Phenotypic Characteristics Associated With the APC Gene I1307K Mutation in Ashkenazi Jewish Patients With Colorectal Polyps

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Context The I1307K mutation of the APC gene is found in approximately 6% of the Ashkenazi Jewish population and is associated with elevated risk of colorectal cancer. The incidence of the mutation in patients with colorectal adenomas is unknown.

Objectives To determine the carrier rate of the I1307K mutation in Ashkenazi Jewish patients with a history of colorectal polyps but without colorectal cancer and to compare phenotypic characteristics and family history of carriers vs noncarriers.

Design, Setting, and Patients A total of 231 patients who had at least 1 large bowel polyp diagnosed between January 1, 1992, and January 31, 1999, at 1 of 5 centers in Boston, Mass, were included, of whom 183 were Ashkenazi Jewish. DNA was isolated from cheek swab samples.

Main Outcome Measures Presence of the I1307K variant in the APC gene.

Results The I1307K variant was identified in 22 (14%) of 161 Ashkenazi Jewish patients with a history of adenomatous polyps and in 1 (5%) of 20 Ashkenazi Jewish patients with hyperplastic polyps. The phenotypic features of adenomas, family history of polyps, colorectal cancer, and other cancers were indistinguishable between I1307K carriers and noncarriers.

Conclusions The frequency of the APC I1307K mutation is elevated in Ashkenazi Jewish patients with adenomatous polyps, but not hyperplastic polyps. The I1307K mutation represents a novel paradigm for cancer-predisposing genes, as it is associated with moderately increased risk of neoplasia without other associated distinguishing phenotypic features.

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overnight mail in a prepaid envelope.

Table 1. I1307K Carrier Rates in Ashkenazi Jewish Patients by Type of Polyps and Family History

<table>
<thead>
<tr>
<th>Total No. of Patients</th>
<th>No. (%): I1307K Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with adenomas</strong></td>
<td></td>
</tr>
<tr>
<td>161</td>
<td>22 (14)</td>
</tr>
<tr>
<td><strong>Patients with adenomas and no family history of colorectal cancer</strong></td>
<td></td>
</tr>
<tr>
<td>87</td>
<td>12 (14)</td>
</tr>
<tr>
<td><strong>Patients with adenomas and a family history of colorectal cancer in a first-degree relative</strong></td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>6 (11)</td>
</tr>
<tr>
<td><strong>Patients with adenomas without knowledge of family history of colorectal cancer</strong></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>4 (18)</td>
</tr>
<tr>
<td><strong>Patients with hyperplastic polyps only</strong></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

I1307K Analysis

DNA was isolated from blood or buccal swab samples using a QIAamp DNA Mini kit (Qiagen Inc., Valencia, Calif). Isolated DNA was amplified using primers specific for exon 15 of the APC gene, including the region that encompassed the published I1307K polymorphism. Amplified material was dot blotted onto Biotrans nylon membranes (ICN, Irvine, Calif) using a Gibco/BRL 96-well dot blot apparatus (Life Technologies, Rockville, Md). Blotted membranes were hybridized with probes specific for either the normal APC gene sequence or the I1307K polymorphism. Results were determined by comparing the hybridization signal of positive controls to patient samples in relation to background.

Assessment of Family History and Ethnicity

Ethnicity was confirmed by patient self-report. Specifically, individuals were asked, “Do you have any Ashkenazi (European-American) Jewish heritage?” Personal and family history of cancer and colorectal polyps were obtained via self-administered questionnaire. Medical records were obtained to confirm all colorectal polyp and cancer diagnoses in index patients; pathological confirmation was obtained for 91% of participants with colorectal adenomas. Pathology and endoscopy reports were reviewed for extraction of phenotypic characteristics of polyps, including size, number, and location.

