Clinical Case Report

Medicine®

OPEN

Compound heterozygous mutations in PARK2 causing early-onset Parkinson disease

A case report

Yu-Qing Fang, MD, Fei Mao, MD, Mei-Jia Zhu, MD, Xiu-Hua Li, MD*

Abstract

Rationale: Parkinson disease (PD) is a complex neurodegenerative movement disorder characterized by resting tremor, muscular rigidity, bradykinesia, and so on. Genetics has been regarded as an important role in the development of PD. PARK2, an autosomal recessive gene, is the most common one referring to early-onset Parkinson disease (EOPD). Strangely, only a single heterozygous mutation in PARK2 was found in a small minority of patients with PD, which has been reported quite rarely and is difficult to explain.

Patient concerns: We described a case of 36-year-old male patient, complaining of progressive tremor for 10 years. He 1st presented uncontrolled resting tremor of his left arm. Besides, he also had trouble in completing fine motor tasks such as writing and buttoning. Six years later, tremor of the ipsilateral leg gradually occurred. On neurologic examinations, pronounced parkinsonian symptoms were noted, including resting tremor, body bradykinesia, and hypomimia. The positron emission tomography-computed tomography showed the distribution of dopamine transporter in both putamens decreased obviously. No family history was indentified. He came to hospital because his disease aggravated in the past 4 months.

Diagnosis: This patient was diagnosed with PD according to the movement disorder society clinical diagnostic criteria for PD.

Interventions and outcomes: With regard to the sequencing of this patient, a heterozygous point mutation of G403C in PARK2 was detected, which was inherited from his unaffected mother, leading to an amino acid alternation of glycine to arginine. Furthermore, deletion mutation of exon 6 in PARK2 was also found in this patient, which was inherited from his normal father. He accepted madopar and benzhexol and showed stable efficacy. To our knowledge, it is the 1st case report to explain the synergistic action of both heterozygous pathogenic point mutation in PARK2 and deletion mutation of exon 6 leading to EOPD.

Lessons: Compound heterozygous mutations in PARK2 with point mutation of G403C and deletion mutation of exon 6 might contribute to the development of EOPD.

Abbreviations: EOPD = early-onset Parkinson disease, MRI = magnetic resonance imaging, PD = Parkinson disease, PET-CT = positron emission tomography-computed tomography.

Keywords: early-onset Parkinson disease, mutation, PARK2

1. Introduction

Parkinson disease (PD) is a common and complex neurodegenerative movement disorder characterized by resting tremor, muscular rigidity, bradykinesia, and so on.[1] About 3.6% of patients with PD develop initial symptoms before the age of 45, which is defined as early-onset PD (EOPD).[2] PD was considered to be caused by environmental factors previously. However, genetics has been regarded as an important role in the development of PD with the discovery of disease causing genes related to PD in recent years. Genetic mutations can be detected in about 3% of patients with parkinsonism, but the proportion can be as high as 77% in groups of patients selected for age at onset, positive family history, and ethnic origin.[3,4] Three autosomal recessive genes (PARK2, PINK1, and DJ-1) are involved in EOPD and PARK2 is the most common one.[2] PARK2 mutations are observed in up to 50% of familial cases and about 15% of sporadic cases.[3] Autosomal recessive PD might result from either homozygous or compound heterozygous mutations in these genes. PARK2 is a large gene with more than 200 known mutations over its 12 exons, including point mutations, small insertions/deletions, and exon rearrangements.[5] Strangely, only a single heterozygous mutation was found in a small minority of patients with PD, which is difficult to explain and needs further studies.[6] Here, we reported a patient with PD with a single heterozygous point mutation in PARK2 inherited from his mother. Maybe another deletion mutation in exon 6 from his father could partly explain this phenomenon.

Editor: N/A.

Y-QF and FM contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

Department of Neurology, Qianfoshan Hospital, Shandong University, Jinan, Shandong, China.

