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Inherited Colorectal Polyposis and Cancer Risk of the *APC I1307K* Polymorphism

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Summary

Germ-line and somatic truncating mutations of the *APC* gene are thought to initiate colorectal tumor formation in familial adenomatous polyposis syndrome and sporadic colorectal carcinogenesis, respectively. Recently, an isoleucine→lysine polymorphism at codon 1307 (*I1307K*) of the *APC* gene has been identified in 6%–7% of the Ashkenazi Jewish population. To assess the risk of this common *APC* allelic variant in colorectal carcinogenesis, we have analyzed a large cohort of unselected Ashkenazi Jewish subjects with adenomatous polyps and.or colorectal cancer, for the *APC I1307K* polymorphism. The *APC I1307K* allele was identified in 48 (10.1%) of 476 patients. Compared with the frequency in two separate population control groups, the *APC I1307K* allele is associated with an estimated relative risk of 1.5–1.7 for colorectal neoplasia (both $P = .01$). Furthermore, compared with noncarriers, *APC I1307K* carriers had increased numbers of adenomas and colorectal cancers per patient ($P = .03$), as well as a younger age at diagnosis. We conclude that the *APC I1307K* variant leads to increased adenoma formation and directly contributes to 3%–4% of all Ashkenazi Jewish colorectal cancer. The estimated relative risk for carriers may justify specific clinical screening for the 360,000 Americans expected to harbor this allele, and genetic testing in the setting of long-term–outcome studies may impact significantly on colorectal cancer prevention in this population.

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Introduction

Approximately 15%–20% of colorectal cancer (CRC), the second leading cause of cancer death in North America, occurs in familial aggregations (Cannon-Albright et al. 1988; Landis et al. 1998). Familial adenomatous polyposis (FAP), caused by an inherited functional mutation of one copy of the adenomatous polyposis coli gene (*APC* [MIM 175100]) is thought to account for <1% of all CRC (Kinzler and Vogelstein 1996). Germline mutation of a DNA mismatch-repair gene, causing hereditary nonpolyposis colorectal cancer (HNPCC), is believed to be responsible for ~2% of CRC (Aaltonen et al. 1998). The majority of the remaining hereditary CRC is unexplained. It is plausible that relatively common but less penetrant alleles may account for a significant proportion of inherited or even seemingly sporadic CRC. The isoleucine→lysine polymorphism at codon 1307 of the *APC* gene (*APC I1307K*) recently has been reported to be carried by 6.1% of New York Ashkenazi Jewish individuals (Laken et al. 1997) and 7.0% of Washington, DC, Ashkenazim (Woodage et al. 1998). In contrast with these control populations, the carrier frequency of this allele was significantly elevated, to 28%, in 28 Ashkenazi persons with a personal and family history of CRC (Laken et al. 1997). Bayesian analysis of genetic linkage in these families confirmed this increased risk of CRC (Peterson et al. 1998).

Mechanistically, the sequence encoded by the *APC I1307K* polymorphism is hypermutable compared with wild-type *APC* sequence (Laken et al. 1997; Gryfe et al. 1998). This mutational susceptibility leads to somatic biallelic inactivation of the *APC* gene and to colorectal tumorigenesis (Gryfe et al. 1998). Despite *APC I1307K* encoding a polyadenine nucleotide repeat, hypermutability of this sequence was not accounted for by tumor microsatellite instability (Gryfe et al. 1998). Although previous findings clearly support the somatic hypermutability of the *APC I1307K* genomic sequence, subtle functional impairment of the *APC I1307K* gene product cannot be excluded.

The actual risk of *APC I1307K* for colorectal neoplasia remains controversial. When data from patients

with a family history of CRC were combined with data from additional individuals not ascertained by family history, a 10.4% *APC I1307K* carrier frequency among 211 patients with CRC was observed (Laken et al. 1997). These findings support a modest odds ratio (OR) of 1.8 (95% confidence interval [95%CI] 1.05–2.8; $P = .03$) for subjects with colorectal neoplasia, compared with controls. A similar but statistically insignificant risk estimate for CRC (OR 1.9; 95%CI 0.84–4.2) was observed among 55 individuals with CRC and 5,026 unaffected controls (Woodage et al. 1998). The *APC I1307K* polymorphism was originally identified in an individual with eight colorectal adenomatous polyps (Laken et al. 1997). More recently, the polymorphism was found to be carried by three (38%) of eight British Ashkenazi Jews with multiple adenomas (Frayling et al. 1998). However, to date there has been no large-scale systematic study of the phenotypic effects of the *APC I1307K* allele. Thus, the relative risk of *APC I1307K* for colorectal polyposis and cancer remains incompletely understood, but it is of great importance to the >360,000 American Ashkenazi Jews estimated to carry this allele.

