

# The APC I1307K allele and breast cancer risk

The I1307K variant of *APC* occurs in approximately 6% of Ashkenazi Jews and has been associated with familial colorectal neoplasia. In four of the eight pedigrees characterized by Laken *et al.*<sup>1</sup>, women who may be heterozygous for this allele were diagnosed with breast cancer. Animal models suggest a relationship between *Min*, a mutant allele of the mouse *Apc* gene, and breast neoplasia, with approximately 5% of B6 *Min*/+ females reported to develop breast tumours<sup>2</sup>. Loss of heterozygosity or comparative genomic hybridization studies have identified 5q or the *APC* region as sites of loss in both *BRCA1*-mutated and *BRCA1* wild-type breast tumours<sup>3-6</sup>, suggesting a possible role for *APC* in the progression of a subset of breast tumours. We speculated that Ashkenazi Jewish women with breast cancer may be more likely to have the I1307K allele than unaffected Ashkenazi Jewish controls.

We determined the frequency of this polymorphism in 632 unrelated women with primary invasive breast cancer who were not selected for a family history of breast or ovarian cancer, and who self-reported as being of Ashkenazi Jewish descent. Cases were diagnosed at three centres: 216 in Toronto, 215 in New York (Memorial Sloan-Kettering Cancer Center (MSKCC)) and 201 in Montreal (SMBD-Jewish General Hospital). The Montreal cases were all diagnosed before age 65, whereas 73 of the 215 MSKCC cases were diagnosed before age 42. The remainder of the 632 cases were unselected for age. For 115 of the MSKCC cases, and all Montreal cases, the field for religion on the medical chart was used to select self-identified individuals of Jewish religion with breast tumour tissue available for study. Paraffin blocks were obtained and analysed anonymously. In 100 cases at MSKCC and all cases at Toronto, questionnaires were used to determine religious and geographical background from individuals with personal histories of breast cancer, irrespective of whether they had a family history of the disease. DNA was obtained from peripheral lymphocytes for these samples.

We studied familial breast cancer cases by recruiting affected Ashkenazi Jewish individuals with at least two first or second degree relatives with breast and/or ovarian cancer from the Fox Chase Cancer Center (n=74), the University of Pennsylvania Medical Center (n=59), MSKCC (n=53) and the Dana-Farber Cancer Center (n=36). The prevalence of the I1307K allele

was estimated in a control group of 4,635 unrelated individuals of self-reported Ashkenazi Jewish ancestry who were participating in a Washington D.C. area genetic epidemiologic study<sup>7</sup> and in 320 volunteers for Tay-Sachs screening in California. IRB approval of the current study was granted at all participating institutions.

Although many techniques (allele specific hybridization, single-strand conformation analysis, conformation-sensitive gel electrophoresis and amplification-created restriction site; refs 8-10) were used to detect the I1307K polymorphism, all positive cases were confirmed by direct sequencing of PCR products. All cases were also analysed for the 185delAG, 5382insC (*BRCA1*) and 6174delT (*BRCA2*) founder mutations. The hypothesis of no disease-mutation exposure was tested using a chi-square test for association; odds ratios, as estimates of the relative risk of breast cancer in association with the I1307K allele, were calculated with 95% confidence intervals.

We first analysed the family history-unselected cases. Sixty-six of 632 breast cancer cases were heterozygous for the I1307K allele (10.4%; Table 1). This proportion was significantly greater than the 7.03% carrier frequency observed in Ashkenazi Jewish volunteers from the Washington D.C. study<sup>7</sup> ( $P=0.003$ ), corresponding to an odds ratio (OR) of 1.5 (95% CI=1.2-2.0). This estimate of the carrier frequency in Ashkenazi Jewish controls is probably high, because the frequency in the Washington study cohort

was 6.8% when individuals with self-reported histories of cancer were excluded from analysis<sup>7</sup>. We also observed a control frequency of 5.6% for the allele in 320 volunteers for Tay-Sachs testing. When the group selected for family history were included in the analysis, the magnitude of the effect decreased (OR=1.4, 95% CI=1.1-1.8), but only 17 individuals from high-risk clinics carried the I1307K allele. Moreover, restricting the analysis to *BRCA* mutation carriers revealed a possible association between the three *BRCA* founder mutations and *APC* polymorphism status; the frequency of the I1307K allele in the subset of patients with *BRCA* mutations was significantly greater than that observed in the control population (OR=1.9, 95% CI=1.2-3.0).

