Establishing a Diagnostic Road Map for MUTYH-Associated Polyposis

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The analysis of MUTYH-associated polyposis cases of the EPIPOLIP cohort confirms the importance of including serrated polyps in the diagnostic work-up of patients with oligopolyposis, suggests a role for screening polyps for the somatic c.34G>T KRAS mutation, and allows the implementation of a genetic testing strategy based on population data. Clin Cancer Res; 20(5); 1061–3. ©2014 AACR.

In this issue of Clinical Cancer Research, Guarinos and colleagues (1) report on a rational genetic workflow that can be applied in cases of suspected MUTYH-associated polyposis (MAP) and confirm the importance of considering polyps with serrated histology, as well as the role of somatic mutations in KRAS as an aid in the diagnosis of MAP.

MAP is an autosomal recessive polyposis syndrome predisposing to colorectal cancer (2) caused by biallelic mutations in the MUTYH gene. MUTYH is involved in the initial steps of the base-excision repair (BER) pathway (3), which prevents somatic mutations induced by oxidative damage (8-oxo-G). MUTYH recognizes 8-oxo-G:A mismatches and excises this error from the DNA. Patients harboring germ-line MUTYH mutations accumulate G:C to T:A (G>T) transversions in secondary genes (4), such as loss-of-function mutations observed in APC and KRAS, which are critical in the early steps of the colonic epithelium’s transition to adenoma and carcinoma (5).

The genetic diagnostic work-up for patients with MAP is complicated because of variations in the genetic features of this disease among populations and the need to exclude other polyposis syndromes. Clinically, most patients with MAP present with ten to hundreds of polyps, which are predominantly located in the proximal colon. The mean age of patients at diagnosis is approximately 45 years, whereas the mean age of patients with MAP who develop colorectal cancer is 50 years, which translates into a simultaneous diagnosis of colorectal cancer and polyposis in 50% of individuals affected by MAP (6). In regard to the histology of the intestinal polyps, it has been reported that patients with MAP present not only with adenomas but also with serrated polyps, such as hyperplastic polyps and sessile serrated adenomas (5, 7). Correlations between the intestinal features (number and type of polyps) and the genotype of patients with MAP vary between populations and are not well characterized, mostly because of the low frequency of this condition. Therefore, there is no consensus on the most appropriate genetic testing workflow for patients with suspected MAP (8).

Guarinos and colleagues aimed to address this problem by analyzing a multi-institutional cohort of patients from Spain presenting with modest colonic polyp burdens (10 or more lesions) in order to establish genotype–phenotype correlates and suggested a diagnostic strategy. A total of 405 patients were included in this cohort. Biallelic mutations in MUTYH were identified in 27 of the patients (7%), with classical mutations c.536A>G, p.Y179C and c.1187G>A, p.G396D as the most frequently found. Of note, 41% of patients with MAP presented with serrated polyps (hyperplastic, traditional serrated adenomas, sessile serrated polyps, and/or mixed hyperplastic/adenomatous polyps) and at least 10% of polyps in 85% of patients with MAP harbored the c.34G>T (p.G12C) KRAS mutation.

On the basis of these findings, the authors devised a genetic testing strategy for MUTYH and proposed an initial step that tested for the most common mutations in their population (c.536A>G, p.Y179C; c.1187G>A, p.G396D; and c.1227_1228dup, p.E410GfsX43). Second, patients found to be heterozygous for one of these alterations underwent whole-gene sequencing. This approach demonstrated good sensitivity (96%) and specificity (100%) in the context of this Caucasian Spanish population. We believe that this strategy could be extrapolated to other countries with a population showing a similar genetic background by including modifications based on the discovery of specific founder mutations. For instance, it is well known that 70% of Caucasian patients with MAP harbor either the p.Y179C or the p.G396D mutation (4). However, at this time, the step-wise approach taken by Guarinos and colleagues may not be applicable to other non-Caucasian populations, such as Asian, African-American, Hispanic, and Jewish populations, in which the mutational spectra have not yet been well studied and for whom, therefore,
whole-gene sequencing will be the most appropriate genetic diagnostic strategy (ref. 4; Fig. 1).

Furthermore, it has been suggested that there is a genotype-phenotype association for common MUTYH mutations in Caucasians, with more significant polypl burden and earlier age of onset in carriers of the p.Y176C allele (9). Guarinos and colleagues reported that patients who were homozygous for the p.Y176C variant had an earlier mean age of onset of polyposis than patients heterozygous or carrying other variants. Also, they reported that the p.G396D variant was strongly associated with the presence of serrated polyps, even in heterozygotes. This observation is consistent with findings in in vitro studies and the fact that p.G396D is less catalytically compromised than the p.Y176C variant (10).

The association of MAP with serrated polyps has been described previously, although in smaller series of patients (5, 7). This association raises an important diagnostic point for clinicians, as the work-up of patients with oligopolyposis would now have to take into consideration not only the total count of polyps, but also the presence of serrated lesions. Based on these two factors, the use of dye-spray colonoscopy in routine surveillance acquires a further dimension. In addition, no patients with serrated polyps were found to have APC mutations, and thus when serrated polyps are identified in the setting of oligopolyposis, the finding of c.34G>T KRAS mutation in codon 12 could facilitate the diagnosis of MAP. In this context, the incorporation of KRAS testing as a first step in the diagnostic work-up of mixed adenomatous and serrated oligopolyposis could be advocated. Of note, this specific C>T transversion is found in less than 8% of colorectal cancer harboring KRAS mutations (4, 11). Nonetheless, although biopsies of polyps usually render sufficient amounts of DNA to perform molecular analysis of KRAS mutations using classical Sanger sequencing or pyrosequencing strategies, the development of alternative strategies based on immunohistochemistry for specific KRAS mutations (similar to the staining for V600E BRAF mutation) would represent a significant advance toward simplifying the diagnosis of MAP.

In many regards, the parallels between the carcinogenesis processes of MAP and the better-known Lynch syndrome may be useful in understanding the biology of MAP. The

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**Figure 1.** Our proposed genetic diagnostic work-up of patients with suspected MAP based on previous reports and the findings presented by Guarinos et al. (1). CRC, colorectal cancer; MAP, MUTYH-associated polyposis; AR, autosomal recessive; HPP, hyperplastic polyps; SSA, sessile serrated adenomas; TSA, traditional serrated adenomas.
similarity between these entities is not restricted to their similar clinical presentation, with frequent involvement of the proximal colon, a higher rate of mucinous histology, and the presence of tumor-infiltrating lymphocytes (12); in addition, they share similar features in their molecular pathogenesis. That is, both syndromes arise because of the presence of germline mutations in genes involved in DNA repair systems (BER in MAP and mismatch repair in Lynch syndrome). These initial mutations introduce secondary hits in key oncogenes or tumor suppressor genes in the form of G>T transversions in MAP or contractions or expansions of microsatellite tracts in Lynch syndrome.

Finally, the application of new technologies such as next-generation sequencing in the routine management of oncologic patients is rapidly becoming a reality. Because steadily decreasing amounts of genomic material are required for these analyses, we expect that gene panels will soon be incorporated into the routine study of samples with low DNA yields such as polyps in high-risk populations. This approach will allow us to detect higher-than-normal rates of G>T transversions in polyps or even in normal mucosa, raising a suspicion for germline defects in the BER pathway and, therefore, enabling early diagnosis and detection of MAP, which will lead to the implementation of screening and preventive measures much earlier and thereby contributing to a decrease in the incidence of colorectal cancer in this population.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Borras
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