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REVIEW

Polymorphisms in IL-4/IL-13 pathway genes and glioma risk: an updated meta-analysis

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Abstract Polymorphisms in interleukin (IL)-4/IL-13 pathway genes have previously been reported to be associated with glioma susceptibility, although results are inconsistent. We therefore performed an updated meta-analysis to determine a more precise estimation of this relationship. Twelve eligible studies were identified by searching PubMed, EMBASE, Web of Science, and the Cochrane Library electronic databases. Nine polymorphisms in genes within the IL-4/IL-13 pathway (*IL-4* rs2243250, rs2070874, rs2243248, *IL-4R* rs1805011, rs1805012, rs1805015, rs1801275, and *IL-13* rs20541 and rs1800925) were assessed for their relationship with glioma risk by computing odds ratios (ORs) and corresponding 95 % confidence intervals (CIs). Akaike's information criterion (AIC) was used to identify the best genetic model for each polymorphism. No association between IL-4/IL-13 pathway genetic polymorphisms and glioma risk was observed in the overall population, although a significant association was found between rs2234248 and glioblastoma when stratified by histological subtype (log-additive model, OR 1.57, 95 % CI 1.11–2.24). This meta-analysis therefore suggested that IL-4/IL-13 pathway genetic polymorphisms are not associated with glioma risk.

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Introduction

Glioma is an uncommon and rapidly fatal disease, for which the etiology remains largely unknown [1]. Exposure to therapeutic doses of ionizing radiation is the strongest known environmental risk factor for glioma but only accounts for a small proportion of cases [2]. Recent studies have consistently indicated an inverse association between self-reported allergies or atopic disease and glioma risk [3–6]. Moreover, evidence has also suggested that elevated immunoglobulin E (IgE) levels are associated with lower glioma risk [7, 8]. Given the consistent epidemiological data supporting the relationship between allergy and glioma, it has been hypothesized that inflammation-related cytokines, which are critical for allergy and IgE production, and their single nucleotide polymorphisms (SNPs) may alter the risk of glioma by affecting the body's immune status.

Interleukin (IL)-4 and IL-13 are cytokines that share immunoregulatory functions and a common IL-4R chain on their receptors. They both play a central role in allergy by stimulating IgE synthesis in B lymphocytes and reducing production of pro-inflammatory cytokines by macrophages [9, 10]. Previous studies have also shown that they have strong antitumor activity in mice and inhibit proliferation of astrocytoma and low-grade glioma in human cell lines [11, 12]. Furthermore, polymorphisms of *IL-4R* and *IL-13* have been reported to be associated with asthma risk [13, 14]. Considering the strong biological rational, several epidemiological studies have investigated the associations between IL-4/IL-13 pathway genetic polymorphisms and risk of glioma but have yielded contradictory results [15–17].

To date, two meta-analyses have been conducted to derive a precise estimation of this relationship [18, 19]. However, these findings have also been inconsistent and evaluated only a limited number of SNPs. Guo et al. reported that *IL-4R* rs1801275 was associated with a decreased risk of glioma [18], but this was not demonstrated in another meta-analysis [19]. Additionally, the published meta-analyses were based on the testing of multiple models (homozygote comparison, heterozygote comparison, recessive model, and dominant model), which are not independent so may increase the risk of false-positive results. Furthermore, some studies were not included in previous meta-analyses [20, 21], including those published later with larger sample sizes and rigorous designs [22, 23]. Considering that these factors could contribute to bias in the final results, we carried out an updated meta-analysis to provide a more reliable correlation between polymorphisms in IL-4/IL-13 pathway genes and glioma risk.

