Abstract

APC-associated polyposis conditions result from a constitutional heterozygous pathogenic variant in the APC gene. These conditions include three main clinical phenotypes: the familial adenomatous polyposis (FAP), the attenuated FAP (AFAP) and the gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This phenotypic variability corresponds to the differences in the location of the pathogenic variant within the APC gene, even though variations among the individuals and within the families with the identical APC pathogenic variant may occur.

Colorectal screening should begin from age 10 to 12 years in FAP and in late teens in AFAP, or earlier if there are gastrointestinal symptoms; the timing of surgery and the extent of resection should be determined on the basis of patient's personal history.

Data to support screening for other cancers and manifestations associated with FAP are limited. The efficacy of the screening for gastric cancer and of prophylactic gastrectomy for patients with GAPPS is currently unknown.

Identity

Other names
Familial adenomatous polyposis (FAP)
Attenuated Familial Adenomatous Polyposis (AFAP)
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)
Gardner syndrome

Note
Inherited cancer susceptibility syndrome characterized by gastrointestinal polyposis.

Inheritance
Autosomal dominant with variable expressivity. About 20-25% of the individuals with FAP harbour a de novo APC pathogenic variant.

The phenotypic variations correlate with the specific location of the APC gene mutation (Nieuwenhuis et Vasen, 2007).

However, variations observed within the families or the groups of individuals with the same pathogenic variant suggest that other modifiers can affect disease expression (Giardiello et al., 1994).

The prevalence of FAP has been estimated between one in 6,850 and one in 31,250 people of the general population (Jasperson et al., 2017). AFAP is likely underdiagnosed, given the milder phenotype.

The prevalence of GAPPS is currently unknown.

Clones

Stomach, GAPPS, APC
Note
The diagnosis of an APC-associated polyposis condition is established by the identification of a heterozygous germline pathogenic variant in the APC gene.

In a cross-sectional study, APC pathogenic variants were found in the 80% (95% CI, 71%-87%) of the individuals with more than 1000 colonic adenomas, 56% (95% CI, 54%-59%) in those with 100-999 adenomas, 10% (95% CI, 9%-11%) in those with 20-99 adenomas, and 5% (95% CI, 4%-7%) in those with 10-19 adenomas (Grover et al., 2012).

Phenotype and clinics
FAP is classically characterized by the development of hundreds to thousands of adenomas in the colon and rectum during the second decade of life. Almost all the patients will develop colorectal cancer (CRC) if they are not treated at an early stage. The mean age at CRC diagnosis in the untreated individuals is 39 years (range 34-43 years).

In addition to the characteristic polyp formation in the colon, individuals with FAP may present extracolonic manifestations such as polyps of the gastric fundus and duodenum, osteomas, dental abnormalities (unerupted teeth, congenital absence of one or more teeth, supernumerary teeth, dentigerous cysts and odontomas), congenital hypertrophy of the retinal pigment epithelium (CHRPE), desmoid tumours, and extracolonic cancers (thyroid, liver, bile ducts and central nervous system). Gardner syndrome is a clinical variant of FAP where the extra-colonic features are prominent. Turcot syndrome is another phenotypic variant characterized by central nervous system tumours occurring together with colonic polyposis (Jasperson et al., 2017).

AFAP is a milder phenotypic variant that is characterized by fewer adenomas, a later age of adenoma development and cancer diagnosis. The extracolonic manifestations, such as gastric and duodenal polyps or cancers, are variably present (Burt et al., 2004; Neklason et al., 2008).

GAPPS is characterized by proximal gastric polyposis and an increased risk of gastric cancer. Colorectal and duodenal involvement is rare (Worthley et al., 2012; Li et al., 2016; Repak et al., 2016).

Differential Diagnosis
MUTYH-Associated polyposis (MAP). The colonic phenotype of MAP can be similar to that of AFAP but the inheritance is autosomal recessive. In a cross-sectional study, the prevalence of biallelic MUTYH pathogenic variants was 2% (95% CI, 0.2%-6%) among the individuals with more than 1000 colonic adenomas, 7% (95% CI, 6%-8%) in those with 100 to 999 adenomas, 7% (95% CI, 6%-8%) in those with 20 to 99 adenomas, and 4% (95% CI, 3%-5%) in those with 10 to 19 adenomas (Grover et al., 2012).

Hamartomatous polyposis syndromes (i.e. Peutz-Jeghers syndrome, PTEN-hamartoma tumour syndrome, Juvenile polyposis syndrome). These conditions are also characterized by gastrointestinal polyposis but can be recognized by the polyp histology and the extracolonic manifestations.

Lynch syndrome (Hereditary non-polyposis colon cancer, HNPC). AFAP could be difficult to distinguish from Lynch syndrome in the individuals with early-onset CRC and few adenomatous colonic polyps (Cao et al, 2002). In this situation, the family history, extracolonic manifestations as well as microsatellite instability and/or immunohistochemistry testing may be helpful in the differential diagnosis.

