Interleukin-10 Promoter Gene Polymorphisms and Susceptibility to Asthma: A Meta-Analysis

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Abstract

Objective: The aim of this study was to explore whether the interleukin (IL)-10 polymorphisms and their haplotypes contribute to asthma susceptibility.

Methods: MEDLINE, EMBASE and the COCHRANE library databases were utilized to identify available articles. A meta-analysis was conducted on IL-10 -1082 G/A, -819 C/T, -592 C/A polymorphisms, and their haplotypes and asthma.

Results: Eleven studies involving 2,215 asthma patients and 2,170 controls were considered in the meta-analysis. The meta-analysis revealed no association between asthma and the IL-10 -1082 G allele [Odds ratio (OR) = 0.87, 95% Confidence interval (CI) = 0.68–1.12, p = 0.28]. However, meta-analysis of the five studies in Hardy-Weinburg equilibrium produced the relationship between the IL-10 -1082 G allele and asthma (OR = 0.71, 95% CI = 0.60–0.83, p < 0.0001). Stratification by ethnicity indicated an association between the IL-10 -1082 G allele and asthma in East Asians (OR = 0.74, 95% CI = 0.57–0.96, p = 0.02), but not in West Asians. Furthermore, stratification by age indicated an association between the IL-10 -1082 G allele and asthma in adults and mixed groups (OR = 0.77, 95% CI = 0.62–0.96, p = 0.02; OR = 0.67, 95% CI = 0.49–0.92, p = 0.01). No association was found between asthma and IL-10 -819 C/T and IL-10 -592 C/A polymorphisms and their haplotypes.

Conclusion: The IL-10 -1082 G/A polymorphism confers susceptibility to asthma in East Asians and in adults. However, the IL-10 -819 C/T, -592 C/A polymorphisms and their haplotypes are not associated with asthma.

Introduction

Asthma is a chronic respiratory disease that is characterized by variable airway obstructions caused by bronchial hyperreactivity [1]. The development of asthma is determined by the interaction between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2]. Although the etiology of asthma remains unknown, an imbalance between host genetic susceptibility and environment [2].
Methods

Identification of Eligible Studies and Data Extraction
We conducted an exhaustive search for studies that examined the association of IL-10 polymorphisms with asthma. We utilized the MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify available articles published up to August 2012 in which IL-10 polymorphisms were studied in asthma patients and controls. The Medical Subject Heading (MeSH) terms and/or text words that were entered were ‘asthma’ or ‘bronchial spasm’ or ‘respiratory hypersensitivity’ or ‘wheezing’, and in combination with ‘polymorphism’ or ‘variant’ or ‘genotype’ or ‘allele’ or ‘mutation’, and in combination with ‘interleukin 10’ or ‘interleukin-10’ or ‘IL-10’ or ‘IL10’ (Supplement S1). Furthermore, all references mentioned in the identified original articles were reviewed by hand-searching in order to investigate additional literature that was not indexed. Genetic association studies that observed the distribution of IL-10 genotypes in asthma patients and controls were eligible for inclusion. Studies were included in this meta-analysis if (1) they were case-control studies, (2) they contained original data and (3) they provided enough data to calculate odds ratios (ORs). There are no restrictions were placed on language, race, ethnicity or geographic area. We excluded the following: (1) studies containing overlapping data; (2) studies in which the number of null and wild genotypes or alleles could not be ascertained and (3) studies in which family members had been studied because their analysis was based on linkage considerations. The PRISMA Checklist and the flow chart for the studies are shown as Supplement S2 and Supplement S3 in the supporting information.

Data were extracted from original studies by two independent reviewers (M.H.H. and C.H.L.) regarding the methods and results of meta-analysis. Discrepancy between the reviewers was resolved by consensus or a third reviewer (Y.H.L). From each study, we extracted following information: first author, year of publication, racial descent and age of the study population, the number of cases and controls, definition of asthma patients, and genotype and allele frequency information for IL-10 polymorphisms.

