Association of IL-10 -1082G>A, -819C>T and -592C>A Polymorphisms with Susceptibility to Asthma in Children: a Systematic Reviews and Meta-Analysis

Abstract
Studies evaluating the association of IL-10 polymorphisms with risk of pediatric asthma found inconsistent data. Here, we performed a meta-analysis to get a precise estimation of the associations. Relevant studies identified in the PubMed, Scopus, CNKI databases were used to perform a meta-analysis. A total of 23 case-control studies including nine studies with 1298 cases and 1079 controls on -1082G>A, four studies with 622 cases and 603 controls on -819C>T and ten studies with 1480 case and 1462 controls on -592C>A were selected. Overall, there was no a significant association between IL-10 polymorphisms with pediatric asthma risk in global population. When stratified by ethnicity, there was a significant association of IL-10 -1082G>A with pediatric asthma in Asians and Chinese. This meta-analysis result revealed that IL-10 -1082G>A, -819C>T and -592C>A polymorphisms were not associated with pediatric asthma risk in the global population.
Keywords: Pediatric Asthma; Interleukin 10; Cytokine; Polymorphism; Association.

List of abbreviations

IL-10- Interleukin 10
NK - Natural Killer
DCs - Dendritic Cells
ISC - World Science Citation Center
SID - Scientific Information Database
CNKI - China National Knowledge Infrastructure
OR - Odds Ratio
CI - Confidence Interval
HWE - Hardy-Weinberg equilibrium

Introduction

Pediatric asthma is a highly heterogeneous disorder with multiple clinical phenotypes and can have very serious consequences for children's health, their families, and the health care system (1–3). It is one of the most common chronic diseases among children and a leading cause of medical expenses (4–6). It is estimated that more than 13% of children had been diagnosed with asthma in Canada and the average direct cost from asthma exacerbations in 2013 was estimated to be around $883.48 per patient per year (10–12). Interleukin 10 (IL-10) is a candidate gene in the mechanism of asthma since it has been shown to regulate both cellular and humoral immunity (13). IL-10 regulates IgE production and reduces IgE switching indirectly as a control point for modulation the effects of inflammatory cytokines (14).

IL-10 is important pleiotropic immunoregulatory cytokine with an anti-inflammatory properties that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis (15). Human IL-10 has a broad-spectrum anti-inflammatory activity which is expressed by activated monocytes/macrophages, natural killer (NK) cells, dendritic cells (DCs), mast cells, B cells, and regulatory T cell subsets (16). Moreover, IL-10 is known to have macrophage-deactivating properties and undermines the Th1-driven pro-inflammatory response by down-regulating the production of several cytokines (17,18). Human IL-10 gene maps to chromosome 1q31-32, contains four introns and five exons, and spans about 4.7 kb (19).

The IL-10 promoter is highly polymorphic [17–20], and three single nucleotide polymorphisms (SNPs) at positions -1082G>A, -819C>T and -592C>A polymorphisms within the promoter region have been shown to correlate with IL-10 production (22,24,25). To date, several genetic epidemiology studies have assessed the association between IL-10 -1082G>A, -819C>T and -592C>A polymorphisms and pediatric asthma in different populations (26,27). But, the results from these studies were often inconsistent and inconclusive. The reason for this inconsistency may derive from a number of issues, including sample size, lack of power, genotyping methods, false-positive errors, and minor impacts of IL-10 gene polymorphisms on risk of pediatric asthma. Thus, we conducted a systematic review and meta-analysis to combine and analyze the available studies in order to get a precise estimation of the association of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms with susceptibility to pediatric asthma.

