RESEARCH ARTICLE

The *ATM* Missense Mutation p.Ser49Cys (c.146C>G) and the Risk of Breast Cancer

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Homozygous mutation in the *ATM* gene causes ataxia telangiectasia and heterozygous mutation carriers may be at increased risk of breast cancer. We studied a total of 22 *ATM* variants; 18 variants were analyzed in one of two large population-based studies from the U.S. and Poland, and four variants were analyzed in all 2,856 breast cancer cases and 3,344 controls from the two studies. The missense mutation Ser49Cys (c.146C>G, p.S49C), carried by approximately 2% of subjects, was more common in cases than controls in both study populations, combined odds ratio (OR) 1.69 (95% CI, 1.19–2.40; P = 0.004). Another missense mutation at approximately 2% frequency, Phe858Leu (c.2572T>C, p.F858L), was associated with a significant increased risk in the U.S. study but not in Poland, and had a combined OR of 1.44 (95% CI, 0.98–2.11; P = 0.06). These analyses provide the most convincing evidence thus far that missense mutations in *ATM*, particularly p.S49C, may be breast cancer susceptibility alleles. Because of their low frequency, even larger sample sizes are required to more firmly establish these associations. Hum Mutat 27(6), 538–544, 2006. Published 2006 Wiley-Liss, Inc.[†]

KEY WORDS: *ATM*; breast cancer; association; epidemiology

INTRODUCTION

Ataxia telangiectasia (AT; MIM♯ 208900) is a rare autosomal recessive disease (frequency of 1/40,000 or less, heterozygote carrier frequency <~1%) characterized predominantly by severe progressive cerebellar degeneration and increased rates of leukemia and lymphoma [McKinnon, 2004]. For nearly 20 years it has been suggested that obligate heterozygote mutation carriers, who are phenotypically normal, are at increased risk of breast cancer [Swift et al., 1987]. Although once controversial [Khanna, 2000], epidemiologic studies among relatives of AT patients have confirmed a modest breast cancer risk among obligate heterozygotes [Swift et al., 1991; Geoffroy-Perez et al., 2001; Olsen et al., 2001; Thompson et al., 2005b].

The *ATM* (ataxia telangiectasia mutated; MIM♯ 607585) gene, cloned in 1995, is very large and mutations occur throughout its amino acid coding portions [Savitsky et al., 1995]. Although somewhat biased, owing to the mutation screening methods applied to such a large gene, such as the protein truncation test, most of the mutations identified thus far in AT patients are protein-truncating. The initial cancer observations in obligate carriers from AT families imply that AT-causing mutations underlie the increased breast cancer risk. Complete mutation screening of the *ATM* gene in breast cancer patients, however, has generally not identified a significant number of AT-related mutations in cases compared to controls, although the diversity and extremely low frequency of detected mutations has resulted in studies of insufficient power [FitzGerald et al., 1997]. Additionally, haplotypes defined by common SNPs across the gene have not shown any association with breast cancer [Tamimi et al., 2004; Lee et al., 2005].

To explain the inability to identify protein-truncating *ATM* mutations in breast cancer patients, a model has been proposed suggesting that missense and truncating mutations could be

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associated with distinct phenotypes, namely, cancer and neurological diseases [Gatti et al., 1999]. This reasoning is not entirely satisfactory, however, because it does not explain how the initial breast cancer risk association was discovered—namely that relatives of AT patients, who necessarily have mutations that are associated with severe neurological symptoms and are usually truncating, are at increased risk of breast cancer. Nonetheless, recent evidence suggests that indeed some missense mutations are functionally relevant and predispose heterozygous carriers to breast cancer. For example, the rare missense mutation c.7271T>G (p.V2424G) has been identified in two British AT patients who have a less severe level of cerebellar degeneration [Stankovic et al., 1998]. It appears to confer an increased risk of breast cancer in these families, and shows "dominant-negative" biochemical effects [Stankovic et al., 1998; Chenevix-Trench et al., 2002; Scott et al., 2002; Thompson et al., 2005a]. Missense mutations p.V2761A, p.R2849P, and p.G2876R, identified in AT patients, also showed dominant-negative effects, whereas of the missense mutations p.S2592C, p.A2274T, p.G2287A, p.C2464R, and p.G2772R, initially identified in breast cancer patients, only p.S2592 showed dominant-negative effects when studied biochemically [Scott et al., 2002]. Although past studies have been underpowered for analysis of low frequency variants, several studies of breast cancer subjects have identified missense mutations more commonly in breast cancer patients, including the p.S49C mutation [Izatt et al., 1999; Atencio et al., 2001; Dork et al., 2001; Teraoka et al., 2001; Maillet et al., 2002; Rodriguez et al., 2002; Sommer et al., 2002; Bretsky et al., 2003; Buchholz et al., 2004].

