Clinical and molecular aspects of MUTYH- and APC-associated polyposis

Nielsen, M.

1.2

Review on *MUTYH*-associated polyposis (MAP)

Maartje Nielsen
Hans Morreau
Hans F.A.Vasen
Frederik .Hes

Crit Rev Oncol Hematol (2010 Jul 19), doi:10.1016/j.critrevonc.2010.05.011

MUTYH-associated polyposis (MAP)

Maartje Nielsen, MD[1], Hans Morreau, PhD MD[2], Hans FA Vasen, PhD MD[3], Frederik J Hes, PhD MD[1]

1 Department Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands
2 Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands
3 Dutch Hereditary Cancer Registry and Department of Gastroenterology, Leiden University Medical Center, Leiden, the Netherlands

Correspondence to: M. Nielsen, LUMC, Department of Clinical Genetics, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands, email: m.nielsen@lumc.nl, fax: 0031-71-5266749

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 i.[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-->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 1p34.3p32.1, 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. [11,12] The C-terminal domain shares homology with the nudix-type motif 1, encoded by the *NUDT1* gene (also known as *MTH1*). This domain plays a role in 8-oxoG recognition.[12–15] Increased expression during the S-phase and interaction of MUTYH with several replication-coupled enzymes, such as PCNA (proliferating cell nuclear antigen) and RPA (replication protein A), suggests a role for MUTYH in replication-coupled long patch repair.[16] Repair during DNA replication also ensures that MUTYH base excision repair is targeted to the daughter DNA strands and not to the parental strands.[17] Recently, in a study with mouse embryonic fibroblast cell lines, it was shown that MUTYH (and OGG1) are likely required under oxidative stress for normal cell-cycle progression and nuclear division, suggesting a role in the maintenance of genome stability and tumor prevention.[18]

3.1 mutation spectrum

To date, 105 unique sequence variants have been reported in the LOVD database for the *MUTYH* gene. These are predominantly missense mutations, but to a lesser extent also small deletions, duplications and one insertion. For all reported mutations see: (www.lovd.nl/*MUTYH*). In the LOVD, mutations are annotated according to the longest possible (hypothetical) coding sequence, NM 001128425.1, as recommended by the Human Genome Variation Society (HGVS) in collaboration with The National Center for Biotechnology Information (NCBI). This sequence differs from the most frequently reported transcript NM 001048171.1 by insertion of 42 nucleotides after c.157 (www.lovd.nl/*MUTYH*). For example: the p.Y165C annotation becomes p.Y179C and p.G382D becomes p.G396D.

In Caucasian populations, a biallelic status for the hot spot mutations p.Y179C and/or p.G396D is reported in up to 70% of MAP patients. Furthermore, 90% of the western MAP population carries at least one of these mutations.[19] Since these mutations were never found in Korean, Japanese or Jewish persons of European origin,[20–24] existence of founder mutations and ethnic differentiation is assumed for *MUTYH* mutations.

Other common mutations are c.1147delC (p.A385fs mutation) in western countries,[19]

p.P405L in Dutch,[25] c.1437 1439del in Italian (p.Glu480del),[26] p.E480X in British Indian, p.Y104X in Pakistani,[27] c.1227 1228dup in Spanish and Portuguese[28] and p.A359V in Japanese and Korean patients.[20,22,29]

3.2 Functionality assays

Functionality assays have been performed for a number of *MUTYH* variants. Studies on other species (like E. coli) show that the equivalent location for the human p.Y179 in the HhH region plays an important role in 8-oxoG recognition and adenine mispair specificity, intercalation into the DNA duplex and stability of the protein-DNA complex. The equivalent location for the human p.G396 in the C-terminal domain is also involved in 8-oxoG recognition and adenine mispair specificity, and is thought to be important for conformational flexibility of the MUTYH protein.[11–14,30] Results of functionality assays on these variants are not consistent, depending on the setting some studies found a complete absence of activity for both variants[31] while others found only partially reduced activity.[32,33] Furthermore the p.G396D variant is significantly less catalytically compromised than the p.Y179C in some studies.[3,33,34] It has been suggested that the effective glycosylase activity of MUTYH is more reduced in vivo because the search process is more demanding, as the size of the chromosomal DNA is larger than the oligonucleotide substrates used in vitro and there is more competition for binding with other DNA binding proteins.[32,35,36] Differences in outcomes might also be explained by lack of consideration and correction of the active enzyme fraction in an in vitro setting. Recently, it was shown that both variants (and other variants) – when corrected for active enzyme fraction – showed the same threefold reduction in glycosylase activity compared to the wild-type protein in a vitro experiment[37] In contrast, in a cellular context using rifampicine resistance assays, different results for the assessed variants were found. While the ability to suppress mutations was reduced only twofold for the p.G396D variant, no mutation suppression was observed upon expression of the p.Y179C variant. These results suggest that the intrinsic activity and active fraction of certain variants may be further compromised in a cellular context because of other factors such as protein stability and folding.[37] Also posttranslational modification, such as phosphorylation, might further reduce glycosylase activity for some variants in a human cell.[16,37]

Severely hampered or completely absent DNA binding and repair activity have subsequently been shown for the c.1147delC,[33,34] p.R185W,[38] p.R241W,[39] p.V246F,[39] p.R245L,[40] p.R245H, p.P295L, p.P405L,[37] p.Y104X, p.Q391X, p.E480X ,[33] p.A473D [41] and p.G286E variants.[22] The p.R274Q is partially active.[33] The c.934-2A>C (IVS10-2A>C) variant causes the production of an aberrant mRNA transcript encoding a truncated

MUTYH protein and immunofluorescence analysis shows the absence of this variant in the nucleus.[42] The mouse MUTYH variant of p.A373V did not show any impaired DNA glycosylase activity.[22]

A number of variants are frequently found in polyposis patient and cancer cases as well as controls, the p.Q338H (previously p.Q324H) is found in 40–45%, the c.504+35G>A (IVS6+35G>A) in 20–25% and the p.V22M variant in 10–15%. The V22M variant showed the same activity as wild-type MUTYH protein in vitro in one study. The pathogenic significance of p.Q338H is disputed. One study also reported no difference with respect to repair activity for the p.Q338H SNP compared to wild type.[43] In contrast, others found that this SNP was partially impaired with regard to adenine removal.[33] Recently it was reported that another variant at the same position, the Q324R variant, showed a reduced rate of adenine excision in the glycosylase assays but the enzyme activity was sufficient to mediate repair and prevent mutations in a cellular context.[37]

In conclusion, the MUTYH BER protein has an important role in DNA repair following oxidative damage. Several different mutations, mainly missense mutations, have been found. The two most common mutations in the Western population are p.Y179C and p.G396D, with probable different effects on MUTYH glycosylase function.

4. Clinical presentation and guidelines for surveillance and molecular genetic testing

Over 500 MAP patients have been reported thus far[19,25,26,28,44–77] [InSiGHT 2009]. Most biallelic *MUTYH* carriers have between 10 and a few hundred polyps, only two MAP cases with more than 500 polyps have been reported so far (Table 1).[56,74] Also, a number of MAP patients with CRC and no polyps have been reported, see Section 4.4 of this review.

About 60% of MAP patients with polyposis have CRC at first presentation, diagnosed at a mean age of 48 years (ranging from 21 to 70 years).[19] In a CRC cohort study, the penetrance of CRC in MAP patients was shown to be 19% at age 50 and 43% at age 60 years.[78] The actual penetrance for CRC is possibly higher because the development of CRC can be prevented through intensive colorectal screening.

4.1 Clinical management of MAP patients

In 2008, a consensus meeting recommended colonoscopic surveillance of MAP patients every 2 years for patients from 18–20 years old. [79] When the number of polyps is greater than is allowed for by endoscopic removal, subtotal colectomy is indicated. Because

of a high risk of metachronous tumors, total colectomy and ileorectal anastomosis or IPAA should be taken into consideration when operating upon a MAP patient. Since hyperplastic polyps and sessile serrated adenomas are a common finding in patients with MAP, and can eventually evolve into more malignant lesions, screening should include the detection and removal of these polyps.[80,81]

Beginning surveillance when patients are 18–20 years old seems sufficient. So far, only two cases have been reported with age of onset <20 years: a 14-year-old boy with hundreds of adenomas throughout the colon and an intramucosal carcinoma (now considered as high-grade dysplasia) and a 13-year-old boy with more than a hundred colon adenomas and gastric cancer at age 17.[57] In these cases, additional genetic or environmental factors might explain the young age of onset. Upper gastrointestinal tract screening is advised to begin from the age of 25–30 years.[79] The recommended intervals between screening depend on the severity of disease according to the Spigelman classification.[79]

4.2 Geno-phenotype correlations

In accordance with a number of functionality assays that show a greater reduction in MUTYH glycosylase activity for p.Y179C as compared to p.G396D (see Section 3.2), we recently showed that the phenotype for MAP patients with biallelic p.G396D mutations was less severe than for p.Y179C homozygotes.[19] Patients with a homozygous p.G396D mutation or compound heterozygous p.G396D/p.Y179C mutations presented with MAP later and had a significantly lower hazard of developing CRC than patients with a homozygous p.Y179C mutation ($P < 0.001$). The mean ages of CRC diagnosis were 58 years (homozygous p.G396D), 52 years (c. heterozygous p.G396D/p.Y179C) and 46 years (homozygous Y179C; $p = 0.001$, linear regression).