Materials and Methods

Literature Search

The ethical approval was not necessary since the current meta-analysis was not a clinical trial study and was based on previously published studies. A comprehensive literature search was performed on major electronic literature databases, including the PubMed, web of sciences, Scopus, Google Scholar, EMBASE, SciELO, Islamic World Science Citation Center (ISC), Scientific Information Database (SID), Wanfang, and VIP, Wanfang and China national knowledge infrastructure (CNKI) databases to find all studies evaluated the association between IL-10 -1082G>A, -819C>T and -592C>A polymorphisms and risk of pediatric asthma published up to May 15, 2020. The following keywords and terms were used: (''Asthma'' OR ''Asthmatic'' OR ''Pediatric'' OR ''Childhood'' OR ''Children'') AND (''Interleukin 10'' OR ''IL-10'' OR ''Cytokine Synthesis Inhibitory Factor'' OR ''CSIF'') AND (''-1082A>G'' OR ''rs1800896'' OR ''g.3943A>G'' OR ''c.-1117A>G'') AND (" -819C>T'' OR ''rs1800871'' OR " g.4206T>C'' OR " c.-854T>C'') AND (" -592C>A'' OR ''rs1800872'' OR ''g.4433A>C'' OR " c.-627A>C'') AND (''Gene'' OR "Polymorphism'' OR ''Single-Nucleotide Polymorphism" OR ''SNPs'' OR ''Mutation'' OR ''Mutant'' OR ''Variant'' OR ''Variation'' OR ''Allele'' OR ''Genotype''). The search was limited to human studies without language restriction. Moreover, no restrictions were placed on the year of publication, and sample size. Moreover, we have also manually reviewed the reference lists of all retrieved articles, reviews and meta-analyses to find missed articles.

Inclusion and Exclusion Criteria

To select eligible studies in the current meta-analysis, the following criteria for inclusion were defined: a) Full-text publications with case-control or cohort design; b) studies evaluated the association of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms with risk of pediatric asthma; and c) provide sufficient data about IL-10 genotypes distributions to estimate the odds ratio (OR) with 95% confidence intervals (95% CI). The exclusion criteria were as follows: a) case only studies (lack of control population); b) lack of eligible genotype frequencies; c) family based studies and linkage studies; d) studies on other polymorphisms of IL-10 gene; e) case reports, posters, abstracts, meeting reports, lectures, editorials, correspondence letters, reviews, previous meta-analyses; and f) overlapped data or duplicated publications. If there were multiple published articles from the same authors, the most recent study or study with larger sample size was included in this meta-analysis. Moreover, different case-control groups or cohorts in one publication were considered as independent studies.

Data extraction

Data of eligible studies were collected by two authors independently and carefully according to the inclusion and exclusion criteria and the third author adjudicated the conflicting data until consensus was reached. The following characteristics were collected from each eligible study: the name of first author,

year of publication, country of origin, ethnicity (categorized as Caucasians, Asians, African, or Mixed), genotyping methods, sample size of cases and controls, allele and genotype frequency of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms in cases and healthy controls, minor allele frequencies (MAFs) and Hardy-Weinberg equilibrium (HWE) in healthy controls.

Statistical Analysis

The strength of the association between the IL-10 -1082G>A, -819C>T and -592C>A polymorphisms and risk of pediatric asthma was measured by odds ratio (OR) with its 95% confidence interval (CI). The significance of pooled ORs was tested by Z-test, in which P<0.05 was considered significant. The association of IL-10 -1082G>A, -819C>T and -592C>A polymorphism was estimated under five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA), and the recessive (BB vs. BA+AA). The between-heterogeneity was examined using chi-square. Moreover, I^2 test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance (I^2<25%, no heterogeneity; I^2 25-50%, moderate heterogeneity; I^2>50%, large or extreme heterogeneity). If the *P* value for heterogeneity tests was >0.01 or I^2 < 50%, a fixed effect model (Mantel-Haenszel method) was used to calculate the pooled OR. Otherwise, a random effect model (DerSimonian-Laird method) was employed to analyze data. The goodness-of-fit Chi-square test for Hardy-Weinberg equilibrium (HWE) was performed in control group and a p-value <0.05 was considered as significant disequilibrium. Sensitivity analysis was performed by removing one study at a time to the stability of the pooled data and the effect of each single study on the conclusions. Moreover, sensitivity analysis was performed by excluding HWE-violating studies. The publication bias among the selected studies was tested by Begg's test, in which an asymmetric plot suggests a possible publication bias. Moreover, Egger's linear regression test was performed to determine the significance of the asymmetry, in which P <0.05 indicated that publication bias was significant. Additionally, if publication bias was seen, the "trim and fill" method which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry was used to further analyses the possible effect of publication bias. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) Software version 2.0 (Biostat, Englewood, USA). All tests were two-sided, and the P< 0.05 was considered statistically significant.