Materials and methods

Identification of eligible studies and SNPs

We performed a systematical search in PubMed, EMBASE, Web of Science, and the Cochrane Library databases for eligible articles with the following terms "glioma," "polymorphism," "IL-4" or "interleukin-4," "IL-4R" or "interleukin-4R," and "IL-13" or "interleukin-13" (last search updated on 10 April 2014). There were no language restrictions. We also reviewed reference lists and papers presented at international conferences for potentially relevant publications. If studies conducted in the same population existed, the most recent one or research with the most complete data was chosen. Inclusion criteria were as follows: (a) case–control or cohort design, (b) associations between relevant polymorphisms and glioma risk already assessed, and (c) sufficient data available for the computation of odds ratios (ORs) and 95 % confidence intervals (CIs). Studies not on human subjects, without available data, or with overlapping data were excluded. SNPs assessed in more than two studies were included for analysis.

Data extraction and assessment of methodological quality

Two reviewers (PQ Chen and K Chen) independently extracted the following data from selected articles: author, year of publication, country of origin, ethnicity, sample size, source of controls, matching criteria, and genotype distribution in cases and controls. We also contacted primary authors for genotype frequency data that were not reported in their articles.

After the concealment of authors, journals, supporting organizations, and funds to avoid subjective bias, two reviewers (K Chen and C Chen) assessed the methodological quality of the respective studies based on a set of criteria modified from previous research (Online Resource 1) [24, 25]. Quality scores ranged from 0 to 10, and studies scoring 6 or more points were considered eligible. Disagreements were resolved by discussion.

Statistical analysis

The strength of the association between IL-4/IL-13 pathway genetic polymorphisms and glioma risk was estimated by ORs with corresponding 95 % CIs. The common genetic models used for evaluating gene–disease associations are dominant, co-dominant, recessive, over-dominant, and log-additive. To avoid the problem of multiple model comparisons, we used Akaike's information criterion (AIC) to determine the best genetic model for each SNP, and then pooled ORs were only calculated for this model. Between-study heterogeneity was determined by the chi-squared (χ^2)-based Q test [26]. $P<0.10$ was considered to be an indicator of a substantial level of heterogeneity, and data were pooled using a random effects model (the DerSimonian and Laird method) [27]; otherwise, the fixed effects model (the Mantel-Haenszel method) was applied [28]. Publication bias was assessed visually using Begger's funnel plots and formally tested using Egger's test [29]. Hardy–Weinberg equilibrium (HWE) of controls was examined by the χ^2 test. Analyses were stratified by glioma histological types to address the differences in genetics and biology of glioblastoma (WHO grade IV) versus medium-grade (WHO grade III) and low-grade (WHO grade II) tumors. All statistical analyses were performed with STATA 12.0 (Stata Corporation, College Station, TX), and all P values were two-sided.

Results

Study characteristics

The selection procedure resulted in the inclusion of 12 published studies in the final meta-analysis (Fig. 1). Eleven studies used a case–control design, and only one used a cohort design [23]. The included studies were carried out in both Caucasian ($n=10$) and Asian ($n=2$) populations. Control subjects were mostly population-based rather than hospital-based and were all frequency-matched to the cases by age and gender. The quality score of included studies ranged from 6 to 9 with the majority scoring 7.5 or more points (Table 1). DNA used for genotyping was mostly extracted from blood samples, although some samples are derived from buccal cells [16]. The distribution of genotypes in the controls was consistent with HWE in all studies. Finally, nine polymorphisms in IL-4/IL-13 pathway genes were evaluated in this study: *IL-4* (rs2243250, rs2070874, and rs2243248), *IL-4R* (rs1805011,

