META-ANALYSIS
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Association between FcεRIβ and IFN-γ Polymorphisms and Asthma in Asian Population: a Meta-Analysis

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ABSTRACT

Polymorphisms in the β subunit of the high affinity receptor for IgE (FcεRIβ) and interferon-γ (IFN-γ) genes may influence the risk of asthma. However, the results in Asian population are still debatable. We performed a meta-analysis to ascertain the association between the FcεRIβ E237G, FcεRIβ -109C/T, and IFN-γ 874T/A polymorphisms and asthma in an Asian population.

Databases including PubMed, Chinese National Knowledge Infrastructure (CNKI), Weipu, and Wan Fang (Chinese) databases were searched to find the relevant studies. The effect summary odds ratio (OR) with 95% confidence interval (CI) was calculated.

There was no significant difference in dominant model and allele model (EG + GG vs. EE: OR = 1.14, 95%CI = 0.94-1.40; G vs. E: OR = 1.13, 95%CI = 0.95-1.34) for FcεRIβ E237G, and no significant association was observed in the subgroup analysis by age and atopic status. A significantly decreased risk of asthma was observed in allelic model (C vs. T: OR=0.88, 95%CI=0.80-0.98) for FcεRIβ -109C/T, significant association was found in dominant model (AT+TT vs. AA: OR=0.56, 95% CI=0.33-0.97) for IFN-γ 874T/A.

This meta-analysis suggested that FcεRIβ E237G is not an influencing factor for asthma in Asian population. FcεRIβ -109C/T and IFN-γ 874T/A polymorphisms may be influencing factors for asthma in the Asian population.

Keywords: Asthma; High affinity receptor; IgE; Interferon-γ; Meta-Analysis; Polymorphism

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INTRODUCTION

Asthma is a chronic inflammatory airway disease, and is characterized by recurrent attacks of breathlessness and wheezing. The World Health Organization (WHO) estimates that there are 235

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million people suffering from asthma, and it occurs in all countries regardless of the level of development.[1] Asthma exhibits a complex etiology, resulting from interactions between genetic and environment factors. Studies indicate that asthma has significant genetic contributions, with heritability estimates varying between 35% and 95%[2]. Therefore, a complete understanding of the genetic risk factors for asthma is important to develop new treatments or prevention strategies. So far, a large number of studies have focused on this field.[3-5]

IgE and an imbalance between T helper cell 1 (Th1) and T helper cell 2 (Th2) are thought to play a key role in the pathogenesis of asthma and other allergic diseases.[6-8] The β subunit of the high affinity receptor for IgE (FcεRIβ), which is expressed in mast cells, basophils, eosinophils, and dendritic cells, was localized to the chromosome 11q13 region and proposed as the most likely candidate gene for asthma.[9,10] Many polymorphisms have been identified in this gene, the E237G in exon 7 and the -109C/T in promoter region of FcεRIβ are two of the most intensively studied.[11-14] In addition, IFN-γ plays a critical role in the development of Th1 subtype, which is also considered playing a critical role in the development of asthma.[15,16] Like most of the cytokines, IFN-γ gene coding region has been found to be variant and the 874T/A polymorphism is a common missense mutation.[17] Recently, a growing number of studies have suggested that the E237G and -109C/T polymorphisms of the FcεRIβ gene and 874T/A polymorphism of the IFN-γ gene are potential risk factors for asthma.[18-21] However, the results are inconclusive and conflicting in Asian populations. Some other studies have suggested that the three single nucleotide polymorphisms (SNPs) are not associated with asthma.[22-25] The discrepancies may be due to a relatively small sample size, different atopic status and population.

Individual studies based on small sample sizes have insufficient statistical power to detect positive associations and are incapable of demonstrating the absence of an association.[26] Meta-analysis is a valuable method to overcome the disadvantages of single studies. One of the advantages is to increase sample size, which may reduce the probability that random error will produce false-positive or false-negative association.[27] Given the number of accumulated data can increase the statistical power and the precision of effect estimates thus, it is necessary to perform a quantitative synthesis of the evidence using rigorous methods. Thus, in order to obtain a more precise conclusion in Asian population, we performed the current meta-analysis to identify the association of FcεRIβ gene and IFN-γ gene and the risk of asthma.

