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Parkinsonism with a double mutation p.L483P in GBA and p.S231P in LRRK2 following acute hypoxic insult

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Abstract

A novel double mutation, c.1448T>A (p.L483P, rs421016) in GBA and c.691T>C (p.S231P, rs201332859) in LRRK2 was identified in a 69-year-old man with Parkinsonism who first developed bradykinesia and rigidity in neck at one month after acute hypoxia insult during mountaineering.

INTRODUCTION

Genetic factor toke an import role in the etiology of idiopathic Parkinson's disease (PD). The glucocerebrosidase gene (GBA) encodes lysosomal enzyme glucocerebrosidase, and its mutation or dysfunction may increase the risk for Gaucher disease, Lewy body dementia and PD[1]. Most GBA mutation carriers in PD showed an earlier-onset, more severe Parkinsonism symptoms, and increased risk of accompanying dementia[1]. Another PD-related gene, leucine-rich repeat kinase 2 (LRRK2), encoded protein interacts with the C-terminal of parkin protein[2]. The 6055G>A (G2019S) mutation in LRRK2 was identified to increase the risk of PD, Crohn's disease and leprosy[3, 4]. The PD patients with G2019S had similar asymmetric resting tremor, bradykinesia, and rigidity with a good response to levodopa[5]. The acute hypoxic insult, classified as an environment factor, was rarely reported to relate with PD before[6]. The acute hypoxic insult following by acute mountain sickness may induce clinical symptoms include headache, nausea, malaise, dizziness, insomnia and cognitive dysfunction[7, 8]. Here, we descripted a Chinese person carrying double mutation included c. 1448T>A (p.L483P) in GBA and c.691T>C (p.S231P) in LRRK2 showed Parkinsonism after acute hypoxic insult.

CASE REPORT

The patient has always lived at Foshan city in China with an elevation about 13 feet and never went to plateau region before. At 69-years-old in 2013, about a month before symptom onset, he travelled to Tibetan Plateau with an elevation about 4,000 feet and stayed 3 days without high altitude reaction at beginning. When climbing to the Mt. Namjagbarwa hill with elevation about 6,700 feet, he suffered headache, vomiting and dizziness following a breeze. After returning home, he experienced an acute hypoxia insult showed as paroxysmal vertigo, bradykinesia and rigidity in the neck. When he was back to lower altitude about 13 feet for one month, vertigo was released but bradykinesia and rigidity continued. He went to hospital, and was found a mask like face, bilateral mild cogwheel rigidity, but no action or rest tremor. The laboratory tests and anal sphincter electromyogram were normal. The brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) scan revealed mild multiple stenosis of bilateral posterior cerebral arteries (PCA) (Figure.1). The patient started drug treatment of levodopa and pramipexole, and his bradykinesia and rigidity symptoms were significant improved with 65% valued by UPDRS motor score. He was considered as Parkinsonism for the first time with UPDRS-III total score of 37.

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After four years in 2017, he developed wearing off phenomena with occasional foot dystonia. We increased the dosage of levodopa and pramipexole, and added amantadine to release the worsening symptoms. After adjusted treatment, he had a better motor function. On examination, he showed hypomimia, mild symmetric bilateral bradykinesia, mild bradykinesia and festination gait. He had normal postural reflexes and no action or rest tremor. The UPDRS-III total score was 21. His other non-motor symptoms included hallucinations, constipation and rapid eye movement sleep behavior disorder (RBD) were shown but without depression and cognitive decline. The laboratory tests were normal. The brain MRI and MRA scan showed the multiple stenosis of PCA was as before. The whole-exome sequencing approach was used to identify potential PD-related genes in his family. His only child is 43-years-old and healthy. The sequencing results showed that he carried both c.1448T>A and c.691T>C mutations (Figure.2), and his wife and son carried c. 1448T>A and c.691T>C mutations separately. His relatives have no history of Parkinsonism. His maternal and paternal families were of Southern Chinese ancestry, and his first degree relatives have no family history of PD. After eight years in 2021, he died from pulmonary infection following aspiration.

DISCUSSION

Here we report a case of Parkinsonism patient with double mutations p.L483P in GBA and p.S231P in LRRK2 genes after hypoxic insults. The persons with GBA mutation (p.L483P) has been reported to increase susceptibility to PD in Chinese[9]. The rs201332859 can induced S231P mutation in lrrk2 protein, but pathogenicity of S231P mutation is not clear yet[9]. It was known little about double mutations included GBA and LRR2 in sporadic PD after hypoxic insults. In this report, we showed one patient, carrying (p.L483P) in GBA and (p.S231P) in LRRK2 mutations, suffered from hypoxic insults and showed Parkinsonism symptoms with festinating gait, asymmetric bradykinesia, and moderate rigidity. It suggested that double mutations included GBA and LRR2 may increase the risk of Parkinsonism and modify the progression of disease.

