

## REVIEW ARTICLE

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# Association between Gene Polymorphisms of T Cell Immunoglobulin Domain and Mucin Domain-3 and Risk of Asthma: A Systematic Review and Meta-analysis

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## ABSTRACT

Previous studies have reported that T cell immunoglobulin domain and mucin domain-3 (TIM-3) 574T>G and 1516G>T are associated with the risk of asthma. However, the results are inconsistent due to the small sample size and varied age in studies. We performed this meta-analysis to systematically evaluate the effect of TIM-3 574T>G and 1516G>T genetic polymorphisms on asthma.

Eligible articles that reported an association between TIM-3 574T>G and 1516G>T genetic polymorphisms and asthma were searched in PubMed, Medline, EMBASE, Google Scholar, and China National Knowledge Infrastructure up to April 2020. Random or fixed-effects models were used to calculate the summary of odds ratios (ORs) and 95% confidence intervals (CIs) to detect any potential associations between TIM-3 genetic polymorphisms and asthma. Subgroup and sensitivity analyses were performed to assess the potential sources of heterogeneity and the robustness of the pooled estimation. Publication bias was analyzed using the Egger test.

A total of 11 case-control studies including 2077 asthma patients and 2122 control subjects were finally analyzed (published data from 2004-2018). The pooled results indicated that TIM-3 574T>G genetic polymorphisms were significantly associated with an increased risk of asthma under the dominant model (GG vs. GT + TT: ORs=2.26, 95% CI 1.09-4.69) and allele model (G vs T: ORs=2.60, 95% CI 1.20-5.64). However, no significant associations between TIM-3 1516G>T genetic polymorphisms with asthma in any model was found. No evidence of publication bias was observed.

Our study indicates that TIM-3 574T>G genetic polymorphisms were associated with increased risk of asthma and the TIM-3 1516G>T genetic polymorphisms may not be correlated with asthma.

**Keywords:** Asthma; Meta-analysis; Polymorphism

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## INTRODUCTION

Asthma is a serious chronic airway inflammatory disease, caused by a combination of genetic and environmental factors, affecting 300 million people all over the world.<sup>1-3</sup> In addition, patients with asthma often report a series of complications such as infection, metabolic disorder, cardiovascular disease, etc; resulting in more complicated conditions and worse prognosis, which will impose a heavy burden on society and family on care.<sup>4</sup> Over the past decades, many extensive genome-wide studies and targeted searches for specific genes had been used to identify common genetic variants associated with susceptibility to asthma.<sup>5</sup>

T cell immunoglobulin domain and mucin domain-3 (TIM-3), one of the members of the TIM family, which was located in chromosome 5q33.2 and had an essential role in Th1-mediated immune responses and macrophage activation.<sup>6</sup> TIM-3 expressed at the highest level on Th1 cells and regulated the autoimmune and alloimmune responses outcome.<sup>7,8</sup> Therefore, TIM-3 is a negative regulatory molecule, which plays an important role in Th1-mediated immune response, and may indirectly regulate the balance between Th1 and Th2 responses to improve autoimmune diseases and asthma.<sup>9-11</sup>

Previous studies had reported that TIM-3 genetic polymorphisms were associated with rheumatoid arthritis,<sup>12</sup> autoimmune diseases,<sup>13</sup> and cancer<sup>14,15</sup> in the general population. During the past decade, several epidemiologic observational studies have investigated the associations between TIM-3 genetic polymorphisms and the occurrence and development of asthma. But the results were controversial due to the small study sample size, study population, or residual confounding among these studies.<sup>16-19</sup> Clarifying these potential associations may have important clinical and public health implications for primary and second prevention of asthma. Therefore, we performed this systematic review and meta-analysis to better assess the associations between TIM-3 genetic polymorphisms and the risk of asthma.

## MATERIALS AND METHODS

### Literature Search Strategy

This present study was performed and reported in accord with the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses Statement, 2009.<sup>20</sup> We conducted a systematic literature search by using the electronic databases including PubMed, Medline, EMBASE, Google Scholar, and China National Knowledge Infrastructure (data up to April 2020). The following search terms were used: T cell immunoglobulin and mucin domain-3, TIM-3, hepatitis A virus cellular receptor 3, HAVCR3 and polymorphism, variant, genotype, allele, and asthma. No language restrictions were imposed. We also conducted manual searches of the reference lists of relevant articles to identify additional eligible studies.

