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Original Article

Association between *ATM* polymorphism and the risk of thyroid cancer: a meta-analysis

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Abstract: Objectives: We performed this meta-analysis aiming to discuss the association of ataxia telangiectasia mutated (*ATM*) rs1801516 polymorphism with the risk of thyroid cancer (TC). Methods: Eligible publications were retrieved through database search. The strength of association between *ATM* rs1801516 polymorphism and the risk of TC was evaluated by pooled odds ratio (OR) with 95% confidence interval (95% CI). In addition, subgroup analyses were also carried out based on ethnicity and control source. Sensitivity analysis was completed to test statistical stability of the final results, and publication bias among included studies was inspected with both Begg's funnel plot and Egger's test. Data syntheses in this meta-analysis were conducted through Stata 12.0 software. Results: A total of 5 published articles including 8 case-control studies were enrolled into our meta-analysis, with 3,175 TC cases and 4,467 controls. The results showed that there was a significant association between decreased TC risk and *ATM* rs1801516 polymorphism in model AA+GA vs. GG (OR=0.88, 95% CI=0.79-0.98). Besides, a similar trend was also detected for the polymorphism in Caucasian group under the same genetic comparison after subgroup analysis by ethnicity. Conclusion: *ATM* rs1801516 polymorphism may reduce the susceptibility to TC, especially in Caucasians.

Keywords: Meta-analysis, *ATM*, polymorphism, thyroid cancer (TC)

Introduction

Thyroid cancer (TC) is the most prevalent malignancy of the endocrine system, accounting for more than 90% of all endocrine malignancies and approximately 1% of all neoplasias [1, 2]. It accounts for about 2.7% of all incident cancers among females and about 0.7% among males around the world [3]. In the United States, a marked increase in TC incidence with nearly 60,000 new cases per year has been observed since the mid-1990s [1, 4]. The incidence and mortality rates of this malignancy have been rising both in industrialized and developing countries over the past few decades, and the annual incidence rate worldwide ranges from 0.5 to 10 cases per 100,000 individuals [5, 6]. Additionally, accumulating evidences from studies on the etiology of TC show that ionizing radiation, body mass index, and work or living environment may impact on the development of TC [7, 8]. Although the pathogenesis of this cancer has not been well characterized yet, TC is believed to be a complex disease resulted from the interactions between environment and genes. Consequently, the genetic susceptibility and several candidate genes have been related to the incidence of TC in recent years [3, 9].

Ataxia telangiectasia mutated (ATM) is a protein kinase which belongs to a member of the phosphoinositide 3-kinase family [10, 11]. Functional experiments have stated that ATM acts as a central mediator of the radioprotective machinery in response to radiation therapy, participating in control of cell cycle checkpoints, cellular stress responses, initiation of apoptosis and repair of DNA double-strand breaks (DSBs) [12]. The human *ATM* gene, coding for this protein kinase, is mapped to chromosome 11q22-23, spanning 150 kb and comprising 66 exons [10]. It has been reported that *ATM* mutations are related to some human disorders, such as

immunodeficiency and cancer [13, 14]. It has been reported that a variety of single-nucleotide polymorphisms (SNPs) in *ATM* gene are associated with the risk of varying radiogenic tumors [2]. With regard to TC, some studies have proposed that the *ATM* genetic polymorphisms may play a critical role in the risk of TC.

However, considerable controversies about the influences of *ATM* polymorphisms on the risk of TC also exist. Given the conflicting evidence on this issue, we designed this meta-analysis with all available case-control studies to explore the association of *ATM* rs1801516 polymorphism with the occurrence and development of TC.

Materials and methods

Identification of publications

With the purpose of identifying all possibly relevant publications addressing the association between *ATM* rs1801516 polymorphism and the onset risk of TC, a comprehensive literature search was performed in the electronic databases of PUBMED, EMBASE, China National Knowledge Infrastructure (CNKI) and Google Scholar. The search strategy adopted the following relevant keywords and subject terms: "thyroid cancer or TC", "ataxia telangiectasia mutated or *ATM*" and "polymorphism or SNP or mutation or variant". No restriction on language, population, sample size or time period was imposed on retrieval of literature. A hand search of references in selected papers was conducted to screen additional papers.

