MEDICINE

BLM Heterozygosity and the Risk of Colorectal Cancer

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Genomic instability is a hallmark of cancer and is featured prominently in Bloom syndrome. Bloom syndrome, the prototype of somatic mutational disorders, is a rare autosomal recessive disorder characterized by a profound predisposition to cancer. Bloom syndrome is caused by inactivating, germline mutations of the RecQ DNA helicase *BLM* (*1*).

Most autosomal recessive disorders require two mutant copies of a gene to express the phenotype, although subtle features of a disorder may be evident in gene carriers with only one mutant allele. To determine whether carriers of *BLM* mutations are at an increased risk of colorectal cancer (CRC), we genotyped 1244 cases of CRC and 1839 controls, both of Ashkenazi Jewish ancestry, to estimate the relative risk of CRC among carriers of the BLM^{Ash} founder mutation. Israeli cases and controls were from the Molecular Epidemiology of Colorectal Cancer study, with incident cases ascertained from all hospitals in a geographically defined region in northern Israel diagnosed since March 1998 and population-based controls without CRC matched by age, gender, clinic, and ethnic heritage. New York cancer cases were identified through a hospital-based series at Memorial Sloan-Kettering Cancer Center beginning in 1997. Controls from New York were ascertained from 1003 healthy volunteers of Ashkenazi descent participating in the New York Cancer Project, an ongoing cohort study of over 17,000 volunteers of varying ethnic backgrounds ages 30 to 69 living in metropolitan New York.

Ashkenazi Jews with CRC were more than twice as likely to carry BLM^{Ash} than Ashkenazi Jewish controls without CRC [odds ratio (OR) =2.45; 95% confidence interval (CI) 1.3 to 4.8; P= 0.0065]. The Israeli controls appeared representative of the Ashkenazi Jewish population, because, as expected, 2.1% carried *BRCA1/2* founder mutations and 6.1% carried the *APC* I1307K allele. In Israel, it was possible to evaluate whether each individual carrying BLM^{Ash} represented a unique kindred; no carriers were related, reducing the possibility that the results could be biased by the presence of one or two large families in which other disease genes might be segregating. To further minimize the possibility that our results arose by chance, we compared the heterozygote frequency in patients with CRC with the total carrier frequency observed in our data and in published surveys of BLM^{Ash}. Again, we found that CRC patients were significantly more likely to carry BLM^{Ash} than the surveyed populations of Ashkenazi Jews, with an OR = 2.34 (95% CI 1.5 to 3.7; P = 0.0002). Analyses using only published controls (excluding our two groups of controls) remained statistically significant (OR = 2.3; 95% CI 1.4 to 3.7, P = 0.0004) (Table 1).

Table 1. BLM^{Ash} heterozygote frequency among Ashkenazi Jews.

Ashkenazi Jews with colorectal cancer	BLM^{Ash}	BLM^{WT}	Total	Carrier frequency
Israel	12	887	899	1/75
New York	11	334	345	1/31
Summary: colorectal cancer	23	1,221	1,244	1/54
Ashkenazi Jewish controls (without colorectal cancer)				
Israel population controls	5	831	836	1/167
New York healthy volunteers	9	994	1,003	1/111
Prenatal screening: Tel Aviv (*4*)	16	1,597	1,613	1/101
Prenatal screening: New York (*5*)	14	1,477	1,491	1/107
Prenatal screening: NYU (*6*)	5	1,150	1,155	1/231
Clinic screening: Tel Aviv (*7*)	36	3,965	4,001	1/111
Summary: controls	85	10,014	10,099	1/118

A founder polymorphism of the *APC* tumor suppressor gene, *APC* I1307K, also doubles the risk of colon cancer among carriers (*2*). To assure that *APC* I1307K did not confound our results, we used logistic regression to adjust for the presence of this allele and found nearly identical results. Adjusting for age, sex, and study center (New York versus Israel) showed an overall OR of 2.76 (95% CI 1.4 to 5.5; P = 0.0045) for BLM^{Ash} carriers.

We also examined the frequency of BLM^{Ash} in other cancers. BLM^{Ash} was observed in 1 of 108 lymphoma cases, 5 of 375 breast, 0 of 154 prostate, 1 of 174 ovarian, and 1 of 149 uterine cancer cases.

A recent mouse model of Bloom syndrome tested for the effect of *Blm* haploinsufficiency; risk of cancer in mutation carriers, because mice heterozygous for *Blm* developed twice the number of intestinal tumors when crossed with mice carrying a mutation of the *Apc* tumor suppressor gene (*3*). Our data similarly show that carriers of a *BLM* mutation have an increased risk for CRC. Possible mechanisms of carcinogenesis include (i) haploinsufficiency, in which a half dose of *BLM* gene product is insufficient for full *BLM* function in the maintenance of genomic integrity, giving rise to an increased mutation rate in the heterozygous cell, and (ii) loss of the normal *BLM* allele in a colonic stem cell, giving rise to a cell clone with the same hypermutability as the Bloom syndrome cell. Whichever the mechanism, our data confirm the importance of genomic instability as a critical element in the pathogenesis of cancer.

References and Notes

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