Risk of colorectal neoplasia associated with the adenomatous polyposis coli E1317Q variant

M. J. Hall¹, E. Liberman²,³, O. Dulkart²,³, L. Galazan², E. Sagiv²,³, E. Shmueli²,³, D. Kazanov², A. Hallak²,³,⁵, M. Moshkovitz²,³,⁵, A. Figer²,³, S. Kraus², M. Inbar²,³,⁴, A. I. Neugut¹ & N. Arber²,⁵*¹

¹Departments of Medicine and Epidemiology, College of Physicians and Surgeons, and the Mailman School of Public Health, Columbia University, New York, NY, USA; ²Integrated Cancer Prevention Center, Tel-Aviv Sourasky Medical Center; ³Sackler Faculty of Medicine, Departments of ⁴Oncology and ⁵Gastroenterology, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Tel Aviv, Israel

Background: Reports of the risk of colorectal neoplasia associated with a variant of the adenomatous polyposis coli (APC E1317Q) gene are conflicting. Using a case–control design, we investigated this relationship within a clinic-based cohort followed through the Integrated Cancer Prevention Center and the Tel-Aviv Sourasky Medical Center.

Materials and Methods: All study subjects were tested for the APC E1317Q variant at enrollment. Subjects underwent colonoscopic evaluation (±biopsy and/or polypectomy) and had cancer history and colorectal neoplasia risk factors assessed. The crude and adjusted risks of neoplasia associated with the E1317Q variant were calculated.

Results: The prevalence of the E1317Q variant was 1.4% in the entire study sample and 3.2% in Sephardic Jews. E1317Q was more prevalent among cases: 15 of 458 (3.3%) cases were carriers compared with 11 of 1431 (0.8%) controls [odds ratio (OR) 4.4, 95% CI 2.0–9.6]. When stratified by neoplasia type, adenoma risk was significantly elevated in carriers (OR 4.1, 95% CI 1.8–9.4) but colorectal cancer risk was not (OR 2.1, 95% CI 0.8–5.3). After adjustment, the E1317Q variant remained a significant predictor of colorectal adenoma (OR 4.6, 95% CI 2.0–10.8).

Conclusions: The APC E1317Q variant is associated with colorectal neoplasia, particularly colorectal adenomas, but further studies are still needed. Variant prevalence is elevated in Sephardic Jews.

Key words: APC gene, colorectal cancer, E1317Q, hereditary risk

introduction

Colorectal cancer (CRC) is the second leading cause of cancer mortality in the Western world, with a cumulative lifetime risk of 6% [1]. Although 15%–20% of CRC occurs in the context of a family history of cancer, a specific genetic cause in most familial cases is unknown [2]. The adenomatous polyposis coli (APC) gene functions in a number of important cellular processes, including serving as a tumor suppressor gene whose protein product is involved in the modulation and sequestration of cytosolic β-catenin as part of the Wnt-signaling pathway [3]. Because several pathways critical to growth, cell division, and signal transduction converge on it, the APC gene plays a central role in both regulated cellular proliferation and carcinogenesis [4].

APC mutations are common in early neoplastic transformation. Somatic mutations in APC have been found in more than two-thirds of colorectal adenomas and CRCs [5, 6]. Germline truncating mutations in APC cause familial adenomatous polyposis (FAP), a complex cancer syndrome characterized by the appearance of hundreds to thousands of colorectal adenomas during adolescence and early-onset CRC [3]. Several putative low-penetrance susceptibility alleles of APC have been investigated in individuals and populations with an elevated risk of colorectal neoplasia [7–9]. The APC E1317Q variant was first described in 1996 by White et al. [10] in an Ashkenazi Jewish family with multiple CRCs, but, unlike the APC I1307K variant [8, 9, 11], founder effects related to E1317Q have not been established in Jewish or other populations. E1317Q has been reported to confer an increased risk of colorectal adenomas and CRCs in some but not all case–control studies [8,12–20]. In the largest study to date (1834 matched cases and controls, 48 E1317Q carriers), Rozek et al. [20] found no association between E1317Q and CRC. To help clarify these divergent findings, the present study investigates the relationship between the E1317Q variant and colorectal neoplasia in a case–control study conducted in Israel.