MATERIALS AND METHODS

Literature Search

PubMed, Chinese National Knowledge Infrastructure (CNKI), Weipu, and Wan Fang (Chinese) databases were searched using the search terms: 'asthma' or 'asthmatic', 'interferon-γ' or 'IFN-γ' or 'high affinity receptor for IgE' or 'FcεRIβ', and 'polymorphism' or 'mutation' or 'variant'. An upper date limit of December 10, 2013 was applied and we used no lower date limit. The reference lists of the identified articles were also examined and the literature retrieval was performed in duplication by two independent reviewers. The results were compared and disagreements were resolved by consensus.

Inclusion and Exclusion Criteria

The following criteria were set to choose the studies included in the current meta-analysis: (1) the publication was a case-control; (2) the study must offer the sample size, distribution of alleles, genotypes or other information that can help us infer the results; (3) Asian population; and (4) publication language was confined to English and Chinese. The exclusion criterions were as follows: (1) review articles; (2) the studies were conducted on animals; (3) genotype distribution of controls were not in Hardy-Weinberg equilibrium (HWE); and (4) the study was based on individuals who were members of the same family. When multiple publications reported on the same or overlapping data, we used the most recent or largest population.

Data Extraction

Data were carefully extracted independently by reviewers according to the inclusion and exclusion criteria. Disagreements were resolved through discussion and arbitration by a third author if necessary. For each study, the following data were recorded: first author, year of publication, country, age, atopic status, number of cases and controls, and genotype distributions in cases and controls.

Statistical Analysis

Hardy–Weinberg equilibrium (HWE) for the E237G and -109C/T genotype distribution of FcεRIβ and the 874T/A genotype distribution of IFN-γ in controls was tested by χ^2 analysis with exact probability. If the χ^2 test showed a significant departure (p<0.05), the study was excluded from further analyses (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The significant of association for dominant model (FcεRIβ E237G: EG + GG vs. EE; FcεRIβ -109C/T: TC + CC vs. TT; IFN-γ874T/A: AT + TT vs. AA) and the allele contrasts (FcεRIβ E237G: G vs. E; FcεRIβ -109C/T: C vs. T; IFN-γ874T/A: T vs. A) were evaluated for each study separately. The pooled odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of the associations between the genetic variants and asthma risk. Heterogeneity assumption was evaluated by a χ^2 based Q-test and I^2 test.[28] A significant Q-test (p <0.10) indicated heterogeneity across studies. I^2 values were classified as low (<25%), moderate (25-50%), and high (>50%) heterogeneity, respectively. When there was no statistical heterogeneity, we used a fixed effects model (the Mantel-Haenszel method).[29] If heterogeneity was present, we used a random effects model (the DerSimonian and Laird method).[30] To evaluate the age-specific and atopic specific effects, subgroup analyses were conducted on the basis of age and atopic status. For the subgroup analysis by age, study population
was divided into three groups: adults (>18 years of age), children (<18 years of age), and mixed (both adults and children). For the subgroup analysis according to atopic status, study population was divided into two groups: atopic and asthma. The Begg rank correlation method and the Egger linear regression method were used to assess potential publication bias.[31,32] The meta-analysis was performed using STATA Version 12.0 (Stata Corp, College Station, TX, USA) softwares. P value less than 0.05 was considered statistically significant. All P values presented are two-tailed.

RESULTS

Characteristics of Studies

The primary search generated 40 potentially relevant articles. After reviewing these articles, 4 articles were excluded for family-based study designs,[11,22,33,34] 4 articles were excluded for data overlapped or duplicated,[35-38] 5 articles were excluded for the people were not Asian people,[17 39-42] 2 articles were excluded for the genotypes in control group not consistent with HWE,[43, 44] 2 articles were excluded because they did not provide sufficient data for the calculation of ORs and 95% CIs.[45,46] 1 article reported three case-control studies[14], 1 article reported two case-control studies.[47] Thus, a total of 26 case-control studies in 23 articles were finally identified[12-15,18-21,25,47-59] (Figure 1). The detailed characteristics of included studies and the genotype and allele distributions are summarized in Tables 1-3. 19 studies focused on the E237G variant, 7 studies on -109C/T genotype distribution of FcεRIβ, and 5 studies on the 874T/A genotype distribution of IFN-γ.

