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NOTE

Association of Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) C1858T gene polymorphism with susceptibility to autoimmune thyroid diseases: a meta-analysis

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Abstract. Results from studies on the association of PTPN22 C1858T polymorphism with AITD risk are conflicting, we thereby perform this meta-analysis to derive a more precise effect on this possible association. Two investigators independently searched the PubMed, Embase, Wanfang and CNKI (China National Knowledge Infrastructure) databases. A total of 11 studies with 3764 AITDs cases and 3328 controls were finally identified. Statistically significant association was observed between PTPN22 C1858T polymorphism and AITD risk based on all studies (TT *vs.* CC, *OR*=2.18, *95%CI*=1.31~3.62; TC *vs.* CC, *OR*=1.50, *95%CI*=1.29~1.73; TT/TC *vs.* CC, *OR*=1.41, *95%CI*=1.12~1.78; TT *vs.* TC/CC, *OR*=2.00, *95%CI*=1.21~3.33). The results of subgroup analysis showed that: (1) regarding ethnic diversity, the variant genotypes TT/TC of C1858T were associated with a significantly increased AITD risk in Caucasians (TT/TC *vs.* CC, *OR*=1.41, *95%CI*=1.09~1.83) (2) regarding different countries, the statistically significantly association was observed in UK (TC *vs.* CC, *OR*=1.64, *95%CI*=1.36~1.98; TT/TC *vs.* CC, *OR*=1.65, *95%CI*=1.37~1.98) and other countries (including Tunisia, Russia, Poland, Japan) (TT *vs.* CC, *OR*=3.65, *95%CI*=1.43~9.33; TT *vs.* TC/CC, *OR*=3.41, *95%CI*=1.34~8.65). (3) regarding the subtypes of AITDs, patients with Graves' disease (GD) had a significant higher degree of C1858T polymorphism (TT *vs.* CC, *OR*=2.35, *95%CI*=1.36~4.05; TC *vs.* CC, *OR*=1.46, *95%CI*=1.12~1.89; TT/TC *vs.* CC, *OR*=1.54, *95%CI*=1.33~1.80; TT *vs.* TC/CC, *OR*=2.16, *95%CI*=1.25~3.72), while no association was observed in patients with Hashimoto's thyroiditis (HT). No publication bias was observed. Our results demonstrated that PTPN22 C1858T polymorphism was associated with AITD risk, especially in Caucasians.

Key words: Protein Tyrosine Phosphatase Nonreceptor 22, Polymorphism, Meta-analysis, Autoimmune thyroid diseases

AUTOIMMUNE THYROID DISEASES (AITDs), classically including Graves' disease (GD) and Hashimoto's thyroiditis (HT), are among the most common human autoimmune diseases. To date, advances have been made in our understanding of the complex interactions between genetic and environmental factors giving rise to AITDs [1], and a number of susceptibility genes have been found to be associated with susceptibility to AITDs [2-4].

In recent years, the polymorphism C1858T (rs2476601) in the Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) gene has been extensively studied and considered as a candidate susceptibility gene to AITDs in different ethnic groups. The PTPN22 gene locates on chromosome 1p13 and encodes the lymphoid protein tyrosine phosphatase (LYP). LYP acts as a powerful T cell activation inhibitor by binding to signal transduction molecules such as Csk kinase that mediate T cell activation. The PTPN22 C1858T SNP results in an arginine (R) to tryptophan (W) residue change at position 620, which leads to less binding efficiency to Csk kinase. As a result, T cells expressing T allele may be hyper-responsive, and leads to autoimmune disorders [5, 6].

However, it remains a common problem that the association of the polymorphism PTPN22 C1858T with AITD susceptibility varies in different studies, negative [7, 8] and positive relationship [9] were coex-

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isted. Due to the underpowered of one single study to detect the overall effects and in an attempt to explain some of the published inconsistencies, we carried out a meta-analysis to gain a greater understanding of the relationship between individual PTPN22 C1815T polymorphism with AITD risk.

Methods

Literature search strategy

We searched the PubMed, Embase, Wanfang and CNKI (China National Knowledge Infrastructure) databases for all articles on the association between PTPN22 polymorphism and AITD (last search update 21st November 2011). The following terms were used in this search: "Protein Tyrosine Phosphatase Nonreceptor 22," "PTPN22," "Rs2476601," "R620W," "thyroid disease," "Graves' disease" and "Hashimoto's disease" limited to humans. All references mentioned were checked for additional relevant studies not indexed by those databases. Review articles were hand-searched to find additionally eligible studies.

