Gastrointestinal Cancer Predisposition Syndromes

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Gastrointestinal cancer is extremely rare in children and adolescents. The etiology in most cases is due to familial syndromes (Saab and Furman 2008).

The two best characterized familial syndromes, hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), are autosomal dominant inherited disorders accounting for approximately 2% and 0.1–1% of all adult cases of colorectal carcinomas, respectively. But also other polyposis syndromes affect children: Peutz–Jeghers syndrome and juvenile polyposis coli. All these syndromes rarely cause malignant colorectal tumors in young carriers, however, extracolonic manifestations and preneoplastic lesions must be considered and often occur in pediatric patients.

30.1 Adenomatous Polyposis Syndrome (FAP)

Familial Adenomatous Polyposis (FAP, OMIM N175100) is a dominantly inherited colorectal cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps (adenomas) and extracolonic manifestations and/or neoplasms (tumors) are variably present.

FAP is generally caused by germline inactivating mutations in the Adenomatous Polyposis Coli gene (APC) at 5q21, which encodes a protein of 2,843 aminoacids (Vasen et al. 2008). APC is a tumor suppressor gene, member of the WNT pathway. Normally, the WNT pathway leads to changes in gene expression profile; in fact, APC is able to form a multiprotein complex with glycogen synthesis kinase-3ß and axin, and to bind ß-catenin, which in turn is phosphorylated

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by glycogen synthase kinase-3ß and subsequently degraded by the proteasome. If APC is mutated, the multiprotein complex could not be formed and, therefore, ß-catenin accumulates into the cytoplasm and then translocates to the nucleus, where it activates the T-cell factor, which in turn causes transcription of target genes, influencing different cellular processes such as cell migration, cell cycle control, differentiation, and apoptosis (Kundu et al. 2006).

APC gene is considered at high penetrance activity so, patients carrying a germline mutation, have theoretically the 100% of risk to develop at early age a colorectal cancer if not adequately treated.

The standard prophylactic approach is still surgical. Generally a total colectomy (extended to the rectum in specific pathological conditions) is required to interrupt the sequence from adenoma to cancer, and the frequent endoscopic screening of the individuals at risk is mandatory from the age of 10–14 years. However, it is imperative to have the best risk estimation and to submit to endoscopy, only individuals that with high probability could develop colorectal lesions, as indicated in the main International Guidelines (Vasen et al. 2008).

FAP affects about 1 in 7,000 individuals. Two types of FAP exist, and a relationship between the location of mutations in the gene and the phenotypic expression of FAP has been established (Vasen et al. 2008; Signoroni et al. 2010): the sparse or attenuated type (generally defined as AFAP) is characterized by hundreds of polyps, and the profuse type presents with thousands of polyps (Fig. 30.1). In general adenomas tend to develop near puberty, although early childhood presentations can occur.

Another polyposis-causing gene was detected on chromosome 1p33-34, the MUTYH gene (OMIM n. 608456). Mutations in this gene have been found to be associated with a milder form of polyposis named MAP. MUTYH germline mutations are related to an attenuated phenotype and have been reported in 10–30% of patients without an APC mutation. For these reasons, it could be considered another important biomarker in identifying polyposis and in particular attenuated phenotype patients. Recent studies have also demonstrated that germline MUTYH mutations predispose to colorectal cancer with an autosomal recessive pattern, accounting for up to 1% of these neoplasms. In this setting, biallelic MUTYH mutations have been found to be associated with a 93-fold excess risk of colorectal cancer, with almost complete penetrance by 60 years of age. Interestingly, in up to one-third of these patients, no associated adenoma was found (Vasen et al. 2008; Kundu et al. 2006; Signoroni et al. 2010; Al-Sukhni et al. 2008). In contrast, the influence