Since complete sequence analysis of the entire *ATM* gene is still prohibitively expensive for an adequately powered breast cancer case–control study, we analyzed 22 individual *ATM* variants, including AT-associated mutations, missense mutations, and noncoding variants, in two independent study populations in the U.S. and Poland.

METHODS

Study Populations

U.S. Radiologic Technologist Study. The study of *ATM* was initiated in a nested breast cancer case–control study within the U.S. Radiologic Technologist (USRT) cohort study, a group with occupational exposure to medical sources of ionizing radiation [Sigurdson et al., 2003, 2004; Yoshinaga et al., 2004]. Eligible subjects included 1,484 prevalent breast cancer cases, both in situ and invasive, identified through questionnaires mailed during 1983–1988 and 1994–1998, and 2,183 control subjects without breast cancer as of 1999, frequency-matched to the cases by year of birth in 5-year strata. Blood samples were collected on 861 cases and 1,048 controls between 1999 and 2004, representing participation rates of 58% among cases and 48% among controls. The calendar year of breast cancer diagnoses ranged from 1955 to 2000.

Breast cancer case–control study in Poland. The second study is a case–control investigation of breast cancer conducted in Poland from 2000–2003 (M. Garcia-Closas, unpublished results). Eligible cases were women 20–74 years of age, residents of Warsaw and Łódź, who were newly diagnosed with either histologically or cytologically confirmed in situ or invasive breast cancer. Population registries were used to randomly select controls, stratified by city and age in 5-year categories. We identified 3,037 eligible cases and 3,639 eligible controls through the study period. Of these, 2,386 (79%) cases and 2,503 (69%) controls agreed to participate in a personal interview on known and suspected breast cancer risk factors. The present study is limited to women with blood DNA samples: 1,995 cases (6% in situ) and 2,296 controls, which represent 84% and 92%, respectively, of those interviewed.

Both study protocols were reviewed and approved by local and NCI Institutional Review Boards. All participants provided written informed consent. Demographic characteristics of the two study populations are shown in Supplementary Table S1 (available online at http://www.interscience.wiley.com/jpages/1059-7794/suppmat). While the prevalence of many risk factors differed considerably between the two populations, the odds ratios (ORs) were similar for both populations and of the expected magnitude and direction [Garcia-Closas, in press].

Laboratory Methods and Variant Selection

We developed Taqman 5′-nuclease allele discrimination, denaturing high-performance liquid chromatography (DHPLC), or PCR-RFLP assays for the following types of nucleotide changes in the *ATM* gene (GenBank reference sequences NP_000042.3 and AP001925.5): potentially AT-associated mutations (n = 6) identified in five or more families of diverse ethnicity (as of 2002) or in British AT patients (www.vmresearch.org/investigators/concannon_patrick/atmut-t.htm); variants with functional significance by biochemical assay (n = 4) [Scott et al., 2002]; and nonconservative missense mutations with a minor allele frequency <5% (n = 5). A single silent mutation, p.P1526P, was also studied because its frequency differed between breast cancer cases and controls in a prior study [Teraoka et al., 2001]. Additional details for all assays are given in Supplementary Table S2.

Interim analyses of association with breast cancer in the USRT study [Struewing et al., 2004] identified four variants (p.S49C, p.S707P, p.F858L, and p.P1526P) with $P \leq 0.1$, prompting us to evaluate these mutations in the Polish breast cancer study. In the Polish study, six additional noncoding SNPs, chosen from among those available at the National Cancer Institute's Core Genotyping Facility (http://snp500cancer.nci.nih.gov), were also assayed [Bonnen et al., 2002; Packer et al., 2004; Tamimi et al., 2004; Lee et al., 2005].