### Inclusion Criteria

Studies were considered eligible if they met the following inclusion criteria: (1) case-control study of asthma patients and control subjects; (2) assessment of the association between TIM-3 574T>G (rs10515746), 1516G>T (rs10053538), and asthma; (3) sufficient genotype data were available for odds ratio and confidence interval calculations. Exclusion criteria were as follow (1) studies without the control groups; (2) studies with no available data to calculated odds ratios (ORs); (3) studies with inappropriate article types (pedigree studies, reviews, editorials, case reports, case series, abstracts, expert opinions, and conference presentations); (4) studies with duplicated data. For those overlapped studies, the largest or most recent publication was included.

### Data Collection and Quality Assessment

Data was collected using a standard electronic spreadsheet. The following data elements were extracted from each included study: first author's last name, publication year, country of origin, the ethnicity of the study population, participants' age type, the number of cases and controls, source of control, distributions of genotypes, and alleles in asthma patients and control subjects and the probability value (*p*-value) of Hardy-Weinberg equilibrium (HWE). The Newcastle-Ottawa Scale (NOS) was used to evaluate methodological quality.<sup>21</sup> Literature search, data extraction, and study quality assessment were independently performed by Wenping Wei and Yu Ma, and independently checked for accuracy by Chuangli Hao.

### Statistical Analysis

Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United

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Kingdom) and STATA 14.0 software (Stata Corp LP, College Station, TX, USA) were utilized for all statistical analyses. HWE was assessed by Fisher's exact test, with the significance level of  $p < 0.05$ . ORs and 95% CIs were used to evaluate associations of TIM-3 574T>G (rs10515746) and 1516G>T (rs10053538) single nucleotide polymorphism and asthma. Pooled ORs results were derived from the combination of each study through comparison in dominant and allele model. The Cochran Q chi-square test and the  $I^2$  statistic were used to assess heterogeneity among the total studies.<sup>22</sup>  $I^2$  values of  $> 50\%$  or  $p$  values of  $< 0.05$  for the Q-statistic were taken to indicate significant heterogeneity and random-effect models would be adopted for analyses. Otherwise, fixed-effect models would be applied for analyses when studies were considered to be homogenous. Subgroup analyses were performed according to participants' age type and sensitivity analyses were performed to verify the stability of overall results by removing each study from the meta-analysis. Publication bias of the studies

included in the final analysis was analyzed using funnel plots and the Egger test.<sup>23</sup> All reported  $p$  values were 2-sided, and  $p < 0.05$  were considered statistically significant.

## RESULTS

### Included Studies

After searching the five databases; using the keywords as well as the relevant reference sections, a total of 151 potentially eligible articles were identified. Of these, 126 articles were excluded after browsing the titles and abstracts and the remaining 25 articles underwent a detailed full-text evaluation. Of these, a total of 11 case-control studies containing 2077 asthmatic patients and 2122 control subjects were ultimately included after application of the inclusion criteria.<sup>16-19,24-30</sup> (Figure 1). Totally, 9/11 were the TIM-3 -574T>G (rs10515746) single nucleotide polymorphism, and 6/11 were the 1516G>T (rs10053538) single nucleotide polymorphism.