Quality Score Assessment
The quality of studies was also independently assessed by the two reviewers (M.H.H. and C.H.L.) who used quality assessment scores of molecular association studies of asthma recommended by Thakkinstian et al (Supplement S4) [28]. These scores were based on both traditional epidemiologic considerations and genetic issues [29]. Total scores ranged from 0 (worst) to 15 (best). Any disagreement was adjudicated by a third author (Y.H.L.). Low quality studies, quality score ≤4, were excluded.

Evaluation of Publication Bias
Funnel plots are commonly used to detect publication bias. However, this method requires a range of studies with varying sizes and subjective judgments. Due to these limitations, we evaluated publication bias using Egger’s linear regression test [30], which measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

Statistical Analysis
Allele frequencies at the IL-10 polymorphisms were determined by the allele counting method. The Chi-square test was used to determine if observed frequencies of genotypes in controls conformed to Hardy-Weinberg (H-W) expectations.

Meta-analysis was executed using (1) allelic contrast and (2) recessive, (3) dominant and (4) homozygote contrasts. Point estimates of risks, ORs, and 95% confidence intervals (CI) were estimated for each study. Cochran’s Q-statistic was also used to assess within- and between study variations and heterogeneity was quantified using $I^2$, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance [31]. $I^2$ values of 25, 50, and 75% were nominally considered low, moderate, and high estimates. The fixed effects model assumes that a genetic factor has a similar effect on asthma susceptibility across all studies are caused by chance alone [32]. Alternatively, the random effects model assumes that different studies shows substantial diversity and assesses both within-study sampling errors and between-study variances [33]. If the result of the heterogeneity was test was p>0.10, ORs were pooled according to the fixed effect model. Otherwise random effect model was used. Statistical manipulations were performed using a Comprehensive Meta-analysis computer program Review Manager 5.1 (Cochrane Collaboration, London, UK).

Results

Studies Included in the Meta-analysis
The flow diagram in Figure 1 outlines of selection process. Briefly, a total 263 articles were identified after eliminating 47 duplications. Two designated reviewers independently excluded definite irrelevant articles. Twenty three articles were enrolled for peer review. After review of the full-text articles, 12 publications were excluded from the meta-analysis for the following reasons: four did not report detailed genotype frequencies, five had family-based study designs, and three did not report case-control studies. Consequently, a total of 11 eligible publications were included in this meta-analysis with a total sample size of 2215 asthma subjects.
Table 1. Characteristics of the individual studies included in the systemic review and meta-analysis.

