

Gastrointestinal Polyposis Syndromes

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Abstract: Colorectal cancer is one of the leading causes of cancer-related death in the Western society, and the incidence is rising. Rare hereditary gastrointestinal polyposis syndromes that predispose to colorectal cancer have provided a model for the investigation of cancer initiation and progression in the general population. Many insights in the molecular genetic basis of cancer have emerged from the study of these syndromes. This review discusses the genetics and clinical manifestations of the three most common syndromes with gastrointestinal polyposis and an increased risk of colorectal cancer: familial adenomatous polyposis (FAP), juvenile polyposis (JP) and Peutz-Jeghers syndrome (PJS).

FAMILIAL ADENOMATOUS POLYPOSIS

Introduction

Familial adenomatous polyposis (FAP) is a syndrome characterized by multiple adenomatous polyps in the large bowel and a virtually 100% lifetime risk of colorectal cancer. It accounts for approximately 1% of all colorectal cancer cases and occurs in about 1/10,000 live births [1]. FAP is inherited in an autosomal dominant fashion and is caused by a germline mutation in one of the *APC* (*adenomatous polyposis coli*) alleles on chromosome 5q21 [2-5]. In about 22-30% of FAP patients no family history of polyposis is noted, indicating that these patients acquired a new spontaneous mutation [6]. In classic FAP, patients have innumerable (>100 to thousands) adenomatous polyps throughout the colorectum. Without prophylactic proctocolectomy, invasive carcinoma usually develops before the 5th decade of life [1]. In addition, a milder variant, termed attenuated FAP (AFAP), has been identified. AFAP is characterized by the presence of less than 100 polyps (oligopolyposis) at presentation and later onset of colorectal cancer (on average 12 years later than in classic FAP). Some of these patients have severe upper gastrointestinal manifestations [1].

Patients with FAP can also develop duodenal and gastric polyps, extra-intestinal malignancies (desmoid tumors, thyroid, pancreatic and biliary tree carcinoma, brain tumors and hepatoblastoma) and benign extra-intestinal lesions (lipomas, fibromas, sebaceous and epidermoid cysts, osteomas, occult radio-opaque jaw lesions, dental abnormalities, congenital hypertrophy of the retinal pigment

epithelium and nasopharyngeal angiofibroma). The combination of colorectal polyposis and a primary central nervous system malignancy (medulloblastoma) is called Crails syndrome [1].

Adenomatous polyps in FAP are mostly sessile and spherical or lobulated and range from barely visible to pedunculated lesions up to 1 cm or more. Dysplasia starts in single crypts, called a dysplastic aberrant crypt focus (ACF), single crypt adenoma or microadenoma (Fig. 1A). Multiple aberrant crypt foci in a colon is unique to FAP. Subsequently, dysplasia progresses following the multistep ACF-adenoma-carcinoma sequence as proposed by Kinzler and Vogelstein in 1996 [7]. Histologically, adenomas in FAP resemble sporadic adenomas.

Clinical Manifestations

Colorectum

The presence of colorectal adenomatous polyposis is the hallmark feature of FAP. Adenomatous polyps develop throughout the colorectum starting in childhood and adolescence. By age 15, about 50% of FAP patients have colorectal adenomas, and by age 35, 95% are affected. If left untreated, invasive carcinoma develops at an average age of 34.5 to 43 years and the lifetime risk of colorectal carcinoma is virtually 100% [1].

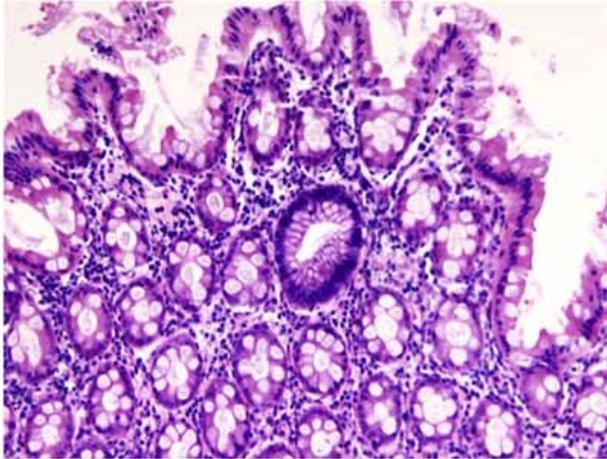
Duodenum

The duodenum is the second most common site of adenoma development in FAP patients with a predilection for the second and third parts and the periampullary region [8]. Duodenal adenomas can be found in 30-70% of FAP patients and the lifetime risk of duodenal adenoma development is nearly 100% [9].

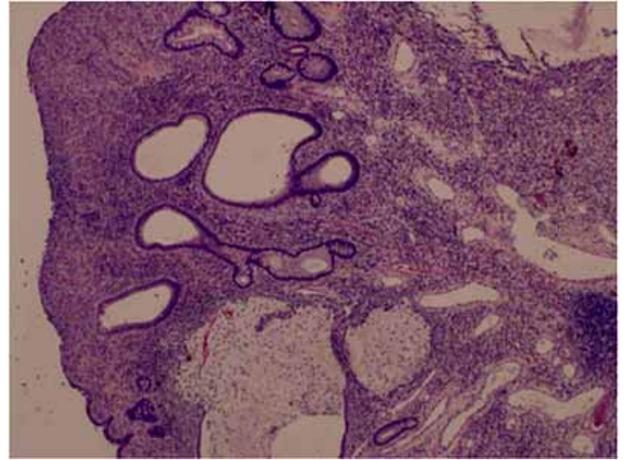
Severity of duodenal polyposis is classified using the Spigelman staging system which describes five

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A)



B)



C)

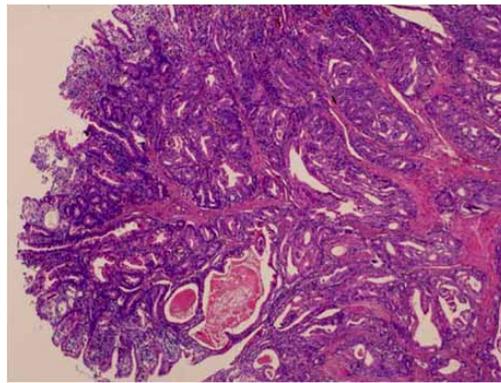


Fig. (1). A) Single crypt adenoma in FAP. B) Typical juvenile polyp with erosion of surface epithelium, expanded mesenchymal stroma and cystically dilated crypts with reactive change. C) Typical microscopic picture of a Peutz-Jeghers polyp with arborizing smooth muscle proliferation and elongated crypts with reactive epithelial cells.

(0-IV) stages (Table 1). Points are assigned for size (1-4, 5-10, >10 mm), number (1-4, 5-20, >20), histology (tubular, tubulovillous, villous) and severity of dysplasia (low-, high-grade). Stage I reflects mild disease, whereas stage III to IV represents severe duodenal polyposis and high risk of developing malignancy [8].

Stage II or stage III duodenal disease is found in 70 to 80% of patients with FAP, and stage I or stage IV disease in 10 to 20%. However, by 70 years of age 52% of FAP patients have stage IV duodenal polyposis [8-10].

Table 1. Spigelman Classification for Duodenal Polyposis in FAP

Criteria	Points		
	1	2	3
Polyp number	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Low-grade		High-grade

Stage 0: 0 points. Stage I: 1-4 points. Stage II: 5-6 points. Stage III: 7-8 points. Stage IV: 9-12 points

The stage of duodenal polyposis progresses over time. In approximately 10 years, progression of duodenal polyposis occurs in 42 to 73% of FAP patients, and the time needed for progression by one stage ranges between 4 to 11 years. Moreover, severity of duodenal polyposis increases with age and the risk of developing stage III or IV disease is exponentially increased after age 40 [9].

Duodenal/periampullary cancer is the leading cause of death in FAP patients after colorectal cancer. Patients have an 100 to 330 fold higher chance to develop duodenal cancer compared to unaffected individuals and estimates of the cumulative risk of duodenal cancer ranges from 4 to 10% at age 60-70 [9, 11, 12]. The risk of developing duodenal malignancy increases with higher Spigelman stages. Stage II and III disease are associated with 2.3% and 2.4% risk, respectively, while stage IV duodenal polyposis carries a 36% risk of developing duodenal cancer [10]. Prophylactic duodenectomy should be considered in patients with stage IV disease.

