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Association of Dopamine Beta-Hydroxylase (DBH) Polymorphisms with Susceptibility to Parkinson's Disease

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Background: The purpose of this study was to explore the association between 2 single-nucleotide polymorphisms (SNPs) in the dopamine β-hydroxylase (DBH) gene (rs1611115 and rs732833) and the susceptibility to Parkinson's disease (PD).

Material/Methods: Polymerase chain reaction direct sequencing (PCR-DS) was used to test the genotypes of *DBH* polymorphisms in 95 PD patients and 100 healthy examinees frequency-matched with the former by age and sex. The genotype and allele distribution differences between the case and control groups were analyzed by chi-square test, and the relative risk of PD in southern Chinese populations was expressed by odds ratio (OR) and 95% confidence interval (CI). Hardy-Weinberg equilibrium (HWE) was also checked by chi-square test.

Results: The genotype and allele distribution frequencies in rs1611115 were obviously different between PD patients and the healthy control group ($P<0.05$). The TT genotype may lead to a 2.95 times higher risk of PD occurrence compared with the common genotype CC (OR=2.95, 95%CI=1.02–8.51), and the C allele increased risk of onset of PD (OR=1.81, 95%CI=1.17–2.82). Cognition of the PD patients was different between CC and CT+TT genotypes of rs1611115 ($P=0.047$).

Conclusions: *DBH* rs1611115 polymorphism was likely to be associated with the susceptibility to PD, but we did not find that rs732833 is a susceptibility marker for PD.

MeSH Keywords: Dopamine beta-Hydroxylase • Parkinson Disease • Polymorphism, Genetic

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Background

Parkinson's disease (PD), also termed "parkinsonism", is a common nervous system degeneration disease presenting in middle-aged individuals, second only to Alzheimer's disease (AD) in prevalence, affecting 0.4% of people over the age of 45 years and 1.0% of people over age 60 [1,2]. It is more common in males than females and the average age at onset is 60 years [3]. In China, the prevalent of PD is 1.7% for those over age 65. It imposes a heavy socio-economic burden on patients, their families, and society [4]. PD pathogenesis is still a mystery and many studies have shown that PD is a complex disease caused by the interaction of various genetic and environmental factors, along with the influences of aging [5]. The pathogenic factors of PD eventually lead to the occurrence of PD through changing the physiological status and functions of dopamine (DA), dopamine receptor (DR), and dopamine transporter (DAT) [6]. Population correlation analysis has been widely used in looking for the susceptibility genes of this disease.

Dopamine β-hydroxylase (DBH) is a rate-limiting enzyme of DA, converting into NE, as well as a catecholamine biosynthetic enzyme first discovered in the blood, which plays an important role in neurotransmission in the adrenergic sympathetic nervous system [7,8]. In the human body, DBH is expressed in adrenal medullary chromaffin granules and the synaptic vesicle of peripheral and central adrenergic neurons' dense nucleus in the forms of dimer and/or tetramer [9]. Each monomer subunit contains 2 copper atoms and 4 submonomers combine into dimer with non-covalent bonds [10].

Abundant evidence proves that the properties of the *DBH* structural gene determine the activity of *DBH* in plasma, and further regulate angiocarpic function by impacting the synthesis of DA and NE [11]. Some SNPs of *DBH* can change the activity of *DBH* and reduce the level of DA in the brain to influence the occurrence of disease. In addition, human *DBH* is apparently polymorphic in different geographic regions or ethnic groups [12]. Susceptibility to attention deficit disorder is closely related to the *DBH* TaqI A2 allele [13]. Therefore, *DBH* polymorphisms are speculated to be correlated with susceptibility to PD, but few studies have investigated the relationship between these, especially in Chinese populations.

In this study, the correlation between *DBH* rs1611115, rs732833, and PD susceptibility was analyzed to provide a basis for the pathological explanation and clinical diagnosis of PD.

