·Informatics Research·

Meta analysis on the relationship between gene polymorphisms of vascular endothelial growth factor and retinal prognosis risk of prematurity

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Abstract

• AIM: To explore the relationship between gene polymorphisms of (VEGF) and retinopathy of prematurity (ROP).

• METHODS: Literature materials related to gene polymorphisms of VEGF and ROP in PubMed, EMBASE, Cochrane and CBM database were retrieved. These materials were screened according to inclusion and exclusion standards. Patients diagnosed with ROP in clinic were regarded as control group and ROP patients who were in treatment were regarded as observation group. The indexes in two groups were matched except birth weight (BW), gender and gestational weeks. Meta5.1 was used to analyze the relationship between gene polymorphisms of VEGF and ROP.

• RESULTS: Four random control tests (RCT) were included in this research, including 2611 patients. Meta analysis results showed that VEGF affected ROP, having statistical significance. The combined ratio was 0.44 (95% CI, 0.07, 0.80), 0.42 (95% CI, 0.09, 0.74) and 0.75 (95% CI, 0.02, 1.49), respectively. Carrying +405 allele might increase the premature infants' risk of having ROP.

• CONCLUSION: ROP may be related to its carrying of +405 allele. Large-scale, multi-factor RCT researches are still needed in order to identify the relation between VEGF and ROP.

• KEYWORDS: polymorphisms of; premature infant; retinopathy; Meta analysis

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INTRODUCTION

Retinopathy of prematurity (ROP) refers to the retinopathy occurs in the infants with premature birth and low birth weight. The clinical manifestations of ROP are retinal ischemia, neovascularization, proliferative retinopathy, which are the main reasons for blindness of newborns in clinic [1]. However, there is significant difference on the prognosis of different ROP. ROP can gradually disappear soon after the born with no need of the treatment. But continued lesions occur in some patients, which need surgery or medicine. What reasons lead to the different prognosis, genetic susceptibility is one of the research focuses in clinic at present. Among these influencing factors, genetic polymorphism of vascular endothelial growth factor (VEGF) is closely related to genetic susceptibility [2-8]. Therefore, to explore the relationship between genetic polymorphisms of VEGF and ROP is helpful to the prognosis of ROP, which also provides reasonable foundations and plans for clinical treating of ROP. Four literatures on VEGF polymorphism were screened in this research. Meta analysis was conducted, investigating the relationship between polymorphism at +405G/C locus of ROP patients and ROP infants.

MATERIALS AND METHODS

Inclusion Standards After screened in PubMed, EMBASE, Cochrane and CBM database, 28 related literatures on polymorphisms of VEGF and ROP infants were retrieved. After the screening, only 4 literatures met the standards. Literatures meeting the following conditions at the same time can be selected: 1) objects: patients diagnosed with ROP; 2) all the research hypothesis and methods were similar; 3) the detection results were expressed by mean ± SD; 4) age, weight, gender and *etc.* should be taken into consideration at grouping and the bias caused by human factor should be excluded.

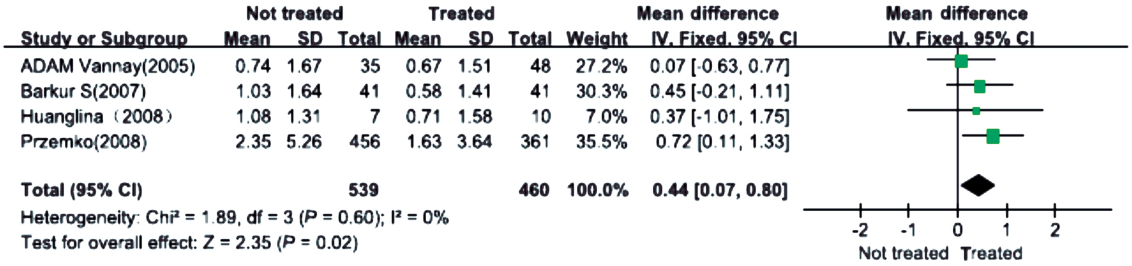

Figure 1 Meta analysis on genetype GG at + 405G/C locus and ROP.