Inclusion and exclusion criteria

All human-associated studies were included in this meta-analysis if they met the following criteria (1) evaluation of PTPN22 C1858T polymorphism and AITD; (2) enough data to calculate *OR*. We excluded the following: (1) overlapping data; (2) no control and (3) no sufficient data reported.

Data extraction

All data were extracted independently by two reviewers (Limei Luo and Bei Cai) according to the inclusion criteria and consensus was achieved for all data. The following data were extracted from each study: the last name of the first author, year of publication, ethnicity of the study population, genotyping methods, study design, numbers of cases and controls, and the genotype and allele frequencies of the PTPN22 C1858T polymorphism, and evidence of Hardy-Weinberg equilibrium (HWE).

Statistical analysis

We firstly assessed HWE in the controls for each study using goodness-of-fit test (chi-square or Fisher's exact test) and a $P < 0.05$ was considered as significant disequilibrium. The strength of the association between AITD and the PTPN22 C1858T polymorphism was estimated using *ORs*, with the corresponding *95% CIs*. The pooled *ORs* were performed for a codominant model (TT *vs.* CC, TC *vs.* CC), a dominant model (TT+ TC *vs.* CC), and a recessive model (TT *vs.* TC+ CC). We also carried out the stratified analyses by ethnicity, types of AITDs (GD or HT), country and HWE in controls.

Both the Cochran's Q statistic [10] to test for heterogeneity and the I^2 statistic to quantify the proportion of the total variation due to heterogeneity[11] were calculated. A *P* value of more than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across studies, allowing for the use of a fixed-effects model (the Mantel–Haenszel method) [12]; if the *P* value in the Cochran's Q statistic was less than 0.10, the random-effects model (the DerSimonian and Laird method) was used [13]. Sensitivity analysis was performed to assess the stability of results.

Several methods were used to assess the potential publication bias. Visual inspection of funnel plot asymmetry was conducted. The Begg's rank correlation method [14] and the Egger's weighted regression method [15] were used to statistically assess publication bias (P <0.05 was considered statistically significant). All analyses were done using STATA software, version 11.0 (STATA Corp., College Station, TX, USA). All the *P* values were two-sided.

Results

Characteristics of studies

Via an extensive search, eleven eligible articles [3, 7, 16-24] were selected for this meta-analysis, including 3764 AITD cases and 3328 controls. Study characteristics were summarized in Table 1. There were four studies with Asian population and seven studies with Caucasian population. Studies had been carried out in China, Japan, Poland, UK, Germany, Tunisia, and Russia. AITD types were distributed as follows: seven studies were concerned with GD, one study concerned with GD and HT separately, one study concerned with HT, and two studies were mixed by GD and HT. The needed DNA for genotyping were extracted from peripheral blood in all studies and the used genotyping methods included the classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay in eight out of eleven studies. The genotype distributions among the controls of all studies were consistent with HWE except for one study [23].

