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Association of STAT6 variants with asthma risk: A systematic review and meta-analysis

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ABSTRACT

A large number of studies have reported that the genetic variants in STAT6 gene may be implicated in susceptibility to asthma, but with inconsistent results. Therefore, the aim of this meta-analysis was to determine the likelihood of developing asthma for the individuals with different STAT6 variants. The database including Pubmed, Embase and CNKI (Chinese National Knowledge Infrastructure) were searched to find the relevant papers. Data were extracted by two independent reviewers and the odds ratios (ORs) were pooled with 95% confidence intervals (CIs), using random effect or fixed effect models as appropriate, to indicate the risk of asthma for different STAT6 variants. The heterogeneity and bias were tested for each pooled result. Data from 19 studies were pooled that reported associations of rs324015, rs71802646 and rs324011 in STAT6 gene with asthma risk. The results demonstrated that 13GT and short GT in rs71802646 were both associated with increased risk of asthma in overall analysis (OR = 1.26 for 13GT and 1.30 for short GT). Further, subgroup analysis showed an increased risk of asthma in Asian population with 13GT (OR = 1.21), 14GT (OR = 1.97) and short GT (OR = 1.27). Besides, 13GT, 14GT and short GT all contributed to higher risk of atopic asthma, with OR 1.50, 2.21 and 1.65 respectively. However, rs324015 (G>A) appeared to be associated with decreased risk for atopic asthma (with OR = 0.83, 0.68 and 0.79 for A, AA and AA+AG respectively). Both overall and subgroup analyses indicated no effect of rs324011 on asthma risk. In conclusion, our meta-analyses suggest that short GT repeats of rs71802646 in STAT6 contribute to higher risk for asthma, while rs324015 may have a protective effect on atopic asthma.

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1. Introduction

Asthma, a phenotypically diverse disease, is characterized by the airway hyperreactivity (AHR), mucus overproduction and chronic eosinophilic inflammation. This disease occurs with high prevalence worldwide. Previous studies have indicated that asthma has a complex heterogeneous origin involving multiple

environmental and genetic factors [1,2], with overall genetic contribution of around 50–60% [1]. In recent years, many susceptibility loci in different genes have been reported to be implicated in the genetic attributions to asthma, but most of them can not be confirmed by replication studies [3].

Human STAT6, a member of STAT transcription factor family, is essential for the functional responses of T helper 2 (Th2) lymphocyte mediated by IL-4 and IL-13. Studies have shown that abnormal production of IL-4 and IL-13 play important roles in the pathogenesis of asthma and upregulation of the IL-4/IL-13-mediated Th2 response is a main characteristic of asthma [4,5]. Besides, STAT6-knockout mice have been shown to be protected from allergic pulmonary manifestations [6]. STAT6 expression was markedly upregulated in the airway epithelial cells in asthma [7–9], and this protein was principally activated by IL-4/IL-13, thus

Abbreviations: STAT6, signal transducer and activator of transcription 6; AHR, airway hyperreactivity; MeSH, Medical Subject Headings; SNPs, single nucleotide polymorphisms; ORs, odds ratios; CIs, confidence intervals.

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mediating a number of responses in Th2 cells [10]. As a consequence, STAT6, a critical molecule in the Th2 signaling pathway, has been thought to be a potential genetic factor contributing to asthma. Previous studies have identified a number of genetic polymorphisms in association with asthma risk, such as GT repeat in exon 1 (rs71802646), C2892T (rs324011) in intron 2 and G2964A (rs324015) in the 3 untranslated region of the human STAT6 gene [11–13]. However, the results from these studies are inconsistent. Some studies demonstrated a significant association of STAT6 polymorphisms with asthma [14–17], but others could not replicate it [18,19]. Considering the inconsistent results across different studies, we performed a meta-analysis of the published studies to clarify the relationship between STAT6 variants and asthma susceptibility.

2. Materials and methods

2.1. Literature search

We searched the database Pubmed, Embase and CNKI (Chinese National Knowledge Infrastructure) to identify the eligible articles published until April, 2013 without language limitation. The search terms covered Medical Subject Headings (MeSH) and/or text words relating to asthma and STAT6 polymorphism. Of all the retrieved papers, the abstracts and titles, as well as the full-text if needed, were screened for fulfillment of the inclusion criteria. Additionally, the reference lists of the retrieved papers were manually identified for other relevant articles.