Material and Methods

The case and control groups

All selected participants were of Chinese Han ethnicity, were from southern China, had no blood relationship each other, and were outpatients in the Neurology Department of the People's Hospital of Haiyang. This clinical trial complied with the Declaration of Helsinki and was approved by the Ethics Committee of the People's Hospital of Haiyang. After participants provided signed informed consent. We recorded participant information into Excel forms, including name, age, sex, birthplace, contact information, previous disease history, family history, and medications, using specially trained epidemiological investigators. Diagnostic standards for PD patients were neuroimaging MRI and conventional ceruloplasmin examinations, and PD was then diagnosed by 2 professional neurologists after excluding other diseases, using the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [14].

The case group consisted of 95 PD patients (55 males and 40 females) aged 45–79 years, with an average age of 61.32±6.51. The exclusion criteria were:

- medical histories of encephalitis, craniocerebral injury, carbon monoxide poisoning, tumor or calcification in the basal nucleus, and poisoning with certain drugs;
- CT scan or MRI showing a focus correlated with clinical manifestations;
- family histories of PD or other diseases;
- antipsychotic or DA depletion drug-taking histories;
- a history of repeating stroke with stair-step progression of PD symptoms.

The control group consisted of 100 healthy people (56 males and 44 females) aged 46–82 years, with an average age of 63.84±7.63, who had physical examinations in this hospital during the same period. The exclusion criteria were:

- PD family history;
- histories of other nervous system diseases (e.g., AD, epilepsy, and cerebrovascular disease);
- previous psychiatric histories (e.g., schizophrenia, major depressive disorder, mental retardation, and mental disorders caused by physical diseases);
- illiteracy, color blindness, language barrier, or failing to communicate due to other reasons;
- cognitive function decline from previous cognitive level.

Methods

Extraction of genomic DNA from peripheral blood

Blood samples were collected by specially trained epidemiological investigators in accordance with national ethics criteria for

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Table 1. Primer sequences of *DBH* rs1611115, rs732833 polymorphisms.

SNP		Primer sequence
rs1611115	For.	5'-GAGGGATCAAGCAGAATGTC-3'
	Rev.	5'-TCAGTCTCACCACGGCAC-3'
rs732833	For.	5'-CGGCTGCAGGACGGCACTGTCC-3'
	Rev.	5'-GAGAGAAGCCCTTTGGAAGCTCC-3'

human genome research. All subjects underwent venipuncture to extract 3 ml of fasting peripheral blood into a blood collection tube with EDTA-2Na anticoagulant. The genomic DNA of all samples was extracted using a Beijing TIANGEN biochemical blood genome DNA extraction kit according to the manufacturer's instructions and then stored at -20°C until use.

The determination of genotypes in DBH polymorphisms

The GeneBank database of NCBI was used to find the complete sequence of *DBH* and the sequences of rs1611115 and rs732833 polymorphisms. The primer was designed by Primer Premier 5 and synthesized by Shanghai Sangon Biotech Co., Ltd. The primer sequences are listed in Table 1.

The PCR reaction system was a 25-μl mixture, including 2.0 μl DNA templates, 0.5 μl forward primer, 0.5 μl reverse primer, 12.5 μl PCR Master Mix, and 9.5 μl sterilized ddH_2O. PCR amplification conditions were: 94°C predegeneration for 3 min; then 30 cycles of 94°C degeneration for 30 s, 59°C annealing for 30 s, and 72°C extension for 1 min; with a final 72°C extension for 5 min. The quality and concentration of PCR products were tested by 1% agarose gel electrophoresis (AGE) and NanoDrop 2000 Scandrop.

The eligible PCR products were directly sequenced by Shanghai Sangon biotech Co., Ltd. to determine the genotypes of *DBH* polymorphisms in every subject.