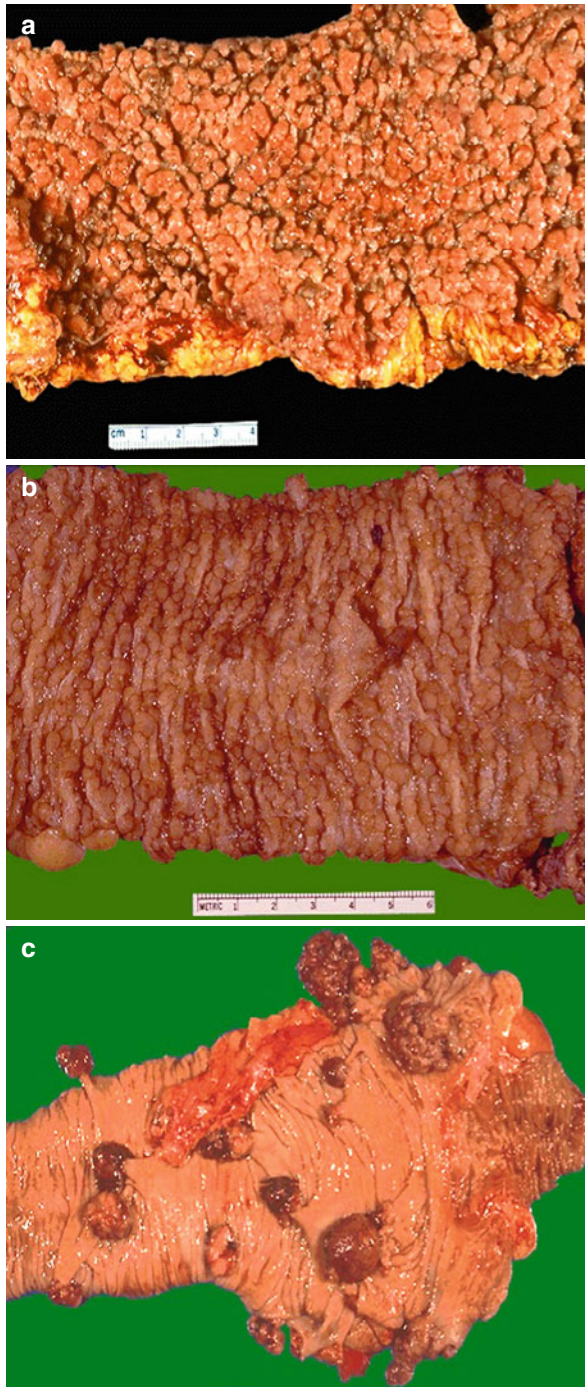

Fig. 30.1 The variability of FAP phenotype: (**a**) severe polyposis, (**b**) classical polyposis, (**c**) attenuated polyposis

of monoallelic MYH mutations on colorectal risk remains controversial, although recent studies suggest a modest effect (Jenkins et al. 2006). The MUTYH gene encodes a member of the base excision repair system. This system is composed of three enzymes (MYH, OGG1, and MTH1) that contribute to protect cells against the mutagenic effects of aerobic metabolism. MUTYH is a DNA glycosylase, which acts at a third level of defense, and is responsible for the removal of adenines mispaired with 8-oxoguanine, one of the most mutagenic DNA products of oxidative DNA damage. Failure to correct these mispairs leads to somatic G:C→T:A transversions in target genes, namely, APC and KRAS. Somatic G:C→T:A transversions in the APC gene were described and in addition, G:C→T:A transversions in the KRAS gene were also observed in adenomas from AFAP patients (David et al. 2007).

Although MAP patients have milder disease, starting later in life, it should be considered that colorectal cancer was frequently found in these subjects and so they need strict surveillance programs like classical FAP patients, to reduce risk of developing cancer. Some reports have identified cases of upper gastrointestinal adenomas/polyps also in MAP patients, so also the upper gastrointestinal tract needs controls (Bouguen et al. 2007).

