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Association of the rs17250932, rs4794067, and rs2240017 polymorphism in the *TBX21* gene with autoimmune diseases: A meta-analysis

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Abstract
Objective: To evaluate systematically the association between *TBX21* gene polymorphisms (rs17250932, rs2240017, and rs4794067) and the risk of autoimmune diseases in Asian populations.
Methods: The Medline, Web of Science, and Chinese Biomedical Literature Database were used to retrieve eligible studies that were published before July 2020. Pooled odds ratios (OR) and 95% confidence intervals (95% CI) were calculated by using the dominant model, heterozygote contrast model, and allelic contrast model. Publication bias was evaluated using contour-enhanced funnel plots and Egger's regression test. Sensitivity analysis was conducted to assess the robustness of this meta-analysis.
Results: A total of 12 eligible studies, including 3834 patients and 4824 healthy controls, were recruited in this meta-analysis. The pooled data demonstrated that *TBX21* rs2240017 and rs4794067 polymorphisms were significantly associated with the risk of autoimmune diseases in Asian populations in allelic contrast model (OR: 1.456, 95% CI: 1.131-1.875, P = 0.004; OR: 0.766, 95% CI: 0.615-0.954, P = 0.017), heterozygote comparison model (OR: 1.647, 95% CI: 1.239-2.189, P = 0.001; OR: 0.796, 95% CI: 0.634-0.999, P = 0.049), and dominant model (OR: 1.572, 95% CI: 1.194-2.071, P = 0.004; OR: 0.767, 95% CI: 0.607-0.970, P = 0.027). The G allele of rs2240017 may be a risk factor for autoimmune diseases, and the T allele of rs4794067 may increase the risk of autoimmune diseases. However, we failed to find evidence of the association between *TBX21* rs17250932 polymorphism and susceptibility to autoimmune diseases. No publication bias was established in this meta-analysis.
Conclusion: This meta-analysis indicated that *TBX21* rs2240017 and rs4794067 polymorphism confer susceptibility to autoimmune diseases, but not rs17250932.

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Introduction

Autoimmune diseases are a kind of chronic complex diseases characterized by loss of autoimmune tolerance; 7.6%–9.4% of general population suffers from autoimmune diseases,[1] and the incidences are still increasing. Autoimmune diseases are now ranked within the top 10 causes of death, resulting in a great economic burden.[2] Although the mechanism of autoimmune diseases is still unclear, the combination of genetic predisposition and environmental factors is thought to play an important role in the etiology of these diseases.[3] Data from human genome-wide association studies (GWAS), linkage, and association studies indicate that autoimmune diseases may share common genetic background.[4]

T cell-specific T-box transcription factor (*TBX21*) gene is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box, and is located on human chromosome 17q21.32. The transcription factor T-bet, encoded by *TBX21* gene, has recently emerged as a central player in autoimmune diseases.[5,6] As a key regulator of Th1 cell differentiation, T-bet can initiate naive Th precursor cells developed to Th1 lineage and play an essential role in promoting IFN-γ production.[7] For example, T-bet transgenic mice avoided developing collagen-induced arthritis,[8] and another mouse model showed an ameliorated Type 1 diabetes in the absence of T-bet.[9] The systemic lupus erythematosus (SLE) was also established to be less susceptibility in T-bet deficient mice.[10] Previous studies have shown that *TBX21* was a strong candidate gene because of its role in Th1/Th2 balance.[11] Collectively, these findings suggest that *TBX21* may play a critical role in multiple immune-mediated diseases.

A number of published case-control studies have been conducted to evaluate the association between *TBX21* rs17250932, rs4794067, and rs2240017 polymorphisms and autoimmune diseases, including SLE,[12,13] rheumatoid arthritis (RA),[14] type 1 diabetes (T1D),[15] Behcet's disease,[16] and autoimmune hepatitis (A1H).[17] However, the results were controversial and inconsistent. This discrepancy might be due to the studies with inadequate statistical power, ethnic differences, publication bias, etc. Therefore, the aim of this meta-analysis was to evaluate the association between *TBX21* rs17250932, rs4794067, and rs2240017 polymorphisms and susceptibility to autoimmune diseases.

Methods and materials

Search strategy

A well-conducted search was performed by two investigators independently to retrieve all the literature examining the association between *TBX21* single nucleotide polymorphisms (SNPs; rs17250932, rs4794067, and rs2240017) and autoimmune diseases. The authors used three bibliographic databases (Medline, Web of Science, and Chinese Biomedical Literature Database) to retrieve eligible studies. The combination of keywords, such as "*TBX21*," "T-bet," "polymorphism," "autoimmune disease," and the names of individual diseases, served as Medical Subject Heading (MeSH) terms and/or text words. Additional studies were supplemented by the references of relevant original research reports and related articles.

