ORIGINAL ARTICLE

Interferon-γ +874A/T Polymorphism Is Associated With Asthma Risk: A Meta-analysis

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Abstract

Background: Results regarding the association between the *interferon-γ* (*IFN-γ*) +874A/T polymorphism and asthma risk are controversial and ambiguous. The aim of this study was to determine with greater precision the relationship between the *IFN-γ* +874A/T polymorphism and asthma using a meta-analysis.
Methods: Published literature was retrieved from 5 databases (PubMed, EMBASE, Wanfang, China National Knowledge Infrastructure [CNKI] and Weipu). ORs with 95% CIs were used to assess the strength of association.
Results: Ten case-control studies involving 697 cases and 1049 controls were identified. In the overall analysis, a significant association between the +874A/T polymorphism and asthma susceptibility was found for AA vs AT + TT (OR, 1.89; 95% CI, 1.37-2.62; *P*=.0001). In the subgroup analysis by ethnicity, significant associations were found among whites (OR, 1.42; 95% CI, 1.04-1.93; *P*=.03) and Asians (OR, 2.52; 95% CI, 1.49-4.25; *P*=.0006). The sensitivity analysis and cumulative meta-analysis further strengthened the validity of this association. No publication bias was observed in this study.
Conclusion: The results of this meta-analysis suggest that the *IFN-γ* +874A/T polymorphism is a risk factor for asthma.

Key words: Interleukin-γ. Asthma. Polymorphism. Meta-analysis.

Resumen

Antecedentes: Los resultados de los estudios publicados sobre la asociación entre el polimorfismo del *interferon-γ* (*IFN-γ*) 874 A/T y el riesgo de asma han sido polémicos y ambiguos. El objetivo de este estudio ha sido determinar, con mayor precisión, la relación entre el polimorfismo del *IFN-γ* 874 A/T y el asma, usando un meta-análisis.
Métodos: Búsqueda de la literatura publicada en Pubmed, EMBASE, Base de Datos Wanfang, Infraestructura Nacional China de Conocimiento (CNKI) y en la base de datos Weipu. Se utilizaron los odds ratios (OR) con intervalos de confianza del 95% (IC) para evaluar la fuerza de la asociación.
Resultados: Se encontraron diez estudios de casos y controles, con 697 casos y 1049 controles. En el análisis general, se halló una asociación significativa entre el polimorfismo 874 A/T y la susceptibilidad al asma, para AA vs AT + TT (OR = 1,89, IC del 95%: 1,37 a 2,62, P = 0,0001). En el análisis de subgrupos, dependiendo de la etnia, se hallaron asociaciones significativas entre los caucásicos (OR = 1,42, IC del 95%: 1,04 a 1,93, P = 0,03) y entre los asiáticos (OR = 2,52, IC del 95%: 1,49 a 4,25, P = 0,0006). El análisis de sensibilidad y un meta-análisis acumulativo reforzaron aún más la validez de esta asociación. No se observaron sesgos de publicación.
Conclusión: Este meta-análisis sugiere que el polimorfismo del *IFN-γ* 874 A/T es un factor de riesgo para el asma.

Palabras clave: Interferón-γ, asma. Polimorfismo. Meta-análisis.

Introduction

Asthma is one of the most common chronic inflammatory diseases. It is characterized by recurrent respiratory symptoms, reversible airway obstruction, airway inflammation, and increased airway responsiveness. It has been suggested that host genetic factors play important roles in the development of this disease [1-3]. A large number of recent studies have investigated the associations between genetic variants and asthma risk, and the *interferon-γ* (*IFN-γ*) gene has been extensively studied.

IFN-γ is a product of type 1 helper T (T_H1) cells and exerts inhibitory effects on T_H2-cell differentiation [4]. Lama et al [5] found that serum levels of *IFN-γ* were significantly lower in asthmatic children compared with healthy controls, while Shahid and coworkers [6] suggested that exhaled *IFN-γ* was significantly lower in patients with asthma compared with healthy individuals [6]. Furthermore, serum *IFN-γ* has been found to be associated with a decline in lung function among adult asthmatics [7]. Thus, *IFN-γ* may contribute to the pathogenesis of asthma.

