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The association between *ATM* D1853N polymorphism and breast cancer susceptibility: a meta-analysis

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Abstract

Background: Emerging evidence suggests that *ataxia telangiectasia-mutated* (*ATM*) is involved in numerous damage repair signaling pathways and cell-cycle checkpoints. Heterozygous carriers of ATM-mutations have an increased risk for the development of breast cancer. The purpose of this study is to evaluate the association between *ATM* exon39 5557G > A (D1853N, rs1801516) polymorphism and breast cancer susceptibility with the use of a meta-analysis.

Methods: By searching PubMed and Embase databases, a total of 9 epidemiological studies with 4,191 cases and 3,780 controls were identified. Crude odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for *ATM* D1853N polymorphism and breast cancer risk were calculated using fixed- or random-effects model based on the degree of heterogeneity among studies.

Results: No significant association between the *ATM* D1853N polymorphism and breast cancer risk was observed in overall analysis (GA versus GG: OR = 1.18; 95% CI, 0.90-1.53; AA versus GG: OR = 0.77; 95% CI, 0.58-1.03; dominant model: OR = 1.16; 95% CI, 0.89-1.51; and recessive model: OR = 0.78; 95% CI, 0.59-1.04, respectively).

Conclusion: Our results indicate that *ATM* D1853N polymorphism is not a risk factor for developing breast cancer.

Background

Ataxia-telangiectasia (A-T) is an autosomal recessive disorder that affects many parts of the body and leads to increased risk of malignancy, including breast cancer [1-3]. A-T is caused by mutations in the *ataxia telangiectasia-mutated* (*ATM*) [4]. ATM, a member of the phosphatidylinositol 3-kinase-like family, plays central roles in the repair of DNA double-strand breaks that was caused by a range of DNA-damaging agents such as ionizing radiation [5].

The *ATM* gene, located on chromosome 11q22-23 and consisting of 66 exons, has been reported to be involved in numerous damage repair signaling pathways and cell-cycle checkpoints [4,6]. Loss of heterozygosity in the region of the *ATM* gene has been detected in

approximately 40% of human sporadic breast tumors [7-11]. Breast cancer patients with the combination of radiation treatment and an *ATM* missense variant resulted in a shorter mean interval to develop a second tumor than patients without radiation treatment and *ATM* germline mutation [12]. Previously, some studies reported that female ATM-heterozygous carriers have an increased risk of breast cancer [1,13-18]. In contrast, some studies failed to find that ATM-heterozygous mutations were more frequent in breast cancer cases.

Recently, Mehdipour et al. reported that a common single nucleotide polymorphism *ATM* exon39 5557G > A (D1853N, rs1801516) may be considered as a predisposition factor for developing breast cancer, especially in cancer-prone pedigrees [19]. To date, a number of studies have been performed to investigate the association between the *ATM* D1853N polymorphism and breast cancer risk, but the evidence regarding the role of *ATM* as a genetic marker for breast cancer is

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conflicting. In order to provide stronger evidence for estimating the association, a meta-analysis was performed.

Materials and methods

Eligible studies and data extraction

We searched the articles using the following terms "*ATM*" and "breast cancer" and "polymorphism" or "variant" in PubMed and Embase databases (last search: 31 May, 2010). Additionally, we checked all relevant publications to retrieve the most eligible literatures.

The inclusion criteria were used for the literature selection: (a) articles about *ATM* D1853N polymorphism and breast cancer risk; (b) case-control studies; (c) sufficient published data for calculating odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). The following information was collected independently by two investigators (Gao LB and Pan XM) from each study: first author's surname, year of publication, country, ethnicity, number of cases and controls with various genotypes, genotyping techniques, quality control for the genotyping methods, Hardy-Weinberg equilibrium (HWE) and minor allele frequency (MAF) in controls (Table 1).

Statistical analysis

The process of meta-analysis in the current study was performed as described previously in detail [20-22]. In brief, crude ORs and corresponding 95% CIs were preformed to assess the association between *ATM* D1853N polymorphism and breast cancer risk. The pooled ORs were calculated for heterozygote comparison (GA versus GG), homozygote comparison (AA versus GG), dominant model (GA/AA versus GG) and recessive model (AA versus GA/GG), respectively. The statistical heterogeneity among studies was checked by Q-test and I^2 statistics [23]. If the P value greater than 0.10 for Q-test,

indicating absence of heterogeneity, the fixed-effects model (the Mantel-Haenszel method) was used to calculate the pooled OR [24]; otherwise, the random-effects model (the DerSimonian and Laird method) was used [25]. Publication bias of literatures was estimated using Begg's funnel plot [26]. All statistical analyses were carried out with STATA software, version 10.0 (STATA Corp., College Station, TX).

Results

Characteristics of studies

Overall, nine studies involving 4,191 cases and 3,780 controls about *ATM* D1853N polymorphism and breast cancer susceptibility were available for this meta-analysis. The main characteristics of eligible studies are summarized in Table 1. There were six studies of European populations, two studies of South American populations, and one study of mixed population that included more than one ethnic descent. Several genotyping methods were used, including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), denatured high performance liquid chromatography (DHPLC), allele-specific oligonucleotide (ASO), PCR-single strand conformation polymorphism (PCR-SSCP), conformation sensitive gel electrophoresis (CSGE), TaqMan, and sequencing. Approximately 67% (6/9) of these studies described quality control for the genotyping assay. The genotype distributions in the controls of all studies were consistent with Hardy-Weinberg equilibrium except for one study [27].

