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Original Research

Superoxide dismutase coding of gene polymorphisms associated with susceptibility to Parkinson's disease

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Oxidative stress linked to the etiology of Parkinson's disease, which is characterized by chronic and progressive neurodegeneration of dopamine neurons. Superoxide dismutase enzymes (SODs) regarded as the first line of defense against oxidative damage. This study assessed the potential associations of gene polymorphisms in *SOD1* (encoding Cu/Zn-SOD), *SOD2* (encoding Mn-SOD) and *SOD3* (encoding extracellular-SOD) with susceptibility to Parkinson's disease. A case-control study, including Parkinson's disease cases (n = 356) and controls (n = 370). Single nucleotide polymorphisms of *SOD1* (*rs*2070424 A/G), *SOD2* (*rs*4880 T/C) and *SOD3* (*rs*1799895, C/G) were genotyped. Results indicated that AG or GG genotype carriers in *SOD1* had a much greater risk of Parkinson's disease compared to corresponding AA genotypes, and allele G carriers had increased risk versus allele A carriers in the single nucleotide polymorphism (*rs*2070424 A/G) in *SOD1*. Further, TC or CC genotype carriers in *SOD2* had a much higher risk of Parkinson's disease compared with corresponding TT genotypes, and the C carriers had an increased risk over allele T carriers in the single nucleotide polymorphism (*rs*4880 T/C) in *SOD2*. Together, carrying allele G in the single nucleotide polymorphism (*rs*2070424 A/G) in *SOD1*, or allele C in the single nucleotide polymorphism (*rs*4880 T/C) in *SOD2*, enhances genetic susceptibility to Parkinson's disease.

Keywords

Parkinson's disease; polymorphisms; superoxide dismutase; genotyping

1. Introduction

Parkinson's disease (PD) is the most prevalent neurodegenerative motor disorder, typically affecting the elderly population. PD is clinically diagnosed based on a combination of classic motor features, including bradykinesia, resting tremor, rigidity, and alternation in gait (Kleinman and Frank, 2013). Conventional dopamine replacement therapy improves motor symptoms but has important limitations that do not slow disease progression and may be associated with fluctuations in motor response and dyskinesia in PD patients (Ferrazzoli et al., 2016; Maier et al., 2014).

Parkinson's disease is a multifactorial disorder that, in most cases, arises from a combination of environmental and genetic factors (Ascherio and Schwarzschild, 2016). Epidemiologic studies suggest a potentially increased risk with long-term pesticide exposure (Pezzoli and Cereda, 2013), dairy consumption (Chen et al., 2007) and traumatic brain injury (Fang et al., 2012), and reduced risk with consumption of caffeine, tobacco and alcohol (Evans et al., 2006; Thacker et al., 2007). Linkage analysis, association studies, and next-generation sequencing have provided convincing evidence for a link between genetic components and PD (Hu et al., 2017). Identification of the genetic basis for occurrence and development of PD would thus contribute new insights into the molecular etiology and pathogenesis of the disease as well as subsequent prevention strategies and therapeutic development.

Oxidative stress plays a key role in the pathogenesis of PD by contributing to degeneration followed by death of dopaminergic neurons (Dias et al., 2013; Zhou et al., 2008). It is caused by disequilibrium between the biological detoxification system and reactive oxygen species (ROS) production, and is a common factor underlying cellular damage (Puspita et al., 2017). ROS is a large family of small and highly reactive molecules, including superoxide anion radical (O_2^{2-}), hydroxyl radical (·OH), and hydrogen peroxide (H_2O_2), which can oxidize proteins, lipids and DNA (Scherz-Shouval and Elazar, 2011). For internal homeostasis, bodies must develop efficient, reducing and detoxification systems, including catalase system, superoxide dismutase (SOD) system, glutathione peroxidase (GPX) system, and glutathione S-transferase (GST) system (Morales et al., 2014). SOD acts an important antioxidant defense mechanism against oxidative stress by catalyzing the dismutation of superoxide (O_2^{2-}) into oxygen and hydrogen peroxide. Three forms of SOD, including cytoplasmic superoxide dismutase (Cu/Zn-SOD, *SOD1*), mitochondrial superoxide dismutase (Mn-SOD, *SOD2*), and extracellular superoxide dismutase (EC-SOD, *SOD3*) are present in mammals (Kim et al., 2015). However, genes for these three SODs (*SOD1, SOD2, SOD3)* are highly polymorphic in human, with certain polymorphisms reported to be associated with serious diseases (Kim et al., 2015; Xu et al., 2012). For example, *SOD1* A/G (*rs*2070424) polymorphism may decrease the risk of (and G allele might protect from) ulcera-