Meta-Analysis of the FcεRIβ E237G Polymorphism and Asthma

19 case-control studies in 16 articles with 7753 individuals (4030 cases and 3723 controls) were included in this meta-analysis. The overall results suggested that the E237G polymorphism wasn't associated with asthma in dominant model and allele model (EG + GG vs. EE: OR= 1.14, 95%CI = 0.94-1.40; G vs. E: OR = 1.13, 95%CI = 0.95-1.34). Subgroup meta-analysis stratified by age and atopic status revealed that significant association was not observed between asthma and FcεRIβ E237G polymorphism. The detailed results of the association between the FcεRIβ E237G polymorphism and asthma were shown in Table 2 and Figure 2.

Meta-Analysis of the FcεRIβ-109C/T Polymorphism and Asthma

7 studies involving the -109C/T polymorphism included 3499 individuals (1859 cases and 1640 controls). In all eligible studies, 3 studies were conducted in children, and 4 in both children and adults. Only one study included atopic asthmatic patients, 6 studies included asthmatic patients. Table 4 and Figure 3 show the results of the association between the FcεRIβ-109C/T polymorphism and asthma. In pooled analysis, a significantly decreased risk of asthma was observed in allelic model (C vs. T: OR=0.88, 95%CI=0.80-0.98), whereas no evidence of association was found in the dominant model (TC+CC vs. TT: OR = 0.87, 95%CI=0.72-1.06).

Table 1. Distribution of FcεRIβ E237G genotype among cases and controls

First author	Year	Country	Age	Atopic status	No. case/con[a]	Case			Control			P_{HWE}[b]
						EE	EG	GG	EE	EG	GG	
Shirakawa T	1996	Japan	Mixed	Asthma	300/100	256	44	0	94	6	0	1.000
Zeng LX	2001	China	Mixed	Asthma	69/28	61	5	3	27	1	0	1.000
Tang Y	2001	China	Mixed	Asthma	61/65	49	11	0	61	4	0	1.000
Wang L	2003	China	Children	Atopic	110/92	65	40	5	70	20	2	0.644
Cui TP	2003	China	Mixed	Atopic	216/198	125	80	11	148	46	4	0.766
Zhao KS	2004	China	Children	Asthma	151/105	126	23	2	92	13	0	1.000
Zhang XZ	2004	China	Adults	Asthma	141/157	81	57	3	108	42	7	0.276
Zhang XZ	2004	Malaysia	Adults	Asthma	68/100	49	19	0	77	23	0	0.353
Zhang XZ	2004	India	Adults	Asthma	82/98	71	10	1	80	18	0	1.000
Liu T	2006	China	Mixed	Asthma	60/50	45	14	1	39	10	1	0.527
Kim SH	2006	Korea	Mixed	Asthma	307/264	235	64	8	177	81	6	0.523
Palikhe NS	2008	Korea	Mixed	Asthma	303/222	230	67	6	151	65	6	1.000
Chan IH	2008	China	Children	Asthma	291/167	267	23	1	154	13	0	1.000
Li H	2009	China	Children	Asthma	192/192	136	38	18	139	45	8	0.101
Wang JY	2009	China	Children	Asthma	446/506	309	121	16	314	165	27	0.362
Kim ES	2009	Korea	Children	Asthma	347/303	244	99	4	217	81	5	0.505
Undarmaa S	2010	Japan	Children	Atopic	322/336	243	70	9	242	85	9	0.673
Undarmaa S	2010	Japan	Adults	Atopic	367/630	256	102	9	440	165	25	0.067
Zheng BQ	2012	China	Children	Asthma	198/110	126	61	11	76	29	5	0.325

[a]Case: asthma, Con: control. [b]*P* value for Hardy-Weinberg equilibrium in control group.