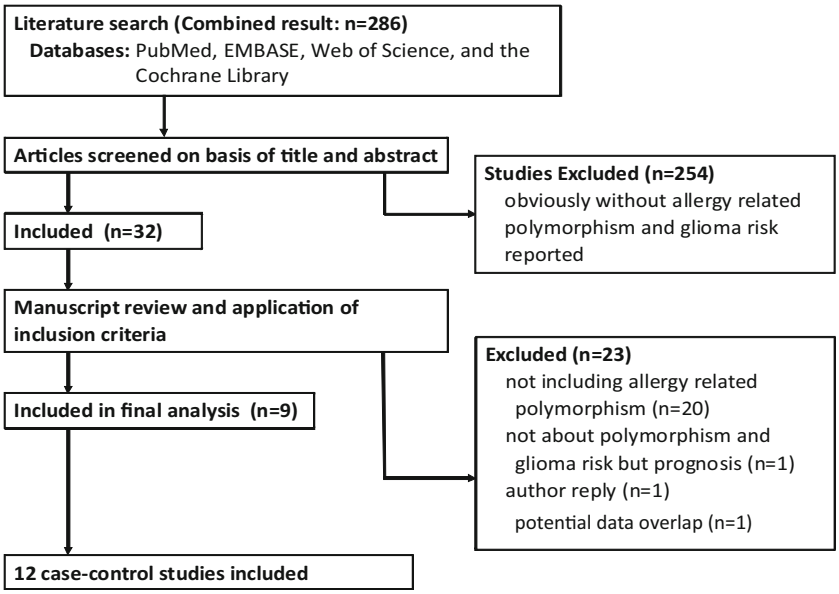

Fig. 1 Flow diagram of the identification of eligible studies

rs1805012, rs1805015, and rs1801275), and *IL-13* (rs20541 and rs1800925).

Meta-analysis results

Overall, no significant association was found between IL-4/IL-13 pathway genetic polymorphisms and glioma risk (Fig. 2). In the case of the *IL-13* rs20541, eight studies were included in the present meta-analysis. The results suggested no association with glioma risk (recessive model, OR 0.88, 95 % CI 0.63–1.24), and a moderate heterogeneity across studies (I^2=46.3 %). Sensitivity analysis found that one study was the main source of heterogeneity [20]. After exclusion of this study, heterogeneity was reduced but there was no significant change to the results (recessive model, I^2=0; OR 0.79, 95 % CI 0.62–1.01).

The meta-analysis of three well-designed studies (including 2312 glioma cases and 2324 controls) found no significant association between *IL-4* rs2243248 and glioma risk (log-additive model, OR 1.31, 95 % CI 0.90–1.91), but strong heterogeneity was evident (I^2=75 %). We considered that publication bias was a possible explanation for this high heterogeneity among studies. Analysis stratified by histological type showed that rs2234248 was associated with an increased risk of glioblastoma (log-additive model, OR 1.57, 95 % CI 1.11–2.24). This was the only IL-4/IL-13 genetic polymorphism to show a significant association with glioblastoma (Table 2 and Online Resource 2).

Table 1 General information of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Case/control	Control source	Matching criteria	Quality score
Schwartzbaum	2005	Sweden	Caucasian	111/422	PB	Age/gender/region	7.5
Schwartzbaum[a]	2007	Finland	Caucasian	44/110	PB	Age/gender/region	7.5
Schwartzbaum[a]	2007	Denmark	Caucasian	66/602	PB	Age/gender/region	7.5
Schwartzbaum[a]	2007	England	Caucasian	107/459	PB	Age/gender/region	7.5
Brenner	2007	America	Caucasian	431/611	HB	Age/gender/ethnicity	7.5
Brenner	2007	America	Caucasian	325/579	PB	Age/gender/region	8.5
Wiemels	2007	America	Caucasian	456/541	PB	Age/gender/ethnicity	8.5
Amirian	2010	America	Caucasian	373/365	PB	Age/gender/ethnicity	8.5
Ruan	2011	China	Asian	677/698	HB	Age/gender/region	6.5
Li	2012	China	Asian	226/254	HB	Age/gender/region	6
Backes	2013	America	Caucasian	143/419	PB	Age/gender/ethnicity	7.5
Walsh	2013	America	Caucasian	1662/1301	PB and HB	Age/gender/ethnicity	9