2.2. Study selection and data abstraction

Eligible studies should meet the following criteria: (a) evaluating association of STAT6 variants with asthma risk, (b) case–control studies, (c) with descriptions of asthma diagnosis and control selection, (d) with genotyping details and sufficient data for meta-analysis. In case of duplicate publication and/or overlapping data, only the larger or more recent publication was included.

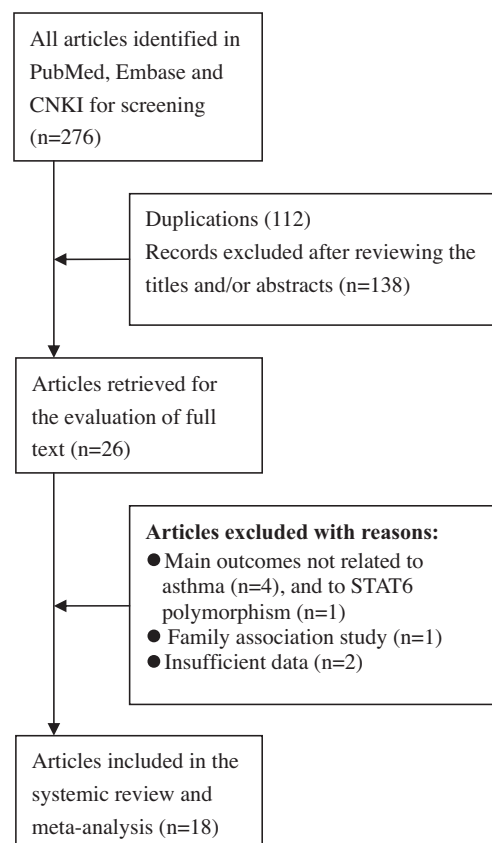


Fig. 1. The flow chart for study selection.

The variables were abstracted from each eligible study according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [20]. Quantitative data for meta-analysis were extracted directly or calculated using information in the original studies [21]. Study selection and data abstraction were per-

Table 1
Characteristics of the included studies.

Author (Year)	Country/ethnicity	Case/control numbers	Case age	Atopic status	Method
rs324015 (G>A)					
Gao et al. (2000)* [11]	Japan/Asian	400/100	Mixed	Mixed	RFLP
Gao et al. (2000)* [11]	British/Caucasian	181/119	Mixed	Mixed	RFLP
Tamura et al. (2003) [13]	Japan/Asian	73/66	Child	Atopic	RFLP
Hu et al. (2005) [32]	China/Asian	135/109	Mixed	Atopic	RFLP
Wu et al. (2006) [33]	China/Asian	42/42	Adult	NA	SSCP
Li et al. (2007) [36]	China/Asian	95/95	Adult	NA	SSCP
Daley et al. (2009) [16]	Australia/Caucasian	644/751	Mixed	Mixed	TaqMan
Ding et al. (2010) [34]	China/Asian	108/115	Adult	NA	RFLP
Murk et al. (2011) [37]	America/Caucasian	100/474	Child	Atopic	RFLP
Lin et al. (2012) [35]	China/Asian	113/87	Child	NA	RFLP
rs71802646 (GT)					
Gao et al. (2004) [14]	British/Caucasian	156/271	NA	Atopic	DS
Shao et al. (2004) [15]	Japan/Asian	114/172	Child	Mixed	DS
Nagarkatti et al. (2004) [39]	Indian/Asian	225/212	Mixed	Mixed	DS
Suzuki et al. (2004) [40]	Japan/Asian	298/166	Mixed	Mixed	CE
Hu et al. (2005) [32]	China/Asian	135/109	Mixed	Atopic	PCR-STR
Wang et al. (2011) [17]	China/Asian	107/96	Child	Mixed	DS
rs324011 (G>A)					
Kabesch et al. (2006) [41]	Germany/Caucasian	73/773	Child	NA	SSCP
Daley et al. (2009) [16]	Australia/Caucasian	664/751	Mixed	Mixed	TaqMan
Wu et al. (2010) [18]	China/Asian	252/227	Child	Mixed	RFLP
Kavalal et al. (2012) [19]	Slovenia/Caucasian	154/71	Child	Mixed	ADA
Godava et al. (2012) [38]	Czech/Caucasian	109/45	Child	Atopic	TaqMan

DS: DNA sequencing; ADA: 5-nuclease allelic discrimination assay; CE: capillary electrophoresis; NA: not available.