Rare individuals carry biallelic pathogenic variants in the mismatch repair genes, leading to a childhood cancer predisposition syndrome. Affected individuals can develop multiple colorectal adenomas mimicking FAP as well as brain tumours, hematologic malignancies, CRC and/or other Lynch syndrome-related cancers. Café au lait macules and/or axillary/inguinal freckling have also been reported (de Vos et al., 2005; Jasperson et al., 2011).

MSH3-associated polyposis. This rare autosomal recessive condition is characterized by colorectal and duodenal adenomas (diagnosed at thirties in most cases), CRC, gastric cancer, and early-onset astrocytoma (Adam et al., 2016).

Polymerase proofreading-associated polyposis (PPAP). This dominantly inherited syndrome is characterized by multiple colorectal adenomas, CRC and other Lynch-syndrome related cancers such as endometrial cancer, ovarian and brain tumours (Palles et al., 2011).

NTHL1-associated polyposis (NAP). This rare autosomal recessive condition is characterized by colorectal and duodenal adenomas and carcinomas. Individuals with NAP may also be at increased risk for multiple extracolonic malignancies (Weren et al., 2015).

Hereditary mixed polyposis syndrome (HMP1). This condition, caused by a duplication upstream of GREM1, is characterized by the presence of a mixture of mixed juvenile-adenomatous, hyperplastic, serrated and adenomatous polyps that are associated with an increased risk of developing CRC if left untreated (Jaeger et al., 2012).

Cronkhite-Canada syndrome. This syndrome is characterized by non-hereditary gastrointestinal hamartomatous polyposis with the cutaneous triad of alopecia, nail changes and hyperpigmentation.

Serrated polyposis syndrome. The diagnosis of this syndrome, characterized by the presence of multiple serrated polyps spread throughout the colorectum and an increased risk of CRC, is based on clinical criteria (Kalady et al., 2011). It is
unknown whether this condition is inherited or acquired.

**Neoplastic risk**
In the individuals with FAP, colorectal polyps begin to appear in the second and third decade. Once they appear, the polyps rapidly increase in number and undergo malignant transformation if untreated. Without treatment, patients with FAP have a nearly 100% lifetime risk of CRC. The average age of CRC development in the untreated patients is 39 years (range 34–43). Inter and intrafamilial phenotypic variability is common (Jasperson et al., 2017).

Individuals with FAP also have an increased risk of other cancers, including duodenal carcinoma (4-12%), especially in the periampullary area (Koornstra, 2012; Aihara et al., 2014), follicular or papillary thyroid cancer (1-12%) (Herreia et al., 2007; Jarrar et al., 2011, Steinhagen et al., 2012; Cetta, 2015), childhood hepatoblastoma (2%) (Aretz et al, 2006), gastric carcinoma (GAPPS syndrome is characterized by fundic gland polyposis and a significant risk for intestinal adenomas, an APC pathogenic variant 3’ of codon 1399, female gender and previous abdominal surgery (Nieuwenhuis et al., 2011; Sinha et al., 2011).

AFAP is characterized by fewer colonic polyps and later age of onset than classic FAP. The cumulative risk for CRC by age 80 years in AFAP is estimated at 70% and the median age at diagnosis is 55 years (Burt et al., 2004; Neklason et al., 2008).

Individuals with AFAP also have an increased risk of upper gastrointestinal cancers, similar to that seen in FAP, and thyroid cancer. Desmoid tumours are rare.

GAPPS syndrome is characterized by fundic gland polyposis and a significant risk for intestinal-type or mixed gastric cancer. The age of onset of gastric cancer is variable, ranging from 23 to 75 years (Worthley et al., 2012; Li et al., 2016; Repak et al., 2016).

**Treatment**
Colectomy is the cornerstone of the therapy in FAP patients. In at risk individuals, large bowel endoscopy is first performed from age 10 to 14 years or earlier if there are gastrointestinal symptoms (Syngal et al., 2015; Gupta et al., 2019). Once the diagnosis has been confirmed, colonoscopy every one to two years is undertaken to assess and monitor polyp burden. The exact timing of surgery depends on the severity of the polyposis, the presence of dysplasia or malignancy, the presence of symptoms, and the intellectual and physical maturity of the patient, with most patients undergoing surgery between ages 15-25. The surgical options for patients with FAP include total colectomy with ileorectal anastomosis, total proctocolectomy with ileal pouch anal anastomosis (IPPA) and total proctocolectomy with permanent ileostomy.

After surgery, those who have had IPPA should undergo pouchoscopy every one to three years, depending on the polyp burden; those who have had IRA should undergo surveillance of the remaining rectum every 6 to 12 months; those who had an ileostomy should undergo ileoscopy every one to three years (Gupta et al., 2019).
For the individuals with AFAP, colorectal screening should begin in late teens; colectomy may be not necessary, and periodic colonoscopic polypectomy could be sufficient to prevent CRC.

Endoscopic or surgical removal of duodenal and/or ampullary adenomas should be considered if polyps exhibit villous change or severe dysplasia, exceed one centimeter in diameter, or cause symptoms. An endoscopic or transduodenal polypectomy is associated with a high rate of recurrence.