Statistical analysis

The statistical analysis was accomplished by PASW Statistics 18.0 software. The chi-square test was used to check whether the genotype distributions matched Hardy-Weinberg equilibrium (HWE) in the control group. Allele and genotype comparisons of *DBH* polymorphisms between the cases and controls were done using the chi-square test. Differences in clinical characteristics between different genotypes were compared by chi-square test or *t* test. The effects of different genotypes and alleles on PD were estimated through odds ratio (OR) and 95% confidence interval (CI), and $P<0.05$ was considered as a statistically significant difference. All data are expressed as $\bar{\chi}\pm s$ or%.

Results

General characteristics of study subjects

We recruited 95 PD patients and 100 healthy controls into this study. In the case group, the sex ratio of males and females was 1.38: 1.00, with an average age of 62.32±6.51. The controls included 56 males and 44 females, at a ratio of 1.27: 1.00 and the average age was 63.84±7.63. The differences in age and sex between the 2 groups had no statistical significance ($P>0.05$), which indicated a well-matched study population.

The genotype distributions of DBH polymorphisms in case and control groups

The genotype distributions of *DBH* rs1611115 and rs732833 polymorphisms in the control group conformed to HWE ($P=0.79$, 0.09 respectively), which indicated our subjects formed a representative group.

The genotype and allele distributions of *DBH* rs1611115 and rs732833 SNPs are shown in Table 2. The CC, CT, and TT genotype frequencies of *DBH* rs1611115 were 42.11%, 44.21%, and 13.68% in the case group and 59.00%, 35.00%, and 6.00%, respectively, in the control group, and the homozygous TT genotype frequency was significantly different between the 2 groups ($P<0.05$), but not CT genotype ($P=0.59$). TT genotype increased risk of PD by 1.95 times compared with the common CC genotype (OR=2.95, 95%CI=1.02–8.51). Moreover, C allele frequencies of PD patients were also higher than that of the controls ($P=0.01$), and C allele carriers had a 1.81 times higher risk of PD than T allele carriers (OR=1.81, 95%CI=1.17–2.82). Regarding rs732833, we learned that GG, AG, and AA genotype frequencies were 32.63%, 54.74%, 12.63% in cases and 37.00%, 54.00%, 9.00% in controls, and G, A allele frequencies were 60.00%, 40.00% and 64.00%, 36.00% in case and control groups, respectively, which demonstrated that the genotype and allele distributions of rs732833 between the 2 groups had no statistical significance ($P>0.05$).

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Table 2. Comparisons of *DBH* rs1611115, rs732833 genotype and allele distributions.

Genotype/allele	Case n=95 (%)	Control n=100 (%)	χ^2	P	OR (95% CI)
rs1611115					
CC	40 (42.11)	59 (59.00)	–	–	1.00
CT	42 (44.21)	35 (35.00)	0.29	0.59	1.17 (0.66–2.07)
TT	13 (13.68)	6 (6.00)	4.26	0.04	2.95 (1.02–8.51)
C	122 (64.21)	153 (76.50)	–	–	1.00
T	68 (35.79)	47 (23.50)	7.08	0.01	1.81 (1.17–2.82)
rs732833					
GG	31 (32.63)	37 (37.00)	–	–	1.00
AG	52 (54.74)	54 (54.00)	0.29	0.59	0.84 (0.44–1.59)
AA	12 (12.63)	9 (9.00)	0.09	0.77	1.16 (0.42–3.18)
G	114 (60.00)	128 (64.00)	–	–	1.00
A	76 (40.00)	72 (36.00)	0.66	0.42	1.19 (0.79–1.79)

Clinical characteristics of PD patients in *DBH* polymorphisms

To obtain an accurate result, the clinical characteristics of PD patients were analyzed in different genotypes of the *DBH* polymorphisms (Table 3). We found that cognition of the PD patients was significantly different between CC and CT+TT genotypes of rs1611115 (P=0.047). However, there was no significant difference in other clinical characteristics (P>0.05), such as sex, age at onset of symptoms, anxiety, and depression. No significant difference in clinical characteristics was observed between the minor allele carriers and non-carriers of rs732833.

