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MINIREVIEW

Current status of the genetic susceptibility in attenuated adenomatous polyposis

Víctor Lorca, Pilar Garre

ORCID number: Víctor Lorca (0000-0002-3681-4319); Pilar Garre (0000-0001-8285-4138).

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Víctor Lorca, Laboratorio de Oncología Molecular, Grupo de Investigación Clínica y Traslacional en Oncología, Hospital Clínico San Carlos, Madrid 28040, Spain

Pilar Garre, Laboratorio de Oncología Molecular, Servicio de Oncología, Hospital Clínico San Carlos, Madrid 28040, Spain

Corresponding author: Pilar Garre, PhD, Research Scientist, Laboratorio de Oncología Molecular, Servicio de Oncología, Hospital Clínico San Carlos, c/Profesor Martín Lagos s/n, Madrid 28040, Spain. pilar_garre@hotmail.com
Telephone: +34-913-303348
Fax: +34-913-302494

Abstract

Adenomatous polyposis (AP) is classified according to cumulative adenoma number in classical AP (CAP) and attenuated AP (AAP). Genetic susceptibility is the major risk factor in CAP due to mutations in the known high predisposition genes *APC* and *MUTYH*. However, the contribution of genetic susceptibility to AAP is lower and less understood. New predisposition genes have been recently proposed, and some of them have been validated, but their scarcity hinders accurate risk estimations and prevalence calculations. AAP is a heterogeneous condition in terms of severity, clinical features and heritability. Therefore, clinicians do not have strong discriminating criteria for the recommendation of the genetic study of known predisposition genes, and the detection rate is low. Elucidation and knowledge of new AAP high predisposition genes are of great importance to offer accurate genetic counseling to the patient and family members. This review aims to update the genetic knowledge of AAP, and to expound the difficulties involved in the genetic analysis of a highly heterogeneous condition such as AAP.

Key words: Attenuated adenomatous polyposis; Genetic susceptibility; High predisposition gene; Genetic heterogeneity; Colorectal cancer

Core tip: Attenuated adenomatous polyposis (AAP) is a highly genetically and clinically heterogeneous condition in terms of severity, clinical features, heritability, and genetics. The major high predisposition genes *APC* and *MUTYH* explain a small fraction of AAP (10%-20%). Several predisposition genes have been recently proposed, and some of

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them have been validated, but studies addressing their global contribution to AAP genetic predisposition is scarce. Clinicians do not have strong discriminating criteria for the recommendation of genetic testing, and the detection rate is low. Therefore, multigene panel testing and a redefinition of strong clinical criteria could improve the outcome of AAP genetic testing.

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INTRODUCTION

Adenomatous polyposis (AP) can be defined as the tendency to develop adenomatous polyps (adenomas) along the large intestine and/or rectum. Although adenomas are benign growths, they are considered the precursor lesions of colorectal carcinoma (CRC)[1]; thus, AP is classified as a cancer risk syndrome with cumulative risks ranging from 40% to 100% depending on the severity of the polyposis (adenoma burden).

AP is usually classified according to the adenoma burden in two major groups: classical AP (CAP) and attenuated AP (AAP). Classical forms are characterized by the detection of hundreds or thousands of adenomas, and have a very low prevalence in the population (1/10000[2]), whereas attenuated forms are defined by the detection of between 10-100 adenomas, and are more prevalent in the adult population. CAP shows aggressive phenotypes, usually triggered during the second decade of life, and with a cumulative absolute cancer risk if adenomas are not removed. Extracolonic manifestations are frequent, and most of the cases show a dominant inheritance pattern[3]. By contrast, AAP is a much more heterogeneous group in terms of polyposis severity and family history[4-6]. Clinical features are distinctive from classical forms; adenoma detection is low or mild, ranging from ten synchronic or 20 cumulative to 100 adenomas, and the polyposis diagnosis age is significantly later than CAP. Cancer risk is also lower and later, ranging from 40% to 80% depending on the adenoma burden. Extracolonic manifestations are uncommon, and a family history of polyposis is frequently absent. AAP is sometimes accompanied by other types of polyps, such as hyperplastic or serrated polyps[3,7].

