



## Review

## Meta-analysis of associations between interleukin-10 polymorphisms and susceptibility to pre-eclampsia

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## ARTICLE INFO

## Article history:

Received 7 May 2014

Received in revised form 6 August 2014

Accepted 9 September 2014

## Keywords:

Pre-eclampsia

Interleukin-10

Polymorphism

Meta-analysis

## ABSTRACT

**Objective:** To investigate whether interleukin-10 (IL-10) polymorphisms are associated with susceptibility to pre-eclampsia.

**Methods:** A meta-analysis was conducted on the associations between IL-10-1082 G/A, -819 C/T and -592 C/A polymorphisms and pre-eclampsia using allele contrast, a recessive model, a dominant model and an additive model.

**Results:** Thirteen groups from 11 papers involving 1534 patients with pre-eclampsia and 2271 controls were considered in the meta-analysis. Meta-analysis of the IL-10-1082 G/A polymorphism in 3500 study subjects revealed no association between pre-eclampsia and the IL-10-1082 G allele [odds ratio (OR) 0.890, 95% confidence interval (CI) 0.729–1.087;  $p = 0.254$ ]. Stratification by ethnicity indicated an association between the IL-10-1082 G allele and pre-eclampsia in the Iranian groups (OR 1.408, 95% CI 1.097–1.807;  $p = 0.007$ ), but not in the European groups (OR 0.759, 95% CI 0.506–1.136;  $p = 0.180$ ). Meta-analysis revealed an association between pre-eclampsia and the IL-10-819 C allele in all study subjects (OR 1.296, 95% CI 1.012–1.661;  $p = 0.040$ ), particularly among the Iranian groups (OR 1.390, 95% CI 1.067–1.811;  $p = 0.015$ ). Meta-analysis showed no association between pre-eclampsia and the IL-10-592 C allele (OR 1.215, 95% CI 0.967–1.527;  $p = 0.094$ ) in any groups, except for the Iranian groups (OR 1.380, 95% CI 1.056–1.805;  $p = 0.018$ ). However, the associations found in the meta-analysis became non-significant after exclusion of the studies in which the controls showed deviation from Hardy–Weinberg equilibrium.

**Conclusions:** This meta-analysis suggests that IL-10-1082 G/A, -819 C/T and -592 C/A polymorphisms are unlikely to be important in susceptibility to pre-eclampsia.

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## Introduction

Pre-eclampsia is a multisystem disorder characterized by hypertension and proteinuria after 20 weeks of gestation. It is a leading cause of maternal and neonatal morbidity and mortality [1]. The cause of pre-eclampsia is not fully understood; however, it is thought to be due to suitable interactions between a susceptible genetic background and environmental factors [2].

Interleukin-10 (IL-10) is a multifunctional cytokine with anti-inflammatory properties, which can downregulate antigen presentation and macrophage activation [3]. IL-10 plays an important role in B-cell activation and auto-antibody production as a survival and differentiation factor, and also acts as an inhibitory factor during the production of T helper 1 cytokines [4]. IL-10 plays a key role in balancing anti-inflammatory and pro-inflammatory milieu at the fetomaternal interface. It can regulate vascular activity and reduce inflammation-mediated vascular dysfunction at the fetomaternal interface as a potent vascular cytokine [5]. IL-10 also plays an important role in the regulation of human trophoblast invasion [6]. Based on these known functions of IL-10, it is thought to be involved in the pathogenesis of pre-eclampsia.