Exclusion Standards 1) experimental data with duplicate publication, comparison study with control before and after treatment and cohort study. 2) unserviceable literatures with poor research quality, little information and incomplete data, for example, case report. 3) the treatment efficacy was not evaluated by original literatures; 4) unreasonable research design of original literatures (such as unreasonable design in control group, incomplete sample materials, non-standard diagnosis or efficacy and *etc.* 5) literatures with duplicate publication.

Statistical Analysis All the literature data including authors, publication time, cases of observation objects and *etc.* were input in Review Manager 5.0 software to conduct heterogeneity and Meta analysis. Funnel plot analysis were made for the number of the included literatures. The publication bias was detected. Clinical heterogeneity and statistical heterogeneity analysis were given to the included literatures. Fixed effect model was used for the analysis if the included researches had no heterogeneity (namely, $P \geqslant 0.1$, $I^2=0$). On the contrary, random effect model was adopted for data analysis. Mantel-Haenszel (Fixed effect model), DerSimonian and Laird (random effect model) were used to calculate the combined effect value. Descriptive analysis was conducted if Meta analysis cannot achieve with the included literatures. OR value was used to express the effectiveness analysis statistics for all the measurement data and the corresponding 95% CI was calculated. $P<0.05$ means that statistical significance exists in the difference of the two treatment plans.

RESULTS

Retrieval results Twenty-eight literatures were preliminarily retrieved. Twenty-four literatures were excluded after reading the titles and abstracts. After further judgment according to inclusion and exclusion standards, 4 literatures were finally included [9-12], the publication years of the literatures was between 2005 and 2008. The general features of the included researches were shown in Table 1.

Meta Analysis on VEGF+405G/C Polymorphism Locus and ROP

Genetype GG at +405G/C locus and ROP After Meta analysis, heterogeneity test was given to 4 researches ($P=0.60$, $I^2=0$), meaning that there was no heterogeneity. The results indicated that there was statistical significance of alleles at +405G/C locus, which can influence ROP ($P<0.05$, Figure 1).

Table 1 Polymorphism distribution at VEGF+405G/C locus

Author(s) and publication time	Genetype at + 405G/C locus	Control group (*n*)	Treatment group(*n*)
Huanglina(2008)	GG	7	10
	GC	9	9
	CC	49	1
ADAM Vannay(2005)	GG	35	48
	GC	48	46
	CC	17	6
Barkur S(2007)	GG	41	41
	GC	20	20
	CC	26	25
Przemko(2008)	GG	456	361
	GC	673	425
	CC	--	290

Potential publication bias The influence of genetype GG at +405G/C locus on ROP was taken as the analysis index and inverted funnel plot was drawn. Due to the small amount of the included research and unobvious distribution trends, the inverted funnel plot showed trend symmetry, indicating that the publication bias was not big (Figure 2).

Potential publication bias The influence of genetype GC at +405G/C locus on ROP was taken as the analysis index and inverted funnel plot was drawn. Due to the small amount of the included research and unobvious distribution trends, the inverted funnel plot showed trend symmetry, indicating that the publication bias was not big (Figure 3).

Genetype GC at +405G/C locus and ROP After Meta analysis, heterogeneity test was given to 4 researches ($P=0.92$, $I^2=0$), with no heterogeneity. The results indicated that there was correlation between genetype GC at +405G/C locus and ROP. Statistical significance of alleles at +405G/C locus was existed, which can influence ROP ($P<0.05$, Figure 4).

