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SHORT COMMUNICATION

Associations of common variants in *TAAR5*, *OR6C70,* and *GBA* with hyposmia in Han Chinese individuals with Parkinson's disease

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Abstract

Hyposmia is one of the cardinal symptoms of Parkinson's disease (PD), with a considerably high prevalence rate in PD individuals. However, some individuals still retain normal olfactory function. Recent studies have shown that genetic factors may play a role in such a phenomenon. This study aimed to explore the potential genetic factors underlying the variation of olfactory function among PD individuals. Two hundred and three Han Chinese individuals with PD were recruited into this study. All the individuals underwent detailed clinical assessment conducted by experienced neurologists. High-throughput sequencing was performed to identify gene variants associated with PD. *TAAR5*, *OR6C70,* and *GBA* were included in the association analysis. In our study, 85 out of 203 individuals (41.9%) reported normal olfaction, and the other 118 (58.1%) reported hyposmia. Genotype and allele logistic regression models were applied to association analysis. We did not find any significant association of *TAAR5* and *OR6C70* with hyposmia. However, we found that *GBA* rs762488 was associated with increased hyposmia risk (P = 0.036, OR = 3.05, 95% CI = 1.08–8.63), while *GBA* rs1800438 was associated with decreased hyposmia risk (P = 0.032, OR = 0.47, 95% CI = 0.24–0.94). In conclusion, this study revealed the association of *GBA* with hyposmia, indicating the genetic involvement in PD hyposmia variation. However, we did not replicate previous results (*TAAR5* and *OR6C70*) in this study. Further studies with larger sample sizes in different populations are warranted.

Keywords: Parkinson's disease; Olfaction; *TAAR5*; *OR6C70*; *GBA*

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1. Introduction

The olfactory system is the bodily structures that serve the sense of smell and enable animals to identify the environmental information from specific odors[1]. Hyposmia is characterized by the loss of odor detection, identification, or memory[2] and is a common symptom in a plethora of neurodegenerative diseases[2,3].

More than half of Parkinson's disease (PD) individuals reported hyposmia[4], which precedes the occurrence of motor symptoms. However, olfactory function remains

normal in some cases long after motor symptoms onset[5]. The detailed mechanism that contributes to the differences in olfactory function in individuals is yet to be clarified; therefore, numerous studies focusing on the underlying genetic variations of olfactory function in PD patients have been conducted[6-8].

Interestingly, a recent whole-genome sequencing analysis revealed that variants in *OR6C70* (encoding the olfactory receptor family six subfamily C member 70) and *TAAR5* (encoding the trace amine associated receptor 5) affect the different perceptions of specific odors between different individuals. Genetic variations in these two genes may partially underlie the olfactory recognition differences[6]. To date, these conclusions have not been replicated in other studies or populations. To our concern, PD is a disease well associated with olfactory dysfunction. Whether the aforementioned gene variants contribute to the differences in olfactory function of PD individuals remains unclear. In our study, we aimed to explore the potential association of *OR6C70* and TAAR5 with hyposmia in Han Chinese individuals with PD. In addition, *GBA* (glucocerebrosidase gene, a common PD causative gene) was also included in this study since previous studies have demonstrated that some PD individuals with mutations in *GBA* have reported hyposmia[8,9].

2. Materials and methods

2.1. Subjects

Two hundred and three Han Chinese individuals with PD, who fulfilled either the 2015 Movement Disorder Society clinical diagnostic criteria[10] or the UK Brain Bank criteria[11] for PD, were recruited consecutively from the Department of Neurology of the Second Affiliated Hospital of Soochow University (Suzhou, China) from January 2013 to December 2019. Individuals with severe cognitive impairment who cannot cooperate with the assessment were excluded from the study. Our study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University (JD-LK-2018-061-01). Detailed clinical data and blood samples were collected after written informed consent were obtained from all the participants.

2.2. Clinical assessment

The demographics, including age, age at onset, duration and gender, of enrolled PD individuals were recorded. Disease severity was assessed by the Unified Parkinson Disease Rating Scale (UPDRS) Part III[12] during the "on" state. Prescribed levodopa equivalent doses of dopaminergic medication were calculated according to the protocol[13]. Non-motor symptoms (NMSs) were assessed by the Non-Motor Symptoms Questionnaire (NMSQ)[14]. We defined hyposmia by the item in NMSQ, "Loss or change in your ability to taste or smell"[15]. PD individuals with taste dysfunction were excluded from the study.