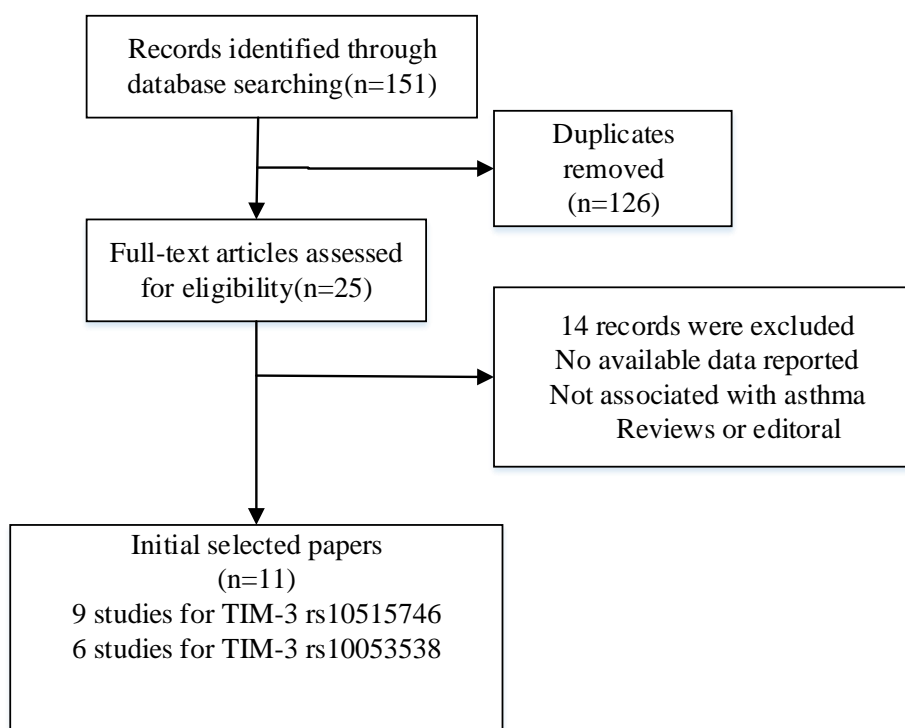


Figure 1. Flowchart of the study selection procedure

**Table 1. Main characteristics of all eligible studies in this meta-analysis**

Authors	Year	Country	Ethnicity	Age group	Cases	Controls	Source of control	NOS score
<b>-574T&gt;G (rs10515746)</b>								
Chae <sup>16</sup>	2004	Korea	Asian	Adult	253	319	HB	7
Chae <sup>17</sup>	2004	Korea	Asian	-	24	24	HB	8
Zhang <sup>18</sup>	2006	China	Asian	Adult	153	130	PB	6
Wu <sup>24</sup>	2006	China	Asian	Adult	202	296	HB	5
Hu <sup>25</sup>	2006	China	Asian	children	143	72	PB	7
Li <sup>26</sup>	2006	China	Asian	Adult	449	386	HB	7
Wu <sup>19</sup>	2012	China	Asian	children	200	215	PB	6
Sadri <sup>27</sup>	2017	Iran	Asian	-	209	201	HB	7
Jin <sup>28</sup>	2018	China	Asian	children	129	130	HB	7
<b>1516G&gt;T (rs10053538)</b>								
Chae <sup>16</sup>	2004	Korea	Asian	Adult	254	319	HB	7
Chae <sup>17</sup>	2004	Korea	Asian	-	24	24	HB	7
Chen <sup>29</sup>	2007	China	Asian	Adult	140	147	PB	7
Hu <sup>30</sup>	2008	China	Asian	Adult	175	202	PB	7
Wu <sup>19</sup>	2012	China	Asian	children	200	215	PB	6
Jin <sup>28</sup>	2018	China	Asian	children	129	130	HB	6

NOS: The Newcastle-Ottawa Scale; HB: hospital-based; PB: population-based

### Characteristics of Included Studies

The main characteristics of the included studies were shown in Table 1. The earliest study began in 2004<sup>16</sup> and the most recent of the included studies ended in 2018.<sup>28</sup> The average NOS score of included studies was 6.73 (range from 4-8), indicating that all eligible studies were of relatively high quality. Of these, 8 studies were carried out among Chinese,<sup>18,19,24-26,28-30</sup> 2 studies were conducted in Korea subjects<sup>16,27</sup> and 1 study on Iran.<sup>27</sup> Six studies were performed on adults,<sup>16,18,26,29,30</sup> 3 studies were conducted on children<sup>19,25,28</sup> and 2 studies did not offer the participants' age information.<sup>17,27</sup> Genotype distribution and HWE examination results are shown in Table 2. The genotypes of TIM-3 574T>G (rs10515746) and 1516G>T (rs10053538) polymorphism in the case and control groups were in agreement with HWE ( $p>0.05$ ).

