

Chapter 2

MUTYH-Associated Polyposis

Maureen E. Mork and Eduardo Vilar

Introduction

Lynch syndrome and familial adenomatous polyposis (FAP) have long been identified as hereditary predisposition syndromes to colorectal cancer (CRC), most easily recognized on the basis of their autosomal dominant inheritance, young age of onset of CRC and other associated malignancies, and, in the case of FAP, the presence of adenomatous polyposis. However, in 2002 the first report of a novel hereditary predisposition to CRC describing a family with three siblings affected with CRC and polyposis who were negative for germline *APC* mutations was published [1]. These siblings were identified to carry biallelic germline mutations in the *MUTYH* gene, also known as *MYH*. This autosomal recessive predisposition to CRC has been termed *MYH*- or *MUTYH*-associated polyposis (MAP, OMIM #608456) and has been recognized as a rare, but important, cause of hereditary CRC, representing less than 1 % of CRC cases [2], and posing challenges in diagnosis, genetic counseling, and surveillance.

M.E. Mork

Clinical Cancer Genetics Program, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

E. Vilar, M.D., Ph.D. (✉)

Department of Clinical Cancer Prevention, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA

e-mail: EVilar@mdanderson.org

Clinical Characteristics

MAP is an autosomal recessive condition caused by biallelic mutations of *MUTYH* with a prevalence of 1:20,000 to 1:40,000 based on the estimated carrier frequency of 1–2 % in the general population [2]. MAP is typically characterized by the development of 10 to 100 adenomatous polyps in the colorectum, most frequently located in the proximal colon, and confers a life-time risk of CRC ranging from 43 % to nearly 100 %, being diagnosed at an average age of 48 [3]. Polyps develop approximately at age 50; therefore, the number of polyps and age of diagnosis have much clinical crossover with attenuated familial adenomatous polyposis (AFAP), associated with germline *APC* mutations [4]. However, patients with biallelic *MUTYH* mutations with an atypical presentation have been described, including patients who present with a single colorectal tumor and absence of polyposis or with less than 10 polyps [5]. In addition, a small percentage of patients who present with polyps with serrated features (hyperplastic/serrated polyps) meeting the threshold for a diagnosis of hyperplastic/serrated polyposis syndrome [6] have been found to have biallelic *MUTYH* mutations [7, 8].

Extracolonic cancer risks in individuals with MAP were assessed in a European multicenter study of 276 cases [9]. The highest reported risk was of cancer of the duodenum. The risk of small bowel polyps, especially in the duodenum, was reported to be 17 %, with an associated 4 % life-time risk of duodenal carcinoma. Gastric polyps were found in 11 % of patients. This study also found a significant increase in ovarian (SIR 5.7), bladder (SIR 7.2), and skin (SIR 2.8) cancers, with a trend of increased risk for breast cancer. Overall, the average life-time risk of extracolonic cancers was reported to be 38 %, although the authors noted the relatively late ages of onset of these cancers (median 51–61 years). Individuals with MAP were also reported to have some features typically seen in patients with FAP, including dental anomalies and congenital hypertrophy of the retinal pigment epithelium. *MUTYH* biallelic carriers have also been reported to have sebaceous neoplasms of the skin [10, 11], again demonstrating the phenotypic overlap between MAP and other hereditary CRC syndromes.

Molecular Genetics

The pairing of the DNA bases (A with T and G with C) is crucial to maintain the stability and the integrity of the information in the genome. However, accurate base pairing is often challenged by environmental toxins and production of reactive oxygen species (ROS) such as hydrogen peroxide, superoxide and hydroxyl radicals secondary to metabolism, cellular respiration, and inflammation. The guanine base is the most susceptible to this “oxidative stress”, generating the product 7,8-dihydro-8-oxoguanine (also known as 8-oxo-G). The base excision repair (BER) pathway is in charge of correcting these errors through the glycosylases OGG1 and

MUTYH. Initially, OGG1 will excise the 8-oxo-G base and then let other enzymes restore the original DNA sequence. However, there is a back-up mechanism involving *MUTYH* that will act in the event that the error is not repaired by OGG1. In the absence of an effective *MUTYH* protein, the presence of 8-oxo-G will generate a transversion from G:C to T:A base pair. The glycosylate *MUTYH* intercepts the incorrect 8-oxo-G:A base pair, removing the A and letting other enzymes in the pathway to restore the DNA to its original configuration [12, 13].