The gastrointestinal tract is also affected in FAP: duodenal, particularly water papilla and gastric polyps seem to be an important and typical manifestation of FAP patients, but generally related to an adult age.

FAP is also associated with the development of extracolonic malignancies including thyroid carcinoma and hepatoblastoma. Clinical phenotype, including the presence of extracolonic abnormalities, appears to vary according to the site of the APC gene mutation and the presentation of modifying genes. After a diagnosis is made, annual sigmoidoscopy is recommended starting about 10 years of age (Table 30.1). As soon as polyps are identified, prophylactic colectomy can be considered at 15 years of age unless suspicious lesions are found earlier (Signoroni et al. 2010).

Two variants of FAP, with the same propensity to progress to CRC and extraintestinal disease manifestations must be considered. One is Gardner syndrome in which FAP is associated with desmoids tumors, epidermoid cysts, fibromas, osteomas, and congenital hypertrophy of the retinal pigment epithelium. Patients with Gardner syndrome are at high risk to develop a desmoid tumor of the abdominal wall or mesentery after colectomy, which can then be a leading cause of morbidity and mortality (Saab and Furman 2008; Vasen et al. 2008; Signoroni et al. 2010).

Table 30.1 Colorectal surveillance protocol in family member at risk for (A) FAP

	Type of investigation	Lower age limit	Interval
Classical FAP	Sigmoidoscopy[a]	10–12 years	2 years[a]
AFAP	Colonoscopy	18–20 years	2 years[a]

From Vasen et al. (2008)
(A)FAP (attenuated) familial adenomatous polyposis
[a]Once adenomas are detected annual colonoscopy should be performed until colectomy is planned

Turcot syndrome is another FAP variant that includes multiple pediatric brain tumors (medulloblastoma, glioma, and ependymoma) in conjunction with FAP (Saab and Furman 2008; Vasen et al. 2008; Signoroni et al. 2010).

30.2 Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are a rare group of hereditary autosomal dominant disorders that comprise less than 1% of all hereditary colorectal cancers (Manfredi 2010). Hamartomatous polyps, in and of themselves, are benign entities; however, these hamartomatous polyposis syndromes have a malignant potential for the development of colorectal cancer as well as extracolonic cancers. Early detection and proper surveillance are vital to minimize the risk of carcinoma.

The hamartomatous polyposis syndromes include juvenile polyposis syndrome (JPS); PTEN hamartoma tumor syndrome, which includes Cowden syndrome (CS) and Bannayan–Riley–Ruvalcaba syndrome (BRRS); and Peutz–Jeghers syndrome (PJS) (Manfredi 2010).

30.2.1 Juvenile Polyposis Syndrome

Juvenile polyps are the most common type of pediatric gastrointestinal polyps. Solitary juvenile polyps can develop at any age, though they appear most frequently in preschool children and have an incidence of 2% in children under 10 years of age. Solitary polyps are

Table 30.2 Juvenile[a] polyposis syndrome (JPS) is diagnosed if at least one of the following clinical criteria is present

Criteria
More than five juvenile polyps of the colorectum
Multiple juvenile polyps of the upper and lower GI tract
Any number of juvenile polyps and a family history of juvenile polyps

[a]The term "juvenile" refers to the type of polyp not the age of onset of polyps. Juvenile polyps are hamartomas that develop from an abnormal collection of tissue elements normally present at this site

generally located in the rectosigmoid area and are usually considered to be a separate entity from JPS, which has an incidence of 1 in 100,000–160,000 individuals (Chow and Macrae 2005). A family history of juvenile polyps is found in 20–50% of patients with JPS, with an autosomal dominant inheritance pattern of variable penetrance (Chow and Macrae 2005; Attard and Young 2006).

The diagnosis of JPS is clinically established based upon the presence of at least 1 of the following criteria (Jass et al. 1988; Giardiello et al. 1991): more than five polyps detected on colonoscopy; polyps located outside of the colon; and any number of polyps in a patient with a family history of juvenile polyps (Table 30.2).

