SYSTEMATIC REVIEW

The Regulated upon Activation Normal T-cell Expressed and Secreted (*RANTES*) −28C/G and −403G/A Polymorphisms and Asthma Risk: A Meta-analysis

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Abstract

Background and Objectives Genetic studies have revealed that the regulated upon activation normal T-cell expressed and secreted (RANTES) −28C/G and −403G/A polymorphisms are associated with asthma risk, but contradictory findings have also been reported. Therefore, we undertook a meta-analysis on this topic.

Methods The PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases were used to identify relevant studies published in the medical literature from 1990 to March 26, 2014. Nine studies (containing 2,103 cases and 2,876 controls) investigated the −28C/G polymorphism, and 11 studies (including 2,015 cases and 1,909 controls) assessed the −403G/A polymorphism.

Results The pooled results demonstrated that the −28C/G polymorphism was not associated with asthma risk in the overall populations (Caucasians, Asians, and a mixed population). However, in subgroup analysis according to age, the −28G allele was associated with an increased risk of asthma in children (odds ratio [OR] 1.27, 95 % confidence interval [CI] 1.03–1.57, P value for heterogeneity $[P_{het}] = 0.163$, P value for the overall effect

$[P_z] = 0.028$). When we further stratified the studies performed in children on the basis of ethnicity, we found that the −28G allele was associated with an increased risk of asthma in Asian children (OR 1.28, 95 % CI 1.02–1.62, $P_{het} = 0.127$, $P_z = 0.035$), but not in Caucasian children (OR 1.20, 95 % CI 0.68–2.12, $P_{het} = 0.137$, $P_z = 0.530$). In subgroup analysis by asthma phenotype, no association between either atopic or non-atopic asthma and the −28C/G polymorphism was identified. For the −403G/A polymorphism, meta-analysis showed no association with asthma risk in the overall populations (Caucasians, Asians, and black people). In subgroup analyses by age, ethnicity, and asthma phenotype, we still did not find any association between the −403G/A polymorphism and asthma.

Conclusion Current findings suggest an association between the −28G allele and asthma risk in Asian children but not in Caucasian children.

> ### Key Findings
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> The G allele of the regulated upon activation normal T-cell expressed and secreted (*RANTES*) −28C/G polymorphism was associated with asthma risk in Asian children but not in Caucasian children
>
> The *RANTES* −403G/A polymorphism was not associated with asthma risk

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1 Introduction

Inflammatory leukocyte recruitment to the lung is a prominent pathological feature of asthma [1]. This process is directed by small inflammatory soluble molecules known as chemokines. Chemokines represent a large

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family of 8–15 kDa chemotactic proteins, which are subdivided into four groups on the basis of the relative position of their first N-terminal cysteine residues and are named CXC, CC, CX3C, and C [2]. Experimental and clinical studies have demonstrated an important role for chemokines in orchestrating multiple aspects of the inflammatory response in asthma, including induction of leukocyte migration, inflammatory mediator release, and promotion of T helper-2 (T_h2) inflammatory responses [3]. This accumulating evidence generates huge scientific interest in investigating the relationship between polymorphisms in chemokine genes and individual genetic predisposition to asthma.

The regulated upon activation normal T-cell expressed and secreted (RANTES) gene, which maps on 17 (q11.2–q12), is considered to be a candidate gene for asthma. Among identified single nucleotide polymorphisms (SNPs) in the RANTES gene, two mutations, a C to G substitution at position −28 (rs2280788) and a G to A substitution at position −403 (rs2107538) in the promoter region, are most frequently evaluated [4, 5]. The association between these two polymorphisms and asthma risk has been investigated in many genetic association studies; however, the results from individual studies remain inconsistent. Meta-analysis is a statistical technique that takes data from a number of independent studies and combines them to permit estimation of an overall effect. Up to now, several meta-analyses on these two SNPs and asthma risk have been performed [6–9], but their results still need to be assessed further. First, some eligible association studies were omitted. Second, studies presenting deviation from Hardy–Weinberg disequilibrium (HWE) in controls were not carefully evaluated, which may have resulted in bias and loss of precision in the estimation of the overall odds ratios (ORs). Third, some studies that had overlapped subjects were also included. Fourth, several new data sets have been published within the last three years. Thus, we conducted an updated meta-analysis to clarify the effect of the −28C/G and −403G/A polymorphisms in the RANTES gene on the risk of asthma.