To elucidate the attributable risk and phenotypic effects of the *APC I1307K* polymorphism, we have evaluated a large cohort of unselected Ashkenazi Jewish patients with either CRC or adenomatous polyps. The *APC I1307K* variant was present in a significantly increased proportion of this colorectal-tumor population, compared with that in controls, and carriers were observed to have significantly elevated numbers of malignant and premalignant colorectal neoplasms, compared to noncarriers. These findings support a significant biological role for this allele in CRC predisposition.

Subjects and Methods

Cohort and Phenotypic Data

Subjects were identified by searching Mount Sinai Hospital records for Jewish patients who had been admitted for surgery during 1977–97 and who had a diagnosis of colorectal adenocarcinoma and/or adenomatous polyps. Additionally, a case series of Jewish patients with either pancreatic and ampullary adenocarcinoma who previously had been analyzed for the BRCA2 mutation (Ozcelik et al. 1997) were further investigated for the current study. It is estimated that >90% of Jews from the greater Toronto area are of Ashkenazi origin (J. Brodbar [Jewish Federation of Greater Toronto, United Jewish Appeal Canada], personal communication). All pathology specimens for each subject were reviewed, and a database was prepared with patient- and pathology-phenotypic features. Individuals with FAP were excluded from analysis, and patients with underlying inflammatory bowel disease were analyzed separately. Because accurate and consistent assessment of family cancer histories could not be ensured by retrospective chart review of this cohort, no attempt was made to obtain this information.

Representative normal and tumor tissues from each individual were identified from paraffin-embedded surgical pathology samples, and unstained and hematoxylin- and eosin-stained sections were prepared for DNA analysis. In accordance with genetic-testing research guidelines (Clayton et al. 1995) and institutional approval, these samples were stripped of identifiers and were coded to anonymously link them to the phenotypic database prepared prior to blinded genetic testing. Patients with the same surname were given consecutive DNA-sample numbers, to indicate that they might be related. Normal genomic DNA was isolated from microdissected paraffin-embedded tissues, by standard proteinase K digestion (Jen et al. 1994).

APC I1307K *Germ-Line Analysis*

Codons 1303–1317 of the *APC* gene were amplified by PCR, from normal genomic DNA template, with the following primers: forward, 5′-AGATTCTGCTAATACCCTGC-3′; and reverse, 5′-GAACTTCGCTCACAGGATC-3′. Single-strand conformation polymorphism (SSCP) analysis of the denatured 83-bp PCR product was performed by means of 9–10-W electrophoretic separation on an 8% polyacrylamide gel with 5% glycerol, at 4°C for 16 h. All positive samples were confirmed by dideoxy chain-termination reaction ThermoSequenase (Amersham) sequencing of an independent PCR amplification product from a newly prepared second genomic DNA sample from the same case. Given the unlinked nature of the samples, neither carriers nor noncarriers were notified of the test results.

Statistical Methods

APC I1307K carrier rates in patients with colorectal tumor and in control populations were compared by either χ^2 or Fisher's exact test, as were other categorical factors (i.e., gender and anatomical site of CRC) in *APC I1307K* carrier and noncarrier patients with colorectal tumor. *APC I1307K* carrier and noncarrier continuous variables (i.e., colorectal and extracolonic tumor number per patient and age at diagnosis) were compared by Student's *t*-test, with Welch's correction for unequal variances when appropriate. Carrier and noncarrier cumulative colorectal-tumor distributions by age at diagnosis were estimated by the Kaplan-Meier method and were compared by the log-rank test.