Results

Characteristics of Eligible Studies

The study screening process was shown in Fig. 1. Initially, a total number of 259 studies were identified from the online databases and by manual search. In accordance with the eligibility criteria, 143 records were left after removing repeated studies and 82 studies were subsequently excluded for title and abstract review. Then, 48 studies were excluded because did not relevant to the IL-10 polymorphisms association with risk of pediatric asthma. In the end, the whole of the rest of the articles were checked based on the inclusion and exclusion criteria. Finally, a total of 23 case-control studies with 3400 pediatrics with asthma and 3144 healthy controls were included in the meta-analysis (28,29,38–42,30–37). Of these studies, nine studies with 1298 cases and 1079 controls were on -1082G>A, four studies with 622 cases and 603 controls on -819C>T and ten studies with 1480 case and 1462 controls were on -592C>A polymorphism. The characteristics of the main studies are shown in Table 1. The studies were published between 2002 and 2017 and sample sizes varied from 30 to 333 in cases with asthma. Of these studies, 18 were conducted on Asians, three studies on African and two studies on Caucasian populations. In the selected studies, seven genotyping methods including PCR-SSP, ARMS-PCR, PCR-

RFLP, MALDI-TOF-MS, MassARRAY, RealTime-PCR, and TaqMan were used to genotyping the IL-10 polymorphisms. The HWE was performed on all of the included studies, and the genotype distributions in the controls for all studies were consistent with the HWE, except for three studies for -1082G>A and one study for -592C>A (Table 2).

Quantitative Data Synthesis

IL-10 -1082G>A

The summary results for the association between IL-10 -1082G>A polymorphism and risk of pediatric asthma are shown in Table 2. Overall, pooled data revealed that IL-10 -1082G>A polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (Fig 2A). Moreover, we performed subgroup analysis based on ethnicity and country of origin. The stratified analysis showed that IL-10 -1082G>A polymorphism was associated with an increased risk of pediatric asthma in Asian (GG vs. AA: OR = 0.784, 95% CI 0.128-0.554, p≤0.001, Fig 2B; GG vs. GA+AA: OR = 0.409, 95% CI 0.229-0.729, p=0.002, Fig 2C) and Chinese (GA vs. AA: OR = 0.098, 95% CI 0.011-0.898, p=0.040). There was no significant association in the African populations (Table 2).

IL-10 -819C>T

The summary results for the association between IL-10 -819C>T polymorphism and risk of pediatric asthma are shown in Table 2. Pooled data showed that IL-10 -819C>T polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (Fig 3A).

IL-10 -592C>A

The summary results for the association between IL-10 -592C>A polymorphism and risk of pediatric asthma are shown in Table 3. Pooled data showed that IL-10 -592C>A polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (Fig 3B). Moreover, we performed subgroup analysis based on ethnicity and country of origin. The subgroup analysis revealed that the IL-10 -592C>A polymorphism was not associated with increased to susceptibility of pediatric asthma in Asians, Caucasians and Chinese (Table 3).

Between-Study Heterogeneity

There was considerable between-study heterogeneity for three IL-10 -1082G>A, -819C>T and -592C>A polymorphisms in this meta-analysis. Thus, we have conducted subgroup analyses by ethnicity and country of origin to describe the potential source of heterogeneity. As shown in Tables 2 and 3, when stratified analyses were conducted, the heterogeneity did not disappear considerably, which indicating that ethnicity and country of origin were not the major sources of heterogeneity in the current meta-analysis.