### Single Nucleotide Polymorphism and Asthma

A total of 9<sup>16-19,24-28</sup> studies including 1762 asthma patients and 1773 control subjects were enrolled to evaluate the association between TIM-3 574T>G (rs10515746) single nucleotide polymorphism and asthma. There was a statistically significant association observed under the dominant model (GT +TT vs GG: OR=2.26, 95% CI 1.09-4.69) (Figure 2A) and allele model (T vs G: OR=2.60, 95% CI 1.20-5.64) (Figure

3A). When stratified population by age, no statistically significant association was found under the dominant model and allele model (Figure 4A). Sensitivity analyses were performed by removing one individual study each time. When the study conducted by Sadri<sup>27</sup> was removed, no significant association with asthma emerged for a dominant model. However, a significant association with asthma was observed when another study was excluded (Table 3). Publication bias was evaluated by funnel plot and Egger's regression test and there was no significant publication bias for the associations of TIM-3 -574T>G (rs10515746) single nucleotide polymorphism and asthma ( $p=0.986$ ) (Figure 5A).

A total of 6<sup>16,18,24,26,29,30</sup> studies with 922 asthma patients and 1036 control subjects were enrolled to evaluate the association between TIM-3-1516G>T (rs10053538) single nucleotide polymorphism and asthma. There was no statistically significant association observed under the dominant model (GT +TT vs GG: OR=1.22, 95% CI 0.94-1.58) and allele model (T vs G: OR=1.05, 95% CI 0.81-1.35) (Figure 2A; Figure 3A). When stratified the study population by age, no statistically significant association was found under the dominant model and allele model (Figure 4B). Sensitivity analyses were performed by removing one individual study each time and no

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significant association was found under the dominant model and allele model (Table 3). There was no significant publication bias for the associations of TIM-

3-1516G>T (rs10053538) single nucleotide polymorphism and asthma ( $p=0.578$ ) (Figure 5B).

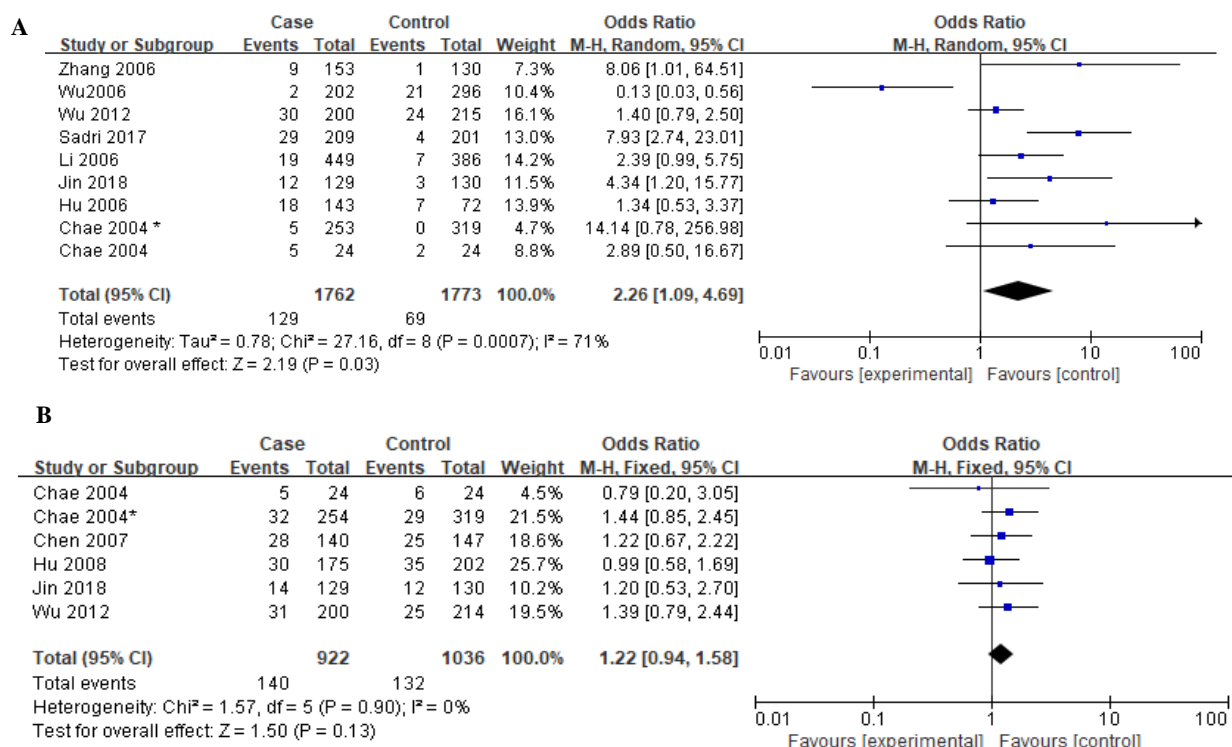
**Table 2. Distributions of T cell immunoglobulin domain and mucin domain-3 (TIM-3) rs10515746 and TIM-3 rs10053538 polymorphisms among asthmatic patients and controls**