materials and methods

study population

The study population included 1889 subjects prospectively enrolled through the multidisciplinary Colorectal Cancer Prevention and Early
Detection Program at the Integrated Cancer Prevention Center and the Departments of Surgery and Oncology at the Tel-Aviv Sourasky Medical Center from October 2000 to September 2007. These facilities include outpatient clinics in an academic hospital-based as well as a community-based setting. Cohort members were self-referred for gastrointestinal symptoms or CRC screening unrelated to known colorectal adenoma or cancer risk or for cancer screening due to a personal or family history of gastrointestinal disease or malignancy. They may also have been referred by a local health care provider for the same indications. Therefore, a spectrum of risk for colorectal neoplasia was represented [21]. All persons attending the Cancer Prevention and Early Detection Program were offered study entry and, if they chose to enroll, signed written informed consent; participation rate was >90%.

assessments of disease and risk factors

At enrollment, cohort members received a physical exam, completed a lifestyle habits questionnaire, and provided a blood sample. The lifestyle habits questionnaire included questions related to established risk factors and risk modifiers of colorectal neoplasia (e.g., cigarette smoking, alcohol consumption, body mass index (BMI), educational attainment, physical activity, and vitamin/antioxidant intake) and has been previously validated in epidemiologic studies [22]. Ethnicity was self-reported. Subjects reported familial ancestral origins from over 30 regions and/or nations. Over 80% of Ashkenazi Jews reported maternal and paternal origins in Eastern/Central Europe. Among Sephardic Jews, the most frequently reported maternal–paternal countries of origin included: maternal [Iraq (17.6%), Morocco (12.6%), Turkey (10.7%), Israel (9.6%), Syria (5.9%), and Bulgaria (5.9%)] and paternal [Iraq (17.8%), Morocco (14.3%), Turkey (11.2%), Yemen (7.1%), Iran (6.7%), and Bulgaria (6.5%)]. Personal and family cancer histories were self-reported and were confirmed by medical records when available. Cohort members underwent full colonoscopy evaluation at the time of enrollment with scheduled follow-up depending on personal–family history and colonoscopy findings. All clinical findings related to colonoscopy (e.g., adenoma histology and tumor histology) were collected, analyzed, and reported through the Tel-Aviv Sourasky Medical Center. Outside medical records were requested and obtained when available if medical care related to adenoma and/or CRC risk occurred outside of this medical system.

Detection of APC E1317Q variant

Testing for the E1317Q variant was instituted for all new cohort members in 2002, with 98.9% of subsequent new enrollees having been tested at the time of this analysis. Physicians were unaware of E1317Q variant status at the time of follow-up visits and exams. Of note, potential study participants were also simultaneously genotyped for the APC I1307K variant; in total, 266 APC E1317Q carriers were identified and excluded from these analyses. No compound heterozygous carriers of APC I1307K and APC E1317Q have been identified to date.

For testing, DNA was extracted from peripheral leukocytes and amplified by real-time PCR (LightCycler gene scanning by high-resolution melting) with primers designed to detect the APC E1317Q variant. The E1317Q variant is a substitution of glutamic acid (E) (common allele) with glutamine (Q) (rare allele) at position 1317 of GenBank Accession No. NP_000029.2, SEQ ID No. 8; which results from the G to C substitution at glutamine (Q) (rare allele) at position 1317 of GenBank Accession No. AP000029.2, SEQ ID No. 8; which results from the G to C substitution at position 1317 of GenBank Accession No. NM_000038.3, SEQ ID No. 7. Genomic DNA was PCR amplified using the following primers: 5'-GAAATAGGATGTAATCAGACG-3' (forward) and 5'-CACCACTTTTGGAGGGAGAT-3' (reverse). Detection of specific polymorphic nucleotide (G/C at position 4006 of SEQ ID No. 7) was by real-time PCR using the anchor primer TGGCTTGAAACTGTCGGAACTTGGC-FL (SEQ ID No. 11) and sensor primer ph-LC-Red705-CACAGGATCTTGGAGCTGACCTAG (SEQ ID No. 12).

case-control analysis

A clinic-based case–control study design was used to examine the association of the APC E1317Q variant to colorectal neoplasia. For the current study, among cohort members tested for the APC E1317Q variant, cases (n = 458) included all persons diagnosed with colorectal adenoma (n = 221) or CRC (n = 237) on screening colonoscopy. Controls included all neoplasia-free subjects. Exclusion criteria included a history of (i) hereditary non-polyposis colon cancer (Lynch Syndrome) fulfilling the revised Amsterdam criteria, (ii) FAP or the attenuated form of this disease, (iii) Peutz–Jeghers Syndrome or Juvenile Polyposis Syndrome, (iv) inflammatory bowel disease (ulcerative colitis and/or Crohn’s disease), or (v) carriers of the APC I1307K variant.