** Correspondence: Xiu-Hua Li, Department of Neurology, Qianfoshan Hospital, Shandong University, Jinan, Shandong, China (e-mail: perfectin2000@163.com).*

Medicine (2019) 98:5(e14228)

Received: 19 September 2018 / Received in final form: 21 December 2018 / Accepted: 1 January 2019

http://dx.doi.org/10.1097/MD.0000000000014228

2. Case report

This was a 36-year-old male patient, who was a teacher, complaining of progressive tremor for 10 years. He 1st presented uncontrolled resting tremor of his left arm which was worse when he felt nervous and disappeared during sleep. He also had trouble in completing fine motor tasks such as writing and buttoning. Six years later, tremor of the ipsilateral leg gradually occurred. Then he was treated with oral madopar and the therapeutic effect was stable. However, his condition fluctuated in the next few years owing to the irregular medication. He came to our hospital because the disease slightly aggravated in the past 4 months and similar symptoms appeared to his right limbs.

On neurologic examinations, pronounced parkinsonian symptoms were noted, including resting tremor, body bradykinesia, and hypomimia. No other neurologic signs were observed, for example, eye movement disorder, rigidity, olfactory sensation loss, myoclonus, or limb weakness. No family history was indentified either. In terms of neuroimaging, the magnetic resonance imaging (MRI) of the brain was normal. The positron emission tomography-computed tomography (PET-CT) showed the distribution of dopamine transporter in both putamens decreased obviously, which was a typical imaging performance of PD (Fig. 1). Then, imaging of dopamine D2 receptor and glucose metabolism was further recommended, but it was not carried out because of patient's noncompliance. Blood tests of this patient were negative. He was diagnosed with PD according to the movement disorder society clinical diagnostic criteria for PD.[7] Then he accepted 750 mg madopar and 6 mg benzhexol per day during hospitalization and showed stable response to the treatment.

2.1. Sequencing

High-throughout sequencing and exon trapping techniques were carried out. Genes related to PD and dystonia were included (Table 1). With regard to the sequencing of this patient, a mutation of G403C was detected. This was a heterozygous point mutation in PARK2, which was inherited from his unaffected mother, leading to an amino acid alternation of glycine to arginine. Furthermore, deletion mutation of exon 6 in PARK2 was also found in this patient, which was inherited from his normal father. The pedigree of the family and sequencing results are shown in Figures 2 and 3.

2.2. Follow-up

Upon being discharged from hospital, medications of madopar and benzhexol have been continued for about 3 months with stable efficacy to this patient. Symptoms of resting tremor and bradykinesia disappeared and no obvious side effects were observed. The patient has provided informed consent for publication of the case.

