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Common ataxia telangiectasia mutated haplotypes and risk of breast cancer: a nested case–control study

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Abstract

Introduction The ataxia telangiectasia mutated (*ATM*) gene is a tumor suppressor gene with functions in cell cycle arrest, apoptosis, and repair of DNA double-strand breaks. Based on family studies, women heterozygous for mutations in the *ATM* gene are reported to have a fourfold to fivefold increased risk of breast cancer compared with noncarriers of the mutations, although not all studies have confirmed this association. Haplotype analysis has been suggested as an efficient method for investigating the role of common variation in the *ATM* gene and breast cancer. Five biallelic haplotype tagging single nucleotide polymorphisms are estimated to capture 99% of the haplotype diversity in Caucasian populations.

Methods We conducted a nested case–control study of breast cancer within the Nurses' Health Study cohort to address the role of common *ATM* haplotypes and breast cancer. Cases and controls were genotyped for five haplotype tagging single nucleotide polymorphisms. Haplotypes were predicted for 1309 cases and 1761 controls for which genotype information was available.

Results Six unique haplotypes were predicted in this study, five of which occur at a frequency of 5% or greater. The overall distribution of haplotypes was not significantly different between cases and controls ($\chi^2 = 3.43$, five degrees of freedom, $P = 0.63$).

Conclusion There was no evidence that common haplotypes of *ATM* are associated with breast cancer risk. Extensive single nucleotide polymorphism detection using the entire genomic sequence of *ATM* will be necessary to rule out less common variation in *ATM* and sporadic breast cancer risk.

Keywords: ataxia telangiectasia mutated gene, breast cancer, haplotype tagging single nucleotide polymorphisms

Introduction

Ataxia telangiectasia (AT) is an autosomal recessive disease characterized by neurodegeneration, cerebral ataxia, oculocutaneous telangiectasia, and sensitivity to radiation. In addition, AT cases are estimated to have a 100-fold increased risk of developing cancer compared with the general population [1]. The most common cancers among AT patients are lymphomas and leukemias, although solid tumors including breast cancer are also found at higher rates. Women heterozygous for mutations in the ataxia telangiectasia mutated (*ATM*) gene, estimated to be about 1% of the population, are reported to have a fourfold to fivefold increased risk of breast cancer compared with noncarriers of the mutations [1-3], although not all studies have confirmed this association [4,5].

Epidemiologic studies examining sequence variation in the *ATM* gene and breast cancer risk have been inconclusive. *ATM* mutations have been reported to be associated with increased breast cancer risk among women with a family history of breast cancer [6,7] and/or early-onset breast cancers [8,9], although not all studies confirm these results [4,10,11]. In addition, two hospital-based studies reported positive associations between *ATM* mutations and breast

AT = ataxia telangiectasia; ATM = ataxia telangiectasia mutated; htSNP = haplotype tagging single nucleotide polymorphism; HWE = Hardy–Weinberg equilibrium; PCR = polymerase chain reaction; SNP = single nucleotide polymorphism.

cancer [12,13]. A recent population-based study provided little support of a role for *ATM* mutations and breast cancer; however, one variant was over-represented in breast cancers among African-American and Latina women [14].

ATM is a tumor suppressor gene with functions in cell cycle arrest, apoptosis, and repair of DNA double-strand breaks. AT cells are sensitive to agents that cause double-strand breaks, due to their defective checkpoint control and inability to repair DNA damage. *In vitro* evidence indicates that cells from AT heterozygotes are intermediate in their sensitivity to X-rays [15]. More than 200 different disease-causing mutations in the *ATM* gene have been identified throughout the coding sequence, most of which are truncation mutations [16,17]. In contrast, *ATM* mutations observed in breast cancer patients are mostly missense mutations postulated to have a dominant negative phenotype [17,18]. *ATM* also plays a role in the regulation of BRCA1, further evidence for a possible association with breast cancer [19,20].

ATM is comprised of 66 exons, distributed over more than 150 kb genomic DNA. Sequence analysis of this gene reveals that the coding sequence has very little nucleotide diversity [21]. Using different methods to identify variations in the gene and different study populations, two independent studies reported that a small number of *ATM* haplotypes exist. Thorstenson and colleagues focused their single nucleotide polymorphism (SNP) discovery on the coding sequence, splice sites and 5' upstream sequences. They predicted seven haplotypes in populations throughout the world, only three of which are found in Europe and the Americas [21]. In contrast, Bonnen and colleagues sequenced randomly dispersed regions of the *ATM* gene primarily in noncoding regions and identified 22 unique haplotypes, seven of which appear in Caucasian populations of European descent [22]. Of those haplotypes appearing in European Caucasian populations, there are five common haplotypes estimated to occur at a frequency greater than 5% [22].