Inclusion and exclusion criteria

We made the following restrictions for the retrieved literatures: (1) published in English or Chinese only, and (2) research published up to November 2018. Studies were included if: (1) unrelated case-control or cohort design; (2) evaluating the association between *TBX21* polymorphism and autoimmune diseases; (3) containing available and sufficient data for comparison and calculating odds ratios (OR) and 95% confidence intervals (CI). Duplicate datasets or studies containing family members were excluded. In addition, autoimmune diseases should be diagnosed according to the respective classification criteria.

Data extraction

First author, year of publication, country and ethnicity of the studied population, demographic information, number of cases and controls, and the allele and genotype frequency of rs17250932, rs4794067, and rs2240017 were extracted from each literature by two authors independently. When the two authors were at odds, the third author was consulted. The studies which contained more than one disease or SNP were treated as separate studies.

Evaluation of statistic association

The meta-analysis aimed to evaluate the strength of association between *TBX21* rs17250932, rs4794067, and rs2240017 polymorphisms and autoimmune diseases by calculating the total OR and 95% CI. Three genetic models were performed, including dominant model, heterozygote contrast model, and allelic contrast model. χ^2 goodness-of-fit tests were used to examine the existence of the Hardy-Weinberg equilibrium (HWE); $P < 0.05$ was considered to be statistically significant.

Heterogeneity was assessed with Cochran's Q test and *I*2 statistic. $P < 0.10$ indicated a significant Q statistic and the existence of within- and between-study variation I^2 statistic values from 0 to 100%; 25%, 50%, and 75% represented a low, moderate, and high heterogeneity, respectively.[18] The pooled OR values and their 95% CIs were obtained by using random effect model in case of significant heterogeneity ($P < 0.10$ or $I^2 > 50\%$), otherwise a fixed effect model ($P < 0.10$ or $I^2 > 50\%$) was used in this meta-analysis.

Contour-enhanced funnel plots were carried out to evaluate the potential publication bias intuitively.[19] The Begg's and Egger's tests were also preformed to quantify the evidence for asymmetry and $P < 0.05$ was considered to be a statistically significant representation of publication bias. By removing one study each time and repeating the analysis, sensitivity analysis was preformed to value the stability of this meta-analysis. All statistical analyses were carried out by STATA 12.0 software (Stata Corp, College Station, TX, USA).

Results

Characteristics of eligible studies

In all, 73 studies were retrieved until July 31, 2020 after a systematical research was done in the above-mentioned bibliographic databases. Among these articles, 20 duplicate articles were excluded; 20 studies were excluded for not mentioning SNPs and autoimmune diseases in the title and on abstract screening. Four animal experimental studies, one non-case control study, and seven reviews were also excluded. After excluding three articles that mainly investigated irrelevant SNPs and six articles whose raw data were unavailable, 12 articles met the inclusion criteria. However, after a careful examination, we determined that two articles should be excluded because one of them was a pedigree study and the other deviated from HWE. Finally, 10 articles[11-17, 20-22] were identified as eligible studies. It is worth noting that one article only provided the frequency of rs17250932 T/C allele in the controls but did not provided data on TT/TC/CC genotypes. Therefore, in this article we included only rs4794067 and rs2240017 for meta-analysis. Of these 10 articles, two articles investigated two types of autoimmune diseases, respectively, so each autoimmune disease was considered to be a separate study. Therefore, 12 eligible studies, including 3834 patients and 4824 healthy controls, were recruited in this meta-analysis. The literature selection process is shown in Figure 1.

The recruited 12 eligible studies contained nine studies for rs17250932, three studies for rs2240017, and 10 studies for rs4794067. Five genotyping methods were used, including polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP), PCR-restriction fragment length polymorphism assay (PCR-RFLP), TaqMan, Sequenom MassArray, and PCR. The characteristics of each study, including first author, year of publication, journal title, disease, ethnicity, genotype method, and demographic characteristics of case and control, are summarized in Table 1.

The association of TBX21 *rs17250932 polymorphism and autoimmune disease susceptibility*

The findings indicated that no relationship existed between rs17259032 polymorphism and autoimmune diseases in the above-mentioned three genetic contrast models, and the pooled OR (95% CI) was 0.842 (0.619-1.144) in allelic contrast model, 0.832 (0.580-1.195) in heterozygote comparison, and 0.830 (0.588-1.171) in dominant model (all P-values >0.05). The results are summarized in Table 2 and Figure 2.

The association of TBX21 *rs2240017 polymorphism and autoimmune disease susceptibility*

A significant association between *TBX21* rs2240017 polymorphism and autoimmune diseases was revealed in allelic contrast model (OR: 1.456, 95% CI: 1.131-1.875, P = 0.004), heterozygote comparison model (OR: 1.647, 95% CI: 1.239-2.189, P = 0.001), and dominant mode (OR: 1.572, 95% CI: 1.194-2.071, P = 0.004) in Asian populations. A summary of meta-analysis findings regarding the association of *TBX21* rs2240017 polymorphism and autoimmune disease susceptibility is provided in Table 2 and Figure 2.