Study	Case			Control			<i>p</i> for HWE
	GG	GT	TT	GG	GT	TT	
<b>-574T&gt;G (rs10515746)</b>							
Chae <sup>16</sup>	248	5	0	319	0	0	0.92
Chae <sup>17</sup>	19	5	0	22	2	0	0.59
Zhang <sup>18</sup>	144	9	0	129	1	0	0.76
Wu <sup>24</sup>	200	2	0	275	21	0	0.60
Hu <sup>25</sup>	125	18	0	65	7	0	0.37
Li <sup>26</sup>	430	19	0	379	7	0	0.65
Wu <sup>19</sup>	185	15	0	210	5	1	0.16
Sadri <sup>27</sup>	180	29	0	197	4	0	0.40
Jin <sup>28</sup>	117	12	0	127	3	0	0.63
<b>1516G&gt;T (rs10053538)</b>							
Chae <sup>16</sup>	222	31	1	290	29	0	0.58
Chae <sup>17</sup>	19	5	0	18	6	0	0.37
Chen <sup>29</sup>	112	28	0	122	25	0	0.08
Hu <sup>30</sup>	145	30	0	167	35	0	0.07
Wu <sup>19</sup>	169	30	1	190	24	1	0.16
Jin <sup>28</sup>	115	14	0	118	12	0	0.40

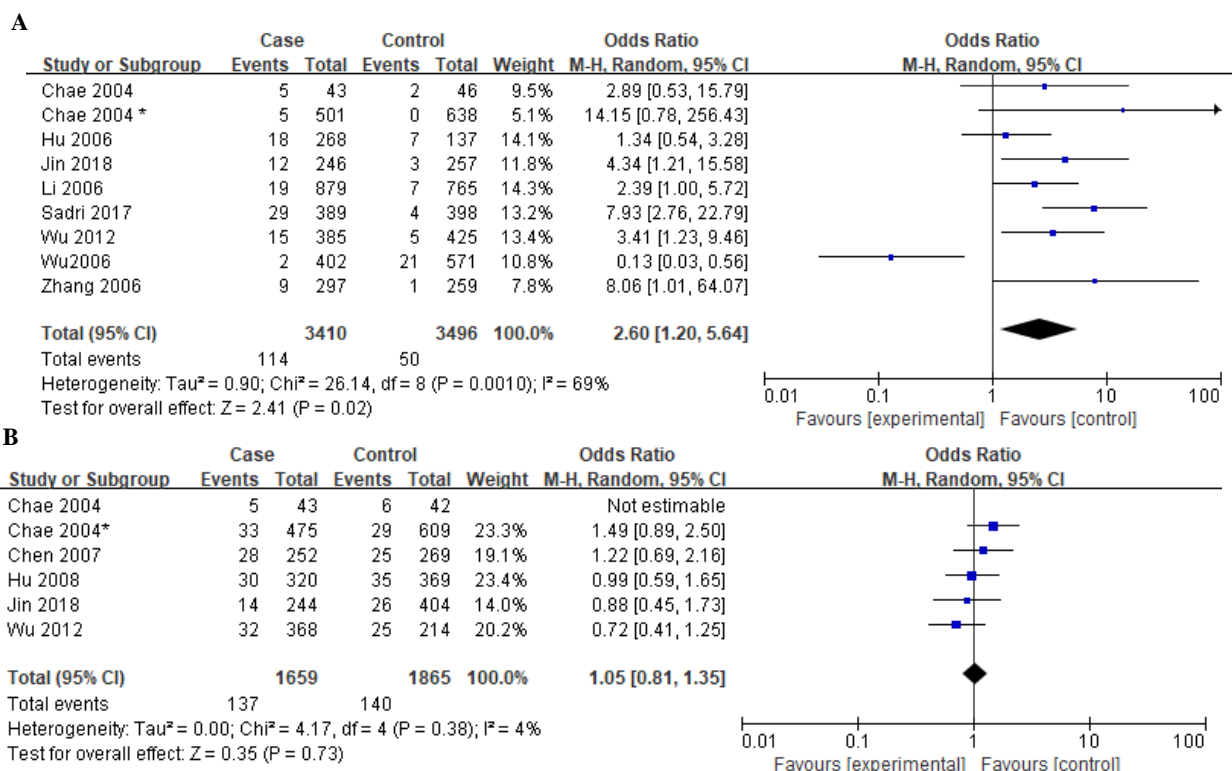
HWE: Hardy–Weinberg equilibrium

**Table 3. Sensitive analyses under a dominant model for the association T cell immunoglobulin domain and mucin domain-3 (TIM-3) single nucleotide polymorphism and asthma**