Because the *ATM* gene is very large, but only a relatively small number of SNPs are required to construct the major haplotypes, a haplotype approach may be a useful method for investigating the role of common variation in *ATM* and breast cancer risk. In the present study, we found no evidence that common *ATM* haplotypes are associated with breast cancer risk.

Materials and methods

We conducted a case–control study nested within the Nurses' Health Study cohort. This cohort was initiated in 1976, when 121,700 US-registered nurses aged 30–55 years returned an initial questionnaire. Information on reproductive variables, cigarette smoking, and exogenous hormone use are updated every 2 years. Incident breast cancer cases were identified through self-report and were confirmed by medical record review. Between 1989 and 1990, blood samples were collected from 32,826 women.

Eligible cases in the present study consist of all women with medical record-confirmed incident breast cancer (both *in situ* and invasive) from the subcohort of women who returned a blood sample and were diagnosed before 1 June 2000. Cases were excluded if they had any other prior cancer diagnosis except for nonmelanoma skin cancer. Controls were randomly selected from the cohort of women returning a blood sample and with no diagnosis of cancer before the case reference date (except for nonmelanoma skin cancer). Controls were matched to cases on year of birth, menopausal status, postmenopausal hormone use at time of blood draw, time of day, month and fasting status at time of blood draw. Although blood draw and menopausal characteristics are unlikely to confound the *ATM*–breast cancer relationship, matching on these characteristics is necessary for analyses involving plasma hormones.

To maximize the efficiency of the overall study design, the selection of breast cancer cases and controls included in this study is identical to those involved in plasma hormone analyses. The study was approved by the Committee on Human Subjects at Brigham and Women's Hospital. This nested case–control study consists of a total of 1318 incident breast cancer cases and 1771 controls. Genotype data were unavailable for nine cases and for 10 controls, and thus results are based on 1309 cases and 1761 controls.

Haplotype tagging single nucleotide polymorphisms (htSNPs) were determined using the BEST program http://genomethods.org/best/[23]. BEST uses an exact method to identify the minimum number of tagging SNPs necessary to capture the haplotype variation in a population. Using the 17 SNPs identified in Bonnen and colleagues' study [22], BEST identified five htSNPs necessary to capture all of the haplotypes occurring in a European Caucasian population at a frequency of greater than 1%.

DNA was extracted from buffy coat fractions using the Qiagen QIAamp Blood kit (Qiagen, Chatsworth, CA, USA). All cases and controls were genotyped for the five ATM htSNPs identified in Table 1 using Taqman® technology (Applied Biosystems, Foster City, CA, USA) with an ABI Prism 7900HT Sequence Detection system (Applied Biosystems). PCR amplification was carried out on 5–20 ng DNA using 1 × TaqMan® universal PCR master mix (No Amp-erase UNG), 900 nM forward and reverse primers, 200 nM FAM-labeled probe and 200 nM VIC-labeled probe in a 5 μl reaction (see Table 2 for primer and probe

Table 1

Location and description of five haplotype tagging single nucleotide polymorphisms (SNPs) used to tag haplotypes in *ATM* in genomic sequence with GenBank Accession number U82828

SNP	Gene location	Change	Location in genomic sequence	RS number[a]
1	Prior to 5' UTR	T→A	10182	228589
2	IVS46-257	A→C	112721	3092992
3	IVS62+60	G→A	142789	664143
4	IVS63-973	A→C	151964	170548
5	IVS63-694	C→A	152243	3092993

UTR, untranslated region. [a] Reference SNP number in the NCBI database.

Table 2

PCR primer sequences and allele specific probe sequences used to genotype the five haplotypes tagging SNPs