Table 1 Characteristics of studies included in the meta-analysis

First author referrnce	Published year	Country	Ethnicity	Genotyping methods	Matching criteria	Types of diseases	Sample size (male/female)		Mean age (±SD) (year)		Genotypes of controls			Genotypes of cases			HWE
							controls	cases	controls	cases	CC	CT	TT	CC	CT	TT	
Gu [3]	2010	China	Asian	Mass-ArrayTM Technology Platform from Sequenom	NA	GD	316 (98/218)	436 (117/319)	49.2±12.7	39.3±12.3	315	0	0	423	0	0	NA
Kahles [7]	2005	Germany	Caucasian	real-time PCR	NA	HT	239 (133/106)	94 (17/77)	49.4±16.6 (23-83)	51.6±17.0 (23-95)	187	50	2	67	25	2	Yes
Zheng [16]	2008	China	Asian	PCR-RFLP	age, sex	GD	218 (77/141)	283 (88/195)	41±12 (15~58)	39 ±13 (11~70)	213	5	0	275	8	0	Yes
Velaga [17]	2004	U.K	Caucasian	PCR-RFLP	NA	GD	429	549 (119/430)	NA	NA	365	61	3	404	139	6	Yes
Chabchoub [18]	2009	Tunisia	Caucasian	PCR-RFLP	NA	AITD	236 (86/150)	204 (54/150)	NA	34.2 (22~58)	224	12		200	4		Yes
Smyth [19]	2004	U.K	Caucasian	PCR-RFLP	ethnically	GD	833	901	NA	NA	669	154	10	661	222	18	Yes
Skórka [20]	2005	Poland	Caucasian	PCR-RFLP	ethnically	GD	310	290 (60/230)	NA	42.5 (6~78)	238	68	4	189	90	11	Yes
Dultz [21]	2009	Germany	Caucasian	PCR-based reverse dot-blot technique	NA	AITD	100 (43/57)	70 (14/56)	38.9±15.6	42.3±13.8	86	12	2	58	12	0	Yes
Ichimura [22]	2008	Japan	Asian	PCR-RFLP	NA	GD	231 (102/129)	414 (90/324)	29.2±8.3 (21-60)	41.9±15.8 (11-87)	231	0	0	414	0	0	NA
Zhebrun [23]	2011	Russia	Caucasian	PCR-RFLP	NA	GD	200	171	NA	NA	132	66	2	115	49	7	No
Zheng [24]	Doctoral Dissertation 2008	China	Asian	PCR-RFLP	NA	GD, HT	216 (76/140)	279 (86/193) (GD) 73(10/63) (HT)	41.46±12.26	39.43±13.64 (GD) 42.13±14.84 (HT)	211	5	0	271 (GD) 73 (HT)	8 (GD) 0 (HT)	0 (GD) 0 (HT)	Yes

PCR–RFLP, polymerase chain reaction–restriction fragment length polymorphism; NA, not available; GD, Graves' disease; HT, Hashimoto's thyroiditis; AITD, autoimmune thyroid disease; HWE, Hardy-Weinberg equilibrium

Quantitative synthesis

Overall, we found that the C/T polymorphism was associated with a significantly increased AITD risk in all genetic models (TT *vs.* CC: *OR*=2.18, *95% CI* =1.31-3.62; TC *vs.* CC: *OR*=1.50, *95% CI* =1.29-1.73; dominant model: *OR*=1.41, *95% CI* =1.12-1.78; recessive model: *OR*=2.00, *95% CI* =1.21-3.33) (Table 2 and Fig. 1).

In the subgroup analysis by ethnicity, the results suggested that the C/T was significantly associated with risk of AITD development among Caucasians (TT *vs.* CC: *OR*=2.18, *95% CI* =1.31-3.62; TC *vs.* CC: OR=1.47, *95% CI* =1.16-1.86; dominant model: *OR*=1.41, *95% CI*=1.09-1.83; recessive model: *OR*=2.00, *95% CI*=1.21-3.33). Moreover, when stratified by types of AITD, a significantly increased risk was observed for GD (Fig. 2) (TT *vs.* CC: OR=2.18, *95% CI* =1.31-3.62; TC *vs.* CC: *OR*=1.47, *95% CI* =1.16-1.86; dominant model: *OR*=1.41, *95% CI*=1.09-1.83; recessive model: *OR*=2.00, *95% CI*=1.21-3.33). Since a large part of the analyzed studies investigated the China, UK, Germany and others populations, we also performed a stratified analysis by country, dividing the groups in China, UK, Germany and others. Interestingly, when stratified by country, a significantly elevated risk was found among UK (TC *vs.* CC: *OR*=1.64, *95% CI*=1.36-1.98; dominant model: *OR*=1.65, *95% CI*=1.37-1.98) and "others" country (TT *vs.* CC: *OR*=3.65, *95% CI* =1.43-9.33; recessive model: *OR*=3.41, *95% CI* =1.34-8.65), but not among China or Germany. Limiting the analysis to the studies within HWE, the results were persistent and robust (Table 2).

Heterogeneity analysis and Sensitivity analysis

No significant heterogeneity between studies was observed in overall comparisons or main subgroup analyses. In the sensitivity analysis, the influence of each study on the pooled *OR* was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure confirmed the stability of our overall results. In addition, when excluding the studies that were not in HWE, the results were persistent and robust (Table 2).

Publication bias

Funnel plot, Begg's and Egger's tests were performed to evaluate publication bias of the literature on AITD. Fig. 3 displayed a funnel plot that examined the

Table 2 Stratified analyses of the Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) 1858 C/T polymorphism on autoimmune thyroid disease (AITD) risk.