There are currently two clearly clinically-actionable genes that can lead to AP: *APC* (MIM#611731) and *MUTYH* (MIM#604933). Thus, prevalence and cancer risk estimations are well-defined, allowing accurate genetic counseling and effective high-risk monitoring programs for carriers. Heterozygous germline truncating mutations in the tumor suppressor gene *APC* mainly give rise to CAP, and sometimes to AAP, with dominant inheritance patterns. In contrast, germline biallelic mutations in the DNA repair gene *MUTYH* mainly lead to AAP and less frequently to CAP, with recessive inheritance patterns. In these cases, identification of *APC* or *MUTYH* carriers is important, not only to define the risks and follow-up strategies for the patient, but also to discriminate between high- and low-risk individuals among the family members who could benefit from high-risk follow-up or, on the contrary, avoid unnecessary and invasive monitoring. Ambiguously, even though both genes explain the vast majority of CAP, together they are only able to explain between 10%-20% of AAP.

AAP incidence is significantly increasing in hospital settings, mainly due to the improvement of imaging techniques and the implementation of CRC population screening programs. This increase translates into a problem in the Genetic Counseling Units due to the high heterogeneity of the disease. On the one hand, it is difficult to discriminate not only between sporadic multiple polyposis and real AP in patients with low adenoma burden, but also between attenuated and classical forms in patients with adenoma counts close to 100. On the other hand, family history is not a discriminant criterion for genetic studies due to the high rate of *de novo* mutations described in *APC* (10%-25%)[8,9] and the recessive inheritance pattern of *MUTYH*[10]. Furthermore, only a minority of AAP cases (< 20%) is explained by germline mutations in *APC* or *MUTYH*[11,12], leaving a substantial fraction of AAP cases unexplained. This means that undiscriminating and invasive follow-up programs will be recommended to all first-degree relatives of these patients.

Under this scenario, the elucidation of genetic susceptibility, which could explain the etiology of the disease and improve the accuracy of genetic counseling, has become a priority for scientists and clinicians. Thanks to the advance of sequencing technologies, new genes have been recently associated with primary predisposition to the development of adenomas by genome/exome sequencing studies in unexplained AP cohorts[13-16]. In the same way, other genetic alterations not detected by conventional coding germline DNA sequencing screening strategies have also been described in the *APC* gene, such as mutations in the promoter[17] or introns[18], large inversions[19] or mosaicism phenomes[20]. In addition, the use of wide gene panels for the genetic diagnosis of AP has incidentally revealed an overlap between different polyposis syndromes[21]. However, all these studies together are only able to explain the etiology of a very small fraction of AAP cases, and the unexplained cases are still a major group that needs to be clarified. Most likely, polygenic inheritance models in which the accumulation of multiple low penetrance alleles[22] and lifestyle risk factors such as smoking, alcohol, body mass index, diet and physical activity[23] play a major role in unexplained AAP cases.

Despite the low frequency of high predisposition genes in AAP, their knowledge is important for the detection of carriers, allowing the discrimination of high- and normal-risk individuals among family members, and leading to accurate and cost-effective monitoring programs.

The aim of this review is to describe the current knowledge of the genetic susceptibility of AAP, with emphasis on genes with a primary predisposition to AP that have been described so far, which are either already implemented in clinical practice, in process, or have recently been proposed.

AP PRIMARY PREDISPOSITION ASSOCIATED GENES

Until recently, *APC* and *MUTYH* were the only known AP syndrome predisposition genes. With the advent of next-generation sequencing (NGS) technologies, new AP predisposition genes have emerged. There are currently three new validated genes [*POLE* (MIM#174762), *POLD1* (MIM#174761), *NTHL1* (MIM#602656)], and two more genes that have been described but not validated [*MSH3* (MIM#600887), *MLH3* (MIM#604395)]. The discovery of new AP predisposition genes has allowed for considerable advancement in the biology of AP development and, therefore, in colorectal carcinogenesis. However, the newly described genes are still poorly implemented in clinical practice, mainly because of their low frequency and the lack of accurate risk estimations. Thus, time is needed to increase the number of described cases that allow better prevalence and risk estimations to be obtained.