| Study [Ref] | Population | Numbers | Age | Asthma definition | Studied polymorphism | Findings† | Quality score |
|-------------|------------|---------|-----|-------------------|----------------------|-----------|--------------|
| Hakimizadeh et al. 2012 [14] | Iran (WA) | 100 | 100 | Mixed ATS criteria | − 592 C/A | − 592 C allele (OR = 3.88, P = 0.001) | 11 |
| Hussein et al. 2011 [15] | Egypt (WA) | 220 | 110 | Children ATS criteria | − 1082 G/A | − 1082 A allele (OR = 1.7, P = 0.01 in atopic asthma, OR = 1.6, P = 0.018 in non-atopic asthma) | 2 |
| Kim et al. 2011 [16] | Korea (EA) | 333 | 248 | Children ATS criteria | − 1082 G/A, − 819 C/T, − 592 C/A, Haplotype* | − 1082 G/A allele (P = NS), − 819 C/T (P = NS), − 592 C/A (P = NS), Haplotype (P = NS) | 9 |
| Trajkov et al. 2009 [17] | Macedonia (EU) | 74 | 301 | Adult NIH criteria | − 1082 G/A, − 819 C/T, − 592 C/A, Haplotype* | − 1082 GG vs. GA+AA (OR = 2.896, P = 0.007), − 819 C/T (P = NS), − 592 C/A (P = NS), Haplotype (P = NS) | 7† |
| Movahedi et al. 2008 [18] | Iran (WA) | 60 | 140 | Children NAEP guideline | − 1082 G/A, − 819 C/T, − 592 C/A, Haplotype* | − 1082 G allele (OR = 1.83, P = 0.008), − 819 T allele (OR = 2.30, P = 0.001), − 592 A allele (OR = 2.37, P = 0.001), ATA haplotype (OR = 2.33, P = 0.001) | 7† |
| Zedan et al. 2008 [19] | Egypt (WA) | 69 | 98 | Children Symptoms, GINA guideline | − 1082 G/A | − 1082 G/A allele (NS), GG vs. GA+AA (OR = 7, 95% CI = 2.4–20, P<0.0001) | 9† |
| Chatterjee et al. 2005 [20] | India (I) | 273 | 307 | Adult NAEP guideline | − 1082 G/A, − 819 C/T, − 592 C/A, Haplotype* | − 1082 A allele (OR = 1.267, P = 0.03), − 819 C/T (P = NS), − 592 A allele (OR = 1.318, P = 0.04), ATA haplotype (OR = 1.385, P = 0.0085) | 11 |
| Park et al. 2004 [21] | Korea (EA) | 532 | 170 | Mixed ATS criteria | − 1082 G/A, − 592 C/A, Haplotype* | − 1082 G/A (P = NS), − 592 C/A (P = NS), ACC Haplotype vs. others (P = NS) | 12 |
| Karjalainen et al. 2003 [22] | Finland (EU) | 242 | 395 | Adult Doctor’s diagnosis | Haplotype* | Haplotype (P = NS) | 9 |
| Hang et al. 2003 [23] | Taiwan (EA) | 117 | 47 | Mixed Symptoms, PFT | Promoter −592 C/A | − 592 AC vs. CC (OR = 1.833, 95% CI = 1.675–13.940), AA vs. CC (OR = 3.599, P = 0.013) | 7 |
| Lim et al. 1998 [24] | UK (EU) | 195 | 241 | Mixed Symptoms, Asthma severity | Haplotype* | ATA haplotype vs. others (OR = 1.5, P = 0.01 in severe asthma, P = NS in mild asthma) | 9 |

Ref references, Vs. versus, NS not significant, WA West Asian, EA East Asian, EU European, OR odds ratio, CI confidential interval, PFT pulmonary function test, ATS american thoracic society, NAEP national asthma education and prevention program, GINA global initiative for asthma, NIH national institute of health.
†Odds ratio indicated asthma versus control group.
*Haplotype of IL-10 -1082 G/A, -819 C/T and -592 C/A.
^Hardy-Weinberg equilibrium in deviation in control groups.

Table 1.jpg
Figure 2. ORs and 95% CIs of individual studies and pooled data for the association between IL-10 -1082 G/A polymorphism and asthma for studies in Hardy-Weinberg equilibrium. (A) G vs. A allele (B) GG vs. GA+AA (recessive) (C) GG+GA vs. AA (dominant model) (D) GG vs. AA (Homozygote contrast).

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Table 2. Meta-analysis of association between the IL-10 -1082 G/A polymorphism and asthma.

