MUTYH associated polyposis

Maartje Nielsen, Frederik J Hes

Department of Clinical Genetics, Leiden University Medical Center (LUMC), Leiden, the Netherlands

Published in Atlas Database: May 2006

Online updated version: http://AtlasGeneticsOncology.org/Kprones/MYHpolyID10121.html

DOI: 10.4267/2042/38368

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence. © 2006 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: MAP (MUTYH-Associated Polyposis).

Inheritance: MUTYH associated polyposis (MAP) is an autosomal recessive disorder, the frequency of heterozygotes carriers is 1-2% and the frequency of bi-allelic mutation carriers (according to Hardy-Weinberg equilibrium) lies between 1 per 10000 and 40000 newborns.

Clinics

Phenotype and clinics

The penetrance for colon polyps is close to 100% and bi-allelic MUTYH mutation carriers generally develop 10-100’s adenomatous polyps/adenomas of the colon and the rectum. Approximately one third of patients also develop polyps/adenomas in the upper gastrointestinal tract.

Other manifestations frequently seen in Familial Adenomatous Polyposis (FAP) are also present in minority of MAP patients: osteomas, pigmented retinal lesions (congenital hypertrophy of the retinal pigment epithelium; CHRPE) and tooth disorders. Recently also sebaceous gland tumors (Muir-Torre syndrome) and pilomatricomas have been reported in MAP-kindreds.

Neoplastic risk

Because of the development of multiple polyps, the risk for colorectal carcinoma is high. About 60-70% of MAP patients were diagnosed with colorectal carcinoma at a mean age of 47 years, most at first presentation. The actual penetrance is probably higher, because the development of colorectal carcinoma can be prevented through intensive colorectal screening. Duodenum carcinoma reported in a minority (2 out of 50 MAP patients in the Netherlands).

Treatment

Colorectal screening, colonoscopy, starting from the age 20-25 years, every 2 years.

Upper gastrointestinal tract screening from the age of 25-30 years, depending of the stage of identified tumours (Spigelman stadia), follow-up every 1-5 years. In case the number of polyps is too large to be endoscopically removed, subtotal colectomy is indicated.

Prognosis

When frequent colorectal and upper gastrointestinal tract screening is performed in a MAP-patient who has not developed (colorectal) carcinoma, the change of developing (colorectal) carcinoma is small and prognosis will be comparable to that of a healthy population.

In MAP patients who have developed colorectal carcinoma, survival will depend on the age of diagnosis and (Dukes) stage of the colorectal carcinoma.

Other findings

Note: In heterozygous MUTYH mutation carriers a (slight) increased risk for developing colorectal carcinoma has been found. A large case control research showed a relative risk of 1.5 for CRC in MUTYH heterozygous carriers aged >55 years. Recently a ~3 fold increased risk in heterozygous carriers was found in a study based on relatives of MAP patients, which was significant in persons aged >55 years and non-significant in persons aged <55 years. So far, there is no conclusive evidence justifying colonoscopic screening in heterozygous MUTYH carriers.

A possible relation between MUTYH and breast cancer has been reported because of a high prevalence of...
breast cancer cases in a group of Dutch female MAP patients (standardised morbidity ratio=3.75). Moreover, MUTYH knockout mouse that also carry heterozygous APC mutations are more prone to develop mammary tumours than APC-heterozygotes only. Case control studies will be necessary to confirm this relation in humans. In 148 gastric cancer cases one bi-allelic splice site mutation encoding a truncated MUTYH protein, c.1VS10-2A>G, was found. However, there was no significant higher number of MUTYH heterozygotes as compared to controls. Furthermore, no overrepresentation of MUTYH mutations (mono or bi-allelic) was found in patients with lung cancer, hepatocellular carcinoma, cholangiocarcinoma and (childhood) leukemia, compared to healthy controls.

A suggested explanation for the relative absence of tumor growth at other places in MAP-patients is that oxidation is a more common effect in the digestive system and that the APC-gene has more sequences (AGAA or TGAA motifs, see heading somatic mutations) which are relatively dependent of MUTYH oxidative damage repair.

**Genes involved and Proteins**

**MUTYH (MUTYH (mutY homolog (E. coli)))**

**Location:** 1p32.1-p34.3

**DNA/RNA**

Description: The MUTYH gene is composed of 16 exons and 15 introns.

Transcription: The MUTYH gene encodes 11.4 kb, and the open reading frame consists of 1854 bp.

**Protein**

Description: The full-length MUTYH protein contains 546 amino acids (60-65kDa). For mutation description the coding sequence is described and used, which differs because of the absence of 11 codons in exon 3. Alternative splicing generates a gene product of 521 amino Acids, referred as type 2. Type 1 is transported to nucleus, while type 2 lacks the first exon containing a mitochondrial targeting signal (MTS) and is transported to nucleus.

Expression: Expression of MUTYH has been found among others in the digestive system, germ cells, thymus,(rat-) brain, (mouse-) liver and (canine-) myocardium. Probably, the MUTYH protein is expressed widely, because the production of reactive oxygen species (ROS) leading to oxidative damage is generated during normal cellular oxygen metabolism and by oxygen stress conditions in all cells.

Localisation: MUTYH is located in the nucleus and mitochondria.

