

## Original Article

# Association between *PEDF* gene polymorphisms and the risk of age-related macular degeneration

Yuanyuan Li, Deliang Wang

Department of Ophthalmology, Shangluo Second People's Hospital, Shangluo, Shanxi, China

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**Abstract:** Objective: Pigment epithelium-derived factor (PEDF) strongly inhibits angiogenesis, and plays an important role in retinoblastoma cells. In this study we detect the association of *PEDF* gene polymorphisms (rs1136287 and rs12150053) and age-related macular degeneration (AMD) risk. Methods: This is a case-control study including 118 AMD patients and 121 healthy controls. *PEDF* gene polymorphisms were genotyped by TaqMan method. Hardy-Weinberg equilibrium (HWE) was used to detect the representativeness of the cases and controls. Differences of genotype and allele distributions of *PEDF* polymorphisms were calculated by Chi-square test. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were used to present the relative risk of AMD. Results: Genotype and allele distributions in controls were in accordance with HWE. Genotype and allele distributions of rs1136287 had no significant association with the susceptibility of AMD under five contrast models ( $P < 0.05$ ). CC genotype and C allele of rs12150053 were higher in cases than that in controls, and rs12150053 was obviously related to the risk of AMD under T vs. C model ( $P = 0.044$ , OR = 1.499, 95% CI = 1.009-2.226). Conclusion: In this study, there was no obvious association between *PEDF* gene rs1136287 polymorphism and AMD susceptibility, and rs12150053T might act as a susceptible allele in the occurrence of AMD.

**Keywords:** *PEDF* gene, polymorphisms, age-related macular degeneration

## Introduction

Age-related macular degeneration (AMD) is an eye disease which usually affects older adults [1, 2]. The disease is based on the disorders of retinal pigment epithelium (RPE) and choroid blood vessel bed, including angiogenesis, lipid deposition, drusen etc. AMD is an irreversible disease which could lead to visual impairment and even blindness. Recent years the morbidity of AMD has an upward trend. At present, there is no complete cure method for AMD. In order to find out an effective therapy method for AMD, explore the pathogenesis of it is necessary. Previous studies demonstrated that AMD is a complex disease, and affects by many factors. Age may be a risk factor for AMD, with the increasing age the incidence of AMD is enhanced. Other factors such as genetic variants, high energy visible light, life style and etc. also contribute to the occurrence of this disease [3-8].

Pigment epithelium-derived factor (PEDF), also known as SERPINF1, is a serpin peptidase inhibitor, belongs to serpin family. PEDF is firstly

discovered in human retinal cell [9, 10], and hereafter researched as a therapy candidate factor for angiogenesis and neurodegeneration [11]. PEDF has various functions including anti-angiogenic, antitumorigenic, and neurotrophic properties [12]. Previous studies indicate that PEDF involves in the development of AMD [13]. *PEDF* gene is located at chromosome 17p13.3, and has 8 exons. Variants of gene might change the expression of gene and/or the function of protein. Single nucleotide polymorphisms (SNPs) of *PEDF* gene relate to many eye diseases [14, 15]. For the above reasons, we speculated that *PEDF* gene polymorphisms were associated with the susceptibility of AMD.

In this study we detected the association of two SNPs of *PEDF* gene (rs1136287 and rs12150053) and the susceptibility of AMD in Chinese Han population.

## Materials and methods

### Subject characteristics

This study was approved by the ethic committee of Shangluo Second People's Hospital. All

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**Table 1.** Genotype and allele distributions in case and control groups

SNP	Case n=118 (%)	Control n=121 (%)	P value
<b>Rs1136287</b>			
CC	41 (34.75)	45 (37.19)	-
CT	51 (43.22)	54 (44.63)	0.902
TT	26 (22.03)	22 (18.18)	0.471
C	133 (56.36)	144 (59.50)	-
T	103 (43.64)	98 (40.50)	0.486
<b>Rs12150053</b>			
TT	56 (47.46)	76 (62.81)	-
TC	48 (40.68)	38 (31.41)	0.053
CC	14 (11.86)	7 (5.78)	0.038
T	160 (67.80)	190 (78.51)	-
C	76 (32.20)	52 (21.49)	0.008

**Table 2.** Correlations between *PEDF* gene polymorphisms and the susceptibility under five contrast models

Model	X <sup>2</sup>	P value	OR (95% CI)
<b>Rs1136287</b>			
TT vs. CC	0.246	0.620	1.182 (0.610-2.289)
TT + TC vs. CC	0.034	0.854	1.039 (0.692-1.559)
TT vs. TC + CC	0.368	0.544	1.212 (0.651-2.257)
TC vs. CC	0.004	0.947	1.016 (0.631-1.637)
T vs. C	0.198	0.656	1.078 (0.775-1.499)
<b>Rs12150053</b>			
TT vs. CC	0.318	0.573	0.874 (0.546-1.397)
TT + TC vs. CC	0.127	0.722	0.935 (0.648-1.351)
TT vs. TC + CC	1.648	0.199	0.756 (0.492-1.160)
TC vs. CC	0.088	0.766	0.917 (0.517-1.626)
T vs. C	4.044	0.044	1.499 (1.009-2.226)

participants were Chinese Han population, and had no relationship between each other. 118 patients who diagnosed as AMD in Shangluo Second People's Hospital from January 2011 to January 2015 were enrolled as cases. 121 healthy individuals who took a healthy examination in the same hospital during the same period were recruited as controls. Controls were consistent with cases in age and gender. Individuals who had any eye disease and cardiovascular disease were excluded from control group. Participants were ≥60 years old, and signed the written informed consent.