* The article by Gao et al. [11] was pooled as two separate studies.

formed by two independent authors (X.B. Qian and Y. Gao), and any disagreement was resolved by discussion.

2.3. Data analysis

ORs and 95% CI were pooled to indicate the likelihood of having asthma for individuals with different allele/genotypes. For the GT repeat length polymorphisms, the alleles with different repeat numbers of 13, 14, 15, 16, and 17 were denoted as 13GT, 14GT, 15GT, 16GT, and 17GT respectively. The GT repeats were divided into short allele (SA) group and long allele (LA) group at a cut-off point of 15GT, with the GT repeats less than 15 being defined as SA and those equal or more than 15 defined as LA. ORs were calculated for each GT repeat allele vs others and for SA vs LA. Each OR was calculated by fixed-effect model or random-effect model as appropriate and statistical significance of the summary OR was determined with Z-test. The model selection was based on the data heterogeneity (evaluated using Cochran Q-statistic) among

included studies [22]. The fixed-effect model (M-H method) would be used if there was no evidence of heterogeneity. Otherwise, the random-effect model (D-L method) would be better when the heterogeneity was significant [23]. Heterogeneity was evaluated by Cochran's Q test and I^2 statistic [22]. Publication bias was analyzed by visual inspection of asymmetry in funnel plots in combination with Egger's test [24]. To evaluate the source of heterogeneity, subgroup analyses were performed by ethnicity, subject age and atopic status of asthma. All statistical tests were performed by using Stata 11.0 (College Station, TX).

3. Results

3.1. Study characteristics

Comprehensive literature search yielded a total of 276 records. After careful screening of the titles and abstracts, 250 articles were