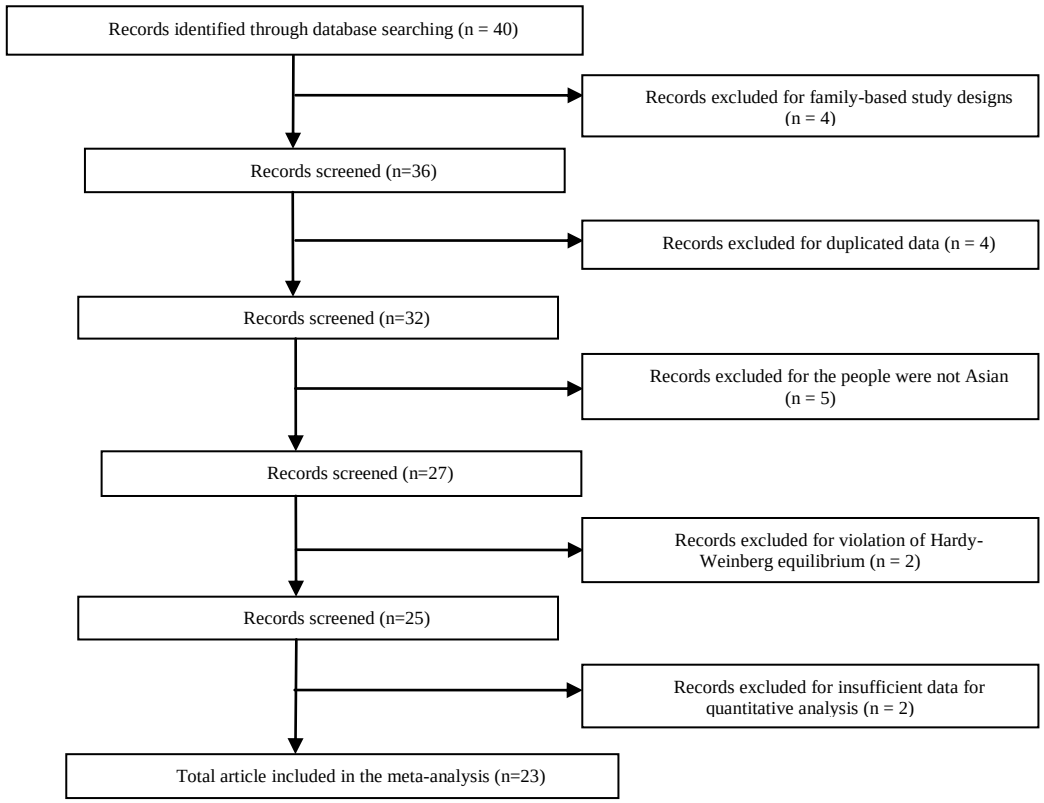

Figure 1. Flow diagram of included/excluded studies

Table 2. Distribution of FcεRIβ -109C/T genotype among patients and controls

First author	Year	Country	Age	Atopic status	No. case/con[a]	Case			Control			P_{HWE}[b]
						TT	TC	CC	TT	TC	CC	
Cui TP	2003	China	Mixed	Atopic	216/198	87	106	23	76	103	19	0.087
Zhao KS	2004	China	Children	Asthma	126/87	46	69	11	40	38	9	1.000
Hizawa N	2006	Japan	Mixed	Asthma	374/374	157	178	39	156	169	49	0.737
Kim SH	2006	Korea	Mixed	Asthma	302/264	146	139	17	113	128	23	0.128
Palikhe NS	2008	Korea	Mixed	Asthma	303/222	154	130	19	99	104	19	0.284
Kim ES	2009	Korea	Children	Asthma	346/303	159	167	20	140	135	28	0.690
Li H	2009	China	Children	Asthma	192/192	110	58	24	78	90	24	0.876

[a]Case: asthma, Con: control.

[b]*P* value for Hardy-Weinberg equilibrium in control group.