2.3. High-throughput sequencing

Genomic DNA of 203 individuals was extracted from the peripheral blood using the QIA ampDNA Blood Maxi Kit (QIAGEN, Valencia, CA, USA). Then, whole-exome sequencing was performed as described in our previous study[16,17]. *TAAR5*, *OR6C70,* and *GBA* were included in our genotype analysis. Single nucleotide polymorphisms (SNPs) and insertions/deletions (Indels) located within the exons and exon-intron boundaries of these three genes were then identified as described previously[17]. After variants calling and annotation, the data were compared to our in-house data to distinguish between common and rare variants[16]. To achieve adequate statistical power, we excluded rare variants[16]. Linkage disequilibrium was estimated using SHEsis (offline version)[18], and SNPs with $r^2 \geq 0.80$ were defined as being in linkage disequilibrium.

2.4. Statistical analysis

In univariate analysis, Kolmogorov–Smirnov test or Shapiro–Wilk test was used to test if the variables were normally distributed in 203 PD individuals. Differences in age, duration, UPDRS-III score, and other variables between hyposmia and non-hyposmia groups were compared using Student's *t*-test (when they were normally distributed) or non-parametric Mann–Whitney U-test (when they were not normally distributed). Gender and other dichotomous variables were compared with Chi-square test or Fisher's exact test. Binary logic regression to hyposmia was used to explore the potential associated factors.

Associations were quantified with the odds ratio (OR) and 95% confidence intervals (CIs). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All tests were performed using IBM SPSS Statistics, version 25.0 (IBM Corporation, NY, USA).

3. Results

Of 203 PD individuals, 118 (58.1%) reported hyposmia, and 85 (41.9%) reported normal olfactory function. According to the demographic analysis, male individuals with and without hyposmia were 76 (57.6%) and 49 (64.4%), respectively. We did not find any significant differences in the demographic profiles between PD individuals with and without hyposmia; these demographic parameters include gender, age, age of onset, duration, disease severity, and prescribed dopaminergic medication dose (Table 1).

In our genotype analyses, we found 91 SNPs and 0 Indel within the exons and exon-intron boundaries of *OR6C70*,

TAAR5, and *GBA*. We did not find the previously reported rare *TAAR5* p.Ser95Pro mutation in any of the individuals. Eighty-three of the 91 SNPs were rare variants (minor allele frequency < 0.10) and were excluded from subsequent analysis for better statistical power. Finally, eight common SNPs (*TAAR5* rs3813355, rs3813354; *OR6C70* rs60683621; *GBA* rs1800473, rs762488, rs2009578, rs2974923, and rs1800438) and 0 Indel were included in our association analyses and none of them was in linkage disequilibrium. In our genotype logistic regression analyses to hyposmia, considering age, gender, duration, motor symptoms and other demographics, we found that none of the SNPs was associated with hyposmia (Table 2).

In our allele logistic regression analyses to hyposmia, considering age, gender, duration, motor symptoms and other demographics, we did not find the three common SNPs in *TAAR5* and *OR6C70* being significantly associated with hyposmia. However, we found that *GBA* rs762488 was associated with increased hyposmia risk (P = 0.036, OR = 3.05, 95% CI = 1.08–8.63), and *GBA* rs1800438 was associated with decreased hyposmia risk (P = 0.032, OR = 0.47, 95% CI = 0.24–0.94) (Table 3).

Table 1. Demographic profiles of PD individuals with/ without hyposmia

	Non-hyposmia (n=85)	Hyposmia (n=118)	P*
Gender (male, %)	49 (57.6%)	76 (64.4%)	0.381
Age (year)	60.59±11.78	63.00±9.22	0.212
Age of onset (year)	56.18±12.74	57.85±9.18	0.598
Duration (month)	52.58±42.42	61.47±53.66	0.471
LED	420.36±250.73	446.71±255.68	0.535
UPDRS-III	20.26±10.40	23.25±13.81	0.153

LED, Levodopa equivalent dose; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale – Part III. *Mann–Whitney U-test

Table 2. Genotype logistic regression analysis of hyposmia in 203 PD individuals

	Regression coefficient	P*	OR	95% CI
Gender (male, %)	−0.382	0.220	0.68	0.37–1.26
Age (year)	−0.028	0.949	0.97	0.41–2.28
Age of onset (year)	0.054	0.902	1.05	0.45–2.47
Duration (month)	0.008	0.834	1.01	0.94–1.08
LED	0.000	0.711	1.00	1.00–1.00
UPDRS-III	0.016	0.250	1.02	0.99–1.04
rs3813355	0.344	0.202	1.41	0.83–2.39
rs3813354	−0.134	0.655	0.87	0.49–1.57
rs60683621	0.109	0.603	1.12	0.74–1.68
rs1800473	−0.378	0.340	0.69	0.32–1.49
rs762488	0.779	0.073	2.18	0.93–5.11
rs2009578	−0.390	0.244	0.68	0.35–1.31
rs2974923	0.074	0.724	1.08	0.71–1.62
rs1800438	−0.412	0.105	0.66	0.40–1.09

CI, Confidence interval; LED, Levodopa equivalent dose; OR, Odds ratio; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale - Part III. *Logistic regression adjusted for gender, age, age of onset, motor symptoms, LED, and UPDRS-III

