The genetics of familial adenomatous polyposis (FAP) and *MutYH*-associated polyposis (MAP)

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Abstract

FAP is characterized by 100-1000s of adenomatous polyps in colon and rectum, and is in 70% of the patients associated with extracolonic manifestations. Attenuated FAP (AFAP) is a less severe form of FAP, marked by the presence of < 100 polyps and a later onset of colorectal cancer (CRC).

(A)FAP is caused by autosomal dominantly inherited mutations in the *APC* (Adenomatous polyposis coli) gene, a tumour suppressor gene that controls β-catenin turnover in the Wnt pathway. *De novo* occurrence is reported in 30-40% of the patients. Mutations are detected in 85% of classical FAP families, while only 20%-30% of AFAP cases will exhibit a germline APC mutation.

***MUTYH* is the second (A)FAP-related gene and is involved with base-excision repair of DNA damaged by oxidative stress. *MUTYH* mutations are inherited in an autosomal recessive way and account for 10%-20% of classical FAP cases without an *APC* mutation and for 30% of AFAP cases.**

Genotype-phenotype correlations exist for mutations in the *APC* gene, however, contradictions in the literature caution against the sole use of the genotype for decisions regarding clinical management.

Once the family's specific *APC* mutation is identified in the proband, predictive testing for first degree relatives is possible from the age of 10 to 12 years on. For AFAP, relatives are tested at age 18 and older. Opinions about the appropriate ages at which to initiate genetic testing may vary.

Physicians must have a discussion about prenatal testing with patients in childbearing age. They may either opt for conventional prenatal diagnosis (amniocentesis or chorionic villous sampling) or for preimplantation genetic diagnosis (PGD). (Acta gastroenterol. belg., **2011**, 74, **421-426**).

Key words : genetics of familial adenomatous polyposis, genetic counseling, APC, MutYH, genotype-phenotype correlations.

Introduction

FAP (Familial adenomatous polyposis) is a colon cancer predisposition syndrome in which hundreds to thousands of precancerous colonic polyps develop, beginning at a mean age of 16 years (range 7-36 years). By age 35 years, 95% of individuals with FAP have polyps. Without colectomy, development of colon cancer is inevitable. The mean age of colon cancer diagnosis in untreated individuals is 39 years (range 34-43 years) (1).

However, attenuated forms of FAP also exist. Attenuated adenomatous polyposis coli (AFAP) is characterized by multiple adenomas (< 100) in most affected family members, later age of disease onset (with cancer occurring on average 15 years later than classical FAP).

(A)FAP is a genetically determined condition that occurs in 1 of 5-10.000 births. FAP is mostly due to a mutation in the *APC* gene on chromosome 5q. Transmission of mutations in the *APC* gene is autosomal dominant.

However, 30-40% of cases are «*de novo*», meaning they arise in the affected individual without clinical or genetic evidence of (A)FAP in the parents (2).

Recently a major breakthrough in cancer genetics has been made by the identification of the *MutYH* gene (1p32.1-p34.3) (3). Biallelic mutations in this gene were reported in (A)FAP cases without an *APC* germline mutation. The syndrome associated with biallelic *MutYH* mutations is called **MAP** (*MutYH*-associated polyposis). MAP is difficult to differentiate clinically from FAP or AFAP. MAP tends to present later with mean and median ages in the mid-50s, although diagnoses at a younger age have been documented. Adenoma numbers range from 5 or fewer to hundreds. MAP is essentially a recessively inherited disorder.

Clinical genetic testing is available for the *APC* and the *MutYH* gene. The discovery of germline mutations in these genes has important clinical implications for the patient and his/her relatives.

The *APC* gene

More than 20 years ago researchers had the first clue about the location of the gene by the detection of an interstitial deletion on chromosome 5q in a patient with Gardner's syndrome (Herrera *et al*., 1986). One year later linkage analysis studies were published by Bodmer

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et al. (1987) (4) and Leppert *et al*. (1987) (5). From that time on it became possible to offer presymptomatic diagnosis on the basis of DNA markers (6). In 1991, Groden *et al*. (7), Kinzler *et al*. (8) and Joslyn *et al*. (9) characterised the *APC* (Adenomoatous Polyposis Coli) gene in detail.

Since then, this gene has been shown to play an integral role in the *Wnt* signalling pathway, especially with regard to the degradation of *β-catenin* within the cell cytoplasm (reviewed in : (10)).

The gene has 15 exons, and encodes a protein of 2843 amino acids (310 kDa). The APC protein occurs in several isoforms within cells, probably as a result of alternative splicing at the mRNA level (11). APC is multifunctional and contains several amino acid motifs and domains allowing it to oligomerize, as well as to interact with numerous other molecules having diverse functions within the cell. Within the cell, the APC protein exists predominantly in the cytoplasm, although nuclear localization has also been reported.