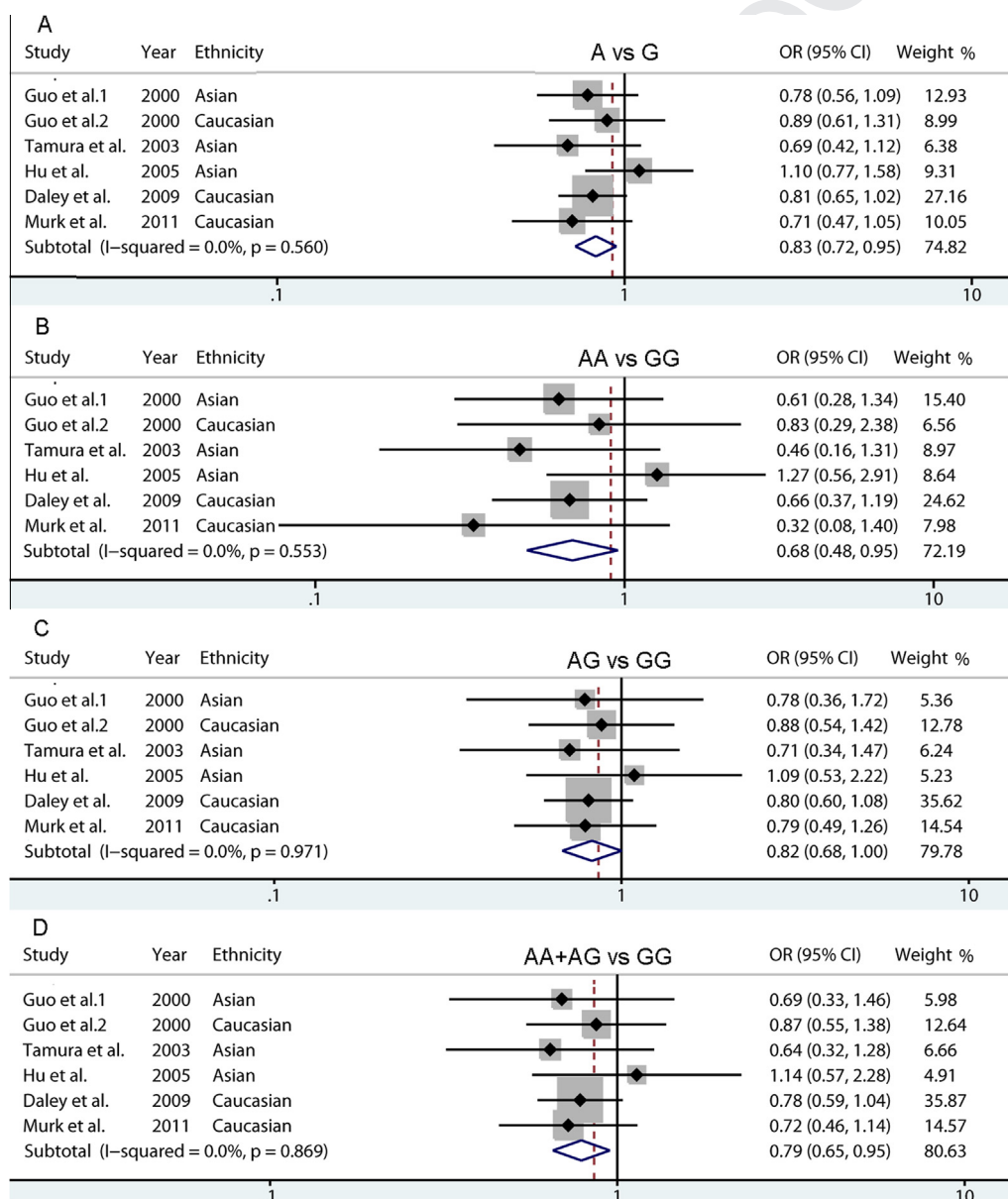


Fig. 2. Association of rs324015 (G>A) with atopic asthma. Summary ORs and 95% CI were calculated in fixed effect model to indicate the risk of atopic asthma for allele A (Fig. 2A) and for genetic model AA (Fig. 2B), AG (Fig. 2C) and AA+AG (Fig. 2D). The heterogeneity and bias were not evident. Solid squares mark the OR from each study with square size proportional to the weight, and the horizontal lines represent 95% CI. Diamond and dotted vertical line indicate summary OR and 95% CI, whereas the solid vertical line indicates the null effect (OR = 1).

excluded, of which 112 were duplications and 138 were not relevant to STAT6 variants and/or asthma. The remaining 26 articles were retrieved for full-text reviewing, and additional 8 articles were excluded because of reasons as following: 4 not relevant to asthma risk [25–28], 1 not relevant to STAT6 variants [29], 2 without sufficient data [30,31] and 1 being family association study [12]. Finally, a total of 18 articles met our inclusion criteria, of which 4 were published in Chinese [32–35] and others in English. Moreover, 11 studies were conducted in Asian and 7 in Caucasian. One article involving Asian and Caucasian populations was treated as two separate studies in the meta-analysis [11]. The process for study selection was provided in Fig. 1. All articles described with details the definition of cases and controls and the genotyping methods. Only some of the included studies provided information for HWE (Hardy-Weinberg equilibrium) test, which stated no evidence of disequilibrium [18,19,32,35–38]. As for other studies, we performed HWE test based on the allele/genotype frequency data from original studies and also found no evidence of disequilibrium in the controls. Of these included studies, 10 reported associations of asthma with rs324015 [11,13,16,32–37], 6 with rs71802646

[14,15,17,32,39,40] and 5 with rs324011 [16,18,19,38,41]. The study characteristics were listed with details in Table 1.

3.2. Data synthesis

3.2.1. STAT6 variant rs324015

Overall, 9 articles reported association of rs324015 with asthma risk, of which one article by Guo et al. involves two cohorts of subjects and thus was treated as two separate studies (Table 1). Therefore, the primary data from 10 studies were abstracted and analyzed for rs324015. Overall analysis showed that rs324015 was not associated with asthma risk for allele A, nor for any other genetic model (Table S1). In addition, subgroup analyses by ethnicity (Asian or Caucasian) and age (child or adult) also demonstrated no association of rs324015 with asthma risk (Table S1). However, rs324015 had a protective effect on atopic asthma (Fig. 2 and Table S1). The bias was not found among the pooled studies, but with heterogeneity for parts of the pooled results (Table S1).