2 Materials and Methods

2.1 Search Strategy

We used the PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang databases to identify relevant studies published in the medical literature from 1990 to March 26, 2014. The search terms included "Regulated upon Activation Normal T-cell Expressed and Secreted", "RANTES", "CCL5", "polymorphism", "genetic variant", "gene", and "asthma". The

search results were limited to publications in English or Chinese. The reference lists in all relevant publications were also hand searched to identify additional studies missed by the database search.

2.2 Inclusion and Exclusion Criteria

Studies were included in our meta-analysis if they met the following criteria: (1) studies on human subjects; and (2) studies reporting genotype or allele frequencies of the −28C/G or −403G/A polymorphisms in subjects with asthma and non-asthma controls. Studies were excluded if one of the following criteria existed: (1) no control; (2) no usable data reported; or (3) studies presenting deviation from HWE in controls.

2.3 Data Extraction

Assessment for eligibility of studies and extraction of data was performed by two independent investigators. Disagreement over eligibility of a study was resolved through evaluation by a third reviewer and discussion until a consensus was reached. For each study, the following data were extracted: (1) first author; (2) publication year; (3) country in which the study was performed; (4) ethnicity; (5) phenotype of asthma; (6) age of subjects; (7) sample size; and (8) individual genotypes and genotype counts in order of preference.

2.4 Statistical Analyses

All statistical tests were performed with Stata version 11.0 software. We used raw data on genotype frequencies, without adjustment for calculation of the study-specific estimates of odds ratios (ORs) and 95 % confidence intervals (CIs). Between-study heterogeneity was assessed by the Q statistic (Cochrane's Q), which is considered significant for $P < 0.1$. In the absence of heterogeneity, pooled estimation of ORs in each study was calculated by the fixed-effects model (Mantel–Haenszel methods) [10], while the random-effects model (DerSimonian and Laird's method) was used to calculate pooled ORs in the case of no significant heterogeneity [11]. The significance of overall ORs was determined by the Z test, with $P < 0.05$ considered statistically significant. For assessing the relation of the −28C/G and −403G/A polymorphisms to asthma risk, the dominant, recessive, homozygote, and allelic comparison models were employed. Subgroup analyses were conducted according to ethnicity, age, and asthma phenotype, respectively. Publication bias was evaluated using funnel plots and Egger's test. HWE in the controls for each study was tested by using a Web-based program (http://www.oege.org/software/hwe-mr-calc.html).

3 Results

3.1 Characteristics of the Included Studies

Figure 1 showed the process of identifying eligible studies. We retrieved 584 published studies, using our search criteria. After screening of the abstracts of these studies, 564 were excluded either because they were irrelevant, the record was a duplicate search result, or the study was not about human subjects. The remaining 20 studies were retrieved for more detailed evaluations, which excluded an additional six studies because no available data for genotypic distribution were reported [12, 13], the studies showed deviation from HWE in controls [14, 15], or the studies had overlapped subjects [16, 17], leaving 14 relevant publications to be included in the final analyses [18–31]. Table 1 shows the characteristics of the eligible studies included in this meta-analysis. Among them, nine studies (including a total of 2,103 cases and 2,876 controls) evaluated the −28C/G polymorphism [19, 21, 22, 24, 26–30], and 11 studies (containing 2,015 cases and 1,909 controls) assessed the −403G/A polymorphism [18–21, 23–27, 29, 31]. The study by Hizawa et al. [20] investigated both the −403G/A and −28C/G polymorphisms, but it had overlapped subjects with those from the study by Kaneko et al. [30], which assessed the −28C/G polymorphism with a larger sample size, so we excluded the data on the −28C/G polymorphism from the study by Hizawa et al. In addition, since the study by Liu et al. [30] presented a deviation from HWE in controls for the −28C/G polymorphism, we did not extract information on genotypic distribution for the −28C/G polymorphism from that study.

In terms of ethnicity, seven studies were conducted in Asians [21–24, 26, 30, 31], four studies were performed in Caucasians [18, 19, 27, 29], one study was undertaken in black people [25], and one study was conducted in a mixed population [28]. Table 2 summarized the genotypic distribution in each study.