statistical analysis

Mean and median values of continuous variables were calculated, with means compared by two-sided Student’s t-test. The χ2 test of independence was used to test associations between binary variables. Confidence intervals are all reported at the 95% significance level, and all P values are two sided (α = 0.05). Multiple logistic regression analysis was used to calculate the risk of colorectal neoplasia, colorectal adenoma, and CRC adjusted for demographic characteristics, social/behavioral modifiers, and dietary supplementation. Multiplicative interactions were evaluated using an interaction term (E1317Q*variable); significance to the logistic model was determined by the log-rank test. Database organization and management was carried out in Microsoft Excel® (Redmond, WA). All statistical analyses were carried out using STATA9SE™ (College Station, TX).

results

demographic characteristics

Characteristics of the study sample are presented in Table 1. The prevalence of the E1317Q variant was 1.3%. Cases were older (P < 0.001); had higher BMI (P < 0.02); were less educated (P < 0.001); more likely to have a personal history of colorectal neoplasia (P = 0.03); and reported less regular alcohol consumption (P < 0.05), dietary calcium (P < 0.03), vitamin C (P < 0.002), and fish oil supplementation (P < 0.05) than controls. No differences in reported family history among cases and controls were observed.

APC E1317Q variant

The E1317Q variant was more common among cases (15 of 458, 3.3%) than controls (11 of 1431, 0.8%) [odds ratio (OR) 4.4, 2.0–9.6]. When stratified by neoplasia type (Table 2), only adenoma risk was significantly elevated [adenoma: OR 4.1 (1.8–9.4); CRC: OR 2.1 (0.8–5.3)]. Adjustment for confounding factors only slightly altered crude estimates of neoplasia risk associated with the E1317Q variant.

When examined by carrier status, E1317Q variant carriers were similar in age and gender to noncarriers (Table 3). The E1317Q variant was more prevalent among Sephardic Jews (3.2% versus 1.0% among Ashkenazi Jews, P < 0.001). Carriers were more likely to report a personal history of both colorectal adenoma (11.5% versus 1.9%, P < 0.001) and CRC (7.7% versus 0.8%, P < 0.001) but not family history of colorectal neoplasia in a first-degree relative (57.7% carriers versus 52.3% noncarriers, P = 0.58).

Among E1317Q variant carriers, CRC was diagnosed in six subjects; three subjects additionally reported a past history of
Age (mean), years 63.8 (SE 13.3) 58.2 (SE 14.2)  <0.001
Sex (male) 246 (53.7) 763 (53.3) 0.88
Ethnicity
  Ashkenazi Jewish 279 (60.9) 904 (63.2) 0.39
  Sephardic Jewish 117 (25.6) 320 (22.4) 0.45
  Others 62 (13.5) 207 (14.5) 0.28
Personal history
  Any colorectal neoplasia 20 (4.4) 35 (2.4) 0.03
  CRC 5 (1.1) 12 (0.8) 0.04
  Colorectal adenoma 15 (3.3) 23 (1.6) 0.23
Family history
  Any colorectal neoplasia 244 (53.3) 745 (52.1) 0.66
  CRC 230 (50.2) 675 (47.2) 0.34
  Colorectal adenoma 14 (3.1) 70 (4.9) 0.01
  BMI (mean) 26.3 (4.6) 25.7 (4.1) 0.02
  Regular physical activity 198 (43.2) 762 (53.3) <0.001
  High school degree 104 (22.7) 227 (15.9) 0.27
  Some graduate 232 (50.7) 726 (50.7) 0.78
  Graduate degree + 122 (26.6) 478 (33.4) <0.001
  Smoking history 190 (41.5) 579 (40.5) 0.70
  Regular alcohol use 48 (10.5) 201 (14.1) 0.05
  Dietary supplementation
    Calcium 49 (10.8) 210 (14.6) 0.03
    Fiber 16 (3.5) 58 (4.0) 0.61
    Vitamin C 28 (6.2) 157 (11.0) 0.02
    Fish oil 17 (3.7) 89 (6.2) 0.05
    APC E1317Q+ carriers 15 (3.3) 11 (0.8) <0.001

*First-degree relatives only.
SE, standard error; CRC, colorectal cancer; BMI, body mass index; APC, aptenomalous polyposis coli gene.