The gross appearance of a juvenile polyp is spherical to slightly lobular in shape, and most are pedunculated with long stalks (Horrilleno et al. 1957). In patients with JPS, polyps may have a multilobulated appearance of a villiform or papillary shape (Desai et al. 1995). Jass and colleagues reported that approximately 20% of polyps have the latter appearance (Jass et al. 1988). Polyp size can range from several millimeters to 3 cm. These polyps are typically very vascular, with a smooth and glistening appearance on the surface; however, they may also have an ulcerated surface from auto-infarction.

Three genes have been associated with JPS: *SMAD4*, *BMPR1A*, and *ENG*, all of which are part of the transforming growth factor-b(TGF-b) superfamily of proteins (18). The *PTEN* gene mutation in patients with juvenile polyposis is a controversial topic. It is generally thought that patients with the *PTEN* gene mutation likely represent CS or BRRS patients who have not yet expressed the extraintestinal clinical features of these conditions (Zbuk and Eng 2007).

Individuals with JPS are at risk for the development of colorectal, gastric, small intestinal, and pancreatic cancers. The risk of developing colorectal cancer from solitary juvenile polyps is thought to be negligible or nonexistent (Coburn et al. 1995). However, individuals with JPS are at risk for developing adenomatous change and carcinoma. The incidence of colorectal cancer has been reported by Jass and associates to be 20.7%, with a mean age of 34 years (age range, 15–59 years) and an estimated cumulative colorectal cancer risk of 68% by 60 years of age (Jass et al. 1988).

30.2.2 PTEN Hamartoma Tumor Syndrome: Cowden Syndrome and Bannayan–Riley–Ruvalcaba Syndrome

Cowden syndrome (CS) is a rare autosomal dominant syndrome, with a reported incidence of 1 in 200,000 individuals (Nelen et al. 1997). This syndrome is characterized by macrocephaly, mucocutaneous lesions (such as facial trichilemmoma), acral keratosis, and papillomatous papules. It is also associated with thyroid, breast, and endometrial manifestations, including cancer in all of these areas (Zbuk and Eng 2007; Calva and Howe 2008; Starink et al. 1986). CS has been linked to Lhermitte–Duclos disease, which is characterized by hamartomas of the cerebellum (Albrecht et al. 1992). Hamartomatous polyps throughout the gastrointestinal tract are associated with this syndrome but are not as common as the extraintestinal findings associated with the syndrome. The incidence of gastrointestinal polyps in CS varies in the literature, ranging anywhere from 30% (Starink et al. 1986; Eng 2000). It is generally thought that the incidence of gastrointestinal polyps in CS is less than that of BRRS, though this belief is debated in the literature (Eng 2000). Another gastrointestinal manifestation of CS is glycogenic acanthosis of the esophagus, which involves large benign glycogen-filled epithelial cells that are gray to white in color (McGarrity et al. 2003).

The Bannayan–Riley–Ruvalcaba Syndrome (BRRS) is characterized by macrocephaly, developmental delays, pigmented speckling of the penis, lipomas, and hamartomatous polyps of the intestine (Gorlin et al. 1992). The incidence of gastrointestinal polyps in BRRS has been reported to be 45% (Gorlin et al. 1992).

CS and BRRS have an autosomal dominant inheritance pattern with variable penetrance. Both syndromes have been associated with the *PTEN* gene, which is located on chromosome 10q22–23 (Eng and Ji 1998).

The *PTEN* gene is a tumor suppressor gene that is also a tyrosine phosphatase that dephosphorylates tyrosine, serine, and threonine (Suzuki et al. 1998). PTEN is a negative regulator of the Akt/PKB signaling pathway (Suzuki et al. 1998; Waite and Eng 2002), which controls the levels of phosphoinositol triphosphate. PTEN is also involved in regulating cell cycle, apoptosis, and angiogenesis (Waite and Eng 2002; Chow and Baker 2006).