Based on the range of age at diagnosis of CRC (37–70 years), it may be appropriate to initiate surveillance later for p.G396D homozygotes and p.G396D/p.Y179C compound heterozygotes as compared to p.Y179C homozygotes. Unexpectedly, the p.G396D mutation in combination with mutations other than p.Y179C did not show a milder phenotype. Severity similar to that of the p.Y179C homozygotes was observed. A later age of CRC diagnosis in p.G382D homozygotes compared to p.Y165C homozygotes was also found by others.[78] Ideally, long-term prospective studies of MAP should be undertaken to extend the evidence for refinement of clinical guidelines.

4.3. Survival

We found that MAP CRC patients have better overall survival than sporadic CRC cases (Nielsen *et al*., submitted). Lynch syndrome patients with CRC have also been shown

to have better survival than sporadic CRC patients.[82,83] Interestingly, MAP carcinomas show some histological similarities to Lynch syndrome carcinomas (see Section 6 of this review for more details). A higher immune response might be the underlying cause of improved survival, induced by accumulation of peptide fragments derived from secondary mutated proteins that are presented at the cell surface as part of the major histocompatibility complex. Because of the activated immune system, a strong selective pressure can be expected to favor the outgrowth of tumor cell clones with an immune evasive phenotype. Recently, it was indeed shown that loss of HLA class I receptor expression (involved in presenting mutated proteins to the immune system) is a frequent event in MAP carcinomas, similar to MMR-deficient colorectal tumors,[84,85] supporting the existence of an anti-tumor immune response.[86]

4.4 Eligibility for MUTYH mutation screening

MUTYH screening should be directed to patients with between 10 and a few hundred polyps (adenomas and/or hyperplastic polyps), especially in the context of a family history that is compatible with recessive inheritance, although a vertical transmission of CRC does not rule out the possibility of biallelic *MUTYH* mutations.[25,87] Biallelic *MUTYH* mutations are found in about 28% of (*APC* germ-line mutation-negative) patients with 10–100 polyps and in 14% of patients with 100–1000 polyps (Table 1). One study showed that the combination of >15 synchronous adenomas and to carry out *MUTYH* mutation analysis before or concomitantly with *APC* analysis in individuals with fewer than 1000 adenomas.

In population-based CRC studies where patients were collected on the basis of the diagnosis of CRC and not on polyps, biallelic *MUTYH* mutations were found in 0.3–2.0% (mean 0.4%) and 0.8–6.2% (mean 1.4%) of patients under 49–55 years when stratified for age (Tables 1 and 2). In eight population-based studies, 28 out of 79 (35%) proven biallelic *MUTYH* mutation carriers had no polyps aside from their CRC while seventeen (22%) had a limited number of adenomas (i.e., <10).[48,49,58–61,66,67,78] Therefore, biallelic *MUTYH* mutations are not invariably associated with a polyposis phenotype and therefore, the practicing pathologist and clinician should also consider biallelic *MUTYH* mutations in CRC patients with zero or less than 10 polyps. However, no biallelic *MUTYH* mutations are found in patients with less than 10–15 polyps and no CRC so far (Table 1). Although, it should be considered that in MAP patients younger than 40 years the polyp development can still be slow, and *MUTYH* DNA analysis might be considered in these cases even if the polyp count is less than 15. A sudden rapid acceleration of adenoma development at age 52 years was recently found in a patient with a single CRC at age 44 years and previously only slow adenoma development.[88] A

pre-screening assay for c.34G>T in *KRAS* in tumor material can also be helpful in these atypical MAP patients (see Section 6 of this review).

Despite the relatively large proportion of population-specific mutations in MAP, it is recommended to screen the entire *MUTYH* gene. About 17% of 185 tested index patients in Germany, the Netherlands and the UK do not carry one of the two most common missense mutations (p.Y179C and p.G396D).[19] In patients of southern European descent, this proportion is even higher (20–33%).[26,28,45,74] In non-western countries, the mutation spectrum is completely different.[22,27.]

When biallelic mutations have been found in a patient, testing should be offered to siblings because they have a 25% chance of having inherited biallelic *MUTYH* mutations. Since *MUTYH* mutations are present in 1–2% of the population, children of mono-or biallelic *MUTYH* mutation carriers have a 0.5–1.0% chance of inheriting two *MUTYH* mutations because the other parent might (also) be a *MUTYH* heterozygote. A cost effectiveness analysis of Dutch MAP patients estimated that *MUTYH* testing in spouses of MAP patients, and to a lesser extent in spouses of *MUTYH* heterozygotes, was acceptable in terms of cost per quality-adjusted life year.[89] Therefore, genetic testing of spouses and children should be discussed with and offered to counselees.

5. MUTYH AND EXTRACOLONIC LESIONS

Since oxidative stress is a common manifestation, it can be expected that a defective *MUTYH* gene leads to cancers and tumors external to the colon as well. Indeed, in *MUTYH* knockout mice, tumors are found in the small intestine.[90] Mice deficient for both MUTYH and APC (APCmin/+) have tumors in the small intestine, breast and lung .[91] In double MUTYH and OGG1 knockout mice ovarian tumors and lymphomas were found.[92]

Recently, extraintestinal lesions were systematically evaluated in a cohort of 276 MAP patients from 181 different European MAP families from three different European countries. The incidence of extraintestinal malignancies as a whole was almost doubled (SIR 1.9; 95% CI 1.4–2.5) with a lifetime risk of 38%. The median age at diagnosis for the different extraintestinal malignancies varied between 51 and 61 years.[93]

5.1. Small bowel lesions

Duodenal polyposis occurred in 17% of 276 MAP patients and the lifetime risk for duodenal cancer was 4% (relative risk (SIR) 129; 95% CI 16–66). Duodenal cancer was also reported in four other patients.[45,77,94] One case report described a MAP patient

with three synchronous jejunal carcinomas at age 39 years.[68] Except for two carcinoid tumors in the small bowel, no other small bowel carcinomas have been reported.[93]

5.2. Gastric cancer

Among 150 endoscopically surveyed patients, 17 (11%) had gastric lesions and a higher risk of gastric cancer was observed, although this trend was not significant (3 out 150 surveyed patients, SIR 4.2, 95% CI 0.9–12).[93] One case described in the literature had gastric cancer at age 17, suggesting the presence of other causative factors. [57] One additional MAP patient with gastric cancer has been reported.[22.] Several Japanese groups studying a possible association of *MUTYH* mutations and gastric cancer show somewhat conflicting results. No biallelic *MUTYH* mutations among 20 familial cases of gastric cancer were found in Japanese patients. However, the authors found a biallelic novel splice site variant (IVS10-2A) in an additional group of 148 consecutive gastric cancer cases. This variant was not present in controls.[42] In 2006 a higher frequency of a specific variant of For now, mutated forms of *MUTYH* do not seem to be a strong causative factor in gastric cancer.

5.3. Endometrial cancer

A non-significant trend towards endometrial cancer in 118 female MAP patients (two patients, SIR 4.6 (95% CI: 0.6–16.5)) was found. The ages at diagnosis were 47 and 54 years.[93] Four endometrial carcinomas in female MAP patients between 46 and 58 years of age have been reported by others.[77,97,98] The tumors in two patients were examined for KRAS mutations. The MAP-specific c.34G>T mutation was found in one patient, underscoring a causative role of defective *MUTYH*.[97] One of these patients was identified in a large series of consecutive endometrial cancers (n = 225.[98] Another study found no biallelic *MUTYH* patients among 213 endometrial cancer patients.[99]

5.4. Breast cancer

An association of breast cancer and *MUTYH* is supported by the fact that BRCA1 and BRCA2 are involved in 8oxoG repair.[100] and breast tumors are found in combined MUTYH/APC deficient mice [91.] The incidence of breast cancer in females in the European cohort with MAP was significantly increased (SIR 3.0; 95%CI 1.5–5.3), but only if the number of cancers rather than the number of affected females was considered. In contrast to hereditary breast and ovarian cancer, breast cancer in MAP patients was a late-onset manifestation occurring between the fifth and eighth decades of life. Breast cancer was also diagnosed at age 56 in one male MAP patient who tested negative for BRCA1 and BRCA2 germ-line mutations (SIR 53.5; 95% CI 1.4–298).[93] In contrast, two large

breast cancer case–control studies (including more than 5000 cases in total) found no association between breast cancer and mono-or biallelic *MUTYH* mutations.[101,102]

5.5. Other cancers

A low to moderate but significant increase in the incidence of ovarian and bladder carcinomas, as well as skin cancer (SIR 5.7, SIR 7.2 and SIR 2.8, respectively), was found in the 276 European MAP patients. Skin cancers included melanomas, squamous epithelial carcinomas and basal cell cancers. The risk of bladder cancer in MAP was similar to the risk of urinary tract cancers in Lynch syndrome. However, in contrast to Lynch syndrome, no cancers were located in the upper part of the urinary tract (renal pelvis, ureter) and the MAP-associated cancers included one squamous cell carcinoma in addition to urothelial cancers.[93] Ovarian cancer was observed three times. In one cancer, the histology was known and involved a mucinous cystadenocarcinoma. Furthermore, two cases of thyroid carcinoma, each with a different histology, were observed in this cohort.[93] One additional case has been reported elsewhere .[103] The two cancers had different histological types, which does not support a clear association of thyroid cancer with MAP, in contrast to the established association with FAP. Furthermore, single MAP patients with scapular chondrosarcoma,[94] a high-grade astrocytoma,[94] and a Schwannoma[45] have been reported.