The human *IFN-γ* gene is located on chromosome 12. Previous sequence analysis revealed several polymorphisms within the *IFN-γ* gene [8] and the most extensively studied was the +874A/T polymorphism (rs2430561). This single nucleotide polymorphism could directly affect the level of *IFN-γ* production. The +874A allele was associated with low production of *IFN-γ* [9]. This T to A polymorphism coincided with the middle of a putative nuclear factor-κB (NF-κB) binding site [9], which could have functional consequences for the transcription of the human *IFN-γ* gene (Figure 1). A number of studies have investigated the association between the +874A/T polymorphism and the risk of asthma [10-19], but the results have been contradictory and inconclusive. One approach to determining whether a gene contributes to asthma susceptibility is to combine all published data in a meta-analysis [20,21]. We conducted what is, to the best of our knowledge, the first meta-analysis of the association between the *IFN-γ* +874A/T polymorphism and asthma risk.

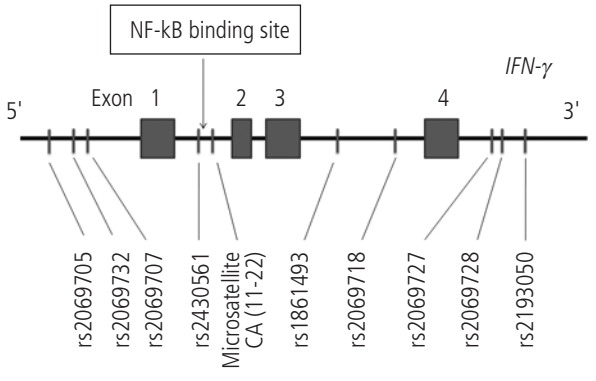

Figure 1. Genetic polymorphisms in the *IFN-γ* region on chromosome 12. Nine single nucleotide polymorphisms and the intron 1 microsatellite are shown, in addition to a putative nuclear factor-κB (NF-κB) binding site, which might have functional consequences for the transcription of the human *IFN-γ* gene.

Methods

Publication Search

We conducted a comprehensive literature search of PubMed, EMBASE, the Wanfang Database, China National Knowledge Infrastructure (CNKI), and the Weipu Database. The last search was updated in February 2013. The search terms used were: (*asthma or asthmatic*) and (*interferon-γ* or *interferon* or *IFN-γ* or *IFN*) and (*polymorphism* or *mutation* or *variant*). Additional studies were identified by a hand search of reference lists from original studies or review articles on this topic.

Inclusion and Exclusion Criteria

Studies included in the meta-analysis had to meet all of the following criteria: *1*) evaluation of the +874A/T polymorphism in the *IFN-γ* gene and asthma risk, *2*) a case-control design, and *3*) sufficient data for estimating an odds ratio (OR) with a 95% CI. Studies were excluded if 1 of the following criteria was present: *1*) it was not relevant to *IFN-γ* or asthma risk, *2*) the design was based on family or sibling pairs, *3*) it was a nonclinical study, *4*) genotype frequencies or numbers were not reported, and *5*) it was a review or abstract. In the case of overlapping studies, the one with the largest sample size was included.

Data Extraction

Two investigators (Nie and Meng) independently extracted the data and subsequently reached consensus on all items. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, age group, atopic status, sample size, genotyping method, and genotype numbers in cases and controls.

Statistical Analysis

ORs and 95% CIs were used to assess the strength of the association between the +874A/T polymorphism and asthma risk. AA vs TT (OR1), AT vs TT (OR2), and AA vs AT (OR3) were estimated for the +874A/T polymorphism and asthma risk. These pairwise differences were used to indicate the most appropriate genetic model as follows: if OR1 = OR3 ≠ 1 and OR2 = 1, a recessive model was suggested; if OR1 = OR2 ≠ 1 and OR3 = 1, a dominant model was suggested; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, a complete overdominant model was suggested; and if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), a codominant model was suggested [22-24]. A random-effects model (Mantel-Haenszel method) was used. The statistical significance of OR was determined by the Z test.

Hardy-Weinberg equilibrium (HWE) in the control group was assessed with the χ^2 test. Heterogeneity among studies was examined using the I^2 statistic and the Q statistic. Subgroup analysis was carried out by ethnicity. The relative influence of each study on the pooled estimate was assessed by omitting 1 study at a time in a sensitivity analysis. A sensitivity analysis was also performed by excluding studies not in HWE. We performed a cumulative meta-analysis by undertaking sequential random-effects pooling, starting with the earliest studies. A Galbraith plot was used to find the

source of heterogeneity. Finally, a funnel plot was employed to evaluate publication bias.

