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APC-associated polyposis conditions

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Olschwang S. Familial adenomatous polyposis (FAP). Atlas Genet Cytogenet Oncol Haematol 1998;2(4)

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.
Esophagogastroduodenoscopy is recommended by age 20-30 years or prior to colon surgery.
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.

Keywords
Familial adenomatous polyposis, FAP, Attenuated familial adenomatous polyposis, AFAP, Gastric Adenocarcinoma and Proximal Polyposis of the Stomach, GAPPS, APC

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.

Clinics

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, HNPCC). 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 (HMPS). 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%) (Herraiz et al., 2007; Jarrar et al., 2011, Steinhagen et al., 2012; Cetta, 2015), childhood hepatoblastoma (2%) (Aretz et al, 2006), gastric carcinoma (

The risk of desmoid tumours in the individuals with FAP is 10-30%. Risk factors for desmoids tumours in FAP patients include a family history of desmoid tumours, 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 IPAA should undergo pouchscopy 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.

Esophagogastroduodenoscopy, including the complete visualization of the ampulla of Vater, is recommended starting at age 20 to 30 years or prior to colectomy (Syngal et al., 2015; Gupta et al., 2019). Post-baseline evaluations are recommended every six months to four years depending on the duodenal adenoma burden according to the Spigelman staging criteria (Spigelman et al., 1989).

The 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. Pancreatico-duodenectomy 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 transcrips): 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 proteasomal 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 mantaining 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 Vasen, 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.

References

Adam R, Spier I, Zhao B, Kloth M, Marquez J, Hinrichsen I, Kirfel J, Tafazzoli A, Horpaopan S, Uhlhaas S, Stienen D, Friedrichs N, Altmüller J, Laner A, Holzapfel S, Peters S, Kayser K, Thiele H, Holinski-Feder E, Marra G, Kristiansen G, Nöthen MM, Büttner R, Möslein G, Betz RC, Brieger A, Lifton RP, Aretz S. Exome Sequencing Identifies Biallelic MSH3 Germline Mutations as a Recessive Subtype of Colorectal Adenomatous Polyposis. Am J Hum Genet. 2016 Aug 4;99(2):337-51

Aihara H, Kumar N, Thompson CC. Diagnosis, surveillance, and treatment strategies for familial adenomatous polyposis: rationale and update. Eur J Gastroenterol Hepatol. 2014 Mar;26(3):255-62

Aretz S, Koch A, Uhlhaas S, Friedl W, Propping P, von Schweinitz D, Pietsch T. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer. 2006 Nov;47(6):811-8

Attard TM, Giglio P, Koppula S, Snyder C, Lynch HT. Brain tumors in individuals with familial adenomatous polyposis: a cancer registry experience and pooled case report analysis. Cancer. 2007 Feb 15;109(4):761-6

Burt RW, Leppert MF, Slattery ML, Samowitz WS, Spirio LN, Kerber RA, Kuwada SK, Neklason DW, Disario JA, Lyon E, Hughes JP, Chey WY, White RL. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology. 2004 Aug;127(2):444-51

Campos FG, Sulbaran M, Safatle-Ribeiro AV, Martinez CA. Duodenal adenoma surveillance in patients with familial adenomatous polyposis. World J Gastrointest Endosc. 2015 Aug 10;7(10):950-9

Cao Y, Pieretti M, Marshall J, Khattar NH, Chen B, Kam-Morgan L, Lynch H. Challenge in the differentiation between attenuated familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer: case report with review of the literature. Am J Gastroenterol. 2002 Jul;97(7):1822-7

Cetta F. FAP Associated Papillary Thyroid Carcinoma: A Peculiar Subtype of Familial Nonmedullary Thyroid Cancer. Patholog Res Int. 2015;2015:309348

Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC Hum Mol Genet 2001 Apr;10(7):721-33

Giardiello FM, Krush AJ, Petersen GM, Booker SV, Kerr M, Tong LL, Hamilton SR. Phenotypic variability of familial adenomatous polyposis in 11 unrelated families with identical APC gene mutation Gastroenterology 1994 Jun;106(6):1542-7

Grover S, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, Wenstrup RJ, Syngal S. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas JAMA 2012 Aug 1;308(5):485-492