Inclusion criteria

The following inclusion criteria were employed to select eligible publications in this meta-analysis: (1) using a case-control design; (2) examining the relationship between the risk of TC and *ATM* rs1801516 polymorphism; (3) full-text publications providing sufficient genotype frequencies both in cases and controls for the evaluation of odds ratio (OR) with its 95% confidence interval (95% CI). If several studies reported the same or overlapping data, the largest or latest one was selected.

Exclusion criteria

Excluded articles correspondingly met at least one of the conditions as follows: (1) duplicates; (2) studies lack of control groups; (3) letters, reviews, comments or meta-analyses; (4) not investigating the association of the occurrence of TC with *ATM* rs1801516 polymorphism, or publications with insufficient data for the evaluation of ORs.

Data extraction

For each eligible case-control study, the following variables were collected: the first author's name, year of publication, country of origin, ethnicities of study populations (Caucasians or mixed), source of controls (hospital-based or population-based), total number of cases and controls, genotyping methods, allele or genotype frequencies in case and control groups and *P* for Hardy-Weinberg equilibrium (HWE) among controls. Two reviewers independently extracted the above-mentioned information using a standardized form. Any discrepancy on each item of extracted data between the two reviewers was resolved via discussion, and if consensus was not reached, a third reviewer would be consulted.

Statistical analysis

Whether genotype frequencies among controls conformed to HWE was estimated by chi-square test and *P* value more than 0.05 represented a fine conformity. The strength of relationship between *ATM* rs1801516 polymorphism and the risk of TC was measured through calculating pooled ORs with its corresponding 95% CIs in five comparison models of AA vs. GG, AA+GA vs. GG, AA vs. GA+GG, allele A vs. allele G and GA vs. GG. Q-statistic test based on chi-square was used to analyze heterogeneity between eligible studies, and $P<0.05$ indicated significant heterogeneity. The pooled ORs were measured using random-effects model if heterogeneity was significant ($P<0.05$). Otherwise, fixed-effects models were employed. Moreover, subgroup analyses were also performed on the basis of ethnicity (Caucasian or mixed) and source of controls (population-based or hospital-based). Additionally, sensitivity was analyzed to evaluate whether the results were substantially affected by any single study, and potential publication bias was assessed by Begg's funnel plot and Egger's linear regression test. All statistical analyses listed above were carried out with Stata software (version 12.0).

