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Role of two common SNPs of *superoxide dismutase 2* gene in the development of primary open angle glaucoma.

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Abstract

Oxidative stress is considered as risk factors for the development of POAG. SOD2 plays an important role in many biological processes caused by ROS. We performed a study to investigate the association of two common SNPs in SOD2 (rs2842980 and rs4880) with the risk of POAG, and the interaction between SOD2 polymorphisms and environmental factors. 170 patients with POAG and 340 matched healthy controls were collected into this study without blood relationship. Genotyping of SOD2 rs2842980 and rs4880 was conducted in a 384-well plate format on the sequenom MassARRAY platform. The association between SOD2 rs2842980 and rs4880 and risk of POAG was analyzed by logistic regression analyses. Compared with the TT individuals, individuals with the TC and CC genotypes have a substantial increased susceptibility for POAG incidence, and adjusted ORs (95% CI) were 1.63 (1.03-2.58) and 6.92 (2.12-22.62), respectively. Moreover, the C allele displayed a 2.09 folds risk of POAG in comparison to the T allele (adjusted OR: 2.09, 95% CI: 1.43-3.06). We found that the rs4880 showed interaction with age. In conclusion, our study suggests a significant association between rs4880 polymorphism and risk of POAG in the Chinese population. SOD2 rs4880 polymorphism could be a susceptibility biomarker for POAG.

Keywords: *Superoxide dismutase 2 (*SOD2), rs2842980, rs4880, Primary open angle glaucoma (POAG).

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Introduction

Glaucoma is the leading cause of irreversible blindness, and this disease has become one of the important public health issues worldwide [1,2]. It is estimated that about 60.5 million people with primary glaucoma by 2010, which may increase to 79.6 million by 2020 with bilateral blindness, in which 5.9 million are Primary Open Angle Glaucoma (POAG) [3]. Almost half of the world's glaucoma population occurs in Asian counties. A recent study suggested that POAG prevalence is about 0.7% in mainland China [4]. The etiology of developing POAG is still uncertain, but it is well known that many environmental and lifestyle factors contribute to the development of this disease, such as intraocular pressure, age, alcohol drinking, cigarette smoking, high body mass index, systemic hypertension [5]. However, many cases suffering from POAG are not related to these risk factors, suggesting that genetic factors contribute to the development of this disease. It is estimated that about 29 genetic variations have been defined by linkage studies on the development of POAG, and about 4% of the glaucoma patients have genetic variation in any one of the potential risk genes [6,7]. Therefore, understood of the role of genetic factors in POAG risk could early predict the high risk individuals of POAG.

Oxidative stress is on behalf of the imbalance of Reactive Oxygen Species (ROS) in human body, and it is considered as a risk factor for the development of POAG [8]. As a second messenger, ROS involves in signal transduction, vascular function and protein regulation, and retinal ganglion cell death signaling pathway [9,10]. The low activity of anti-oxidative enzymes and low molecular weight of antioxidants reveal the oxidative stress in the pathogenesis of POAG [11,12]. Superoxide Dismutase (SOD) is an antioxidant enzyme with a high activity on catalytic dismutation of superoxide radical anion, and plays an important role in many biological processes caused by ROS [13]. Three types of SOD were observed, including SOD1, SOD2 and SOD3. SOD has been reported to have a protective role in cells and extracellular components from damages related to inflammatory process in the pathogenesis of many diseases [14,15]. Previous studies have reported that the expression of SOD2 was changed in the aqueous humor of POAG patients [16,17]. Genetic polymorphisms of *SOD* genes have been widely investigated, and reported to be involving in many diseases [18,19]. Three previous studies have been reported the association between

SOD2 polymorphisms and risk of POAG, but the results are inconsistent [20-22]. In this study, we performed a study to investigate the association of two common SNPs in SOD2 (rs2842980 and rs4880) with the risk of POAG, and interaction between SOD2 polymorphisms and environmental factors.

Materials and Methods

Ethics statement

The protocol of this study was approved by the Institutional Review Board of the Inner Mongolia Autonomous Region People's Hospital, Hohhot, China. The informed consent was obtained from all subjects prior to enrolment.