Sensitivity Analysis

Sensitivity analysis was conducted to check the influence of individual studies on the stability of the pooled data by excluding one study at a time. The exclusion of any single study did not significantly affect the pooled ORs or 95% CIs for three IL-10 -1082G>A, -819C>T and -592C>A polymorphisms. Then, sensitivity analysis was performed by excluding those four HWE-violating studies for IL-10 -1082G>A and -592C>A polymorphisms. The results showed that none of the pooled data for IL-10 -1082G>A and -592C>A polymorphisms under all five genetic models were significantly changed by excluding the HWE-

violating studies. Hence, results of the sensitivity analysis indicated that our pooled data for IL-10 -1082G>A, -819C>T and -592C>A polymorphisms were statistically stable and reliable.

Publication Bias

The Begg's and Egger's linear regression tests were applied to test the potential publication bias for association of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms with risk of pediatric asthma in the global population. Table 2 lists the publication bias assessment method with its respective P-value for three IL-10 polymorphisms. The shapes of the funnel plots did not show any evidence of publication bias in the global population for IL-10 -1082G>A polymorphism. However, there was evidence of publication bias under the recessive model (AC vs. CC: P_{Beggs} = 0.089; P_{Eggers} =0.024) for IL-10 -819C>T and under the heterozygote model (AC vs. CC: P_{Beggs} = 0.031; P_{Eggers} =0.044) for IL-10 -592C>A polymorphisms. Thus, we applied the Duval and Tweedie nonparametric ''trim and fill'' method to adjust the pooled risk for association of IL-10 -819C>T and -592C>A polymorphisms and pediatric asthma under the recessive model and heterozygote model, respectively (Fig. 4). However, the "trim and fill" method did not significantly change results, indicating that our pooled data were statistically robust and reliable.

Discussion

The results of the current meta-analysis may improve our understanding of the role of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms in susceptibility to pediatric asthma. Our pooled data revealed that three -1082G>A, -819C>T and -592C>A polymorphisms at promoter region of IL-10 gene were not significantly associated with risk of pediatric asthma in the global population. However, the stratified analyses by ethnicity and country of origin found a significant association between IL-10 -1082G>A polymorphism and an increased risk of pediatric asthma in Asians and Chinese children.

In 2016, Huang et al., in meta-analysis of 16 case control studies including 2494 cases and 2160 controls evaluated the association of IL-10 promoter polymorphisms with the risk of pediatric asthma. Their pooled data showed that IL-10 promoter polymorphisms were not significantly associated with a risk of pediatric asthma in any of the genetic models in the global population. Moreover, their stratified analyses based on ethnicity revealed that IL -1082G>A polymorphism was associated with the risk of pediatric asthma in Asians under the dominant model (OR = 3.607, 95%CI = 1.141-11.407, P = 0.029) and non-Asian populations under the recessive model (OR = 2.429, 95%CI = 1.620-3.642, P < 0.001) (26). However, our subgroup analysis showed that IL -1082G>A polymorphism was not significantly associated with risk of pediatric asthma in non-Asian populations (Table 2). In 2014, Zheng et al., in a meta-analysis based on A total of 4,716 asthmatic patients and 5,093 controls revealed that -1082G>A and -592C>A polymorphisms and their haplotypes at IL-10 gene were correlated with asthma risk in the overall population, but not -819C>T polymorphism. However, their subgroup analysis based on eleven studies showed that IL-10 -1082G>A and -592C>A polymorphisms were not associated with risk of asthma in children (27).

Between-study heterogeneity is to be expected in a meta-analysis, which may have affected result when interpreting of the pooled data (43–45). It is described that several factors such as study design, ethnicity, sample size, source of controls, genotyping method, and HWE may be among the major causes of the heterogeneity (45,46). In this meta-analysis, there was a significant heterogeneity under most genetic models for three -1082G>A, -819C>T and -592C>A polymorphisms at promoter region of IL-10 gene. When subgroup analyses by ethnicity and country of origin were performed the heterogeneity still existed with a slight reduction. Thus, ethnicity and country of origin could not be considered as the source of the heterogeneity, suggesting the existence of other unknown factors influencing the heterogeneity among included studies.

