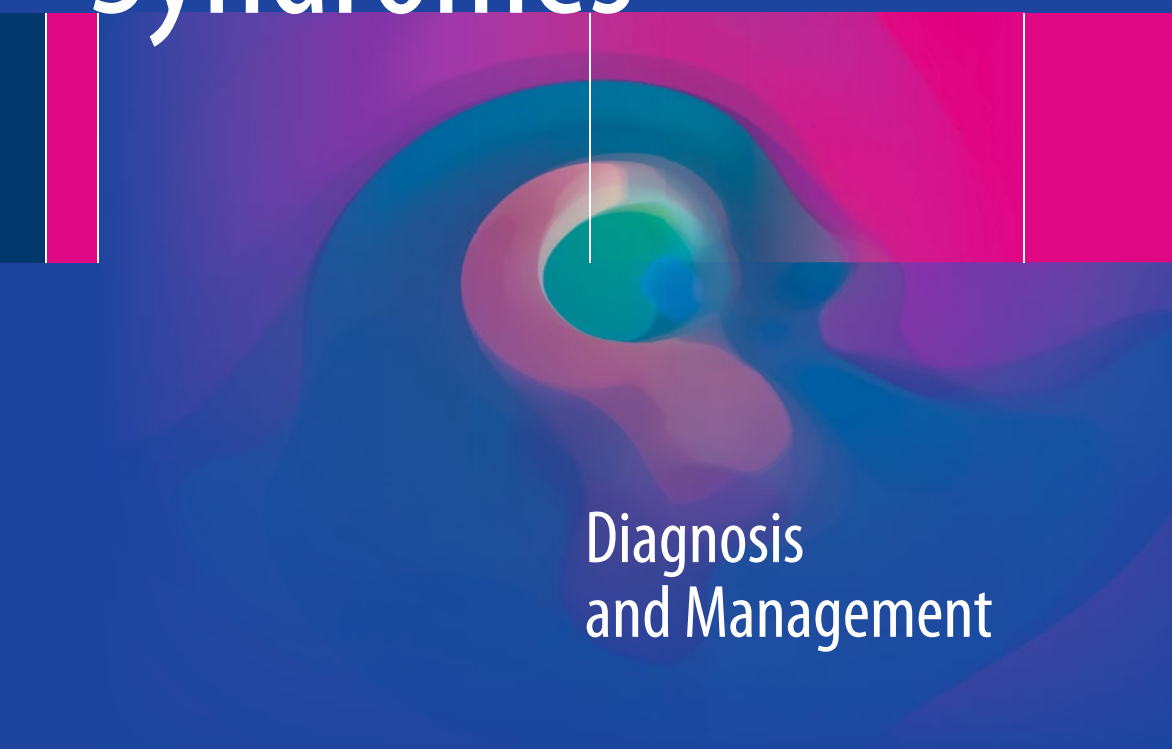
Lisa A. Boardman
Editor

Intestinal Polyposis Syndromes



Diagnosis and Management

Springer

Intestinal Polyposis Syndromes

Lisa A. Boardman
Editor

Intestinal Polyposis Syndromes

Diagnosis and Management

Springer

Editor
Lisa A. Boardman
Division of Gastroenterology
Mayo Clinic
Rochester, MN, USA

ISBN 978-3-319-28101-8 ISBN 978-3-319-28103-2 (eBook)
DOI 10.1007/978-3-319-28103-2

Library of Congress Control Number: 2016932399

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

The majority of colorectal cancers arise from sporadic polyps which are likely secondary to a combination of underlying acquired genetic mutations potentiated by environmental exposures. However, approximately 5 % of people who develop colorectal cancer will have an underlying hereditary colon cancer syndrome that is associated with an increased polyp burden. Classification of a patient into a specific polyposis syndrome is based on both clinical features and when possible genetic test results, yet determining the precise diagnosis is no small task, given the complexity of the histological variations and clinical features that may overlap between these syndromes. Similarly, the risks for extracolonic polyps or cancers as well as the risk for the development of colorectal cancer necessitate an extensive knowledge of how best to diagnose and manage polyp and cancer screening and surveillance for these patients.

This book outlines the known hereditary polyposis syndromes including familial adenomatous polyposis (FAP) syndrome, attenuated FAP, *MUTYH*-associated polyposis, juvenile polyposis syndrome, Peutz–Jeghers syndrome, hereditary mixed polyposis syndrome, inflammatory cap polyposis, PTEN hamartoma syndrome, serrated polyposis syndrome, polymerase proofreading-associated polyposis, and several other newly identified polyposis syndromes of hereditary colorectal cancer. Though not known to be hereditary, Cronkhite–Canada syndrome is also included as an intestinal polyposis condition that is associated with an increased risk for colorectal cancer. The first chapter of the book is an overview of these intestinal polyposis syndromes, demonstrating the degree of overlap among polyp histologies and cancer risks while highlighting the diversity of these conditions. Following this overview, a chapter is dedicated to each of the known polyposis syndromes and outlines the clinical features that are associated with the polyps, the histologic features of these polyps, the risk for colorectal and extraintestinal malignancies, the known molecular genetic mechanisms that lead to the development of the polyps and likely the associated malignancies, cancer surveillance and screening recommendations, and, when available, chemopreventive therapies.

The future for those who have an intestinal polyposis syndrome and those who care for them will evolve as these intestinal polyposis syndromes are more

meticulously categorized. Ultimately, the molecular etiologies and even the definition of how few polyps constitute a polyposis syndrome will be expanded as whole genome and other "omics" technologies are applied to all patients who have developed polyps and/or colorectal cancer. In fact, during the development of this book, four new germline genetic mutations were found to cause intestinal polyposis.

Colorectal cancer screening has proved invaluable, and, in fact, the incidence of colorectal cancer in the general population has decreased with the use of colonoscopy and polypectomy. This is particularly useful in some of the polyposis syndromes, but, unfortunately, for patients with polyps that cannot be managed endoscopically, the need for surgery continues to be a necessity. The long-term hope for patients with polyposis syndromes may be met by further development of chemopreventive agents directed at genetically relevant targets, more tailored screening and surveillance programs, and possibly methodologies for gene editing or correction of genetic defects that may ultimately help these patients avoid the need for invasive surgeries. In the meantime, our intention is to provide a clear, comprehensive guide for recognition and management of individuals with polyposis syndromes.

Rochester, MN, USA Lisa A. Boardman

Contents

Contributors

Badr F. Al Bawardy Division of Gastroenterology, Mayo Clinic College of Medicine, Rochester, MN, USA

Veroushka Ballester-Vargas Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Randall W. Burt Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, UT, USA

Division of Gastroenterology and Hepatology, University of Utah, Salt Lake City, UT, USA

James Church Sanford R. Weiss Center for Hereditary Colorectal Neoplasia, Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, OH, USA

Thomas G. Cotter Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Giovanni De Petris Mountain State Pathology Corp., Penrose Hospital, Colorado Springs, CO, USA

Maurizio Genuardi "A. Gemelli" School of Medicine, Institute of Medical Genetics, Catholic University of the Sacred Heart, Rome, Italy

Eva Hernández-Illán Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain

James R. Howe University of Iowa Carver College of Medicine, Iowa City, IA, USA

Kory W. Jasperson Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, UT, USA

Rodrigo Jover Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain

Miriam Juárez Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain

Kendall Keck University of Iowa Carver College of Medicine, Iowa City, IA, USA

Jessica L. Mester GeneDx Laboratories, Cleveland, OH, USA

BioReference Laboratories, Elmwood Park, NJ, USA

Maureen E. Mork Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Oscar Murcia Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain

Shahrooz Rashtak Mayo Clinic College of Medicine, Rochester, MN, USA

William Rengifo-Cam Division of Digestive and Liver Diseases, University of Texas Southwestern, Dallas, TX, USA

Douglas Riegert-Johnson Mayo Clinic College of Medicine, Jacksonville, FL, USA

María Rodríguez-Soler Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Alicante, Spain

N. Jewel Samadder Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, UT, USA

Division of Gastroenterology and Hepatology, University of Utah, Salt Lake City, UT, USA

Seth Sweetser Division of Gastroenterology, Mayo Clinic College of Medicine, Rochester, MN, USA

Ian Tomlinson Molecular and Population Genetics Laboratory, Oxford Centre for Cancer Gene Research, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

Tiziana Venesio Department of Pathology, Institute for Cancer Research and Treatment, University of Torino, Candiolo, Italy

Eduardo Vilar Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Chapter 1
The Intestinal Polyposes: Clinical and Molecular Overview

Tiziana Venesio and Maurizio Genuardi

Introduction

The intestinal polyposes are a heterogeneous group of conditions characterized by the growth of multiple tumors in the colorectum. Like their isolated counterparts, these tumors can undergo stepwise transformation from benign to malignant stages.

The first description of a patient with multiple colonic polyps, a 15-year-old boy, dates back to 1721 [1]. A few additional single reports were published throughout the nineteenth century, but it was not until 1885 that the first histologically verified case of familial adenomatous polyposis (FAP) was published in Russia [2]. This was soon followed by the first reports of familial recurrence of polyposis either in siblings or across generations [3–5].

Traditionally, the different forms of polyposes have been recognized based on their phenotypic characteristics: number, location, and histological subtype of polyps; risk of progression to colorectal carcinoma (CRC); development of polyps and cancer in other gastrointestinal (GI) locations (stomach, small bowel); extraintestinal cancerous and non-cancerous manifestations. Although parent-to-child transmission was apparently not documented for the first familial cases, who were affected siblings [3, 4], colorectal polyposis has been considered for a long time as an autosomal dominant trait. Of note, the first reported pedigree showing parent-to-child transmission had characteristics of a very rare condition, juvenile polyposis [5]. Autosomal recessive transmission was recognized for the first time in 2002 [6].

T. Venesio
Department of Pathology, Institute for Cancer Research and Treatment, University of Torino, Candiolo, Italy

M. Genuardi (✉)
Institute of Medical Genetics, "A. Gemelli" School of Medicine, Catholic University of the Sacred Heart, Largo Francesco Vito 1, 00168 Rome, Italy
e-mail: maurizio.genuardi@dfc.unifi.it

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_1

Since then, the type of family history (vertical or horizontal involvement; sporadic presentation) has become an important component of the diagnostic process.

However, the intestinal polyposes have substantial phenotypic overlap, which can hamper clinical diagnosis (Table 1.1). In addition, as patients affected with classical syndromes are now often diagnosed at presymptomatic stages in the setting of predictive genetic testing, a growing proportion of the cases identified through endoscopy presents with phenotypes that cannot be easily assigned to one of the known polyposis conditions.

Classification based on the underlying genetic bases can bypass the difficulties met with phenotypic categorization and provides clues on the molecular pathways underlying pathogenesis.

Furthermore, one of the consequences of the introduction of massive parallel sequencing technologies for genetic diagnosis is a faster turnaround time of genetic test reports compared to traditional Sanger sequencing. Results can be available even before the clinical phenotype has been fully defined; consequently, early diagnosis by means of genetic testing can inform clinical evaluation to establish disease extent.

At the same time, histopathological characterization is still a cornerstone in the diagnosis of intestinal polyposis. Therefore, before addressing single genetic entities and outlining their distinctive clinical and molecular features, the main morphological aspects of colorectal polyps will be briefly examined.

Types of Colorectal Polyps

Colorectal polyps associated with inherited syndromes can be grouped into three main categories: adenomatous, serrated, and hamartomatous [7].

Adenomatous polyps (*adenomas*) (Fig. 1.1a, b) are the precursors of the majority of CRCs. Depending on their structure and growth pattern (pedunculated or sessile) they are defined as tubular, tubulovillous, and villous adenomas. The potential of malignant evolution increases from tubular to villous adenomas. While a polyp is by definition a lesion protruding in the lumen of a hollow organ, they can also grow as flat or even depressed lesions in the colorectal mucosa. These are more difficult to detect and, compared to the polyps protruding into the lumen, they may evolve more rapidly to carcinoma.

Serrated polyps are defined by infolded epithelial tufts in the upper crypts and on the luminal surface, imparting a saw-tooth configuration. Two main types of serrated polyps can be recognized: *hyperplastic polyps* and *sessile serrated adenomas/polyps* (Fig. 1.1c, d); the former display minimal architectural changes without cytological atypia and are usually located in the sigmoid colon and rectum, while the latter are often right-sided and large-sized (>1 cm) in which the sawtooth outline is accompanied by dysplastic changes in the epithelium lining the upper portion of the crypts and luminal surface. The two types are also distinguished for their potential of malignant transformation, which is high for sessile serrated and

Table 1.1 Molecular, clinical, and histological features of the intestinal polyposis

Syndrome[a]	Inheritance mode[b]	Gene(s)	Colorectal polyps		Other GI polyps[c]	CRC risk (%)	Other cancers	Other manifestations[d]	Somatic mutation signature[e]
			N	Type[c]					
AAP/ FAP-AFAP	AD	*APC*	>100 (classical form); ≥10 to <100 (attenuated form)	AP; occasionally HP or SSA	DA. GFGP. Gastric AP	100 (FAP) 69 (AFAP)	Duodenum. Thyroid. Hepatoblastoma. Medulloblastoma.	Desmoids. Osteomas. Absent, unerupted or supernumerary teeth. Fibromas. Epidermoid cysts. CHRPE	–
MAP	AR	*MUTYH*	>100 (classical); ≥10 to <100 (attenuated); occasionally 0–9	AP; SSA; HP	DA. GFGP	43–100	Duodenum	Skin and jaw lesions described but incidence to be verified	Excess of *KRAS* and *APC* G>T transversions
NAP	AR	*NTHL1*	<10 to 50	AP	DA	?	Endometrium	–	Excess of C>T transitions

(continued)

Table 1.1 (continued)

Syndrome[a]	Inheritance mode[b]	Gene(s)	Colorectal polyps		Other GI polyps[c]	CRC risk (%)	Other cancers	Other manifestations[d]	Somatic mutation signature[e]
			N	Type[c]					
PPAP	AD	*POLD1* *POLE*	<10 to 100 or none	AP; occasionally HP	DA	?	Endometrium. Brain (gliomas)	–	Increased frequency of all base substitutions, namely C:G>T:A and A:T>C:G
JPS	AD	*SMAD4* *BMPR1A*	<5 to >100	JP; occasionally AP, HP, mixed	Gastric and small bowel JP	38–68	Stomach. Pancreas	Telangiectasias. Arteriovenous malformations	–
PJS	AD	*STK11*	>	PJP	Gastric and small bowel PJP	12–39	Breast. Pancreas. Small bowel. Stomach. Sex cord tumors with annular tubules of the ovary. Adenoma malignum of the cervix. Large calcifying Sertoli cell tumors of the testis. Lung	Mucocutaneous pigmentation	–

PHTS	AD	*PTEN*	≥3	Atypical JP; HP; AP; Ganglioneuroma; Lipoma	Gastric JP, HP, AP. Ganglioneuroma	9–16	Breast. Thyroid. Endometrium. Melanoma. Kidney	Macrocephaly. Mucocutaneous hamartomas (trichilemmomas; papillomatous papules). Acral keratoses. Benign thyroid disease. Breast fibrocystic disease. Hemangiomas. Lhermitte–Duclos disease. Lipomas. Penile freckling. Autism spectrum disorder	–
HMPS	AD	*GREM1* *BMPR1A*	?	Mixed; HP; AP; IP	–	?	–	–	–
SPS	?	?	≥5	SSA; HP; occasionally AP	–	~>50 %	–	–	CIMP. *BRAF* mutation

[a]See text for abbreviations

[b]*AD* autosomal dominant, *AR* autosomal recessive

[c]*AP* adenomatous polyps, *JP* juvenile polyps, *HP* hyperplastic polyps, *PJP* Peutz–Jeghers polyps, *SSA* sessile serrated adenomas, *IP* inflammatory polyps, *DA* duodenal adenomas, *GFGP* gastric fundic gland polyps

[d]*CHRPE* congenital hypertrophy of the retinal pigmented epithelium

[e]*CIMP* CpG island methylator phenotype

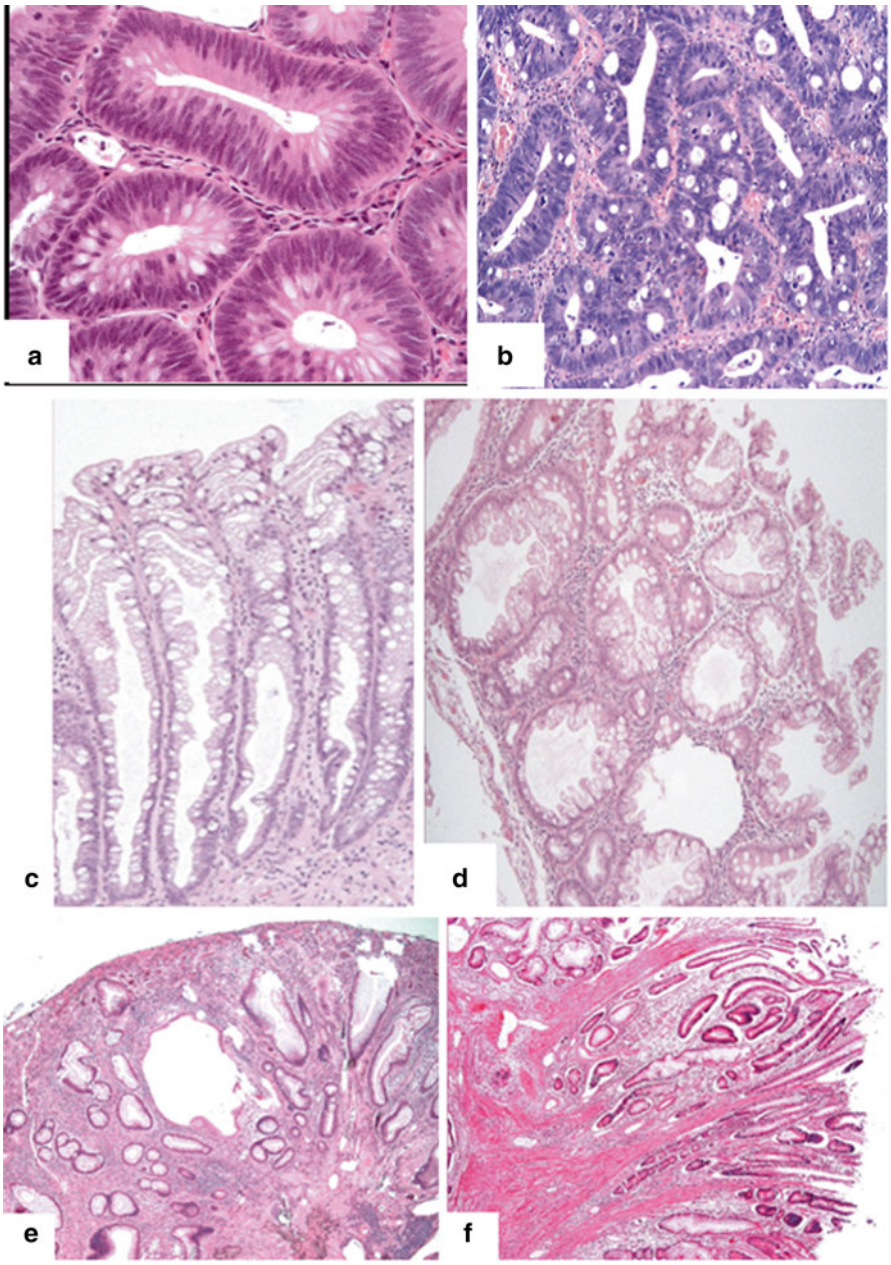


Fig. 1.1 Histological appearance of colorectal polyps. Villous adenomas with low grade (**a**) and high grade (**b**) dysplasia. Hyperplastic polyp (**c**). Sessile serrated adenoma (**d**). Juvenile polyp (**e**). Peutz–Jeghers polyp (**f**). Modified from Ref. [7]

negligible for hyperplastic polyps. In mixed hyperplastic polyp/adenomas, one or more serrated components (hyperplastic or sessile serrated) are associated and/or intermingled with classical adenomatous tissue, with separate identifiable areas of each histopathological type [8–10].

Hamartomatous polyps are characterized by a disorganized overgrowth of the tissues that normally make up the colorectum. Two main types can be recognized: *juvenile polyps,* which are spherical lesions containing edematous tissue that surrounds cystically dilated glands filled with mucin (Fig. 1.1e), and *Peutz–Jeghers polyps*, characterized by a central core of arborizing bands of smooth muscle covered by normal or hyperplastic glandular epithelium (Fig. 1.1f). Juvenile polyps are the main clinical component of juvenile polyposis syndrome. A variety characterized by a predominance of myofibroblasts and often difficult to distinguish from the classical juvenile polyps is associated with Cowden syndrome and other conditions due to mutations of the *PTEN* gene [11].

Inflammatory polyps are another not infrequent type, but they usually arise in patients with inflammatory bowel disease or other rare conditions, and are very rarely found in patients with hereditary polyposes. These are reactive lesions, sharing some histological similarity with juvenile polyps, and devoid of malignant potential.

On the other hand, some rare lesions, such as *intestinal lipomas* and *ganglioneuromas*, can be found in hereditary syndromes.

The inherited polyposes can be classified into three main subcategories, adenomatous, hamartomatous, and serrated, based on the predominant type of polyps. Although serrated polyposis is a well-recognized entity, its genetic basis is still largely unknown, so that it currently cannot be considered a proper "genetic" syndrome.

Adenomatous Polyposes

APC *Associated Polyposis (AAP)*

Clinical Aspects

This definition encompasses a set of heterogeneous autosomal dominant presentations characterized by the tendency to develop colorectal adenomas. These can be differentiated based on the number of polyps (*attenuated*, *classical*, *profuse*). The classical form, characterized by the presence of ≥100 adenomas, has been traditionally termed *familial adenomatous polyposis* (FAP). However, since the FAP phenotype is also common to other adenomatous polyposes, herewith the term AAP is used to define the condition caused by *APC* constitutional mutations. This also applies to the attenuated form (known as *attenuated familial adenomatous polyposis* or AFAP), which is defined by a lower number of adenomas (<100). Although AAP is associated by definition with conventional adenomas, serrated polyps are also occasionally found [12]. Before the introduction of prophylactic surgery, the

risk of CRC in classical AAP was 100 %, with a median age at diagnosis of 39 years [13]. Attenuated forms are also at high CRC risk, albeit at later ages.

AAP is associated with a range of extracolonic manifestations, including benign and malignant GI and extra-GI tumors (Table 1.1). Subtypes of AAP characterized by the presence of specific non-GI tumors have been recognized for a long time. In Gardner syndrome GI manifestations are associated with osteomas, epidermoid cysts, fibromas, and desmoids. Another subtype is Turcot syndrome (TS), which is defined by the presence of colorectal polyps and brain tumors. However, TS is phenotypically and genetically heterogeneous. The typical brain cancer in patients with *APC* mutations is medulloblastoma, while the other forms of TS, which are due to DNA repair defects, are associated with tumors of glial origin (see below).

Molecular Aspects

APC is a large gene, coding for a full-length protein containing 2843 amino acids, and the spectrum of mutations in AAP is highly heterogeneous. Genotype–phenotype correlations are well established and explain at least in part the variable phenotype [14].

In the past two decades the characterization of the genetic pathways involved in the progression of hereditary CRC syndromes has largely contributed to understand the carcinogenesis of CRC. To date three distinct molecular pathways have been recognized in sporadic CRC: the chromosomal instability (CIN), the microsatellite instability (MSI), and the CpG island phenotype (CIMP) pathway; two of these pathways, CIN and CIMP, have been characterized by studying polyposis syndromes.

The first model was associated with AAP/FAP: it was proposed as a reference for the adenoma-carcinoma sequence by Fearon and Vogelstein in 1990 [15]. In this model, *APC* and the Wnt pathway play a central role in the process leading to the formation of small adenomas.

According to this sequence, the key initiating step would be provided by complete *APC* loss, which is achieved by somatic inactivation of the second allele. The somatic hit of the *APC* gene is a non-random event which strictly depends on the position of the *APC* germline mutation and is selected for conferring the best growth advantage to the colonocytes [16]. The APC protein mainly acts as a negative regulator of β-catenin, the effector of the Wnt pathway; as a consequence, the greatest growth advantage is conferred by germline mutations in the β-catenin binding domain, around codon 1300, the so-called *Mutation Cluster Region* (MCR). Loss of heterozygosity (LOH), which has been reported in 20 % of FAP adenomas, is the somatic hit preferentially associated with MCR germline mutations. By converse, patients carrying constitutional alterations located in other regions of the *APC* gene tend to select second, or even third, hits in the MCR to compensate for the weaker selective advantage of the first germline alteration [17]. In addition, it has been shown that even single mutated *APC* alleles can create changes in the precancerous colon crypt, such as increased number of stem cells and increased crypt fission, which are accompanied by changes in DNA methylation and increased mutation rates [18].

APC loss is followed by increased activation of the Wnt signaling pathway through the stabilization and nuclear localization of β-catenin. Supporting this model, the expression of β-catenin and related proliferative and apoptotic target genes (CYCLIND1, BCL-2, CASPASE-3, and KI-67) have been reported in adenomas but not in the corresponding healthy tissues from FAP patients [19].

So far, questions about the order of the events following *APC* loss have been raised and additional Wnt-independent functions of *APC* as well as the activation of other genes have been proposed to contribute to both initiation and development of adenomas [20]. Accordingly, polyclonal genetic defects have been found in advanced FAP adenomas, supporting the notion that independent mutated clones can arise during adenoma development [21].

It is known that Wnt activation may occur in the absence of detectable nuclear β-catenin accumulation since loss of *APC* function can be insufficient for nuclear β-catenin translocation; in early adenomas this accumulation might be influenced by the position of the cells, with the involvement of paracrine factors [22]. In addition, copy number changes of *APC* and/or activating mutations in the *KRAS* or *BRAF* proto-oncogenes could also contribute in enhancing Wnt signaling and nuclear β-catenin translocation through the activity of RAC and JNK [23, 24]

According to in vitro analyses, adenoma initiation would be supported by the interaction of APC with the transcriptional co-repressor CTBP1, whereas nuclear β-catenin localization would be achieved later through *KRAS* activation [25]. However, it has been reported that nuclear β-catenin staining can be observed in a vast majority of FAP adenomas, whereas *KRAS* mutations are detectable in only 10 % of these cases, independently of beta-catenin subcellular localization [26]. Although the type of synergism is still unknown, when *APC* is lost, *KRAS* activation results in larger, more aggressive lesions. Accordingly, an in vivo mouse model has recently shown that activated *KRAS* can accelerate *APC*-initiated intestinal adenomagenesis with a striking tumor promotion in large intestines [27].

Chromosomal aberrations contribute early to the progression of adenomatous polyposis, after biallelic inactivation of *APC* [28]. Loss or truncation of *APC* causes mitotic spindle defects that, upon somatic inactivation of other putative CIN genes (e.g., spindle and cell cycle checkpoint genes, DNA repair, telomere maintenance, etc.), cause the onset of chromosomal aberrations and aneuploidy [29].

MUTYH-*Associated Polyposis (MAP)*

Clinical Aspects

This condition is transmitted as an autosomal recessive trait. The phenotype tends to be milder compared to AAP (Table 1.1). The number of adenomas can be >100, but profuse polyposis, with thousands of polyps, is never observed. More often the presentation is similar to attenuated AAP/AFAP, with predominant involvement of the proximal colon [30]. Usually ≥10 polyps are found; although in population-based

series of CRC, up to one-third of patients diagnosed with MAP have none or <10 polyps at presentation [31]. In fact the phenotype can overlap that of Lynch syndrome. Although adenomas usually represent the major histologic type of polyps in MAP, nearly half of MAP patients have hyperplastic polyps and sessile serrated adenomas [32–34], with a phenotype resembling serrated polyposis (see below). The incidence of extraintestinal manifestations is lower than in FAP or AFAP [35].

Molecular Aspects

MAP is caused by biallelic mutations of *MUTYH*, which codes for a DNA glycosylase involved in the base excision (BER) system. MUTYH repairs mismatches induced by the variant base 8-oxo-guanine, a product of DNA oxidation. *MUTYH* mutations found in MAP patients cause reduced or absent enzymatic activity. Consequently, secondary mutations accumulate in somatic cells and can affect genes that initiate or drive neoplastic transformation [36].

Phenotypic variability in MAP may be partly related to the effects of the different *MUTYH* mutations. Two variants, p.Tyr179Cys and p.Gly396Asp, account for approximately 70 % of *MUTYH* alterations in the patients of European ancestry. p.Tyr179Cys completely abolishes enzymatic activity and is associated on average with a classical phenotype, whereas p.Gly396Asp is a hypomorphic variant more frequently found in patients with an attenuated presentation. p.Gly396Asp is more frequent than p.Tyr179Cys in the general population, while the opposite is found in MAP patients, suggesting the existence of a stronger selective pressure against p. Tyr179Cys [37].

Presently, *MUTYH* driven carcinogenesis is only partly known, but it appears that it follows a distinct progression compared to the pathways involved in other types of polyposis or hereditary colorectal syndromes. Some features overlap with the adenoma-carcinoma sequence and the CIN phenotype, including frequent *APC*/*KRAS* mutations, LOH of *APC* and near-diploid karyotype, while some others, including loss of HLA class I expression, are shared with the MSI phenotype, [36, 38–40].

As a consequence of the inability to repair mismatches induced by 8-oxo-guanine, deficiency of *MUTYH* results in adenomas and colorectal tumors with an excess of the specific c.34G>T transversion in *KRAS*, which can be considered the hallmark of this syndrome; the *APC* gene can also be affected by G>T transversions, which mainly occur in the context of GAA sequences, resulting in stop codon formation and gene inactivation [41].

It has been observed that MAP-associated hyperplastic polyps and sessile serrated adenomas have a characteristic molecular background [34]. In particular, *KRAS* gene mutations were found in 70 % of these lesions; of relevance, G>T transversions accounted for 94 % of the mutations in hyperplastic/sessile serrated polyps, whereas *APC* mutations were detected only in adenomas of the same patients, suggesting two independent tumor pathways, one leading to adenomas *via APC*, and the other leading to hyperplastic/sessile serrated polyps *via KRAS* mutations.

Similar to Lynch syndrome, MAP patients have a high risk for the development of CRC, even under surveillance, which suggests accelerated progression [42]. The high prevalence of G>T transversions could have a role in this acceleration. In support of this hypothesis, it has been recently shown that MAP tumor progression can be characterized by the early onset of specific *KRAS* mutations in association with non-random and potentially pathogenetic mutations in mitochondrial DNA involved in oxidative phosphorylation [43].

NTHL1 *Associated Polyposis (NAP)*

Like MAP, this form of polyposis is autosomal recessive and is caused by biallelic mutations in a BER gene. This entity has been described only very recently [44] following whole exome sequencing analyses of 51 patients from 48 families with multiple colonic adenomas who had turned out negative upon molecular screening of known genes. Homozygosity for the same nonsense mutation (c.268C>T; p.Gln90*) was found in seven patients from three families, all of Dutch origin. The clinical characteristics were: polyp range 8–50 (all adenomatous), multiple primary CRCs from 40 years of age, endometrial cancer or complex hyperplasia in all three affected females, and duodenal adenomas and cancer in one individual each (Table 1.1).

Tumors showed a specific mutation signature, characterized by an excess of C>T transitions. The different somatic mutation pattern compared to MAP tumors can be explained by different repair specificities of *MUTYH* and *NTHL1*. However, more data are needed to gain a deeper insight on the clinical and molecular characteristics of this condition. By analogy to MAP, we propose the use of the acronym NAP for this condition.

Polymerase Proofreading Associated Polyposis (PPAP)

Clinical Aspects

An autosomal dominant condition caused by monoallelic mutations of the DNA polymerase subunit genes *POLD1* and *POLE* has recently been identified using a whole genome sequencing approach in patients with unexplained multiple adenomas and/or young onset CRC [45]. Based on a review of 69 carriers from 29 families [46], the colorectal phenotype is variable, ranging from oligopolyposis (<10 polyps) to attenuated polyposis (≥10–100) with or without CRC, to isolated young onset CRC or large adenomas, or a family history fulfilling type I Amsterdam criteria for Lynch syndrome [47] in the absence of constitutional mismatch repair (MMR) gene mutations (Table 1.1). Hyperplastic polyps can also been detected, and in patients with oligopolyposis, they can occasionally represent the only polyp type. Although there are no available estimates as yet, pedigree analysis strongly suggests an increased risk for

cancers outside the GI tract, namely endometrial carcinoma for *POLD1* mutation carriers and brain tumors (gliomas) for *POLE* (and possibly also *POLD1*) carriers. Therefore, PPAP can present with an autosomal dominant TS phenotype characterized by the tendency to develop tumors of glial derivation. The combination of gliomas, colorectal adenomas, and CRC can also be observed in individuals with MMR gene pathogenetic variants, either monoallelic or biallelic; the former are associated with Lynch syndrome, and the latter with the more severe and rare constitutional mismatch repair deficiency syndrome and very young age onset adenomas and CRC.

Molecular Aspects

So far only a few mutations have been detected in *POLD1* and *POLE* [46], the most common being *POLD1* p.Ser478Asn and *POLE* p.Leu424Pro. All mutations occur in the exonuclease proofreading domain of the two proteins. These determine a mutator phenotype, as shown by the very high frequency of somatic mutations observed in tumors with *POLD1* or *POLE* defects [45].

POLE and *POLD1* do not seem to act as classical tumor suppressor genes since only a minority of tumors from carriers of constitutional mutations show LOH or other inactivating alterations acting as second "hits." In addition, somatic mutations of the MMR genes *MSH2* and *MSH6* have been found in CRCs harboring *POLE* or *POLD1* constitutional mutations. Interestingly, the Cancer Genome Atlas (TCGA) exome sequencing project has provided evidence for *POLE* being the target of recurrent somatic mutations in the DNA binding pocket, adjacent to the exonuclease active site, in MMR-proficient, but "ultramutated" CRCs (3 % of CRCs) [48]. Compared to *POLE*-wild-type tumors, these neoplasms show an increased number of somatic base substitutions of all types, with C:G>T:A changes being the most common [45, 48, 49]. Moreover, the presence of *POLE* mutations seems to affect the spectrum of somatic alterations in target genes, which is characterized by the onset of unusual driver missense substitutions, such as mutations on codons 117 and 146 in *KRAS* and codon 88 in *PIK3CA*; these alterations, probably suboptimal for conferring growth advantage with respect to the classical mutations, such as those on *KRAS* codons 12 and 13, would be sufficient in proofreading deficient cells to rapidly acquire additional mutations [45, 50].

The Hamartomatous Polyposes

Juvenile Polyposis Syndrome (JPS)

Clinical Aspects

JPS is a rare autosomal dominant condition characterized by the development of juvenile polyps. As juvenile polyps can occur in individuals not affected with JPS, specific diagnostic criteria have been devised for this condition [51]. The polyps usually have the typical spherical appearance of juvenile polyps, but some are

larger, up to 5 cm diameter, multilobulated, and can contain foci of adenomatous dysplasia, which are deemed to be the precursors of carcinomas in this condition [11]. Occasionally other types of polyps, adenomatous, hyperplastic and of mixed histology are observed. Individuals with JPS have a 9–50 % risk of developing GI cancers [52], including CRC and, less frequently, carcinomas of the upper GI tract, namely of the stomach or pancreas (Table 1.1).

Molecular Aspects

A constitutional mutation in the *SMAD4* or *BMPR1A* genes can be found in 50 % of JPS patients [53, 54]. Both genes are involved in the BMP/TGF-beta signaling pathway; however, their role in leading to polyp formation is still poorly understood. According to Haramis et al. [55] (2004), polyps could develop through the defective cell population lying in the stromal compartment, and tumor growth of the epithelial cells would be a result of this abnormal microenvironment. Interestingly, inactivation of the second allele of *SMAD4* or *BMPR1*A in the epithelial cell compartment does not seem to be the initiating event of polyp formation or cancer progression [56].

The TGF-beta signaling pathway is also affected in hereditary hemorrhagic telangiectasia (HHT). So, it is not surprising that a fraction up to 22 %, and possibly higher, of JPS patients have a mixed JPS-HHT phenotype.

Peutz–Jeghers Syndrome (PJS)

PJS is an autosomal dominant condition defined by a characteristic mucocutaneous melanotic pigmentation and hamartomatous polyps of the Peutz–Jeghers type [57] (Table 1.1). Peutz–Jeghers polyps develop mainly in the small bowel, but they can also occur in the colorectum and stomach. The most common disease presentation is with small bowel obstruction or intussusceptions in the second or third decades. PJS patients are at markedly increased risk of CRC and other cancers. The relative and the cumulative risk for any cancer range from 9.9 to 18 and 37 % to 93 %, respectively [58].

Constitutional mutations of the *STK11* (*LKB1*) gene are found in about 80–94 % of the families. The inactivation of this tumor-suppressor gene would play a role in the hamartoma-carcinoma transition by up-regulating Wnt signaling pathway via GSK3beta [59].

PTEN *Hamartoma Tumor Syndrome (PHTS)*

Clinical Aspects

PHTS encompasses a heterogeneous set of autosomal dominant conditions characterized by the development of hamartomatous lesions and other manifestations, caused by alterations of the *PTEN* gene [60] (Table 1.1). The main clinical presentations are

Cowden syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome (BRRS); these can be distinguished based on the phenotype, which is partially overlapping, and on age at onset, childhood for BRRS and usually adolescence/young adulthood for CS. Macrocephaly is very common in all clinical presentations; developmental delay and intellectual disability are associated with BRRS, while CS shows characteristic mucocutaneous lesions. From a literature review of 107 PHTS patients who underwent colonoscopies, colonic polyps were detected in 92.5–95 % of patients [61]. Polyps can be of different histological types: hyperplastic (43.6 %), adenoma (40.4 %), hamartoma (38.3 %), ganglioneuroma (33 %), and inflammatory (24.5 %) [62, 63]. Intestinal lipomas can also occur. More than half of the patients present with multiple histological types. Actually, the lesions defined as ganglioneuromas in PHTS are deemed to be JPs with a very abundant stromal ganglion cell component [64, 65]. PHTS patients are at increased risk of CRC as well as other cancers.

Molecular Aspects

Inactivation of a single copy of *PTEN* is sufficient to promote tumor growth in experimental models [66, 67]. Therefore *PTEN* can act through a haploinsufficiency mechanism and is not a classical tumor suppressor gene. It is still unclear whether the development of the intestinal lesions in PHTS is driven by loss of *PTEN* expression in the epithelial or stromal compartment. Recently it has been shown that epithelial-specific *PTEN* deletion could cause formation of juvenile polyps in the colon-rectum of Cowden syndrome patients without the involvement of stromal *PTEN* loss [68].

Juvenile Polyposis of Infancy

This is a very rare and extremely severe form of polyposis caused by microdeletions of the 10q23.2–10q23.3 region, which contains the *BMPR1A* and *PTEN* genes [69, 70]. Polyps develop early in childhood throughout the GI tract (stomach, small bowel, and colon). It is associated with variable degrees of developmental delay and intellectual disability, as well as with congenital anomalies, namely congenital heart disease. The facial appearance, with macrocephaly, is similar to PHTS.

Hereditary Mixed Polyposis Syndrome (HMPS)

Clinical Aspects

HMPS is defined by the development of polyps of different histology confined to the colon-rectum and an increased risk of CRC, with mean age at diagnosis of 48 years. The following types of polyps are found in this condition: adenomas,

including flat lesions, hyperplastic polyps, inflammatory polyps, and, characteristically, atypical juvenile polyps, with mixed features of hamartomas and adenomas (Table 1.1). The condition was originally described in a large family of Ashkenazi origin with an autosomal dominant transmission pattern [71]. The phenotypes of JPS and HMPS may therefore overlap and be indistinguishable in some cases.

Molecular Aspects

HMPS and JPS share a common pathogenesis, related to the disruption of the bone morphogenetic protein pathway. The molecular defect identified in the original Ashkenazi HMPS family is a 40 kb duplication on chromosome 15q13.3 [72]. The duplication segregated with the HMPS phenotype in the family and has been subsequently detected in additional HMPS Ashkenazi families. More recently, it has also been found in an Ashkenazi individual with a family history of LS [73], suggesting that it can underlie also other phenotypic presentations. The duplication encompasses a large segment of the *SCG5* gene, and ends just upstream of the CpG island of the *GREM1* gene. Functional analyses have demonstrated that it has no effects on *SCG5* expression, whereas the expression of *GREM1* mRNA and protein is increased and ectopic in intestinal crypt cells [74]. A subset of HMPS, noted in four Singapore Chinese families and one Irish pedigree, is instead associated with mutations of *BMPR1A* [75, 76].

Polyposes of Unknown Etiology

Serrated Polyposis (SPS) Syndrome

Clinical Aspects

Described four decades ago, SPS is a relatively rare condition, characterized by multiple and/or large serrated polyps that has been associated with an increased personal and familial risk of CRC [77, 78]. SPS diagnosis is clinical and requires the following: (1) ≥5 serrated polyps proximal to the sigmoid colon, of which two or more greater than 10 mm in diameter, or (2) any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first degree relative with SPS; or (3) >20 serrated polyps of any size, but distributed throughout the colon [79]. Hyperplastic polyps are frequently reported, and occasionally also adenomas (Table 1.1). The higher the numbers of hyperplastic polyps and adenomas, the higher is the risk of CRC [80]. No extraintestinal manifestations have been reported so far [81], and the mode of inheritance, if any, has not yet been established. Occasionally, familial aggregations of SPS have been observed, but more commonly relatives develop CRC in the absence of SPS [33, 78, 82–85].

Molecular Aspects

SPS presently remains one of the most poorly molecularly understood of all intestinal polyposes, which suggests that it may be a group of diseases rather than a single entity. The somatic genetic alterations found in this condition are mostly activating mutations of the *BRAF* oncogene and a widespread gene promoter hypermethylation (CIMP) which can affect several genes, including *MGMT*, *MLH1*, *APC*, and *MCC* [77]. Sessile serrated adenomas can exhibit both early *BRAF* mutations and the CIMP pattern.

It has been shown by in vitro analysis that activated *BRAF* induces an initial burst of MEK-dependent proliferation leading to the formation of hyperplastic crypts. These crypts remain dormant for a prolonged period due to the upregulation of senescence–associated beta–galactosidase and p16(Ink4a); subsequent tumor progression is thought to be associated with down-regulation of p16(Ink4a) by CpG methylation of exon 1 [86]. CIMP is also an early event since it has been reported in the normal colonic mucosa of individuals with a high burden of hyperplastic polyps [87].

Hyperplastic polyps have traditionally been considered not to have malignant potential, but they frequently harbor *KRAS* mutations. In a study performed on aberrant crypt foci, a strong inverse relation was found between the presence of *BRAF* and *KRAS* mutations and the serrated and hyperplastic components, with *BRAF* strictly associated with the serrated component [88]. However, it has been shown that the frequency of *BRAF* or *KRAS* mutations cannot differentiate phenotypes of SPS [89]. It has also been observed that independent of the number of serrated polyps, only a few CRCs demonstrate a *BRAF* mutation, thus suggesting that tumors can arise within lesions other than serrated adenomas [90]. It is conceivable that an alternative pathway driven by *KRAS* mutations could contribute to the carcinogenesis in both hyperplastic and serrated polyposis [84].

Cap Inflammatory Polyposis

Cap polyposis is mainly confined to the sigmoid colon, with or without diverticular disease. The specific localization and the absence of inflammatory bowel disease distinguish it from the more common secondary inflammatory polyposis. Polyps may histologically display smooth muscle proliferation within the lamina propria, erosion of the surface epithelium, or reactive epithelium with serration, hence showing similarities with Peutz–Jeghers, juvenile, and serrated polyps. The definition derives from the presence of a “cap” of granulation tissue on the surface [90]. Its pathogenesis is currently unknown and no extraintestinal manifestations have been reported.

Cronkhite–Canada Syndrome

Cronkhite–Canada syndrome is a rare disease characterized by diffuse polyposis of the GI tract, diarrhea, weight loss, abdominal pain, cutaneous hyperpigmentation, dystrophic changes of fingernails, and alopecia [91, 92]. Most polyps are juvenile-like, with not infrequent adenomatous changes. Conventional and serrated adenomas have also been described. The etiology is unknown, although an autoimmune pathogenesis has been proposed.

A Practical Approach to the Intestinal Polyposes

The correct diagnosis of an intestinal polyposis syndrome requires careful assessment of the following characteristics (Box 1.1):

- Number, histology, and location of polyps
- Age at diagnosis
- Family history (including evidence of consanguinity and ethnic background)
- Other GI and extra GI clinical manifestations.

Box 1.1: Clinical Assessment of the Hereditary Colorectal Polyposes
Polyp characteristics: number, type, histology, and distribution in the colorectum and throughout the GI tract. Profuse (>5000 synchronous lesions) polyposis is only associated with *APC* mutations, and polyps are mainly adenomatous. Attenuated adenomatous polyposes, especially MAP, preferentially involve the right bowel. By definition, juvenile and Peutz–Jeghers polyps are associated with JPS and PJS, respectively. However, the juvenile polyps can be found in other genetic forms and they can also occur as sporadic non-genetic lesions. More rarely, the presence of unusual lesions, such as the ganglioneuromas associated with PHTS, can point to a specific condition.

Age at diagnosis. PJS and JPS can present in childhood, the first with intussusception due to the growth of polyps in the small bowel, and the second with bleeding, anemia, and protein losing enteropathy. The adenomatous polyposes, mainly AAP, can present in adolescence, young adulthood, or later in life, depending on polyp burden. AAP rarely presents in childhood; when this occurs, the initial manifestation is a rare tumor (hepatoblastoma or medulloblastoma).

Family history. In the adenomatous polyposes, vertical transmission is indicative of AAP. Involvement of siblings with no affected parent is suggestive of autosomal recessive inheritance (MAP or NAP). However, occasional MAP pedigrees can show apparent autosomal dominant transmission of ade-

(continued)

nomatous polyposis due to marriage between affected individuals and unrelated healthy carriers, who are not rare in the general population (1:100–1:50). Sporadic cases of adenomatous polyposis can be due to *APC* mutations, acquired either through de novo mutation or post-zygotic constitutional mosaicism, or to biallelic mutations of *MUTYH* or *NTHL1*. If there is consanguinity between the parents of a sporadic case or of affected siblings, an autosomal recessive form (MAP or NAP) should be suspected. Positive family history of PJS or JPS is major criteria for the diagnosis of these conditions. Although PPAP is autosomal dominant, its penetrance and phenotype are not yet defined.

Other GI and non-GI manifestations. Extracolonic manifestations are more frequent in *APC* mutation carriers than in MAP; these may involve the GI tract (duodenal adenomas, gastric fundic polyps, and more rarely gastric adenomas) or other organs (osteomas, supernumerary teeth, epidermoid cysts). Desmoids are associated with AAP. Pilomatricomas and sebaceous tumors have been observed in MAP, but they are not specific. Multiple congenital hypertrophy of the pigmented epithelium of the retina (CHRPE) lesions are found in up to 90 % of classical or profuse AAP patients; these were once used as a marker of the presence of the gene in young children, but they can also occur in MAP, though more rarely (<10 % of the cases). PJS patients can be easily identified through the presence of the typical pigmentation, although this can occur in individuals who do not have this disease. PHTS is usually recognized for non-GI manifestations (macrocephaly, characteristics mucocutaneous hamartomas and other skin lesions, Lhermitte–Duclos disease or dysplastic gangliocytoma of the cerebellum).

In some cases the diagnosis can be easily made based on the clinical presentation. For instance, classical or profuse adenomatous polyposis with parent-to-child transmission in multiple generations is associated with AAP/FAP. However, genetic diagnosis is still mandatory, especially for the purpose of familial follow-up, as there is a small fraction of such pedigrees in which pathogenetic variants of *APC* cannot be detected despite intensive laboratory investigations.

The accuracy of genetic tests and their increasing availability have moved molecular diagnosis to the forefront of the clinical work up of patients with a recent diagnosis of polyposis. Molecular diagnosis does not replace thorough clinical evaluation, but it can reduce unnecessary tests and procedures.

The role of genetic analyses for the diagnosis of colorectal polyposis is likely to expand. One of the reasons is the possibility that an increasing number of new polyposis genes will be identified. The most recent discoveries in the field of hereditary CRC and polyposis [44, 45, 93] indicate that the newly detected genes account for only very small numbers of cases, especially when compared to the genes—i.e., *APC*

and the MMR genes—that were first identified in the last 25 years. Therefore it is not unreasonable to expect that the fraction of the as yet unexplained genetic polyposes might comprise a high number of ultra-rare conditions, each caused by a different gene. Should this happen, the use of high-throughput molecular tests will become instrumental to obtain an accurate diagnosis and to allow the identification of at risk relatives for the implementation of adequate surveillance and preventative actions.

Molecular tests performed on tumor tissue can be useful for diagnosis and for the prediction of treatment response. Somatic tests—i.e., MSI and immunohistochemical analysis of MMR gene products—are commonly used to identify Lynch Syndrome, but they are also predictors of response to 5-fluoruracil and, more recently, to PD-1 inhibitors [94]. Other genetic markers (i.e., *KRAS* and *BRAF* mutations) are commonly searched for in CRC DNA to tailor therapy. Likewise, knowledge of somatic mutation patterns—i.e., the specific base substitutions associated with MAP, PPAP, or NAP—can be useful for the correct identification of a polyposis syndrome [95].

Finally, it is not unrealistic to expect that targeted pharmacological therapies will become available for the intestinal polyposes [96], by analogy to recent advances in precision medicine that have proven to be useful for other hereditary cancers [97–99]. In this case, knowledge of the genetic cause of the polyposis and/or of the molecular blueprint of the tumors would become essential to establish appropriate treatment.

References

1. Menzel D. De excrescentiis verrucoso cristosis copiose in intestinis crassis dysenteriam passi observatis. Acta Med Berol. 1721;68–71.
2. Sklifasowski NW. Polyadenoma tractus intestinalis. Vrac. 1881;4:55–7.
3. Cripps WH. Two cases of disseminated polypus of the rectum. Trans Path Soc London. 1882;33:165–8.
4. Smith T. Three cases of multiple polypi of the lower bowel occurring in one family. St Bartholomew's Hosp Rep. 1887;23:225–9.
5. Bickersteth RA. Multiple polypi of the rectum occurring in a mother and child. St Bartholomew's Hosp Rep. 1890;26:299–301.
6. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, et al. Inherited variants of MYH associated with somatic G:C→T:A mutations in colorectal tumors. Nat Genet. 2002;30:227–32.
7. Lucci-Cordisco E, Risio M, Venesio T, Genuardi M. The growing complexity of intestinal polyposis syndromes. Am J Med Genet A. 2013;161A:2777–87. doi:10.1002/ajmg.a.36253.
8. Snover DC. Serrated polyps of the large intestine. Semin Diagn Pathol. 2005;22:301–8.
9. Torlakovic EE, Gomez JD, Driman DK, Parfitt JR, Wang C, Benerjee T, Snover DC. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). Am J Surg Pathol. 2008;32:21–9.
10. Lanza G, Messerini L, Gafà R, Risio M. Colorectal tumors: the histology report. Dig Liver Dis. 2011;43 Suppl 4:S344–55. doi:10.1016/S1590-8658(11)60590-2.
11. Jass JR. Colorectal polyposis: from phenotype to diagnosis. Pathol Res Pract. 2008;204:431–47.
12. Matsumoto T, Iida M, Kobori Y, Mizuno M, Nakamura S, Hizawa K, Yao T. Serrated adenoma in familial adenomatous polyposis: relation to germline APC gene mutation. Gut. 2002;50:402–4.

13. Cruz-Correa M, Giardiello FM. Familial adenomatous polyposis. Gastrointest Endosc. 2003;58:885–94.
14. Friedl W, Aretz S. Familial adenomatous polyposis: experience from a study of 1164 unrelated German polyposis patients. Hered Cancer Clin Pract. 2005;3:95–114. doi:10.1186/1897-4287-3-3-95.
15. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61:759–67.
16. Lamlum H, Ilyas M, Rowan A, Clark S, Johnson V, Bell J, et al. The type of somatic mutation at APC in familial adenomatous polyposis is determined by the site of the germline mutation: a new facet to Knudson's 'two-hit' hypothesis. Nat Med. 1999;5:1071–5.
17. Segditsas S, Rowan AJ, Howarth K, Jones A, Leedham S, Wright NA, et al. APC and the three-hit hypothesis. Oncogene. 2009;28:146–55. doi:10.1038/onc.2008.361.
18. Kim K-M, Calabrese P, Tavare S, Shibata D. Enhanced stem cell survival in familial adenomatous polyposis. Am J Pathol. 2004;164:1369–77.
19. Wang J, El-Masry N, Talbot I, Tomlinson I, Alison MR, El-Bahrawy M. Expression profiling of proliferation and apoptotic markers along the Adenoma-Carcinoma sequence in familial adenomatous polyposis patients. Gastroenterol Res Pract. 2013;2013:107534. doi:10.1155/2013/107534.
20. Fodde R, Tomlinson I. Nuclear beta-catenin expression and Wnt signalling: in defence of the dogma. J Pathol. 2010;221:239–41. doi:10.1002/path.2718.
21. Thirlwell C, Will OC, Domingo E, Graham TA, McDonald SA, Oukrif D, et al. Clonality assessment and clonal ordering of individual neoplastic crypts shows polyclonality of colorectal adenomas. Gastroenterology. 2010;138:1441–54. doi:10.1053/j.gastro.2010.01.033.
22. Fodde R, Brabletz T. Wnt/beta-catenin signaling in cancer stemness and malignant behavior. Curr Opin Cell Biol. 2007;19:150–8.
23. Janssen KP, Alberici P, Fsihi H, Gaspar C, Breukel C, Franken P, et al. APC and oncogenic KRAS are synergistic in enhancing Wnt signaling in intestinal tumor formation and progression. Gastroenterology. 2006;131:1096–109.
24. James RG, Conrad WH, Moon RT. Beta-catenin-independent Wnt pathways: signals, core proteins, and effectors. Methods Mol Biol. 2008;468:131–44. doi:10.1007/978-1-59745-249-6_10.
25. Phelps RA, Chidester S, Dehghanizadeh S, Phelps J, Sandoval IT, Rai K, et al. A two-step model for colon adenoma initiation and progression caused by APC loss. Cell. 2009;137:623–34. doi:10.1016/j.cell.2009.02.037.
26. Obrador-Hevia A, Chin SF, González S, Rees J, Vilardell F, Greenson JK, et al. Oncogenic KRAS is not necessary for Wnt signalling activation in APC-associated FAP adenomas. J Pathol. 2010;221:57–67. doi:10.1002/path.2685.
27. Luo F, Poulogiannis G, Ye H, Hamoudi R, Arends MJ. Synergism between K-rasVal12 and mutant Apc accelerates murine large intestinal tumourigenesis. Oncol Rep. 2011;26:125–33. doi:10.3892/or.2011.1288.
28. Bläker H, Scholten M, Sutter C, Otto HF, Penzel R. Somatic mutations in familial adenomatous polyps. Nuclear translocation of beta-catenin requires more than biallelic APC inactivation. Am J Clin Pathol. 2003;120:418–23.
29. Alberici P, de Pater E, Cardoso J, Bevelander M, Molenaar L, Jonkers J, Fodde R. Aneuploidy arises at early stages of Apc-driven intestinal tumorigenesis and pinpoints conserved chromosomal loci of allelic imbalance between mouse and human. Am J Pathol. 2007;170:377–87.
30. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutations. J Clin Oncol. 2009;27:3975–80. doi:10.1200/JCO.2008.21.6853.
31. Cleary SP, Cotterchio M, Jenkins MA, Kim H, Bristow R, Green R, et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. Gastroenterology. 2009;136:1251–60. doi:10.1053/j.gastro.2008.12.050.
32. Lipton L, Tomlinson I. The multiple colorectal adenoma phenotype and MYH, a base excision repair gene. Clin Gastroenterol Hepatol. 2004;2:633–8.
33. Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, Brown G, Winship I, Barker M, Buchanan D, Cowie S, Nasioulas S, du Sart D, Young J, Leggett B, Jass J, Macrae F. Hyperplastic polyposis: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006;131:30–9.

34. Boparai KS, Dekker E, Van Eeden S, Polak MM, Bartelsman JF, Mathus-Vliegen EM, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology. 2008;135:2014–8. doi:10.1053/j.gastro.2008.09.020.
35. Vogt S, Jones N, Christian D, Engel C, Nielsen M, Kaufman A, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009;137:1976–85. doi:10.1053/j.gastro.2009.08.052.
36. Lipton L, Halford SE, Johnson V, Novelli MR, Jones A, Cummings C, et al. Carcinogenesis in MYH-associated polyposis follows a distinct genetic pathway. Cancer Res. 2003;63:7595–9.
37. Aretz S, Tricarico R, Papi L, Spier I, Pin E, Horpaopan S, et al. *MUTYH*-associated polyposis (MAP): evidence for the origin of the common European mutations p.Tyr179Cys and p. Gly396Asp by founder events. Eur J Hum Genet. 2014;22:923–9. doi:10.1038/ejhg.2012.309.
38. Jones S, Lambert S, Williams GT, Best JM, Sampson JR, Cheadle JP. Increased frequency of the k-ras G12C mutation in MYH polyposis colorectal adenomas. Br J Cancer. 2004;90:1591–3.
39. Middeldorp A, van Puijenbroek M, Nielsen M, Corver WE, Jordanova ES, ter Haar N, et al. High frequency of copy-neutral LOH in MUTYH-associated polyposis carcinomas. J Pathol. 2008;216:25–31. doi:10.1002/path.2375.
40. de Miranda NF, Nielsen M, Pereira D, van Puijenbroek M, Vasen HF, Hes FJ, et al. MUTYH-associated polyposis carcinomas frequently lose HLA class I expression – a common event amongst DNA-repair-deficient colorectal cancers. J Pathol. 2009;219:69–76. doi:10.1002/path.2569.
41. Jones S, Emmerson P, Maynard J, Best JM, Jordan S, Williams GT, Sampson JR, Cheadle JP. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C⟶T:A mutations. Hum Mol Genet. 2002;11:2961–7.
42. Nieuwenhuis MH, Vogt S, Jones N, Nielsen M, Hes FJ, Sampson JR, et al. Evidence for accelerated colorectal adenoma--carcinoma progression in MUTYH-associated polyposis? Gut. 2012;61:734–8. doi:10.1136/gut.2010.229104.
43. Venesio T, Balsamo A, Errichiello E, Ranzani GN, Risio M. Oxidative DNA damage drives carcinogenesis in MUTYH-associated-polyposis by specific mutations of mitochondrial and MAPK genes. Mod Pathol. 2013;26:1371–81. doi:10.1038/modpathol.2013.66.
44. Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, et al. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. Nat Genet. 2015;47:668–71. doi:10.1038/ng.3287.
45. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45:136–44. doi:10.1038/ng.2503.
46. Bellido F, Pineda M, Aiza G, Valdés-Mas R, Navarro M, Puente DA, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 2015. doi:10.1038/gim.2015.75.
47. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology. 1999;116:1453–6.
48. Network CGA. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487:330–7. doi:10.1038/nature11252.
49. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2:401–4. doi:10.1158/2159-8290.CD-12-0095.
50. Donehower LA, Creighton CJ, Schultz N, Shinbrot E, Chang K, Gunaratne PH, et al. MLH1-silenced and non-silenced subgroups of hypermutated colorectal carcinomas have distinct mutational landscapes. J Pathol. 2013;229:99–110. doi:10.1002/path.4087.
51. Offerhaus GJA, Howe JR. Juvenile polyposis. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. World Health Organization classification of tumours of the digestive system. Lyon, France: IARC Press; 2010. p. 166–7.
52. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5:751–6.

53. Aretz S, Stienen D, Uhlhaas S, Stolte M, Entius MM, Loff S, et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007;44:702–9.
54. van Hattem WA, Brosens LA, de Leng WW, Morsink FH, Lens S, Carvalho R, et al. Large genomic deletions of SMAD4, BMPR1A and PTEN in juvenile polyposis. Gut. 2008;57:623–7. doi:10.1136/gut.2007.
55. Haramis AP, Begthel H, van den Born M, van Es J, Jonkheer S, Offerhaus GJ, Clevers H. De novo crypt formation and juvenile polyposis on BMP inhibition in mouse intestine. Science. 2004;303:1684–6.
56. Langeveld D, van Hattem WA, de Leng WW, Morsink FH, Ten Kate FJ, Giardiello FM, et al. SMAD4 immunohistochemistry reflects genetic status in juvenile polyposis syndrome. Clin Cancer Res. 2010;16:4126–34. doi:10.1158/1078-0432.CCR-10-0168.
57. McGarrity TJ, Kulin HE, Zaino RJ. Peutz-Jeghers syndrome. Am J Gastroenterol. 2000;95:596–604.
58. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105:1258–64. doi:10.1038/ajg.2009.725.
59. Lin-Marq N, Borel C, Antonarakis SE. Peutz-Jeghers LKB1 mutants fail to activate GSK-3beta, preventing it from inhibiting Wnt signaling. Mol Genet Genomics. 2005;273:184–96.
60. Eng C. PTEN: one gene, many syndromes. Hum Mutat. 2003;22:183–98.
61. Stanich PP, Pilarski R, Rock J, Frankel WL, El-Dika S, Meyer MM. Colonic manifestations of the *PTEN* hamartoma tumor syndrome: case series and systematic review. World J Gastroenterol. 2014;20:1833–8. doi:10.3748/wjg.v20.i7.1833.
62. Heald B, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139:1927–33. doi:10.1053/j.gastro.2010.06.061.
63. Ponz de Leon M, Di Gregorio C, Giunti L, Roncucci L, Pedroni M, Tinca AC, et al. Duodenal carcinoma in a 37-year-old man with Cowden/Bannayan syndrome. Dig Liver Dis. 2013;45:75–8. doi: 10.1016/j.dld.2012.09.017.
64. Trufant JW, Greene L, Cook DL, McKinnon W, Greenblatt M, Bosenberg MW. Colonic ganglioneuromatous polyposis and metastatic adenocarcinoma in the setting of Cowden syndrome: a case report and literature review. Hum Pathol. 2012;43:601–4. doi:10.1016/j.humpath.2011.06.022.
65. Ngeow J, Heald B, Rybicki LA, Orloff MS, Chen JL, Liu X, et al. Prevalence of germline PTEN, BMPR1A, SMAD4, STK11, and ENG mutations in patients with moderate-load colorectal polyps. Gastroenterology. 2013;144:1402–9. doi:10.1053/j.gastro.2013.02.001.
66. Ma L, Teruya-Feldstein J, Behrendt N, Chen Z, Noda T, Hino O, et al. Genetic analysis of Pten and Tsc2 functional interactions in the mouse reveals asymmetrical haploinsufficiency in tumor suppression. Genes Dev. 2005;19:1779–86.
67. Berger AH, Pandolfi PP. Haplo-insufficiency: a driving force in cancer. J Pathol. 2011;223:137–46.
68. Marsh Durban V, Jansen M, Davies EJ, Morsink FH, Offerhaus GJ, Clarke AR. Epithelial-specific loss of PTEN results in colorectal juvenile polyp formation and invasive cancer. Am J Pathol. 2014;184:86–91. doi:10.1016/j.ajpath.2013.10.003.
69. Delnatte C, Sanlaville D, Mougenot JF, Vermeesch JR, Houdayer C, Blois MC, et al. Contiguous gene deletion within chromosome arm 10q is associated with juvenile polyposis of infancy, reflecting cooperation between the BMPR1A and PTEN tumor-suppressor genes. Am J Hum Genet. 2006;78:1066–74.
70. Dahdaleh FS, Carr JC, Calva D, Howe JR. Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23. Clin Genet. 2012;81:110–6. doi:10.1111/j.1399-0004.2011.01763.x.
71. Whitelaw SC, Murday VA, Tomlinson IPM, Thomas HJW, Cottrell S, Ginsberg A, et al. Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology. 1997;112:327–34.

72. Jaeger E, Leedham S, Lewis A, Segditsas S, Becker M, Cuadrado PR, et al. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist *GREM1*. Nat Genet. 2012;44:699–703. doi:10.1038/ng.2263.
73. Laitman Y, Jaeger E, Katz L, Tomlinson I, Friedman E. GREM1 germline mutation screening in Ashkenazi Jewish patients with familial colorectal cancer. Genet Res. 2015;97, e11. doi:10.1017/S0016672315000105.
74. Davis H, Irshad S, Bansal M, Rafferty H, Boitsova T, Bardella C, et al. Aberrant epithelial GREM1 expression initiates colonic tumorigenesis from cells outside the stem cell niche. Nat Med. 2015;21:62–70. doi:10.1038/nm.3750.
75. Cheah PY, Wong YH, Chau YP, Loi C, Lim KH, Lim JF, et al. Germline bone morphogenesis protein receptor 1A mutation causes colorectal tumorigenesis in hereditary mixed polyposis syndrome. Am J Gastroenterol. 2009;104:3027–33. doi:10.1038/ajg.2009.542.
76. O'Riordan JM, O'Donoghue D, Green A, Keegan D, Hawkes LA, Payne SJ, et al. Hereditary mixed polyposis syndrome due to a BMPR1A mutation. Colorectal Dis. 2010;12:570–3. doi:10.1111/j.1463-1318.2009.01931.x.
77. Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. Gastroenterology. 2002;123:862–76.
78. Young J, Jass JR. The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. Cancer Epidemiol Biomarkers Prev. 2006;15:1778–84.
79. Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. World Health Organization classification of tumours of the digestive system. Lyon, France: IARC Press; 2010. p. 160–5.
80. Boparai KS, Mathus-Vliegen EM, Koornstra JJ, Nagengast FM, van Leerdam M, van Noesel CJ, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut. 2010;59:1094–100. doi:10.1136/gut.2009.185884.
81. Hazewinkel Y, Reitsma JB, Nagengast FM, Vasen HF, van Os TA, van Leerdam ME, et al. Extracolonic cancer risk in patients with serrated polyposis syndrome and their first-degree relatives. Fam Cancer. 2013;12:669–73. doi:10.1007/s10689-013-9643-x.
82. Lage P, Cravo M, Sousa R, Chaves P, Salazar M, Fonseca R, et al. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. Am J Gastroenterol. 2004;99:1779–84.
83. Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. Endoscopy. 2006;38:266–70.
84. Carvajal-Carmona LG, Howarth KM, Lockett M, Polanco-Echeverry GM, Volikos E, Gorman M, et al. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. J Pathol. 2007;212:378–85.
85. Kalady MF, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, Church JM. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. Dis Colon Rectum. 2011;54:164–70. doi:10.1007/DCR.0b013e3181fd4c15.
86. Carragher LA, Snell KR, Giblett SM, Aldridge VS, Patel B, Cook SJ, et al. V600EBraf induces gastrointestinal crypt senescence and promotes tumour progression through enhanced CpG methylation of p16INK4a. EMBO Mol Med. 2010;2:458–71. doi:10.1002/emmm.201000099.
87. Minoo P, Baker K, Goswami R, Chong G, Foulkes WD, Ruszkiewicz AR, et al. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. Gut. 2006;55:1467–74.
88. Rosenberg DW, Yang S, Pleau DC, Greenspan EJ, Stevens RG, Rajan TV, et al. Mutations in BRAF and KRAS differentially distinguish serrated versus non-serrated hyperplastic aberrant crypt foci in humans. Cancer Res. 2007;67:3551–4.
89. Guarinos C, Sánchez-Fortún C, Rodríguez-Soler M, Pérez-Carbonell L, Egoavil C, Juárez M, et al. Clinical subtypes and molecular characteristics of serrated polyposis syndrome. Clin Gastroenterol Hepatol. 2013;11:705–11. doi:10.1016/j.cgh.2012.12.045.