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Table 1. PCR primer pairs and restriction enzymes used for *SOD1*, *SOD2* and *SOD3* gene polymorphisms analysis

Polymorphism (genes)	Primer sequence (5' - 3')	Annealing temp (°C)	Amplicon size (bp)	Restriction enzyme	Restriction products (bp)
*rs*2070424, A/G (*SOD1*)	AGTACTGTCAACCACTAGCA CCAGTGTGCGGCCAATGATG	64	570	*MspI*	570 or 369 + 201
*rs*4880, T/C (*SOD2*)	GCTGTGCTTTCTCGTCTTCAG TGGTACTTCTCCTCGGTGACG	58	208	*BsaWI*	41/167 or 208
*rs*1799895, C/G (*SOD3*)	GGCTGGCCTGCTGCGTGGTGG CCTTGCACTCGCTCTCGCGCG	65	104	*Eco52I*	23/81 or 104

tive colitis (El-Kheshen et al., 2016) and gastric cancer (Ebrahimpour and Saadat, 2014). Further, *SOD2* T/C (*rs*4880) is reported to be associated with noise-induced hearing loss in humans (Liu et al., 2010), while *SOD3* C/G (*rs*1799895) is associated with cardiovascular disease (Naganuma et al., 2008) and preeclampsia (Procopciuc et al., 2012).

The potential associations of *SOD1*, *SOD2* and *SOD3* polymorphisms with the risk of PD are unknown. Our research focuses on investigating the possible associations of *SOD1* (*rs*2070424 A/G), *SOD2* (*rs*4880 T/C) and *SOD3* (*rs*1799895, C/G) polymorphisms with susceptibility to PD in a population.

2. Materials and methods

2.1 Clinical samples

A total of 356 patient blood specimens were obtained from sporadic adults diagnosed with PD, and confirmed by a senior neurologist specializing in movement disorders, according to the Consensus Statement of the Movement Disorders Society in 1998 (Bhatia et al., 2018), or treated for PD in the West China Hospital of Sichuan University, between June 1, 2012 and May 30, 2015. Accordingly, 370 age- and sex-matched healthy individuals with no evidence of PD enrolled as controls for this study. All participants' data about major risk factors, including age, family history of neurological diseases, living environment conditions, and smoking, were obtained from questionnaires. The research approved by the ethics committee of the West China Hospital of Sichuan University and informed consent of each participant was obtained either directly from patients themselves or their guardian.

2.2 Inclusion and exclusion criteria

The diagnosis made according to the criteria in the "guidelines for the treatment of Parkinson's disease in China (Second Edition)" issued by the Parkinson's disease and dyskinesia group of the Chinese Medical Association Neurology Branch. All patients diagnosed with PD were symptomatic to clinical symptoms and signs, combined with auxiliary examinations such as brain CT or MRI. Meanwhile, patients of severe organic diseases such as liver and kidney failure, malignant tumors, and nutritional, metabolic diseases, as well as neurological diseases such as vascular dementia and idiopathic tremor, were excluded.

2.3 PCR amplification and genotyping

Genomic DNA was extracted from peripheral venous blood by the Axygen DNA isolation kit (Axygen, CA, catalog number: APGX50) according to the recommended protocol, and stored at -80°C for subsequent analysis. The three common single nucleotide polymorphisms (SNPs) of *SOD1* (*rs*2070424 A/G), *SOD2* (*rs*4880 T/C) and *SOD3* (*rs*1799895, C/G) genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. All PCR primers were synthesized by Sangon Biotech (Shanghai, China). Corresponding theoretical annealing temperatures and PCR amplified fragment lengths listed in Table 1.

