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...
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 (controls) | HWE (controls) | MAF |
|------------------|------|---------|-------------------|----------------------------------|----------------|-----|
| Angele [30]      | 2003 | France  | European          | GG 192 GA 56 AA 6 GG 240 GA 65 AA 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
showing that another polymorphism of ATM with the finding from a previous meta-analysis in the overall study populations. Our result was consistent with the finding between this polymorphism and breast cancer risk was observed even though positive association was found in South American population. On the other hand, data were not available 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.

**Acknowledgements**

This work was supported by the National Natural Science Foundation of China (No. 30801317), and Science & Technology Pillar Program of Sichuan Province (No. 20105ZD012).

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| Ethnicity          | n   | Cases/controls | GA versus GG | AA versus GG | GA/AA versus GG (dominant) | AA versus GA/GG (recessive) | P b   | P b   | P b   | 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.
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Authors’ contributions
GB, 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.

Received: 14 August 2010 Accepted: 27 August 2010
Published: 27 August 2010

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doi:10.1186/1756-9966-29-117
Cite this article as: Gao et al.: The association between ATM D1853N polymorphism and breast cancer susceptibility: a meta-analysis. Journal of Experimental & Clinical Cancer Research 2010 29:117.