Stomach

In contrast to duodenal polyps, gastric polyps in FAP patients are usually benign fundic gland polyps. These lesions occur in the fundus and the body of the stomach in about 50% of FAP patients. Histologically, these polyps are characterized by dilatation and cystic change of the fundic glands. Although dysplasia has been described, fundic gland polyps rarely show malignant transformation [13]. Approximately 10% of the gastric polyps are adenomas, which can be found throughout the stomach [8, 9]. Interestingly, in Japan, a high-risk country for gastric cancer, adenomatous stomach polyps in FAP patients occur more frequently than in western countries. In Japanese and Korean FAP patients a 3 to 4 times higher risk of gastric cancer was found compared to the general population [14, 15]. In contrast, person-year analysis revealed that western FAP patients have no increased risk of gastric cancer [12].

Desmoid Tumors

Desmoid tumors (or fibromatosis) are slow growing tumors originating from the mesenchymal primordial germ-cell layer. They are composed of sheets of elongated myofibroblasts, arranged in fascicles and whorls with abundant collagen matrix. Desmoids occur in approximately 10% of FAP patients most frequently within the abdomen and small intestinal mesentery, but also in the abdominal wall or in the extremities. FAP patients have an 852 times higher risk of developing desmoids compared to the general population [16, 17].

Although desmoids have no metastatic potential, they can cause obstructive complications as a result of local growth. Desmoid tumors are the cause of death in a significant proportion of patients with FAP treated by colectomy. In particular, intra-abdominal

desmoid tumors have a poor prognosis compared to those of the abdominal wall. Death can result from local expansion and invasive growth with resulting damage to intra-abdominal structures, such as intestines, ureters and blood vessels. In addition, peri-operative complications in patients undergoing surgery for intra-abdominal desmoids are an important cause of death [17].

The exact etiology of desmoid tumors is unclear. However, surgical trauma is considered as a major risk factor since these lesions frequently develop after a patient has had surgery. Also, recurrence rates after incomplete resection are high. In addition, sex hormones, in particular estrogens, may play a role in the development of these tumors [16, 17].

Extra-Intestinal Malignancies

Extra-intestinal malignancies that have been associated with FAP, include thyroid, pancreatic [18], biliary tree [19, 20], hepatoblastoma [21], and medulloblastoma [22]. Thyroid cancer, predominantly papillary carcinoma, can be found in 1-2% of FAP patients. The relative risk of developing this malignancy ranges from 7.6 to 20.9, although the absolute life time risk is low (2.1%) [15, 18, 23]. Thyroid cancer in FAP is typically diagnosed in the third decade of life and female patients are at a higher risk than males [23, 24]. Annual physical examination of the thyroid is recommended and ultrasonography should be considered [18]. The relative risk of pancreatic adenocarcinoma is 4.5. The absolute life time risk, however, is low (1.7%) [18]. Hepatoblastoma occurs during the first seven years of life in about 0.3% of patients with FAP or at-risk for FAP, with an 800-fold higher risk of this rare tumor compared to the general population [21].

Finally, the presence of a brain tumor and multiple colorectal polyps is called Crails syndrome. FAP patients usually present at young age with medulloblastoma and colorectal polyposis. Central nervous system malignancies have also been associated with hereditary non-polyposis coli cancer (HNPPC), but tumors in these patients are usually astrocytomas or glioblastomas and present later in life. The association of glioblastoma with HNPPC is known as Turcot's syndrome [22, 25].

Benign Extra-Intestinal Manifestations

A variety of benign extra-intestinal lesions have been described in association with FAP. Some of these phenotypic markers can be used as diagnostic tools in the examination of first degree relatives of FAP patients [26].

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) can be found in more than 90% of patients with FAP. CHRPE are discrete round to oval darkly pigmented areas in the ocular fundus ranging in size from 0.1 to 1 optic-disc diameter. They consist of multiple hyperplastic layers of retinal pigment epithelium with hypertrophied cells filled with large spherical melanosomes. Although these

lesions are asymptomatic, the presence of bilateral and/or multiple (>4) CHRPE can be used as a specific clinical marker for the identification of asymptomatic carriers in FAP families [26, 27].

Osteomas of the maxilla and mandibula are noted in approximately 80% of FAP patients [28]. Occult radio-opaque jaw lesions are osteosclerotic bone lesions that can be demonstrated by panoramic radiographs of the jaw. These lesions can be used as predictors for polyp development in families with FAP and jaw lesions [29].

In addition, a variety of dental abnormalities, including impacted teeth, supernumerary or congenitally missing teeth, and fused roots of molars, can occur in 17 to 75% FAP patients [28]. FAP patients can also develop cutaneous lesions including lipomas, fibromas, sebaceous and epidermoid cysts [30, 31]. Finally, nasopharyngeal angiofibroma is a highly vascular locally invasive tumor most often occurring in the nares or nasopharynx of adolescent boys. It is 25 times more common in FAP patients than in the general population [32].

Genetic Defect

In 1987 the genetic defect causing FAP was linked to chromosome 5q21 [2] and in 1991 the *APC* gene was identified [3-5]. The *APC* gene is a tumor-suppressor gene with 15 exons, encoding a 2843 amino acid protein with a key function in the Wnt signaling pathway. Wnt signaling is involved in repression of apoptosis, induction of proliferation and cell cycle progression [33].

More than 300 different *APC* gene mutations have been reported in FAP. Germline mutations are mainly found in the 5' half of the *APC* gene, particularly in codons 1061 and 1309. Most mutations are frameshifts due to insertions or deletions, or nonsense mutations, leading to truncated *APC* proteins [1, 34]. A high frequency of somatic *APC* mutations is found in the so-called mutation cluster region in the 5' part of exon 15, between codons 1286 and 1513 (Fig. 2) [35].

Germline mutations in the *APC* gene are found in about 80-90% of patients with classic FAP and in about 10-30% of patients with AFAP [34, 36]. Until recently, no other genetic cause for the remainder of patients with classic or attenuated FAP was known. However, in 2002 defects in the base excision repair gene *MYH* were identified in patients with both classic and attenuated FAP in which no germline *APC* mutation could be found. Adenomatous polyposis in these patients is inherited in an autosomal recessive way with biallelic inactivation needed to develop the phenotype. *MYH* has a repair function critical for *APC*, and the *APC* gene is particularly vulnerable to loss of function [37, 38].

Genotype-Phenotype Correlations

Several genotype-phenotype correlations have been established in FAP. Classic FAP is caused by *APC* mutations between codons 169 and 1393, and mutations between codon 1250 and codon 1464 are associated with severe polyposis (>1000 colorectal polyps) [1, 39]. Moreover, mutations at the 5' and 3' extremes and in exon 9 of the *APC* gene tend to present as attenuated FAP, characterized by less

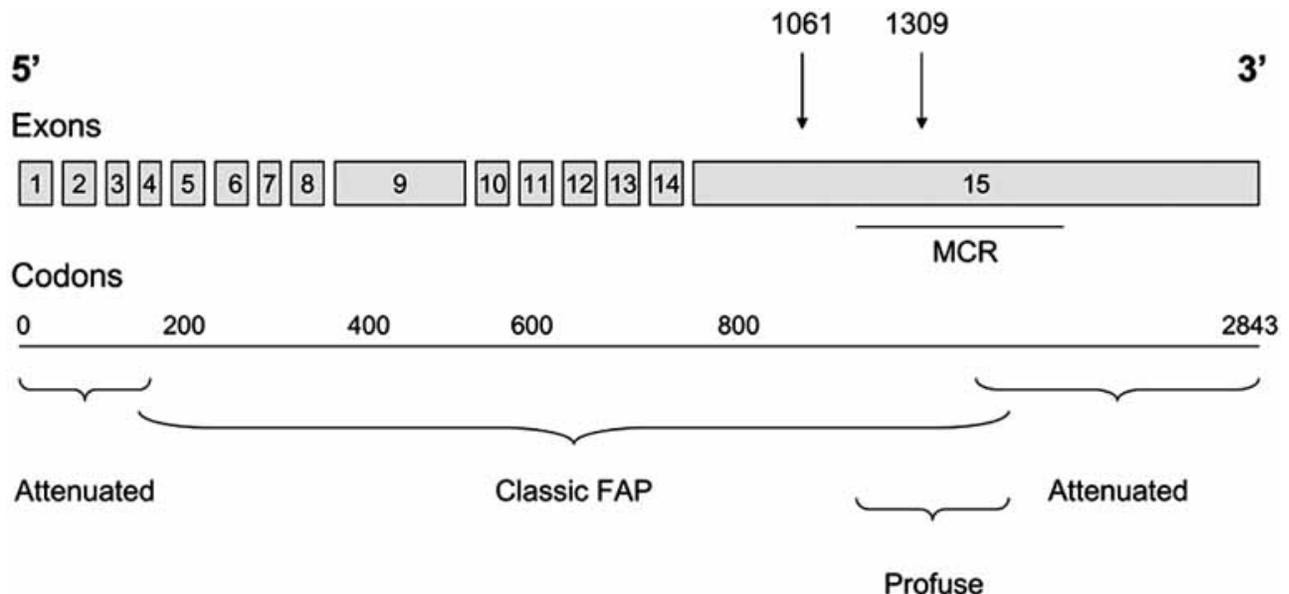


Fig. (2). Schematic representation of the *APC* gene, consisting of 15 exons and 2843 codons. Most germline mutations are found in the 5' half the *APC* gene, particularly in codons 1061 and 1309. A high frequency of somatic *APC* mutations is found in the so-called mutation cluster region between codons 1286 and 1513. Germline mutations in the central part of the gene represent classic FAP. Germline mutations between codons 1250 and 1464 associate with profuse polyposis, whereas mutations in the extremities of the *APC* gene cause attenuated FAP.

than 100 colorectal polyps and malignant transformation occurring 10-20 years later than in patients with classic FAP (Fig. 2) [1, 40, 41].