Excluded studies	ORs(95%CI)	I <sup>2</sup> (%)	<i>p</i>
Chae <sup>16</sup>	2.46(1.09-5.53)	72	<0.001
Chae <sup>17</sup>	2.25(1.06-4.76)	70	0.001
Zhang <sup>18</sup>	2.24(1.04-4.83)	71	<0.001
Wu <sup>24</sup>	2.37(1.01-5.54)	71	<0.001
Hu <sup>25</sup>	2.74(1.18-6.38)	69	0.002
Li <sup>26</sup>	2.50(1.04-6.03)	72	<0.001
Wu <sup>19</sup>	3.08(1.90-5.00)	25	0.23
Sadri <sup>27</sup>	2.08(0.97-4.48)	65	0.005
Jin <sup>28</sup>	2.30(1.02-5.22)	71	0.001
<b>1516G&gt;T (rs10053538)</b>			
Chae <sup>16</sup>	1.24(0.95-1.61)	0	0.880
Chae <sup>17</sup>	1.16(0.86-1.55)	0	0.900
Chen <sup>29</sup>	1.22(0.92-1.62)	0	0.810
Hu <sup>30</sup>	1.30(0.97-1.74)	0	0.940
Wu <sup>19</sup>	1.18(0.99-1.57)	0	0.860
Jin <sup>28</sup>	1.22(0.93-1.60)	0	0.810

