

Association Analyses of *SNAP25*, *HNMT*, *FCHSD1*, and *DBH* Single-Nucleotide Polymorphisms with Parkinson's Disease in a Northern Chinese Population

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Purpose: Sequencing potentially causal and susceptible genes and genome-wide association studies in samples from Parkinson's disease (PD) patients has revealed several related loci. The genes for synaptosome-associated protein of 25 kDa (*SNAP25*), histamine-N-methyltransferase (*HNMT*), FCH and double SH3 domains 1 (*FCHSD1*) and dopamine β -hydroxylase (*DBH*) are candidate loci and have not been studied in a northern Chinese population. We explored the genetic distribution of four single-nucleotide polymorphisms (rs3746544, rs11558538, rs456998, rs129882) located on *SNAP25*, *HNMT*, *FCHSD1* and *DBH*, respectively.

Patients and Methods: A total of 330 patients with sporadic PD and 332 healthy controls (HCs) were recruited from a northern Chinese population. Polymerase chain reaction restriction fragment length polymorphism was used to genotype these four SNPs.

Results: After statistical analyses and correction of the genotyping results, the mutant-allele T in rs456998 of *FCHSD1* was found to be significantly related to reducing the PD risk ($P = 0.029$, OR = 0.754, 95% CI = 0.586–0.971, power = 0.591). However, rs3746544, rs11558538, and rs129882 did not show an association with PD.

Conclusion: *FCHSD1* rs456998 may have a protective role in PD in a northern Chinese population, but more studies are needed to support this suggestion.

Keywords: Parkinson's disease, single nucleotide polymorphism, *SNAP25*, *HNMT*, *FCHSD1*, *DBH*, association study

Introduction

Parkinson's disease (PD) is a neurological disease. It is characterized mainly by degeneration of dopaminergic neurons and noradrenergic neurons, and deposition of Lewy bodies in surviving neurons. Researchers have found that PD is related to genetics, ethnicity, geographical variation, tobacco smoking, pesticide exposure, fat, and other risk factors.^{1–3} PD pathogenesis is incompletely understood. However, numerous studies have shown that PD is associated with toxic dysregulation of α -synuclein, mitochondrial dysfunction, and oxidative stress.^{4–6} Complex interactions between genetic and environmental factors are believed to contribute to the development of PD.⁷ Many causal and susceptible loci were found and duplicated based on GWAS. However, simple genetic factors may cause PD (or be associated with PD) and a genetic contribution to PD onset has been established.

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There were a large number of studies aimed at finding accurate association between PD and genes in different populations. Nevertheless, most PD cases are sporadic. In particular, the predominant sporadic variant of PD seems to be associated with a combination of common variants within several genes. In addition, like many genetics-related diseases, genome-wide association studies (GWAS) on PD have been extensive. Increasing numbers of studies have highlighted a clear genetic contribution among PD patients. Several causal loci and susceptible loci have been found and duplicated in different ethnicities and populations based on GWAS and the function of individual genes.

Studies on the level of synaptosome-associated protein of 25 kDa (SNAP25) in the presynaptic plasma membrane have demonstrated synaptic dysfunction to be an initial event of the subsequent neurodegeneration in several neurodegenerative diseases of the central nervous system. Also, *SNAP25* polymorphisms have been associated with distinct neuropsychiatric and neurological disorders, such as PD.⁸ Histamine-N-methyltransferase (HNMT) can degrade the small-molecule neurotransmitter histamine, and a common genetic polymorphism in exon 4 of *HNMT* is associated with PD.^{9,10} FCH and double SH3 domains 1 (*FCHSD1*) is predicted to function in actin dynamics. Fernandez-Santiago et al showed that rs456998 of *FCHSD1* combined with rs8111699 of serine/threonine kinase 11 (*STK11*), rs1732170 of glycogen synthase kinase 3 beta (*GSK3B*), and rs356219 of synuclein alpha (*SNCA*) genes were related to PD in a Spanish population.¹¹ Dopamine (DA) in synaptic vesicles is converted to norepinephrine (NE) by the enzyme dopamine β -hydroxylase (*DBH*). A GWAS of PD-sibling pairs among a UK population revealed linkage to the chromosomal location 9q, which overlaps with the *DBH* locus.¹² Moreover, Ghosh et al proposed that *DBH* is a modifier gene of PD in a study in an eastern Indian population.¹³

In recent years, we have published the results of association analyses with PD in northern China based on the candidate genes and GWAS of PD.^{14–17} However, accurate research on the correlation between these four gene loci (*SNAP25*, *HNMT*, *FCHSD1*, and *DBH*) and PD in China is lacking. Several studies have aimed to find an accurate association between PD and genes in different populations. Furthermore, thorough understanding of the genetic architecture of the common, complex forms of PD in northern China and data accumulation are rational and important aims.