Genotype-phenotype correlations for duodenal polyposis in FAP are less clear. However, a severe duodenal phenotype appears to be associated with mutations in exon 15 of the *APC* gene, particularly distal to codon 1400 [9]. Desmoid tumors have been associated with mutations 3' of codon 1444 of the *APC* gene [42, 43], although other investigators have not found this relationship [16, 44]. Thyroid cancer appears associated with germline mutations in the 5' part of exon 15, outside codons 1286-1513, and with an increased frequency at codon 1061 [23]. A multiplicity of extra-intestinal lesions has been associated with mutations in codons 1465, 1546 and 2621 and ocular fundus lesions (CHRPE) are associated with mutations between codons 463 and 1444 of the *APC* gene [27, 44, 45].

To conclude, understanding genotype-phenotype correlations can be helpful in predictive testing of at-risk subjects. However, caution should be taken in genetic counseling of patients with FAP, since considerable phenotypic variability occurs among individuals and families with identical *APC* mutations [46]. Therapeutic decisions should, therefore, be based on the clinical findings in individual patients, not site of gene mutation [34].

Cancer Pathogenesis

The *APC* gene is a key tumor-suppressor gene in the Wnt signaling pathway. In the absence of Wnt signaling, *APC* functions in a multiprotein complex with axin and glycogen synthase kinase 3 (GSK-3) that targets β -catenin for proteasomal degradation. Inactivation of *APC* leads to disturbed regulation of intracellular β -catenin levels, nuclear translocation of β -catenin and Wnt target gene transcription. Wnt target genes are involved in repression of apoptosis, induction of proliferation, and cell cycle progression [7, 33].

In 1996, Kinzler and Vogelstein proposed a paradigm for carcinoma development in FAP and sporadic colorectal cancer. In this model, intestinal carcinogenesis follows a stepwise progression through the so-called ACF-adenoma-carcinoma sequence. *APC* acts as the "gatekeeper" in the

initiation of this oncogenic sequence. Once the *APC* gene is mutated, additional mutations in tumor-suppressor genes (e.g. *p53* and *SMAD4*) and proto-oncogenes (e.g. *K-Ras*) drive the progression of the adenoma-carcinoma sequence (Fig. 3) [7]. Also, expression of cell regulatory proteins is changed, including cyclooxygenase-2 (COX-2), which is increasingly expressed in consecutive stages of the adenoma-carcinoma sequence [47]. COX-2 is a key enzyme in the conversion of arachidonic acid to prostaglandin, which regulates cellular functions such as cell proliferation, apoptosis and angiogenesis. Recently, a direct link between COX-2 upregulation and Wnt signaling was shown. In the absence of functional *APC*, binding of prostaglandin E2 to its receptor EP2 promotes the release of GSK-3 from its complex with axin, leading to increased intracellular β -catenin levels, Wnt target gene transcription and colon cancer cell proliferation [48]. Selective and non-selective inhibition of COX-2 has been studied in chemoprevention trials and causes regression of adenomas in FAP [49, 50].

Management

Colorectum

Screening and Surveillance

First degree relatives of patients with FAP should be screened for FAP between age 10-12. For these individuals, *APC* gene testing is the test of choice (Table 2). However, at-risk individuals in which no informative genetic test can be obtained should be enrolled in an endoscopic screening program. These patients should have a yearly sigmoidoscopy starting at 12 years of age, with reduced screening frequency each subsequent decade up to age 50. After 50 years of age, patients should follow guidelines for colorectal cancer screening in average-risk patients [1, 51]. For individuals suspected of AFAP, gene testing is recommended if 20 or more cumulative colorectal adenomas are found [1]. Endoscopic screening with colonoscopy in patients at risk for AFAP should occur at age 12, 15, 18 and 21, and then every 2 years [51].

Treatment

To prevent colorectal carcinoma in FAP patients, prophylactic colectomy should be performed shortly

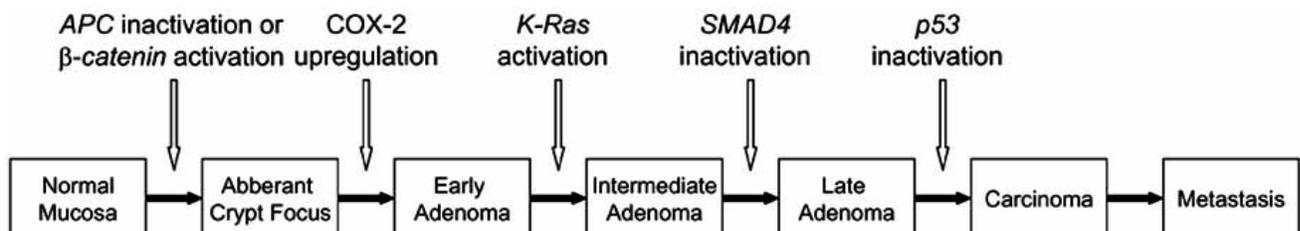


Fig. (3). The adenoma-carcinoma sequence. Activation of the Wnt signaling pathway, by an inactivating *APC* mutation or an activating β -catenin mutation, is regarded as the first step in the adenoma-carcinoma sequence. Then, additional mutations in oncogenes (e.g. *K-Ras*) and tumor-suppressor genes (e.g. *p53* and *SMAD4*) drive further progression of the adenoma-carcinoma sequence.

after diagnosis of adenomatous polyposis. Surgical options include subtotal colectomy with ileorectal anastomosis, total proctocolectomy with Brooke ileostomy (or with continent ileostomy) and total proctocolectomy with mucosal proctectomy and ileo-anal pull-through (with pouch formation). Patients who have subtotal colectomy and ileorectal anastomosis should have life-long endoscopic surveillance of the remaining rectal segment every six months, since cancer in the retained rectum develops in approximately 25% of these patients. In about 16% of these individuals, proctocolectomy is eventually needed. Patients with dense polyposis and carcinoma at the time of subtotal colectomy have a particularly high risk of developing rectal cancer. Therefore, these patients should have total proctocolectomy with either ileostomy or restorative proctocolectomy [51-53].

Table 2. Indications for APC Gene Testing

100 colorectal adenomas
First-degree relatives (>10 years old) of FAP patients
20 cumulative colorectal adenomas (suspected for AFAP)
First-degree relatives (>10 years old) of AFAP patients

Chemoprevention

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used in chemoprevention studies of colorectal adenoma development. Chemoprevention of polyps in the retained rectum of patients with FAP with selective and non-selective COX-2 inhibitors has been shown to reduce the number and size of polyps in short-term [49, 50], and long-term studies with sulindac [54]. However, the effects are variable and endoscopic surveillance should still be performed stringently. The main benefit obtained by the use of NSAIDs is that endoscopic surveillance is more straightforward due to decreased numbers and smaller polyps [54]. Primary chemoprevention of adenomas in phenotypically unaffected *APC* gene mutation positive patients did not prevent development of polyposis [55].

Upper Gastrointestinal Tract

Screening and Surveillance

Baseline upper gastrointestinal endoscopy is recommended between age 25 and 30 [51].

Thereafter, endoscopic surveillance of duodenal polyposis should be adjusted to the Spigelman-stage of duodenal polyposis. In general, recommendations include: stage 0 and stage I every four years, stage II every 2 to 3 years, stage III every 6 to 12 months and for stage IV surgery should be considered (Table 3) [10, 51].

Treatment

Treatment options for duodenal polyposis are pharmacologic therapy, endoscopic treatment (including snare-excision, laser therapy, photodynamic therapy and argon-plasma therapy), and surgery.

Endoscopic treatment of duodenal polyposis is fraught with high recurrence rates, varying from 50 to 100%. Therefore, the benefit of endoscopic therapy is controversial, but it may be useful in individual cases and to postpone surgery [9].