3.2 Association Between the −28C/G Polymorphism and Asthma Risk

All of the eligible studies for this SNP presented no deviation from HWE in controls. Pooling data provided no evidence of a relationship between this polymorphism and asthma risk in the overall populations (Caucasians, Asians, and a mixed group) in the dominant model (OR 1.22, 95 % CI 0.74–2.00, P value for heterogeneity [P_{het}] = 0.276, P value for the overall effect [P_z] = 0.117), recessive model (OR 1.21, 95 % CI 0.81–1.81, P_{het} = 0.228, P_z = 0.346), homozygote model (OR 1.25, 95 % CI 0.84–1.87, P_{het} = 0.214, P_z = 0.277), and allelic comparison model (OR 1.12, 95 % CI 0.98–1.28, P_{het} = 0.222, P_z = 0.094) [Fig. 2]. In subgroup analysis stratified by ethnicity, we did not find an association between the −28C/G polymorphism and asthma risk in Caucasians (506 cases and 583 controls) and Asians (1,497 cases and 1,811 controls), respectively (Table 2). In the stratified analysis based on age, we found that the G allele was associated with an increased risk of asthma in children (OR 1.27, 95 % CI 1.03–1.57, P_{het} = 0.163, P_z = 0.028) [Table 2]. However, no association was identified in the dominant, recessive, and homozygote models (Table 2). When we further stratified studies performed in children according to

Fig. 1 Flow chart of the study selection process. *HWE* Hardy–Weinberg equilibrium
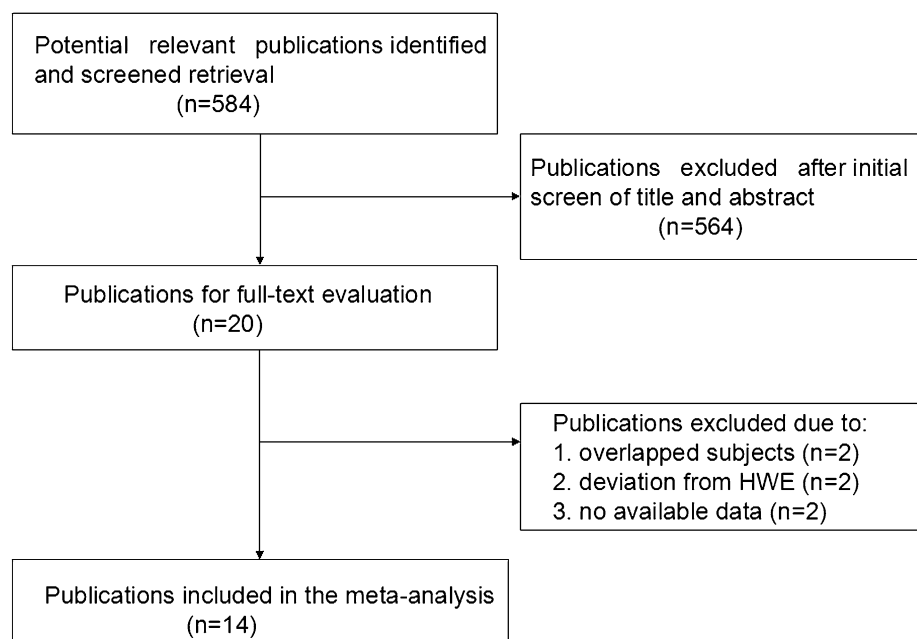
Table 1 Characteristics of included studies

First author of study	Year	Country or Area	Ethnicity	Asthma phenotype	Age	Patients (*n*)		Controls (*n*)	
						−403G/A	−28C/G	−403G/A	−28C/G
Fryer	2000	UK	Caucasians	Atopic and non-atopic	Adults	120	NE	74	NE
Szalai	2001	Hungry	Caucasians	Atopic and non-atopic	Children	160	160	303	303
Hizawa	2002	Japan	Asians	Atopic and non-atopic	Adults and Children	298	EX	311	EX
Yao	2003	Taiwan	Asians	NR	Children	182	182	107	107
Wang	2004	China	Asians	Atopic	Children	NE	100	NE	90
Leung	2005	Hong Kong	Asians	Atopic and non-atopic	Children	129	NA	66	NA
Moissidis	2005	USA	Black people	NR	Adults and Children	38	NA	131	NA
Liu	2005	China	Asians	NR	Children	32	32	32	32
Muro	2008	Spain	Caucasians	Atopic and non-atopic	Adults	306	242	306	242
Sohn	2008	Korea	Asians	Atopic and non-atopic	Children	326	253	326	253
Murk	2011	USA	Mixed	Atopic	Children	NE	100	NE	482
Nahas	2012	Lebanon	Caucasians	Atopic and non-atopic	Adults and Children	40	38	40	38
Kaneko	2013	Japan	Asians	Atopic and non-atopic	Adults and Children	NE	880	NE	1,329
Liu	2013	China	Asians	NR	Adults and Children	384	EX	384	EX

EX excluded, *NA* not applicable, *NE* not evaluated, *NR* not reported

ethnicity, we found that the G allele was associated with an increased risk of asthma in Asian children (OR 1.28, 95 % CI 1.02–1.62, $P_{het} = 0.127$, $P_z = 0.035$) but not in Caucasian children (OR 1.20, 95 % CI 0.68–2.12, $P_{het} = 0.137$, $P_z = 0.530$). Because of the limited availability of published results, we were unable to evaluate this SNP in adults. Finally, we conducted subgroup analysis according to asthma phenotype. There was no significant association between either atopic or non-atopic asthma and the −28C/G polymorphism (Table 2).