All PCRs were carried out in 50 μL reaction mixture, containing 200 ng template DNA, 1× buffer (Tris-HCl 100 mmol/L, pH 8.3; KCl 500 mmol/L), 0.50 μmol/L primers, 2.0 mmol/L $MgCl_2$, 0.25 mmol/L dNTPs and 1.0 U rTaq DNA polymerase (Promega, Madison, WI, USA). PCRs were performed through the following steps: first at 94 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, annealing at the corresponding temperature (shown in Table 1) for 30 s, and 72 °C for 30 s, and lastly the extension step at 72 °C for 5 min. Amplified PCR products were preliminary checked by electrophoresis on 2.0% agarose gel and then analyzed under UV light.

Some 20 μL aliquots of amplified PCR products were digested with 4U restriction enzymes, *Msp*I, *Bsa*WI, or *Eco*52I (MBI Fermentas, St. Leon-Rot, Germany) at the corresponding temperatures for 10 h following the recommendations in the supplier manual. Digested products were separated by 2.5% agarose gel electrophoresis and analyzed under UV light. For quality control, about 10-15% of randomly selected samples were re-analyzed by DNA sequencing method (ABI3730xl DNA Analyzer, Applied Biosystems, Foster City, CA, USA) to ensure concordance with genotyping results from PCR-RFLP.

2.4 Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences software for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). The chi-squared (χ^2) test was utilized to evaluate the Hardy-Weinberg equilibrium in genotypic distributions and clinical characteristics. A level of $^*P < 0.05$ was considered statistically significant.

3. Results

3.1 Population characteristics

The demographic and clinical characteristics of the study population summarized in Table 2. There are no significant differences in age and gender between the PD patient group and the healthy control group. The average age of the PD group was 64.23 (ranging from 45 to 87 years), while that of the healthy control group was 61.72 (ranging from 41 to 88 years). The percentage of individuals with a previous history of eye disease was 7.87% in the

Table 2. Characteristics of the PD group and the healthy control group in this study

Characteristics	PD group (n = 356)	Healthy control group (n = 370)	*P*-value
Age mean (Range) (years)	64.23 ± 11.35 (45-87)	61.72 ± 14.55 (41-88)	NS[a]
Gender (male/female)	185/171	191/179	NS[a]
Previous history of eye disease (Y/N)[b]	28/356	0/370	$P < 0.001^{*}$
Living condition(Rural/ Urban)	156/200	168/202	NS[a]
Smoking (Y/N)	78/278	79/291	NS[a]

Abbreviations: NS, Not significant; Y/N, Yes/No; *Represents statistically significant.

PD group, and 0% in the healthy control group – a statistically significant difference ($^{***}P = 0.00023$). As for the living conditions, there is no significant difference between the two groups – the ratio of individuals living in rural to urban environments is 156/200 in the PD group and 168/202 in the control group ($P = 0.59$). The rate of smoking was also not statistically significant between the two groups - 21.91% in PD group to 21.35% in healthy controls ($P = 0.78$).

3.2 Genotyping

The frequencies of *SOD1*, *SOD2*, and *SOD3* gene polymorphisms in the PD and healthy control group were detected by PCR-RFLP, and subsequently compared by the chi-squared (χ^2) test method. The results are shown in Table 3.

For the *rs*2070424 A/G SNP in *SOD1*, which is an Ala9Val polymorphism, the genotypic frequencies of AA, AG and GG were 54.21%, 35.96%, and 9.83% in the PD group, and 84.05%, 13.78%, and 2.16% in the healthy control group. These genotype distribution frequencies were statistically significant between the PD patients and the healthy controls ($\chi^2 = 77.462$, $^{***}P = 0.00023$). The corresponding allelic frequencies between these two groups were also statistically significant, with 72.19% to 90.95% for A allele, and 27.81% to 9.05% for G allele, in the PD group and healthy control group, respectively. These results suggest that the G-allele is associated with a higher risk of PD than the A-allele ($\chi^2 = 85.549$, $^{***}P = 0.00067$).