Similar to other meta-analysis, there were several limitations in the current study. First, no restrictions were placed on the language. However, we have found only studies published in English or Chinese language, which might introduce potential selection bias. Second, the majority of the included studies in the current meta-analysis were conducted in Asian and Africans populations, which may introduce ethnicity bias, and further studies should conduct on Caucasian and mixed populations. Third, in view of the limited number of studies for IL-10 -819C>T polymorphism, the power used to detect the association of this polymorphism with risk of pediatric asthma may not be strong enough. Thus, our pooled data revealed that IL-10 -819C>T polymorphism might be associated with an increased risk of pediatric asthma in the global population and by ethnicity. Fourth, there was significant between-study heterogeneity under most genetic models for IL-10 -1082G>A, -819C>T and -592C>A polymorphisms in the global population, which could be owing to the fact that the analysis included few studies in the analysis or due to insufficient data that limited further subgroup analysis. Therefore, more relevant case-control studies are required to be performed and then included in the meta-analysis so as to get a more reliable and scientific data. Finally, this meta-analysis exclusively concentrated on the association of IL-10 -1082G>A, -819C>T and -592C>A polymorphisms with risk of pediatric asthma without considering gene-gene or gene-environment interactions. Hence, in order to comprehensively demonstrate the etiology of pediatric asthma, it is extremely required to study the combined interaction of the related genes.

Conclusions

Our pooled data revealed that the IL-10 -1082G>A, -819C>T and -592C>A polymorphisms were not significantly associated with risk of pediatric asthma in the global population. However, the stratified analyses by ethnicity and country of origin revealed a significant association between IL-10 -1082G>A polymorphism and risk of pediatric asthma in Asians and Chinese children. Due to limitations mentioned above in the meta-analysis, it is critical that larger and well-designed studies in different ethnicities are needed to confirm our data.

Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research or publication of this article.

Acknowledgments

We thank the anonymous reviewers for reviewing this manuscript.

Funding

The authors received no financial support for the research or publication of this article.

References

1. Hoch HE, Hornin PR, Stillwell PC. Asthma in children: A brief review for primary care providers. Pediatric Annals. Slack Incorporated; 2019;48: e103–e109. doi:10.3928/19382359-20190219-01
2. Oksel C, Haider S, Fontanella S, Frainay C, Custovic A. Classification of pediatric asthma: From phenotype discovery to clinical practice. Frontiers in Pediatrics. Frontiers Media S.A.; 2018. doi:10.3389/fped.2018.00258
3. Papadopoulos NG, Čustović A, Cabana MD, Dell SD, Deschildre A, Hedlin G, et al. Pediatric asthma: An unmet need for more effective, focused treatments. Kalayci Ö, editor. Pediatric

