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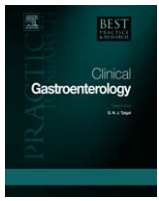

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Hereditary colorectal cancer: MYH-associated polyposis and other newly identified disorders

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Historically, discussions of familial adenomatous polyposis and hereditary non-polyposis colon cancer have dominated lectures and writings on hereditary predisposition to colorectal cancer. In the last decade, the subject has grown well beyond the two entities. In this paper, five topics relevant to genetic risk assessment for colorectal cancer are reviewed. These include the autosomal recessive MYH-associated polyposis, hyperplastic polyposis and serrated pathway syndrome, the association of autosomal dominant juvenile polyposis with hereditary hemorrhagic telangiectasia, familial colorectal cancer type X, and the syndrome of biallelic DNA mismatch repair gene mutations. Knowledge of these entities may assist clinicians to recognize and manage cases that do not fit into the more common syndromes of colorectal cancer predisposition.

Introduction

Until recently, only two disorders were routinely discussed when the topic of hereditary predisposition to colorectal cancer was raised. These were familial adenomatous polyposis (FAP) and the hereditary DNA mismatch repair deficiency, commonly called hereditary non-polyposis colon cancer (HNPCC), or Lynch syndrome. In the last few years, other clinical entities or associations have emerged. Each of these are reviewed here, including: (1) *MYH*-associated polyposis, (2) hyperplastic polyposis and serrated pathway syndrome, (3) juvenile polyposis associated with hereditary hemorrhagic telangiectasia, (4) familial colorectal cancer type X, and (5) biallelic mutations DNA mismatch repair genes.

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MYH: Success of a candidate gene approach

Take-home message

Biallelic mutations in *MYH* (a base excision repair gene) cause an autosomal recessively inherited disorder that can be a phenocopy of familial adenomatous polyposis (FAP), with both classical and attenuated polyposis, along with FAP-like extra-colonic manifestations, or just colorectal cancer.

Background

Until 2002, *APC* was the only recognized gene in which germline mutations were shown to cause adenomatous polyposis of the colorectum. At that time, a family was reported in which three of seven siblings had multiple adenomatous colorectal polyps or adenocarcinoma without germline *APC* mutation [1]. Somatic *APC* mutation analysis of the neoplasms revealed a molecular signature consisting of a high proportion of G:C to T:A transversions, which are characteristic of defective base-excision repair (BER). Germline analysis of three BER genes *MYH*, *OGG1* and *MTH1* led to the identification of biallelic mutations in *MYH*: Y165C and G382D, in all affected individuals. Unaffected relatives were heterozygous for *MYH* mutations or wild type, supporting evidence of an autosomal recessive pattern of disease inheritance. This new disorder is known as *MUTYH*- or *MYH*-associated polyposis (MAP).

Genetics of base-excision repair

Reactive oxygen species (ROS) produced during cellular metabolism or through exposure to ionizing radiation or chemicals damages DNA. Cells with deficient BER, thus, are susceptible to DNA damage by ROS. There are multiple proteins that interact in human BER (reviewed by Tudek [2] and Frosina[3]) but three main components that prevent ROS-induced DNA damage: *MTH1*, *OGG1* and *MYH* (also known as *MUTYH)* [2,3]. Each enzyme has a specific function following oxidative damage to the cell. *MYH*, a DNA glycosylase, identifies and removes adenine residues that have been incorrectly paired with 8-oxoG, a highly mutagenic ROS. Failure to correct 8-oxoG:A mispairing in the next cycle of DNA replication leads to the characteristic G:C to T:A transversions seen in BER deficiency [4].

More than 80 germline *MYH* variants have now been reported [5]. The most commonly reported mutations are Y165C and G382D which account for ~80% of *MYH* mutations reported in Caucasian populations [6,7]. The heterozygote population frequency for these mutations is 0.3–2% [1,7–9].

Cancer development in MAP

Chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator (CIMP) are three pathways through which the majority of colorectal cancers develop. Of the hereditary syndromes, neoplasia in familial adenomatous polyposis (FAP) tends to evolve via the CIN pathway, whereas neoplasia in Lynch syndrome/hereditary non-polyposis colorectal cancer (HNPCC) evolves through the MSI pathway. The CIN pathway, which accounts for the majority of colorectal cancers, is characterized by mutations in *APC*, p53, K-ras or *SMAD4*, loss of 18q and an aneuploid karyotype. The pathways associated with defective MYH lead to colorectal cancers that contain acquired mutations in *APC* caused by G:C to T:A transversions, particularly at GAA sequences which lead to a stop codon, TAA [1,10,11]. The fact that *APC* is a target of mutations that cannot be repaired in cells with defective BER explains the clinical similarity between FAP and MAP. MAP tumours have a high frequency of mutations in K-ras with the same type of transversion; it has been suggested that this somatic finding could be used to identify atypical MAP patients [12]. MAP tumours are generally microsatellite stable, but unlike CIN-type tumours, MAP tumours are diploid [10].

MYH inactivation is unusual in colorectal cancers in general. Among 75 unselected sporadic colorectal cancers no *MYH* mutations were identified and *MYH* mRNA and protein expression was found at normal levels in 35 CRC cell lines [13].