For *rs*4880 T/C position in *SOD2*, which is a Val16Ala polymorphism, the genotypic frequencies of TT, TC and CC were 73.60%, 23.31%, and 3.09% in the PD group, versus 85.68%, 13.78%, and 0.54% in the healthy control group. These genotype distribution frequencies in *SOD2* were statistically significant between PD patients and healthy controls ($\chi^2 = 18.834$, $^{***}P = 0.00051$). The corresponding allelic frequencies between these two groups were also statistically significant: 85.25% to 92.57% for the T allele, and 14.75% to 7.43% for C allele, in the PD group and healthy control group, respectively. Thus, the C-allele was associated with a much higher PD risk than the T-allele ($\chi^2 = 19.801$, $^{***}P = 0.00079$).

Finally, for the *rs*1799895 C/G SNP in *SOD3*, which is an Arg213Gly polymorphism, the CC, CG and GG genotypes occurred at a frequency of 39.89%, 44.10%, and 16.01% in the PD group, and 39.46%, 42.70%, and 17.84% in the healthy control group. No statistically significant differences in the distribution of these *SOD3* genotypes were observed between the PD patients and healthy controls ($\chi^2 = 0.447$, $P = 0.800$). The corresponding allelic frequencies also displayed no statistically significant differences between the two groups, with 61.94% to 60.81% for the C allele, and 38.06% to 39.19% for the G allele in the PD group and healthy control group, respectively. This indicates that the *rs*1799895 C/G SNP of *SOD3* may not be associated with risk of PD ($\chi^2 = 0.195$, $P = 0.659$).

4. Discussion

As a common but serious neurodegenerative and movement disorder, PD often occurs in the elderly and develops slowly as a result of aging. In previous studies, many factors have been shown to be associated with susceptibility to PD, such as age (Nalls et al., 2014), smoking (Chen et al., 2010), alcohol consumption (Liu et al., 2013), ultraviolet radiation (Gatto et al., 2015) among others (Kalia and Lang, 2015). The genetic background has also been demonstrated to be an important factor in the development of PD (Nalls et al., 2014; Spatola and Wider, 2014). In this case-control study, we analyzed the distribution of genetic polymorphisms of three *SOD* genes in PD patients versus healthy controls, to determine the potential association of these polymorphisms with susceptibility to PD. The results indicate that carriage of allele G in the SNP (*rs*2070424 A/G) in *SOD1*, or allele C in the SNP (*rs*4880 T/C) in *SOD*2, may enhance genetic susceptibility to PD. We suggest that these two genetic polymorphisms applied as molecular markers for PD susceptibility detection.

Our data indicated that the distribution of genotype and allele frequencies of *SOD1* (*rs*2070424 A/G) and *SOD2* (*rs*4880 T/C) altered in a statistically significant manner in PD patients versus healthy controls. For *SOD1* (*rs*2070424 A/G), the frequency of AG or GG genotypes was up to 2.61- or 4.55-fold higher in PD patients compared to healthy controls. Further, the frequency of the G allele in PD patients (27.81%) was 3.07-fold higher than that in healthy controls (9.05%). This suggested that the *SOD1* (*rs*2070424 A/G) SNP is associated with the risk of PD ($\chi^2 = 77.462$, $^{***}P = 0.00023$), while G allele carriers may have a higher risk of PD than A allele carriers ($\chi^2 = 85.549$, $^{***}P = 0.00067$).

For *SOD2* (*rs*4880 T/C), the frequency of TC or CC genotypes was up to 1.69- or 5.72-fold higher in PD patients than in healthy controls. The frequency of C allele was 14.75% in PD patients - 1.99-fold of that in the healthy controls (7.43%) -- suggesting that *SOD2* (*rs*4880 T/C) is also associated with risk of PD ($\chi^2 = 18.834$, $^{***}P = 0.00051$), with C allele carriers at a higher risk than T allele carriers ($\chi^2 = 19.801$, $^{***}P = 0.00079$). However, unlike *SOD1* (*rs*2070424 A/G) and *SOD2* (*rs*4880 T/C), there were no statistically significant differences in the genotype frequencies and allele frequency of the hypothesized risk factor *SOD3* (*rs*1799895, C/G) between the PD patient group and the healthy controls, suggesting this SNP may not be associated with the risk of PD.