3.3 No Association Between the −403G/A Polymorphism and Asthma Risk

No deviation from HWE was observed in any of the 11 independent studies. We found no association between the −403G/A polymorphism and asthma risk in the overall populations (Caucasians, Asians, and black people) in the dominant model (OR 1.04, 95 % CI 0.91–1.19, $P_{het} = 0.202$, $P_z = 0.602$), recessive model (OR 1.15, 95 % CI 0.93–1.42, $P_{het} = 0.823$, $P_z = 0.206$), homozygote model (OR 1.17, 95 % CI 0.93–1.46, $P_{het} = 0.836$, $P_z = 0.183$), and allelic comparison model (OR 1.05, 95 % CI 0.95–1.17, $P_{het} = 0.356$, $P_z = 0.315$) [Fig. 3]. In subgroup analysis stratified by ethnicity, no association between the −403G/A

polymorphism and asthma risk was identified in Caucasians (626 cases and 625 controls) in the dominant model (OR 1.06, 95 % CI 0.82–1.36, $P_{het} = 0.037$, $P_z = 0.676$), recessive model (OR 1.31, 95 % CI 0.67–2.54, $P_{het} = 0.825$, $P_z = 0.428$), homozygote model (OR 1.33, 95 % CI 0.68–2.58, $P_{het} = 0.746$, $P_z = 0.402$), and allelic comparison model (OR 1.07, 95 % CI 0.86–1.34, $P_{het} = 0.077$, $P_z = 0.528$). We also did not find an association between the −403G/A polymorphism and asthma risk in Asians (1,351 cases and 1,153 controls), with similar ORs in these genetic models (Table 2). Age-specific analysis showed that the −403G/A polymorphism was not associated with asthma risk in either adults or children (Table 2). We further performed subgroup analysis according to asthma phenotype, finding that the −403G/A polymorphism was not associated with atopic or non-atopic asthma (Table 2).

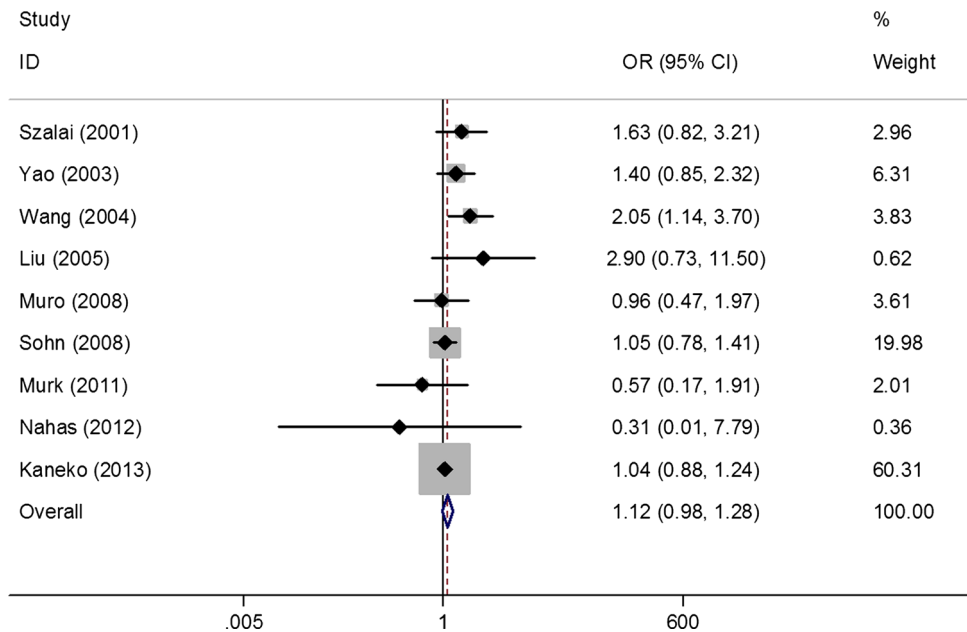### 3.4 Heterogeneity and Publication Bias

