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Association between polymorphisms in *interleukin-4Rα* and *interleukin-13* and glioma risk: A meta-analysis

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ABSTRACT

Introduction: It has been suggested that allergies are inversely associated with glioma risk. Single nucleotide polymorphisms in two allergy-related genes [*interleukin* (*IL*)*-4Rα*, *IL-13*] have been implicated in susceptibility to glioma; however, results from the published studies remained inconclusive. *Methods*: To derive a more precise relationship, we conducted a meta-analysis including seven case–control studies that investigated the influence of *IL-4Rα* rs1801275 and *IL13* rs20541 polymorphisms on glioma risk. Data were extracted from these studies and pooled odds ratios (OR) with 95% confidence intervals (CI) were used to investigate the strength of the association. *Results*: Overall, the pooled analysis showed that there was no significant association between the *IL-4Rα* rs1801275 polymorphism and glioma risk (OR = 0.99, 95%CI: 0.79–1.25, AG/GG *vs.* AA). However, we found that the *IL13* rs20541 variant genotypes (GA/AA) were significantly associated with reduced risk for glioma (OR = 0.85, 95%CI: 0.75–0.97, GA/AA *vs.* GG). In the stratified analyses by ethnicity, marginally significant association between the *IL13* rs20541 polymorphism and decreased glioma risk was found among Asian populations in dominant models (OR = 0.84, 95%CI: 0.70–1.00, GA/AA *vs.* GG). *Conclusions*: This meta-analysis suggests that the *IL13* rs20541 but not the *IL-4Rα* rs1801275 polymorphism may be a genetic predictor for glioma. More studies with larger sample size are warranted to further elucidate the impact of the *IL13* rs20541 polymorphism on glioma risk.

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1. Introduction

Gliomas are aggressive lethal disease and account for approximately 80% of primary malignant brain tumors [1]. Gliomas derive from glial cells that surround and support neurons in the brain [2]. The most established risk factor for glioma is a high dose of ionizing radiation [1], however, this risk factor accounts for only a small proportion of cases. Evidence from several epidemiological studies consistently suggests an inverse association between allergic conditions (IgE levels) and risk of glioma [3]. It has been shown that single nucleotide polymorphisms (SNPs) in inflammation-related genes influence the risk of various cancer [4–6], including glioma [7]. Particularly, several SNPs in inflammation-related genes that confer asthma risk have been found to confer glioma risk [7]. Of these genes, previous meta-analyses have identified *IL-4Rα* rs1801275 and *IL13* rs20541 as risk factors for asthma [8,9].

IL-4 and IL-13 are cytokines which share a common IL-4RA chain on their receptors and immunoregulatory functions. They both play a central role in allergy by stimulating IgE synthesis [10] and reducing the production of pro-inflammatory cytokines by macrophages [11]. It has been showed that IL-4 and IL-13 have strong anti-tumor activity in mice and can inhibit proliferation of low-grade glioma in human cell lines [12,13]. Studies investigating polymorphisms in the *IL-4Rα* and *IL-13* genes provide strong evidence for a role of these genes in IgE production or allergy [8,14]. Because of the important association of allergic disease and glioma, and the influences of the *IL13* rs20541 and the *IL-4Rα* rs1801275 on asthma risk, several molecular epidemiological studies have been conducted to investigate the association between these two polymorphisms and the risk of glioma [15–19]. However, the results from these studies remained inconclusive. To detect a true association of polymorphism with small effect on glioma risk, a single study may be underpowered, particularly for those studies with inadequate sample size.

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Table 1
Characteristics of studies included in the meta-analysis.

ID	First author	Year	Country	Source of controls	Ethnic group	Case/control		HWE
						IL-4Rα rs1801275	*IL13* rs20541	
1	Schwartzbaum	2007	Sweden	Population	Caucasian	109/418	110/434	C
2	Schwartzbaum	2007	England	Population	Caucasian	106/455	107/459	C
3	Schwartzbaum	2007	Denmark	Population	Caucasian	66/601	66/599	C
4	Schwartzbaum	2007	Finland	Population	Caucasian	44/109	44/109	C
5	Wiemels	2007	USA	Population	Caucasian	384/469	385/468	C
6	Ruan	2011	China	Hospital	Asian	672/696	672/693	C
7	Li	2011	China	Population	Asian	225/250	225/254	C

HWE: Hardy–Weinberg equilibrium of genotype of control. C: conformed to HWE.

Therefore, we conducted a meta-analysis of all eligible case–control studies that have been published to clarify the effects of the *IL13* rs20541 and the *IL-4Rα* rs1801275 on glioma risk.