No overrepresentation of mono-or biallelic *MUTYH* mutations was found in patients with hepatocellular carcinoma,[104] cholangiocellular carcinoma,[104] (childhood) leukaemia,[105] prostate cancer[106,107] sporadic squamous oral/oropharyngeal carcinoma[108] or sporadic pancreatic cancer[109] as compared to healthy controls. In 276 patients with lung cancer, no overrepresentation of *MUTYH* mutations (mono-or biallelic) was found.[110] However, in a recent study, biallelic *MUTYH* p.Q338H (previously p.Q324H) showed a significant association with lung cancer risk in smokers (adjusted OR 3.82, p = 0.022).[111]

5.6. Sebaceous gland tumors

Sebaceous gland tumors (adenomas, epitheliomas and carcinomas), which are a well-known characteristic of the Muir–Torre variant of Lynch syndrome and are very rare in the general population, have been reported in four MAP patients. [44,103,112] In the European cohort, sebaceous gland tumors occurred in five patients (1.8% of all included MAP patients).[93] Furthermore, sebaceous gland hyperplasia (SGH), which is not part of the Muir–Torre syndrome clinical definition, has been reported in four MAP patients. In all of these cases, a somatic *BRAF* p.V600E mutation was detected.[51] The authors suggest that detection of *BRAF* mutations in sebaceous hyperplasia can help identify MAP cases.[51] Notably, the mutation found concerned a T > A transversion, which is not associated with MUTYH deficiency.

5.7. FAP manifestations

Some manifestations also seen in familial adenomatous polyposis (FAP) have been reported in a small number of MAP patients; lipomas in 3% (8/276);[93] congenital hypertrophy of the retinal pigment epithelium (CHRPE) in 5.5% (3/62 analyzed patients[93] and 5 more cases in the literature);[26,54,62] osteomas in two cases;[26] jaw-bone cyst in 11 cases;[93] epidermoid cyst in 3 cases:[93] desmoid tumor in 1 case; [68] and pilomatrixomas (pilomatricomas) in three siblings.[113] Overall, the incidence of FAP-related manifestations in MAP patients seems to be low.

In conclusion, several extracolonic tumors have been reported in MAP, but significantly higher risks were only observed for duodenal carcinoma, ovarian, bladder and skin cancer. Although extracolonic tumors are less prevalent than in Lynch syndrome patients, the extracolonic tumor spectrum is somewhat similar to that found in Lynch syndrome patients. The spectrum of cancers and their advanced age at onset in MAP do not suggest specific surveillance recommendations other than frequent upper gastrointestinal tract screening.

6. MAP CARCINOMA, MOLECULAR AND HISTOLOGICAL CHARACTERISTICS

One can expect specific molecular and histological characteristics for MAP carcinoma because they follow, at least in part, a different genetic pathway than that followed by sporadic tumors. A dysfunctional MUTYH protein is expected to generate specifically somatic G > T transversions in other genes. In fact, G > T transversions in the *APC* gene in polyps of a Welsh family led to the initial discovery of the *MUTYH* gene.

6.1. MAP colorectal carcinomas

In further studies, *APC* mutations were found in 14–83% of MAP CRCs, all G > T transversions with a predilection for G bases in AGAA or TGAA motifs. A specific *KRAS* mutation (the c.34G>T in codon 12) is present in 64% of CRCs.[54,114,115] In contrast, *KRAS* mutations are found in 29% of sporadic CRCs and 22% of sporadic MSI-high carcinomas. Furthermore, the c.34G>T transversion represents just 8% of KRAS mutations in sporadic CRCs and 0% of KRAS mutations in MSI-high CRCs.[16] P53 and *SMAD4* mutations were found in MAP CRCs less frequently (21–60 and 0–26%, respectively). These were not predominantly G > T changes.[114,115]

In contrast to sporadic colon cancer, where physical loss of genetic material is the main characteristic, MAP CRCs are often near-diploid (52–92%) [114,117] and commonly

contain chromosomal regions of copy-neutral loss of heterozygosity (LOH) (71%) [117]. In contrast, another study found aneuploidy in 80% of MAP-adenomas,[118] although another study did not.[119] One possible explanation for the difference is that different technical platforms were used.[117]

Several studies investigated microsatellite instability (MSI) in MAP cancers. Two small studies found MSI-high phenotypes in 33 and 16% of patients (1/3 and 1/6 MAP CRCs, respectively) [54,75] and suggested an MSI pathway (by inactivation of MLH1) in some MAP CRCs. Others found the MSI-high phenotype in a minority of cancers (0–18%, mean: 4%, 3/77). [67,78,81,115] One study found that CRCs of mono-and biallelic *MUTYH* carriers are more often MSI-low than sporadic CRCs (23.5% vs. 9%). However, only one carcinoma (6%, 1/17) was characterized as MSI-high.[67] Although the MSI pathway does not appear a common pathway in MAP tumors, we recently found that MAP CRCs show some histological similarities to cancers characterized by MSI (Lynch syndrome or sporadic MSI-high). A preferential proximal location was found in 69% (40/58), (meta) synchronous tumors in 23% (10/44), a high rate of mucinous histotype in 21% (9/42), and high frequency of tumor infiltrating lymphocytes (TILs) in 74% (marked in 17%)[115] (see Fig. 2 for examples of MAP carcinomas). A frequent proximal location, metachronous CRC and high numbers of TILs in comparison to sporadic CRCs were also shown by others.[67,114]

Previously, MUTYH nuclear immunohistochemistry (IHC) staining was shown to discriminate between MUTYH-proficient and MUTYH-deficient carcinomas.[120] However, others were not able to replicate these results and concluded that MUTYH IHC is not a feasible technique to discriminate *MUTYH*-associated CRCs from sporadic CRCs.[81,121]

In conclusion, a *KRAS* hotspot mutation (c.34G>T in codon 12) is present in 64% of MAP CRCs and, less frequently, G > T transversions are found in the *APC* gene. Since G > T transversions are found predominantly in genes mutated in early tumor development (*KRAS* and *APC*), but not in *P53* and *SMAD4* (implicated in tumor progression), this finding might indicate a predominant MUTYH effect in early carcinogenesis. Furthermore, MAP CRCs have some specific molecular and histological features that differentiate them from sporadic CRCs, and show overlap with MSI-high and Lynch syndrome CRCs, such as a preferential proximal location, mucinous histotype and increased presence of TILs. These features should direct the pathologist towards a MAP etiology of CRC as an alternative cause of deficient mismatch repair, especially when diagnosed at a young age and in combination with polyps and/or a recessive inheritance pattern. *KRAS* analysis can be implemented as a pre-screening test that helps select patients with CRC who are eligible for *MUTYH* mutation screening.[66]

6.2. Adenomas, hyperplastic polyps and sessile serrated adenoma

MAP patients can present with conventional adenomas as well as serrated adenomas, hyperplastic polyps and mixed (hyperplastic and adenomatous) polyps.[62,73,80,81,103,122] In 47% (8/17) of MAP patients 1 or more hyperplastic polyps and/or sessile serrated adenoma (SSAs) were found. Three of these patients fulfilled the criteria for the hyperplastic polyposis syndrome.[80]

Mutations in *KRAS* are present in 18–23% of MAP adenomas.[80,123] Similar to *MUTYH*-associated carcinomas, the hotspot mutation is a c.34G>T transversion in codon 12. This mutation was found in 100% of MAP adenomas with a *KRAS* mutation compared to only 13% of *KRAS* mutations in sporadic adenomas. [23] Another research group also found exclusively G:C to T:A transversions in MAP adenomas, although the proportion of c.34G>T transversions was not mentioned.[80] The frequency of *KRAS* mutation increases with the degree of dysplasia, villous content and size.[123] *APC* mutations are found in 41% of MAP adenomas and comprise exclusively G:C to T:A transversions [80]. No G:C to T:A transversions in *APC* were found in sporadic adenomas in this study.[80] In *MUTYH*-associated HPs and SSAs, no *APC* mutations were found, but KRAS mutations in codon 12 were present in 70% of patients (51/73); 94% of mutations comprised G:C to T:A transversions. In the control group, *KRAS* mutations were present in only 17% (7/41) of patients and no *APC* mutations were present. The authors concluded that HPs and SSAs are a common finding in patients with MAP and are causally related to biallelic *MUTYH* mutations. They subsequently suggested the existence of two distinct pathways, one leading to conventional adenomas with *APC* and/or *KRAS* mutations and one separate non-*APC* route leading to HPs and SSAs with *KRAS* mutations.[80.] Another study found *MUTYH* biallelic mutations in 1 out of 38 patients with hyperplastic polyposis syndrome,[73] suggesting that this gene should be considered in individuals with both adenomatous and hyperplastic polyposis. Further investigation is necessary to evaluate the prevalence of *MUTYH* mutations in patients with hyperplastic polyposis syndrome.

6.3. Somatic MUTYH mutations

Somatic inactivation of *MUTYH* in CRC is reported by one group (2 out of 48 sporadic CRC cases)[124] but not by others.[47,63,64] It does not seem to be a frequent occurrence in CRC. One study found somatic *MUTYH* mutations in both alleles of 2 out of 95 sporadic gastric cancer cases.[125] A recent study found that the nuclear expression of MUTYH was attenuated in the mucosa of ulcerative colitis (UC)-associated neoplasia and UC without neoplasms compared to mucosa unaffected by UC. No pathological *MUTYH* mutations were detected in any of the UC-associated neoplasia cases.[126]

7. HETEROZYGOUS MUTYH MUTATIONS AND CRC

There has been much debate regarding whether monoallelic (heterozygous) mutation carriers also have a higher risk for developing colorectal cancer, possibly at a later age. The carrier rate for *MUTYH* monoallelic mutations in controls is 1.5–2.0% for all mutations [67] [Farrington InSiGHT] and, more specifically, 1.1–1.6% for p.G396D, 0.4–0.6% for p.Y179C, [Farrington InSiGHT] and less than 0.1% for other mutations.[67] The risk for CRC in these *MUTYH* heterozygotes would arise from a second somatic hit in *MUTYH*, leading to BER-defective cells that would consequently acquire additional somatic mutations in genes, such as *APC* and *KRAS*. These somatic mutations could, in turn, induce tumorigenesis.