90. Rosty C, Parry S, Young JP. Serrated polyposis: an enigmatic model of colorectal cancer predisposition. Pathol Res Int. 2011;2011:157073. doi:10.4061/2011/157073.
91. Li JH, Leong MY, Phua KB, Low Y, Kader A, Logarajah V, et al. Cap polyposis: further experience and review. World J Gastroenterol. 2013;119:4185–91. doi:10.3748/wjg.v19.i26.4185.
92. Slavik T, Montgomery EA. Cronkhite–Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol. 2014;67:891–7.
93. Seguí N, Mina LB, Lázaro C, Sanz-Pamplona R, Pons T, Navarro M, et al. Germline mutations in FAN1 cause hereditary colorectal cancer by impairing DNA repair. Gastroenterology. 2015. pii: S0016-5085(15)00783-0. doi:10.1053/j.gastro.2015.05.056.
94. Wong A, Ma BB. Personalizing therapy for colorectal cancer. Clin Gastroenterol Hepatol. 2014;12:139–44. doi: 10.1016/j.cgh.2013.08.040.
95. van Puijenbroek M, Nielsen M, Tops CM, Halfwerk H, Vasen HF, Weiss MM, et al. Identification of patients with (atypical) MUTYH-associated polyposis by KRAS2 c.34G>T prescreening followed by MUTYH hotspot analysis in formalin-fixed paraffin-embedded tissue. Clin Cancer Res. 2008;14:139–42. doi:10.1158/1078-0432.CCR-07-1705.
96. Lesko AC, Goss KH, Prosperi JR. Exploiting APC function as a novel cancer therapy. Curr Drug Targets. 2014;15(1):90–102.
97. Xie J, Bartels CM, Barton SW, Gu D. Targeting hedgehog signaling in cancer: research and clinical developments. Oncol Targets Ther. 2013;6:1425–35. doi:10.2147/OTT.S34678.
98. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20. doi:10.1056/NEJMoa1500596.
99. Lord CJ, Tutt AN, Ashworth A. Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. Annu Rev Med. 2015;66:455–70. doi:10.1146/annurev-med-050913-022545.

Chapter 2
MUTYH-Associated Polyposis

Maureen E. Mork and Eduardo Vilar

Introduction

Lynch syndrome and familial adenomatous polyposis (FAP) have long been identified as hereditary predisposition syndromes to colorectal cancer (CRC), most easily recognized on the basis of their autosomal dominant inheritance, young age of onset of CRC and other associated malignancies, and, in the case of FAP, the presence of adenomatous polyposis. However, in 2002 the first report of a novel hereditary predisposition to CRC describing a family with three siblings affected with CRC and polyposis who were negative for germline *APC* mutations was published [1]. These siblings were identified to carry biallelic germline mutations in the *MUTYH* gene, also known as *MYH*. This autosomal recessive predisposition to CRC has been termed *MYH*- or *MUTYH*-associated polyposis (MAP, OMIM #608456) and has been recognized as a rare, but important, cause of hereditary CRC, representing less than 1 % of CRC cases [2], and posing challenges in diagnosis, genetic counseling, and surveillance.

M.E. Mork
Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

E. Vilar, M.D., Ph.D. (✉)
Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA
e-mail: EVilar@mdanderson.org

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_2

Clinical Characteristics

MAP is an autosomal recessive condition caused by biallelic mutations of *MUTYH* with a prevalence of 1:20,000 to 1:40,000 based on the estimated carrier frequency of 1–2 % in the general population [2]. MAP is typically characterized by the development of 10 to 100 adenomatous polyps in the colorectum, most frequently located in the proximal colon, and confers a life-time risk of CRC ranging from 43 % to nearly 100 %, being diagnosed at an average age of 48 [3]. Polyps develop approximately at age 50; therefore, the number of polyps and age of diagnosis have much clinical crossover with attenuated familial adenomatous polyposis (AFAP), associated with germline *APC* mutations [4]. However, patients with biallelic *MUTYH* mutations with an atypical presentation have been described, including patients who present with a single colorectal tumor and absence of polyposis or with less than 10 polyps [5]. In addition, a small percentage of patients who present with polyps with serrated features (hyperplastic/serrated polyps) meeting the threshold for a diagnosis of hyperplastic/serrated polyposis syndrome [6] have been found to have biallelic *MUTYH* mutations [7, 8].

Extracolonic cancer risks in individuals with MAP were assessed in a European multicenter study of 276 cases [9]. The highest reported risk was of cancer of the duodenum. The risk of small bowel polyps, especially in the duodenum, was reported to be 17 %, with an associated 4 % life-time risk of duodenal carcinoma. Gastric polyps were found in 11 % of patients. This study also found a significant increase in ovarian (SIR 5.7), bladder (SIR 7.2), and skin (SIR 2.8) cancers, with a trend of increased risk for breast cancer. Overall, the average life-time risk of extracolonic cancers was reported to be 38 %, although the authors noted the relatively late ages of onset of these cancers (median 51–61 years). Individuals with MAP were also reported to have some features typically seen in patients with FAP, including dental anomalies and congenital hypertrophy of the retinal pigment epithelium. *MUTYH* biallelic carriers have also been reported to have sebaceous neoplasms of the skin [10, 11], again demonstrating the phenotypic overlap between MAP and other hereditary CRC syndromes.

Molecular Genetics

The pairing of the DNA bases (A with T and G with C) is crucial to maintain the stability and the integrity of the information in the genome. However, accurate base paring is often challenged by environmental toxins and production of reactive oxygen species (ROS) such as hydrogen peroxide, superoxide and hydroxyl radicals secondary to metabolism, cellular respiration, and inflammation. The guanine base is the most susceptible to this "oxidative stress", generating the product 7,8-dihydro-8-oxoguanine (also known as 8-oxo-G). The base excision repair (BER) pathway is in charge of correcting these errors through the glycosylases OGG1 and

MUTYH. Initially, OGG1 will excise the 8-oxo-G base and then let other enzymes restore the original DNA sequence. However, there is a back-up mechanism involving MUTYH that will act in the event that the error is not repaired by OGG1. In the absence of an effective MUTYH protein, the presence of 8-oxo-G will generate a transversion from G:C to T:A base pair. The glycosylate MUTYH intercepts the incorrect 8-oxo-G:A base pair, removing the A and letting other enzymes in the pathway to restore the DNA to its original configuration [12, 13].

The gene *MUTYH*, also known as *MYH* (mutY homolog), is located on chromosome 1 (mapping to 45,794,835–45,806,142 in the GRCh37 coordinates, which is located between 1p34.3 and p32.1) and has a total of 16 exons, encoding a protein with 535 amino acids [13]. The partial homology of the human protein with the *E. coli* and *B. stearothermophilus* has allowed obtaining an accurate idea of the functioning of the BER pathway and, in some instances, predicting the functional consequences of mutations identified in patients and families. In fact, a total of 82 germline mutations have been identified in *MUTYH* alleles of patients diagnosed with CRC and polyposis [12]. Consistent with the known biology and functioning of *MUTYH* in the BER pathway, patients diagnosed with MAP have been found to have a higher rate of somatic G:C to T:A transversions in the *APC* and *KRAS* genes. In fact, studies have shown that adenomatous polyps and serrated polyps identified in MAP individuals present in a high proportion with G:T transversion in the first G base of the codon 12 (*KRAS* c.34G>T) [3, 12]. This type of change has also been able to link the presence of polyps with serrated features (both hyperplastic and sessile serrated) with MAP, thus establishing a causal relation between the biallelic loss of *MUTYH* and the presence of serrated polyposis [8]. Finally, several studies have analyzed the microsatellite status of premalignant lesions and tumors from MAP patients. Although the number of patients and samples analyzed is not large, thus precluding to obtain definite conclusions, it is clear that the majority displayed a mismatch repair proficient status. In addition, one study observed a higher frequency for microsatellite instability-low tumors among MAP compared to the sporadic setting. A minority of cases reported showed high levels of microsatellite instability which is puzzling as the BER pathway is not involved in the correction of mismatches in microsatellite tracts [3].

Genetic Testing and Genetic Counseling

Identifying individuals with MAP is a complex task, as there is phenotypic overlap with other polyposis syndromes (i.e., AFAP) and due to its variable phenotypic expression. Genetic testing for MAP is typically considered in individuals who present with oligopolyposis, although the spectrum of presentation expands from 10 to 100 polyps [14]. Traditionally, genetic testing for MAP has begun with testing for the two founder *MUTYH* mutations in northern European populations, G382D and Y165C, which represents the genotypes of approximately 70 % of affected individuals [15]. However, full sequencing and rearrangement testing of *MUTYH* are

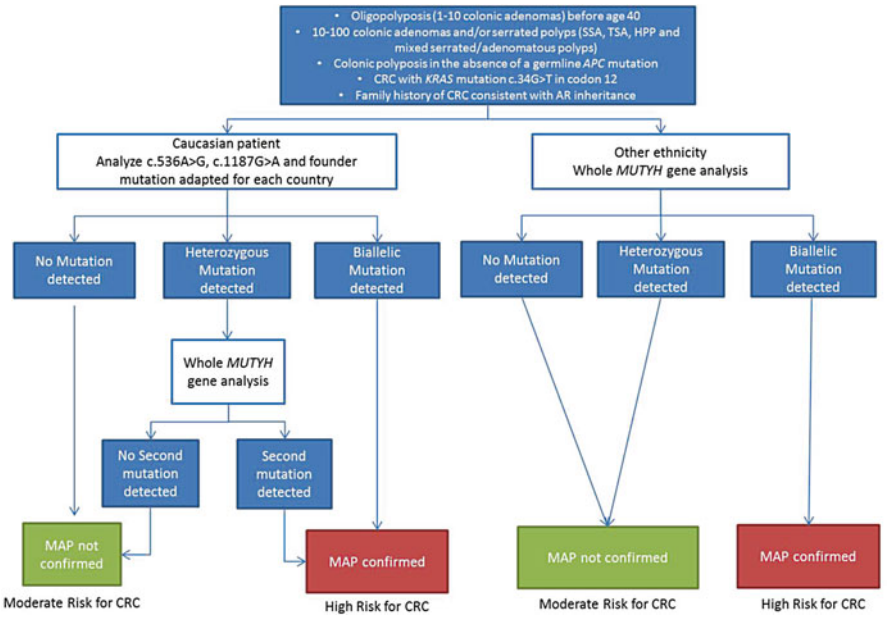


Fig. 2.1 Proposed genetic diagnosis work-up for patients with suspected MAP based on the available literature. *CRC* colorectal cancer, *MAP MUTYH*-associated polyposis, *AR* autosomal recessive, *HPP* hyperplastic polyps, *SSA* sessile serrated adenomas, *TSA* traditional serrated adenomas. Figure adapted from Borras et al., Clin Cancer Res (2014);20(5):1061–3

also available, although most individuals with MAP present with point mutations with large deletions rarely reported [16]. Given the admixture of populations, comprehensive testing may be advantageous rather than founder mutation testing, especially if a patient is not of Northern European ancestry [17]. However, if a patient is Caucasian, then an algorithm of founder mutation testing with reflex to full testing may be followed (Fig. 2.1). In addition, testing for MAP may be performed in conjunction with *APC* germline testing, and is offered quite frequently as an "adenomatous polyposis" genetic testing panel included along with *APC* by many commercial genetic testing companies. If an individual presents with a family history consistent with autosomal dominant FAP, then testing *APC* alone would be the most appropriate course of action [14]. However, an individual with a simplex case of adenomatous polyposis may represent with autosomal recessive inheritance, like MAP, or a *de novo APC* mutation [18]. Therefore, concurrent testing of *APC* and *MUTYH* is appropriate in such individuals.

In addition to testing individuals with multiple adenomatous polyps, the developing description of the atypical MAP phenotype may expand the spectrum of patients appropriate for *MUTYH* testing. It has been proposed that individuals with CRC without polyposis or patients with polyps numbering less than 10 be evaluated for MAP, especially with the syndrome's variable presentation (Fig. 2.1) [5]. To this end, *MUTYH* has been included in many next-generation sequencing panels of

hereditary cancer genes. While the inclusion of this gene has found many heterozygote carriers, it may continue to expand the MAP phenotype as more individuals with an atypical phenotype are identified. In addition, as sebaceous lesions of the skin have been reported in individuals with MAP as well as tumors with mismatch repair deficiency [19], patients with a Lynch syndrome phenotype with no mismatch repair mutation may also warrant MAP evaluation. Patients with CRC demonstrating *KRAS* mutations in codon 12 with G to T transversions (c.34G>T) in the absence of polyposis may also be considered for testing.

MAP is unique among hereditary predispositions to CRC due to its autosomal recessive inheritance. For an individual to inherit biallelic mutations of the *MUTYH* gene, his or her parents must each carry a single *MUTYH* mutation. Full siblings of an individual with MAP each have a 25 % chance of also having biallelic mutations and therefore MAP, 50 % chance of being a *MUTYH* carrier, and 25 % chance of having two wild-type alleles. Children of an individual with MAP are obligate heterozygote carriers. The status of the other allele, however, depends on the mutation status of the unaffected parent. Therefore, the genetic testing algorithm in a family identified to have MAP is more complex than in a family with an autosomal dominant condition.

Siblings of an affected individual are recommended to undergo site-specific testing for the *MUTYH* mutation(s) identified in the proband. However, single-site testing in obligate heterozygote children will not evaluate for the possibility of a mutation in the other parent. Therefore, it may be more cost-effective for the unaffected parent to undergo carrier testing of *MUTYH*. If the other parent is negative for *MUTYH* mutations, this negates the need for testing in children. This algorithm introduces some complexity into results disclosure and recommendations for family members, as education regarding a recessive condition may not be as straightforward as an autosomal dominant condition; therefore, careful genetic counseling is important to impart accurate information to the patient and his or her family.

Colonic Surveillance and Surgical Recommendations

Surveillance recommendations for biallelic *MUTYH* carriers have been issued by a number of expert groups (i.e., National Comprehensive Cancer Network, American Medical Association/National Coalition for Health Professional Education in Genetics). Per the guidelines of the National Comprehensive Cancer Network (NCCN), colonoscopy is recommended beginning at 25–30 years and repeating every 2–3 years if negative [20]. If polyps are identified, then colonoscopy should be repeated every 1–2 years. If the polyp burden becomes too burdensome to be managed endoscopically with polypectomy, then surgical intervention is recommended, with consideration of colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileorectal pouch anastomosis (IPAA) depending on rectal polyp burden. Post-colectomy, endoscopy of any remaining rectum is recommended every 6–12 months.

Chemoprevention

There are results from randomized placebo-controlled clinical trials proving the effect of aspirin [21], non-steroidal anti-inflammatory agents such as Sulindac [22] and cyclo-oxygenase-2 (COX-2) inhibitors [23, 24] in the regression and modulation of adenomatous polyps in patients diagnosed with polyposis secondary to a diagnosis of FAP. However, there is virtually no controlled data generated for patients and families diagnosed with MAP. There is a case report in the literature that reports the successful modulation of polyposis using COX-2 inhibitors indicated for the treatment of arthritis in a patient with MAP [25]. After the discontinuation of Celecoxib the patient presented with progression of the polyp counts and required prophylactic surgery. There is some low level scientific evidence supporting the use of NSAIDs such as the finding of upregulation by both immunohistochemistry and RNA expression of COX-2 in polyps and CRCs of patients with MAP, which is an analogous situation to the FAP context [26]. Although there is no evidence to support the prophylactic use of NSAIDs or COX-2 inhibitors, the implementation of clinical trials testing this intervention should be encouraged in this patient population. It could be reasonable to try this group of agents as prophylaxis in selected situations under the condition of close endoscopic surveillance and clinical management attentive to potential side effects, always keeping in mind the relatively low frequency of this syndrome (N of 1 trials).

Extracolonic Surveillance

Few recommendations have been made regarding extracolonic cancer risks for individuals with MAP. As the highest reported extracolonic risk is for small bowel polyps and cancer, biallelic *MUTYH* carriers are recommended to undergo baseline esophagogastroduodenoscopy (EGD) beginning at age 30–35 years, following FAP recommendations based on duodenoscopic findings [20]. In addition, individuals with MAP are recommended to undergo annual physical exam. No recommendations have been made regarding surveillance for the other cancers associated with MAP.

MUTYH Heterozygotes

As genetic testing for *MUTYH* has entered the algorithm for germline testing, either through cancer-specific genetic testing or via next-generation sequencing panels of hereditary cancer genes, this has led to the identification of monoallelic carriers of *MUTYH* mutations. The risk of CRC to *MUTYH* carriers was initially studied in parents of patients with biallelic *MUTYH* mutations and was estimated to be approximately twofold the general population incidence [27]. However, a more recent

study of 2,332 patients with monoallelic *MUTYH* mutations found that the risk to carriers was dependent upon the family history of CRC. In fact, the risk for CRC, irrespective of family history, was 5.6 % for females and 7.2 % for males, while CRC risk for individuals with a first-degree relative with CRC was 10 % for women and 12.5 % for men [28]. Current surveillance guidelines recommend that *MUTYH* heterozygotes follow general population screening practices for CRC [20]. Extracolonic cancer risks in *MUTYH* carriers have not been well studied and no additional surveillance guidelines have been issued.

References

1. Al-Tassan N, Chmiel NH, Maynard J, Fleming N, Livingston AL, Williams GT, et al. Inherited variants of MYH associated with somatic G:C→T:A mutations in colorectal tumors. Nat Genet. 2002;30(2):227–32.
2. Cleary SP, Cotterchio M, Jenkins MA, Kim H, Bristow R, Green R, et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. Gastroenterology. 2009;136(4):1251–60.
3. Nielsen M, Joerink-van de Beld MC, Jones N, Vogt S, Tops CM, Vasen HF, et al. Analysis of MUTYH genotypes and colorectal phenotypes in patients With MUTYH-associated polyposis. Gastroenterology. 2009;136(2):471–6.
4. Aretz S, Uhlhaas S, Goergens H, Siberg K, Vogel M, Pagenstecher C, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer. 2006;119(4):807–14.
5. Landon M, Ceulemans S, Saraiya DS, Strike B, Arnell C, Burbidge LA, et al. Analysis of current testing practices for biallelic MUTYH mutations in MUTYH-associated polyposis. Clin Genet. 2015;87(4):368–72.
6. Guarinos C, Sanchez-Fortun C, Rodriguez-Soler M, Alenda C, Paya A, Jover R. Serrated polyposis syndrome: molecular, pathological and clinical aspects. World J Gastroenterol. 2012;18(20):2452–61.
7. Guarinos C, Juarez M, Egoavil C, Rodriguez-Soler M, Perez-Carbonell L, Salas R, et al. Prevalence and characteristics of MUTYH-associated polyposis in patients with multiple adenomatous and serrated polyps. Clin Cancer Res. 2014;20(5):1158–68.
8. Boparai KS, Dekker E, Van Eeden S, Polak MM, Bartelsman JF, Mathus-Vliegen EM, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology. 2008;135(6):2014–8. Epub 2008/11/18.
9. Vogt S, Jones N, Christian D, Engel C, Nielsen M, Kaufmann A, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009;137(6):1976–85 e1-10.
10. Guillen-Ponce C, Castillejo A, Barbera VM, Pascual-Ramirez JC, Andrada E, Castillejo MI, et al. Biallelic MYH germline mutations as cause of Muir-Torre syndrome. Fam Cancer. 2010;9(2):151–4. Epub 2009/12/10.
11. Morak M, Heidenreich B, Keller G, Hampel H, Laner A, de la Chapelle A, et al. Biallelic MUTYH mutations can mimic Lynch syndrome. Eur J Hum Genet. 2014;22(11):1334–7.
12. David SS, O'Shea VL, Kundu S. Base-excision repair of oxidative DNA damage. Nature. 2007;447(7147):941–50. Epub 2007/06/22.
13. Lipton L, Tomlinson I. The genetics of FAP and FAP-like syndromes. Fam Cancer. 2006;5(3):221–6. Epub 2006/09/26.
14. Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A. Working Group of the American College of Medical G, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med. 2014;16(1):101–16.

15. Nielsen M, Morreau H, Vasen HF, Hes FJ. MUTYH-associated polyposis (MAP). Crit Rev Oncol Hematol. 2011;79(1):1–16.
16. Rouleau E, Zattara H, Lefol C, Noguchi T, Briaux A, Buecher B, et al. First large rearrangement in the MUTYH gene and attenuated familial adenomatous polyposis syndrome. Clin Genet. 2011;80(3):301–3.
17. Borras E, Taggart MW, Lynch PM, Vilar E. Establishing a diagnostic road map for MUTYH-associated polyposis. Clin Cancer Res. 2014;20(5):1061–3.
18. Bisgaard ML, Fenger K, Bulow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat. 1994;3(2):121–5.
19. Castillejo A, Vargas G, Castillejo MI, Navarro M, Barbera VM, Gonzalez S, et al. Prevalence of germline MUTYH mutations among Lynch-like syndrome patients. Eur J Cancer. 2014;50(13):2241–50.
20. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Genetic/familial high-risk assessment: Colorectal. National Comprehensive Cancer Network. 2014.
21. Burn J, Bishop DT, Chapman PD, Elliott F, Bertario L, Dunlop MG, et al. A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. Cancer Prev Res (Phila). 2011;4(5):655–65. Epub 2011/05/06.
22. Giardiello FM, Yang VW, Hylind LM, Krush AJ, Petersen GM, Trimbath JD, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. N Engl J Med. 2002;346(14):1054–9. Epub 2002/04/05.
23. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000;342(26):1946–52. Epub 2000/06/30.
24. Lynch PM, Ayers GD, Hawk E, Richmond E, Eagle C, Woloj M, et al. The safety and efficacy of celecoxib in children with familial adenomatous polyposis. Am J Gastroenterol. 2010;105(6):1437–43. Epub 2010/03/18.
25. Sturgeon D, Herline AJ, Wise PE. Do NSAIDs suppress polyps in MUTYH-associated polyposis? A case report. Hered Cancer Clin Pr. 2011;9(Suppl 1):36.
26. Frattini M, Carnevali I, Signoroni S, Balestra D, Moiraghi ML, Radice P, et al. Cyclooxygenase-2 expression in FAP patients carrying germ line MYH mutations. Cancer Epidemiol Biomarkers Prev. 2005;14(8):2049–52. Epub 2005/08/17.
27. Jones N, Vogt S, Nielsen M, Christian D, Wark PA, Eccles D, et al. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. Gastroenterology. 2009;137(2):489–94, 94 e1; quiz 725–6.
28. Win AK, Dowty JG, Cleary SP, Kim H, Buchanan DD, Young JP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. Gastroenterology. 2014;146(5):1208–11 e1–5.

Chapter 3
Inflammatory "Cap" Polyposis

Giovanni De Petris and Shahrooz Rashtak

Introduction

Polyposes of the gastrointestinal tract not currently linked to specific molecular alterations include Cronkhite–Canada syndrome (CCS), inflammatory "cap" polyposis (ICP), inflammatory polyposis of inflammatory bowel disease (IBD), and the exceptional pyogenic granulomatosis associated with endocrine tumors [1].

ICP is an uncommonly recognized sporadic polyposis limited usually to the colon (indeed only two cases were found associated with gastric polyposis and a single case manifested as isolated gastric polyposis) [2]. It is characterized by red- and white-capped polyp(s), usually sessile, with elongated, only slightly tortuous, crypts, and superficial erosion. The number of polyps spans from one [3] to hundreds per patient.

The epidemiology of ICP is limited due to the low number of cases, mainly reported in small case series or case reports. Less than 100 cases have appeared in the literature since the first description of 15 patients with mucous diarrhea and hematochezia by Williams, Bussey, and Morson about three decades ago [4]. The rarity of the disease, and/or the difficulty in diagnosis, can be appreciated by the fact that 8 years passed after the initial report when two additional cases were found [5] and by the observation that several different conditions are confused with ICP. Additionally nonspecific endoscopic and pathology findings of ICP may lead to under recognition of the disease and contribute to poor understanding of the etiology, natural course, and effective treatment of this condition. ICP affects women more than men and is most frequent during the fifth decade of life with preponderance of cases originating from Asia. The age of the patients ranges from 5 to 90 years [4, 6].

G. De Petris, M.D. (✉)
Mountain State Pathology Corp., Penrose Hospital,
2222 North Nevada Avenue, Colorado Springs, CO 80907, USA
e-mail: Pathgdp@gmail.com

S. Rashtak, M.D.
Mayo Clinic College of Medicine, Rochester, MN 55905, USA

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_3

Etiology

The etiology of ICP is unknown. Williams et al. [4] suggested that the polyps are caused by chronic mucosal prolapse. The endoscopic appearance of the polyps, their common location in the left colon (especially in the rectum) and association with constipation, all overlap with mucosal prolapse syndrome. However given the documented occasional association of ICP with colitis and colorectal cancer, it can be hypothesized that ICP is a nonspecific abnormal response to an underlying inflammatory process [7] rather than a consequence of prolapse injury. The resolution of several ICP cases after treatment with anti-inflammatory agents, antibiotics, and therapy of coexistent *Helicobacter pylori* (*H. pylori*) infection [8], as well as reported cases of polyps extending all the way to the cecum and the association with gastric ICP, all argue against ICP being caused by motility disorder of the rectum.

ICP epithelial cells secrete a different type of mucus compared to normal colonic mucosa. ICP polyps produce predominantly non-sulphated mucins and exhibit abnormal expression of MUC4, MUC3, and MUC5ac genes [9]. These differences are not specific to ICP. The proliferative compartment of the crypts in ICP is irregular and extends along the crypts [10]. In addition focal p16 expression is seen in ICP which is similar to hyperplastic polyps and sessile serrated adenoma without dysplasia [10, 11]. The expression of claudin-2, a pore-forming claudin, was found to be abnormally upregulated in a single case of ICP with protein losing enteropathy [12] and claudin-7, a pore-sealing claudin, was found to be down-regulated. These observations suggest that ICP is an abnormal inflammatory response to various stimuli, but the underlying mechanisms leading to this dysregulated response remain unknown.

Endoscopic Appearance

Polyps of ICP preferentially present in the left colon, particularly in the rectum, but they may arise throughout the colon. It has been observed that polyps form first in the rectum before "marching" proximally. Approximately 36 % of subjects have rectal polyps detectable on digital rectal examination [13]. The proximal polyps typically are smaller than distal ones [14]. Polyps can reach several centimeters in size, especially in the rectum. On visual inspection at colonoscopy, polyps are flat or protruding flat-topped, even plaque-like formations due to aggregation of several polyps, less commonly they are pedunculated or semi-pedunculated. The polyps typically straddle the colonic plicae (Fig. 3.1) and are covered by a cap of whitish fibrin: rinsing off the fibrin cap reveals a dark red friable surface. The mucosa between polyps is generally unremarkable (Fig. 3.1) but occasionally may be dotted with a few white specks [14]. A milder form of the disease typified by erythematous and edematous patches of mucosa scattered throughout the colon has been reported [15].

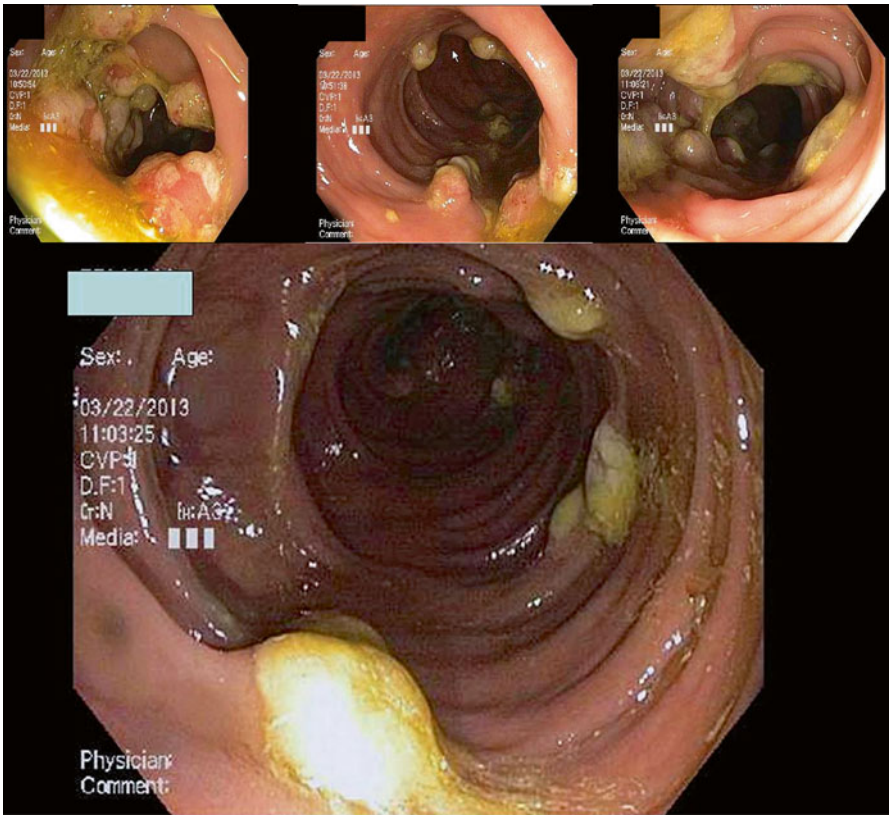


Fig. 3.1 Endoscopic appearance of ICP. The polyps show uniformly a whitish or red cap, have variable dimensions, in the top left photograph there is suggestion of fusion of polyps to create a plaque-like area. The larger photograph at the bottom shows the preference of the polyps to straddles across the colonic plicae. The larger photograph is reproduced with permission from De Petris G et al. International Journal of Surgical Pathology 22(4), 378–382, 2014

Histology

The histological features of the cap polyp include the presence of elongated crypts; enlargement of the luminal third into cup-shaped or cystic-shaped crypts; attenuation or erosion of the surface epithelium; and a cap on the eroded surface of the majority of polyps consisting of mucus, inflammatory, and detached epithelial cells and fibrin. Dysplasia has never been reported in ICP. Serration of the contour of the crypt is minimal, usually in the mid crypt, just below the dilated portion of the crypt (Figs. 3.2 and 3.3). The crypt lining epithelium appears eosinophilic and mucin-poor cells line the dilated portion of the crypts (Fig. 3.3). Regenerative changes are likely secondary to the erosion and loss of surface epithelium that characterize this condition. Only the larger polyps display smooth muscle fibers emanating from the

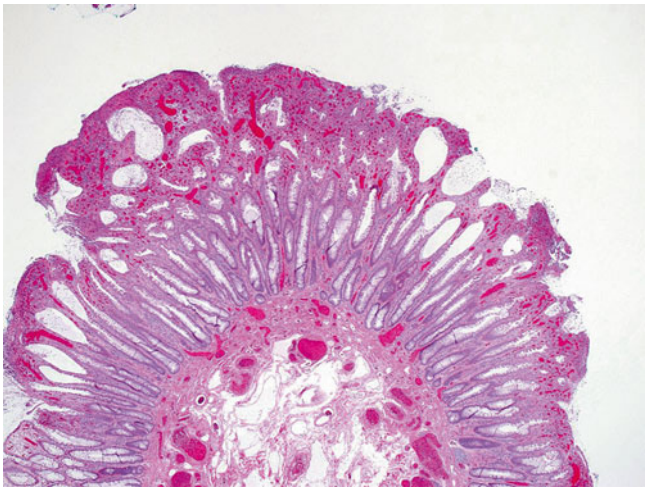


Fig. 3.2 Typical inflammatory cap polyp (Hematoxylin–Eosin stain, 4× magnification). Notice the elongated crypts with dilatation in the upper third with erosion and fibrin, the minimal serration of the crypts profile in the mid third. Boot- or L-shaped crypts are not present as also absent is fibromuscularization of the lamina propria. The lamina propria is not edematous or expanded, as is the case in juvenile polyps or Cronkhite–Canada syndrome polyps, and is not particularly inflamed. Dysplasia is absent. Reproduced with permission from De Petris G et al. International Journal of Surgical Pathology 22(4), 378–382, 2014

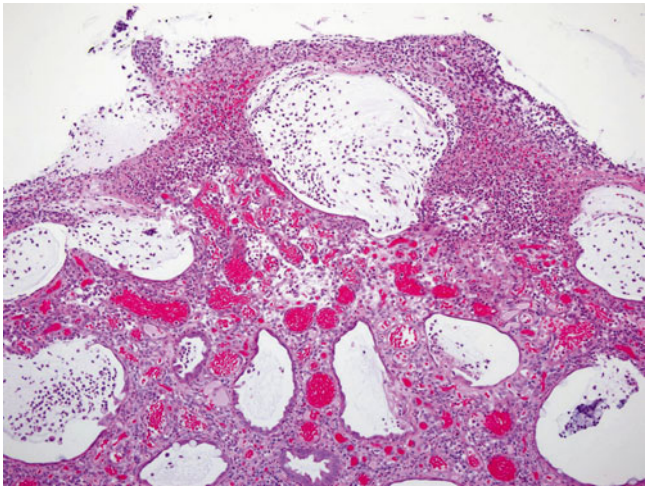


Fig. 3.3 Higher magnification (Hematoxylin–Eosin stain, 10× magnification) of the upper third of an inflammatory cap polyp. Typical cystic dilatation of the glands that have attenuated or missing epithelium lining their walls and are filled by muco-inflammatory exudate. The surface (upper aspect) of the polyp is eroded. Reproduced with permission from De Petris G et al. International Journal of Surgical Pathology 22(4), 378–382, 2014

muscularis mucosae into the epithelium but the muscularis mucosae of the intervening colon is intact. The presence of smooth muscle fibers in the large polyps may be secondary to prolapse of the polyp itself, and most polyps are otherwise devoid of smooth muscle in the lamina propria. Remarkably only mild inflammation due to mononuclear cells, more prominent in the luminal aspect of the mucosa, are elicited by the erosion seen in these polyps. Rarely colitis cystica profunda develops and can arise in direct association with the polyps or in the nonpolypoid areas of the colon [16].

Clinical Aspects and Differential Diagnosis

ICP may develop at any age with female predominance. Affected individuals usually have no family history of polyposes. Rarely ICP is asymptomatic [17], but the condition is more likely to present with rectal bleeding (82 %), mucoid diarrhea (46 %), chronic straining and/or constipation (both 64 %) [13]. In a series from Singapore, rectal bleeding was found in all pediatric patients [18]. Mucoid diarrhea can be abundant and lead to incontinence and protein losing enteropathy, characterized by weight loss, fat soluble vitamin deficiencies, and hypoalbuminemia with resultant lower extremity pitting edema. The chronicity of the bloody diarrhea can result in anemia.

The natural history of ICP is unknown, but occasionally spontaneous resolution occurs, irrespective of the extent of disease [19]. Treatment with simple polypectomy, medical therapy, or surgery to remove affected portions of the colon may be required in symptomatic patients.

Overlapping histologic features of mucosal prolapse may lead to a misdiagnosis of ICP. This condition is also often confused by polyposis syndromes such as Serrated Polyposis Syndrome, (SPS), CCS, Juvenile Polyposis Syndrome (JPS), Cowden Syndrome (CS), or IBD with pseudopolyps.

The features of ICP are distinct from those of SPS, in which the majority of lesions are sessile serrated polyps (SSP). The SSP has a typical L- or inverted T-shaped crypt appearance and marked serration with flask- or booth-shaped crypts, in contrast to the modest serration in the mid portion of the crypts in ICP. SPS polyps lack the diffuse surface erosion of ICP. In addition other types of polyps such as hyperplastic and adenomatous polyps also arise in SPS. Nor do ICP polyps resemble traditional serrated adenoma (TSA) which exhibit small lateral gland outpouching, complex villiform growth, eosinophilia, or the penicillate nuclei of TSA.

CCS can be differentiated from ICP by the phenotypical manifestations of nail dystrophy, dysgeusia, and hair loss associated with CCS but not present in ICP patients. The histology of CCS is distinctive with edematous and atrophic mucosa in both nonpolypoid and polypoid mucosa, as is the clinical feature of involvement of the entire digestive tract in CCS while polyps are confined to the colon in ICP patients.

The superficial cystic dilatation of the crypts and the adherent mucin cap present in ICP are not seen in JPS. Instead, in JPS polyps the gland dilatation is basal, and the stroma of the polyp has marked inflammation often with eosinophils, while ICP polyps are scantily infiltrated by inflammatory cells.

Cowden Syndrome (CS) polyps can mimic ICP; however, in CS cryptic cystic dilatation can be seen throughout the polyp. CS is an hereditary syndrome characterized by macrocephaly, skin lesions including trichilemmoma, and an increased risk for breast (often bilateral), uterine, thyroid, and colorectal cancers. CS is one manifestation of the PTEN Hamartoma Tumor Syndrome (PHTS) caused by germline mutations in the *PTEN* tumor suppressor gene. The second manifestation of PHTS is Bannayan–Riley–Ruvalcaba Syndrome, a condition that presents at a younger age of onset and more often arises in males compared to the adult onset, female predominant presentation of CS, but which shares the same benign tumor and cancer risks associated with CS. These extra intestinal manifestations are absent in ICP and may guide the clinicians to the proper diagnosis.

The lack of mucosal changes of chronic colitis injury in the nonpolypoid mucosa distinguishes the majority of cases of ICP from IBD. Pseudomembranous colitis could be confused with ICP by both endoscopist and pathologists not well versed in ICP but evaluation for Clostridium difficile infection may help direct the care provider to the diagnosis.

Treatment

Only a minority of cases of ICP resolve spontaneously. The optimal therapy of ICP in the majority of patients remains to be established and is presented in Table 3.1. The possibility of ICP as a nonspecific response to an infection has been put forth. Oiya et al. recently showed cure of ICP by eradication of *H. pylori* [8], an observation repeated in multiple case reports and small series mainly from Japan [15, 20]. Shimizu suggested ICP may be due to *Escherichia coli* (*E. coli*) infection [7]. It is possible that another infectious agent that responds to antibiotic therapy for *H. pylori* is associated with ICP. However, cure of this condition by antibiotics is not universally achieved, and recurrence after initial remission is documented [21]. The response of ICP to metronidazole reported which may be due to the anti-inflammatory capability of the drug rather than its anti-microbial activity. ICP may respond to treatment of prolapse (such as simple avoidance of straining) [19], steroids [21], infliximab [22], endoscopic or surgical resection [5, 23]. However, the results are inconsistent, and the dosage and duration of drug treatments have not been standardized, since no randomized, placebo controlled clinical trials have been performed.

Resolution of polyps and symptoms after steroids (e.g., prednisolone 40 mg/day at start) can occur in 1–2 months [21] but the rate of early relapse is high. Treatment with the TNF alpha inhibitor, infliximab was reported to be highly effective in several patients following either 4 infusions at 8 weeks intervals or a single infusion [22, 24]. However, treatment failures to infliximab associated with no impact of the drug

Table 3.1 Therapeutic considerations for CAP polyposis

Intervention/Medication	Mechanism of action	Indication/Efficacy	Reference
Biofeedback treating constipation Avoid straining	Avoiding intraluminal trauma	Symptomatic relief	Oriuchi et al. [26] Konishi et al. [27]
Antibiotics Metronidazole *H. pylori* eradication	Anti-microbial effect and reducing inflammation (may have direct anti-inflammatory effect)	Controversial remission or response	Shimizu et al. [7] Akamatsu et al. [15] Oiya H, et al. [8] Takeshima et al. [20]
Anti-inflammatory/ Immunomodulators Oral aminosalicylates Topical steroids(betamethasone enemas) Systemic steroids	Preventing mucosal injury	Ineffective Controversial Controversial, associated with high recurrence rate	Akamatsu et al. [15] Chang et al. [21] Suzuki et al. [28]
Biologics Infliximab	Anti TNF	Controversial	Bookman et al. [22] Kim et al. [24] Maunoury et al. [25]
Endoscopic approach	Polypectomy/argon plasma coagulation	For <10 polyps, High recurrence rate unless solitary	Ng et al. [13]
Surgical resection	Proctocolectomy	For refractory symptoms, recurrence possible following resection	Konishi et al. [27]

on TNF alpha levels in the tissue [25] have also been described. Limited by the small numbers of treated patients and the unknown natural history of ICP, these therapeutic reports have been unable to discern which patients will be resistant to therapy.

In practice, initial treatment approach is focused on symptomatic relief directed toward reducing excessive straining and treating constipation. Polypectomy generally is recommended. Eradication of *H. pylori* can be considered in *H. pylori*-positive patients that remain symptomatic. This may be followed by anti-inflammatory agents such as steroids and infliximab, with the goal of achieving remission and avoiding surgery which may be considered in case of failure to the above-mentioned therapies. ICP has been shown to recur in the colon in up to 37 % of patients undergoing limited resection of the affected area [7].

In summary ICP remains a disease of unknown etiology with the natural course and lack of established therapeutic guidelines.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Allibone RO, Hoffman J, Gosney JR, Helliwell TR. Granulation tissue polyposis associated with carcinoid tumours of the small intestine. Histopathology. 1993;22:475–80.
2. Iguchi E, Tsumura T, Sekikawa A, Wakasa T, Maruo T, Okabe Y, Kimura T, Osaki Y. Cap-polyposis-like gastropathy with hypoproteinemia treated with H. pylori eradication. Intern Med. 2013;52:2215–8.
3. Papaconstantinou I, Karakatsanis A, Benia X, Polymeneas G, Kostopoulou E. Solitary rectal cap polyp: case report and review of the literature. World J Gastrointest Surg. 2012;4:157–62.
4. Williams GT, Bussey HJR, Morson BC. Inflammatory "cap" polyposis of the large intestine. Br J Surg. 1985;72:s133.
5. Campbell AP, Cobb CA, Chapman RW, Kettlewell M, Hoang P, Haot BJ, Jewell DP. Cap polyposis--an unusual cause of diarrhoea. Gut. 1993;34:562–4.
6. Peny MO, Noel JC, Haot J, Sokolow Y, Zalcman M, Houben JJ, Vanderwinden JM, Finne R, Adler M. Cap polyposis: a rare syndrome. Gastroenterol Clin Biol. 1998;22:349–52.
7. Shimizu K, Koga H, Iida M, Yao T, Hirakawa K, Hoshika K, Mikami Y, Haruma K. Does metronidazole cure cap polyposis by its antiinflammatory actions instead of by its antibiotic action? a case study. Dig Dis Sci. 2002;47:1465–8.
8. Oiya H, Okawa K, Aoki T, Nebiki H, Inoue T. Cap polyposis cured by Helicobacter pylori eradication therapy. J Gastroenterol. 2002;37:463–6.
9. Buisine MP, Colombel JF, Lecomte-Houcke M, Gower P, Aubert JP, Porchet N, Janin A. Abnormal mucus in cap polyposis. Gut. 1998;42:135–8.
10. De Petris G, Dhungel BM, Chen L, Pasha SF. Inflammatory "cap" polyposis: a case report of a rare nonneoplastic colonic polyposis. Int J Surg Pathol. 2013;22:378–82.
11. Kriegl L, Neumann J, Vieth M, Greten FR, Reu S, Jung A, Kirchner T. Up and downregulation of p16(Ink4a) expression in BRAF-mutated polyps/adenomas indicates a senescence barrier in the serrated route to colon cancer. Mod Pathol. 2011;24:1015–22.
12. Arimura Y, Isshiki H, Hirayama D, Onodera K, Murakami K, Yamashita K, Shinomura Y. Polypectomy to eradicate cap polyposis with protein-losing enteropathy. Am J Gastroenterol. 2014;109:1689–91.
13. Ng KH, Mathur P, Kumarasinghe MP, Eu KW, Seow-Choen F. Cap polyposis: further experience and review. Dis Colon Rectum. 2004;47:1208–15.
14. Esaki M, Matsumoto T, Kobayashi H, Yao T, Nakamura S, Mizuno M, Iida M, Fujishima M. Cap polyposis of the colon and rectum: an analysis of endoscopic findings. Endoscopy. 2001;33:262–6.
15. Akamatsu T, Nakamura N, Kawamura Y, Shinji A, Tateiwa N, Ochi Y, Katsuyama T, Kiyosawa K. Possible relationship between Helicobacter pylori infection and cap polyposis of the colon. Helicobacter. 2004;9:651–6.
16. Arana R, Flejou JF, Parc Y, El-Murr N, Cosnes J, Svrcek M. Cap polyposis and colitis cystica profunda: a rare association. Histopathology. 2014;64:604–7.
17. Sadamoto Y, Jimi S, Harada N, Sakai K, Minoda S, Kohno S, Nawata H. Asymptomatic cap polyposis from the sigmoid colon to the cecum. Gastrointest Endosc. 2001;54:654–6.
18. Li JH, Leong MY, Phua KB, Low Y, Kader A, Logarajah V, Ong LY, Chua JH, Ong C. Cap polyposis: a rare cause of rectal bleeding in children. World J Gastroenterol WJG. 2013;19:4185–91.

19. Sasaki Y, Takeda H, Fujishima S, Sato T, Nishise S, Abe Y, Ajioka Y, Kawata S, Ueno Y. Nine-year follow-up from onset to spontaneous complete remission of cap polyposis. Intern Med. 2013;52:351–4.
20. Takeshima F, Senoo T, Matsushima K, Akazawa Y, Yamaguchi N, Shiozawa K, Ohnita K, Ichikawa T, Isomoto H, Nakao K. Successful management of cap polyposis with eradication of Helicobacter pylori relapsing 15 years after remission on steroid therapy. Intern Med. 2012;51:435–9.
21. Chang HS, Yang SK, Kim MJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Long-term outcome of cap polyposis, with special reference to the effects of steroid therapy. Gastrointest Endosc. 2012;75:211–6.
22. Bookman ID, Redston MS, Greenberg GR. Successful treatment of cap polyposis with infliximab. Gastroenterology. 2004;126:1868–71.
23. Nakagawa Y, Nagai T, Okawara H, Nakashima H, Tasaki T, Soma W, Hisamatsu A, Watada M, Murakami K, Fujioka T. Cap polyposis (CP) which relapsed after remission by avoiding straining at defecation, and was cured by Helicobacter pylori eradication therapy. Intern Med. 2009;48:2009–13.
24. Kim ES, Jeen YT, Keum B, Seo YS, Chun HJ, Um SH, Kim CD, Ryu HS. Remission of cap polyposis maintained for more than three years after infliximab treatment. Gut Liver. 2009;3:325–8.
25. Maunoury V, Breisse M, Desreumaux P, Gambiez L, Colombel JF. Infliximab failure in cap polyposis. Gut. 2005;54:313–4.
26. Oriuchi T, Kinouchi Y, Kimura M, et al. Successful treatment of cap polyposis by avoidance of intraluminal trauma: clues to pathogenesis. Am J Gastroenterol. 2000;95:2095.
27. Konishi T, Watanabe T, Takei Y, et al. Cap polyposis: an inflammatory disorder or a spectrum of mucosal prolapse syndrome? Gut. 2005;54:1342.
28. Suzuki H, Sato M, Akutsu D, et al. A case of cap polyposis remission by betamethasone enema after antibiotics therapy including Helicobacter pylori eradication. J Gastrointestin Liver Dis. 2014;23:203–6.

Chapter 4
Serrated Polyposis Syndrome

Miriam Juárez, Eva Hernández-Illán, Oscar Murcia, María Rodríguez-Soler, and Rodrigo Jover

Introduction

Serrated polyposis syndrome (SPS), formerly known as hyperplastic polyposis syndrome, is an uncommon disease characterized by the presence of multiple serrated polyps throughout the colorectum [1]. Although SPS was described for the first time in the early 1970s [2], until now, its genetics, molecular, and clinical characteristics continue to be unknown. Nevertheless, SPS shows differential characteristics that suggest a genetic predisposition, such as multiplicity of lesions, young-age onset, and family history of this disease [3]. Consistent with this, several studies have previously reported families from which both an autosomal recessive and autosomal dominant inheritance could be considered [4–6].

The real prevalence of SPS in the general population is difficult to be determined due to several factors, such as the lack of recognition of this syndrome among the physician community [7]. Even so, the prevalence of patients diagnosed with this syndrome is estimated as less than 1 %, with a range from 0.033 % to 0.055 % [8, 9].

Traditionally, the main pathway toward CRC has been attributed to activation of WNT signalling which leads to transformation from a pre-neoplastic adenoma to carcinoma. This "traditional pathway," which represents between 70 % and 80 % of CRC, is initiated with a mutation of the *APC* gene, with adenomatous polyps being precursor lesions to adenocarcinoma in the colon [10–12]. However, a newly described alternative pathway known as the serrated pathway of carcinogenesis, via progression of serrated polyps to CRC, has been found to be responsible for about a quarter of all CRC cases [11]. This pathway is characterized by somatic mutations

M. Juárez • E. Hernández-Illán • O. Murcia • M. Rodríguez-Soler • R. Jover (✉)
Unidad de Gastroenterología, Servicio de Medicina Digestiva, Hospital General Universitario de Alicante, Universidad Miguel Hernández, Pintor Baeza, 12, 03010 Alicante, Spain
e-mail: rodrigojover@gmail.com

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_4

in *BRAF* or *KRAS*, microsatellite instability (MSI) and epigenetic silencing of tumor suppressor genes. Recently, there is growing recognition that there are different types of serrated polyps which can be subdivided with respect to their morphologic appearance, molecular alterations, and risk of malignant transformation. Several studies have shown the dominance of the serrated pathway of carcinogenesis in patients diagnosed with SPS [13, 14]. For that reason, this syndrome could be considered as the paradigm of the serrated pathway of carcinogenesis. Patients with SPS could provide a valuable model to achieve a deeper understanding of the features that drive progression from serrated (hyperplastic) polyps to CRC through this pathway [12, 15].

Epidemiology and Clinical Characteristics

Epidemiology

There are substantial differences in the published data about the real prevalence of this disease in the population. Several studies have suggested that the prevalence of SPS, estimated out of CRC endoscopy-based screening programs on average risk individuals, is relatively low. Lockett [16] described a prevalence rate of 1 in 3000 individuals. However, this prevalence is based on individuals in whom more than 20 distal hyperplastic polyps (HP) were previously found during a flexible sigmoidoscopy screening trial [16]. In another study carried out in a population-based screening program, only 28 patients out of 50,148 participants, met clinical criteria for SPS (0.056 %) [8].

In addition, two studies have recently published the prevalence of SPS in two prospective cohorts of patients under CRC screening programmes. On one hand, Biswas et al. [17] evaluated the prevalence of this syndrome in 755 patients who undertook screening flexible sigmoidoscopy between April 2010 and January 2012, finding the prevalence of this disease to be 0.66 %, a 20-fold increase compared to the previously described rate [17]. On the other hand, in the study made by Moreira et al. [18], 8 cases of SPS were diagnosed in a cohort of 2,355 patients between 50 and 69 years (1/294, 0.34 %), with positive fecal immunochemical testing (FIT) in the CRC screening programme of Barcelona [18].

In spite of this diversity in the prevalence rates, it seems that this syndrome occurs at a frequency comparable with other familial polyposes, such as familial adenomatous polyposis or *MUTYH*-associated polyposis. These differences in the rates between studies can be explained by several factors that may be determinant, such as: endoscopists' experience and their ability to detect serrated lesions, adequate bowel preparation, health and pre-colonoscopy counselling, use of high-definition instruments and knowledge about this syndrome in the physician community.

Table 4.1 The World Health Organization's clinical criteria for the identification of serrated polyposis syndrome

A	At least five serrated polyps proximal to the sigmoid colon, with two or more of these being larger than 10 mm
B	Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with SPS
C	More than 20 serrated polyps of any size, distributed throughout the colon

Diagnostic Criteria

The clinical criteria for diagnosis of SPS were firstly described by Burt and Jass [19] for the World Health Organization (WHO). These criteria were redefined in Berlin in 2010 [1]. The clinical diagnosis of this syndrome is established when patients fulfill, at least, one of the three WHO criteria (Table 4.1).

In general population, the proportion of patients who meet these three individual criteria remains unknown [7]. It is important to note that the number of polyps is cumulative over time for the C criterion, and polyps detected should be counted toward the total number of colonoscopies [20]. Moreover, these 20 polyps must be distributed throughout the colon, excluding patients with only HPs located within the sigmoid and rectum.

However, these criteria have been considered arbitrary and restrictive [1], possibly leading to an underestimation of the frequency of this syndrome [21]. Because of that, patients with multiple but fewer than 20 HPs, as well as patients with several serrated lesions who do not fulfill the A criterion, are excluded from the definition of SPS [22]. Moreover, because of the difficulty of diagnosis and the low frequency of this syndrome, many patients do not know whether their relatives have this disease. Hence, a recent study suggests that SPS may be largely unrecognized during colonoscopy in community and academic endoscopic practices [7]. This circumstance could be due to the lack of knowledge of the WHO criteria for the diagnosis among physician community. In this sense, the mentioned study found that only 1 out of 20 patients who fulfilled the WHO criteria for SPS, was correctly identified by the referring physician and half of those patients (50 %) by the endoscopist [7]. Other important factors contributing for the probable under-diagnosis of this syndrome can be the difficulty of endoscopic detection of serrated lesions and the lack of consensus about the histological classification of this type of polyps.

Clinical Features

This syndrome is present in similar proportions in men and women but it has a higher prevalence in north-western European countries [23]. The mean age at diagnosis is between 40 and 60 years of age [4, 22, 24–27] with a range between 11 and 83 years of age [28–30].

Although the majority of polyps in patients diagnosed with SPS are serrated, the presence of synchronous adenomatous polyps has also been described in up to approximately 70 % of SPS patients [22, 31].

There is substantial phenotypic diversity in patients harboring SPS [1, 26]. This phenotypic heterogeneity in SPS has been suggested to result from different subjacent molecular backgrounds [22]. The WHO recognizes the existence of two different phenotypes within the SPS according to the location of the serrated polyps throughout the colon: **Type 1** is the right-sided phenotype with the presence of a limited number of large serrated polyps, whereas in **Type 2,** a higher number of small serrated polyps are present throughout the colon [1]. The risk of cancer in patients classified as Type 1 is considered by some authors to be substantially higher than in patients with Type 2 [1, 32]. However, other studies do not find differences between both types [33]. This study did not find substantial differences according to demographic, pathological, or molecular characteristics between both phenotypes [33]. Finally, Kalady et al. in a recent study suggested the existence of a third "mixed" phenotype, which shares features with the Type 1 and 2 phenotypes and is present in slightly more than one-third of patients with SPS [22].

Characteristics of Serrated Lesions

Histological and Morphological Features of Serrated Lesions

Serrated polyps are defined as epithelial lesions with a serrated "saw-tooth" appearance on histological section due to infolding of colonic crypts [15]. According to the latest WHO classification in 2010 [1], serrated polyps can be classified into three groups: hyperplastic polyps (HPs), sessile serrated adenomas/polyps (SSAs), and traditional serrated adenomas (TSAs) [1].

HPs are the most frequent colorectal polyps. They are typically small (2–5 mm), can become numerous and are mainly distributed in the sigmoid colon and rectum [24, 34]. This group is divided into three histological groups: microvesicular hyperplastic polyps (MVHPs), in which columnar cells have mucin-filled vesicles within atypical cytoplasm; goblet cell hyperplastic polyps (GCHPs) with conspicuous goblet cells and predominantly distal colon location; and the least frequent mucin-poor hyperplastic polyps (MPHP) [12, 34, 35] (Table 4.2).

SSAs are usually larger than HPs and mainly right-sided. They are histologically distinguished from HPs by the presence of inverted T- or L-shaped crypt bases that reflect disordered proliferation [15]. Other features include dilated crypts and serration extending into the lower third of the crypts, increased mucin production, absence of enteroendocrine cells, and absence of a thickened basement membrane under the surface (Fig. 4.1) [36]. SSAs can progress to dysplasia and cancer [37] and they represent around 18 % of all the serrated lesions (Table 4.2) [38]. MVHPs seem to be their precursor lesions, especially when they are located into the right colon [39]. In fact, both entities, MVHPs and SSAs, share their molecular profile harboring *BRAF* mutations, and being MSI-H and CpG Island Methylator Phenotype (CIMP) positive.

Table 4.2 Features of serrated polyps

Polyp subtype		Proportion (%)	Morphology	Location	Molecular features
HP	GCHP	20–30 %	Conspicuous goblet cells	Distal	Frequent *KRAS* mutations (54)
	MVHP	40–50 %	Columnar cells with mucin-filled vesicles within atypical cytoplasm	Distal	Frequent *BRAF* mutation (76) and CIMP-H (68)
SSA		17–30 %	Advanced type of serrated polyps with architecture and abnormal proliferation. Dilated crypts and serration extending, mucin production, absence of enteroendocrine cells, and absence of a thickened basement membrane under the surface	Proximal	Frequent *BRAF* mutations (75–82) and CIMP-H (92); MSI-H
TSA		2–5 %	Serrated architecture with dysplasia. Presence of crypts with bases not seated adjacent to the muscularis mucosae	Distal	Molecular heterogeneity. Associated with *KRAS* mutation and *BRAF* mutations, MSI-L and CIMP-L
MP		–	Two different components: a hyperplastic component and another dysplastic adenomatous component	–	Frequent mutations in *BRAF* especially when SSA is part of the lesion

HP hyperplastic polyps, *GCHP* goblet cell hyperplastic polyps, *MVHP* microvesicular hyperplastic polyp, *CIMP-H* CpG island methylator phenotype high, *SSA* sessile serrated adenoma, *MSI-H* microsatellite instability-high, *TSA* traditional serrated adenoma, *MSI-L* microsatellite instability-low, *CIMP-L* CpG island methylator phenotype low, *MP* mixed polyp

TSAs are less frequent and usually located in the left colon. They are dysplastic polyps with patterns more similar to conventional tubulovillous adenoma architecture [12, 34, 40]. Ectopic crypt formation, defined by the presence of crypts with bases not seated adjacent to the muscularis mucosae, is a feature that makes possible to distinguish between TSAs and SSAs (Fig. 4.2) [12]. TSAs are more frequently associated with *KRAS* mutation, and are MSI-L and CIMP-L [37] (Table 4.2). Malignancy risk and rate of progression to carcinoma are unknown in these lesions [35]. GCHPs usually mimic SSAs and seem to be the precursors of these dysplastic TSAs [40, 41].

Endoscopic Features of Serrated Lesions

Serrated polyps show endoscopic features that help physicians to distinguish them from adenomatous polyps. HPs are typically diminutive and located in the distal colon and rectum (Fig. 4.3). They are characteristically pale, translucent, glistening and flat

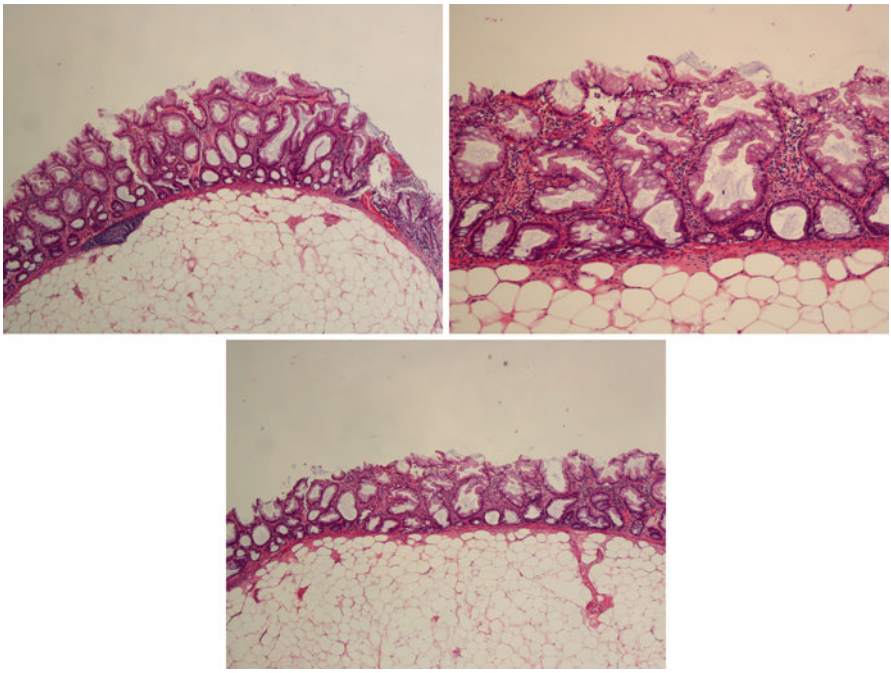


Fig. 4.1 Histology of sessile serrated adenoma (SSA)

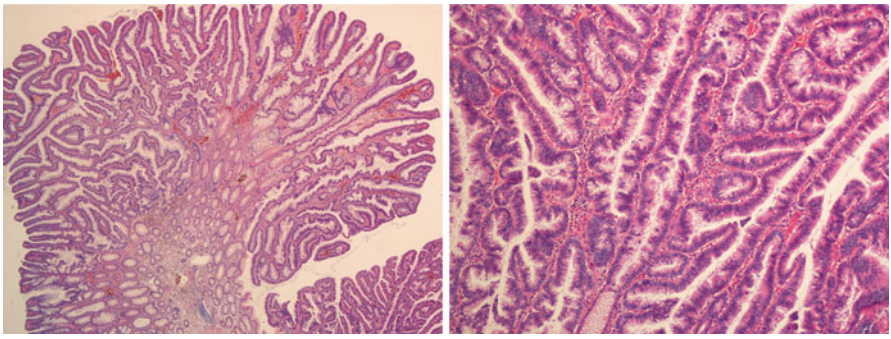


Fig. 4.2 Histology of traditional serrated adenoma (TSA)

or sessile, and usually covered by mucus. Their vascular network is weak, in contrast to that of hypervascular adenomas. In total, these make HPs look very similar to the surrounding mucosa and less visible with insufflations [15, 39] (Fig. 4.4).

SSAs are typically flat or with non-polypoid morphology, making their detection even more difficult [37]. They often have the appearance of redundant or thickened mucosa altering the contour of a fold. Moreover, they have a mucus layer as a distinctive feature, which is adherent to the surface of the lesion, giving it a yellow or rust-colored appearance in contrast to the surrounding mucosa, which can help to

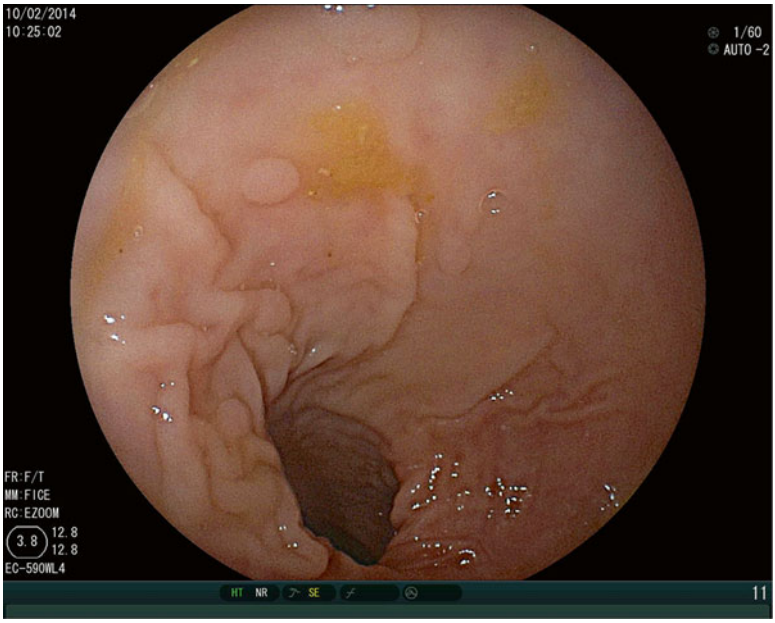


Fig. 4.3 Multiple hyperplastic polyps in the colorectum

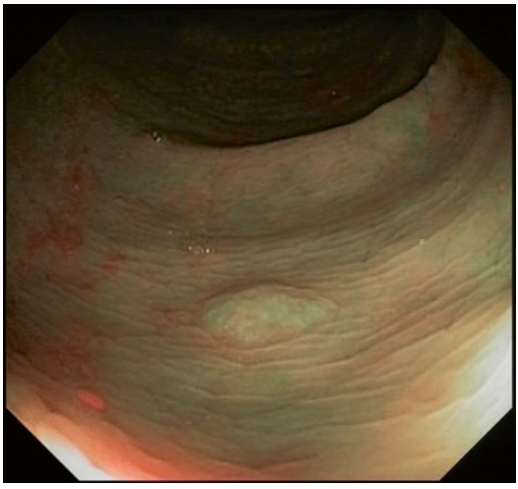


Fig. 4.4 Hyperplastic polyp with sessile morphology

delineate the lesion [15, 39]. Their flat morphology may make them difficult to be detected and completely excised by endoscopists, what may explain the variation in detection rates. In this sense, it has been shown that the miss-rate of polyps smaller than 10 mm can be as high as 23 % [42]. In fact, incomplete colonoscopy detection has become an important issue in the proximal colon, where the effectiveness of colonoscopy to prevent CRC is clearly lower than within the distal colon and rectum,

possibly related to failures into SSAs recognition and resection [39]. In this regard, it is not surprising that there has been suggested a link between the serrated pathway and risk for interval cancers [43].

Newly advanced endoscopic techniques, such as chromoendoscopy or narrow-band imaging (NBI), may significantly improve the detection rate of serrated lesions [15]. Indeed, areas of dysplasia within an SSA can be distinguishable with image enhancement techniques and/or optical magnification colonoscopies [39]. Published randomized trials have shown that pancolonic chromoendoscopy almost doubles the rate of detection of sporadic serrated polyps compared to conventional endoscopy [44–46]. Toyoshima et al. [47] found a prevalence of SPS of 8.4 % in a cohort of 249 patients with HPs using chromoendoscopy [47]. NBI is also useful to differentiate adenomas from HPs [48, 49], and the prospective study made by Boparai et al. [50] in SPS patients showed promising results supporting the use of this technology.

The Serrated Pathway of Colorectal Carcinogenesis

The serrated pathway of carcinogenesis is an alternative and recently recognized tumorigenesis pathway that involves the malignant transformation of serrated polyps into CRC. This serrated pathway accounts for 15–30 % of all of CRCs [43]. The serrated pathway of carcinogenesis is considered a distinct entity from the other two classical CRC pathways—chromosomal instability (CIN) and MSI pathways—where adenomas are traditionally considered the precursor lesions. The serrated pathway involves epigenetic hypermethylation of CpG islands within promoter regions of tumor suppressor genes. This mechanism results in the silencing of these genes, and these tumors are known as CIMP-positive tumors. This epigenetic event is usually the first step of a cumulative set of alterations in which *BRAF* V600E mutation has been suggested as a precursor step. The role of this mutation could be related to apoptosis evasion [51, 52], that may result in the development of cancer.

