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Title

The heterozygous R1441C mutation of leucine-rich repeat kinase 2 gene in a Chinese patient with Parkinson disease: a five-year follow-up and literatures review

Running title

a Chinese PD patient with R1441C mutation of *LRRK2*

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Abstract

Background: Leucine-rich repeat kinase 2 gene (*LRRK2*) was recognized associated with both familial and sporadic Parkinson Disease (PD). Seven missense mutations (G2019S, R1441C, R1441G, R1441H, Y1699C, I2020T, N1437H) of it have been confirmed disease-causing. They were common amongst Caucasian PD patients, but rarely reported in Asian, especially in Chinese Han population.

Objectives: We aimed to identify the frequencies of these seven mutations of *LRRK2* in Chinese early-onset PD (EOPD) patients and analyze the phenotypes.

Methods: One hundred and thirty seven EOPD patients were enrolled for genetic testing. The seven disease-causing mutations of *LRRK2* were carried out by target sequencing using Illumina HiSeq 2000 Sequencer. The identified variants were further confirmed by Sanger sequence. The clinical materials were investigated retrospectively.

Results: Only one patient (0.73%) was found carrying pathogenetic *LRRK2* mutation of R1441C. The age at onset of the female patient was 44. She manifested typical motor symptoms of PD and responded well to levodopa therapy. Longitudinal evaluation showed progression of motor symptoms and depression but no cognitive impairment. The dopamine transporter (DAT) imaging via [¹¹C]-2β-carbomethoxy-3β-(4-fluorophenyl) tropan (CFT) and Positron emission computed tomography (PET) revealed typical dopamine transporter uptake reduction.

Conclusions: The *LRRK2* R1441C mutation was found in a Chinese EOPD patient for the first time. The manifestations of *LRRK2*-R1441C carriers were indistinguishable from sporadic PD patients.

Key Words: Parkinson disease; R1441C mutation; Leucine-rich repeat kinase 2 gene; early-onset PD; Dopamine transporter imaging; Positron emission computed tomography

1.Introduction

Parkinson disease (PD) is the second most common progressive neurodegenerative disorder with the motor syndrome of bradykinesia, muscular rigidity, resting tremor, and postural instability[1]. Over the past years, genetic factors have been set a connection with the pathogenesis of PD. Among these genes, leucine-rich repeat kinase 2 gene (*LRRK2*) was considered as the most common cause for familial and sporadic PD[2]. Up to date, abundant variants in *LRRK2* have been reported as causes of PD, but only seven mutations of G2019S[2], R1441C [3], R1441G [4], R1441H[5], Y1699C[4], I2020T[3], and N1437H[6] were demonstrated as disease-causing with overwhelming proof. These mutations were distributed mostly in Caucasian population, rarely found in Asian, except for G2019S was reported in two Japanese patients[7], R1441C in one Chinese Han patient from Singapore[8], R1441H in one Taiwanese patient[9], and I2020T in several Sagamihara pedigrees[10].

Though the incomplete penetrance made *LRRK2* mutations be found mostly in late-onset PD (LOPD, age at onset ≥ 50), a small part of early-onset PD (EOPD, age at onset < 50) patients was found carrying *LRRK2* mutations[11]. There was no such investigation in Chinese EOPD patients. Here, we performed genetic testing in 137 Chinese Han EOPD patients to investigate their carrying status of *LRRK2* disease-causing mutations[12]. We found only one patient with a heterozygous R1441C mutation. Her clinical characteristics and the disease progression were demonstrated retrospectively.

2.Methods

2.1 Subjects and clinical assessments

New and routine follow-up EOPD patients were enrolled for genetic testing from June 2014 to March 2016. The assessments of these patients included Unified Parkinson's Disease Rating Scale motor examination (item 18-31) (UPDRS-III) and Hoehn and Yahr (H&Y) for the motor symptoms[13], non-motor symptoms scale (NMSS)[14], Epworth

sleepiness scale (ESS)[15], Geriatric Depression Rating Scale (GDS)[16], rapid eye movement sleep behavior disorder (RBD) screening questionnaire (RBDSQ)[17], 12-item identification test from Sniffin's Sticks (SS-12)[18] and 39 item Parkinson's disease questionnaire (PDQ39)[19] for the non-motor symptoms. The assessments of general and five subdomains of cognitive function were performed as previously reported[20].