Genotyping quality control (QC) was assessed with duplicated DNA samples intermixed with study samples (87 DNA aliquots from eight nonstudy subjects in the USRT study, and 100 DNA pairs in the Polish study). Laboratory personnel were blinded as to the QC samples, which showed ≥99% concordance for all but one *ATM* assay (rs600329 in IVS31; 97% concordance). We observed no significant departures from Hardy-Weinberg equilibrium in the control populations for any of the assays.

Statistical Methods

We compared genotype frequencies between cases and controls using contingency table analyses and unconditional logistic regression modeling, adjusting for age and study site. Adjustment for additional variables, such as age at menarche, parity, and age at first birth within the individual study groups did not appreciably alter the estimated genotype ORs. For age-adjusted analyses, age was considered the age at diagnosis for cases; for controls from Poland, age was considered the age at interview, and in the USRT study, the age as of 1999. For variants in which all three genotype possibilities were observed, we tested for overall differences in genotype frequency between cases and controls using a likelihood ratio chi-squared test with two degrees of freedom (this does not assume dominant or recessive inheritance model). We tested for homogeneity of ORs between study groups using the Breslow-Day test as implemented in SAS 9.1 (SAS Institute, Inc., Cary, NC).

We calculated the probability of a false association, or false-positive report probability (FPRP) [Wacholder et al., 2004], to assess whether our findings were "noteworthy" and reflect true associations. The FPRP was calculated for prior probabilities ranging from 0.1 to 0.0001, based on the statistical power to detect a true OR of 1.5. This range of probabilities was chosen to reflect our prior results for the SNPs under study, i.e., 0.1 for the AT-related and missense mutations and 0.0001 for the noncoding mutations. We considered associations with an FPRP below 0.20 (i.e., less than 20% probability of being false positive findings) to be noteworthy.

Genotype frequencies were compared for cases with various survival times in the USRT study and there were no statistically significant differences. For example, the prevalence of p.S49C heterozygotes was 3.6% in subjects recruited within 10 years of their breast cancer diagnosis and 4.1% among those diagnosed more than 10 years prior to recruitment and blood collection (P = 0.8). We also noted no statistically significant differences in the genotype frequencies for any variant between invasive and in situ cases for either study group (data not shown). Therefore, estimates of relative risk are presented for both types of tumors combined.

RESULTS

We observed a significantly increased risk of breast cancer among women who were heterozygous carriers of the rare missense mutation p.S49C (Table 1). Among USRT subjects, 3.9% of cases and 2.6% of controls were heterozygous for p.S49C, while in Polish subjects 2.3% of cases and 1.2% of controls carried this mutation. Estimated ORs were not significantly different between the two study populations (P = 0.5), and the adjusted OR for the combined data was 1.69 (95% CI, 1.19–2.40; P = 0.004). p.S49C heterozygotes were found more commonly among cases under age 50 years than among older cases, whereas the frequency was similar among controls (Table 2), resulting in a stronger association with breast cancer risk in younger (OR, 2.21; 95% CI, 1.09–4.46) than older (OR 1.53; 95% CI, 0.99–2.38) women (P = 0.1 for heterogeneity of ORs). The p.F858L missense mutation was associated with significantly increased breast cancer risk in the USRT study, being carried by 3.5% of cases and 1.8% of controls (P = 0.03) (Table 1). Its frequency did not vary significantly between cases and controls in the Polish study. The study-specific ORs for p.F858L were not significantly different from each other (P = 0.2), however, and the combined OR was 1.44 (95% CI, 0.98–2.11; P = 0.06).

Table 2 shows p.S49C and p.F858L heterozygote frequencies for various subgroups of subjects. The two SNPs were slightly more common in the U.S. subjects, but generally showed consistency in their association with breast cancer. Heterozygote frequencies for p.F858L were slightly higher in subjects with a first degree relative with breast cancer compared to those with a negative family history, but p.S49C did not vary by family history.

The FPRP, or the probability that the observed association with p.S49C is a false-positive finding, was 11%, assuming the true effect size was 1.5 and the prior probability of it being associated was 0.1. Since the prior probability is as estimated quantity, we also calculated FPRPs for other priors: the FPRP was 20% or below for prior probabilities as low as 0.05, but was 57% for a prior probability of 0.01. The FPRP for the borderline significant association for p.F858L was above 20%, even for high priors (FPRPs 49% to >99%, for priors of 0.1 to 0.0001, respectively, and true OR of 1.5), indicating that this finding is likely to be a false positive.

