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MUTYH-associated polyposis (MAP)

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Abstract

The human mutY homologue (MUTYH) gene is responsible for inheritable polyposis and colorectal cancer. This review discusses the molecular genetic aspects of the MUTYH gene and protein, the clinical impact of mono- and biallelic MUTYH mutations and histological aspects of the MUTYH tumors. Furthermore, the relationship between MUTYH and the mismatch repair genes in colorectal cancer (CRC) families is examined. Finally, the role of other base excision repair genes in polyposis and CRC patients is discussed.

Keywords: MUTYH-associated polyposis; MUTYH gene; MAP; Colorectal cancer; Polyposis

1. Introduction

Colorectal adenomas are a common manifestation in the general population, primarily at an older age, and are thought to be the requisite precursor for colorectal cancer (CRC) [1]. In addition to adenoma size and grade of dysplasia, the chance of malignancy among these lesions grows with larger numbers of adenomas [2]. When adenomas or other polyps are numerous or manifest at a relatively young age, an inheritable form of polyposis should be considered.

MUTYH-associated polyposis (MAP) (OMIM #608456) is the most recent reported CRC and polyposis syndrome. It was discovered in 2002 by a Welsh research group [3]. An earlier identified other polyposis and CRC syndrome is familial adenomatous polyposis (FAP), caused by mutations in the adenomatous polyposis coli (APC) gene. Lynch syndrome, or hereditary non-polyposis colorectal carcinoma (HNPCC), is a tumor predisposition syndrome associated with colorectal and endometrial cancer and several other extracolonic malignancies, caused by mutations in the 'mismatch repair' (MMR) genes, predominantly MLH1, MSH2, MSH6 and PMS2. Less prevalent syndromes are Peutz–Jeghers (caused by mutations in LKB1), juvenile polyposis (SMAD4, BMPR1A, ENG-genes), hereditary mixed polyposis (BMPR1A-gene), and hyperplastic polyposis syndrome (HPS) [4].

Intriguingly, the latter are all dominantly inherited syndromes (except HPS, inheritance and gene unknown); MAP is the first known polyposis syndrome with a recessive mode of inheritance. Mutations in both MUTYH genes predispose patients to the development of polyps. The disease is, in principal, restricted to one generation; see Section 4 for more clinical details. Since its discovery, multiple international research groups have investigated the consequences of mono- and biallelic mutations in the MUTYH gene in humans, bacteria and other species. Several aspects of the natural history and pathophysiology of MAP have been elucidated and a possible CRC risk in MUTYH heterozygotes has been analyzed in large case–control studies.

MUTYH has been shown to cooperate with other proteins involved in DNA repair, such as MSH6. MUTYH might act as a causative factor or modifier in Lynch syndrome families. Furthermore, it has been suggested that other base excision repair genes might be involved in the development of adenomas and CRC.

2. Methods

The computerized PubMed database was searched for the literature published from 1980 to August 2009, looking for publications that concern MYH, hMYH, MutY homolog or MUTYH. Additional relevant articles were identified by reviewing the references of retrieved publications. Proceedings of the Meeting of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) 2009 in Dusseldorf were also included; see the website for more information http://www.insight2009.info/.

3. Functional studies and the mutation spectrum

In 1988, the mutY gene was cloned in *Escherichia coli* [5]. The equivalent gene, which was identified from human HeLa cells, was described in 1991 [6] and named MYH. Later, the name MYH was replaced by MUTYH because MYH was already in use for another group of genes: the myosin heavy chain genes. The role of the MUTYH gene in polyposis was discovered in a family of 3 siblings in 2002 by Al Tassan et al. In 11 tumors of these siblings, a significantly greater proportion of G:C to T:A transversions (83%, 15/18 of somatic APC mutations) was found than in sporadic tumors which lead to the suspicion of a deficient MUTYH protein. This finding reinforced the need for research on the functionality of this protein.

The MUTYH gene, located at chromosome locus 1p34.3-p32.1, is 11.2 kb long and has 16 exons (www.lovd.nl/mutyh). The MUTYH protein is a base excision repair (BER) glycosylase 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). When an oxoG:A mismatch is present in the DNA-template in the next round of replication, a G:C to T:A transversion will occur [7]. MUTYH recognizes an oxoG:A mismatch and excises the undamaged adenine base using a base–flipping mechanism. DNA polymerases can subsequently restore an oxoG:C pair that can be acted upon by another BER-glycosylase, OGG1, to replace the oxidized guanine with a guanine (see Fig. 1) [8–10].

The MUTYH protein consists of different functional domains. On the N-terminal domain lies the catalytic region with the helix–hairpin–helix (HhH) motif, as well as the pseudo-HhH region and the iron–sulfur cluster loop motif