7.1. Case–control studies

Seventeen case–control studies addressing this question have been performed to date.[47–49,58–61,63,65,67,71,75,76,78,127–129] The majority of studies found a small overrepresentation of *MUTYH* heterozygotes in CRC cases with odds ratios between 0.78 and 4.7, although independent statistical significance was reached in only three.[58,59,71] Among CRC patients under age 50 or patients with familial CRC and/or less than 10 polyps no [49,60] or only a slight overrepresentation of heterozygotes is seen.[60,69,72]

To achieve more statistical power, several meta-analyses have been performed, with ORs or RRs between 1.11 and 1.27.[61,127,130] Of these, only one reached (borderline) statistical significance (OR 1.27; 95% CI 1.01–1.61).[130] There are several possible biases in these studies. One possible weak point in a number of these studies is that genetic screening was limited to the two common mutations (p.Y179D and p.G396D) or a subset of mutations in most studies. In a recent study, the entire *MUTYH* gene was screened and a significant odds ratio of 1.48 (95% CI.1.02–2.16) was found.[67] If screening had been limited to the two common mutations, the authors state that they would have failed to detect a significant increase (including only p.G396D and p.Y179C; RR 1.45; 95% CI 0.95–2.3). The authors also speculated that the less common variants may be more penetrant than the two common mutations. The mutational spectrum of MAP patients might not be completely representative of the unselected CRC patient spectrum.[67] Therefore, restricted genotyping for the most common mutations in MAP patients might lead to an underestimation of the risk for CRC in *MUTYH* heterozygotes. By contrast, the OR might also be overestimated when no or limited additional screening was performed because p.Y179C or p.G396D heterozygotes will be compound heterozygotes.[61,127] For example, in two studies additional rare *MUTYH* variants were found in p.Y179C and p.G396D heterozygotes.[48,59]

Stratification by mutations or age might be needed to find a significant effect of *MUTYH* heterozygotic mutations (with correction for multiple testing). Two studies found a lower OR in p.G396D carriers (1.1 and 1.3) than in p.Y179C carriers (1.24 and 2.1), although these numbers did not reach significance.[48,58] A large case–control study showed a significant relative risk after stratification for age: a risk ratio of 1.68 (95% CI of 1.07–2.95) for CRC in *MUTYH* heterozygous carriers aged >55 years.[59] This result was not confirmed by Webb *et al.,*[127] who stratified 10-year age bands in a large case–control study and found no evidence for a relationship between cancer risk and age.

One small study suggested an association of the p.Q338H polymorphism with colorectal cancer susceptibility in patients with no smoking history (adjusted OR 4.08, p = 0.022). [131] Recently a significantly increased risk for rectal carcinoma (but not for colon) was found for p.Q338H homozygotes (OR:1,52, 95% CI:1.06–2.17) in a Swedish cohort (1785 cases and 1722 controls).[132] Previously, the same research group reported in a smaller cohort (412 CRC cases and 188 controls) no evidence of an increased colorectal cancer risk for p.Q338H homo-or heterozygotes.[76] This research group also noted that three (until that time unreported) variants at codon 437 (previously codon 423) were found to be overrepresented in CRC cases compared to healthy controls (5/447 vs. 0/478, p = 0.02, Chi-square test). The pathological relevance of variants at this codon needs to be further studied. Another study demonstrated an increased CRC risk for the c.IVS1+11T *MUTYH* variant (OR 1.43, p = 0.042) and a specific haplotype containing, amongst others, the c.IVS1+11T and p.Q338H variants (OR 1.43, p = 0.046.[133]

7.2. Family studies

Another strategy to examine whether *MUTYH* heterozygotes have an increased CRC risk is to study family members of MAP patients. One research group found a twofold significant increase in the incidence of colorectal cancer in 347-obligate *MUTYH*-heterozygous parents compared to the general population (standardized incidence ratio (SIR), 2.12). Their colorectal cancer mortality was not significantly increased (standardized mortality ratio (SMR), 1.02), nor was overall cancer risk (SIR 0.92), cancer mortality (SMR 1.12) or overall mortality (SMR 0.94).[87] Another research group used a kin-cohort design to estimate CRC risk among 300 first-degree relatives of 39 CRC cases with either monoallelic or biallelic *MUTYH* mutations. An approximately threefold increased risk was found among monoallelic carriers, which was significant in persons aged >55 years and non-significant in persons aged >55 years.[134] A similar kin-cohort approach was used by two other large research groups. A somewhat – though non-significant – higher CRC prevalence (ratios of around 1.7) was found for first-degree relatives of *MUTYH* mutation carriers compared to CRC controls.[78,127]

7.3. Somatic inactivation of the wild-type MUTYH allele?

A possible mechanism underlying CRC in *MUTYH* heterozygotes might be somatic inactivation of the wild-type *MUTYH* allele through loss of heterozygosity (LOH) at chromosome 1 (corresponding to the chromosomal location of *MUTYH*). LOH of this region was found in 8 (47%) of 17 colorectal tumors from monoallelic *MUTYH* gene mutation carriers but in only 2 (20%) of 10 sporadic colorectal tumors.[48] This argument was disputed by others because LOH at chromosome 1p in tumors is highly variable and subject to confounding.[135] In seven adenomas from a heterozygous p.G396D mutation carrier two somatic *APC* changes were found; neither change was a G:C > T:A transversion, thus providing no evidence of defective MUTYH activity.[62] Another study showed a significant positive correlation between the presence of monoallelic germ-line *MUTYH* variants and G:C > T:A transversions in *KRAS* or *APC* and 1p LOH. They suggest that single germ-line *MUTYH* variants may influence genetic pathways in CRC.[65]

In conclusion, the risk of CRC among *MUTYH* heterozygotes in the population seems to be only marginally increased and present data do not justify colonoscopic screening in heterozygous *MUTYH* carriers. For heterozygous relatives of MAP patients available data suggest that such individuals have a two or at most threefold increase in their risk of CRC at an age similar to that in the general population and thus are expected to benefit from population screening measures or could be offered average moderate-risk colorectal screening based on their family history. Furthermore, heterozygotes do not seem to have an increased overall risk of cancer.

8. SYNERGY BETWEEN MUTYH AND THE MISMATCH REPAIR SYSTEM

The occurrence of sebaceous gland tumors and other Lynch syndrome-associated tumors (ovarian, bladder and endometrial) in MAP patients points to a phenotypic overlap with Lynch syndrome.

In Lynch syndrome patients with proven pathogenic MMR mutations (mainly *MLH1* and *MSH2*), no overrepresentation of mono-or biallelic *MUTYH* mutations has been found,[49,136] arguing against a modifying effect of *MUTYH*. Furthermore, in CRC families without mismatch repair mutations (Amsterdam positive HNPCC families or HNPCC-like families), few *MUTYH* biallelics have been found (0–1.3%).[77,136–139]

8.1. Association MUTYH and MSH6

On a molecular level, *MUTYH* has been shown to be physically associated with the MSH2/MSH6 complex via the MSH6 subunit. The MSH6 binding site is mapped to a conserved region in the *MUTYH* gene and the binding and glycosylase activities of MUTYH are enhanced by the MSH2/MSH6 complex.[17] Moreover, the MSH2/MSH6 complex can also bind DNA duplexes containing oxoG:A mispairs [140,141] and overexpression of the MSH2/MSH6 complex significantly decreased the rate of G:C > T:A transversions in MUTYH mutant E. coli cells.[142] Based on this interaction, it was hypothesized that both genes act cooperatively to confer an increased CRC risk. Indeed, patients with a mild *MSH6* missense mutation had an *MUTYH* monoallelic mutation more frequently than controls, suggesting a contribution to adenomas and/or CRC development.[143]

In addition, mutations in MSH6 were also more frequently found in heterozygote *MUTYH* CRC patients than in control CRC patients (11.5% vs. 0%).[144] However, a different study did not find overrepresentation of *MUTYH* heterozygotes among MSH6 missense carriers.[145]

On the other hand, abrogation of both *MSH6* DNA mismatch repair and base repair might be mutually exclusive, as we previously showed in a patient with compound heterozygous *MUTYH* mutations and a pathogenic *MSH6* germ-line mutation. This patient had an extremely mild clinical phenotype with only a few adenomas at age 56 years. No second hit of *MSH6* was apparent in any of the adenomas, due to retained MSH6 nuclear expression and a lack of microsatellite instability.[146]

For now it seems that biallelic or monoallelic germ-line mutations of *MUTYH* are unlikely to play a significant role in Lynch syndrome, HNPCC and HNPCC-like patients. It remains to be determined whether interaction between MUTYH and MSH6 contributes to the cause of polyps and/or CRC. Previously, the p.G396D and p.Y179C *MUTYH* mutations were not found in *APC*-positive FAP patients, suggesting that mutations in *MUTYH* do not play a modifying role in *APC*-driven FAP either.[147]

9. OTHER GENES INVOLVED IN BASE EXCISION REPAIR (BER) MACHINERY

A number of other enzymes (OGG1, NTH1, NUDT1, NEIL1, 2 and 3) are involved in BER and oxidative DNA damage and represent candidate predisposition genes for colorectal carcinoma and polyposis.[148,149] Until now however, no clear association between pathogenic mutations in these associated genes and CRC development has been found, also not in combination with mutations in *MUTYH*.[3,62,64,129,139,150,151]

In a review on *OGG1*, it was concluded that although functional and epidemiological studies indicated identified polymorphisms in *OGG1*, particularly S326C, may play a role in 8-OHdG-induced carcinogenesis, much remains unknown and the literature is not consistent.[152]

10. CONCLUSIONS

Most biallelic *MUTYH* patients described to date developed between 10 and 500 polyps. In addition, a number of MAP patients have been described with CRC and none or only a few polyps. The CRC risk in MAP patients is about 43% at age 60 and the life-time risk is assumed to be close to 100% in the absence of timely surveillance. The lifetime risk for duodenal cancer is about 4% and a significantly increased incidence has been shown for ovarian, bladder and skin cancers (SIR 5.7, SIR 7.2 and SIR2.8). Lynch syndrome-associated sebaceous gland tumors are found in about 2% of the population. There seems to be a consensus in the literature to suggest surveillance in MAP patients, according to attenuated familial adenomatous polyposis (AFAP) protocols. Colonic surveillance should start at age 18–20 years and gastroduodenal surveillance at age 25–30 years. The spectrum and age of presentation of extraintestinal tumors does not support other forms of screening at the moment.