Discussion

PD usually occurs after the age of 60, with major clinical features of tremor, hypermyotonia, and decreased movement. The primary pathological features are decoloration, degeneration, and deletion of dopaminergic neurons in the substantia nigra pars compacta, and degeneration of substantia nigra-striatum, which leads to significant decrease in the content of striatum DA and relative hyperfunction of acetylcholine systemic function. When striatum DA content declines to 80%, patients appear hypermyotonia and action is reduced. The clear reduction in DA content in mesolimbic and cerebral cortex systems may result in advanced neural activity disorders, such as hypophrenia, abnormal emotional behavior, and paraphasia. It is reported that the average survival time from PD diagnosis to death is 15 years [15]. The pathogenesis of PD is very complex and is still not completely understood. Studies have reported that the occurrence of PD is correlated with genetic variation and environmental factors [16–18]. Many studies have shown that environmental toxins induce the degeneration of substantia nigra-striatum dopaminergic neurons, and air and heavy metal pollution also influence PD [19,20]. Recently, genetic factors were studied widely for influence on PD susceptibility.

DBH, a mixed oxidase, makes use of the hydroxyl group (–OH) formed by molecular oxygen to join into dopamine β carbon atom and form NE enzyme, which is a biosynthetic enzyme in the CA metabolic system. Biochemical and immunological functions of DBH in blood circulation are similar to that in the nervous system and adrenal medulla. *DBH* activity increases when *DBH* and NE are released from sympathetic nerve endings in sympathetic activation. In consequence, *DBH* can act as the index of sympathetic nerve functional activities and it can be used in studies of neurology, pathology, the mechanism of acupuncture analgesia, and other fields (e.g., endocrine system diseases). The changes in *DBH* activity and number can give rise to abnormal DA and NE metabolic function. Furthermore, 19bp in the 5' end of *DBH* is an insertion deletion fragment that regulates promoter activity, thereby modulating *DBH* activity and level of plasma and cerebrospinal fluid [21]. *DBH* is highly polymorphic and is associated with the activity of *DBH*, which is a major quantitative trait locus that controls enzyme activity in serum and cerebrospinal fluid [12,22,23]. A number of *DBH* SNPs that lead to different genotypes in individuals have been found. *DBH* genotypes can determine the differences of *DBH* expressions and functions between diverse individuals and affect the ultimate biological effect *in vivo*.

Sternberg et al. measured the *DBH* activity of cerebrospinal fluid in 30 patients with schizophrenia and schizoaffective disorder

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Table 3. Clinical characteristics of PD patients in *DBH* polymorphisms.

Characteristics	rs1611115 genotypes		*P*	rs732833 genotypes		*P*
	CC	CT+TT		GG	GA+AA	
Gender			0.438			0.981
Male (%)	25 (62.50)	30 (54.55)		18 (58.06)	37 (57.81)	
Female (%)	15 (37.50)	25 (45.45)		13 (41.94)	27 (42.19)	
Onset age	61.97±5.87	60.93±7.64	0.794	61.76±7.14	60.81±6.14	0.816
Onset symptoms			0.986			0.944
Static tremor (%)	19 (47.50)	28 (50.91)		15 (48.39)	34 (53.12)	
Bradykinesia (%)	9 (22.50)	11 (20.00)		9 (29.03)	16 (25.00)	
Rigidity (%)	7 (17.50)	9 (16.36)		6 (19.35)	11 (17.19)	
Others (%)	5 (12.50)	7 (12.73)		1 (3.23)	3 (4.69)	
Cognition (%)			0.047			0.110
Normal (%)	22 (55.00)	19 (34.55)		17 (54.84)	24 (37.50)	
Abnormal (%)	18 (45.00)	36 (65.45)		14 (45.16)	40 (62.50)	
Anxiety			0.644			0.372
Absence (%)	23 (57.50)	29 (52.73)		19 (61.29)	33 (51.56)	
Presence (%)	17 (42.50)	26 (47.27)		12 (38.71)	31 (48.44)	
Depression			0.151			0.679
Absence (%)	11 (27.50)	23 (41.82)		12 (38.71)	22 (34.38)	
Presence (%)	29 (72.50)	32 (51.18)		19 (61.29)	42 (65.62)	