RESULTS

Between May 1998 and May 1999, we mailed a total of 836 study packets to potentially eligible patients. A total of 272 individuals enrolled in the study, for a participation rate of 32%. Participation rates were similar across sites (ranging from 28% to 35%) and did not vary by type of practice or referring physician. Forty-one individuals were excluded from the study: 5 because of insufficient data, 19 because of a history of CRC; and 17 because of polymerase chain reaction amplification failure.

Of the remaining 231 participants, 27 were not Ashkenazi Jewish and 21 were of unknown ethnicity. There were 20 participants with hyperplastic polyps and 2 with inflammatory polyps. The 161 Ashkenazi Jewish patients with adenomatous polyps are the main focus of this report. A total of 153 (95%) were Ashkenazi Jewish on both maternal and paternal sides of the family; 8 (5%) were Ashkenazi only on 1 side of the family. There were 99 men (61%) and 62 women (39%). The mean age at first adenoma diagnosis was 63 years. Fifty-two individuals (32%) reported a first-degree relative with colorectal cancer, and 22 individuals (14%) had a first-degree relative with colorectal polyps.

To compare the characteristics of participants and those individuals who chose not to enroll, we randomly sampled 83 records (14%) of nonresponders. Comparison of demographic characteristics and findings on colonoscopy revealed no significant difference between the 2 groups except that the mean age of participants was 4 years younger than nonresponders.

Carrier rates were determined for several risk groups (Table 2). Among Ashkenazi Jewish patients with adenomas, 22 (14%) of 161 carried the I1307K mutation, whereas the alteration was found in only 1 (5%) of 20 Ashkenazi Jewish individuals with hyperplastic polyps. The 14% mutation rate in adenomatous polyps was significantly higher than reported mutation rates of 6.1% to 7.0% in 2 large series of Ashkenazi Jewish controls without CRC (2-sided P by Pearson χ² = .005). The results were not significantly different when the analysis was performed with the inclusion of data from the 19 patients who had been excluded because of a history of CRC.

Analysis of the characteristics of adenomatous polyps in Ashkenazi Jewish patients with colorectal polyps is presented in Table 2. Comparison of the
mean age at first diagnosis of adenomas, the mean number of adenomas per colonoscopy, the mean size of adenomas, and the location of adenomas revealed no significant differences between carriers and noncarriers. Furthermore, there were no significant differences in the frequency of CRC, non-CRCs, or colorectal polyps in first-degree relatives between carriers and noncarriers (Table 3).

**COMMENT**

Cancer-predisposition genes have classically been associated with striking phenotypic features, such as early age at onset of neoplasia, multiple affected family members, rare tumors, and the presence of multiple tumors in the same individual. Therefore, we hypothesized that patients with adenomatous polyps who carried the I1307K mutation would exhibit unusual clinical characteristics and be more likely to have a positive family history of colorectal polyps or cancer than noncarriers. The I1307K carrier rate in Ashkenazi Jewish patients with adenomatous polyps (but not hyperplastic polyps) was increased compared with the population prevalence of the mutation and similar to the rate found in Ashkenazi Jewish patients with CRC, confirming its role early in the pathogenesis of colorectal neoplasia. However, in contrast to previous reports and our expectations, we found no differences in family history of colorectal neoplasia or any phenotypic features of adenomas in terms of age of onset and location, size, and number of polyps in I1307K mutation carriers vs noncarriers.

Multiple issues may affect patients' willingness to participate in genetics studies, including fear of confidentiality of individual results and stigmatization of the Jewish community, and these factors may have led to the suboptimal participation rate observed in our study. We attempted to address this issue with an analysis of nonresponders, which revealed similar demographic and polyp characteristics (except for a small difference in age) between eligible patients who chose and did not choose to participate. Ascertainment bias may still have affected enrollment, with a bias toward those who were undergoing endoscopic surveillance or had a family history of the disease. However, such a bias should not affect comparisons between carriers and noncarriers, since they would not be expected to differ between the mutation carrier and noncarrier groups.