Genetype CC at +405G/C locus and ROP After Meta analysis, heterogeneity test was given to 4 researches ($P=0.94$, $I^2=0$), meaning that there was no heterogeneity. The results indicated that there was correlation between genetype CC at +405G/C locus and ROP. $P<0.05$ meant that there existed statistical significance of alleles at +405G/C locus, which can influence ROP (Figure 5).

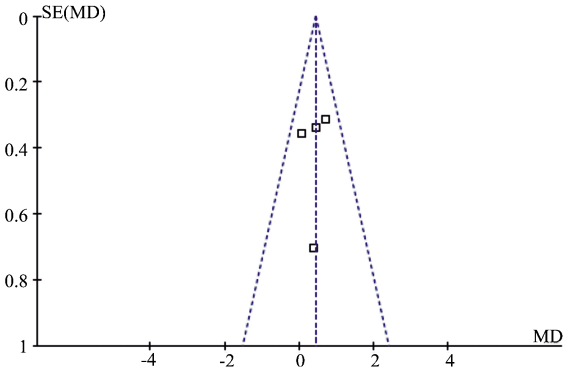

Figure 2 Bias analysis for the influence of genetype GG at +405G/C locus on ROP.

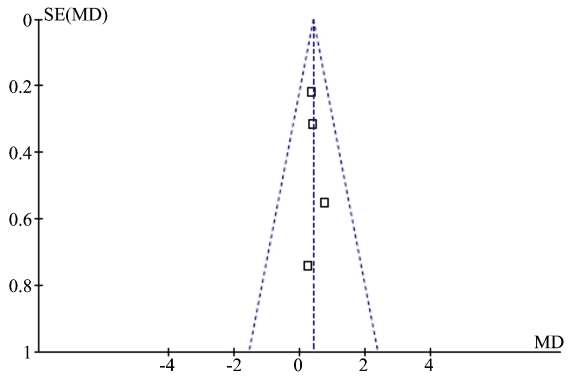

Figure 3 Bias analysis for the influence of genetype GC at +405G/C locus on ROP.

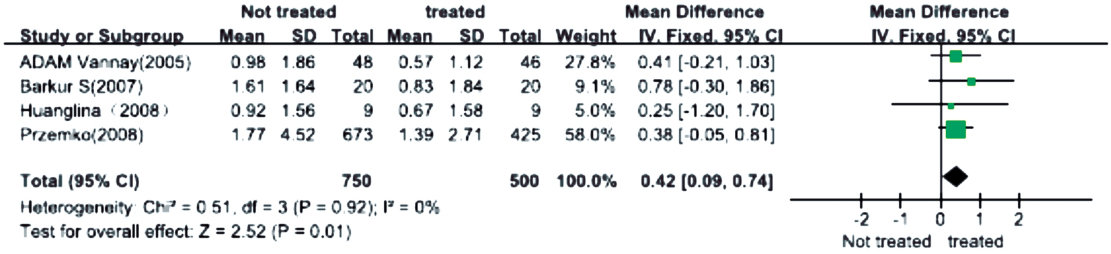

Figure 4 Results of Meta analysis on genetype GC at+405G/C locus and ROP.

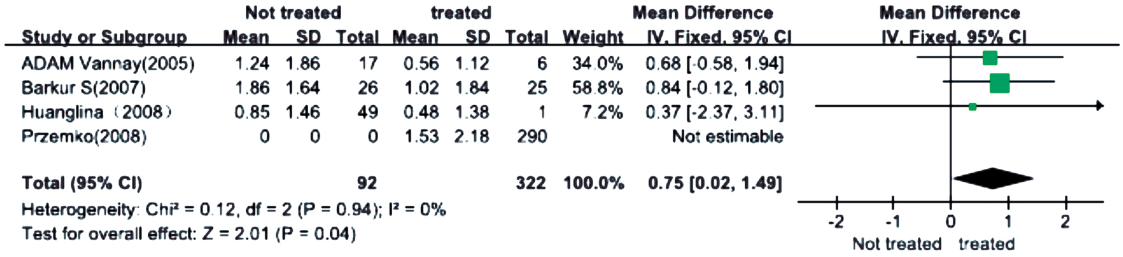

Figure 5 Meta analysis on genetype CC at +405G/C locus and ROP.