Segmental duodenal resection and pancreas-sparing duodenectomy may have a role in patients with limited disease. Pancreatoduodenectomy remains the last resort for advanced duodenal and ampullary adenomatosis, but the risks of this complex procedure are high (van Heumen et al., 2012; Campos et al., 2015).
If there is a family history of desmoids, abdominal MRI or CT scan should be considered within one to three years post colectomy and then every five to ten years (Gupta et al., 2019). Available treatments for desmoid tumours include surgical excision (associated with high rate of recurrence), non-steroidal anti-inflammatory drugs, hormonal therapy, radiotherapy, and cytotoxic chemotherapy (Vasen et al., 2008). Data to support screening and treatment of desmoid tumours are limited.

The evidence for efficacy of surveillance for thyroid cancer, hepatoblastoma and CNS neoplasm is limited. There are currently no guidelines on the screening and timing of prophylactic gastrectomy for GAPPS. Due to the extent of gastric polyposis and the rapid progression of fundic gland polyposis, endoscopic surveillance in this condition may have limited effectiveness (Repak et al., 2016).
**Prognosis**

Untreated FAP patients have a median life expectancy of 42 years. Life expectancy is extended greatly in those treated with colectomy. Upper gastrointestinal cancer, desmoid tumour and rectal stump cancer are the most common causes of death in patients who have undergone colectomy. Individuals diagnosed with APC-associated conditions as a result of having an affected relative have a significantly greater life expectancy than those diagnosed on the basis of symptoms (Heiskanen et al., 2000).

**Genes involved and proteins**

**APC (adenomatosis polyposis coli, APC regulator of WNT signaling pathway)**

**Alias**
GS; DP2; DP3; BTPS2; DP2.5; PPP1R46

**Location**
5q22.2

**DNA/RNA**

**Description**
The APC gene spans 108 kb of genomic DNA, with 15 coding exons and 3 upstream noncoding exons.

**Transcription**
The transcribed mRNA has 8532 bps. 13 distinct transcripts have been described.

**Protein**

**Description**
Size (primary transcripts): 2843 aminoacids; Molecular Mass: 311,646 Da. From the N terminus to the C terminus, there is an oligomerization domain, an armadillo repeat-domain, a 15- or 20-residue repeat domain, a SAMP repeats domain, a basic domain and C-terminal domains. The oligomerization domain has been shown to be a binding site for APC mutants and is critical for the dominant negative effect of the APC protein. The armadillo repeat domain is the most conserved domain and binds to several proteins, contributing to stimulation of cell migration and cell adhesion. The following 15-, 20-residue repeat domain and the SAMP repeats domain play central roles in the negative regulation of the canonical Wnt signaling pathway by aiding in the proteosomal degradation of the beta-catenin. The basic and C-terminal domains bind, directly or indirectly, to the microtubules and are important for the microtubule stabilization, kinetochore function, and chromosomal segregation (Sieber et al., 2000; Fearnhead et al., 2001).

**Expression**
Ubiquitous, more specifically throughout the large intestine and central nervous system

**Localisation**
Nucleus and membrane/cytoskeleton

**Function**
The APC protein acts as a tumour suppressor protein and plays a critical role in maintaining normal apoptosis. APC functions as a negative regulator of Wnt signaling by mediating the proteolytic degradation of the CTNNB1 (beta-catenin). The APC protein forms a complex with the axin protein AXIN1, serine/threonine kinases glycogen synthase kinase 3 (GSK3) and casein kinase 1 (CK1). This 'destruction complex' targets beta-catenin for the phosphorylation and the subsequent ubiquitin-mediated proteolysis (Lipton and Tomlinson, 2006). APC also interacts with actin- and microtubule-associated proteins and stabilizes microtubules. In addition, the APC protein is also involved in other processes including cell migration, adhesion, chromosome segregation, spindle assembly, apoptosis, and neuronal differentiation (Fearnhead et al., 2001).

**Homology**
APC homologs are present in eukaryotes.

**Mutations**

**Germinal**
More than 1100 different APC pathogenic variants have been described to date (http://www.lovd.nl/apc). The great majority result in a premature truncation of the APC protein, usually through single amino-acid substitutions or frameshifts (Hegde et al., 2014). Large genomic rearrangements have been reported to account for about 10% of the alterations. While pathogenic variants have been found scattered throughout the gene, they are predominantly clustered in the 5’ end of the gene. The most common germline pathogenic variant is a 5-bp deletion that results in a frameshift at codon 1309. Although variations may occur among the individuals and within the families with the identical APC pathogenic variant, a correlation between the location of the mutation in the APC gene and the colonic phenotype severity, the age of onset and the appearance of extracolonic manifestations has been described (Giardiello et al., 1994; Nieuwenhuis et Vase, 2007).

**Somatic**
Somatic mutations in the APC gene are an early, if not the initiating, event for 80%-85% of the sporadic CRCs (Macrae at al, 2009). Sporadic cancers show a broader clustering of somatic APC mutations in codons 1281-1556, the so-called mutation cluster region (MCR), contained within regions involved in the beta-catenin downregulation. Somatic mutations of this gene are also implicated in extracolonic
cancers such as those of the pancreas, stomach, and esophagus.

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