Gupta S, Provenzale D, Llor X, Halverson AL, Grady W, Chung DC, Haraldsdottir S, Markowitz AJ, Slavin TP Jr, Hampel H; CGC, Ness RM, Weiss JM, Ahnen DJ, Chen LM, Cooper G, Early DS, Giardiello FM, Hall MJ, Hamilton SR, Kanth P, Klapman JB, Lazenby AJ, Lynch PM, Mayer RJ, Mikkelson J; CGC, Peter S, Regenbogen SE, Dwyer MA; CGC, Ogba N. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 2 2019 J Natl Compr Canc Netw

Hegde M, Ferber M, Mao R, Samowitz W, Ganguly A; Working Group of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis) Genet Med 2014 Jan;16(1):101-16

Heiskanen I, Luostarinen T, Järvinen HJ. Impact of screening examinations on survival in familial adenomatous polyposis Scand J Gastroenterol 2000 Dec;35(12):1284-7

Herraiz M, Barbesino G, Faquin W, Chan-Smutko G, Patel D, Shannon KM, Daniels GH, Chung DC. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations Clin Gastroenterol Hepatol 2007 Mar;5(3):367-73

Jaeger E, Leedham S, Lewis A, Segditsas S, Becker M, Cuadrado PR, Davis H, Kaur K, Heinimann K, Howarth K; HMPS Collaboration, East J, Taylor J, Thomas H, Tomlinson I. Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1 Nat Genet 2012 May 6;44(6):699-703

Jarrar AM, Milas M, Mitchell J, Laguardia L, O'Malley M, Berber E, Siperstein A, Burke C, Church JM. Screening for thyroid cancer in patients with familial adenomatous polyposis Ann Surg 2011 Mar;253(3):515-21

Jasperson KW, Samowitz WS, Burt RW. Constitutional mismatch repair-deficiency syndrome presenting as colonic adenomatous polyposis: clues from the skin Clin Genet 2011 Oct;80(4):394-7

Kabasawa Y, Ishii A, Murata H, Takaoka M. Clinical significance of the house dust mite (Dermatophagoides pteronyssinus) in asthmatic children in Japan Acta Allergol 1976 Dec;31(6):442-54

Kalady MF, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, Church JM. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome Dis Colon Rectum 2011 Feb;54(2):164-70

Koornstra JJ. Small bowel endoscopy in familial adenomatous polyposis and Lynch syndrome Best Pract Res Clin Gastroenterol 2012 Jun;26(3):359-68

Li J, Woods SL, Healey S, Beesley J, Chen X, Lee JS, Sivakumaran H, Wayte N, Nones K, Waterfall JJ, Pearson J, Patch AM, Senz J, Ferreira MA, Kaurah P, Mackenzie R, Heravi-Moussavi A, Hansford S, Lannagan TRM, Spurdle AB, Simpson PT, da Silva L, Lakhani SR, Clouston AD, Bettington M, Grimpen F, Busuttil RA, Di Costanzo N, Boussioutas A, Jeanjean M, Chong G, Fabre A, Olschwang S, Faulkner GJ, Bellos E, Coin L, Rioux K, Bathe OF, Wen X, Martin HC, Neklason DW, Davis SR, Walker RL, Calzone KA, Avital I, Heller T, Koh C, Pineda M, Rudloff U, Quezado M, Pichurin PN, Hulick PJ, Weissman SM, Newlin A, Rubinstein WS, Sampson JE, Hamman K, Goldgar D, Poplawski N, Phillips K, Schofield

L, Armstrong J, Kiraly-Borri C, Suthers GK, Huntsman DG, Foulkes WD, Carneiro F, Lindor NM, Edwards SL, French JD, Waddell N, Meltzer PS, Worthley DL, Schrader KA, Chenevix-Trench G. Point Mutations in Exon 1B of APC Reveal Gastric Adenocarcinoma and Proximal Polyposis of the Stomach as a Familial Adenomatous Polyposis Variant Am J Hum Genet 2016 May 5;98(5):830-842

Lipton L, Tomlinson I. The genetics of FAP and FAP-like syndromes Fam Cancer 2006;5(3):221-6

Macrae F, du Sart D, Nasioulas S. Familial adenomatous polyposis Best Pract Res Clin Gastroenterol 2009;23(2):197-207