APC

APC is a tumor suppressor gene closely involved in colorectal carcinogenesis; *APC* somatic mutations are the first event in the canonical CRC carcinogenesis model, which is followed by more than 80% of all CRCs[24]. The *APC* gene encodes a multifunctional protein that is mainly involved in signal transduction, cell adhesion and migration, microtubule assembly and chromosome segregation[25]. Its tumor-suppressing ability relies on its capacity to negatively regulate intracellular β-catenin levels, the main effector of the Wnt pathway. Therefore, inactivation of APC leads to increased β-catenin levels and overexpression of its different target genes involved in cell proliferation, differentiation, migration and apoptosis[26], which histologically correlates with adenoma formation.

APC is located on the long arm of chromosome 5 (5q21), has 15 exons, and encodes a 2,843 amino acid protein[27]. Most of the somatic mutations lie in the mutation cluster region (MCR), which is located between amino acids 1286 and 1513 and overlaps with the β-catenin binding region[28]. Heterozygous *APC* germline mutations have been associated with AP predisposition in a gene location-dependent manner[29]. Most of the germline *APC* mutations are truncating variants lying between codons 178 and 1580, and give rise to stable mutant peptides that exert a dominant-negative effect on the wild-type protein[30,31]. These mutations lead to classical forms of the disease called familial AP (FAP), whereas germline mutations located at both the 5′ and 3′ ends of the transcript, as well as splicing mutations that lead to exon 9 skipping, give rise to attenuated forms of the disease called attenuated familial AP (AFAP) (Figure 1A). Germline mutations at the 3′ end give rise to stable proteins with a certain capability to regulate β-catenin levels[30], and 5′ end mutations upstream of codon 177 produce functional proteins by initiation of translation at codon 184[31,32]. This internal initiation of translation is relatively inefficient, leading to a haploinsufficient phenotype rather than a dominant-negative phenotype. Mutations at the splice donor site in intron 9

lead to inefficient exon skipping with some expression of normal transcript, and therefore with an attenuated form of the disease[33].

Both FAP and AFAP show autosomal dominant inheritance patterns. However, there are some exceptions without any family history. *De novo* mutations have been described in 10%-25% of *APC* carriers[8,9], and recent studies report *APC* mosaicism rates of 20%-50% in unexplained AP cases[20,34]. Whereas *de novo* mutations have been observed in both FAP and AFAP, it is noteworthy that mosaicism carriers present an attenuated form of the disease[20], likely due to the nonubiquitous distribution of the mutant allele.

MUTYH

MUTYH is a DNA repair gene involved in the base excision repair (BER) pathway[35]. It encodes a monofunctional DNA glycosylase responsible for the recognition and excision of the deoxyadenosine misincorporated with 8-hydroxy-2' -deoxyguanosine (8-OHdG) in the DNA molecule. 8-OHdG arises as a consequence of the oxidation of deoxyguanosine, which is a mutagenic base because it has the ability to pair indiscriminately with deoxycytosine or deoxyadenosine, leading to an increase in somatic G>T transversions[36]. Therefore, inactivation of *MUTYH* leads to an increase in the G>T mutation rate, which especially affects known cancer driver genes such as *KRAS* or *APC*[37], both of which are involved in adenoma formation.

MUTYH is located on the short arm of chromosome 1 (1p34.1) and is formed by 6 exons, encoding two major transcripts, which leads to 546 and 535 amino acid isoforms[35]. Biallelic *MUTYH* germline mutations have been associated with AP predisposition, leading to an autosomal recessive syndrome[10]. Because it is a recessive condition, there is no vertical transmission of the disease, and family history is often absent or is presented horizontally (siblings)[38]. *MUTYH*-associated polyposis (MAP) is characterized by the presence of 10–100 adenomatous polyps in the colon rectum resembling AFAP, but in some cases it may be accompanied by hyperplastic or serrated polyps[39]. A minor fraction of MAP presents classical forms of the disease with the detection of more than 100 adenomas. In contrast to *APC*, no relationship has been observed between the location of the mutation and the phenotype of the disease. Mutations located throughout the entire *MUTYH* have been described in MAP, but only two missense mutations, NM_001128425: c.1187G>A p.(Gly396Asp) and c.536A>G p.(Tyr179Cys), are the most prevalent in Caucasians. Other recurrent mutations have been described in more specific populations[40] (Figure 1B).