Adenomas as well as hyperplastic polyps can be present in MAP patients. CRCs are often right-sided and multiple at presentation. MSI is present in a minority of CRCs and CRCs are often diploid. A relatively high number of TILs are present, indicating an activated immune response, which might explain better survival in MAP CRC patients compared to sporadic CRC cases. There seems to be an overlap between the *MUTYH* phenotype and Lynch syndrome phenotype with regard to tumor spectrum, histological characteristics and molecular biology.

The CRC risk for *MUTYH* heterozygotes, regardless of significance is only marginally increased in population-based studies (OR 1.1–1.2 in meta-analyses), although the risk in heterozygote family members is higher (OR 2–3). Also, no clear overrepresentation of *MUTYH* mutations (mono-or biallelic) has been shown in CRC families without MMR mutations (HNPCC or HNPCC-like). In any case, the potential increased risk and age at presentation in *MUTYH* CRC heterozygotes do not justify screening other than population-based screening.

Table 1. Percentage of *MUTYH* biallelics according to the number of polyps and CRC in *APC*- and MRR-negative patients.
Cumulating data from all published clinical *MUTYH* studies (see section 4 of this review for references). *AFAP as defined by Nielsen et al.[55]

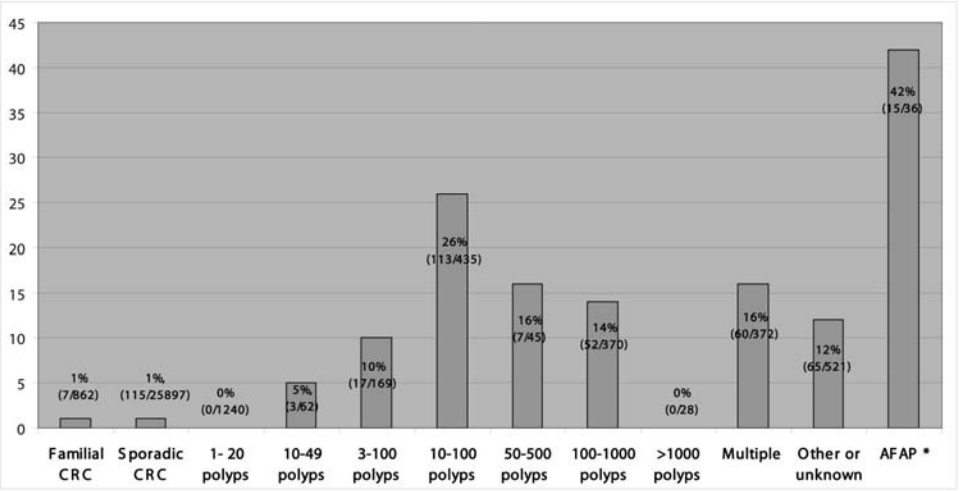


Table 2 Percentage of *MUTYH* biallelics in CRC patients according to age. Cumulating data from eight studies. [49;54;58;59;63;69;72;78]

polyps / age	CRC with or without polyps
<50 years	1.1% (29/2605) Range 0.8-6.2%
>50 years	0.3% (28/11150) Range 0.0-0.6%*

Figure 1. Three-component system of 8-oxoG repair.
Based on figure from [12].The *MUTYH* protein recognizes 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 excises the 8-oxoG from the 8-oxoG:C base-pair (a). MTH1 (also known as NUDT1) works separately and cleanses the cellular nucleotide pool of oxidized guanine precursors (d°GTP), which prevents incorporation of 8-oxo G in the DNA (b). The three-component 'base excision repair' mechanism thereby prevents the incorporation of d°GTP in the DNA and thus eliminates G:C>T:A and A:T>C:G transversions.

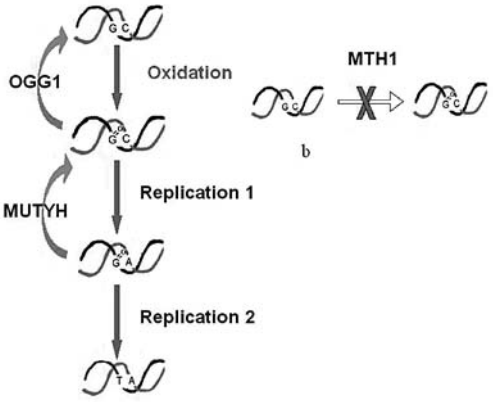
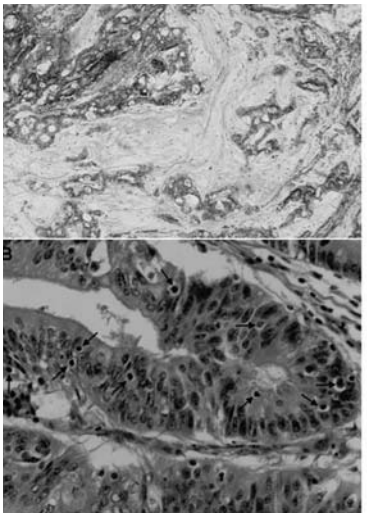


Figure 2A and B



References

1 Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996;87:159–70.

2 Gilbertsen VA. Proctosigmoidoscopy and polypectomy in reducing the incidence of rectal cancer. Cancer 1973;34(Suppl. 9).

3 Al Tassan N, Chmiel NH, Maynard J, *et al*. Inherited variants of MYH associated with somatic G:C →T:A mutations in colorectal tumors. Nat Genet 2002;30:227–32.

4 Jass JR. Colorectal polyposes: from phenotype to diagnosis. Pathol Res Pract 2008;204:431–47.

5 Nghiem Y, Cabrera M, Cupples CG, Miller JH. The mutY gene: a mutator locus in Escherichia coli that generates G.C→T.A transversions. Proc Natl Acad Sci USA 1988;85:2709–13.

6 Yeh YC, Chang DY, Masin J, Lu AL. Two nicking enzyme systems specific for mismatch-containing DNA in nuclear extracts from human cells. J Biol Chem 1991;266:6480–4.

7 Shibutani S, Takeshita M, Grollman AP. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. Nature 1991;349:431–4.

8 Michaels ML, Miller JH. The GO system protects organisms from the mutagenic effect of the spontaneous lesion 8-hydroxyguanine (7,8dihydro-8-oxoguanine). J Bacteriol 1992;174:6321–5. [9] Boiteux S, Radicella JP. The human OGG1 gene: structure, functions, and its implication in the process of carcinogenesis. Arch Biochem Biophys 2000;377:1–8.

10 Slupska MM, Luther WM, Chiang JH, Yang H, Miller JH. Functional expression of hMYH, a human homolog of the Escherichia coli MutY protein. J Bacteriol 1999;181:6210–3.

11 Guan Y, Manuel RC, Arvai AS, *et al*. MutY catalytic core, mutant and bound adenine structures define specificity for DNA repair enzyme superfamily. Nat Struct Biol 1998;5:1058–64.

12 Fromme JC, Banerjee A, Huang SJ, Verdine GL. Structural basis for removal of adenine mispaired with 8-oxoguanine by MutY adenine DNA glycosylase. Nature 2004;427:652–6.

13 Noll DM, Gogos A, Granek JA, Clarke ND. The C-terminal domain of the adenine-DNA glycosylase MutY confers specificity for 8oxoguanine.adenine mispairs and may have evolved from MutT, an 8-oxo-dGTPase. Biochemistry 1999;38:6374–9.

14 Chmiel NH, Livingston AL, David SS. Insight into the functional consequences of inherited variants of the hMYH adenine glycosylase associated with colorectal cancer: complementation assays with hMYH variants and pre-steady-state kinetics of the corresponding mutated E. coli enzymes. J Mol Biol 2003;327:431–43.

15 Volk DE, House PG, Thiviyanathan V, *et al*. Structural similarities between MutT and the C-terminal domain of MutY. Biochemistry 2000;39:7331–6.

16 Parker A, Gu Y, Mahoney W, Lee SH, Singh KK, Lu AL. Human homolog of the MutY repair protein (hMYH) physically interacts with proteins involved in long patch DNA base excision repair. J Biol Chem 2001;276:5547–55.

17 Gu Y, Parker A, Wilson TM, Bai H, Chang DY, Lu AL. Human MutY homolog, a DNA glycosylase involved in base excision repair, physically and functionally interacts with mismatch repair proteins human MutS homolog 2/human MutS homolog 6. J Biol Chem 2002;277:11135–42.

18 Xie Y, Yang H, Miller JH, *et al*. Cells deficient in oxidative DNA damage repair genes Myh and Ogg1 are sensitive to oxidants with increased G2/M arrest and multinucleation. Carcinogenesis 2008;29:722–8.