The gene *MUTYH*, also known as *MYH* (mutY homolog), is located on chromosome 1 (mapping to 45,794,835–45,806,142 in the GRCh37 coordinates, which is located between 1p34.3 and p32.1) and has a total of 16 exons, encoding a protein with 535 amino acids [13]. The partial homology of the human protein with the *E. coli* and *B. stearotherophilus* has allowed obtaining an accurate idea of the functioning of the BER pathway and, in some instances, predicting the functional consequences of mutations identified in patients and families. In fact, a total of 82 germline mutations have been identified in *MUTYH* alleles of patients diagnosed with CRC and polyposis [12]. Consistent with the known biology and functioning of *MUTYH* in the BER pathway, patients diagnosed with MAP have been found to have a higher rate of somatic G:C to T:A transversions in the *APC* and *KRAS* genes. In fact, studies have shown that adenomatous polyps and serrated polyps identified in MAP individuals present in a high proportion with G:T transversion in the first G base of the codon 12 (*KRAS* c.34G>T) [3, 12]. This type of change has also been able to link the presence of polyps with serrated features (both hyperplastic and sessile serrated) with MAP, thus establishing a causal relation between the biallelic loss of *MUTYH* and the presence of serrated polyposis [8]. Finally, several studies have analyzed the microsatellite status of premalignant lesions and tumors from MAP patients. Although the number of patients and samples analyzed is not large, thus precluding to obtain definite conclusions, it is clear that the majority displayed a mismatch repair proficient status. In addition, one study observed a higher frequency for microsatellite instability-low tumors among MAP compared to the sporadic setting. A minority of cases reported showed high levels of microsatellite instability which is puzzling as the BER pathway is not involved in the correction of mismatches in microsatellite tracts [3].

Genetic Testing and Genetic Counseling

Identifying individuals with MAP is a complex task, as there is phenotypic overlap with other polyposis syndromes (i.e., AFAP) and due to its variable phenotypic expression. Genetic testing for MAP is typically considered in individuals who present with oligopolyposis, although the spectrum of presentation expands from 10 to 100 polyps [14]. Traditionally, genetic testing for MAP has begun with testing for the two founder *MUTYH* mutations in northern European populations, G382D and Y165C, which represents the genotypes of approximately 70 % of affected individuals [15]. However, full sequencing and rearrangement testing of *MUTYH* are

