Chapter 1
The Intestinal Polyposes: Clinical and Molecular Overview

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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].

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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

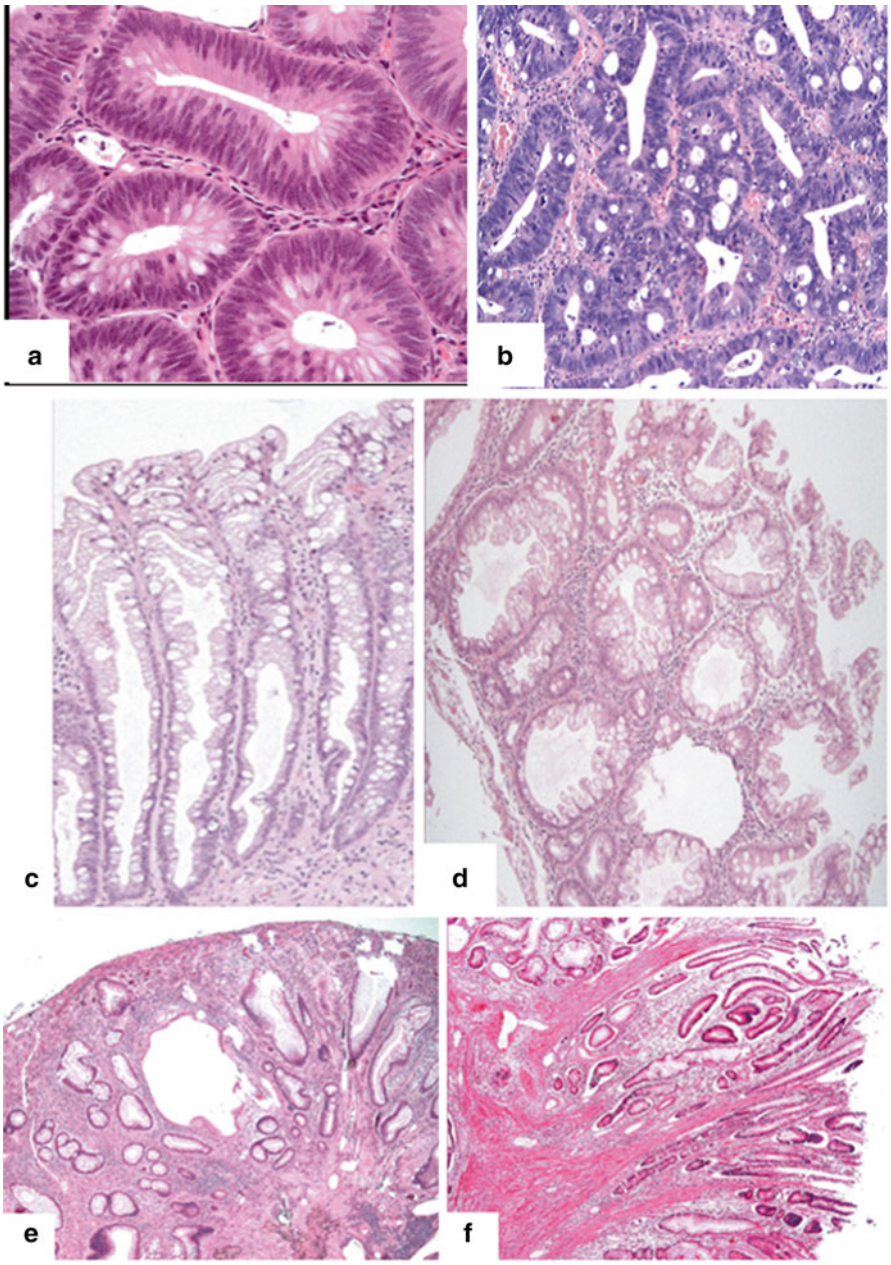

Fig. 1.1 Histological appearance of colorectal polyps. Villous adenomas with low grade (**a**) and high grade (**b**) dysplasia. Hyperplastic polyp (**c**). Sessile serrated adenoma (**d**). Juvenile polyp (**e**). Peutz–Jeghers polyp (**f**). Modified from Ref. [7]

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.

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