These data, and the similar frequencies of the *APC* polymorphism in patients without *BRCA* mutations compared with the control population (OR=1.4, 95% CI=1.0-1.8; Table 1), suggest that the effect of the I1307K allele on breast cancer risk is largely or entirely limited to those with *BRCA* founder mutations. This effect does not appear to operate through a shift in age-dependent penetrance, as double heterozygotes for *BRCA* founder mutations and the I1307K allele had the same mean age as women heterozygous only for *BRCA* founder mutations. In addition, in the combined group of 751 cases with a known age at diagnosis, as well as in subgroups sorted by age or family history, there was no significant difference be-

Table 1 • Frequency of I1307K in populations studied

Group	Subgroup	I1307K carriers	Total	%	OR	95% CI	P
Controls <sup>a</sup>		326 <sup>b</sup>	4635	7.0	1.0	—	—
Unselected cases							
	<i>BRCA1</i> /+	11	65	16.9	2.7	1.4-5.2	0.005
	<i>BRCA2</i> /+	5	26	19.2	3.1	1.2-8.4	0.04
	<i>BRCA1</i> /+	16	91	17.6	2.6	1.5-4.6	0.001
	+/(wt)	50	541	9.2	1.4	1.0-1.8	0.07
	All	66	632	10.4	1.5	1.2-2.0	0.003
High risk clinic cases <sup>c</sup>							
	<i>BRCA1</i> /+	8	81	9.9	1.5	0.7-3.0	0.4
	<i>BRCA2</i> /+	0	17	0.0	—	—	—
	<i>BRCA1</i> /+	8	98	8.2	1.2	0.6-2.4	0.8
	+/(wt)	9	124	7.3	1.0	0.5-2.1	0.9
	All	17	222	7.7	1.1	0.7-1.8	0.8

*BRCA1*/+ signifies heterozygotes for either the 185delAG, 5382insC *BRCA1* and 6174delT *BRCA2* mutations; +/(wt) signifies wild type (for *BRCA1/2*). <sup>a</sup>Population controls from Woodage *et al.*<sup>7</sup> <sup>b</sup>Two controls were homozygous for the I1307K allele; percentage is carrier frequency from series by Woodage *et al.*<sup>7</sup> <sup>c</sup>MSKCC, Fox Chase Cancer Center, the Cancer Risk Evaluation Program at the University of Pennsylvania and the Dana-Farber Cancer Center.

tween age at onset of breast cancer in I1307K heterozygotes compared to APC wild-type patients. These findings are consistent with possible interactions of the I1307K APC polymorphism with other as-yet-unidentified modifying factors, including both high- and low-penetrance alleles associated with familial cancer risk. Such modifiers, if over-represented in cases selected for extensive family history of disease, could account for the lower observed prevalence of the APC variant allele in this group.

A previous study did not find an excess of the I1307K polymorphic allele in 158 Ashkenazi Jewish kindreds with breast or colorectal cancers, but was not able to exclude co-segregation of the polymorphism with breast cancers in 9 of 10 pedigrees shown<sup>11</sup>. When combined with the results reported by Woodage *et al.* in this issue<sup>7</sup>, the I1307K polymorphism emerges as a candidate low-penetrance breast cancer susceptibility allele or a genetic modifier of risk in BRCA heterozygotes. In the current study, there was no significant association between breast cancer risk and the APC polymorphism in patients without germline BRCA mutations. If we assume that the effect of the I1307K allele is restricted to BRCA mutation carriers (approximately 2.5% of the Ashkenazi Jewish population), then 6% of breast cancers among BRCA heterozygotes are attributable to the I1307K allele. Therefore, although of genetic epidemiologic interest, these findings indicate that for the substantial majority of individuals of

Ashkenazi Jewish background, clinical testing for the I1307K allele is not justified outside of a research context.

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