19 Nielsen M, Joerink-van de Beld MC, Jones N, *et al*. Analysis of *MUTYH* genotypes and colorectal phenotypes in patients With *MUTYH*-associated polyposis. Gastroenterology 2009;136: 471–6.

20 Kim DW, Kim IJ, Kang HC, *et al*. Germline mutations of the MYH gene in Korean patients with multiple colorectal adenomas. Int J Colorectal Dis 2007;22:1173–8.

21 Kim H, Kim HJ, Chi SG, *et al*. Absence of MutY homologue mutation in patients with multiple sporadic adenomatous polyps in Korea. World J Gastroenterol 2006;12:951–5.

22 Yanaru-Fujisawa R, Matsumoto T, Ushijima Y, *et al*. Genomic and functional analyses of *MUTYH* in Japanese patients with adenomatous polyposis. Clin Genet 2008;73:545–53.

23 Miyaki M, Iijima T, Yamaguchi T, *et al*. Germline mutations of the MYH gene in Japanese patients with multiple colorectal adenomas. Mutat Res 2005;578:430–3.

24 Peterlongo P, Mitra N, Sanchez de AA, *et al*. Increased frequency of disease-causing MYH mutations in colon cancer families. Carcinogenesis 2006;27:2243–9.

25 Nielsen M, Franken PF, Reinards TH, *et al*. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet 2005;42:e54.

26 Gismondi V, Meta M, Bonelli L, *et al*. Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MYH gene in Please cite this article in press as: Nielsen M, *et al*. *MUTYH*-associated polyposis (MAP). Crit Rev Oncol/Hematol (2010), doi:10.1016/j.critrevonc.2010.05.011 M. Nielsen *et al*. / Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx Italian patients with adenomatous polyposis coli and colorectal adenomas. Int J Cancer 2004;109:680–4.

27 Dolwani S, Williams GT, West KP, *et al*. Analysis of inherited MYH/(*MUTYH*) mutations in British Asian patients with colorectal cancer. Gut 2007;56:593.

28 Gomez-Fernandez N, Castellvi-Bel S, Fernandez-Rozadilla C, *et al*. Molecular analysis of the *APC* and *MUTYH* genes in Galician and Catalonian FAP families: a different spectrum of mutations? BMC Med Genet 2009;10:57.

29 Kim JC, Ka IH, Lee YM, *et al*. MYH, OGG1, MTH1, and *APC* alterations involved in the colorectal tumorigenesis of Korean patients with multiple adenomas. Virchows Arch 2007;450:311–9.

30 Livingston AL, Kundu S, Henderson PM, Anderson DW, David SS. Insight into the roles of tyrosine 82 and glycine 253 in the Escherichia coli adenine glycosylase MutY. Biochemistry 2005;44: 14179–90.

31 Wooden SH, Bassett HM, Wood TG, McCullough AK. Identification of critical residues required for the mutation avoidance function of human MutY (hMYH) and implications in colorectal cancer. Cancer Lett 2004;205:89–95. [32] Pope MA, Chmiel NH, David SS. Insight into the functional consequences of hMYH variants associated with colorectal cancer: distinct differences in the adenine glycosylase activity and the response to AP endonucleases of Y150C and G365D murine MYH. DNA Repair (Amst) 2005;4:315–25.

33 Ali M, Kim H, Cleary S, Cupples C, Gallinger S, Bristow R. Characterization of mutant *MUTYH* proteins associated with familial colorectal cancer. Gastroenterology 2008;135:499–507.

34 Parker AR, Sieber OM, Shi C, *et al*. Cells with pathogenic biallelic mutations in the human *MUTYH* gene are defective in DNA damage binding and repair. Carcinogenesis 2005;26:2010–8.

35 Francis AW, David SS. Escherichia coli MutY and Fpg utilize a processive mechanism for target location. Biochemistry 2003;42: 801–10.

36 Tominaga Y, Ushijima Y, Tsuchimoto D, *et al*. *MUTYH* prevents OGG1 or APEX1 from inappropriately processing its substrate or reaction product with its C-terminal domain. Nucleic Acids Res 2004;32:3198–211.

37 Kundu S, Brinkmeyer MK, Livingston AL, David SS. Adenine removal activity and bacterial complementation with the human MutY homologue (*MUTYH*) and Y165C, G382D, P391L and Q324R variants associated with colorectal cancer. DNA Repair (Amst) 2009;8:1400–10.

38 Molatore S, Russo MT, D'Agostino VG, *et al*. *MUTYH* mutations associated with familial adenomatous polyposis: functional characterization by a mammalian cell-based assay. Hum Mutat 2010;31(2):159–66.

39 Bai H, Jones S, Guan X, *et al*. Functional characterization of two human MutY homolog (hMYH) missense mutations (R227W and V232F) that lie within the putative hMSH6 binding domain and are associated with hMYH polyposis. Nucleic Acids Res 2005;33:597–604.

40 Bai H, Grist S, Gardner J, Suthers G, Wilson TM, Lu AL. Functional characterization of human MutY homolog (hMYH) missense mutation (R231L) that is linked with hMYH-associated polyposis. Cancer Lett 2007;250:74–81.

41 Alhopuro P, Parker AR, Lehtonen R, *et al*. A novel functionally deficient MYH variant in individuals with colorectal adenomatous polyposis. Hum Mutat 2005;26:393.

42 Tao H, Shinmura K, Hanaoka T, *et al*. A novel splice-site variant of the base excision repair gene MYH is associated with production of an aberrant mRNA transcript encoding a truncated MYH protein not localized in the nucleus. Carcinogenesis 2004;25:1859–66.

43 Shinmura K, Yamaguchi S, Saitoh T, *et al*. Adenine excisional repair function of MYH protein on the adenine:8-hydroxyguanine base pair in double-stranded DNA. Nucleic Acids Res 2000;28: 4912–8.

44 Guillen-Ponce C, Castillejo A, Barbera VM, *et al*. Biallelic MYH germline mutations as cause of Muir-Torre syndrome. Fam Cancer 2010;9(2):151–4.

45 Croitoru ME, Cleary SP, Berk T, *et al*. Germline MYH mutations in a clinic-based series of Canadian multiple colorectal adenoma patients. J Surg Oncol 2007;95:499–506.

46 Sulova M, Zidkova K, Kleibl Z, *et al*. Mutation analysis of the MYH gene in unrelated Czech *APC* mutation-negative polyposis patients. Eur J Cancer 2007;43:1617–21.

47 Enholm S, Hienonen T, Suomalainen A, *et al*. Proportion and phenotype of MYH-associated colorectal neoplasia in a population-based series of Finnish colorectal cancer patients. Am J Pathol 2003;163:827–32.

48 Croitoru ME, Cleary SP, Di Nicola N, *et al*. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J Natl Cancer Inst 2004;96:1631–4.

49 Wang L, Baudhuin LM, Boardman LA, *et al*. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. Gastroenterology 2004;127:9–16.

50 Russell AM, Zhang J, Luz J, *et al*. Prevalence of MYH germline mutations in Swiss *APC* mutation-negative polyposis patients. Int J Cancer 2006;118:1937–40.

51 Ponti G, Venesio T, Losi L, *et al*. BRAF mutations in multiple sebaceous hyperplasias of patients belonging to MYH-associated polyposis pedigrees. J Invest Dermatol 2007;127:1387–91.

52 Lejeune S, Guillemot F, Triboulet JP, *et al*. Low frequency of AXIN2 mutations and high frequency of *MUTYH* mutations in patients with multiple polyposis. Hum Mutat 2006;27:1064.

53 enesio T, Molatore S, Cattaneo F, Arrigoni A, Risio M, Ranzani GN. High frequency of MYH gene mutations in a subset of patients with familial adenomatous polyposis. Gastroenterology 2004;126:1681–5.

54 Lefevre JH, Rodrigue CM, Mourra N, *et al*. Implication of MYH in colorectal polyposis. Ann Surg 2006;244:874–9.

55 Nielsen M, Hes FJ, Nagengast FM, *et al*. Germline mutations in *APC* and *MUTYH* are responsible for the majority of families with attenuated familial adenomatous polyposis (AFAP). Clin Genet 2007;71:427–33.

56 Aretz S, Uhlhaas S, Goergens H, *et al*. *MUTYH*-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 2006;119:807–14.

57 Sampson JR, Dolwani S, Jones S, *et al*. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. Lancet 2003;362:39–41.

58 Balaguer F, Castellvi-Bel S, Castells A, *et al*. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case–control, population-based study. Clin Gastroenterol Hepatol 2007;5:379–87.

59 Farrington SM, Tenesa A, Barnetson R, *et al*. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 2005;77:112–9.

60 Grunhage F, Jungck M, Lamberti C, *et al*. Contribution of common monoallelic *MUTYH* gene variants in German patients with familial colorectal cancer. Cancer Biomark 2008;4:55–61.

61 Avezzu A, Agostini M, Pucciarelli S, *et al*. The role of MYH gene in genetic predisposition to colorectal cancer: another piece of the puzzle. Cancer Lett 2008;268:308–13.

62 Sieber OM, Lipton L, Crabtree M, *et al*. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003;348:791–9.

63 Fleischmann C, Peto J, Cheadle J, Shah B, Sampson J, Houlston RS. Comprehensive analysis of the contribution of germline MYH variation to early-onset colorectal cancer. Int J Cancer 2004;109:554–8.

64 Halford SE, Rowan AJ, Lipton L, *et al*. Germline mutations but not somatic changes at the MYH locus contribute to the pathogenesis of unselected colorectal cancers. Am J Pathol 2003;162:1545–8.