Individuals with CS are at risk for developing breast, thyroid, and endometrial cancers. The risk of adenocarcinoma of the breast has been reported to range from 30% to 50% in women with CS (Zbuk and Eng 2007; Starink et al. 1986; Eng 2000). In addition, there are reports of breast cancer in men with CS (Fackenthal et al. 2001). Individuals with CS are also subject to benign conditions of the breast such as fibrocystic disease (Starink et al. 1986). Thyroid abnormalities such as multinodular goiter and thyroglossal duct cysts are associated with this syndrome, as well as a 10% risk of thyroid cancer. CS patients also have a risk of leiomyomas, as well as an up-to-10% risk of endometrial cancer (Starink et al. 1986). Renal cell cancer has also been associated with CS (Starink et al. 1986). The risk of developing gastrointestinal carcinoma in CS is unclear at this point. It has been reported by some studies that there is no increased risk of gastrointestinal cancer; however, there are multiple case reports of gastric and colorectal cancer (Starink et al. 1986; Carlson et al. 1984).

In BRRS, the cancer risk is unclear. The limited number of patients with this disease makes it difficult to determine the risk; however, there have been case reports of breast and endometrial cancer (Marsh et al. 1999; Longy et al. 1998). With additional evidence supporting the idea that CS and BRRS are variable phenotypic expressions in the *PTEN* gene, it is therefore recommended that individuals with BRRS be considered at risk for malignancy, as with CS.

30.2.3 Peutz–Jeghers Syndrome

PJS, as with the other hamartomatous syndromes, is an autosomal dominant syndrome that is typified by its characteristic mucocutaneous pigmentation and intestinal hamartomatous polyps. The incidence of PJS is reported to be 1 in 150,000–200,000 individuals (Boardman 2002; Kutscher et al. 1960). Pigmentation

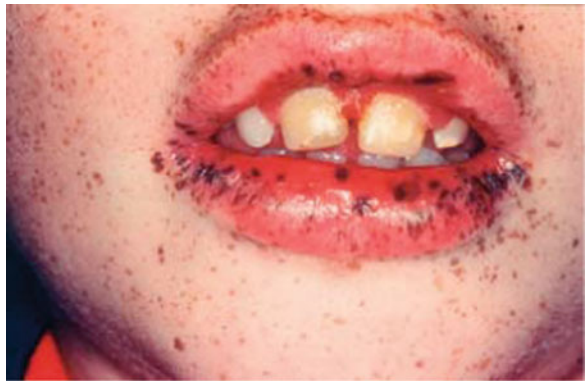

Fig. 30.2 Mucocutaneous pigmentation around lips in Peutz–Jeghers syndrome

is seen around the vermilion border of the lips in over 95% of cases, with the buccal mucosa being the second most common site (80%) (Traboulsi and Maumenee 1986; Utsunomiya et al. 1975) (Fig. 30.2). Other areas of pigmentation include the hands, feet, genitals, and around the nose and eyes. Pigmentation typically presents in early childhood and starts to fade with age usually after the start of puberty (Giardiello and Trimbath 2006).

Hamartomatous polyps in PJS are commonly found in the small intestine; however, they are also found in the stomach and colon. The number of polyps in the intestine may range from 1 to a complete carpeting of the gastrointestinal tract (Utsunomiya et al. 1975; Westerman and Wilson 1999). The most common presentation of PJS is abdominal pain secondary to intussusception. Other clinical presentations include anemia, melena, hematochezia, hematemesis, and obstruction. Approximately one-third of PJS patients present in the first decade of life, with up to 60% presenting by the second or third decade (Giardiello and Trimbath 2006; Brosens et al. 2007).

The diagnosis of PJS is clinically established on the presence of histologic tissue that is consistent with hamartomatous polyps and two of the following criteria (Giardiello et al. 1987): a family history of PJS; the presence of mucocutaneous pigmentation and the presence of small-bowel polyps.