| Population | No | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het |
|------------|----|-------------|-------|--------|-------------|-------|--------|-------------|-------|--------|-------------|-------|--------|
| Overall    | 8  | 0.87 (0.68–1.28) | <0.01 | 0.69 | 0.85 (0.38–1.90) | <0.01 | 0.72 (0.49–1.06) | <0.01 | 0.66 (0.38–1.16) | 0.24 | 0.05 |
| In HWE*    | 5  | 0.71 (0.60–0.83) | <0.001 | 0.66 | 0.58 (0.40–0.83) | 0.003 | 0.51 | 0.70 (0.57–0.85) | <0.001 | 0.58 | 0.45 (0.30–0.68) | <0.001 | 0.80 |
| Subgroup by ethnicity | | | | | | | | | | | | | |
| EA         | 3  | 0.74 (0.57–0.96) | 0.02 | 0.49 | 0.32 (0.14–0.71) | 0.005 | 0.71 | 0.79 (0.59–1.06) | 0.12 | 0.31 | 0.35 (0.15–0.80) | 0.01 | 0.83 |
| WA         | 3  | 1.13 (0.57–2.25) | 0.73 | 0.73 | 2.08 (0.40–10.7) | 0.38 | <0.01 | 1.53 (0.20–11.4) | 0.68 | <0.01 | 0.97 (0.15–6.25) | 0.97 | 0.01 |
| Subgroup by age | | | | | | | | | | | | | |
| Adult      | 2  | 0.77 (0.62–0.96) | 0.02 | 0.67 | 1.42 (0.36–5.64) | 0.62 | <0.01 | 0.62 (0.47–0.83) | 0.001 | 0.13 | 0.91 (0.39–2.11) | 0.82 | 0.13 |
| Child      | 4  | 1.07 (0.64–1.76) | 0.80 | <0.01 | 0.88 (0.18–4.30) | 0.87 | <0.01 | 1.09 (0.37–3.20) | 0.87 | <0.01 | 0.78 (0.22–2.75) | 0.70 | 0.04 |
| Mixed      | 2  | 0.67 (0.49–0.92) | 0.01 | 0.59 | 0.28 (0.12–0.69) | 0.006 | 0.52 | 0.72 (0.50–1.04) | 0.08 | 0.21 | 0.31 (0.12–0.79) | 0.01 | 0.67 |

No number, Vs. versus, OR odds ratio, CI confidential interval, P_eff P value of pooled effect, P_Het P value of heterogeneity test. HWE Hardy-Weinberg equilibrium, EA East Asian, WA West Asian.

*Random effects model was used when P_Het <0.1; otherwise, fixed effects model was used.

Three studies of control groups were deviated from Hardy-Weinberg equilibrium.

Table 3. Meta-analysis of association between the IL-10 -819 C/T polymorphism and asthma.

| Population | No | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het | OR (95% CI) | P_eff | P_Het |
|------------|----|-------------|-------|--------|-------------|-------|--------|-------------|-------|--------|-------------|-------|--------|
| Overall†  | 4  | 0.78 (0.58–1.04) | 0.09 | 0.02 | 0.54 (0.25–1.16) | 0.11 | <0.01 | 0.95 (0.75–1.22) | 0.70 | 0.34 | 0.84 (0.60–1.18) | 0.31 | 0.68 |
| Subgroup by age | | | | | | | | | | | | | |
| Adult     | 2  | 0.84 (0.69–1.03) | 0.09 | 0.95 | 0.76 (0.57–1.02) | 0.06 | 0.62 | 0.84 (0.57–1.23) | 0.37 | 0.71 | 0.71 (0.46–1.10) | 0.13 | 0.73 |
| Child     | 2  | 0.68 (0.30–1.53) | 0.35 | <0.01 | 0.20 (0.00–8.61) | 0.41 | <0.01 | 1.04 (0.76–1.43) | 0.81 | 0.10 | 1.07 (0.63–1.84) | 0.80 | 0.90 |

No number, Vs. versus, OR odds ratio, CI confidential interval, P_eff P value of pooled effect, P_Het P value of heterogeneity test.

†Random effects model was used when P_Het <0.1; otherwise, fixed effects model was used.

*All studies were in Hardy-Weinberg equilibrium in control group.

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IL-10 Polymorphisms and Asthma

A summary of findings concerning the associations between IL-10 -819 C/T polymorphism and asthma is shown in Table 3. Four studies with 740 asthmatic subjects and 996 control subjects were included in this meta-analysis. No association was found between asthma and IL-10 -819 C/T polymorphism using the allele contrast, recessive, dominant, or homozygote contrast (OR for C allele = 0.78, 95% CI = 0.58–1.04, p = 0.09) (Table 3). In addition, meta-analysis stratified by age revealed no association between asthma and IL-10 -819 C/T polymorphism (Table 3).