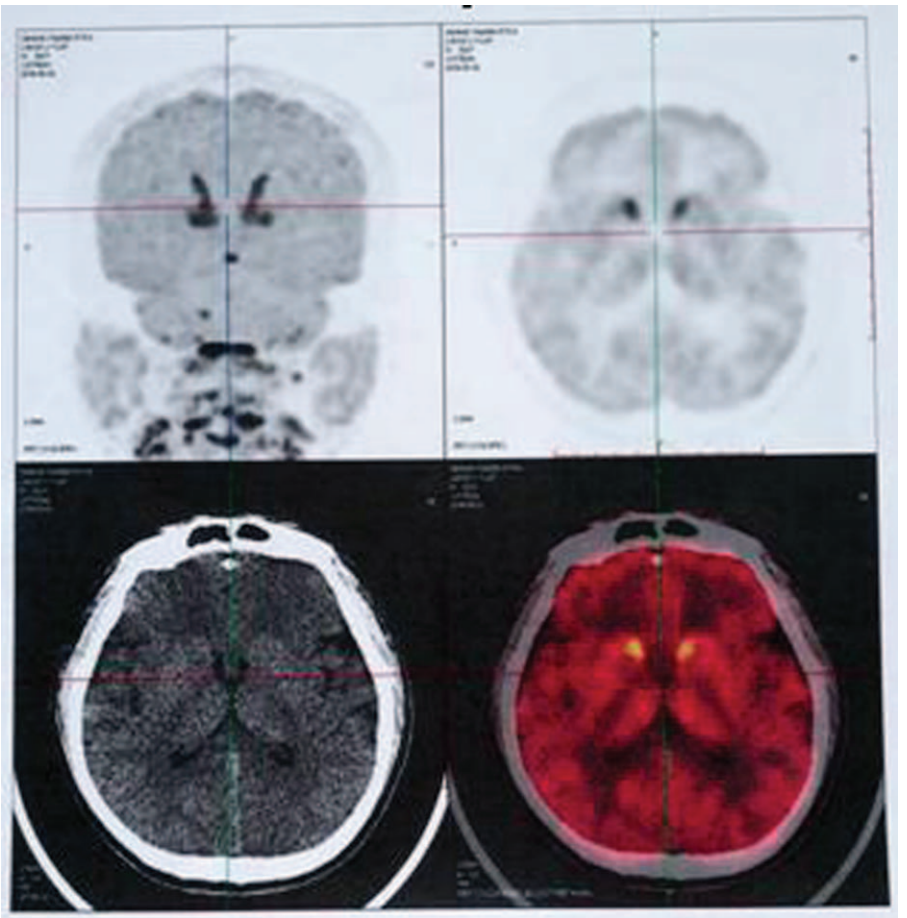

Figure 1. The positron emission tomography-computed tomography of the patient.

Table 1

Genes related to PD and dystonia.

Classification of subtypes	Gene	Mode of inheritance
Parkinson 1	SNCA	AD
Parkinson 2	PARK2	AR
Parkinson 3	Unknown	AD
Parkinson 4	SNCA	AD
Parkinson 5	UCHL1	AD
Parkinson 6	PINK1	AR
Parkinson 7	DJ1	AR
Parkinson 8	LRRK2	AD
Parkinson 9/KUFOR–RAKEB syndrome	ATP13A2	AR
Parkinson 10	Unknown	AR
Parkinson 11	GIGYF2	AD
Parkinson 12	Unknown	XR
Parkinson 13	HTRA2	Susceptible
Parkinson 14	PLA2G6	AR
Parkinson 15	FBXO7	AR
Parkinson 16	Unknown	–
Parkinson 17	VPS35	AD
Parkinson 18	EIF4G1	AD
Parkinson 20	SYNJ1	AR
Parkinson	GBA	Susceptible
Parkinson	ADH1C	Susceptible
Parkinson	MAPT	Susceptible
Parkinson	TBP	Susceptible
Parkinsonism-dystonia, infantile	SLC6A3	AR
HARP syndrome	PANK2	AR
PERRY syndrome	DCTN1	AD
DYT 1	TOR1A	AD
DYT 2	Unknown	AR
DYT 3	TAF1	XR
DYT 4	TUBB4A	AD
DYT 5	GCH1	AD
DYT 6	THAP1	AD
DYT 7	Unknown	AD
DYT 8	MR1	AD
DYT 9	SLC2A1	AD
DYT 10	PRRT2	AD
DYT 11	SGCE	AD
DYT 12	ATP1A3	AD
DYT 13	Unknown	AD
DYT 15	Unknown	AD
DYT 16	PRKRA	AR
DYT 17	Unknown	AR
DYT 19	Unknown	AD
DYT 20	Unknown	AD
DYT 21	Unknown	AR
DYT 23	CIZ1	AD
DYT 24	ANO3	AD
DYT 25	GNAL	AD
DYT, myoclonic	DRD2	AR/AD
THD	TH	AR

AD = autosomal dominant, AR = autosomal recessive, PD = Parkinson disease, XR = X-linked recessive.

3. Discussion

Mutations of PARK2 are the commonest autosomal recessive forms in PD and have been found in numerous families of different ethnic backgrounds.[1]. Unlike autosomal dominant PD, which tends to have an age of onset similar to sporadic PD, recessively inherited parkinsonism is more frequently associated with early onset.[8] The large number and wide spectrum of PARK2 mutations include changes in each of its 12 exons. Here, we reported a patient with compound heterozygous mutation in PARK2.