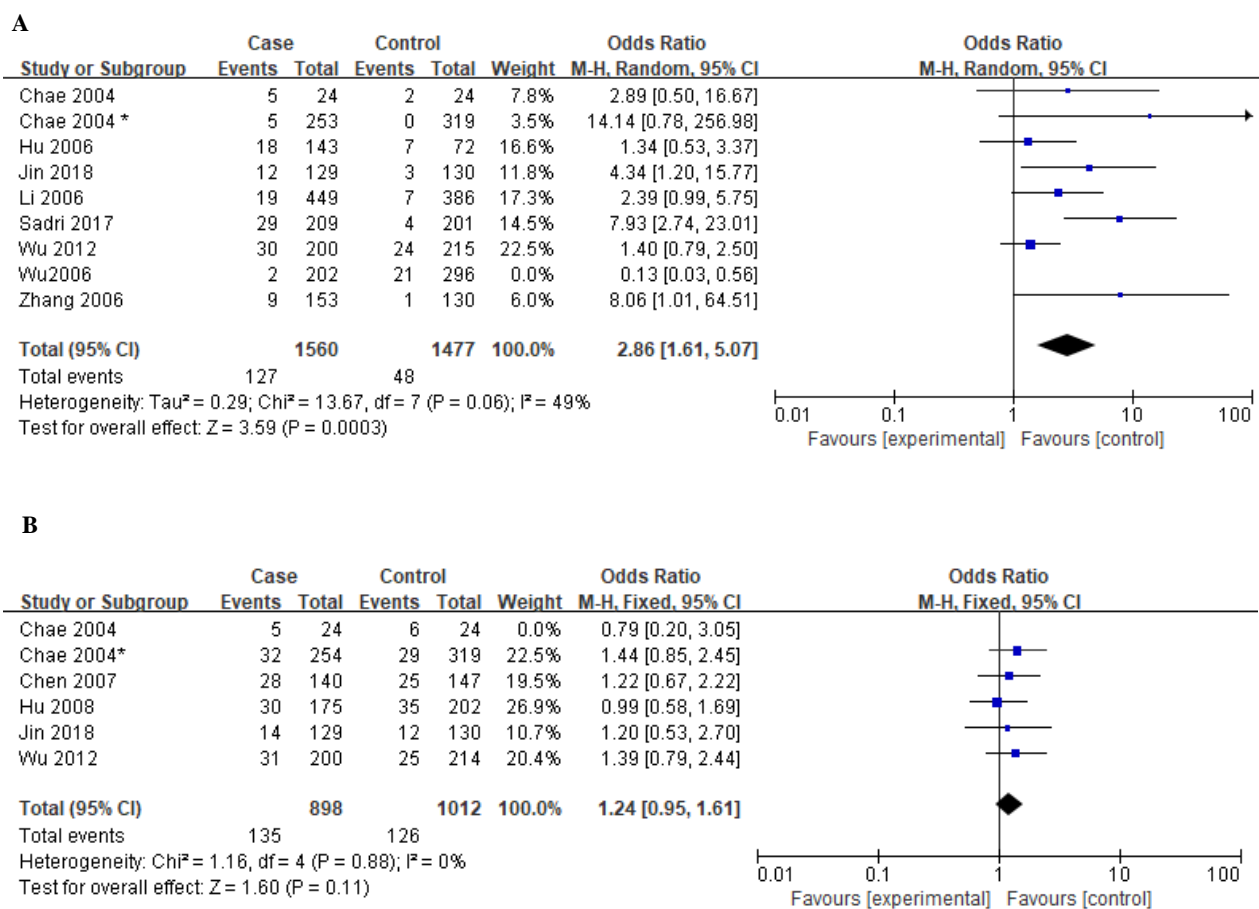


**Figure 2. Meta-analyses under a dominant model for the association T cell immunoglobulin domain and mucin domain-3 (TIM-3) single nucleotide polymorphism and asthma, A: TIM-3 rs10515746 B: TIM-3 rs10053538**

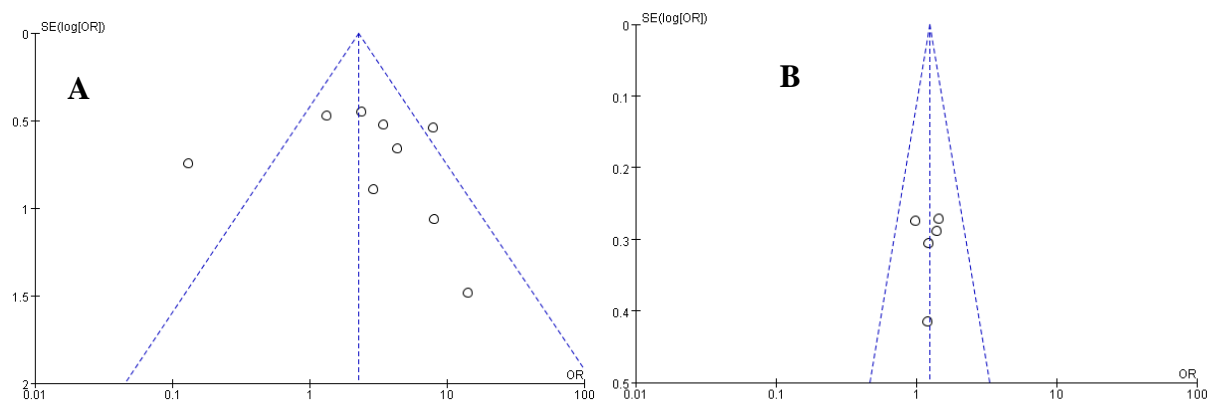


**Figure 3. Meta-analyses under allele model for the association T cell immunoglobulin domain and mucin domain-3 (TIM-3) single nucleotide polymorphism and asthma, A: TIM-3 rs10515746 B: TIM-3 rs10053538.**

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**Figure 4. Sensitive analyses under a dominant model for the association of T cell immunoglobulin domain and mucin domain-3 (TIM-3) single nucleotide polymorphism and asthma, A: TIM-3 rs10515746 B: TIM-3 rs10053538.**



**Figure 5. Begg's funnel plots of publication bias for the association between T cell immunoglobulin domain and mucin domain-3 (TIM-3) single nucleotide polymorphism and asthma. A: TIM-3 rs10515746 B: TIM-3 rs10053538.**

## DISCUSSION

As far as we know, this is the first systematic review of the association between TIM-3 574T>G (rs10515746) and 1516G>T (rs10053538) polymorphisms and risk of asthma. Our present study indicated that there was a significant association between TIM-3 574 T>G (rs10515746) polymorphism and the risk of asthma. However, no significant association between TIM-3 1516 G>T (rs10053538) polymorphism and asthma susceptibility was found in overall analyses.