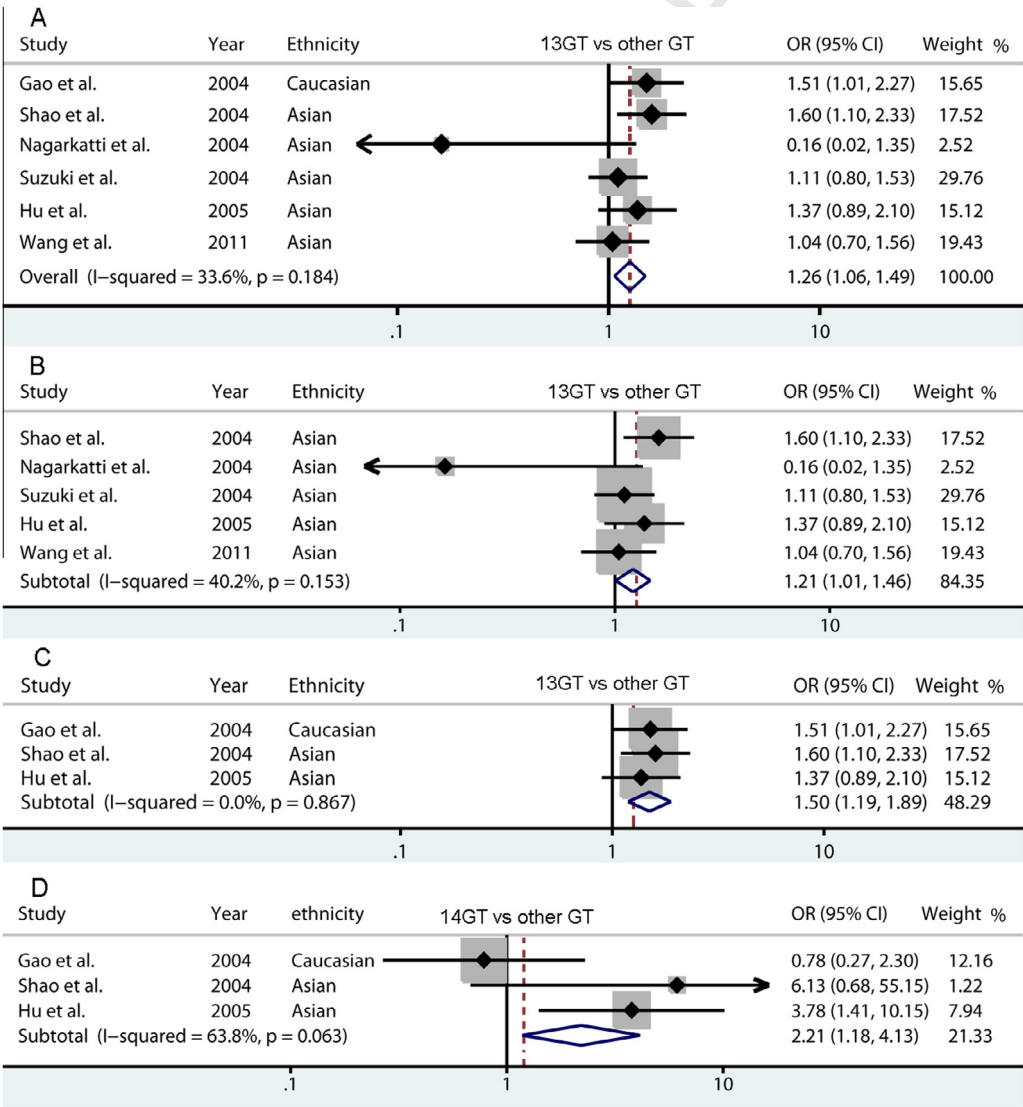


Fig. 3. Association of rs71802646 (each GT vs other GT) with asthma. Summary ORs and 95% CI were calculated in fixed effect model for 13GT vs other GT by overall analysis (A) as well as by subgroup analysis in Asian (B) and in atopic asthma (C). Additionally, summary ORs and 95% CI were calculated in fixed effect model for 14GT vs other GT by subgroup analysis in atopic asthma (D). The heterogeneity and bias were not evident. Other details of the plots are the same as Fig. 2.