TABLE 1. Association Between Four *ATM* Variants and Breast Cancer

SNP Name[a] (rs num)	Genotype[b]	USRT				Poland				Combined					
		Cases (N)	Controls (N)	OR (95% CI)[c]	P	Cases (N)	Controls (N)	OR (95% CI)[c]	P	Cases N	Cases %	Controls N	Controls %	OR (95% CI)[d]	P[e]
p.S49C (1800054)	Hz WT	821	1013	1.0		1933	2258	1.0		2754	97.2	3271	98.4	1.0	
	Het	33	27	1.60 (0.88–2.90)	0.1	45	28	1.88 (1.17–3.02)	0.009	78	2.8	55	1.7	1.69 (1.19–2.40)	0.004
p.S707P (4986761)	Hz WT	837	999	1.0		1923	2231	1.0		2760	98.0	3230	97.8	1.0	
	Het	14	34	0.47 (0.23–0.93)	0.03	42	39	1.25 (0.80–1.94)	0.3	56	2.0	73	2.2	0.92 (0.65–1.32)	0.7
p.F858L (1800056)	Hz WT	826	1023	1.0		1924	2230	1.0		2750	97.9	3253	98.5	1.0	
	Het	30	19	2.03 (1.05–3.90)	0.03	30	31	1.12 (0.67–1.86)	0.7	60	2.1	50	1.5	1.44 (0.98–2.11)	0.06
p.P1526P (1800889)	Hz WT	791	951	1.0		1702	1962	1.0		2493	88.3	2913	87.7	1.0	
	Het	47	87	0.75 (0.49–1.13)		273	308	1.02 (0.86–1.22)		320	11.3	395	11.9	0.93 (0.79–1.09)	
	Hz Var	2	0	Inf.		7	14	0.58 (0.23–1.43)		9	0.3	14	0.4	0.75 (0.32–1.74)	
					0.4 (df = 2)[f]				0.5 (df = 2)[f]						0.5 (df = 2)[f]

[a]Protein name based on NP_000042.3, rs number in parentheses is reference SNP number (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db = Snp).
[b]Hz WT subjects are homozygous for the reference/wild-type allele; Het subjects are heterozygous for the variation; Hz Var subjects are homozygous for the nonreference/variant allele.
[c]Odds ratio, adjusted for age (below 50, 50–59, 60–69, 70+ years).
[d]Adjusted for study group (USRT or Poland) and age (below 50, 50–59, 60–69, 70+ years).
[e]P value for Breslow-Day test for homogeneity of the ORs across study groups (USRT vs. Poland).
[f]P value for unadjusted likelihood ratio chi squared-test with two degrees of freedom for overall difference in genotype frequencies between cases and controls.

TABLE 2. Heterozygote Frequencies for the Two *ATM* Missense Mutations p.S49C and p.F858L Among Subgroups of Study Subjects

		ATM SNP					
		p.S49C			p.F858L		
Breast cancer case/control	Subgroup	Total (N)	No. Het	% Het	Total (N)	No. Het	% Het
Cases	All	2832	78	2.8	2810	60	2.1
Controls	All	3326	55	1.7	3303	50	1.5
Cases	USRT[a]	854	33	3.9	856	30	3.5
	Warsaw[b]	1255	31	2.5	1242	18	1.4
	Łódź[b]	723	14	1.9	712	12	1.7
Controls	USRT	1040	27	2.6	1042	19	1.8
	Warsaw	1467	20	1.4	1450	17	1.2
	Łódź	819	8	1.0	811	14	1.7
Cases	Age <50	1095	37	3.4	1089	27	2.5
	Age 50+	1736	41	2.4	1720	33	1.9
Controls	Age <50	807	11	1.4	803	11	1.4
	Age 50+	2519	44	1.7	2500	39	1.6
Cases	FH+[c]	398	10	2.5	395	10	2.5
	FH−	2432	68	2.8	2413	50	2.1
Controls	FH+	296	5	1.7	294	5	1.7
	FH−	3028	50	1.7	3007	45	1.5
Cases	Invasive, USRT	729	28	3.8	731	28	3.8
	In situ USRT	125	5	4.0	125	2	1.6
	Invasive, Poland	1862	41	2.2	1839	30	1.6
	In situ Poland	116	4	3.4	115	0	0.0

[a]U.S. Radiologic Technologist Study subjects.
[b]Warsaw and Łódź are the two study sites for the Polish Breast Cancer Case–Control Study.
[c]FH+, subjects report at least one first degree relative with breast cancer; FH−, subjects have no first degree relatives with breast cancer.