POLE and POLD1

POLE and *POLD1* encode the catalytic subunits of the polymerase enzyme complexes ε (Polε) and δ (Polδ), respectively, which are the principal leading- and lagging-strand DNA polymerases during S phase[41]. In addition, they also catalyze DNA synthesis in several DNA repair pathways, such as nucleotide excision repair (NER) or mismatch repair (MMR). Both POLE and POLD1 encompass not only a binding DNA region and polymerase domain, but also an exonuclease domain, which confers proofreading capability by the recognition and removal of misincorporated nucleotides during DNA replication[42]. Polymerase proofreading activity, together with high base selectivity and the MMR pathway, are the main cellular mechanisms responsible for minimizing errors during DNA replication[43]. Inactivating point mutations within the exonuclease domains lead to proteins with an active polymerase domain that lack proofreading activity, which causes high genetic instability during DNA replication. Indeed, somatic mutations within the exonuclease domains have been described in human cancer, leading to a high increase in mutational rates[44]. Tumor mutations in the *POLE* exonuclease domain have been identified in 1%-2% of sporadic CRC and in 7%-12% of endometrial cancers, as well as in tumors of the brain, pancreas, ovary, breast and stomach, showing ultramutated and microsatellite-stable tumors[45].

POLE is located on the long arm of chromosome 12 (12q24.33), consists of 49 exons, and encodes a 2,286 amino acid protein. Its exonuclease domain lies between codons 268 and 471[46]. *POLD1* is located on the long arm of chromosome 19 (19q13.33) and consists of 27 exons, encoding an 1,133 amino acid protein. Its exonuclease domain is located between codons 304 and 517[47]. Heterozygous germline mutations within the exonuclease (proofreading) domains of both *POLE* and *POLD1* were recently associated with AAP[13], leading to an autosomal dominant inheritance condition that is characterized by high-penetrance predisposition to multiple colorectal adenomas, large adenomas, early-onset CRC, or multiple CRCs, as well as other extracolonic tumors such as endometrial tumors[48].

Since the first association of *POLE* and *POLD1* with AAP, several studies have validated the results and found new germline mutations in the exonuclease domains[49-55] (Figures 1C and 1D). However, due to the small number of families described so far, accurate risk estimations and the contribution of polymerases to AP