Results

We identified 3,535 patients who had undergone surgical resection for either CRC or adenoma, and, in their admitting record, 491 (13.9%) of these individuals indicated that they were Jewish. Blocks were retrieved, and amplifiable DNA was obtained in 476 (96.9%) of these 491 cases (fig. 1). The *APC I1307K* polymorphism was detected in the germ line of 48 (10.1%) of these 476 patients (table 1). The frequency of this *APC* allelic variant was similar in both the patients with cancer and the patients with only adenoma. Although no CRC family-history data was available, none of the 48 *APC I1307K* carriers had redundant surnames.

APC I1307K-carrier demographic features and tumor phenotype were compared with those of noncarriers (table 2). No significant difference was found in either patient gender or anatomic location of CRC. Mean age at CRC diagnosis was ~2 years younger in *APC I1307K* carriers than in noncarriers ($P = .13$). Comparison of the cumulative distribution curves (fig. 2) revealed a significantly younger age at tumor diagnosis in *APC I1307K* carriers compared with noncarriers (hazard ratio 1.45; 95%CI 1.09–2.21; $P = .01$).

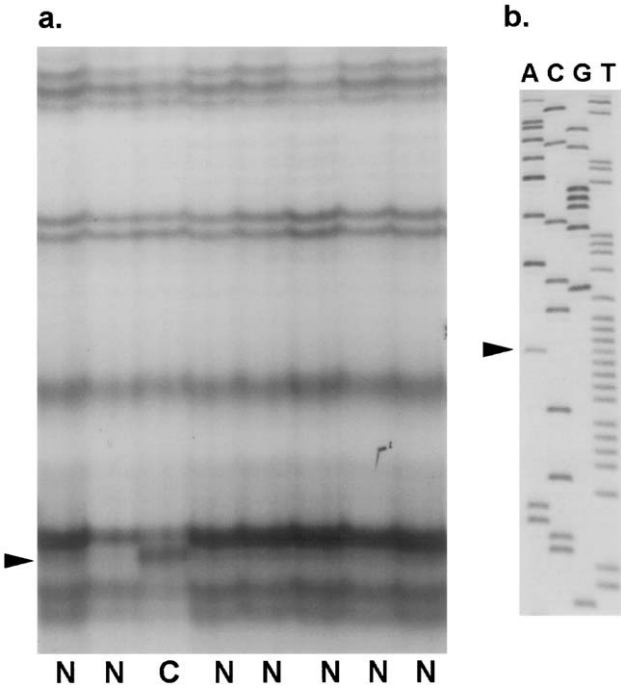

Figure 1 *a*, SSCP analysis of *APC* codons 1303–1317. Lanes N, PCR product from patients without *APC* alteration. Lane C, PCR product from a carrier of the *APC I1307K* alteration. The arrowhead points to the *APC I1307K* band with altered electrophoretic mobility. *b*, Reverse-primer sequence of *APC* of germ-line tissue from an *APC I1307K* carrier. The arrowhead points to the polymorphic T→A substitution.

Table 1

***APC I1307K* Carrier Rates**

Category	No. (%)	
	I1307K Carriers	Total
Patients with CRC	41 (10.1)	404
Patients with adenoma	7 (9.7)	72
Total	48 (10.1)	476

Analysis of tumor numbers revealed striking differences between *APC I1307K* carriers and noncarriers (table 2). The 48 *APC I1307K* carriers were found to have 139 colorectal cancers and adenomatous polyps, compared with 835 colorectal neoplasms identified in 428 noncarriers. In terms of OR, this corresponds to a relative-risk estimate of 1.48 (95%CI 1.05–2.10; $P = .03$) for colorectal neoplasia in *APC I1307K* carriers. Furthermore, the *APC I1307K* carrier rate steadily increased with colorectal neoplasm number (fig. 3; for the trend, $P = .001$). Of the four patients with >10 colonic neoplasms, two were found to be *APC I1307K* carriers. In contrast to FAP, no microscopic adenomas were identified in routine histologic sections of flat mucosa from any of the *APC I1307K* carriers.

APC I1307K carriers were no more likely to have extracolonic cancers than were noncarriers (table 2). The only extracolonic cancers present in carriers were one breast cancer and one bladder cancer, and these were also present, at a similar frequency, in noncarriers (seven breast cancers and eight bladder cancers). All other extracolonic cancers in the noncarriers were present at frequencies <1%.