Patients and controls

In this study, 170 patients with POAG were collected into this study without blood relationship. Patients were enrolled from the Inner Mongolia Autonomous Region People's hospital between May 2013 and 2016. All the patients were primarily diagnosed by the following criteria: I) Appearance of the disc or retinal nerve fiber layer; II) Visual field loss in line with optic nerve damage; III) Glaucomatous optic nerve damage with cup-to-disc ratio>0.5; IV) Intraocular pressure above 21 mmHg in any one eye, and visual acuity<0.05. The exclusion criteria for patients were those with evidence of secondary glaucoma, congenital glaucoma, a history of steroid use, or ocular trauma.

During the same period, 340 healthy controls were enrolled from the clinics and healthy examination center of the Inner Mongolia Autonomous Region People's Hospital. All the controls are free from glaucoma by health examination. All the healthy controls were matched with patients with POAG by sex and age (± 5 y). The demographic variables and clinical information were collected from medical records and a self-designed questionnaire with face to face investigation. The demographic and clinical information included sex, age, and family history of glaucoma, alcohol drinking, tobacco smoking, intraocular pressures and cup-to-disc ratio. Tobacco smoking was divided into never and ever smoking, and ever smoking was defined as those who smoked at least one cigarette per day for more than six months. Alcohol drinking was categorized as never and ever drinking, and ever drinking was defined as those who consumed at least one alcoholic drink a day for more than six months.

DNA extraction and genotyping

3-5 ml peripheral venous blood sample was collected from each participant after agreement of participation. Genomic DNA was extracted from peripheral blood by DNA blood mini kit (Tiangen, Beijing, China) following manufacturer's protocol, and the DNA samples were kept at -20°C in refrigerator. Genotyping of SOD2 rs2842980 and rs4880 was conducted in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). The PCR amplification reaction for genotyping SOD2 rs2842980 and rs4880 was performed in 5 μL mixture. The DNA samples were desalted, and robotically dispensed onto a silicon chip (SpectroCHIP), and finally analyzed with MALDI-TOF MS.

Statistical analysis

All data were analyzed by SAS (version 9.2, SAS Institute Inc., Cary, NC, USA). Differences of demographic and clinical variables were analyzed by Chi-square (χ^2) test or student t-test. In order to confirm the effectiveness of SNP allele frequency, hardy-Weinberg equilibrium of SOD2 rs2842980 and rs4880 was analyzed by a goodness-of-fit chi-square. The association between SOD2 rs2842980 and rs4880 and risk of POAG was analyzed by logistic regression analyses, after adjusting potential confounding factors. The interaction between SOD2 rs2842980 and rs4880 and environmental factors in the risk of POAG was analyzed by Chi-square (χ^2) test. Two tailed and P<0.05 was considered as statistical significance.

Results

The demographic and clinical variables of 170 patients with POAG and 340 healthy controls are shown in Table 1. There was no significant difference between patients with POAG and controls in terms of sex, age, smoking habits. However, a significant difference was found between the two study groups in a family history of glaucoma (χ^2: 8.14, P<0.001), alcohol drinking (χ^2: 6.70, P: 0.01), intraocular pressures (t: 41.27, P<0.001) and cup-to-disc ratio (t: 45.00, P<0.001).

Table 1. *Demographic and clinical information of investigated subjects.*

Variables	Patients N=170	%	Controls N=340	%	t or χ^2 test	P value
Sex						
Female	71	41.76	153	45		0.49
Male	99	58.24	187	55	0.48	
Age, y						
<45	31	18.24	50	14.7		0.78
45-60	48	28.24	102	30		
60-75	64	37.64	133	39.12		
>75	27	15.88	55	16.18	1.08	
Family history of glaucoma						
No	163	95.88	338	99.41		<0.001
Yes	7	4.12	2	0.59	8.14	
Tobacco smoking						
Ever	110	64.71	211	62.06		0.56
Never	60	35.29	129	37.94	0.34	
Alcohol drinking						

No	93	54.71	226	66.47		0.01
Yes	77	45.29	114	33.53	6.7	
Intraocular pressures	26.51 ± 2.27		15.93 ± 2.93		41.27	<0.001
Cup-to-disc ratio	0.75 ± 0.11		0.34 ± 0.09		45.00	<0.001

The TT, TC and CC genotypes of SOD2 rs4880 in patients with POAG were significant difference from controls (χ^2: 22.80, P<0.001), while no significant difference was found in SOD2 rs2842980 (χ^2: 0.85, P: 0.65) between the two study groups (Table 2). SOD2 rs2842980 and rs4880 did not deviate from Hardy-Weinberg equilibrium both in patients with POAG and controls.

