

Original article

# Association between VEGF polymorphisms (–460 T/C and +936 C/T) and retinopathy of prematurity risk: A meta-analysis



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## Abstract

**Purpose:** Vascular endothelial growth factor (VEGF) contributes to the development of retinopathy of prematurity (ROP). A number of studies investigated the association of ROP with VEGF –460 T/C and +936 C/T polymorphisms but the results were conflicting. In order to derive a more precise estimation of the associations, we performed a meta-analysis of the relationship between VEGF –460 T/C and +936 C/T polymorphisms with ROP in all published studies.

**Methods:** A literature search was performed systematically using electronic databases. Published literature from PubMed and other databases was retrieved. The odds ratio (OR) with 95% confidence interval (CI) was used to estimate the pooled effect. Each –460 T/C and +936 C/T polymorphism included four case-control studies including case/control 249/308 and 179/250 respectively.

**Results:** Through literature search, we found that both VEGF –460 T/C and +936 C/T polymorphisms were not associated with ROP risk at allelic, co-dominant, dominant and recessive models.

**Conclusions:** This meta-analysis suggests that the VEGF –460 T/C and +936 C/T polymorphism might contribute to genetic susceptibility of ROP. The association between VEGF –460 T/C and +936 C/T polymorphism and ROP risk awaits further investigation.

**Keywords:** VEGF, ROP, Polymorphism, Meta-analysis

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## Introduction

Retinopathy of prematurity (ROP) is a disorder in which retinal blood vessels fail to develop normally, sometimes resulting in visual impairment and blindness in premature infants. In the early stages of retinal vascular development, premature neonates are exposed to higher oxygen levels eliminating physiological hypoxia, thus down-regulating angiogenic factors that are required for the growth of the

vasculature. ROP occurs in premature infants with disruption of this angiogenic phase. Vascular endothelial growth factor (VEGF) plays an important role in both physiological and pathologic angiogenesis. Discovery of growth factors acting on the vascular endothelium has coincided with application of powerful new genetic approaches to the problem of vascular development. A number of studies have investigated and observed that VEGF messenger ribonucleic acid (mRNA) and protein were significantly higher in ROP, which supported

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a key role for VEGF in the pathological angiogenesis in ROP.<sup>1,2</sup>

The human VEGF gene (OMIM 192240) is located on chromosome 6p12. Many polymorphisms of the VEGF gene have been reported, although most are relatively rare. Single nucleotide polymorphisms (SNPs) in the VEGF -460 T/C (rs833061) and +936 C/T (rs3025039) in the respective 5' and 3' untranslated region (UTR) have been reported in different populations.<sup>3</sup> Some studies have found association of VEGF -460 T/C or +936 C/T polymorphism with ROP risk,<sup>4-6</sup> but some other studies show no association between VEGF -460 T/C or +936 C/T polymorphism and risk of ROP.<sup>7-11</sup> These studies revealed a conflicting conclusion, probably due to the relatively small size of subjects, since individual studies are usually underpowered in detecting the effect of low penetrance genes. Therefore, in this study we conducted a meta-analysis to investigate the association between VEGF -460 T/C and +936 C/T polymorphism and the risk for ROP.

## Materials and methods

### Identification and eligibility of relevant studies

To identify all articles that examined the association of VEGF -460 T/C and +936 C/T polymorphism with ROP, we conducted a literature search in the PubMed, EMBASE, Cochrane Library, Google, dogpile and CBM database, up to July 2015 using the following terms and keywords: "VEGF", "vascular endothelial growth factor", "-460 T/C", "rs833061", "+936 C/T", "rs3025039" polymorphism" and "retinopathy of prematurity". Additional studies were identified by a manual search from other sources (e.g., Web of Knowledge), references of original studies or review articles on this topic.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies are limited to VEGF -460 T/C and +936 C/T polymorphism and ROP; (2) Independent case-control studies using either a hospital-based or a population based design; (3) complete data with genotype and allele frequencies; (4) the literature having a comprehensive statistical index, sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (5) the genotype frequency of cases and controls was within Hardy-Weinberg equilibrium (HWE); (6) papers published in English and (7) all the studies included were according to tenets of the Declaration of Helsinki.

The major reasons for exclusion of studies were (1) studies which were not possible to extract data from the published results; (2) studies that did not report appropriate outcomes; (3) Duplicated studies were also excluded; (4) case-only studies; (5) all three genotype frequency missing and (6) family based studies.

### Data extraction

Authors independently reviewed all the potentially relevant papers through assessing the eligibility of each article and abstracting data with standardized data-abstraction forms. For each study, the following information was

extracted: name of the first author; publication year; ethnicity; sample size; types of disease; sources of samples; genotyping methods; and the minor allele frequency in the controls with the Hardy-Weinberg Equilibrium (HWE) *p*-value, respectively. Disagreements were resolved through discussion. The characteristics of these studies included in this meta-analysis on the association of ROP with VEGF -460 T/C and +936 C/T polymorphism are shown in [Tables 1 and 2](#). The VEGF -460 T/C and +936 C/T polymorphism genotype distributions from each study is presented in [Tables 3 and 4](#) respectively.

### Statistical analysis

ORs and relevant 95% CIs were computed using review manager (comprehensive meta-analysis version 3).<sup>12</sup> ORs were used to measure association across the studies. The risk of VEGF -460 T/C CC genotype on retinopathy of prematurity was evaluated by comparing with their reference wild type homozygote and then evaluated the risks of TC + CC vs. TT and TT + TC vs. CC on retinopathy of prematurity, assuming dominant and recessive effects of the variant C allele, respectively. And the risk of VEGF +936 C/T and TT genotype on retinopathy of prematurity was evaluated by comparing with their reference wild type homozygote and then evaluated the risks of CT + TT vs. CC and CC + CT vs. TT on retinopathy of prematurity, assuming dominant and recessive effects of the variant T allele, respectively. If moderate or high level heterogeneity exists, a random-effects meta-analysis was performed, unless using fixed-effects models. Publication bias was assessed by visually inspecting a funnel plot. A *p* value less than 0.05 was considered statistically significant.<sup>13</sup>

## Results

### Association of the VEGF -460 T/C polymorphism with ROP

This meta-analysis included four eligible studies of the association of the VEGF -460 T/C polymorphism with ROP. The genetic models all used fixed-effects models. In the overall analysis, no significant associations were found in any of the comparison models including the allele model: T vs. C (OR = 0.931, 95% CI = 0.726–1.195, *P* = 0.576) ([Fig. 1](#)), dominant model: TC + CC vs. TT (OR = 0.895, 95% CI = 0.629–1.273, *P* = 0.536) ([Fig. 2](#)), recessive model: TT + TC vs. CC (OR = 1.048, 95% CI = 0.646–1.699, *P* = 0.849) ([Fig. 3](#)) and co-dominant model: TT vs. CC (OR = 0.911, 95% CI = 0.537–1.544, *P* = 0.729) ([Fig. 4](#)).

### Association of the VEGF +936 C/T polymorphism with ROP

A total of four studies were included in this meta-analysis. No significant associations between the VEGF +936 C/T polymorphism with ROP were identified in any comparison models, including the allele model: C vs. T (OR = 0.882, 95% CI = 0.610–1.274, *P* = 0.502) ([Fig. 5](#)), dominant model: CT + TT vs. CC (OR = 0.866, 95% CI = 0.558–1.344, *P* = 0.521) ([Fig. 6](#)), recessive model: CC + CT vs. TT (OR = 1.139, 95% CI = 0.487–2.665, *P* = 0.764) ([Fig. 7](#)) and

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