Table 3 shows between-study heterogeneity in detail. We found no heterogeneity in most analyses. We evaluated the −28C/G and −403G/A polymorphisms in the overall populations in the allelic comparison model for publication bias. Since publication bias was hard to detect when the number of studies were small, analysis for bias was not

Table 2 Genotypic distribution in cases and controls

Polymorphism	Cases					Controls					HWE
−28C/G	**CC**	**CG**	**GG**	**C allele**	**G allele**	**CC**	**CG**	**GG**	**C allele**	**G allele**	
Szalai (2001)	144	16	0	304	16	284	19	0	587	19	Yes
Yao (2003)	134	39	9	307	57	83	23	1	189	25	Yes
Wang (2004)	65	31	4	161	39	72	17	1	161	19	Yes
Liu (2005)	25	6	1	56	8	29	3	0	61	3	Yes
Muro (2008)	289	17	0	595	17	228	14	0	470	14	Yes
Sohn (2008)	218	93	15	529	123	174	66	13	414	92	Yes
Murk (2011)	98	1	1	197	3	457	25	0	939	25	Yes
Nahas (2012)	40	0	0	80	0	37	1	0	75	1	Yes
Kaneko (2013)	625	210	22	1,460	254	984	310	35	2,278	380	Yes
−403G/A	**GG**	**GA**	**AA**	**G allele**	**A allele**	**GG**	**GA**	**AA**	**G allele**	**A allele**	
Fryer (2000)	75	39	6	189	51	35	6	1	76	8	Yes
Szalai (2001)	122	32	6	276	44	211	84	8	506	100	Yes
Hizawa (2002)	146	108	44	400	196	140	137	34	417	205	Yes
Yao (2003)	98	65	19	261	103	60	41	6	161	53	Yes
Leung (2005)	60	53	16	173	85	37	21	8	95	37	Yes
Moissidis (2005)	13	21	4	47	29	35	72	24	142	120	Yes
Liu (2005)	17	13	2	47	17	16	14	2	46	18	Yes
Muro (2008)	202	93	11	497	115	165	69	8	399	85	Yes
Sohn (2008)	109	146	71	364	288	97	107	49	301	205	Yes
Nahas (2012)	30	10	0	70	10	30	8	0	68	8	Yes
Liu (2013)	148	186	50	482	286	149	183	52	481	287	Yes

HWE Hardy–Weinberg equilibrium

Fig. 2 Meta-analysis with a fixed-effects model for the association between the −28C/G polymorphism and asthma risk in the overall populations in the allelic comparison model (G allele versus C allele). *CI* confidence interval, *OR* odds ratio

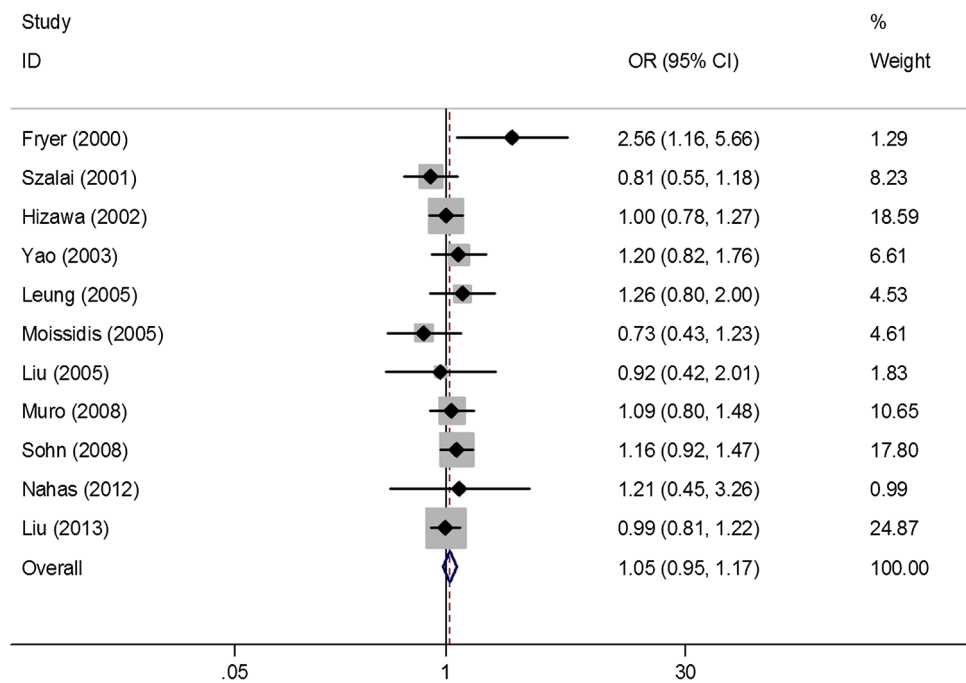| Study ID	OR (95% CI)	% Weight
Szalai (2001)	1.63 (0.82, 3.21)	2.96
Yao (2003)	1.40 (0.85, 2.32)	6.31
Wang (2004)	2.05 (1.14, 3.70)	3.83
Liu (2005)	2.90 (0.73, 11.50)	0.62
Muro (2008)	0.96 (0.47, 1.97)	3.61
Sohn (2008)	1.05 (0.78, 1.41)	19.98
Murk (2011)	0.57 (0.17, 1.91)	2.01
Nahas (2012)	0.31 (0.01, 7.79)	0.36
Kaneko (2013)	1.04 (0.88, 1.24)	60.31
Overall	1.12 (0.98, 1.28)	100.00