We analyzed the single-nucleotide polymorphisms (SNPs) on *SNAP25*, *HNMT*, *FCHSD1*, and *DBH* genes in a cohort of Chinese patients with sporadic PD to ascertain their possible involvement in PD.

Patients and Methods

Ethical Approval of the Study Protocol

This study was conducted in accordance with the Helsinki Declaration, and was approved by the Ethics Association of China Medical University (Shenyang, China). Participants provided written informed consent.

Study Cohort

A total of 330 PD patients (164 males and 166 females) and 332 healthy controls (HCs; 193 males and 139 females) from northern China were recruited randomly. The age at enrollment of PD patients was 62.42 ± 9.59 years, and the age at PD onset was 60.98 ± 10.23 years. The age at enrollment of the HC group was 68.95 ± 13.97 years. Patients were diagnosed with idiopathic PD by a very experienced neurologist at the First Affiliated Hospital of China Medical University. Patients met the diagnostic criteria for PD set by the British Brain Bank.¹⁸ HCs did not have a neurodegenerative disease.

Genotyping

Samples of peripheral blood were collected from all participants. Genomic DNA was extracted using the sodium dodecyl sulfate–protease K–phenol–chloroform method. According to published sequences in GenBank, we designed forward primers and reverse (Table S1). We synthetically generated a *Xho* I restriction endonuclease site in the amplified product of the rs3746544 locus using a mismatched polymerase chain reaction (PCR) primer based on published sequences. The products of PCR amplification and enzyme digestion were verified by sequencing.

Polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) was used to identify SNPs. The PCR system (in a final volume of 10 μ L) consisted of 5 μ L of 2 \times DreamTaq[®] Green Master Mix (Thermo Scientific, Waltham, MA, USA), 10 ng of genomic DNA, 0.2 μ M of forward primer, and 0.2 μ M of reverse primer (Genewiz, Tianjin, China). For rs3746544 and rs129882, PCR amplification was done with an initial denaturation step at 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 30 s, annealing at 60°C for 30

s, extension at 72°C for 30 s, and an eventual elongation at 72°C for 4 min. For rs456998 and rs11558538, PCR amplification was undertaken with annealing at 62°C for 30 s, and the other steps were the same as those for the loci stated above. The PCR products of rs3746544 on *SNAP25*, rs11558538 on *HNMT*, and rs129882 on *DBH* were digested at 37°C for 1 h in 10 µL of H buffer containing 2 µL of PCR product, 1 µL of 10× H buffer, 6.75 µL of double-distilled H₂O, and 0.25 µL of restriction enzymes (*Xho* I, *Eco*R V, *Sph* I), all of which were from TaKaRa Biotechnology (Shiga, Japan). The PCR product of rs456998 on *FCHSD1* was digested at 37°C for 1 h in 10 µL of T buffer containing 2 µL of PCR product, 1 µL of 10× T buffer, 1 µL of bovine serum albumin (0.1%), 5.75 µL of double-distilled H₂O, and 0.25 µL of *Afa* I, all of which were from TaKaRa Biotechnology. The enzyme-digested products of rs129882 and rs11558538 were separated on 1% agarose gel. The enzyme-digested products of rs3746544 and rs456998 were isolated on 2% agarose gel. Then, fragments were viewed on a gel-imaging system (Tanon 2500R, Shanghai, China).

For rs3746544 of *SNAP25*, the PCR products of length 225 bp (which represent the undigested mutant-type allele T) were digested into 205-bp and 20-bp fragments (which represent the digested wild-type allele G). The loci of other SNPs were genotyped in the same manner. For rs11558538 of *HNMT*, PCR products of length 307 bp (which represent the undigested wild-type allele C) were digested into 259-bp and 48-bp fragments (which represent the mutant-type allele T). For rs456998 of *FCHSD1*, PCR products of length 195 bp (which represent the undigested mutant-type allele T) were digested into 128-bp and 67-bp fragments (which represent the wild-type allele G). For rs129882 of *DBH*, PCR products of length 517 bp (which represent the undigested wild-type allele C) were digested into 369-bp and 148-bp fragments (which represent the mutant-type allele T).

Statistical Analyses

First, the Hardy–Weinberg equilibrium was tested in samples from the PD patients and HCs. Then, the results were analyzed by SPSS 20.0 (IBM, Armonk, NY, USA) and PS 3.1.6 (Power and Sample Size Calculations; <https://biostat.app.vumc.org/wiki/Main/PowerSampleSize/>). Multiple comparisons necessitated application of the Bonferroni correction ($\alpha = 0.05/4 = 0.0125$). $P \leq 0.05$ (two-sided) was considered significant.