Table 2. Characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (N = 458)</th>
<th>Controls (N = 1431)</th>
<th>Pn (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean), years</td>
<td>63.8 (SE 13.3)</td>
<td>58.2 (SE 14.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>246 (53.7)</td>
<td>763 (53.3)</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>279 (60.9)</td>
<td>904 (63.2)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Sephardic Jewish</td>
<td>117 (25.6)</td>
<td>320 (22.4)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>62 (13.5)</td>
<td>207 (14.5)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any colorectal neoplasia</td>
<td>20 (4.4)</td>
<td>35 (2.4)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>5 (1.1)</td>
<td>12 (0.8)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Colorectal adenoma</td>
<td>15 (3.3)</td>
<td>23 (1.6)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any colorectal neoplasia</td>
<td>244 (53.3)</td>
<td>745 (52.1)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>230 (50.2)</td>
<td>675 (47.2)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Colorectal adenoma</td>
<td>14 (3.1)</td>
<td>70 (4.9)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>BMI (mean)</td>
<td>26.3 (4.6)</td>
<td>25.7 (4.1)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>198 (43.2)</td>
<td>762 (53.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>High school degree</td>
<td>104 (22.7)</td>
<td>227 (15.9)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Some graduate</td>
<td>232 (50.7)</td>
<td>726 (50.7)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Graduate degree +</td>
<td>122 (26.6)</td>
<td>478 (33.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>190 (41.5)</td>
<td>579 (40.5)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Regular alcohol use</td>
<td>48 (10.5)</td>
<td>201 (14.1)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Dietary supplementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>49 (10.8)</td>
<td>210 (14.6)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Fiber</td>
<td>16 (3.5)</td>
<td>58 (4.0)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>28 (6.2)</td>
<td>157 (11.0)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Fish oil</td>
<td>17 (3.7)</td>
<td>89 (6.2)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>APC E1317Q+ carriers</td>
<td>15 (3.3)</td>
<td>11 (0.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Selected characteristics in E1317Q variant carriers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>E1317Q+ (N = 26)</th>
<th>Noncarriers (N = 1863)</th>
<th>Pn (%)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.8 (SE 11.9)</td>
<td>59.6 (SE 14.3)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>15 (57.7)</td>
<td>994 (53.4)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>12 (46.2)</td>
<td>1171 (62.9)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Sephardic Jewish</td>
<td>14 (53.8)</td>
<td>423 (22.7)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0)</td>
<td>269 (14.4)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td>15 (57.7)</td>
<td>974 (52.3)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>2 (7.7)</td>
<td>15 (0.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>3 (11.5)</td>
<td>35 (1.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

interactions
The presence of multiplicative interactions between APC E1317Q and risk modifiers (BMI, educational attainment, physical activity, alcohol intake, smoking, and dietary supplementation with calcium, fiber, and fish oil) was evaluated for CRC, adenomas, and combined neoplasia. No significant interactions were identified.

discussion
The overall prevalence of E1317Q in this predominantly Jewish sample (63% Ashkenazi and 23% Sephardic) was 1.3% (1.0% among Ashkenazi Jews and 3.2% among Sephardic Jews) with a higher carrier rate in cases with colorectal neoplasia (3.3%) and a lower carrier rate in colonoscopy-negative controls (0.8%). Our findings are similar to those of Hahnloser et al. [14], who found an E1317Q carrier rate of 2.4% among individuals with a history of colorectal neoplasia and 0.3% among colonoscopy-negative controls. Because these authors did not report race/ethnicity, it is unknown whether E1317Q carriers included Sephardic subjects. Nonetheless, the Mayo Clinic population is unlikely to be as highly concentrated in Ashkenazi and Sephardic Jews as our own.