PJS, as with the other hamartomatous syndromes, has an autosomal dominant pattern of inheritance with both familial and sporadic transmission. The gene associated with PJS is a serine-threonine kinase that is located on chromosome 19p13.3 (Hemminki et al. 1997;

Mehenni et al. 1997). Hemminki and coworkers and Jenne and associates independently identified the gene in this region as *LKB1/STK11* (Hemminki et al. 1998; Jenne et al. 1998). This gene has been reported in 80% of patients with PJS. Common mutations are frameshift and nonsense mutations in exons 1–6; however, large deletion mutations missed by direct sequencing have been recently described using multiple ligation probes (Volikos et al. 2006).

LKB1/STK11 is a tumor suppressor gene that encodes a serine-threonine kinase that phosphorylates and activates members of the AMPK-related subfamily of protein kinases (Forcet et al. 2005). LKB1/STK11 has an essential role in G1 cell cycle arrest, cell polarity, p53-dependent apoptosis, and cellular energy levels (Forcet and Billaud 2007; Marignani 2005). *LKB1* (+/–) mice develop gastrointestinal polyps with histologic characteristics resembling those of human PJS polyps (Miyoshi et al. 2002).

Individuals with PJS are at risk for the development of colorectal, gastric, small intestinal, esophageal, and pancreatic cancers but generally not in pediatric age. PJS patients are also at risk for extraintestinal cancer such as lung, breast, ovarian, testicular, and endometrial cancers (Saab and Furman 2008; Zbuk and Eng 2007; Giardiello and Trimbath 2006). A meta-analysis showed that the risk of developing any type of cancer by 64 years of age was 93% (relative risk of 15) (giardiello et al. 2000).

30.3 Hereditary Non-polyposis Colorectal Cancer (HNPCC)

Hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome is a rare hereditary disease that accounts for about 1–5% of all colorectal cancers (Gryfe 2009). It is an autosomal dominant condition caused by the mutation of one of several DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, and PMS2, leading to microsatellite instability (MSI). The average age of colorectal cancer diagnosis in Lynch syndrome mutation carriers is 44 years, compared with 64 years in sporadic colorectal cancer. Individuals with a Lynch syndrome gene mutation have an estimated 80% lifetime risk of developing colorectal cancer. The identification of Lynch syndrome patients is fundamental to address them to correct intensive surveillance programs and to the right therapeutic strategies (Gryfe 2009).

The research criteria for defining Lynch syndrome were established by the International Collaborative Group (ICG) meeting in Amsterdam in 1990, and are known as the Amsterdam Criteria. However, these criteria are not considered comprehensive; a number of families who do not meet these criteria, but have germline MMR gene mutations, have been reported. For this reason, another set of clinical criteria that can be used to identify Lynch syndrome families is the revised Bethesda guidelines. These criteria are less stringent for identifying families with microsatellite instability (MSI) and germline mutations in one of the MMR genes (Mukherjee et al. 2010).

It is difficult to precisely determine the prevalence of HNPCC in children and adolescents with colorectal carcinoma. Case series reporting children and adolescents with colorectal cancer have not focused on the underlying genetic aspects of the tumor or genetic susceptibility of the families (Bethel et al. 1997; Vastyan et al. 2001; Kam et al. 2004). Single case reports describe adolescents with colorectal carcinoma with HNPCC, one 13-years old with an MSH2 mutation (Madlensky et al. 1997), another 13-year old with a PMS2 mutation (Hamilton et al. 1995) and a 14-year old with an MLH1 mutation (Huang et al. 2001).

Extremely rarely MMR genes mutations can occur in homozygosis. Generally, homozygous or compound heterozygous MMR gene mutation carriers develop hematologic malignancies, brain tumors, or both in their first decade of life (Durno and Gallinger 2006).

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