Surgery for duodenal polyposis is generally offered to patients with stage IV duodenal polyposis. Surgical options include local surgical treatment (duodenotomy with polypectomy and/or ampullectomy), pancreas and pylorus preserving duodenectomy or classical pancreaticoduodenectomy. High recurrence rates have been reported in patients treated with local surgery. Therefore, pancreas and pylorus preserving duodenectomy or classical pancreaticoduodenectomy is indicated in patients with severe duodenal disease, failed endoscopic or local surgical management, and carcinoma development. However, morbidity and mortality of these surgical procedures must be weighed against the risk of developing duodenal malignancy [9, 51].

Chemoprevention

Chemoprevention trials of duodenal polyps with NSAIDs show conflicting result. Some groups find modest regression of small duodenal adenomas in patients treated with 400 mg sulindac or 800 mg celecoxib, however, most reports find no significant effect on duodenal polyposis [9].

Desmoid Tumors

Desmoids in the abdominal wall and extremities can usually be excised with few complications, although recurrence rates are high (10-70%). In case of recurrence, re-resection, or treatment with sulindac and anti-estrogens can be considered. In addition,

Table 3. Recommendations for Management of Duodenal Polyposis in FAP, Adjusted to the Spigelman Stage of Duodenal Polyposis

Spigelman Stage	Endoscopic frequency	Chemoprevention	Surgery
Stage 0	4 years	No	No
Stage I	2-3 years	No	No
Stage II	2-3 years	+/-	No
Stage III	6-12 months	+/-	+/-
Stage IV	6-12 months	+/-	Yes

radiotherapy can be used for recurrence of desmoids on the extremities [17].

The usual first line treatment of symptomatic mesenteric or retroperitoneal desmoids is medical treatment with regimens such as combination of sulindac (200 mg/day) and an anti-estrogen (e.g. tamoxifen 20-40 mg/day). The effect of treatment should be evaluated every three to six months by CT scan. In addition, kidney function should be controlled and stenting should be considered in case of ureteric obstruction from desmoid disease. Radical resection of mesenteric or retroperitoneal desmoids is often impossible. Also, major complications occur in about half of the patients and post-operative mortality rates vary from 10 to 60%. In almost 80% of these patients, desmoids will recur within 5 years. However, surgery can be considered if considerable symptoms result from small, well-defined desmoids. Intestinal by-pass surgery is indicated in patients with signs of intestinal ischemia or bowel obstruction. Larger desmoids, that involve vital structures, should be attacked with cytotoxic agents [17].

Life-Expectancy and Causes of Death

As a result of screening and prophylactic surgery, life expectancy of patients with FAP has significantly improved in the last several decades. However, FAP patients still have a 3.35 fold elevated risk of dying compared to the general population [56]. The main causes of death are upper gastrointestinal malignancy, peri-operative complications and desmoid disease [56, 57].

JUVENILE POLYPOSIS

Introduction

Juvenile polyposis is an autosomal dominant syndrome characterised by multiple juvenile polyps primarily in the colorectum but also elsewhere in the gastrointestinal tract. It is the most common hamartomatous polyposis syndrome, occurring in approximately 1/100,000 live births. The first histological description of a juvenile polyp was by Diamond in 1939 [58], and McColl *et al.* introduced the term juvenile polyposis in 1964 [59].

Solitary juvenile polyps occur in approximately 2% of the pediatric population and are not associated with an increased risk of colorectal cancer [60]. In contrast, in the setting of juvenile polyposis, there is an increased risk of gastrointestinal malignancy. JP is generally defined as: A) more than 3-5 juvenile polyps in the colorectum, and/or B) juvenile polyps throughout the gastrointestinal tract, and/or C) any number of juvenile polyps with a positive family history of juvenile polyposis [61, 62].

Other syndromes to be excluded and associated with colorectal juvenile polyps include Bannayan-Ruvalcaba-Riley, Cowden, and Gorlin syndrome. Each of these disorders is characterized by specific extra-intestinal features in addition to intestinal polyps. In some patients, however, exclusion of one these syndromes can be difficult since extra-

intestinal characteristics may only appear at later age [63].

Macroscopically, juvenile polyps typically have a spherical, lobulated and pedunculated appearance and vary in size from 5 to 50 mm, often with surface erosion. On histology, solitary juvenile polyps have abundant stroma composed of inflamed and oedematous granulation tissue surrounding cystically dilated glands containing mucin. The glands are lined by cuboidal to columnar epithelium with reactive changes. Juvenile polyps in juvenile polyposis may have similar appearances as sporadic juvenile polyps, but often have a frond-like growth pattern with relatively less stroma, fewer dilated glands and more proliferative smaller glands (Fig. 1B) [64].

Clinical Manifestations

Presentation

Juvenile polyposis typically presents in the first or second decade of life with rectal bleeding, a prolapsed rectal polyp, abdominal pain, diarrhea or anemia. In 20-50% of these patients a family history of juvenile polyposis is present [62, 65, 66]. JP can also present in infancy with severe gastrointestinal bleeding, diarrhea, protein-losing enteropathy and failure to thrive. Death may occur at a young age in these patients if supportive care is not provided. Family history is usually negative. This latter form is also called JP of infancy [62, 66].

Polyps most commonly occur in the colorectum and vary in number from three to several hundreds. Polyps can also be found in the upper gastrointestinal tract, particularly in the stomach [67-69]. Howe *et al.* report an incidence of upper gastrointestinal polyps in about 40 to 65% [70]. Rarely, profuse gastric juvenile polyposis is found in the absence colonic polyps [71].

Cancer Risk

Previously, juvenile polyps were thought to harbour no malignant potential. This appears true for sporadic solitary juvenile polyps [60], but not in juvenile polyposis. Reports describing adenomatous change in colonic juvenile polyps [61, 67, 72-74], adenomas [61, 67, 74], and colorectal carcinoma in patients with JP [61, 67, 72-74], suggest an increased risk of colorectal cancer. In addition, gastric [70, 75, 76], duodenal [70], and pancreatic cancer [70, 77] have been described in these patients.

Few studies estimate the colorectal cancer risk in JP, and these calculations vary widely. Jass *et al.* found colorectal cancer in 18 of 87 (20.7%) JP patients at a mean age of 34 years (range 15-59) [62]. However, since most of these patients had undergone colectomy, the cumulative risk of colorectal cancer was estimated as high as 68% at age 60 [66].

A review of medical records of the Iowa JP kindred of 29 patients with juvenile polyposis

revealed 11 patients with colorectal cancer (38%), 4 with gastric (13.7%), 1 with duodenal (3.4%), and 1 with pancreatic cancer (3.4%). The cumulative risk of colorectal and upper gastrointestinal malignancy was 55% with a median age of colorectal and upper gastrointestinal cancer of 42 (range 17.4-68.2) and 57.6 (range 20.5-72.8) years, respectively [70]. In the same report, a literature review revealed 42 cases of colorectal cancer (31.5%), 15 cases of stomach cancer (11.3%), one case of duodenal (0.75%), and one pancreatic carcinoma (0.75%) in 133 patients with familial juvenile polyposis from 22 families [70].

In a review of published reports, Coburn *et al.* found 34 colorectal cancers in 218 JP patients (15.5%) and a mean age of cancer diagnosis of 35.5 (range 4-60) years. In addition, they found one gastric and one duodenal carcinoma [65].

Although considerable variation in reports exists, it seems evident that JP patients carry an increased risk of colorectal and possibly gastric cancer.

Extra-Intestinal Manifestations

A variety of extra-intestinal manifestations in JP have been described, although most are based on case reports. Also, extra-intestinal features in JP are difficult to interpret due to an unclear distinction between JP, Cowden, and Bannayan-Ruvalcaba-Riley syndrome.

Extra-intestinal manifestations have been reported in about 10 to 78% of JP patients [66, 78]. Anomalies described, include hypertelorism, macrocephaly, digital clubbing, polydactily, mental retardation, hydrocephalus, congenital cardiac anomalies, pulmonary arteriovenous malformations, pulmonary stenosis, teleangiectasias, Meckels diverticulum, intestinal malrotation, cryptorchidism, and bifid uterus and vagina [59, 65, 71, 77, 78].