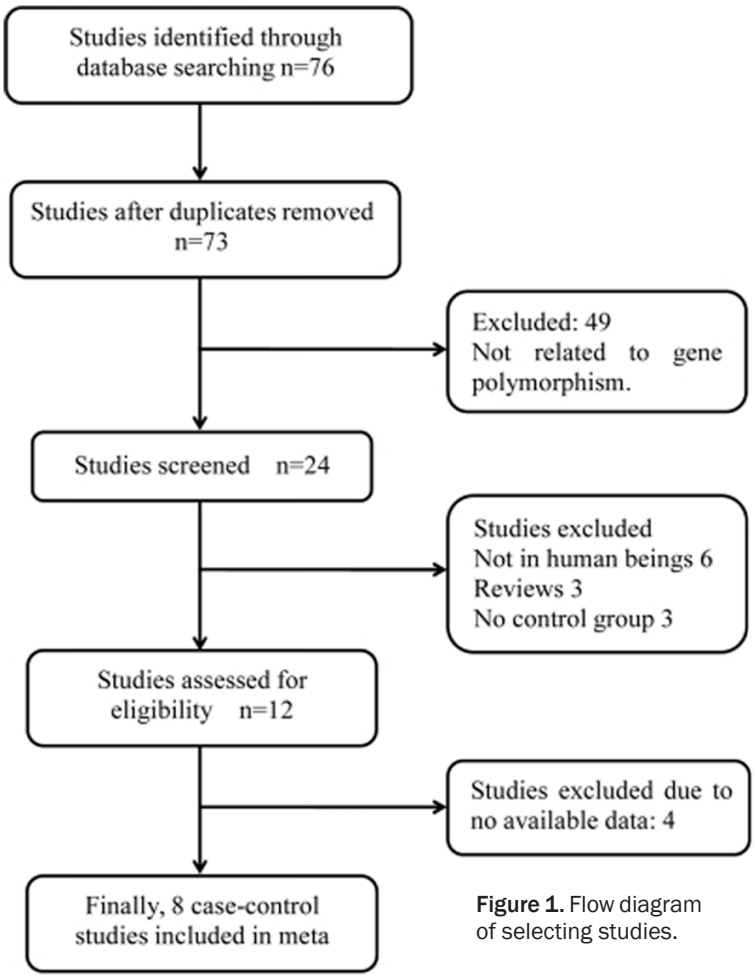

Figure 1. Flow diagram of selecting studies.

Results

Study selection and characteristics

A total of 76 potentially relevant publications involving the association between *ATM* rs1801516 polymorphism and the relative risk of TC were retrieved after the initial search of the online databases, meanwhile 3 duplicates were deleted first. Then, 49 publications were excluded for not relating to *ATM* rs1801516 polymorphism. Subsequently, 12 reports, including 6 animal studies, 3 reviews and 3 studies without control group, were eliminated. Finally, 4 studies without available data were removed. Therefore, 5 publications containing 8 case-control studies with 3,175 TC cases and 4,467 controls were recruited into this meta-analysis [1-4, 15] (**Figure 1**).

Of the 8 case-control studies, 5 studies were performed in Caucasian population while 3 in mixed populations; 6 studies were in a hospital-based design while 2 in a population-based design. The study characteristics were clearly summarized in **Table 1**.

Results of the meta-analysis

As informed in **Table 2**, *ATM* rs1801516 polymorphism was associated with decreased risk of developing TC in model AA+GA vs. GG (OR=0.88, 95% CI=0.79-0.98) in total analysis (**Figure 2**). In addition, such negative relationship was also detected in Caucasian subgroup under AA+GA vs. GG genetic comparisonafterstratifiedanalysis by ethnicity (OR=0.73, 95% CI=0.54-0.99).

Heterogeneity evaluation

Significant heterogeneity was observed in models allele A vs. allele G and GA vs. GG (*P*=0.017; *P*=0.016; respectively), so the random-effects model was applied to calculate pooled ORs. As for the other three genetic models, the fixed-effects model was used due to the lack of significant heterogeneity.

Sensitivity analysis

The reliability of outcomes in the current study was estimated by sensitivity analysis via excluding one single study from our meta-analysis each time in order to reflect the influence of individual data on pooled ORs. The overall results were not altered qualitatively (data not shown), which demonstrated the stability of our results.

Publication bias

Underlying publication bias was detected both by Begg's funnel plot and Egger's linear regression test. The visual inspection of Begg's funnel plot showed no distinct symmetry (**Figure 3**), which indicated the absence of significant publication bias. Besides, the results of Egger's test statistically supported these indications (*P*=0.149).

Table 1. Principal characteristics of the studies included in the meta-analysis

First author	Year	Country	Ethnicity	Control source	Genotyping method	Cancer type	Case			Control		
							GG	GA	AA	GG	GA	AA
Akulevich	2009	Russia, Belarus	Caucasian	HB	PCR-RFLP	IR-induced PTC	95	25	2	138	53	7
Akulevich	2009	Russia, Belarus	Caucasian	HB	PCR-RFLP	Sporadic PTC	105	24	3	293	90	15
Damiola	2014	Belarus	Caucasian	PB	PCR-HRM	PTC (exposed to radiation)	63	6	1	177	66	7
Pereda	2015	Cuba	Mixed	PB	PCR-HRM	DTC	153	44	0	162	42	2
Wojcicka	2014	Poland	Caucasian	HB	Sequenom MassARRAY	PTC	1261	319	23	1455	357	32
Xu	2012	United States, Brazil	Caucasian	HB	PCR-RFLP	DTC	366	93		519	167	
Xu	2012	United States	Mixed	HB	PCR-RFLP	DTC	244	45		305	69	
Xu	2012	Brazil	Mixed	HB	PCR-RFLP	DTC	239	64		392	119	