65 Kambara T, Whitehall VL, Spring KJ, *et al*. Role of inherited defects of MYH in the development of sporadic colorectal cancer. Genes Chromosomes Cancer 2004;40:1–9. Please cite this article in press as: Nielsen M, *et al*. *MUTYH*-associated polyposis (MAP). Crit Rev Oncol/Hematol (2010), doi:10.1016/j.critrevonc.2010.05.011 M. Nielsen *et al*. / Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx

66 Van Puijenbroek M, Nielsen M, Tops CM, *et al*. Identification of patients with (atypical) *MUTYH*-associated polyposis by *KRAS2* c.34G>T prescreening followed by *MUTYH* Hotspot analysis in formalin-fixed paraffin-embedded tissue. Clin Cancer Res 2008;14:139–42.

67 Cleary SP, Cotterchio M, Jenkins MA, *et al*. Germline MutY human homologue mutations and colorectal cancer: a multisite case–control study. Gastroenterology 2009;136:1251–60.

68 de Ferro SM, Suspiro A, Fidalgo P, *et al*. Aggressive phenotype of MYH-associated polyposis with jejunal cancer and intra-abdominal desmoid tumor: report of a case. Dis Colon Rectum 2009;52: 742–5.

69 Jo WS, Bandipalliam P, Shannon KM, *et al*. Correlation of polyp number and family history of colon cancer with germline MYH mutations. Clin Gastroenterol Hepatol 2005;3:1022–8.

70 De Rosa M, Dourisboure RJ, Morelli G, *et al*. First genotype characterization of Argentinean FAP patients: identification of 14 novel *APC* mutations. Hum Mutat 2004;23:523–4.

71 Peterlongo P, Mitra N, Chuai S, *et al*. Colorectal cancer risk in individuals with biallelic or monoallelic mutations of MYH. Int J Cancer 2005;114:505–7.

72 Riegert-Johnson DL, Johnson RA, Rabe KG, *et al*. The value of *MUTYH* testing in patients with early onset microsatellite stable colorectal cancer referred for hereditary nonpolyposis colon cancer syndrome testing. Genet Test 2007;11:361–5.

73 Chow E, Lipton L, Lynch E, *et al*. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30–9.

74 Isidro G, Laranjeira F, Pires A, *et al*. Germline *MUTYH* (MYH) mutations in Portuguese individuals with multiple colorectal adenomas. Hum Mutat 2004;24:353–4.

75 Colebatch A, Hitchins M, Williams R, Meagher A, Hawkins NJ, Ward RL. The role of MYH and microsatellite instability in the development of sporadic colorectal cancer. Br J Cancer 2006;95:1239–43.

76 Zhou XL, Djureinovic T, Werelius B, Lindmark G, Sun XF, Lindblom A. Germline mutations in the MYH gene in Swedish familial and sporadic colorectal cancer. Genet Test 2005;9:147–51.

77 Stormorken A, Heintz K, Andresen PA, Møller P. *MUTYH* mutations do not cause HNPCC or late onset familial colorectal cancer. Hered Cancer Clin Pract 2006;4:90–3.

78 Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with *MUTYH* mutation. J Clin Oncol 2009;27:3975–80.

79 Vasen HF, Moslein G, Alonso A, *et al*. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704–13.

80 Boparai KS, Dekker E, Eeden van S, *et al*. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis (Map). Gastroenterology 2008;135(6):2014–8.

81 O'Shea AM, Cleary SP, Croitoru MA, *et al*. Pathological features of colorectal carcinomas in MYH-associated polyposis. Histopathology 2008;53(2):184–94.

82 Sankila R, Aaltonen LA, Jarvinen HJ, Mecklin JP. Better survival rates in patients with MLH1-associated hereditary colorectal cancer. Gastroenterology 1996;110:682–7.

83 Stigliano V, Assisi D, Cosimelli M, *et al*. Survival of hereditary non-polyposis colorectal cancer patients compared with sporadic colorectal cancer patients. J Exp Clin Cancer Res 2008;27:39.

84 Dierssen JW, de Miranda NF, Ferrone S, *et al*. HNPCC versus sporadic microsatellite-unstable colon cancers follow different routes toward loss of HLA class I expression. BMC Cancer 2007;7:33.

85 Kloor M, Becker C, Benner A, *et al*. Immunoselective pressure and human leukocyte antigen class I antigen machinery defects in microsatellite unstable colorectal cancers. Cancer Res 2005;65:6418–24.

86 de Miranda NF, Nielsen M, Pereira D, *et al*. *MUTYH*-associated polyposis carcinomas frequently lose HLA class I expression-a common event amongst DNA-repair-deficient colorectal cancers. J Pathol 2009;219(1):69–76.

87 Jones N, Vogt S, Nielsen M, *et al*. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in *MUTYH*. Gastroenterology 2009;137:489–94.

88 Casper M, Plotz G, Juengling B, Trojan J, Lammert F, Raedle J. Adenoma development in a patient with *MUTYH*-associated polyposis (MAP): new insights into the natural course of polyp development. Dig Dis Sci 2010;55(6):1711–5.

89 Nielsen M, Hes FJ, Vasen HF, Van Den Hout WB. Cost-utility analysis of genetic screening in families of patients with germline *MUTYH* mutations. BMC Med Genet 2007;8:42.

90 Sakamoto K, Tominaga Y, Yamauchi K, *et al*. *MUTYH*-null mice are susceptible to spontaneous and oxidative stress induced intestinal tumorigenesis. Cancer Res 2007;67:6599–604.

91 Sieber OM, Howarth KM, Thirlwell C, *et al*. Myh deficiency enhances intestinal tumorigenesis in multiple intestinal neoplasia (*APC*Min/+) mice. Cancer Res 2004;64:8876–81.

92 Xie Y, Yang H, Cunanan C, *et al*. Deficiencies in mouse Myh and Ogg1 result in tumor predisposition and G to T mutations in codon 12 of the K-ras oncogene in lung tumors. Cancer Res 2004;64:3096–102.

93 Vogt S, Jones N, Christian D, *et al*. Expanded extracolonic tumor spectrum in *MUTYH*-associated polyposis. Gastroenterology 2009;137:1976–85.

94 Buecher B, Baert-Desurmont S, Leborgne J, Humeau B, Olschwang S, Frebourg T. Duodenal adenocarcinoma and Mut Y human homologue-associated polyposis. Eur J Gastroenterol Hepatol 2008;20:1024–7.

95 Zhang Y, Liu X, Fan Y, *et al*. Germline mutations and polymorphic variants in MMR, E-cadherin and MYH genes associated with familial gastric cancer in Jiangsu of China. Int J Cancer 2006;119:2592–6.

96 Goto M, Shinmura K, Yamada H, Tsuneyoshi T, Sugimura H. OGG1, MYH and MTH1 gene variants identified in gastric cancer patients exhibiting both 8-hydroxy-2'-deoxyguanosine accumulation and low inflammatory cell infiltration in their gastric mucosa. J Genet 2008;87:181–6.

97 Tricarico R, Bet P, Ciambotti B, *et al*. Endometrial cancer and somatic G > T KRAS transversion in patients with constitutional *MUTYH* biallelic mutations. Cancer Lett 2009;274:266–70.

98 Barnetson RA, Devlin L, Miller J, *et al*. Germline mutation prevalence in the base excision repair gene, MYH, in patients with endometrial cancer. Clin Genet 2007;72:551–5.

99 Ashton KA, Proietto A, Otton G, Symonds I, Scott RJ. Genetic variants in *MUTYH* are not associated with endometrial cancer risk. Hered Cancer Clin Pract 2009;7:3.

100 Le Page F, Randrianarison V, Marot D, *et al*. BRCA1 and BRCA2 are necessary for the transcription-coupled repair of the oxidative 8-oxoguanine lesion in human cells. Cancer Res 2000;60:5548–52.

101 Zhang Y, Newcomb PA, Egan KM, *et al*. Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2006;15:353–8.

102 Beiner ME, Zhang WW, Zhang S, Gallinger S, Sun P, Narod SA. Mutations of the MYH gene do not substantially contribute to the risk of breast cancer. Breast Cancer Res Treat 2009;114:575–8.

103 Ponti G, Ponz DL, Maffei S, *et al*. Attenuated familial adenomatous polyposis and Muir–Torre syndrome linked to compound biallelic constitutional MYH gene mutations. Clin Genet 2005;68:442–7.

104 Baudhuin LM, Roberts LR, Enders FT, *et al*. MYH Y165C and G382D mutations in hepatocellular carcinoma and cholangiocarcinoma patients. J Cancer Res Clin Oncol 2006;132:159–62.

105 Akyerli CB, Ozbek U, Aydin-Sayitoglu M, Sirma S, Ozcelik T. Analysis of MYH Tyr165Cys and Gly382Asp variants in childhood leukemias. J Cancer Res Clin Oncol 2003;129:604–5.

106 Shin EJ, Chappell E, Pethe V, *et al*. MYH mutations are rare in prostate cancer. J Cancer Res Clin Oncol 2007;133:373–8.

107 Agalliu I, Kwon EM, Salinas CA, Koopmeiners JS, Ostrander EA, Stanford JL. Genetic variation in DNA repair genes and prostate can-Please cite this article in press as: Nielsen M, *et al*. *MUTYH*-associated polyposis (MAP). Crit Rev Oncol/Hematol (2010), doi:10.1016/j.critrevonc.2010.05.011 M. Nielsen *et al*. / Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx cer risk: results from a population-based study. Cancer Causes Control 2009;21:289–300.

108 Gorgens H, Muller A, Kruger S, *et al*. Analysis of the base excision repair genes MTH1, OGG1 and *MUTYH* in patients with squamous oral carcinomas. Oral Oncol 2007;43:791–5.

