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Short communication

Juvenile-onset parkinsonism with pyramidal signs due to compound heterozygous mutations in the F-Box only protein 7 gene

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ABSTRACT

Background: Juvenile-onset parkinsonism is often caused by genetic factors. Mutations in several autosomal genes, including the F-box only protein 7 (FBXO7) gene, have been found in patients suffering from juvenile-onset parkinsonism with pyramidal signs. Only five types of FBXO7 mutations have been described. Here, we present a case report about a Chinese patient presenting with juvenile-onset parkinsonism likely caused by FBXO7 mutations.

Methods: The patient was a 32-year-old Chinese male. DNA samples were extracted from the patient and his parents. Exons in parkinsonism-related genes were amplified and sequenced.

Results: The patient began experiencing a progressive involuntary tremor in his left hand at 16 years of age, which was followed by the development of gait dysfunction, dysarthria, and rapid eye movement sleep behavior disorder. A neurological examination of the patient revealed cogwheel rigidity, bradykinesia, static and postural tremor and bilateral Babinski signs. The patient responded to dopaminergic therapies but was affected by psychiatric side effects. Further genetic analysis of the patient and his parents revealed compound heterozygous mutations of the FBXO7 gene (NM_012179.3) in the patient (a nonsense c.1408G > T (p.E470X) mutation and a missense c.152A > G (p.N51S) mutation coming from the patient's mother and father, respectively).

Conclusions: This is the first case harboring FBXO7 mutations that presented with juvenile-onset parkinsonism in the Chinese population.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. The neuropathological features of PD are progressive loss of dopaminergic neurons in the substantia nigra (SN) and aggregation of α-synuclein-positive Lewy bodies (LBs) in surviving neurons [1]. Despite that PD has been heavily researched over the last two decades, the precise etiology and pathogenesis of the disease remain not very clear. Growing evidence has confirmed the role of genetic factors in the pathogenesis of PD and related parkinsonian disorders [2,3]. To date, at least 23 loci and 18 pathogenic genes have been identified to exhibit roles in the monogenic transmission of PD [1]. Among these genes, homozygous or compound heterozygous mutations in the F-box only protein 7 (FBXO7) gene cause juvenile-onset parkinsonism or early-onset parkinsonism with variable degrees of pyramidal disturbances (PARK15) [4]. The main clinical PARK15 phenotype is juvenile-onset parkinsonism with pyramidal signs, but these symptoms are often accompanied by atypical symptoms, such as mental retardation, eyelid apraxia and chorea [3–6]. In previous studies, all patients with PARK15 responded well to dopaminergic therapies, but they often experienced severe treatment-induced side effects [2,3].

Several articles have reported FBXO7 mutations in patients with PD [2–9]. At present, only five types of FBXO7 mutation have been described [3]. The first, the p.R378G mutation, was identified in an Iranian family that presented with early-onset PD with pyramidal features [2]. The remaining four FBXO7 mutations include IVS7 11G > T and p.T22M, which were identified in the compound heterozygous state in a Dutch family [5]; p.R498X, which was

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identified in the homozygous state in Italian [5], Pakistani [8], and Turkish families [3,6,8,9]; and p.L34R, which was identified in the homozygous state in Turkish families [4]. All the above-mentioned cases exhibited additional various atypical clinical symptoms. However, to the best of our knowledge, there have been no reports of Chinese patients with FBXO7 mutations presenting with juvenile-onset PD. Here, we present a case report of a Chinese patient with juvenile-onset parkinsonism with a compound heterozygous mutation in the FBXO7 gene.

2. Materials and methods

2.1. Genotyping

Genomic DNA was extracted from the blood leukocytes of the patient and his parents using standard protocols. Written informed consent was obtained from all subjects. This study was approved by the institutional review board of the Third Affiliated Hospital of Sun Yat-sen University.

Exons in parkinsonism-related genes, including LRRK2, FBXO7, PINK1, SNCA, ANG, ATP13A2, TP1A3, ATXN2, CYP27A1, DCTN1, DNAJC6, EIF4G1, FOXG1, FTH1, GBA, GRN, HTRA2, MAPT, NDUFV2, PARK2, PARK7, PARL, PITX3, PLA2G6, POLG, PRKAG2, PRKRA, PSEN1, PSEN2, SLC30A10, SLC41A1, SLC6A3, SNCAI P, TBP, TH, TRPM2, UCHL1, USP24, VPS35, and ZFYVE26, were amplified via PCR, and the products were sequenced using dideoxynucleotide chain termination with a DNA sequencer (ABI 3100; Applied Biosystems, Foster City, CA, USA).

We also detected the copy numbers of exons of parkinsonism-related genes including SNCA, PARK2, UCHL1, PINK1, PARK7 (DJ1), LRRK2, GCH1 and ATP13A2 using multiplex ligation-dependent probe amplification (MLPA) technique, with the DNA of health subjects as control.