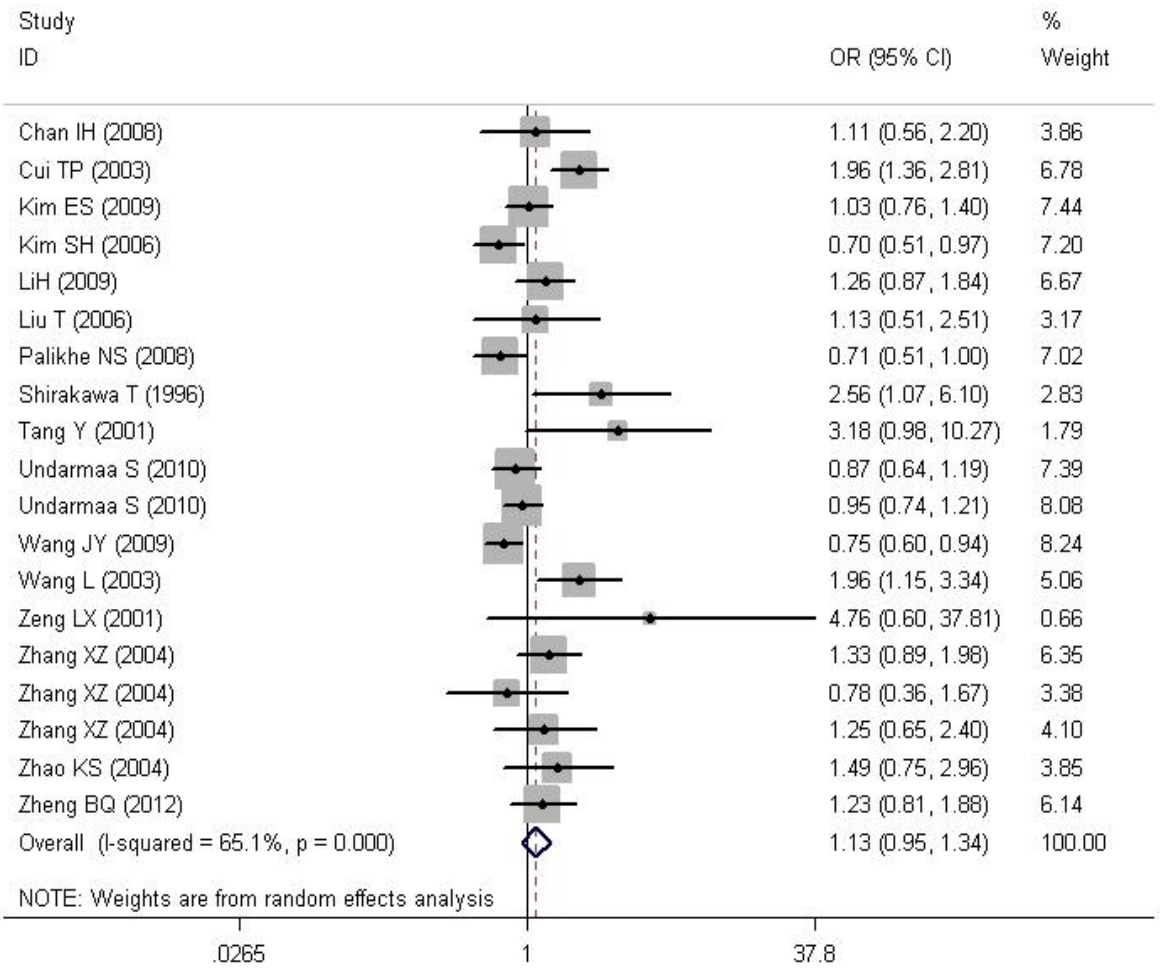

Figure 2. Forest plot for FcεRIβ E237G polymorphism (G vs. E) and asthma

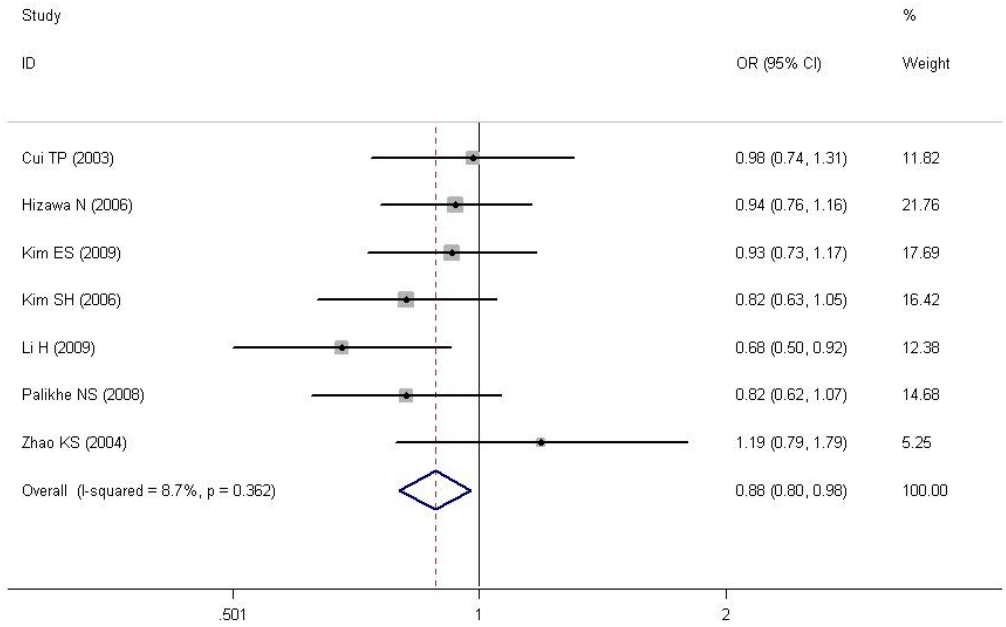

Figure 3. Forest plot for FcεRIβ -109C/T polymorphism (C vs. T) and asthma

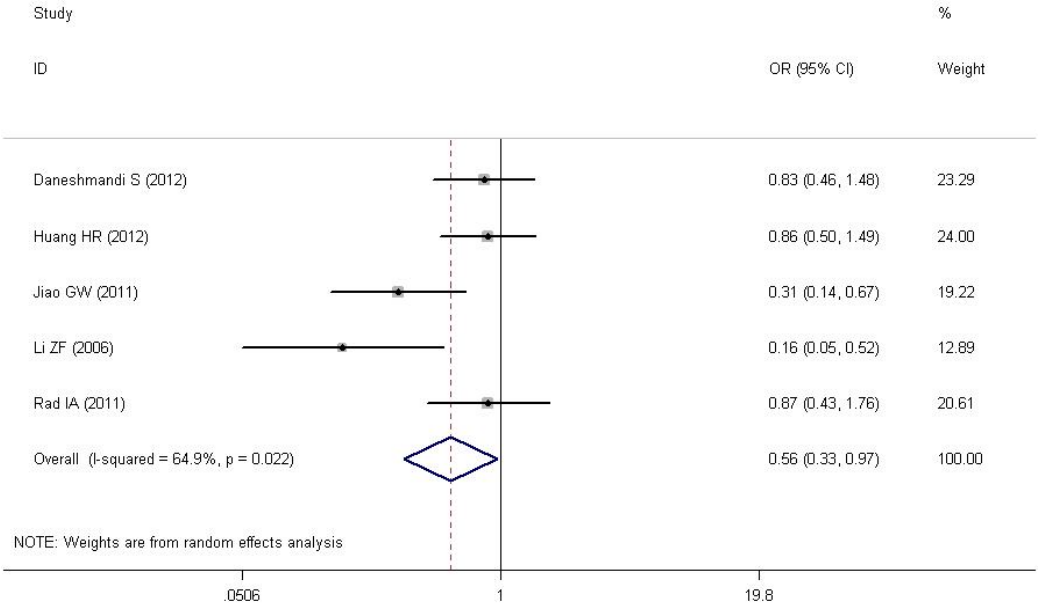

Figure 4. Forest plot for IFN-γ +874T/A polymorphism (AT + TT vs. AA) and asthma

Table 3. Distribution of IFN-γ+874T/A genotype among patients and controls

First author	Year	Country	Age	Atopic status	No. case/con[a]	Case			Control			P_{HWE}[b]
						AA	AT	TT	AA	AT	TT	
Li ZF	2006	China	Children	Asthma	30/26	22	7	1	8	11	7	0.449
Rad IA	2011	Iran	Adult	Asthma	64/109	17	31	16	26	59	24	0.447
Jiao GW	2011	China	Adult	Asthma	75/73	63	12	0	45	28	0	0.058
Daneshmandi S	2012	Iran	Adult	Asthma	81/124	31	31	19	42	53	29	0.146
Huang HR	2012	China	Children	Asthma	100/122	65	33	2	75	43	4	0.591

[a]Case: asthma, Con: control.

[b]*P* value for Hardy-Weinberg equilibrium in control group.