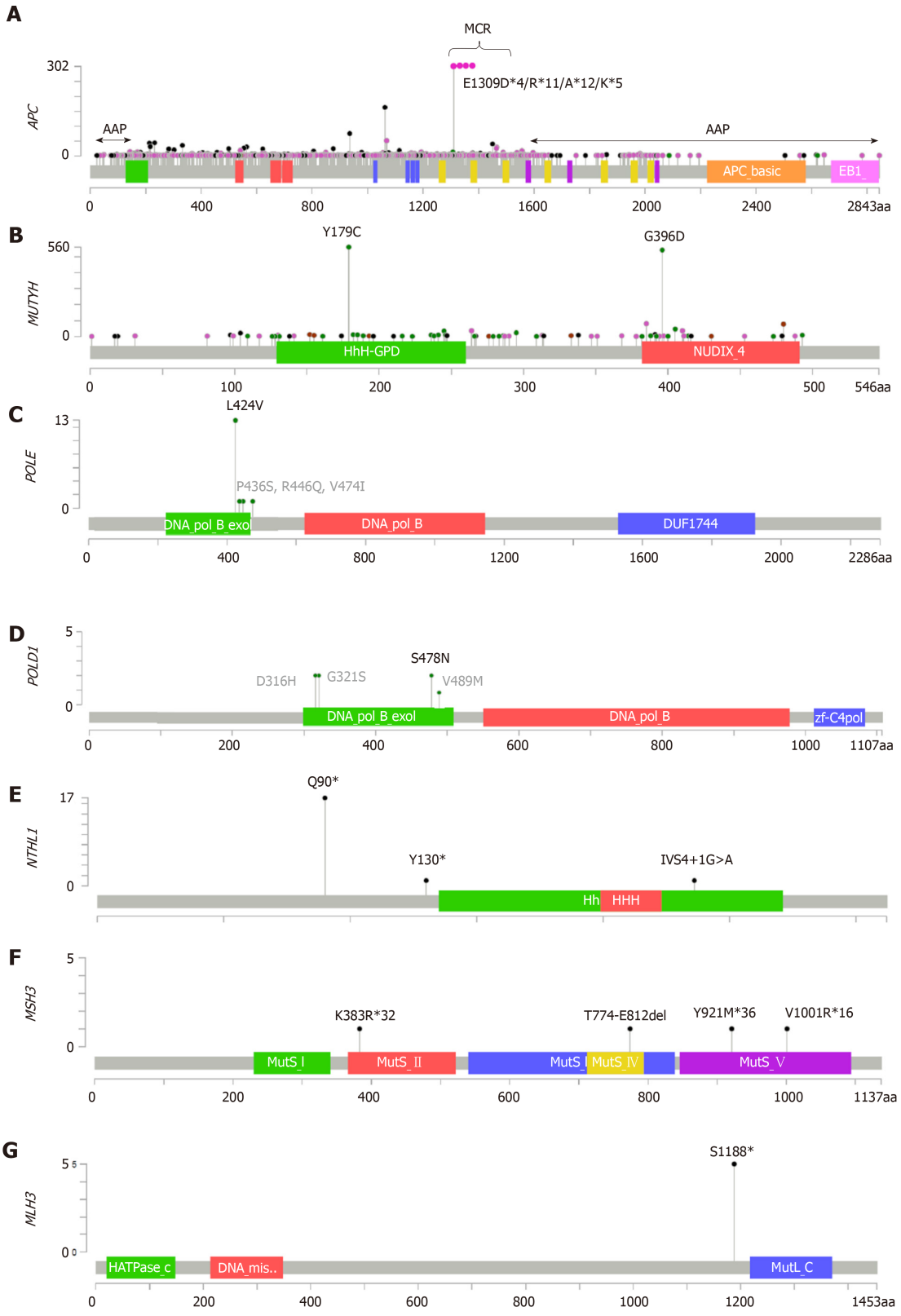

Figure 1 Distribution of germline mutations in attenuated adenomatous polyposis predisposition genes across protein domains. A: *APC* likely pathogenic and pathogenic variants described in the LOVD database[115]. Most of the mutations are truncating variants. Mutations associated with AAP are located at both the 3'-end and 5'-end of the gene (indicated with arrows); B: *MUTYH* likely pathogenic and pathogenic mutations described in the LOVD database[115]. The two most prevalent mutations in Caucasians are shown; C-G: *POLE*, *POLD1*, *NTHL1*, *MSH3* and *MLH3* likely pathogenic and pathogenic mutations described in the literature and associated with AAP. Unclassified variants in the polymerase proofreading POLE and POLD1 domains are in gray. All lollipops were designed with The cBio Cancer Genomics Portal[116,117]. Mutation types are coded as follows: black dots for nonsense variants; pink dots for frameshift and splicing variants; green dots for missense mutations; brown dots for in-frame indels. Reference sequences: *APC*: NM_000038, NP_000029; *MUTYH*: NM_001128425, NP_036354; *POLE*: NM_006231, NP_006222; *POLD1*: NM_001256849, NP_001121897; *NTHL1*: NM_002528, NP_002519; *MSH3*: NM_002439, NP_002430; *MLH3*: NM_001040108, NP_001035197.

are still not well-defined.

NTHL1

Similar to *MUTYH*, *NTHL1* is a DNA repair gene involved in the BER pathway. It encodes a bifunctional N-glycosylase protein that recognizes and removes oxidized pyrimidines, such as 2'-deoxy-5-hydroxycytldine (5-OHdC) and ring-opened purines[56]. 5-OHdC arises as a consequence of the oxidation of deoxycytosine, and it has the ability to pair both deoxyguanosine and deoxyadenine, leading to an accumulation of somatic C>T transitions, which can affect important CRC driver genes such as *APC*, *TP53* or *KRAS*, among others.

NTHL1 is located on the short arm of chromosome 16 (16p13.3), consists of 6 exons, and encodes a 312 amino acid protein[57]. *NTHL1* homozygous or compound heterozygous germline mutations have been recently detected in AAP, delineating an autosomal recessive polyposis syndrome called *NTHL1*-associated polyposis (NAP)[14]. All *NTHL1* biallelic carriers described so far showed AAP, and also frequently showed other extracolonic tumors such as endometrial or breast[58]. One nonsense mutation at codon 90 seems to be involved in nearly all the biallelic carriers described; however, novel pathogenic mutations are arising as new studies emerge[58-62] (Figure 1E).