When first identified, I1307K was hailed as the cause of a significant proportion of CRC in Jewish patients, and clinical recommendations were made advocating genetic testing for the mutation and intensified surveillance for carriers. Our detailed comparison of mutation carriers and noncarriers indicates that the I1307K mutation is distinctly different than classic high-penetration cancer susceptibility genes, which are typically rare, segregate with disease, and are sufficient on their own to substantially increase risk with only minimal impact by environmental factors. With completion of the elucidation of the human genetic code, scientists will continue to identify other polymorphisms such as I1307K that are common and increase risk of cancer and other common diseases but can be strongly influenced by association with other genetic or environmental factors.

### Table 2. Characteristics of Adenomatous Polyps in Ashkenazi Jewish I1307K Carriers vs Noncarriers

| Characteristic | I1307K Positive (n = 22) | I1307K Negative (n = 139) | P Value*
|---------------|-------------------------|--------------------------|--------
| Indication for colonoscopy, No. (%) | | | |
| Screening† | 13 (59) | 76 (55) | .70
| Evaluation of symptoms | 4 (18) | 35 (25) | .48
| Unknown | 5 (23) | 28 (20) | .78
| Mean age at first adenoma diagnosis, y | 62.3 | 62.1 | .94
| Mean total No. of adenomas per patient | 3.18 | 2.76 | .49
| Mean No. of adenomas per colonoscopy | 1.66 | 1.86 | .33
| Mean size of adenomas, mm | 5.81 | 5.50 | .99
| Location of polyps, No. (%) | | | |
| Rectosigmoid | 25 (52) | 100 (73) | .10
| Descending or splenic flexure | 8 (17) | 42 (31) | .97
| Transverse | 6 (13) | 40 (29) | .57
| Right | 9 (19) | 73 (52) | .16

*Comparisons were made using χ² test for categorical variables and t test for continuous variables.
†Screening group comprises patients undergoing colonoscopy because of a family history of colorectal cancer or adenomas, personal polyp history, or a polyp found on screening flexible sigmoidoscopy.

### Table 3. Family History Characteristics of Ashkenazi Jewish Adenomatous Polyp I1307K Carriers and Noncarriers

| Characteristic | I1307K Positive (n = 22) | I1307K Negative (n = 139) | P Value
|---------------|-------------------------|--------------------------|--------
| First-degree relative with colorectal cancer | | | |
| Yes | 6 (27) | 46 (33) | .59
| No | 12 (55) | 75 (54) | .96
| Do not know | 4 (18) | 18 (13) | .51
| First-degree relative with noncolorectal cancer | | | |
| Yes | 12 (55) | 70 (50) | .72
| No | 10 (46) | 53 (38) | .51
| Do not know | 0 (0) | 16 (12) | .09
| First-degree relative with polyps | | | |
| Yes | 4 (18) | 31 (22) | .66
| No | 7 (32) | 40 (33) | .91
| Do not know | 11 (50) | 62 (45) | .64
| Two or more relatives with colorectal cancer | 3 (14) | 20 (14) | .93
| Two or more relatives with colorectal cancer and/or polyps | 3 (14) | 28 (20) | .47

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Ultimately, the best estimation of risk is likely to be made by assessment of the combination and interaction of multiple low-penetrance mutations, behavioral factors, and personal medical history. In the meantime, it is important that patients who elect to undergo testing for I1307K appreciate that although the test is relatively cheap and easy to obtain, the results need to be interpreted in the context of a variety of other factors. A positive result does not mean the inevitability of cancer, and risk may be significantly affected by screening practices and behavioral factors, such as physical activity and diet. Equally important, however, is that a negative result does not imply protection from CRC, since there are surely other low-penetrance genes affecting CRC risk that have not yet been identified. The study of these complex interactions and clinical implementation of testing of low-penetrance genes clearly pose novel challenges for genetic epidemiologists, physicians, and patients.

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**REFERENCES**


Absence of thought is indeed a powerful factor in human affairs—statistically speaking the most powerful.

—Hannah Arendt (1906–1975)