This study is the first to report an enrichment of the E1317Q variant in Sephardic Jews. Previous studies examining E1317Q prevalence have identified variable carrier rates in self-reported Jewish (1.1%–1.4% Ashkenazi men and women [12, 13]) and non-Jewish (0.0% Swedish [18] and Chinese [23]) control groups. A concentration of the E1317Q variant in Sephardic but not Ashkenazi Jews would indicate that this variant entered the population after the fragmentation of Central/Eastern European Jews (Ashkenazim) from the Sephardim. We have yet to carry out haplotype analysis to determine whether the variants detected in Sephardic subjects share a common ancestor and whether they are related to those detected in our Ashkenazi subjects. Whether the risk of colorectal neoplasia associated with E1317Q may be unique to Sephardic Jewish carriers is unknown; however, the positive findings of Hahnloser et al. [14] (likely few Sephardic Jews) and the negative findings of Rozek et al. [20] (approximately one-third of Sephardic Jews) go against this.
Several groups have evaluated the risk of CRCs and/or adenomas associated with APC E1317Q in a case–control or case series format, but most have identified fewer than five carriers among case and/or control populations [8,10–13,15–19, 24]. Lamium et al. [25] reported the strongest association to date in a select population with multiple adenomas (3–96 adenomas; OR 11.17, 2.30–54.3); results of other studies examining subjects with multiple adenomas (≥23 adenomas) have been nonsignificant but suggestive of an increased risk (OR 2.0 and RR 1.3) [17, 19.1]. Phenotypically, carriers exhibit a range of adenoma burden (6 to 25+ adenomas per patient), and adenoma incidence may accelerate with increased age [16, 24, 25]. No difference in E1317Q prevalence among subjects with single (2%) versus multiple (0.7%) adenomas has been reported [19].

In our study, neoplasia risk was elevated in E1317Q variant carriers (OR 4.8, 2.1–10.9). When examined by neoplasia type, adenoma risk was significantly increased (OR 4.6, 2.0–10.8) whereas CRC risk was not (OR 2.1, 0.8–5.6). A recent population-based study of 1834 matched cases and polyp-free controls also found no association between CRC and E1317Q [20]. In our sample, CRCs occurred earlier than usual (mean age 56 years) and were primarily left sided; adenomas were generally solitary, small, and displayed low-grade dysplasia. When these data are considered along with the existing literature, the E1317Q variant appears to have variable penetrance, with adenoma risk outweighing CRC risk. The increased magnitude of adenoma risk may be due to the degree of polyp burden in variant carriers, with those carriers manifesting a higher polyp burden being at greater risk for cancer. Adenomas in E1317Q variant carriers may also be more plentiful but may have a lower malignant potential than in noncarriers.

We found that family history of neoplasia in a first-degree relative was not associated with the presence of the E1317Q variant. Equally, the absence of difference among cases and controls (P = 0.66) for family history versus personal history (4.4% cases versus 2.4% controls, P = 0.03) also warrants further investigation. Several authors have reported E1317Q carriers with a personal history of adenomas but little or no family history [17, 24, 25]. Low-penetrance gene variants may be less likely to produce strong family history, particularly when family history is not a criterion for study ascertainment [26]. Family members may also be less aware of familial precancer risk (adenoma) than cancer risk, and healthy individuals often misclassify familial cancer history, even among close relatives [27]. Finally, when total family size is small, as is common among Israeli Jews, the utility of family history as a marker of inherited cancer predisposition is diminished because fewer at-risk individuals are available to develop disease [28].

Our results may be limited by selection bias. Selection biases can occur in referral populations (differential referral), screening studies (differential participation), and cohort studies (differential follow-up). Our efforts to minimize selection bias (diagnosis-blind open enrollment through both tertiary care and community-based sites) are unlikely to fully correct these issues. Additionally, while selective screening practices, with E1317Q carriers receiving more intensive screening than noncarriers, could also impact these findings, our subjects and practitioners were blinded to E1317Q status. Overall, cohort participation rates were high (>90%), and nearly all subjects completed an enrollment colonoscopy and genetic testing for E1317Q once testing began (>98%). Finally, while several pathological characteristics of adenomas in E1317Q variant carriers are reported here (see ‘Results’ section), a comprehensive review of CRC histopathologic characteristics, including several with known prognostic significance (e.g. tumor differentiation), is to date still under development.

While the clinical implications of this work are considerable, further studies are needed to confirm our findings and to better characterize the risk of colorectal neoplasia secondary to APC E1317Q. If the neoplasia risk and increased prevalence of E1317Q in the Sephardim are corroborated, population screening for the variant could be considered as a means to improve early detection of colorectal adenomas and CRCs by initiating colorectal screening measures in variant carriers at an early age. In this setting, we would suggest that carriers be offered screening colonoscopy beginning at 40 years of age and that all first-degree relatives of known carriers be evaluated for this mutation.

funding
Israel Cancer Association to NA; Israel Science Foundation (1156/05) to NA; Israeli Academia to NA; American Cancer Society (MRSG-07-232-01-CPHPS) to MJH.

references