Variables	N[a]	TT *versus* CC		TC *versus* CC		TT+TC *versus* CC		TT *versus* TC+CC	
		OR(95%CI)	P^b	OR(95%CI)	P^b	OR(95%CI)	P^b	OR(95%CI)	P^b
Total	11	2.18(1.31,3.62)	0.68	1.50(1.29,1.73)	0.17	1.41(1.12,1.78)	0.07	2.00(1.21,3.33)	0.65
Ethnicity									
Asian	4	NA	NA	1.24(0.56,2.77)	1.00	1.24(0.56,2.77)	1.00	NA	NA
Caucasian	7	2.18(1.31,3.62)	0.68	1.47(1.16,1.86)	0.07	1.41(1.09,1.83)	0.03	2.00(1.21,3.33)	0.65
Country									
China	3	NA	NA	1.24(0.56,2.77)	1.00	1.24(0.56,2.77)	1.00	NA	NA
UK	2	1.82(0.92,3.59)	0.99	1.64(1.36,1.98)	0.10	1.65(1.37,1.98)	0.11	1.65(0.84,3.26)	0.93
Germany	2	1.16(0.25,5.30)	0.22	1.42(0.89,2.77)	0.91	1.39(0.88,2.20)	0.80	1.08(0.24,4.96)	0.22
Others	4	3.65(1.43,9.33)	0.88	1.21(0.63,2.33)	0.02	1.01(0.51,2.00)	0.01	3.41(1.34,8.65)	0.74
HWE in controls									
Yes	10	2.01(1.17,3.44)	0.64	1.60(1.37,1.87)	0.74	1.57(1.35,1.83)	0.20	1.81(1.06,3.11)	0.67
No	1	4.02(0.82,19.72)	NA	0.85(0.55,1.33)	NA	0.95(0.61,1.46)	NA	4.23(0.87,20.62)	NA
Types of AITD									
GD	8	2.35(1.36,4.05)	0.70	1.46(1.12,1.89)	0.07	1.54(1.33,1.80)	0.12	2.16(1.25,3.72)	0.66
HT	2	2.79(0.39,20.21)	NA	1.26(0.74,2.15)	0.26	1.31(0.78,2.21)	0.25	2.58(0.36,18.56)	NA

AITDs, autoimmune thyroid diseases; GD, Graves' disease; HT, Hashimoto's thyroiditis; NA, not available. [a]Number of comparisons. [b] *P* value of Q-test for heterogeneity test. Random-effects model was used when *P* value for heterogeneity test <0.1; otherwise, fixed-effects model was used.