An association between JP and hereditary hemorrhagic teleangiectasias (HHT) exists. Hereditary hemorrhagic teleangiectasia (Osler-Weber-Rendu syndrome) is an autosomal dominant

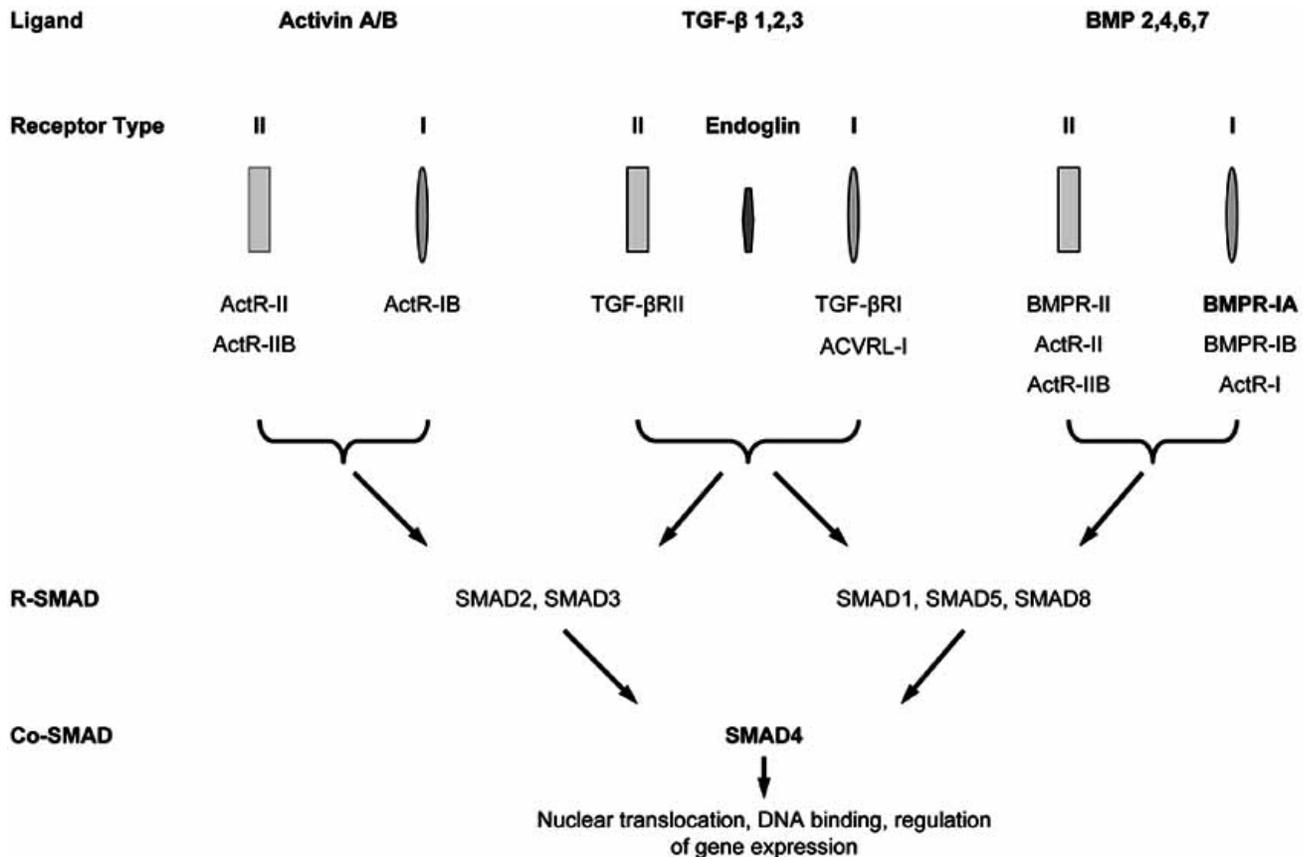


Fig. (4). The TGF-β signaling pathway. Binding of a TGF-β ligand to a type II receptor results in recruitment of a type I receptor and subsequent phosphorylation of the type I receptor by the type II receptor. The type I receptor then phosphorylates and activates receptor-regulated SMADs (R-SMADs) which subsequently form complexes with the common SMAD (Co-SMAD) SMAD4. The activated SMAD complexes translocate to the nucleus where they regulate target gene transcription. Inhibitory SMADs (I-SMADs) SMAD6 and SMAD 7 inhibit TGF-β signaling by competing with R-SMADs for receptor or Co-SMAD interaction and by targeting the receptors for degradation. Endoglin is a co-receptor for TGF-β 1 and TGF-β 3.

Abbreviations: Act: activin, ActR: Activin receptor, ALK: Activin-like kinase, BMP: Bone morphogenetic protein, BMPR: BMP receptor, TGF- R: TGF- receptor, ACVRL-1: Activin A receptor type-II like 1. Commonly used synonyms are: ActR-1/ALK2, ActR-IB/ALK4, TGF- R-I/ALK5, ACVRL1/ALK1, BMPR-IA/ALK3, BMPR-IB/ALK6.

disorder of vascular dysplasia affecting many organs. Characteristic features are teleangiectasias of skin and mucosal surfaces, pulmonary, cerebral and hepatic arteriovenous malformations and hemorrhage as a consequence of these lesions. HHT is caused by mutations in two endothelial-specific receptors for TGF- β : *ENG* (*Endoglin*) and *ACVRL1* (*ALK1*) (Fig. 4) [79]. Case reports of juvenile polyposis patients with symptoms of HHT, including arteriovenous malformations in the lung [80-83], liver [82, 83], and skin [83] and gastrointestinal teleangiectasias [81, 82], raised the suggestion of a common genetic cause for these two syndromes. In 2004, HHT and juvenile polyposis were genetically linked by the discovery of *SMAD4* mutations in patients with both conditions [84], and germline mutations in *ENG* were recently described in two JP patients [85].

In JP patients with germline *SMAD4* or *ENG* mutations, screening should be considered for arteriovenous malformations using chest radiography, magnetic resonance imaging of the brain and liver sonography [82, 84]. In addition, digital clubbing and pulmonary osteoarthropathy are frequently described in combination with arteriovenous malformations [78, 80].

Bannayan-Riley-Ruvalcaba Syndrome and Cowden Syndrome

Bannayan-Riley-Ruvalcaba syndrome (BRRS) and, to a lesser extent, Cowden syndrome (CS) share the intestinal phenotype of juvenile polyposis. Hamartomatous intestinal polyps occur in about 45% of BRRS patients [86]. In CS, intestinal polyps occur less frequently, although the incidence is unclear. In addition, polyps in CS are usually less abundant and asymptomatic, and typical juvenile polyps in CS are rare [87].

Intestinal polyposis is not pathognomonic for BRRS or CS and both syndromes are marked by specific extra-intestinal features. BRRS is characterized by macrocephaly, developmental retardation, genital pigmentation, hemangiomas, lipomas, intestinal polyps and lipid myopathy [86]. Clinical features of CS include mucocutaneous lesions (facial trichilemmoma, acral keratoses, papillomatous papules and mucosal lesions are pathognomonic), increased risk of breast and thyroid carcinoma, macrocephaly and a range of minor features, including gastrointestinal hamartomas. About 75% of CS patients have thyroid disease, usually goiter and/or adenoma. CS patients are at increased risk of breast cancer (25-50%), non-medullary thyroid malignancy (10%), and possibly endometrial carcinoma [87].

CS and BRRS are autosomal dominant diseases caused by a germline defect in the *PTEN* gene, which is found in approximately 80% of CS and 60% of BRRS patients [88, 89]. Since patients fulfilling criteria for both CS and BRRS have been described, and CS and BRRS are caused by mutations in the same gene these two syndromes are likely two

variable expressions of the same genetic alteration [89].

Genetic Defect

Currently alterations in two genes, *SMAD4* and *BMPR1A*, are identified causes of JP. Both encode proteins involved in TGF- β /BMP signaling (Fig. 4). In 1998, Howe *et al.* discovered *SMAD4*, located on chromosome 18q21.1, as a gene responsible for JP [90]. Germline mutations in *SMAD4* are found in 16-24% of JP patients, most in the 3' half of the gene, encoding the highly conserved MH2 domain, which is involved in SMAD oligomerization and transcriptional activation [90-93]. In 2001, *bone morphogenetic protein receptor 1A* (*BMPR1A*), located on chromosome 10q22.3, was identified as a second JP gene [94]. Germline *BMPR1A* mutations are noted in 17-24% of JP patients [91-93]. Since germline mutations in *SMAD4* or *BMPR1A* are identified in a minority of patients with clinically defined juvenile polyposis [91], other components of the TGF- β signaling pathway have been studied. Other *SMAD* genes, including *SMAD1*, *SMAD2*, *SMAD3*, *SMAD5* and *SMAD7* were analysed, but no germline mutations in these genes were found in JP patients [95, 96]. In addition, germline *BMPR2*, *BMPR1B* and *ACVRL1* mutations were excluded as a cause for JP [91]. Recently, germline mutations in the HHT gene *ENG*, encoding the TGF- β co-receptor endoglin, were reported in two patients with JP [85].