Theoretical estimations of NAP suggest a prevalence of at least five times lower than that of MAP[62]. Due to the limited number of NAP families described until now, the phenotypic spectrum and cancer risk estimates have not been properly established.

MSH3

MSH3 is one of the six *MMR* genes identified to date in eukaryotic cells[63]. It is involved in the detection of replication errors in microsatellite sequences together with *MSH2* and *MSH6*. *MSH3* encodes an alternative binding partner for MSH2, which is required for the specific detection of insertion or deletion loops of two or more nucleotides[64], as well as for double strand break repair[65]. MSH2 requires the binding of MSH6 or MSH3 to exercise its function. The MSH2-MSH6 dimer recognizes single substitutions and small indel mispairs, whereas MSH2-MSH3 recognizes errors in di- and larger nucleotide repeats[66]. Inactivation of *MSH3* leads to a high microsatellite instability of di- and tetranucleotides (EMAST), which has been associated with a characteristic somatic *APC* mutation spectrum in colorectal adenoma from AAP patients[15].

The *MSH3* gene is located in the long arm of chromosome 5 (5q14.1) and consists of 24 exons, encoding an 1,137 amino acid protein[67]. Biallelic truncating variants in *MSH3* have been recently reported in two patients with AAP, suggesting an additional recessive subtype of colorectal AP[15] (Figure 1F).

Until now, no more studies have validated these results, so its association with AAP and phenotype estimations remain to be defined.

MLH3

MLH3 is a member of the MutL homolog family of MMR proteins[63]. MLH3 dimerizes with MLH1, resulting in the MutLγ complex, which is primarily involved in meiotic recombination rather than in mitotic genetic stability[68].

The *MLH3* gene is located in the long arm of chromosome 14 (14q24.3), consists of 13 exons, and encodes a 1,453 amino acid protein. The homozygous truncating germline variant S1188* was first detected in an unexplained Swedish AAP case[21], and more recently in one more AAP and two CAP subjects from Finland, suggesting a founder effect[16] (Figure 1G). Authors hypothesize the involvement of a defective DNA damage response and/or recombination-related processes in the pathogenesis of these cases[16].

Once again, research on additional cohorts is needed to reinforce the significance of *MLH3* as an AP predisposition gene.

OTHER CANDIDATE GENES SUGGESTED FOR AP PREDISPOSITION

Other candidate genes, including AXIN2 (MIM#604025), *FOCAD* (MIM#614606), *GALNT12* (MIM#610290) and *BUB1* (MIM#602452) /*BUB3* (*MIM*#603719), are involved in the AP predisposition. However, evidence for these genes is not as thorough as those previously discussed.

AXIN2

AXIN2 encodes the Wnt pathway component conductin; it is the scaffold protein of the β-catenin destruction complex and main negative regulator of the pathway[69]. Mutations in this gene have been described in CRC, and similar to *APC*, they increase β-catenin levels and activate β-catenin/T-cell factor signaling, thus promoting CRC development[70]. A*XIN2* is located on the long arm of chromosome 17 (17q24.1), consists of 11 exons, and encodes two major transcripts, which leads to 843 and 778 amino acid isoforms[69]. Deleterious germline mutations have been reported in four families, showing a strong association with oligodontia as well as gastrointestinal neoplasias[71-73]. More recently, a novel missense variant has been described in an AAP family without signs of oligodontia or ectodermal dysplasia, suggesting the possibility of different phenotypes depending on the protein domain affected[74]. Two other works have screened mutations for *AXIN2* in different CRC populations, both in polyposis and nonpolyposis, without any success[75,76]. Therefore, although there is a clear association between *AXIN2* and oligodontia, further studies are needed to clarify its role in CRC syndromes, particularly with AAP.

FOCAD

FOCAD encodes a focal adhesion protein with a potential tumor suppressor function in glyomas[77]. The *FOCAD* gene is located on the short arm of chromosome 9 (9p21.3) and is formed by 46 exons encoding an 1,801 amino acid protein[77]. Two studies identified large deletions and truncating point mutations in a total of five CRC cases: 2/221 cases of unexplained AP[78] and 3/1232 early-onset and familial CRC cases[79]. Altogether, four cases had a diagnosis of AAP. Since *FOCAD* shows high expression levels in colonic epithelial cells and has been involved in cell survival and proliferation, the authors suggest a potential role of this gene in polyposis/CRC susceptibility[79]. Regardless, this association and its contribution to AAP predisposition requires further clarification.