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Table 4. Summary of comparative results of FcεRIβ and IFN-γ genes

SNP	Comparison	Subgroup	NO. of Studies	Test of association			Heterogeneity		
				OR (95%CI)	Z	P	χ^2	P value	I^2 (%)
FcεRIβ E237G	EG + GG vs. EE	Overall	19	1.14(0.94-1.40)	1.31	0.189	53.74	0.000	66.5
		Children	8	1.06(0.84-1.34)	0.52	0.605	14.83	0.038	52.8
		Mixed	7	1.40(0.79-2.48)	1.16	0.246	33.49	0.000	82.1
		Adults	4	1.14(0.83-1.55)	0.81	0.416	4.54	0.209	33.9
		Atopic	4	2.17(1.54-1.37)	1.29	0.198	16.94	0.001	82.3
		Asthma	15	1.06(0.82-1.61)	0.60	0.550	33.00	0.003	57.6
	G vs. E	Overall	19	1.13(0.95-1.34)	1.38	0.167	51.59	0.000	65.1
		Children	8	1.09(0.88-1.35)	0.80	0.425	16.78	0.019	58.3
		Mixed	7	1.38(0.83-2.28)	1.25	0.212	31.85	0.000	81.2
		Adults	4	1.04(0.86-1.26)	0.37	0.712	2.77	0.428	0.0
		Atopic	4	1.29(0.85-1.95)	1.22	0.224	17.51	0.001	82.9
		Asthma	15	1.07(0.88-1.29)	0.69	0.493	31.10	0.005	55.0
FcεRIβ -109C/T	TC + CC vs. TT	Overall	7	0.87(0.72-1.06)	1.35	0.178	12.52	0.051	52.1
	C vs. T	Overall	7	0.88(0.80-0.98)	2.39	0.017	6.57	0.362	8.7
IFN-γ +874T/A	AT + TT vs. AA	Overrall	5	0.56(0.33-0.97)	2.08	0.037	11.41	0.022	64.9
	T vs. A	Overrall	5	0.63(0.39-1.02)	1.89	0.059	15.85	0.003	74.8

SNP:Single Nucleotide Polymorphism OR: Oddis Ratio

Meta-Analysis of the IFN-γ 874T/A Polymorphism and Asthma

We identified 5 studies on the association between IFN-γ 874T/A polymorphism and asthma, including 350 cases and 454 controls. Table 3 and Figure 4 showed the results of the meta-analysis for the association between the polymorphism of IFN-γ and asthma. This meta-analysis indicated that significant association was found in dominant model (AT+TT vs. AA: OR=0.56, 95%CI= 0.33-0.97).

Heterogeneity and Publication Bias

Table 2 showed the heterogeneity of studies in each comparison. We found that the significant heterogeneity existed in the dominant model (FcεRIβ E237G: p=0.000, I^2=66.5%; FcεRIβ -109C/T: p=0.051, I^2=52.1%; IFN-γ874T/A: p=0.022, I^2=64.9%) and allelic model (FcεRIβ E237G: p=0.000, I^2=65.1%; IFN-γ874T/A: P=0.003, I^2 = 74.8%). Heterogeneity was not found in allelic model of FcεRIβ -109C/T (p=0.362, I^2=8.7%). Subgroup analyses of FcεRIβ E237G revealed that heterogeneity was decreased or removed in the analyses of adults, children, and asthma. The Begg rank correlation method and the Egger linear regression method was performed to access the publication bias of literatures. Begg rank correlation method indicated that there was no publication bias for FcεRIβ -109C/T (TC + CC vs. TT: P=0.764; C vs. T: p = 1.000), and IFN-γ874T/A (T vs. A: p=0.086), but not for FcεRIβ E237G (EG + GG vs. EE: p=0.005; G vs. E: p=0.036), The Egger linear regression method suggested significant publication biases for FcεRIβ E237G (EG+GG vs. EE: p=0.036; G vs. E: p=0.023) and IFN-γ874T/A (AT+TT vs. AA: p=0.047; T vs. A: p=0.003).

