DNA REPAIR 6 (2007) 274–279

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/dnarepair

Mini-review

MUTYH-associated polyposis—From defect in base excision repair to clinical genetic testing

Jeremy P. Cheadle, Julian R. Sampson*

Institute of Medical Genetics, Cardiff University, Heath Park, Cardiff CF14 4XN, UK

ARTICLE INFO

Article history:
Received 1 November 2006
Accepted 1 November 2006
Published on line 11 December 2006

Keywords:
MUTYH-associated polyposis
MUTYH
MAP
Colorectal cancer
Base excision repair
MYH

ABSTRACT

Established predisposition genes account for only a small proportion of familial colorectal cancer. Recently, it has been shown that germline mutations in *MUTYH* predispose to *MUTYH*-associated polyposis (MAP), an autosomal recessive disorder characterised by multiple colorectal adenomas and carcinomas. MUTYH functions as a base excision repair DNA glycosylase that excises adenines misincorporated opposite 8-oxo-7,8-dihydro-2′-deoxyguanosine, one of the most stable products of oxidative DNA damage. It is the failure to correct this mispair that is thought to give rise to the characteristic signature of G:C → T:A mutations found in MAP-associated tumours. Here, we review the germline mutation spectrum at the *MUTYH* locus (comprising 30 truncating and 55 missense/inframe insertion/deletion variants) and the molecular mechanism and biochemical defect(s) underlying this disorder. We also discuss the application of molecular genetic analysis of *MUTYH* in clinical practice.

Contents

* *Corresponding author*. Tel.: +44 2920742652; fax: +44 2920746551.
E-mail address: cheadlejp@cardiff.ac.uk (J.P. Cheadle).
1568-7864/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.dnarep.2006.11.001

1. Inherited predisposition to colorectal cancer

Inherited factors are thought to play a significant role in up to one third of colorectal cancers (CRCs), but only a minority of these can be accounted for by established CRC predisposition genes [1]. Familial adenomatous polyposis (FAP) (MIM 175100) is an autosomal dominant disorder characterised by the development of hundreds or thousands of colorectal adenomas, some of which progress to cancer. FAP is caused by inherited mutations in the adenomatous polyposis coli (*APC*) gene that acts as a gatekeeper regulating proliferation of colonic cells [2]. A milder form of this disorder termed attenuated FAP (AFAP) is associated with smaller numbers of adenomas and is caused by germline mutations in the extreme 5′ or 3′ ends of *APC* or in the alternatively spliced region of exon 9 [2]. Hereditary non-polyposis CRC (HNPCC; MIM 114500) is an autosomal dominant disorder characterised by early onset CRC (in the absence of florid polyposis) and other extra-colonic cancers, notably endometrial cancer and cancers of the stomach, small bowel, ureter and renal pelvis. HNPCC is caused by inherited deficiencies in the mismatch repair pathway [3], primarily within the genes *MSH2* and *MLH1*.

2. Inherited mutations in *MUTYH* predispose to colorectal tumours

In 2002, Al-Tassan and colleagues studied a British family (Family N) with three affected siblings with multiple colorectal adenomas (CRAs) and carcinoma [4]. Sequencing of the entire *APC* open reading frame (ORF) in germline DNA samples from two of the affected siblings, together with haplotype and expression analyses, excluded an inherited *APC* gene defect. To provide a clue as to the underlying genetic defect, the investigators examined colorectal tumours from Family N and found an unusually high proportion of somatic G:C → T:A mutations in *APC* [4]. Previous studies in bacteria and yeast had shown a mutator phenotype with this characteristic in *MutY* and *Ogg1*-deficient strains and subsequent studies of the corresponding human orthologues showed that patients from Family N were germline compound heterozygotes for the missense variants Y165C and G382D in the human orthologue of *MutY* [4]. This gene is called *MUTYH* (and often, incorrectly, *hMYH* or *MYH*). In a follow up study, Jones et al. [5] identified seven further unrelated patients with multiple CRAs (six with CRC) and biallelic germline *MUTYH* mutations, including four cases homozygous for truncating mutations. Again, colorectal tumours from the affected individuals displayed a highly significant excess of somatic G:C → T:A mutations in *APC*, as compared to sporadic or FAP-associated colorectal tumours. These findings supported the role of biallelic inherited mutations in *MUTYH* in causing an AFAP-like syndrome characterised by multiple CRA and CRC (reviewed in [6]). This disorder has been termed *MUTYH*-associated polyposis (MAP).

3. The phenotype of MAP

Mutation analysis of *MUTYH* has now been undertaken in several series of patients with FAP-like and AFAP-like phenotypes and in whom no inherited *APC* mutation could be identified [5,7–12]. Biallelic *MUTYH* mutations have been identified in approximately 25% of such cases and, in general, segregation has been consistent with transmission of MAP as an autosomal recessive trait with high and probably complete penetrance. The colorectal phenotype of MAP closely resembles AFAP (10–100 adenomas), or FAP (100–1000 adenomas), but not severe FAP (>1000 adenomas). In addition, some cases appear to develop fewer than 10 macroscopic adenomas by middle age and to have developed CRC in the absence of obvious polyposis [7,13,14]. As expected for a recessive trait, many cases appear to be sporadic and hence present symptomatically. CRC was found at presentation in ∼50% of cases reported by Sampson et al. [7] and by Sieber et al. [8].

A possible explanation for the predominantly colorectal phenotype in MAP is the high level of oxidative damage that occurs in the large bowel since *MUTYH* functions in the oxidative damage repair pathway. An alternative or additional factor was proposed after careful examination of the target sequence surrounding the somatic G:C → T:A mutations in MAP tumours—the two bases immediately 3′ to the mutated G are almost always AA and this preponderance of G:C → T:A mutations at GAA sequences is highly significant [4,5]. *APC*, the key gatekeeper in colorectal tumourigenesis, has a total of 216 GAA sites in which G:C → T:A mutations could lead to termination codons. By comparison *TP53*, *PTCH*, *RB1*, *NF1* and *VHL* (that are frequently mutated during tumourigenesis in the brain/breast/lung, skin, retina, Schwann cells and kidney) have significantly fewer target sites and therefore *APC* may be a particularly vulnerable target for mutagenesis in MAP [6].

4. Mutation spectrum in *MUTYH* and diagnostic implications

As of November 2006, 30 mutations that are predicted to truncate the protein product have been reported in *MUTYH*, comprising 11 nonsense, 9 small insertion/deletions and 10 splice site variants (Fig. 1). In addition, 52 missense variants and three small inframe insertion/deletions have been reported that are distributed throughout the gene (Fig. 1) [4,5,7–12,15–34]. Although there is some reporting bias, the missense variants Y165C and G382D together account for approximately 73% of all *MUTYH* mutations reported to-date, and have been identified commonly in the British, Italian, American, Portuguese and Dutch populations (reviewed in [35]). In addition, specific mutations in *MUTYH* have been identified in different populations and diagnostic screening strategies will have to be optimised accordingly. For example, recurrent mutations have been identified in Italian (1395delGGA), Portuguese (1186–1187insGG) and Dutch patients (P391L) and the truncating mutation E466X has been identified in at least four unrelated Gujarati families [7,9,11,25]. Apart from Y165C and G382D, most missense variants are rare. However, their collective frequency and the lack of functional data for the vast majority pose major difficulties for molecular diagnostics since many will be benign polymorphisms. Most of these variants remain ‘of uncertain pathogenicity’ and genetic counselling for patients carrying them is problematic.