The role for germline *PTEN* (chromosome 10q23.3) mutations in juvenile polyposis is unclear. Some investigators suggested that *PTEN* could be involved in JP [97], while others disagree [98]. Discriminating between JP and CS can be difficult since the penetrance of CS is less than 10% below age 15 [63]. Currently, *PTEN* mutations in patients with JP likely represent CS or BRRS patients that have not yet expressed the clinical features of these conditions [99].

Genotype-Phenotype Correlation

Since juvenile polyposis is a rare disorder, only a few genotype-phenotype studies exist. Patients with either a *SMAD4* or *BMPR1A* germline mutation express a more prominent juvenile polyposis phenotype (i.e. more family history of JP, >10 polyps, and higher frequency of family history of gastrointestinal cancer) compared to those without an identified germline mutation [92]. Moreover, *SMAD4* mutations have been associated with a more aggressive gastrointestinal phenotype compared to *BMPR1A* mutation carriers. Handra-Luca and colleagues, found a higher incidence of colonic adenomas in carriers of *SMAD4* mutations compared to those with *BMPR1A* or *PTEN* mutations, and carcinoma was only found in patients with *SMAD4* mutations [100].

In addition, carriers of germline *SMAD4* mutations have more severe gastric polyposis than patients

with a *BMPR1A* mutation or those in whom no germline mutation could be identified [92, 93, 100]. Finally, the combined syndrome of JP and hereditary hemorrhagic teleangiectasia has been associated with germline mutations in *SMAD4* [84].

Cancer Pathogenesis

Malignant transformation in JP likely occurs in adenomatous foci within juvenile polyps, and/or in adenomas that arise as separate lesions. Reports describing adenomatous foci in juvenile polyps [61, 67, 72-74] suggest that these polyps can undergo neoplastic change. In addition, carcinoma *in situ* and adenocarcinoma have been described within juvenile polyps [68, 101, 102].

Goodman and colleagues first proposed a model for polyp development and neoplastic transformation in juvenile polyps. They suggested a pathogenic sequence from epithelial hyperplasia, leading to hyperplastic polyps which become inflamed and enlarge, forming juvenile polyps. Subsequently, focal adenomatous areas develop in some juvenile polyps giving rise to adenoma and eventually adenocarcinoma [67]. Moreover, Jass *et al.* showed that dysplasia could be found frequently in juvenile polyps, particularly in atypical juvenile polyps. Adenomatous epithelium was found in 9% of typical juvenile polyps, but 47% of atypical juvenile polyps (i.e. multilobulated, relatively less lamina propria and more epithelium and villous or papillary configuration) [62].

Although alterations in genes with a function in the TGF- β /BMP signaling pathway cause JP, molecular mechanisms of polyp development are still poorly understood. The TGF- β signaling pathway is a key tumor-suppressor pathway, regulating cellular functions such as cell proliferation, adhesion and differentiation. The TGF- β family comprises several structurally related secreted cytokines, including TGF- β isoforms, activins, and BMPs. Signal transduction is mediated through binding of these cytokines to membrane bound receptors and subsequent intracellular signal transduction mediated by SMAD proteins. Of these proteins, SMAD4 has a central role in TGF- β , activin, and BMP signaling (Fig. 4) [103].

In 1998, Kinzler and Vogelstein introduced the "landscaper" hypothesis. Based on the observation that the genetic alterations at chromosome 10q22 (*BMPR1A* locus) occur predominantly in the stroma [104], they hypothesized that stromal changes provide an abnormal environment influencing behaviour of adjacent epithelium and ultimately leading to an increased risk of neoplastic transformation [105]. Recently, BMP-4 has been localized exclusively to the mesenchymal compartment of the intestine in mice. Disrupted BMP signaling resulted in development of ectopic crypts perpendicular to the crypt-villus axis, leading to polyps resembling juvenile polyps [106, 107]. Consequently, disrupted mesenchymal-epithelial

communication, by defective BMP signaling, is hypothesized to cause the "landscaper" defect [106]. Interestingly, in long term observation, neoplastic change was observed in the polyps of these mice. Nuclear translocation of β -catenin and overexpression of Wnt targets in these dysplastic foci suggested Wnt activation. This was interpreted as compelling evidence that stromal-epithelial cross-talk in these polyps underlies conventional adenoma-carcinoma sequence initiation. Furthermore, BMP signaling appeared to restrict ectopic crypt formation by antagonizing Wnt signaling. He *et al.* proposed that BMP-4 promotes PTEN activation in intestinal stem cells, which in turn represses β -catenin/TCF4 through the PI3 kinase-AKT pathway [107]. Lastly, disturbed stromal TGF- β signaling ultimately leads to epithelial neoplasia of the prostate in mice [108].

Whether germline *SMAD4* mutations in JP also act *via* a landscaper mechanism is unclear. Historically, *SMAD4* is known as a tumor-suppressor gene in several cancer types [109]. One study found homozygous *SMAD4* deletions primarily in the epithelium, but also in stromal fibroblasts and pericryptal myofibroblasts, of juvenile polyps of JP patients with germline *SMAD4* mutations. These findings suggest that SMAD4 acts as a "gatekeeper", instead of a "landscaper" and that juvenile polyps are not just stromal lesions, but epithelium is also involved in hamartoma development [110].

LOH of *SMAD4* was found in 1 out of 11 polyps from five JP patients [90]. Also heterozygous *SMAD4* knockout mice showed LOH in epithelium of polyps resembling juvenile polyps [111]. Finally, SMAD4 protein expression was absent in almost all polyps from *SMAD4* mutation carriers, suggesting a second-hit mechanism in polyp formation in JP [112]. In contrast, no LOH of *BMPR1A* was found in either epithelial or stromal cells of JP polyps, arguing against a typical two-hit tumor-suppressor function for *BMPR1A* [94].

Management

Screening

Patients at risk or with a high suspicion of JP should have endoscopic screening of the colon and upper gastrointestinal tract at age 15 or at the time of first symptoms [6, 113, 114]. At the time of diagnosis of JP, the entire gastrointestinal tract should be examined for the presence of polyps [68]. Genetic testing can be useful for at-risk members from families where germline mutations have been identified. If no germline mutation is found in such an at-risk person, they do not have JP and can be enrolled in screening programs for the general population [113].

Surveillance and Treatment

Endoscopic examination of the colon and upper gastrointestinal tract is recommended every two to three years in patients with JP. In patients with polyps, endoscopic screening should be performed

yearly, until the patient is polyp free [6, 113-115]. Patients with mild polyposis can be managed by frequent endoscopic examinations and polypectomy [115].

Prophylactic surgery is indicated in patients with polyposis (>50-100) unable to be managed endoscopically, severe gastrointestinal bleeding or diarrhea, juvenile polyps with adenomatous changes, and patients with a strong family history of colorectal cancer [114-116]. Surgical options include subtotal colectomy with ileorectal anastomosis (IRA) or total proctocolectomy with pouch [115, 116]. It is unclear which type of surgery is preferable but, in analogy with FAP, may depend on the extent of rectal polyposis [117]. However, no relationship was found between rectal polyp burden and the type of surgery [116]. Moreover, recurrence of rectal polyps in patients with subtotal colectomy is frequent [115] and recent data show that about half of these individuals require subsequent proctectomy [116]. Therefore, total proctocolectomy has been advocated as the initial surgery for patients with massive juvenile polyposis, unable to be managed endoscopically [115]. Although the surgery of choice in JP remains debatable, patients need frequent post-operative endoscopic surveillance because of high recurrence rates of polyps in the remnant rectum and the pouch [116].

Endoscopic treatment of gastric polyps is often difficult, and patients with symptomatic gastric polyposis (e.g. severe anemia) eventually need subtotal or total gastrectomy.

Chemoprevention

Recently noted, COX-2 expression is higher in JP polyps than in sporadic juvenile polyps and correlates with polyp size and dysplasia [118]. This observation suggests that chemoprevention using selective or non-selective COX-2 inhibitors could be beneficial in JP. Currently, NSAID chemoprevention in JP has not been studied systematically. Anecdotally, Oncel *et al.* described the use of sulindac 300 mg per day in two JP patients who had proctocolectomy with a pouch and subsequent polypectomy from the pouch. These patients were followed for 2 and 9 years with no further polyp development in the pouch [116]. The value of NSAID chemoprevention in JP requires further investigation.