3. Results

3.1. Case report

The patient was a 32-year-old Chinese man who showed no abnormalities in neurological function at birth. His mental development, language and motor development were also normal. However, he performed poorly in school. There was no history of parental consanguinity in his family. At 16 years of age, he began experiencing a progressive involuntary tremor (static tremor and postural tremor) in his left hand. Some movements, such as writing and using chopsticks, were mildly affected. For a long period of time, he was still qualified for his job of assembling electronic components. At 25 years of age, the involuntary tremor progressed and began to affect the rest of his limbs.

From 29 years of age, the patient developed gait dysfunction and dysarthria. According to his parents, the patient presented with small shuffling steps and a general slowness of movement. He began to develop rapid eye movement sleep behavior disorders (RBD) at the age of 29 with the frequency varies from once a week to four times a week. He did not see a doctor until he was 31 years old and was diagnosed with Parkinson's syndrome. After 1 week of a low-dose dopaminergic treatment (levodopa-benserazide 300-75 mg/day), the tremors were improved, but the patient developed manic behavior that led to the withdrawal of the dopaminergic treatment. When he came to our department (June 2016), the parkinsonism symptoms had become aggravated and were depriving him of the ability to do his job.

Neurological examination revealed monotonous, rapid tachyphemic speech with impaired articulation; hypomimia, festination, bilateral static and postural tremor of the hands; generalized cogwheel rigidity and hyperreflexia; slowness of finger-to-nose movements and bilateral Babinski signs. A cognitive assessment revealed impairment (Mini-Mental State Examination (MMSE) score 21/30). A low-dose L-dopa treatment (levodopa-benserazide 150–37.5 mg/day and piribedil 50 mg/day) was effective (UPDRS scores: 54 pre- and 32 post-treatment). Routine blood tests, including Wilson's disease screening, and an electroencephalogram (EEG) were normal. The patient's brain MRI scan was unremarkable, with the exception of mild, general atrophy (Fig. 1).

A clinical evaluation of the patient's parents, a 60-year-old male (I-1) and a 63-year-old female (I-2), was normal. Their MMSE scores were also within the normal range (29/30 for his father and 28/30 for his mother) (Fig. 1).

The patient's elder sister (II-1) and two elder brothers (II-2 and II-3) were healthy (Fig. 1). Because his siblings lived elsewhere, their blood samples were unavailable. Their information was collected according to descriptions provided by the parents.

3.2. Genetic findings

Exome sequencing analysis of the patient (II-4) and his parents (I-1 and I-2) identified compound heterozygosity for the two following novel FBXO7 mutations (NM_012179.3): c.1408G > T in exon 9 from his mother and c.152A > G in exon 2 from his father (Fig. 1). The c.1408G > T mutation is considered a pathogenic variation because it causes a nonsense mutation (p.E470X) in exon 9. The c.152A > G mutation causes a missense mutation (p.N51S) in exon 2. Based on PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) prediction and Combined Annotation Dependent Depletion (CADD) v1.3 (http://cadd.gs.washington.edu/) analysis, the missense mutation c.152A > G (p.N51S) was likely pathogenic. These two mutations were absent from the Exome Aggregation Consortium (ExAC, http://exac.broadinstitute.org/), dbSNP (www.ncbi.nlm.nih.gov/snp/), 1000 Genomes Project (http://browser.1000genomes.org/) and NHLBI exome sequencing project (https://evs.gs.washington.edu/EVS) databases, as well as from previous literature. No other potentially or reported pathogenic variant in other PD-related genes was identified (data not shown). The MLPA results did not show any duplications or deletions of exons in common genes related to parkinsonism including SNCA, PARK2, UCHL1, PINK1, PARK7 (DJ1), LRRK2, GCH1 and ATP13A2 (Supplementary file).

3.3. Clinical phenotypes of currently reported patients carrying FBXO7 mutations

We summarized previously reported cases with FBXO7 mutations along with our data (Table 1). The results showed a male-to-female ratio of 8–9 and an average age at onset of 20.0 ± 10.8 years. A total of 64.7% (11/17) of the patients had a history of parental consanguinity. All patients exhibited rigidity and bradykinesia, while 64.7% (11/17) manifested tremor (static or postural), and 87.5% (14/16) showed postural instability. Pyramidal signs and hyperreflexia were present in 64.7% (11/17) and 75.0% (9/12) of the patients, respectively. Most of the patients (88.2%, 15/17) responded well to dopaminergic therapy and exhibited side effects.

4. Discussion

Juvenile-onset parkinsonism or early-onset parkinsonism are terms used to describe patients with parkinsonism with an age of onset earlier than 40 years. Generally, the younger the age of onset of parkinsonism, the more likely it is that the patient has an inherited form of parkinsonism. In this study, we report a case of juvenile-onset parkinsonism with two novel mutations in a

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