Notes: PCR, polymerase chain reaction; PCR-RFLP, PCR-restriction fragment length polymorphism; PCR-HRM, PCR-high-resolution melting curve; PTC, papillary thyroid carcinoma; IR-induced PTC, irradiated induced papillary thyroid carcinoma; DTC, differentiated thyroid carcinoma; HWE, Hardy-Weinberg equilibrium.

Table 2. *ATM* rs1801516 polymorphism and TC risk

Genotype/ Allele	Reference	Group	OR (95% CI)	P_h	Model for analysis
AA	GG	Caucasian	0.70 (0.44, 1.11)	0.758	FEM
		Mix	0.21 (0.01, 4.45)	/	
		Hospital	0.73 (0.45, 1.16)	0.646	
		Population	0.32 (0.06, 1.85)	0.735	
		Total	0.68 (0.43, 1.06)	0.775	
AA+GA	GG	Caucasian	0.73 (0.54, 0.99)*	0.010	FEM
		Mix	0.90 (0.71, 1.13)	0.709	
		Hospital	0.90 (0.80, 1.01)	0.371	
		Population	0.56 (0.14, 2.16)*	0.004	
		Total	0.88 (0.79, 0.98)	0.052	
GA	GG	Caucasian	0.69 (0.44, 1.10)	0.009	REM
		Mix	1.11 (0.69, 1.79)	/	
		Hospital	0.89 (0.68, 1.17)	0.207	
		Population	0.56 (0.13, 2.39)	0.004	
		Total	0.78 (0.55, 1.11)	0.016	
AA	GG+GA	Caucasian	0.72 (0.46, 1.14)	0.858	FEM
		Mix	0.21 (0.01, 4.34)	/	
		Hospital	0.74 (0.46, 1.18)	0.729	
		Population	0.37 (0.07, 2.11)	0.638	
		Total	0.70 (0.44, 1.09)	0.842	
A	G	Caucasian	0.71 (0.45, 1.12)	0.008	REM
		Mix	1.00 (0.65, 1.55)	/	
		Hospital	0.84 (0.63, 1.11)	0.122	
		Population	0.59 (0.19, 1.83)	0.009	
		Total	0.76 (0.56, 1.04)	0.017	

Notes: OR, odds ratio; CI, confidence interval; Ph, *P* value for heterogeneity; *Represents values calculated with random-effects model; FEM, fixed-effects model; REM, random-effects model.

Discussion

TC, the most common endocrine malignancy, is the most rapidly rising incident cancer in females and the second most rapidly rising incident cancer in males in the United States [16, 17]. TC can be histologically classified into four main groups, namely papillary thyroid cancer (PTC), follicular (FTC), medullary (MTC) and undifferentiated thyroid carcinomas, with PTC (80-85%) and FTC (10-15%) accounting for the vast majority of all TC cases [18]. Besides, this cancer is more and more prevalent in females with a female-to-male ratio of about 3 to 1. Furthermore, TC incidence has shown an upward trend among people under 20 years old, according to the data provided by the National Cancer Institute Surveillance, Epidemiology and End Results registry [19, 20]. Family history studies have indicated that this cancer may have a greater familial component than other cancers with an estimated risk of 3-4 folds or more for people having a family history of such cancer in first-degree relatives [21, 22]. Generally, TC is recognized as a multi-factorial disease caused by complicated interactions between environmental and genetic components, what's more, the identification and further evaluation of genetic variations are essential for understanding the potential mechanisms involved in thyroid carcinogenesis [23].