PB population-based, *HB* hospital-based

[a] Data provided by these studies can only be calculated for dominant model

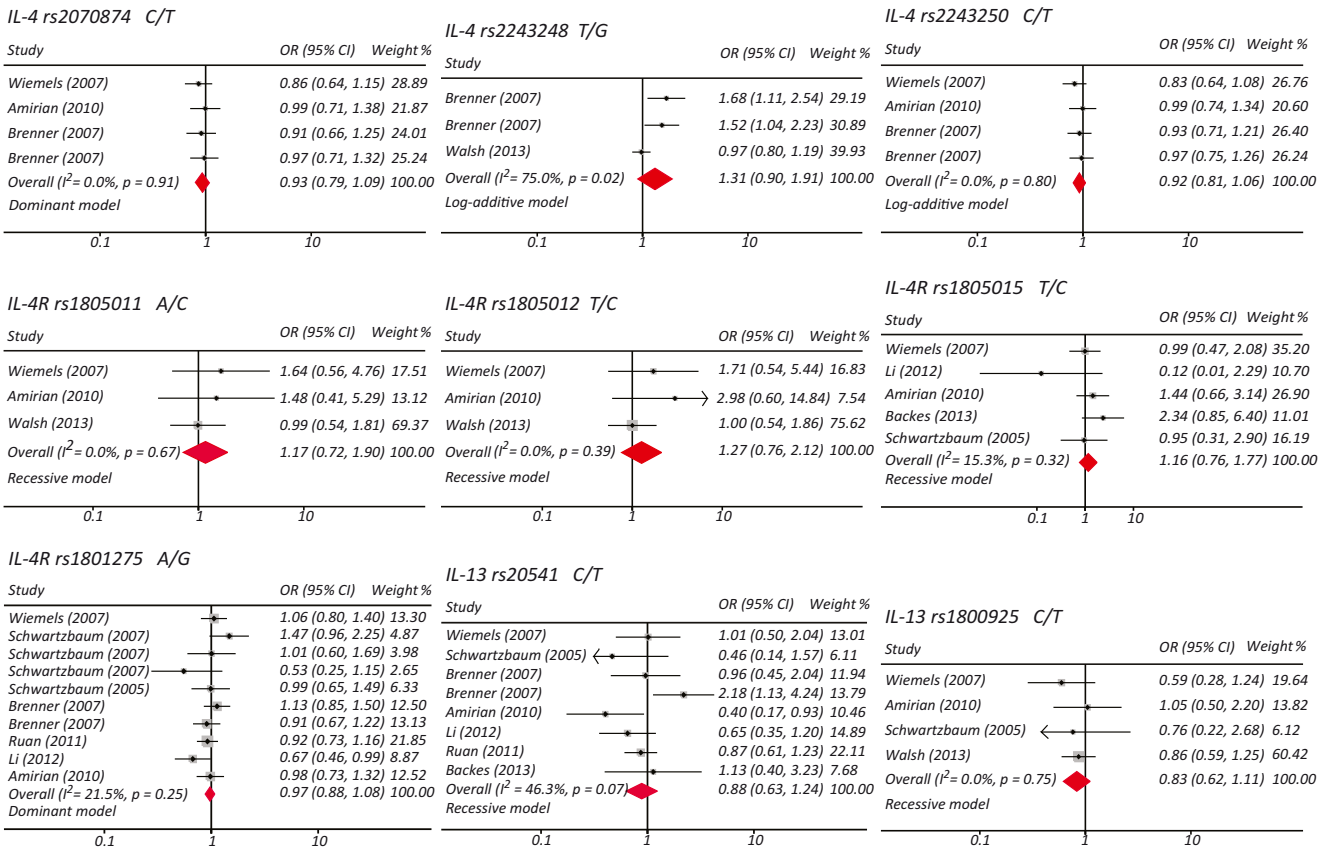

Fig. 2 Meta-analysis for the association between IL-4/IL-13 pathway genetic polymorphisms and glioma risk

The meta-analysis of ten studies of *IL-4R* rs1801275 yielded no significant association with glioma risk (dominant model, OR 0.97, 95 % CI 0.88–1.08). When we restricted the study type to an analysis of Caucasians, high-quality score (quality score >8), or case sample >300, the results did not substantially alter.