Results

Genetic Parameters and Association Analyses

The Hardy–Weinberg equilibrium was tested on samples from the PD group and HC group. The P -value for rs3746544, rs11558538, rs456998, and rs129882 in the PD group was 0.6262, 0.0944, 0.2247, and 0.3507, whereas it was 0.0605, 0.4399, 0.6551, and 0.1824, respectively, in the HC group. The allelic and genotypic frequencies of the PD group and HC group, as well as the allelic and genotypic frequencies of rs456998 based on sex, are shown in Table 1. The frequency of rs456998 on *FCHSD1* was significantly different between the PD group and HC group. The T allele in the PD group ($P = 0.029$, odds ratio (OR) = 0.754, 95% confidence interval (CI) = 0.586–0.971, power = 0.591) was less frequent than that in the HC group. However, other SNPs showed no significant association between the PD group and HC group (rs3746544: $P = 0.07$, OR = 0.796, 95% CI = 0.622–1.018, power = 0.443; rs11558538: 0.687, 1.123, 0.660–1.911, 0.071; rs129882: 0.773, 1.037, 0.827–1.299, 0.061). Then, we investigated the sex differences of rs456998 (Table 1) between PD patients and HCs, but there was no obvious difference (males: $P = 0.066$, OR = 0.713, 95% CI = 0.504–1.009, power = 0.481; females: 0.294, 0.806, 0.555–1.171, 0.206).

Genotype Distributions of rs456998 Between PD Patients and HCs Based on Four Genetic Models

There was no significant difference between the PD group and HC group based on a homozygous co-dominant model ($P = 0.411$, OR = 0.738, 95% CI = 0.387–1.409, power = 0.259), heterozygous co-dominant model (0.017, 0.669, 0.483–0.926, 0.942), dominant model (0.015, 0.679, 0.498–0.925, 0.935) and recessive model (0.748, 0.861, 0.457–1.622, 0.108) after application of the Bonferroni correction ($\alpha = 0.05/4 = 0.0125$) (Table 2).

Discussion

PD is the second most common progressive neurodegenerative disorder (after Alzheimer's disease).¹⁹ Several studies have attempted to reveal the relationship between genes and PD. A wealth of loci of candidate genes have been found to be associated with PD, and this connection has been confirmed in different populations. However,

Table 1 Distribution of Allelic and Genotypic Frequencies in Four Investigated SNPs and One of rs456998 Based on Sex

SNPs	Types	PD (%)	Control (%)	OR (95% CI)	p value	Power
rs3746544	T	474 (71.820)	506 (76.200)	0.796 (0.622–1.018)	0.07	0.443
	GG	28 (8.480)	25 (7.530)			
	GT	130 (39.390)	108 (32.530)	NA	0.126	NA
	TT	172 (52.120)	199 (59.940)			
rs11558538	T	30 (4.550)	27 (4.070)	1.123 (0.660–1.911)	0.687	0.071
	CC	302 (91.520)	305 (91.870)			
	CT	26 (7.880)	27 (8.130)	NA	0.569	NA
	TT	2 (0.600)	0		(corrected)	
rs456998	T	142 (21.520)	177 (26.660)	0.754 (0.586–0.971)	0.029	0.591
	GG	207 (62.730)	177 (53.310)			
	GT	104 (31.520)	133 (40.060)	NA	0.046	NA
	TT	19 (5.750)	22 (6.630)			
Male	T	69	105 (0.272)	0.713 (0.504–1.009)	0.066	0.481
	Number	328	386			
	GG	103	104			
	GT	53	73			
	TT	8	16	NA	0.170	NA
	Number	164	193			
Female	T	73	72 (0.259)	0.806 (0.555–1.171)	0.294	0.206
	Number	332	278			
	GG	104	73			
	GT	51	60			
	TT	11	6	NA	0.074	NA
	Number	166	139			
rs129882	T	233 (35.300)	229 (34.490)	1.037 (0.827–1.299)	0.773	0.061
	CC	142 (43.030)	137 (41.270)			
	CT	143 (43.330)	161 (48.490)	NA	0.259	NA
	TT	45 (13.640)	34 (10.240)			

Note: Total PD and control numbers are 330 and 332, respectively.

Table 2 Analysis Under Different Genetic Models for rs456998 Locus

Genetic Model	Types	PD	Control	p value	OR (95% CI)	Power
Homozygous	TT	19	22 (0.111)	0.411	0.738	0.259
Co-dominant	GG	207	177		(0.387–1.409)	
Heterozygous	GT	104	133	0.017	0.669	0.942
Co-dominant	GG	207	177		(0.483–0.926)	
Dominant	GG	207	177	0.015	0.679	0.935
	TT+TG	123	155 (0.467)		(0.498–0.925)	
Recessive	TT	19	22	0.748	0.861	0.108
	GG+TG	311	310		(0.457–1.622)	

Note: $\alpha = 0.05/4 = 0.0125$.