All statistical tests were performed using Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX). A *P* value of less than .05 was considered statistically significant, except for tests of heterogeneity, where a level of 0.10 was used. All tests were 2-sided.

Results

Study Characteristics

The literature search and study selection procedures are shown in Figure 2. Ten studies were identified to evaluate the relationship between the *IFN-γ* +874A/T polymorphism and asthma risk. In total, 697 asthma patients and 1049 healthy controls were included. The detailed characteristics of the 10 studies are shown in Table 1. There were 5 studies in Asians [10-12,18,19] and 5 studies in whites [13-17]. One study included atopic asthma patients [15], 1 study included atopic and nonatopic patients [17], and 8 studies did not offer detailed information [10-14,16,18,19]. Genotype numbers and HWE examination results are shown in Table 2.

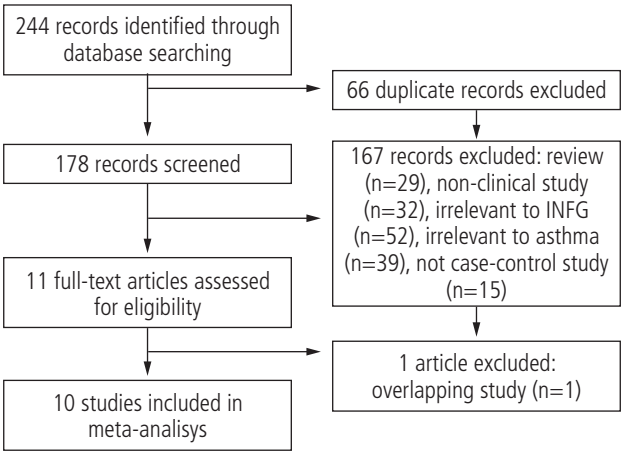

Figure 2. Flow chart showing selection of studies included in the meta-analysis.

Quantitative Data Synthesis

For the *IFN-γ* +874A/T polymorphism, OR1, OR2, and OR3 were 1.77 (*P*=.05), 1.07 (*P*=.84), and 1.99 (*P*<.0001), respectively. These estimates suggested a recessive genetic model, and therefore AT and TT were combined and compared with AA. As shown in Figure 3, the pooled OR was 1.89 (95% CI, 1.37-2.62; *P*=.0001). There was significant heterogeneity ($P_{heterogeneity}$ = 0.04 and I =48%).

In the subgroup analysis by ethnicity, significant associations were found among whites (OR, 1.42; 95% CI, 1.04-1.93; *P*=.03) and Asians (OR, 2.52; 95% CI, 1.49-4.25; *P*=.0006). The results of the other genetic comparisons are summarized in Table 3.

Sensitivity Analysis

In order to assess the stability of the results of the meta-analysis, we performed a sensitivity analysis by omitting 1 study at a time. None of the results were materially changed (Figure 4). In addition, when studies that were not in HWE were omitted [11,13,19], the statistical significance of the result did not change (OR, 1.74; 95% CI, 1.15-2.63; *P*=.009).

Cumulative Meta-Analysis

A cumulative meta-analysis of the association between the *IFN-γ* +874A/T polymorphism and asthma risk was conducted by arranging the studies by publication date. As shown in Figure 5, there has been a shift over time toward a significant association with asthma risk.

Table 1. Characteristics of Case-Control Studies Included in the Meta-Analysis

First Author	Year	Country	Ethnicity	Age Group	Atopic Status	No. of Cases	No. of Controls	Genotyping Method
Li [10]	2006	China	Asian	Children	NA	30	26	PCR-SSP
Li [11]	2007	China	Asian	Adults	NA	95	95	PCR-SSP
Liu [12]	2008	China	Asian	Mixed	NA	108	88	PCR-SSP
Movahedi [13]	2008	Iran	Caucasian	Adults	NA	60	140	PCR-SSP
Trajkov [14]	2008	Macedonia	Caucasian	Adults	NA	74	249	PCR-SSP
Hussein [15]	2009	Egypt	Caucasian	NA	Atopic	25	25	ARMS-PCR
Rad [16]	2010	Iran	Caucasian	Adult	NA	64	65	PCR-RFLP
Daneshmandi [17]	2011	Iran	Caucasian	Adult	Mixed	81	124	PCR-RFLP
Huang [18]	2011	China	Asian	Children	NA	100	122	PCR-RFLP
Jiao [19]	2011	China	Asian	Adult	NA	75	73	PCR-SSP

Abbreviations: ARMS, amplification refractory mutation system; PCR, polymerase chain reaction; SSP, sequence-specific primers; RFLP, restriction fragment length polymorphism; NA, not available.