### Genotyping method

Peripheral venous blood was collected from every fasting participant and anticoagulated by

EDTA. Genomic DNA was extracted from 1 ml peripheral blood using a TIANamp Blood DNA Kit (Tiangen, Beijing, China). Genotypes of *PEDF* gene polymorphisms (rs1136287 and rs12150053) were genotyped using TaqMan method with an ABI 3730XL genetic analyzer (Applied Biosystems, Foster City, CA, USA).

### Statistic method

Representativeness of cases and controls were detected by Hardy-Weinberg equilibrium (HWE) examination. Differences of genotype and allele distributions between case and control groups were assessed by Chi-square test. Odds ratios (ORs) with corresponding 95% confidence intervals (95% CI) were used to present the relative risk of AMD. All of the calculations were performed by PASW 18.0 software. P value less than 0.05 indicated a significantly result.

### Results

Genotype and allele distributions in controls were in accordance with HWE, demonstrating the controls had well goodness of fit and representativeness.

Genotype and allele distributions of rs1136287 had no obvious difference between case and control groups (**Table 1**,  $P > 0.05$ ). CC genotype and C allele of rs12150053 were significantly higher in cases than that in controls (**Table 1**,  $P < 0.05$ ). In order to certify the association of *PEDF* gene polymorphisms (rs1136287 and rs12150053) with the susceptibility of AMD, we detected the association under five contrast models (**Table 2**). Rs1136287 had no significant association with the susceptibility of AMD under five contrast models ( $P > 0.05$ ). *PEDF* gene rs12150053 polymorphism could increase the risk of AMD under T vs. C model ( $P = 0.044$ , OR=1.499, 95% CI=1.009-2.226). Under other models, rs12150053 didn't relate to AMD susceptibility ( $P > 0.05$ ).

### Discussion

AMD is a tardive and progressive eye disease, and characterized by non-infectious injury around macular area. AMD could be classified into two types: dry (or atrophic) AMD and wet AMD (or exudative AMD). Symptoms of AMD mainly include retinal nerve degeneration, pathological changes of RPE cells, Bruch membrane and choroid, lipid deposition and neoangiogenesis. AMD begins with the presence of

drusen. With advancing age, the presence of small drusen is common. However, numerous and larger drusen in macular region is an early symptom of AMD. Previous study showed that family history had a significant association with the incidence of AMD [16]. Therefore it suggested that genetic factors may be related to the occurrence of AMD. Etiology of AMD has not yet been certified, but it is currently considered as a complex disease induced by gene and environment factors and/or their interactions [17-19].

To our knowledge, PEDF could inhibit the proliferation and migration of endothelial cells in retinal tissue [20, 21], and also has an effective inhibition for angiogenesis [22, 23]. With the functions of antiangiogenic, antitumorigenic, and neurotrophic properties [12], PEDF might involve in the development of AMD. It is known that the polymorphisms of gene can influence the expression of gene and might change the amino acid of the protein. Genetic may be an important factor for the pathogenesis of many diseases. Rs1136287, rs12150053, rs12948385 and rs9913583 were widely studied SNPs of *PEDF* gene in the association with the incidence of AMD [24, 25]. Rs1136287 is a functional amino acid change at codon 72 in 3<sup>rd</sup> exon of *PEDF* gene (Met72Thr). In 2005, it was first proposed to be associated with the risk of AMD [26]. Another *PEDF* gene polymorphism, rs12150053 (-5736T>C) was on the promoter region of the gene. Research has shown that rs12150053 was associated with the incidence of diabetic retinopathy [27]. However, there were very little researches focusing on the association of rs1215003 and the susceptibility of AMD. In this study, we detected the association of the two polymorphisms of *PEDF* gene (rs1136287 and rs12150053) with the susceptibility of AMD.

In our study, genotype and allele distributions of rs1136287 were not obviously different between case and control groups. Analyzing the association between rs1136287 SNP and the susceptibility of AMD under five contrast models, the results indicated that rs1136287 polymorphism had no significant association with the susceptibility of AMD. That was consistent with previous studies [28, 29]. But this result was different from another study, which suggested that T allele of rs1136287 was significantly associated with wet AMD in Taiwan

Chinese population [30]. For *PEDF* gene rs12150053 polymorphism, CC genotype and C allele distributions were obviously different between case and control groups. Five contrast model analysis results demonstrated that rs12150053 polymorphism was associated with 1.499 times increased risk of AMD under T vs. C model. However under other models the SNP had no association with the susceptibility of AMD. That was different from previous studies, which demonstrated that rs12150053 had no significant association with the susceptibility of AMD [24, 28]. Above all, we suggested that rs1136287 polymorphism had no association with the occurrence of AMD, and T allele of rs12150053 was the risk allele for the development of AMD in Chinese Han population.

Other factors such as the linkage disequilibrium between *PEDF* gene polymorphisms, gene-gene and gene-environment interactions were not assessed in this study. The results of our study was unadjusted by other risk factors. Although we obtained a meaningful result, the evidence was insufficient to certify the etiology of AMD. So, in the future, a well designed study considering multiple risk factors and larger sample size is necessary.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Yuanyuan Li, Department of Ophthalmology, Shangluo Second People's Hospital, Shangluo 726000, Shanxi, China. E-mail: yuanjiem@yeah.net

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