Allergy and Immunology. Blackwell Publishing Ltd; 2018;30: pai.12990. doi:10.1111/pai.12990
4. Baye TM, Kovacic MB, Myers JM, Martin LJ, Lindsey M, Patterson TL, et al. Differences in candidate gene association between European ancestry and African American asthmatic children. PLoS ONE. 2011;6: e16522. doi:10.1371/journal.pone.0016522
5. Mirsadraee R, Gharagozlou M, Movahedi M, Behniafard N, Nasiri R. Evaluation of factors contributed in nonadherence to medication therapy in children asthma. Iranian journal of allergy, asthma, and immunology. 2012;11: 23–7. doi:011.01/ijaai.2327
6. Nourijelyani K, Aghamohammadi A, Salehi Sadaghiani M, Behniafard N, Abolhassani H, Pourjabar S, et al. Physicians awareness on primary immunodeficiency disorders in Iran. Iranian journal of allergy, asthma, and immunology. 2012;11: 57–64. doi:011.01/ijaai.5764
7. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: A systematic review. BMC Pulmonary Medicine. 2013;13. doi:10.1186/1471-2466-13-70
8. Shefrin AE, Goldman RD. Use of dexamethasone and prednisone in acute asthma exacerbations in pediatric patients. Canadian Family Physician. 2009. pp. 704–706.
9. Garner R, Kohen D. Changes in the prevalence of asthma among Canadian children. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la santé / Statistique Canada, Centre canadien d'information sur la santé. 2008;19: 45–50.
10. Lyon H, Lange C, Lake S, Silverman EK, Randolph AG, Kwiatkowski D, et al. IL10 Gene Polymorphisms Are Associated with Asthma Phenotypes in Children. Genetic Epidemiology. NIH Public Access; 2004;26: 155–165. doi:10.1002/gepi.10298
11. Hawrylowicz CM, O'Garra A. Potential role of interleukin-10-secreting regulatory T cells in allergy and asthma. Nature Reviews Immunology. Nature Publishing Group; 2005. pp. 271–283. doi:10.1038/nri1589
12. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical reviews in immunology. 2012;32: 23–63. Available: http://www.ncbi.nlm.nih.gov/pubmed/22428854
13. Mosser DM, Zhang X. Interleukin-10: New perspectives on an old cytokine. Immunological Reviews. NIH Public Access; 2008. pp. 205–218. doi:10.1111/j.1600-065X.2008.00706.x
14. DiMeo D, Tian J, Zhang J, Narushima S, Berg DJ. Increased interleukin-10 production and Th2 skewing in the absence of 5-lipoxygenase. Immunology. Wiley-Blackwell; 2008;123: 250–262. doi:10.1111/j.1365-2567.2007.02694.x
15. Schülke S. Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. Frontiers in Immunology. Frontiers Media S.A.; 2018;9. doi:10.3389/fimmu.2018.02455
16. Trifunović J, Miller L, Debeljak Ž, Horvat V. Pathologic patterns of interleukin 10 expression – A review. Biochemia Medica. 2015;25: 36–48. doi:10.11613/BM.2015.004
17. Aflatoonian M, Sivandzadeh G, Morovati-Sharifabad M, Mirjalili SR, Akbarian-Bafghi MJ, Neamatzadeh H. Associations of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with susceptibility to celiac disease: evidence from a meta-analysis and literature review. Arquivos de gastroenterologia. 2019;56: 323–328. doi:10.1590/S0004-2803.201900000-60
18. Jafari-Nedooshan J, Moghimi M, Zare M, Heiranizadeh N, Morovati-Sharifabad M, Akbarian-Bafghi MJ, et al. Association of Promoter Region Polymorphisms of IL-10 Gene with Susceptibility to Lung Cancer: Systematic Review and Meta-Analysis. Asian Pac J Cancer Prev. 2019;20: 1951–1957. doi:10.31557/APJCP.2019.20.7.1951
19. Fereydan F, Dastgheib SA, Morovati-Sharifabad M, Lookzadeh MH, Noorishadkam M, Mirjalili SR, et al. Cumulative Evidence for Association between IL-10 Polymorphisms and Kawasaki Disease Susceptibility: A Systematic Review and Meta-Analysis. Fetal and Pediatric Pathology. Taylor and Francis Ltd; 2019; 1–13. doi:10.1080/15513815.2019.1686789. Online ahead of print.