The *MutYH* gene

The contribution of *MutYH* to the multiple adenoma phenotype was first documented in a study of a Caucasian sib ship with multiple colorectal adenomas and carcinomas but no inherited *APC* or mismatch repair mutations (3). The *MutYH* gene has 16 exons and encodes a 535 amino acid protein. Analysis of the somatic mutation spectrum of *APC* in tumour samples revealed an unusually high frequency of G :C to T :A transversions resulting in nonsense or splice site mutations in *APC*. This suggested faulty repair of 7,8-dihydro-8-oxo-2'deoxyguanosine (8-oxoG). 8-oxoG is one of the most stable deleterious products of oxidative DNA damage. It readily mispairs with adenine (A) residues leading to G :C to T :A transversions. The MutYH glycosylase provides defense against oxidation-induced DNA damage by scanning the daughter strand after replication, removing A mispaired with G or a 8-oxoG. MutYH acts together with MTH1 and OGG1 as part of the base excision repair machinery (12).

Practical and clinical implications of molecular screening

The authors feel that because of the high frequency of *de novo APC* mutations in FAP and the autosomal recessive nature of MAP, all individuals with multiple (synchronous or metachronous) polyps, regardless of family history, should be referred for genetic counseling and possible testing. Eliciting detailed information about family history of polyps and cancer is important when considering which genetic tests to offer and whether to start with *APC* or *MutYH* testing. Elements to consider include the number and location of polyps in the proband and his or her relatives, the exact types of cancers in the family, the presence of extracolonic features indicative of FAP, and the ages of diagnosis. Also noteworthy is whether transmission appears to be autosomal dominant, autosomal recessive, or sporadic. Trends of neoplasia and patterns of inheritance in families are more easily visualized by constructing a detailed pedigree. These details are usually obtained before or during the initial genetic counseling appointment.

Medical management decisions for individuals with multiple polyps can be made without a genetic diagnosis, but confirming a suspected diagnosis through genetic testing can lead to more specific screening recommendations. In addition, if a mutation for a particular hereditary syndrome is identified, then at-risk relatives can consider predictive genetic testing (13,14,15).

In about 70-90% of FAP cases and families truncating germline mutations in the *APC* gene are found, depending on the range of molecular techniques applied in the analysis ((16-18) and own unpublished data). Techniques relying on PCR amplification, including sequencing, will miss a significant minority of mutations (deletions and rearrangements that involve the PCR primer binding sites are found in about 10% of the patients) (19). Therefore, the optimal mutation detection strategy should include a combination of the traditional PCR-based methods (like sequencing) and a method to detect large deletions and rearrangements (such as MLPA, multiplex-ligation dependent probe amplification).

An attenuated form of FAP was found to be also linked to the *APC* locus in about 30% of the families (20).

Somatic mosaicism is described in cases with "*de novo*" mutations (21). In mutation negative cases, an increase in mutation detection rate can be obtained by analyzing also the adenomas.

If no mutation in the *APC* gene is shown and in case of a recessive inheritance pattern, mutation analysis of the *MutYH* gene is performed. In about 20% of the patients with adenomatous polyposis without an *APC* mutation, biallelic *MutYH* mutations are identified (representing about 1.4% of all adenomatous polyposis patients) (22). Table 1 summarizes mutation detection rates for patients who should be referred for genetic testing.

Identification of the disease-causing mutations requires the DNA of an affected patient. Once the family specific mutation has been identified, directed DNA diagnostic techniques can be readily applied as a predictive test for FAP in other family members of unknown or uncertain genetic status.

Patients in whom an *APC* mutation is identified, have a 50% risk of transmitting the mutation to each of their children (autosomal dominant inheritance).

However, if the diagnosis of MAP is confirmed the risk of disease in a sibling is about 1 in 4, but is much lower (about 0.005) in offspring. A small effect of *MutYH* heterozygosity on cancer risk has been published. A 2-fold increase in the incidence of colorectal cancer among parents of MAP cases is reported,

Table 1. — **When should a patient being referred for genetic counseling ?**

	Chance to detect *APC* mutation	Chance to detect biallelic *MutYH* mutations
Patient with 15-100 polyps, regardless of family history	20-30% (20,36)	30% (37)
Patient with > 100 polyps, regardless of family history	70-90% (36)	10-20% of *APC*-negative patients (1.4% of all adenomatous polyposis patients) (22)

compared with the general population (SIR, 2.12 ; 95% confidence interval (CI) : 1.30-3.28). Their colorectal cancer mortality was not significantly increased (SMR, 1.02 ; 95% CI : 0.41-2.10) nor was overall cancer risk (SIR, 0.92 ; 95% CI : 0.70-1.18), cancer mortality (SMR, 1.12 ; 95% CI : 0.83-1.48), or overall mortality (SMR, 0.94 ; 95% CI : 0.80-1.08) (23). Therefore, it may be prudent to screen these patients, yet there is little justification for aggressive colonoscopic screening of heterozygote family members. Screening recommendations for unaffected individuals with monoallelic *MutYH* mutations are the same as for the general population. Management recommendations for MAP are based on current literature but are not yet recognized as official protocols or standard of care. With further research, they will undoubtedly evolve.