Single nucleotide polymorphism	Primer/Probe sequence
Primers used for PCR	
SNP1, F1	5'-AGCATAGCCGGGTCCAATAA-3'
SNP1, R1	5'-CCCGGCTTGTATTGGGTAAG-3'
SNP2, F2	5'-CAGAAGAGTATTTAGAAGGGCTGCTT-3'
SNP2, R2	5'-AGGTCACAGATGACAAACATCAAAA-3'
SNP3, F5	5'-GGAAGACTTTATTTTTTTTCTTACCAGGTA-3'
SNP3, R5	5'-AGCAGTGCTCTTCACATCAGTGA-3'
SNP4, F3	5'-GGAGGACACTCAAAACAGCATTAAA-3'
SNP4, R3	5'-TTAGCAGATTTAGTTTCAGGACACGTA-3'
SNP5, F4	5'-CCAGAGCAGTTAGCTGTTCTGAACT-3'
SNP5, R4	5'-GAGCAAGTAGCTTTAGGTCGTAAATTTT-3'
FAM-labeled allele-specific probes	
SNP1	CCTCCATCCCGCG
SNP2	TGTCAGCGTATTAAA
SNP3	TTCCTGATGAGATACAC
SNP4	AATAGAGAGATTTTGGTTCT
SNP5	CATGATGAATTTCTG
VIC-labeled allele-specific probes	
SNP1	CCCTCCTTCCCGC
SNP2	TGTCAGAGTATTAAAAAT
SNP3	TTCCTGACGAGATACA
SNP4	AATAGAGCGATTTTGG
SNP5	CATGAGGAATTTC

sequences). Amplification conditions on an ABI 9700 dual plate thermal cycler (Applied Biosystems) were as follows: one cycle of 95°C for 10 min, followed by 50 cycles of 92°C for 15 s and 58°C for 1 min. TaqMan® primers and probes were designed using the Primer Express® Oligo Design software version 2.0 (Applied Biosystem). Approxi-

mately 10% of the samples were included as duplicates to serve as quality control samples. Quality control samples served as internal controls to validate the genotyping method; there was 100% concordance of the quality control samples. Laboratory personnel were blinded to the status (case, control or quality control) of samples.

Conditional logistic regression models were used to assess the relative risk and 95% confidence intervals of individual htSNPs for the risk of developing breast cancer.

Employing an expectation–maximization algorithm for multilocus data when the phase was unknown, we utilized PROC HAPLOTYPE in the SAS/Genetics Software (SAS Institute, Cary, NC, USA) to estimate haplotypes. Because the algorithm is capable of handling missing data, our primary analysis included all cases and controls for which genotype data on at least one of the five SNPs were available. Haplotype prediction relied on 1309 cases and 1761 controls, which were estimated as separate populations. Haplotypes predicted at frequencies less than 1% were excluded from further analyses. A secondary analysis, in which haplotype estimation was restricted to individuals with only complete genotype data across all five SNPs (1199 cases and 1535 controls), gave essentially similar frequencies. Haplotype estimation restricted to cases with invasive breast cancer (excluding *in situ* cancers) (n = 1056) also demonstrated almost identical case frequencies. Using an expectation substitution [24,25] approach, we also examined haplotype interactions with family history of breast cancer and menopausal status at diagnosis.

The International HapMap Project has genotyped 29 SNPs in the *ATM* gene in 60 individuals from the CEPH-30-trios panel http://www.hapmap.org. Using these data and the Haploview software http://www.broad.mit.edu/personal/jcbarret/haploview/, we predicted the number of haplotype blocks and the number of common haplotypes across the *ATM* gene.

Results and discussion

ATM genotype data were available for 1309 cases and 1761 controls. At the time of blood collection, 596 women (272 cases) were premenopausal with a mean age of 48.6 years (standard deviation = 3.3) and 2185 women (901 cases) were postmenopausal with a mean age of 60.8 years (standard deviation = 5.1). The median age of the breast cancer cases was 63 years (range, 44–79 years).

Compared with controls, cases tended to have an earlier age at menarche ($P < 0.05$), a later age at first birth, a later age at menopause, lower mean parity ($P < 0.05$), a lower body mass index and a greater weight gain since age 18. Cases were significantly more likely to have a history of benign breast disease as compared with controls (64% versus 51%, $P < 0.001$), and were also more likely to have a family history of breast cancer (21% versus 15%, $P < 0.001$).

Among controls, genotypes for SNP2, SNP3, SNP4, and SNP5 were consistent with Hardy–Weinberg equilibrium (HWE). In both the controls and the cases there was evidence that SNP1 may diverge from HWE ($P = 0.03$ and $P = 0.008$, respectively). Among the cases, there was also evidence that SNP3 may diverge from HWE ($P = 0.006$). SNP1 and SNP3 are in high linkage disequilibrium ($P < 0.001$) [22]. It is thus not surprising that both SNPs would perform similarly in the test for HWE. In addition, the genotype distributions in cases are similar to those observed in controls, and there was 100% genotype concordance between duplicate quality control samples, suggesting that the divergence from HWE for these SNPs is not likely to be due to genotyping error.