4. Discussion

PD is the second most common neurodegenerative disease with many motor and non-motor symptoms[19,20]. Hyposmia is one of the core non-motor symptoms of PD and is part of the critical clinical diagnostic criteria for PD[10]. Nevertheless, hyposmia is a condition with incomplete penetrance and different PD individuals with hyposmia may have a varying degree of olfactory loss[21-23]. The detailed mechanism of hyposmia occurrence remains undetermined. So far, there have been limited studies unraveling the specific genetic background of hyposmia in PD. Since hyposmia is a prevalent non-motor symptom in PD, increasing attention has been devoted to investigating olfaction in PD. Recently, Gisladottir *et al.* found that *TAAR5* p.Ser95Pro mutation is associated with a reduced intensity rating of fish odor containing trimethylamine[6]. *TAAR5* is a G protein-coupled receptor, which shares 35% of the sequence with 5-HT-1D receptor[24] and 33% with dopamine D2 receptor[25], which may contribute to PD pathology[26]. Besides, Gisladottir *et al.* also found that *OR6C70* p.Lys233Asn (rs60683621) is associated with increased intensity and identification of licorice odor[6]. However, the associations of *OR6C70* and *TAAR5* with PD have not been reported previously. Such results highlighted that sequence diversity in olfactory receptor genes can lead to enhanced olfactory ability.

In our study, the sequencing covered exon and exon-intron boundary regions of *TAAR5* and *OR6C70,* but we were not able to find any significant association between hyposmia and common variants (including the reported rs60683621) in these two genes. We did not replicate the reported association between rs60683621 and olfactory function, which merely a consequence of global hyposmia assessment previously instead of an assessment scale with specific olfactory domain evaluation in our study, which warrants further investigations in future studies.

GBA encodes glucocerebrosidase, a lysosomal protein that cleaves the beta-glycosidic bond of glucosylceramide and contributes to Gaucher's disease and PD. Thaler *et al.* and da Silva *et al.* found that mutations in *GBA*

Table 3. Allele logistic regression analysis of hyposmia in 203 PD individuals

	Regression coefficient	*P**	OR	95% CI
Gender (male, %)	−0.358	0.101	0.70	0.46–1.07
Age (year)	−0.044	0.886	0.96	0.53–1.74
Age of onset (year)	0.068	0.824	1.07	0.59–1.95
Duration (month)	0.008	0.738	1.01	0.96–1.06
LED	0.000	0.679	1.00	1.00–1.00
UPDRS-III	0.015	0.116	1.02	1.00–1.03
rs3813355	0.316	0.235	1.37	0.81–2.31
rs3813354	−0.142	0.629	0.87	0.49–1.54
rs60683621	0.048	0.827	1.05	0.68–1.62
rs1800473	−0.725	0.129	0.48	0.19–1.23
rs762488	1.115	0.036	3.05	1.08–8.63
rs2009578	−0.503	0.208	0.60	0.28–1.32
rs2974923	0.163	0.529	1.18	0.71–1.95
rs1800438	−0.749	0.032	0.47	0.24–0.94

CI, Confidence interval; LED, Levodopa equivalent dose; OR, Odds ratio; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale - Part III. *Logistic regression adjusted for gender, age, age of onset, motor symptoms, LED, and UPDRS-III

were associated with hyposmia in PD[8,9]. In our study, we found that *GBA* rs1800438 was associated with decreased hyposmia risk, while *GBA* rs762488 was associated with increased hyposmia risk. It is possible that rs762488 and rs1800438 are located in different introns, which may lead to different expression levels of *GBA*. This deserves further investigation with functional experiment. In summary, this is the first report concerning the associations between common variants in *GBA* and hyposmia in PD. We consider that associations between PD and *GBA*, including its common and rare variants, should be studied in future.

Our study has some limitations. First, the sample size is limited. The collection of a larger sample size was limited due to the fact that this is a single-center cross-sectional study. Second, the prevalence rate of hyposmia in our study is not comparable to that in some epidemiological studies[4,27]. This may be partially attributed to ethnicity factor. In general, marked differences in allele frequencies had been discerned between different populations. Geological conditions, as well as social customs, may also lead to different odor recognition[28,29]. In addition, we applied a single-question method for screening olfactory dysfunction, which could be further improved. In general, in accordance with the study by Gisladottir *et al.*, more studies with larger sample sizes and standardized assessments of olfactory function are warranted in different populations in the future, which may help us differentiate different subtypes of PD and facilitate precise treatment.

5. Conclusion

In our study, we found that *GBA* is associated with hyposmia in PD, indicating genetic involvement in PD hyposmia variation. However, we did not replicate the previous results (loci in *TAAR5* and *OR6C70*) in this study. More studies with larger sample sizes concerning the above genes need to be implemented to explore the potential association between hyposmia in different populations.

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Conflict of interest

None.

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