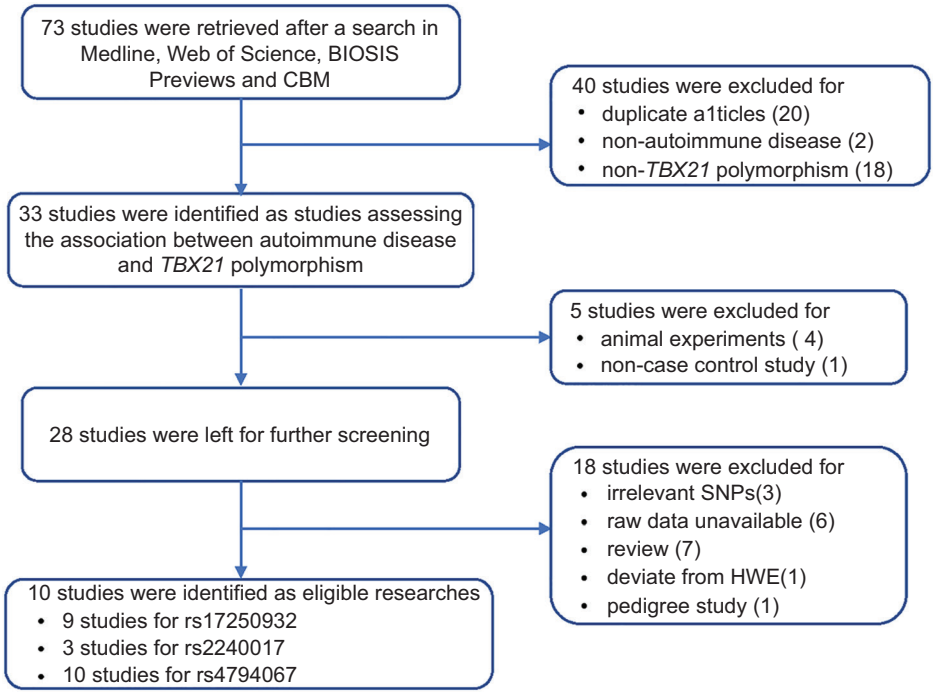

Figure 1 Flowchart for identification of studies in the meta-analysis.

Table 1 Characteristics of individual studies included in the meta-analysis.

SNP	First author	Year	Disease	Country	Genotyping methods	Sample size (Case/control)	Genotypes (Case/control)			Allele (Case/control)		HWE
							MM	Mm	mm	M	m	
rs17250932												
	You Y	2010	SLE	China	PCR-RFLP	248/261	226/210	20/50	2/1	472/470	24/52	Yes
	Chae SC	2009	RA	Korean	PCR-RFLP	367/572	332/546	33/26	0/0	697/1118	33/26	Yes
	Chen S	2011	AIH	China	PCR-RFLP	84/318	72/267	12/50	0/1	156/584	12/52	Yes
	Morita M	2012	HD	Japan	PCR	90/79	58/60	3/9	0/0	119/129	3/9	Yes
	Morita M	2012	GD	Japan	PCR	113/79	81/60	3/9	0/0	165/129	3/9	Yes
	Zhang D	2014	ITP	China	PCR-RFLP	275/261	241/224	34/37	0/0	516/485	34/37	Yes
	Liao D	2015	BD	China	PCR-RFLP	401/613	338/508	65/78	0/6	741/1094	65/90	Yes
	Liao D	2015	VKH	China	PCR-RFLP	401/613	347/508	50/78	2/6	744/1094	54/90	Yes
	Ge ML	2012	AA	China	PCR-RFLP	202/195	177/167	25/28	0/0	379/362	25/28	Yes
rs2240017												
	Chae SC	2009	RA	Korean	PCR-RFLP	367/572	247/457	71/81	4/6	565/995	79/93	Yes
	Sasaki Y	2004	T1D	Japan	PCR-RFLP	153/200	108/162	43/34	2/4	259/358	45/38	Yes
	Takahashi Y	2013	RS	Japan	PCR	29/44	25/35	3/6	1/3	53/76	5/12	Yes
rs4794067												
	You Y	2010	SLE	China	PCR-RFLP	248/261	202/192	43/63	3/6	447/447	49/75	Yes
	Chen S	2010	AIH	China	PCR-RFLP	84/318	79/247	5/67	0/4	163/561	5/75	Yes
	Leng RX	2016	SLE	China	Sequenom MassArray	1466/2266	1118/1732	314/494	34/40	2550/3958	382/574	Yes
	Morita M	2012	HD	Japan	PCR	90/79	57/43	13/14	0/3	127/100	13/20	Yes
	Morita M	2012	GD	Japan	PCR	113/79	75/43	21/14	1/3	171/100	23/20	Yes
	Zhang D	2014	ITP	China	PCR-RFLP	275/261	228/193	46/66	1/2	502/452	48/70	Yes
	Takahashi Y	2013	RS	Japan	PCR	29/113	23/96	6/16	0/1	52/208	6/18	Yes
	Liao D	2015	BD	China	PCR-RFLP	406/613	303/464	92/116	8/13	698/1044	108/142	Yes
	Liao D	2015	VKH	China	PCR-RFLP	406/613	319/464	75/116	6/13	713/1044	87/142	Yes
	Ge ML	2012	AA	China	PCR-RFLP	202/195	172/149	30/46	0/0	374/344	30/46	Yes