It is well established that CIMP-H is strongly associated with *BRAF* mutations as well as with MSI, probably through *MLH1* methylation. On the other hand, CIMP-L phenotype is associated with *KRAS* mutations [53], mainly involving codons 12 and 13. Both *KRAS* and *BRAF* are proto-oncogenes involved in the upstream activation of the mitogen activated protein kinase (MAPK) pathway, which promotes proliferation, cell survival, and gene expression. These oncogene-activating mutations, together with the development of the CIMP phenotype, promote accumulation of alterations in serrated precursor lesions that can finally lead to carcinoma formation [39]. These CIMP-positive tumors seem to be associated with a good prognosis [54], although it has been shown that they do not respond to 5-FU-based chemotherapy [55]. Molecular events leading to these clinicopathological differences remain unknown.

Molecular Hallmarks of Serrated Pathway

There is some evidence to hypothesize the coexistence of two different serrated pathways regarding their different molecular profiles. One of them involves *BRAF* mutation and usually leads to CIMP-H tumors. These tumors are usually MSI, although their MSI status will depend on the somatic hypermethylation of the *MLH1* promoter [12, 34, 36, 56]. This hypermethylation could precede the development of cytologic dysplasia [57]. This pathway usually results in neoplasia in the proximal colon [34, 37].

The precursor lesions in this serrated pathway would be first MVHP that would progress next to SSA [58]. *BRAF* mutation and CIMP-H status are molecular events shared by both type of polyps, thus supporting this theory [59]. The role of *BRAF* mutation evading apoptosis [51, 52]; and the silencing of genes involved in cellular cycle silencing through methylation of their promoters (such as *CDKN2A*, I*GFBP7*, and *TP53*) could help these cells to escape senescence [12].

In the second serrated pathway subtype, microsatellite stable (MSS) tumors could evolve from TSAs when the *MLH1* promoter is not affected (and thus MSI is not developed). These tumors harbor *KRAS* mutations more frequently than *BRAF* mutations, possibly due to silencing of *MGMT* gene [34, 60]. This pathway is usually CIMP-L and results in more distal colon neoplasia.

Finally, although both *BRAF* and *KRAS* mutations are associated with pathogenesis of SSAs and TSAs respectively, the progression to highly dysplastic lesions or invasive carcinomas requires the presence of additional alterations in tumor suppressor genes, including *p53* or β-*Catenin* [61]. In fact, aberrant nuclear accumulation of *p53*, which regulates cellular response to stress throughout cell cycle control, correlates with dysplastic changes in a proportion of SSAs and TSAs [39, 61, 62]. *p53* has been found more commonly mutated in CIMP-L MSS cancers, compared to MSI ones, which could explain the aggressiveness and worse prognosis of those tumors [12, 34, 39]. It is possible that *MLH1* methylation and *p53* mutation are critical alterations leading to neoplastic change and transition to either MSI or MSS CRC, respectively [39] (Fig. 4.5).

Molecular Markers of Serrated Pathway in SPS Patients

Some studies have evaluated the use of *BRAF* and *KRAS* mutation and CIMP status as biomarkers of SPS [56, 63]. This would become particularly useful considering the difficulties for SPS diagnosis due to the stringent WHO criteria. Guarinos et al. [33] detected a high rate of somatic *BRAF* mutations and CIMP-H phenotype in the polyps of 50 SPS patients. Moreover, all these SPS patients had mutations in either *KRAS* or *BRAF* in at least 25 % of their polyps, suggesting these mutations as potential biomarkers for this disease. Similarly, Carvajal-Carmona et al. [9] proposed

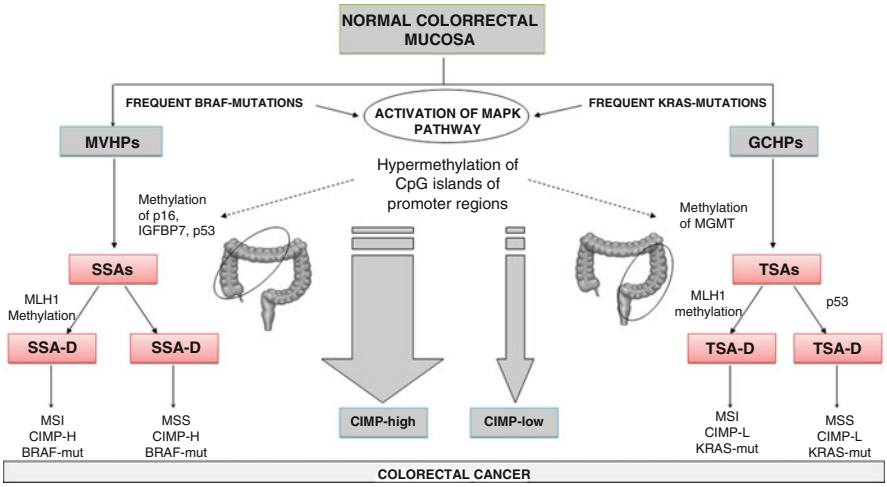


Fig. 4.5 Model of serrated pathway of carcinogenesis. *MVHP* microvesicular hyperplastic polyp, *SSA* sessile serrated adenoma, *SSA-D* sessile serrated adenoma with dysplasia, *MSI* microsatellite instability, *MSS* microsatellite stable, *CIMP* CpG island methylator phenotype, *GCHP* goblet cell serrated polyp, *TSA* traditional serrated adenoma, *TSA-D* traditional serrated adenoma with dysplasia

those molecular criteria as complementary to the clinical WHO criteria for SPS diagnosis. They recommended SPS to be diagnosed if either somatic *BRAF* or *KRAS* mutations are present in a high frequency in HPs; and conversely, to be excluded if both mutations were present in less than 10 % of HPs, or if less than 5 % of HPs were MSI-H.

Nevertheless, there is still some controversy about the usefulness of these molecular markers for SPS, since the SPS-related CRCs do not exhibit consistent molecular patterns in this regard. Rosty et al. reported that only half of the CRCs of SPS patients—those with distally located and MMR proficient cancers—had somatic *BRAF* or *KRAS* mutations [31]. This discrepancy in the molecular profile between polyps and CRC of SPS patients could be explained if a proportion of the CRCs of SPS patients do not develop through the serrated pathway but the traditional adenoma–carcinoma pathway instead.

Methylation of Normal Colorectal Mucosa in SPS Patients

BRAF mutation and DNA methylation seem to be the earliest events of the serrated pathway of carcinogenesis. Extensive DNA methylation in normal colorectal mucosa has been described in patients with SPS compared to patients with sporadic serrated polyps [52]. This suggests a field defect in epigenetic regulation associated with senescence and inappropriate rapid aging of the colonic mucosa, which would

drive an underlying genetic predisposition to extensive DNA methylation. Thus, this phenomenon would be associated with a predisposition to young-onset multiple serrated polyps and conventional adenomas, and finally to CRC arising through the serrated pathway [15, 64]. However, the sequence of events involved in this constitutive epigenetic disorder has not been elucidated yet [15, 65].

Risk of Cancer in SPS

CRC Risk in SPS Patients

Although SPS was originally considered to have no clinical consequences [66], it is now accepted that there is a substantial risk of CRC among patients with this syndrome. Nevertheless, the magnitude of this risk has still to be precisely determined [67]. Several studies have reported different CRC risks in SPS patients, ranging from 20 to 70 %, depending on the moment of its determination, which can be at the time of diagnosis or during polyps surveillance [3, 4, 16, 24–26, 33, 68] (Table 4.3).

In a recent retrospective study of 77 SPS patients, up to 35 % had CRC, of which 28.5 % were detected at time of SPS diagnosis, and 6.5 % developed it during the subsequent 5 years of polyps surveillance [26]. The cumulative risk of CRC was 6.5 % during a follow-up of a mean of 5.6 years [26]. Similar rates were found in another cohort of 44 patients, where 4.5 % of them were diagnosed with CRC in surveillance colonoscopies [68].

It is important to note that, due to the phenotypic heterogeneity of this disorder, the risk of CRC is not likely to be uniform [69]. Moreover, it seems that the occurrence and the risk of cancer increase with the number and size of serrated polyps [26, 70]. This situation acquires significant relevance because the number of polyps detected in surveillance colonoscopies increases 40 % per year over the baseline polyp number [68]. In addition, these patients can also have synchronous conventional adenomas [25, 71]. In fact, the presence of at least one adenoma in patients with multiple serrated

Table 4.3 Colorectal cancer (CRC) risk in patients fulfilling World Health Organization (WHO) criteria for serrated polyposis syndrome (SPS)

Author (year)	Number of SPS patients	Diagnostic (mean, years)	WHO	CRC (% patients)
Ferrandez [24]	15	52	Yes	–
Rubio [25]	10	61	Yes	70 %
Chow [4]	38	44	Yes	26 %
Boparai [26]	77	56	Yes	35 %
Win [3]	100	48	No (>5 serrated polyps)	69 %
Edelstein [68]	44	52	Yes	7.6 %
Guarinos [33]	50	49	Yes	18 %

polyps is associated with a 4 times higher risk of CRC [72]. The existence of missed lesions in previous colonoscopies or rapidly growing tumors following the serrated pathway of carcinogenesis have been suggested as possible causes of this high risk of CRC development in SPS patients [73].

Risk of Extracolonic Cancers in SPS patients

Several studies have reported incidence rates of extracolonic cancers between 16 % and 28 % in patients with SPS [22, 27, 74, 75]. Edelstein et al. reported that 16 % of 64 SPS patients developed extracolonic cancers [74] and Jasperson et al. found that 24 % of SPS patients had a history of an extracolonic tumor [27]. Breast, lung and prostate cancers are the most common extracolonic cancers seen in SPS families [22]. Pancreatic cancer is also associated with this syndrome [3]. Supporting that, Kalady et al. reported, in a cohort of SPS patients, that pancreatic cancer was the most common cancer overall, affecting 15 % of male patients. In the same study, 9 % of the pedigrees analyzed had gastric cancers [22].

However, other series do not show any increase of the risk of extracolonic neoplasms in SPS patients either in their first-degree relatives [76]. Environmental factors may partly be responsible for the phenotypic differences of SPS patients and they may be interacting with the genetic predisposition to both colonic and extracolonic cancers. Several studies have suggested that factors such as smoking, overweight or use of certain drugs may be potential risk factors for the development of hyperplastic polyps and serrated polyposis [72, 77–79].

Risk in Relatives of SPS Patients

Serrated polyposis has many features suggestive of an underlying genetic predisposition, including young-onset of CRC, multiplicity of neoplastic lesions, and an ethnicity and familial aggregation of SPS and CRC. However, the pattern of inheritance and the exact familial risk of SPS remain unknown and both dominant and recessive patterns have been described [4, 22, 50]. Published case series indicate that the rate of CRC in first-degree relatives of SPS patients ranges between 0 % and 59 % [4, 5, 22, 25, 27]. Reasons for this high variability in reported family history of CRC are largely unknown, but they may be secondary to selection bias. Boparai et al. have recently reported an increased risk for both CRC and SPS in first-degree relatives of SPS patients, compared to general population. They estimated that first-degree relatives of SPS patients had a five-fold greater risk of CRC and 39 times higher incidence of SPS compared to general population [50]. Win et al. observed similar findings in a retrospective cohort of 1,639 first and second-degree relatives of 100 index cases with SPS from different countries. Second-degree relatives of these SPS index cases also had an increased risk of CRC [3]. In a prospective study,

the incidence of SPS among first-degree relatives of the SPS patients analyzed was 32 % [80]. Besides, in the 11 SPS families described by Young et al., six of them fulfilled Amsterdam criteria I for Lynch Syndrome. The phenotype of these tumors was variable in MSI status, and 70 % of them showed mutation in *BRAF* and 80 % hypermethylation of *MINT31*. Moreover, CRCs were associated with young age of onset and a serrated architecture in those cases [81].

Some patients with *MUTYH*-associated polyposis (MAP) fulfill the WHO criteria for SPS [4, 82, 83]. These MAP patients account for approximately 1 % of all the SPS patients, and these individuals commonly show a mixed phenotype, with both hyperplastic and serrated polyps. Mutations in other tumor suppressor genes have also been reported. Sweet et al. found mutations in *PTEN* in 2/23 patients with a combination of hyperplastic and adenomatous polyps [84]. Moreover, one case with a missense mutation in *EPHB2* has also been reported [85]. Germline whole exome sequencing in 20 patients with multiple SSAs detected mutations in 35 % of these patients in six genes involved in oncogene-induced senescence (*ATM*, *PIF1*, *TELO2*, *XAF1*, *RBL1*, and *RNF43*) [86]. Other studies that aimed to identify specific genes in target regions for SPS or for multiple serrated polyps did not find any germline candidates [4, 87, 88].

Recommendations for Treatment and Surveillance

Recommendations for SPS Patients and Relatives

Recommendation for surveillance and management of SPS patients are exclusively based on experts opinions, although CRC surveillance guidelines do have recommendations regarding management of SSAs outside the context of SPS.

Recent guidelines for CRC screening recommend a complete polypectomy of all the polyps larger than 5 mm and located in proximal colon [89]. Surveillance colonoscopy is recommended after 1 to 3 years depending on the features of polyps found, being especially important a high number, SSA histology, proximal location or large size of polyps [5, 23–25, 70]. In this sense, a recent study shows that annual endoscopic surveillance with removal of all polyps greater than 3 mm prevents CRC in SPS patients [76].

Surgery with total colectomy and ileorectal anastomosis is indicated when CRC is diagnosed, or the number and/or size of polyps make the endoscopic management unfeasible, either there is no possibility of surveillance [35]. Annual follow-up colonoscopies are indicated post-surgery for the assessment of the remaining colon and rectum.

In first-degree relatives, a screening colonoscopy is recommended from the age of 35–40 or 10 years younger than the index case with SSAs or HPs. In the same way, surveillance colonoscopies are recommended in these relatives every 5 years, with shorter intervals when polyps are detected [35, 50, 89].

In any case, the management of patients with SPS and their relatives requires a multidisciplinary assessment in a context of high-risk units of CRC prevention. High quality colonoscopy with use of complementary techniques in order to improve polyp detection should be guaranteed for SPS patients and their relatives.

References

1. Snover DC, Ahnen AD, Burt RW, Odze RD. WHO classification of tumours of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, editors. Berlin: Springer; 2010.
2. Goldman H, Ming S, Hickock DF. Nature and significance of hyperplastic polyps of the human colon. Arch Pathol. 1970;89(4):349–54.
3. Win AK, Walters RJ, Buchanan DD, Jenkins MA, Sweet K, Frankel WL, et al. Cancer risks for relatives of patients with serrated polyposis. Am J Gastroenterol. 2012;107(5):770–8.
4. Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006;131(1):30–9.
5. Lage P, Cravo M, Sousa R, Chaves P, Salazar M, Fonseca R, et al. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. Am J Gastroenterol. 2004;99(9):1779–84.
6. Jeevaratnam P, Cottier DS, Browett PJ, Van De Water NS, Pokos V, Jass JR. Familial giant hyperplastic polyposis predisposing to colorectal cancer: a new hereditary bowel cancer syndrome. J Pathol. 1996;179(1):20–5.
7. Vemulapalli KC, Rex DK. Failure to recognize serrated polyposis syndrome in a cohort with large sessile colorectal polyps. Gastrointest Endosc. 2012;75(6):1206–10.
8. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med. 2006;355(18):1863–72.
9. Carvajal-Carmona LG, Howarth KM, Lockett M, Polanco-Echeverry GM, Volikos E, Gorman M, et al. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. J Pathol. 2007;212(4):378–85.
10. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759–67.
11. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology. 2007;50(1):113–30.
12. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138(6):2088–100.
13. Boparai KS, Dekker E, Polak MM, Musler AR, van Eeden S, van Noesel CJ. A serrated colorectal cancer pathway predominates over the classic WNT pathway in patients with hyperplastic polyposis syndrome. Am J Pathol. 2011;178(6):2700–7.
14. Margulies M, Egholm M, Altman WE, Attiya S, Bader JS, Bemben LA, et al. Genome sequencing in microfabricated high-density picolitre reactors. Nature. 2005;437(7057):376–80.
15. Guarinos C, Sanchez-Fortun C, Rodriguez-Soler M, Alenda C, Paya A, Jover R. Serrated polyposis syndrome: molecular, pathological and clinical aspects. World J Gastroenterol. 2012;18(20):2452–61.
16. Lockett MAW. Hyperplastic polyposis: prevalence and cancer risk. Gut. 2011;48 Suppl 1:A11:A1–A5.
17. Biswas S, Ellis AJ, Guy R, Savage H, Madronal K, East JE. High prevalence of hyperplastic polyposis syndrome (serrated polyposis) in the NHS bowel cancer screening programme. Gut. 2013;62(3):475.
18. Moreira L, Pellise M, Carballal S, Bessa X, Ocana T, Serradesanferm A, et al. High prevalence of serrated polyposis syndrome in FIT-based colorectal cancer screening programmes. Gut. 2013;62(3):476–7.

19. Burt RW, Jass JR. Hyperplastic polyposis. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours pathology and genetics tumours of the digestive system. Berlin: Springer; 2000. p. 135–6.
20. Higuchi T, Jass JR. My approach to serrated polyps of the colorectum. J Clin Pathol. 2004;57(7):682–6.
21. Crowder CD, Sweet K, Lehman A, Frankel WL. Serrated polyposis is an underdiagnosed and unclear syndrome: the surgical pathologist has a role in improving detection. Am J Surg Pathol. 2012;36(8):1178–85.
22. Kalady MF, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, et al. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. Dis Colon Rectum. 2011;54(2):164–70.
23. Yeoman A, Young J, Arnold J, Jass J, Parry S. Hyperplastic polyposis in the New Zealand population: a condition associated with increased colorectal cancer risk and European ancestry. N Z Med J. 2007;120(1266):U2827.
24. Ferrandez A, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol. 2004;99(10):2012–8.
25. Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. Endoscopy. 2006;38(3):266–70.
26. Boparai KS, Mathus-Vliegen EM, Koornstra JJ, Nagengast FM, van Leerdam M, van Noesel CJ, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut. 2010;59(8):1094–100.
27. Jasperson KW, Kanth P, Kirchhoff AC, Huismann D, Gammon A, Kohlmann W, et al. Serrated polyposis: colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum. 2013;56(11):1211–6.
28. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology. 1996;110(3):748–55.
29. Bengoechea O, Martinez-Penuela JM, Larrinaga B, Valerdi J, Borda F. Hyperplastic polyposis of the colorectum and adenocarcinoma in a 24-year-old man. Am J Surg Pathol. 1987;| 11(4):323–7.
30. Keljo DJ, Weinberg AG, Winick N, Tomlinson G. Rectal cancer in an 11-year-old girl with hyperplastic polyposis. J Pediatr Gastroenterol Nutr. 1999;28(3):327–32.
31. Rosty C, Walsh MD, Walters RJ, Clendenning M, Pearson SA, Jenkins MA, et al. Multiplicity and molecular heterogeneity of colorectal carcinomas in individuals with serrated polyposis. Am J Surg Pathol. 2013;37(3):434–42.
32. Jass JR. Gastrointestinal polyposes: clinical, pathological and molecular features. Gastroenterol Clin North Am. 2007;36(4):927–46. viii.
33. Guarinos C, Sanchez-Fortun C, Rodriguez-Soler M, Perez-Carbonell L, Egoavil C, Juarez M, et al. Clinical subtypes and molecular characteristics of serrated polyposis syndrome. Clin Gastroenterol Hepatol. 2013;11 6:705–11; quiz e46.
34. Huang CS, Farraye FA, Yang S, O'Brien MJ. The clinical significance of serrated polyps. Am J Gastroenterol. 2011;106(2):229–40. quiz 41.
35. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012;107(9):1315–29; quiz 4, 30.
36. Jass JR. Hyperplastic polyps and colorectal cancer: is there a link? Clin Gastroenterol Hepatol. 2004;2(1):1–8.
37. East JE, Saunders BP, Jass JR. Sporadic and syndromic hyperplastic polyps and serrated adenomas of the colon: classification, molecular genetics, natural history, and clinical management. Gastroenterol Clin North Am. 2008;37(1):25–46. v.
38. Liang JJ, Alrawi S, Tan D. Nomenclature, molecular genetics and clinical significance of the precursor lesions in the serrated polyp pathway of colorectal carcinoma. Int J Clin Exp Pathol. 2008;1(4):317–24.
39. Rosty C, Hewett DG, Brown IS, Leggett BA, Whitehall VL. Serrated polyps of the large intestine: current understanding of diagnosis, pathogenesis, and clinical management. J Gastroenterol. 2013;48(3):287–302.

40. Sandmeier D, Benhattar J, Martin P, Bouzourene H. Serrated polyps of the large intestine: a molecular study comparing sessile serrated adenomas and hyperplastic polyps. Histopathology. 2009;55(2):206–13.
41. Hiraoka S, Kato J, Fujiki S, Kaji E, Morikawa T, Murakami T, et al. The presence of large serrated polyps increases risk for colorectal cancer. Gastroenterology. 2010;139(5):1503–10, 10 e1–3.
42. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101(2):343–50.
43. Anderson JC. Pathogenesis and management of serrated polyps: current status and future directions. Gut Liver. 2014;8(6):582–9.
44. Brooker JC, Saunders BP, Shah SG, Thapar CJ, Thomas HJ, Atkin WS, et al. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc. 2002;56(3):333–8.
45. Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut. 2004;53(3):376–80.
46. Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy. 2006;38(5):444–8.
47. Toyoshima N, Sakamoto T, Makazu M, Nakajima T, Matsuda T, Kushima R, et al. Prevalence of serrated polyposis syndrome and its association with synchronous advanced adenoma and lifestyle. Mol Clin Oncol. 2015;3(1):69–72.
48. Rastogi A, Bansal A, Wani S, Callahan P, McGregor DH, Cherian R, et al. Narrow-band imaging colonoscopy--a pilot feasibility study for the detection of polyps and correlation of surface patterns with polyp histologic diagnosis. Gastrointest Endosc. 2008;67(2):280–6.
49. Tischendorf JJ, Wasmuth HE, Koch A, Hecker H, Trautwein C, Winograd R. Value of magnifying chromoendoscopy and narrow band imaging (NBI) in classifying colorectal polyps: a prospective controlled study. Endoscopy. 2007;39(12):1092–6.
50. Boparai KS, Reitsma JB, Lemmens V, van Os TA, Mathus-Vliegen EM, Koornstra JJ, et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. Gut. 2010;59(9):1222–5.
51. Kambara T, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut. 2004;53(8):1137–44.
52. Minoo P, Moyer MP, Jass JR. Role of BRAF-V600E in the serrated pathway of colorectal tumourigenesis. J Pathol. 2007;212(2):124–33.
53. Shen L, Toyota M, Kondo Y, Lin E, Zhang L, Guo Y, et al. Integrated genetic and epigenetic analysis identifies three different subclasses of colon cancer. Proc Natl Acad Sci USA. 2007;104(47):18654–9.
54. Ogino S, Nosho K, Kirkner GJ, Kawasaki T, Meyerhardt JA, Loda M, et al. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. Gut. 2009;58(1):90–6.
55. Jover R, Nguyen TP, Perez-Carbonell L, Zapater P, Paya A, Alenda C, et al. 5-Fluorouracil adjuvant chemotherapy does not increase survival in patients with CpG island methylator phenotype colorectal cancer. Gastroenterology. 2011;140(4):1174–81.
56. Chan AO, Issa JP, Morris JS, Hamilton SR, Rashid A. Concordant CpG island methylation in hyperplastic polyposis. Am J Pathol. 2002;160(2):529–36.
57. Hawkins NJ, Ward RL. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. J Natl Cancer Inst. 2001;93(17):1307–13.
58. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology. 2013;62(3):367–86.

59. O'Brien MJ, Yang S, Mack C, Xu H, Huang CS, Mulcahy E, et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. Am J Surg Pathol. 2006;30(12):1491–501.
60. Whitehall VL, Walsh MD, Young J, Leggett BA, Jass JR. Methylation of O-6-methylguanine DNA methyltransferase characterizes a subset of colorectal cancer with low-level DNA microsatellite instability. Cancer Res. 2001;61(3):827–30.
61. Fujita K, Yamamoto H, Matsumoto T, Hirahashi M, Gushima M, Kishimoto J, et al. Sessile serrated adenoma with early neoplastic progression: a clinicopathologic and molecular study. Am J Surg Pathol. 2011;35(2):295–304.
62. Fu B, Yachida S, Morgan R, Zhong Y, Montgomery EA, Iacobuzio-Donahue CA. Clinicopathologic and genetic characterization of traditional serrated adenomas of the colon. Am J Clin Pathol. 2012;138(3):356–66.
63. Wynter CV, Walsh MD, Higuchi T, Leggett BA, Young J, Jass JR. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. Gut. 2004;53(4):573–80.
64. Worthley D, Whitehall V, Buttenshaw R, Irahara N, Greco S, Ramsnes I, et al. DNA methylation within the normal colorectal mucosa is associated with pathway-specific predisposition to cancer. Oncogene. 2010;29:10.
65. Hesson LB, Hitchins MP, Ward RL. Epimutations and cancer predisposition: importance and mechanisms. Curr Opin Genet Dev. 2010;20(3):290–8.
66. Williams GT, Arthur JF, Bussey HJ, Morson BC. Metaplastic polyps and polyposis of the colorectum. Histopathology. 1980;4(2):155–70.
67. Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology. 2006;130(6):1872–85.
68. Edelstein DL, Axilbund JE, Hylind LM, Romans K, Griffin CA, Cruz-Correa M, et al. Serrated polyposis: rapid and relentless development of colorectal neoplasia. Gut. 2013;62(3):404–8.
69. Rashid A, Houlihan PS, Booker S, Petersen GM, Giardiello FM, Hamilton SR. Phenotypic and molecular characteristics of hyperplastic polyposis. Gastroenterology. 2000;119(2):323–32.
70. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. Gastroenterology. 2010;139(5):1497–502.
71. Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol. 2001;25(2):177–84.
72. Buchanan DD, Sweet K, Drini M, Jenkins MA, Win AK, English DR, et al. Risk factors for colorectal cancer in patients with multiple serrated polyps: a cross-sectional case series from genetics clinics. PLoS One. 2010;5(7), e11636.
73. Sanduleanu S, Masclee AM, Meijer GA. Interval cancers after colonoscopy-insights and recommendations. Nat Rev Gastroenterol Hepatol. 2012;9(9):550–4.
74. Edelstein DL, Cruz-Correa M, Soto-Salgado M, Axilbund JE, Hylind LM, Romans K, et al. Risk of colorectal and other cancers in patients with serrated polyposis. Clin Gastroenterol Hepatol. 2015;13(9):1697–9.
75. Elorza G, Enriquez-Navascues JM, Bujanda L, Larzabal M, Gil Lasa I, Marti L. Phenotype characteristics of patients with colonic serrated polyposis syndrome: a study of 23 cases. Cir Esp. 2014;92(10):659–64.
76. Hazewinkel Y, Tytgat KM, van Eeden S, Bastiaansen B, Tanis PJ, Boparai KS, et al. Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. Gastroenterology. 2014;147(1):88–95.
77. Samowitz WS, Albertsen H, Sweeney C, Herrick J, Caan BJ, Anderson KE, et al. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. J Natl Cancer Inst. 2006;98(23):1731–8.
78. Walker RG, Landmann JK, Hewett DG, Worthley DL, Buttenshaw RL, Knight N, et al. Hyperplastic polyposis syndrome is associated with cigarette smoking, which may be a modifiable risk factor. Am J Gastroenterol. 2010;105(7):1642–7.

79. Wallace K, Grau MV, Ahnen D, Snover DC, Robertson DJ, Mahnke D, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiol Biomarkers Prev. 2009;18(8):2310–7.
80. Oquinena S, Guerra A, Pueyo A, Eguaras J, Montes M, Razquin S, et al. Serrated polyposis: prospective study of first-degree relatives. Eur J Gastroenterol Hepatol. 2013;25(1):28–32.
81. Young J, Barker MA, Simms LA, Walsh MD, Biden KG, Buchanan D, et al. Evidence for BRAF mutation and variable levels of microsatellite instability in a syndrome of familial colorectal cancer. Clin Gastroenterol Hepatol. 2005;3(3):254–63.
82. Guarinos C, Juarez M, Egoavil C, Rodriguez-Soler M, Perez-Carbonell L, Salas R, et al. Prevalence and characteristics of MUTYH-associated polyposis in patients with multiple adenomatous and serrated polyps. Clin Cancer Res. 2014;20(5):1158–68.
83. Jarrar AM, Church JM, Fay S, Kalady MF. Is the phenotype mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. Dis Colon Rectum. 2009;52(12):1949–55.
84. Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, Alhopuro P, et al. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA. 2005;294(19):2465–73.
85. Kokko A, Laiho P, Lehtonen R, Korja S, Carvajal-Carmona LG, Jarvinen H, et al. EPHB2 germline variants in patients with colorectal cancer or hyperplastic polyposis. BMC Cancer. 2006;6:145.
86. Gala MK, Mizukami Y, Le LP, Moriichi K, Austin T, Yamamoto M, et al. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. Gastroenterology. 2014;146(2):520–9.
87. Clendenning M, Young JP, Walsh MD, Woodall S, Arnold J, Jenkins M, et al. Germline mutations in the polyposis-associated genes, and are not common in individuals with serrated polyposis syndrome. PLoS One. 2013;8(6), e66705.
88. Roberts A, Nancarrow D, Clendenning M, Buchanan DD, Jenkins MA, Duggan D, et al. Linkage to chromosome 2q32.2-q33.3 in familial serrated neoplasia (Jass syndrome). Fam Cancer. 2011;10(2):245–54.
89. Burt RW, Barthel JS, Dunn KB, David DS, Drelichman E, Ford JM, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. J Natl Compr Canc Netw. 2010;8(1):8–61.

Chapter 5
Polymerase Proofreading Associated Polyposis, and Other New Syndromes of Hereditary Colorectal Cancer

James Church

Introduction

The hallmarks of hereditary colorectal cancer include multiple neoplasms in multiple organs, cancer arising at a young age, and a family history suggestive of inheritance. When a patient and family present in this way, genetic counseling and testing sometimes reveal the mutation causing the syndrome. The most common hereditary polyposis syndromes are familial adenomatous polyposis (FAP) and *MYH* associated polyposis (MAP). Recently new syndromes of inherited colorectal cancer have been reported, involving germline mutations in genes coding for proteins that help to maintain the fidelity of DNA reproduction. This chapter will describe these syndromes: polymerase proofreading associated polyposis (PPAP) [1], *NTHL1* associated polyposis (NAP) [2], polyposis associated with mutations in *FAN1* [3], and hereditary colon cancer associated with mutations in *BUB1*/*BUB3*. They are summarized in Table 5.1. However before discussing the syndromes it is important to emphasize the critical nature of DNA repair to health in general, and carcinogenesis in particular.

The Importance of Faithful DNA Reproduction

Whenever a cell divides its genetic material is passed into the daughter cells. Ideally there should be an exact replication of the sequence of nucleotide bases that constitute the DNA. Of course there is considerable redundancy in the genetic code and

J. Church, M.B.Ch.B., F.R.A.C.S. (✉)
Sanford R. Weiss Center for Hereditary Colorectal Neoplasia, Department of Colorectal Surgery, Cleveland Clinic Foundation,
James Church, Desk A30, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: churchj@ccf.org

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_5

Table 5.1 Newly described syndromes of hereditary colorectal neoplasia

Syndrome	Gene(s)	Mechanism	Inheritance	Phenotype
Polymerase proofreading associated polyposis (PPAP)	*POLE, POLD1*	DNA polymerase proofreading	Dominant	>5 adenomas, young age of onset colorectal cancer, endometrial cancer (*POLD1*)
NTHL1 associated polyposis (NAP)	*NTHL1*	Base-excision repair	Recessive	Oligopolyposis, young age of onset colorectal cancer
FAN1 associated young colorectal cancer	*FAN1*	Interstrand crosslink repair	Dominant	Young age of onset colorectal cancer
BUB1/BUB3 young colorectal cancer	*BUB1, BUB3*	Spindle checkpoint assembly		Young age of onset colorectal cancer

so some discrepancy is tolerated, but sometimes even a change in one base is harmful. There are multiple systems of DNA proofreading and repair that are highly conserved between species. This conservation and the redundancy in the genetic code reflect the importance of faithful DNA replication to the survival of the organism.

Failure of DNA repair has serious implications for the genome of the daughter cells as the mistakes that go uncorrected become incorporated into the DNA and are passed on to all subsequent generations of the affected clones as mutations: permanent structural changes. The results of DNA repair failure are often characteristic of the repair system involved. For example, failure of mismatch repair causes unstable DNA microsatellites and is recognized clinically as microsatellite instability in tumors [4]. Genes that contain microsatellites are at risk of acquiring mutations. Failure of base-excision repair due to loss of MYH function results in GC:AT transversions (substitution of two ring purines for one ring for pyrimidines) that cause mutations in multiple genes. Typically *APC* is affected, and these *APC* mutations act as a driver for colorectal carcinogenesis, producing the clinical picture of attenuated FAP that is termed *MYH* Associated Polyposis (MAP) [5]. However the phenotype varies according to the spectrum of genes involved by the effects of the germline mutation. For example, if *KRAS* acquires the GC:AT transversions, patients tend to develop serrated polyps. A second gene involved in base-excision repair—*NTHL1*—has been described in association with a MAP-like syndrome characterized by recessive inheritance, attenuated adenomatous polyposis, and extracolonic tumors. This syndrome has been named *NTHL1* associated polyposis (NAP) [2]. Another mechanism of DNA repair that, when failing, has downstream effects on multiple genes, is DNA polymerase proofreading. As the new strand of DNA is formed, proofreading proteins check for mistakes in nucleotide base incorporation. When proofreading fails, mutations occur in multiple genes, including *APC, KRAS*, and *BRAF*. When the failure is inherited as a germline mutation in a proofreading gene, it leads to a dominantly inherited syndrome of young onset colorectal cancer and

adenomatous polyps. This is PPAP [1]. Finally a recent report describes germline mutations in a gene associated with DNA interstrand crosslink repair (*FAN1*) in patients with Amsterdam positive colorectal cancer families with microsatellite stable tumors [3].

This relative plethora of new syndromes of hereditary colorectal cancer increases the complexity of the field, but at the same time fills in gaps that existed in our ability to find a molecular explanation for inheritance of the disease. In the context of the increasing use of Nextgen sequencing and cancer panels, variants in rare genes may be identified in families and so an increase in knowledge and understanding of the implications of these gene mutations is important.

Polymerase Proofreading Polyposis

DNA polymerases are responsible for replication of the DNA molecule. This is a complex process involving multiple isomers of the polymerase proteins. The process of replication is begun by Polα and continued by Polε on the leading strand and Polδ on the lagging strand. Inherent to the accurate replication of DNA by Polδ and Polε is a 3′ exonuclease function that corrects mistakes in the process. Mutations that interfere with the proofreading function of these genes produce a mutator phenotype that has been associated with a dominantly inherited syndrome of young onset colorectal cancer, oligopolyposis, and endometrial cancer [1, 6–11].

In February 2013, Palles et al. published the results of whole genome sequencing of 15 probands who presented with at least 10 adenomas diagnosed before they turned 60 years of age [1]. Five relatives of the probands were also sequenced. Eight of these 20 patients had developed colorectal cancer, and the remaining 12 each had an affected first degree relative. Patients had been screened for germline mutations in *APC*, *MYH*, and the DNA mismatch repair genes: one patient had attenuated FAP and another had Lynch syndrome. Analysis of the remaining patients revealed a variant at *POLE* L424V that was predicted to have severe deleterious effects on protein function.

Clinical and genetic analysis of the affected patients and their tumors followed. There was variability in the severity of the phenotype but the kindreds showed dominant inheritance of multiple adenomas and young onset, microsatellite stable cancer. Ages at diagnosis of cancer ranged from 28 to 53 years (median 33 years), the range of number of adenomas was from 1 to 68 (median 10), and the time during which the adenomas accumulated was from 10 to 22 years. Thirty-nine tumors from 11 carriers were genetically analyzed, and base substitution mutations were found in multiple genes including *KRAS*, *BRAF*, and *APC*. This *APC* mutation pattern was different to that found in sporadic tumors, where the majority of mutations are frameshifts. A second variant was found in three other families: *POLD1* S478N. Tumors in these patients were similar to those found in *POLE* mutation carriers but the cancer spectrum for *POLD1* included endometrial and brain cancer [1].

Since this original report, others have screened various groups of patients for germline mutations in *POLE* or *POLD1*. Elsayed et al. tested 1188 genetically undiagnosed patients with familial colorectal cancer or polyposis for the variants *POLE* p.L424V and *POLD* p.S478N [6]. They found three index cases with POLE p.L424V, one of which seemed to be de novo. Neoplasms from three patients in two of the families were microsatellite unstable and on immunohistochemistry lacked expression of MSH2/MSH6. There were no germline mutations in these DNA mismatch repair genes and the authors theorized that this mismatch repair deficiency was due to the hypermutator phenotype caused by the *POLE* mutation, the same phenomenon that is sometimes seen in patients with biallelic *MYH* mutations.

Valle et al. screened 858 patients with polyposis and familial/young age of onset colorectal cancer and found a de novo *POLE* p.L424V mutation in a 28 years old with polyposis and colorectal cancer [7]. In addition a new mutation (*POLD1* p.L474P) was found in a mismatch repair proficient family fulfilling Amsterdam II criteria. Chubb et al. [8] studied 646 unrelated individuals with colorectal cancer diagnosed under 56 years old and with at least one affected first degree relative, and found pathogenic mutations in *POLE* in two and *POLD1* in one. Age at diagnosis ranged from 28 to 45 years, and there was an average of 4 affected relatives for *POLE* and 2 for *POLD1*. These large studies by Elsayed et al., Valle et al., and Chubb et al. show that PPAP is rare, even in families with a suggestive family history. They show that mutations in polymerase proofreading genes can occur de novo (that is, without a family history), and that they can produce tumors with a Lynch syndrome phenotype. These are all important findings in the context of investigating patients and families that may have an hereditary colorectal cancer syndrome.

Whole exome sequencing is a technique that limits testing to the protein coding regions of the DNA (the exome); 5 % of the whole genome. It identifies variants segregating with disease that are likely to have a deleterious effect on protein formation [13]. At a recent meeting of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT), four abstracts reported the results of exome sequencing in families with apparent dominant inheritance of adenomatous polyposis and/or young age of onset colorectal cancer [8–11]. While this work does not establish the incidence of *POLE* and *POLD1* mutations in patients and families with this phenotype, it does increase our knowledge of the phenotype. This is shown in Table 5.2.

Diagnosis, Surveillance, and Treatment

The clinical features of PPAP seem to be variable but include a dominantly inherited pattern of predisposition to colorectal neoplasia, such as attenuated polyposis, multiple advanced adenomas, microsatellite stable or unstable colorectal cancer, and endometrial cancer, all happening at relatively young ages. Thus PPAP can account for an unknown percentage of patients currently defined as Familial Colorectal

Table 5.2 Genotype and phenotype of patients and families with polymerase proofreading associated polyposis (PPAP)

Authors	Gene(s)	Colorectal phenotype	Extracolonic cancers	Family history of cancers
Spier [9]	*POLE* Leu 424Val	3/77 with Amsterdam positive families, 2/30 with adenomatous polyposis	Duodenal adenomas (63 %), duodenal cancer, ovarian cancer, glioblastoma	
Hansen [12]	*POLE* p.Tyr458Phe	Variable	Ovaries, small intestine pancreas	
Rosner [10]	*POLD1* p.V759I, *POLE* p.E277G	Adenomas, advanced adenomas, hyperplastic polyps, left sided colorectal cancer	Glioblastoma multiforme, café au lait spots (POLE)	Lung cancer, lymphoma, skin, and gum cancer
Nordling [11]	*POLE* p.Asn363Lys p.Lys425Arg	Young onset CRC	Ovary, endometrium, brain	
Elsayed [6]	*POLE p.*L424V	Multiple adenomas, young age of onset colorectal cancer (MSS and MSI)	Endometrium, brain	Liver cancer
Valle [7]	*POLE* p.L424V *POLD1* p.L474P	Polyposis and colorectal cancer		Endometrial, gastric, brain, bladder
Chubb [14]	*POLE* p.L424V *POLD1* p.S478N 6 other variants	Young age of onset colorectal cancer with affected first degree relative		

Cancer Type X, and for some patients with MSI cancers lacking MSH2/MSH6 expression but without germline mutations in the corresponding genes. The option of sequencing *POLD1* and *POLE* is beginning to be added to Nextgen panels by commercial genetic testing companies. This will make the diagnosis easier. Once a genetic diagnosis is made, patients can be followed yearly with colonoscopy and pelvic ultrasound. Prophylactic colectomy and hysterectomy can be discussed though there is very little data on which to make an informed recommendation to the patient and family. The number of adenomas reported by Palles et al. suggests that many patients can potentially be managed by colonoscopy, either of the intact colon or after a segmental colectomy for a presenting cancer.

Management of an existing colorectal cancer can be segmental colectomy or total colectomy and ileorectal anastomosis. The limited literature suggests a highly penetrant disease, but there is no long-term follow-up on gene carriers to look at the risk of metachronous tumors. The following suggested surveillance program is extrapolated from other syndromes and falls on the more aggressive side of surveillance.

Management of the at risk relatives requires colonoscopic screening from the lower age of 25 years, or 5 years younger than the youngest affected relative. For *POLD1* families, or untested families with endometrial cancer as part of the phenotype, yearly pelvic examinations with ultrasound should begin at age 30. Hysterectomy should be considered after childbearing has been completed. A baseline EGD should be done at diagnosis, and repeated every 5 years or more often if there are polyps. When there is a Familial Colorectal Cancer Type X family, in whom genetic testing is uninformative, a similar surveillance program should apply to all at risk relatives. When genetic testing identifies a deleterious mutation, at risk relatives can be triaged by screening for the mutation.

NTHL1 Associated Polyposis

In a recent letter to Nature Genetics, Weren et al. reported the results of whole exome sequencing in 51 unrelated patients with multiple adenomas [2]. They found homozygous germline mutations in a base-excision repair gene (*NTHL1*) in seven affected individuals from three unrelated families. All three families showed recessive inheritance of adenomas and predisposition to colorectal and endometrial cancer. The carrier state of the mutation (heterozygous mutation) occurred in 0.0036 % of 2329 controls. Examination of tumors in affected individuals showed an excess of CG:TA transversions in the DNA, different to the CG:AT transversions seen with MAP. Affected genes included *APC, TP53, KRAS*, and *PIK3CA*, typical driver genes for colorectal neoplasia. Clinical features of the homozygous mutation carriers included multiple colorectal adenomas and multiple metachronous colorectal cancers, premalignant or malignant endometrial tumors, and duodenal neoplasia. Serrated polyps were not seen.

In this one study, NAP is behaving in a similar way to MAP, with early onset of colorectal cancer, multiple adenomas, endometrial cancer, and a picture reminiscent of attenuated FAP. This is not surprising because the molecular mechanism of the disease is very similar. For the moment, patients and families can be managed similarly to those with MAP. The colon may be managed endoscopically and surveyed yearly if this is practicable given the ease of the examination and the aggressiveness of the polyposis. EGD and thyroid screening are performed as indicated by findings on the early examination. If endoscopic treatment is impossible or inadequate for cancer prevention, prophylactic surgery is performed. *NTHL1* sequencing is not yet commercially available, but may come in to colorectal cancer testing panels in the relatively near future.

FAN1 and *BUB1/BUB3*

Whole exome sequencing of Familial Colorectal Cancer Type X families (Amsterdam positive family history and microsatellite stable tumors) has recently uncovered germline mutations in *FAN1*, a gene which encodes a nuclease involved

in DNA interstrand crosslink repair [3]. The FAN1 protein interacts with components of DNA mismatch repair such as MLH1, PMS2, and PMS1. Germline *FAN1* mutations were detected in approximately 3 % of familial colorectal cancer Type X families, offering another molecular explanation for this genetically heterogeneous group. *BUB1* and *BUB3* are spindle assembly checkpoint genes, ensuring normal chromosome segregation during mitosis and preventing aneuploidy. De Voer et al. found haploinsufficiencies or heterozygous germline mutations in 2.9 % of 208 patients with colorectal cancer under the age of 40 years, or with familial aggregation of the disease [14]. In addition to the colorectal cancer these patients showed variegated aneuploidy in multiple tissues. We await more detailed reporting of the phenotypes and the incidence of the genotypes of *FAN1* and *BUB1*/*BUB3* associated colorectal cancer. In the meantime their inclusion in genetic panels will make the genetic diagnosis of hereditary colorectal cancer more complete.

References

1. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45:136–44.
2. Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, et al. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. Nat Genet. 2015;47:668–71.
3. Seguí N, Mina LB, Lázaro C, Sanz-Pamplona R, Pons T, Navarro M, et al. Germline mutations in FAN1 cause hereditary colorectal cancer by impairing DNA repair. Gastroenterology. 2015 Jun 4. pii: S0016-5085(15)00783-0. doi: 10.1053/j.gastro.2015.05.056.
4. Sameer AS, Nissar S, Fatima K. Mismatch repair pathway: molecules, functions, and role in colorectal carcinogenesis. Eur J Cancer Prev. 2014;23:246–57.
5. Sereno M, Merino M, López-Gómez M, Gómez-Raposo C, Zambrana Tébar F, Moreno Rubio J, et al. MYH polyposis syndrome: clinical findings, genetics issues and management. Clin Trans Oncol. 2014;16:675–9.
6. Elsayed FA, Kets CM, Ruano D, van den Akker B, Mensenkamp AR, Schrumpf M, et al. Germline variants in POLE are associated with early onset mismatch repair deficient colorectal cancer. Eur J Hum Genet. 2014. doi:10.1038/ejhg.2014.242.
7. Valle L, Hernandez-Illan E, Bellido F, Aiza G, Castillejo A, Castillejo MI, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet. 2014;23(13):3506–12.
8. Chubb D, Broderick P, Frampton M, Kinnersley B, Sherborne A, Penegar S, Lloyd A, Ma YP, Dobbins SE, Houlston RS. Genetic diagnosis of high-penetrance susceptibility for colorectal cancer (CRC) is achievable for a high proportion of familial CRC by exome sequencing. J Clin Oncol. 2015;33(5):426–32.
9. Spier I, Holzapfel S, Altmüller J, Zhao B, Horpaopan S, Vogt S, et al. Frequency and phenotypic spectrum of germline mutations in POLE and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas. Int J Cancer. 2015;137:320–31.
10. Rosner G, Elya R, Bercovich D, Santo E, Halpern Z, Kariv R. Mutations in DNA polymerase genes (POLD1 and POLE) in individuals having early-onset colorectal cancer and/or multiple adenomas. Familial Cancer. 2015;14 Suppl 1:S29.
11. Nordling M, Rohlin A, Zagoras T, Eiengard F, Engwall Y, Nilsson S, et al. Causative novel POLE mutations in hereditary colorectal cancer syndromes. Familial Cancer. 2015;14 Suppl 1:S68.

12. Hansen ME, Johansen J, Bjornevoll I, Sylvander A, Syeinsbekk K, Saetrom P, et al. A novel POLE variant, identified by exome sequencing, causes colorectal and extracolonic cancers. Familial Cancer. 2015;14 Suppl 1:S44.
13. Ng S, Buckingham K, Lee C, Bigham A, Tabor H, Dent K, Huff C, Paul T, Shannon P, et al. Exome sequencing identifies the cause of a Mendelian disorder. Nat Genet. 2010;42:30–35.
14. de Voer RM, Geurts van Kessel A, Weren RD, Ligtenberg MJ, Smeets D, Fu L, et al. Germline mutations in the spindle assembly checkpoint genes BUB1 and BUB3 are risk factors for colorectal cancer. Gastroenterology. 2013;145:544–7.

Chapter 6
Juvenile Polyposis Syndrome

Kendall Keck and James R. Howe

Introduction

Juvenile polyps are the most common polyps seen in children [1]. It has been estimated that as many as 1 % of the population will have one of these polyps in their lifetime, but in most cases these disappear, and patients do not have ongoing issues related to them, such as bleeding or prolapse. In some individuals, these polyps are multiple, and may continue to form throughout a person's life. These people have a different situation, where they are born with an autosomal dominant syndrome predisposing them to developing these polyps. It has been estimated that this condition, Juvenile Polyposis (JP), affects approximately 1 in 100,000 individuals [2]. There is an equal incidence between males and females, and an increased incidence in individuals of Northern European descent [3]. JP patients most commonly develop hamartomatous polyps throughout the colon (Fig. 6.1), but may also have polyps in other portions of the GI tract as well, usually within the stomach (Fig. 6.2). Patients with JP have an increased risk of GI cancers, with the highest risk being for colorectal cancers, but there is also increased risk for gastric and pancreatic tumors.

The earliest case of JP described in the literature is unclear, but some attribute this to Hertz et al. in 1914. He described a family consisting of four children all having rectal polyps and bleeding, and asymptomatic parents [4]. These polyps were never confirmed to be juvenile histologically, but this was very likely the earliest description of a JP family. In 1939, Diamond reported a 30-month-old child with constipation and hematochezia with a pedunculated, sessile polyp of the rectum, prone to prolapse [5]. This 2.5 cm polyp, although described as an adenoma, had the histologic features we have come to know as a juvenile polyp.

K. Keck, M.D. • J.R. Howe, M.D. (✉)
University of Iowa Carver College of Medicine,
4644 JCP, 200 Hawkins Drive, Iowa City, IA 52242, USA
e-mail: james-howe@uiowa.edu

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_6

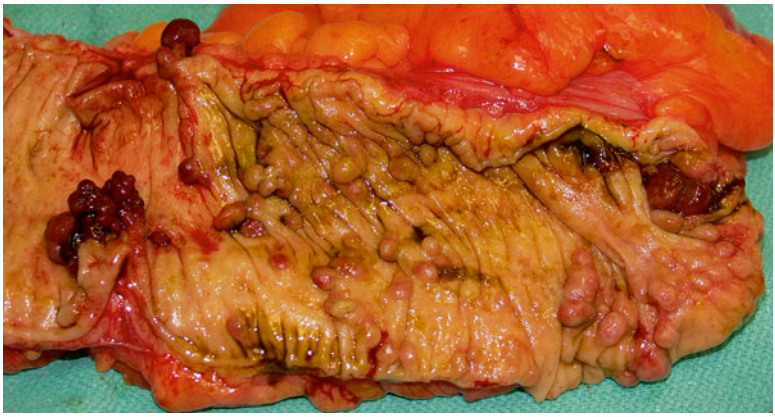


Fig. 6.1 Multiple juvenile polyps in the cecum. Note many diminutive polyps and several larger, red, pedunculated, and multilobular polyps

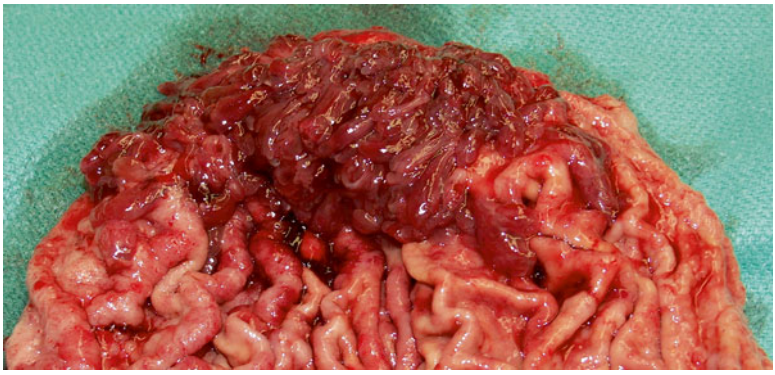


Fig. 6.2 Gastric polyposis at the GE junction, sparing the more distal stomach in a JP patient. Note the diffuse, frond-like nature, rather than the pedunculated polyps as seen in the colon

Helwig described the histologic findings of hamartomatous polyps in 1946, including stroma embedded with mucus-filled, glandular structures, and associated inflammatory cell infiltration. There were no dysplastic or adenomatous changes noted within the epithelium [6]. Ravitch described a 10 month old with upper and lower GI juvenile polyps in 1948, who suffered from severe anemia, malnutrition, and prolapsing rectal polyps, and subsequently died from this at an early age [7]. In 1957, Horilleno first introduced the term hamartomatous polyp [8], and shortly thereafter, Morson spelled out the differences between adenomatous, inflammatory, Peutz-Jeghers, and Juvenile polyps [9].

Despite these previous observations and Hertz's early report, it was not until 1966 that an autosomal dominant inheritance pattern was suggested by Smilow and associates, after studying a three generation family with JP [10]. This was further

reinforced by a 1975 report by Stemper and associates, who described a kindred with ten affected individuals with colorectal or gastric polyps. There were also 11 members of the family who developed GI cancer, predominantly of the colon, but also of the stomach, duodenum, and pancreas [11]. The link between hamartomatous polyps and GI cancer was strengthened by the finding of Liu et al. of a focus of signet ring cell carcinoma within a juvenile polyp in a 16-year-old boy [12]. Since then, multiple reports have confirmed this relationship between JP and the development of GI cancer [13–16].

Morphology and Histology

Juvenile polyps are frequently rounded and pedunculated on a stalk. They may range in size from a few mm to up to 5 cm. They can also be sessile, especially when in the stomach. Their surface has a thin mucosa, which may become eroded, leading to bleeding [17, 18]. In those with JP, there may be just a few polyps at a time, or there may be a 100 or more, even within members of the same family. Looking at them microscopically, there is an expansion of the lamina propria with abundant stroma, cystically dilated glands, and infiltration of inflammatory cells (Fig. 6.3). Overlying this markedly expanded lamina propria is a relatively normal layer of epithelium. This epithelium can occasionally become dysplastic, but this is relatively rare. When biopsied, these hamartomatous polyps may be diagnosed as

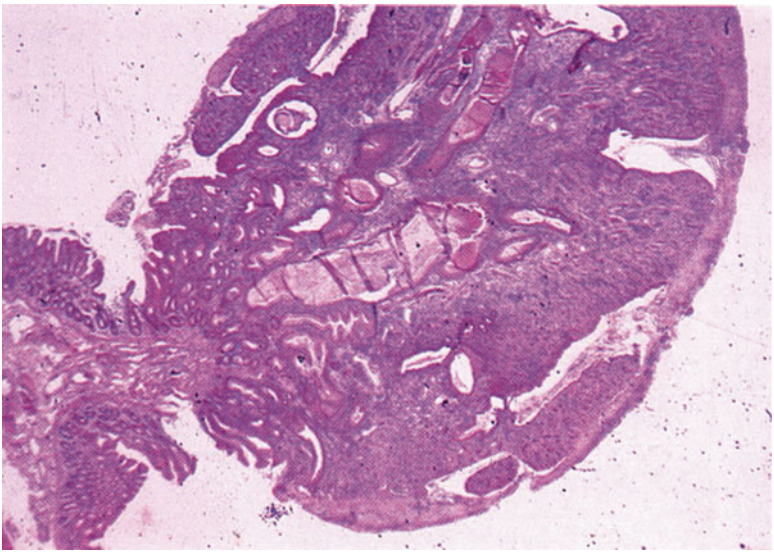


Fig. 6.3 Microscopic view of a polyp showing an expanded lamina propria with cystically dilated glands with inflammatory infiltrate, covered by thin layer of epithelium

juvenile polyps, hyperplastic polyps, or inflammatory polyps. They differ from hamartomatous polyps in Peutz-Jeghers patients in that the latter contain areas of smooth muscle within the lamina propria.

Clinical Presentation

The most common presentation is anemia, which is often accompanied by rectal bleeding. Other signs and symptoms may also include abdominal pain, diarrhea, prolapse of a rectal polyp, and intussusception [19, 20]. The most frequent associated anomalies include macrocephaly, mental retardation, Meckel's diverticulum, malrotation, pulmonary arteriovenous malformations (AVMs), telangiectasias, atrial and ventricular septal defects, pulmonic stenosis, and cryptorchidism [21, 22]. The diagnosis of JP is made based on the clinical criteria initially proposed by Sachatello et al. [23], with the number of polyps later reduced from 10 to 5 by Jass and colleagues [24]. These criteria for JP require

1. At least 5 juvenile polyps within the colorectum; or
2. Juvenile polyps in both the upper and lower GI tract; or
3. Any number of juvenile polyps in a patient with a family history of JP

After one of these conditions is satisfied, JP patients can be further subclassified into Juvenile Polyposis Coli (where patients have only colorectal polyps), generalized Juvenile Polyposis (where patients have polyps in both the upper and lower GI tract), and JP of infancy. These first two usually present with rectal bleeding, prolapse, anemia, diarrhea, or abdominal pain within the first two decades of life [25, 26]. The latter condition is uncommon, but has an earlier and more severe presentation, including protein losing enteropathy, anemia, anasarca, bloody diarrhea, failure to thrive, and often death before age 1 [23, 27, 28].

Other conditions that may present in a similar fashion include the PTEN Hamartoma Tumor syndromes of Bannayan–Riley–Ruvalcaba syndrome (BRRS) and Cowden syndrome (CS). Polyps in patients with these conditions are histologically indistinguishable, but these syndromes can be differentiated by genetic testing and other characteristic phenotypic features. Patients with BRRS may have macrocephaly, developmental delay, prominent corneal nerves, lipid myopathy, lipomas, genital pigmentation, and angiolipomas [29]. Patients with CS have facial trichilemmomas, acral keratoses, papules, breast cancer, fibrocystic disease of the breast, benign or malignant thyroid lesions, mental retardation, lipomas, or fibromas [30].

Genetics

The autosomal dominant inheritance pattern for JP was first revealed in the 1966 publication of three affected members in three generations by Smilow et al. [10]. Approximately 75 % of patients with JP have a family history, and the remainder

have de novo mutations leading to JP [31]. Clues to the genes predisposing to JP remained elusive until the late 1990s. In 1997, Jacoby described a patient with features of JP and macrocephaly, who had a deletion of chromosome 10q22 [32]. Olschwang et al. then reported three patients with germline *PTEN* mutations (which maps to 10q22) thought to have JP [33], but further scrutiny suggested that these patients might actually have had CS rather than JP [34]. Additional studies examining JP patients for germline *PTEN* mutations were negative, confirming the idea that *PTEN* was not the JP gene [35, 36].

SMAD4

It was in 1998 that the first hard evidence for the location of a JP gene was established. Howe et al. studied 43 members (including 13 affected) of the family originally reported by Stemper et al. [11], and established genetic linkage with 6 markers from chromosome 18q21, with a maximum lod score of 5.00 with *D18S1099* (at $\theta = 0.001$). Critical recombinants placed the JP gene within a 11 cM region between *D18S118* and *D18S487* [37, 38]. Sequencing of candidate genes from this region revealed that all affected members of this kindred shared a frameshift mutation, a 4 base pair deletion in exon 9 of the *SMAD4* gene. In this report, 5 of 9 total JP families tested were found to have germline *SMAD4* mutations [39]. This finding was soon confirmed by several other investigators in additional JP families [40–42].

SMAD4 was originally called deleted in pancreatic cancer 4 (*DPC4*), because of the fact that it is inactivated in approximately 50 % of pancreatic adenocarcinoma specimens [43]. *DPC4* was later renamed *SMAD4* when it became clear that this was the common intracellular mediator of the transforming growth factor-beta (TGFβ) superfamily, which signals through *SMAD* genes [44, 45]. *SMAD4* is comprised of 11 coding exons, encoding a 552-amino acid cytoplasmic protein. Within the TGFβ, activin, bone morphogenetic protein (BMP), and inhibin pathways, the function of SMAD4 is to bind to SMAD proteins phosphorylated by the type 1 receptor, after it has been phosphorylated by the type 2 receptor following ligand binding. SMAD4 binds to co-SMADs 1, 5, and 8 in the BMP pathway, and with co-SMADs 2 and 3 in the TGFβ pathway. The complex of SMAD4 and these co-SMADs then migrates to the nucleus, where it recruits a DNA-binding protein, and then binds directly to specific promoters to regulate transcription (Fig. 6.4).

In a 2009 paper by Calva et al., 77 of 357 JP probands (21.6 %) were found to have germline *SMAD4* mutations by sequencing. Of these mutations, 78 % were within exons 8–11 (encoding for the mad homology 2 domain), 17 % within exons 3–7, and 5 % in exons 1 and 2 (Fig. 6.5) [46]. A smaller percentage of JP patients have been found to have deletions of *SMAD4*, which have been identified using the mixed ligation-dependent probe amplification assay (MLPA) [47, 48]. Combining the largest studies using this technique, 7 of 128 (7 %) of JP probands were found to have *SMAD4* deletions [31].

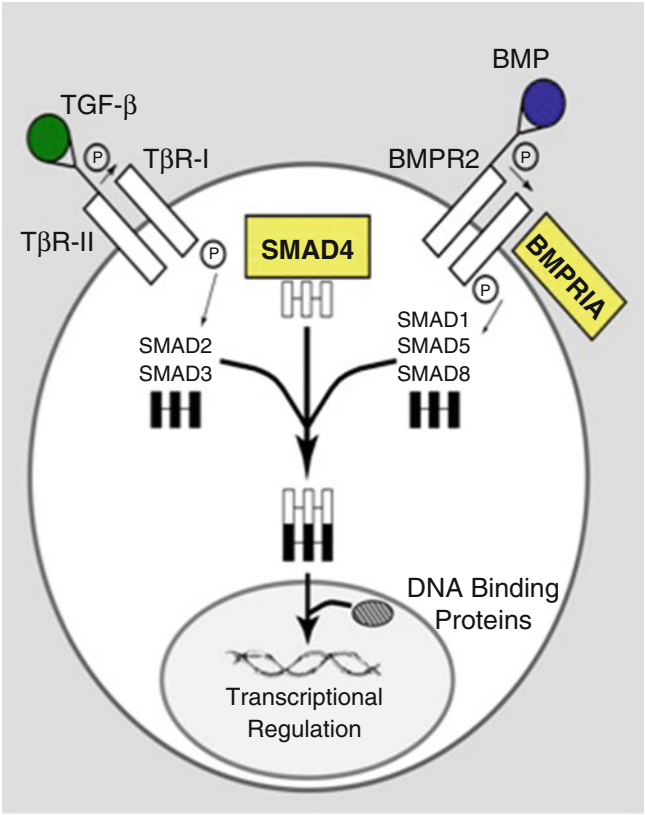


Fig. 6.4 Diagram of the signaling pathway of TGFβ depicting its interactions with BMPR1A and SMAD 4 to facilitate changes in nuclear transcription. BMPR1A works via SMAD 1, 5, and 8 while TGFβ works through SMAD 2 and 3. These join a common pathway with SMAD4 which creates an oligomer that translocates into the nucleus to regulate transcription [31]

BMPR1A

After it became apparent that only 20 % of JP families had germline changes in *SMAD4*, it seemed likely that there must be other JP genes. In 2001, Howe et al. found a suggestion of a second JP locus in four unrelated JP families, with a lod score of 2.33 at $\theta = 0.10$ with the marker *D10S573*. This was in the vicinity of the *PTEN* gene on chromosome 10q22-23, but these families had already been sequenced for *PTEN* and found to not have mutations. Another gene involved in the TGFβ superfamily was found to map to this general region, and they identified 2 polymorphic simple tandem repeat markers 49 and 76 kb upstream from this gene. When these markers were tested in these four families, the maximum lod scores were 4.17 and 4.74 at $\theta = 0$, proving linkage at this locus. Sequencing in these families revealed that all affected members had germline mutations of *BMPR1A*, which

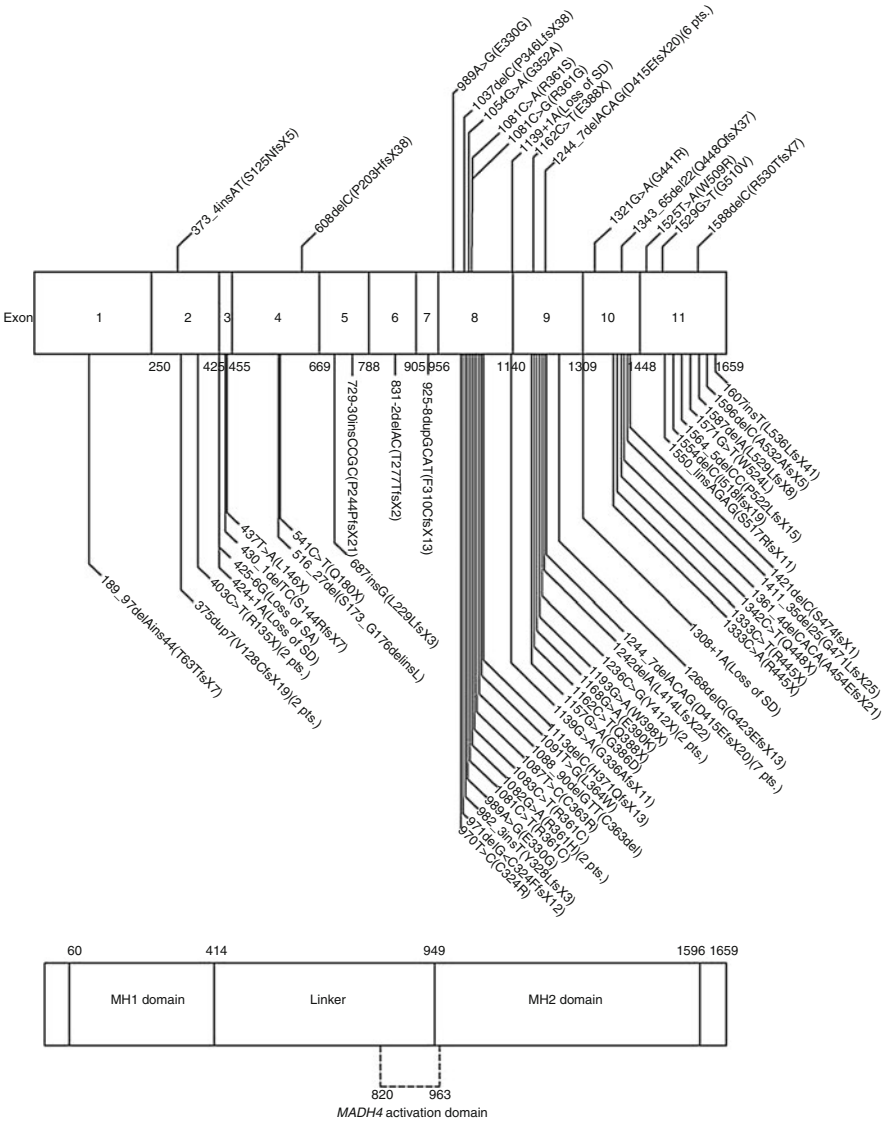


Fig. 6.5 Distribution of mutations in *SMAD4*. The rectangle above represents the coding exons of the gene, with nucleotides at each exon boundary shown underneath. The rectangle below represents the protein, with corresponding nucleotide numbers listed above and below domain boundaries. Mutations listed above the exons are those described in the present study, and those below the exons are from the literature. MH1, mad homology 1; MH2, mad homology 2 (Figure originally from *Clinical Genetics*) [46]

were frameshift in two families and nonsense mutations in the two others [49]. This finding was confirmed in other JP families shortly thereafter [50, 51]. *BMPR1A* encodes for the type I receptor in the BMP pathway, and is comprised of 11 coding exons. This receptor is a 532-amino acid transmembrane protein that associates with and is phosphorylated by the type II receptor (BMPR2) after it binds to extracellular BMP ligands. BMPR1A then phosphorylates co-SMADs 1, 5, and 8, which form oligomers that bind to intracellular SMAD4. This complex then migrates to the nucleus, recruits DNA-binding proteins, then binds directly to promoters to activate transcription (Fig. 6.4) [31, 37].