Main results

The main results of this meta-analysis are shown in Table 2. Overall, no significant association between the *ATM* D1853N polymorphism and breast cancer risk was observed. After subgroup analyses according to ethnicity, significantly increased risk was observed in South

Table 1 Characteristics of literatures included in the meta-analysis

References	Year	Country	Ethnicity	Genotype distribution						HWE (controls)	MAF
				case			control				
				GG	GA	AA	GG	GA	AA		
Angele [30]	2003	France	European	192	56	6	240	65	7	Yes	0.13
Buchholz [31]	2004	USA	Mixed	39	17	2	394	119	15	Yes	0.14
Dork [32]	2001	Germany	European	753	235	12	422	74	4	Yes	0.08
Gonzalez-Hormazabal [29]	2008	Chile	South American	100	26	0	174	26	0	Yes	0.07
Heikkinen [33]	2005	Finland	European	68	44	9	174	109	23	Yes	0.25
Renwick [34]	2006	UK	European	339	98	6	371	131	19	Yes	0.16
Schrauder [35]	2008	Germany	European	406	99	9	369	129	13	Yes	0.15
Tapia [27]	2008	Chile	South American	74	19	1	183	15	2	No	0.05
Tommiska [36]	2006	Finland	European	954	561	66	404	260	38	Yes	0.24

HWE, Hardy-Weinberg equilibrium

MAF, minor allele frequency

Table 2 Main results of pooled ORs in the meta-analysis

	n[a]	Cases/controls	GA versus GG		AA versus GG		GA/AA versus GG (dominant)		AA versus GA/GG (recessive)	
			OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]	OR (95%CI)	P[b]
Total	9	4,191/3,780	1.18 (0.90-1.53)	< 0.001	0.77 (0.58-1.03)	0.50	1.16 (0.89-1.51)	< 0.001	0.78 (0.59-1.04)	0.66
Ethnicity										
European	6	3,913/2,852	1.00 (0.77-1.31)	< 0.001	0.75 (0.56-1.01)	0.34	0.98 (0.75-1.29)	< 0.001	0.77 (0.57-1.02)	0.46
South American	2	220/400	2.19 (1.38-3.47)	0.22	1.24 (0.11-13.84)	-	2.15 (1.37-3.38)	0.27	1.07 (0.10-11.89)	-
Mixed	1	58/528	1.44 (0.79-2.64)	-	1.35 (0.30-6.11)	-	1.43 (0.80-2.56)	-	1.22 (0.27-5.48)	-

[a] Number of comparisons
[b] P value of Q-test for heterogeneity test. Random-effects model was used if the P value <0.10; otherwise, fixed-effects model was used

American population (GA versus GG: OR = 2.19; 95% CI, 1.38-3.47; and dominant model: OR = 2.15; 95% CI, 1.37-3.38, respectively) but not in European and mixed populations.

Publication bias
Begg's funnel plot was used to identify the potential publication bias of literatures on breast cancer, and the results did not show any evidence of publication bias in any comparison model (*P* > 0.05).

Discussion
Previous studies have inconclusive results about the association between *ATM* D1853N polymorphism and breast cancer risk, which might be caused by relatively small sample size in a single study. Meta-analysis offers a rational and helpful way to solve this practical problem by combination the findings from independent studies. In the current meta-analysis, we cumulated the data from nine case-control studies to explore the association between *ATM* D1853N polymorphism and breast cancer risk. No significant association between this polymorphism and breast cancer risk was observed in the overall study populations. Our result was consistent with the finding from a previous meta-analysis showing that another polymorphism of *ATM* (S49C, rs1800054) was not significantly associated with breast cancer susceptibility [28]. This finding indicates that the *ATM* D1853N polymorphism is not a risk factor for developing breast cancer, although a significantly increased risk of breast cancer in ATM-heterozygous carriers has been reported [1,13-18].

After subgroup analyses according to ethnicity, we found that the *ATM* D1853N polymorphism was associated with a significantly increased risk of breast cancer in South American population (heterozygote comparison and dominant model) but not in European and mixed populations. The reason for these discrepancies is not very clear. There are, however, some possible reasons. Firstly, the *ATM* D1853N polymorphism may present with different frequencies in different populations and

as a result may be associated with different degrees of breast cancer risk among different ethnic populations. Secondly, the genotype distribution in the controls of a South American study was departed from Hardy-Weinberg equilibrium [27], indicating that there was a high risk of selection bias because the controls may not be representative of the general population very well. Thirdly, the positive association might have occurred by chance due to the insufficient statistical power with only two South American studies eligible in this meta-analysis [27,29]. Therefore, additional studies with larger sample size are of great importance to clarify this finding.

Some limitations of this meta-analysis should be taken into consideration. On the one hand, the numbers of cases and controls analyzed for D1853N (rs1801516) found in the literature is still very small and might not precisely answer the given question. Especially, for some subgroup analyses, the statistical power is so low that caution should be taken in interpreting these results, even though positive association was found in South American population. On the other hand, data were not stratified by age at menarche, number of full-term pregnancies, menopausal status, and other suspected factors due to absence of available information.

In conclusion, the overall outcomes of this meta-analysis have shown that the *ATM* D1853N polymorphism is not associated with breast cancer risk, indicating that this polymorphism is not an independent risk factor for the development of breast cancer. Well-designed, unbiased studies with a wider spectrum of subjects should be of great value to explore other potential risk factors.

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Authors' contributions

GLB, PXM, and Zhang L designed the study, and wrote the manuscript; SH, WX, and RL performed data acquisition; LLJ performed quality control of data; LWB, LML, and YWZ performed statistical analysis and interpretation. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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