20. Mirjalili SA, Moghimi M, Aghili K, Jafari M, Abolbaghaei SM, Neamatzadeh H, et al. Association of promoter region polymorphisms of interleukin-10 gene with susceptibility to colorectal cancer: a systematic review and meta-analysis. Arquivos de gastroenterologia. 2018;55: 306–313. doi:10.1590/S0004-2803.201800000-66
21. Veisian M, Tabatabaei RS, Javaheri A, Abbasi H, Salimi E, Hadadan A, et al. Association of Interleukin-10 -1082G > A Polymorphism with Susceptibility to Preeclampsia: A Systematic Review and Meta-Analysis Based on 21 Studies. Fetal and Pediatric Pathology. Taylor and Francis Ltd; 2019. doi:10.1080/15513815.2019.1683919 [Epub ahead of print]
22. Soleimani-Jadidi S, Abbasi H, Javaheri A, Behforouz A, Zanbagh L, Meibodi B, et al. Cumulative Evidence for Association of IL-10-1082G>A Polymorphism with Susceptibility to Recurrent Pregnancy Loss: A Systematic Review and Meta-Analysis. Fetal Pediatr Pathol. 2020; 1–15. doi:doi: 10.1080/15513815.2020.1716903. [Epub ahead of print]
23. Huang ZY, Cheng BJ, Wan Y, Zhou C. Meta-analysis of the IL-10 promoter polymorphisms and pediatric asthma susceptibility. Genetics and Molecular Research. Fundacao de Pesquisas Cientificas de Ribeirao Preto; 2016;15. doi:10.4238/gmr.15028310
24. Zheng XY, Guan WJ, Mao C, Chen HF, Ding H, Zheng JP, et al. Interleukin-10 promoter 1082/-819/-592 polymorphisms are associated with asthma susceptibility in Asians and atopic asthma: A meta-analysis. Lung. 2014;192: 65–73. doi:10.1007/s00408-013-9519-8
25. Li ZF, Lu JH LJ and LB. Lack of association between childhood asthma and interleukin-10 polymorphism gene. Marson L, editor. Central Plains Med. Public Library of Science; 2007;34: 4–5.
26. Movahedi M, Mahdaviani SA, Rezaei N, Moradi B, Dorkhosh S, Amirzargar AA. IL-10, TGF-β, IL-2, IL-12, and IFN-γ cytokine gene polymorphisms in asthma. Journal of Asthma. 2008;45: 790–794. doi:10.1080/02770900802207261
27. Zedan M, Settin A, Farag MK, El-Bayoumi M, El Kegal ME, El Baz R, et al. Gene polymorphisms of tumor necrosis factor alpha-308 and interleukin-10-1082 among asthmatic Egyptian children. Allergy and Asthma Proceedings. 2008;29: 268–273. doi:10.2500/aap.2008.29.3123
28. Hussein YM, Shalaby SM, Mohamed RH, Hassan TH. Association between genes encoding components of the IL-10/IL-0 receptor pathway and asthma in children. Annals of Allergy, Asthma and Immunology. 2011;106: 474–480. doi:10.1016/j.anai.2011.02.021
29. Kim KW, Lee KE, Hong JY, Kim MN, Yeo W Il, Sohn MH, et al. Involvement of IL-10 gene promoter polymorphisms in the susceptibility for childhood asthma. Lung. 2011;189: 417–23. doi:10.1007/s00408-011-9312-5
30. Tan J, Huang X, Li D, Chen J. Association between IL-10 and IL-33 single nucleotide polymorphisms and asthma susceptibility in Han children in Zhongshan city. Guangdong Med J. 2013;34: 1239-1242.
31. Hussein YM, Alzahrani SS, Alharthi AA, Ghonaim MM, Alhazmi AS, Eed EM, et al. Association of serum cytokines levels, interleukin 10 -1082G/A and interferon-γ +874T/A polymorphisms with atopic asthma children from Saudi Arabia. Cellular Immunology. Academic Press Inc.; 2014;289: 21–26. doi:10.1016/j.cellimm.2014.03.006
32. Xu J, Shi F, Li L. Polymorphisms and susceptibility to asthma in children study of Interleukin-10 gene single nucleotide. China J Chin Med. Academic Press Inc.; 2014;29: 639–641.
33. Shahin RS, Gouda RM. The Association between Interleukin-10 Gene Polymorphism (-1082 G/A) and Bronchial Asthma with the Relation to Spirometric Parameters in Egyptian Children. American Journal of Biochemistry. 2017;7: 127–133.
34. Schubert K, von Bonnsdorf H, Burke M, Ahlert I, Braun S, Berner R, et al. A comprehensive candidate gene study on bronchial asthma and juvenile idiopathic arthritis. Disease markers. 2006;22: 127–32. doi:10.1155/2006/373620