Calva et al. found that 62 of 336 JP probands (18.5 %) had germline *BMPR1A* mutations by sequencing. Of these mutations, 52 % were within the intracellular protein kinase domain (exons 7–11), and 31 % in the Mad homology I domain (exons 2–4). No mutations have been described within the transmembrane region of the receptor, and the mutations seen in *BMPR1A* are more uniformly spread out and more likely to be unique than seen with *SMAD4* mutations in JP patients (Fig. 6.6) [46]. A small percentage of JP patients have been found to have larger deletions of *BMPR1A* by MLPA, affecting 8 of 128 probands tested (6.3 %) [31, 47, 48]. Another small group of JP patients have been found with mutations in the promoter of *BMPR1A*, including one family with ten affected individuals all sharing a 12,433 bp deletion lying 119 kb upstream from the coding region, deleting a non-coding exon and a promoter. This paper reported five unrelated probands with deletion or missense mutations of the *BMPR1A* promoter which led to reduced luciferase activity in in vitro promoter constructs [52]. One study recreating JP patient *BMPR1A* missense mutations in a cell line demonstrated that the protein was held up intracellularly and did not efficiently translocate to the cell membrane, suggesting one potential mechanism through which BMP signaling may be reduced [53].

Other JP Genes

Sweet et al. reported that 2 of 14 JP patients that did not have either *SMAD4* or *BMPR1A* germline mutations had changes in the endoglin (ENG) gene, one of the genes responsible for hemorrhagic hereditary telangiectasia (HHT); neither of these two probands had signs of HHT [54]. Howe et al., by sequencing *ENG*, found substitutions in *ENG* in 6 of 31 JP probands (without *SMAD4* or *BMPR1A* mutations), but these substitutions were also found in control patients, and this study concluded that it was not clear whether *ENG* was a predisposing gene for JP [55]. No confirmatory studies have been published since these reports to confirm that *ENG* really is a gene predisposing to JP.

The confusion surrounding whether *PTEN* is a JP gene was discussed earlier, and patients with juvenile polyps and germline *PTEN* mutations are likely to have CS or BRRS rather than JP. However, some patients with JP have been described that have contiguous deletions of both *PTEN* and *BMPR1A*, which lie within 1.1 Mb of one

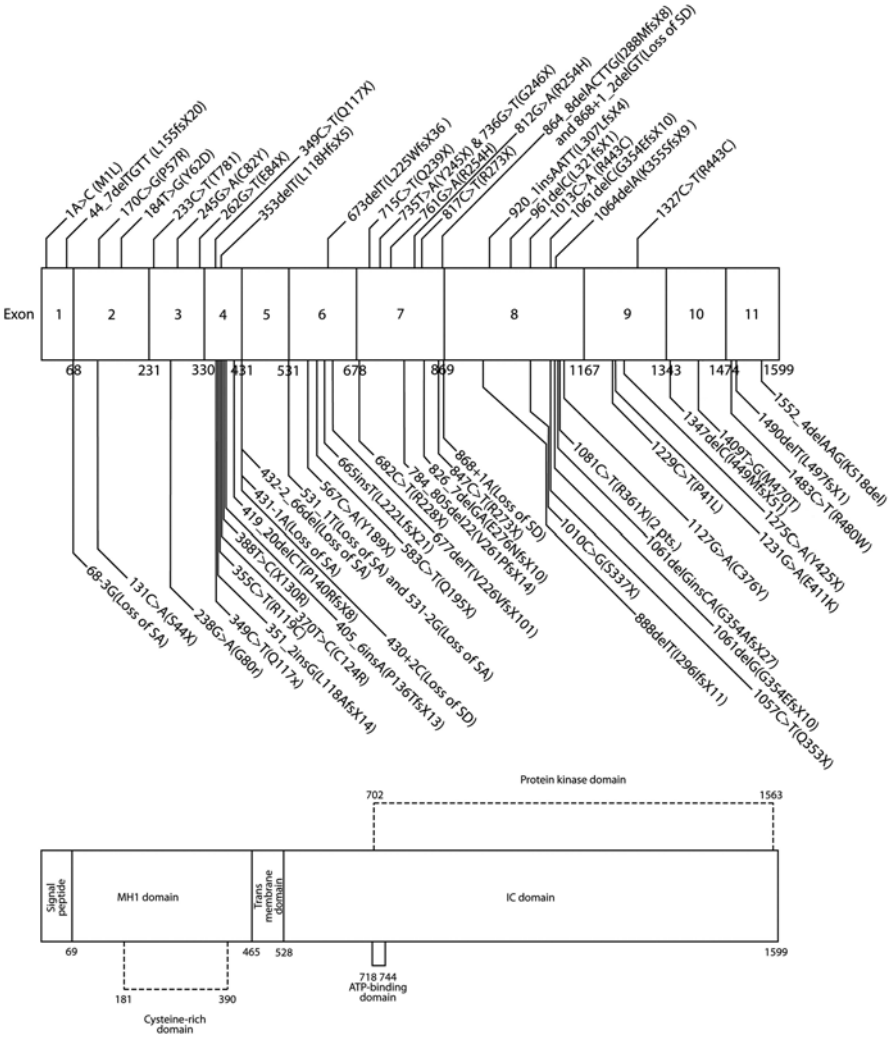


Fig. 6.6 Distribution of mutations in *BMPR1A*. The *rectangle* above represents the coding exons of the gene, with nucleotides at each exon boundary shown underneath. The *rectangle* below represents the protein, with corresponding nucleotide numbers listed above and below domain boundaries. Mutations listed above the exons are those described in the present study, and those below the exons are from the literature (Figure originally from *Clinical Genetics*) [46]

another on chromosome 10q22-23. Delnatte et al. described four patients with deletions of both these genes, all of who had presentation at an early age, upper and lower GI juvenile polyps, and macrocephaly, suggestive of JP of infancy [56]. Salviati et al. described a JP patient with deletion of both genes, presenting at age 3 with mild dysmorphic features, but not macrocephaly [57]. Menko et al. described four additional cases, in which all patients had macrocephaly and dysmorphic

features [58]. The effect of contiguous deletion of these two genes is not entirely clear, but appears to result in a more severe phenotype, combining some features of BRRS with those of JP, and sometimes with JP of infancy [59].

Genotype–Phenotype Correlations

Patients with mutations of *SMAD4* are more likely to have gastric polyposis than patients with *BMPR1A* mutations [48, 51, 60, 61]. In 2007, Aretz et al. found that 72 % of patients who had upper endoscopy results and a *SMAD4* mutation were found to have gastric polyps while only 8 % of patients with *BMPR1A* mutations that had upper endoscopy were found to have polyps. On average, gastric polyps were found much later in life with a median age of 41 years at the time of discovery [48]. Sayed et al. showed that JP patients with germline *SMAD4* mutations had a higher rate of positive family history of UGI polyps than those with *BMPR1A* mutations (86 % vs. 10 %, $p<0.01$) [60]. Juvenile polyps from patients with *SMAD4* germline mutations generally have a more proliferative epithelium and decreased stroma when compared to polyps from patients with *BMPR1A* germline mutations [62]. Handra-Luca et al. found that patients with germline *SMAD4* mutations had more low-grade adenomas than those with *BMPR1A* mutations, and that only patients with *SMAD4* mutations had high-grade dysplasia or carcinomas within their polyps [61].

Combined JP and HHT

In the early 1980s, Cox et al. and Conte et al. described individuals with JP that also had pulmonary AVMs, telangiectasias, and digital clubbing [63, 64]. In 1999, Inoue described a teenage girl who presented with nosebleeds beginning at age 6 and rectal bleeding at age 14. Work-up revealed 30 colonic juvenile polyps, and features of HHT (telangiectasias of the skin, a dilated hepatic artery, and pulmonary AVMs) [65].

Gallione et al. studied 14 individuals from 7 families with combined JP and HHT, none of whom had mutations of the two known HHT genes, *ENG* or the activin receptor type I (*ACVR1*). All of the patients were found to have germline *SMAD4* mutations, three of which were de novo [66]. Gallione et al. later tested 30 unselected patients with HHT who did not have *ENG* or *ACVR1* mutations and found that 3 had *SMAD4* mutations and endoscopic evidence of JP [67]. The frequency of HHT in JP patients with known *SMAD4* mutations has been reported to be between 15 % and 22 % [48, 66]. The majority of the *SMAD4* mutations resulting in this combined syndrome are within the MH2 domain of the gene involving exons 8–11 [66]. Mutations at other sites within the gene have been described but are less common [68]. The phenotypic presentation of combined JP/HHT due to *SMAD4*

mutations is variable, but includes multiple juvenile polyps, mucocutaneous telangiectasias, pulmonary AVMs, hepatic AVMs, cerebral AVMs, GI AVMs, and epistaxis [37]. O'Malley et al. analyzed 21 individuals with JP/HHT and found epistaxis in 71 %, pulmonary AVMs in 81 %, visceral AVMs in 86 %, and telangiectasias in 57 % of patients [69]. Wain et al. found that 76 % of JP patients with *SMAD4* mutations had some feature of HHT [70]. Based upon the results of this study, combined JP and HHT appears to be much more common than originally thought, and screening for HHT should be strongly considered in any JP patient found with germline *SMAD4* mutation.

The Malignant Potential of Juvenile Polyps

When JP was first described, most people felt that since these polyps were hamartomatous, that they had no malignant potential. This continued despite several examples of patients having both JP and GI cancers, and even the publication of the large Iowa kindred in 1975 with 11 individuals with GI cancer was careful not to stress the connection between juvenile polyps and GI cancer [11]. Further histologic investigation of 1032 polyps from 80 JP patients by Jass et al. revealed that 840 were typical juvenile polyps, 169 were multilobulated or villous polyps, 21 were adenomas, and 2 hyperplastic polyps. A total of 9 % of the juvenile polyps harbored dysplastic changes while 47 % of the villous polyps had dysplasia. They estimated the risk of developing colorectal cancer to be greater than 50 % for patients with JP, with a mean age of onset of colorectal cancer at 34 years of age [24]. Giardiello and colleagues found that only 4 % of patients with 1–2 juvenile polyps and no family history of JP had adenomas or adenocarcinoma, versus 29 % of those with $\geq$3 polyps or a family history of JP. The mean age at diagnosis of neoplasia was 37 years old for the JP patients within this study [71].

Further evidence that carcinoma may develop from juvenile polyps has been provided by several case reports. In 1978, Liu et al. described a 16 years old with an adenocarcinoma arising from within a juvenile polyp [12]. In 1979, Goodman et al. described a case of a 23-year-old woman with multiple upper and lower GI juvenile polyps who underwent proctocolectomy and antrectomy. Several different kinds of polyps were seen, including small hyperplastic polyps, typical juvenile polyps, juvenile polyps with adenomatous epithelium, and adenomas. There was a rectal adenocarcinoma among the polyps, and the authors suggested that there was likely a progression from hyperplastic to adenomatous change in JP that eventually leads to adenocarcinoma [13]. In support of this, Jarvinen and Fransilla reported 2 JP patients with severe dysplastic change in juvenile polyps [14] and Ramaswamy et al. described a 19 years old with generalized JP and dysplastic changes with carcinoma in situ [15]. Jones et al. described a case of an intramucosal carcinoma arising within a typical juvenile polyp in a patient without JP, suggesting that cancer can arise in these lesions, albeit very rarely [72]. Longo et al. reported a case of a patient with generalized JP and osteoarthropathy who had a subtotal colectomy at

age 6, and then a proctectomy and Swenson pull-through at age 12 (leaving 2 cm of rectum). At age 17, he developed a large tubulovillous adenoma in the rectal remnant which was removed, then 2 years later underwent completion proctectomy for what proved to be a poorly differentiated adenocarcinoma arising within a juvenile polyp [73].

Coburn studied 218 JP patients and found that the mean age of diagnosis was 18.5 years for JP and 35.5 years for GI cancer. A total of 36 patients (17 %) developed GI cancer, 34 of the colorectum, 1 gastric, and 1 duodenal [74]. Howe et al. found that within the Iowa JP kindred, that 16/29 affected members (55 %) developed GI cancers, including 11 (38 %) with colorectal cancer, and 6 (21 %) with upper GI cancers (4 gastric, 1 pancreatic, 1 duodenal). The median age at presentation or diagnosis of JP was 32.7 years (range 6.0–68.2 years), and the median age of colorectal cancer was 42.0 years (the youngest was 17.4 years old) and 57.6 years for upper GI cancers (the youngest was 20.5 years old) [75]. Brosens et al. studied 84 patients from 44 families and found 8 with colorectal cancer (mean age of 43.9 years) and calculated the lifetime colorectal cancer risk to be 38 % (and a 34-fold increased relative risk compared to the normal population). They had no cases of upper GI cancer in their cohort [76].

The process by which juvenile polyps undergo transformation to malignant polyps has not been thoroughly established, although the development of adenomatous elements and later adenocarcinoma as suggested by Goodman et al. seems most plausible [13]. The specific mechanisms of how germline mutations in *SMAD4* or *BMPR1A* lead to polyps and cancer continue to be a matter of speculation. One theory, the landscaper hypothesis, postulates that stromal changes lead to cancer in the overlying epithelium. This is based upon the observation that the majority of histologic changes within juvenile polyps are found within the stroma, which might then create an abnormal landscape, and aberrant signaling (presumably in the BMP or TGFβ pathway) in this layer leads to neoplastic change within the adjacent epithelium [77]. Another possibility is a tumor suppressor model, where germline mutation of one copy followed by somatic loss of the other within epithelial cells leads to cancer [78, 79]. Although neither of these models has been definitively proven, both should be considered useful paradigms of how polyps may transform into cancers.

Management

Patients presenting with symptoms of JP, including rectal bleeding, changes in stool, abdominal pain, and intussusception should be worked up with a thorough history and physical. If colonoscopic evaluation yields findings consistent with a possible diagnosis of JP (see diagnostic criteria) then follow-up should be performed as described below. In addition, individuals who are first-degree relatives of those with JP should also be worked up.

Individuals from a JP family with a known mutation in either *SMAD4* or *BMPR1A* should undergo genetic testing within the first 5 years of life [31]. If the results of

the genetic test are negative, then the patient does not need enhanced surveillance and may follow the same recommendations for colorectal cancer screening as the normal population. Patients who are found to have a mutation should follow the same screening regimen recommended for all JP patients. This includes colonoscopy and upper endoscopy beginning either at age 15 or earlier if symptoms develop (such as anemia, bleeding, and abdominal pain). If an individual is found to have polyps, the gastroenterologist or surgeon should attempt to remove them colonoscopically. If polyps are found, then repeat screening in 1 year is recommended, unless the polyps cannot be cleared. If no polyps are found, then colonoscopy and upper endoscopy can be extended out to every 3 years. If no mutation has been found within a family with JP, but a patient is at risk by virtue of having an affected first-degree relative, then this person should undergo the same surveillance as recommended for someone with a known mutation above (Fig. 6.7) [80].

When polyps are found, the management has been evolving. The early recommendations from Sachatello et al. were for polypectomy or fulguration with resection of the affected bowel outside the rectum [28]. Grosfield et al. were more

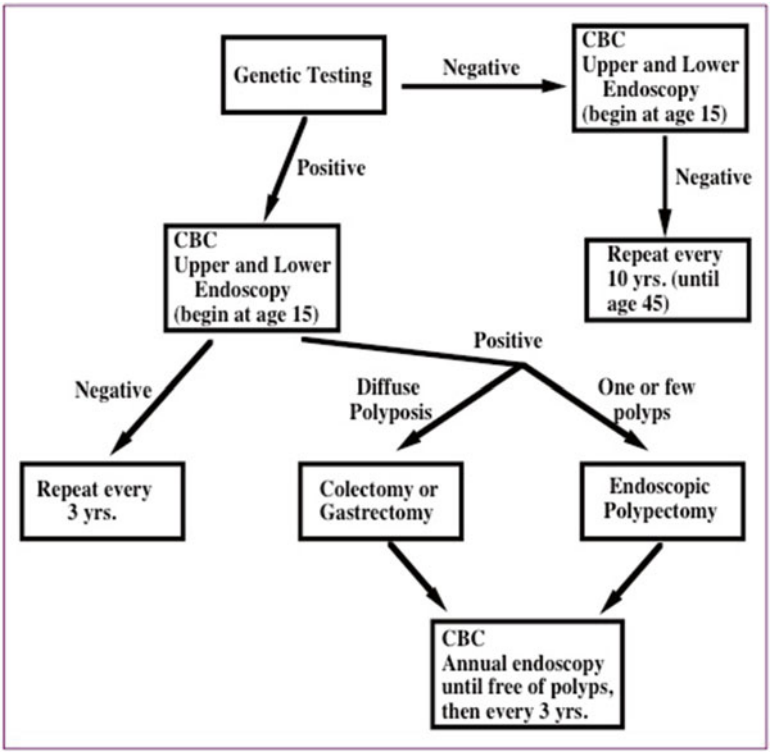


Fig. 6.7 Recommended screening algorithm for patients at risk for JP. This screening guideline is recommended for anyone who meets the criteria for JP or who otherwise has a family history of JP with unknown polyp status. *CBC* complete blood count (Figure originally from *Surgery*) [79]

aggressive and recommended subtotal colectomy with ileorectal anastomosis (IRA) for patients with anemia from chronic rectal bleeding, hypoproteinemia resulting in failure to thrive, and recurrent intussusceptions [81]. These indications were expanded to all JP patients by Jarvinen et al. in 1993 when they recommended prophylactic colectomy with IRA for patients with JP in their early 20s, in order to reduce the risk of colorectal cancer [82]. Oncel et al. compared their results of performing subtotal colectomy with IRA with total proctocolectomy and ileoanal pouch (IPAA) in JP patients. The functional results were better with IRA, and although 4 of 7 IRA patients eventually underwent completion proctectomy, the authors concluded that both procedures were reasonable options [83]. Howe et al. supported the use of subtotal colectomy with IRA in severe cases (100 or more polyps, significant anemia, dysplasia), but recommended aggressive colonoscopic polypectomy as initial treatment for colorectal polyps in JP patients. In those having resection and IRA, screening would include flexible sigmoidoscopy and upper endoscopy every 3 years [75]. Patients who have colonoscopic polypectomy should be screened yearly until polyp free, and then every 3 years thereafter.

The treatment of gastric polyps is more technically difficult due to their sessile nature and the fact that polyps are more diffuse and without well-defined stalks. If significant anemia develops, or polyps develop dysplastic changes, then subtotal or total gastrectomy is recommended. As described earlier, patients with *SMAD4* mutations are at increased risk and may need more frequent screening than patients with *BMPR1A* or unknown mutations.

Summary

Our understanding of JP has come a long way over the past 2 decades. It has been recognized that despite the fact that patients have hamartomatous polyps, they are at significant risk for colorectal and upper GI malignancies. Two predisposing genes have been clearly identified which cause JP, and there are likely others since these only explain roughly one-half of cases. Understanding the genetics of JP has helped clarify and allowed separation from other hamartomatous polyposis syndromes, and suggested potential mechanisms by which cancers may develop in these patients. Screening algorithms have been suggested for JP based upon the age of onset of cancers and symptoms, and taking into account the results of genetic testing.

References

1. Adolph VR, Bernabe K. Polyps in children. Clin Colon Rectal Surg. 2008;21(4):280–5.
2. Burt RW, Bishop DT, Lynch HT, Rozen P, Winawer SJ. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. Bull World Health Organ. 1990;68(5):655–65.

3. Jass J. Pathology of polyposis syndromes with special reference to juvenile polyposis. Hereditary Colorectal Cancer. 1990;345–250.
4. Hertz AF. Four cases of rectal polypus occurring in one family. Proc R Soc Med. 1914;7(Surg Sect):255–6.
5. Diamond M. Adenoma of the rectum in children: report of a case in a thirty month old girl. Am J Dis Child. 1939;57:360–7.
6. Helwig EB. Adenomas of the large intestine in children. Am J Dis Child. 1946;72:289–95.
7. Ravitch MM. Polypoid adenomatosis of the entire gastrointestinal tract. Ann Surg. 1948;128(2):283–98.
8. Horrilleno EG, Eckert C, Ackerman LV. Polyps of the rectum and colon in children. Cancer. 1957;10(6):1210–20.
9. Morson BC. Some prominent personalities in the history of St. Mark's Hospital. Dis Colon Rectum. 1962;5:173–83.
10. Smilow PC, Pryor Jr CA, Swinton NW. Juvenile polyposis coli. A report of three patients in three generations of one family. Dis Colon Rectum. 1966;9(4):248–54.
11. Stemper TJ, Kent TH, Summers RW. Juvenile polyposis and gastrointestinal carcinoma. A study of a kindred. Ann Intern Med. 1975;83(5):639–46.
12. Liu TH, Chen MC, Tseng HC, Chou L, Lu C. Malignant change of juvenile polyp of colon: a case report. Chin Med J (Engl). 1978;4(6):434–9.
13. Goodman ZD, Yardley JH, Milligan FD. Pathogenesis of colonic polyps in multiple juvenile polyposis: report of a case associated with gastric polyps and carcinoma of the rectum. Cancer. 1979;43(5):1906–13.
14. Jarvinen H, Franssila KO. Familial juvenile polyposis coli; increased risk of colorectal cancer. Gut. 1984;25(7):792–800.
15. Ramaswamy G, Elhosseiny AA, Tchertkoff V. Juvenile polyposis of the colon with atypical adenomatous changes and carcinoma in situ. Report of a case and review of the literature. Dis Colon Rectum. 1984;27(6):393–8.
16. Rozen P, Baratz M. Familial juvenile colonic polyposis with associated colon cancer. Cancer. 1982;49(7):1500–3.
17. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62. quiz 63.
18. Brosens LA, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJ. Juvenile polyposis syndrome. World J Gastroenterol. 2011;17(44):4839–44.
19. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 2005;100(2):476–90.
20. Chow E, Macrae F. A review of juvenile polyposis syndrome. J Gastroenterol Hepatol. 2005;20(11):1634–40.
21. Brosens LA, van Hattem WA, Jansen M, de Leng WW, Giardiello FM, Offerhaus GJ. Gastrointestinal polyposis syndromes. Curr Mol Med. 2007;7(1):29–46.
22. Desai DC, Murday V, Phillips RK, Neale KF, Milla P, Hodgson SV. A survey of phenotypic features in juvenile polyposis. J Med Genet. 1998;35(6):476–81.
23. Sachatello CR. Polypoid diseases of the gastrointestinal tract. J Ky Med Assoc. 1972;70(7):540–4.
24. Jass JR, Williams CB, Bussey HJ, Morson BC. Juvenile polyposis—a precancerous condition. Histopathology. 1988;13(6):619–30.
25. Roth SI, Helwig EB. Juvenile polyps of the colon and rectum. Cancer. 1963;16:468–79.
26. Reed K, Vose PC. Diffuse juvenile polyposis of the colon: a premalignant condition? Dis Colon Rectum. 1981;24(3):205–10.
27. Soper RT, Kent TH. Fatal juvenile polyposis in infancy. Surgery. 1971;69(5):692–8.
28. Sachatello CR, Hahn IS, Carrington CB. Juvenile gastrointestinal polyposis in a female infant: report of a case and review of the literature of a recently recognized syndrome. Surgery. 1974;75(1):107–14.

29. Gorlin RJ, Cohen Jr MM, Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet. 1992;44(3):307–14.
30. Waite KA, Eng C. Protean PTEN: form and function. Am J Hum Genet. 2002;70(4):829–44.
31. Calva D, Howe J. Juvenile polyposis. In Riegert-Johnson DL, Boardman LA, Hefferon T, Roberts M, editors. Cancer syndromes. Bethesda MD: National Center for Biotechnology Information, USA; 2009.
32. Jacoby RF, Schlack S, Cole CE, Skarbek M, Harris C, Meisner LF. A juvenile polyposis tumor suppressor locus at 10q22 is deleted from nonepithelial cells in the lamina propria. Gastroenterology. 1997;112(4):1398–403.
33. Olschwang S, Serova-Sinilnikova OM, Lenoir GM, Thomas G. PTEN germ-line mutations in juvenile polyposis coli. Nat Genet. 1998;18(1):12–4.
34. Eng C, Peacocke M. PTEN and inherited hamartoma-cancer syndromes. Nat Genet. 1998;19(3):223.
35. Marsh DJ, Roth S, Lunetta KL, Hemminki A, Dahia PL, Sistonen P, et al. Exclusion of PTEN and 10q22-24 as the susceptibility locus for juvenile polyposis syndrome. Cancer Res. 1997;57(22):5017–21.
36. Riggins GJ, Kinzler KW, Vogelstein B, Thiagalingam S. Frequency of Smad gene mutations in human cancers. Cancer Res. 1997;57(13):2578–80.
37. Larsen Haidle J, Howe JR. Juvenile polyposis syndrome. In Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. GeneReviews(R). Seattle, WA: University of Washington, Seattle; 1993.
38. Howe JR, Ringold JC, Summers RW, Mitros FA, Nishimura DY, Stone EM. A gene for familial juvenile polyposis maps to chromosome 18q21.1. Am J Hum Genet. 1998;62(5):1129–36.
39. Howe JR, Roth S, Ringold JC, Summers RW, Jarvinen HJ, Sistonen P, et al. Mutations in the SMAD4/DPC4 gene in juvenile polyposis. Science. 1998;280(5366):1086–8.
40. Houlston RS, Tomlinson IP. Modifier genes in humans: strategies for identification. Eur J Hum Genet. 1998;6(1):80–8.
41. Roth S, Sistonen P, Salovaara R, Hemminki A, Loukola A, Johansson M, et al. SMAD genes in juvenile polyposis. Genes Chromosomes Cancer. 1999;26(1):54–61.
42. Friedl W, Kruse R, Uhlhaas S, Stolte M, Schartmann B, Keller KM, et al. Frequent 4-bp deletion in exon 9 of the SMAD4/MADH4 gene in familial juvenile polyposis patients. Genes Chromosomes Cancer. 1999;25(4):403–6.
43. Hahn SA, Schutte M, Hoque AT, Moskaluk CA, da Costa LT, Rozenblum E, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science. 1996;271(5247):350–3.
44. Massaous J, Hata A. TGF-beta signalling through the Smad pathway. Trends Cell Biol. 1997;7(5):187–92.
45. Heldin CH, Miyazono K, ten Dijke P. TGF-beta signalling from cell membrane to nucleus through SMAD proteins. Nature. 1997;390(6659):465–71.
46. Calva-Cerqueira D, Chinnathambi S, Pechman B, Bair J, Larsen-Haidle J, Howe JR. The rate of germline mutations and large deletions of SMAD4 and BMPR1A in juvenile polyposis. Clin Genet. 2009;75(1):79–85.
47. van Hattem WA, Brosens LA, de Leng WW, Morsink FH, Lens S, Carvalho R, et al. Large genomic deletions of SMAD4, BMPR1A and PTEN in juvenile polyposis. Gut. 2008;57(5):623–7.
48. Aretz S, Stienen D, Uhlhaas S, Stolte M, Entius MM, Loff S, et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. J Med Genet. 2007;44(11):702–9.
49. Howe JR, Bair JL, Sayed MG, Anderson ME, Mitros FA, Petersen GM, et al. Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. Nat Genet. 2001;28(2):184–7.
50. Zhou XP, Woodford-Richens K, Lehtonen R, Kurose K, Aldred M, Hampel H, et al. Germline mutations in BMPR1A/ALK3 cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan-Riley-Ruvalcaba syndromes. Am J Hum Genet. 2001;69(4):704–11.

51. Friedl W, Uhlhaas S, Schulmann K, Stolte M, Loff S, Back W, et al. Juvenile polyposis: massive gastric polyposis is more common in MADH4 mutation carriers than in BMPR1A mutation carriers. Hum Genet. 2002;111(1):108–11.
52. Calva-Cerqueira D, Dahdaleh FS, Woodfield G, Chinnathambi S, Nagy PL, Larsen-Haidle J, et al. Discovery of the BMPR1A promoter and germline mutations that cause juvenile polyposis. Hum Mol Genet. 2010;19(23):4654–62.
53. Howe JR, Dahdaleh FS, Carr JC, Wang D, Sherman SK, Howe JR. BMPR1A mutations in juvenile polyposis affect cellular localization. J Surg Res. 2013;184(2):739–45.
54. Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, Alhopuro P, et al. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA. 2005;294(19):2465–73.
55. Howe JR, Haidle JL, Lal G, Bair J, Song C, Pechman B, et al. ENG mutations in MADH4/BMPR1A mutation negative patients with juvenile polyposis. Clin Genet. 2007;71(1):91–2.
56. Delnatte C, Sanlaville D, Mougenot JF, Vermeesch JR, Houdayer C, Blois MC, et al. Contiguous gene deletion within chromosome arm 10q is associated with juvenile polyposis of infancy, reflecting cooperation between the BMPR1A and PTEN tumor-suppressor genes. Am J Hum Genet. 2006;78(6):1066–74.
57. Salviati L, Patricelli M, Guariso G, Sturniolo GC, Alaggio R, Bernardi F, et al. Deletion of PTEN and BMPR1A on chromosome 10q23 is not always associated with juvenile polyposis of infancy. Am J Hum Genet. 2006;79(3):593–6. author reply 6-7.
58. Menko FH, Kneepkens CM, de Leeuw N, Peeters EA, Van Maldergem L, Kamsteeg EJ, et al. Variable phenotypes associated with 10q23 microdeletions involving the PTEN and BMPR1A genes. Clin Genet. 2008;74(2):145–54.
59. Dahdaleh FS, Carr JC, Calva D, Howe JR. Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23. Clin Genet. 2012;81(2):110–6.
60. Sayed MG, Ahmed AF, Ringold JR, Anderson ME, Bair JL, Mitros FA, et al. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. Ann Surg Oncol. 2002;9(9):901–6.
61. Handra-Luca A, Condroyer C, de Moncuit C, Tepper M, Flejou JF, Thomas G, et al. Vessels' morphology in SMAD4 and BMPR1A-related juvenile polyposis. Am J Med Genet A. 2005;138A(2):113–7.
62. van Hattem WA, Langeveld D, de Leng WW, Morsink FH, van Diest PJ, Iacobuzio-Donahue CA, et al. Histologic variations in juvenile polyp phenotype correlate with genetic defect underlying juvenile polyposis. Am J Surg Pathol. 2011;35(4):530–6.
63. Conte WJ, Rotter RJ, Schwartz AG, Congelton JE. Hereditary generalized juvenile polyposis, arteriovenous malformations and colonic carcinoma. Clin Res. 1982;30(93A).
64. Cox KL, Frates Jr RC, Wong A, Gandhi G. Hereditary generalized juvenile polyposis associated with pulmonary arteriovenous malformation. Gastroenterology. 1980;78(6):1566–70.
65. Inoue S, Matsumoto T, Iida M, Hoshika K, Shimizu M, Hisamoto N, et al. Juvenile polyposis occurring in hereditary hemorrhagic telangiectasia. Am J Med Sci. 1999;317(1):59–62.
66. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, et al. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet. 2004;363(9412):852–9.
67. Gallione CJ, Richards JA, Letteboer TG, Rushlow D, Prigoda NL, Leedom TP, et al. SMAD4 mutations found in unselected HHT patients. J Med Genet. 2006;43(10):793–7.
68. Gallione C, Aylsworth AS, Beis J, Berk T, Bernhardt B, Clark RD, et al. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. Am J Med Genet A. 2010;152A(2):333–9.
69. O'Malley M, LaGuardia L, Kalady MF, Parambil J, Heald B, Eng C, et al. The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. Dis Colon Rectum. 2012;55(8):886–92.
70. Wain KE, Ellingson MS, McDonald J, Gammon A, Roberts M, Pichurin P, et al. Appreciating the broad clinical features of SMAD4 mutation carriers: a multicenter chart review. Genet Med. 2014;16(8):588–93.

71. Giardiello FM, Hamilton SR, Kern SE, Offerhaus GJ, Green PA, Celano P, et al. Colorectal neoplasia in juvenile polyposis or juvenile polyps. Arch Dis Child. 1991;66(8):971–5.
72. Jones MA, Hebert JC, Trainer TD. Juvenile polyp with intramucosal carcinoma. Arch Pathol Lab Med. 1987;111(2):200–1.
73. Longo WE, Touloukian RJ, West AB, Ballantyne GH. Malignant potential of juvenile polyposis coli. Report of a case and review of the literature. Dis Colon Rectum. 1990;33(11):980–4.
74. Coburn MC, Pricolo VE, DeLuca FG, Bland KI. Malignant potential in intestinal juvenile polyposis syndromes. Ann Surg Oncol. 1995;2(5):386–91.
75. Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8):751–6.
76. Brosens LA, van Hattem A, Hylind LM, Iacobuzio-Donahue C, Romans KE, Axilbund J, et al. Risk of colorectal cancer in juvenile polyposis. Gut. 2007;56(7):965–7.
77. Kinzler KW, Vogelstein B. Landscaping the cancer terrain. Science. 1998;280(5366):1036–7.
78. Langeveld D, van Hattem WA, de Leng WW, Morsink FH, Ten Kate FJ, Giardiello FM, et al. SMAD4 immunohistochemistry reflects genetic status in juvenile polyposis syndrome. Clin Cancer Res. 2010;16(16):4126–34.
79. Woodford-Richens K, Williamson J, Bevan S, Young J, Leggett B, Frayling I, et al. Allelic loss at SMAD4 in polyps from juvenile polyposis patients and use of fluorescence in situ hybridization to demonstrate clonal origin of the epithelium. Cancer Res. 2000;60(9):2477–82.
80. Howe JR, Ringold JC, Hughes JH, Summers RW. Direct genetic testing for Smad4 mutations in patients at risk for juvenile polyposis. Surgery. 1999;126(2):162–70.
81. Grosfeld JL, West KW. Generalized juvenile polyposis coli. Clinical management based on long-term observations. Arch Surg. 1986;121(5):530–4.
82. Jarvinen H. Juvenile gastrointestinal polyposis. Probl Gen Surg. 1993;10:749–57.
83. Oncel M, Church JM, Remzi FH, Fazio VW. Colonic surgery in patients with juvenile polyposis syndrome: a case series. Dis Colon Rectum. 2005;48(1):49–55; discussion -6.

Chapter 7
PTEN Hamartoma Tumor Syndrome

Jessica L. Mester

Introduction and Overview

PTEN Hamartoma Tumor syndrome (PHTS, OMIM +601728) includes individuals with diverse clinical diagnoses, most commonly Cowden syndrome (CS, OMIM #158350) or Bannayan–Riley–Ruvalcaba syndrome (BRRS, OMIM #153480), found to have germline mutation of the *PTEN* tumor suppressor gene. *PTEN* was first described as a tumor suppressor through studies identifying loss of heterozygosity and somatic mutations in glioma, prostate, breast, kidney, and endometrial tumors and cell lines [1–4]. *PTEN* acts as a dual-specificity phosphatase that interacts with both lipid and protein substrates [5, 6]. Its canonical function is to inhibit the AKT/mTOR pathway, and it also has an inhibitory role in the MAPK pathway. When *PTEN* is not functioning properly, these pathways become upregulated, leading to tumorigenesis through prolonged cell survival and enhanced cell migration [7–9].

At approximately the same time its tumor suppressor role was elucidated, linkage studies led to the identification of *PTEN* as the causative gene for CS, and germline mutations were identified in affected families [10, 11]. Given its clinical overlap as another hamartomatous polyposis syndrome, *PTEN* was interrogated in individuals with BRRS and mutations were identified, some of which had been observed in CS kindreds [12, 13]. The features which typified CS tended to occur in adulthood and more often in women, and the opposite was true in BRRS (Table 7.1), leading to gender- and age-related biases in clinical diagnosis [14]. Thus PHTS is currently used as the unifying diagnostic term for any person with a germline *PTEN*

J.L. Mester, M.S., L.G.C. (✉)
GeneDx Laboratories, Cleveland, OH, USA

BioReference Laboratories, 481 Edward H. Ross Drive,
Elmwood Park, NJ 07407, USA
e-mail: jmester@genedx.com

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_7

Table 7.1 Features of PTEN Hamartoma Tumor syndrome by age of onset and gender-specificity

	Affected gender		Typical age of onset	
	Female	Male	Pediatric	Adult
Malignancies				
Breast cancer	✓	Rare		✓
Thyroid cancer	✓	✓	Rare	✓
Renal cancer	✓	✓		✓
Endometrial cancer	✓			✓
Colorectal cancer	✓	✓		✓
Melanoma	✓	✓		✓
Benign Neoplasias				
Vascular malformations/hemangiomas	✓	✓	✓	
Lhermitte–Duclos disease	✓	✓		✓
Gastrointestinal polyposis	✓	✓	Rare	✓
Oral papillomatosis	✓	✓	✓	✓
Palmoplantar keratosis	✓	✓		✓
Trichilemmomas	✓	✓		✓
Lipomas	✓	✓	✓	✓
Fibromas	✓	✓		✓
Freckling of the glans penis		✓	✓	
Benign breast lesions	✓	Rare	Rare	✓
Thyroid goiter/nodules/Hashimoto's thyroiditis	✓	✓	✓	✓
Other genitourinary tumors	✓	✓	✓	✓
Neurologic				
Macrocephaly	✓	✓	✓	
Autism/developmental delay	✓	✓	✓	

mutation and therefore the same risk assessment and management guidelines apply to any patients with PHTS regardless of clinical presentation.

Several individuals with other seemingly separate phenotypes—Lhermitte–Duclos disease and macrocephaly plus autism—have also been identified as having germline *PTEN* mutations, further expanding the phenotypic spectrum of PHTS [15–19].

Cancer Risks, Other Syndrome Features, and Management Recommendations

When first described, CS was considered primarily to be a dermatologic disease, and as more affected individuals were identified and described in the literature, associations with cancer risks and other phenotypes began to be recognized. The characteristics of PHTS can now be grouped into three main categories—malignancies, benign neoplasias, and neurodevelopmental features. As previewed in Table 7.1, many of the organs susceptible to benign neoplasia in PHTS are those in which risk

for malignancy is also increased. Thus we will first focus on reviewing the overall cancer risks in PHTS, and then discuss management recommendations which apply to both malignant and non-malignant findings together.

Cancer Risks in PHTS

In patients with germline *PTEN* mutations and thus PHTS, three studies to date have examined risks for malignancy (Table 7.2) [20–22]. Interestingly, some of the component cancers with the highest lifetime risks—breast, endometrial, and renal—were among the first to be commonly associated with somatic PTEN loss or alterations. To date, strong genotype–phenotype correlations have not been elucidated [22], and significant intrafamilial variability as well as overlapping mutation spectra have been observed [14]. These findings reinforce the need for every individual with PHTS to be offered high-risk management options for all associated cancers regardless of mutation type, family history, or clinical presentation.

Diverse other malignancies have been described in isolated case reports of individuals with PHTS, but none at a frequency requiring investigation into lifetime risk for that cancer type or addition to screening recommendations.

System-Based Management of PHTS

Breast With risk estimates for breast cancer ranging from 67 % to 85 %, overlapping with the risk quoted to women with Hereditary Breast and Ovarian Cancer syndrome (caused by mutation of the *BRCA1* or *BRCA2* genes), it makes sense for women with PHTS to be offered similar screening and management options. Both

Table 7.2 Results from studies analyzing lifetime cancer risks in patients with PHTS [20–22]

	Tan et al. [23] (*N* = 368)	Bubien et al. [20] (*N* = 146)	Nieuwenhuis et al. [21] (*N* = 180)
Median age of dataset (years)	39	36	32
Lifetime cancer risks[a]			
Female breast	85 %	77 %	67 %
Thyroid	35 %	38 %	Women: 25 % Men: 6 %
Renal	34 %	Elevated in women	Women: 9 % Men: 2 %
Endometrial	28 %	Elevated	21 %
Colorectal	9 %	Elevated in men	Women: 17 % Men: 20 %
Melanoma	6 %	Elevated	Men: 2 %

[a]Lifetime risks calculated to age 70 by Tan and Bubien; to age 60 by Nieuwenhuis

the National Comprehensive Cancer Network (NCCN) and PHTS experts recommend imaging surveillance begin by age 30, and that this should include both mammography and MRI [22, 24]. Some women with PHTS have a striking degree of benign breast lesions, leading to difficult radiologic interpretation and need for multiple call-backs and biopsies [25–27]. For these reasons, some women may wish to consider prophylactic mastectomy, which within the Hereditary Breast and Ovarian Cancer syndrome population has been shown to reduce breast cancer risk by 90 % [28]. Women with PHTS who have already had one breast cancer diagnosis are at 29 % risk for another primary breast cancer within the next 10 years [29]; this reinforces a need for continued high-risk surveillance following a first breast cancer diagnosis and for mastectomy and contralateral prophylactic mastectomy to be offered as surgical options.

Thyroid By early adolescence, most individuals with PHTS have some form of thyroid disease, presenting with multiple nodules, Hashimoto's thyroiditis, or a combination of the two [30]. Among those cancers seen most often in PHTS, thyroid cancer has the earliest age of onset, and several diagnoses in the pediatric population have been reported, the youngest being at age 6 [31, 32]. Given that risk for thyroid cancer begins to elevate in childhood and that ultrasound is a no-risk screening option, both syndrome experts and the NCCN recommend all patients begin routine thyroid ultrasound at the age of diagnosis, with follow-up on a yearly basis if normal [22, 24]. If surgery becomes necessary—either due to positive FNA or if compressive symptoms occur—total thyroidectomy is recommended, even if only one side of the thyroid appears affected, due to the high likelihood for additional disease and need for future surgery. Prophylactic thyroidectomy has also been proposed as an option for patients with autism or other cognitive defects who will not tolerate thyroid ultrasound without sedation [30].

Endometrial While most endometrial cancer diagnoses in PHTS have occurred after the age when most women have completed childbearing, earlier diagnoses have been reported, with one case report describing a diagnosis at age 14 [33]. Prophylactic hysterectomy can be considered as a surgical option. Ovarian cancer has not been over-reported in women with PHTS, implicating that simultaneous oophorectomy need not be performed, helping these women avoid the morbidity incurred by surgically induced menopause. Both NCCN and syndrome experts also give blind endometrial biopsy and ultrasound surveillance as screening options to begin at age 30–35, but it bears recognition that these screening modalities have not been proven in PHTS or other syndromes causing high endometrial cancer risk to reduce morbidity or mortality [22, 24].

Renal While small patient series and case reports described occasional patients with CS or PHTS and renal cancer, it was not until the recent studies analyzing lifetime cancer risks in individuals with PHTS that a true syndrome-associated risk was appreciated. On review by a dedicated genitourinary pathologist, most of the renal cancers in patients with PHTS are either papillary or chromophobe in nature,

and PTEN protein expression is absent in papillary tumors, indicating a possible future role for immunohistochemistry screening similar to that performed in Lynch syndrome [34]. While bilateral tumors have been reported, metastatic disease has not. Both syndrome experts and NCCN recommend imaging surveillance begin at age 40 with repeat every 1–2 years [22, 24]. While ultrasound will likely detect most tumors, CT may be considered given its enhanced ability to detect smaller papillary lesions [35]. With individuals with PHTS being at risk for multiple primary tumors, identifying lesions when small enough to permit nephron-sparing surgery may reduce need for renal dialysis secondary to nephrectomies if bilateral tumors occur.

Gastrointestinal While risk for colorectal cancer is not as high as the other cancer types seen in PHTS, gastrointestinal polyposis is a common occurrence. In series of individuals with PHTS who had undergone endoscopy, 80–93 % had polyps [36–38]. The number and type of polyps vary dramatically among affected individuals. While some have only a few hyperplastic polyps, others have thousands of polyps of diverse histologies including multiple adenomas. Hamartomatous polyps were the histologic subtype first associated with CS, BRRS, and PHTS, and are second in frequency to hyperplastic polyps in the series of patients cited above, followed by ganglioneuromas, adenomas, inflammatory, and juvenile polyps. Upper endoscopy frequently reveals polyps as well, most often hyperplastic and hamartomatous, and may also identify glycogenic acanthosis.

Both NCCN and syndrome experts recommend first colonoscopy to occur at age 35–40 with frequency no less than every 5 years and follow-up interval determined by the number and type of polyps identified [22, 24]. At this time, prophylactic colectomy is not routine and does not appear warranted for the average patient. It could be considered for the patient having several adenomas on subsequent scopes, with such a large number of other polyps that there is concern adenomas will be missed among the field of hamartomatous, hyperplastic, and other polyp types.

PTEN is adjacent to BMPR1A, one of the genes causing Juvenile Polyposis syndrome (JPS), and patients with chromosome deletions including both genes have been reported [39, 40]. With these individuals having absence of both the PTEN and BMPR1A genes, they are at risk to develop the cancers and other features associated with both PHTS and JPS, and should be managed accordingly.

Dermatologic A slight increase in risk for melanoma (6 % compared to 2 % in the general population) has also been reported for patients with PTEN mutations [22]. Yearly dermatologic examination is recommended for this purpose and can also prove useful in monitoring the many benign skin lesions characteristic of PHTS (summarized in Table 7.1), most of which increase in number and type as an individual progresses through adulthood. Fortunately these lesions are not at high risk to undergo malignant transformation and should not require removal unless they are painful or bothersome to the patient or appear to be undergoing rapid growth [41]. Biopsy of skin lesions can be helpful when histologic confirmation is needed to help clinicians decide whether to refer the patients for genetics evaluation and can help genetics providers understand whether *PTEN* gene testing is appropriate.

Hemangiomas requiring surgical intervention have been described in series of patients with PHTS [42, 43]. The unique pathologic nature of these lesions has recently been elucidated. As opposed to solely involving vascular tissue, in persons with PHTS lipomatous and muscular tissues are also involved in a disorganized growth pattern, giving rise to the moniker PTEN-related Hamartoma of Soft Tissue (PHOST) as an appropriate descriptor [44]. Unfortunately some patients develop multiple troublesome PHOSTs which have not responded well to surgical management via resection or embolization and have tended to recur post-treatment [42]. PHOSTs affecting the limbs have caused some patients significantly reduced mobility and troubles with daily living activities.

Neurologic Macrocephaly and developmental delay or autism spectrum disorders (ASD) are the findings which prompt genetics referral for many children ultimately diagnosed with PHTS. Approximately 94 % of persons with PHTS have head circumference which measures >2 standard deviations from the norm for age and gender. Average head circumference for children measures +4.89 standard deviations above the mean and for adult men and women measures 62.8 and 60.0 cm, respectively [45]. Case reports and small imaging series have found the enlarged head circumference in PHTS is owed to overgrowth of brain tissue as opposed to hydrocephalus [46, 47].

Within series of children with macrocephaly and autism, up to 17 % are found to have PHTS [19]. Ascertainment bias creates difficulty when attempting to estimate the percent of individuals with PHTS and neurocognitive delay, as this can be a driving force behind genetics referral and syndrome recognition. Neurodevelopmental evaluation should be performed for children with PHTS so that any needed therapeutic interventions may begin as early as possible [22, 24]. In comparison with individuals with idiopathic ASDs, persons with PHTS and autism demonstrated reduced processing speed and working memory [48]. In older individuals with PHTS not selected for ASD phenotype and with normal IQ range, Busch et al. [49] found deficits in motor function, executive function, and memory recall, suggesting an underlying issue with frontal lobe circuitry.

Lhermitte–Duclos disease, also known as dysplastic cerebellar gangliocytoma, is a rare benign brain tumor occurring in less than 10 % of individuals with PHTS [21]. Cerebrovascular malformations including dural arteriovenous fistulas, cavernous hemangiomas, small developmental venous anomalies, and paraspinal arteriovenous malformations have been reported in individuals with PHTS and in some cases have been difficult to treat [43, 50–53]. While routine MRI imaging is not currently recommended, symptoms concerning for either of these issues (especially onset of seizure, unresolved/worsening headache, or vertigo) warrant immediate attention and investigation.

Keys to Recognizing Individuals at Risk for PHTS

PHTS can be difficult to recognize due to the diverse presentations observed among affected individuals and the subtle nature of some presenting features. Additionally, detecting at-risk patients may require asking questions or checking for findings such

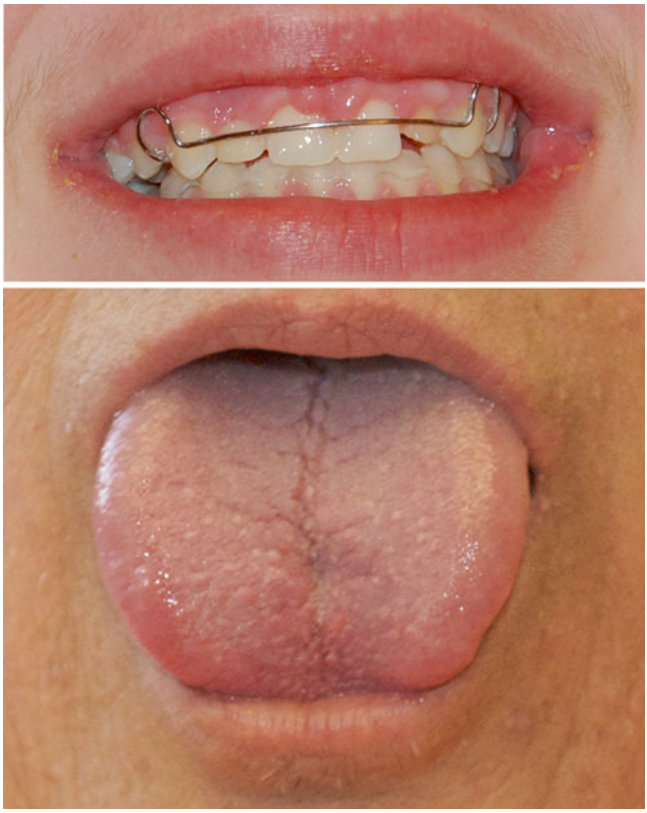


Fig. 7.1 Papillomas of the gums (*top*) and tongue (*bottom*) in persons with PHTS

as enlarged head circumference, that while easy to assess, are unlikely to be part of the office visit routine. However, there are some characteristics which should raise strong clinical suspicion for PHTS given their rarity in the general population and are easily identifiable through quick pathology/history review or brief physical examination:

- Lhermitte–Duclos disease (dysplastic cerebellar gangliocytoma)
- Extreme macrocephaly (children, +5 standard deviations above the mean or higher; adult women >60 cm, adult men >63 cm)
- Oral mucosal papillomatosis (Fig. 7.1)
- Penile freckling
- Hamartomatous gastrointestinal polyps
- Pediatric non-medullary thyroid carcinoma

These findings were among the highest-scoring components on the Cleveland Clinic PTEN Risk Calculation tool, which calculates a patient's a priori *PTEN* mutation risk [23]. This tool, freely available online at http://www.lerner.ccf.org/gmi/ccscore, awarded a weighted score for each characteristic after comparing

age-related prevalence within mutation positive and negative research participants to expected community frequencies as derived from published literature and the Surveillance Epidemiology and End Results database. The calculation provides a percentage risk for PTEN mutation in adults and recommendation whether or not to pursue PTEN testing/genetics referral for both pediatric and adult patients.

The generic "red flags" for cancer genetics referral can also be useful in identifying patients at risk for PHTS. These include

- Early onset diagnosis for the cancer type
- Multiple primary tumors
- Multifocal/bilateral tumors
- Rare histologies
- Family history of similarly affected relatives

Additionally, any individual who reports a family member previously diagnosed with Cowden syndrome, BRRS, PHTS, or any other hereditary cancer predisposition syndrome should always be referred to cancer genetics for further evaluation and testing.

Inheritance, Genetic Testing, and Genetic Counseling

PHTS is inherited in an autosomal dominant manner. For conditions with this inheritance pattern, each child of an affected individual has a 50 % chance to inherit the mutation and thus share their parent's disease predisposition. An individual's *PTEN* mutation might have been inherited from their parent or could have been a de novo occurrence, meaning that neither parent was affected, and the gene mutation occurred sporadically in either the sperm or egg cell or very early in embryonic development. In PHTS, the condition is estimated to occur in a de novo manner in 10–44 % of cases [54], meaning that in most cases the mutation is shared by one of the individual's parents and could have been present for several generations.

Disease-causing *PTEN* mutations have been identified in all nine *PTEN* exons and include mutations causing gene truncation, a single amino acid change (missense mutation), or large deletion or duplication [55]. Genetic variants have also been identified in the *PTEN* promoter region. Gene sequencing is the most common methodology employed by laboratories for mutation detection, but this technology cannot detect large deletions or duplications involving one or more exons. To detect these types of mutations a second methodology such as targeted microarray or multiplex-ligation probe amplification (MLPA) is required. Care should be taken to select a laboratory whose test methodology would allow detection of all mutation types.

Analysis of the entire gene is needed to discover the location and exact sequence change involved for only the first member of a family to undergo *PTEN* testing. After one family member's mutation is identified, it is possible for his or her relatives to pursue targeted testing which only investigates the region of the gene where

the family member's mutation was found. This targeted testing is highly accurate, less expensive than full gene analysis, tends to be well-covered by insurance carriers, and provides family members with a direct "yes or no" answer regarding their mutation status. Family members found to share their relative's mutation would then also be granted a PHTS diagnosis, and the same disease risk and management recommendations would also apply. If they are negative, their risks for PHTS-associated cancers and other complications would revert to that of any other person in the general population.

With thyroid cancer risk beginning to elevate during childhood for individuals with PHTS, predictive testing of children in a family with a known *PTEN* mutation is permitted, as opposed to conditions like Hereditary Breast and Ovarian Cancer syndrome, where management would not change until adulthood and testing is not offered until that time. The American Society of Clinical Oncology, American College of Gastroenterology, and other professional societies recommend genetic testing occur in the setting of both pre- and post-test genetic counseling [56, 57]. During pre-test counseling, the genetic counselor reviews the syndrome in question and helps the individual (or for children unable to consent themselves, their parents) understand whether the decision to pursue testing is the right one at this juncture of their life. The counselor also follows up to disclose results and if positive, explains the implications of these results for their care and helps guide them to appropriate subspecialists for needed management.

Receiving a diagnosis of PHTS or any other genetic condition can cause a strong emotional reaction in some individuals. Genetic counselors are equipped to help their patients understand how to accept their new diagnosis and use this information in a positive and empowering manner. After a genetic diagnosis is made, a genetic counselor will identify available support resources such as disease-specific support groups that the patient and their family may wish to connect with. Some individuals may have inaccurate preconceptions about risk for genetic discrimination. Genetic counselors are equipped to explain the risks and benefits of testing and protective laws such as the Genetic Information and Nondiscrimination Act, which makes it illegal for most employers and health insurance companies to discriminate against a person or treat them differently based on genetic testing or family history information (http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf).

Summary and Resources

Early recognition of individuals at risk for PHTS and timely genetics referral has the potential to prevent cancer diagnoses and lessen disease morbidity and mortality for the affected patient as well as at-risk family members. Screening and management guidelines have been developed to assist health care providers as they work to care for affected individuals in their practice. Partnering with a genetic counselor to ensure patients receive appropriate pre- and post-test counseling can ensure patients

make informed decisions regarding genetic testing and have access to a health care professional able to explain the results and implications for their care. The resources listed below may also be helpful to health care providers as well as individuals affected with PHTS.

PHTS Patient/Advocacy Groups

PTEN Hamartoma Tumor Syndrome Foundation: www.ptenfoundation.org. 501(c)3 non-profit organization developed to promote research for and awareness of PHTS and provide financial assistance for research efforts and affected individuals.

PTEN World: www.ptenworld.com. Discussion forum-based resource providing support and connection to individuals with PHTS, their family members/loved ones, and health care providers. To protect privacy, membership and access granted following submission of application to group leadership.

PTEN Life: www.ptenlife.com. Posts recent news and research articles of interest to PHTS community. Also provides individuals an opportunity to share their or their affected child's story and pictures.

Facebook: www.facebook.com. Searches using the terms "PTEN," "PHTS," "Cowden syndrome," or "BRRS" will identify multiple groups of interest.

Medical Resources/Research Studies

PTEN/Cowden Clinic: www.clevelandclinic.org/ptenclinic. Multi-disciplinary team through the Cleveland Clinic in Cleveland, OH. Provides care coordination for patients/families wishing to arrange medical visits with specialists knowledgeable about PHTS.

Natural History Study of Individuals with Autism and Germline Heterozygous PTEN Mutations: https://clinicaltrials.gov/show/NCT02461446. NIH-supported prospective observational cohort study with multiple recruitment sites across the USA. Purpose of study: to determine cross-sectional and longitudinal medical, behavioral, and cognitive differences between individuals with PHTS and ASD and other groups, as well as to identify cognitive, neural systems, and molecular biomarkers specific ASD in individuals with PHTS. In addition, this study will be creating and maintaining a biorepository and linked phenotypic database for individuals with PHTS and ASD.

The PTEN Study: www.lerner.ccf.org/gmi/research/pten. Multi-faceted research study housed at the Cleveland Clinic. Combines clinical patient information with DNA, RNA, and protein studies of the PTEN gene and related pathways. Provides *PTEN* mutation analysis in a research laboratory setting and can forward results to clinical laboratories for targeted mutation confirmation testing.

Resources for Health Care Professionals

National Society of Genetic Counselors: www.nsgc.org. Contains searchable directory to assist in locating area genetic counselors.

National Cancer Institute Cancer Genetics Service Directory: http://www.cancer.gov/about-cancer/causes-prevention/genetics/directory. Searchable list of professionals providing services related to cancer genetics.

References

1. Li DM, Sun H. TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. Cancer Res. 1997;57(11):2124–9.
2. Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science. 1997;275(5308):1943–7.
3. Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. Cancer Res. 1997;57(21):4736–8.
4. Steck PA, Pershouse MA, Jasser SA, Yung WK, Lin H, Ligon AH, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet. 1997;15(4):356–62.
5. Maehama T, Dixon JE. The tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. J Biol Chem. 1998;273(22):13375–8.
6. Myers MP, Stolarov JP, Eng C, Li J, Wang SI, Wigler MH, et al. P-TEN, the tumor suppressor from human chromosome 10q23, is a dual-specificity phosphatase. Proc Natl Acad Sci USA. 1997;94(17):9052–7.
7. Gu J, Tamura M, Yamada KM. Tumor suppressor PTEN inhibits integrin- and growth factor-mediated mitogen-activated protein (MAP) kinase signaling pathways. J Cell Biol. 1998;143(5):1375–83.
8. Stambolic V, Suzuki A, de la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell. 1998;95(1):29–39.
9. Weng L, Brown J, Eng C. PTEN induces apoptosis and cell cycle arrest through phosphoinositol-3-kinase/Akt-dependent and -independent pathways. Hum Mol Genet. 2001;10(3):237–42.
10. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet. 1997;16(1):64–7.
11. Nelen MR, Padberg GW, Peeters EA, Lin AY, van den Helm B, Frants RR, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet. 1996;13(1):114–6.
12. Marsh DJ, Dahia PL, Zheng Z, Liaw D, Parsons R, Gorlin RJ, et al. Germline mutations in PTEN are present in Bannayan-Zonana syndrome. Nat Genet. 1997;16(4):333–4.
13. Marsh DJ, Kum JB, Lunetta KL, Bennett MJ, Gorlin RJ, Ahmed SF, et al. PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet. 1999;8(8):1461–72.
14. Lachlan KL, Lucassen AM, Bunyan D, Temple IK. Cowden syndrome and Bannayan Riley Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of PTEN mutation carriers. J Med Genet. 2007;44(9):579–85.

15. Koch R, Scholz M, Nelen MR, Schwechheimer K, Epplen JT, Harders AG. Lhermitte-Duclos disease as a component of Cowden's syndrome. Case report and review of the literature. J Neurosurg. 1999;90(4):776–9.
16. McBride KL, Varga EA, Pastore MT, Prior TW, Manickam K, Atkin JF, et al. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. Autism Res. 2010;3(3):137–41. doi:10.1002/aur.132.
17. Pérez-Núñez A, Lagares A, Benítez J, Urioste M, Lobato RD, Ricoy JR, et al. Lhermitte-Duclos disease and Cowden disease: clinical and genetic study in five patients with Lhermitte-Duclos disease and literature review. Acta Neurochir (Wien). 2004;146(7):679–90.
18. Robinson S, Cohen AR. Cowden disease and Lhermitte-Duclos disease: an update. Case report and review of the literature. Neurosurg Focus. 2006;20(1), E6.
19. Varga EA, Pastore M, Prior T, Herman GE, McBride KL. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. Genet Med. 2009;11(2):111–7. doi:10.1097/GIM.0b013e31818fd762.
20. Bubien V, Bonnet F, Brouste V, Hoppe S, Barouk-Simonet E, David A, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet. 2013;50(4):255–63. doi:10.1136/jmedgenet-2012-101339.
21. Nieuwenhuis MH, Kets CM, Murphy-Ryan M, Yntema HG, Evans DG, Colas C, et al. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. Fam Cancer. 2014;13(1):57–63. doi:10.1007/s10689-013-9674-3.
22. Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400–7. doi:10.1158/1078-0432.CCR-11-2283.
23. Tan MH, Mester J, Peterson C, Yang Y, Chen JL, Rybicki LA, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. Am J Hum Genet. 2011;88(1):42–56. doi:10.1016/j.ajhg.2010.11.013.
24. National Comprehensive Cancer Network. Genetic/Familial High Risk Assessment: Breast and Ovarian (Version 2.2015). http://www.nccn.org. Accessed 7 July 2015.
25. Gómez García EB, Lobbes MB, van de Vijver K, Keymeulen K, van der Ent F, Yntema HG, et al. occult breast cancer due to multiple calcified hamartomas in a patient with Cowden syndrome. Case Rep Radiol. 2012;2012:638725. doi:10.1155/2012/638725.
26. Sabaté JM, Gómez A, Torrubia S, Blancas C, Sánchez G, Alonso MC, et al. Evaluation of breast involvement in relation to Cowden syndrome: a radiological and clinicopathological study of patients with PTEN germ-line mutations. Eur Radiol. 2006;16(3):702–6.
27. Schrager CA, Schneider D, Gruener AC, Tsou HC, Peacocke M. Clinical and pathological features of breast disease in Cowden's syndrome: an underrecognized syndrome with an increased risk of breast cancer. Hum Pathol. 1998;29(1):47–53.
28. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2004;22(6):1055–62.
29. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C. Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations. J Clin Oncol. 2014;32(17):1818–24. doi:10.1200/JCO.2013.53.6656.
30. Milas M, Mester J, Metzger R, Shin J, Mitchell J, Berber E, et al. Should patients with Cowden syndrome undergo prophylactic thyroidectomy? Surgery. 2012;152(6):1201–10. doi:10.1016/j.surg.2012.08.055.
31. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96(12):E2063–71. doi:10.1210/jc.2011-1616.
32. Smith JR, Marqusee E, Webb S, Nose V, Fishman SJ, Shamberger RC, et al. Thyroid nodules and cancer in children with PTEN hamartoma tumor syndrome. J Clin Endocrinol Metab. 2011;96(1):34–7. doi:10.1210/jc.2010-1315.

33. Baker WD, Soisson AP, Dodson MK. Endometrial cancer in a 14-year-old girl with Cowden syndrome: a case report. J Obstet Gynaecol Res. 2013;39(4):876–8. doi:10.1111/j.1447-0756.2012.02052.x.
34. Mester JL, Zhou M, Prescott N, Eng C. Papillary renal cell carcinoma is associated with PTEN hamartoma tumor syndrome. Urology. 2012;79(5):1187. e1–7. doi: 10.1016/j.urology.2011.12.025.
35. Choyke PL, Walther MM, Glenn GM, Wagner JR, Venzon DJ, Lubensky IA, et al. Imaging features of hereditary papillary renal cancers. J Comput Assist Tomogr. 1997;21(5):737–41.
36. Heald B, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139(6):1927–33. doi:10.1053/j.gastro.2010.06.061.
37. Levi Z, Baris HN, Kedar I, Niv Y, Geller A, Gal E, et al. Upper and lower gastrointestinal findings in PTEN mutation-positive Cowden syndrome patients participating in an active surveillance program. Clin Trans Gastroenterol. 2011;2, e5. doi:10.1038/ctg.2011.4.
38. Stanich PP, Owens VL, Sweetser S, Khambatta S, Smyrk TC, Richardson RL, et al. Colonic polyposis and neoplasia in Cowden syndrome. Mayo Clin Proc. 2011;86(6):489–92. doi:10.4065/mcp.2010.0816.
39. Alimi A, Weeth-Feinstein LA, Stettner A, Caldera F, Weiss JM. Overlap of juvenile polyposis syndrome and Cowden syndrome due to de novo chromosome 10 deletion involving BMPR1A and PTEN: implications for treatment and surveillance. Am J Med Genet A. 2015;167(6):1305–8. doi:10.1002/ajmg.a.36876.
40. Tsuchiya KD, Wiesner G, Cassidy SB, Limwongse C, Boyle JT, Schwartz S. Deletion 10q23.2-q23.33 in a patient with gastrointestinal juvenile polyposis and other features of a Cowden-like syndrome. Genes Chromosomes Cancer. 1998;21(2):113–8.
41. Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille JJ, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet. 1986;29(3):222–33.
42. Greene AK, Orbach DB. Management of arteriovenous malformations. Clin Plast Surg. 2011;38(1):95–106. doi:10.1016/j.cps.2010.08.005.
43. Tan WH, Baris HN, Burrows PE, Robson CD, Alomari AI, Mulliken JB, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. J Med Genet. 2007;44(9):594–602.
44. Kurek KC, Howard E, Tennant LB, Upton J, Alomari AI, Burrows PE, et al. PTEN hamartoma of soft tissue: a distinctive lesion in PTEN syndromes. Am J Surg Pathol. 2012;36(5):671–87. doi:10.1097/PAS.0b013e31824dd86c.
45. Mester JL, Tilot AK, Rybicki LA, Frazier 2nd TW, Eng C. Analysis of prevalence and degree of macrocephaly in patients with germline PTEN mutations and of brain weight in Pten knock-in murine model. Eur J Hum Genet. 2011;19(7):763–8. doi:10.1038/ejhg.2011.20.
46. Lok C, Viseux V, Avril MF, Richard MA, Gondry-Jouet C, Deramond H, et al. Brain magnetic resonance imaging in patients with Cowden syndrome. Med (Baltimore). 2005;84(2):129–36.
47. Padberg GW, Schot JD, Vielvoye GJ, Bots GT, de Beer FC. Lhermitte-Duclos disease and Cowden disease: a single phakomatosis. Ann Neurol. 1991;29(5):517–23.
48. Frazier TW, Embacher R, Tilot AK, Koenig K, Mester J, Eng C. Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism. Mol Psychiatry. 2015;20:1132–8. doi:10.1038/mp.2014.125.
49. Busch RM, Chapin JS, Mester J, Ferguson L, Haut JS, Frazier TW, et al. Cognitive characteristics of PTEN hamartoma tumor syndromes. Genet Med. 2013;15(7):548–53. doi:10.1038/gim.2013.1.
50. Bae BG, Kim HJ, Lee SG, Choi JR, Hwang C, Lee JH, et al. A novel PTEN mutation in a Korean patient with Cowden syndrome and vascular anomalies. Acta Derm Venereol. 2011;91(1):88–90. doi:10.2340/00015555-0994.
51. Moon K, Ducruet AF, Crowley RW, Klas K, Bristol R, Albuquerque FC. Complex dural arteriovenous fistula in Bannayan-Riley-Ruvalcaba syndrome. J Neurosurg Pediatr. 2013;12(1):87–92. doi:10.3171/2013.3.PEDS12551.
52. Sadahiro H, Ishihara H, Goto H, Oka F, Shirao S, Yoneda H, et al. Postoperative dural arteriovenous fistula in a patient with Cowden disease: a case report. J Stroke Cerebrovasc Dis. 2014;23(3):572–5. doi:10.1016/j.jstrokecerebrovasdis.2013.04.021.