SLE: systemic lupus erythematosus; SNP: single nucleotide polymorphism; RA: rheumatoid arthritis; AIH: autoimmune hepatitis; HD: Hashimoto's disease; GD: Graves' disease; ITP: primary immune thrombocytopenia; BD: Behcet's disease; VKH: Vogt-Koyanagi-Harada; AA: aplastic anemia; RS: Rasmussen syndrome; HWE: Hardy-Weinberg equilibrium; PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism assay.
Note: For rs17250932 and rs4794067, MM, Mm and mm stand for TT, TC and CC genotypes, respectively. For rs2240017, MM, Mm and mm stand for CC, CG and GG genotypes, respectively.

Table 2 Meta-analysis of the association between the *TBX21* rs17250932, rs2240017, and rs4794067 polymorphism and autoimmune diseases.

SNP	Comparison	No. of studies	Test of association			Model	Test of heterogeneity			Begg's test		Egger's test	
			OR (95% CI)	*z*	P		Q	P	I^2 (%)	*z*	P	*t*	P
rs17250932	Allelic contrast model	9	0.842 (0.619-1.144)	1.10	0.271	R	22.58	0.004	64.6	1.15	0.251	0.383	0.232
	Heterozygote comparison	9	0.832 (0.580-1.195)	0.99	0.320	R	28.22	0.000	71.7	1.36	0.175	−1.63	0.147
	Dominant model	9	0.830 (0.588-1.171)	1.06	0.288	R	26.02	0.001	69.3	1.56	0.118	−1.490	0.180
rs2240017	Allelic contrast model	3	1.456 (1.131-1.875)	2.91	**0.004**	F	2.79	0.248	28.4	0.00	1.000	0.220	0.359
	Heterozygote comparison	3	1.647 (1.239-2.189)	3.44	**0.001**	F	1.59	0.452	0.0	0.00	1.000	−1.09	0.473
	Dominant model	3	1.572 (1.194-2.071)	2.86	**0.004**	F	2.24	0.326	10.7	0.00	1.000	−1.50	0.374
rs4794067	Allelic contrast model	10	0.766 (0.615-0.954)	2.38	**0.017**	R	27.82	0.001	67.6	1.25	0.210	−2.90	0.020
	Heterozygote comparison	10	0.796 (0.634-0.999)	1.97	**0.049**	R	23.45	0.005	61.6	1.07	0.283	−1.72	0.125
	Dominant model	10	0.767 (0.607-0.970)	2.22	**0.027**	R	26.27	0.002	65.7	1.25	0.210	−2.26	0.054

SNP: single nucleotide polymorphism; R: random effect model; F: fixed effect model.

The association of TBX21 *rs4794067 polymorphism and autoimmune disease susceptibility*

A significant association was found between *TBX21* rs4794067 polymorphism and autoimmune diseases by using allelic contrast model (OR: 0.766, 95% CI: 0.615–0.954, P = 0.017), heterozygote comparison model (OR: 0.796, 95% CI: 0.634–0.999, P = 0.049), and dominant model (OR: 0.767, 95% CI: 0.607–0.970, P = 0.027) in Asian populations. However, it should be noted that the marginal value was approximately equal to 1 in the heterozygote comparison model. Meta-analysis results concerning the association of *TBX21* rs4794067 polymorphism and autoimmune disease susceptibility is given in Table 2 and Figure 2.

Test of heterogeneity

As shown in Table 2, heterogeneity was found when analyzing the *TBX21* polymorphisms rs17250932 and rs4794067 and autoimmune diseases in allelic contrast model, heterozygote comparison model, and dominant model (all P-values <0.05), but no heterogeneity was found in rs2240017 in the three genetic models (all P-values >0.05). Subgroup analyses and meta-regression were conducted to explore the potential sources of heterogeneity. The results showed that the year of publication and genotyping methods were not able to explain heterogeneity for rs17250932 (all P-values >0.05), and the genotyping methods and country were not statistically correlated with heterogeneity for rs4794067. However, we established that South Korea could be responsible for heterogeneity for rs17250932, and the year of publication may statistically correlate with heterogeneity for rs4794067.