The p.S49C and p.F858L mutations were two of four coding mutations genotyped in both the USRT and Poland study groups because they showed some evidence of association ($P \leq 0.1$) in an interim analysis of the USRT data [Struewing et al., 2004] (Supplementary Tables S3 and S4. The p.P1526P silent mutation, observed commonly in a previous series of breast cancer cases [Teraoka et al., 2001], was somewhat less common among cases in USRT but was observed at the same frequency among the Polish cases and controls. The p.S707P missense mutation was significantly less common among USRT cases compared to controls (OR, 0.47; 95% CI, 0.23–0.93) but showed the opposite effect in the Polish study group (OR, 1.25; 95% CI, 0.80–1.94). Overall, there was no significant association between p.S707P with breast cancer risk, but there was evidence for significant heterogeneity in the OR between study groups ($P = 0.02$).

Of the 10 potentially AT-related mutations studied in the USRT population, only four were heterozygous in at least one subject: one case carried the c.1563-1564delG mutation and one carried the c.7636-7644del9 mutation, both clearly AT-associated mutations; three cases and four controls were heterozygous for g.82970C>T (IVS10-6T>G); and four cases and three controls carried rs800059 (S1691R), both variants now thought likely to be polymorphisms. In total, nine cases and seven controls carried one of these mutations specified a priori as likely to be causally related to the AT phenotype, an insignificant difference. The frequency of all variants studied in the USRT study group are shown in Supplementary Table S3. In the Poland study group, there were no differences in genotype frequency between cases and controls for the noncoding variants, as shown in Supplementary Table S4.

DISCUSSION

We have analyzed a number of rare (heterozygote frequencies $<10\%$) coding variants in the *ATM* gene in two large breast cancer studies of 2,856 breast cancer cases and 3,344 controls from the U.S. and Poland. We provide evidence that at least one of them, p.S49C, may be a breast cancer susceptibility allele. The p.S49C missense mutation, carried by less than 3% of subjects, was associated with a significantly elevated OR of 1.69 (95% CI, 1.19–2.40; $P = 0.004$). False-positive report probability calculations indicated that this association is unlikely to be a false positive: assuming the prior probability of this variant being a breast cancer susceptibility allele was 1 in 10, there is only an 11% chance that the significant association we observed is a false positive, and the chance that it is a false finding is 20% or below for prior probabilities as low as 1 in 20. The variant was slightly more common in U.S. compared to Polish subjects, but the association with breast cancer risk was consistent between the two study populations. The variant was more common among early-onset breast cancer cases (diagnosed before age 50 years), but there was little difference for subjects with and without a first-degree relative with breast cancer.

p.F858L, another missense mutation at about the same frequency as p.S49C, was also more common among cases but the association did not reach even nominal statistical significance. The association was mostly driven by the U.S. study group, although the test for heterogeneity of the ORs between studies was not statistically significant. The p.S707P mutation was significantly less common in cases than controls in the USRT study, but is was more common in cases than controls in the Polish study. The p.P1526P variant was significantly lower in cases from the USRT study in an interim analysis, but upon analysis of the complete data set and when combined with the Polish data, was not associated with breast cancer risk.

Because complete sequence analysis of the *ATM* gene is prohibitively expensive in large epidemiologic studies, we developed assays for a set of individual AT-causing mutations. While individually rare, we hoped that combining less frequent AT-related mutations would permit us to determine whether they are associated with breast cancer. Most of the mutations we assayed

were not detected in any of the USRT subjects and the summed frequency of AT-related mutations was not different between cases and controls. Two of the mutations included in our a priori list, rs800059 (S1691R) and the intron 10 splicing mutation (g.82970T>G), were detected in more than one subject, but it may be that neither of them are true mutations: studies of the intron 10 splicing mutation published since we initiated our analyses suggests it may not increase the risk of breast cancer [Bernstein et al., 2003; Szabo et al., 2004], and the S1691R was studied because it was identified in a single British AT patient, which may, in fact, not be the AT-causing mutation in this subject. Excluding these two variants, we detected two clear AT-causing mutations in cases and none in controls. We thus were not able to contribute much information on whether truncating, AT-causing mutations are more common in breast cancer patients compared to controls.