GBA mutations are a common risk factor for PD. The OR for any GBA mutation in patients with PD was about 5.4 compared with control without PD[10]. The PD carrying pathogenic GBA mutations had about 5 years younger on disease onset, more advanced H&Y score, higher problility to suffer postural instability gait difficulty, but similar respond to levodopa compared with the non-carried[10]. In Chinese Han population, L444P is a most important GBA mutation with increased risk for PD[11]. The GBA was known to regulate the lysosomal-autophagy pathway and involve with the formation of Lewy bodies in PD pathogenesis[12]. The molecular mechanism of L444P mutation on GBA is not clear yet. But the L444P mutation may affect the GBA function involved with PD[11]. In our report, we showed one PD patient with double mutations contained L444P. His initial symptoms were bradykinesia and rigidity which were not released well only by levodopa. It suggested that another mutation of S231P in LRRK2 may have an interaction with L444P which may alter the PD pathogenesis and symptoms.

The LRRK2 gene encodes a serine/threonine kinase with GTPase activity, and its pathogenic mutations are a cause of familial Parkinson's disease[2]. LRRK2 is a multi-domain protein kinase included an armadillo repeat domain from residue 150 to residue 510, and serine/threonine protein kinase domain from residues 1879 to residue 2138[2]. The G2019S was a common pathogenic mutation lied in the kinase domain and increases kinase activity of LRRK2 involved with PD pathogenesis[5]. In this report, we found a rare heterozygous mutation, S231P, which produces a serine to proline aminoacid substitution at residue 231. In epidemiological investigation, S231P was found only 0.041healthy samples from different countries[13]. A recent study showed one multiple system atrophy patient carried S231P mutation in 1137 samples, but none in 619 healthy controls in Aisa population[13]. Here, we showed a PD patient carried S231P mutation for first time. It is not clear the function change brought by S231P mutation yet. Base on the limit clinic data, more evidences still need to confirm the association between S231P and risk of PD.

Acute mountain sickness is an illness related with acute hypoxic insult, and always occurred after climbing to an altitude above 2,500 meter without prior acclimatization[7]. Its clinical recoverable symptoms contain headache, malaise, nausea, dizziness, and insomnia[7]. LRRK2 and GBA both contribute to oxidative stress-related signal pathway[14, 15]. But their relationship with environment factor is unclear. Here, we showed a PD patient, carried L444P and S231P mutations, had a different clinic profiles with unrecoverable symptoms

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after acute hypoxia insult. The symptoms can partly release by combination therapy with levodopa and pramipexole. The GBA (L444P) with LRRK2 (R1628P) interaction may affect the clinical profiles and pathogenesis[16]. We hypothesized that combination mutations of L444P and S231P may impaired the function of oxidative stress-related signal pathway which makes the acute hypoxic insult more seriously. Reveal this mechanism may help to renew the interaction between genetic and environment factors in PD help to clinic treatments.

CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

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Figure.1 Brain structure of Parkinsonism patient by magnetic resonance imaging

The MRI imaging performed transverse scan of T1-weighted (A), T2-weighted (B), T2-weighted Flair (C), and sagittal scan of T2-weighted (D) in 2017. No severe morphological change in brain was reported.