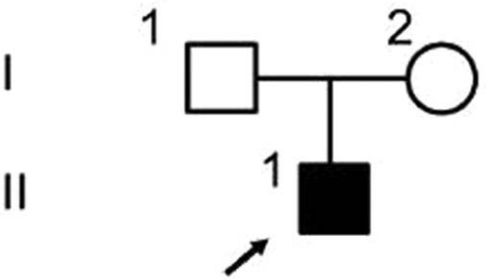

Figure 2. The pedigree of the family. (I:1) The father with heterozygous deletion mutation of exon 6 in PARK2. (I:2) The mother with heterozygous point mutation of G403C in PARK2. (II:1) The Parkinson disease patient with point mutation and deletion mutation.

Some study has already revealed that homozygous point mutation of G403C contributes to the development of EOPD.[9] HGMDpro database also recorded that this point mutation was a pathogenic gene mutation for EOPD and showed autosomal recessive inheritance. As to this patient, his mother was a carrier with heterozygous point mutation of G403C, while his father with heterozygous deletion mutation in exon 6. Neither of his parents presented clinical symptoms of PD. Unfortunately, the patient inherited G403C point mutation from his mother and deletion mutation from father, and the symptoms of PD occurred to him at the age of 24. It revealed that a person with either heterozygous point mutation of G403C or heterozygous deletion mutation in exon 6 alone was just a carrier, which intended to be normal. However, people with both mutations could promote the development of PD.

Parkin protein seems to function as an E3-type, E2-enzyme-dependent ubiquitin ligase in ex vivo and in vitro studies; it is thought to be involved in the monoubiquitination or poly-ubiquitination of several putative target proteins.[10,11] Numerous studies have provided evidence that wild-type parkin can protect against various pathogenetic changes, such as SNCA-mediated toxicity and Pael-R-induced degeneration.[12,13] Likewise, the mechanisms by which loss of wild-type parkin protein in vivo results in the selective loss of catecholaminergic neurons in the substantia nigra and locus coeruleus of mouse.[14] The patient in our case report inherited both mutations from his mother and father, so he had no functions of wild-type parkin protein. In contrast, either his father or mother still harbored a normal autosome and was protected by wild-type parkin protein. It could partly explain why the son was a patient with PD but his parents were not.

Single heterozygous mutation of 1 autosome in PARK2 usually showed no clinical symptoms, while homozygous point mutation of G403C was pathogenic.[9,15] Previous studies have already showed that single heterozygous mutation could lead to parkinsonism with mystery. No reasonable explanation can elaborate the phenomenon before. We tried to explain this with a case of heterozygous point mutation in PARK2 as well as deletion mutation of exon 6. To our knowledge, it is the 1st case report to explain the synergistic action of both heterozygous pathogenic point mutation in PARK2 and deletion mutation of exon 6 leading to EOPD, and further investigations should still be performed.