Asthma is a very complex and heterogeneous disease, the causes of which are not yet known. Recent studies have shown that genetic factors are one of the risk factors associated with asthma.<sup>31,32</sup> Previous studies have shown that several TIM-3 genetic polymorphisms were associated with an increased risk of asthma. Of these, 574 T>G (rs10515746) and 1516 G>T (rs10053538) single nucleotide polymorphism were the two most intensively investigated locations. The location of 574T>G (rs10515746) and 1516G>T (rs10053538) were in promoter region of Tim-3 gene. Although polymorphisms in promoter regions do not alter the coding sequence of specific genes, they control the initiation and promotion of gene expression and are therefore potentially pathogenic. The potential role of TIM-3 promoter polymorphisms in allergic phenotypes has been investigated in previous studies. Those two single nucleotide polymorphisms were significantly associated with asthma susceptibility in Korean and Chinese populations. TIM-3 binds to its ligand, galectin-9, and the interaction between TIM-3 and galectin-9 induces Th1 apoptosis and downregulates Th1 responses. Subsequently, it shifts the immune response towards Th2-dominant immunity. The single nucleotide polymorphisms may involve the regulation of Th1/Th2 balance.<sup>33,34</sup> Despite these potential mechanisms, the results about associations of certain TIM-3 genetic polymorphisms and asthma were still contradictory. Therefore, we performed the current meta-analysis to obtain more convincing results. The present study found that TIM-3-574T>G (rs10515746) single nucleotide polymorphism was significantly associated with asthma, whereas TIM-3-1516G>T (rs10053538) single nucleotide polymorphism was not significantly associated with asthma.

To our knowledge, no previous Meta-analysis has comprehensively examined the relationship between TIM-3-574T>G (rs10515746) and 1516G>T (rs10053538) polymorphisms and asthma risk. Although the prevalence of asthma in children and adults in China is lower than in developed countries, China is the most populous country with 40% of asthma patients uncontrolled, resulting in increased hospitalizations, emergency department visits, and absences from work or school.<sup>35</sup> The present study showed that TIM-3-574T>G (rs10515746) polymorphism was significantly associated with the risk of asthma development. Our results suggest that TIM-3-574T>G (rs10515746) may play a role in the development of asthma, suggesting that TIM-3 may be a promising asthma biomarker and therapeutic option.

Several limitations must be mentioned. First, all studies were conducted in Asia and the sample size in this meta-analysis was small, which might result in bias of the results when evaluating the association TIM-3 574T>G (rs10515746) and TIM-3-1516G>T (rs10053538) gene polymorphisms with susceptibility to asthma. Second, significant between-study heterogeneity was found in TIM-3-574T>G (rs10515746) pooled analyses. Further subgroup analysis based on age, heterogeneity was not resolved, suggesting that other potentially relevant factors, such as gender, genotyping methods, and disease phenotypes, may contribute to the heterogeneity. Third, asthma is a heterogeneous disease with various genotypes and phenotypes. Although a genetic basis for asthma is undeniable, only a small proportion of heritability can be explained by the previously identified genetic polymorphisms associated with asthma because of the variability of the clinical phenotype. At last, although funnel plots and Egger's test revealed no apparent publication bias, we still could not eliminate the possibility of publication bias since only published studies were retrieved in the meta-analysis.

In conclusion, our meta-analysis indicated that TIM-3-574T>G (rs10515746) single nucleotide polymorphism was correlated with the risk of asthma in Asian ethnicity under the dominant and allele model. However, TIM-3-1516G>T (rs10053538) single nucleotide polymorphism may not be associated with the susceptibility to asthma. Considering that the current results are based on a limited number of case-



control studies, most of which were conducted among Asians, further well-designed studies with larger sample sizes, especially those conducted among other ethnicities, are necessary to better understand the potential linkages between TIM-3-574T>G (rs10515746) and TIM-3-1516G>T (rs10053538) gene polymorphisms with asthma. Furthermore, other studies should focus on the potential association between other TIM-3 genetic polymorphisms and asthma.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

### ACKNOWLEDGEMENTS

Not applicable.

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