IL-10 -592 C/A Polymorphism and Asthma

Six publications (1372 asthmatic subjects and 1266 control subjects) reported on the genotype frequency of IL-10 -592 C/A polymorphism and asthma (Table 4). Meta-analysis of the IL-10 -592 C/A polymorphism showed no association between asthma and IL-10 -592 C/A polymorphism (Table 4). Meta-analysis of homozygous GCC, ACC, ATA haplotypes failed to show a significant association with asthma (OR = 0.97, 95% CI = 0.77–1.23, p = 0.97; OR = 1.00, 95% CI = 0.80–1.25, p = 0.97; OR = 1.25, 95% CI = 0.97–1.60, p = 0.08, respectively). Subgroup analysis based on ethnicity and age did not show statistical significance between GCC, ACC, ATA haplotypes and asthma risk (Table 4). In the stratified analysis by ethnicity, no association was found between asthma and IL-10 -592 C/A polymorphisms in East Asian, and West Asian groups, only except for West Asians using homozygote contrast (OR = 5.70, 95% CI = 2.38–13.6, p<0.0001) (Table 4).

IL-10 Promoter Haplotype and Asthma

Three single nucleotide polymorphisms (SNPs) at the promoter region (−1082 G/A, −819 C/T and −592 C/A) were in complete linkage disequilibrium and three haplotypes were present (GCC, ACC, ATA). Seven case-control studies (1802 asthmatic subjects and 1709 control subjects) were included on the relationship between IL-10 promoter haplotype and the susceptibility of asthma (Table 5). Meta-analysis of homozygous GCC, ACC, ATA haplotypes failed to show a significant association with asthma (OR = 0.97, 95% CI = 0.77–1.23, p = 0.81; OR = 1.00, 95% CI = 0.80–1.25, p = 0.97; OR = 1.25, 95% CI = 0.97–1.60, p = 0.08, respectively). Subgroup analysis based on ethnicity and age did not show statistical significance between GCC, ACC, ATA haplotypes and asthma risk (Table 5).

Table 4. Meta-analysis of association between the IL-10 -592 C/A polymorphism and asthma.

| Population | No | −592 C/A C vs. A | CC vs. CA+AA (Recessive) | CC+CA vs. AA (Dominant) | CC vs. AA (Additive) |
|------------|----|-----------------|--------------------------|-------------------------|---------------------|
|            | OR (95% CI) | P_eff | P_het | OR (95% CI) | P_eff | P_het | OR (95% CI) | P_eff | P_het |
| Overall    | 6  | 1.01 (0.66–1.54) | 0.98 | <0.01 | 1.01 (0.96–1.06) | 0.52 | <0.01 | 1.01 (0.77–1.31) | 0.52 | <0.01 |
| Subgroup by ethnicity | | | | | | | | | | |
| EA         | 2  | 0.96 (0.80–1.14) | 0.64 | 0.36 | 0.95 (0.67–1.35) | 0.77 | 0.50 | 0.97 (0.80–1.17) | 0.74 | 0.55 |
| WA         | 2  | 1.28 (1.14–1.17) | 0.83 | <0.01 | 0.35 (0.00–206.1) | 0.75 | <0.01 | 1.24 (0.92–1.66) | 0.15 | 0.80 |
| Subgroup by age | | | | | | | | | | |
| Adult      | 2  | 0.82 (0.67–1.00) | 0.05 | 0.46 | 0.79 (0.62–1.02) | 0.07 | 0.50 | 0.96 (0.78–1.16) | 0.65 | 0.65 |
| Child      | 2  | 0.67 (0.28–1.63) | 0.38 | <0.01 | 0.18 (0.00–15.2) | 0.45 | <0.01 | 1.06 (0.85–1.33) | 0.58 | 0.56 |
| Mixed      | 2  | 1.83 (0.43–7.82) | 0.42 | <0.01 | 1.88 (0.38–9.34) | 0.44 | <0.01 | 1.02 (0.81–1.27) | 0.89 | 0.17 |

No number, Vs. versus, OR odds ratio, CI confidential interval, P_eff P value of pooled effect, P_het P value of heterogeneity test, EA East Asian, WA West Asian. 