To assess the contribution of *APC I1307K* to colitis-associated neoplasia and pancreatic and ampullary carcinomas, we separately analyzed Ashkenazi Jewish individuals affected by these conditions. Of seven patients with underlying inflammatory bowel disease and either CRC or adenoma/dysplasia, none were found to be *APC I1307K* carriers. Two (5.7%) of 35 patients with pancreatic cancer and 0 of 6 patients with ampullary cancer were identified as being *APC I1307K* carriers.

Discussion

Our study provides several lines of evidence that *APC I1307K* is associated with a modest but clinically significant increase in the risk of CRC. The 10.1% *APC I1307K* carrier frequency observed in our unselected patients with either CRC or adenoma is significantly elevated compared with the previously published 6.1% (47/766) carrier rate in non-CRC Ashkenazi Jewish controls

Table 2

***APC I1307K* Carrier and Tumor Phenotype**

	No. (%) of Individuals	
	I1307K	Non-*I1307K*
Gender:		
Male	26 (54)	239 (56)
Female	22 (46)	189 (44)
CRC site:		
Right	13 (28)	141 (36)
Left	20 (43)	149 (38)
Rectum	14 (30)	101 (26)
Mean age of patients ± SE (years)	70.2 ± 1.2	72.2 ± .5
Tumor types (per patient ± SE):		
CRCs	.98 ± .42	.91 ± .02
Adenomas[a]	1.92 ± .08	1.04 ± .08
Total[a]	2.90 ± .42	1.95 ± .08
Extracolonic cancers	2 (4.2)	32 (7.5)

[a] There was a significant difference between *APC I1307K* carriers and noncarriers ($P < .05$).

ascertained through a New York Tay-Sachs screening program ($P = .01$; Laken et al. 1997). On the basis of the OR, the estimated relative risk for colorectal neoplasia in *APC I1307K* carriers is 1.72 (95%CI 1.13–2.61). Recently, a Washington, DC, series, which included both unaffected individuals and those with a variety of cancers, demonstrated an *APC I1307K* carrier rate of 7.0% (326/4,635 [Woodage et al. 1998]). Compared with this control estimate, our observed rate of *APC I1307K* in patients with colorectal tumor is significantly elevated, to a similar degree (OR 1.48; 95%CI 1.08–2.04; $P = .01$). Furthermore, because the *APC I1307K* polymorphism predisposes to adenoma formation that is often asymptomatic, the carrier rate in control populations may overestimate the true unaffected-carrier rate—and thus lead to an underestimate of the risk of *APC I1307K* for colorectal neoplasia.

Testing of a large Toronto control group to establish the local carrier rate of *APC I1307K* was not possible for the current study. However, results of previous studies of founder mutations in North American Ashkenazi populations make feasible the comparison of our Toronto *APC I1307K* data with data on previously published controls. First, no significant difference was observed in *APC I1307K* control carrier frequencies derived from the large New York and Washington, DC, studies (Laken et al. 1997; Woodage et al. 1998). Second, previous studies have revealed that the rates of three founder mutations of the hexosaminidase gene were similar in five urban American and Canadian Ashkenazi populations, including that of Toronto (Fernandes et al. 1992). Third, the rates of three BRCA1 and BRCA2 founder mutations have been observed to be similar in different American Ashkenazi control populations (Roa et al. 1996; Oddoux et al. 1996; Struewing et al. 1997). Presumably, carrier rates of all these allelic variants are similar in various urban centers because they arose in Ashkenazi ancestors long ago and were not significantly influenced by later migration to North America.

Our OR estimate of 1.72 is slightly lower than previous risk estimates of the *APC I1307K* allele but is supported by both a tighter confidence interval and more-powerful statistical association. The number of patients with colorectal tumors who were included in the present study is more than double that in previous studies, and the inclusion of only unselected cases avoids the potential biases of family-history selection (Laken et al. 1997) and volunteers (Woodage et al. 1998) that are present in previous *APC I1307K* CRC analyses. Our 10.1% carrier frequency is significantly lower than either the 28% rate observed in individuals with a personal and family history of CRC ($P = .02$; Laken et al. 1997) or the 38% rate observed in persons with multiple adenomas ($P = .04$; Frayling 1998). However, both these selected populations were very small and may have been influenced by other environmental or genetic modifiers.