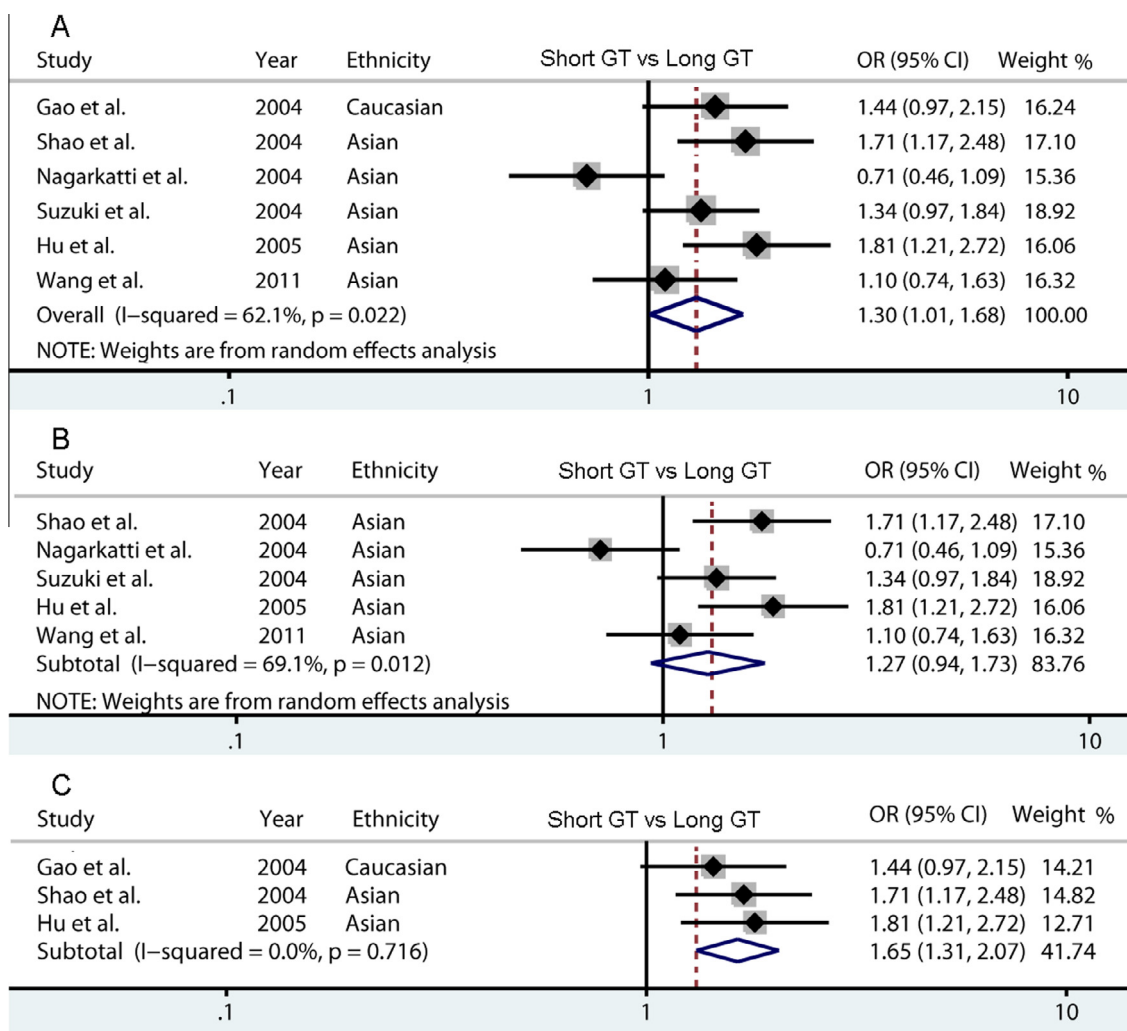


Fig. 4. Association of rs71802646 (short GT vs long GT) with asthma. Summary ORs and 95% CI were calculated for rs71802646 (short GT vs long GT) by overall analysis in random effect model (A) as well as by subgroup analysis in Asian in random effect model (B) and in atopic asthma in fixed effect model (C). The heterogeneity and bias were not evident. Other details of the plots are the same as Fig. 2.

3.2.2. STAT6 variant rs71802646

Overall, 6 studies reported association of STAT6 variant rs71802646 with asthma risk. As shown in Figs. 3 and 4 and Table S2, overall analysis showed that rs71802646 was associated with increased risk of asthma, with OR 1.26 (95% CI 1.07–1.49, $P = 0.007$) for 13GT vs others and OR 1.30 (95% CI 1.01–1.68, $P = 0.043$) for SA (short GT) vs LA (long GT). Subgroup analyses in Asian population demonstrated that only 13GT had association with asthma risk (Figs. 3 and 4 and Table S2). Moreover, 13GT, 14GT and SA were associated with increased risk of atopic asthma (Figs. 3 and 4 and Table S2). The heterogeneity was found among the studies for some of the pooled results, but publication bias was not evident according to Begg's funnel plot and Egger's test (Figs. 3 and 4 and Table S2).