Genetic testing of adenomatous polyposis patients is very important to determine the cancer risks for the patients and their relatives. Knowledge about the gene involved in the phenotype has direct implications for the patients' and their relatives' surveillance.

Genotype-phenotype correlations

Within the *APC* gene genotype-phenotype correlations exist with regard to the location of the germline mutation. Protein-truncating germline mutations throughout the gene have been described in FAP, and, whilst most are fully penetrant, they differ in their severity of polyposis and the expression of extra-colonic features. Generally, mutations in the central region of the gene (codons 1290-1400) give a profuse polyposis phenotype with thousands of intestinal polyps. Two codons, 1061 and 1309 are mutational hotspots and account for approximately 11% and 17% of all germline mutations. CHRPE (congenital hypertrophy of the retinal pigment epithelium) is associated with germline mutations between codons 457 and 1444 approximately and mandibular osteomas and desmoid tumours are more prevalent in patients with mutations after codon 1400. Mutations occurring in the 5' (codons 78-167) and 3' (1581-2843) regions of the *APC* gene and in exon 9 are associated with AFAP (for review : (24)) (Fig. 1). However, intrafamilial and interfamilial phenotypic differences have been observed due to unknown modifying genes, which warrant further research (25-27). Polyp numbers may be highly variable with some mutation carriers developing hundreds of polyps and others very few. In conclusion, the correlations between mutation position and phenotype are not strong enough to restrict mutation analysis to specific regions of the *APC* gene in individual patients with an AFAP phenotype. Furthermore, the mutation position cannot be used for "tailored" counseling and clinical follow-up. For all patients the general guidelines should be followed.

For mutations in the *MutYH* gene no genotype-phenotype correlations have been described associated with the location of the mutation and/or mutation type. Generally, a large intrafamilial variation in the number of adenomas and age at diagnosis is observed in the MAP families (28,29).

Attitudes toward predictive and prenatal genetic testing

Predictive genetic testing offers an opportunity to focus on cancer prevention. Family members who test negative do not need further investigations for follow-up and cannot transmit the mutation to the next generation.

When the proband has classic FAP and the family's specific *APC* mutation is identified, genetic testing is offered to children of 10 to 12 years of age as at this age the diagnosis begins to gain clinical relevance in terms of surgical intervention, and the child is mature enough to understand the reason for a test and is compliant for evaluation. The managing clinician may occasionally ask for an earlier test if there are suspicious symptoms in the child or extreme anxiety of the parents (30).

For AFAP, relatives are tested at age 18 and older. Opinions about the appropriate ages at which to initiate genetic testing may vary.

High uptake rates for predictive genetic testing of up to 82% have been reported in asymptomatic at-risk adults with FAP (95% uptake in minors) enrolled in a cancer registry in the United States (31). This has been attributed to the high penetrance of *APC* mutations, early onset of disease, and possibly the greater awareness of the disease given the increased experience with multiple affected family members.

MAP is an autosomal recessive inherited condition. Individuals with 15-100 synchronous or metachronous adenomas confirmed by pathology and a family history indicative of autosomal recessive inheritance should consider genetic testing for *MutYH* mutations using full gene sequencing. Two common mutations, Y165C and G382D, account for over 80% of all *MutYH* mutations in Caucasians. The carrier frequency of these two mutations in the general population is estimated at 1% to 2% (32). Therefore, to partners and spouses of individuals with (biallelic) *MutYH* mutation(s), carrier testing