35. Undarmaa S, Mashimo Y, Hattori S, Shimojo N, Fujita K, Miyatake A, et al. Replication of genetic association studies in asthma and related phenotypes. Journal of Human Genetics. 2010;55: 342–349. doi:10.1038/jhg.2010.32
36. Wei B, Li-li Z, Ding-fang D. Association between Polymorphisms in Promoter Region of Interleukin-10 and Interleukin-17 Gene and Childhood Asthma. Progress in Modern Biomedicine. 2011;11: 307-309,313.
37. Xie Q. Study of the correlation between IL-10 gene-627C/A polymorphism and childhood asthma. Md Med J. 2012;40: 51–53.
38. Ji J, Guan L, Wang L, Liu C. Association of interleukin-10 gene-592C/A polymorphism with concentration of interleukin-10 in children with bronchial asthma. Clin J Appl Clin Pediatr. 2013;28: 261–264. doi:10.1111/j.1399-0039.2008.01037.x
39. Smolnikova M V., Smirnova S V., Freidin MB, Tyutina OS. Immunological parameters and gene polymorphisms (C-590T IL4, C-597A IL10) in severe bronchial asthma in children from the Krasnoyarsk region, West Siberia. International Journal of Circumpolar Health. 2013;72. doi:10.3402/ijch.v72i0.21159
40. Bahrami R, Dastgheib SA, Niktabar SM, Amooee A, Lookzadeh MH, Mirjalili SR, et al. Association of BMP4 rs17563 Polymorphism with Nonsyndromic Cleft Lip with or without Cleft Palate Risk: Literature Review and Comprehensive Meta-Analysis. Fetal Pediatr Pathol. 2020; 1-15. doi:10.1080/15513815.2019.1707916. Online ahead of print.
41. Namazi A, Abedinzadeh M, Nourbaksh P, Neamatzadeh H. Association between the XRCC3 Thr241Met polymorphism and risk of colorectal cancer: A meta analysis of 5,193 cases and 6,645 controls. Asian Pac J Cancer Prev. 2015;16: 2263–2268. doi:10.7314/APJCP.2015.16.6.2263
42. Kamali M, Hamadani S, Neamatzadeh H, Mazaheri M, Shehneh MZ, Gilani MM, et al. Association of XRCC2 rs3218536 polymorphism with susceptibility of breast and ovarian cancer: A systematic review and meta-analysis. Asian Pac J Cancer Prev. 2017;18: 1743–1749. doi:10.22034/APJCP.2017.18.7.1743
43. Khoram-Abadi KM, Forat-Yazdi M, Kheradisan S, Saeidi N, Zarezade Z, Mehrabi N, et al. DNMT3B -149 C>T and -579 G>T Polymorphisms and Risk of Gastric and Colorectal Cancer: a Meta-analysis. Asian Pac J Cancer Prev. 2016;17: 3015–20. Available: http://www.ncbi.nlm.nih.gov/pubmed/27356727

Figures Legends:

Figure 1. Flowchart of literature search and selection process.
Figure 2. Forest plot for association of IL-10 -1082G>A polymorphism with risk of pediatric asthma. **A:** global population (allele model: G vs. A); **B:** Asians (homozygote model: GG vs. AA); and **C:** Asians (recessive model: GG vs. GA+AA).
Figure 3. Forest plot for association of IL-10 -819C>T and -592C>A polymorphism with risk of pediatric asthma in the global population. **A:** -819C>T (homozygote model: TT vs. CC); and **B:** -592C>A (dominant model: AA+AC vs. CC).

Figure 4. The funnel plots of publication bias for association of the IL-10 -819C>T polymorphism with risk of pediatric asthma in the global population under the homozygote model (AC vs. CC), before (hollow circles) and after (solid circles) ''Trim-and-Fill'' method.