Table 3. Genotype distribution of *SOD1*, *SOD2* and *SOD3* gene polymorphisms in the PD group and the healthy controls

Genotypes	PD group (n = 312)	Control group (n = 256)	OR (95% CI)	χ^2 and *P*-value
*SOD1 rs*2070424 A/G				
AA[a]	193 (54.21%)	311 (84.05%)		
AG	128 (35.96%)	51 (13.78%)	0.247 (0.171-0.358)	χ^2 = 77.462
GG	35 (9.83%)	8 (2.16%)	0.142 (0.064-0.312)	$^{***}P$ = 0.00023
A[a]	514 (72.19%)	673 (90.95%)		χ^2 = 85.549
G	198 (27.81%)	67 (9.05%)	0.258 (0.191-0.349)	$^{***}P$ = 0.00067
*SOD2 rs*4880 T/C				
TT[a]	262 (73.60%)	317 (85.68%)		
TC	83 (23.31%)	51 (13.78%)	0.508 (1.345-0.746)	χ^2 = 18.834
CC	11 (3.09%)	2 (0.54%)	0.150 (0.033-50.684)	$^{***}P$ = 0.00051
T[a]	607 (85.25%)	685 (92.57%)		χ^2 = 19.801
C	105 (14.75%)	55 (7.43%)	0.997 (0.591-1.681)	$^{***}P$ = 0.00079
*SOD3 rs*1799895 C/G				
CC[a]	142 (39.89%)	146 (39.46%)		
CG	157 (44.10%)	158 (42.70%)	0.979 (0.711-1.347)	χ^2 = 0.447
GG	57 (16.01%)	66 (17.84%)	1.126 (0.738-1.719)	P = 0.800
C[a]	441 (61.94%)	450 (60.81%)		χ^2 = 0.195
G	271 (38.06%)	290 (39.19%)	1.049 (0.849-1.296)	P = 0.659

[a] homozygous genotypes were used as reference group

OR, odds ratio and CI, confidence interval.

Although the results have shown a statistically significant enrichment of specific SNPs in SOD genes across the PD population compared to control, the use of such polymorphisms as screening and genetic markers to detect PD is probably limited based on the fact that some of these genetic anomalies are also present in a fair number of the non-PD population. However, it is possible that the presence of these polymorphisms increases the probability or enhances the development of PD through other unknown genetic mutations (such as polymorphic genes coding for enzymes involved in the metabolism of foreign chemicals (xenobiotics)) as well as external factors (including pesticides, organic solvents, and metals including iron, copper, and manganese) (Dick et al., 2007).

Many studies have shown that oxidative damage may contribute to the development of PD. Several reducing and detoxification systems, such as the SOD (Yan et al., 2013), GPX (Bellinger et al., 2011), and GST systems (Kiyohara et al., 2010), may play a role in inhibiting the pathogenesis of PD. Our study showed that gene polymorphisms in *SOD1* (*rs*2070424 A/G) and *SOD2* (*rs*4880 T/C) are associated with the risk of PD, while no such risk is associated with the polymorphism in *SOD3* (*rs*1799895, C/G), implying that there may be other underlying mechanisms. Although previous studies failed to reveal an association between the clinical outcome of acute paraquat intoxication and the genetic polymorphism or enzyme activity of superoxide dismutase (V16A). The functional polymorphisms of the Mn-SOD gene were not linked to changes in erythrocyte SOD (Hong et al., 2010), so we cannot ascertain if all three SOD polymorphisms are closely linked to corresponding enzyme activities and paraquat exposure.

5. Conclusion

The results provide a framework into the role of SOD gene polymorphisms, and genotypic variants of other reducing and detoxification genes, in susceptibility to PD in humans. Larger prospective studies aimed at evaluating the association between gene polymorphisms of *SOD1-3* and susceptibility to PD are needed to confirm these findings to elucidate the underlying molecular mechanisms.

Ethics approval and consent to participate

The research undertaken was approved by the West China Hospital of Sichuan University.

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Conflict of interest

The authors declare no conflict of interest.

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