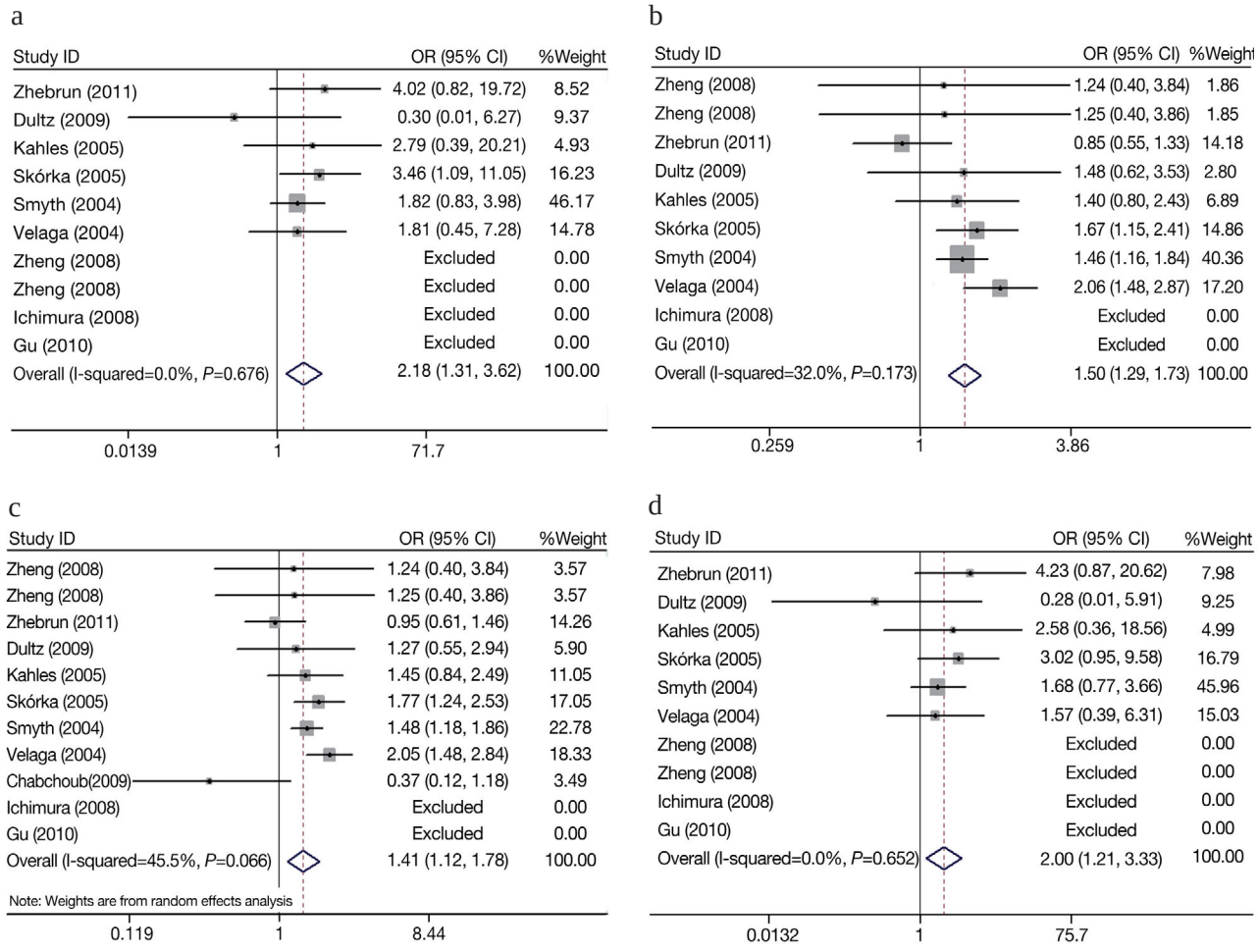

Fig. 1 Forest plots of *ORs* with *95% CIs* for protein tyrosine phosphatase nonreceptor 22 (PTPN22)1858 C/T polymorphism and risk for autoimmune thyroid diseases (AITDs). The center of each square represents the *OR*, the area of the square is the number of sample and thus the weight used in the meta-analysis, and the horizontal line indicates the 95%CI. (a) TT *vs.* CC. (b) TC *vs.* CC. (c) TT + TC *vs.* CC. (d) TT *vs.* TC+ CC.

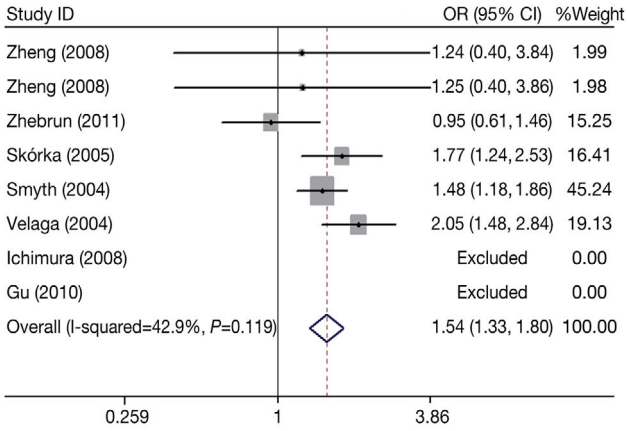

Fig. 2 Forest plots of *ORs* with *95% CIs* for Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22)1858 C/T polymorphism and risk for Graves' disease (GD) (TT + TC *vs.* CC).

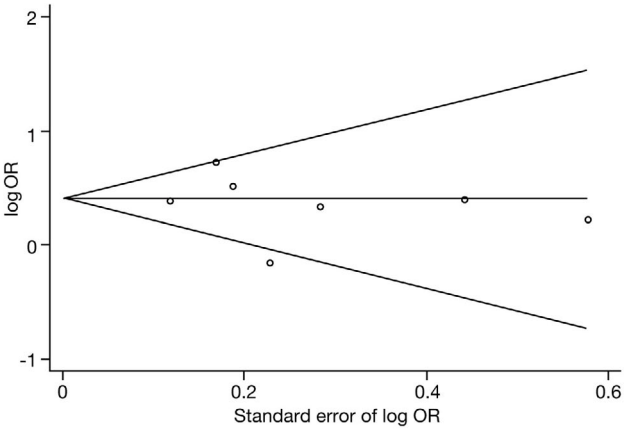

Fig. 3 Begg's funnel plot with pseudo 95% confidence limits Funnel plot for publication bias test (TC *vs.* CC). Each point represents a separate study for the indicated association.