109 Smith LM, Sharif S, Brand R, Fink E, Lamb J, Whitcomb DC. *MUTYH* exon 7 and 13 mutations associated with colorectal cancer (MAP syndrome) are not commonly associated with sporadic pancreatic cancer. Pancreatology 2010;9:793–6.

110 Al Tassan N, Eisen T, Maynard J, *et al*. Inherited variants in MYH are unlikely to contribute to the risk of lung carcinoma. Hum Genet 2004;114:207–10.

111 Miyaishi A, Osawa K, Osawa Y, *et al*. *MUTYH* Gln324His gene polymorphism and genetic susceptibility for lung cancer in a Japanese population. J Exp Clin Cancer Res 2009;28:10.

112 jith Kumar VK, Gold JA, Mallon E, Thomas S, Hodgson SV. Sebaceous adenomas in an MYH associated polyposis patient of Indian (Gujarati) origin. Fam Cancer 2008;7:187–9.

113 Baglioni S, Melean G, Gensini F, *et al*. A kindred with MYH-associated polyposis and pilomatricomas. Am J Med Genet A 2005;134:212–4.

114 Lipton L, Halford SE, Johnson V, *et al*. Carcinogenesis in MYH-associated polyposis follows a distinct genetic pathway. Cancer Res 2003;63:7595–9.

115 Nielsen M, de Miranda NF, van PM, *et al*. Colorectal carcinomas in *MUTYH*-associated polyposis display histopathological similarities to microsatellite unstable carcinomas. BMC Cancer 2009;9: 184.

116 Andreyev HJ, Norman AR, Cunningham D, *et al*. Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. Br J Cancer 2001;85:692–6.

117 Middeldorp A, van PM, Nielsen M, *et al*. High frequency of copy-neutral LOH in *MUTYH*-associated polyposis carcinomas. J Pathol 2008;216:25–31.

118 Cardoso J, Molenaar L, de Menezes RX, *et al*. Chromosomal instability in MYH-and *APC*-mutant adenomatous polyps. Cancer Res 2006;66:2514–9.

119 Jones AM, Thirlwell C, Howarth KM, *et al*. Analysis of copy number changes suggests chromosomal instability in a minority of large colorectal adenomas. J Pathol 2007;213:249–56.

120 Di Gregorio C, Frattini M, Maffei S, *et al*. Immunohistochemical expression of MYH protein can be used to identify patients with MYH-associated polyposis. Gastroenterology 2006;131:439–44.

121 van der Post RS, Kets CM, Ligtenberg MJ, van Krieken JH, Hoogerbrugge N. Immunohistochemistry is not an accurate first step towards the molecular diagnosis of *MUTYH*-associated polyposis. Virchows Arch 2009;454:25–9.

122 Johnson V, Lipton LR, Cummings C, *et al*. Analysis of somatic molecular changes, clinicopathological features, family history, and germline mutations in colorectal cancer families: evidence for efficient diagnosis of HNPCC and for the existence of distinct groups of non-HNPCC families. J Med Genet 2005;42:756–62.

123 Jones S, Emmerson P, Maynard J, *et al*. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C– > T:A mutations. Hum Mol Genet 2002;11:2961–7.

124 Bougatef K, Marrakchi R, Kourda N, *et al*. Somatic mutation of *MUTYH* in Tunisian patients with sporadic colorectal cancer. J Clin Lab Anal 2007;21:372–4.

125 Kim CJ, Cho YG, Park CH, *et al*. Genetic alterations of the MYH gene in gastric cancer. Oncogene 2004;23:6820–2.

126 Gushima M, Hirahashi M, Matsumoto T, *et al*. Altered expression of *MUTYH* and an increase in 8-hydroxydeoxyguanosine are early events in ulcerative colitis-associated carcinogenesis. J Pathol 2009;219:77–86.

127 Webb EL, Rudd MF, Houlston RS. Colorectal cancer risk in monoallelic carriers of MYH variants. Am J Hum Genet 2006;79: 768–71.

128 Kury S, Buecher B, Robiou-du-Pont S, *et al*. The thorough screening of the *MUTYH* gene in a large French cohort of sporadic colorectal cancers. Genet Test 2007;11:373–9.

129 Schafmayer C, Buch S, Egberts JH, *et al*. Genetic investigation of DNA-repair pathway genes PMS2, MLH1, MSH2, MSH6, *MUTYH*, OGG1 and MTH1 in sporadic colon cancer. Int J Cancer 2007;121:555–8.

130 Tenesa A, Campbell H, Barnetson R, Porteous M, Dunlop M, Farrington SM. Association of *MUTYH* and colorectal cancer. Br J Cancer 2006;95:239–42.

131 Kasahara M, Osawa K, Yoshida K, *et al*. Association of *MUTYH* Gln324His and APEX1 Asp148Glu with colorectal cancer and smoking in a Japanese population. J Exp Clin Cancer Res 2008;27:49.

132 Picelli S, Zajac P, Zhou XL, *et al*. Common variants in human CRC genes as low-risk alleles. Eur J Cancer 2010;46(6):1041–8.

133 Tao H, Shinmura K, Suzuki M, *et al*. Association between genetic polymorphisms of the base excision repair gene *MUTYH* and increased colorectal cancer risk in a Japanese population. Cancer Sci 2008;99:355–60.

134 Jenkins MA, Croitoru ME, Monga N, *et al*. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 2006;15:312–4.

135 Tenesa A, Farrington SM, Dunlop MG: Re:. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. J Natl Cancer Inst 2005;97:320–1.

136 Ashton KA, Meldrum CJ, McPhillips L, Kairupan CF, Scott J. Frequency of the common MYH mutations (G382D and Y165C) in MMR mutation positive and negative HNPCC patients. Hered Cancer Clin Pract 2005;3:65–70.

137 Gorgens H, Kruger S, Kuhlisch E, *et al*. Microsatellite stable colorectal cancers in clinically suspected hereditary nonpolyposis colorectal cancer patients without vertical transmission of disease are unlikely to be caused by biallelic germline mutations in MYH. J Mol Diagn 2006;8:178–82.

138 Eliason K, Hendrickson BC, Judkins T, *et al*. The potential for increased clinical sensitivity in genetic testing for polyposis colorectal cancer through the analysis of MYH mutations in North American patients. J Med Genet 2005;42:95–6.

139 Kim IJ, Ku JL, Kang HC, *et al*. Mutational analysis of OGG1, MYH, MTH1 in FAP, HNPCC and sporadic colorectal cancer patients: R154H OGG1 polymorphism is associated with sporadic colorectal cancer patients. Hum Genet 2004;115:498–503.

140 Mazurek A, Berardini M, Fishel R. Activation of human MutS homologs by 8-oxo-guanine DNA damage. J Biol Chem 2002;277:8260–6. Macpherson P, Barone F, Maga G, Mazzei F, Karran P, Bignami 8-oxoguanine incorporation into DNA repeats in vitro and mismatch recognition by MutSalpha. Nucleic Acids Res 2005;33: 5094–105.

142 Zhao J, Winkler ME. Reduction of GC → TA transversion mutation by overexpression of MutS in Escherichia coli K-12. J Bacteriol 2000;182:5025–8.

143 Niessen RC, Sijmons RH, Ou J, *et al*. *MUTYH* and the mismatch repair system: partners in crime? Hum Genet 2006;119:206–11.

144 Giraldez MD, Balaguer F, Caldes T, *et al*. Association of *MUTYH* and MSH6 germline mutations in colorectal cancer patients. Fam Cancer 2009;8:525–31.

145 Steinke V, Rahner N, Morak M, *et al*. No association between *MUTYH* and MSH6 germline mutations in 64 HNPCC patients. Eur J Hum Genet 2008;16:587–92.

146 Van Puijenbroek M, Nielsen M, Reinards TH, *et al*. The natural history of a combined defect in MSH6 and *MUTYH* in a HNPCC family. Fam Cancer 2007;6(1):43–51.

147 Kairupan CF, Meldrum CJ, Crooks R, *et al*. Mutation analysis of the MYH gene in an Australian series of colorectal polyposis patients with or without germline *APC* mutations. Int J Cancer 2005;116:73–7. Please cite this article in press as: Nielsen M, *et al*. *MUTYH*-associated polyposis (MAP). Crit Rev Oncol/Hematol (2010), doi:10.1016/j.critrevonc.2010.05.011 M. Nielsen *et al*. / Critical Reviews in Oncology/Hematology xxx (2010) xxx–xxx

148 Matsumoto Y, Zhang QM, Takao M, Yasui A, Yonei S. Escherichia coli Nth and human hNTH1 DNA glycosylases are involved in removal of 8-oxoguanine from 8-oxoguanine/guanine mispairs in DNA. Nucleic Acids Res 2001;29:1975–81.

149 Hazra TK, Das A, Das S, Choudhury S, Kow YW, Roy R. Oxidative DNA damage repair in mammalian cells: a new perspective. DNA Repair (Amst) 2007;6:470–80.

150 Dallosso AR, Dolwani S, Jones N, *et al*. Inherited predisposition to colorectal adenomas caused by multiple rare alleles of *MUTYH* but not OGG1, NUDT1, NTH1 or NEIL 1, 2 or 3. Gut 2008;57:1252–5.

151 Broderick P, Bagratuni T, Vijayakrishnan J, Lubbe S, Chandler I, Houlston RS. Evaluation of NTHL1, NEIL1, NEIL2, MPG, TDG, UNG and SMUG1 genes in familial colorectal cancer predisposition. BMC Cancer 2006;6:243.

152 Weiss JM, Goode EL, Ladiges WC, Ulrich CM. Polymorphic variation in hOGG1 and risk of cancer: a review of the functional and epidemiologic literature. Mol Carcinog 2005;42:127–41.