Table 2. Distribution of *IFN-γ* +874A/G Genotype Among Patients and Controls

First Author	Asthma Patients			Controls			HWE
	AA	AT	TT	AA	AT	TT	(*P* Value)
Li [10]	22	7	1	8	11	7	.437
Li [11]	27	34	34	12	30	53	.029
Liu [12]	91	17	0	59	29	0	.064
Movahedi [13]	19	17	11	43	54	41	.010
Trajkov [14]	26	10	36	64	111	74	.091
Hussein [15]	6	8	11	0	4	21	.663
Rad [16]	17	31	16	26	59	24	.387
Daneshmandi [17]	31	31	19	42	53	29	.131
Huang [18]	65	33	2	75	43	4	.466
Jiao [19]	63	12	0	45	28	0	.043

Abbreviation: HWE, Hardy-Weinberg equilibrium.

Table 3. Determination of the Genetic Effect of *IFN-γ* +874A/T on Asthma and Subgroup Analysis

Comparison	Study	Sample Size		No. of Studies	Test of Association			Model	Heterogeneity		
		Cases	Controls		OR (95% CI)	Z	*P* Value		χ^2	*P* Value	I^2 (%)
AA vs TT	Overall	497	627	10	1.77 (0.99-3.18)	1.92	.05	R	17.90	.01	61.0
AT vs TT	Overall	330	675	10	1.07 (0.54-2.11)	0.20	.84	R	27.54	.0003	75.0
AA vs AT	Overall	567	796	10	1.99 (1.41-2.81)	3.91	<.0001	R	16.34	.06	45.0
AA vs AT + TT	Overall	697	1049	10	1.89 (1.37-2.62)	3.84	.0001	R	17.35	.04	48.0
AA vs AT + TT	Asian	408	404	5	2.52 (1.49-4.25)	3.45	.0006	R	9.80	.04	59.0
AA vs AT + TT	White	289	645	5	1.42 (1.04-1.93)	2.20	.03	R	3.67	.45	0.0

Abbreviation: R, random-effects model.

Heterogeneity Analysis

Statistically significant between-study heterogeneity was observed in the recessive genetic model ($P_{heterogeneity}$ = 0.04 and I^2 = 48%). The study performed by Li et al [10] was the outlier in this genetic model (Figure 6). After excluding this study, the level of heterogeneity decreased markedly ($P_{heterogeneity}$ = 0.12 and I^2 = 37%).

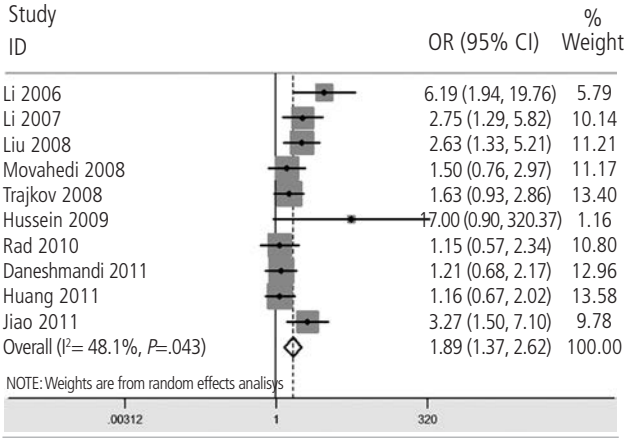

Figure 3. Forest plot of asthma risk associated with the *IFN-γ* +874A/T polymorphism (AA vs AT + TT) using the random effects model. For each study, the estimates of ORs and 95% CIs were plotted with a box and a horizontal line. The filled diamond symbol indicates the pooled OR and its 95% CI.