Abbreviations: OR, odds ratio; CI, confidence interval; NA, not available.

research on *SNAP25*, *HNMT*, *FCHSD1*, and *DBH* in northern China is lacking. Studies have shown that these four genes may be involved in PD pathogenesis.^{8,10,11,13} To assess the genetic background related to PD more

comprehensively, we conducted genotype analyses and correlation studies on the newly discovered SNPs of the four genes to accumulate genetic information on PD in a Chinese population.

SNAP25 is located on chromosome 20p12.2. It encodes a 25-kDa presynaptic plasma-membrane protein involved in the regulation of neurotransmitter release. *SNAP25* has been found to be associated with neuropsychiatric and neurological disorders such as autism and Alzheimer's disease.²⁰ Agliardi et al investigated five SNPs (rs363050, rs363039, rs363043, rs3746544, and rs1051312) on *SNAP25* to analyze a possible correlation with PD. They found that the interaction of these five SNPs had an effect on reducing the PD risk in a case-control study in Italy (2019). We discovered that genotypic and allelic frequencies on the rs3746544 locus were not significantly different between the PD group and HC group.

HNMT is located on chromosome 2q22.1 and is responsible for encoding HNMT. Histamine is a small-molecule neurotransmitter synthesized from histidine by decarboxylase and degraded by HNMT. Studies have shown that histamine infusion can induce the death of brain neurons in rats, whereas HNMT can inactivate histamine in the brain.²¹ The SNP rs11558538 of *HNMT* is also known as Thr105Ile, which denotes a rs11558538 C > T mutation. The association of this SNP with PD is controversial. Keeling et al suggested that the Thr105Ile variant was not a factor in PD progression in North American Caucasians.²² However, in a study of populations in the USA and Europe, Palada et al suggested a lower frequency of the rs11558538 C allele in a PD group.¹⁰ Based on genotypic and allele frequencies on the rs11558538 locus, we found no significant differences between PD patients and HCs in a northern Chinese population after correction of the genotyping results.

FCHSD1 is located on chromosome 5q31.3. It is a member of a gene group involved in the synthesis of a protein from the mechanistic target of rapamycin kinase (mTOR) signaling pathway. How the mTOR signaling pathway affects PD is not known, but accumulating evidence suggests that the mTOR signaling pathway plays a significant part in the growth, death, survival, metabolism, and proliferation of cells.^{23,24} In recent years, studies have suggested that dysregulation of the mTOR signaling pathway is involved in PD.^{25,26} However, whether the mTOR signaling pathway has a protective role or toxic effect in PD is controversial. Fernandez-Santiago et al suggested that genetic linkage of the loci of *SKT11* rs8111699, *FCHSD1* rs456998, *GSK3B* rs1732170, and *SNCA* rs356219 was significantly associated with an increased risk of PD in a Spanish population.¹¹ However, in other research, over-expression of wild-type mTOR has been shown to protect

neurons from damage.^{25–27} Intriguingly, in the present study, distributions of genotypic and allelic frequencies on the *FCHSD1* rs456998 locus were significantly different between the PD group and HC group, data that are consistent with results from PDGene ($P < 0.05$) (www.pdgene.org/). However, the four genetic models we created were not significantly different after application of the Bonferroni correction. Our results suggested that the minor allele T of rs456998 might have a protective role in PD. However, the influence of the power value after statistical analyses suggests that more association studies are needed to verify our results.

DBH is located on chromosome 9q34.2 and encodes a 69.065-kDa DBH protein. DBH is an enzyme that converts DA to NE in catecholaminergic neurons.^{13,28,29} DBH regulates DA storage in synaptic vesicles, thereby maintaining the DA:NE ratio in vesicles for appropriate synaptic transmission.³⁰ Thus, an abnormality in *DBH* may be related to susceptibility to PD. Several SNPs that may be related to PD have been reported: rs1611115 (–1021 T > C), rs2283123, rs2007153, rs1611131, rs129882, rs1108580, rs732833, and rs5302.^{13,31–34} An investigation in an east Indian population by Ghosh et al found that the rs129882 T allele of *DBH* was more frequent in the case group than that in the control group. However, this genetic locus did not show differences in genotypic and allelic frequencies between the PD group and HC group in the present study.

Conclusions

Our results indicated that rs456998 might be related to PD. However, the other three SNPs tested did not show an obvious association. Beyond enriching the genetic profile associated with PD in a northern Chinese population, our results suggest that, with the help of GWAS, more candidate loci can be researched in PD, and that this is a valuable research direction.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors have declared that no competing interests exist.

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