Neklason DW, Stevens J, Boucher KM, Kerber RA, Matsunami N, Barlow J, Mineau G, Leppert MF, Burt RW. American founder mutation for attenuated familial adenomatous polyposis Clin Gastroenterol Hepatol 2008 Jan;6(1):46-52

Nieuwenhuis MH, Mathus-Vliegen EM, Baeten CG, Nagengast FM, van der Bijl J, van Dalsen AD, Kleibeuker JH, Dekker E, Langers AM, Vecht J, Peters FT, van Dam R, van Gemert WG, Stuifbergen WN, Schouten WR, Gelderblom H, Vasen HF. Evaluation of management of desmoid tumours associated with familial adenomatous polyposis in Dutch patients Br J Cancer 2011 Jan 4;104(1):37-42

Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, Kemp Z, Spain SL, Guarino E, Salguero I, Sherborne A, Chubb D, Carvajal-Carmona LG, Ma Y, Kaur K, Dobbins S, Barclay E, Gorman M, Martin L, Kovac MB, Humphray S; CORGI Consortium; WGS500 Consortium, Lucassen A, Holmes CC, Bentley D, Donnelly P, Taylor J, Petridis C, Roylance R, Sawyer EJ, Kerr DJ, Clark S, Grimes J, Kearsey SE, Thomas HJ, McVean G, Houlston RS, Tomlinson I. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas Nat Genet 2013 Feb;45(2):136-44

Repak R, Kohoutova D, Podhola M, Rejchrt S, Minarik M, Benesova L, Lesko M, Bures J. The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature Gastrointest Endosc 2016 Oct;84(4):718-25

Sieber OM, Tomlinson IP, Lamlum H. The adenomatous polyposis coli (APC) tumour suppressor--genetics, function and disease Mol Med Today 2000 Dec;6(12):462-9

Sinha A, Tekkis PP, Gibbons DC, Phillips RK, Clark SK. Risk factors predicting desmoid occurrence in patients with familial adenomatous polyposis: a meta-analysis Colorectal Dis 2011 Nov;13(11):1222-9

Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis Lancet 1989 Sep 30;2(8666):783-5

Steinhagen E, Guillem JG, Chang G, Salo-Mullen EE, Shia J, Fish S, Stadler ZK, Markowitz AJ. The prevalence of thyroid cancer and benign thyroid disease in patients with familial adenomatous polyposis may be higher than previously recognized Clin Colorectal Cancer 2012 Dec;11(4):304-8

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263

Vasen HF, Möslein G, Alonso A, Aretz S, Bernstein I, Bertario L, Blanco I, Bülow S, Burn J, Capella G, Colas C, Engel C, Frayling I, Friedl W, Hes FJ, Hodgson S, Järvinen H, Mecklin JP, Møller P, Myrhøi T, Nagengast FM, Parc Y, Phillips R, Clark SK, de Leon MP, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen J. Guidelines for the clinical management of familial adenomatous polyposis (FAP) Gut 2008 May;57(5):704-13

Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, van Zelst-Stams WA, Jongmans MC, Gilissen C, Hehir-Kwa JY, Hoischen A, Shendure J, Boyle EA, Kamping EJ, Nagtegaal ID, Tops BB, Nagengast FM, Geurts van Kessel A, van Krieken JH, Kuiper RP, Hoogerbrugge N. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer Nat Genet 2015 Jun;47(6):668-71

Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, Shulkes A, Grimpen F, Clouston A, Moore D, Cullen D, Ormonde D, Mounkley D, Wen X, Lindor N, Carneiro F, Huntsman DG, Chenevix-Trench G, Suthers GK. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome Gut 2012 May;61(5):774-9

de Vos M, Hayward B, Bonthron DT, Sheridan E. Phenotype associated with recessively inherited mutations in DNA mismatch repair (MMR) genes Biochem Soc Trans 2005 Aug;33(Pt 4):718-20

van Heumen BW, Nieuwenhuis MH, van Goor H, Mathus-Vliegen LE, Dekker E, Gouma DJ, Dees J, van Eijck CH, Vasen HF, Nagengast FM. Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: a nationwide retrospective cohort study Surgery 2012 May;151(5):681-90

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