Table 5. Meta-analysis of association between the IL-10 promoter haplotype (−1082 G/A, −819 C/T, −592 C/A) and asthma.

| Population No | GCC vs. others | ACC vs. others | ATA vs. others |
|---------------|----------------|----------------|----------------|
| OR (95% CI)   | P_eff | P_het | OR (95% CI) | P_eff | P_het | OR (95% CI) | P_eff | P_het |
| Overall       | 6   | 0.97 (0.77–1.23) | 0.81 | <0.01 | 7   | 1.00 (0.80–1.25) | 0.97 | <0.01 | 6   | 1.25 (0.97–1.60) | 0.08 | <0.01 |
| Subgroup by ethnicity | | | | | | | | | | |
| EU            | 3   | 0.86 (0.65–1.14) | 0.28 | 0.05 | 3   | 1.03 (0.87–1.22) | 0.70 | 0.78 | 3   | 1.14 (0.95–1.36) | 0.17 | 0.11 |
| EA            | 1   | NA | NA | 2   | 1.08 (0.89–1.31) | 0.43 | 0.47 | 1   | NA | NA |
| Subgroup by age | | | | | | | | | | |
| Adult          | 3   | 0.95 (0.81–1.11) | 0.51 | 0.30 | 3   | 1.00 (0.86–1.17) | 0.97 | 0.84 | 3   | 1.16 (0.99–1.37) | 0.06 | 0.10 |
| Child          | 2   | 1.37 (0.74–2.52) | 0.32 | 0.05 | 2   | 0.15 (0.00–22.1) | 0.45 | <0.01 | 2   | 1.41 (0.54–3.65) | 0.48 | <0.01 |
| Mixed          | 1   | NA | NA | 2   | 1.04 (0.85–1.27) | 0.71 | 0.70 | 1   | NA | NA |

No number, Vs. versus, OR odds ratio, CI confidential interval, P_eff P value of pooled effect, P_het P value of heterogeneity test, EU European, EA East Asian, NA not applicable. 

1Random effects model was used when P_het <0.1; otherwise, fixed effects model was used. 

*One study was only available for ACC haplotype frequency [21]. 

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Heterogeneity and Publication Bias

Some between-study heterogeneity was found during the meta-analyses, but no evidence of heterogeneity was found for analyses of IL-10 -1082 G/A, -819 C/T and -592 C/A polymorphisms. It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was small. Egger's regression test showed no evidence of publication bias in this meta-analysis (Egger's regression test p>0.1). The distributions of genotypes in the normal control groups were not consistent with the H-W equilibrium in three studies of the IL-10 -1082 G/A polymorphism [17–19]. Deviation from H-W equilibrium among controls implies potential bias during control selection, or genotyping errors, but excluding these studies did affect our result for an association between the IL-10 -1082 G/A polymorphism and asthma (Table 2, Figure 2). All studies were in H-W equilibrium for the IL-10 -819 C/T and -592 C/A polymorphisms.

Discussion

IL-10 is a potent immunomodulatory molecule that inhibits the synthesis of pro-inflammatory cytokines, and upregulates of B cell production and differentiation [34]. Its association of airway tone regulation is evident from various observations including human and animal model [35,36]. Low levels of IL-10 expression have a role on the pathogenesis of asthma [37,38]. On the other hand, high level of IL-10 from regulatory T cells has a protective effect against airway hyperreactivity and inflammation [39]. Since cytokine production is genetically controlled at the transcription level, the association of IL-10 polymorphisms at the genotypic or haplotypic levels with asthma has been reported in a numerous studies [14–24]. Three SNPs (-1082 G/A, -819 C/T, and -592 C/A) have been implicated as potential risk factors for asthma [7,8].