53. Srinivasa RN, Burrows PE. Dural arteriovenous malformation in a child with Bannayan-Riley-Ruvalcaba Syndrome. AJNR Am J Neuroradiol. 2006;27(9):1927–9.
54. Mester J, Eng C. Estimate of de novo mutation frequency in probands with PTEN hamartoma tumor syndrome. Genet Med. 2012;14(9):819–22. doi:10.1038/gim.2012.51.
55. Mester J, Eng C. When overgrowth bumps into cancer: the PTEN-opathies. Am J Med Genet C Semin Med Genet. 2013;163C(2):114–21. doi:10.1002/ajmg.c.31364.
56. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K, American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2010;28(5):893–901. doi:10.1200/JCO.2009.27.0660.
57. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62. doi:10.1038/ajg.2014.435. quiz 263.

Chapter 8
Cronkhite–Canada Syndrome

Thomas G. Cotter, Badr F. Al Bawardy, and Seth Sweetser

Introduction

Background

Cronkhite–Canada syndrome (CCS) is a rare, noninherited condition, associated with high morbidity. It is characterized by gastrointestinal inflammatory polyposis, alopecia, onychodystrophy, cutaneous hyperpigmentation, and diarrhea. The disease was first described in 1955 by the American internist, Leonard Wolsey Cronkhite, and the American radiologist, Wilma Jeanne Canada, in the *New England Journal of Medicine* [1]. They described two cases of an unusual fatal syndrome consisting of generalized gastrointestinal polyps, cutaneous pigmentation, alopecia, and onychodystrophy. The term CCS was first coined in 1966 by Jarnum and Jensen in describing two new observations in CCS patients: protein-losing enteropathy with electrolyte disturbances and the presence of non-adenomatous cystic polyps [2]. Since then, several case reports and a few small series have been published including the largest study by Goto on 100 Japanese cases of CCS in 1995 [3]. In this study, Goto divided the disease into five groups according to the leading symptom; type 1: diarrhea, type 2: dysgeusia, type 3: abnormal sensation in the mouth with thirst, type 4: abdominal symptoms other than diarrhea, and type 5: alopecia. At this time, about 450 cases of CCS have been described in the literature.

T.G. Cotter, M.D.
Department of Internal Medicine, Mayo Clinic, Rochester, MN USA
e-mail: cotter.thomas@mayo.edu

B.F. Al Bawardy, M.D. • S. Sweetser, M.D. (✉)
Division of Gastroenterology, Mayo Clinic College of Medicine,
200 First Street S.W., Rochester, MN 55905, USA
e-mail: AlBawardy.Badr@mayo.edu; sweetser.seth@mayo.edu

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_8

Epidemiology

The estimated incidence of CCS is one per million according to the aforementioned study by Goto [3]. CCS occurs worldwide, however, 75 % of reports come from Japan, for an unknown reason. It is typically seen in adults between ages 31 and 80, with a mean age of onset of symptomatic disease of 60 years [3]. The youngest case reported was in a 17-year-old man [4]. There is a slight male predominance with a ratio of 3:2 [5].

Etiology and Risk Factors

The etiology of CCS is currently unknown. There is no strong evidence to suggest a familial predisposition. Evidence continues to emerge supporting an autoimmune basis. Infection is another theory suggested in the literature. Mental and physical stress have been confirmed to be among the most important risk factors for this syndrome [3].

CCS appears to be an inflammatory condition and treatment with immunosuppressing anti-inflammatory regimens often leads to complete clinical response and polyp regression [3, 6–9]. Immunologic dysfunction as an etiology first raised the possibility of an autoimmune basis in the 1980s [10]. A number of CCS cases have been associated with autoimmune disorders including hypothyroidism [6, 11], systemic lupus erythematous (SLE) [12], and membranous glomerulonephritis [13]. Patients with CCS have also been shown to possess elevated antinuclear antibodies (ANA) and anti-Saccharomyces cerevisiae antibodies (ASCA) [13–16]. Recently, research has centered on the relationship between Immunoglobulin G4 (IgG4) autoimmunity and CCS. IgG4-associated systemic disease is an increasingly recognized multisystem immune-mediated disorder characterized by IgG4 plasma cell infiltration with manifestations including autoimmune pancreatitis (AIP), sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis, and papillitis [17–19]. IgG4 plasma cell infiltration of CCS polyps was first reported in 2007 [20]. A larger study reaffirmed this finding with autoimmune-related IgG4 antibody increased in CCS polyps compared to other diseases and normal control tissues [21]. However, a recent study of seven CCS patients found that all had histologic features commonly found in other immune disorders of the gastrointestinal tract, with only one patient having significantly increased IgG4-positive plasma cells. The authors concluded that this further supported the hypothesis that CCS may represent an immune dysregulation syndrome, and suggested CCS is different from IgG4-related disease [22]. Regardless of whether this finding is linked to IgG4-related autoimmune disease or not, this finding provides a clue to the pathophysiology of CCS. Furthermore, it is postulated that this could be clinically useful when more information is needed to exclude or include the diagnosis of CCS. To surmise, the acknowledged response of CCS to immunosuppressing anti-inflammatory regimens, the association with

autoimmune disorders and autoimmune serum markers combined with the recent evidence of IgG4 infiltration of CCS polyps is strong evidence of an autoimmune inflammatory process underlying the etiology of CCS.

The possibility of an infectious cause has been suggested on the basis of inflammatory cell infiltration with mononuclear cells and eosinophils [5, 23]. One series reported two cases of CCS with combined infection with two or more pathogens [14]. However, the authors did acknowledge that the relationship of these pathogens with diarrhea and CCS was difficult to determine. *Helicobacter pylori* infection has also been implicated in the number of case reports [24–26]. An allergic component of CCS has been proposed with the observation that after stopping the use of inducers—hair dye and topical medications, IgE and eosinophils levels decreased, and symptoms improved in CCS patients [14]. Furthermore, CCS has been described in association with arsenic poisoning [27]. Familial incidence has been described only once, in two members of one family—a 50-year-old man and his 22-year-old son [28].

Clinical Manifestations

The clinical manifestations of CCS can vary, but classically it is characterized by diffuse gastrointestinal inflammatory polyposis (sparing the esophagus), diarrhea, weight loss, and the dermatologic triad of cutaneous hyperpigmentation, alopecia, and dystrophic nails [1, 6, 29–31]. Regarding the unique ectodermal abnormalities, dystrophic nails present with thinning, splitting, and separation from the nail beds [32]. Alopecia affects the scalp and body hair with biopsy revealing a marked noninflammatory loss of follicular units with dilated follicles and deposition of glycosaminoglycans [6]. The diffuse cutaneous hyperpigmentation manifests with light to dark brown macular lesions most frequently observed on the extremities, face, neck, palms, and soles [6]. Microscopic examination of biopsied skin reveals abnormally increased melanin deposition with or without increased melanocyte proliferation [33, 34].

An epidemiological study of the clinical features on 110 CCS patients by *Goto et al.* found that 35.4 % of people presented with diarrhea (Type I), 40.9 % with hypogeusia (Type II), 6.4 % with xerostomia (Type III), 9.1 % with abdominal discomfort (Type IV), and 8.2 % with alopecia (Type V) [3]. The hypogeusia is thought to be related to zinc and copper deficiencies in some patients [35]. Other common symptoms include edema (due to a protein-losing enteropathy), progressive anorexia, anemia, glossitis and neurological symptoms of paraesthesias, seizures, and tetany related to electrolyte abnormalities [6].

There is a high morbidity associated with CCS, with the long-term prognosis being quite poor according to early studies. The 5-year survival rate has been reported at 55 % [3]. However, with improvement in medical therapy and increased recognition of the syndrome, the prognosis is now better compared to earlier case reports [36]. A number of possible complications may occur with CCS and can contribute to the poor outcome. These include potentially fatal gastrointestinal

bleeding, intussusception, and prolapse [6, 37]. Electrolyte abnormalities, dehydration, protein-losing enteropathy, and other nutritional deficiencies due to malabsorption can also complicate the course of the disease. Patients with CCS are also predisposed to recurrent infections, however, it is not known whether this is related to malnutrition or is a primary immunological deficiency [10].

Associated Syndromes

Although CCS has characteristic clinicopathological features, the differential diagnosis includes a number of polyposis syndromes, including familial adenomatous polyposis (FAP) and variants Turcot and Gardner syndrome, Peutz–Jeghers syndrome (PJS), Cowden disease, juvenile polyposis syndrome (JPS), and serrated polyposis syndrome. Clinically, these diagnoses exhibit characteristics that distinguish them from CCS [38] (Table 8.1). However, the endoscopic and histologic features of CCS polyps and juvenile polyps overlap and may appear identical and distinguishing them requires the presence of the classic ectodermal changes of CCS [39]. There are also significant similarities between the features of CCS and PJS, in particular in the morphology of intestinal hamartomatous polyps, mandating attention to detail to ensure the correct diagnosis is made [39, 40]. Such is the phenotypic overlap between CCS, JPS, and PJS, some authors have suggested that CCS might be related to PJS and JPS [41].

In CCS, the polypoid lesions are non-neoplastic inflammatory polyps with cystic dilation and typical glandular changes and are similar to hamartomatous polyps seen with either sporadic juvenile polyps or those associated with JPS [42]. The polyps occur throughout the entire gastrointestinal tract, with the exception of the esophagus [6]. There can be hundreds of polyps ranging in size from 1 mm to 3 cm. The colonic polyps are almost always sessile, even when large, which can assist in differentiating them from juvenile polyps [39]. Another useful distinction between these polyps is that the mucosa of polyps in CCS is histologically abnormal, revealing edema, congestion, and inflammation of the lamina propria [39]. By contrast, the mucosa of juvenile polyps is histologically normal. More recently, IgG4 plasma cell infiltration of CCS polyps has been described [20, 21] and IgG4 staining of intestinal polyps can provide histologic evidence when more information is needed to exclude or include the diagnosis of CCS [20, 21]. Due to these histological similarities between JPS and CCS, one needs to take the clinical picture into account when making the diagnosis, rather than relying on polyp histology alone. JPS is an inherited condition associated with mutations in the MADH4 and BMPR1A genes and presents in the first or second decades in life [42]. Furthermore, JPS is associated with an increased risk of gastrointestinal malignancy but lacks the ectodermal changes typical of CCS, and JPS polyps do not regress with steroid treatment [42, 43]. Cancers appear to arise from adenomatous components present in some juvenile polyps [44]. Despite these differences, CCS and JPS can occasionally be confused both clinically and histologically.

Table 8.1 Polyposis Colonic Syndromes and distribution of polyps in the gastrointestinal tract (Modified from *Seshadri et al.* [76])

Syndrome	Age of symptom onset	Transmission	Distribution of polyps			Histology	Extraintestinal manifestations	Prognosis
			Stomach (%)	Small bowel (%)	Colon (%)			
Serrated polyposis syndrome	>40 years	Familial clusters	0	0	100	Hyperplastic polyps, sessile serrated adenomas	None	Colon cancer (mostly right-sided)
Cronkhite–Canada syndrome	50–60 years	Sporadic	100	50	100	Hamartomatous polyps (juvenile type) exhibiting glandular hyperplasia, cystic dilation, mucosal edema, and eosinophilic inflammation	Alopecia, dermal hyperpigmentation, onychodystrophy, diarrhea, protein-losing enteropathy, dysgeusia	Cachexia, colon cancer (mostly left-sided)
Peutz–Jeghers syndrome	10–30 years	Autosomal dominant	25	64–96	25–35	Hamartomas in the stomach and small bowel, adenomatous polyps in the colon	Mucocutaneous melanosis (mostly in the lips and buccal mucosa)	Colon, gastric, pancreatic, breast, and/or gynecologic cancers
Familial adenomatous polyposis	15–20 years	Autosomal dominant	10–30	10	100	Adenomas	Hypertrophy of retinal pigment epithelium, brain tumors (Turcot syndrome), epidermoid cysts, mandibular osteomas, desmoids, thyroid tumors (Gardner syndrome)	Colon, duodenal, and/or thyroid cancers

(continued)

Table 8.1 (continued)

Syndrome	Age of symptom onset	Transmission	Distribution of polyps			Histology	Extraintestinal manifestations	Prognosis
			Stomach (%)	Small bowel (%)	Colon (%)			
Juvenile polyposis syndrome	<10 years	Autosomal dominant	14	<10	100	Hamartomas with an inflammatory component, usually solitary in nature, and commonly found in the rectum. Adenomas and hyperplastic polyps are less common.	Rectal bleeding, protein-losing enteropathy, intussusception	Colon and/or gastric cancers
Cowden syndrome	9–20 years	Autosomal dominant	20	20	30	Hamartomas	Facial trichilemmomas, macrocephaly, mucocutaneous lesions, acral keratoses, thyroid disease, breast disease	Breast, thyroid, reproductive organ, and/or colon cancers

Reproduced with permission from Seshadri D, Karagiorgos N, Hyser MJ. A case of Cronkhite–Canada syndrome and a review of gastrointestinal polyposis syndromes. Gastroenterol Hepatol (N Y). 2012 Mar; 8(3): 197–201

PJS is another similar hamartomatous polyposis syndrome inherited in an autosomal-dominant fashion [38]. The polyps are present throughout the entire GI tract (mostly in the small bowel) along with mucocutaneous melanin pigmentation spots that appear most commonly on the lips and buccal mucosa. Symptom onset usually occurs prior to 30 years of age. Many organs are prone to cancer in these patients with colorectal cancer being common in these patients.

Serrated polyposis syndrome is an entity in which serrated polyps are found in abundance throughout the colon in the absence of gastric or small bowel involvement and is more common in patients over 40 years of age. Usually, the polyps are large, flat, and found along haustral folds. CCS polyps have been described and interpreted as serrated in appearance, but they are most appropriately characterized as inflammatory and are distinct from serrated polyps.

Distinguishing CCS from adenomatous polyposis syndromes is often straight forward as the polyps are histologically distinct. Adenomatous polyposis syndromes are characterized by inheritance of an abnormal autosomal-dominant gene that results in multiple colorectal adenomatous polyps. FAP usually involves the colorectum, duodenum and, to a much lesser extent, the stomach and small bowel. In FAP patients, the risk of colorectal cancer approaches 100 % by the time these patients are 50 years of age.

While PJS and JPS have a proven genetic component, CCS is still thought to be nonhereditary. The other entities of the noninherited, non-adenomatous polyposis each exhibit unique clinical and pathological features helping to distinguish them from one another [5]. These conditions include CCS, lipomatous polyposis, nodular lymphoid hyperplasia, inflammatory polyposis, and lymphomatous polyposis.

Diagnosis

There are no clear diagnostic tools for CCS. CCS is a clinicopathologic diagnosis based on features of malabsorption in the setting of characteristic clinical, endoscopic, radiologic, and histologic findings.

Clinical Findings

Diarrhea and hypogeusia are the most common initial symptoms, with the dermatological changes of alopecia, cutaneous hyperpigmentation, and onychodystrophy occurring after a few weeks or months [6]. The main clinical effects of the gastrointestinal disease are protein-losing enteropathy caused by excess mucous secretion by intestinal crypt cells [45] with resultant hypoproteinemia and malnutrition. Laboratory findings are non-specific; however, they may include electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia), depressed serum levels of zinc, iron, copper and vitamin B12, anemia, hypoalbuminemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), elevated ANA, and raised serum levels of gastrin.

Endoscopic and Radiographic Findings

Endoscopy reveals polypoid lesions of the sessile or semipedunculated type throughout the entire gastrointestinal tract, except for characteristic sparing of the esophagus [6]. Endoscopic appearance of CCS varies according to current literature. Gastric mucosa can reveal red and edematous granular polyps with thickened mucosal folds (Fig. 8.1), mimicking Menetrier's disease, to atrophic appearing with polypoid lesions [46]. Similar polyps can be found in the small intestine with some small denuded areas without villi being typical (Fig. 8.2). Colonic polyps are characterized as sessile and can be "strawberry-like" according to some studies (Fig. 8.3) [47–50].

Other imaging studies which may be helpful in diagnosing CCS include abdominal CT scanning which may reveal thickened gastric folds and CT enterography or enteroclysis, capsule endoscopy or small intestine double-contrast radiology examination which may reveal small intestinal polypoid lesions. Multidetector CT (MDCT) imaging has also been shown to be useful for the detection of CCS polyps and for the monitoring of effects of therapy [51].

Histologic Findings

As described in detail previously when comparing CCS to other polyposis syndromes, CCS polyps are typically hamartomatous or juvenile type characterized by their broad sessile base and exhibit glandular hyperplasia (Fig. 8.4), cystic dilation,

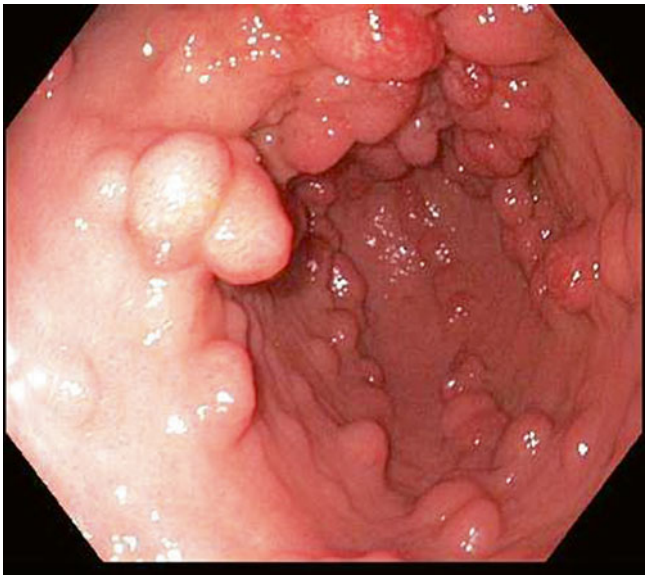


Fig. 8.1 CCS with extensive inflammatory gastric polyps

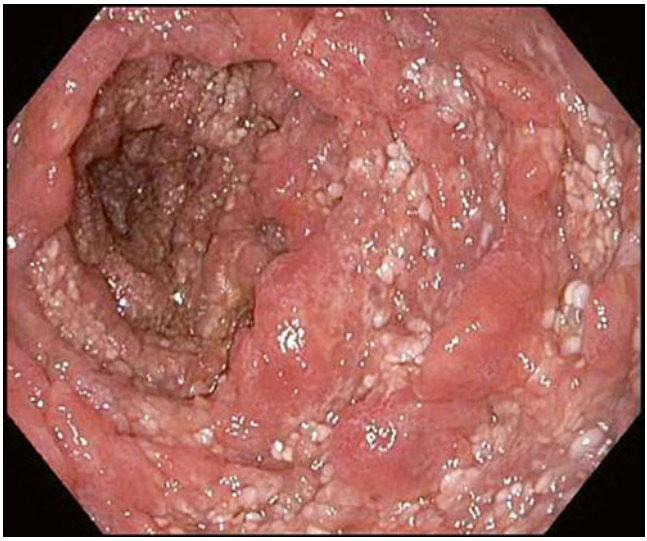


Fig. 8.2 Severe inflammatory duodenopathy in CCS

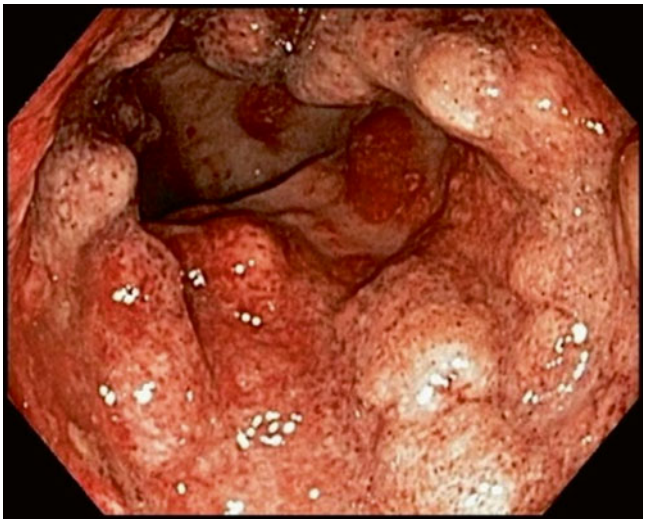


Fig. 8.3 CCS colon polyps

mucosal dilation with edema of the lamina propria (Fig. 8.5), and eosinophilic inflammation [6, 9, 15, 23, 39]. Interestingly, the surface of duodenal, jejunal, and ileal mucosa can be rather flat due to subtotal and/or total atrophy of villi. CCS polyps have been shown to be infiltrated with IgG4 plasma cells [20, 21] which may help distinguish it from JPS.

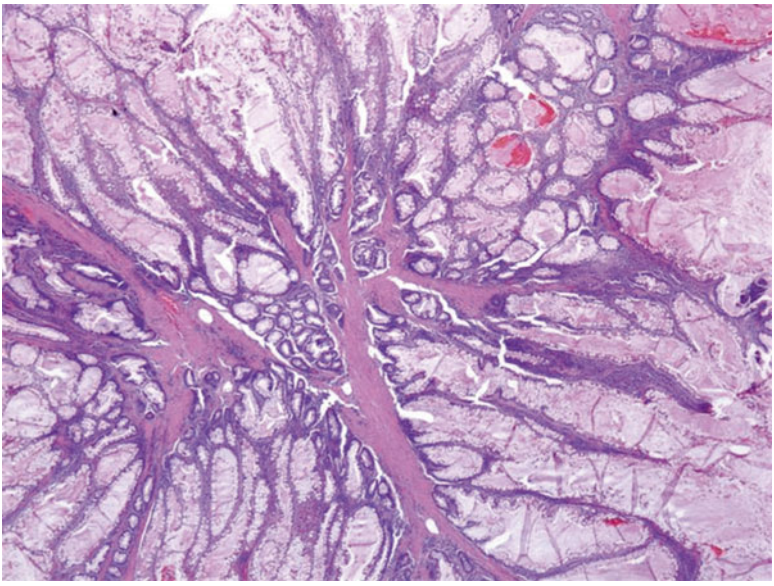


Fig. 8.4 Proliferative, tortuous glands in CCS polyp. Courtesy of Thomas C. Smyrk, M.D., Department of Pathology, Mayo Clinic, Rochester, Minnesota

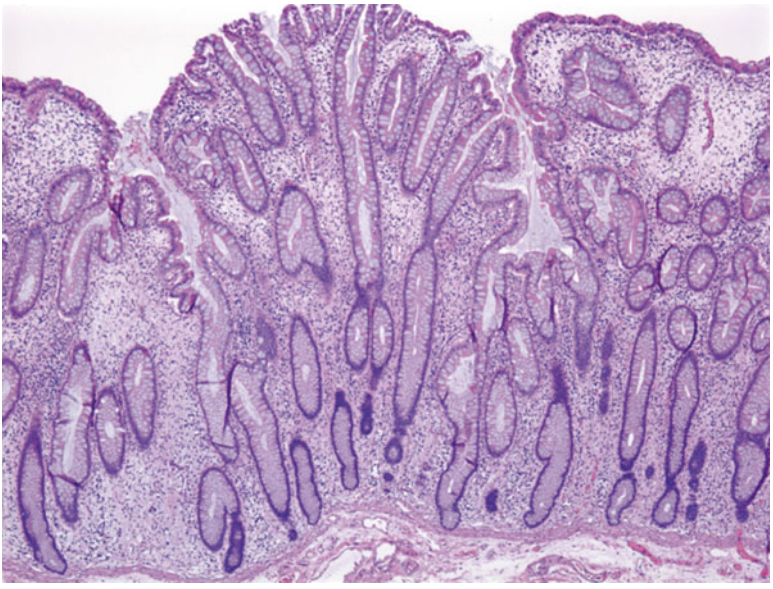


Fig. 8.5 Edematous lamina propria in CCS. Courtesy of Thomas C. Smyrk, M.D., Department of Pathology, Mayo Clinic, Rochester, Minnesota

Management

Given the rarity of CCS, there are no evidence-based therapies, and no systematic investigations of medical or surgical interventions have been conducted to guide management. Interestingly, one case of spontaneous remission has been described [52]. However, this is extremely rare and intervention is usually mandated. Several different treatment approaches have been attempted, with varying degrees of success. Such treatments include hyperalimentation, corticosteroids, H2-receptor antagonists, antibiotics, acid suppression, cromolyn sodium, anabolic steroids, surgery, and combinations of these therapies [53].

As weight loss, malabsorption and micronutrient deficiencies are common in patients with CCS, aggressive nutritional support, and electrolyte replacement is required in the majority of patients. Nutritional support is the cornerstone of patient management. In fact, there are reports of complete and sustained remission being achieved with nutritional support alone in the form of enteral feeding or parenteral nutrition with complete symptomatic improvement and resolution of ectodermal changes [6, 54–57]. Traditionally, total parenteral nutrition has been preferred to enteral nutrition because of the supposed effect of bowel rest, however, this is not evidence based [58]. Most patients, however, do not respond to nutritional therapy alone, and current literature favors a combination therapy based on nutritional support and corticosteroids [7].

Corticosteroids are frequently used and are considered the mainstay of medical treatment for CCS, in combination with nutritional supplementation. Notably, steroids produced a transient response in one of the first two reported cases of CCS [1]. Corticosteroids have been shown to induce sustained remission in patients [7, 53, 59]. However, the specific preparation, dose and duration of corticosteroid treatment used have varied widely in the literature [6]. Once a sustained response is achieved, corticosteroids should be tapered and discontinued. Duration of therapy is determined by a patient's response to therapy and the resolution of disease manifestations [53]. The typical steroid treatment regimen is 40 mg of prednisone for 1 week, with a 5-mg decrease every week until the patient is tapered off. In one study, a symptomatic response was seen within 3 months in 10 of 11 CCS patients treated with this regimen [21]. However, relapse of symptoms is common during the taper of corticosteroids; therefore, a steroid-sparing strategy can be employed using immunomodulatory agents such as azathioprine, which was used in the previously mentioned study [21]. Five CCS patients who responded to corticosteroid treatment were placed on azathioprine (2 mg/kg/day) with achievement of clinical remission and no relapse after 5 years of follow-up [21]. Recurrence of disease may require corticosteroid re-treatment [53].

Multiple other agents have been described in the literature for treating CCS. Various antibiotics, usually in combination with other modalities, have been used with varying degrees of success [6]. Disease remission has also been reported after *H. pylori* eradication and acid-suppressive therapy with histamine receptor antagonists [24, 25, 60, 61]. It has been hypothesized that mast cells may play a role

in the development of CCS and accordingly a patient has been described who improved with cromolyn sulfate, a mast cell stabilizer. Specifically, a combination therapy including cromolyn sulfate, histamine receptor antagonists, corticosteroids, and antibiotics was used [53, 60]. The use of mesalazine has also been reported to be effective in one case study [62]. Due to the suspected autoimmune component, azathioprine in combination with tacrolimus or cyclosporin has also been administered to some patients with improvement reported [46, 63]. An anti-TNF-α therapy was considered in one paper due to strong intracellular expression of TNF-α in the small intestinal mucosa, however, before the medication could be introduced, the patient died [47]. Subsequently, the use of infliximab was described in another patient with refractory CCS with remission achieved leading the authors to conclude that infliximab offers both a promising new therapy and potential insight into the pathogenesis [64]. The use of the antifibrinolytic, tranexamic acid, resulted in symptomatic improvement in one patient [65]. The proposed mechanism is that this agent impairs fibrinolysis in the gastrointestinal tract, thereby reducing the loss of proteins. Unfortunately, due to the rarity of CCS, randomized controlled trials to determine optimal treatment will likely never be possible. Anecdotal evidence with careful tailoring of the treatment regimen to the individual patient, with the likely use of corticosteroids, will have to suffice.

The role of surgery in the treatment of CCS is undefined. Surgical treatment for the complications of CCS has been advocated as resection of the specific sections of the gastrointestinal tract that appears to be responsible for particular complications and appears to be beneficial in some cases. There have been case reports describing improvement in hypoalbuminemia, resulting from protein-losing enteropathy, in patients with CCS after undergoing a right hemicolectomy and a subtotal colectomy [66, 67].

The question of whether polyps in CCS possess malignant potential is controversial. However, colorectal neoplasia risk appears to be increased in CCS. There are case reports to suggest that both typical adenomatous and serrated polyp pathways may be involved, and the overall risk of colorectal cancer has ranged from 14 % to 25 % in the literature [21, 68–72]. The histology of these cancers is adenocarcinoma. It is unknown whether the duration and/or extent of polyp formation accelerate the risk of neoplasia in CCS patients. There is debate also as to whether these cancers are coincidental or if they begin as inflammatory polyps and then develop malignant transformation. One study suggested the possibility of serrated polyps, a precursor to adenocarcinoma, being more common in CCS than conventional adenomatous polyps. In these cases of CCS, both the serrated polyps and the adenocarcinoma demonstrated microsatellite instability and overexpression of the p53 protein [72]. The serrated-adenoma–carcinoma sequence is a recognized pathway of colon carcinogenesis. A mechanistic explanation for a serrated-adenoma–carcinoma sequence in patients with CCS is that both CCS and serrated adenomas arise from abnormal intestinal crypt cell proliferation. Pathologic studies in patients with CCS have suggested that selective damage to the crypt epithelium occurs with the aberrant maturation of crypt cells [45]. Similarly, serrated polyps have crypt abnormalities that are demonstrated histologically by saw-toothed, elongated, and dilated

crypts with a high proliferative activity [73]. Aberrant crypt maturation in CCS and the high proliferative rate of serrated polyps may be the common pathway that predisposes to mutations and the development of neoplasia. Other theories include the possibility that chronic generalized mucosal inflammation in CCS may increase neoplastic transformation similar to the inflammation-induced mutagenesis of idiopathic inflammatory bowel disease [74] and the theory of sporadic adenocarcinomas occurring in a background of non-adenomatous polyps.

Unfortunately, due to the rarity of this disease, optimal screening protocols have not been developed for CCS patients. Careful follow-up is recommended. Surveillance endoscopies should be employed to assess the response to treatment and for the early detection of gastrointestinal and colorectal neoplasia, with most clinicians recommending annual surveillance [53]. This schedule is optimally aimed at controlling polyp burden and detecting colorectal cancer. Early detection of malignancy can be challenging against the backdrop of hundreds of inflammatory polyps that may persist despite treatment. A recommended solution to this dilemma is to perform a repeat endoscopy after successful treatment, as treatment causes remission of most CCS polyps that are potentially inflammatory and non-neoplastic. Anecdotally, some clinicians have advised systematic resection of all polyps that are >1 cm in diameter at colonoscopy, as these are more likely to contain an adenomatous component than smaller polyps [25, 75], and this approach in conjunction with effective medical therapy may possibly help prevent the development of colorectal cancer [53]. Despite prolonged corticosteroid treatment, inflammatory CCS polyps may not regress. If repeat biopsy samples of persistent polyps in CCS patients show any degree of dysplasia, intestinal resection should be considered.

References

1. Cronkhite Jr LW, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med. 1955;252(24):1011–5.
2. Jarnum S, Jensen H. Diffuse gastrointestinal polyposis with ectodermal changes. A case with severe malabsorption and enteric loss of plasma proteins and electrolytes. Gastroenterology. 1966;50(1):107–18.
3. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Nihon Geka Hokan. 1995;64(1):3–14.
4. Vernia P, Marcheggiano A, Marinaro V, Morabito S, Guzzo I, Pierucci A. Is Cronkhite-Canada Syndrome necessarily a late-onset disease? Eur J Gastroenterol Hepatol. 2005;17(10):1139–41.
5. Ward EM, Wolfsen HC. Review article: the non-inherited gastrointestinal polyposis syndromes. Aliment Pharmacol Ther. 2002;16(3):333–42.
6. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The Cronkhite-Canada syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. Medicine. 1982;61(5):293–309.
7. Chadalavada R, Brown DK, Walker AN, Sedghi S. Cronkhite-Canada syndrome: sustained remission after corticosteroid treatment. Am J Gastroenterol. 2003;98(6):1444–6.
8. Doyle T, Jarvis R. Reversal of changes in Cronkhite-Canada syndrome. Australas Radiol. 1984;28(1):19–22.

9. Goto A. Cronkhite-Canada syndrome: observations about treatment, course and prognosis of 123 cases reported in Japan. Nihon Geka Hokan. 1988;57(5):427–33.
10. Lin HJ, Tsai YT, Lee SD, Lai KH, Ng WW, Tam TN, et al. The Cronkhite-Canada syndrome with focus on immunity and infection. Report of a case. J Clin Gastroenterol. 1987;9(5): 568–70.
11. Qiao M, Lei Z, Nai-Zhong H, Jian-Ming X. Cronkhite-Canada syndrome with hypothyroidism. South Med J. 2005;98(5):575–6.
12. Kubo T, Hirose S, Aoki S, Kaji T, Kitagawa M. Canada-Cronkhite syndrome associated with systemic lupus erythematosus. Arch Intern Med. 1986;146(5):995–6.
13. Takeuchi Y, Yoshikawa M, Tsukamoto N, Shiroi A, Hoshida Y, Enomoto Y, et al. Cronkhite-Canada syndrome with colon cancer, portal thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis. J Gastroenterol. 2003;38(8):791–5.
14. Wen XH, Wang L, Wang YX, Qian JM. Cronkhite-Canada syndrome: report of six cases and review of literature. World J Gastroenterol WJG. 2014;20(23):7518–22.
15. Murata I, Yoshikawa I, Endo M, Tai M, Toyoda C, Abe S, et al. Cronkhite-Canada syndrome: report of two cases. J Gastroenterol. 2000;35(9):706–11.
16. Sampson JE, Harmon ML, Cushman M, Krawitt EL. Corticosteroid-responsive Cronkhite-Canada syndrome complicated by thrombosis. Dig Dis Sci. 2007;52(4):1137–40.
17. Takahashi H, Yamamoto M, Suzuki C, Naishiro Y, Shinomura Y, Imai K. The birthday of a new syndrome: IgG4-related diseases constitute a clinical entity. Autoimmun Rev. 2010;9(9):591–4.
18. Nishimori I, Otsuki M. Autoimmune pancreatitis and IgG4-associated sclerosing cholangitis. Best Pract Res Clin Gastroenterol. 2009;23(1):11–23.
19. Kim MH, Moon SH, Kamisawa T. Major duodenal papilla in autoimmune pancreatitis. Dig Surg. 2010;27(2):110–4.
20. Riegert-Johnson DL, Osborn N, Smyrk T, Boardman LA. Cronkhite-Canada syndrome hamartomatous polyps are infiltrated with IgG4 plasma cells. Digestion. 2007;75(2-3):96–7.
21. Sweetser S, Ahlquist DA, Osborn NK, Sanderson SO, Smyrk TC, Chari ST, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Dig Dis Sci. 2012;57(2):496–502.
22. Bettington M, Brown IS, Kumarasinghe MP, de Boer B, Bettington A, Rosty C. The challenging diagnosis of Cronkhite-Canada syndrome in the upper gastrointestinal tract: a series of 7 cases with clinical follow-up. Am J Surg Pathol. 2014;38(2):215–23.
23. Johnson GK, Soergel KH, Hensley GT, Dodds WJ, Hogan WJ. Cronkite-Canada syndrome: gastrointestinal pathophysiology and morphology. Gastroenterology. 1972;63(1):140–52.
24. Kato K, Ishii Y, Mazaki T, Uehara T, Nakamura H, Kikuchi H, et al. Spontaneous regression of polyposis following abdominal colectomy and helicobacter pylori eradication for Cronkhite-Canada syndrome. Case Rep Gastroenterol. 2013;7(1):140–6.
25. Okamoto K, Isomoto H, Shikuwa S, Nishiyama H, Ito M, Kohno S. A case of Cronkhite-Canada syndrome: remission after treatment with anti-Helicobacter pylori regimen. Digestion. 2008;78(2-3):82–7.
26. Kim MS, Jung HK, Jung HS, Choi JY, Na YJ, Pyun GW, et al. A case of Cronkhite-Canada syndrome showing resolution with Helicobacter pylori eradication and omeprazole. Korean J Gastroenterol. 2006;47(1):59–64.
27. Senesse P, Justrabo E, Boschi F, Goegebeur G, Collet E, Boutron MC, et al. Cronkhite-Canada syndrome and arsenic poisoning: fortuitous association or new etiological hypothesis? Gastroenterol Clin Biol. 1999;23(3):399–402.
28. Patil V, Patil LS, Jakareddy R, Verma A, Gupta AB. Cronkhite-Canada syndrome: a report of two familial cases. Indian J Gastroenterol. 2013;32(2):119–22.
29. Blonski WC, Furth EE, Kinosian BP, Compher C, Metz DC. A case of Cronkhite-Canada syndrome with taste disturbance as a leading complaint. Digestion. 2005;71(4):201–5.
30. Kao KT, Patel JK, Pampati V. Cronkhite-Canada syndrome: a case report and review of literature. Gastroenterol Res Pract. 2009;2009:619378.

31. Goto A, Mimoto H, Shibuya C, Matsunami E. Cronkhite-Canada syndrome: an analysis of clinical features and follow-up studies of 80 cases reported in Japan. Nihon Geka Hokan. 1988;57(6):506–26.
32. Nyam DC, Ho MS, Goh HS. Progressive ectodermal changes in the Cronkhite-Canada syndrome. Aust N Z J Surg. 1996;66(11):780–1.
33. Herzberg AJ, Kaplan DL. Cronkhite-Canada syndrome. Light and electron microscopy of the cutaneous pigmentary abnormalities. Int J Dermatol. 1990;29(2):121–5.
34. Ortonne JP, Bazex J, Berbis P. Cronkhite-Canada disease. Discussion apropos of a case and study of the pigmentation. Ann Dermatol Venereol. 1985;112(12):951–8.
35. Berzin TM, Greenberger NJ, Levy BD, Loscalzo J. Clinical problem-solving. Worth a second look. N Engl J Med. 2012;366(5):463–8.
36. Watanabe C, Narimatsu K, Sato H, Usui S, Komoto S, Tomita K, Hokari R, Miura S. Clinical response to medical treatment and prognosis of Cronkhite-Canada syndrome – a Japanese nationwide survey. Gastroenterology. 2014;1:S-795.
37. Ishikawa E, Kudo M, Minami Y, Ueshima K, Kitai S, Ueda K. Cecal intussusception in an adult with Cronkhite-Canada syndrome relieved by colonoscopy. Intern Med. 2010;49(12): 1123–6.
38. Macaron C, Leach BH, Burke CA. Hereditary colorectal cancer syndromes and genetic testing. J Surg Oncol. 2015;111(1):103–11.
39. Burke AP, Sobin LH. The pathology of Cronkhite-Canada polyps. A comparison to juvenile polyposis. Am J Surg Pathol. 1989;13(11):940–6.
40. de la Chapelle A. Genetic predisposition to colorectal cancer. Nat Rev Cancer. 2004;4(10): 769–80.
41. Samoha S, Arber N. Cronkhite-Canada syndrome. Digestion. 2005;71(4):199–200.
42. Boardman LA. Heritable colorectal cancer syndromes: recognition and preventive management. Gastroenterol Clin North Am. 2002;31(4):1107–31.
43. Schreibman IR, Baker M, Amos C, McGarrity TJ. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol. 2005;100(2):476–90.
44. Half EE, Bresalier RS. Clinical management of hereditary colorectal cancer syndromes. Curr Opin Gastroenterol. 2004;20(1):32–42.
45. Jenkins D, Stephenson PM, Scott BB. The Cronkhite-Canada syndrome: an ultrastructural study of pathogenesis. J Clin Pathol. 1985;38(3):271–6.
46. Anderson RD, Patel R, Hamilton JK, Boland CR. Cronkhite-Canada syndrome presenting as eosinophilic gastroenteritis. Proc Natl Acad Sci USA. 2006;19(3):209–12.
47. Martinek J, Chvatalova T, Zavada F, Vankova P, Tuckova I, Zavoral M. A fulminant course of Cronkhite-Canada syndrome. Endoscopy. 2010;42 Suppl 2:E350–1.
48. Yuan B, Jin X, Zhu R, Zhang X, Liu J, Wan H, et al. Cronkhite-Canada syndrome associated with rib fractures: a case report. BMC Gastroenterol. 2010;10:121.
49. Cao XC, Zhou B, Ding JJ, Lian J, Lu N, Wang BM. Clinical characteristics of Cronkhite-Canada syndrome in Chinese: meta-analysis of 35 cases. Zhonghua Yi Xue Za Zhi. 2007; 87(44):3130–2.
50. Monkemuller K, Neumann H, Evert M. Cronkhite-Canada syndrome: panendoscopic characterization with esophagogastroduodenoscopy, endoscopic ultrasound, colonoscopy, and double balloon enteroscopy. Clin Gastroenterol Hepatol. 2008;6(10):A26.
51. Samet JD, Horton KM, Fishman EK, Iacobuzio-Donahue CA. Cronkhite-Canada syndrome: gastric involvement diagnosed by MDCT. Case Rep Med. 2009;2009:148795.
52. Peart Jr AG, Sivak Jr MV, Rankin GB, Kish LS, Steck WD. Spontaneous improvement of Cronkhite-Canada syndrome in a postpartum female. Dig Dis Sci. 1984;29(5):470–4.
53. Ward EM, Wolfsen HC. Pharmacological management of Cronkhite-Canada syndrome. Expert Opin Pharmacother. 2003;4(3):385–9.
54. Jones AF, Paone DB. Canada-Cronkhite syndrome in an 82-year-old woman. Am J Med. 1984;77(3):555–7.
55. Ferney DM, DeSchryver-Kecskemeti K, Clouse RE. Treatment of Cronkhite-Canada syndrome with home total parenteral nutrition. Ann Intern Med. 1986;104(4):588.

56. Russell DM, Bhathal PS, St John DJ. Complete remission in Cronkhite-Canada syndrome. Gastroenterology. 1983;85(1):180–5.
57. Russell DM, Bhathal PS, St John DJ. Sustained remission in Cronkhite-Canada syndrome. Gastroenterology. 1986;91(6):1580.
58. Kopacova M, Urban O, Cyrany J, Laco J, Bures J, Rejchrt S, et al. Cronkhite-Canada syndrome: review of the literature. Gastroenterol Res Pract. 2013;2013:856873.
59. Goo YS, Lee YC, Shin MS, Kim WH, Kim H, Park IS. A case of Cronkhite-Canada syndrome involving the entire gastrointestinal tract. Endoscopy. 2001;33(4):385.
60. Ward E, Wolfsen HC, Ng C. Medical management of Cronkhite-Canada syndrome. South Med J. 2002;95(2):272–4.
61. Allbritton J, Simmons-O'Brien E, Hutcheons D, Whitmore SE. Cronkhite-Canada syndrome: report of two cases, biopsy findings in the associated alopecia, and a new treatment option. Cutis. 1998;61(4):229–32.
62. Takakura M, Adachi H, Tsuchihashi N, Miyazaki E, Yoshioka Y, Yoshida K, Oryo F, Sawada T. A case of Cronkhite-Canada syndrome markedly improved with mesalazine therapy. Dig Endosc. 2004;16:74–8.
63. Ohmiya N, Nakamura M, Yamamura T, Yamada K, Nagura A, Yoshimura T, et al. Steroid-resistant Cronkhite-Canada syndrome successfully treated by cyclosporine and azathioprine. J Clin Gastroenterol. 2014;48(5):463–4.
64. Tran VT, Reicher S, Chung DS, Eysselein VE, Pham BV. Infliximab therapy in refractory Cronkhite-Canada syndrome. Gastroenterology. 2010;1:S364.
65. Nakayama M, Muta H, Somada S, Maeda T, Mutoh T, Shimizu K, et al. Cronkhite-Canada syndrome associated with schizophrenia. Intern Med. 2007;46(4):175–80.
66. Hanzawa M, Yoshikawa N, Tezuka T, Konishi K, Kaneko K, Akita Y, et al. Surgical treatment of Cronkhite-Canada syndrome associated with protein-losing enteropathy: report of a case. Dis Colon Rectum. 1998;41(7):932–4.
67. Samalavicius NE, Lunevicius R, Klimovskij M, Kildusis E, Zazeckis H. Subtotal colectomy for severe protein-losing enteropathy associated with Cronkhite-Canada syndrome: a case report. Colorectal Dis. 2013;15(3):e164–5.
68. Nagata J, Kijima H, Hasumi K, Suzuki T, Shirai T, Mine T. Adenocarcinoma and multiple adenomas of the large intestine, associated with Cronkhite-Canada syndrome. Dig Liver Dis. 2003;35(6):434–8.
69. Katayama Y, Kimura M, Konn M. Cronkhite-Canada syndrome associated with a rectal cancer and adenomatous changes in colonic polyps. Am J Surg Pathol. 1985;9(1):65–71.
70. Malhotra R, Sheffield A. Cronkhite-Canada syndrome associated with colon carcinoma and adenomatous changes in C-C polyps. Am J Gastroenterol. 1988;83(7):772–6.
71. Jain A, Nanda S, Chakraborty P, Kundra A, Anuradha S, Reddy BS, et al. Cronkhite-Canada syndrome with adenomatous and carcinomatous transformation of colonic polyp. Indian J Gastroenterol. 2003;22(5):189–90.
72. Yashiro M, Kobayashi H, Kubo N, Nishiguchi Y, Wakasa K, Hirakawa K. Cronkhite-Canada syndrome containing colon cancer and serrated adenoma lesions. Digestion. 2004;69(1): 57–62.
73. Fujishima N. Proliferative activity of mixed hyperplastic adenomatous polyp/serrated adenoma in the large intestine, measured by PCNA (proliferating cell nuclear antigen). J Gastroenterol. 1996;31(2):207–13.
74. Tlsty TD, Coussens LM. Tumor stroma and regulation of cancer development. Annu Rev Pathol. 2006;1:119–50.
75. Sweetser S, Boardman LA. Cronkhite-Canada syndrome: an acquired condition of gastrointestinal polyposis and dermatologic abnormalities. Gastroenterol Hepatol. 2012;8(3):201–3.
76. Seshadri D, Karagiorgos N, Hyser MJ. A case of Cronkhite-Canada syndrome and a review of gastrointestinal polyposis syndromes. Gastroenterol Hepatol. 2012;8(3):197–201.

Chapter 9
Peutz-Jeghers Syndrome

Douglas Riegert-Johnson

Introduction

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by melanotic macules, intestinal polyps, and an increased cancer risk. It is caused by mutations in the serine/threonine kinase 11 gene (*LKB1*, *STK11*).

Epidemiology

PJS is a rare disease. ("Peutz-Jeghers syndrome is no frequent nosological unit" [1].) There are no high-quality estimates of the prevalence or incidence of PJS. Estimates have included 1 in 8500 to 23,000 live births [2], 1 in 50,000 to 1 in 100,000 in Finland [3], and 1 in 200,000 [4]. At Mayo Clinic from 1945 to 1996 the incidence of PJS was 0.9 PJS patients per 100,000 patients. PJS has been reported in Western Europeans [5], African Americans [5], Nigerians [6], Japanese [7], Chinese [8, 9], Indians [10, 11], and other populations [12–15]. PJS occurs equally in males and females [7].

Historical Background

PJS was first reported in a pair of identical twins with melanotic macules (MMs) described by Connor in 1895 and illustrated by Hutchinson in 1896 (Fig. 9.1) [16, 17]. Later in life, the twins developed what are now known to be additional

D. Riegert-Johnson (✉)
Mayo Clinic College of Medicine, 4500 San Pablo Road, Jacksonville, FL 32082, USA
e-mail: riegertjohnson.douglas@mayo.edu

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_9

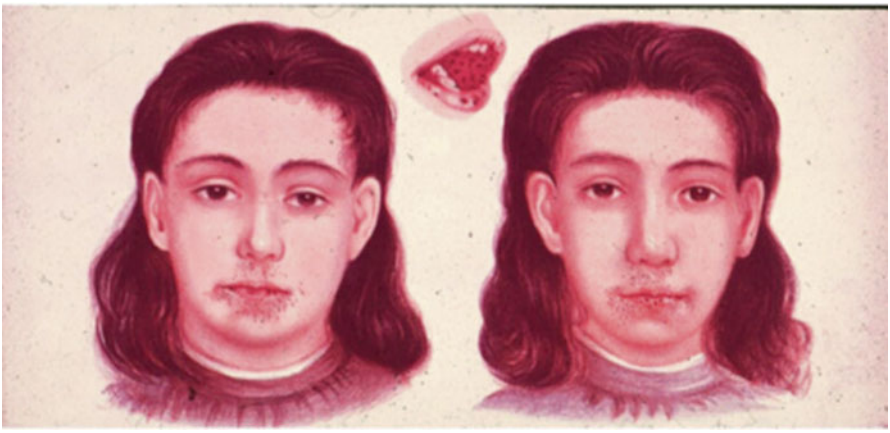


Fig. 9.1 Illustration of the identical twins reported by Conner as rendered by Sir Jonathan Hutchinson's artist. Connor's report was published in *Lancet* (1895;2:1169) and the illustration was published in *Archives of Surgery* (London 7:290,1896). Note the perioral melanotic macules. The text of Connor's report reads, "Dr. J. T. Connor showed two cases of Pigmentation, of the Lips and the Mouth, in twins, both girls, aged 12 years, of dark complexion and anaemic. The pigment spots, which were only noticed 2 years ago, were ink black in colour, mostly of very small size and scattered over the lips, (especially the lower), gums, hard palate, and not on the tongue." Later in life, the twins developed additional features of PJS—one died of intussusception at age 20, the other died of breast cancer at age 52 [5, 18]. Courtesy of Victor McKusick, MD, Johns Hopkins Hospital

features of PJS—one died of intussusception at age 20, the other died of breast cancer at age 52 [5, 18].

Johannes Peutz reported two boys who were members of the same family with MMs and small intestine polyps in 1921 (Fig. 9.2) [19]. An English translation of Peutz's paper is available online (http://www.ncbi.nlm.nih.gov/books/NBK7027/). In 1949, Harold Jeghers and others reported an additional ten cases from several families (Fig. 9.3) [5]. The eponym PJS was coined in 1957 at the Mayo Clinic [20]. A history of PJS with biographies of Peutz and Jeghers has been published, and many early PJS papers have been made available online by the Jeghers Medical Index (http://www.jeghers.com/pj_pubmed.aspx) [21].

Although Peutz described early jejunal adenocarcinoma in one of his patient's polyps, it was controversial whether or not there was an increased cancer risk associated with PJS until the 1980s [22–27]. The author of a 1974 JAMA editorial estimated the lifetime intestinal cancer risk for PJS at only 2–3 %, whereas the most recent estimate is 57 % [23, 28].

In 1997 the *PJS* locus was localized to 19p13.3 using comparative genome hybridization, loss of heterozygosity (LOH) studies, and targeted linkage analysis [29]. One year later, mutations in the *LKB1* gene at that locus were identified in PJS patients by two groups [30, 31]. A follow-up study of Peutz's original pedigree identified an *LKB1* mutation in affected family members [32].

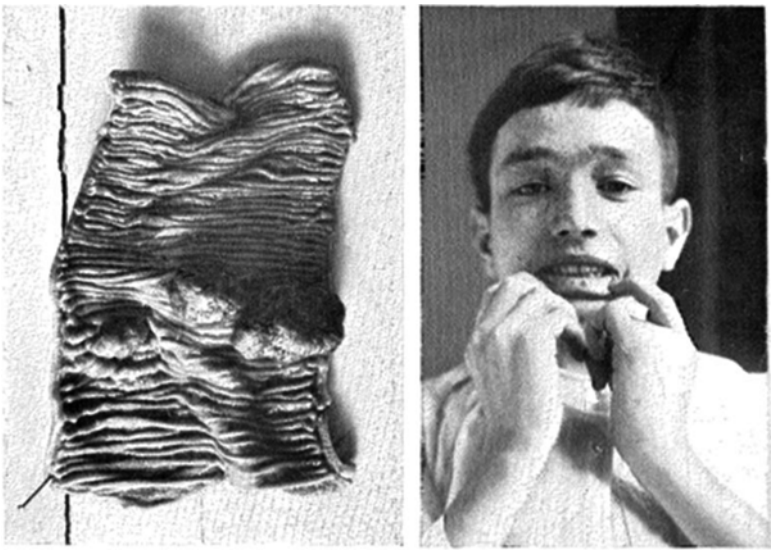


Fig. 9.2 Reproduction of the single figure from Dr. Johannes Peutz's 1921 paper. Pictured are a segment of jejunum with polyps and the patient demonstrating melanotic macules on his lower lip. The original caption read, "Concerning the unusual syndrome of familial polyposis of the gastro-intestinal mucosa with that of the nasal cavity also in combination with strange pigmentation of the skin and mucosa." The entire text of Peutz's original paper in English is available by linking to Appendix I. Translation from Dutch by Wytske Westra, MD

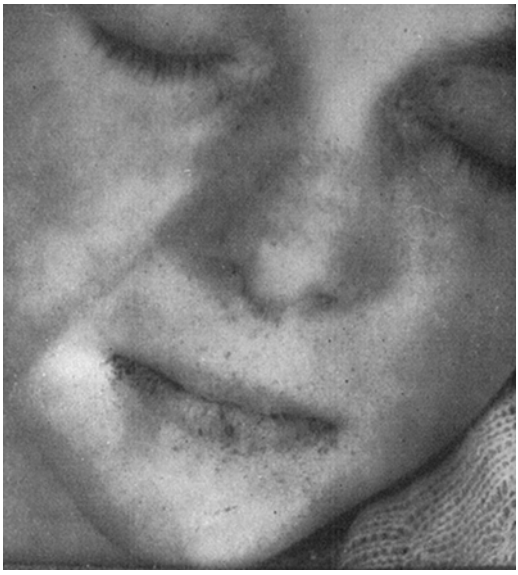


Fig. 9.3 Photo of the patient described in case 5 from the 1949 *New England Journal of Medicine* report by Drs. Jeghers, McKusick and Katz (this photo was not included in that publication). Note the perioral and periocular melanotic macules. Provided by Lori M. Gawdyda, Medical Librarian, Jeghers Medical Index, St. Elizabeth Health Center, Youngstown, Ohio. (http://www.jeghers.com/)

Table 9.1 Identification of LKB1 mutations in Peutz-Jeghers syndrome patients

Reference	Patients with mutations	Mutation by sequencing	Mutation by MLPA[a]
Hearle et al. [98]	28/46 (61 %)	19/46	9/18
Aretz et al. [208]	54/71 (76 %)	37/71	17/34
Volikos et al. [209]	59/76 (78 %)	48/76	11/28
Chow et al. [210]	24/33 (73 %)	14/33	10/14
Total	165/226 (74 %)	118/226 (52 %)	47/226 (21 %)[b]

[a]In the studies listed, MLPA was only performed on patients who did not have mutations identifiable by sequencing

[b]For the percentage of mutations detected by MLPA, the number of mutations detected by MLPA was divided by the total number of patients, not the number tested by MLPA. *MLPA* multiplex ligation-dependent probe amplification

LKB1 is the original gene designation and is still used. *SKT11* is the official designation for *LKB1* by the Human Genome Organization (HUGO) (http://www.genenames.org/data/hgnc_data.php?hgnc_id=11389). *LKB1* is the only gene associated with PJS. Mutations in *LKB1* can be found in about 75 % of PJS patients using sequencing and multiplex ligation-dependent probe amplification (MLPA) (Table 9.1).

Support Group

A group of PJS patients holds annual meetings in the USA. The website for the PJS support group is https://www.smartpatients.com/communities/peutz-jeghers-syndrome.

Pathophysiology

LKB1

The LKB1 protein is a serine/threonine kinase. It is the only known tumor suppressor kinase. *LKB1* consists of ten exons covering 22.6 kb of genomic DNA located at 19p13.3 (Fig. 9.4). Nine exons are coding; the final exon is non-coding. Only one transcript isoform is known. *LKB1* codes for the 433 amino acid LKB1 protein that is expressed in most epithelial tissues, myocytes, glia cells, and the cells of the seminiferous tubules (Fig. 9.5) [33, 34]. Fetal tissues have higher expression than adult tissues [33]. LKB1 is present primarily in the cytoplasm [35].

A multispecies alignment of the amino acid sequence of LKB1 across human, chimpanzee, dog, rat, mouse, chicken, xenopus, zebrafish, and drosophila reveals a highly conserved core of 245 amino acids, corresponding to the C-terminal portion of the LKB1 kinase domain (Figs. 9.5 and 9.6). Human and mouse share 98 % identity and 99 % similarity across this region, versus 89 % identity and 93 % similarity across the entire protein.

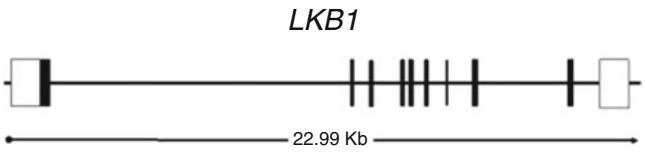


Fig. 9.4 *LKB1* consists of 10 exons covering 22.6 kb of genomic DNA located at 19p13.3. Nine exons are coding; the final exon is non-coding

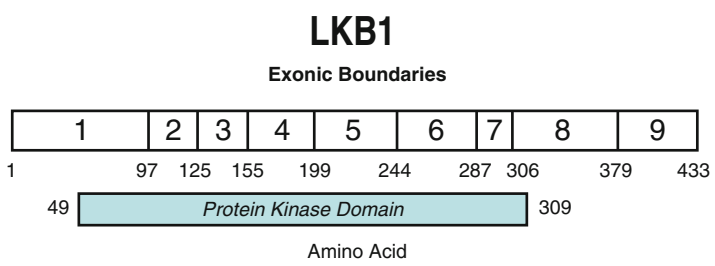


Fig. 9.5 Exonic boundaries and the protein kinase domain of LKB1

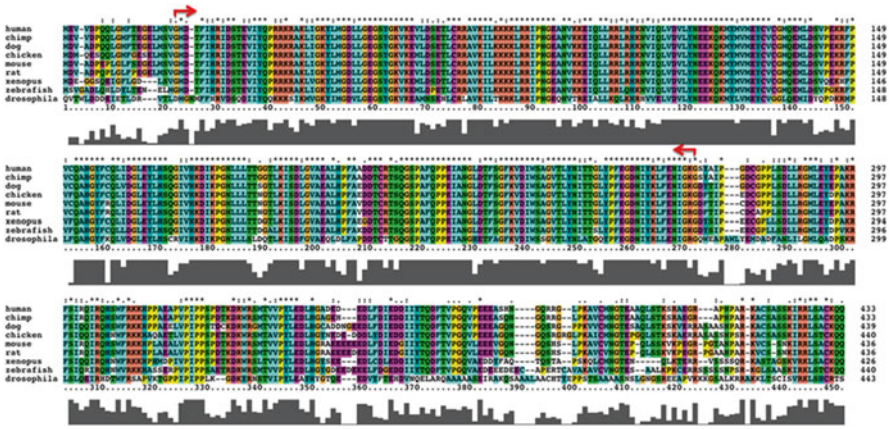


Fig. 9.6 Sequence conservation of LKB1. A multispecies alignment of LKB1 amino acid sequence from nine vertebrates and one insect. *Drosophila* and *Xenopus* sequences have been truncated at C-terminal end for clarity. *Colors* denote amino acids with similar biochemical properties; an *asterisk* indicates amino acid identity; *two dots* indicate strong conservation; *one dot* indicates weak conservation; *bars beneath alignment* indicate degree of conservation. Note the highly conserved region between residues 27 and 272 (corresponding to human residues 25–270) bounded by *red arrows*. This region corresponds to a portion of the LKB1 kinase domain. Alignment was generated by ClustalX 2.0.5 (www.clustal.org)

Peutz-Jeghers Syndrome Patients Without Identifiable LKB1 Mutations

Twenty-five percent of PJS patients do not have detectable *LKB1* mutations (Table 9.1). These patients probably have large rearrangements of *LKB1*, including deletions, duplications, and inversions of areas larger than an exon. Large rearrangements are common in familial cancer syndrome patients who do not have mutations detected by sequencing. Most of these will be detected by MLPA, while some may not be. Conversion technology has increased the mutation detection rate in familial cancer syndromes, but to date there are no reports of the use of conversion to identify *LKB1* mutations [36].

Other possibilities less likely than large rearrangements include *LKB1* promoter mutations, mosaicism, *LKB1* intronic mutations, or a PJS locus other than *LKB1*. A search for promoter mutations in 33 PJS patients without an identifiable *LKB1* mutation was negative, and *LKB1* mutation mosaicism has never been described [37]. Three lines of evidence support the hypothesis that there is another PJS locus in addition to *LKB1*. First, there are three PJS families reported that do not show linkage to the *LKB1* locus and one PJS family with linkage to 19p13.4 [38, 39]. In the 19p13.4 family, analysis of four genes at 19q13.4 did not identify a mutation [40]. Second, *LKB1* sequencing has been able to identify a mutation in only 75 % of patients with a diagnosis of PJS (Table 9.1). Finally, a chromosomal translocation at the previously identified 19p13.4 locus was identified in a PJS-type polyp taken from a 6-day-old PJS patient [41]. Despite this data, identification of a second PJS locus has been elusive, and no mutations have been found in any of the genes investigated. These include genes whose protein products interact with LKB1 (*STRAD25*, *MO25*, *BRG1*, *LIP*), proteins activated by LKB1 (MARK family of microtubule associated kinases), and candidate genes identified in mouse models (*CDX2*) [40, 42–45].

LKB1 in Normal Physiology

LKB1 complexes with STE-20 related adaptor (STRAD) and mouse protein 25 (MO25). STRAD is an inactive pseudokinase and MO25 is an armadillo repeat scaffolding protein. The catalytic activity of LKB1 increases when bound to STRAD, and when LKB1 is complexed with STRAD/MO25, it is sequestered in the cytoplasm [35].

LKB1 functions are mediated through at least 13 downstream kinases that LKB1 activates by phosphorylation of threonine residues in a lysine-X-threonine motif (AMPK, MARK1, MARK2, MARK3, MARK4, NUAK1, NUAK2, BRSK1, BRSK2, QIK, QSK, SIK, MELK) [46]. The most well-described functions of LKB1 are as a sensor and regulator of cellular energy and in establishing cellular polarity. In stress conditions such as hypoglycemia or hypoxemia LKB1 down regulates protein synthesis. The measure of energy availability that activates LKB1 is an increased AMP/ATP ratio. When activated, LKB1 phosphorylates AMPK, which in turn down regulates the mammalian target of rapamycin (mTOR) pathway through tuberin (*TSC2*) [47].

LKB1 has also been shown to have a role in cellular polarity in cell systems, *Drosophila*, *Caenorhabditis elegans*, and mouse oocytes. Experiments in cell systems have shown that activation of LKB1 by inducing STRAD causes the formation of an apical brush border and that LKB1 is necessary for mammalian brain axonal polarization [48–50]. Mutations in the *Drosophila* homolog of LKB1, AMPKα, result in the loss of epithelial cell polarity [51]. Limited data support a role for LKB1 orthologs in the development of asymmetry in *C. elegans* and in mouse embryogenesis [52, 53].

Lkb1-Deficient Mouse Models

Lkb1-/- mice die in utero between 8.5 and 9.5 days post coitum [54–57]. These embryos have abnormal placental development, neural tube defects, vascular malformations, and a hypoblastic or absent first brachial arch [56].

Lkb1+/- mice recapitulate the human polyp phenotype. By 6.5 months of life they have developed hamartomatous polyps of the stomach; most are at the pylorus (Fig. 9.7) [58]. They have a median life expectancy of 14 months. Histologically, polyps from *lkb1*+/- mice consist of mucus, pyloric gland epithelium, and arborization of connective tissue similar to the unique smooth muscle arborization seen in human PJS polyps (Fig. 9.8). Unlike human PJS patients, *lkb1*+/- mice rarely have small bowel polyps and do not have colon polyps or develop gastrointestinal, pancreatic, breast, or other carcinomas.

After 50 weeks of life, some *lkb1*+/- mice do develop hepatocellular carcinoma (HCC) [59]. Analysis of the HCCs in these mice identified LOH at the *lkb1* locus. *Lkb1*-/+ mice have been crossed onto COX-2 and P53 deficient backgrounds showing decreased and increased neoplasia, respectively [58, 60, 61].

It has recently been reported that 12 *lkb1*+/- asymptomatic mice sacrificed at 300 days all had asymptomatic osteogenic tumors of the vertebral column [62].

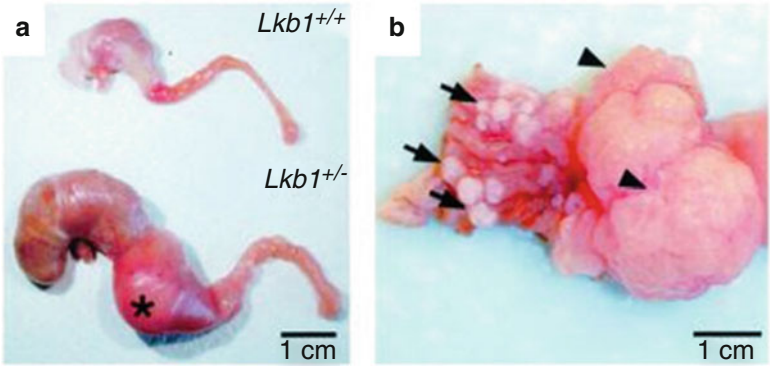


Fig. 9.7 Panel (**a**) *above*, control mouse stomach and proximal small intestine; *below*, distended stomach of the *lkb1*+/- mouse. Panel (**b**) Pyloric polyps in *lkb1*+/- mouse (*arrows*). Reproduced from Rossi and others, Proc Natl Acad Sci USA 2002: 12327–12332

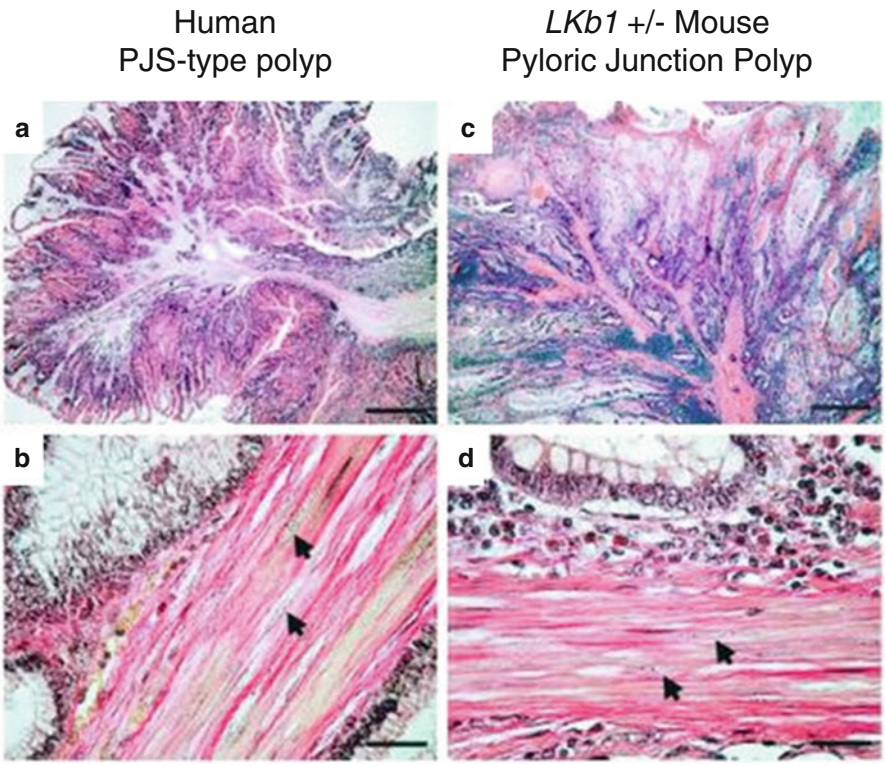


Fig. 9.8 Panels (**a**) and (**b**) are low and high power microscopic views, respectively, of a PJS-type polyp from a PJS patient. Panels (**c**) and (**d**) are low and high power microscopic views, respectively, of pyloric junction polyp from an *lkb1+/-* mouse. *Arrows* in panels (**b**) and (**d**) indicate smooth muscle nuclei. Reproduced from Rossi and others, Proc Natl Acad Sci USA 2002: 12327–12332

Hypomorphic Lkb1 mice ($Lkb^{fl/fl}$) have been created that express 10 % of the normal amount of Lkb1. These mice do not develop tumors or polyps [63].