Publication bias

Publication bias was detected by Egger's test in *IL-4* rs2243248 (P=0.01) and *IL-4R* 1805012 (P=0.03). We found no evidence of publication bias in the other SNPs using Begger's or Egger's test (Fig. 3).

Table 2 Meta-analysis results for associations between polymorphisms of IL-4/IL-13 pathway and glioma risk

Gene	SNP ID	Model	Genotype	Glioma		Glioblastoma	
				OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
IL-4	rs2070874	Dominant	TT/CT vs CC	0.93 (0.79–1.09)	0.35	0.96 (0.72–1.29)	0.80
	rs2243248	Log-additive		1.31 (0.90–1.91)	0.16	**1.57 (1.11–2.24)**	0.01
	rs2243250	Log-additive		0.92 (0.81–1.06)	0.25	0.95 (0.75–1.21)	0.66
IL-4R	rs1805011	Recessive	CC vs AA/AC	1.17 (0.72–1.90)	0.53	–[a]	–
	rs1805012	Recessive	CC vs TT/CT	1.27 (0.76–2.12)	0.36	–	–
	rs1805015	Recessive	CC vs TT/CT	1.16 (0.76–1.77)	0.49	1.61 (0.76–3.39)	0.21
	rs1801275	Dominant	GG/AG vs AA	0.97 (0.88–1.08)	0.61	1.03 (0.88–1.20)	0.72
IL-13	rs20541	Recessive	TT vs CT/CC	0.88 (0.63–1.24)	0.47	0.92 (0.64–1.32)	0.66
	rs1800925	Recessive	TT vs CT/CC	0.83 (0.62–1.11)	0.21	0.76 (0.22–2.68)	0.67

The Akaike's information criterion was used to determine the best genetic model for each SNP, for which the pooled ORs were only calculated. Bold values indicate the odds ratios that are statistically significant