In the present study, we addressed associations between the IL-10 -1082 G/A, -819 C/T, -592 C/A polymorphisms, and their haplotypes and asthma susceptibility. The IL-10 -1082 G/A polymorphism conferred susceptibility to asthma in East Asians and adult asthmatics. However, the meta-analysis revealed no association between IL-10 -819 C/T, -592 C/A polymorphisms, and their haplotypes and asthma.

In the polymorphism at position -1082 G/A, which lies within a putative ETS-like transcription factor binding site, it has been reported that G position may be associated with a higher expression of the IL-10 gene [40,41]. Clinically, a suggestive association between -1082 G/A and both IgE, FEV1 as a percentage of predicted (FEV1PP) has been reported [12]. The data demonstrated in this meta-analysis should be interpreted with some caution. Even though we revealed significant associations by sensitivity analysis for studies in H-W equilibrium, which excluded potential bias during the control selection, there were only five studies were in H-W equilibrium, which is a limited population. Discrepancy between East or West Asians, as well as adult or child population. The relative importance of the -1082 G/A polymorphisms during the development of asthma may vary between ethnic and age groups, but we did not perform subgroup meta-analysis on the -1082 G/A polymorphism in H-W equilibrium due to limited data.

Besides, we failed to find any association between IL-10 -819 C/T and -592 C/A polymorphisms and asthma risk under different contrast models with subgroup analysis on the basis of age and ethnicity. In addition, haplotype analysis which has provided more information than single polymorphism showed that no evidence of association was found between the haplotypes of the GCC, ACC, ATA and asthma. A previous study concerning the function of SNPs of regulatory T cells showed that analyses of gene-to-gene interactions about –819T/C and –592A/C polymorphisms did not show any association with asthma and atopy that supporting this result [42]. It seems -819 C/T and -592 C/A were relatively less affect to asthma unlike other inflammatory disease including rheumatoid arthritis and systemic sclerosis [43,44]. It has been shown that the effect of the ATA haplotype on asthma in Caucasian and Finnish populations with various eosinophilic count and serum IgE levels is contentious [22,24]. The conclusion that -819 C/T and 592 C/A polymorphisms and ATA haplotype were of no role in asthma risk could be premature due to limited number of studies included in this meta-analysis. There should be additional large scale studies about asthma to clarify these relationships.

There are several limitations that should be considered when interpreting our results. Heterogeneity and confounding factors may have affected the meta-analysis. Because asthma itself is heterogeneous disease, asthma phenotype should be fully specified. Divergent patient group inclusion criteria and enrollment of control group without asthma screening test could have distorted the results. Publication bias may also have affected the analysis. Since studies that produced negative results may not have been published, we could not eliminate the possibility of bias even though we performed Egger’s regression test. Finally, IL-10 polymorphisms may be associated with asthma severity as well as susceptibility. However, the small amount of data available did not allow us to perform meta-analysis this association.

In conclusion, this meta-analysis demonstrates that IL-10 -1082 G/A polymorphism confers susceptibility to asthma in East Asians and adult asthmatics. However, IL-10 -819 C/T, -592 C/A polymorphisms, and their haplotypes were not associated with asthma. Further well designed high quality researches with larger scale and various ethnicities are required to explore the potential roles of these polymorphisms and pathogeneses of asthma.

Supporting Information

Supplement S1 Search strategy for meta-analysis of association between interleukin-10 gene polymorphisms and the risk of asthma.

Supplement S2 PRISMA 2009 Checklist of items to include when reporting a systematic review or meta-analysis.

Supplement S3 The flow chart of the included studies in accordance to the PRISMA 2009 statement.

Supplement S4 Criteria of methodological quality assessment for molecular association case/control study for asthma.

Supplement S5 Quality score assessment results.

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Author Contributions
Conceived and designed the experiments: MHH YHL. Performed the experiments: MHH CHL MHK BKP. Analyzed the data: MHH CHL MHK BKP. Contributed reagents/materials/analysis tools: MHK BKP. Wrote the paper: MHH CHL YHL.

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