Publication bias

Contour-enhanced funnel plots and the Begg's and Egger's tests were carried out to evaluate the potential publication bias in this meta-analysis. The results revealed that nonstatistically significant asymmetry was found in the Asian populations for rs17250932 (Egger's test: $t = 0.383$, P = 0.232 > 0.05; Begg's test: $z = 1.15$; P = 0.251 > 0.05), and for rs2240017 (Egger's test: $t = 0.220$, P = 0.359 > 0.05; Begg's test: $z = 0.00$; P = 1.000 > 0.05). There seems to be no significant asymmetry in the Asian populations for rs4794067 based on the intuitive observation of the contour-enhanced funnel plots, and the results of the Berger's test also supported that no significant publication bias was found (Begg's test: $z = 1.25$; P = 0.210 > 0.05); however, a statistically significant asymmetry was found in Egger's test (Egger's test: $t = -2.90$, P = 0.020 < 0.05). Therefore, we preformed trim and fill funnel plot for further verification (data not shown), and the results showed that there was no evidence of missing studies, thus confirming the absence of publication bias (Figure 3).

Sensitivity analysis

After the single study was excluded, nonstatistically significant change was observed in the recalculated pooled ORs

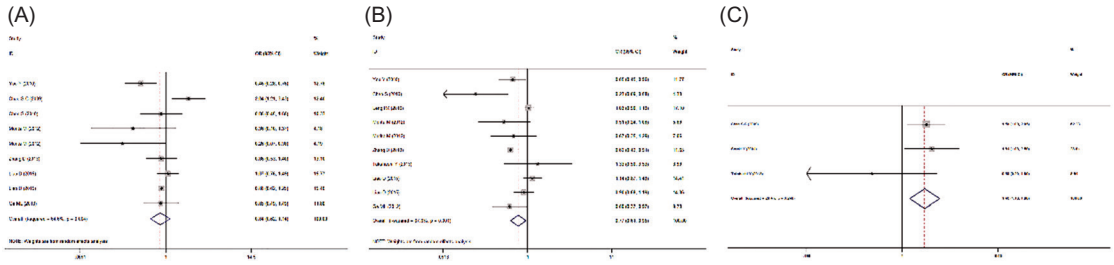

Figure 2 Forest plots regarding the association between *TBX21* rs17250932, rs2240017, and rs4794067 polymorphism and autoimmune disease susceptibility in allelic contrast model. (A) rs17250932; (B) rs4794067; (C) rs224017

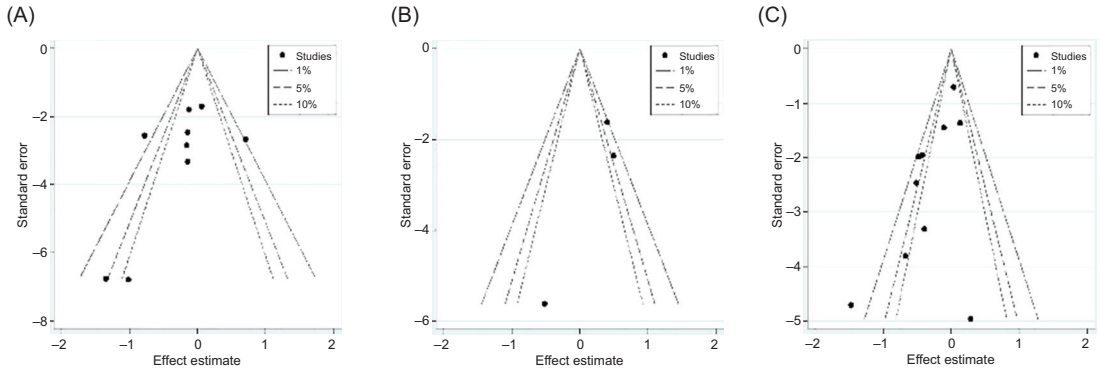

Figure 3 Contour-enhanced funnel plot assessing the publication bias of the included studies that evaluate the association between rs17250932, rs2240017, and rs4794067 and autoimmune diseases in allelic contrast model. (A) rs17250923; (B) rs2240017; (C) rs4794067

in the Asian populations for rs4794067 in allelic contrast model, indicating that the results of this meta-analysis were stable. For rs17250932, after excluding the study done by Chae et al.,[14] a marginal statistically significant change (P = 0.046) was shown and the pooled OR (95% CI) changed from 0.842 (0.619–1.144) to 0.772 (0.599–0.995) by using allelic contrast model. Since only three articles about rs2240017 were included in the meta-analysis, we did not include them in sensitivity analysis (Figure 4).