None of the htSNPs were significantly associated with breast cancer risk (Table 3). Six unique haplotypes were estimated from the control population, revealing five common haplotypes occurring at a frequency of 5% or more (Table 4). Haplotypes 1, 3, 4, 5, and 6 in Table 4 are concordant with the five common haplotypes predicted by Bonnen and colleagues in Caucasian populations at relatively similar frequencies (Table 4) [22]. The overall distribution of haplotypes was not significantly different between cases and controls ($\chi^2 = 3.43$, five degrees of freedom, $P = 0.63$).

Haplotypes 1, 4 and 5 represent > 80% of the haplotypes in the study population. These results are consistent with previous studies identifying three major *ATM* haplotypes [13,21,22]. In addition, Haploview analysis of 29 SNPs across the *ATM* gene in a CEPH (Centre d'Etude du Polymorphisme Humain) panel of 60 individuals also revealed three major haplotypes and one haplotype block. Together, these data suggest that the majority of *ATM* variation can be explained by three major haplotypes.

There was no evidence that any of the five common haplotypes (haplotypes 1, 3, 4, 5 and 6) were associated with breast cancer risk (Table 4). In contrast, Angèle and colleagues identified three SNPs that were associated with three major haplotypes, and one major haplotype that was significantly associated with breast cancer risk [13]. The Angèle and colleagues' study recruited cases (n = 254) from a radiotherapy clinic and controls from blood donors in the hospital's catchment area.

Our results are consistent with a recent population-based case–control study that examined the relationship between 20 missense mutations and polymorphisms and breast cancer [14]. In that study, only one variant was associated

Table 3

Relative risk of breast cancer and 95% confidence intervals according to genotype of ATM haplotype tagging single nucleotide polymorphisms (SNPs) in the Nurses' Health Study (1989–2000)

SNP	Genotype	Cases[a]	Controls[a]	Relative risk[b]	Relative risk[c]
SNP1	T/T	450 (35.3)	556 (33.9)	1.00 (Reference)	1.00 (Reference)
	T/A	575 (45.1)	762 (46.4)	0.94 (0.79–1.11)	0.94 (0.79–1.12)
	A/A	249 (19.5)	324 (19.7)	0.95 (0.77–1.17)	0.94 (0.75–1.17)
SNP2	A/A	1158 (90.5)	1495 (90.5)	1.00 (Reference)	1.00 (Reference)
	A/C	118 (9.2)	154 (9.3)	1.00 (0.77–1.30)	1.02 (0.78–1.34)
	C/C	4 (0.3)	3 (0.2)	1.64 (0.36–7.45)	2.07 (0.42–10.26)
SNP3	G/G	455 (35.8)	553 (34.3)	1.00 (Reference)	1.00 (Reference)
	G/A	570 (44.9)	755 (46.8)	0.99 (0.83–1.17)	0.99 (0.83–1.18)
	A/A	245 (19.3)	306 (19.0)	1.03 (0.83–1.28)	1.03 (0.82–1.29)
SNP4	A/A	164 (12.7)	189 (11.0)	1.00 (Reference)	1.00 (Reference)
	A/C	565 (43.9)	759 (44.0)	0.88 (0.69–1.12)	0.87 (0.68–1.12)
	C/C	559 (43.4)	778 (45.1)	0.86 (0.67–1.09)	0.85 (0.66–1.09)
SNP5	C/C	970 (75.7)	1207 (73.1)	1.00 (Reference)	1.00 (Reference)
	C/A	292 (22.8)	417 (25.2)	0.87 (0.73–1.04)	0.86 (0.72–1.04)
	A/A	20 (1.6)	28 (1.7)	0.81 (0.45–1.47)	0.81 (0.44–1.50)

[a] Data presented as *n* (%). Numbers may not add to totals due to missing genotype data. [b] Relative risks are crude odds ratios from conditional logistic regression models (95% confidence interval). [c] Relative risks (95% confidence interval) are from conditional logistic regression models adjusted for age at menarche (< 12 years, 12 years, 13 years, > 13 years), age at menopause (≤ 45 years, 46–50 years, 51–60 years), first-degree family history of breast cancer (yes/no), personal history of benign breast disease (yes/no), weight gain since age 18 (< 5 kg, ≥ 5 to < 20 kg, ≥ 20 kg), body mass index at age 18 (continuous), age at first birth/parity (nulliparous, one to four children/age at first birth ≤ 24 years, one to four children/age at first birth > 24 years, five or more children/age at first birth ≤ 24 years, five or more children/age at first birth > 24 years), and duration of postmenopausal hormone use (premenopausal, never, past user < 5 years duration, past user ≥ 5 years duration, current user < 5 years duration, current user ≥ 5 years duration).

with increased risk of breast cancer, and this was among African-American women only. This variant was only present in African-American and Latina women, and therefore could not be addressed in the current study comprised of primarily Caucasian women.