ATM is a serine threonine protein kinase and a key initiator of the DNA damage response [15, 24]. In addition, it is also a critical protein in the

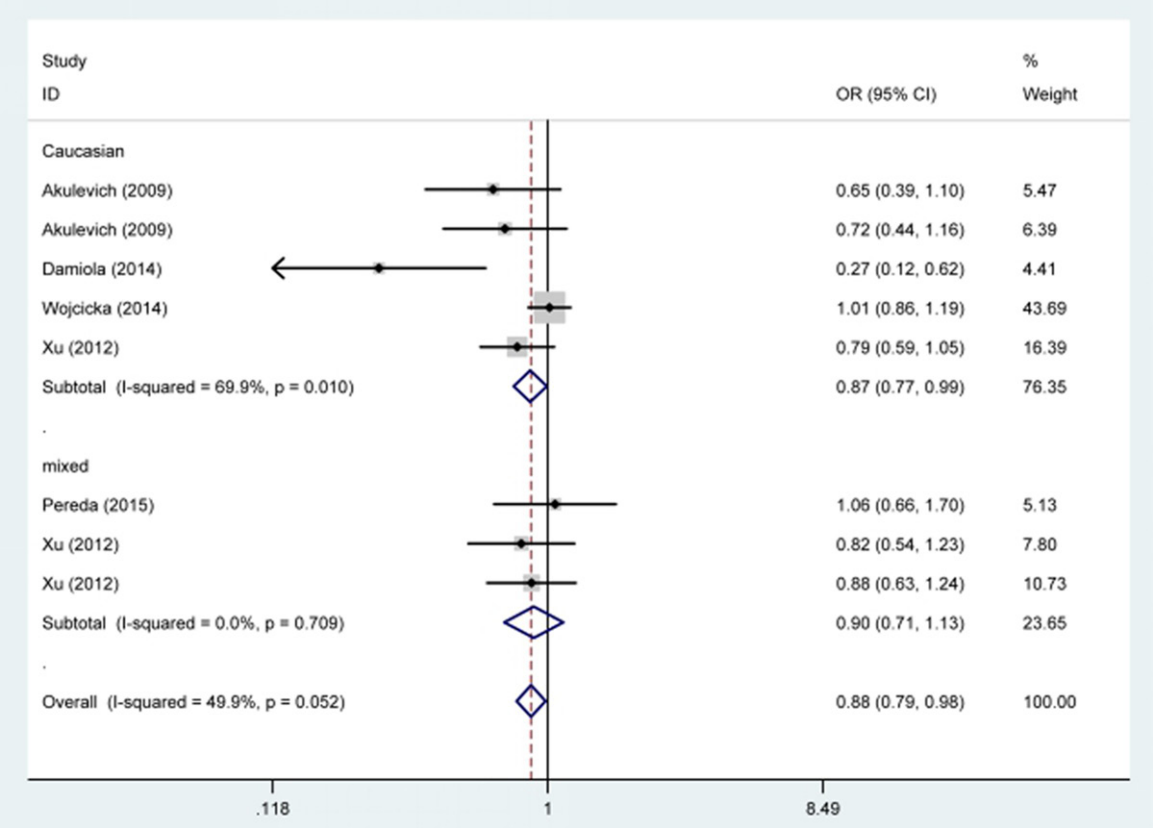

Figure 2. Forest plot of *ATM* rs1801516 polymorphism and TC risk under model AA+GA vs. GG.