Compared with the TT genotypes, individuals with the TC and CC genotypes had a substantial increased susceptibility for POAG incidence, and adjusted ORs (95% CI) were 1.63 (1.03-2.58) and 6.92 (2.12-22.62), respectively (Table 3). Moreover, the C allele displayed a 2.09 folds risk of POAG in comparison to the T allele (adjusted OR: 2.09, 95% CI: 1.43-3.06). These results suggested that SOD2 rs4880 had an influence on the occurrence of PAH. However, no significant difference was observed between SOD2 rs2842980 polymorphisms and susceptibility for POAG incidence.

Table 2. *Genotype frequencies of SOD2 rs2842980 and rs4880 between patients with POAG and controls.*

Genes	Patients N=170	%	Controls N=340	%	χ^2	P value	P for HWE	
							POAG Patients	Controls
rs2842980								
AA	73	42.94	160	47.06	0.85	0.65	0.47	0.93
AT	80	47.06	146	42.94				
TT	17	10	34	10				
rs4880								
TT	116	68.24	278	81.76	22.80	<0.001	0.06	0.75
TC	42	24.71	60	17.65				
CC	12	7.06	2	0.59				

Table 3. *Association of SOD2 rs2842980 and rs4880 with the risk of POAG.*

Genes	Patients N=170	%	Controls N=340	%	Crude OR (95% CI)	P value	Adjusted OR (95% CI)[1]	P value
rs2842980								
AA	70.89	41.7	154.36	45.4	1.0		1.0	
AT	81.26	47.8	156.06	45.9	1.15 (0.77-1.71)	0.36	1.19 (0.79-1.78)	0.4
TT	17.85	10.5	29.58	8.7	1.04 (0.54-2.01)	0.78	1.09 (0.55-2.14)	0.81
Allele								
A	226	66.47	466	68.53	1.0		1.0	
T	114	33.53	214	31.47	1.10 (0.83-1.45)	0.51	1.02 (0.77-1.37)	0.87
rs4880								
TT	115	67.65	277	81.47	1.0		1.0	
TC	44	25.88	60	17.65	1.76 (1.13-2.75)	0.01	1.63 (1.03-2.58)	0.04
CC	11	6.47	3	0.88	6.60 (2.06-21.16)	0.001	6.92 (2.12-22.62)	0.001
Allele								
T	274	80.59	612	90	1.0		1.0	
C	66	19.41	68	10	2.17 (1.50-3.13)	<0.001	2.09 (1.43-3.06)	<0.001

[1]Adjusted for alcohol drinking and family history of glaucoma.

The associations between rs4880 and environmental factors were shown in Table 4. We found that genotype frequencies of rs4880 showed difference in the four age groups, and the younger age was associated with more TC and CC genotypes of rs4880 in patients with POAG than controls (for <45 y: P=0.02; 45-60 y: P=0.03; 60-75 y: P=0.04; >75 y: P=0.36). Moreover, no significant difference was found in genotype distribution of rs4880 among those with family history of glaucoma (χ^2: 0.03, P: 0.86), while a significant difference was observed in those without family history (χ^2: 19.4, P<0.001).

Table 4. Gene-environmental interaction between rs4880 and environmental factors in the risk of POAG.