conforming to research diagnostic criterion (RDC), and found that the *DBH* activity of patients with better effect of classic antipsychotic drugs is apparently lower than that of other patients [24]. Additionally, the adaptation level of patients with low activity is usually better before the patient becomes ill. van Kammen et al. [25] reported that serum *DBH* level of patients with schizophrenia is obviously lower than that of non-schizophrenia controls, and this result has been confirmed in a schizophrenia autopsy study [26]. Nevertheless, some subsequent studies adopted rigorous diagnostic criteria for case diagnosis, and found that there is no difference in the expression of *DBH* between patients with schizophrenia and controls [24,27]. Goldin et al. demonstrated that there is evidence to prove the linkage between the *loci* influencing plasma *DBH* level and blood type [28]. TaqI polymorphism A2/A2 genotype in *DBH* intron 5 is positively related to PD susceptibility, while C-1021T-T/T genotype (serum low-enzyme activity type) of 5' end is negatively associated with the susceptibility to PD [29]. Therefore, the correlation between *DBH* and mental illness has heterogeneity and may interact with multiple genes. Experiments have discovered that *DBH* activity is clearly lower in cerebrospinal fluid of PD patients, which shows that *DBH* may be involved in the pathological process of PD [30]. In addition, A2 allele and A2/A2 genotype frequencies of *DBH* are more frequent in PD patients than in controls in Han populations from Shanghai, and individuals with A2 allele had higher risk of PD [11].

In the present study, TT genotype and T allele frequencies of *DBH* rs1611115 (–1021T>C) polymorphism were higher in PD patients than in controls. These differences indicate that the rs1611115 TT genotype is correlated with susceptibility to PD in the Han population in southern China. TT genotype and T allele may increase the risk of PD by about 2.95 and 1.81 times, respectively. However, Chun et al. suggested that both the genotypes and alleles of rs1611115 had no significant associations with the risk of PD [31]. Ross et al. indicated that T allele of rs1611115 increased the PD risk in Polish subjects, decreased the PD risk in Norse subjects, and had no significant association with PD in Irish and American subjects [32]. These differences may be caused by sample size and ethnicity. We found that cognition of PD patients was different between CC and CT+TT genotypes of rs1611115, with 2-sided *P*=0.047. However, because the sample size was small, this result does not prove

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that rs1611115 is associated with the cognition of PD patients. For rs732833, the number of AA genotypes and A alleles were higher in cases than in controls, but the differences had no statistical significance. Our data show that the rs732833 polymorphism has no significant association with the onset of PD. The present study explored the effect of rs732833 on PD for the first time. Our study population was restricted to Han people in southern China. The association of DBH rs1611115 and rs732833 polymorphisms with PD in other populations needs to be further studied with larger sample sizes.

This study provides an elementary understanding of the role of *DBH* polymorphisms in the occurrence of PD. This study had many limitations, although the representativeness of our subjects was good. Firstly, the sample size was small. Secondly, the results were not adjusted for confounding factors. Thirdly, our study only included people of 1 race. Finally, gene-gene and gene-environment interactions were not examined. All of these limitations might have affected the accuracy of the presented results.

Conclusions

DBH mutation may be involved in PD development, but this conclusion needs to be confirmed by further studies. The association between *DBH* rs1611115, but not rs732833, polymorphism and PD susceptibility is proven in the Han population in southern China. To obtain more accurate and convincing results and achieve the goals of early diagnosis and timely treatment, further well-designed studies should be conducted.

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