Our most interesting association was p.S49C and breast cancer. This mutation, initially identified in a small series of 38 sporadic breast cancer cases [Vorechovsky et al., 1996], has also been detected in 1.6% of 192 hospital-based breast cancer cases [Dork et al., 2001] and in a study of 92 North American AT patients [Castellvi-Bel et al., 1999]. It has been evaluated in at least two previous epidemiologic studies of breast cancer. Its frequency did not differ between breast cancer cases and controls in the Multiethnic Cohort study [Bretsky et al., 2003], although there were two or fewer carriers in each of the four ethnic groups. p.S49C was significantly more common among 75 Caucasian breast cancer patients, oversampled for second cancers and positive breast cancer family history, studied at M. D. Anderson Cancer Center, as compared to 940 blood bank donor controls (6.7% vs. 1.3%) [Buchholz et al., 2004].

The Ser-to-Cys mutation is a nonconservative amino acid substitution at residue 49, but there have been no biochemical studies of its effect on ATM function. This amino acid maps to the recently described chromatin association domain [Young et al., 2005], but does not map to the well-known functional domains of this protein. In silico analysis of the potential functional significance of this and other missense mutations were inconclusive: the p.S49C has a potentially intolerant "sorting intolerant from tolerant" (SIFT) score, but is not predicted to be pathological with PolyPhen, while the p.F858L was possibly damaging in PolyPhen analyses but tolerated in SIFT analyses [Ng and Henikoff 2001; Ramensky et al., 2002].

The other coding SNPs that we evaluated have been studied previously in epidemiologic settings, but owing largely to their small sample size, the results have been inconsistent. For example, p.F858L has sometimes been observed more frequently in breast cancer cases than controls (3.6% vs. 2.6%; 1,500 total subjects) [Dork et al., 2001], while in another setting it was less frequent (2.1% vs. 7.4%; 223 total subjects) [Teraoka et al., 2001]. In the Multiethnic Cohort study, its frequency was similar between cases and controls (1.3% vs. 1.1%; 854 total subjects) but there were only nine heterozygote carriers [Bretsky et al., 2003]. The p.S707P mutation has been observed more frequently in breast cancer cases than controls in some [Dork et al., 2001; Teraoka et al., 2001; Bretsky et al., 2003], but not all studies [Thorstenson et al., 2003], and it was significantly less frequent in cases from our USRT study. Whether the observed differences in our two study populations might reflect true differences in the effect of p.S707P on breast cancer risk due to different environmental or genetic backgrounds is unknown. We did not find any evidence for associations with two of the more common missense variants, p.P1054R and p.L1420F, which have shown inconsistent results in previous studies, nor with the very common noncoding polymorphisms studied previously [Dork et al., 2001; Teraoka et al., 2001; Bretsky et al., 2003; Tamimi et al., 2004; Lee et al., 2005].

The USRT cohort study participants are a unique occupational group exposed to fractionated, low-dose ionizing radiation not present in most other study settings, including the Polish study participants analyzed here. Such differences in environmental exposures may underlie some of the heterogeneity observed between study populations, for example for p.F858L, and it will be of great interest to study *ATM*-radiation gene–environment interactions. Exploratory analyses with interim radiation dose estimates yielded likelihood ratio test P values >0.5 for an interaction term with the p.S49C, and P values of 0.2 or greater for p.F858L and p.S707P, but final radiation dose estimates, based on individual work histories, radiation badge measurements, and modeling, are underway, and further analyses with the improved radiation doses are planned.

In summary, we find that the *ATM* missense mutation p.S49C is likely to be a breast cancer susceptibility allele. The mutation is rare, and even in our combined study population of 6,200 subjects, we observed it in only 133. It will be important to confirm this association, and to further analyze the p.F858L variant, in even larger study populations that can be attained through data pooling efforts, such as the Breast Cancer Association Consortium, and to conduct functional studies of the impact of these changes on the protein. Because of *ATM*'s function in the repair of DNA damage, there is also interest in its potential impact on treatment [Smilenov et al., 2001; Andreassen et al., 2005; Choudhury et al., 2006], but further biochemical, clinical, and epidemiologic studies are required before mutation and polymorphism information are used for prevention or treatment decisions.

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