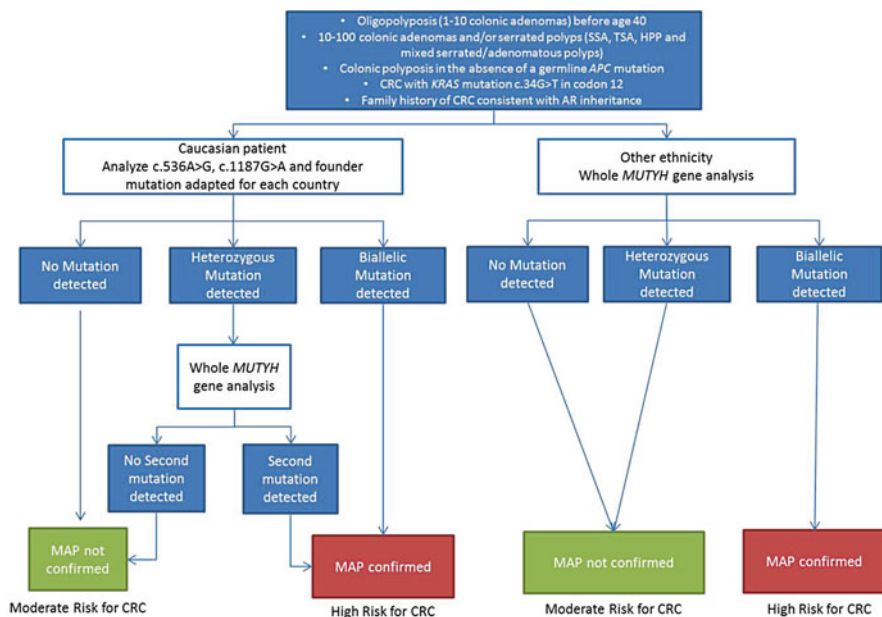


Fig. 2.1 Proposed genetic diagnosis work-up for patients with suspected MAP based on the available literature. CRC colorectal cancer, MAP *MUTYH*-associated polyposis, AR autosomal recessive, HPP hyperplastic polyps, SSA sessile serrated adenomas, TSA traditional serrated adenomas. Figure adapted from Borrás et al., Clin Cancer Res (2014);20(5):1061–3

also available, although most individuals with MAP present with point mutations with large deletions rarely reported [16]. Given the admixture of populations, comprehensive testing may be advantageous rather than founder mutation testing, especially if a patient is not of Northern European ancestry [17]. However, if a patient is Caucasian, then an algorithm of founder mutation testing with reflex to full testing may be followed (Fig. 2.1). In addition, testing for MAP may be performed in conjunction with *APC* germline testing, and is offered quite frequently as an “adenomatous polyposis” genetic testing panel included along with *APC* by many commercial genetic testing companies. If an individual presents with a family history consistent with autosomal dominant FAP, then testing *APC* alone would be the most appropriate course of action [14]. However, an individual with a simplex case of adenomatous polyposis may represent with autosomal recessive inheritance, like MAP, or a *de novo APC* mutation [18]. Therefore, concurrent testing of *APC* and *MUTYH* is appropriate in such individuals.

In addition to testing individuals with multiple adenomatous polyps, the developing description of the atypical MAP phenotype may expand the spectrum of patients appropriate for *MUTYH* testing. It has been proposed that individuals with CRC without polyposis or patients with polyps numbering less than 10 be evaluated for MAP, especially with the syndrome’s variable presentation (Fig. 2.1) [5]. To this end, *MUTYH* has been included in many next-generation sequencing panels of

hereditary cancer genes. While the inclusion of this gene has found many heterozygote carriers, it may continue to expand the MAP phenotype as more individuals with an atypical phenotype are identified. In addition, as sebaceous lesions of the skin have been reported in individuals with MAP as well as tumors with mismatch repair deficiency [19], patients with a Lynch syndrome phenotype with no mismatch repair mutation may also warrant MAP evaluation. Patients with CRC demonstrating *KRAS* mutations in codon 12 with G to T transversions (c.34G>T) in the absence of polyposis may also be considered for testing.

MAP is unique among hereditary predispositions to CRC due to its autosomal recessive inheritance. For an individual to inherit biallelic mutations of the *MUTYH* gene, his or her parents must each carry a single *MUTYH* mutation. Full siblings of an individual with MAP each have a 25 % chance of also having biallelic mutations and therefore MAP, 50 % chance of being a *MUTYH* carrier, and 25 % chance of having two wild-type alleles. Children of an individual with MAP are obligate heterozygote carriers. The status of the other allele, however, depends on the mutation status of the unaffected parent. Therefore, the genetic testing algorithm in a family identified to have MAP is more complex than in a family with an autosomal dominant condition.

Siblings of an affected individual are recommended to undergo site-specific testing for the *MUTYH* mutation(s) identified in the proband. However, single-site testing in obligate heterozygote children will not evaluate for the possibility of a mutation in the other parent. Therefore, it may be more cost-effective for the unaffected parent to undergo carrier testing of *MUTYH*. If the other parent is negative for *MUTYH* mutations, this negates the need for testing in children. This algorithm introduces some complexity into results disclosure and recommendations for family members, as education regarding a recessive condition may not be as straightforward as an autosomal dominant condition; therefore, careful genetic counseling is important to impart accurate information to the patient and his or her family.