The *IL-10* gene maps to 1q31-32 and exhibits polymorphisms in its promoter region, which appear to be correlated with variations in transcription. Three IL-10 polymorphisms have been studied in detail: IL-10-1082 G to A (rs1800896), IL-10-819 C to T (rs1800871) and IL-10-592 C to A (rs1800872). All three of these polymorphisms are located at the putative regulatory regions of the IL-10 promoter [7]. The IL-10-1082 G/A polymorphism lies within a putative Ets transcription-factor-binding site, the IL-10-819 C/T polymorphism lies within a putative positive regulatory region, and the IL-10-592 C/A polymorphism lies within a putative STAT-3-binding site and a negative regulatory region [8,9]. Thus, polymorphisms at these sites may modify the transcription-factor-binding sites and affect IL-10 production. The *IL-10* gene is considered to be an attractive candidate gene for pre-eclampsia because of its chromosomal location and functional relevance. Several studies have examined the association between IL-10 polymorphisms and pre-eclampsia, albeit with contradictory results, probably due to low statistical power of the individual studies [10–20]. Therefore, the authors undertook a meta-analysis in order to overcome the limitations of interpreting individual studies, resolve inconsistencies in reported data, and reduce the probability of random errors that cause false-positive or false-negative associations [21–23]. Meta-analysis was used to investigate whether IL-10-1082 G/A, -819 C/T and -592 C/A polymorphisms are associated with susceptibility to pre-eclampsia.

## Methods

### Identification of eligible studies and data extraction

A literature search for published studies that examined the associations between IL-10 polymorphisms and pre-eclampsia was undertaken using MEDLINE and EMBASE; this included articles in which IL-10 polymorphisms were analysed in patients with pre-eclampsia. Different combinations of keywords, such as 'interleukin-10', 'IL-10', 'polymorphism' and 'pre-eclampsia', were entered as medical subject heading components and as text words. The references cited in the obtained papers were also examined to identify additional studies that were not indexed by MEDLINE or EMBASE. Genetic association studies that determined the distributions of IL-10-1082 G/A, -819 C/T and -592 C/A polymorphisms in patients with pre-eclampsia and controls were also included. Overall, the inclusion criteria were: case-control study design; original data; and sufficient genotype data to calculate odds ratios (ORs). No language restrictions were applied. The

exclusion criteria were: overlapping data; inability to ascertain the number of null and wild genotypes; and studies of family members, because the analysis was based on linkage considerations. Two independent reviewers extracted the data on the methods and results from the original studies for meta-analysis. Any discrepancies were resolved by consensus between the two reviewers or by intervention of a third reviewer. The following information was extracted from each study: author name; year of publication; ethnicity of the study population; demographics; number of cases and controls; and genotype and allele frequencies of IL-10-1082 G/A, -819 C/T and -592 C/A polymorphisms.

### Evaluations of statistical associations

Allele frequencies of IL-10 polymorphisms were determined using the allele counting method. Chi-squared test was used to ascertain whether the observed frequencies of genotypes in the controls conformed to Hardy–Weinberg equilibrium (HWE). Meta-analyses were performed using allelic contrast, and recessive, dominant and additive models. Point estimates of risks, ORs and 95% confidence intervals (CI) were estimated for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. The effect of 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 to chance [24].  $I^2$  values of 25%, 50% and 75% were nominally considered as low, moderate and high estimates, respectively. The fixed-effects model assumes that a genetic factor has a similar effect on susceptibility to pre-eclampsia across all investigated studies, and that the observed variations between the studies are caused by chance alone [25]. However, the random-effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [26]. When the study groups are homogeneous, the two models are similar. In contrast, when the groups are not homogeneous, the random-effects model usually provides wider CIs than the fixed-effects model. The random-effects model is best used in the presence of significant between-study heterogeneity [26]. Statistical manipulations were performed using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ, USA).

### Evaluation of heterogeneity and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by omitting each individual study, and to investigate statistically robust results from this meta-analysis. To examine the potential source of heterogeneity observed in this meta-analysis, meta-regression was performed using HWE, ethnicity, publication year and sample size. While funnel plots are often used to detect publication bias, funnel plotting requires diverse study types of varying sample sizes and involves subjective judgements. Accordingly, this study evaluated any publication bias using Egger's linear regression test [27], which measures funnel plot asymmetry using a natural logarithm scale of ORs.

## Results

### Studies included in the meta-analysis

Fifty-five studies were identified by electronic and manual searches, and 15 studies were selected for full-text review based on the title and abstract details. Four studies were excluded because they discussed IL-10 polymorphisms other than those considered

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