2. Materials and methods

2.1. Identification and eligibility of relevant studies:

Relevant publications were identified by a literature search using the keywords "*IL-4Rα*" "*IL13*", "inflammation genes", "polymorphism" and "glioma" in the Medline and Embase databases (the last search update was October, 2012). Potentially additional study was identified by a hand search of the references of the original studies. The following criteria were used for inclusion of the identified articles in the present meta-analysis: (1) use a case–control design and (2) contain available genotype frequency. The major reasons for exclusion of studies were (1) not case–control study [20–22] and (2) no usable data reported [7]. Finally, the data for the analysis were available from 7 case–control studies [15–19], including 1606 cancer cases and 2998 controls for the *IL-4Rα* rs1801275 polymorphism and 1609 cancer cases and 3016 controls for the *IL13* rs20541 polymorphism.

2.2. Data extraction

Two investigators independently extracted data and reached a consensus on all of the items. The following information was sought from each article: the first author's name, year of publication, country of origin, ethnicity, source of controls, number of cases and controls, genotype frequencies for cases and controls and Hardy–Weinberg equilibrium (HWE) of controls.

2.3. Meta-analysis

The strength of the association between *IL-4Rα* rs1801275 and *IL13* rs20541 polymorphisms and glioma risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). Four different ORs were calculated using the following models: the dominant genetic model, the recessive genetic model, the homozygote comparison and the heterozygote comparison. Since four of the included studies [15] only reported the dominant model analysis for the *IL-4Rα* rs1801275 and the *IL13* rs20541 polymorphisms, so in the meta-analysis all of the 7 data-sets were included in the dominant model analysis contained, but only 3 data-sets were included in the recessive genetic model, the homozygote and heterozygote comparison. Heterogeneity assumption was evaluated with a chi-square-based *Q*-test. If the *P* value is greater than 0.100 of the *Q*-test, which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by a fixed effects model (the Mantel–Haenszel method) [23]. Otherwise, the random-effects model (the DerSimoniane and Laird method) [24] was performed. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias. All statistical analysis were done with the Stata software (version 10.0; StataCorp LP, College Station, TX), using two-sided *P* values.

3. Results

3.1. Characteristics of studies

According to the criteria for inclusion and exclusion, 7 case–control studies investigating the association between the two polymorphisms and risk of glioma were finally included in the present meta-analysis. The characteristics of the studies were listed in Table 1. Of the 7 studies, 5 studies were conducted in Caucasian population and 2 conducted in Asian populations. Six of the studies used population-based design and 1 study used hospital-based design. The genotype frequencies of the two polymorphisms were extracted from the studies. The *IL-4Rα* rs1801275 and the *IL13* rs20541 genotype distributions in the controls from all of the studies were conformed to Hardy–Weinberg equilibrium.

3.2. The IL-4Rα *rs1801275 polymorphism*

As shown in Table 2, the results of the meta-analysis did not suggest any statistical evidence of an association between the

Table 2
Meta-analysis of the *IL-4Rα* rs1801275 polymorphism and glioma risk association.

IL-4Rα rs1801275	Study	Sample size		*N*[a]	Test of association			Model[c]	Test of heterogeneity		
		Case	Control		OR (95% CI)	*Z*	*P* value		χ^2	*P*[b]	I^2 (%)
GG *vs.* AA[d]		1281	1415	3	0.66 (0.42–1.04)	1.81	0.071	F	1.13	0.567	0.0
AG *vs.* AA[d]		1281	1415	3	0.94 (0.80–1.11)	0.68	0.494	F	3.49	0.175	42.7
GG/AG *vs.* AA	Overall	1606	2998	7	0.99 (0.79–1.25)	0.06	0.951	R	14.77	0.022	59.4
	Asian	897	946	2	1.18 (0.97–1.43)	1.64	0.100	F	1.91	0.167	47.7
	Caucasian	709	2052	5	0.87 (0.72–1.04)	1.52	0.128	F	7.75	0.101	48.4
GG *vs.* AA/AG [d]		1281	1415	3	0.66 (0.42–1.04)	1.81	0.071	F	0.85	0.655	0.0

[a] Number of data sets included.
[b] *P* value of *Q*-test for heterogeneity test.
[c] Random-effects model (R) was used when *P* value for heterogeneity test <0.10; otherwise, fix-effects model (F) was used.
[d] Stratified analysis was not performed since only 3 studies (Refs. [16,18,19]) were included in the models.

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