GALNT12

GALNT12 encodes a hexosyltransferase involved in the initial steps of the mucin-type O-glycosylation process[80]. Alterations in this process lead to aberrant glycosylation, which has been associated with alterations in cell growth, differentiation, transformation, adhesion, metastasis and immune surveillance in cancers[81]. *GALNT12* is highly expressed in the digestive tract, and is frequently downregulated in CRC[82]. The *GALNT12* gene is located on the long arm of chromosome 9 (9q22.33), has 10 exons, and encodes a 581 amino acid protein[80]. Evidence for the association between *GALNT12* and CRC has been reported[83], but its association with familial CRC, particularly AP, remains a controversial issue. Partially inactivating variants have been detected in familial CRC along with a mild polyp burden, suggesting the involvement of this gene in CRC predisposition[84]. However, later studies do not support its involvement in nonpolyposis and polyposis CRC predisposition[85,86].

BUB1 and *BUB3 (mitotic checkpoint serine/threonine kinases)*

BUB1 and *BUB3* encode components of the spindle assembly checkpoint complex, which controls chromosome biorientation on the mitotic spindle, delaying the anaphase transition until all kinetochores are properly attached[87]. Alterations in the activity of this complex lead to alterations in chromosome copy number, *i.e*. aneuploidies[88]. The *BUB1* gene is located on the long arm of chromosome 2 (2q13), consists of 25 exons, and encodes a 1,085 amino acid protein, whereas *BUB3* is located on the long arm of chromosome 10 (10q26.13), has 8 exons, and encodes a 328 amino acid protein[89]. Deleterious germline mutations in both genes have been associated not only with increased levels of constitutive aneuploidy, but also with gastrointestinal neoplasms, including adenocarcinomas and adenomas[90,91]. Furthermore, aneuploidy caused by Bub1 insufficiency has been proven to drive colorectal adenoma formation in mice through *APC* loss of heterozygosity (LOH)[92]. Screening of the *BUB1* and *BUB3* genes in familial and AP CRC cohorts has shown functionally relevant germline mutations in a low fraction of patients with CRC who also presented increased levels of constitutive aneuploidy[93,94]. However, the causality of these mutations in CRC/adenoma susceptibility remains unproven.

AAP INCIDENTAL TO OTHER CANCER RISK SYNDROMES

Although phenotypes for related CRC risk syndromes are generally well-defined, there are some overlapping features that can lead to confusion in the clinical suspicion and subsequent misdirection of the genetic testing approach. The cancer risk syndromes prone to phenotypically overlap with AAP are described below.

Lynch syndrome is the main hereditary nonpolyposis colorectal cancer syndrome

caused by heterozygous deleterious mutations in MMR genes (*MSH2*, *MLH1*, *MSH6* and *PMS2*) that can be accompanied by early-onset adenomas[95]. Usually, the adenoma burden does not exceed 10, but it can sometimes mimic AAP.

Constitutional MMR deficiency is due to loss-of-function biallelic germline mutations in the main *MMR* genes. It is an aggressive recessive cancer predisposition syndrome with a wide tumor spectrum, very early age of onset and poor outcome[96]. In addition, nearly 36% of affected subjects develop colorectal AP ranging from a few up to 100 adenomas[97].

Hereditary mixed polyposis syndrome is characterized by multiple colon polyps of mixed pathologic subtypes and an increased risk for CRC[98]. It is caused by large duplications in the 5' regulatory region of *GREM1* (MIM 603054), leading to an excess of coding protein expression[99]. GREM1 is an antagonist of bone morphogenic protein (BMP), so its overexpression can lead to inactivation of the BMP pathway and subsequent hyperproliferation of colonic epithelium[100].

The pathogenesis of polyps in hereditary mixed polyposis syndrome likely overlaps with that of juvenile polyposis syndrome (JPS), which is caused by inactivating mutations in other genes of the BMP pathway, including *BMPR1A* (MIM 601299), *SMAD4* (MIM 600993), *ENG* (MIM 131195) and *BMP4* (MIM 112262)[101-104]. JPS is a hamartomatous polyposis syndrome with an increased risk of CRC as well as other digestive cancers. Cancer risk arises from adenomatous components present in the juvenile polyps, which can sometimes lead to misinterpretations[105].