Variables	Patients			Controls			χ^2 test	P value
	TT	TC	CC	TT	TC	CC		
Sex								
Female	50	18	3	126	25	2	4.78	0.09
Male	65	26	8	151	35	1	15.39	<0.001
Age, y								
<45	17	11	3	39	11	0	7.6	0.02
45-60	33	12	3	87	14	1	6.91	0.03
60-75	44	17	3	109	23	1	6.09	0.04
>75	21	4	2	42	12	1	2.01	0.36
Family history of glaucoma								
No	111	41	11	276	59	3	19.4	<0.001
Yes	4	3	0	1	1	0	0.03	0.86
Tobacco smoking								
Ever	78	25	7	171	39	1	11.67	0.003
Never	37	19	4	106	21	2	10.23	0.006
Alcohol drinking								
No	67	20	6	183	40	3	7.31	0.03
Yes	48	24	5	94	20	0	13.61	0.001

Discussion

In this study, we observed a significant association between SOD2 rs4880 polymorphism and risk of POAG. Our study suggests that the TC and CC genotypes of rs4880 were significantly correlated with POAG susceptibility when compared TT genotype, and the C allele of SOD2 rs4880 was closely related to an increased risk of POAG. Moreover, a significant interaction was found between age and family history of glaucoma. These results suggested that SOD2 rs4880 was associated with an increased incidence of POAG among Chinese population, and this SNP could be a susceptibility biomarker for POAG.

SOD2 is the major form of SODs expressed in mitochondria of human body, and it is involved in cellular processes, such as metabolism, progression, proliferation, invasion and apoptosis [23-25]. SOD2 plays a role in eliminating ROS in mitochondria to prevent oxidative stress response. Currently, many studies have indicated an directly correlation between ROS and occurrence of POAG [11,26,27]. In humans, eyes are too sensitive to oxidative stress, and extensive light, ultraviolet radiation and environmental pollution are usually cause for the failure of oxidation, and then the ROS could damage the eye tissue lipid, protein and nucleic acid. Previous studies have shown that the activity of SOD2 and other antioxidant enzymes, but the underline mechanism of decreased activity of SOD2 is unclear [28].

rs4880 is a widely studied SNP, which is located at the exon region of SOD2 and induces an amino acid substitution. The C allele of rs4880 is considered to reduce the SOD2's transport efficiency in mitochondria, and individuals with the TT genotype is associated with a higher activity level of SOD2 in comparison to those carrying the TC and CC genotypes [29]. Several epidemiological studies have investigated the relationship between rs4880 and susceptibility to many diseases, such as oral squamous cell carcinoma, pancreatic cancer, Alzheimer's disease, adult brain tumors and diabetes as well as osteoporosis [30-35].

Moreover, for the correlation between rs4880 and risk of POAG, and only three studies reported their relationship, but the results are inconsistent [20-22]. Amero et al. performed a study with 226 unrelated POAG patients and 403 control

subjects in a Saudi population, and revealed that the CC genotype of rs4880 was associated with an increased risk of POAG [36]. Zhou et al. performed a study in a Chinese population, and they revealed that the rs4880 and rs2842980 polymorphism were not related to the pathogenesis of glaucoma [21]. In a recent study, Zhang et al. performed a study with 261 patients with POAG and 312 healthy controls. They reported that rs2842980 polymorphism was associated with risk of POAG, but rs4880 was not, and significant linkage disequilibrium was found between rs6917589 and rs4880 [22]. In our study, we reported a significant association between rs4880 and risk of POAG. The differences of these results might be attributed to the differences of population, study design, sample size or random by chance.

Moreover, our study reported an interaction between rs4880 and age, and the younger age was associated with more TC and CC genotypes of rs4880 in patients with POAG than controls. These results suggested that in younger age individuals, those carried the TC and CC genotype was associated with higher risk of POAG. In older age individuals, other factors excepted for rs4880 may contribute more to the pathogenesis of this disease. Further studies are greatly needed to confirm our findings.

Some potential limitations of this study existed. First, only 170 patients of POAG were enrolled. The relatively small sample size might lead to lower statistical power to identify differences between groups in our study. Second, the patients were enrolled from only one hospital in China, which may cause selection bias in this study.

Conclusions

Our study suggests a significant association between rs4880 polymorphism and risk of POAG in the Chinese population. However, no significant association was observed between rs2842980 and development of POAG. SOD2 rs4880 polymorphism could be a susceptibility biomarker for POAG.

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