The objective of the present study was to assess the role of common variation in *ATM* and breast cancer risk. Based on these results, it does not appear that any common haplotypes are associated with breast cancer. In addition, there were no significant interactions between common haplotypes and family history ($P = 0.51$) or menopausal status ($P = 0.29$). The AT syndrome is caused by multiple rare mutations, and our data do not exclude the possibility that rare mutations of this gene may alter breast cancer risk.

The accuracy of the estimated haplotypes relies heavily on the precision with which the five htSNPs are able to correctly identify common haplotypes in this mainly Caucasian population. The two groups that undertook the task of identifying variation in the *ATM* gene employed two different methods: one relying on coding sequence and splice sites, and the other focusing on intronic sequences. Bonnen and colleagues resequenced approximately 13.5 kb genomic DNA from 29 regions randomly dispersed across the gene, containing regions of minimal repetitive sequence [22]. Thorstenson and colleagues resequenced all 62 coding exons as well as 14.6 kb noncoding sequence [21]. There was 25% overlap in the sequence covered by the two groups [21]. These two independent methods used for SNP discovery and subsequent haplotype prediction came to similar conclusions regarding the number of common haplotypes. Because neither of these groups or any other groups have resequenced this gene entirely, it is still possible that other common haplotypes of *ATM* exist.

The expectation–maximization algorithm utilized to estimate haplotypes assumes that both case and control genotypes are in HWE. Among the controls the htSNPs were in HWE except for SNP1, and SNP1 and SNP3 diverged from HWE among the case population. Because the haplotypes predicted among the cases are, in general, identical to those in the controls and those predicted by Bonnen and colleagues, it does not appear that this violation of the assumption results in misspecified haplotypes. In addition, the accuracy of the expectation–maximization estimation is reported to be very high even when the loci are not in HWE if the population size is moderately large [26].

Table 4

Estimated case and control frequencies of predicted *ATM* haplotypes in the Nurses' Health Study (1989–2000) in comparison with *ATM* haplotypes in Bonnen and colleagues' study [22]

Haplotype	Sequence[a]	Previously published[b]		Current study[c]		
		White European American ($n = 154$)	CEPH ($n = 70$)	Controls ($n = 3522$)	Cases ($n = 2618$)	P value
1	A A A C C	0.292	0.394	0.367	0.359	0.51
2	A A G C C	0.013	0.015	0.015	0.014	0.83
3	A C A C C	0.065	0.061	0.048	0.049	0.85
4	T A G A C	0.351	0.273	0.324	0.340	0.22
5	T A G C A	0.175	0.227	0.142	0.130	0.16
6	T A G C C	0.097	0.015	0.096	0.101	0.50

-, the haplotype was not predicted in that population; CEPH (Centre d'Etude du Polymorphisme Humain). [a] Sequence corresponds to the nucleotide at haplotype tagging single nucleotide polymorphisms 1–5. [b] From Bonnen and colleagues' study [22]. [c] Frequencies do not add to 1.0 because rare haplotypes of frequencies less than 0.01 were excluded.

The individual htSNPs and the haplotypes they define in the present study were not associated with breast cancer, although it is possible that unidentified functional SNPs not in linkage disequilibrium with the selected htSNPs exist and could be associated with breast cancer risk. The efficiency of the haplotype tagging approach depends on the density of the markers used to choose the tagging SNPs. In this case, we used the markers from Bonnen and colleagues, which had an average density of about one SNP per 10 kb. This may not be sufficient to tag all common variants in ATM. For example, Letrero and colleagues demonstrated that carriers of the S49C SNP, a nonconservative SNP in the ATM coding region, were just as likely to be carriers of one of the common Bonnen and colleagues' haplotypes as noncarriers of the SNP, suggesting that it is possible for association studies to miss functional SNPs [27].

In addition, it is possible that *ATM* may play a more important role in specific subsets of breast cancer such as familial, early-onset or radiosensitive breast cancers. This study is not designed to examine these hypotheses.

Conclusion

We observed no evidence that common *ATM* haplotypes are associated with breast cancer risk. Extensive SNP detection using the entire genomic sequence of *ATM* will be necessary to rule out less common variation in *ATM* and sporadic breast cancer risk.

Competing interests

None declared.

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