Two additional independent findings support a predisposition to colorectal neoplasia in *APC I1307K* carriers. First, cumulative colorectal-tumor distribution by age at diagnosis was significantly shifted to a younger age in carriers, compared with that in noncarriers. Although this effect was small in terms of absolute mean age at diagnosis, it supports a definite biological effect and is in agreement with previous findings (Laken et al. 1997). Second, carriers were found to have an increase

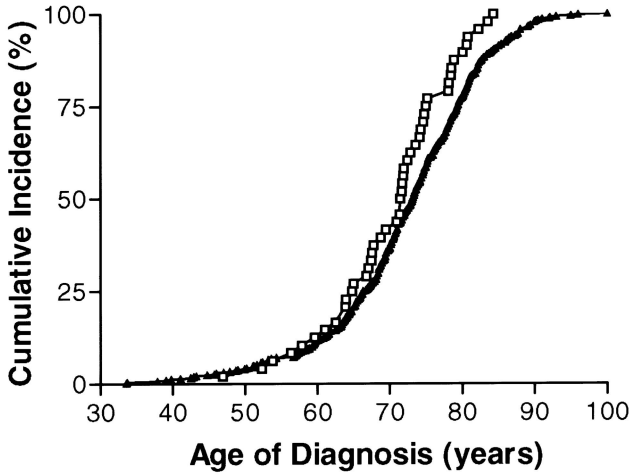

Figure 2 Cumulative distribution of time until colorectal-tumor diagnosis, for *APC I1307K* carriers (□) and noncarriers (▲). The time until colorectal-tumor diagnosis in *APC I1307K* carriers is significantly shifted to a younger age, compared with that in noncarriers ($P = .01$).

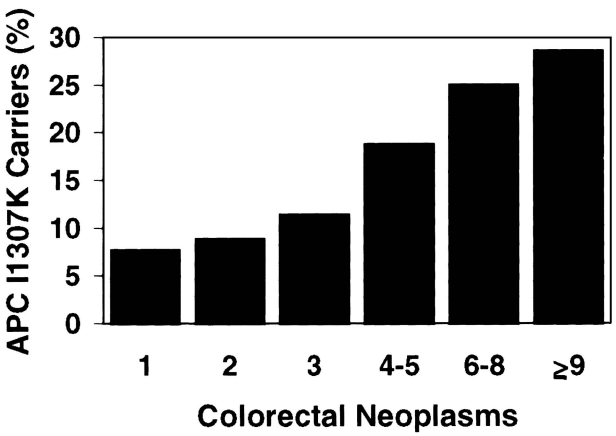

Figure 3 *APC I1307K* carrier rate and number of colorectal neoplasms. A significant correlation between *APC I1307K* carrier frequency and an increasing number of colorectal neoplasms is observable ($P = .001$).

in the number of colorectal neoplasms, with an estimated relative risk of 1.48. This value closely parallels the relative risk predicted from carrier-rate data and introduces a novel and potentially powerful method to independently quantify risk of colorectal-tumor initiation from low-penetrant exposures (either genetic or environmental).

If it is assumed that CRC risk in the Ashkenazi Jewish population is the same as that in the general American population, then the estimated relative risks suggest that the lifetime risk that *APC I1307K* carriers will develop CRC is ~9%–10% (Landis et al. 1998). Although these relative-risk estimates are consistent with a low-penetrant predisposition allele, there is a significant associated clinical effect due to the common occurrence of this allele in the population. In fact, both our carrier frequency and our previously published allele-specific somatic mutation rate (Gryfe et al. 1998) suggest that 3%–4% of all Ashkenazi Jewish colorectal neoplasia may be directly attributable to *APC I1307K*. Thus, although lifetime risks to the individual carrier are only 9%–10%, this likely represents a more significant contribution to the overall burden of colorectal neoplasia in this population than is imparted by FAP and HNPCC combined. However, one consequence of the relatively low penetrance of the *APC I1307K* allele predicted from the present study is that analyses of allele frequency in probands not ascertained for CRC—such as those analyses that recently have been published (Petrukhin et al. 1997; Abrahamson et al. 1998; Woodage et al. 1998)—are unlikely to detect a significant association with a positive family history of CRC, unless very large numbers of individuals are tested.