C/T polymorphism and overall AITD risk included in the meta-analysis in the homozygote comparison. The shape of funnel plot did not reveal any evidence of funnel plot asymmetry. The statistical results still did not show publication bias except for in recessive model. (TT *vs.* CC: Begg's test P=0.71, Egger's test P=0.72; TC *vs.* CC: Begg's test P=0.27, Egger's test P=0.56; dominant model: Begg's test P=0.08, Egger's test P=0.18; recessive model: Begg's test P=1.00, Egger's test P=0.76).

Discussion

It has been reported that the PTPN22 locus is one of the strongest risk factors outside of the major histocompatability complex that associates with various autoimmune diseases, autoimmune thyroid diseases for example (AITDs) [25]. Despite a wealth of genetic studies implicating PTPN22 C1858T polymorphism as risk factor for AITDs, the results differed among different studies as previously mentioned, which might be partly due to different genetic backgrounds among various populations or other potential confounding factors. To derive a more precise effect on the association between the PTPN22 C1858T polymorphism and AITD susceptibility, we conducted this meta-analysis. At the same time, stratified analysis by ethnicity, country, and subgroups of AITDs were carried out to adjust for potential confounding factors.

Our results provided strong evidence for an association of the PTPN22 missense SNP with risk of AITDs with *ORs* of 1.41 and 2.00 in dominant model and recessive model, respectively. It has been reported that the T1858 allele was almost absent in African American and Asian populations [26], which raises interesting questions to researchers about the origin of the polymorphism and different selective susceptibility to the disease. In the present study, the association was seen in Caucasian when stratified by ethnicity. Due to small sample size possibly, both the positive result of Caucasian populations and negative result of Asian populations should be interpreted seriously, rather than coming to a confirmed conclusion. Further more, we evaluated the PTPN22 C1858T polymorphism and AITD risk in different types of AITDs and countries. The results showed that a significantly increased risk was observed for GD, and a significantly elevated risk was found among the British but not among the Chinese or the German. While several environmental factors contributing to the etiology of AITD have been identified [1], additional studies should be performed to evaluate the interactions between genes and environmental factors in the etiology of AITDs in the future to better explain the difference between different populations or countries or disease subtypes.

We only focused on AITDs but not overall autoimmune diseases. Our analysis differed from a previous meta-analysis on the PTPN22 C1858T polymorphism and autoimmune diseases including AITD risk performed by Lee YH *et al.* [27], as we included eight more comparisons, and we conducted subgroup analysis not only in different ethnic groups but also the types

of AITDs. There were some limitations that should be considered in the study. First, our ethnic-specific meta-analysis included data from Caucasians and Asian patients, thus our results were applicable only to these ethnic groups. Second, data on matching criteria of age or sex were not sufficiently standardized across studies to allow controlling of sex-related effect modification or gender differences. Third, the PTPN22 gene contains many more SNPs than C1858T mentioned in this article. Given the limited evidence available on other PTPN22 gene polymorphisms, this meta-analysis was restricted to PTPN22 C1858T polymorphism, and future studies should be performed to capture more of the diversity within the PTPN22 gene.

Furthermore, the thyroid is highly vulnerable to autoimmune diseases, resulting from a complex interplay of genetic, environmental, and endogenous factors [28]. It has been reported that approximately 10% of individuals have thyroid-specific autoantibodies (TgAb about 10.4±0.5% and TPOAb about 11.3±0.4%) [29]. To ensure the reliability of each study, the ideal healthy controls should be euthyroidism, negative for thyroid-specific autoantibodies, and no history of thyroid disorders. However, only two studies met this reliable criterion [7, 22] and subgroup analysis for reliability controls could not be performed because the T allele was absent in one study [22]. Although genetic factors predominate, accounting for approximately 80% of the likelihood of developing AITDs [28], at least 20% is still due to environmental factors, so more strict study protocols and selection criteria of healthy controls should be carried out to overcome other possible factors and explore the more precise gene effect on AITDs risk.

In conclusion, this meta-analysis demonstrated that the PTPN22 C1858T polymorphism confers susceptibility to AITDs in Caucasians. Due to small sample size possibly, it is critical that larger studies based on various ethnic groups are needed to confirm our results.

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