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Clinical profiles of Parkinson's disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals

Chaodong Wang [a,b,c,d], Yanning Cai [a], Zhuqin Gu [b,c], Jinghong Ma [a,b,c], Zheng Zheng [a], Bei-Sha Tang [e], Yanming Xu [f], Yongtao Zhou [b], Tao Feng [g], Tao Wang [a], Sheng-Di Chen [h], Piu Chan [a,b,c,*], Chinese Parkinson Study Group

[a] Department of Neurobiology, Beijing Institute of Geriatrics, Xuanwu Hospital of Capital Medical University, Beijing, China
[b] Department of Neurology, Beijing Institute of Geriatrics, Xuanwu Hospital of Capital Medical University, Beijing, China
[c] Key Laboratory on Neurodegenerative Disease of Ministry of Education and Key Laboratory on Parkinson's Disease of Beijing, Beijing, China
[d] Department of Neurology, The Affiliated Sanming First Hospital of Fujian Medical University, Sanming, Fujian, China
[e] Department of Neurology, Xiangya Hospital of Central South University, Changsha, China
[f] Department of Neurology, West China Hospital of Sichuang University, Chengdu, China
[g] Department of Neurology, Beijing Titan Hospital Affiliated to Capital Medical University, Beijing, China
[h] Institute of Neurology, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China

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ABSTRACT

Clinical profiles of Parkinson's disease (PD) related to LRRK2 (LRRK2-PD), and GBA (GBA-PD) genes have not been reported in Chinese individuals. In this study, we have investigated motor and non-motor aspects in 1638 Chinese PD patients who carried LRRK2 G2385R or R1628P (LRRK2-PD, n = 223), GBA L444P variant (GBA-PD, n = 49), or none of the variants (idiopathic PD [IPD], n = 1366). As a result, age at onset and motor and non-motor features of LRRK2-PD patients were similar to IPD patients except for milder non-motor symptoms. In contrast, GBA-PD patients had a significantly younger age at onset and higher Unified Parkinson's Disease Rating Scale scores than LRRK2-PD and IPD patients. In addition, postural instability and gait disorders, motor complications, cognitive decline, hallucination, sexual dysfunction, and constipation were more frequent in GBA-PD than in LRRK2-PD and IPD patients, and GBA-PD patients had a worse performance for social functioning and role-emotional scores. Our study represents the first large-scale clinical study of LRRK2-PD and GBA-PD in ethnic Chinese individuals. The data suggest that both LRRK2-PD and GBA-PD are similar to IPD, except for an earlier age at onset and relatively more common non-motor symptoms in GBA-PD patients. These findings strengthen our understanding of the clinical heterogeneity of PD, and may have implications for molecular classification of the disease.

1. Introduction

The clinical presentation and course of Parkinson's disease (PD) is heterogeneous, with variability in onset, progression, and severity of motor and non-motor symptoms. The basis for the variation in PD phenotype is unknown, but is thought to be a result of environmental and genetic factors (De Michele et al., 1996; Dick et al., 2007; Gasser, 2005; Tan and Skipper, 2007; Zorzon et al., 2002). Phenotypes of genetically defined subtypes of PD have been reported recently. In particular, Parkinsonism related to mutations in genes encoding leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) have attracted increasing attention. Mutations in the LRRK2 gene are the most frequent genetic cause associated with autosomal dominant PD, accounting for about 6% of familial cases and roughly 2% of sporadic PD in the white population (Di Fonzo et al., 2005; Gilks et al., 2005; Nichols et al., 2005). Moreover, clinical features of LRRK2-related PD (LRRK2-PD) resemble those of late-onset sporadic PD (Healy et al., 2008; San Luciano et al., 2010). A detailed clinical as well as pathological characterization of PD patients carrying the G2019S and other LRRK2 mutations is warranted to investigate whether LRRK2-related disease represents the classical PD or a different entity.