[a] Not determined

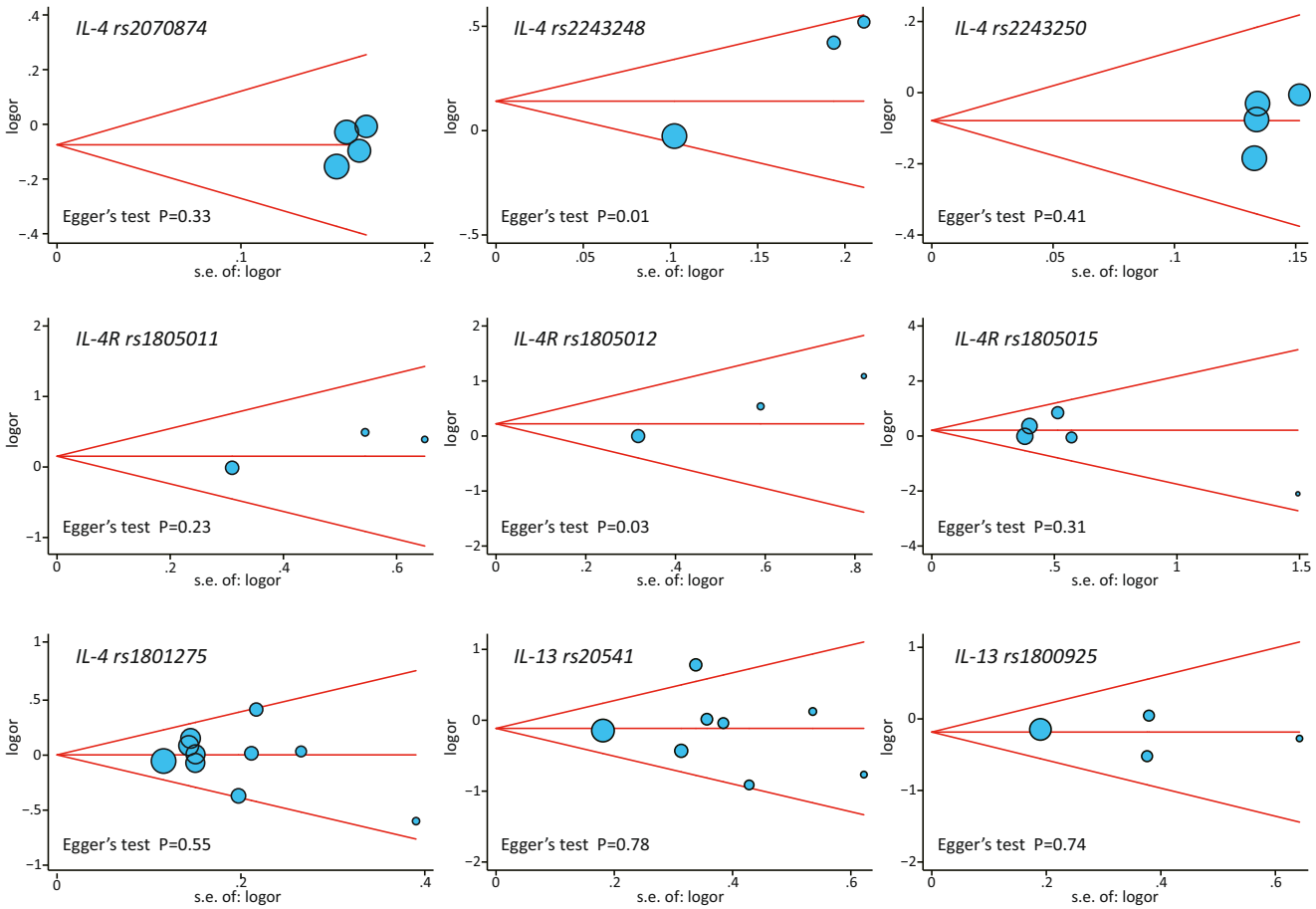

Fig. 3 Publication bias examinations by Begger's funnel plots and Egger's test. Asymmetrical plots or $P<0.10$ suggest potential bias. *Each point* represents a separate study for the indicated association, and the *horizontal line* depicts mean effect size. *logor* natural logarithm of OR, *s.e.* standard error

Discussion

Since the IgE-glioma or allergy-glioma association was discovered, the role of polymorphisms in cytokine genes, which are critical for allergy and IgE synthesis, has been extensively studied on glioma risk but with mixed findings. The motivation of the present study is to define a precise estimation of this association. Our results revealed that IL-4/IL-13 pathway genetic polymorphisms were not associated with glioma risk in the overall population.

In recent years, genome-wide association studies (GWAS), which are not contingent on prior information concerning candidate genes or pathways, have made great progress in discovering the underlying architecture of genetic susceptibility to glioma. Previous GWAS have demonstrated that genetic variant mapping to 9p21.3 (*CDKN2A/CDKN2B*) [30], 7p11.2 (*EGFR*) [31], 5p15.33 (*TERT*) [32], 20q13.33 (*RTEL1*) [30], 8q24.21 (*CCDC26*) [33], and 11q23.3 (*PHLDB1*) [33] contribute to the heritable risk of glioma. However, they have thus far not identified a significant association between glioma and allergy-related genes, which further supports our present work.

In our study, rs2243248 was found to have a significant association only when analyses were restricted to the glioblastoma subgroup, which indicated that this variant might have a subtype-specific effect on the risk of glioma development. Although the specific functional relevance of rs2243248 is not completely understood, a previous study identified it as a risk factor for sporadic Alzheimer's disease in the Chinese Han population [34]. Moreover, it has also been associated with a decreased risk of juvenile idiopathic arthritis [35]. Thus, an opposite association between rs2243248 and glioblastoma appears to be consistent with expectations from previous epidemiologic studies [36, 37]. Nevertheless, the significant publication bias ($P=0.01$) observed for this polymorphism in the present study may have introduced serious bias to the pooled results. Thus, the association warrants replication in a larger population.