3.2.3. STAT6 variant rs324011

Overall, 5 studies reported association of STAT6 variant rs324011 with asthma risk. As shown in Table S3, overall analysis demonstrated no association between rs324011 and increased risk of asthma for allele T and other genetic models (CT, TT and dominant CT+TT). Similarly, the subgroup analyses by atopic status, age and ethnicity did not show any relationship between rs324011 and asthma risk (Table S3). The heterogeneity was not found among

the pooled studies, but the bias was evident for the studies of AG in Caucasian according to Egger's test with $P < 0.01$ (Table S3).

4. Discussion

Several lines of evidence from experimental studies have revealed a critical role of STAT6 defects in the pathogenesis of asthma, but the results from different genetic association studies are still inconsistent. Based on a comprehensive review and meta-analyses, our results indicate that the genetic variants rs71802646, but not rs324015 and rs324011, in STAT6 gene are associated with increased asthma risk. In detail, rs71802646 was found to be associated with increased risk of asthma for 13GT vs others and for SA (short GT) vs LA (long GT) by overall analysis. Further, subgroup analyses also demonstrated an association of 13GT with asthma in Asian population, and concurrently an association of 13GT, 14GT and SA with atopic asthma respectively. Interestingly, although rs324015 had no relation with asthma overall, it was demonstrated to have protective effect on atopic asthma by subgroup analysis.

Recently, one meta-analysis by Zhu et al. has documented association of STAT6 polymorphisms with asthma risk [42]. This meta-analysis involved two variants (rs324015 and rs71802646), and

showed an increased risk of asthma for short GT (13GT and 14GT) of rs71802646, but not significantly for rs324015. Therefore, the summary results from this meta-analysis are consistent with our findings as for rs71802646, both indicating a critical role of GT length variants in asthma. Moreover, we also demonstrated no association of rs324015 with asthma based on the overall analysis or the subgroup analysis by ethnicity or age. Interestingly, our results showed that rs324015 appear to have a protective effect on atopic asthma by subgroup analysis. However, this finding should be taken with caution and needs further confirmation, since the pooled results generated from only three studies that involved a relatively small number of the subjects.

In general, small sample size in the genetic association study of complex disease is a major concern, which may yield false results. Meta-analysis, when pooling the data from individual studies, will enhance the statistical power to detect relatively small effects of any genetic variant on complex disease. This meta-analysis performed data pooling in different genetic models, which may ensure a relatively reliable conclusion. The strength also stems from other aspects including the comprehensive literature search without language limitation and bias protection in study selection and data abstraction.

The heterogeneity was evident for parts of the summary results, but the source of heterogeneity could not be explored in further analysis. However, the small sample size in some of the involved studies and insufficient study numbers and differences in subject definitions may be the sources of heterogeneity. It should be noted that the heterogeneity was present mostly for those SNPs without any relation to asthma risk, but the 14GT at rs71802646 was a notable exception that was demonstrated to be risk allele for asthma. Therefore, the heterogeneity seems to bias the results towards the null and the significant associations found in the present meta-analysis are most likely valid. Publication bias was only present for rs324011 in the studies of Caucasian.

Several other limitations should be also taken into account when interpreting the summary results of our meta-analysis. First, asthma is a complex disorder with heterogeneous characteristics, and so individual studies may employ divergent criteria for patient recruitment. Second, the atopic status of asthma patients varied in different studies. As consequence, these factors may be other source of heterogeneity. Additionally, the number of the included studies for each outcome was relatively small and heterogeneity was evident for some of the pooled effect size, which probably makes the summary results less conclusive. Finally, the meta-analysis could not address gene-gene and gene-environment interactions, due to insufficient data from the primary studies.

In conclusion, the meta-analyses indicate that rs71802646 (13GT, 14GT and short GT), but not rs324011, in STAT6 contribute to high risk for asthma. Interestingly, rs324015 appears to have protective effect on atopic asthma. Future studies with large sample size should focus on the interactions of STAT6 variants with environmental factors, thus helping to clarify the relationship between STAT6 variants and asthma risk.

5. Competing interest

The authors declared no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.humimm.2014.06.007>.

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