carried out in the subgroup analyses. The shapes of the funnel plots seemed to be symmetrical (Fig. 4). The P values for the −28C/G polymorphism (P = 0.437) and the −403G/A polymorphism (P = 0.511) were not significant.

4 Discussion

The main findings of this meta-analysis were as follows: (1) there was no significant association between the *RANTES* −28C/G SNP and asthma risk in the overall

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Fig. 3 Meta-analysis with a fixed-effects model for the association between the −403G/A polymorphism and asthma risk in the overall populations in the allelic comparison model (A allele versus G allele). *CI* confidence interval, *OR* odds ratio

Study ID	OR (95% CI)	% Weight
Fryer (2000)	2.56 (1.16, 5.66)	1.29
Szalai (2001)	0.81 (0.55, 1.18)	8.23
Hizawa (2002)	1.00 (0.78, 1.27)	18.59
Yao (2003)	1.20 (0.82, 1.76)	6.61
Leung (2005)	1.26 (0.80, 2.00)	4.53
Moissidis (2005)	0.73 (0.43, 1.23)	4.61
Liu (2005)	0.92 (0.42, 2.01)	1.83
Muro (2008)	1.09 (0.80, 1.48)	10.65
Sohn (2008)	1.16 (0.92, 1.47)	17.80
Nahas (2012)	1.21 (0.45, 3.26)	0.99
Liu (2013)	0.99 (0.81, 1.22)	24.87
Overall	1.05 (0.95, 1.17)	100.00

.05   1   30

populations; (2) in subgroup analysis according to age and ethnicity, the G allele of the −28C/G polymorphism was associated with an increased risk of asthma in Asian children but not in Caucasian children; and (3) no association between the *RANTES* −403G/A polymorphism and asthma risk was identified in the overall populations. In subgroup analysis based on ethnicity, age, and asthma phenotype, we still did not find an association.

As increased infiltration of inflammatory cells into the lung is closely associated with development of asthma, the involvement of RANTES in asthma has attracted considerable interest. In vitro and animal studies have demonstrated that RANTES is a major chemotactic factor produced during the asthmatic response and contributes to exacerbation of allergic airway inflammation [32–34]. Increased levels of RANTES were observed in bronchial lavage fluid from patients with active asthma [35]. In addition, significantly higher plasma levels of RANTES were also detected in asthmatic patients during acute attacks [36]. Thus, the *RANTES* gene is thought to be a candidate gene for asthma susceptibility. The −28C/G and −403G/A polymorphisms are two functional variants that increase transcriptional activity and subsequent RANTES expression in human cell lines. In this meta-analysis, we first identified a positive association between the G allele of the −28C/G variant and asthma risk in Asian children but not in Caucasian children. It was reported that the −28G allele was associated with elevated *RANTES* messenger RNA and protein expression, an increased blood eosinophil count, and a higher degree of bronchial hyper-responsiveness. Therefore, it may increase the individual

genetic predisposition to develop asthma. The discrepancy of the −28G allele association between Asian children and Caucasian children indicated that this SNP may have different effects on asthma risk according to the ethnic genetic background. In subgroup analysis according to age, because of the limited availability of published results, we were unable to investigate the association between the −28G allele and asthma in adults. We expect that as more studies become available, an accurate estimation of the relationship between the −28G allele and asthma in adults will be obtained.

Two previous meta-analysis obtained similar findings for the −28C/G polymorphism [7, 8]. With a smaller number of subjects, a meta-analysis by Fang et al. [7] found an association between the −28G allele and asthma risk in Asians. An ethnicity-specific meta-analysis [8] reported an association between the −28C/G polymorphism and asthma in Chinese populations. However, neither of those two meta-analyses further stratified Asian subjects according to age to assess the relationship between the −28C/G polymorphism and asthma. Therefore, they were unable to simultaneously evaluate the impact of ethnicity and age, which were considered to be the two most important factors accounting for heterogeneity in the *RANTES* association with asthma risk. The Lu et al. meta-analysis [9] focused on the association between the *RANTES* polymorphisms and the risk of pediatric asthma. However, because of the small number of subjects, that meta-analysis did not identify a significant association between the *RANTES* polymorphisms and pediatric asthma in Asians and Caucasians. The Zhang et al. meta-analysis

Table 3 Meta-analysis of regulated upon activation normal T-cell expressed and secreted (*RANTES*) polymorphisms and asthma risk[a]

| Polymorphism	Dominant			Recessive			Homozygote			Allelic comparison		
	OR (95 % CI)	P_{het}	P_z	OR (95 % CI)	P_{het}	P_z	OR (95 % CI)	P_{het}	P_z	OR (95 % CI)	P_{het}	P_z
−28C/G[b]												
Total	1.22 (0.74–2.00)	0.276	0.117	1.21 (0.81–1.81)	0.228	0.346	1.25 (0.84–1.87)	0.214	0.277	1.12 (0.98–1.28)	0.222	0.094
Subanalysis by ethnicity												
Caucasians	1.22 (0.74–2.00)	0.391	0.435	NA	NA	NA	NA	NA	NA	1.21 (0.74–1.97)	0.405	0.443
Asians	1.14 (0.97–1.33)	0.229	0.105	1.16 (0.77–1.74)	0.350	0.474	1.20 (0.80–1.80)	0.312	0.388	1.12 (0.98–1.29)	0.111	0.096
Subanalysis by age												
Children	1.27 (1.00–1.62)	0.185	0.052	1.59 (0.86–2.94)	0.188	0.140	1.67 (0.90–3.10)	0.184	0.105	1.27 (1.03–1.57)	0.163	**0.028**
Subanalysis by phenotype												
Atopic asthma	1.14 (0.85–1.52)	0.105	0.384	1.23 (0.62–2.43)	0.140	0.547	1.14 (0.57–2.29)	0.419	0.703	1.13 (0.89–1.44)	0.133	0.308
Non-atopic asthma	1.15 (0.70–1.90)	0.612	0.588	NA	NA	NA	NA	NA	NA	1.03 (0.78–1.36)	0.827	0.818
−403G/A[c]												
Total	1.04 (0.91–1.19)	0.202	0.602	1.15 (0.93–1.42)	0.823	0.206	1.17 (0.93–1.46)	0.836	0.183	1.05 (0.95–1.17)	0.356	0.315
Subanalysis by ethnicity												
Caucasians	1.06 (0.82–1.36)	0.037	0.676	1.31 (0.67–2.54)	0.825	0.428	1.33 (0.68–2.58)	0.746	0.402	1.07 (0.86–1.34)	0.077	0.528
Asians	1.05 (0.89–1.23)	0.556	0.587	1.17 (0.93–1.48)	0.741	0.174	1.20 (0.93–1.53)	0.852	0.155	1.07 (0.95–1.20)	0.814	0.274
Subanalysis by age												
Adults	1.30 (0.93–1.80)	0.041	0.120	1.24 (0.54–2.87)	0.566	0.615	1.35 (0.58–3.12)	0.443	0.489	1.25 (0.94–1.66)	0.047	0.130
Children	1.06 (0.86–1.31)	0.269	0.571	1.24 (0.90–1.72)	0.864	0.193	1.35 (0.95–1.91)	0.948	0.095	1.09 (0.93–1.29)	0.487	0.277
Subanalysis by phenotype												
Atopic asthma	1.29 (0.99–1.67)	0.127	0.057	1.14 (0.77–1.68)	0.863	0.513	1.29 (0.85–1.98)	0.791	0.236	1.19 (0.98–1.45)	0.146	0.077
Non-atopic asthma	1.23 (0.87–1.71)	0.296	0.258	1.32 (0.75–2.34)	0.733	0.340	1.35 (0.73–2.51)	0.721	0.343	1.21 (0.92–1.58)	0.286	0.171

CI confidence interval, *NA* not available, *OR* odds ratio, P_{het} *P* value for heterogeneity, P_z *P* value for the overall effect

[a] Significant associations are indicated in bold text

[b] For the −28C/G polymorphism: dominant is GG + CG versus CC; recessive is GG versus CG + CC; homozygote is GG versus CC; and allelic comparison is G allele versus C allele

[c] For the −403G/A polymorphism: dominant is AA + GA versus GG; recessive is AA versus GA + GG; homozygote is AA versus GG; and allelic comparison is A allele versus G allele

Fig. 4 a Begg's funnel plot for the −28C/G polymorphism and asthma risk under allelic comparison model; **b** Begg's funnel plot for the −403G/A polymorphism and asthma risk under allelic comparison model. *logor* log(odds ratio), *s.e.* standard error
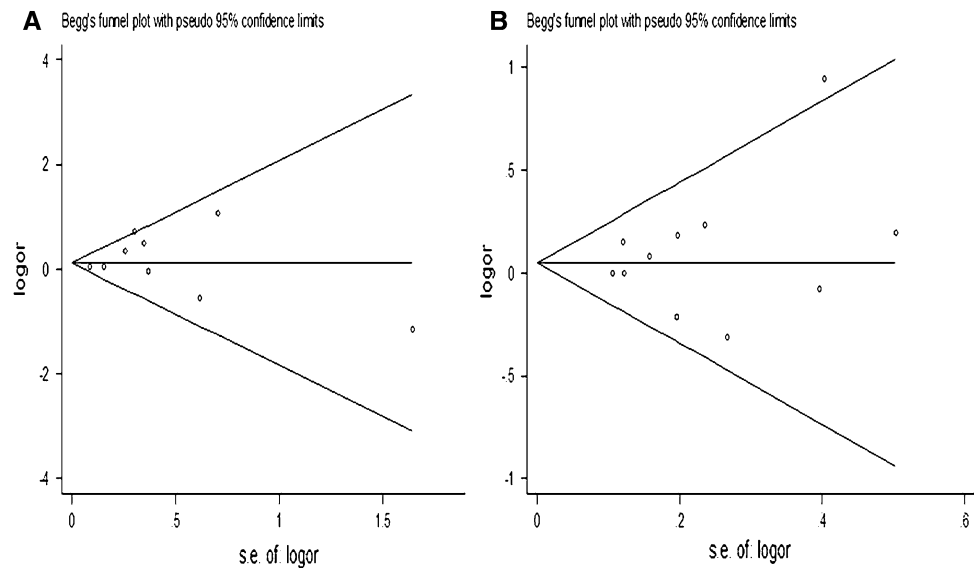
[6] summarizing studies on the relation of the two *RANTES* SNPs, published up until November 2009, found an association between the −403G/A polymorphism and atopic asthma. However, four new studies have been published since 2009, dramatically increasing the numbers of asthma patients and controls with relevant genetic information [28–31]. In our updated meta-analysis including the newly available published studies, we did not find an association between either atopic or non-atopic asthma and the two *RANTES* polymorphisms.

This meta-analysis represents an updated and comprehensive review of the literature on the two most studied *RANTES* polymorphisms and asthma risk. There were some advantages in this study. Besides performing pooled analysis in the overall populations, we also conducted subgroup analyses based on ethnicity, age, and asthma phenotype. In order not to miss any potential literatures, besides electronic databases, we manually searched the reference lists in all relevant publications. We excluded studies containing overlapped subjects with a smaller sample size. For example, the Tölgyesi study [17] was excluded from our analysis in that it had overlapped subjects with those of the Szalai study [19]. The study by Huang [16] was also excluded for a similar reason. In addition, we excluded studies deviating from HWE in controls. Two studies were excluded for this reason [14, 15]. In terms of between-study heterogeneity and publication bias, most analyses showed no or very low heterogeneity, and there was no evidence of publication bias. Therefore, the results of our study were reliable to some extent.

Some limitations of this meta-analysis should be mentioned. First, the small sample size in some of the included studies might have influenced the statistical power to better evaluate the association between the −28C/G and −403G/A polymorphisms and asthma risk, especially in subgroup analysis. Second, because of the limited availability of published results, gene–gene and gene–environment interactions were not analyzed in this meta-analysis. Third, we evaluated only the −28C/G and 403G/A polymorphisms. It is also possible that other polymorphisms in the *RANTES* gene influence the risk of asthma.

5 Conclusion

The results of our meta-analysis demonstrate that the G allele of the *RANTES* −28C/G polymorphism is associated with an increased risk of asthma in Asian children but not in Caucasian children. There is no association between the *RANTES* −403G/A polymorphism and asthma risk.

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