The overrepresentation of carriers in the subgroup of individuals with multiple colorectal neoplasms is particularly interesting from a clinical viewpoint. Overall, there were 59 patients with four or more colorectal neoplasms, who represented 12% of the total cohort, and 13 (22%) of these 59 were *APC I1307K* carriers. Of the four patients with ⩾10 colorectal neoplasms (range 10–19), two were found to be *APC I1307K* carriers. Attenuated adenomatous polyposis coli (AAPC) has previously been characterized by both increased adenoma formation (range 10–99) and nonsense germ-line mutations at the extreme 5′ and 3′ ends of the *APC* gene (Spirio et al. 1993; van der Luijt et al. 1996). Our findings suggest that, in addition to these previously observed *AAPC* mutations, other mechanisms may contribute to the appearance of multiple adenomas. We predict that a significant fraction of patients with multiple polyps may have an important inherited predisposition due to either less-penetrant *APC* alterations or other modifier genes. Results of our study indicate that careful examination of the pathological phenotype may be a powerful method to accurately identify these patients and characterize the contribution from their inherited predisposition.

Using several independent lines of evidence, we have demonstrated relative-risk estimates of ~1.5–1.7 for colorectal neoplasia in *APC I1307K* carriers. These results raise important public-health issues regarding clinical screening and genetic-testing recommendations. Our risk estimates are similar to those that have been calculated for persons with a family history of either CRC or adenoma in a first-degree relative (Fuchs et al. 1994; Winawer et al. 1996), for whom the American Gastroenterology Association (AGA) has advocated more-stringent clinical screening (Winawer et al. 1997). The CRC age-at-diagnosis data from the present study (fig. 2) suggest that standard AGA clinical screening beginning at age 50 years (Winawer et al. 1997) is likely to be effective for *APC I1307K* carriers who do not have a significant family history but who do have a modestly increased risk for development of CRC. However, in view of previous findings in individuals with a family history of either CRC or adenomatous polyps (Laken et al. 1997), more-rigorous clinical screening beginning at a younger age should be recommended to *APC I1307K* carriers who have a significant family history.

Genetic testing for the *APC I1307K* polymorphism in the Ashkenazi Jewish population is a more contentious issue and of great importance to the 360,000 predicted carriers in the United States. Issues surrounding positive genetic tests—such as potential negative psychological effects and difficulties in obtaining insurance—have led the American Society of Clinical Oncology (ASCO) to support genetic testing for cancer predisposition only in the setting of a strong family history (American Society of Clinical Oncology 1996). Such histories are likely to

be absent, with the lower penetrance of *APC I1307K*. Furthermore, neither a positive nor a negative genetic result for this allele is likely to have an impact on clinical screening recommendations in individuals with a strong family history. However, several additional factors must be considered before recommendations regarding testing for the *APC I1307K* allele are made. First, CRC is a common and often fatal disease that is potentially preventable by endoscopic screening. Second, >80% of CRC occurs in the absence of a family history for this disease (Cannon-Albright et al. 1988). Third, in accordance with ASCO guidelines (American Society of Clinical Oncology 1996), *APC I1307K* testing is easily interpreted, and positive test results are likely to influence medical management in the majority of individuals. Despite both the common occurrence of CRC and the effectiveness of colonoscopy, screening compliance remains poor (Centers for Disease Control and Prevention 1996). However, individuals without a family history of CRC who are aware of their *APC I1307K* carrier status and who are at modestly increased risk for development of CRC may be more motivated to undergo colonoscopic screening. Our data indicate that genetic testing of Ashkenazi Jews with or without a family history of CRC, followed by appropriate clinical screening, might significantly benefit the 9%–10% of carriers expected to develop CRC. Similarly, screening of these individuals could potentially lead to either the prevention or early diagnosis of ~10% of all Askenazi Jewish CRC. Because the full impact of genetic testing on this population is not currently known, it should only be conducted in conjunction with pre- and posttest genetic counseling and in the setting of long-term–outcome research studies. Further studies will be required to accurately determine how family history and other genetic and environmental factors could influence neoplasia risks in *APC I1307K* carriers.

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Electronic-Database Information

The accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for *APC* [MIM 175100])

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