Discussion

Autoimmune diseases are a group of diseases with similar pathogenesis and characterized by abnormal immunity and tissue destruction.[23] Although there are many hypotheses about the pathogenesis of autoimmune diseases, increasingly data have shown that the interaction of environmental and genetic factors may have an important effect on the occurrence and development of autoimmune diseases.[24] As one of the most common genetic variations in human genome, SNP may play an important role in autoimmune diseases.[25] Previous studies on genetic association have shown that autoimmune diseases may share susceptibility genes.[26]

T-bet, encoded by the *TBX21* gene, is an important Th1 transcription factor closely related to the occurrence and treatment of autoimmune diseases.[27] More specifically, two important polymorphisms rs17250932 and rs4794067 in the promoter region of the *TBX21* gene and rs2240017 in the nonpromoter region are considered to be one of the possible genetic risk factors for autoimmune diseases, and many studies have reported that the above SNPs may be associated with genetic susceptibility to autoimmune diseases in Asian populations. However, the results of some studies could be contradictory. For example, You et al. found that rs17250932 T allele was a risk factor for SLE,[13] while Chae et al. showed that rs17250932C allele was a risk factor for RA,[14] but Leng et al. failed to find a relationship between rs17250932 and SLE.[12] Therefore, in order to comprehensively evaluate the relationship between *TBX21* rs17250932, rs2240017, and rs4794067 polymorphisms and the risk of autoimmune diseases, we conducted this meta-analysis. To the best of our knowledge, this is the first meta-analysis to evaluate the relationship between *TBX21* gene polymorphism and genetic susceptibility to autoimmune diseases, and is more effective than any previous case-control study.

In this meta-analysis, we demonstrated that *TBX21* rs2240017 and rs4794067 polymorphisms were significantly associated with the risk of autoimmune diseases in Asian populations. The results demonstrated that the G allele of rs2240017 may be a risk factor for autoimmune diseases, and the T allele of rs4794067 may increase the risk of autoimmune diseases. However, we failed to find evidence of the association between *TBX21* rs17250932 polymorphism and susceptibility to autoimmune diseases. T-bet is considered to be the main regulator of CD4+ Th1 cell differentiation and can promote the production of IFN-γ by Th1 cells

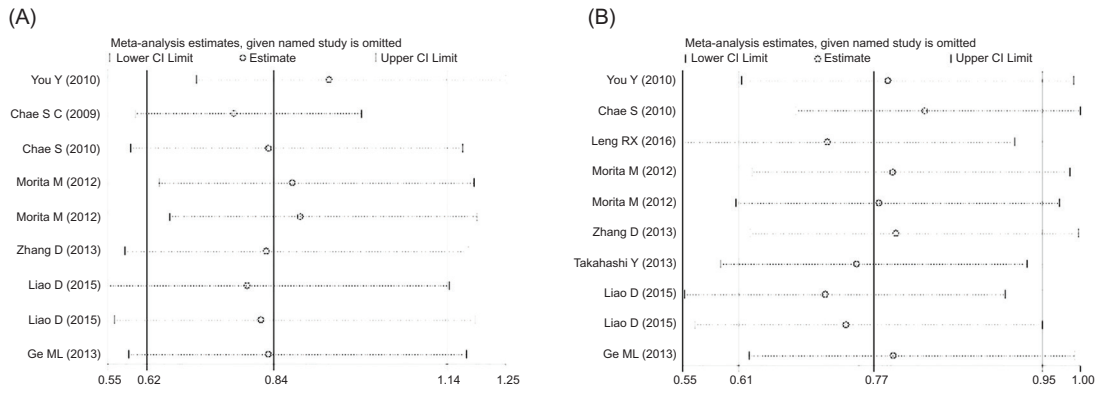

Figure 4 Sensitivity analysis plot assessing the stability of the included studies that evaluate the association between rs17250932 and rs4794067 and autoimmune diseases in allelic contrast model. (A) rs17250923; (B) rs4794067

and NK cells.[28] At the same time, T-bet also has a regulatory effect on IgG2a produced by B cells, although this effect may be based on the action of IFN-γ.[29] These function of T-bet are considered to affect the process of autoimmunity. Both rs17250932 and rs4794067 are located in the promoter region of *TBX21*. These SNP variants may be related to the translation of mRNA, thus regulating the expression or function of T-bet. Therefore, the polymorphism of *TBX21* gene may change the expression level of mRNA, resulting in changes in protein expression or the production of autoantibodies or other immune diseases.[30] All these make *TBX21* an interesting candidate for autoimmune diseases. However, the future studies could confirm this hypothesis. It is worth mentioning that there is heterogeneity in our study. In the meta-analysis of rs17250932, we found strong heterogeneity, but after excluding the study done by Chae et al.,[14] the heterogeneity disappeared and there was a significant association between rs17250932 and autoimmune diseases, and the T allele was the potential risk factor. However, after a careful review of Chae et al.,[14] we did not find any difference between this and other articles, so we concluded that rs17250932 polymorphism has nothing to do with autoimmune diseases, and more related studies need to be included to confirm this view.