PEUTZ-JEGHERS SYNDROME

Introduction

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder, characterized by hamartomatous intestinal polyposis and mucocutaneous skin pigmentation. After juvenile polyposis, it is the most common hamartomatous syndrome with an incidence of one per 120,000-200,000 live births [6, 119, 120]. First described as an inherited condition by Dr Peutz in 1921, followed by a comprehensive report by Dr

Jeghers in 1949, the eponym Peutz-Jeghers was assigned to this disorder in 1954 [119, 121].

Diagnostic criteria for PJS are: A) three or more histologically confirmed Peutz-Jeghers polyps, or B) any number of Peutz-Jeghers polyps with a family history of PJS, or C) characteristic, prominent, mucocutaneous pigmentation with a family history of PJS, or D) any number of Peutz-Jeghers polyps and characteristic, prominent, mucocutaneous pigmentation [119, 122].

Peutz-Jeghers polyps typically occur in the small intestine, although these lesions can also be found in the stomach, large intestine, and rarely in the gallbladder, respiratory and urinary tract [123]. Macroscopically, the polyps are 5 to 50 mm in size and can be pedunculated or sessile. On histology, the center of the polyp is composed of smooth muscle with a tree-like branching pattern. Overlying the smooth muscle core, is mucosa native to the region, heaped into folds producing a villous pattern (Fig. 1C). Pseudo-invasion (epithelial misplacement involving all layers of the bowel wall) has been described in 10% of the small intestinal PJS polyps, and may, thereby, mimic a well differentiated adenocarcinoma [122, 124].

Clinical Manifestations

Presentation

Presenting symptoms of Peutz-Jeghers syndrome include bowel obstruction, polyp intussusception, abdominal pain, rectal bleeding and anemia. About 50% will present with obstruction or intussusception, 25% presents with abdominal pain, and rectal bleeding and polyp extrusion are found in 13 and 7%, respectively [120, 125]. Symptoms usually occur during the first decade of life, and 50-60% of patients will have complaints before the age of 20 [126]. In addition, PJS patients can present with gastrointestinal malignancy [120].

Mucocutaneous skin pigmentation, characterized by increased melanocytes at the epidermal-dermal junction and increased melanin in the basal cells, is the hallmark feature of Peutz-Jeghers syndrome. These pigmented macules are usually between 1 and 5 mm in size and cluster around the mouth, eyes, nostrils, and the peri-anal area. Pigmented spots can also be found on the fingers and toes and rarely on the dorsal and volar aspects of the hands and feet. Pigmentation can be present from birth, but may develop in early infancy, and is usually present before gastrointestinal manifestations arise. Although buccal pigmentation tends to persist, skin pigmentation can fade with age [120].

The presence of multiple hamartomatous polyps with typical Peutz-Jeghers histology in the large and/or small intestine is diagnostic for PJS. Polyps in PJS are less numerous than in FAP, ranging from zero to several dozens per intestinal segment. Polyps are most prevalent in the small intestine (64-

96% of patients), but can also be found in the colon (27-53% of patients) and stomach (24-49% of patients) [120, 125]. Solitary Peutz-Jeghers polyps can occur as sporadic lesions in patients without a family history or any other features of PJS. In addition to intestinal polyps, hamartomas have been described in the gallbladder, nasopharynx, trachea, bladder, and ureter [123].

Cancer Risk

Peutz-Jeghers patients have an increased risk for several malignancies including small intestinal, stomach, pancreas, colon, esophagus, ovary, uterus, lung, and breast cancer [127-130]. Several investigators have estimated the cancer risk in PJS.

Giardiello *et al.* reported 15 malignancies in 31 PJS patients (48%). Most cancers were extra-intestinal and only 4 gastrointestinal cancers were found. They reported a 18 times greater risk of cancer development in PJS patients compared to the general population [127].

Spigelman *et al.* studied 72 PJS patients and found 16 cancers (22%), of which 9 were gastrointestinal and 7 were extra-intestinal malignancies. The estimated relative risk of death was 13 due to gastrointestinal malignancy, and 9 due to any malignancy. The chance of dying of cancer was 48% at age 57 [129].

Boardman *et al.* found a relative risk of cancer of 18.5 in women and 6.2 in men with PJS (overall relative risk of 9.9). Men had a relative risk of gastrointestinal cancer of 30.3 and women of 150.9, the total relative risk was 50.5 for men and women together. The relative risk of breast and gynecologic cancer in women was 20.3 [130].

In 2000 Giardiello and colleagues reviewed the literature and estimated the risk of cancer in PJS based on 210 PJS patients described in 6 publications. They found a relative risk of all cancers of 15.2 and a cumulative risk of developing cancer of 93% from age 15 to 64. Moreover, PJS patients were at a significantly greater relative risk of cancer of the small intestine (RR 520), stomach (RR 213), pancreas (RR 132), colon (RR 84), esophagus (RR 57), ovary (RR 27), uterus (RR 16), lung (RR 17), and breast (RR 15.2) [128].

Recently, a large study among 240 patients with Peutz-Jeghers syndrome carrying germline *LKB1/STK11* mutations found an overall risk of developing cancer at ages 20, 30, 40, 50, 60 and 70 years of 1%, 3%, 19%, 32%, 63% and 81%, respectively. The most common cancers found were gastroesophageal, small bowel, colorectal and pancreatic cancer. Women had an increased risk of breast cancer of 32% at age 60 [131].

In summary, these studies show that PJS patients are at high risk for cancer, although exact figures remain unclear. The relative risk of developing cancer ranges between 9.9 and 18 fold [127, 128,

130] and the cumulative risk between 80-90% at age 70 [128, 131].

Genital Tract Tumors

Several gonadal malignancies occur in PJS patients [132, 133]. In female patients, sex cord tumors with annular tubes (SCTAT) are found in almost all individuals in whom the ovaries are examined. Patients with these tumors can present with menstrual irregularity, hyperestrogenism or sexual precocity. These lesions occur bilaterally and usually have a benign behavior, although a clinically malignant course has been reported [132].

In male PJS patients calcifying Sertoli cell tumors, also referred to as testicular tumors resembling SCTAT, have been described. Presenting symptoms are gynecomastia, rapid growth and advanced bone age due to hyperestrogenism. Patients often present at a young age, between age 2-6 years old. Although a benign tumor, it does have malignant potential. Orchiectomy is the curative treatment [134, 135].

Finally, adenoma malignum, or minimal deviation adenocarcinoma of the cervix, has been reported in PJS patients. Presenting symptoms include abnormal vaginal bleeding or a mucoid vaginal discharge. It is an extremely well differentiated adenocarcinoma of the cervix, usually of mucinous type, with malignant behavior and a poor prognosis [132, 133].

Genetic Defect

In 1998 two groups independently identified the serine-threonine kinase gene (*STK11/LKB1*), located on chromosome 19p13.3, as responsible for the Peutz-Jeghers syndrome [136, 137]. *LKB1* is a tumor-suppressor involved in intracellular signal transduction and cellular polarity [138]. Mutations in *LKB1* result in inactivation of the kinase activity [139], although germline mutations that allow retention of kinase activity have recently been reported [140].

LKB1 is composed of nine exons, coding a 433 amino acid protein. Although mutations can occur throughout exons 1 to 9, about 40% are found in exon 1 to 6 [131, 141, 142]. More than 75% of the mutations in *LKB1* are frameshift or nonsense mutations, resulting in a truncated protein. In-frame deletions or missense mutations occur less commonly at conserved amino acids within the kinase core of the protein [136, 137, 139, 140, 142-144].

Germline mutation in *LKB1* can be identified in about 50 to 70% of PJS patients. Although shortcomings in mutational analyses and patient selection have been suggested to account for the large proportion of germline mutation-negative PJS patients, genetic heterogeneity has also been considered [140-143, 145]. A possible second locus was proposed at chromosome 19q13.4. However, no

germline mutations in this region have been identified [146, 147]. In addition, several LKB1/STK11-interacting proteins, including STRAD on chromosome 17q23.3 [148, 149], BRG1, MO25 [149], and LIP1 (LKB1-interacting protein) on chromosome 2q36 [147], were excluded as PJS genes. A recent study found germline *LKB1* defects in 94% of patients who clinically met the criteria of Peutz-Jeghers, arguing against the existence of a second PJS locus [150].

Genotype-Phenotype Correlations

Considerable inter- and intra-familial phenotypic variation of expression exists in PJS kindreds and little is known about the natural course of PJS in relationship to site and type of *LKB1* germline mutation. Several studies have evaluated genotype-phenotype correlations in PJS.

Some studies found that cancer risk differs between PJS patients with and without detectable *LKB1* mutations [140, 143, 145]. However, a recent large multi center study did not find such correlation [151].