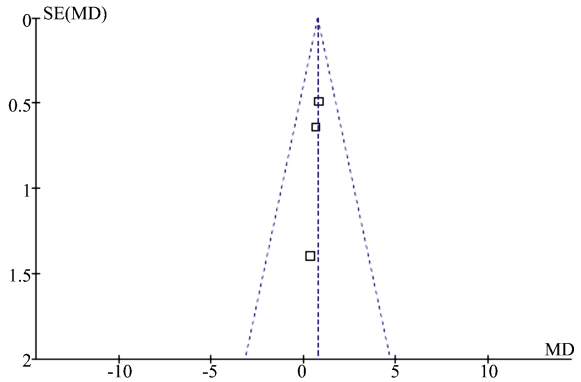

Figure 6 Bias analysis for the influence of genetype CC at +405G/C locus on ROP.

Potential publication bias The influence of genetype CC at + 405G/C locus on ROP was taken as the analysis index and inverted funnel plot was drawn. Due to the small amount of the included research and unobvious distribution trends, the inverted funnel plot showed trend symmetry, indicating that the publication bias was not big (Figure 6).

DISCUSSION

As we all know, the occurrence and development of ROP is directly related to VEGF [13]. VEGF plays an important role in and vessel leakage during ROP disease course. The development of ROP mainly divides into two stages. The first stage: relative high-oxygen environment inhibits the normal secretion of VEGF, making retinal stop; the second stage: due to the of normal retinal , the tissue is relatively short of oxygen, promoting high-expression of VEGF and stimulating abnormal from retina to vitreous cavity. At the same time, fibroplasia occurs. A lot of case-control studies verified that single nucleotide polymorphisms of VEGF are related to many kinds of diseases such as breast cancer, oral carcinoma, senile dementia, kidney disease and etc. Similarly, many researches also detect that single nucleotide polymorphisms of VEGF are related to the changes of protein expression during ROP threshold lesions. Cooke *et al* [2] pointed out in their case-control researches that VEGF-634G allele in 5'non-transcribed domain of VEGF is the independent risk factor in ROP threshold period. The risk of homozygous G allele developing into ROP threshold is twice times than other genetypes. On the contrary, Vanny *et al* [3] put forward the opposite opinion that VEGF-634C

allele is more common in patients during ROP threshold lesions and C allele is the severe independent risk factor of ROP. But other researchers did not repeat these results [11-15].

Researches in recent years show that up-regulation of VEGF gene may play an important role in the occurrence and development of ROP [16, 17]. The retinal growth of premature infants and low birth weight babies is not mature. As a result, a large amount of avascular area exists. Due to the following features [18], VEGF is regarded as the most important factor promoting : 1) VEGF has signal peptide that is essential to extracellular transport and promotes division and hyperplasia of endothelial cells; 2) VEGF enhances the permeability of . such as and *etc.* can enter into and form , which supports endothelial cell growth of [19]; 3) VEGF is produced under [20]. But pathological retinal neovascularization is usually companied with non-perfusion of capillary; 4) the expression level of VEGF receptor in retinal endothelial cells increases under . Retinal vessel system of premature infants is gradually mature after the birth. Therefore, its growth process can be observed by funduscope and technology.

The risk and influencing factors of VEGF on ROP were explored in this research. Through the analysis of VEGF expression during retinal growth of premature infants, we hope to further explore the effects and mechanisms of VEGF in angiogenesis of premature infants. Thus, in the clinical judgment of ROP prognosis, the combination of genetic polymorphism detection of VEGF gene at +405G/C locus and comprehensive consideration of other related factors may be helpful, providing for making correct clinical treatment plans.

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