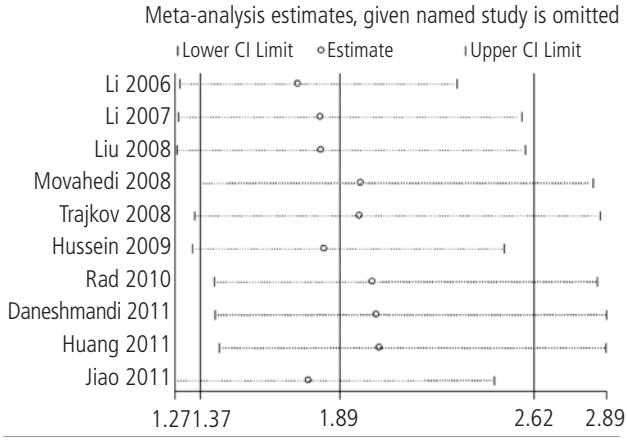

Figure 4. Sensitivity analysis for the association between asthma risk and the *IFN-γ* +874A/T polymorphism (AA vs AT + TT). Results were computed by omitting each study (left column) in turn. Bars, 95% CI. Meta-analysis random-effects estimates (exponential form) were used.

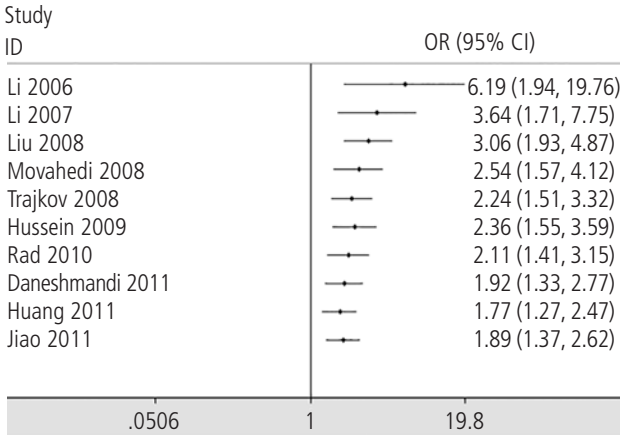

Figure 5. Cumulative meta-analysis of associations between the *IFN-γ* +874AA genotype, as compared with the combined AT + TT genotype, and asthma risk classified by publication year and total sample size. Horizontal line, accumulation of estimates as each study was added rather than the estimate of a single study.

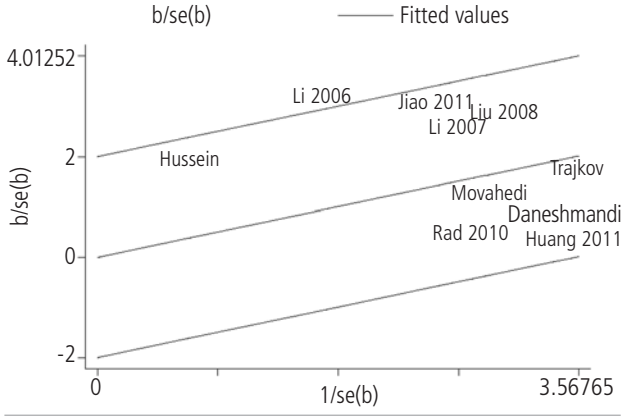

Figure 6. Galbraith plot of the *IFN-γ* +874A/T polymorphism and asthma risk (AA vs AT + TT). Each name represents a separate study included in the meta-analysis. One study [10] was spotted as the outlier and possibly the main source of heterogeneity.

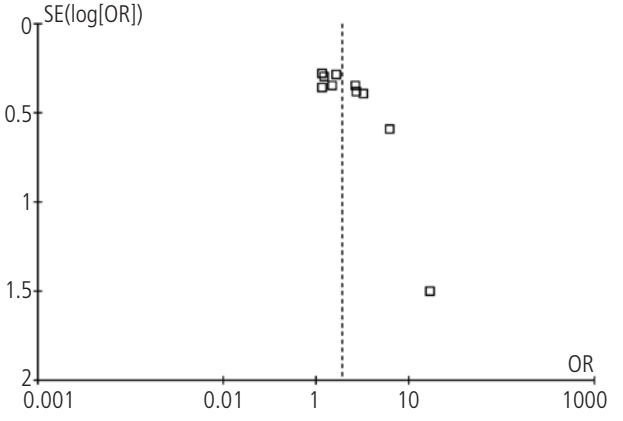

Figure 7. Funnel plot for studies of the association between asthma risk and the *IFN-γ* +874A/T polymorphism (AA vs AT + TT). The horizontal and vertical axis correspond to the OR and 95% CI.

Publication Bias

The funnel plot showed symmetry, suggesting the absence of publication bias among the studies included (Figure 7).

