Published in final edited form as:
Gastroenterology. 2009 June ; 136(7): 2407–2408. doi:10.1053/j.gastro.2008.12.076.

A Perspective on Bi-allelic *MUTYH* Mutations in Patients with Hyperplastic Polyposis Syndrome

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Dear Sir

We read with interest the article by Dr Boparai and colleagues, and its accompanying editorial in the December 2008 edition of *Gastroenterology*[1, 2]. The work describes a series of 17 bi-allelic *MUTYH* mutation carriers where 8 of these (47%) had at least one hyperplastic polyp and 3 (18%) fulfilled the current criteria for hyperplastic polyposis syndrome (HPS)[3]. Importantly, the particular somatic mutations identified in the *KRAS* gene [G:C->T:A transversions] which featured prominently in the serrated polyps in this series when compared with unselected controls, raise the possibility that at least a proportion of HPS might be attributed to germline mutations in *MUTYH*.

The WHO criteria were originally introduced to distinguish HPS from the common observations of both satellite hyperplastic polyps around rectal cancers, and diminutive distal-only hyperplastic polyps[4]. However, the cases reported here suggest that predominantly distal hyperplastic polyps may be a defining characteristic of such patients, and these patients may also be distinguished by the frequency of the particular *KRAS* variant observed in their polyps and possibly the magnitude of their polyp multiplicity. This finding is also consistent with previous reports of *KRAS* mutation-rich serrated polyps being more frequent in this region of the colon[5]. In contrast, much of the HPS reported in the literature features a pan-colonic or proximal distribution, and concordant mutation in the *BRAF* gene[6]. Several patients with concordant *KRAS* mutation however, have been reported[7, 8] suggesting that this variant is either relatively rare, or, as has been proposed[1], may have been overlooked in the presence of multiple adenomas, due to the low malignant potential of distal hyperplastic polyps. The possibility of heterogeneity in HPS was first raised over a decade ago[9] and was subsequently explored by Rashid and colleagues[10]. An important relevant finding which emerged from these studies was that *KRAS* mutation was likely to be observed in hyperplastic polyps from HPS subjects with multiple small lesions, but was not found in cases where large hyperplastic polyps were seen. Also consistent with this, the sessile serrated adenomas with *KRAS* mutation described by Boparai *et al* are of relatively diminutive proportions[1].

In their detailed report, Boparai and colleagues have presented an estimate of the frequency of HPS among *MUTYH* bi-allelic mutation carriers[1]. The question now arises as to the frequency of *MUTYH* bi-allelic mutation carriers amongst patients with HPS. We had previously screened a group of 126 patients with HPS, for the two common mutations of northern Europeans occurring in the *MUTYH* gene (Y165C and G382D) (Buchanan and Young, unpublished observations). During this exercise, we found only a single bi-allelic mutation carrier and this patient was homozygous for Y165C, however, in testing for only the common mutations, we

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Declaration: The authors have no conflict of interest to declare with respect to this work.

may have failed to identify patients who carry less common variants. Synchronous adenomas were present in 88% of the 106 patients in our current series where information was available, and, except for the bi-allelic mutation carrier described above, all other patients in this series had less than 25 adenomas, a criterion proposed by the authors of the paper under discussion here[1]. The bi-allelic mutation carrier had been reported in 2006, and had at least 40 adenomas as well as more than 30 hyperplastic polyps throughout the colon[11].

The important issue in both *MUTYH*-associated polyposis (MAP) and HPS is recognition of the condition, and its resultant benefits for prevention of CRC in both the patients and their relatives through screening. The different modes of inheritance however have implications for which relatives are offered colonoscopic surveillance or in the case of MAP genetic testing. An observation in *MUTYH* bi-allelic mutation carriers which has emerged from a large population-based study is that even though up to one-third do not manifest adenomas, almost all will develop a CRC by age 60[12]. Lack of this important portent however can be overcome in part because pre-symptomatic mutation testing can be carried out thereby identifying any individual or relative carrying two *MUTYH* alleles. Though there is debate regarding the matter of single mutant allele carriers in some families, their risk for CRC is not considered to be high. In contrast, there is no definitive genetic test for HPS. The risk of CRC in HPS is considerable, but has been difficult to quantitate[4]. In addition, the two largest series of HPS patients published to date [70 patients in total] suggest that the risk to first-degree relatives of CRC is also considerable[7, 11]. The features of both MAP and HPS therefore may need to be considered in patients with evidence of overlapping conditions.

The report by Boparai *et al* highlights a subset of HPS patients in which a germline defect in *MUTYH* is likely to be a contributing factor. The report prompts more extensive studies to fully understand the nature and magnitude of this apparent phenotypic overlap and its clinical implications. Whether the HPS phenotype seen in the bi-allelic mutation carriers results directly from *MUTYH* mutation or from an interaction between the *MUTYH* variants and an independently-segregating genetic predisposition remains to be discovered.

Acknowledgment

Joanne Young is supported by a Cancer Council Queensland Senior Research Fellowship. This work was supported by a grant from the National Cancer Institute 1R01CA123010 (Genetics of Serrated Neoplasia).

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