Germline alterations in genes involved in the PTEN/PI3K/AKT pathway are also associated with hamartomatous polyposis syndromes. Cowden syndrome is caused by heterozygous *PTEN* (MIM 601728) germline mutations, and is characterized by the development of hamartomatous and neoplastic lesions of the skin, mucous membranes, thyroid, breast, endometrium, and brain[106]. Although hamartomatous polyps are the most characteristic gastrointestinal lesions in Cowden syndrome, adenomatous polyps in the colon have been detected in 30% of affected individuals[107].

In contrast, germline heterozygous mutations in *STK11* (MIM 602216) lead to Peutz-Jeghers syndrome (PJS), which is characterized by mucocutaneous pigmentation and diffuse gastrointestinal hamartomas[108]. Similar to other hamartomatous syndromes, polyps with large adenomatous transformation areas and adenomatous polyps have been described in PJS[109].

Currently, thanks to NGS technology and the widespread use of multigene panels for hereditary cancer testing, the detection of overlapping phenotypes between different CRC syndromes is greatly increasing, improving the diagnosis and follow-up of these patients[12,21,110].

CONCLUSION

AAP is a highly heterogeneous disease, covering both moderate and mild forms of AP, as well as hereditary and sporadic forms, recessive and dominant conditions, and the presence or absence of other gastrointestinal or extracolonic manifestations. Thus, the genetic heterogeneity of the syndrome, where several high predisposition genes are involved in the polyposis predisposition of a minor subset of AAP, is not surprising. Two previous studies have investigated the prevalence of pathogenic mutations in large cohorts of AP, detecting approximately 6%-15% of pathogenic mutations in either the *APC* or *MUTYH* genes when analyzing patients with an adenoma burden between 10 and 99[11,12]. These detection rates were decreased (2%-9%, respectively) when only patients between 10 and 19 adenomas were considered, showing that adenoma burden and the likelihood of detecting pathogenic mutations in *APC* and *MUTYH* are directly proportional in AAP. Regarding the prevalence of the new AP predisposition genes, Stanich and collaborators included the analysis of *POLE* and *POLD1* in their cohorts, but the contribution of these genes was scarce (one detection in 2,979 AAP cases), and it did not alter the overall mutation detection rate[12]. The *NTHL1* contribution to AAP has been recently estimated to be five times less prevalent than that of *MUTYH*[62]. Therefore, it seems that the heritability of AAP lies in different predisposition genes, each of which explains a small fraction of the total. Recently, other newly associated genes have been described, but the contribution of genetics to the etiology of the disease, as well as its heritability, are difficult to estimate. The high clinical and genetic heterogeneity, as well as the low prevalence of pathogenic mutations in the described genes, reflects the necessity of multigene panel testing for the effective genetic diagnosis of AAP.

To increase diagnostic sensitivity in such a heterogeneous syndrome, clinical guidelines have been developed with broad criteria, recommending genetic testing in

patients with more than 10 adenomas, even in those patients with oligopolyposis (< 10 adenomas) or early CRC[111-113]. These criteria increase the genetic testing requests in diagnostic laboratories, thus decreasing the mutation detection rate, which makes genetic studies not cost-effective, even if they are performed by multigene panel testing. Furthermore, most of the genetic testing results are not informative, and the probability of unclassified variant detection with multigene panel testing is high, which leads to a major group of patients with anxiety and confusion. Therefore, more stringent clinical criteria, especially in the cumulative number of adenomas, should be redefined to ascertain those patients who are most likely to harbor a hereditary polyposis syndrome. The stricter the recommendation criteria for the genetic study is, the greater the mutation detection rate and lower the ambiguous results. We are in agreement with the last guideline of the American Society of Colon and Rectal Surgeons (ASCRS) that a cutoff of 20 cumulative adenomas should be used to prompt genetic counseling and testing[114].

In conclusion, the contribution of genetics to the etiology of the disease and its heritability are difficult to estimate. The high clinical and genetic heterogeneity, as well as the low prevalence of each AP predisposing gene, reflects the necessity of multigene panel testing for an effective diagnosis of AAP. Nevertheless, the decline in diagnosis rates that comes with the decrease in adenoma burden shows the necessity of stricter clinical criteria when genetic testing is recommended for AAP predisposition genes.

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