Function: The MUTYH protein is a base excision repair glycosylase which is involved in the repair of one of the most frequent and stable forms of oxidative damage, oxidation of a guanine leading to 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxoG). Other base excision repair glycosylases involved in oxidised guanine repair are the OGG1 and MTH1 protein (figure 1).

MUTYH recognizes an oxoG:A mismatch and subsequently excises the undamaged adenine base using a base-flipping mechanism. To a lesser extent also G:A, C:A, 8-oxoG:G and 8-oxoA:G mispairs are recognised and catalysed by MUTYH. The MUTYH protein consists of different functional domains. The N-terminal domain on the 5' side contains the catalytic region and includes a helix-hairpin-helix (HhH), pseudo HhH and an iron-sulfur cluster loop motif, which are also common motifs in other BER glycosylases. The C-terminal domain on the 3' side is shares homology with MTH1 and plays a role in 8-oxoG recognition.

Furthermore, MUTYH has binding sites for PCNA (proliferating cell nuclear antigen), RPA (replication protein A) and AP (apurinic/apyrimidinic) endonuclease. The interaction with these replication enzymes and a reported increase of expression during the S phase suggests a role for MUTYH especially in the replication-coupled repair. In E.coli it was demonstrated that the MUTYH homologue, mutY, recognizes the nascent strand in association with various cellular proteins such as PCNA or a mismatch repair genes complex. Remarkably, it was demonstrated that amino acid residues 232-254 of MUTYH interacts with the MSH2/MSH6 heterodimer via MSH6 and this interaction stimulates the glycosylase activities of MUTYH.

Homology: The percentage of similarity between the human muty gene (MUTYH) and that of various organisms is: 99% in chimpanzee, 80% in dog, 79% in mouse, 77% in rat, 66% in chicken and 41% in E.coli.

**Mutations**

Germinal: About thirty pathogenic mutations in the MUTYH gene have been described; predominantly missense mutations, but to a lesser extent also small deletions, small insertions, (putative) splice site mutations and one gross deletion. Most common mutations found (in Western population) are the Tyr165Cys (Y165C) and Gly382Asp (G382D), which compromise about 70-75% of mutations in Western MAP patients.

Other common mutations are: A371fs (c.1105delC, sometimes referred to as 1103delC); c.891+3A>C; P391L in Dutch patients (14%); Glu466del (c.1395delGGA) in Italian and the E466X in Indian people.

The Y165C mutation is located in the pseudo HhH region that is involved in mismatch specificity and flipping of the adenine into the base specificity pocket. The G382D is located in the C-terminal domain.
involved in 8-oxoG recognition. In functional tests especially the Y165C, but also the G382D variants, have shown to be devoid of glycosylase activity directed towards 8-oxoG:A. The corresponding variant of G382D in mice, G365D, does not suppress the elevated spontaneous mutations in MUTHY-null ES cells and failed to prevent OGG1 from excising 8-oxoG opposite the generated AP site-which would then result in double strand DNA breaks.

Recently, the 1105 delC variant showed significantly lowered binding and cleavage activities with heteroduplex oligonucleotides containing A:8-oxoG and 8-oxoA:G mispairs.

Several SNP’s (single nucleotide polymorphism) with amino acid substitutions have been registered in the NCBI database. Most frequently found in cases and controls: His 324Gln (Q324H) in 40-45% and IVS6+35 (462 +35) G>A in 20-25%. Pathogenic significance of the V22M SNP is disputed; it’s prevalence in controls and in cases is comparable (10-15%).

Somatic: In the tumours of MAP patients specific G:C>T:A somatic transversions are found in APC and KRAS2 genes in up to 40% and 64% of cases, respectively. In APC G>T transversions have a predilection for G bases in AGAA or TGAA motifs, whereas in KRAS2 a preferential GGT>TGT transition of codon 12 (p.Gly12Cys) is found.

All MAP tumours examined so far are MSI stable. One study found 18q LOH and P53 over-expression in the same frequency as in sporadic carcinomas. Few P53 mutations were found however and predominantly not G>T changes. No BRAF, SMAD4 or TGFBIIIR mutations were detected in the same group of MAP-carcinomas. Twelve out of 13 MAP cancers tested were near-diploid. This last finding is in contrast with a more recent study that found aneuploidy in 80% of MAP-adenomas and also frequent losses at chromosome 1p, 17, 19, and 22 and gains affecting chromosomes 7 and 13. Authors explained the difference in outcomes because of the use of more sensitive and specific techniques in the last.

Three component system of 8-oxoG repair.

The MUTHY-protein recognizes the 8-oxoG:A base-pair and excises the improperly incorporated adenine during replication, after which other reparation proteins can place a cytosine opposite the 8-oxoG. OGG1 then can excise the 8-oxoG from the 8-oxoG:C base-pair.

(a) MTH1 works separately, and cleanses the cellular nucleotide pool from oxidized precursors of guanine (dGTP) en prevents incorporation of 8-oxo G in the DNA.

(b) The three components ‘base excision repair’ mechanism thus prevents the incorporation of dGTP in the DNA and subsequently G:C naar T:A and A:T to C:G transversions. Based on figure from Michaels 1992.
References


This article should be referenced as such: