Association between Interleukin-4 Receptor α Chain (IL4RA) I50V and Q551R Polymorphisms and Asthma Risk: An Update Meta-Analysis

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Abstract

Background: The associations between the interleukin-4 receptor α chain (IL4RA) I50V and Q551R polymorphisms and asthma risk remained controversial.

Methods: We searched the Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang databases for studies published before February 2013. The strengths of the associations were calculated using odds ratios (ORs) with 95% confidence intervals (CIs).

Results: A total of 50 studies were included in this meta-analysis. There was a significant association between the IL4RA I50V polymorphism and asthma risk in a dominant genetic model (OR = 1.13, 95% CI 1.04–1.23, P = 0.005). The IL4RA Q551R polymorphism was associated with a significantly elevated asthma risk in a recessive genetic model (OR = 1.46, 95% CI 1.22–1.75, P<0.0001). Subgroup analyses found that the IL4RA I50V polymorphism was significantly associated with asthma risk in Asians (OR = 1.72, 95% CI 1.31–2.25, P<0.0001), pediatric asthma risk (OR = 1.50, 95% CI 1.13–1.99, P = 0.005), and atopic asthma risk (OR = 1.88, 95% CI 1.27–2.79, P = 0.002).

Conclusions: The results of this meta-analysis suggested that the IL4RA I50V and Q551R polymorphisms may be risk factors for developing asthma.

Introduction

Asthma is a complex, persistent, inflammatory disease characterized by airway hyper-responsiveness and inflammation. Asthma currently represents a major public health burden in many countries [1]. Thus an understanding of the causes of this disease is an area of intense interest. Cumulative evidence supports an important genetic role in determining asthma risk [2].

T helper-2 (Th2) cytokines, such as interleukin-4 (IL-4) and IL-13, play central roles in allergic inflammation and asthma. They exert their biological activities by binding to their respective cell surface receptors, both of which share the α chain of the IL-4 receptor (IL4Rα) [3]. Kotsimbos et al. [4] showed that expression levels of IL4Rα messenger RNA and protein were significantly increased in the epithelium and subepithelium of biopsy specimens from subjects with atopic asthma, compared with atopic control subjects. Additionally, IL4Rα-deficient mice were unable to produce immunoglobulin E (IgE) and the Th2 inflammatory reaction was markedly diminished [5]. Furthermore, IL4Rα-targeted antibodies could reduce lung inflammation, airway hyper-responsiveness and goblet-cell hyperplasia in mice models of asthma [6]. Therefore, these results indicated that IL-4Rα may play an important role in the pathogenesis of asthma and suggested that IL4RA may be a strong candidate gene for asthma susceptibility.

IL4RA is located on chromosome 16p12.1. Many studies have investigated the associations between the IL4RA polymorphisms and susceptibility to asthma [7–56]. Most of these studies focused on two polymorphisms: I50V (rs1805010) and Q551R (rs1801275). However, the results of these studies have been controversial and inconclusive. A single study may not have sufficient power to detect slight effects of these polymorphisms on asthma because of relatively small sample sizes; however, a meta-analysis may provide more credible evidence by systematically summarizing the existing data. In 2007, Loza and Chang conducted a meta-analysis and concluded that IL-4RA Q551R polymorphism, but not the I50V polymorphism, was associated with asthma risk [57]. However, that meta-analysis only included 13 studies, and several new studies with more data have been published since 2007. We therefore conducted an up-to-date...
meta-analysis to re-investigate the association between \textit{IL4RA} polymorphisms and asthma risk.

\textbf{Methods}

\textbf{Publication search}

A literature search of the PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases was conducted for studies published before February 2013 using combinations of the following terms: (asthma or asthmatic) and (interleukin-4 receptor \( \alpha \) chain or IL-4R\( \alpha \) or IL4R\( \alpha \) or IL4RA) and (polymorphism or mutation or variant). All eligible articles were retrieved, and their references were checked for other relevant studies.

\textbf{Study selection}

All selected studies complied with the following three criteria: (1) evaluation of the \textit{IL4RA} I50V and Q551R polymorphisms and asthma risk; (2) using a case-control design; and (3) genotype distributions in both cases and controls available for estimating an odds ratio (OR) with a 95\% confidence interval (CI). If serial studies of the same population from the same group were reported, the largest study was included.

\textbf{Data extraction}

Two investigators (Nie and Chen) independently extracted data from the included studies. The following information was collected from each study: first author’s name, year of publication, original country, ethnicity, age group, atopic status, sample size, and genotype number in cases and controls. We verified the accuracy of the data by comparing collection forms between investigators. If different results were generated, the full text of the article was checked.

\textbf{Qualitative assessment}

The quality of included studies was assessed independently by two investigators (Nie and Chen). \textbf{Table S1} shows the criteria for quality appraisal. The quality scoring system was based on traditional epidemiological considerations and asthma genetic issues [58]. The criteria covered the representativeness of cases and controls, the ascertainment of cases and controls, genotyping examination, Hardy-Weinberg equilibrium (HWE), and association assessment. Scores ranged from the lowest zero to the highest thirteen.

\textbf{Statistical analysis}

A meta-analysis was performed when data from at least three similar studies were available. The strengths of the associations between the \textit{IL4RA} polymorphisms and asthma risk were measured by ORs and 95\% CIs. The statistical significance of summary OR was determined using the \( Z \) test. OR1, OR2, and OR3 were calculated for the genotypes: 1) II vs. VV (OR1), IV vs. VV (OR2), and II vs. IV (OR3) for the I50V polymorphism, 2). RR vs. QQ (OR1), QR vs. QQ (OR2), and RR vs. QR (OR3) for the Q551R polymorphism. These pairwise differences were used to indicate the most appropriate genetic model [59–63]. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a co-dominant model) and to pool the results.

HWE was evaluated using the Chi-square test. \( P<0.05 \) was considered representative of a departure from HWE. Heterogeneity of effects across studies was assessed using the Chi-square statistic and quantified by \( I^2 \), which represented the percentage of total variation across studies that was attributable to heterogeneity rather than chance \( (P<0.10 \) was considered representative of statistically significant heterogeneity). A fixed-effect model was used when there was no heterogeneity in the studies. Otherwise, the random-effect model was used. Subgroup analyses were performed by stratifying according to ethnicity, age group, and atopic status. The stability of the results was assessed by performing a sensitivity analysis using sequential omission of individual studies. A cumulative meta-analysis was conducted by undertaking sequential pooling, starting with the earliest studies. Funnel plots were performed to estimate the potential publication bias, with an asymmetrical plot suggesting a possible publication bias. The asymmetry was assessed using the Egger’s linear
Table 1. Characteristics of the case-control studies included in meta-analysis.

| First author/Year/Country/Ethnicity/Group/Age | Atopic status | Case (n) | Control (n) | IL4RA polymorphism | Score |
|-----------------------------------------------|---------------|---------|-------------|---------------------|-------|
| Mitsuyasu [7] 1998 Japan Asian Mixed* | Mixed*         | 360     | 120         | IS0V               | 7     |
| Mitsuyasu [8] 1999 Japan Asian Mixed* | Mixed*         | 300     | 100         | QS51R              | 7     |
| Noguchi [9] 1999 Japan Asian Mixed | Atopic         | 101     | 101         | IS0V               | 9     |
| Rosa-Rosa [10] 1999 USA Caucasian Adults | Mixed*         | 149     | 57          | QS51R              | 7     |
| Heinzmann [11] 2000 Japan Asian Adults | Mixed*         | 200     | 100         | QS51R              | 8     |
| Sandford [12] 2000 Canada Caucasian Adults | NA            | 221     | 143         | QS51R              | 10    |
| Takabayashi [13] 2000 Japan Asian Children | Atopic         | 100     | 100         | IS0V, QS51R        | 7     |
| Hakonarson [14] 2001 Iceland Caucasian Mixed | Atopic         | 94      | 94          | QS51R              | 10    |
| Howard [15] 2002 Netherlands Caucasian Adults | NA            | 151     | 114         | IS0V, QS51R        | 9     |
| Leung [16] 2002 China Asian Children | NA            | 76      | 70          | IS0V               | 9     |
| Mújica-López [17] 2002 Mexico Mexican Children | Atopic         | 30      | 32          | IS0V               | 6     |
| Risma [18] 2002 USA Caucasian Adults | Mixed*         | 200     | 65          | IS0V, QS51R        | 7     |
| Beghe [19] 2003 USA Caucasian Mixed | Atopic         | 186     | 670         | IS0V, QS51R        | 7     |
| Cui [20] 2003 China Asian Mixed | Atopic         | 241     | 175         | QS51R              | 7     |
| Hytonen [21] 2004 Sweden Caucasian Adults | Atopic         | 170     | 100         | IS0V, QS51R        | 6     |
| Lee [22] 2004 Korea Asian Children | Mixed*         | 256     | 100         | IS0V, QS51R        | 9     |
| Yang [23] 2004 China Asian Adults | NA            | 34      | 29          | IS0V               | 5     |
| Isidoro-García [24] 2005 Spain Caucasian Adults | Mixed*         | 133     | 79          | QS51R              | 8     |
| Hu [25] 2005 China Asian Children | Atopic         | 175     | 175         | QS51R              | 6     |
| Sun [26] 2005 China Asian Children | NA            | 82      | 59          | QS51R              | 6     |
| Bernstein [27] 2006 USA Caucasian Adults | NA            | 62      | 75          | IS0V, QS51R        | 9     |
| Kabesch [28] 2006 Germany Caucasian Children | NA            | 73      | 773         | IS0V               | 9     |
| Melen [29] 2006 Sweden Caucasian Children | NA            | 521     | 509         | IS0V, QS51R        | 7     |
| Deng [30] 2006 China Asian Mixed | NA            | 100     | 100         | IS0V               | 6     |
| Gui [31] 2006 China Asian Children | NA            | 50      | 50          | QS51R              | 7     |
| Tang [32] 2006 China Asian Mixed | NA            | 103     | 62          | IS0V               | 5     |
| Battle [33] 2006 USA African American Mixed | NA            | 264     | 176         | IS0V               | 11    |
| López [34] 2007 Mexico Mexican Children | NA            | 88      | 88          | IS0V, QS51R        | 7     |
| Mak [45] 2007 China Asian Adults | Mixed*         | 285     | 291         | QS51R              | 9     |
| Zhang [36] 2007 China Asian Adults | NA            | 303     | 355         | IS0V, QS51R        | 8     |
| Zhang [37] 2007 China Asian Mixed | NA            | 423     | 114         | IS0V, QS51R        | 7     |
| Chan [38] 2008 China Asian Children | NA            | 295     | 167         | IS0V               | 9     |
| de Faria [39] 2008 Brazil Mixed Children | Atopic         | 88      | 202         | IS0V               | 6     |
| Liu [40] 2008 China Asian Adults | NA            | 108     | 88          | QS51R              | 5     |
| Trajkov [41] 2008 Macedonia Caucasian Adults | NA            | 74      | 249         | QS51R              | 8     |
| Sun [42] 2008 China Asian Adults | NA            | 82      | 50          | QS51R              | 6     |
| Amirzargar [43] 2009 Iran Caucasian Children | NA            | 59      | 139         | QS51R              | 8     |
| Llanes [44] 2009 Spain Caucasian Adults | Atopic         | 109     | 50          | IS0V, QS51R        | 8     |
| Wang [45] 2009 China Asian Children | NA            | 449     | 512         | IS0V, QS51R        | 10    |
| Xu [46] 2009 China Asian Children | NA            | 128     | 82          | IS0V, QS51R        | 7     |
| Beghe [47] 2010 UK Italy Caucasian Adults | Mixed*         | 299     | 176         | IS0V, QS51R        | 9     |
| Berce [48] 2010 Slovenia Caucasian Children | Mixed*         | 106     | 89          | QS51R              | 8     |
| Bottema [49] 2010 Netherlands Caucasian Adults | Atopic         | 118     | 102         | IS0V, QS51R        | 9     |
| Michel [50] 2010 German Caucasian | NA            | 703     | 658         | IS0V               | 11    |
| Undarmaa 1 [51] 2010 Japan Asian Children | Atopic         | 325     | 336         | IS0V, QS51R        | 9     |
| Undarmaa 2 [51] 2010 Japan Asian Adults | Atopic         | 367     | 676         | IS0V, QS51R        | 9     |
| Wu [52] 2010 China Asian Children | NA            | 252     | 227         | IS0V, QS51R        | 8     |
| Fan [53] 2010 China Asian Adults | NA            | 62      | 30          | QS51R              | 5     |
regression test and \( P < 0.05 \) was considered to represent statistically significant publication bias [64]. All statistical tests were performed using STATA 11.0 software (Stata Corporation, College Station, TX). The Bonferroni correction of critical \( P \) values for two genetic models was applied when performing a high number of comparisons.

**Results**

**Study characteristics**

Fifty studies met the inclusion criteria [7–56]. A flowchart detailing the process for study identification and selection is shown in Figure 1. A study by Undarmaa et al. [51] presented two independent case-control studies, each of which was considered separately for analysis. There were 33 studies of the IL4V polymorphism and 35 36 studies of the Q551R polymorphism. Twenty-seven studies were performed in Asians, 19 in Caucasians, two in Mexicans, and one in African Americans. Nineteen studies were performed in adults, and 21 in children. Twelve studies included atopic asthma patients and nine included both atopic and non-atopic asthma patients, but data for these patients could be extracted separately. The quality scores ranged from 5 to 11, suggesting that the methodological quality was generally acceptable. The characteristics of each study are presented in Table 1. Genotype frequencies and HWE examination results are listed in Table 2. Seven studies were not in HWE, and these studies were not included in the meta-analysis.

**Quantitative data synthesis**

**IL4RA I50V polymorphism.** Thirty studies investigated the association between the I50V polymorphism and asthma risk. The total sample sizes for case and control groups were 6442 and 7240, respectively. The estimated OR1, OR2 and OR3 values were 1.14 (\( P = 0.08 \)), 1.09 (\( P = 0.06 \)), and 1.06 (\( P = 0.35 \)), respectively (Table 3). These estimates suggested a dominant genetic model; therefore II and IV were combined and compared with VV. The pooled OR was 1.13 (95% CI 1.04–1.23, \( P = 0.005 \)) (Figure 2). There was no significant heterogeneity \( (I^2 = 5\%, P = 0.38) \). In the stratified analysis by ethnicity, no significant association was found for the studies in Asians (OR = 1.23, 95% CI 1.05–1.45, \( P = 0.01 \)) or Caucasians (OR = 1.10, 95% CI 0.96–1.26, \( P = 0.15 \)). In the subgroup analysis by age, the IL4RA I50V polymorphism was not associated with pediatric asthma risk (OR = 1.15, 95% CI 1.03–1.29, \( P = 0.01 \)) or adult asthma risk (OR = 1.08, 95% CI 0.91–1.27, \( P = 0.39 \)). In the subgroup analysis according to atopic status, the IL4RA I50 V polymorphism was not significantly associated with the risk of atopic asthma (OR = 1.19, 95% CI 1.01–1.40, \( P = 0.04 \)) or non-atopic asthma risk (OR = 0.92, 95% CI 0.63–1.35, \( P = 0.67 \)).

Cumulative meta-analyses were conducted. A tendency toward significant association with asthma risk was found (Figure S1). We performed a sensitivity analysis to evaluate the stability of the meta-analysis. As shown in Figure S2, the statistical significance of the result was not altered when any single study was omitted. The funnel plot did not reveal evidence of obvious asymmetry (Figure S3). The result was further supported by Egger’s test (\( P = 0.601 \)).

**IL4RA Q551R polymorphism.** Thirty-two studies identified an association between the IL4RA Q551R polymorphism and asthma risk. A total of 6750 cases and 8594 controls were included in this meta-analysis. The estimated OR1, OR2 and OR3 values were 1.46 (\( P = 0.002 \)), 1.11 (\( P = 0.05 \)), and 1.35 (\( P = 0.002 \)), respectively (Table 3). Thus, these estimates suggested a recessive genetic model; therefore QR and QQ were combined and compared with RR. The pooled OR was 1.46 (95% CI 1.22–1.75, \( P < 0.0001 \)) (Figure 3). No significant heterogeneity was observed \( (I^2 = 16\%, P = 0.21) \). Subgroup analysis was performed by ethnicity. Statistically significant findings were found in Asians (OR = 1.72, 95% CI 1.31–2.25, \( P < 0.0001 \)) but not in Caucasians (OR = 1.09, 95% CI 0.86–1.38, \( P = 0.48 \)). In the stratified analysis by age group, a statistically significantly increased asthma risk was found among children (OR = 1.50, 95% CI 1.13–1.99, \( P = 0.005 \)), but no significant risk was found among adult asthmatic patients (OR = 1.36, 95% CI 1.00–1.84, \( P = 0.05 \)). In terms of atopic status, we found a significant association between this polymorphism and atopic asthma risk (OR = 1.88, 95% CI 1.27–2.79, \( P = 0.002 \)). However, there was no significant association with non-atopic asthma (OR = 1.90, 95% CI 0.94–3.84, \( P = 0.07 \)). Evidence from a cumulative meta-analysis showed that the results were consistent over time (Figure S4). A sensitivity analysis showed no substantial modification of the estimates after exclusion of individual studies (Figure S5). The shape of the funnel plot was symmetrical (Figure S6). Egger’s test indicated the absence of publication bias \( (P = 0.773) \).

**Discussion**

On the basis of 50 eligible case-control studies, this meta-analysis comprehensively evaluated the association between the IL4RA I50V and Q551R polymorphisms and asthma risk. In terms of the IL4RA I50V polymorphism, we found that individuals with the 50I allele \( (\text{II} \text{ or IV}) \) showed an increased risk of asthma in the overall population. However, in the subgroup analyses based on ethnicity, age group, and atopic status, no significant associations were observed after Bonferroni correction. A significant association was also noted for the IL4RA Q551R polymorphism. This result suggests that individuals carrying the RR genotype had an increased asthma risk. There is no significant
difference in the frequencies of IL4RA Q551R alleles between Asians and Caucasians with asthma (http://asia.ensembl.org); however, analysis stratified by ethnicity showed a significant association with asthma in Asians, but not in Caucasians. It is possible that different lifestyles, diets, and environments may account for this apparent discrepancy. These issues should be investigated in future studies. In the subgroup analysis stratified by age group, the IL4RA Q551R polymorphism was associated with increased pediatric asthma risk. These results demonstrate that even the same variant in the same gene may have a different effect on the pathogenesis and occurrence of asthma in different individuals. To the best of our knowledge, no previous study has assessed the age-specific influence of IL4RA Q551R on asthma risk, and further studies are needed to address the effect of this polymorphism on asthma risk in different age groups. We also carried out a subgroup analysis according to atopic status. There was a significant association between this polymorphism and atopic asthma risk, suggesting that the IL4RA Q551R polymorphism may play a role in the etiology of atopic asthma. IgE-mediated immune responses are best known for their involvement in allergies. Cornejo-Garcia et al. [65] showed that the IL4RA Q551R polymorphism was associated with IgE against prevalent

Table 2. Distribution of IL4RA I50V and Q551R polymorphisms among patients and controls.

| IL4RA I50V | Asthma | Control | HWE (P value) |
|------------|--------|---------|---------------|
| II IV VV   | II IV VV |         |               |
| Mitsuyasu  | 142 125 93 | 20 57 43 | 0.880         |
| Noguchi    | 10 57 34 | 16 44 41 | 0.470         |
| Takabayashi | 17 49 34 | 16 36 48 | 0.048         |
| Howard     | 30 53 26 | 25 42 20 | 0.770         |
| Leung      | 23 38 15 | 19 35 16 | 0.968         |
| Mujica-López | 15 13 2 | 19 11 2 | 0.811         |
| Risma      | 67 98 35 | 20 32 13 | 0.975         |
| Beghe      | 46 101 39 | 199 340 131 | 0.509 |
| Hytonen    | 28 49 23 | 29 51 20 | 0.777         |
| Lee        | 54 133 69 | 20 51 29 | 0.777         |
| Yang       | 6 21 7 8 | 16 5 3 | 0.534         |
| Bernstein  | 24 29 9 | 19 43 13 | 0.182         |
| Kabesch    | 25 32 16 | 256 375 142 | 0.820 |
| Melen      | 169 256 96 | 148 253 108 | 0.995 |
| Deng       | 24 47 29 | 9 33 58 | 0.189         |
| Tang       | 33 36 34 | 18 23 21 | 0.044         |
| Battle     | 76 131 55 | 56 86 32 | 0.919         |
| López      | 29 42 17 | 34 47 15 | 0.852         |
| Zhang W    | 84 154 65 | 99 180 76 | 0.729         |
| Zhang H    | 78 168 106 | 17 53 44 | 0.873         |
| Chan       | 79 159 57 | 49 80 38 | 0.626         |
| de Faria   | 20 52 16 | 67 96 39 | 0.661         |
| Llanes     | 35 52 22 | 16 23 11 | 0.617         |
| Wang       | 139 201 105 | 136 250 124 | 0.667 |
| Xu         | 50 54 24 | 18 43 21 | 0.649         |
| Beghe      | 84 149 66 | 51 88 37 | 0.933         |
| Bottema    | 34 59 25 | 30 51 21 | 0.937         |
| Michel     | 162 351 190 | 122 322 214 | 0.964 |
| Undarmaa 1 | 133 150 42 | 127 159 50 | 0.984         |
| Undarmaa 2 | 138 174 55 | 238 326 112 | 0.984         |
| Wu         | 46 131 75 | 59 110 58 | 0.642         |
| Murk       | 28 49 23 | 142 236 106 | 0.670 |
| Su         | 80 101 54 | 280 505 290 | 0.048         |
| IL4RA Q551R | RR QR QQ | RR QR QQ |               |
| Mitsuyasu  | 7 76 217 1 | 21 78 78 | 0.751         |
| Rosa-Rosa  | 19 49 81 | 1 20 36 | 0.339         |
| Heinzmann  | 16 80 104 5 | 34 61 92 | 0.926         |
| Sandford   | 7 69 145 5 | 43 95 961 | 0.961         |
| Takabayashi | 2 27 71 | 5 16 79 | 0.003         |
| Hakonarson | 3 28 63 4 | 37 57 505 | 0.505         |
| Howard     | 8 39 104 5 | 36 73 834 | 0.834         |
| Risma      | 19 84 97 | 3 20 42 | 0.765         |
| Beghe      | 11 62 114 36 | 229 404 635 | 0.635 |
| Cui        | 23 89 129 4 | 41 130 720 | 0.720         |
| Hytonen    | 6 35 59 3 | 30 67 871 | 0.871         |
| Lee        | 9 58 189 5 | 11 84 800 | 0.000         |

Table 2. Cont.

| IL4RA I50V | Asthma | Control | HWE (P value) |
|------------|--------|---------|---------------|
| II IV VV   | II IV VV |         |               |
| Isidoro-Garcia | 1 41 91 | 4 26 49 | 0.820         |
| Hu         | 19 66 90 | 4 41 130 | 0.720         |
| Sun        | 4 19 59 | 3 10 46 | 0.033         |
| Bernstein  | 4 17 40 | 2 30 43 | 0.222         |
| Melen      | 28 184 309 | 25 174 310 | 0.927 |
| Gui        | 2 15 33 | 2 14 34 | 0.716         |
| López      | 8 39 49 | 6 42 38 | 0.215         |
| Mak        | 4 81 200 | 9 91 191 | 0.642         |
| Zhang W    | 19 87 197 | 22 93 240 | 0.003         |
| Zhang H    | 8 87 257 | 0 27 87 | 0.152         |
| Liu        | 15 79 54 | 0 78 10 | 0.000         |
| Trakov     | 3 27 44 | 11 78 212 | 0.262         |
| Sun        | 2 15 65 | 0 8 42 | 0.539         |
| Amirzargar | 1 25 32 | 2 30 106 | 0.941         |
| Llanes     | 3 37 69 | 2 14 34 | 0.716         |
| Wang       | 9 112 326 | 12 140 360 | 0.710         |
| Xu         | 8 49 71 | 2 29 51 | 0.364         |
| Beghe      | 14 103 182 | 8 58 110 | 0.920         |
| Berce      | 6 28 72 | 6 27 56 | 0.285         |
| Bottema    | 7 43 68 | 7 41 54 | 0.835         |
| Undarmaa 1 | 7 73 245 | 8 86 242 | 0.913         |
| Undarmaa 2 | 12 102 253 | 10 154 512 | 0.681         |
| Wu         | 8 61 183 | 4 55 168 | 0.837         |
| Fan        | 6 8 48 | 3 2 25 | 0.000         |
| GeMDBJ     | 20 194 556 | 46 588 1741 | 0.655         |
| Murk       | 16 38 45 | 31 186 263 | 0.806         |