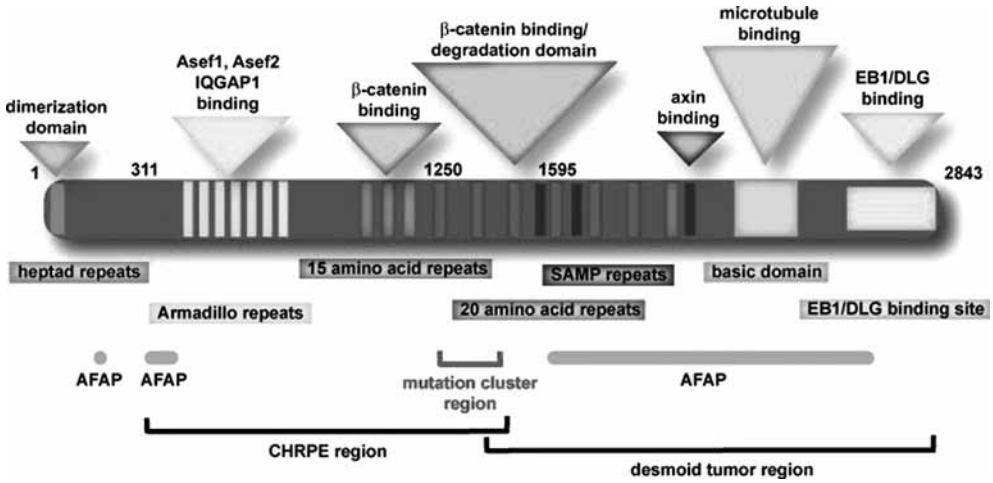

Fig. 1. — (Reprinted from (38) with permission from Elsevier) : The APC protein domains and FAP phenotype association with germline mutation position.
APC germline mutations in AFAP patients tend to cluster in three regions of the gene : (i) the 5' end, particularly in the regions spanning exons 3 and 4, (ii) within exon 9, most frequently within a region of exon 9 that is alternatively spliced, and (iii) the very 3' end of the gene beyond codon 1595. It is not immediately obvious why mutations in these regions of the gene would lead to a milder form of the disease.
All extracolonic manifestations can be associated with mutations anywhere in the *APC* gene, except for CHRPE and desmoid tumours, which are more likely to be associated with certain regions of the gene, but may also occur with other mutations throughout the gene.
The studies of AFAP families are still too limited and multiple studies note both intra- and inter-family variation in AFAP phenotype. Therefore, mutation position should not solely be used to make decisions regarding the clinical management of patients.

should be offered, at least for these two common mutations (33). Genetic testing of spouses and/or children should be discussed with and offered to counselees.

Physicians caring for FAP patients must be aware of the implications associated with predictive genetic testing, including its use in prenatal testing. Prenatal diagnosis has been offered for decades to families at risk of having children with chromosomal defects or genetic disease. Conventional prenatal diagnosis such as amniocentesis and chorionic villous sampling (CVS) could indicate whether a fetus is affected, giving the opportunity to selectively terminate the pregnancy. However, pregnancy termination for couples carrying a cancer predisposing gene mutation has been controversial and thought to be unacceptable because affected children are often healthy and remain so for many years before manifesting any symptoms. However, although colon cancer is "preventable" in FAP patients, many patients with FAP argue that colectomy and lifelong invasive screening procedures, as well as the potential for multiple surgical procedures for extracolonic processes do not constitute treatment and do not define a cancer-free condition.

Recent progress in assisted reproductive technology, gamete and embryo micromanipulations, and molecular biology have now made the diagnosis of genetic diseases possible in the preimplantation period. Preimplantation genetic diagnosis (PGD) is an early form of prenatal diagnosis where embryos are created through *in vitro* fertilization (IVF) and are analysed for well-defined genetic defects. Created embryos are allowed to divide and multiply for 3-5 days, by which stage they contain about eight cells. At that time, one or two cells are removed from the embryo, amplified and analysed for the gene-specific condition in question. Only embryos that would not result in an affected child are transferred to the uterus where a pregnancy can be established.

This reproductive option can offer individuals with a hereditary predisposition to cancer the chance to have an unaffected, genetically related child without having to consider selective pregnancy termination. In 1998, the first reported diagnosis of an inherited cancer predisposition syndrome using PGD was for FAP (34). A recent study showed that an overwhelming majority of patients with FAP are willing to consider prenatal testing for their condition and feel that their diagnosis has had an impact on their decisions regarding childbearing (35).

Prenatal testing to prevent transmission of FAP to their children is a discussion that physicians must have with patients of childbearing age.

Our knowledge of the molecular pathogenesis of colorectal polyposis is becoming increasingly broad with new entities such as MAP. Nonetheless, several other more rare syndromes exist (like Peutz-Jeghers syndrome, Juvenile Polyposis syndrome, etc.) and a large group of polyp-forming patients remain without specific genetic diagnosis. It seems likely that there exist other, high-penetrance colorectal tumour predisposition genes that remain to be found. With the current fast evolution of genome-wide techniques, our knowledge on cancer predisposing genes is expected to rapidly increase. The

discovery of new genetic defects, new genes and signaling pathways will possibly lead to new therapeutic molecular targets, which on their turn could lead to the development of new compounds which can reduce colorectal cancer risk. As genomic medicine becomes an integrated part of health care delivery, use of personalized genomics in the clinical treatment of colorectal cancer will increase.

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