Neoplasia in Peutz-Jeghers Syndrome

Cancer Paradigm: Two Hits or One?

The paradigm for neoplasia in familial cancer syndromes is the two-hit model (Knudsen hypothesis) [64]. The first hit is inherited as a germline mutation, and the second hit occurs by chromosomal deletion (LOH), chromosomal rearrangement, hypermethylation, or somatic mutation. PJS differs from other familial cancer syndromes in that there is data supporting both a one-hit (haploinsufficiency) and two-hit model. Data supporting the one-hit model includes that there is no LOH of

Table 9.2 Loss of heterozygosity at the *LKB1* locus in Peutz-Jeghers syndrome-associated polyps and cancers

Reference	LOH in PJS polyps	LOH in PJS cancers	Notes
De Leng et al. [84]	7/22	8/22	
Enitus et al. [102]	15/39	5/5	
Miyaki et al. [68]	19/27	1/1	
Nakanishi et al. [197]	–	1/1	Single breast cancer
Nakamura et al. [211]	–	1/1	Single duodenal cancer
Wang et al. [212]	1/4	7/11	
Gruber et al. [78][a]	8/9	3/3	
Total[a]	50/101 (50 %)	27/45 (60 %)	

[a]Gruber et al. reported results for polyps and carcinomas as a single group. Combined results were LOH in 11 of 12 PJS polyps or carcinomas. In calculations of totals using results from Gruber et al., it was assumed that 8 of 9 polyps had LOH and 3 of 3 cancers had LOH

lkb1 and 50 % Lkb1 expression in *lkb1*+/- mouse polyps, LOH at the *LKB1* locus is seen in only some human PJS polyps, and smooth muscle limited *Lkb1* mouse knockouts have the same polyp formation regardless if one or both *lkb1* alleles are knocked out [54, 65].

Some data from human PJS patients supports the two-hit model. Immunohistochemistry studies of PJS polyps show some have a complete loss of LKB1 staining, and *LKB1* LOH is seen in about 50 % of PJS polyps and cancers studied (Table 9.2) [66, 67]. In the polyps without LOH there is evidence that either somatic mutations or hypermethylation are the second hit in some cases. In a study of 27 PJS polyps, 19 had LOH of *LKB1*, 5 had somatic mutations of *LKB1*, and 3 had neither [68]. In the only study of *LKB1* hypermethylation, 4 of 22 PJS polyps showed *LKB1* hypermethylation [69].

Precursor Lesions and Pathways (Hamartoma → Carcinoma Sequence)

Cancer precursors and pathways have only been well studied for intestinal cancer in PJS. The canonical precursor for cancer in PJS is the PJS hamartomatous polyp, and the canonical pathway for intestinal cancer in PJS is the hamartoma → carcinoma sequence (hamartoma → low grade dysplasia → high grade dysplasia → carcinoma). The hamartoma → carcinoma sequence also proposes that with each histological step toward carcinoma there are corresponding cumulative molecular events (e.g., *KRAS* mutations followed by *APC* mutations). This pathway is analogous to the adenoma → carcinoma sequence for sporadic colorectal neoplasia (Vogelstein paradigm).

The histological evidence supporting the hamartoma → carcinoma sequence includes reports of cancer developing in hamartomatous PJS polyps and no reports of cancer not associated with polyps. Also, dysplasia in PJS polyps is only seen in larger polyps which would agree with hamartoma → carcinoma sequence hypothesis that as polyps become larger there are more molecular events leading to the

development of cancer. Many reports have followed the initial report of cancer in a PJS polyp in Peutz's original description, and a 1994 review identified 24 reports in 20 patients [7, 8, 70–75]. Other than data showing somatic inactivation of LKB1 (reviewed above), there is little molecular data supporting the underlying cumulative molecular events presumed to be the basis of the hamartoma → carcinoma sequence.

An alternative theory to the hamartoma → carcinoma sequence was put forward by the authors of papers in 2006 and 2007 [76, 77]. The authors proposed that PJS polyposis occurs through loss of cellular polarization and is not the result of cumulative genetic events as seen with sporadic colon polyps or the polyps of other colorectal familial cancer syndromes. They propose carcinogenesis in PJS occurs by well-established pathways, probably the Wnt/APC/β-catenin pathway, and is unrelated to events causing hamartomatous polyposis. Data supporting this hypothesis comes from their study of polyps from two PJS patients. The polyps were found by them to be polyclonal with an expanded progenitor zone. The authors interpret the polyclonality of the polyps as not supporting hamartoma → carcinoma sequence, as polyps progressing through a pathway would be monoclonal, and they speculate that the expanded progenitor zone indicates asymmetrical cell division as the pathway for carcinogenesis in PJS.

Molecular Pathways (Wnt/APC/β-Catenin, DNA Mismatch Repair and COX-2)

It is unclear whether the molecular pathways involved in other familial cancer syndromes are also involved in PJS. PJS polyps do not have evidence of DNA mismatch repair defects as seen in Lynch syndrome [78]. *APC* somatic mutations and *APC* LOH with resulting nuclear β-catenin accumulation are characteristic of familial adenomatous polyposis (FAP) [79]. Somatic APC inactivation as a result of LOH or somatic mutations is rare in PJS (Table 9.3). Two of three studies of β-catenin nuclear accumulation in PJS polyps have found abnormal accumulation (Table 9.4).

Table 9.3 *APC* mutations and 5 q loss of heterozygosity in Peutz-Jeghers syndrome polyps and cancers

Reference	PJS polyps		PJS cancers	
	5 q LOH	*APC* mutations	5 q LOH	*APC* mutations
De Leng et al. [84]	–	0/22	–	2/11
Entius et al. [213]	–	12/12	–	4/5
Miyaki et al. [214]	0/27	0/27	–	–
Gruber et al. [78][a]	0/9	–	0/9	–

[a]For Gruber et al. results for polyps and carcinomas were not reported separately. In calculations of totals using results from Gruber, the assumption was that 9 were polyps and 9 were cancers

Table 9.4 Nuclear β-catenin in Peutz-Jeghers syndrome polyps and cancers

Reference	PJS polyps	PJS cancers
De Leng et al. [84]	4/22	5/11
Back et al. [213]	12/12	–
Herter et al. [215]	0/6	–
Total	16/40 (40 %)	5/11 (46 %)

Table 9.5 COX-2 expression in Peutz-Jeghers syndrome polyps

Reference	PJS polyps with COX-2 over expression
Wei et al. [67]	28/33
Rossi et al. [216]	16/23
McGarrity et al. [217]	7/11

Of the several downstream pathways of LKB1, it has not been possible to conclusively isolate which if any of them are responsible for PJS-associated neoplasia. Knockout mice of two of the downstream kinases activated by LKB1, AMPK α1/α2, and Emk/Park-1 (mouse homolog of LKB1 target MARK2), have not reproduced the PJS phenotype [80–82]. As noted above, LKB1 is a proximal member of the mTOR pathway, and treatment of *lkb1*+/- mice with the mTOR inhibitor rapamycin has been shown to suppress polyp formation [83].

Investigations in PJS patients and the *lkb1*+/- mouse show a role for COX-2 in PJS neoplasia. COX-2 is over expressed in 60–80 % of PJS polyps (Table 9.5). One study showed COX-2 expression correlated with dysplasia, 24 % of hamartomas compared to 64 % of carcinomas having moderate or strong COX-2 expression [84]. Another study found a correlation between COX-2 and LKB1 staining in PJS polyps [67]. Crossing *lkb1*+/- mice onto a *COX-2-/+* or *COX-2-/-* background or treating them with a COX-2 inhibitor decreases polyp burden [61]. In the only study of chemoprevention in PJS patients, six patients were treated for 6 months with celecoxib 200 mg twice daily [61]. Two of six patients met the primary endpoint of a decrease in gastric polyps as assessed by endoscopy.

Pathology

PJS-type intestinal polyps are disorganized normal tissue (*hamartomas*). PJS-associated polyps can be differentiated from sporadic hamartomatous polyps and hamartomatous polyps associated with other syndromes by a unique smooth muscle core that arborizes throughout the polyp (Fig. 9.9). PJS-type polyps do not have specific endoscopic features and can only reliably be distinguished from other types of polyps by histopathology.

The unique PJS polyp pathology is best appreciated in PJS small intestine polyps [85]. The histopathology of PJS-associated gastric polyps can be similar to hyperplastic

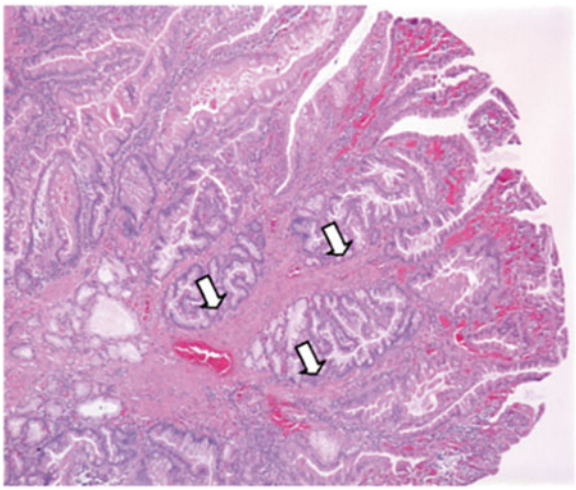


Fig. 9.9 PJS-type polyp histology. Note the arborizing smooth muscle architecture unique to PJS-type intestinal polyps (*arrows*). See also Figs. 9.10, 9.11, and 9.12

gastric polyps. Mucosal prolapse colon polyps can have a smooth muscle core similar to the one seen in PJS-associated polyps. A few PJS patients have been reported to also have adenomatous and hyperplastic polyps, and there is one case report of osseous metaplasia of PJS-type polyps [26, 86, 87].

Pseudo-Invasion

The epithelium of PJS polyps can invade into the wall of the intestine without transforming into cancer (Figs. 9.10, 9.11, and 9.12) [88, 89]. This is termed *pseudo-invasion*. Pseudo-invasion can mimic malignant invasion and has been misdiagnosed as small intestine cancer. It has been reported only in PJS small intestine polyps and not in PJS colon or stomach polyps [90]. In a review of PJS-type polyps at St. Mark's Hospital, 10 % had pseudo-invasion [90].

Sporadic Peutz-Jeghers-Type Polyps not Associated with PJS

Sporadic PJS-type polyps not associated with PJS are rare. Only 12 sporadic PJS duodenal polyps have been reported [91]. A study of 121 PJS-type polyps at Johns Hopkins Hospital was unable to definitively identify a patient with a PJS-type polyp who did not have PJS [85]. At the Cleveland Clinic, over a period of approximately 20 years, eight patients with solitary PJS-type polyps were identified. On follow-up, none of these patients developed features of PJS, although one patient died of colon cancer 12 years after identification of the solitary PJS polyp.

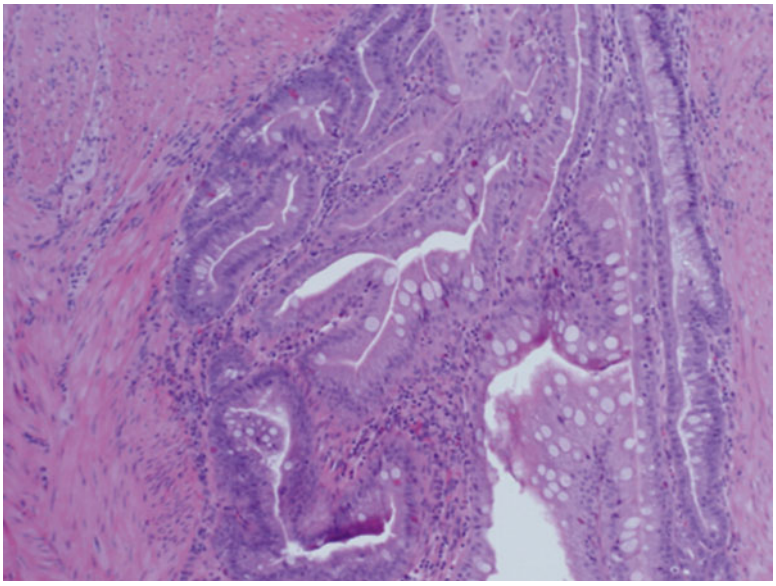


Fig. 9.10 High power microscopic view of a PJS-type jejunal polyp with pseudo-invasion. *Arrow* indicates an area of low grade dysplasia. For lower power views see Figs. 9.11 and 9.12

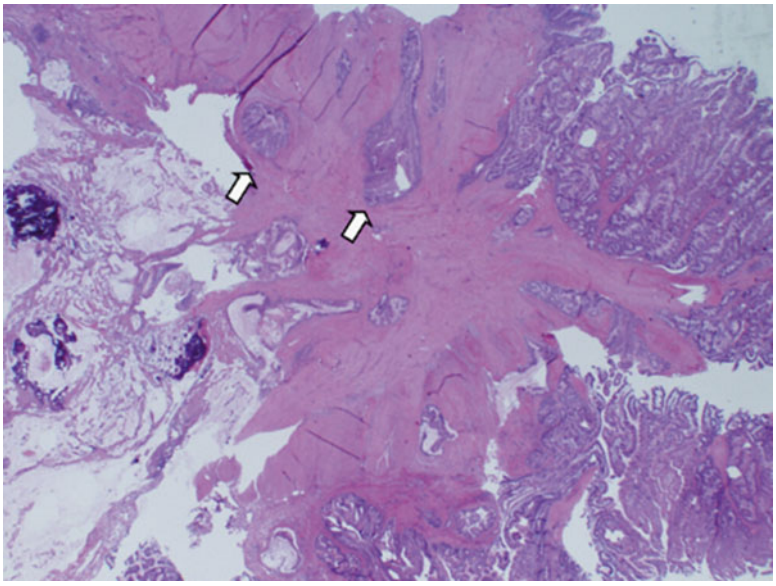


Fig. 9.11 Low power microscopic view of a PJS-type jejunal polyp with pseudo-invasion. *Arrows* indicate hamartomatous small intestine mucosa in the intestinal wall. See also Figs. 9.10 and 9.12

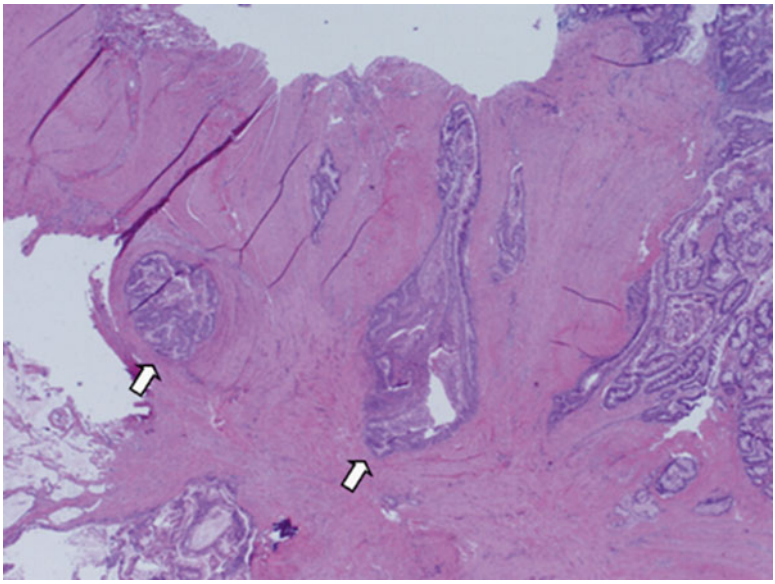


Fig. 9.12 Medium power microscopic view of a PJS-type jejunal polyp with pseudo-invasion. *Arrows* indicate hamartomatous small intestine mucosa in the intestinal wall. See also Figs. 9.10 and 9.11

The most common location for sporadic PJS-type polyps is the colon, followed by the rectum and the duodenum. Patients typically present later in life; in one study the mean age of presentation was 55 years [92]. The malignant potential of sporadic PJS-type polyps is unknown. Two sporadic PJS-type polyps have been reported to have a focus of adenocarcinoma [91, 93]. The authors recommend that all patients with a solitary PJS-type polyp be evaluated for PJS.

Melanotic Macules

PJS MMs have increased basal pigmentation and melanocytes with long pigment-filled dendrites [94]. Electron microscopy has shown a blockage in pigment transfer from melanocytes to keratinocytes in MMs of the fingers and toes [95].

Diagnosis

PJS is a clinical diagnosis based on MMs, PJS-type intestinal polyps, and family history. Genetic testing is usually not necessary (see *LKB1 Genetic testing in the diagnosis and management of Peutz-Jeghers Syndrome*). There is no consensus or society-endorsed diagnostic criteria. Table 9.6 shows the diagnostic criteria used at Mayo Clinic and that of Tomlinson and Houston.

Table 9.6 Diagnostic criteria for Peutz-Jeghers syndrome

Mayo Clinic
A diagnosis of PJS can be made
In patients **without** a family history of PJS if either of the following are present:
• characteristic melanotic macules and one or more intestinal polyps with PJS-type histology, or • two intestinal polyps with PJS-type histology
In patients **with** a family history of PJS in a parent or sibling, if any of the following are present:
• characteristic melanotic macules, or • one intestinal polyp with PJS-type histology, or • an *LKB1* mutation
Tomlinson and Houston [130]
A diagnosis of PJS can be made if there are
• two or more intestinal polyps with PJS histology, or • one intestinal polyp with PJS-type histology with either typical melanotic macules or a family history of PJS, or • a family history of PJS and characteristic melanotic macules

PJS Peutz-Jeghers Syndrome

Clinical Genetics

LKB1 Mutations in PJS Patients

Approximately 75 % of PJS patients have identifiable mutations in *LKB1* (Table 9.1). Two-thirds of mutations are detectable by sequencing and one-third by MLPA. A review of 145 germline PJS *LKB1* mutations found that 34 % were deletions, 21 % missense, 14.5 % insertions, 12 % nonsense, 14 % splice site, and 4.5 % deletions/insertions, inversions, genomic rearrangements, and others [96]. One PJS family with a complete deletion of *LKB1* has been reported [97]. Seven percent of PJS families have been found to have either a 1-bp deletion or 1-bp insertion in a 6-cysteine repeat mutation hotspot (c.837–c.842) [13, 96].

A higher proportion of PJS patients has new mutations and no family history than do patients with other inherited cancer syndromes. The percentage of PJS patients without a family history is about 45 % [98]. For comparison, only 15 % of FAP patients do not have a family history. The reason for the high degree of new mutations in PJS is probably the low reproductive fitness of PJS patients prior to the introduction of effective treatment for intussusception.

LKB1 Genetic Testing in Diagnosis and Management

LKB1 genetic testing plays a limited role in the diagnosis and management of PJS patients (see *Diagnosis*). As 25 % of confirmed PJS patients will have a negative genetic test, a clinical diagnosis of PJS stands even when genetic testing is negative.

As there are no clinically significant genotype/phenotype correlations, a positive or negative genetic test does not change management.

Molecular diagnostic laboratories advertise *LKB1* testing for PJS, including sequencing of coding regions, deletion/duplication testing by MLPA, linkage analysis, prenatal and preimplantation testing. A list of laboratories offering *LKB1* testing can be found at www.geneclinics.org. *LKB1* genetic testing can be difficult to coordinate and is expensive (>1000 US$).

Genotype/Phenotype Correlations

LKB1/PJS genotype/phenotype correlations are of great interest as they could allow for targeted cancer surveillance. Unfortunately, no clinically significant genotype/phenotype correlations for *LKB1*/PJS have been identified. A review of the largest cohort of PJS patients to date, 416 patients, found a nonsignificant trend for increased cancer risk in patients with truncating mutations as compared with nontruncating mutations [28]. Other reports of genotype/phenotype correlations have included an association between *LKB1* exon six mutations and increased cancer risk, an increased risk for bile duct cancer in patients without detectable mutations, and no genotype/phenotype association [99–101].

A somatic mutation/phenotype correlation for cancer has been reported. Enius and others found that polyps from PJS patients with cancer had a higher proportion of LOH at the *LKB1* locus than PJS patients without cancer [102]. Studies are contradictory on the presence of a genotype/phenotype correlation for intussusception in PJS [103, 104].

Penetrance, Expressivity, Mosaicism, and Modifiers

PJS is highly penetrant with variable expression. Only one case of nonpenetrance of an *LKB1* mutation has been reported [38]. Almost all PJS patients will display the two cardinal features of the disease (MMs and PJS-type intestinal polyps) and most will develop a PJS-related cancer (Fig. 9.13). There is significant variability in the timing and extent of the MMs, polyps, and cancers[1] (Tables 9.7 and 9.8, and Fig. 9.14). Germline or somatic mosaicism of *LKB1* mutations has not been reported, and no genetic or environmental modifiers of the *LKB1*/PJS phenotype have been identified.

[1] "… for each living being has his own individual peculiarities and whatever his disease it must be necessarily peculiar to himself – a new and complex malady unknown to medicine …"—*War and Peace*, Leo Tolstoy.

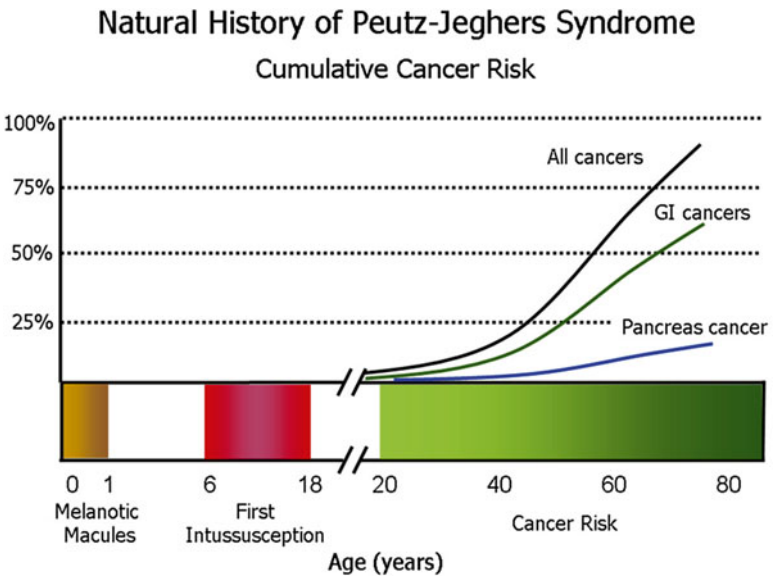


Fig. 9.13 A graphical representation of the natural history of Peutz-Jeghers syndrome. Most patients will develop melanotic macules during the first year of life and a patient's first intussusception usually occurs between the ages of 6 and 18 years old. Cumulative lifetime cancer risk begins to rise in middle age. Cumulative risks by age 70 for all cancers, gastrointestinal (GI) cancers, and pancreatic cancer are 85 %, 57 %, and 11 %, respectively

Table 9.7 Intra- and inter-familial variability of Peutz-Jeghers syndrome

Kindred	Age at onset of MMs (years)	Age at onset of abdominal symptoms (years)	Status and notes
Peutz	First months	25	Dead, 50, breast cancer
Pedigree [32][a]	"Young age"	17	Dead, 40, colon cancer
	<1	<24	Dead, 40, squamous cell carcinoma of the nasopharynx
	2 years	8	Dead, 70, peritonitis
	<1	6	Dead, 30, gastrointestinal adenocarcinoma
	<1	<10	Dead, 70, pneumothorax
	First weeks	15	Living, 60
Harrisburg	–	–	Dead, 40, gastric adenocarcinoma
Family [218][a]	–	8	Dead, 29, metastatic adenocarcinoma
	–	20	Living, 68
Syracuse	Present at 8	–	Living, 26
Pedigree [147]	Present at 2	17	Living, 29
	Present at 2	19	Living, 28
	Present at 3	3?	Living, 30, SCTATs
	Present at 6	–	Living, 33
	Present at 12	12	Dead, 38, breast cancer age 36, jejunal adenocarcinoma 38
	Present	19	Dead, 19, acute peritonitis of unknown cause
	Present		Dead, 63, breast cancer

[a]Some family members not included. Also see Fig. 9.14 for graphical representation of data. *MMs* melanotic macules. *SCTATs* sex cord tumor with annular tubules

Table 9.8 Youngest and oldest reports of cancer in Peutz-Jeghers syndrome patients

Cancer	Youngest reported case in a PJS patient (years)	Oldest reported case in a PJS patient (years)
Bile duct (cholangiocarcinoma)	6 [130]	–
Colorectal	10 [219]	71 [175][a]
Small intestine	21 [175][a]	84 [175][a]
Stomach	13 [70]	61 [175][a]
Breast	19 [175][a]	57 [147]
Pancreatic	16 [220]	91 [221]
Invasive large cell calcifying Sertoli cell tumor of the testis	1 year, 7 months old [222]	14 [223]
Lung	41 [175]	70 [175]

[a]Secondary reference. *PJS* Peutz-Jeghers syndrome

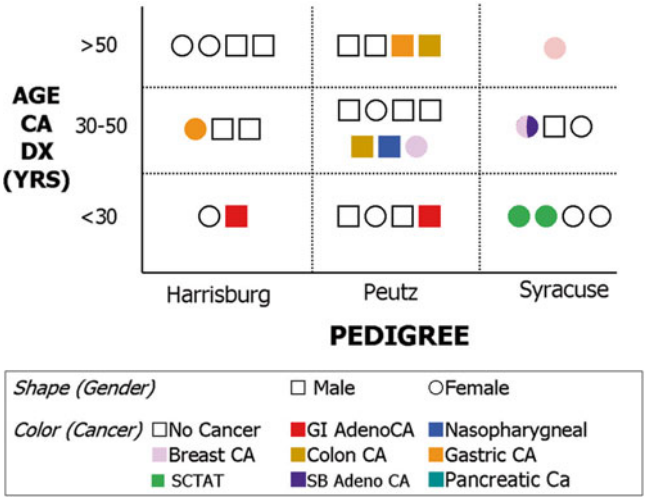


Fig. 9.14 Cancer diagnosis in three well-described Peutz-Jeghers syndrome families. Some family members who died at a young age from causes other than cancer are not included. See Table 9.7 for source data

Natural History

Overview

MMs usually develop on the lips by the end of the first year of life and are almost always present by 5 years of age (Fig. 9.1, 9.2, and 9.3) [32]. Unless a family history of PJS is present, the MMs are usually interpreted as freckles and a diagnosis of PJS is not made.

Between the ages of 6 and 18 years most PJS patients will present with symptoms of obstruction due to small intestine intussusception. Some patients will present subacutely with intermittent bouts of abdominal pain while others present emergently with severe abdominal pain, nausea, and vomiting. Most patients will undergo surgery at their initial presentation with abdominal pain, often before the diagnosis of PJS is made. Rarely patients will initially present with rectal bleeding or a prolapsing rectal polyp [105].

Almost all PJS patients will be diagnosed with one or more cancers during their lives, usually in middle age or later. There is no current data available on the long-term survival of PJS patients. In a report of 72 PJS patients published in 1989, 48 % had died from cancer by the age of 57 years [25]. A study of the psychosocial impact of PJS found patients had mild depression but did not feel physically impacted by PJS [106].

Melanotic Macules

Melanotic macules (MMs) on and around the lips are a cardinal feature of PJS (Figs. 9.1, 9.2, and 9.3). They can also be seen on the buccal mucosa, surrounding the eyes and ears, on the tips of the dorsal surface of fingers and toes, on the eyelids, and surrounding the anus and genitals. In a Japanese cohort, 94 % of patients had MMs surrounding the lips, 65 % on the buccal mucosa, 73 % on the finger tips, 62 % on the toe tips, and 21 % on other locations [7].

The facial distribution of the MMs is the inverse to that of freckles (ephilides); they have been referred to as *ephilides inversae* [107]. PJS MMs also can be distinguished from freckles by their presence on the buccal mucosa and hard palate. The macules are usually 1–5 mm in diameter and vary in color from “ink black” to dark chocolate to latte (Fig. 9.1 caption [16]).

MMs typically develop on the lips by the end of the first year of life and are almost always present by 5 years (Table 9.7) [32]. They are rarely present at birth [108]. In puberty and adulthood PJS MMs fade and in many cases can disappear. Therefore, the absence of MMs in an adult patient presenting for PJS evaluation should not rule out the diagnosis of PJS. There is wide variation between patients in the distribution, intensity, and timing of appearance and disappearance of the macules.

A few PJS patients will not have MMs at anytime. In a series of 170 PJS patients, there were two cases of PJS with documented *LKB1* mutations without MMs [84]. Possible explanations include incomplete expressivity, slightly noticeable pigmentation in childhood that was not noted and then faded, or mosaicism.

PJS-associated MMs can be removed for cosmetic reasons with laser treatment [109–111]. MMs associated with PJS have never been reported to develop into melanoma or other malignancy. Two patients with PJS have been diagnosed with melanoma not associated with a melanotic macule [112, 113]. MMs have been reported in the psoriatic plaques of PJS patients with psoriasis [94, 114].

Laugier-Hunziker syndrome (LHS) and isolated mucocutaneous melanotic pigmentation (IMMP) patients can have MMs on the lips similar to PJS. LHS can be differentiated from PJS by a later onset of pigmentation in adulthood, pigmentation of the finger nails (longitudinal melanonychia), and lack of family history [115]. LHS is not associated with an increased risk of cancer or PJS-type intestinal polyps. The etiology of LHS is unknown; sequencing of *LKB1* in a patient with LHS did not identify a mutation [115]. IMMP patients have PJS-type MMs without any PJS-associated polyps, malignancies, or *LKB1* mutations. Female IMMP patients have an increased risk for gynecological cancers [116].

For discussion of the pathology of MMs see *Pathology*.

Nasal Polyposis and Other Sites of Extra-Intestinal Polyps

Nasal Polyposis and Nasopharyngeal Carcinoma

A study found nasal polyps in 15 % of PJS patients studied (8 of 52) [117]. Six of 22 members of the original Peutz pedigree have been diagnosed with nasal polyposis [32]. Three PJS patients with nasopharyngeal carcinoma have been reported [32, 99].

Nasal polyposis has been molecularly confirmed as a manifestation of PJS by LOH at the *LKB1* locus in the nasal polyps of PJS patients [118]. A comparative histological study of PJS-associated nasal polyps and sporadic nasal polyps found fewer eosinophils in the PJS polyps [117]. In the same study, 11 of 12 PJS-associated nasal polyps were found to express COX-2 compared with 19 of 28 sporadic nasal polyps.

There are no published recommendations for the surveillance and management of PJS nasal polyps. St. Mark's Hospital, Johns Hopkins Hospital, and Mayo Clinic Florida PJS management protocols do not recommend routinely evaluating PJS patients for nasal polyps. PJS patients with sinus obstruction caused by polyps have been treated with surgery [119, 120].

Gallbladder and Bile Duct Polyps and Cancer

In a series of 72 PJS patients, three (4.1 %) had gallbladder polyps [11]. Also reported are one PJS patient requiring cholecystectomy for gallbladder obstruction by polyps and one PJS patient with common bile duct obstruction by polyps [121, 122]. Two PJS patients with gallbladder cancer have been reported; one had gallbladder cancer arising near but not in hamartomatous gallbladder polyps [7, 123]. Several PJS patients have been reported with bile duct cancer (cholangiocarcinoma) [89, 100].

There are no published recommendations for the surveillance and management of PJS gallbladder and common bile duct polyps. We recommend that gallbladder polyps greater than 10 mm be removed by cholecystectomy. Smaller gallbladder polyps should be monitored at 3 and 6 months after diagnosis, and if stable then yearly.

Rare Sites of Extra-Intestinal Polyps in PJS Patients

Hamartomatous polyps in PJS patients have also been reported in the ureter [124], respiratory tract [125, 126], and on the tonsils [127].

PJS-Type Polyps

PJS patients have polyps throughout the gastrointestinal tract. The jejunum is the most common location, followed by the ileum, colon, rectum, stomach, duodenum, appendix, and esophagus (Figs. 9.15, 9.16, 9.17, 9.18, and 9.19) [128]. Some patients may develop thousands of small polyps carpeting the small intestine, others only a handful of polyps. The natural history of PJS-type polyps has not been well studied. From the authors' and anecdotal experience, polyp growth is erratic, with polyps remaining the same size for many years. Some polyps may regress or autoamputate and spontaneously pass [7]. The pathology and surveillance regimens for PJS-type polyps are discussed separately (*Pathology, Small intestine polyp and cancer surveillance*).

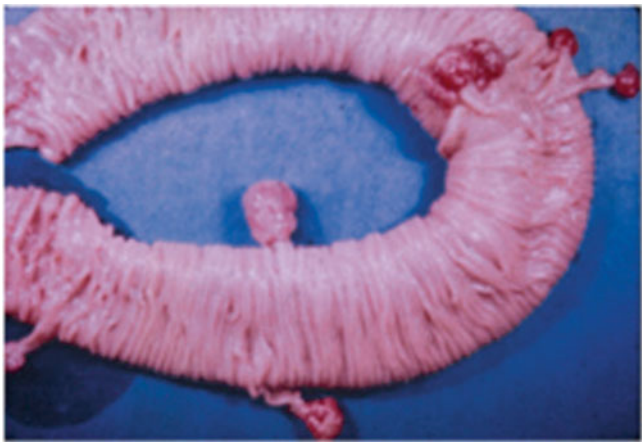


Fig. 9.15 Section of jejunum removed from a Peutz-Jeghers patient at surgery with multiple pedunculated polyps. Courtesy of Victor McKusick, MD, Johns Hopkins Hospital

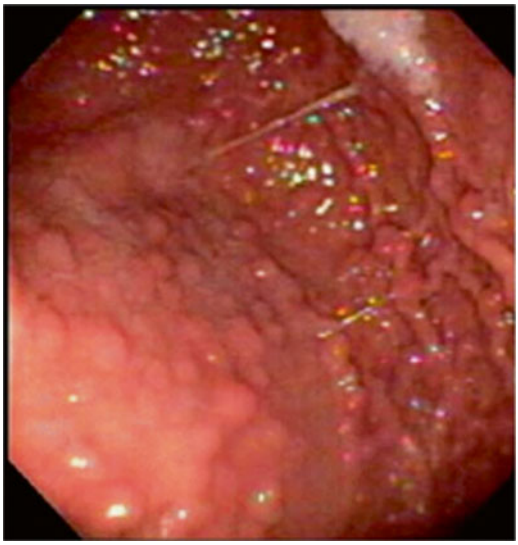


Fig. 9.16 Stomach polyps in a Peutz-Jeghers syndrome patient

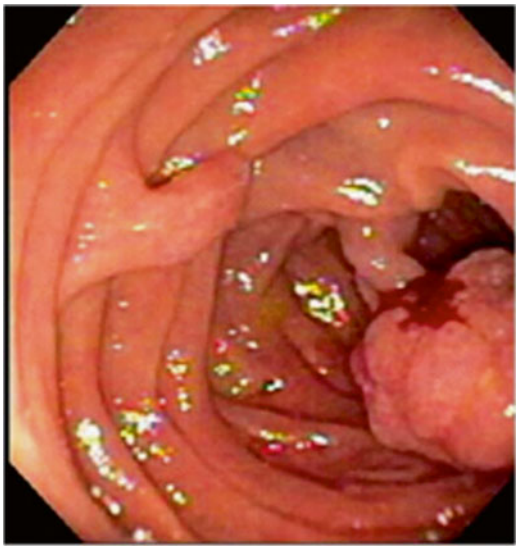


Fig. 9.17 Duodenal polyp in a Peutz-Jeghers syndrome patient

PJS polyps should be removed before they cause intussusception/obstruction, develop dysplasia, or become too large to remove endoscopically. Polyps occurring in the stomach, duodenum, and colon are easily reached and removed by standard endoscopy. The authors recommend polyps in these areas usually be removed. Small intestine PJS polyps can be much more difficult, if not impossible, to remove by endoscopy. Therefore, a cutoff for which small intestine polyps to invest the resources to attempt to remove has great clinical importance.

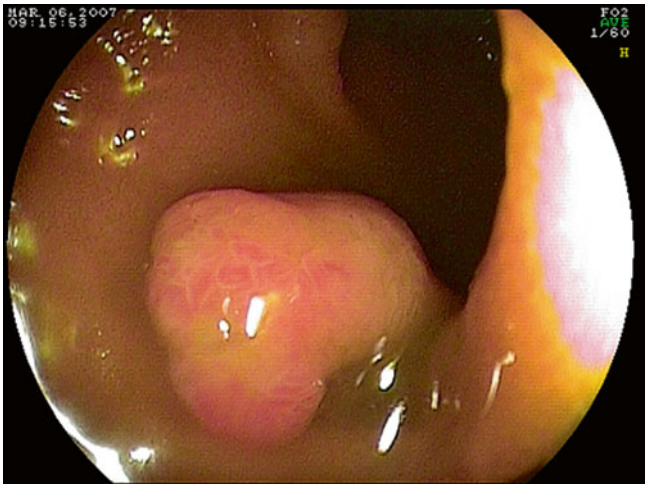


Fig. 9.18 Ileal polyp in a Peutz-Jeghers syndrome patient

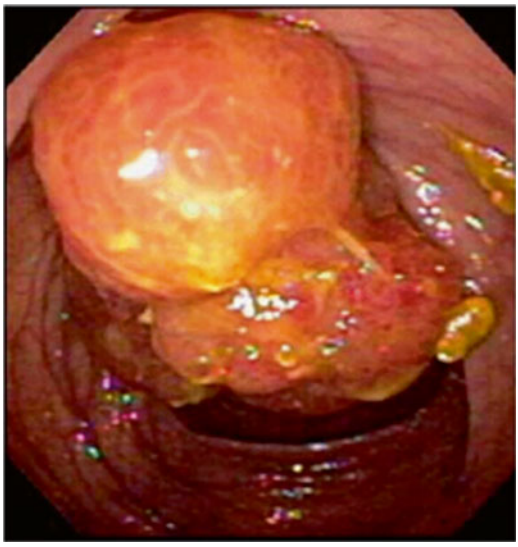


Fig. 9.19 Colon polyp in a Peutz-Jeghers syndrome patient

The first proposed cutoff for small intestine polyp removal was 1.5 cm, proposed in 1994 by the Danish polyposis registry [129]. Further reports have expanded the cutoff range to between 1.0 and 1.5 cm [76, 129, 130]. In the authors' experience, the 1.5 cm cutoff is appropriate. Small intestine polyps rarely intussuscept in adults until they are larger than 1.5 cm, dysplasia is rare until polyps are larger than 3.0 cm, and double balloon endoscopy (DBE) has been used to remove polyps as large as 3 cm. The authors have developed a protocol for management of PJS small intestine polyps using extended endoscopy, DBE, and laparoscopic intraoperative endoscopic polypectomy (Fig. 9.20).

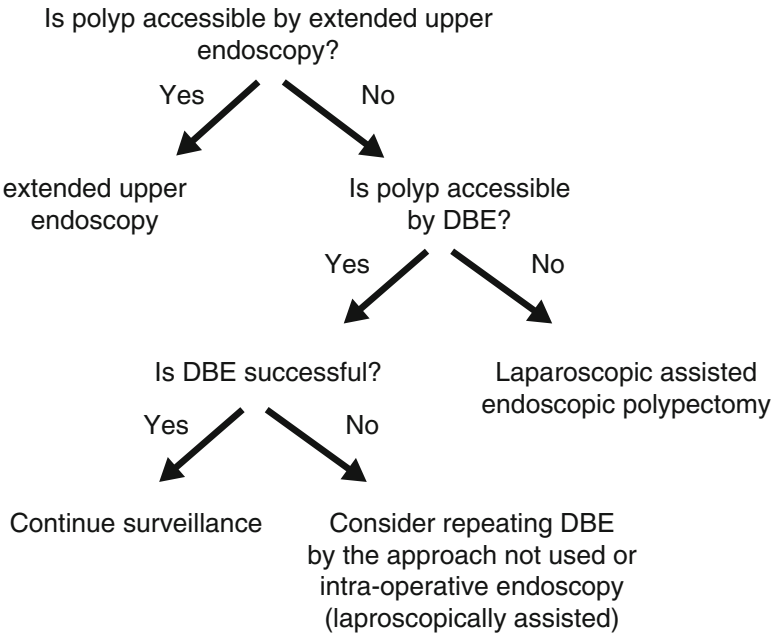


Fig. 9.20 Mayo Clinic Peutz-Jeghers syndrome small intestine polyp management algorithm

Double Balloon Endoscopy

DBE was approved by the US Food and Drug Administration in 2004, and the first DBE procedure for PJS was reported in 2005 [54]. Since then, several case reports or small case series of DBE for the removal of small intestine polyps in PJS patients have been published [131–134]. There is no data on the long-term efficacy of DBE-assisted polyp removal in PJS patients in preventing intussusceptions or cancer.

Pre-DBE imaging with MRI enterography and other small intestine imaging techniques provides the information needed to plan either an antegrade (oral) or retrograde (anal) approach in order to target the largest polyps. The primary objective at DBE is to remove the large polyps inaccessible to standard endoscopy. The authors do not usually remove small polyps (≤5 mm).

The DBE system (Fujinon Inc., Saitama, Japan) consists of a 200-cm long endoscope, an overtube, and a balloon pump controller to inflate and deflate two balloons affixed at the tip of the endoscope and overtube (Fig. 9.21). The objective is to advance and reduce the endoscope and overtube in a repetitive sequential fashion that allows pleating of the small intestine onto the overtube. Yamamoto has published a review of the technical details [135]. The DBE procedure can be performed via the antegrade (oral) or retrograde (anal) approaches without or with intraoperative assistance [136]. The insertion route is selected according to the estimated location of the target polyps based on clinical impression and imaging studies. With antegrade DBE, the scope can usually be inserted to the distal jejunum

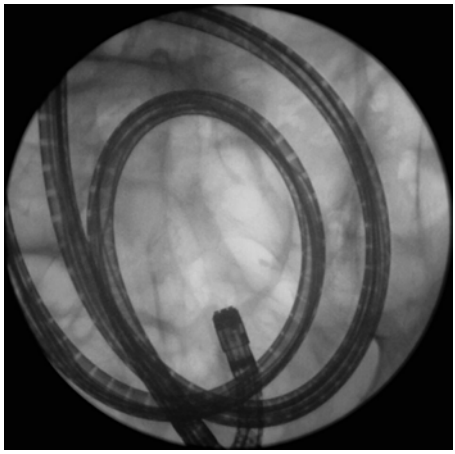


Fig. 9.21 Fluoroscopic image of a retrograde double balloon endoscope at maximum insertion

or proximal ileum. With retrograde DBE, the scope can typically be advanced to the proximal ileum. Using both ante- and retrograde approaches, complete small bowel examination can be performed in 30–60 % of patients [137, 138]. For patients with polyps unresectable by the ante- or retrograde approaches, intraoperative endoscopy with standard or DBE is recommended [136].

DBE is a safe procedure and serious complications are rare. The risk of perforation is approximately 0.5 %. Thirty percent of cases will be complicated by post-procedure abdominal pain, 46 % by asymptomatic hyperamylasemia, and 1 % or less by pancreatitis [139, 140]. Most PJS patients have intra-abdominal adhesions from multiple surgeries. Adhesions can cause sharp intestinal bending, hinder effective small bowel pleating, and limit the depth of insertion. Adhesions may also increase the risk of perforation. The only DBE complication reported in a PJS patient was an intestinal perforation in an infant [141].

Intraoperative Endoscopy

During intraoperative endoscopy the surgeon guides the endoscope through the small bowel and can lyse adhesions blocking the endoscope. These maneuvers increase the reach of the endoscope, and often the entire small bowel can be seen using a combination of antegrade and retrograde approaches. Usually standard endoscopes are used for intraoperative endoscopy, but double balloon scopes have also been used [136].

Intraoperative endoscopy can be used during open or laparoscopic surgery to remove polyps that cannot be removed using standard endoscopy or performed as an additional procedure when abdominal surgery is being performed for another indication. When PJS patients do undergo surgical polypectomy or other abdominal surgical procedures, it is recommended that the opportunity be used to perform a total polyp clearance (“clean sweep”) by intraoperative endoscopy.

Two retrospective studies have confirmed the value of intraoperative endoscopy in PJS patients [142, 143]. In one, 25 PJS patients who underwent small bowel clearance by intraoperative endoscopy had a significantly decreased reoperation rate compared with historical controls [142]. In another, intraoperative endoscopy was superior to palpation for polyp detection, with a median of 12 additional polyps that could not be palpated removed endoscopically.

Intussusception

The distribution of intussusceptions follows the distribution of polyps: jejunum, ileum, and colon. Rare and unusual intussusceptions have also been reported in PJS patients including gastroduodenal intussusceptions [9, 105, 144], double and triple intussusceptions (patients presenting with two or more different intussusceptions at the same time) [1, 105], appendiceal intussusceptions [145–147], and retrograde intussusceptions [144]. Most PJS patients present with an intussusception between the ages of 6 and 18. Patients as young as 15 days old and as old as 35 years have presented with their first intussusception [108, 148].

Symptoms of intussusception include abdominal pain, nausea, vomiting, and bloody stool. PJS patients presenting with symptoms of intussusception should have an emergency evaluation with an abdominal computerized tomography (CT) scan and surgical consultation [149]. Treatment of acute intussusception with intestinal obstruction is surgical. Endoscopic management is not recommended.

The surgical approach is dependent on the location and extent of the intussusception, suspicion for malignancy, and extent of associated inflammation, edema, and ischemia [150]. For the most common intussusception in PJS, jejunal/jejunal by a nonmalignant polyp, the recommended surgical technique is reduction, enterotomy, and polyp resection. After reduction, the base of the polyp that served as the lead point can be identified by a dimple in the wall of the small intestine [7]. The polyp can be removed through a small incision adjacent to the dimple. If there is concern for malignant invasion after the incision is made, the base of the polyp and adjacent small bowel can be excised by extending the initial incision. In the rare case where the lead point of the intussusception is suspected to be a polyp with cancer, reduction should not be performed before the enterotomy is made to prevent dissemination of malignant cells. If possible, intraoperative endoscopy should also be performed to remove other polyps. One group recommends prolapsing the small intestine through the enterotomy incision so that 2 or 3 feet of mucosa can be inspected for polyps [143].

Cancer Risk

PJS patients have an increased risk for cancers of the colon, stomach, small intestine, pancreas, breast, and other organs. The most current and complete data on cancer risk in PJS patients is from a multicenter collaborative series of 416 PJS

patients published in 2006 [28]. The cumulative cancer risk for a PJS patient was 85 % by age 70 (control population risk 18 %). Thirteen percent to 15 % of PJS patients will be diagnosed with two cancers [28, 101].

Rare Cancers that Have a Special Association with PJS

Several cancers have a special association with PJS. In female PJS patients these include a rare tumor of the cervix called adenoma malignum (ADM) and a rare tumor of the ovary known as sex cord tumor with annular tubules (SCTATs). In male PJS patients the corresponding tumors to SCTATs are Sertoli cell testicular tumors. ADM and SCTATs sometimes occur in association with one another; eight patients with both SCTATs and ADM have been reported [151]. Therefore, patients presenting with either SCTATs or ADM should be carefully followed for development of the other.

Adenoma Malignum (ADM)

ADM is a very rare, highly differentiated adenocarcinoma of the endocervical glands. The number of female PJS patients who develop ADM is low, probably 5 % or less. Several large case series of PJS patients have not reported a single case [25]. About 10 % of patients with ADM have PJS [152].

Patients with ADM present with a watery vaginal discharge or vaginal bleeding. Establishing the diagnosis of ADM can be difficult. On examination the cervix has alternatively been described as being normal, having a firm or nodular appearance, or resembling a polypoid mass [153]. Papanicolaou smear or cervical biopsy can be diagnostic in some but not all cases [153]. Imaging studies show multiple cervical cysts [153, 154].

Histologically, ADM closely resembles normal endocervical glands and for this reason it is sometimes referred to as a *minimal deviation adenocarcinoma*. Histological clues to the diagnosis of ADM include an associated desmoplastic response, nuclear atypia, deep invasion of the cervical wall, and identification of a focus of undifferentiated adenocarcinoma. Using a standard criteria for ADM, the diagnosis of ADM has been found to be reproducible between pathologists [155]. Staining with Alcian blue periodic acid Schiff and with the HIK1803 monoclonal antibody to gastric gland mucous cell-mucin endocervical glands has been reported to help make the distinction between ADM and normal endocervical glands [156, 157].

Surveillance for ADM should include a yearly gynecological exam with Papanicolaou smear and pelvic ultrasound (Table 9.9). If the diagnosis of ADM is suspected or confirmed, the patient should be referred to a gynecologic oncology surgeon. In the most recent series of ADM patients, published 5-year survival was 60 % [155].

Sex Cord Tumors with Annular Tubules (SCTATs)

Most female PJS patients of reproductive age have ovarian cysts. It is unclear how many of these represent physiological cysts versus stable SCTATs. The authors estimate about 10 % of female PJS patients will develop SCTATs that require surgery. About one-third of patients with SCTATs have PJS [158].

Histologically, SCTATs are either simple or complex tubules lined by cells with peripherally placed nuclei that surround a hyaline-filled lumen. PJS-associated SCTATs are bilateral, multifocal, often microscopic, and contain focal calcifications. Sporadic SCTATs are large and unilateral. PJS-associated SCTATs have a low malignant potential and a good prognosis. Only two cases of malignant SCTATs have been reported in PJS patients [159, 160].

PJS patients with SCTATs usually present with an asymptomatic adnexal cyst or mass identified by cancer surveillance testing. SCTATs sometimes produce estrogen, causing precocious puberty. Most PJS patients with SCTATs are young. A conservative approach with preservation of fertility and avoidance of surgical menopause is recommended [161]. PJS patients with known or suspected SCTATs should be referred to both a gynecologic oncology surgeon and a reproductive endocrinologist.

Sertoli Cell Testicular Tumors

These tumors probably are the corresponding male tumor to the SCTATs seen in female PJS patients. The authors' experience is that most male PJS patients will have bilateral multifocal testicular calcifications on testicular ultrasound consistent with asymptomatic Sertoli cell testicular neoplasia (Fig. 9.22). These lesions rarely progress to invasive large calcifying Sertoli cell tumors (ILCST), and only six cases of ILCST have been reported in PJS patients [162]. ILCST patients typically present as children with testicular enlargement or prepubertal gynecomasty (ages ranging from 1 to 14 years, Table 9.8) [162]. (Sertoli cells express aromatase, which converts testosterone to an estrogen precursor, causing prepubertal gynecomasty.)

Yearly surveillance with testicular ultrasound for ILCST is recommended (Table 9.9). The authors do not recommend routine testicular biopsy of asymptomatic PJS patients with microcalcifications on testicular ultrasound. Historical treatment has been orchiectomy, but as with SCTATs, given the usually benign nature of these tumors in PJS patients, conservative observation of asymptomatic non-large calcifying tumors is recommended [162]. There is a single report of successful treatment with the aromatase inhibitor anastrozole and use of inhibin-alpha as a tumor marker [163].

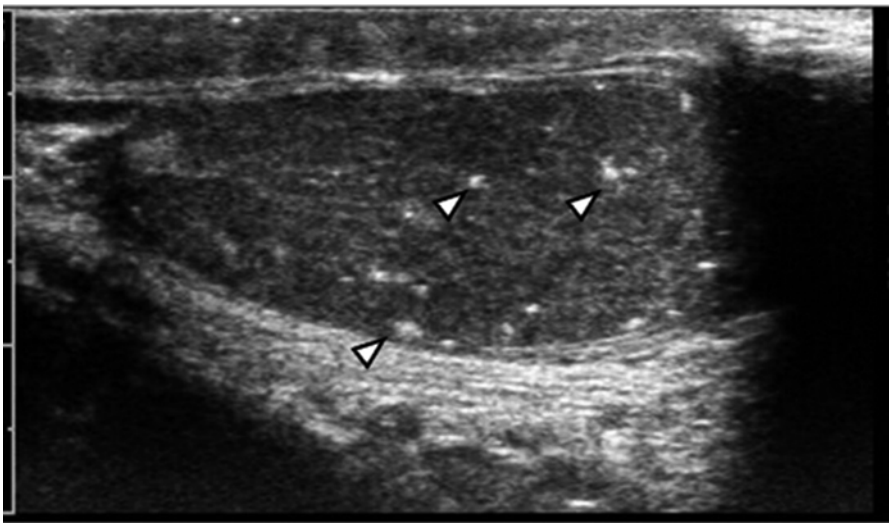


Fig. 9.22 Testicular ultrasound of a PJS patient showing multifocal microcalcifications consistent with Sertoli cell testicular neoplasia

Table 9.9 Peutz-Jeghers syndrome management protocols

Organ	Mayo Clinic (Jacksonville, Rochester, USA)
Multi system and lifestyle modification	Birth. Annual history and physical examination 18 years. Annual hemogram, electrolytes, and hepatobiliary tests. Patients should be counseled on smoking cessation, alcohol intake, exercise, and weight loss as indicated.
Breast	18 years. Monthly breast self exam 25 years. Clinical breast exam semiannually and annual mammography with the option of breast MRI for dense breasts, discuss prophylactic mastectomy
Stomach	8 years. Baseline upper endoscopy 18 years. Annual extended upper endoscopy using a pediatric colonoscope
Small intestine	8 years. Screening upper endoscopy and MR enterography. Follow-up variable depending on findings. 18 years. Annual extended upper endoscopy using pediatric colonoscope. MR enterography every 1–3 years depending on findings. Follow-up DBE if any polyps greater than 1.0 to 1.5 cm identified by MR enterography
Colon	18 years. Initial colonoscopy. Screening interval is determined by presence of polyps. If colon polyps present, screening interval is 1 year; if no polyps, then screening interval is 2 years.
Pancreas	18 years. Annual MR of the abdomen and CA19-9
Lung	18 years. Annual chest radiograph

(continued)

Table 9.9 (continued)

Organ	Mayo Clinic (Jacksonville, Rochester, USA)
Ovary	18 years. Annual MR of the pelvis, transvaginal ultrasound, serum CA-125, discuss prophylactic hysterectomy and oophorectomy
Cervix and uterus	18 years. Annual MR of the pelvis, transvaginal ultrasound, pelvic exam with Pap smear by a gynecologist, discuss prophylactic hysterectomy and oophorectomy
Testicles	Birth. Annual examination and ultrasound of the testicles
Nasopharynx	18 years. Annual screen for symptoms and refer to an ear, nose, and throat physician as indicated

Recommended age of initiation of testing is followed by recommended tests. There is no consensus or organization-approved guideline for cancer surveillance in PJS patients. Whichever protocol is used, it should be modified according to available resources, an individual patient's disease manifestations, psychosocial situation, and personal preferences. *MR* magnetic resonance, *MRI* magnetic resonance imaging, *DBE* double balloon endoscopy

Other Cancers and Neoplasia Associated with PJS

Cancers and other neoplasia associated with PJS and reported as a single case or as a few cases are shown in Table 9.10.

Cancer Surveillance Protocols

Cancer surveillance is standard of care for PJS patients. However, no cancer surveillance protocol has been shown to decrease cancer incidence or increase survival in PJS patients. Highlighting the limitations of surveillance, only one of 96 cancers was identified in a surveillance program in the largest cohort of PJS patients reported to date [28]. It was not reported how many patients were under surveillance or what surveillance protocol was used.

There is no consensus or organization-approved guideline for cancer surveillance in PJS patients. Table 9.9 summarizes the PJS cancer surveillance and management protocols used at Mayo Clinic Florida [164–166]. The University of Edinburgh, Danish polyposis registry, and the University of Newcastle (Australia) have also published protocols [129, 167, 168]. Whichever protocol is used, it should be modified according to available resources, an individual patient's disease manifestations, psychosocial situation, and personal preferences (see footnote 1).

Screening of At-Risk Individuals

At-risk groups for PJS include the children and other relatives of PJS patients. For other hereditary cancer syndromes (e.g., Lynch syndrome), there are many individuals at risk for whom the diagnosis can neither be proved nor disproved. These

Table 9.10 Neoplasia reported in a single or few Peutz-Jeghers syndrome patients

Neoplasia	Reference(s)
Gastrointestinal/Hepatobiliary	
Appendix carcinoid (appendiceal)	[224]
Oral papilloma	[225]
Gallbladder adenocarcinoma	[7, 123]
Bile duct (cholangiocarcinoma)	[89, 100]
Biliary hamartoma of the liver	[226]
Esophageal adenocarcinoma	[227]
Breast/Ovarian/Fallopian	
Male breast cancer	[28]
Ovarian gonadoblastoma	[228, 229]
Lobular breast cancer occurring in the setting of a fibroadenoma	[147]
Malignant Mullerian tumor of fallopian tube	[230]
Mucinous cystadenoma of the fallopian tube	[231]
Endometrial stromal sarcoma	[203]
Pancreas	
Pancreatic cystadenocarcinoma	[145, 146]
Papillary adenoma of the pancreatic duct	[226]
Villous adenoma of the pancreatic duct	[89]
Other	
Cervical adenocarcinoma	[130]
Ganglioglioma	[232]
Prostate cancer	[26]
Multiple myeloma	[27]
Tonsillar cancer	[89]
Renal cancer	[100, 233]
Melanoma	[112, 113]
Thyroid cancer	[25, 26]
Bronchoalveolar	[234]
Osteosarcoma	[7]
Leiomyosarcoma	[158]

at-risk individuals also require cancer surveillance even though it is unclear whether or not they are affected. However, for PJS there are very few at-risk individuals as the diagnosis is usually easily made by the presence of MMs and by screening for PJS-type intestinal polyps.

Small Intestine Polyp and Cancer Surveillance

The purpose of small intestine surveillance in PJS is to identify polyps before they serve as the lead point for an intussusception, develop dysplasia, or become too large to remove endoscopically. The current standard for adult PJS patients is to remove all polyps 1.0–1.5 cm or larger. (For discussion, see *PJS-type polyps.*) For

pediatric patients, polyp management is individualized depending on symptoms, age, previous surgeries, location, and size of the polyp(s) in question, and available resources.

The small intestine can be screened for polyps using magnetic resonance (MR) and CT enterography and enteroclysis, capsule endoscopy, and small intestine X-ray (Figs. 9.23, 9.24, and 9.25). The characteristics of small intestine polyp screening tests are shown in Table 9.11.

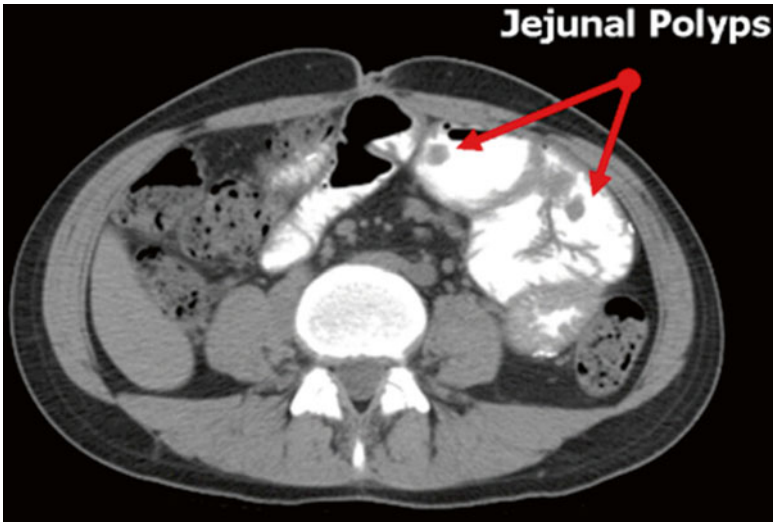


Fig. 9.23 CT enteroclysis study of a 29-year-old Peutz-Jeghers syndrome patient showing several large jejunal polyps

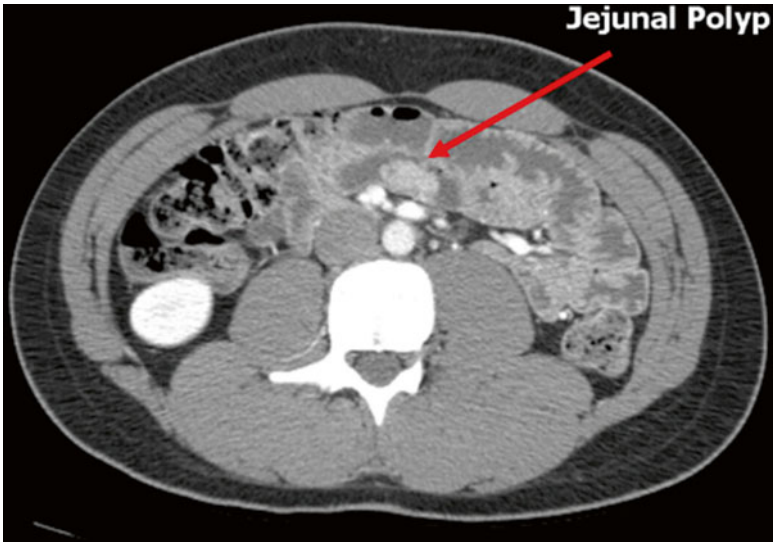


Fig. 9.24 CT enterography study of a Peutz-Jeghers syndrome patient showing 1.2 cm jejunal polyp

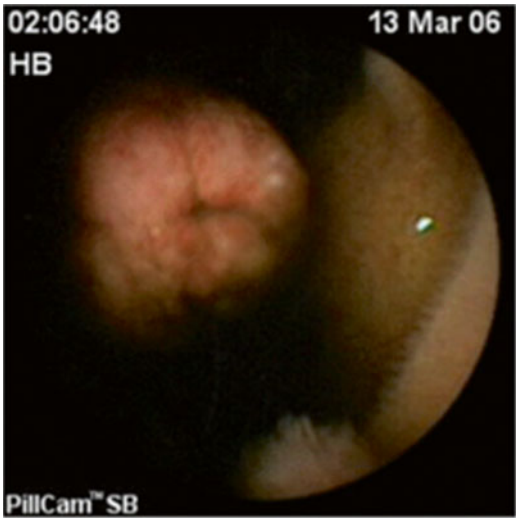


Fig. 9.25 Capsule endoscopy image from a Peutz-Jeghers syndrome patient showing small intestine polyp. Courtesy Mark Stark, MD, Mayo Clinic, Jacksonville

Table 9.11 Characteristics of small intestine imaging tests

Imaging study	Small intestine polyp detection	Radiation exposure [191]	Naso-intestinal tube	Extraluminal imaging
MR enterography	++	None	No	Yes
MR enteroclysis	++	None	Yes	Yes
Barium study	+	+	No	No
Capsule endoscopy	+++	None	No	No
CT enteroclysis	+++	++	Yes	Yes
CT enterography	++	++	No	Yes

MR enterography is preferred by the Mayo Clinic for small intestine polyp surveillance in Peutz-Jeghers syndrome patients. Other tests or combinations of other tests are also acceptable. Characteristics of tests taken from references and the authors' experience [169, 170]. *MR* magnetic resonance, *CT* computed tomography

Mayo Clinic recommends MR enterography for small intestine surveillance. It has adequate sensitivity for 1.5 cm polyps, surveys the extraluminal abdominal organs, and does not involve exposure to radiation [169, 170]. MR enterography is not widely available, so screening with CT enteroclysis or enterography are acceptable alternatives. CT enteroclysis is also used at Mayo Clinic. In the authors' opinion, it provides the highest quality images but is associated with radiation exposure and the discomfort of a naso-small intestine tube. Patients should be forewarned that CT and MR enteroclysis require insertion of a naso-small intestine tube that is unpleasant for all and not tolerated by some.

Few studies have compared the different techniques for detecting small intestine polyps. One study showed similar information was gained from enteroclysis and enterography techniques for both CT and MR, but small intestine polyp detection was not specifically studied [171]. Other studies in PJS patients have shown MR

enterography and capsule endoscopy equivalent in identifying small intestine polyps greater than 1.5 cm and that capsule endoscopy detects more polyps than small intestine X-ray [172, 173].

Pancreatic Cancer Surveillance

Background

More than 90 % of sporadic and PJS-associated pancreatic cancers are pancreatic ductal adenocarcinomas. Pancreatic cancer in a PJS patient was first reported in 1957, and an increased incidence of pancreatic cancer in PJS patients was reported in 1987 [27, 174]. Eighty-five percent of PJS patients with pancreatic cancer are diagnosed over the age of 40 (ranging from 16 to 91 years old) (Table 9.8). The cumulative lifetime risk of pancreatic cancer for PJS in the study with the most patient follow-up was 11 % [28].

The most quoted estimate of the lifetime pancreatic cancer risk in PJS is 40 %. This comes from a 36 % estimate reported in a review of six published case series published in 2000 [98]. This may be an overestimate due to selection bias. In that study, six cases of pancreatic cancer were reported in a total of 201 patients. One study included in the analysis contributed 31 of the 201 patients and a very disproportionate four of the six pancreatic cancer cases. Other studies have not confirmed the high pancreatic cancer risk reported in 2000. As noted above, the most comprehensive natural history study of PJS found an 11 % risk, and a study of 147 PJS patients with proven *LKB1* mutations published in 2006 identified no cases of pancreatic cancer [99, 175]. No PJS patient followed at Mayo Clinic has ever been diagnosed with pancreatic cancer. Other than selection bias, another explanation for the different rates of pancreatic cancer reported is that populations under intensive surveillance for colon and other preventable cancers may have a higher rate of pancreatic cancer because of the low number of deaths due to colon and other cancers.