HWE, Hardy-Weinberg equilibrium. doi:10.1371/journal.pone.0069120.t002
Table 3. Determination of the genetic effects of IL4RA polymorphisms on asthma and subgroup analysis.

| Polymorphisms | Study          | Sample size | No. of Test of association | Heterogeneity |
|---------------|----------------|-------------|-----------------------------|---------------|
|               |                | case | control | studies | OR (95 % CI) | Z     | p Value | Model | $\chi^2$ | p Value | I² (%) |
| IL4RA I50V    | Overall        | 3314 | 3707 | 29    | 1.14 (0.98–1.33) | 1.76  | 0.08 | R       | 51.82 | 0.006 | 44.0   |
|               | IV vs. VV      | 4564 | 5172 | 29    | 1.09 (1.00–1.20) | 1.90  | 0.06 | F       | 18.52 | 0.93  | 0.0    |
|               | II vs. IV      | 5006 | 5601 | 29    | 1.06 (0.94–1.19) | 0.94  | 0.35 | R       | 45.83 | 0.02  | 37.0   |
|               | II+IV vs. VV   | 6442 | 7420 | 29    | 1.13 (1.04–1.23) | 2.78  | 0.005 | F       | 30.63 | 0.38  | 5.0    |
|               | II+IV vs. VV   | 3394 | 2987 | 14    | 1.23 (1.05–1.45) | 2.51  | 0.01 | R       | 21.06 | 0.07  | 38.0   |
|               | II+IV vs. VV   | 2480 | 3265 | 11    | 1.10 (0.96–1.27) | 1.44  | 0.15 | F       | 5.71  | 0.84  | 0.0    |
|               | II+IV vs. VV   | 3500 | 4366 | 15    | 1.15 (1.03–1.29) | 2.46  | 0.01 | F       | 16.56 | 0.28  | 15.0   |
|               | II+IV vs. VV   | 1821 | 1835 | 11    | 1.08 (0.91–1.27) | 0.86  | 0.39 | R       | 5.13  | 0.88  | 0.0    |
|               | II+IV vs. VV   | 1919 | 2368 | 12    | 1.19 (1.01–1.40) | 2.10  | 0.04 | F       | 9.13  | 0.61  | 0.0    |
|               | II+IV vs. VV   | 235  | 285  | 3     | 0.92 (0.63–1.35) | 0.42  | 0.67 | F       | 0.78  | 0.68  | 0.0    |
| IL4RA Q551R   | RR vs. QQ      | 4702 | 6144 | 32    | 1.46 (1.15–1.87) | 3.05  | 0.002 | R       | 44.54 | 0.05  | 30.0   |
|               | QR vs. QQ      | 6441 | 8326 | 32    | 1.11 (1.00–1.24) | 1.92  | 0.05 | R       | 53.54 | 0.007 | 42.0   |
|               | RR vs. QR      | 2357 | 2718 | 32    | 1.35 (1.12–1.63) | 3.11  | 0.002 | F       | 24.09 | 0.81  | 0.0    |
|               | RR vs. QR+QQ   | 6750 | 8594 | 32    | 1.46 (1.22–1.75) | 4.14  | <0.0001 | F     | 37.07 | 0.21  | 16.0   |
|               | RR vs. QQQ+QQ  | 3974 | 5263 | 14    | 1.72 (1.31–2.25) | 3.91  | <0.0001 | F     | 17.54 | 0.18  | 26.0   |
|               | RR vs. QQ      | 2642 | 3185 | 17    | 1.09 (0.86–1.38) | 0.71  | 0.48 | F       | 11.96 | 0.75  | 0.0    |
|               | RR vs. QQ      | 2357 | 2784 | 12    | 1.50 (1.13–1.99) | 2.78  | 0.005 | F       | 14.21 | 0.22  | 23.0   |
|               | RR vs. QQ      | 2749 | 2479 | 16    | 1.36 (1.00–1.84) | 1.98  | 0.05 | F       | 16.32 | 0.36  | 8.0    |
|               | RR vs. QQ      | 2533 | 2868 | 16    | 1.88 (1.27–2.79) | 3.15  | 0.002 | R       | 22.95 | 0.09  | 35.0   |
|               | RR vs. QQ      | 445  | 747  | 7     | 1.77 (0.97–3.23) | 1.85  | 0.06 | F       | 6.41  | 0.38  | 6.0    |

