PostScript

LETTERS

Analysis of inherited MYH/ (MutYH) mutations in British Asian patients with colorectal cancer

Biallelic inherited mutations of the MYH gene (also known as MutYH or human MutY homologue) are associated with multiple colorectal adenomas and a high risk of colorectal cancer that approaches 100%.^{1,2} This recessive disorder has become known as MYH-associated polyposis (MAP) to distinguish it from dominantly inherited familial adenomatous polyposis. The risk of colorectal cancer in heterozygotes seems to be only marginally increased, if at all.² During a review of the Wales Polyposis Register we noted that although only 4 of the 115 recorded families were of Asian origin, all four had MAP. This was in contrast to the 111 indigenous families, only 12 of which had MAP. All affected members of three unrelated British Indian families were homozygous for the mutation E466X and one patient of Pakistani descent was homozygous for Y90X.³ These mutations have not been observed in other ethnic groups. As the overall incidence of colorectal cancer among Asians living in England and Wales is markedly below that of the general population,⁴ we postulated that MYH mutations might contribute more significantly to colorectal cancer among British Asians than among indigenous northern Europeans. We conducted a retrospective study to assess the contribution of MYH mutations to colorectal cancer among British Asians.

Multicentre research ethics Committee approval was obtained (Wales MREC 03/9/033). Cases were ascertained through departments of pathology at five participating UK centres, three in Wales and two centres in Leicester and Birmingham, which were selected for their large Asian populations. In each centre, we identified archived paraffin-wax-embedded blocks of tissue from cases of colorectal cancer by searching by forename and surname for cases of Indian subcontinent origin.^{5,6} All cases were anonymised before despatch for laboratory analysis. Of the 143 identified cases, 120 yielded DNA suitable for polymerase chain reaction (PCR) amplification. From the same centres, 174 control paraffin-wax-embedded colonic mucosa samples were also identified from individuals with names of Indian subcontinent origin, in whom colonic biopsy specimens had revealed a histopathological diagnosis of inflammation without neoplasia. Of these, 100 yielded DNA suitable for PCR analysis. In view of the difficulties inherent in obtaining adequate numbers of samples with a relatively rare condition in a minority ethnic group, we did not attempt to age match the groups. All samples in the case group were subjected to histopathological re-examination to ensure analysis of only normal background tissue. PCR and restriction enzyme digestion were used to identify of the Asian mutations E466X (using *ApoI*) and Y90X (using *RsaI*), and also to identify the common northern European mutation G382D (using *BglII*).

Amplification refractory mutation system PCR was used to detect the second most common European mutation, Y165C (details of primers and PCR conditions are available online at (http://www.cardiff.ac.uk/medicine/medical_genetics/genetics_research/tmg/projects/Dolwani2006/). Positive results were confirmed by bidirectional sequencing (ABI Prism 3100). Raw data for all phenotypic features wherever available and results in all cases and controls is given in supplementary table A (available at <http://www.gutjnl.com/supplemental>).

One case (1/120) and one control (1/100) sample were found to be heterozygous for the E466X variant of MYH. No cases or controls had biallelic mutations or carried any of the other mutations tested (Y165C, G382D and Y90X). Sequencing of the rest of the coding region was possible only for exons 2, 3, 11, 14 and 16 of MYH in these two individuals, and did not reveal any other mutation. Owing to the nature of the ethical approval, we were unable to follow up the two heterozygotes for further sampling and more details of phenotype or family history apart from that mentioned. We conclude that these four MYH mutations are unlikely to be a major contributor to colorectal cancer in British Asians. A much larger series would be required to quantify accurately the proportion of colorectal cancer attributable to MYH in this group. Nonetheless, previous studies have identified homozygotes for the E466X allele of MYH in British Asians with MAP, and our observation of this allele in the heterozygous state both in unselected cases and controls strengthens the case for initial testing for this mutation in patients from this population with polyposis or apparently recessive colorectal cancer.^{2,3,7} Studies in other ethnic subgroups have also suggested that the identification and characterisation of population-specific ancestral variants such as 1395delGGA in Italians^{8,9} will be helpful for the provision of molecular diagnostics for MAP.

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Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they?

In a recent version of *Gut*, Mainie and colleagues report on patients with persistent symptoms despite acid suppressive therapy.¹ This is often presented as a considerable problem and impedance seems useful in the evaluation of these patients. The importance of the phenomenon of proton pump inhibitor (PPI)-refractory symptoms is also stressed in studies in which the need for a new anti-reflux drug is propagated. However, we think some caution is appropriate when speaking of PPI-refractory gastro-oesophageal reflux disease (GORD) symptoms, in particular when it is decided that new reflux-inhibiting drugs are warranted to treat the "PPI-resistant reflux symptoms".

Firstly, the term PPI-resistant GORD is often used for patients that are not fully investigated,