Colonic Surveillance and Surgical Recommendations

Surveillance recommendations for biallelic *MUTYH* carriers have been issued by a number of expert groups (i.e., National Comprehensive Cancer Network, American Medical Association/National Coalition for Health Professional Education in Genetics). Per the guidelines of the National Comprehensive Cancer Network (NCCN), colonoscopy is recommended beginning at 25–30 years and repeating every 2–3 years if negative [20]. If polyps are identified, then colonoscopy should be repeated every 1–2 years. If the polyp burden becomes too burdensome to be managed endoscopically with polypectomy, then surgical intervention is recommended, with consideration of colectomy with ileorectal anastomosis (IRA) or proctocolectomy with ileorectal pouch anastomosis (IPAA) depending on rectal polyp burden. Post-colectomy, endoscopy of any remaining rectum is recommended every 6–12 months.

Chemoprevention

There are results from randomized placebo-controlled clinical trials proving the effect of aspirin [21], non-steroidal anti-inflammatory agents such as Sulindac [22] and cyclo-oxygenase-2 (COX-2) inhibitors [23, 24] in the regression and modulation of adenomatous polyps in patients diagnosed with polyposis secondary to a diagnosis of FAP. However, there is virtually no controlled data generated for patients and families diagnosed with MAP. There is a case report in the literature that reports the successful modulation of polyposis using COX-2 inhibitors indicated for the treatment of arthritis in a patient with MAP [25]. After the discontinuation of Celecoxib the patient presented with progression of the polyp counts and required prophylactic surgery. There is some low level scientific evidence supporting the use of NSAIDs such as the finding of upregulation by both immunohistochemistry and RNA expression of COX-2 in polyps and CRCs of patients with MAP, which is an analogous situation to the FAP context [26]. Although there is no evidence to support the prophylactic use of NSAIDs or COX-2 inhibitors, the implementation of clinical trials testing this intervention should be encouraged in this patient population. It could be reasonable to try this group of agents as prophylaxis in selected situations under the condition of close endoscopic surveillance and clinical management attentive to potential side effects, always keeping in mind the relatively low frequency of this syndrome (N of 1 trials).

Extracolonic Surveillance

Few recommendations have been made regarding extracolonic cancer risks for individuals with MAP. As the highest reported extracolonic risk is for small bowel polyps and cancer, biallelic *MUTYH* carriers are recommended to undergo baseline esophagogastroduodenoscopy (EGD) beginning at age 30–35 years, following FAP recommendations based on duodenoscopic findings [20]. In addition, individuals with MAP are recommended to undergo annual physical exam. No recommendations have been made regarding surveillance for the other cancers associated with MAP.

MUTYH Heterozygotes

As genetic testing for *MUTYH* has entered the algorithm for germline testing, either through cancer-specific genetic testing or via next-generation sequencing panels of hereditary cancer genes, this has led to the identification of monoallelic carriers of *MUTYH* mutations. The risk of CRC to *MUTYH* carriers was initially studied in parents of patients with biallelic *MUTYH* mutations and was estimated to be approximately twofold the general population incidence [27]. However, a more recent

study of 2,332 patients with monoallelic *MUTYH* mutations found that the risk to carriers was dependent upon the family history of CRC. In fact, the risk for CRC, irrespective of family history, was 5.6 % for females and 7.2 % for males, while CRC risk for individuals with a first-degree relative with CRC was 10 % for women and 12.5 % for men [28]. Current surveillance guidelines recommend that *MUTYH* heterozygotes follow general population screening practices for CRC [20]. Extracolonic cancer risks in *MUTYH* carriers have not been well studied and no additional surveillance guidelines have been issued.

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