Bonferroni correction was applied (P<0.00714). vs., versus; R, random-effects model; F, fixed-effects model; HWE, Hardy-Weinberg equilibrium.

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Figure 2. Meta-analysis for the association between asthma risk and the IL4RA I50V polymorphism.
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allergens and with total IgE. The \textit{IL4RA} Q551R polymorphism may therefore be a relevant marker for allergies and atopic asthma development.

\textit{IL-4R} α has been shown to play a pivotal role in the pathogenesis of Th2 inflammation and asthma. For example, Kelly-Welch et al. [66] reported that \textit{IL-4R}α-deficient mice engrafted with bone marrow derived from \textit{IL-4R}α-expressing mice failed to develop goblet-cell metaplasia in response to allergic airway inflammation. In addition, deletion of the gene encoding \textit{IL-4R}α rendered mice resistant to the induction of experimental allergic asthma [67]. Mitsuyasu et al. [7] documented that the \textit{IL-4R}α 50I variant significantly upregulated the receptor response to IL-4, with resultant increased activation of STAT6, and hence increased cell proliferation and increased IgE production. Furthermore, Rosenwasser et al. [68] showed that peripheral blood mononuclear cells derived from individuals carrying the 551R variant had enhanced IL-4 responsiveness compared with 551Q. It is therefore possible that these two polymorphisms could influence the susceptibility to asthma. The 50I and 551Q variants may be associated with increased asthma risk. The results of this meta-analysis strongly support this hypothesis.

A previous meta-analysis by Loza and Chang has focused on the relationship between these polymorphisms and asthma risk [57], and concluded that the I50 V polymorphism was not significant associated with asthma. However, only six studies of the I50 V polymorphism were included in that meta-analysis. A positive association between this polymorphism and asthma could therefore not be ruled out, because studies with small sample sizes may have had insufficient statistical power to detect any slight effect. Our current meta-analysis included 30 studies (6442 cases and 7240 controls), and found a moderate but significant association. Furthermore, this meta-analysis addressed the methodological issues such as cumulative meta-analysis and sensitivity analysis.

Results from our meta-analysis were stable and reliable. First, sensitivity analyses and cumulative meta-analyses revealed that the results were robust. Second, there was no significant heterogeneity in most of the comparisons. Third, funnel plots and Egger’s tests found no significant publication bias. However, some limitations should be addressed. First, the numbers of published studies involving African Americans and Mexicans were limited. Second, the overall outcome was based on unadjusted data, whereas a baseline risk-adjusted analysis could be performed if individual data were available to allow adjustment. Third, asthma is a complex disease with multifactorial etiology. A lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and gene-environment interactions during asthma development. These gene-environment and gene-gene interactions should be further evaluated. Fourth, even though no significant
publication bias was found by funnel plot analysis and formal statistical tests, it was impossible to exclude potential publication bias completely, because small studies with null results tend not to be published. Finally, all the studies included in this meta-analysis used a case-control design, which was susceptible to recall and selection biases. In addition, there was a risk of residual confounding by unmeasured factors.

In conclusion, this meta-analysis found significant associations between the IL4RA I50V and Q551R polymorphisms and asthma risk. Further studies in more ethnic groups, especially African Americans and Mexicans, are warranted to validate these results.

Supporting Information

Figure S1 Cumulative meta-analysis of associations between the IL4RA I50V polymorphism and asthma risk. (TIFF)

Figure S2 Sensitivity analysis for the IL4RA I50V polymorphism with asthma risk. (TIFF)

Figure S3 Funnel plot for asthma risk and the IL4RA I50V polymorphism. (TIFF)

Figure S4 Cumulative meta-analysis of associations between the IL4RA R551Q polymorphism and asthma risk. (TIFF)

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