DISCUSSION

Asthma is a common and complex pulmonary disorder. It was thought that asthma is a result of a combination of environmental factors and the accumulation of genetic variation. Several candidate genes have been reported to be involved in asthma susceptibility, such as STAT6, ADAM33.[60] A growing number of studies have recently suggested the FcεRIβ[52, 61] and IFN-γ gene[62] are potential risk factors for asthma. However, the results have been inconsistent and inconclusive in Asian populations. In order to resolve the conflicting results, meta-analysis should be preformed to provide a quantitative approach to combine comparable studies in an attempt to reduce the pernicious influence on false-positive and false-negative associations. Although there are several SNPs in the FcεRIβ and IFN-γ gene, only three extensively investigated SNPs (FcεRIβ E237G, FcεRIβ-109C/T, and IFN-γ 874T/A) were included in this meta-analysis,

considering that small numbers of studies could weaken the conclusions.

This meta-analysis of summarized 19 case-control studies including 4030 cases and 3723 controls systematically evaluated the association between FcεRIβ E237G polymorphism and asthma risk. The result showed that no significant association was indicated in the Asian population, which is different with previous meta-analysis in Chinese population.[63] The reason for the discrepancy stemmed from the fact that Li and coworkers only included 9 studies with 1434 asthma cases and 1276 controls. Another reason for the inconsistency was related to some mistakes in reporting the genotype numbers in their meta-analysis, such as the genotype numbers extracted from Cui TP's study. There were several studies which supported the positive association between the FcεRIβ E237G polymorphism with atopic asthma and asthma in children [36, 38]. However, no significant association was found in subgroup analysis by age or atopic status in this meta-analysis. More studies should be performed focusing on different classified asthma patients in the future.

With respect to FcεRIβ -109C/T polymorphism, a significantly decreased risk of asthma was observed in allelic model. This result suggested that individuals who carry the C allele may have a 12% decreased asthma risk compared with T allele in Asian population. The result was consistent with Li H et al, which included only three case-control studies on -109C/T polymorphism.[63] In the present meta-analysis, we first assessed the relationship between IFN-γ 874T/A and the risk of asthma in Asian population. The results showed that significant association was found in dominant model. It has been demonstrated that IFN-γ 874T/A polymorphisms may play an important role in pathophysiologic mechanisms and be a useful marker of asthma phenotype.

Heterogeneity is one of the important things when performing meta-analysis. The results should be interpreted with caution when heterogeneity exists. There was high heterogeneity among most of the meta-analysis. Considering that differences in age and atopic status may affect the results, we performed subgroup analysis by age and atopic status. After subgroup analysis, the heterogeneity was decreased or removed in the analyses of adults and asthmatic patients. It showed that the source of heterogeneity may be from different ages and atopic status. Another important factor for heterogeneity was that homogeneity in either the case and control groups was not totally clear. Although all parameters such as sex and environmental exposures in the cases and controls should be matched, this cannot be confirmed because of the insufficient clinical information for individual persons. Publication bias is another important thing which should also be discussed in meta-analysis. In this meta-analysis, the Begg rank correlation method and the Egger linear regression method showed that there was publication bias in part of meta-analysis for the FcεRIβ E237G and IFN-γ 874T/A polymorphism. Negative studies were less likely to be published in journals and be available in computerized database, resulting in potential overestimation of effect sizes.[64] Thus, our results should be interpreted with caution and more studies are still needed to evaluate the effect of FcεRIβ E237G and IFN-γ 874T/A polymorphism on asthma risk.

Some limitations of the present study should be mentioned. First, publication bias existed in part of meta-analysis for the FcεRIβ E237G and IFN-γ 874T/A polymorphism. Only studies that were indexed by the selected databases were included for this meta-analysis, some relevant published studies or unpublished studies with null results were missed. This might have biased the results. Second, the relationship between the three SNPs and asthma risk did not consider the confounding factors, such as sex, lifestyle factors, and other risk factors. Third, asthma is the result of the interaction of multiple genetic and environmental factors. However, insufficient information could be extracted from the primary publications. Thus, this meta-analysis could not address gene-gene and gene-environment interactions. More studies should be designed to analyze these associations in the future. In view of the limitation of this meta-analysis, it is necessary to conduct a large sample study using homogeneous asthma patients and well-matched controls in the future.

This meta-analysis suggested that FcεRIβ E237G is not an influential factor for asthma in an Asian population. FcεRIβ -109C/T and IFN-γ 874T/A polymorphisms maybe influential factor for asthma in an Asian population.

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