Written consents were obtained from all the subjects or their legally authorized caregivers. This study was approved by the ethics committee of Huashan Hospital.

2.2 Genetic test

The genomic DNA was extracted from peripheral blood of the patients. Target sequencing of PD and related genes including *LRRK2* were carried out by Illumina HiSeq 2000 Sequencer as previously reported[20]. The seven disease-causing mutations of *LRRK2* were investigated in each patient.

3.Results

3.1 Characteristics of patients for genetic testing

A total of 137 EOPD patients were enrolled. Among them, 43 (31.4%) had a positive family history, with 31 presenting autosomal dominant inherited mode (having PD patients in different generations) and 12 autosomal recessive mode (having PD patients only in the same generation). The age at onset was 36.0 ± 9.66 . Only one heterozygous mutation of R1441C was identified. The frequency of *LRRK2* mutations in our subjects was 0.73%.

3.2 Clinical characteristics of the patient

This 50-year old female patient had been followed up in our clinic for 5 years. She first presented stiffness in the lower left limb at the age of 44, followed by bradykinesia and rigidity in the upper left limb. She came to our clinic at 45. Her UPDRS-III (off medication) was 12/108. H&Y was stage 1. During the 5 years, her motor function had been continually worsened according to the ever-increasing scores of UPDRS-III (off medication) with 8.0 ± 3.00 points per year and her non-motor symptoms had also presented a mild deterioration,

especially depression and life quality (PDQ39). She had no signs of cognitive impairment because the scores in five different subdomains were almost normal. She performed dopamine transporter (DAT) imaging twice, and the images showed dopaminergic loss in one side first and two years later pre-synaptic dopaminergic loss involved two sides, much severe in the right (**Figure**).

This patient was an orphan and was adopted, so the information of her biological parents or siblings were unavailable. Whether this mutation was inherited or de novo could not be determined.

3.3 Literatures review

We reviewed the previously literatures of the PD patients carrying R1441C in *LRRK2* (**Table**). The mean onset age was from 30 to 79. Most R1441C carriers were Caucasian with or without family history, barely in Asian population except for the only one Chinese LOPD male patient in Singapore [8]. R1441C patients manifested typical PD symptoms and good response to levodopa. And PET or SPECT was only reported in three studies, all of which revealed the reduction of dopamine uptake in striatum.

4. Discussion

R1441C was the second most common mutation within *LRRK2*. This mutation was demonstrated decreasing the GTPase activity of *LRRK2*[21], altering the folding properties of the ROC domain to lower its thermodynamic stability[22], and could induce Substantia Nigra (SN) dopaminergic neurons degeneration, which might contribute to the pathogenesis of *LRRK2*-related PD[23].

The PD patients carrying R1441C mutation usually showed typical parkinsonian symptoms, slow progression, less cognitive impairment, good responsive to levodopa and typical DAT uptake reduction. Common non-motor symptoms included depression, anxiety and hallucinations[11]. Though mild cognitive impairment was presented in a few patients, severe cognitive function impairment was uncommon and only one patient was reported to

have dementia[24]. Our patient showed typical PD motor symptoms and depression and no signs of cognitive impairment, which was the same as the phenotype reported before. The DAT images showed pre-synaptic dopaminergic loss in both putamen and caudate nucleus, much severe in the right side. These images indicated the disease progression and were consistent with the increasing scores of UPDRS-III.

LRRK2 mutations were kept screening in Chinese PD patients, mainly in autosomal dominant inherited PD families, but no confirmed pathogenic mutations were found[25]. A novel mutation K616R was considered to be probably pathogenic due to the co-segregation[26]. The variants identified frequently were G2385R, R1628P and A419V which were considered as risk factors and genetic modifiers of PD[27-29]. The ethnic difference might cause the low frequency of *LRRK2* mutation and different risk factors in Chinese PD patients, but further investigations in sporadic PD and LOPD should be performed.