However, because of the possible limitations of this meta-analysis, it is necessary to be cautious in drawing conclusions based on this study. First, autoimmune disease is a complex illness caused by the interaction of genetic and environmental factors. The current polymorphism may affect the occurrence of autoimmune diseases to some extent, which is difficult to be detected by meta-analysis. Second, the article retrieval in this meta-analysis was limited to three electronic databases (Medline, Web of Science, and Chinese Biomedical Literature Database), and the search languages were limited to English and Chinese. Owing to the limitations of search databases and languages, there could be a possibility of publication bias. Third, all the original studies were based on Asian populations. Although two articles reported the association between rs17250932 and rs2240017 and autoimmune diseases in the Caucasian population, neither of them was included in this study because one of them was a family study and the other did not conform to HWE. Fourth, the number of studies included in this meta-analysis was small, and lacked sufficient research to carry out subgroup analysis according to the type of disease. Fifth, significant heterogeneity was found in the analysis for rs17250932 and rs4794067 by using three genetic models.

According to the results of subgroup analyses and meta-regression, the year of publication were considered to be the main sources of rs4794067 heterogeneity, while South Korea could be responsible for heterogeneity for rs17250932.. Sixth, owing to data limitations or the unavailability of data, this meta-analysis did not take into account the impact of gender, age, and other environmental factors on autoimmune diseases.

Overall, results of our meta-analysis showed that *TBX21* rs2240017 and rs4794067 polymorphisms may be associated with susceptibility to autoimmune diseases in Asian populations, but we failed to found an association between rs17250932 and autoimmune diseases. In Asian populations, the T allele of rs4794067 in the promoter region may be associated with increased susceptibility to autoimmune diseases, while the G allele of rs2240017 is shown to be a potential risk factor. However, this study has some limitations in exploring the exact mechanism of *TBX21* gene polymorphism affecting the susceptibility to autoimmune diseases. Therefore, further studies, including larger sample sizes and well-designed case controls in different ethnic groups, are needed to reveal the exact role of *TBX21* SNPs in the pathogenesis of autoimmune diseases.

Acknowledgments

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Conflict of interest

Authors declare that they have no conflict of interest.

Author contributions

Hai-li Wang and Hong Wang: literature search, manuscript preparation, statistical analysis. Yue Wu, Hua-yun Ling and

Ling-ling Wu: manuscript preparation. Bin Wang and Dong-qing Ye: manuscript revision, final language editing.