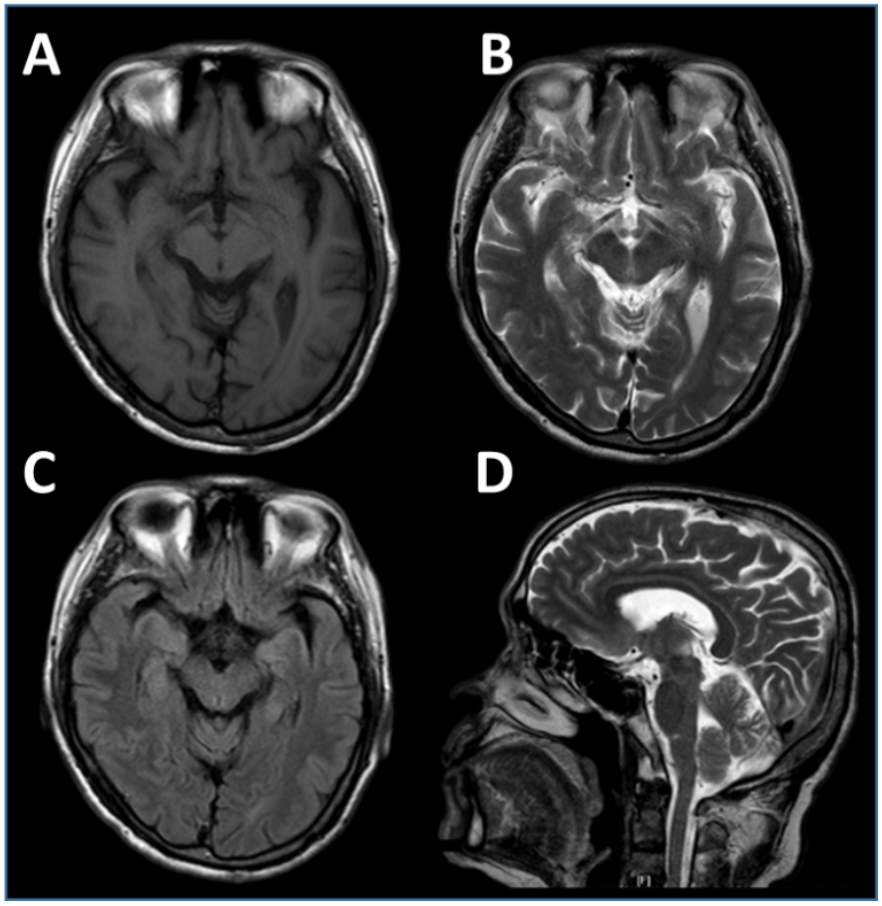

Figure.2 Genotype of Parkinsonism patient by whole-exome sequencing

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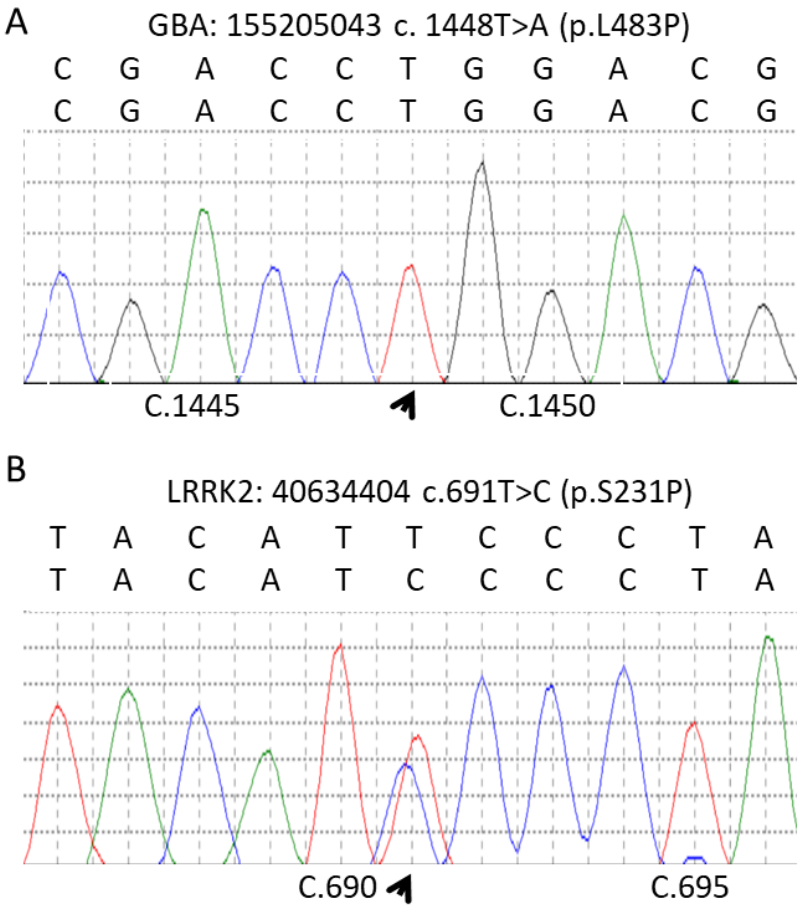

The whole-exome sequencing result showed that Parkinsonism patient had double mutations, included c.1448T>A (p.L483P, rs421016) in GBA (A) and c.691T>C (p.S231P, rs201332859) in LRRK2 (B). The arrow pointed to the polymorphism mutation site.