Pancreatic cancer has the worst prognosis of any of the PJS-associated cancers. The median lifespan for sporadic pancreatic cancer patients treated with neoadjuvant therapy is 9–11 months [176]. Less than 5 % of pancreatic cancer patients are long-term survivors (>5 years). No PJS patient has been reported to be a long-term survivor of pancreatic cancer. A review of 14 PJS patients diagnosed with pancreatic cancer found surgery was attempted in only three; the remaining 11 are assumed to have died of pancreatic cancer. Of the three surgically managed patients, one had locally advanced disease and is assumed to have died from pancreatic cancer. The two remaining patients had pancreatic cystadenocarcinoma, a rare tumor of the pancreas associated with a better prognosis than pancreatic ductal adenocarcinoma [145, 146].

The only chance for cure of pancreatic cancer is early surgery in the narrow window of resectability prior to the development of locally advanced or metastatic disease. Therefore, any successful screening test for pancreatic cancer must be able to identify a premalignant lesion or cancer in the narrow time window when surgical

cure is possible. Two candidates for the premalignant lesion of pancreatic cancer in PJS are pancreatic intraepithelial neoplasia (PanINs) [177] and intraductal papillary mucous neoplasms (IPMNs) [178]. PanINs are microscopic areas of intraductal neoplasia and are graded from low (grade 1) to high grade dysplasia (grade 3). Only PanINs-3 are clearly associated with pancreatic cancers; PanINs-1 and -2 can be seen in normal pancreas parenchyma and in acute and chronic pancreatitis. PanINs cannot be reliably detected on imaging, and IPMNs have a cystic mucinous component that may be detected by imaging.

Although both PanINs and IPMN have been reported in individual PJS patients, it is unclear which one, if either, is the premalignant lesion of PJS-associated pancreatic cancer. Limited molecular evidence supports the conclusion that IPMNs are a manifestation of PJS. A study of IPMNs from two PJS patients showed LOH at the *LKB1* locus [178].

Screening Tests

Potential screening tests for pancreatic cancer include serum CA19-9 and imaging studies including CT, MRI (magnetic resonance imaging), and endoscopic ultrasound (EUS). CA19-9 is the only blood-based pancreatic cancer biomarker in use. The positive predictive value of CA19-9 is 59 % in patients undergoing imaging of the pancreas and 0.9 % in the general population [179, 180]. CA19-9 is of limited value as it usually is only elevated when the tumor is unresectable. The value of CA19-9 testing in PJS patients has never been reported, and the American Society for Clinical Oncology does not recommend that CA19-9 be used for screening in the general population [181]. Other serum biomarkers proposed for pancreatic cancer detection include glucose intolerance [182], serum RCAS1 [183], PGK1 [184], REG4 [185], and CEACAM1 [186]. The utility of these biomarkers in PJS has not been reported.

Pancreatic cancer imaging screening strategies for high-risk groups, including PJS patients, were recently reviewed by Canto [187]. Limited data is available concerning CT and EUS screening in the PJS patients from two studies. A third collaborative multisite EUS-CT study for pancreatic cancer surveillance in high-risk groups, including PJS patients, is ongoing. The first study of CT and EUS screening for pancreatic cancer in high-risk individuals included six PJS patients. One PJS patient had a cystic lesion identified in the head of the pancreas by both EUS and CT [188]. This patient underwent a pancreatic duodenectomy and was found to have an IPMN with carcinoma in situ. In a second high-risk pancreatic cancer CT and EUS study, a mass was identified in the pancreatic head of a PJS patient by CT and EUS [177]. The patient had a pancreatic duodenectomy, and pathology showed diffuse grade 1–2 PanINs *without* evidence of pancreatic cancer. The limitations of EUS were further shown in a study of interoperator variability in interpreting surveillance EUS studies performed on hereditary pancreatic cancer syndrome patients including PJS [189]. There was significant interoperator variability for features other than cysts. There are no reports of the value of MRI screening in PJS patients.

Two studies of the effectiveness of pancreatic cancer screening in PJS or similar populations have been published. A Markov model analysis studied surveillance strategies for patients with hereditary pancreatic cancer [190]. Approaches studied included "do nothing," total pancreatectomy, EUS, and EUS with fine needle aspiration. The "do nothing" approach provided the longest number of years of life. The second study, a review and cost-effectiveness evaluation of pancreatic cancer screening specifically in PJS, found that EUS screening was not cost-effective and recommended it only be performed on a research basis [166].

In summary, all pancreatic cancer screening tests have significant limitations, and it is unclear if any of them, or any combination of them, would decrease pancreatic cancer mortality and morbidity in PJS patients.

Recommendations

St. Mark's Hospital recommends no screening. Mayo Clinic and Johns Hopkins Hospital recommend CA19-9 in combination with MRI or EUS evaluation, respectively. The Mayo Clinic protocol recommends MRI over EUS because of the low specificity and interobserver variability with EUS. In contrast to EUS, MRI surveys the entire abdomen, does not require sedation, and has less interobserver variability. However, MRI is not as sensitive as EUS and is less likely to identify premalignant lesions and pancreatic cancers when they are small enough to still be cured by surgery.

In reference to MRI versus CT, all pancreatic neoplasms identified in PJS patients participating in the EUS/CT studies over time have been seen by CT and should also be seen by MRI. A key benefit of MRI over CT in younger PJS patients is that MRI does not expose the patient to possibly carcinogenic doses of ionizing radiation [191].

Chemoprevention and Chemotherapy

COX-2 Inhibitors

Chemoprevention using the COX-2 inhibitor celecoxib has been studied in the *lkb1*+/- PJS mouse model and in PJS patients. *Lkb1*+/- mice treated with celecoxib have both a decrease in the formation of new polyps and the size of preexisting polyps [61]. In the only study of chemoprevention in PJS patients, 6 patients were treated for 6 months with celecoxib 200 mg twice daily [61]. The primary endpoint was decrease in gastric polyps as assessed by endoscopy. Two of six patients had a significant decrease in gastric polyps at the end of the study.

The authors do not recommend treating PJS patients with celecoxib or other COX-2 inhibitors. This recommendation is based on the lack of any data showing

COX-2 inhibitors impact any clinically significant endpoint (e.g., cancer, intussusception), advances in endoscopic therapy for PJS polyps, and the increased risk of myocardial infarction and stroke associated with COX-2 inhibitors [192].

Selective Estrogen Receptor Modulators (SERMs) and Prophylactic Oophorectomy

Tamoxifen and raloxifene are selective estrogen receptor modulators (SERMs). Tamoxifen is effective for primary and secondary breast cancer prevention in high-risk patients [193]. In a case-control study of *BRCA*1/2 patients who had had breast cancer, tamoxifen reduced a second contralateral breast cancer by 75 % [194].

Presumably, tamoxifen decreases breast cancer risk by blocking the action of estrogen. However, data from BRCA1/2 patients is mixed on whether tamoxifen decreases the incidence of ER-expressing breast cancers or all breast cancers [195, 196]. In the one case of PJS-associated breast cancer where tumor estrogen receptor status was reported, the tumor did not express estrogen receptors [197]. Chemoprevention of breast cancer in PJS using SERMS has not been reported.

In retrospective and prospective studies, prophylactic oophorectomy decreases breast cancer in *BRCA*1/2 mutation carriers [198, 199]. Prophylactic oophorectomy for breast cancer prevention has not been reported in PJS. Side effects of SERMs and oophorectomy include deep venous thrombosis, infertility, and osteoporosis. Given these adverse side effects and that their efficacy in PJS is unproven, the authors do not recommend SERMs be used for chemoprevention in PJS patients.

Rapamycin and Rapalogs

The cause of PJS MMs, polyps, and cancers are DNA mutations in the *LKB1* gene, resulting in decreased function or absence of the LKB1 protein. Decreased LKB1 function results in more signaling through the mTOR (mammalian target of rapamycin) pathway. Drugs that suppress signaling through the mTOR pathway are called rapalogs. Rapamycin was the first mTOR inhibitor identified and so this eponymous class of drugs [200].

Mice with lack of function in the mouse gene corresponding to the human *LKB1* gene have been treated with rapamycin (*lkb1*+/- mice) [201]. In one study, 50 mice were treated with rapamycin and 50 mice were not (controls). Mean polyp weight was much less in the mice treated with rapamycin (mean 203 gm vs, 323 gm, $p = 0.0001$).

Patients with PJS have also been treated with rapalogs. RAD001, also known as everolimus, is a rapalog approved in the USA for the treatment of cancers and suppression of the immune system after organ transplantation. An open label clinical trial of RAD001 for treatment and prevention of PJS polyps was conducted at the

University of Utah (NCT00811590) [202]. The study began in November of 2008 and ended in March of 2011. Three patients, all female, completed 12 months of treatment with RAD001. The investigators were unable to enroll more patients as the study criteria only allowed them to enroll patients who had not had a history of cancer, and many PJS patients have had a history of cancer. The initial dose of RAD001 was 10 mg by mouth daily. All three patients developed stomatitis and the dose for all of them was changed to 10 mg by mouth every other day. With data from only three patients the investigators could not determine if the effect, if any, of RAD001 on PJS polyps.

There are two reports of PJS patients with cancer being treated with RAD001. One patient was a 46-year-old woman with PJS and endometrial stromal sarcoma [203]. She was treated with RAD001, other chemotherapy drugs, radiation, and surgery. There was no clinical response to RAD001 and the patient died about 30 months after diagnosis. The other patient was also 46 years old and was a man with acinar cell pancreatic cancer [204]. This patient had partial response to RAD001 at 3 and 6 months, but follow-up at 9 months showed progressive disease. His physicians noted a decrease in colon polyp growth with RAD001 treatment. Further follow-up was not reported for this patient.

Metformin

Metformin has been shown to inhibit mTOR activity in breast cancer cells but was unable to inhibit mTOR in cells lacking *LKB1* [205]. Based on this data, it is unclear how effective metformin would be in PJS patients who are germline haploinsufficient for *LKB1* and in PJS neoplastic tissue that does not express *LKB1*.

Prophylactic Surgery

Prophylactic surgery has been shown to be effective in patients with Lynch syndrome and the *BRCA*1/2 syndromes [206, 207]. Prophylactic surgery in PJS patients has not been reported. The authors review the option of prophylactic bilateral mastectomy, hysterectomy, and oophorectomy with female PJS patients.

Lifestyle Modification

Lifestyle factors including excess weight, lack of exercise, smoking, and alcohol use are risk factors for the cancers associated with PJS. Although no study of PJS patients has shown that modification of these risk factors reduces cancer risk, all PJS patients should be advised to adopt a healthy lifestyle.

References

1. Mergl V. Simultaneous multiple invagination in Peutz-Jeghers syndrome. Int Surg. 1971; 55(5):357–60.
2. Mallory SB, Stough DB. Genodermatoses with malignant potential. Dermatol Clin. 1987;5(1):221–30.
3. Hemminki A. The molecular basis and clinical aspects of Peutz-Jeghers syndrome. Cell Mol Life Sci. 1999;55(5):735–50.
4. Burt R. Polyposis syndromes. Clin Persp Gastro 2002;5(1):51–9.
5. Jeghers H. McKusick V, Katz K. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. New Engl J Med. 1949;241:993–1005 and 1031–36.
6. Anyanwu SN. Sporadic Peutz-Jeghers syndrome in a Nigerian. Cent Afr J Med. 1999; 45(7):182–4.
7. Utsunomiya J et al. Peutz-Jeghers syndrome: its natural course and management. Johns Hopkins Med J. 1975;136(2):71–82.
8. Dong K, Li B. Peutz-Jeghers syndrome: case reports and update on diagnosis and treatment. Chin J Dig Dis. 2004;5(4):160–4.
9. Wu YK et al. Gastroduodenal intussusception due to Peutz-Jeghers syndrome. A case report. Hepatogastroenterology. 1994;41(2):134–6.
10. Basu AK. Familial intestinal polyposis with pigmentation of skin and mucous membrane. Lancet. 1952;2:586–7.
11. Vogel T et al. Extraintestinal polyps in Peutz-Jeghers syndrome: presentation of four cases and review of the literature. Int J Colorectal Dis. 2000;15(2):118–23.
12. Kieselstein M et al. Mucocutaneous pigmentation and intestinal polyposis (Peutz-Jeghers syndrome) in a family of Iraqi Jews with polycystic kidney disease. With a chromosome study. Isr J Med Sci. 1969;5(1):81–90.
13. Bartosova Z et al. STK11/LKB1 germline mutations in the first Peutz-Jeghers syndrome patients identified in Slovakia. Neoplasma. 2007;54(2):101–7.
14. Trau H et al. Peutz-Jeghers syndrome and bilateral breast carcinoma. Cancer. 1982; 50(4):788–92.
15. Yoon KA et al. Germline mutations of the STK11 gene in Korean Peutz-Jeghers syndrome patients. Br J Cancer. 2000;82(8):1403–6.
16. Connor J. Aesculapian society of London. Lancet. 1895;2:1169.
17. Hutchinson J. Pigmentation of lips and mouth. Arch Surg (Lond). 1896;7:290.
18. Weber FP. Patches of deep pigmentation of oral mucous membrane not connected with Addison's disease. Quart J Med. 1919;12:404.
19. Peutz J. Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentations of skin and mucous membrane. Nederl Maandschr Geneesk. 1921;10:134–46.
20. Bruwer A, Bargen J, Kierland R. Surface pigmentation and generalized intestinal polyposis (Peutz-Jeghers syndrome). Proc Staff Meet Mayo Clin. 1954;29:168–71.
21. Keller JJ et al. Jan Peutz, Harold Jeghers and a remarkable combination of polyposis and pigmentation of the skin and mucous membranes. Fam Cancer. 2001;1(3–4):181–5.
22. Dozois RR et al. The Peutz-Jeghers syndrome. Is there a predisposition to the development of intestinal malignancy? Arch Surg. 1969;98(4):509–17.
23. Reid J. Intestinal carcinoma in Peutz Jeghers syndrome. JAMA. 1974;229:833–4.
24. Linos DA et al. Does Peutz-Jeghers syndrome predispose to gastrointestinal malignancy? A later look. Arch Surg. 1981;116(9):1182–4.
25. Spigelman AD, Murday V, Phillips RK. Cancer and the Peutz-Jeghers syndrome. Gut. 1989;30(11):1588–90.
26. Boardman LA et al. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med. 1998;128(11):896–9.

27. Giardiello FM et al. Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med. 1987;316(24):1511–4.
28. Hearle N et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. Clin Cancer Res. 2006;12(10):3209–15.
29. Hemminki A et al. Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. Nat Genet. 1997;15(1):87–90.
30. Hemminki A et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature. 1998;391(6663):184–7.
31. Jenne DE et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet. 1998;18(1):38–43.
32. Westerman AM et al. Peutz-Jeghers syndrome: 78-year follow-up of the original family. Lancet. 1999;353(9160):1211–5.
33. Rowan A et al. In situ analysis of LKB1/STK11 mRNA expression in human normal tissues and tumours. J Pathol. 2000;192(2):203–6.
34. Conde E et al. Specific pattern of LKB1 and phospho-acetyl-CoA carboxylase protein immunostaining in human normal tissues and lung carcinomas. Hum Pathol. 2007;38(9):1351–60.
35. Boudeau J et al. MO25alpha/beta interact with STRADalpha/beta enhancing their ability to bind, activate and localize LKB1 in the cytoplasm. EMBO J. 2003;22(19):5102–14.
36. Casey G et al. Conversion analysis for mutation detection in MLH1 and MSH2 in patients with colorectal cancer. JAMA. 2005;293(7):799–809.
37. Hearle NC et al. Sequence changes in predicted promoter elements of STK11/LKB1 are unlikely to contribute to Peutz-Jeghers syndrome. BMC Genomics. 2005;6(1):38.
38. Olschwang S et al. Peutz-Jeghers disease: most, but not all, families are compatible with linkage to 19p13.3. J Med Genet. 1998;35(1):42–4.
39. Mehenni H et al. Peutz-Jeghers syndrome: confirmation of linkage to chromosome 19p13.3 and identification of a potential second locus, on 19q13.4. Am J Hum Genet. 1997;61(6):1327–34.
40. Buchet-Poyau K et al. Search for the second Peutz-Jeghers syndrome locus: exclusion of the STK13, PRKCG, KLK10, and PSCD2 genes on chromosome 19 and the STK11IP gene on chromosome 2. Cytogenet Genome Res. 2002;97(3–4):171–8.
41. Hearle N et al. Mapping of a translocation breakpoint in a Peutz-Jeghers hamartoma to the putative PJS locus at 19q13.4 and mutation analysis of candidate genes in polyp and STK11-negative PJS cases. Genes Chromosomes Cancer. 2004;41(2):163–9.
42. Alhopuro P et al. Mutation analysis of three genes encoding novel LKB1-interacting proteins, BRG1, STRADalpha, and MO25alpha, in Peutz-Jeghers syndrome. Br J Cancer. 2005;92(6):1126–9.
43. de Leng WW et al. STRAD in Peutz-Jeghers syndrome and sporadic cancers. J Clin Pathol. 2005;58(10):1091–5.
44. de Leng WW et al. Genetic defects underlying Peutz-Jeghers syndrome (PJS) and exclusion of the polarity-associated MARK/Par1 gene family as potential PJS candidates. Clin Genet. 2007;72(6):568–73.
45. Woodford-Richens KL et al. CDX2 mutations do not account for juvenile polyposis or Peutz-Jeghers syndrome and occur infrequently in sporadic colorectal cancers. Br J Cancer. 2001;84(10):1314–6.
46. Lizcano JM et al. LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. EMBO J. 2004;23(4):833–43.
47. Hawley SA et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol. 2003;2(4):28.
48. Baas AF et al. Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD. Cell. 2004;116(3):457–66.
49. Barnes AP et al. LKB1 and SAD kinases define a pathway required for the polarization of cortical neurons. Cell. 2007;129(3):549–63.

50. Shelly M et al. LKB1/STRAD promotes axon initiation during neuronal polarization. Cell. 2007;129(3):565–77.
51. Mirouse V et al. LKB1 and AMPK maintain epithelial cell polarity under energetic stress. J Cell Biol. 2007;177(3):387–92.
52. Szczepanska K, Maleszewski M. LKB1/PAR4 protein is asymmetrically localized in mouse oocytes and associates with meiotic spindle. Gene Expr Patterns. 2005;6(1):86–93.
53. Watts JL et al. The C. elegans par-4 gene encodes a putative serine-threonine kinase required for establishing embryonic asymmetry. Development. 2000;127(7):1467–75.
54. Jishage K et al. Role of Lkb1, the causative gene of Peutz-Jegher's syndrome, in embryogenesis and polyposis. Proc Natl Acad Sci U S A. 2002;99(13):8903–8.
55. Miyoshi H et al. Gastrointestinal hamartomatous polyposis in Lkb1 heterozygous knockout mice. Cancer Res. 2002;62(8):2261–6.
56. Ylikorkala A et al. Vascular abnormalities and deregulation of VEGF in Lkb1-deficient mice. Science. 2001;293(5533):1323–6.
57. Bardeesy N et al. Loss of the Lkb1 tumour suppressor provokes intestinal polyposis but resistance to transformation. Nature. 2002;419(6903):162–7.
58. Wei C et al. Mutation of Lkb1 and p53 genes exert a cooperative effect on tumorigenesis. Cancer Res. 2005;65(24):11297–303.
59. Nakau M et al. Hepatocellular carcinoma caused by loss of heterozygosity in Lkb1 gene knockout mice. Cancer Res. 2002;62(16):4549–53.
60. Takeda H et al. Accelerated onsets of gastric hamartomas and hepatic adenomas/carcinomas in Lkb1+/-p53-/- compound mutant mice. Oncogene. 2006;25(12):1816–20.
61. Udd L et al. Suppression of Peutz-Jeghers polyposis by inhibition of cyclooxygenase-2. Gastroenterology. 2004;127(4):1030–7.
62. Robinson J et al. Osteogenic tumours in Lkb1-deficient mice. Exp Mol Pathol. 2008; 85:223–6.
63. Alessi DR, Sakamoto K, Bayascas JR. LKB1-dependent signaling pathways. Annu Rev Biochem. 2006;75:137–63.
64. Ponder BA. Cancer genetics. Nature. 2001;411(6835):336–41.
65. Katajisto P et al. LKB1 signaling in mesenchymal cells required for suppression of gastrointestinal polyposis. Nat Genet. 2008;40(4):455–9.
66. Karuman P et al. The Peutz-Jeghers gene product LKB1 is a mediator of p53-dependent cell death. Mol Cell. 2001;7(6):1307–19.
67. Wei C et al. Correlation of staining for LKB1 and COX-2 in hamartomatous polyps and carcinomas from patients with Peutz-Jeghers syndrome. J Histochem Cytochem. 2003;51(12):1665–72.
68. Miyaki M et al. Somatic mutations of LKB1 and beta-catenin genes in gastrointestinal polyps from patients with Peutz-Jeghers syndrome. Cancer Res. 2000;60(22):6311–3.
69. Esteller M et al. Epigenetic inactivation of LKB1 in primary tumors associated with the Peutz-Jeghers syndrome. Oncogene. 2000;19(1):164–8.
70. Achord JL, Proctor HD. Malignant degeneration and metastasis and degeneration in the Peutz-Jeghers syndrome. Arch Intern Med. 1963;111:498–502.
71. Williams JP, Knudsen A. Peutz-Jeghers syndrome with metastasizing duodenal adenocarcinoma. Gut. 1965;6:179–84.
72. Miller LJ et al. Adenocarcinoma of the rectum arising in a hamartomatous polyp in a patient with Peutz-Jeghers syndrome. Dig Dis Sci. 1983;28(11):1047–51.
73. Erdas E et al. Peutz-Jeghers syndrome: an account of 3 cases in the same family and a review of the literature. Chir Ital. 2005;57(4):425–36.
74. Perzin KH, Bridge MF. Adenomatous and carcinomatous changes in hamartomatous polyps of the small intestine (Peutz-Jeghers syndrome): report of a case and review of the literature. Cancer. 1982;49(5):971–83.
75. Flageole H et al. Progression toward malignancy of hamartomas in a patient with Peutz-Jeghers syndrome: case report and literature review. Can J Surg. 1994;37(3):231–6.

76. Jansen M et al. Mucosal prolapse in the pathogenesis of Peutz-Jeghers polyposis. Gut. 2006;55(1):1–5.
77. de Leng WW et al. Peutz-Jeghers syndrome polyps are polyclonal with expanded progenitor cell compartment. Gut. 2007;56(10):1475–6.
78. Gruber SB et al. Pathogenesis of adenocarcinoma in Peutz-Jeghers syndrome. Cancer Res. 1998;58(23):5267–70.
79. Kimelman D, Xu W. Beta-catenin destruction complex: insights and questions from a structural perspective. Oncogene. 2006;25(57):7482–91.
80. Viollet B et al. The AMP-activated protein kinase alpha2 catalytic subunit controls whole-body insulin sensitivity. J Clin Invest. 2003;111(1):91–8.
81. Jorgensen SB et al. Knockout of the alpha2 but not alpha1 5′-AMP-activated protein kinase isoform abolishes 5-aminoimidazole-4-carboxamide-1-beta-4-ribofuranoside but not contraction-induced glucose uptake in skeletal muscle. J Biol Chem. 2004;279(2):1070–9.
82. Hurov JB et al. Immune system dysfunction and autoimmune disease in mice lacking Emk (Par-1) protein kinase. Mol Cell Biol. 2001;21(9):3206–19.
83. Wei C et al. Suppression of Peutz-Jeghers polyposis by targeting mammalian target of rapamycin signaling. Clin Cancer Res. 2008;14(4):1167–71.
84. De Leng WW et al. Cyclooxygenase 2 expression and molecular alterations in Peutz-Jeghers hamartomas and carcinomas. Clin Cancer Res. 2003;9(8):3065–72.
85. Burkart AL et al. Do sporadic Peutz-Jeghers polyps exist? Experience of a large teaching hospital. Am J Surg Pathol. 2007;31(8):1209–14.
86. Qanungo S, Haldar S, Basu A. Restoration of silenced Peutz-Jeghers syndrome gene, LKB1, induces apoptosis in pancreatic carcinoma cells. Neoplasia. 2003;5(4):367–74.
87. Narita T, Ohnuma H, Yokoyama S. Peutz-Jeghers syndrome with osseous metaplasia of the intestinal polyps. Pathol Int. 1995;45(5):388–92.
88. Westerman AM et al. Malignancy in Peutz-Jeghers syndrome? The pitfall of pseudo-invasion. J Clin Gastroenterol. 1997;25(1):387–90.
89. Bolwell JS, James PD. Peutz-Jeghers syndrome with pseudoinvasion of hamartomatous polyps and multiple epithelial neoplasms. Histopathology. 1979;3(1):39–50.
90. Shepherd NA, Bussey HJ, Jass JR. Epithelial misplacement in Peutz-Jeghers polyps. A diagnostic pitfall. Am J Surg Pathol. 1987;11(10):743–9.
91. Suzuki S et al. Three cases of solitary Peutz-Jeghers-type hamartomatous polyp in the duodenum. World J Gastroenterol. 2008;14(6):944–7.
92. Nakayama H et al. A solitary Peutz-Jeghers-type hamartomatous polyp of the rectum: report of a case and review of the literature. Jpn J Clin Oncol. 1996;26(4):273–6.
93. Ichiyoshi Y et al. Solitary Peutz-Jeghers type polyp of the duodenum containing a focus of adenocarcinoma. Ital J Gastroenterol. 1996;28(2):95–7.
94. Banse-Kupin LA, Douglass MC. Localization of Peutz-Jeghers macules to psoriatic plaques. Arch Dermatol. 1986;122(6):679–83.
95. Yamada K et al. Ultrastructural studies on pigmented macules of Peutz-Jeghers syndrome. J Dermatol. 1981;8(5):367–77.
96. Launonen V. Mutations in the human LKB1/STK11 gene. Hum Mutat. 2005;26(4):291–7.
97. Le Meur N et al. Complete germline deletion of the STK11 gene in a family with Peutz-Jeghers syndrome. Eur J Hum Genet. 2004;12(5):415–8.
98. Hearle NC et al. Exonic STK11 deletions are not a rare cause of Peutz-Jeghers syndrome. J Med Genet. 2006;43(4), e15.
99. Mehenni H et al. Cancer risks in LKB1 germline mutation carriers. Gut. 2006;55(7): 984–90.
100. Olschwang S, Boisson C, Thomas G. Peutz-Jeghers families unlinked to STK11/LKB1 gene mutations are highly predisposed to primitive biliary adenocarcinoma. J Med Genet. 2001;38(6):356–60.
101. Mehenni H et al. Molecular and clinical characteristics in 46 families affected with Peutz-Jeghers syndrome. Dig Dis Sci. 2007;52(8):1924–33.

102. Entius MM et al. Molecular genetic alterations in hamartomatous polyps and carcinomas of patients with Peutz-Jeghers syndrome. J Clin Pathol. 2001;54(2):126–31.
103. Amos CI et al. Genotype-phenotype correlations in Peutz-Jeghers syndrome. J Med Genet. 2004;41(5):327–33.
104. Hearle N et al. STK11 status and intussusception risk in Peutz-Jeghers syndrome. J Med Genet. 2006;43(8), e41.
105. Tovar JA et al. Peutz-Jeghers syndrome in children: report of two cases and review of the literature. J Pediatr Surg. 1983;18(1):1–6.
106. Woo A et al. Psychosocial impact of Peutz-Jeghers Syndrome. Fam Cancer. 2008;8(1):59–65.
107. Seimens H. Zur klinish-aetiologischen Analyse und Systematik kleinfleckiger Pigmentierungen, nebst Beschreibung einer besonderen Form von Epheliden. Dermat Ztschr. 1928;53:575–91.
108. Sarlos P, Kiraly A, Nagy L. Family study in Peutz-Jeghers syndrome. Orv Hetil. 2007; 148(6):255–8.
109. Kato S et al. Ruby laser therapy for labial lentigines in Peutz-Jeghers syndrome. Eur J Pediatr. 1998;157(8):622–4.
110. Zaheri S, Chong SK, Harland CC. Treatment of mucocutaneous pigmentation in Peutz-Jeghers syndrome with potassium titanyl phosphate (KTP) laser. Clin Exp Dermatol. 2005;30(6):710–2.
111. Benedict LM, Cohen B. Treatment of Peutz-Jeghers lentigines with the carbon dioxide laser. J Dermatol Surg Oncol. 1991;17(12):954–5.
112. Braitman M. Subungual malignant melanoma. Cutis. 1979;23(5):617–23.
113. Wong SS, Rajakulendran S. Peutz-Jeghers syndrome associated with primary malignant melanoma of the rectum. Br J Dermatol. 1996;135(3):439–42.
114. McKenna KE, Walsh MY, Burrows D. Pigmentation of Peutz-Jeghers syndrome occurring in psoriatic plaques. Dermatology. 1994;189(3):297–300.
115. Lampe AK et al. Laugier-Hunziker syndrome: an important differential diagnosis for Peutz-Jeghers syndrome. J Med Genet. 2003;40(6):e77.
116. Boardman LA et al. Association of Peutz-Jeghers-like mucocutaneous pigmentation with breast and gynecologic carcinomas in women. Medicine (Baltimore). 2000;79(5):293–8.
117. de Leng WW et al. Nasal polyposis in Peutz-Jeghers syndrome: a distinct histopathological and molecular genetic entity. J Clin Pathol. 2007;60(4):392–6.
118. Keller JJ et al. Molecular genetic evidence of an association between nasal polyposis and the Peutz-Jeghers syndrome. Ann Intern Med. 2002;136(11):855–6.
119. De Facq L et al. A case of Peutz-Jeghers syndrome with nasal polyposis, extreme iron deficiency anemia, and hamartoma-adenoma transformation: management by combined surgical and endoscopic approach. Am J Gastroenterol. 1995;90(8):1330–2.
120. Saxena PK et al. Peutz-Jeghers syndrome with unusual features (a case report). J Postgrad Med. 1986;32(4):236–8.
121. Trojan J et al. Peutz-Jeghers syndrome: molecular analysis of a three-generation kindred with a novel defect in the serine threonine kinase gene STK11. Am J Gastroenterol. 1999;94(1):257–61.
122. Parker MC, Knight M. Peutz-Jeghers syndrome causing obstructive jaundice due to polyp in common bile duct. J R Soc Med. 1983;76(8):701–3.
123. Wada K et al. Carcinoma and polyps of the gallbladder associated with Peutz-Jeghers syndrome. Dig Dis Sci. 1987;32(8):943–6.
124. Sommerhaug RG, Mason T. Peutz-Jeghers syndrome and ureteral polyposis. JAMA. 1970;211(1):120–2.
125. Jancu J. Peutz-Jeghers syndrome. Involvement of the gastrointestinal and upper respiratory tracts. Am J Gastroenterol. 1971;56(6):545–9.
126. Hartweg H, Goerlich R. On the Peutz syndrome. Fortschr Geb Rontgenstr Nuklearmed. 1960;93:203–11.
127. Humpheries AL, Shephard MH, Peters HJ. Peutz-Jeghers syndrome with colonic adenocarcinoma and ovarian tumor. JAMA. 1966;197:296–8.
128. Bartholomew LG, Dahlin DC, Waugh JM. Intestinal polyposis associated with mucocutaneous melanin pigmentation Peutz-Jeghers syndrome; review of literature and report of six cases with special reference to pathologic findings. Gastroenterology. 1957;32:434–51.

129. Rebsdorf Pedersen I et al. Management of Peutz-Jeghers syndrome. Experience with patients from the Danish polyposis register. Int J Colorectal Dis. 1994;9(4):177–9.
130. Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet. 1997;34(12):1007–11.
131. Matsumoto Y et al. Small-intestinal Peutz-Jeghers polyps resected by endoscopic polypectomy with double-balloon enteroscopy and removal confirmed by ultrasonography. Dig Dis Sci. 2006;51(12):2337–40.
132. Ohmiya N et al. Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without laparotomy. Gastrointest Endosc. 2005;61(1):140–7.
133. Terauchi S, Snowberger N, Demarco D. Double-balloon endoscopy and Peutz-Jeghers syndrome: a new look at an old disease. Proc (Bayl Univ Med Cent). 2006;19(4):335–7.
134. Ullerich H et al. Small intestinal obstruction by a Peutz-Jeghers polyp – double-balloon enteroscopic removal. Endoscopy. 2007;39, Suppl 1:E193.
135. Yamamoto H et al. New system of double-balloon enteroscopy for diagnosis and treatment of small intestinal disorders. Gastroenterology. 2003;125(5):1556.
136. Ross AS, Dye C, Prachand VN. Laparoscopic-assisted double-balloon enteroscopy for small-bowel polyp surveillance and treatment in patients with Peutz-Jeghers syndrome. Gastrointest Endosc. 2006;64(6):984–8.
137. Rajua GS et al. American gastroenterological association (AGA) institute technical review on obscure gastrointestinal bleeding. Gastroenterology. 2007;133(5):1694–96.
138. Gross SA, Stark ME. Initial experience with double-balloon enteroscopy at a U.S. center. Gastrointest Endosc. 2008;67:890–7.
139. Honda K et al. Acute pancreatitis associated with peroral double-balloon enteroscopy: a case report. World J Gastroenterol. 2006;12(11):1802–4.
140. Honda K et al. An increase in the serum amylase level in patients after peroral double-balloon enteroscopy: an association with the development of pancreatitis. Endoscopy. 2006;38(10): 1040–3.
141. Spahn TW et al. Small-bowel perforation after endoscopic resection of a Peutz-Jeghers polyp in an infant using double-balloon enteroscopy. Endoscopy. 2007;39, Suppl 1:E217.
142. Edwards DP et al. Long-term results of polyp clearance by intraoperative enteroscopy in the Peutz-Jeghers syndrome. Dis Colon Rectum. 2003;46(1):48–50.
143. Oncel M et al. Benefits of 'clean sweep' in Peutz-Jeghers patients. Colorectal Dis. 2004; 6(5):332–5.
144. Talwar N et al. Prograde and retrograde intussusception: a rarity in Peutz-Jeghers syndrome. Int Surg. 2006;91(5):265–6.
145. Pauwels M et al. Pancreatic cystadenocarcinoma in Peutz-Jeghers syndrome. J Clin Gastroenterol. 1997;25(2):485–6.
146. Yoshikawa A et al. Peutz-Jeghers syndrome manifesting complete intussusception of the appendix and associated with a focal cancer of the duodenum and a cystadenocarcinoma of the pancreas: report of a case. Dis Colon Rectum. 1998;41(4):517–21.
147. Burdick D, Prior JT. Peutz-Jeghers syndrome. A clinicopathologic study of a large family with a 27-year follow-up. Cancer. 1982;50(10):2139–46.
148. Fernandez Seara MJ et al. Peutz-Jeghers syndrome in a neonate. J Pediatr. 1995;126(6):965–7.
149. Barussaud M et al. Clinical spectrum and surgical approach of adult intussusceptions: a multicentric study. Int J Colorectal Dis. 2006;21(8):834–9.
150. Nagorney DM, Sarr MG, McIlrath DC. Surgical management of intussusception in the adult. Ann Surg. 1981;193(2):230–6.
151. Srivatsa PJ, Keeney GL, Podratz KC. Disseminated cervical adenoma malignum and bilateral ovarian sex cord tumors with annular tubules associated with Peutz-Jeghers syndrome. Gynecol Oncol. 1994;53(2):256–64.
152. Gilks CB et al. Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol. 1989;13(9):717–29.
153. Tsuruchi N et al. Adenoma malignum of the uterine cervix detected by imaging methods in a patient with Peutz-Jeghers syndrome. Gynecol Oncol. 1994;54(2):232–6.

154. Okamoto Y et al. MR imaging of the uterine cervix: imaging-pathologic correlation. Radiographics. 2003;23(2):425–45. quiz 534-5.
155. Tsuda H et al. Reproducible and clinically meaningful differential diagnosis is possible between lobular endocervical glandular hyperplasia and 'adenoma malignum' based on common histopathological criteria. Pathol Int. 2005;55(7):412–8.
156. Ishii K et al. A new diagnostic method for adenoma malignum and related lesions: latex agglutination test with a new monoclonal antibody, HIK1083. Clin Chim Acta. 2001;312(1–2):231–3.
157. McCluggage WG. Endocervical glandular lesions: controversial aspects and ancillary techniques. J Clin Pathol. 2003;56(3):164–73.
158. Young RH, Scully RE. Ovarian sex cord-stromal tumors: recent progress. Int J Gynecol Pathol. 1982;1(1):101–23.
159. Lele SM et al. Malignant ovarian sex cord tumor with annular tubules in a patient with Peutz-Jeghers syndrome: a case report. Mod Pathol. 2000;13(4):466–70.
160. Rodu B, Martinez Jr MG. Peutz-Jeghers syndrome and cancer. Oral Surg Oral Med Oral Pathol. 1984;58(5):584–8.
161. Gibbon DG. Conservative management of sex cord tumors with annular tubules of the ovary in women with Peutz-Jeghers syndrome. J Pediatr Hematol Oncol. 2005;27(11):630–2.
162. Ulbright TM, Amin MB, Young RH. Intratubular large cell hyalinizing sertoli cell neoplasia of the testis: a report of 8 cases of a distinctive lesion of the Peutz-Jeghers syndrome. Am J Surg Pathol. 2007;31(6):827–35.
163. Lefevre H et al. Prepubertal gynecomastia in Peutz-Jeghers syndrome: incomplete penetrance in a familial case and management with an aromatase inhibitor. Eur J Endocrinol. 2006;154(2):221–7.
164. Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. Clin Gastroenterol Hepatol. 2006;4(4):408–15.
165. Spigelman AD, Arese P, Phillips RK. Polyposis: the Peutz-Jeghers syndrome. Br J Surg. 1995;82(10):1311–4.
166. Latchford A et al. Peutz-Jeghers syndrome and screening for pancreatic cancer. Br J Surg. 2006;93(12):1446–55.
167. Dunlop MG. Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polypolis, juvenile polyposis, and Peutz-Jeghers syndrome. Gut. 2002;51 Suppl 5:V21–7.
168. McGrath DR, Spigelman AD. Preventive measures in Peutz-Jeghers syndrome. Fam Cancer. 2001;1(2):121–5.
169. Fidler J. MR imaging of the small bowel. Radiol Clin North Am. 2007;45(2):317–31.
170. Wold PB et al. Assessment of small bowel Crohn disease: noninvasive peroral CT enterography compared with other imaging methods and endoscopy-feasibility study. Radiology. 2003;229(1):275–81.
171. Schreyer AG et al. Abdominal MRI after enteroclysis or with oral contrast in patients with suspected or proven Crohn's disease. Clin Gastroenterol Hepatol. 2004;2(6):491–7.
172. Caspari R et al. Comparison of capsule endoscopy and magnetic resonance imaging for the detection of polyps of the small intestine in patients with familial adenomatous polyposis or with Peutz-Jeghers' syndrome. Endoscopy. 2004;36(12):1054–9.
173. Brown G et al. Video capsule endoscopy in Peutz-Jeghers syndrome: a blinded comparison with barium follow-through for detection of small-bowel polyps. Endoscopy. 2006;38(4):385–90.
174. Dormandy T. Gastrointestinal polyposis with mucocutaneous pigmentation (Peutz-Jeghers Syndrome) New Engl J Med. 1957;256:1093–1103, 1141–46, 1186–90.
175. Giardiello FM et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447–53.
176. Tse RV et al. Neoadjuvant treatment for pancreatic cancer—a review. Crit Rev Oncol Hematol. 2008;65(3):263–74.
177. Canto MI et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol. 2004;2(7):606–21.

178. Sato N et al. STK11/LKB1 Peutz-Jeghers gene inactivation in intraductal papillary-mucinous neoplasms of the pancreas. Am J Pathol. 2001;159(6):2017–22.
179. Pleskow DK et al. Evaluation of a serologic marker, CA19-9, in the diagnosis of pancreatic cancer. Ann Intern Med. 1989;110(9):704–9.
180. Kim JE et al. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol. 2004;19(2):182–6.
181. Locker GY et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313–27.
182. Pelaez-Luna M et al. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. Am J Gastroenterol. 2007;102(10):2157–63.
183. Akashi T et al. Expression and diagnostic evaluation of the human tumor-associated antigen RCAS1 in pancreatic cancer. Pancreas. 2003;26(1):49–55.
184. Hwang TL et al. Overexpression and elevated serum levels of phosphoglycerate kinase 1 in pancreatic ductal adenocarcinoma. Proteomics. 2006;6(7):2259–72.
185. Takehara A et al. Novel tumor marker REG4 detected in serum of patients with resectable pancreatic cancer and feasibility for antibody therapy targeting REG4. Cancer Sci. 2006;97(11):1191–7.
186. Simeone DM et al. CEACAM1, a novel serum biomarker for pancreatic cancer. Pancreas. 2007;34(4):436–43.
187. Canto MI. Strategies for screening for pancreatic adenocarcinoma in high-risk patients. Semin Oncol. 2007;34(4):295–302.
188. Canto MI et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol. 2006;4(6):766–81. quiz 665.
189. Topazian M et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc. 2007;66(1):62–7.
190. Rubenstein JH, Scheiman JM, Anderson MA. A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology. 2007;7(5-6):514–25.
191. Jaffe TA et al. Radiation doses from small-bowel follow-through and abdominopelvic MDCT in Crohn's disease. AJR Am J Roentgenol. 2007;189(5):1015–22.
192. Solomon SD et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071–80.
193. Fisher B et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371–88.
194. Narod SA et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet. 2000;356(9245):1876–81.
195. King MC et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA. 2001;286(18):2251–6.
196. Foulkes WD et al. Tamoxifen may be an effective adjuvant treatment for BRCA1-related breast cancer irrespective of estrogen receptor status. J Natl Cancer Inst. 2002;94(19):1504–6.
197. Nakanishi C et al. Germline mutation of the LKB1/STK11 gene with loss of the normal allele in an aggressive breast cancer of Peutz-Jeghers syndrome. Oncology. 2004;67(5–6):476–9.
198. Scheuer L et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol. 2002;20(5):1260–8.
199. Rebbeck TR et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346(21):1616–22.
200. Inoki K, Corradetti MN, Guan KL. Dysregulation of the TSC-mTOR pathway in human disease. Nat Genet. 2005;37(1):19–24.
201. Robinson J et al. Oral rapamycin reduces tumour burden and vascularization in Lkb1(+/-) mice. J Pathol. 2009;219(1):35–40.

202. Kuwada SK, Burt R. A rationale for mTOR inhibitors as chemoprevention agents in Peutz-Jeghers syndrome. Fam Cancer. 2011;10(3):469–72.
203. Noriega-Iriondo MF et al. High-grade endometrial stromal sarcoma as the initial presentation of an adult patient with Peutz-Jeghers Syndrome: a case report. Hered Cancer Clin Pract. 2015;13(1):6.
204. Klumpen HJ et al. mTOR inhibitor treatment of pancreatic cancer in a patient with Peutz-Jeghers syndrome. J Clin Oncol. 2011;29(6):e150–3.
205. Dowling RJ et al. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Res. 2007;67(22):10804–12.
206. Schmeler KM et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261–9.
207. Bermejo-Perez MJ, Marquez-Calderon S, Llanos-Mendez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer. 2007;121(2):225–31.
208. Aretz S et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat. 2005;26(6):513–9.
209. Volikos E et al. LKB1 exonic and whole gene deletions are a common cause of Peutz-Jeghers syndrome. J Med Genet. 2006;43(5), e18.
210. Chow E et al. An updated mutation spectrum in an Australian series of PJS patients provides further evidence for only one gene locus. Clin Genet. 2006;70(5):409–14.
211. Nakamura T et al. Duodenal cancer in a patient with Peutz-Jeghers syndrome: molecular analysis. J Gastroenterol. 2002;37(5):376–80.
212. Wang ZJ et al. Allelic imbalance at the LKB1 (STK11) locus in tumours from patients with Peutz-Jeghers' syndrome provides evidence for a hamartoma-(adenoma)-carcinoma sequence. J Pathol. 1999;188(1):9–13.
213. Back W et al. Immunolocalization of beta catenin in intestinal polyps of Peutz-Jeghers and juvenile polyposis syndromes. J Clin Pathol. 1999;52(5):345–9.
214. Miyaki M et al. Frequent mutation of beta-catenin and APC genes in primary colorectal tumors from patients with hereditary nonpolyposis colorectal cancer. Cancer Res. 1999; 59(18):4506–9.
215. Herter P et al. Intracellular distribution of beta-catenin in colorectal adenomas, carcinomas and Peutz-Jeghers polyps. J Cancer Res Clin Oncol. 1999;125(5):297–304.
216. Rossi DJ et al. Induction of cyclooxygenase-2 in a mouse model of Peutz-Jeghers polyposis. Proc Natl Acad Sci U S A. 2002;99(19):12327–32.
217. McGarrity TJ et al. Overexpression of cyclooxygenase 2 in hamartomatous polyps of Peutz-Jeghers syndrome. Am J Gastroenterol. 2003;98(3):671–8.
218. Foley TR, McGarrity TJ, Abt AB. Peutz-Jeghers syndrome: a clinicopathologic survey of the "Harrisburg family" with a 49-year follow-up. Gastroenterology. 1988;95(6):1535–40.
219. Saranrittichai S. Peutz-Jeghers syndrome and colon cancer in a 10-year-old girl: implications for when and how to start screening? Asian Pac J Cancer Prev. 2008;9(1):159–61.
220. Bowlby LS. Pancreatic adenocarcinoma in an adolescent male with Peutz-Jeghers syndrome. Hum Pathol. 1986;17(1):97–9.
221. Brinster DR, Raper SE. Synchronous colon and pancreatic cancers in a patient with Peutz-Jeghers syndrome: report of a case and review of the literature. Surgery. 2004;135(3):352–4.
222. Dubois RS et al. Feminizing sex cord tumor with annular tubules in a boy with Peutz-Jeghers syndrome. J Pediatr. 1982;101(4):568–71.
223. Venara M et al. Sertoli cell proliferations of the infantile testis: an intratubular form of Sertoli cell tumor? Am J Surg Pathol. 2001;25(10):1237–44.
224. Hofmann S et al. Appendix carcinoid associated with the Peutz-Jeghers syndrome. Int J Surg Case Rep. 2014;5(12):964–7.
225. Lowe NJ. Peutz-Jeghers syndrome with pigmented oral papillomas. Arch Dermatol. 1975;111(4):503–5.
226. Cochet B et al. Peutz-Jeghers syndrome associated with gastrointestinal carcinoma. Report of two cases in a family. Gut. 1979;20(2):169–75.

227. Eng A et al. Peutz-Jeghers-like melanotic macules associated with esophageal adenocarcinoma. Am J Dermatopathol. 1991;13(2):152–7.
228. Kilic-Okman T et al. Breast cancer, ovarian gonadoblastoma and cervical cancer in a patient with Peutz-Jeghers Syndrome. Arch Gynecol Obstet. 2008;278(1):75–77.
229. Tokatli F et al. Peutz-Jeghers syndrome combined with breast cancer, cervical carcinoma and ovarian gonadoblastoma: a case report. J Buon. 2004;9(4):469–72.
230. Maitra RN et al. Malignant mixed Mullerian tumour of the fallopian tube occurring in a patient with Peutz-Jegher's syndrome. Aust N Z J Obstet Gynaecol. 2004;44(1):77–9.
231. Seidman JD. Mucinous lesions of the fallopian tube. A report of seven cases. Am J Surg Pathol. 1994;18(12):1205–12.
232. Resta N et al. Ganglioglioma arising in a Peutz-Jeghers patient: a case report with molecular implications. Acta Neuropathol. 2006;112(1):106–11.
233. Kataoka H et al. Digestive. Endoscopy. 2006;18(4):294–7.
234. von Herbay A et al. Bronchioloalveolar carcinoma: a new cancer in Peutz-Jeghers syndrome. Lung Cancer. 2005;47(2):283–8.

Chapter 10
Hereditary Mixed Polyposis Syndrome

Veroushka Ballester-Vargas and Ian Tomlinson

Introduction

Hereditary cancer syndromes are generally the result of high-penetrance germline mutations in genes that directly restrain uncontrolled growth or preserve the integrity of the genome. A number of such syndromes exist that have colorectal cancer (CRC) and/or polyps as their primary feature. Examples (with their genes) include Lynch syndrome (*MSH2, MLH1, MSH6, PMS2*), familial adenomatous polyposis (*APC*), Peutz-Jeghers syndrome (*STK11*), and juvenile polyposis syndrome (JPS) (*SMAD4, BMPR1A*), among others. Each syndrome is associated with distinctive clinical phenotypic features as well as tumors of a particular morphology [1, 2]. Hereditary mixed polyposis syndrome (HMPS) is a rare CRC syndrome that is inherited in an autosomal dominant fashion. It does not have a pathognomonic clinical phenotype, but the patients develop colorectal polyps of several different histological types, including individual tumors that combine different morphologies. HMPS polyps include atypical juvenile polyps, adenomas, and a variety of serrated/hyperplastic polyps [3].

HMPS was first described in a large Ashkenazi kindred, St. Mark's family 96 (SM96), who had a dominantly inherited predisposition to multiple large bowel polyps and early onset CRC. Many questioned whether these patients had an atypical variant of an established polyposis syndrome, or a distinct disorder [2]. The disease in this pedigree was found not to be linked to loci associated with other polyposis syndromes such as *APC* or mismatch repair genes (MMR genes) *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and its phenotype did not include extracolonic features [3].

V. Ballester-Vargas, M.D.
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

I. Tomlinson, M.D. (✉)
Molecular and Population Genetics Laboratory, Oxford Centre for Cancer Gene Research, Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK
e-mail: iant@well.ox.ac.uk

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_10

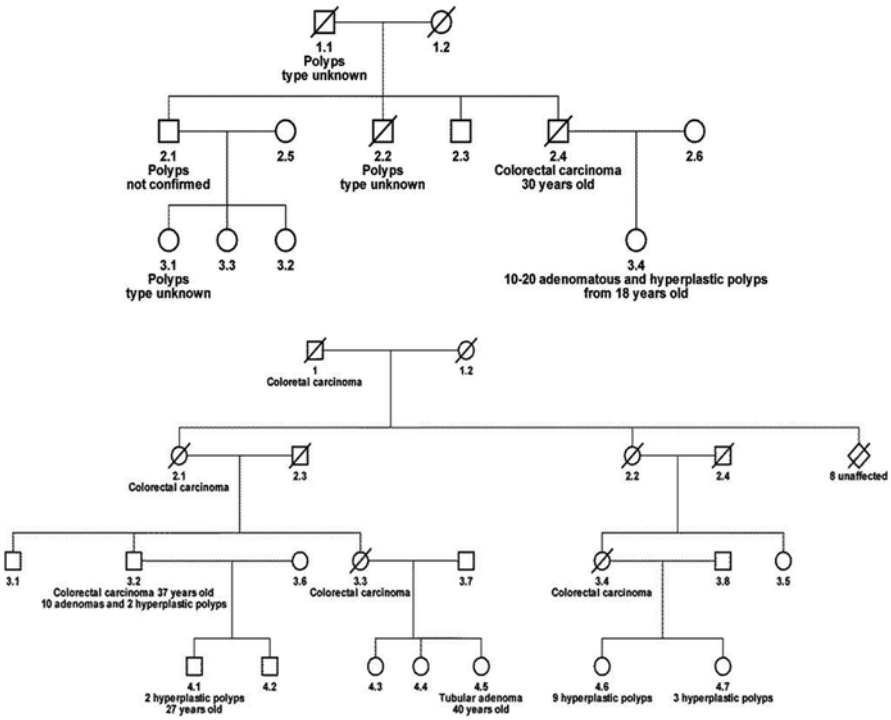


Fig. 10.1 Pedigrees and phenotypes of some HMPS families showing variation in the phenotype and sometimes relatively mild clinical features

These findings provided support for a distinct syndrome. A molecular diagnosis was ultimately needed for the characterization of this syndrome. Initially, studies mapped the *HMPS* locus to chromosome 6q16-21 [4]. More recently, progress was made regarding the molecular mechanisms underlying HMPS showing that the HMPS gene is not located at 6q16-61 as previously thought, but at 15q13-q14 (Fig. 10.1).

Clinico-Pathological Features of Hereditary Mixed Polyposis Syndrome

The SM96 pedigree was followed for nearly 40 years. It consisted of more than 20 second degree generation, 64 third generation, 102 fourth generation, and 42 fifth generation individuals [2]. Individuals from this pedigree presented at a median age of 40 years (range 23–65 years) [2]. Clinical presentation consisted of changed bowel habit, passing blood per rectum, abdominal pain, obstruction, or anemia [2]. The median age at diagnosis of CRC was 47 years (range 32–74 years) [2].

On colonoscopic examination, affected individuals presented with a combination of polyp histologies including atypical juvenile polyps, which are perhaps the most characteristic tumors, but also adenomatous and hyperplastic polyps. Affected individuals had no upper gastrointestinal or extraintestinal manifestations.

To describe the characteristics of polyps in individuals with HMPS, 159 from the SM96 pedigree were evaluated and classified according to the World Health Organization of Morson and Sabin [5]. Individuals with HMPS usually presented with less than 15 polyps at initial endoscopic evaluation, although the number of polyps varied among patients. The polyps were distributed throughout the colon, as were the CRCs. Metachronous and synchronous polyps of different histopathologic types were identified. Examples are shown in Fig. 10.2.

Molecular Features and Genetics

The classification of individuals with HMPS was challenging, particularly when these individuals did not present with a characteristic phenotype and/or had synchronous and metachronous polyps of various histopathologic types. In an effort to assess whether these patients had an atypical presentation of an already established polyposis syndrome, or a distinct disorder, molecular diagnosis was needed for further classification. Initial linkage analysis on SM96 pedigree excluded most of the mutations at candidate loci, which were known to be associated with hereditary or sporadic colorectal tumors, as the cause of HMPS [2]. Linkage of the HMPS locus to the FAP locus, *APC*, as well as other candidate loci, including *MSH2*, *TP53*, and *DCC*, were excluded on the basis of logarithm of the odds (LOD) score [2], a LOD score of >3.0 conventionally being considered evidence of genetic linkage between the disease and the test loci [2].

Data from previous studies initially mapped the HMPS locus to chromosome 6q16-q21 [4]. A genetic linkage analysis was performed on 46 members of the HMPS kindred, SM96. This analysis showed that the only significant positive LOD score was found at the D6S283 locus on chromosome 6q [4]. SM96 was subsequently retested. A genome wide linkage screen was performed in the SM96 kindred, which confirmed that HMPS and 6q16-q21 alleles did not co-segregate [6]. However, the genome wide screen showed that the only site in the genome with evidence of linkage to HMPS was on chromosome 15q13-q21 [6].

Individuals from another Ashkenazi kindred SM1311 had a similar phenotypic presentation to HMPS. Affected members of SM1311 presented with polyps of multiple histopathological types and CRC, throughout the colon, without evidence of extracolonic features. Genetic linkage and mutational analysis were done to locate a novel susceptibility gene in this Ashkenazi pedigree (SM1311). Genetic linkage analysis showed evidence for a new susceptibility gene *CRAC1*, which mapped to chromosome 15q14-q22 [7]. This raised the question of whether *HMPS*

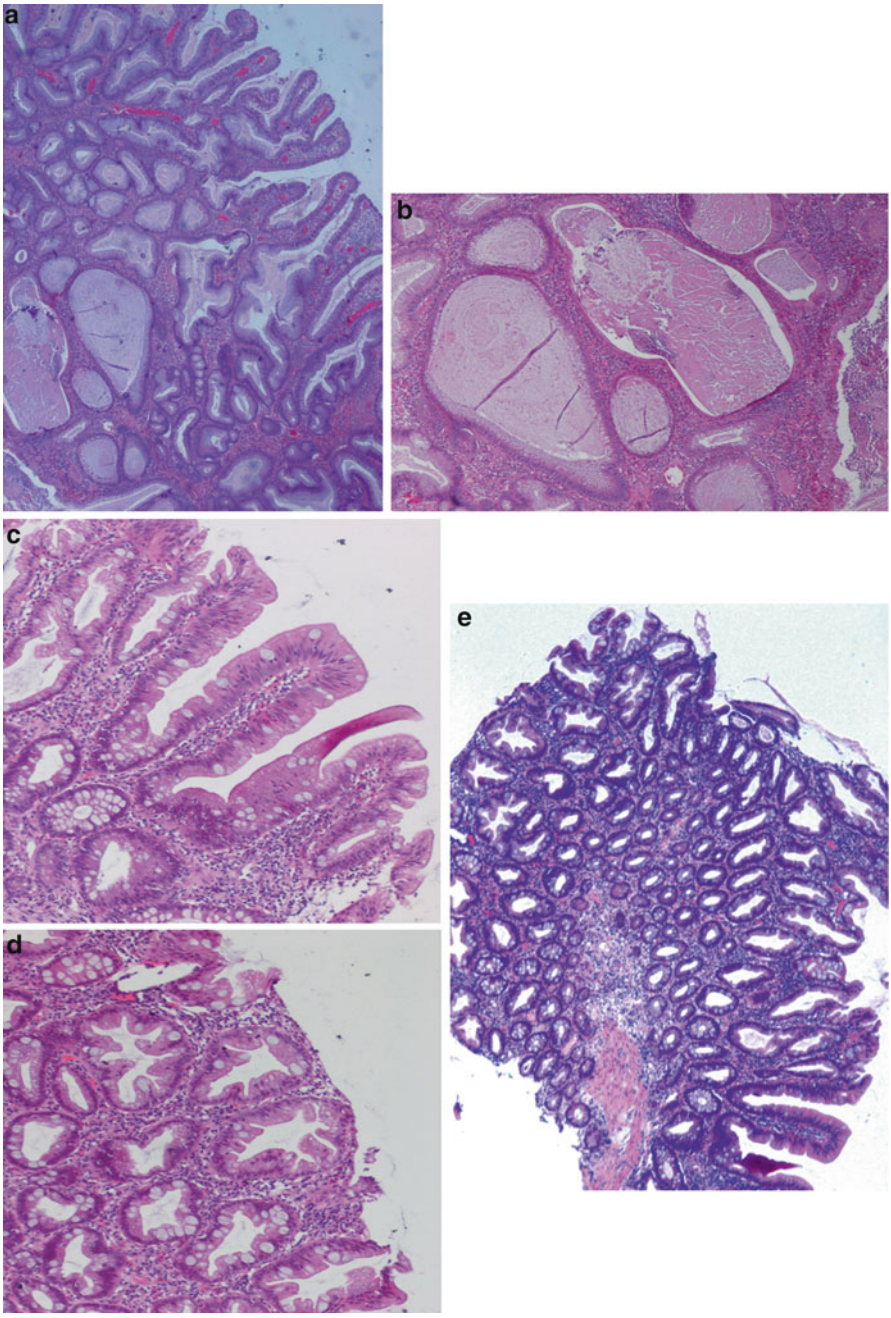


Fig. 10.2 Histopathological features of HMPS polyps. (**a**) Mixed juvenile-hyperplastic-adenomatous polyp. (**b**) Juvenile polyp. (**c**) Adenoma with serrated features. (**d**) Hyperplastic polyp. (**e**) Mixed hyperplastic-adenomatous polyp

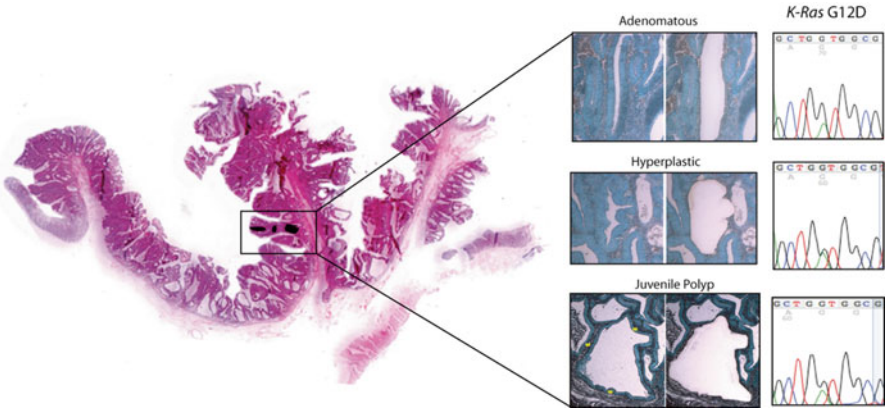


Fig. 10.3 Somatic KRAS mutations variably present in different areas of an HMPS polyps

and *CRAC1* might be the same locus. Jaeger et al. compared the *CRAC1* and SM96 disease-associated haplotypes, and found that they were identical for markers shared within a region between microsatellite markers D15S1031 and D15S118 on chromosome 15, suggesting that the *HMPS* and *CRAC1* genes were the same [6]. Subsequently, several additional Ashkenazi families that presented with colorectal adenomas were examined (Fig. 10.1). All affected members were found to have the HMPS/CRAC1 haplotype between D15S1031 and D15S118, and this was rare in the general Ashkenazi population [6]. The data indicated that these families most likely shared an ancestral mutation that was responsible for their disease.

The causative germline mutation for HMPS was identified by Jaeger et al. The authors showed that HMPS results from an unusual duplication of approximately 40 kb upstream of the gene that encodes the bone morphogenetic protein (BMP) agonist *GREM1* [1]. This duplication, which contains a variety of gene regulatory elements, causes greatly increased *GREM1* expression and ectopic expression in the epithelium of the colon as well as the normal location in the mesenchyme. Excess GREM1 is predicted to cause reduced BMP pathway activity, thus resembling the inactivation of BMP pathway components (SMAD4 and BMPR1A) thought to underlie tumor formation in JPS [1]. The ancestral Ashkenazi HMPS duplication can be identified using a single PCR based on the finding that there exists a short unique DNA sequence between the duplicated regions. However, such testing is unlikely to be sufficient, since recently, an independent, slightly smaller duplication upstream of *GREM1* has been reported in a northern European family without known Jewish ancestry.

The molecular pathways of polyp formation and progression to cancer in HMPS are not well characterized. *GREM1* does not appear to be a tumor suppressor, but a "landscaper" gene that alters the microenvironment to make it permissive for colorectal tumorigenesis. The available evidence suggests that the initial HMPS lesion is usually a hyperplastic polyp that carries a somatically acquired *KRAS* or *BRAF* mutation (Fig. 10.3). This may become dysplastic owing to *APC* mutations

and progress to carcinoma. Whether juvenile polyps can develop without the requirement for further somatic mutations remains unclear.

Overlap Between HMPS and Juvenile Polyposis

Given their related functional gene defects, it is perhaps not surprising that the phenotypic features of HMPS and JPS overlap, and juvenile polyps can occur in both syndromes. Such overlapping features are common in cancer syndromes. There are, however, clear differences between HMPS and JPS, including: (1) the presence of important extracolonic features in JPS; (2) the predominance of serrated/hyperplastic polyps in HMPS; (3) the generally older age of presentation in HMPS; and (4) disease prevalence. Recent claims that *BMPR1A* mutations can cause HMPS [8] have little utility, not least because HMPS patients can also present with very similar disease to patients with germline mutations in *APC and MUYTH, NTHL1, POLE, POLD1*, and the MMR genes. These syndromes are best defined by their underlying mutations, even if the phenotypic features share similarities.

Recommendations for Surveillance in HMPS

For asymptomatic HMPS mutation carriers, the age at which screening should be started and the surveillance interval are unclear owing to the rarity of the disease and its young history as a defined entity still need to be elucidated. Existing data show that the earliest age at which polyps have been diagnosed in an affected individual was 18 years. Therefore, it might be reasonable to start screening at the age of 18 years, based on the available data [2]. Currently there are no established guidelines for surveillance. Biennial colonoscopy is recommended based on the finding that an individual from the SM96 pedigree developed 12 adenomas in a two-year interval [2]. Since half of the cancers diagnosed in SM96 were found proximal to the mid-transverse colon, colonoscopy is considered the screening modality of choice [2]. Extracolonic screening is not currently recommended. Colonoscopy appears sufficient to manage the polyp burden and risk of progression according to the limited available evidence, and prophylactic surgery is not currently recommended.

Summary

HMPS is a Mendelian dominant CRC predisposition syndrome, characterized by multiple colorectal polyps. The distinctive clinical phenotype of polyps of mixed histopathological type is not reliably present, and mixed polyps (e.g.,

serrated + adenomatous, juvenile + adenomatous) can be present in other conditions. It is therefore recommended that duplications upstream of *GREM1* are included in gene panels for testing the Mendelian CRC genes, unless there is a sufficient clinical suspicion and a dominant pedigree of Ashkenazi origins, in which case early, focussed *GREM1* screening could be performed. Although screening and surveillance algorithms still need to be elucidated, early recognition of individuals at risk for this syndrome will potentially help decrease morbidity and mortality of CRC, as early screening implementation should be effective in detecting premalignant lesions and early stage CRC.

References

1. Jaeger E, Leedham S, Lewis A, et al. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Nat Genet. 2012;44(6):699–703.
2. Whitelaw SC, Murday VA, Tomlinson IP, et al. Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology. 1997;112(2):327–34.
3. Giardiello FM, Hamilton SR. Hereditary mixed polyposis syndrome: A zebra or a horse dressed in pinstripes. Gastroenterology. 1997;112(2):643–5.
4. Thomas HJ, Whitelaw SC, Cottrell SE, et al. Genetic mapping of hereditary mixed polyposis syndrome to chromosome 6q. Am J Hum Genet. 1996;58(4):770–6.
5. Morson BC, Sobin LH. Histological typing of intestinal tumours (International histological classification of tumours, No 15). Geneva: World Health Organization; 1976.
6. Jaeger EE, Woodford-Richens KL, Lockett M, et al. An ancestral Ashkenazi haplotype at the HMPS/CRAC1 locus on 15q13-q14 is associated with hereditary mixed polyposis syndrome. Am J Hum Genet. 2003;72(5):1261–7.
7. Tomlinson I, Rahman N, Frayling I, et al. Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. Gastroenterology. 1999;116(4):789–95.
8. Cao X, Eu KW, Kumarasinghe MP, Li HH, Loi C, Cheah PY. Mapping of hereditary mixed polyposis syndrome (HMPS) to chromosome 10q23 by genomewide high-density single nucleotide polymorphism (SNP) scan and identification of BMPR1A loss of function. J Med Genet. 2006;43(3), e13.

Chapter 11
Familial Adenomatous Polyposis

William Rengifo-Cam, Kory W. Jasperson, Randall W. Burt, and N. Jewel Samadder

Definition

FAP is an autosomal dominant disease with a prevalence of about one in 10,000 live births. It is classically characterized by the development of hundreds to thousands of adenomas in the colon and rectum that progress to colorectal cancer (CRC) in almost all individuals if left untreated.

FAP is the second most common hereditary CRC syndrome, but only a small fraction (<1 %) of all CRCs are due to FAP. Adequate colonoscopy surveillance and prophylactic colectomy has reduced the incidence of CRC cases in FAP. It typically presents in early adolescence and without any intervention, 95 % of patients will develop CRC by age 50 [1].

Attenuated FAP (AFAP) is a less severe form of the same disease with a nearly 70 % lifetime risk of CRC, characterized by later age of adenoma and CRC development, fewer adenomas (0–100 colon adenomatous polyps with an average of 30) and development of more proximal colonic neoplasms [2].