Heterozygous mutations in the GBA gene represent the second most common genetic risk factor for sporadic PD (Aharon-Peretz et al., 2004; Sidransky et al., 2009). In contrast to LRRK2-PD, PD patients carrying the GBA L444P and N370S

* Corresponding author at: Xuanwu Hospital of Capital Medical University, #45 Changchun Street, 100053 Beijing, China. Tel.: +86 10 83198677; fax: +86 10 83161294.
E-mail address: pbchan90@gmail.com (P. Chan).

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Table 1
Demographic data and baseline clinical information for the 3 groups of PD patients

	LRRK2-PD (n = 223)	GBA-PD (n = 49)	IPD (n = 1366)	*p*	*p*1	*p*2	*p*3
Age, y	61.61 ± 10.90	55.67 ± 8.91	62.43 ± 10.71	**<0.001**	**<0.001**	0.286	**<0.001**
Sex, male (%)	143 (64.1)	27 (55.1)	842 (61.6)	0.483	0.237	0.478	0.356
Age at onset, y	57.96 ± 10.97	51.45 ± 9.14	58.41 ± 11.03	**<0.001**	**<0.001**	0.586	**<0.001**
Duration, y	3.65 ± 3.22	4.22 ± 3.17	4.02 ± 3.61	0.309	0.304	0.147	0.693
Hoehn and Yahr stage	1.84 ± 0.83	2.02 ± 0.68	1.94 ± 0.78	0.183	0.152	0.104	0.455
UPDRS total	34.48 ± 20.72	40.31 ± 18.76	35.97 ± 20.24	0.180	0.052	0.647	**0.024**
UPDRS I	1.95 ± 2.06	2.73 ± 2.54	2.12 ± 2.09	0.060	**0.027**	0.374	**0.033**
UPDRS II	9.99 ± 6.26	11.78 ± 5.46	10.49 ± 6.22	0.173	0.050	0.625	**0.015**
UPDRS III	22.53 ± 14.17	25.80 ± 13.49	23.35 ± 13.95	0.324	0.107	0.759	0.066

For *p* values, comparisons among all 3 groups were as follows: *p*1: LRRK2-PD versus GBA-PD; *p*2: LRRK2-PD versus IPD; *p*3: GBA-PD versus IPD. Comparisons for UPDRS were conducted using a binary logistic model adjusted for age, gender and duration. *p* Values <0.05 are shown in boldface type.
Key: IPD, idiopathic Parkinson disease; PD, Parkinson disease; UPDRS, Unified Parkinson's Disease Rating Scale.

mutation present with an earlier age at onset and a higher prevalence of non-motor symptoms such as cognitive impairment compared to nonmutation carriers (Neumann et al., 2009). These results support the hypothesis that LRRK2-PD and GBA-PD may represent distinct subtypes of Parkinsonism. However, such reports have been confined to Western populations and Ashkenazi Jews. A systematic study of the clinical profiles of LRRK2-PD or GBA-PD in Asians has been lacking. Because the PD-associated LRRK2 and GBA mutations/variations identified in Asians were distinct from those reported in other ethnicities (i.e., LRRK2 G2385A and R1628P specific for Asians while LRRK2 G2019S specific for Caucasians; GBA N370S mutations only for individuals of White and of Ashkenazi Jewish ethnicity) (Farrer et al., 2007; Lu et al., 2008; Sidransky et al., 2009), it is compelling to investigate whether the phenotypes of PD related to the 2 genes are also distinct in this population.