5. Conclusion

R1441C mutation of *LRRK2* was rare in Chinese Han EOPD patients. We reported the first case of a Chinese Han EOPD patient carrying it and gave a longitudinal picture of this patient. Her clinical manifestations and DAT uptake reduction were indistinguishable from sporadic PD. Our study expanded the clinical and genetic spectrums of *LRRK2* in Chinese PD patients.

Figure legend

Fig. PET-DAT of the patient with *LRRK2* R1441C mutation. (A) Images at the age of 45: severe pre-synaptic dopaminergic loss in the right putamen. (B) Images at the age of 47: more significant pre-synaptic dopaminergic loss in both putamen and caudate nucleus, much severe in the right side.

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Conflicts of interest

The authors declare no conflicts of interest.

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Table Literatures review of reported Parkinson disease patients with R1441C mutation in *LRRK2*

Study (year)	R1441C Case No./Total case No.	gender	het/ hom	Populations of R1441C patient(s)	Family number with positive family History	Definitions of EOPD or LOPD	Age at onset (range)	Initial symptpm	Response to levodopa	MCI or Dementia	Psychiatric disorders	CT/MRI	PET-DAT/SPECT
Zimprich A,et al ¹ .(2004)	18/NA	NA	het	Western Nebraska	1	NA	65 (48-78)	rest tremor and bradyskinesia	+	NA	NA	NA	NA
Di Fonzo A,et al ² .(2006)	3/60 families	NA	het	Italy	3	NA	63-65	NA	2good, 1NA	-	NA	1 symmetric frontal atrophy	NA
Tan EK,et al ³ .(2006)	1/384	1M	het	Chinese	0	Late-onset ≥56y	58	rest tremor,rigidity,bradykinesia	good	-	No	NA	NA
Gosal D,et al ⁴ .(2007)	1/1	1M	het	Irish	1	NA	35	rest tremor	modest	NA	occasional hallucinations	Normal	NA
Floris G,et al ⁵ .(2008)	2/356	2F	het	sardinian	0	Early-onset≤45y; Late-onset>45y	59, 60	tremor	good	1MCI	both depression and anxiety	NA	SPECT: bilateral reduction of tracer uptake mainly involving the putamen and more pronounced to one side
Nuytemans K,et al ⁶ . (2008)	6/304	NA	het	Belgian	6	NA	39-73	5 tremor and 1 rigidity	3 good, 1 NA	NA	NA	NA	NA

Haugarvoll K, et al ⁷ .(2008),	33/NA	NA	het	Italian, German, Spanish, American, Belgian, Irish, Singapore	29	NA	60±13 (30-79)	rest tremor (57%), bradykinesia (18%), mixed motor symptoms (18%)	25 good, 8NA	4 MCI, 1 dementia	9 Depression, 6 anxiety, 2 hallucinations	NA	NA
Pchelina SN, et al ⁸ .(2008)	1/274	1M	het	Russia	0	20y<Early-onset≤50y; Late-onset>50y	61	tremor-rigidity	NA	NA	NA	NA	NA
Criscuolo C, et al ⁹ .(2011)	8/192	3M 5F	het	southern Italy	6	Early-onset≤45y; Late-onset>45y	55.4±11.6	Tremor (67%) , akinesia (58%), pain (25%)	good	Mild/moderate (17%) Severe (8%)	anxiety/depression (33%)	NA	NA
Borroni B, et al ¹⁰ .(2013)	1/1	1F	het	Italy	1	NA	56	tremor choreo-athetotic movements	good	-	NA	Normal	SPECT DAT: severe pre-synaptic dopaminergic loss, more prevalent on the right side, whilst brain PET-FDG was normal
De Rosa A, et al ¹¹ .(2014)	13/513	8M 5F	het	Campania	9	NA	53.7±10.8 (36-69)	tremor	good	NA	NA	NA	NA

EOPD: early-onset PD; F: Female; het: heterozygous; hom: homozygous; LOPD: late-onset PD; M: Male; NA: Not Available;

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Figure