W. Rengifo-Cam
Division of Digestive and Liver Diseases, University of Texas Southwestern, Dallas, TX, USA

K.W. Jasperson
Cancer Control and Population Sciences, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City, UT 84112, USA

R.W. Burt • N.J. Samadder, M.D., M.Sc., F.R.C.P.C. (✉)
Cancer Control and Population Sciences, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City, UT 84112, USA

Division of Gastroenterology and Hepatology, University of Utah, Salt Lake City, UT, USA
e-mail: Jewel.samadder@hsc.utah.edu

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2_11

Epidemiology and Clinical Presentation

The highest incidence of CRC is in Western and industrialized countries. About 85 % of CRCs are sporadic and 15 % are considered to be familial with FAP accounting for less than 1 %. Nonetheless, FAP is one of the highest risk, best known and best understood of the inherited colon cancer conditions. There are many countries with FAP registries but no country has accurate nation-wide data.

Colonic Manifestations

Classic FAP is characterized by the presence of hundreds to thousands of colorectal adenomas of different sizes (Figs. 11.1, 11.2, and 11.3) [3]. In the majority of patients, polyps begin to develop during childhood, mostly in the distal colon as small intramucosal nodules. Polyps thereafter increase in size and numbers. By adolescence, polyps are usually present throughout the entire colon. Children and adolescents rarely present with symptoms. CRC starts to develop a decade after the appearance of polyps, thus the importance of colonoscopy surveillance. Rectal bleeding or even anemia may present when the adenomas are large and numerous. Patients may complain of non-specific symptoms such as change in bowel habits, constipation or diarrhea, abdominal discomfort, palpable abdominal masses, or weight loss. Any of these symptoms may prompt colon examination that will identify multiple polyps suggestive of FAP. If the colon is left untreated, the majority of patients with classical FAP will develop CRC by age 50 years. Although uncommon, CRC has been described in children [4].

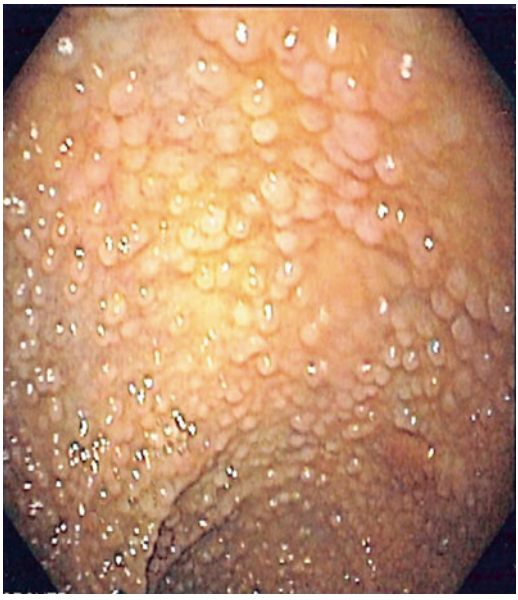


Fig. 11.1 Endoscopic view of the colon. FAP is characterized by the presence of hundreds or thousands of adenomatous polyps in the colons of affected individuals, which often start in adolescence

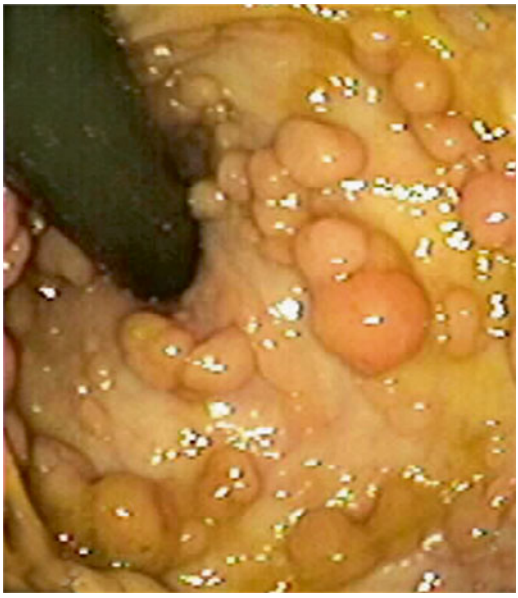


Fig. 11.2 Endoscopic view of the rectum in a patient with FAP, characterized by numerous adenomatous polyps

Fig. 11.3 Gross pathology specimen from a FAP patient undergoing total colectomy and carpeted with thousands of adenomatous polyps. FAP is characterized by the presence of hundreds or thousands of adenomatous polyps in the colons of affected individuals, which often start in adolescence

Gastric Manifestations

Gastric fundic gland polyps (FGP) develop in 90 % of patients with FAP. Although 40 % of these lesions in FAP patients have been shown to have focal adenomatous features, the polyps progress to cancer in only 1 or 2 % of cases [5]. Early diagnosis of gastric cancer is difficult in part due to the large numbers of FGPs [6, 7]. It is well established that FGPs in FAP are pathogenetically distinct from sporadic FGPs. Morphological dysplasia in the FGP of FAP is usually preceded by mutational inactivation of the normal *APC* allele further indicating the polyp's neoplastic potential [8].

Small Bowel Manifestations

The presence of adenomatous polyps in the second and third portions of the duodenum and in the periampullary area has been well described (Fig. 11.4) [9]. It is estimated that they occur in 90 % of patients with FAP and often develop 10–20 years after the appearance of colorectal polyps [10]. Spigelman created a scale for classification of duodenal polyps, based on polyp number, size, histology, and severity of dysplasia (Table 11.1) [10]. Approximately 4–12 % of patients will develop duodenal/periampullary cancer within 10 years if polyps are left untreated [11–13]. Although Spigelman staging is useful to evaluate the progression of duodenal polyposis, cancer can present even in patients with lower Spigelman stages [11, 14]. The colorectal polyp severity cannot be used as a guide to duodenal polyp

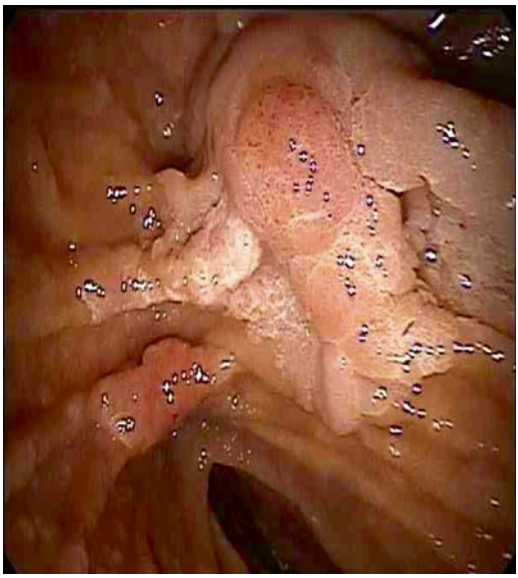


Fig. 11.4 Periampullary region in a patient with FAP showing a large adenomatous polyp with beard-like extension developing from the ampulla

Table 11.1 Spigelman's score and stage

Factor	1 Point	2 Points	3 Points
Number of polyps	1–4	5–20	>20
Polyp size in mm	1–4	5–10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	–	High grade

Stage 0: no polyps; Stage 1: 1–4 points; Stage 2: 5–6 points; Stage 3: 7–8 points; Stage 4: 9–12 points

severity in individual patients as they are frequently disparate. Nonetheless, the coexistence of populations with severe duodenal and rectal polyposis suggests that environmental factors are important in phenotypic expression in FAP [15]. Ampullary carcinoma may present as biliary obstruction or acute pancreatitis in FAP patients with severe duodenal adenomatosis [16]. The main cause of cancer death in FAP after removal of the colon is duodenal malignancy. Thus, the aim of duodenal surveillance is to target individuals with more advanced duodenal polyposis and endoscopically remove polyps or identify early cancers [17, 18].

Although, the risk of pancreatitis after routine screening and biopsy of the ampulla of Vater has been described [19], endoscopic treatment of severe duodenal polyposis in patients with FAP produces few adverse events and allows efficient down staging of the polyposis. Long-term follow-up of patients so managed has shown little risk of invasive duodenal cancer [20].

Jejunal and ileal adenomas can also be observed in patients with FAP undergoing push enteroscopy, double balloon enteroscopy, or capsule endoscopy, with an incidence rate of 30–75 % depending on the evaluation modality [21–23]. Cancer risk in the distal small bowel is much lower than the duodenum, but it occurs and if there is concern for these lesions because of polyp numbers and/or size, adequate surveillance should be implemented.

Extra-Intestinal Manifestations

Although there are many extra-intestinal manifestations of FAP, these lesions are rarely malignant [24]. Gardner syndrome (GS) is a historical variant of FAP and exhibits a number of benign findings including osteomas, fibromas, desmoid tumors (DTs), and cutaneous lesions including pilomatricomas, sebaceous and epidermoid cysts [25, 26]. GS has also been associated with juvenile nasopharyngeal angiofibromas (JNA). JNA is a rare, histologically benign but locally aggressive tumor of the nasal cavity presenting almost exclusively in adolescent males [27–29]. All physicians involved in the care of patients with FAP should be aware that JNA, although rare, is a gender-dependent extra colonic manifestation of substantial consequence. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) can also be associated with GS or FAP without other extra-intestinal manifestations

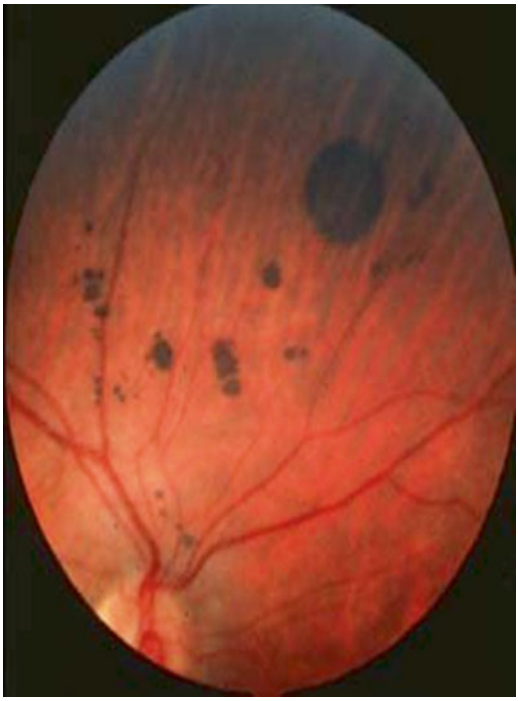


Fig. 11.5 Fundus photography of congenital hypertrophy of the retinal pigment epithelium (CHRPE) lesions. One large and multiple peripheral punctiform CHRPE lesions

and is characterized by bilateral ocular lesions with depigmented halos observed during funduscopic examination (Fig. 11.5) [30–32]. CHRPE was considered to be a benign and stationary lesion, however, there have been reports of low-grade adenocarcinoma arising from these lesions [33, 34]. Gardner syndrome is now considered a historical term, and not a distinct clinical entity separate from FAP as it arises from *APC* mutations as other persons and families with FAP. Nonetheless, there are some correlations between the appearance of extra-intestinal manifestations described above and location of the causative mutation in the *APC* gene.

Desmoid tumors (benign soft tissue tumors of fibroblast growth) may develop in the mesentery, abdominal wall, limbs, and/or areas of scars (Fig. 11.6). Because these tumors can arise from trauma, decreased incidence of DTs has been seen with laparoscopic compared to open colectomy [35]. DTs affect up to 26 % of patients and contribute significantly to morbidity and mortality [36]. Female patients appear to have a higher risk of DT independent of the *APC* mutation site, whereas in male patients the mutation site seems to correlate better with DT occurrence [36]. It has been shown that a multidisciplinary approach to DT treatment is important, including nonsteroidal anti-inflammatory drugs, anti-estrogens, cytotoxic agents, surgery, and in some cases radiation therapy. DT unrelated to surgical trauma has a relatively poor prognosis [37]. Although DTs are considered benign, they grow along aponeurotic tissue planes and by progressive enlargement and consequent pressure and even encasement of gastrointestinal, urinary, nervous, or vascular tissues and structures, they can be life threatening.

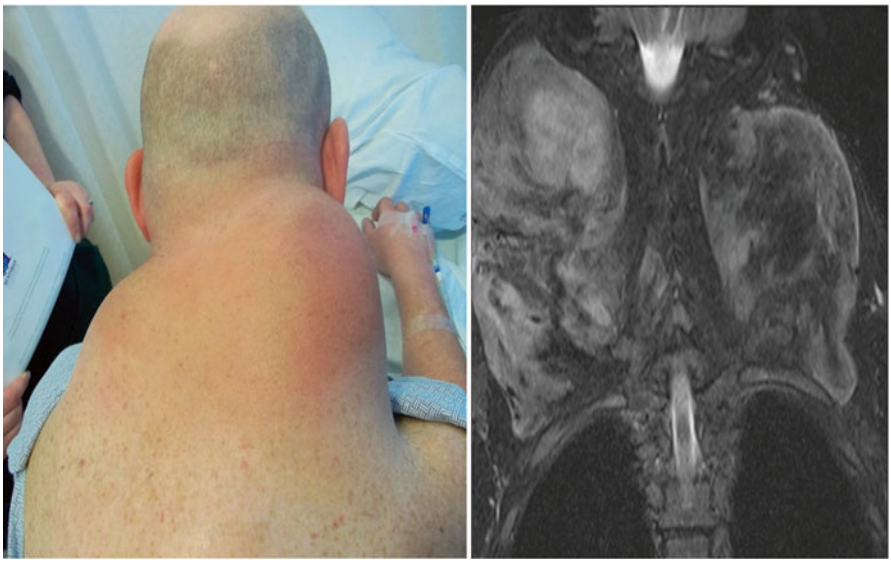


Fig. 11.6 An FAP patient with a 10–13 cm left neck mass and multiple growths on his back. MRI of the neck revealed a diffusely infiltrating soft tissue fibrous tumor involving the upper back and posterior paraspinous soft tissues, consistent with a desmoid tumor

Extra-Intestinal Malignancies

These include pancreatic mucinous adenocarcinomas, hepatoblastomas, brain tumors, and thyroid cancer.

- IPMT (intraductal papillary and mucinous pancreatic tumor) has been described in patients with FAP [38]. It may manifest with typical symptoms of pancreatic tumor including epigastric pain, nausea and vomiting, weight loss, and new onset diabetes mellitus. Spiral computed tomography scan may reveal a large tumor in the pancreas and depending on the location, it may cause an upstream main pancreatic duct dilatation. Endoscopic ultrasonography can confirm these findings. Mucous secretion can be seen at duodenoscopy and a lesion in the main pancreatic duct can be confirmed by retrograde pancreatography. The treatment is pancreaticoduodenectomy [38].
- Compared to the general population, the risk of hepatoblastoma is 750–7500 times higher in children with FAP, almost always occurring in the first decade of life. The effectiveness of surveillance for hepatoblastoma is unclear. In a substantial fraction of sporadic HB, the disease appears to be the first manifestation of a de novo FAP [39]. Genetic testing of *APC* should therefore be considered in individuals with hepatoblastomas [39, 40].
- Another variant of FAP is Turcot syndrome, which includes the association of typical FAP colorectal polyposis with the occurrence of medulloblastoma [41, 42]. Similar to GS, Turcot syndrome is an historical term and no longer considered

a separate entity from FAP. Additionally, some persons and families previously designated as Turcot syndrome have been found to represent Lynch syndrome, in which case, LS patients develop glioblastoma multiforme.

- Several studies have estimated the rate of thyroid cancer in FAP to be five times higher than that seen in the general population [43]. The cribriform morular variant of papillary thyroid carcinoma is a rare subtype of papillary thyroid cancer that occurs most often in FAP patients with a concomitant *RAS* mutation in the tumor [44]. No current consensus defines screening for thyroid cancer in FAP. However, a recent study has shown that screening-detected cases (by ultrasound) showed smaller-sized cancers that required less radical therapy compared to nonscreened cases. Therefore, a baseline and subsequent thyroid US surveillance in all FAP patients should be considered, in addition to annual thyroid palpation [45, 46]. Benign thyroid lesions (hypothyroidism, nodules, cysts, goiter, thyroiditis) have also been reported in FAP with a female preponderance [43, 47].
- Benign cutaneous lesions have been reported as noted above under GS. These include epidermoid cysts, fibromas, and pilomatricomas. They do not appear to have malignant potential but may cause pain and/or cosmetic concern depending on size and location [48, 49].
- Craniomaxillofacial manifestations (osteoma formation, tooth impaction, diffuse opacities in the skull, mandible and maxilla, scalp tumors) usually precede polyposis [50]. Dental pathology observed in 17 % of individuals with FAP include unerupted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts, and odontomas [51].
- Adrenal masses were found in 7.4–13 % of individuals with FAP [52, 53]. These masses are asymptomatic adenomas and found incidentally, however, functional lesions and carcinoma may also occur but appear to be rare [54, 55].
- Other rare tumors that have also been described include bilateral Sertoli cell tumors of the testis [56], low-grade neuroendocrine tumors [57], mucoepidermoid carcinoma of the parotid gland [58], gastrointestinal stromal tumor [59], breast fibromatosis [60], and ovarian steroid cell tumors [61].

Attenuated Familial Adenomatous Polyposis (AFAP)

AFAP is a less aggressive variant of FAP that is characterized by fewer colorectal adenomatous polyps (usually 10–100) in addition to later age of adenoma appearance (mean age 44 years old) and cancer (mean age 56 years). The mutation detection rate in AFAP is lower than in classic FAP and mutations in these patients are most often located in the proximal and distal portions of the *APC* gene, as well as in certain locations of exon 9. The polyps are predominant in the proximal colon and are infrequent in the rectum [62, 63]. Due to the propensity for proximal colon polyps, a sigmoidoscopy in a patient with AFAP (which often cannot be distinguished prior to colonoscopy) may inappropriately judge their risk of cancer to be low based on visualization limited to the rectosigmoid colon. Colonoscopy is the preferred option for screening in both attenuated and classic forms of FAP. In the

majority of patients, prophylactic colectomy and ileorectal anastomosis (IRA) are recommended at the age of 20–25 years depending on polyp number, size, and histology [64]. As in FAP the most common extracolonic findings are duodenal and gastric adenomas and FGP. Gastric and duodenal cancers also occur. Other extracolonic lesions of FAP are rare, but have been described [64].

Differential Diagnosis

FAP may be distinguished from other polyposis syndromes by molecular genetic testing, histopathology findings, and phenotypic characteristics. Hereditary disorders to consider in the differential diagnosis include the following:

1. ***MUTYH*-associated polyposis (MAP)**. MAP was first described in 2002. *MUTYH* is a component of a base excision repair system that protects the genomic information from oxidative damage [65]. When the *MUTYH* gene product is impaired by biallelic germline mutation, it leads to the mutation of cancer-related genes, such as the *APC* and/or the *KRAS* genes, via G to T transversions. MAP is a hereditary CRC syndrome inherited in an autosomal-recessive fashion. Patients can have either homozygous or compound heterozygous germline *MUTYH* mutations. Biallelic germline mutations of the *MUTYH* gene occur in 18 % of *APC* gene mutation-negative patients with an attenuated polyposis phenotype [66]. Colorectal surveillance starting at about 18 years of age is recommended in MAP [67, 68]. The clinical features of MAP include the presence of 10–100 s of adenomatous polyps in the colon, and young-onset of CRC. The frequency of duodenal polyposis is between 4 % and 25 % among individuals with biallelic *MUTYH* pathogenic variants; extra-intestinal findings are also noted on occasion [67]. If an *APC* pathogenic mutation is not identified in a patient who has a phenotype compatible with AFAP, molecular genetic testing of *MUTYH* should be considered [69].
2. **Lynch syndrome.** It is caused by a heterozygous germline mutation in one of four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or the *EPCAM* gene causing an increased risk for CRC and other cancers (e.g., of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, skin). Family history of extracolonic cancers as well as microsatellite instability testing and/or immunohistochemistry testing on tumor tissue from a colon or uterine cancer may help to differentiate from AFAP especially if few polyps are present [70]. Constitutional mismatch repair deficiency (CMMRD) syndrome results from biallelic germline mutations in these same genes. The tumor spectrum is very broad, including mainly hematological, brain, and intestinal tract tumors. Patients also show a variety of non-malignant features that are indicative of CMMRD including multiple hyperpigmented spots (café au lait macules) and hypopigmented skin areas, neurofibromas, axillary and inguinal freckling, brain malformations, pilomatricomas, and multiple colorectal adenomas mimicking AFAP [71, 72].

3. **Peutz–Jeghers syndrome (PJS).** This is an autosomal dominant inherited condition, characterized by hamartomatous gastrointestinal polyposis and mucocutaneous pigmentation, neither of which are present in FAP/AFAP [73]. It is linked to mutations in the *STK 11/LKB1* gene. Patients affected by PJS have an increased risk of developing a variety of cancers. Extra-intestinal malignancies are mostly breast cancer in women, followed closely by pancreatic cancer. Peutz-Jeghers polyps may result in acute gastrointestinal bleeding, intussusception, and bowel obstruction [74].
4. **PTEN hamartoma tumor syndrome (PHTS).** Cowden syndrome (CS), the most common presentation of PHTS, is an autosomal dominant hereditary cancer syndrome causing increased risk for breast, thyroid, renal, uterine, and other cancers as well as benign neoplasias and neurodevelopmental concerns. Unlike FAP/AFAP, hamartomatous polyps (juvenile polyps, lipomas, and ganglioneuromas) predominate, and colon cancer is uncommon [75].
5. **Juvenile polyposis syndrome (JPS).** It is an autosomal dominant predisposition to the occurrence of juvenile type hamartomatous polyps in the gastrointestinal tract. Diagnosis of JPS is based on the occurrence of multiple juvenile polyps or any number of these polyps with family history of JPS. JPS is caused by mutations in *the SMAD4* or *BMPR1A genes*. The *SMAD4* genotype is associated with a more aggressive upper gastrointestinal malignancy risk [76]. JPS belongs to the group of hamartomatous polyposis conditions, compared to FAP/AFAP which are associated with adenomatous polyposis [76, 77].
6. **Hereditary mixed polyposis syndrome (HMPS).** This condition is an autosomal dominant disorder caused by a duplication upstream of *GREM1* gene [78, 79]. It is characterized by an increased risk for colorectal tumors and cancer. The characteristic lesions are mixed juvenile-adenomatous colon polyps. However, adenomas, hyperplastic, serrated adenomas, and mixed hyperplastic-adenomatous polyps may also occur [80].
7. **Neurofibromatosis type 1 (NF1).** NF1 is an autosomal dominant inherited disorder characterized by both benign and malignant tumors. They exhibit multiple intestinal polypoid neurofibromas or ganglioneuromas in the small bowel, stomach, and colon. Colon adenocarcinomas have rarely been reported [81].
8. **Serrated polyposis (SP).** SP is characterized by serrated polyps distributed throughout the colorectum. These patients may also have synchronous colorectal adenomas and CRCs [82]. A recent study suggested that the risk of extracolonic cancer may also be increased including breast, ovarian, cervical, and prostate cancer [83, 84]. The genetic etiology of SP remains unknown.
9. **Cronkhite–Canada syndrome.** This is a rare acquired gastro-enterocolopathy of uncertain etiology and characterized by diffuse gastrointestinal polyposis sparing only the esophagus, ectodermal abnormalities, and an unpredictable but often fatal clinical course. The disease may demonstrate extremely diverse clinical and endoscopic features [85]. Comprehensive treatment led by corticosteroids can result in partial remission of clinical symptoms [86].
10. **Nodular lymphoid hyperplasia.** It is a very rare disease characterized by a diffuse nodular lymphoid hyperplasia of the gastrointestinal tract resulting in

diffuse detectable small polypoid masses distributed in the small intestine, colon, or both. It may be associated with common variable immunodeficiency syndrome [87, 88].

11. **Lymphomatous polyposis.** The gastrointestinal tract is the predominant site of extranodal non-Hodgkin lymphomas. Multiple lymphomatous polyposis is a type of appearance of mantle cell lymphoma. It is characterized by multiple polypoid lesions involving long gastrointestinal tracts and it accounts for only approximately 1–2 % of non-Hodgkin lymphomas [89, 90].
12. **Inflammatory polyposis.** These are acquired, non-neoplastic polyps associated with inflammatory bowel disease.
13. **Sporadic colorectal tumors.** The majority of sporadic colorectal tumors have been associated with a somatic pathogenic mutation in the *APC* gene that is believed to occur early during tumorigenesis.

Genetics and Diagnosis

Both, FAP and AFAP are caused by germline mutations in the *APC* gene, which encodes the tumor suppressor protein APC, recognized as an important part of the WNT signaling cascade [91]. Genetic testing of *APC* should be considered when more than ten adenomatous colon polyps are found at a single examination or over time. Detection rate of *APC* mutations is strongly associated with polyp numbers [92]. Other findings that may suggest the presence of *APC* mutation include family history of CRC or colonic polyposis, onset of polyps and CRC at younger ages, and extracolonic findings [93]. However, 30 % of newly diagnosed FAP are due to de novo *APC* mutations. Several studies have evaluated a genotype–phenotype correlation, suggesting that the location of the mutation within the *APC* gene is associated with the severity of colonic polyposis and the presence of extra-intestinal manifestations including desmoid tumors and CHRPE [94]. Although there are no formal recommendations on the use of genotype–phenotype correlations in the management of patients with germline *APC* mutations, it has been suggested that mutation analysis might predict severity of polyposis and be helpful in the surgical decision [95].

A genetic diagnosis of FAP and AFAP depends on finding a disease-causing mutation in the *APC* gene. Greater than 100 colonic adenomas is often used as the cutoff for determining the "classic" form of FAP while AFAP is often suspected when less than 100 adenomas are found in a person with an *APC* mutation. But AFAP can overlap with classic FAP and with MAP [69]. Therefore, genetic testing is necessary in order to differentiate AFAP and FAP from MAP because the tumor risks and inheritance patterns are different.

The possibility of detecting an *APC* pathogenic variant depends on the severity of colonic polyposis and family history. Several reports have shown higher detection rates in individuals with classic polyposis than in attenuated colonic phenotypes [67, 96–98] and higher in individuals with other relatives affected with polyposis compared to de novo cases without family history in the previous generation [99–101].

In fact, less than 30 % of individuals with attenuated phenotypes are expected to have an identifiable APC mutation [102].

Most *APC* pathogenic variants are nonsense or frameshift and cause premature truncation of the *APC* protein.

It has been reported that a proportion of mutation-negative FAP cases bear molecular changes in deep intronic and regulatory sequences and that approximately 20 % of individuals with de novo *APC* mutation have somatic mosaicism [101]. In individuals with somatic mosaicism, genetic sequencing of *APC* from DNA extracted from peripheral blood lymphocytes may fail to detect any alteration because of weak mutation signals [100, 101]. It has been reported that protein truncation test (PTT) may be useful in identifying mutations in apparently *APC* mutation-negative FAP patients with mosaicism [103]. Furthermore, individuals with mutation-negative FAP should also be evaluated for *APC* promoter 1B mutations [104–106]. Interstitial deletions of chromosome 5q that include *APC* have been identified in a number of patients with colonic polyposis, intellectual disability, and other findings [107]. A classic or attenuated colonic phenotype is possible in cases with whole *APC* gene deletions [108].

When no pathogenic variant is identified in an affected individual, linkage analysis can be considered in families with more than one affected family member belonging to different generations. Linkage studies are based on an accurate clinical diagnosis of an *APC*-associated polyposis condition in the affected family members and accurate understanding of genetic relationships in the family. For this reason, linkage analysis is not possible in individuals with de novo gene mutations [109, 110].

Genotype–Phenotype Correlations

A great effort has gone into making genotype–phenotype correlations to design management strategies based on these associations [111]. However, some studies have suggested that therapeutic decisions should not be based on genotype [112].

There is not routine use at present but there are several correlations that may become important for patient management in the future.

- The most frequent *APC* pathogenic variant is located at codon 1309 (c.3927_3931delAAAGA) and has been associated with a high number of colonic adenomas at an early age [112–114].
- The average age of onset for colonic symptoms varies depending on the pathogenic variant location [112]:
  - Codon 1309: age 20 years
  - Between codon 168 and 1580 (excluding 1309): age 30 years
  - 5′ of codon 168 and 3′ of codon 1580: age 52 years

- Severe polyposis (about 5000 polyps): codon 1250–1464 [115]
- Attenuated FAP has been related to:
  - Truncating mutations in the 5′ part of the gene (codons 1–77) [116], exon 9 [116–118], and the distal 3′ end of the gene [116, 119–121].
  - Deletions of chromosome 5q22 that include *APC* [108]
  - Specific in-frame deletions [122]
  - Somatic mosaicism for *APC* pathogenic variant [100, 101, 123]
- Risk for duodenal adenomas: pathogenic variant between codons 976 and 1067 [114].
- Desmoid tumors have been related to:
  - pathogenic variants 3′ to codon 1399 [124].
  - 20 % of individuals with pathogenic variants 5′ to codon 1444, 49 % of individuals with pathogenic variants 3′ to codon 1444, and 61 % of individuals with pathogenic variants in codons 1445–1580 [112].
  - Pathogenic variants at the extreme 3′ end of the gene (codon 1924) [125–127].
  - Pathogenic variants distal to codon 1444 [94, 128].
  - Pathogenic variants in codons 1395–1493 have significantly higher rate of desmoid tumors, osteomas, and epidermoid cysts [129].
  - Pathogenic variants in codons 1445–1578 developed desmoid tumors [123].
  - Pathogenic variants found in a Korean population in codon 1280 [130]
- CHRPE is associated with:
  - Pathogenic variants between codons 148–2043 [48]
  - Whole *APC* gene deletions [97]
- Hepatoblastoma and/or brain tumors are associated with:
  - Pathogenic variants in codons 457–1309 [129]
- Thyroid cancer is associated with:
  - Pathogenic variants 5′ to codon 1220 [131]
  - Pathogenic variants proximal to the mutation cluster region (codons 1286–1513) [132].
  - Pathogenic variants in codon 180 [130].
  - Pathogenic variants c.3183_87delACAAA and del9-10 (del9080dup11) [133].
- Survival:
  - Patients with a pathogenic variant in codons 1249–1549 develop polyposis at an early age and have a worse survival. Patients with a pathogenic variant in codons 0–178 or 312–412 develop polyposis later and have an improved survival [134].

Colorectal Surveillance and Management

Classic FAP has nearly 100 % lifetime risk of CRC, therefore screening and early diagnosis are essential. Several studies have compared the incidence of CRC in screened versus symptomatic patients with FAP as part of national polyposis registries in Europe, Australia, and North America [135–138]. These studies showed that the incidence of CRC was higher in symptomatic FAP cases (50–70 %) compared with those in a registry-based surveillance (3–10 %) [137, 139–141]. Therefore, there is overwhelming evidence that colonoscopy/sigmoidoscopy screening is efficacious at identifying patients who should have prophylactic colectomy. Unfortunately, studies have shown that the colonoscopy adherence in FAP and AFAP patients is low [142].

The age of initiation of CRC surveillance in FAP is between 10 and 12 years old. This is based on studies involving large case series of FAP families from the 1970s and 1980s suggesting that development of CRC before the age of 20 years is very rare, but possible [143]. A small number of cases with high grade dysplasia or cancer have been described in children [144–146].

Interestingly, individual colon adenomas in patients with FAP are histologically identical to sporadic adenomatous polyps and do not seem to have an increased malignant potential. The adenoma to carcinoma timeline has an average of 10–15 years for any one individual adenoma. The increased cancer risk arises from the large number of adenomas that form in this condition. This supports the current recommendation to perform a colonoscopy evaluation every 1–2 years initially and then increased to annual surveillance once adenomatous polyps are found.

AFAP may have rectal and distal colon sparing with a propensity for proximal colon polyps. For this reason colonoscopy is the preferred option for screening and not sigmoidoscopy. Experts have recommended initiating colonoscopy evaluation in their late teens (18 years old) and an interval of 1–2 years. This recommendation is based on the observation that the mean age of CRC diagnosis is older in AFAP compared with classic FAP (54 years versus 39 years old) and no cases of CRC below 29 years old were found in a large Utah AFAP kindred [2]. Approximately 33 % of patients with AFAP can be managed with colonoscopy and polypectomy because of the lower polyp density (median of 25 colorectal adenomas), thus preventing the need of colectomy.

Surgical consideration should be considered early in FAP patients who present with >20 adenomas, when adenomas are >1 cm in size or when advanced histology appears (villous or high grade dysplasia) [65]. The two surgical options are total colectomy with IRA or proctocolectomy with ileal pouch-anal anastomosis (IPAA). IPAA is preferred when numerous rectal adenomas are found. If IRA is selected, at least annual (or more frequent) endoscopic surveillance must be performed to ensure that cancer does not develop in the remaining rectal segment. In these cases, the use of Sulindac can effectively regress polyps in the remaining rectal mucosa, making surveillance easier [147–149]. A meta-analysis found that patients subjected to IRA have less negative quality of life issues than patients who underwent IPAA, though fecal urgency was reduced in the IPAA group. There were no significant

differences between the two techniques regarding sexual dysfunction or postoperative complications. Rectal cancer only occurred in the IRA group [150].

Screening for Extracolonic Cancer Sites

The Spigelman staging criteria is helpful in determining the risk of duodenal malignancy, interval for endoscopy follow-up, and need for future therapeutic endoscopy or surgical management of duodenal and ampullary adenomas [10]. Current recommendations advise upper gastrointestinal endoscopy, including side-viewing endoscopy, to be performed every 1–3 years for patients with either AFAP or FAP, starting at age 25–30 years.

Annual thyroid examination with ultrasound should also be considered for patients with AFAP or FAP due to increased risk of thyroid cancer [45, 151]. There is no evidence to recommend screening for adrenal masses in FAP [152]. Screening for hepatoblastoma in FAP may be considered with abdominal ultrasound and measurements of serum alpha-fetoprotein levels from infancy to age 5 years every 3 months. However its efficacy remains to be seen [40, 100, 153].

Chemopreventive strategies have been studied in FAP patients in an effort to delay the development of adenomas in the upper and the lower gastrointestinal tract and to prevent recurrence of adenomas in the retained rectum of patients after IRA prophylactic surgery. Sulindac, a nonsteroidal anti-inflammatory drug, causes regression of colorectal adenomas in the retained rectal segment of FAP patients [154]. Further studies are needed to establish if sulindac may also be effective in reducing the size and the number of colonic polyps in patients with FAP without a prophylactic colectomy and polypectomy [149, 155].

Preimplantation genetic diagnosis (PGD) is a technology that allows embryos without a deleterious mutation associated with a hereditary cancer syndrome to be identified and implanted. The parent's disease-causing allele must be identified before PGD can be performed [156].

Conclusions

FAP is an autosomal-dominant syndrome, caused by a germline mutation in the *APC* gene. It is characterized by hundreds to thousands of adenomatous polyps, with an inevitable progression to CRC if left untreated. Associated features include upper gastrointestinal tract polyps, CHRPE, desmoid tumors, and other extracolonic malignancies. Gardner syndrome is more of a historical subdivision of FAP, characterized by osteomas, dental anomalies, epidermal cysts, and soft tissue tumors. Turcot syndrome refers to polyposis associated with medulloblastoma. Several genotype–phenotype correlations have been observed. AFAP presents with fewer than 100 adenomas. Multiple colorectal adenomas can also be caused by

mutations in the human *MUTYH* gene in an autosomal-recessive condition referred to as MAP. Endoscopic screening of FAP probands and relatives is advocated as early as the ages of 10–12 years, with the objective of reducing the occurrence of CRC. Colectomy remains the optimal prophylactic treatment. The major challenges for the future are identifying better chemopreventive agents and optimizing screening of extracolonic cancers.

References

1. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044–58.
2. Burt RW, Leppert MF, Slattery ML, Samowitz WS, Spirio LN, Kerber RA, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology. 2004;127(2):444–51.
3. Jasperson KW, Burt RW. APC-associated polyposis conditions. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, et al. editors. GeneReviews(R). Seattle, WA: University of Washington; 1993.
4. Vaynsthein G, Gurlanik L, Markel A. Gardner's syndrome in a 75-year-old woman. Intern Med. 2008;47(16):1491–4.
5. Bianchi LK, Burke CA, Bennett AE, Lopez R, Hasson H, Church JM. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2008;6(2):180–5.
6. Lynch HT, Snyder C, Davies JM, Lanspa S, Lynch J, Gatalica Z, et al. FAP, gastric cancer, and genetic counseling featuring children and young adults: a family study and review. Fam Cancer. 2010;9(4):581–8.
7. Shibata C, Ogawa H, Miura K, Naitoh T, Yamauchi J, Unno M. Clinical characteristics of gastric cancer in patients with familial adenomatous polyposis. Tohoku J Exp Med. 2013;229(2):143–6.
8. Abraham SC, Nobukawa B, Giardiello FM, Hamilton SR, Wu TT. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. Am J Pathol. 2000;157(3):747–54.
9. Domizio P, Talbot IC, Spigelman AD, Williams CB, Phillips RK. Upper gastrointestinal pathology in familial adenomatous polyposis: results from a prospective study of 102 patients. J Clin Pathol. 1990;43(9):738–43.
10. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet. 1989;2(8666):783–5.
11. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. Gut. 2002;50(5):636–41.
12. Bulow S, Alm T, Fausa O, Hultcrantz R, Jarvinen H, Vasen H. Duodenal adenomatosis in familial adenomatous polyposis. DAF Project Group. Int J Colorectal Dis. 1995;10(1):43–6.
13. Biasco G, Pantaleo MA, Di Febo G, Calabrese C, Brandi G, Bulow S. Risk of duodenal cancer in patients with familial adenomatous polyposis. Gut. 2004;53:1547. author reply.
14. Bulow S, Bjork J, Christensen IJ, Fausa O, Jarvinen H, Moesgaard F, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004;53(3):381–6.
15. Spigelman AD, Williams CB, Phillips RK. Rectal polyposis as a guide to duodenal polyposis in familial adenomatous polyposis. J R Soc Med. 1992;85(2):77–9.
16. Vasiliadisl K, Papavasiliou C, Pervana S, Nikopoulos K, Makridis C. Acute pancreatitis as the initial manifestation of an adenocarcinoma of the major duodenal papilla in a patient with

familial adenomatous polyposis syndrome: a case report and literature review. Acta Chir Belg. 2013;113(6):463–7.
17. Debinski HS, Spigelman AD, Hatfield A, Williams CB, Phillips RK. Upper intestinal surveillance in familial adenomatous polyposis. Eur J Cancer. 1995;31a(7–8):1149–53.
18. Nugent KP, Spigelman AD, Williams CB, Talbot IC, Phillips RK. Surveillance of duodenal polyps in familial adenomatous polyposis: progress report. J R Soc Med. 1994;87(11):704–6.
19. Nugent KP, Spigelman AD, Williams CB, Phillips RK. Latrogenic pancreatitis in familial adenomatous polyposis. Gut. 1993;34(9):1269–70.
20. Moussata D, Napoleon B, Lepilliez V, Klich A, Ecochard R, Lapalus MG, et al. Endoscopic treatment of severe duodenal polyposis as an alternative to surgery for patients with familial adenomatous polyposis. Gastrointest Endosc. 2014;80(5):817–25.
21. Matsumoto T, Esaki M, Yanaru-Fujisawa R, Moriyama T, Yada S, Nakamura S, et al. Small-intestinal involvement in familial adenomatous polyposis: evaluation by double-balloon endoscopy and intraoperative enteroscopy. Gastrointest Endosc. 2008;68(5):911–9.
22. Iaquinto G, Fornasarig M, Quaia M, Giardullo N, D'Onofrio V, Iaquinto S, et al. Capsule endoscopy is useful and safe for small-bowel surveillance in familial adenomatous polyposis. Gastrointest Endosc. 2008;67(1):61–7.
23. Alderlieste YA, Rauws EA, Mathus-Vliegen EM, Fockens P, Dekker E. Prospective enteroscopic evaluation of jejunal polyposis in patients with familial adenomatous polyposis and advanced duodenal polyposis. Fam Cancer. 2013;12(1):51–6.
24. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis. 2009;4:22.
25. Juhn E, Khachemoune A. Gardner syndrome: skin manifestations, differential diagnosis and management. Am J Clin Dermatol. 2010;11(2):117–22.
26. Gomez Garcia EB, Knoers NV. Gardner's syndrome (familial adenomatous polyposis): a cilia-related disorder. Lancet Oncol. 2009;10(7):727–35.
27. Valanzano R, Curia MC, Aceto G, Veschi S, De Lellis L, Catalano T, et al. Genetic evidence that juvenile nasopharyngeal angiofibroma is an integral FAP tumour. Gut. 2005;54:1046–7.
28. Ponti G, Losi L, Pellacani G, Rossi GB, Presutti L, Mattioli F, et al. Wnt pathway, angiogenetic and hormonal markers in sporadic and familial adenomatous polyposis-associated juvenile nasopharyngeal angiofibromas (JNA). Appl Immunohistochem Mol Morphol. 2008;16(2):173–8.
29. Waterhouse D. Nasopharyngeal angiofibroma: a manifestation of familial adenomatous polyposis. ANZ J Surg. 2013;83(5):387–8.
30. Nusliha A, Dalpatadu U, Amarasinghe B, Chandrasinghe PC, Deen KI. Congenital hypertrophy of retinal pigment epithelium (CHRPE) in patients with familial adenomatous polyposis (FAP); a polyposis registry experience. BMC Res Notes. 2014;7:734.
31. Chen CS, Phillips KD, Grist S, Bennet G, Craig JE, Muecke JS, et al. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) in familial colorectal cancer. Fam Cancer. 2006;5(4):397–404.
32. Tourino R, Conde-Freire R, Cabezas-Agricola JM, Rodriguez-Aves T, Lopez-Valladares MJ, Otero-Cepeda JL, et al. Value of the congenital hypertrophy of the retinal pigment epithelium in the diagnosis of familial adenomatous polyposis. Int Ophthalmol. 2004;25(2):101–12.
33. Shields JA, Shields CL, Eagle Jr RC, Singh AD. Adenocarcinoma arising from congenital hypertrophy of retinal pigment epithelium. Arch Ophthalmol. 2001;119(4):597–602.
34. Shields JA, Eagle Jr RC, Shields CL, Brown GC, Lally SE. Malignant transformation of congenital hypertrophy of the retinal pigment epithelium. Ophthalmology. 2009;116(11):2213–6.
35. Vitellaro M, Sala P, Signoroni S, Radice P, Fortuzzi S, Civelli EM, et al. Risk of desmoid tumours after open and laparoscopic colectomy in patients with familial adenomatous polyposis. Br J Surg. 2014;101(5):558–65.
36. Schiessling S, Kihm M, Ganschow P, Kadmon G, Buchler MW, Kadmon M. Desmoid tumour biology in patients with familial adenomatous polyposis coli. Br J Surg. 2013;100(5):694–703.
37. Jung WB, Kim CW, Kim JC. Clinical characteristics and adequate treatment of familial adenomatous polyposis combined with desmoid tumors. Cancer Res Treat. 2014;46(4):366–73.

38. Maire F, Hammel P, Terris B, Olschwang S, O'Toole D, Sauvanet A, et al. Intraductal papillary and mucinous pancreatic tumour: a new extracolonic tumour in familial adenomatous polyposis. Gut. 2002;51(3):446–9.
39. Aretz S, Koch A, Uhlhaas S, Friedl W, Propping P, von Schweinitz D, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer. 2006;47(6):811–8.
40. Moore SW, Tshifularo N, Grobbelaar J. Lessons from the hepatoblastoma-familial polyposis connection. S Afr Med J. 2012;102(11 Pt 2):888–9.
41. Gorovoy IR, de Alba Campomanes A. A potential life-saving diagnosis--recognizing Turcot syndrome. J AAPOS. 2014;18(2):186–8.
42. Turcot J, Despres JP, St Pierre F. Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. Dis Colon Rectum. 1959;2:465–8.
43. Steinhagen E, Guillem JG, Chang G, Salo-Mullen EE, Shia J, Fish S, et al. The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized. Clin Colorectal Cancer. 2012;11(4):304–8.
44. Giannelli SM, McPhaul L, Nakamoto J, Gianoukakis AG. Familial adenomatous polyposis-associated, cribriform morular variant of papillary thyroid carcinoma harboring a K-RAS mutation: case presentation and review of molecular mechanisms. Thyroid. 2014;24(7):1184–9.
45. Feng X, Milas M, O'Malley M, LaGuardia L, Berber E, Jin J, et al. Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. Thyroid. 2015;25(3):325–32.
46. Septer S, Slowik V, Morgan R, Dai H, Attard T. Thyroid cancer complicating familial adenomatous polyposis: mutation spectrum of at-risk individuals. Hered Cancer Clin Pract. 2013;11(1):13.
47. Jarrar AM, Milas M, Mitchell J, Laguardia L, O'Malley M, Berber E, et al. Screening for thyroid cancer in patients with familial adenomatous polyposis. Ann Surg. 2011;253(3): 515–21.
48. Burger B, Cattani N, Trueb S, de Lorenzo R, Albertini M, Bontognali E, et al. Prevalence of skin lesions in familial adenomatous polyposis: a marker for presymptomatic diagnosis? Oncologist. 2011;16(12):1698–705.
49. Pujol RM, Casanova JM, Egido R, Pujol J, de Moragas JM. Multiple familial pilomatricomas: a cutaneous marker for Gardner syndrome? Pediatr Dermatol. 1995;12(4):331–5.
50. de Oliveira RM, Martins WD, de Sousa MH, de Aguiar Koubik AC, Avila LF, Zanferrari FL, et al. Oral and maxillofacial manifestations of familial adenomatous polyposis (Gardner's syndrome): a report of two cases. J Contemp Dent Pract. 2009;10(1):82–90.
51. Carl W, Sullivan MA. Dental abnormalities and bone lesions associated with familial adenomatous polyposis: report of cases. J Am Dent Assoc. 1989;119(1):137–9.
52. Marchesa P, Fazio VW, Church JM, McGannon E. Adrenal masses in patients with familial adenomatous polyposis. Dis Colon Rectum. 1997;40(9):1023–8.
53. Rekik NM, Ben Salah S, Kallel N, Kamoun M, Charfi N, Abid M. Adrenocortical secreting mass in a patient with Gardner's syndrome: a case report. Case Rep Med. 2010;2010:682081.
54. Pines Corrales PJ, Gonzalez-Albarran O, Peralta M, Roa C, Anton T. Clinically inapparent adrenal mass in a patient with familial adenomatous polyposis. Horm Res. 2006;66(5):207–10.
55. Else T. Association of adrenocortical carcinoma with familial cancer susceptibility syndromes. Mol Cell Endocrinol. 2012;351(1):66–70.
56. Xiao GQ, Granato RC, Unger PD. Bilateral Sertoli cell tumors of the testis-a likely new extracolonic manifestation of familial adenomatous polyposis. Virchows Arch. 2012;461(6):713–5.
57. Estrella JS, Taggart MW, Rashid A, Abraham SC. Low-grade neuroendocrine tumors arising in intestinal adenomas: evidence for alterations in the adenomatous polyposis coli/beta-catenin pathway. Hum Pathol. 2014;45(10):2051–8.
58. Cazorla A, Viennet G, Uro-Coste E, Valmary-Degano S. Mucoepidermoid carcinoma: A yet unreported cancer associated with familial adenomatous polyposis. J Craniomaxillofac Surg. 2014;42(3):262–4.

59. Bassorgun CI, Ozbudak IH, Erdogan G, Elpek GO, Erdogan O, Gelen T. Familial adenomatous polyposis associated with gastrointestinal stromal tumor: report of a case. Turk J Gastroenterol. 2012;23(3):262–6.
60. Abraham SC, Reynolds C, Lee JH, Montgomery EA, Baisden BL, Krasinskas AM, et al. Fibromatosis of the breast and mutations involving the APC/beta-catenin pathway. Hum Pathol. 2002;33(1):39–46.
61. Hu PJ, Knoepp SM, Wu R, Cho KR. Ovarian steroid cell tumor with biallelic adenomatous polyposis coli inactivation in a patient with familial adenomatous polyposis. Genes Chromosomes Cancer. 2012;51(3):283–9.
62. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62.
63. Ibrahim A, Barnes DR, Dunlop J, Barrowdale D, Antoniou AC, Berg JN. Attenuated familial adenomatous polyposis manifests as autosomal dominant late-onset colorectal cancer. Eur J Hum Genet. 2014;22(11):1330–3.
64. Knudsen AL, Bulow S, Tomlinson I, Moslein G, Heinimann K, Christensen IJ. Attenuated familial adenomatous polyposis: results from an international collaborative study. Colorectal Dis. 2010;12(10 Online):e243–9.
65. Samadder NJ, Jasperson K, Burt RW. Hereditary and common familial colorectal cancer: evidence for colorectal screening. Dig Dis Sci. 2015;60(3):734–47.
66. Sampson JR, Jones S, Dolwani S, Cheadle JP. MutYH (MYH) and colorectal cancer. Biochem Soc Trans. 2005;33(Pt 4):679–83.
67. Aretz S, Uhlhaas S, Goergens H, Siberg K, Vogel M, Pagenstecher C, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer. 2006;119(4):807–14.
68. Jenkins MA, Croitoru ME, Monga N, Cleary SP, Cotterchio M, Hopper JL, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev. 2006;15(2):312–4.
69. Sieber OM, Lipton L, Crabtree M, Heinimann K, Fidalgo P, Phillips RK, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med. 2003;348(9):791–9.
70. Vasen HF, Tomlinson I, Castells A. Clinical management of hereditary colorectal cancer syndromes. Nat Rev Gastroenterol Hepatol. 2015;12:88–97.
71. Wimmer K, Kratz CP, Vasen HF, Caron O, Colas C, Entz-Werle N, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014;51(6):355–65.
72. Jasperson KW, Samowitz WS, Burt RW. Constitutional mismatch repair-deficiency syndrome presenting as colonic adenomatous polyposis: clues from the skin. Clin Genet. 2011;80(4):394–7.
73. Maslyankov S, Trifonov G, Kyoseva D, Fidoshev I, Tzoneva D, Velev G, et al. Peutz-Jeghers syndrome—a rare case and a literature review. Khirurgiia (Sofiia). 2014;(1):43–8.
74. Tomas C, Soyer P, Dohan A, Dray X, Boudiaf M, Hoeffel C. Update on imaging of Peutz-Jeghers syndrome. World J Gastroenterol. 2014;20(31):10864–75.
75. Mester J, Eng C. Cowden syndrome: recognizing and managing a not-so-rare hereditary cancer syndrome. J Surg Oncol. 2015;111(1):125–30.
76. Cichy W, Klincewicz B, Plawski A. Juvenile polyposis syndrome. Arch Med Sci. 2014; 10(3):570–7.
77. Aytac E, Sulu B, Heald B, O'Malley M, LaGuardia L, Remzi FH, et al. Genotype-defined cancer risk in juvenile polyposis syndrome. Br J Surg. 2015;102(1):114–8.
78. Jaeger E, Leedham S, Lewis A, Segditsas S, Becker M, Cuadrado PR, et al. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Nat Genet. 2012;44(6):699–703.
79. Davis H, Irshad S, Bansal M, Rafferty H, Boitsova T, Bardella C, et al. Aberrant epithelial GREM1 expression initiates colonic tumorigenesis from cells outside the stem cell niche. Nat Med. 2015;21(1):62–70.

80. Lucci-Cordisco E, Risio M, Venesio T, Genuardi M. The growing complexity of the intestinal polyposis syndromes. Am J Med Genet A. 2013;161a(11):2777–87.
81. Kim IY, Cho MY, Kim YW. Synchronous multiple colonic adenocarcinomas arising in patient with neurofibromatosis type 1. Ann Surg Treat Res. 2014;87(3):156–60.
82. Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006;131(1):30–9.
83. Edelstein DL, Cruz-Correa M, Soto-Salgado M, Axilbund JE, Hylind LM, Romans K et al. Risk of colorectal and other cancers in patients with serrated polyposis. Clin Gastroenterol Hepatol. 2015;13(9):1697–9.
84. Jasperson KW, Kanth P, Kirchhoff AC, Huismann D, Gammon A, Kohlmann W, et al. Serrated polyposis: colonic phenotype, extracolonic features, and familial risk in a large cohort. Dis Colon Rectum. 2013;56(11):1211–6.
85. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. J Clin Pathol. 2014;67(10):891–7.
86. Wen XH, Wang L, Wang YX, Qian JM. Cronkhite-Canada syndrome: report of six cases and review of literature. World J Gastroenterol. 2014;20(23):7518–22.
87. Hablolvarid MH. Nodular lymphoid hyperplasia of the colon in a vervet monkey (Cholorocebous aethiops). J Med Primatol. 2014;43(6):498–502.
88. Gurkan OE, Yilmaz G, Aksu AU, Demirtas Z, Akyol G, Dalgic B. Colonic lymphoid nodular hyperplasia in childhood: causes of familial Mediterranean fever need extra attention. J Pediatr Gastroenterol Nutr. 2013;57(6):817–21.
89. Cestaro G, De Rosa M, Vitiello C, Galloro G, Gentile M. Multiple lymphomatous polyposis with diffuse involvement of the gastrointestinal tract. Case report. G Chir. 2013;34(5–6):173–5.
90. Aiman S, Chakrapani A, Sawaimoon S, Sen S, Chandy M, Chatterjee S. Multiple lymphomatous polyposis: characteristic endoscopic features. Indian J Gastroenterol. 2014.
91. Nielsen M, Hes FJ, Nagengast FM, Weiss MM, Mathus-Vliegen EM, Morreau H, et al. Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis. Clin Genet. 2007;71(5):427–33.
92. Grover S, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012;308(5):485–92.
93. Jasperson KW. Genetic testing by cancer site: colon (polyposis syndromes). Cancer J. 2012;18(4):328–33.
94. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol. 2007;61(2):153–61.
95. Nieuwenhuis MH, Mathus-Vliegen LM, Slors FJ, Griffioen G, Nagengast FM, Schouten WR, et al. Genotype-phenotype correlations as a guide in the management of familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2007;5(3):374–8.
96. Sieber OM, Lamlum H, Crabtree MD, Rowan AJ, Barclay E, Lipton L, et al. Whole-gene APC deletions cause classical familial adenomatous polyposis, but not attenuated polyposis or "multiple" colorectal adenomas. Proc Natl Acad Sci USA. 2002;99(5):2954–8.
97. Aretz S, Stienen D, Uhlhaas S, Pagenstecher C, Mangold E, Caspari R, et al. Large submicroscopic genomic APC deletions are a common cause of typical familial adenomatous polyposis. J Med Genet. 2005;42:185–92.
98. Michils G, Tejpar S, Thoelen R, van Cutsem E, Vermeesch JR, Fryns JP, et al. Large deletions of the APC gene in 15% of mutation-negative patients with classical polyposis (FAP): a Belgian study. Hum Mutat. 2005;25(2):125–34.
99. Truta B, Allen BA, Conrad PG, Weinberg V, Miller GA, Pomponio R, et al. A comparison of the phenotype and genotype in adenomatous polyposis patients with and without a family history. Fam Cancer. 2005;4(2):127–33.
100. Aretz S, Stienen D, Friedrichs N, Stemmler S, Uhlhaas S, Rahner N, et al. Somatic APC mosaicism: a frequent cause of familial adenomatous polyposis (FAP). Hum Mutat. 2007; 28(10):985–92.

101. Hes FJ, Nielsen M, Bik EC, Konvalinka D, Wijnen JT, Bakker E, et al. Somatic APC mosaicism: an underestimated cause of polyposis coli. Gut. 2008;57(1):71–6.
102. Lefevre JH, Rodrigue CM, Mourra N, Bennis M, Flejou JF, Parc R, et al. Implication of MYH in colorectal polyposis. Ann Surg. 2006;244(6):874–9. discussion 9-80.
103. Necker J, Kovac M, Attenhofer M, Reichlin B, Heinimann K. Detection of APC germ line mosaicism in patients with de novo familial adenomatous polyposis: a plea for the protein truncation test. J Med Genet. 2011;48(8):526–9.
104. Rohlin A, Engwall Y, Fritzell K, Goransson K, Bergsten A, Einbeigi Z, et al. Inactivation of promoter 1B of APC causes partial gene silencing: evidence for a significant role of the promoter in regulation and causative of familial adenomatous polyposis. Oncogene. 2011;30(50): 4977–89.
105. Snow AK, Tuohy TM, Sargent NR, Smith LJ, Burt RW, Neklason DW. APC promoter 1B deletion in seven American families with familial adenomatous polyposis. Clin Genet. 2014.
106. Kadiyska TK, Todorov TP, Bichev SN, Vazharova RV, Nossikoff AV, Savov AS, et al. APC promoter 1B deletion in familial polyposis--implications for mutation-negative families. Clin Genet. 2014;85(5):452–7.
107. Heald B, Moran R, Milas M, Burke C, Eng C. Familial adenomatous polyposis in a patient with unexplained mental retardation. Nat Clin Pract Neurol. 2007;3(12):694–700.
108. Pilarski RT, Brothman AR, Benn P, Shulman RS. Attenuated familial adenomatous polyposis in a man with an interstitial deletion of chromosome arm 5q. Am J Med Genet. 1999;86(4):321–4.
109. Kartheuser A, West S, Walon C, Curtis A, Hamzehloei T, Lannoy N, et al. The genetic background of familial adenomatous polyposis. Linkage analysis, the APC gene identification and mutation screening. Acta Gastroenterol Belg. 1995;58(5–6):433–51.
110. Petersen GM, Slack J, Nakamura Y. Screening guidelines and premorbid diagnosis of familial adenomatous polyposis using linkage. Gastroenterology. 1991;100(6):1658–64.
111. Vasen HF, van der Luijt RB, Slors JF, Buskens E, de Ruiter P, Baeten CG, et al. Molecular genetic tests as a guide to surgical management of familial adenomatous polyposis. Lancet. 1996;348(9025):433–5.
112. Friedl W, Caspari R, Sengteller M, Uhlhaas S, Lamberti C, Jungck M, et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? experience from 680 FAP families. Gut. 2001;48(4):515–21.
113. Friedl W, Aretz S. Familial adenomatous polyposis: experience from a study of 1164 unrelated German polyposis patients. Hered Cancer Clin Pract. 2005;3(3):95–114.
114. Bertario L, Russo A, Sala P, Varesco L, Giarola M, Mondini P, et al. Multiple approach to the exploration of genotype-phenotype correlations in familial adenomatous polyposis. J Clin Oncol. 2003;21(9):1698–707.
115. Nagase H, Miyoshi Y, Horii A, Aoki T, Ogawa M, Utsunomiya J, et al. Correlation between the location of germ-line mutations in the APC gene and the number of colorectal polyps in familial adenomatous polyposis patients. Cancer Res. 1992;52(14):4055–7.
116. Sieber OM, Segditsas S, Knudsen AL, Zhang J, Luz J, Rowan AJ, et al. Disease severity and genetic pathways in attenuated familial adenomatous polyposis vary greatly but depend on the site of the germline mutation. Gut. 2006;55(10):1440–8.
117. van der Luijt RB, Vasen HF, Tops CM, Breukel C, Fodde R, Meera KP. APC mutation in the alternatively spliced region of exon 9 associated with late onset familial adenomatous polyposis. Hum Genet. 1995;96(6):705–10.
118. Soravia C, Berk T, Madlensky L, Mitri A, Cheng H, Gallinger S, et al. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. Am J Hum Genet. 1998;62(6):1290–301.
119. van der Luijt RB, Meera Khan P, Vasen HF, Breukel C, Tops CM, Scott RJ, et al. Germline mutations in the 3′ part of APC exon 15 do not result in truncated proteins and are associated with attenuated adenomatous polyposis coli. Hum Genet. 1996;98(6):727–34.
120. Friedl W, Meuschel S, Caspari R, Lamberti C, Krieger S, Sengteller M, et al. Attenuated familial adenomatous polyposis due to a mutation in the 3′ part of the APC gene. A clue for understanding the function of the APC protein. Hum Genet. 1996;97(5):579–84.

121. Walon C, Kartheuser A, Michils G, Smaers M, Lannoy N, Ngounou P, et al. Novel germline mutations in the APC gene and their phenotypic spectrum in familial adenomatous polyposis kindreds. Hum Genet. 1997;100(5–6):601–5.
122. Nielsen M, Bik E, Hes FJ, Breuning MH, Vasen HF, Bakker E, et al. Genotype-phenotype correlations in 19 Dutch cases with APC gene deletions and a literature review. Eur J Hum Genet. 2007;15(10):1034–42.
123. Caspari R, Olschwang S, Friedl W, Mandl M, Boisson C, Boker T, et al. Familial adenomatous polyposis: desmoid tumours and lack of ophthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet. 1995;4(3):337–40.
124. Sinha A, Tekkis PP, Gibbons DC, Phillips RK, Clark SK. Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis. Colorectal Dis. 2011;13(11):1222–9.
125. Eccles DM, van der Luijt R, Breukel C, Bullman H, Bunyan D, Fisher A, et al. Hereditary desmoid disease due to a frameshift mutation at codon 1924 of the APC gene. Am J Hum Genet. 1996;59(6):1193–201.
126. Scott RJ, Froggatt NJ, Trembath RC, Evans DG, Hodgson SV, Maher ER. Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3′ APC gene mutation. Hum Mol Genet. 1996;5(12):1921–4.
127. Couture J, Mitri A, Lagace R, Smits R, Berk T, Bouchard HL, et al. A germline mutation at the extreme 3′ end of the APC gene results in a severe desmoid phenotype and is associated with overexpression of beta-catenin in the desmoid tumor. Clin Genet. 2000;57(3):205–12.
128. Nieuwenhuis MH, Lefevre JH, Bulow S, Jarvinen H, Bertario L, Kerneis S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum. 2011;54(10):1229–34.
129. Wallis YL, Morton DG, McKeown CM, Macdonald F. Molecular analysis of the APC gene in 205 families: extended genotype-phenotype correlations in FAP and evidence for the role of APC amino acid changes in colorectal cancer predisposition. J Med Genet. 1999;36(1):14–20.
130. Han SH, Ryu JS, Kim YJ, Cho HI, Yang YH, Lee KR. Mutation analysis of the APC gene in unrelated Korean patients with FAP: four novel mutations with unusual phenotype. Fam Cancer. 2011;10(1):21–6.
131. Cetta F, Montalto G, Gori M, Curia MC, Cama A, Olschwang S. Germline mutations of the APC gene in patients with familial adenomatous polyposis-associated thyroid carcinoma: results from a European cooperative study. J Clin Endocrinol Metab. 2000;85(1):286–92.
132. Truta B, Allen BA, Conrad PG, Kim YS, Berk T, Gallinger S, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. Fam Cancer. 2003;2(2):95–9.
133. Martayan A, Sanchez-Mete L, Baldelli R, Falvo E, Barnabei A, Conti L, et al. Gene variants associated to malignant thyroid disease in familial adenomatous polyposis: a novel APC germline mutation. J Endocrinol Invest. 2010;33(9):603–6.
134. Newton KF, Mallinson EK, Bowen J, Lalloo F, Clancy T, Hill J, et al. Genotype-phenotype correlation in colorectal polyposis. Clin Genet. 2012;81(6):521–31.
135. Alm T. Surgical treatment of hereditary adenomatosis of the colon and rectum in Sweden during the last 20 years. Part II. Patients with prophylactic operations, primary and late results. Discussion and summary. Acta Chir Scand. 1975;141(3):228–37.
136. Bulow S. Clinical features in familial polyposis coli. Results of the Danish polyposis register. Dis Colon Rectum. 1986;29(2):102–7.
137. Jarvinen HJ, Husa A, Aukee S, Laitinen S, Matikainen M, Havia T. Finnish registry for familial adenomatosis coli. Scand J Gastroenterol. 1984;19(7):941–6.
138. Vasen HF, Griffioen G, Offerhaus GJ, Den Hartog Jager FC, Van Leeuwen-Cornelisse IS, Meera Khan P, et al. The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. Dis Colon Rectum. 1990;33(3):227–30.
139. Rhodes M, Chapman PD, Burn J, Gunn A. Role of a regional register for familial adenomatous polyposis: experience in the northern region. Br J Surg. 1991;78(4):451–2.

140. Morton DG, Macdonald F, Haydon J, Cullen R, Barker G, Hulten M, et al. Screening practice for familial adenomatous polyposis: the potential for regional registers. Br J Surg. 1993;80(2): 255–8.
141. Mallinson EK, Newton KF, Bowen J, Lalloo F, Clancy T, Hill J, et al. The impact of screening and genetic registration on mortality and colorectal cancer incidence in familial adenomatous polyposis. Gut. 2010;59(10):1378–82.
142. Kinney AY, Hicken B, Simonsen SE, Venne V, Lowstuter K, Balzotti J, et al. Colorectal cancer surveillance behaviors among members of typical and attenuated FAP families. Am J Gastroenterol. 2007;102(1):153–62.
143. Heald RJ, Bussey HJ. Clinical experiences at St. Mark's Hospital with multiple synchronous cancers of the colon and rectum. Dis Colon Rectum. 1975;18(1):6–10.
144. Ruttenberg D, Elliot MS, Bolding E. Severe colonic dysplasia in a child with familial adenomatous polyposis. Int J Colorectal Dis. 1991;6(3):169–70.
145. Jerkic S, Rosewich H, Scharf JG, Perske C, Fuzesi L, Wilichowski E, et al. Colorectal cancer in two pre-teenage siblings with familial adenomatous polyposis. Eur J Pediatr. 2005;164(5): 306–10.
146. Boskovic A, Djuricic S, Grujic B, Stankovic I. Early onset of dysplasia in polyps in children with familial adenomatous polyposis: case report and literature review. Arab J Gastroenterol. 2014;15(2):88–90.
147. Cruz-Correa M, Hylind LM, Romans KE, Booker SV, Giardiello FM. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. Gastroenterology. 2002;122(3):641–5.
148. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328(18):1313–6.
149. Giardiello FM, Yang VW, Hylind LM, Krush AJ, Petersen GM, Trimbath JD, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. N Engl J Med. 2002;346(14):1054–9.
150. Aziz O, Athanasiou T, Fazio VW, Nicholls RJ, Darzi AW, Church J, et al. Meta-analysis of observational studies of ileorectal versus ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg. 2006;93(4):407–17.
151. Herraiz M, Barbesino G, Faquin W, Chan-Smutko G, Patel D, Shannon KM, et al. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol. 2007;5(3):367–73.
152. Ferrandez A, Pho L, Solomon C, Samowitz WS, Kuwada SK, Knecht TP, et al. An evidence-based, multidisciplinary approach to the clinical considerations, management, and surveillance of adrenal lesions in familial adenomatous polyposis: report of three cases. Dis Colon Rectum. 2006;49(11):1781–90.
153. Hirschman BA, Pollock BH, Tomlinson GE. The spectrum of APC mutations in children with hepatoblastoma from familial adenomatous polyposis kindreds. J Pediatr. 2005;147(2):263–6.
154. Lang M, Gasche C. Chemoprevention of colorectal cancer. Dig Dis. 2015;33(1):58–67.
155. Kim KY, Jeon SW, Park JG, Yu CH, Jang SY, Lee JK, et al. Regression of colonic adenomas after treatment with sulindac in familial adenomatous polyposis: a case with a 2-year follow-up without a prophylactic colectomy. Ann Coloproctol. 2014;30(4):201–4.
156. Davis T, Song B, Cram DS. Preimplantation genetic diagnosis of familial adenomatous polyposis. Reprod Biomed Online. 2006;13(5):707–11.

Index

L.A. Boardman (ed.), *Intestinal Polyposis Syndromes*,
DOI 10.1007/978-3-319-28103-2