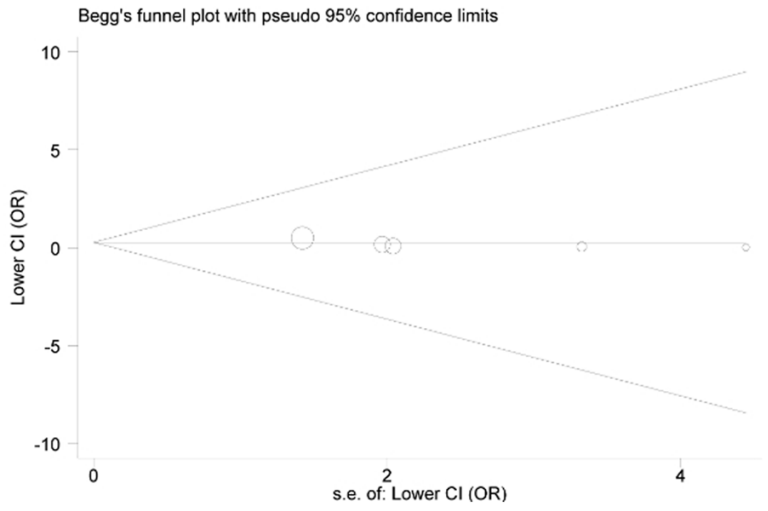

Figure 3. Begg's funnel plot for publication bias.

p53 pathway, and has been reported to be a key protein involved in several signaling pathways, including cell cycle control, DNA damage recognition, induction of apoptosis and meiotic recombination [13]. In response to the induction of DSBs, ATM is rapidly activated and can phosphorylate various downstream substrates, some of which are key factors in the regulation of cell-cycle arrest, apoptosis and DNA repair. For instance, ATM, as an upstream factor of tumor-suppressor protein TP53, can not only regulate the progression of cell cycle and apoptosis through activating and stabilizing p53 [25], but also interact with phosphorylate oncogenic protein MDM2, DNA-repair protein NBS1, checkpoint kinase CHK2 and tumor-suppressor protein BRCA1 [26, 27]. Since the identification of the gene *ATM* in 1995, several population-based studies have confirmed the relationship between specific *ATM* alleles and several common cancers like breast, lung and prostate cancer [28-30].

It has been hypothesized that exposure to environmental components have great influences on the incidence of TC, and exposure to ionizing radiation in childhood or adolescence is the only established environmental risk factor for this malignancy until now. Moreover, the familial aggregation of TC and thyroid diseases proves that genetic factors may also contribute to the susceptibility to TC [3]. In addition, numerous epidemiological studies have stated that the rs1801516 polymorphism in *ATM* possibly causes inefficient repair of ionizing radiation-induced DNA breaks and predisposes people to a variety of cancers [1]. Akulevich et al. suggested that *ATM* rs1801516 polymorphism might be associated with decreased risk of developing TC [2]. In contrast, Damiola et al. informed that *ATM* rs1801516 polymorphism appeared to act as independent multiplicative risk factors for TC [3]. Nonetheless, the results provided by Wojcicka et al. revealed no significant association between the onset risk of TC and *ATM* rs1801516 polymorphism, neither did the study conducted by Pereda et al. [1, 15]. Due to the conflict between these conclusions, we analyzed the role of *ATM* rs1801516 polymorphism in TC susceptibility using a meta-analysis including 8 case-control studies with 3,175 TC patients and 4,467 controls, and found a statistically significant association between *ATM* polymorphism and decreased TC risk in model AA+GA vs. GG. Additionally, a similar effect of the polymorphism was also detected in Caucasian subgroup after stratification analysis by ethnicity.

This meta-analysis had stronger statistical power compared with previous single studies, but some limitations might affect our conclusions. Firstly, only papers published were selected in the current study, which might lead to some bias in our results. Secondly, potential effects of gene-gene and gene-environment interactions on the relative risk of TC were not evaluated owing to the lack of original data. Thirdly, limited studies included in the meta-analysis restricted us to perform further subgroup analyses by other factors than ethnicity and control source. Eventually, the small sample size in the analyses perhaps restricted the statistical power of the final outcomes.

Briefly, our meta-analysis concluded that the rs1801516 polymorphism in *ATM* might provide protection against the risk of developing TC. However, more well-designed studies are needed to further confirm our results in different ethnic populations with larger sample sizes and consideration of gene-gene and gene-environment interactions.

Disclosure of conflict of interest

None.

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