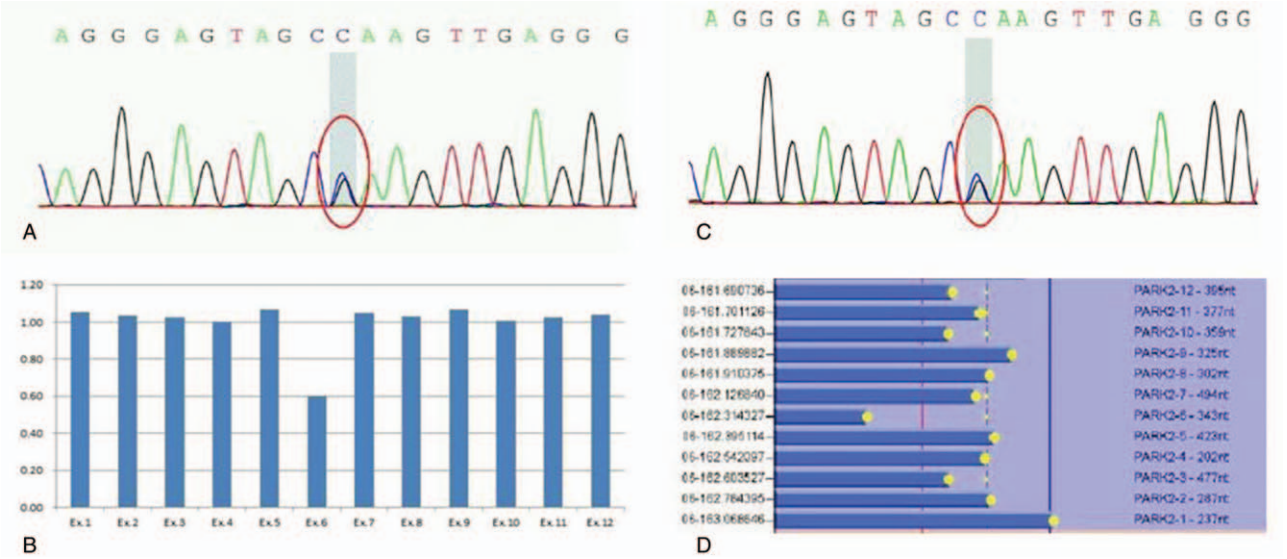

Figure 3. Sequencing results. (A) The point mutation of G403C of the patient with Parkinson disease (PD). (B) The deletion mutation in exon 6 of the patient with PD. (C) The point mutation of G403C of the mother. (D) The deletion mutation in exon 6 of the father.

Author contributions

Supervision: Mei-Jia Zhu, Xiu-Hua Li.
Writing – original draft: Yu-Qing Fang.
Writing – review & editing: Fei Mao.

References

[1] Kalia LV, Lang AE. Parkinson's disease. Lancet 2015;386:896–912.
[2] Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol 2006;5:355–63.
[3] Lucking CB, Durr A, Bonifati V, et al. Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med 2000;342:1560–7.
[4] Thaler A, Ash E, Gan-Or Z, et al. The LRRK2 G2019S mutation as the cause of Parkinson's disease in Ashkenazi Jews. J Neural Transm (Vienna) 2009;116:1473–82.
[5] Kilarski LL, Pearson JP, Newsway V, et al. Systematic review and UK-based study of PARK2 (parkin), PINK1, PARK7 (DJ-1) and LRRK2 in early-onset Parkinson's disease. Mov Disord 2012;27:1522–9.
[6] Hedrich K, Marder K, Harris J, et al. Evaluation of 50 probands with early-onset Parkinson's disease for Parkin mutations. Neurology 2002;58:1239–46.
[7] Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591–601.
[8] Erer S, Egeli U, Zarifoglu M, et al. Mutation analysis of the PARKIN, PINK1, DJ1, and SNCA genes in Turkish early-onset Parkinson's patients and genotype-phenotype correlations. Clin Neurol Neurosurg 2016;148:147–53.
[9] Wang T, Liang Z, Sun S, et al. A novel point mutation in parkin gene was identified in an early-onset case of Parkinson's disease. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2003;20:111–3.
[10] Shimura H, Hattori N, Kubo S, et al. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet 2000;25:302–5.
[11] Hampe C, Ardila-Osorio H, Fournier M, et al. Biochemical analysis of Parkinson's disease-causing variants of Parkin, an E3 ubiquitin-protein ligase with monoubiquitylation capacity. Hum Mol Genet 2006;15:2059–75.
[12] Petrucelli L, O'Farrell C, Lockhart PJ, et al. Parkin protects against the toxicity associated with mutant alpha-synuclein: proteasome dysfunction selectively affects catecholaminergic neurons. Neuron 2002;36:1007–19.
[13] Yang Y, Nishimura I, Imai Y, et al. Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in *Drosophila*. Neuron 2003;37:911–24.
[14] Periquet M, Corti O, Jacquier S, et al. Proteomic analysis of parkin knockout mice: alterations in energy metabolism, protein handling and synaptic function. J Neurochem 2005;95:1259–76.
[15] Klein C, Lohmann-Hedrich K, Rogaeva E, et al. Deciphering the role of heterozygous mutations in genes associated with parkinsonism. Lancet Neurol 2007;6:652–62.