Also the site and type of mutation have been associated with differences in cancer risk for patients with PJS in some small studies. One study found that PJS patients with missense mutations had a later age of onset of gastrointestinal symptoms, gastric polyposis, and first polypectomy compared to patients with truncating mutations or with no detectable mutation [145]. Another group reported that in-frame deletions, splice site mutations, and missense mutations in the part of the gene encoding protein domains important for ATP binding (codon 49-106) and the site of catalysis (codon 123-171) were rarely associated with cancer, whereas mutations in the C-terminus and in the part of the gene encoding protein domains important for substrate recognition (codon 171-225) were more frequently associated with malignancies [140]. A recent large collaborative study, however, did not find a correlation between type or site of *LKB1* mutation and cancer risk [151].

Cancer Pathogenesis

The pathogenic mechanisms involved in gastrointestinal polyp development and carcinogenesis in PJS are largely unknown. Reports describing adenomatous and carcinomatous change within hamartomas, suggest that malignancy develops within hamartomas, following a hamartoma-adenoma-carcinoma sequence, comparable to that in FAP, [152-155]. In addition, several studies provided molecular evidence of a hamartoma-adenoma-carcinoma sequence in PJS. A second hit in *LKB1* causing loss of heterozygosity (LOH) in adenomatous and carcinomatous lesions in PJS polyps was noted by several investigators [144, 156, 157]. Consequently, *LKB1* was thought to act as a typical tumor-suppressor gene [158]. In addition,

LOH of *p53*, and *K-Ras* and β -*catenin* mutations were found in adenomas developing in hamartomatous polyps, indicating that molecular alterations in these genes drive carcinogenesis in PJS as well [144, 157].

However, the precise frequency of LOH of *LKB1* in PJS polyps in humans remains unclear, and studies in mice showed that loss of the wild-type *LKB1* allele is not a prerequisite for the formation of hamartomatous polyps [159]. Therefore, the need for a second-hit in *LKB1* during polyp development in PJS and, hence, the role of *LKB1* as a typical 'Knudson' two-hit tumor-suppressor gene, is questioned.

The identification of *LKB1* as important in cellular polarity [138] may provide new insights in the molecular mechanism of polyp and carcinoma development in PJS. One theory suggests mucosal prolapse as a pathogenic mechanism underlying the development of typical hamartomatous polyps in PJS. In this hypothesis PJS hamartomatous polyps represent an epiphenomenon to the cancer-prone condition and the hamartoma-adenoma-carcinoma sequence as such does not exist [160]. Loss of polarity function may also affect asymmetric stem cell division in PJS and lead to expansion of the stem cell pool [161]. This could contribute to polyp formation and explain the increased cancer risk as well.

Management

Screening and surveillance of PJS patients is essential since complications of polyposis resulting in repeated acute laparotomy with the risk of short-bowel syndrome can be prevented [162]. In addition, PJS patients are at increased risk for numerous malignancies. Management of small bowel polyps is problematic, since most endoscopic techniques fail to visualize and treat polyps in this region. However, modern endoscopic techniques have improved surveillance and treatment of small bowel polyposis.

Screening

Genetic testing of at-risk offspring of PJS patients is indicated at the time symptoms occur or in the late teens if symptoms do not occur. In addition, in patients with a negative family history, genetic testing is indicated in patients with Peutz-Jeghers polyps or typical pigmentation [6, 145].

Surveillance and Treatment

Most authors recommend endoscopic surveillance of the upper gastrointestinal tract at a two year interval starting at age 10 [6, 119, 120]. However, others recommend upper gastrointestinal endoscopic surveillance every three years, starting at age 25 [114]. In addition, a barium study is recommended every 2 years to evaluate small intestinal polyposis. Polyps larger than 1.5 cm should be removed by push enteroscopy and/or laparotomy with intra-operative enteroscopy. Small polyps can be removed

by snare polypectomy, larger polyps may require enterotomy [119, 120, 162]. In the future, wireless capsule endoscopy may prove to be an effective method for evaluating small bowel polyposis in PJS.

Colonoscopic examination should occur every three years starting at the time of first symptoms or in the late teens in patients that did not develop symptoms [6, 114].

Multiple bowel resections due to gastrointestinal complications of polyps may eventually result in short-bowel syndrome. Therefore, prevention of surgery is key in the treatment of PJS. However, surgery may be inevitable in acute situations, or in case of malignancy.

To evaluate presence of pancreatic tumors, endoscopic or abdominal ultrasound is indicated every one or two years, starting at age 30 [119, 120]. Female patients should perform regular breast self-examination, and undergo breast radiology every 5 years from 25 to 45 years. Thereafter, breast radiology should occur every two years between age 45 and 50, and yearly after the age of 50 [119]. In addition, pelvic ultrasound, and cervical smears should be performed yearly [119, 120]. Finally, affected or at-risk males should perform regular self examination of the testes and have scrotal ultrasound until puberty or in the presence of feminising symptoms [119].

Chemoprevention

Several investigators showed increased levels of COX-2 in hamartomas [163-165] and carcinomas [163, 165] of PJS patients. Udd *et al.* studied the effect of COX-2 inhibition in *LKB*^{+/-} mice and PJS patients. They observed decreased numbers of polyps larger than 2 mm in *LKB1*^{+/-} mice treated with celecoxib or *LKB*^{+/-} mice in which one or two COX-2 alleles were knocked out. Interestingly, the effect of celecoxib treatment on polyp burden was greater than the effect that was observed in COX-2 deficient mice, indicating an effect of a COX-2 independent mechanism. Moreover, no effect on polyps smaller than 2 mm was observed, which points to a role for COX-2 in polyp progression rather than polyp initiation [166]. In addition, they performed a pilot clinical trial in which eight PJS patients were treated with 400 mg celecoxib per day for 6 months. Gastroscopy was performed before and after 6 months of treatment. Clinical data from 6 patients were used in the final analysis. In 2 of 6 patients a significant reduction of gastric polyp burden was observed [166]. These results indicate that COX-2 inhibition may be beneficial in at least a subset of PJS patients. However, a randomized study is necessary to further evaluate the potential of long-term COX-2 treatment in PJS.

SUMMARY AND CONCLUDING REMARKS

FAP, JP and PJS are the most well-known and clinically relevant gastrointestinal polyposis

syndromes. Although rare, recognition of these conditions is important in view of the consequences for the patients as well as family members. These hereditary gastrointestinal polyposis syndromes also serve as paradigms for understanding gastrointestinal carcinogenesis. FAP was the first polyposis syndrome molecularly characterized by the discovery of the APC gene. Tumorigenesis in FAP is considered the prototype of the adenoma-carcinoma sequence in the large bowel due to disrupted 'gatekeeper' function of APC and subsequent Wnt activation accompanied by an accumulation of genetic changes and resultant clonal expansion. The molecular genetics of juvenile polyposis and Peutz-Jeghers syndrome are less well understood. In JP the primary defect may be stromal rather than epithelial and this so-called 'landscaper' defect may ultimately lead to neoplastic transformation in the overlying epithelium, though the polyps are not neoplastic per se. On the contrary, they may be considered true hamartomas, i.e. anomalies in the developmental patterning of the gut. In PJS loss of polarity function may be a critical pathogenic mechanism underlying polyp formation and tumorigenesis. Loss of proper polarity regulation may affect asymmetric stem cell division, leading to an expanded stem cell compartment. Secondary changes due to mucosal prolapse of the bowel mucosa may then contribute to the typical appearance of the polyps. Whether or not the polyps are preneoplastic remains to be determined.

Future studies on the molecular and clinical aspects of these syndromes may eventually result in a better understanding of gastrointestinal polyposis and carcinogenesis, and improved management of patients afflicted by these disorders.

ACKNOWLEDGEMENTS

This work was supported by The Netherlands Digestive Disease Foundation (MLDS) grant 04-06. We thank Wilfried Meun for his help in preparing the figures.

ABBREVIATIONS

FAP	= familial adenomatous polyposis
PJS	= Peutz-Jeghers syndrome
JP	= juvenile polyposis
HNPCC	= Hereditary Non-Polyposis Colorectal Cancer
BRRS	= Bannayan-Riley-Ruvalcaba syndrome
CS	= Cowden syndrome
APC	= adenomatous polyposis coli
ACF	= aberrant crypt focus
CHRPE	= Congenital Hypertrophy of Retinal Pigment Epithelium
NSAID	= non-steroidal anti-inflammatory drug

COX-2 = cyclooxygenase-2
 IRA = ileorectal anastomosis
 TGF- = transforming growth factor-
 BMPR1A = Bone Morphogenetic Protein Receptor 1A
 ENG = Endoglin
 STK11 = Serine/Threonine-protein kinase 11
 LOH = loss of heterozygosity
 HHT = hereditary hemorrhagic teleangiectasias

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