A previous meta-analysis including 1609 cases and 3016 controls identified *IL-13* rs20541 as a protective factor for glioma [19], but this was not replicated in our study. Our meta-analysis had a larger sample size than the previous one, which might have altered the overall results. In addition, the previous meta-analysis tested multiple genetic models and did not

correct for multiple comparisons, which may have increased the risk of false-positive results. By contrast, pooled ORs were only calculated for the recessive model in our study, which was determined from AIC to avoid the problems of multiple comparisons. Our findings are therefore likely to be more reliable than those of the previous study. Although rs20541 has been reported to play a role in IgE synthesis and asthma risk, our results suggest that it is unlikely to affect glioma development.

Four *IL-4R* polymorphisms (rs1805011, rs1805012, rs1805015, and rs1801275) were assessed in our study. No previous studies identified a significant association between rs1805011, rs1805012, or rs1805015 and glioma risk, and the results were still insignificant when we pooled data from these studies. An earlier meta-analysis revealed a significant association between rs1801275 and glioma risk [18], but this was not replicated in another meta-analysis [19] or our own. Even after restricting the study type to a Caucasian population, high-quality score (>8), or case sample >300, the OR for an association between rs1801275 and glioma risk was barely altered, strengthening the possibility that the lack of association was not caused by chance.

Consistent evidence supports a correlation between allergic conditions and glioma, so it is conceivable that genetic susceptibility to allergies is also related to the risk of glioma. However, this is not borne out by our current findings. One reason for this is that maybe the SNPs assessed in our study are not functional variants in the IL-4/IL-13 pathway, such that single base substitutions at these loci have no effect on the functions of target genes. Thus, other functional SNPs not in linkage disequilibrium could be investigated in future analyses.

Another potential reason is that although certain SNPs assessed are good candidates for affecting IgE levels and allergies such as rs20541 and rs1801275, they only account for some of the factors that affect IgE levels. For example, *IL-13* haplotypes are estimated to be responsible for only 0.59 % of total IgE levels [38]. The point measurement of total IgE is also determined by other factors such as seasonality, diet, and circadian rhythms, so an individual SNP in the IL-4/IL-13 pathway might not substantially alter glioma risk through its small influence on the immune system.

To our knowledge, this is the most comprehensive study of polymorphisms in the IL-4/IL-13 pathway and glioma risk. Most of the nine polymorphisms assessed in our study have never been included in a meta-analysis before. Additional strengths of our study included the use of AIC to determine the best genetic model for each SNP and performing a methodology assessment to ensure the quality of included studies. However, there were some limitations that merit attention. First, because of the lack of original data, the effects of gene–gene and gene–environment interactions were not taken into consideration, yet these could modulate glioma risk. Second, although we undertook an extensive search to limit bias in the review process, publication bias was still detected for polymorphisms such as *IL-4* rs2243248 and *IL-4R* rs1805012, so these results should be interpreted with caution. Third, only two studies conducted in Asian populations were included in our meta-analysis, so we were unable to perform a subgroup analysis by ethnicity. Finally, our meta-analysis was subject to the same multiple testing issues as a single-sample study. However, because correction for multiple testing is usually applied to eliminate false-positive results, our results are unlikely to differ after adjusting for multiple testing as we did not observe any significant associations.

In conclusion, our study revealed that IL-4/IL-13 pathway genetic polymorphisms are not associated with glioma risk in the overall population. However, studies with larger sample sizes, standardized unbiased homogenous patients, and well-matched controls are required to draw more comprehensive conclusions. Differences in genetic risk profiles between histological subtypes and tumor grades should also be considered in future studies.

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Conflicts of interest None

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