The potential for increased clinical sensitivity in genetic testing for polyposis colorectal cancer through the analysis of MYH mutations in North American patients

K Eliason, B C Hendrickson, T Judkins, M Norton, B Leclair, E Lyon, B Ward, W Noll, T Scholl

Mutations in the base excision repair gene MYH were recently implicated in recessive inheritance of colorectal adenomas and carcinomas.1 The majority of patient specimens screened for MYH and described in published reports derive from the United Kingdom, where two missense variants—Y165C and G382D—are the most prevalent mutations in the white population.2–5 The carrier frequency for these two mutations is approximately 2% in the British population.1, 4 Some additional mutations were detected at lower frequency in these patients. Two other protein truncating mutations—E466X and Y90X—have been found in individuals of Indian and Pakistani descent, respectively.2 Finally, a mutation that deletes codon Glu-466 was reported to be prevalent in Italian patients.6 This evidence supports the view that additional mutations will be discovered showing differences in prevalence between ancestries.

We determined the mutation spectrum for MYH by direct DNA sequencing in 219 anonymous North American patient specimens found negative for APC mutations during clinical genetic testing for risk assessment for familial adenomatous polyposis (FAP). All specimens were first sequenced for exons 7 and 13, where 13 instances (5.9%) of biallelic mutations and 15 instances (6.8%) of heterozygous mutations of either Y165C or G382D were detected (table 1).

The remaining 202 specimens with one or no mutations and with sufficient DNA were sequenced at MYH for all exons and Intron–exon boundaries. Sequencing identified a second mutation in nine of the 15 heterozygous carriers of Y165C and G382D. Two of these mutations—891+3A→C and 1103delC—have been described previously,3, 4 while others (E182X, Q500X and IVS13+25del30) are novel. IVS13+25del30 was considered a mutation because it deletes 30 bases from an 85 base intron and therefore seems likely to interfere with RNA splicing. Also, one homozygous patient each for two previously reported mutations—E466X and 1395delGGA—were detected. Small deletions affecting exons within the MYH locus were excluded as potential causes for an apparent homozygous result in these patients by long range polymerase chain reaction extending from exons 1 to 16. A North American population frequency of 2% was determined by identifying three Y165C and seven G382D heterozygous carriers when 497 anonymous samples that were negative for clinical factor V Leiden tests were screened at exons 7 and 13. This carrier frequency is similar to that reported in two European studies.1, 4

MYH mutations were also assessed in 306 anonymous North American specimens found negative for clinical testing in hMLH1 and hMSH2 as part of an analysis of risk for hereditary non-polyposis colorectal cancer (HNPCC). All 306 specimens were initially screened for Y165C and G382D; three specimens (1.0%) carried biallelic mutations and 10 specimens (3.3%) were heterozygotes. One instance of the 891+3A→C mutation was found when the entire MYH gene was sequenced in these 10 heterozygous specimens. When an additional 50 of the HNPCC negative specimens were fully sequenced for MYH, one heterozygous carrier for 1103delC was detected.

These results confirm other reports associating MYH mutations with colon cancer. In this set of 219 patients undergoing polyposis colon cancer genetic testing, 24 (11.0%) carried biallelic MYH mutations. This percentage could increase if clinically uncertain missense variants detected in these patients are shown to cause disease (data not shown). Within these 24 patients, three reported having 6 to 19 polyps, nine had 20 to 99 polyps, three had 100 or more, and for nine the polyp status was unknown. APC testing alone identified deleterious mutations in 34.4% of all patients referred for FAP testing. When MYH testing was included, the positive rate increased to 41.3%. It is reasonable to conclude that MYH testing represents an important component of comprehensive genetic testing for polyposis colorectal cancer.

Additional mutations in MYH will probably be discovered; screening methods should be capable of detecting novel mutations as they come to light.

Key points

• MYH testing represents an important component of comprehensive genetic testing for polyposis colorectal cancer.

• If an initial screen for highly prevalent MYH mutations is used, then whole gene analysis of heterozygous carriers is necessary to identify other low prevalence mutations in order to obtain the maximum clinical sensitivity.

• Additional mutations in MYH will probably be discovered; screening methods should be capable of detecting novel mutations as they come to light.

Abbreviations: FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer.
Table 1 Results of MYH sequencing in North American populations

<table>
<thead>
<tr>
<th>Genotype</th>
<th>FAP negative samples (n = 219)*</th>
<th>HNPPCC negative samples (n = 306)**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First mutation</td>
<td>Second mutation</td>
</tr>
<tr>
<td>Y165C</td>
<td>Y165C</td>
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</tr>
<tr>
<td>G382D</td>
<td>G382D</td>
<td>2</td>
</tr>
<tr>
<td>Y165C</td>
<td>891+3A→C</td>
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</tr>
<tr>
<td>Y165C</td>
<td>1103delC</td>
<td>1</td>
</tr>
<tr>
<td>Y165C</td>
<td>IVS12–2 A→G</td>
<td>7</td>
</tr>
<tr>
<td>Y165C</td>
<td>1395delGGA</td>
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<tr>
<td>G382D</td>
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<tr>
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<tr>
<td>Y165C</td>
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<td>1103delC</td>
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</tr>
<tr>
<td>IVS12–2 A→G</td>
<td>IVS12–2 A→G</td>
<td>1</td>
</tr>
</tbody>
</table>

All specimens were negative for whole gene clinical sequencing of APC for FAP specimens and hMLH1 and hMSH2 for HNPPCC specimens. Mutations in bold were detected by whole gene sequencing of MYH. A dash (–) accompanies heterozygous carriers in the “second mutation” column.

*All heterozygotes after testing for Y165C and G382D and 187 samples without mutations received full sequence testing.

**All heterozygotes after testing for Y165C and G382D and 50 randomly selected samples without mutations received full sequence testing.

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American patients

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