Discussion

T_H2 cytokines are known to activate a cascade of events that are necessary for allergic inflammation, and *IFN-γ* is known to counter-regulate T_H2 immune response. Administration of exogenous *IFN-γ* prevented airway eosinophilia and hyperresponsiveness following allergen exposure in mice [25,26]. Additionally, Li et al [27] showed that mucosal *IFN-γ* gene transfer was effective in modulating pulmonary allergic responses. *IFN-γ* receptor knockout mice have also been seen to exhibit prolonged airway eosinophilia in response to an allergen challenge [28]. Taken together, these results suggested that *IFN-γ* was a critical cytokine in the pathogenesis of atopy and asthma. An early study had reported that a functional mutation in the *IFN-γ* gene (the +874A/T polymorphism) could influence expression of this gene [9]. The TT genotype has been linked to higher *IFN-γ* levels, compared with the AA genotype, while the heterozygous genotype has been associated with intermediate levels [9]. In asthmatic patients, *IFN-γ* expression was lower among patients with the AA genotype than in those with the AT genotype [18]. We therefore speculated that the *IFN-γ* +874A/T polymorphism might influence susceptibility to asthma and confirmed this hypothesis in our meta-analysis.

This meta-analysis of 10 case-control studies indicates that the +874A/T polymorphism is a modest risk factor for developing asthma. The results suggest that individuals who carry the AA genotype may have an increased risk of asthma compared with T allele carriers. Subgroup analysis stratified by ethnicity was also performed, and asthma risk was found to be increased in whites and Asians with the AA genotype. We noted that more than a third of the Asian population were children. Whether age could influence asthma risk through the +874A/T polymorphism remains unclear. We did not perform subgroup analyses according to age because there were only 2 studies that included a pediatric population. More studies are needed to determine the association between this polymorphism and asthma risk in children.

Inhaled corticosteroids and β_2-agonists have been the mainstay of asthma treatment for 30 years, but they are not effective in all patients. Furthermore, high costs and adverse effects also drive the need for more targeted treatment. Pharmacogenetics is the study of the genetic basis for interindividual differences in response to therapeutic drugs and the goal is to personalize therapeutic regimens to enhance drug efficacy and reduce adverse effects. A study of the *TBX21* gene, which encodes the transcription factor T-bet, found that an amino acid substitution was associated with improvement in airway hyperresponsiveness after inhaled corticosteroid treatment [29]. In addition, several studies have shown that individuals who were homozygous for *ADRB2* Arg16 had a greater response to salbutamol than those homozygous for Gly16 [30-32]. The number of genes identified for the various asthma drug response phenotypes remains small and

no pharmacogenomics studies of the *IFN-γ* gene have been performed to date. More studies should be designed to predict individual response to anti-asthma therapies.

There was modest heterogeneity in the overall comparison for the +874A/T polymorphism. We used the Galbraith plot to explore the source of heterogeneity. After excluding the outlier [10], we found that the I^2 value decreased, suggesting that the outlying study [10] was possibly the main source of heterogeneity. Furthermore, heterogeneity did not influence the result, as it remained significant after exclusion of this outlier. In addition, we carried out a sensitivity analysis. Removal of each study and of studies not in HWE did not alter the strength of the association between the +874A/T polymorphism and asthma risk, suggesting the high reliability of this result. The cumulative meta-analyses showed that the pooled ORs tended to be stable, suggesting the robustness of our results. Finally, the shape of the funnel plot was symmetrical, indicating absence of publication bias.

This present meta-analysis had some limitations. First, the number of studies that qualified for inclusion was modest, despite a comprehensive search to find all relevant studies. Second, only published studies were included, so it is possible that we missed out on some relevant unpublished studies. Third, all of the studies were conducted in whites and Asians, and our results may therefore be applicable only to these ethnic groups. Fourth, the meta-analysis was not carried out with other polymorphisms. We also did not address the association between the *IFN-γ* +874A/T polymorphism and atopic asthma risk because of a lack of information. Finally, due to a lack of data, we were unable to address gene-gene and gene-environment interactions.

In conclusion, our meta-analysis found a significant association between the *IFN-γ* +874A/T polymorphism and asthma risk. Large, well-designed studies are needed to confirm this association. As studies in other ethnic groups are limited, further studies including a wider spectrum of individuals should also be performed to investigate the role of this functional polymorphism in other populations. Moreover, gene-environment and gene-gene interactions should also be considered.

Funding

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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