References

1. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. J Autoimmun. 2009;33(3-4):197-207. http://dx.doi.org/10.1016/j.jaut.2009.09.008.
2. Fazal SA, Khan M, Nishi SE, Alam F, Zarin N, Bari MT, et al. A clinical update and global economic burden of rheumatoid arthritis. Endocr Metab Immune Disord Drug Targets. 2018;18(2):98-109. http://dx.doi.org/10.2174/1871530317666171114122417.
3. Farh KK-H, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature. 2015;518(7539):337-43. http://dx.doi.org/10.1038/nature13835.
4. Lettre G, Rioux JD. Autoimmune diseases: Insights from genome-wide association studies. Hum Mol Genet. 2008;17(2):R116-21. http://dx.doi.org/10.1093/hmg/ddn246.
5. Peng SL. The T-box transcription factor T-bet in immunity and autoimmunity. Cell Mol Immunol. 2006;3(2):87-95. http://dx.doi.org/10.4049/jimmunol.0802887.
6. Ji N, Sosa RA, Forsthuber TG. More than just a T-box: The role of T-bet as a possible biomarker and therapeutic target in autoimmune diseases. Immunotherapy. 2011;3(3):435-41. http://dx.doi.org/10.2217/imt.10.111.
7. Dardalhon V, Korn T, Kuchroo VK, Anderson AC. Role of Th1 and Th17 cells in organ-specific autoimmunity. J Autoimmun. 2008;31(3):252-6. http://dx.doi.org/10.1016/j.jaut.2008.04.017.
8. Kondo Y, Iizuka M, Wakamatsu E, Yao Z, Tahara M, Tsuboi H, et al. Overexpression of T-bet gene regulates murine autoimmune arthritis. Arthritis Rheum. 2012;64(1):162-72. http://dx.doi.org/10.1002/art.33335.
9. Juedes AE, Rodrigo E, Togher L, Glimcher LH, Herrath MG von. T-bet controls autoaggressive CD8 lymphocyte responses in type I diabetes. J Exp Med. 2004;199(8):1153-62. http://dx.doi.org/10.1084/jem.20031873.
10. Rubtsova K, Rubtsov AV, Thurman JM, Mennona JM, Kappler JW, Marrack P. B cells expressing the transcription factor T-bet drive lupus-like autoimmunity. J Clin Invest. 2017;127(4):1392-404. http://dx.doi.org/10.1172/JCI91250.
11. Morita M, Watanabe M, Inoue N, Inaoka C, Akamizu T, Tatsumi K-I, et al. Functional polymorphisms in *TBX21* and *HLX* are associated with development and prognosis of Graves' disease. Autoimmunity. 2012;45(2):129-36. http://dx.doi.org/10.3109/08916934.2011.622013.
12. Leng R-X, Pan H-F, Liu J, Yang X-K, Zhang C, Tao S-S, et al. Evidence for genetic association of *TBX21* and *IFNG* with systemic lupus erythematosus in a Chinese Han population. Sci Rep. 2016;6:22081. http://dx.doi.org/10.1038/srep22081.
13. You Y, Zhao W, Chen S, Tan W, Dan Y, Hao F, et al. Association of *TBX21* gene haplotypes in a Chinese population with systemic lupus erythematosus. Scand J Rheumatol. 2010;39(3):254-8. http://dx.doi.org/10.3109/03009740903347983.
14. Chae SC, Shim SC, Chung HT. Association of *TBX21* polymorphisms in a Korean population with rheumatoid arthritis. Exp Mol Med. 2009;41(1):33-41. http://dx.doi.org/10.3858/emm.2009.41.1.005.
15. Sasaki Y, Ihara K, Matsuura N, Kohno H, Nagafuchi S, Kuromaru R, et al. Identification of a novel type 1 diabetes susceptibility gene, T-bet. Hum Genet. 2004;115(3):177-84. http://dx.doi.org/10.1007/s00439-004-1146-2.
16. Liao D, Hou S, Zhang J, Fang J, Liu Y, Bai L, et al. Copy number variants and genetic polymorphisms in *TBX21*, *GATA3*, *Rorc*, *Foxp3* and susceptibility to Behcet's disease and Vogt-Koyanagi-Harada syndrome. Sci Rep. 2015;5:9511. http://dx.doi.org/10.1038/srep09511.
17. Chen S, Zhao W, Tan W, Luo X, Dan Y, You Z, et al. Association of *TBX21* promoter polymorphisms with type 1 autoimmune hepatitis in a Chinese population. Hum Immunol. 2011;72(1):69-73. http://dx.doi.org/10.1016/j.humimm.2010.10.019.
18. Wang H, Yuan F-F, Dai Z-W, Wang B, Ye D-Q. Association between rheumatoid arthritis and genetic variants of natural resistance-associated macrophage protein 1 gene: A meta-analysis. Int J Rheum Dis. 2018;21(9):1651-58. http://dx.doi.org/10.1111/1756-185X.13366.
19. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008;61(10):991-6. http://dx.doi.org/10.1016/j.jclinepi.2007.11.010.
20. Takahashi Y, Mogami Y, Mine J, Imai K, Koide Y, Matsuda K, et al. Genetic variations of immunoregulatory genes associated with Rasmussen syndrome. Epilepsy Res. 2013;107(3):238-43. http://dx.doi.org/10.1016/j.eplepsyres.2013.09.004.
21. Ge M, Zheng Y, Li X, Shi J, Ge J, Li H, et al. The polymorphisms of T cell-specific TBX21 and STAT4 genes may contribute to the susceptibility of Chinese individuals to aplastic anemia. Hum Immunol. 2012;73(1):118-21. http://dx.doi.org/10.1016/j.humimm.2011.11.007.
22. Zhang D, Zhang X, Ge M, Xuan M, Li H, Yang Y, et al. The polymorphisms of T cell-specific TBX21 gene may contribute to the susceptibility of chronic immune thrombocytopenia in Chinese population. Hum Immunol. 2014;75(2):129-33. http://dx.doi.org/10.1016/j.humimm.2013.11.011.
23. Mackay IR. Clustering and commonalities among autoimmune diseases. J Autoimmun. 2009;33(3-4, SI):170-7. http://dx.doi.org/10.1016/j.jaut.2009.09.006.
24. Goodnow CC, Sprent J, Fazekas de St Groth, B, Vinuesa CG. Cellular and genetic mechanisms of self-tolerance and autoimmunity. Nature. 2005;435(7042):590-7. http://dx.doi.org/10.1038/nature03724.
25. Bentham J, Morris DL, Graham DSC, Pinder CL, Tombleson P, Behrens TW, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet. 2015;47(12):1457+. http://dx.doi.org/10.1038/ng.3434.
26. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. Nat Genet. 2010;42(6):508-56. http://dx.doi.org/10.1038/ng.582.
27. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T-cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015;74(1):5-17. http://dx.doi.org/10.1016/j.cyto.2014.09.011.
28. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000;100(6):655-69. http://dx.doi.org/10.1016/s0092-8674(00)80702-3.
29. Lugo-Villarino G, Maldonado-Lopez R, Possemato R, Penaranda C, Glimcher LH. T-bet is required for optimal production of IFN-gamma and antigen-specific T cell activation by dendritic cells. Proc Natl Acad Sci USA. 2003;100(13):7749-54. http://dx.doi.org/10.1073/pnas.1332767100.
30. Li J-R, Li J-G, Deng G-H, Zhao W-L, Dan Y-J, Wang Y-M, et al. A common promoter variant of *TBX21* is associated with allele specific binding to Yin-Yang 1 and reduced gene expression. Scand J Immunol. 2011;73(5):449-58. http://dx.doi.org/10.1111/j.1365-3083.2011.02520.x.