One challenge hampering the identification of relatively "pure" genetic subtype of PD might be the significant overlapping of carriers for mutations/variants of multiple PD-associated genes. In a previous multigenic study (Wang et al., 2012), we have demonstrated that carriers for risk variants of the SNCA, MAPT, BST1, and PARK16 gene frequently overlapped with each other, making it difficult to distinguish the PD subtype associated with one gene from another. In contrast, carriers for GBA and LRRK2 variants rarely overlap, warranting a molecular and clinical differentiation of the PD subtypes related to the two genes. In a large Chinese cohort, we have systematically evaluated the motor performance, cognitive impairment, neuropsychiatric symptoms, and autonomic dysfunctions for the molecular subtypes of PD related to the Asian-specific LRRK2 variants (G2385R and R1628P) and the GBA L444P mutation in large Chinese cohort, to achieve a clinical characterization of patients with different genetic factors.

2. Methods

PD patients were recruited from the PD cohort of the Chinese National Consortium on Neurodegenerative Diseases (CNCPD), established by the Chinese Parkinson Study Group (CPSG), a collaboration of 42 clinical centers managed by the coordination center at Xuanwu Hospital of Capital Medical University in Beijing. PD was diagnosed by movement disorder specialists using the United Kingdom PD Society Brain Bank Criteria (Hughes et al., 1992). Patients with a family history of PD in a first- or second-degree relative were not included. Patients meeting these criteria were enrolled between January 2008 and April 2010, and their DNA samples were collected. Subjects with incomplete clinical information were excluded from the study. This study was approved by the Ethics Committee of XuanWu Hospital of Capital Medical University. The use of human subjects was carried out with adequate understanding and written consent of the subjects or their legal guardians.

PD patients were genotyped for the R1628P and G2385A variants of LRRK2 and the GBA L444P variant as described previously (Wang et al., 2012). Patients carrying the risk allele of either of the LRRK2 variants were classified as LRRK2-PD, and those carrying the GBA L444P variant were classified as GBA-PD. The remaining patients carrying none of the LRRK2 or GBA variants were defined as those with sporadic or idiopathic PD.

Exposures to environmental factors including head trauma, carbon monoxide, pesticide, chemical solvents, heavy metals, smoking, alchoholic beverages, tea, and coffee, were surveyed for all PD patients by questionnaire during a person-to-person interview. The frequency for each exposure by LRRK2-PD, GBA-PD, and IPD patients were calculated and compared between groups (Table 2).

All patients were examined by movement disorder neurologists. Disease severity was assessed by Unified Parkinson's Disease Rating Scale (UPDRS), in which motor symptoms were assessed by the

Table 2
Environmental exposures in the 3 groups of PD patients

	LRRK2-PD		GBA-PD		IPD		*p*	*p*1	*p*2	*p*3
	n	Frequency (%)	n	Frequency (%)	n	Frequency (%)				
Head Trauma	89	6.7	21	4.8	645	6.0	0.936	0.556	0.825	0.804
CO exposure	89	21.3	21	19.0	642	11.5	0.024	0.501	**0.017**	0.598
Pesticide exposure	176	12.1	41	14.6	1132	12.5	0.905	0.947	0.767	0.784
Chemical solvent	174	6.3	41	4.9	1129	7.5	0.708	0.83	0.531	0.489
Heavy metal	174	4.6	41	2.4	1126	3.6	0.724	0.496	0.540	0.713
Smoking	179	31.3	44	34.1	1115	30.3	0.846	0.971	0.995	0.548
Alchohol	141	32.6	36	36.1	925	30.1	0.632	0.651	0.819	0.476
Alcholic beverage	128	83.6	35	85.7	855	80.6	0.561	0.716	0.301	0.331
Tea drinking	180	38.3	44	45.5	1117	43.2	0.444	0.548	0.202	0.656
Coffee drinking	176	11.9	44	15.9	1111	15.6	0.451	0.637	0.202	0.891

For *p* values, p: comparisons among all 3 groups; p1: LRRK2-PD versus GBA-PD; p2: LRRK2-PD versus IPD; p3: GBA-PD versus idiopathic PD. *p* Values <0.05 are shown in boldface type.
Key: IPD, idiopathic Parkinson's disease; PD, Parkinson's disease; n, number of patients whose information on environmental exposure was available.