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Novel *PLA2G6* mutations and clinical heterogeneity in Chinese cases with phospholipase A2-associated neurodegeneration

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ABSTRACT

Introduction: Phospholipase A2-associated neurodegeneration (PLAN) is an autosomal recessive movement disorder with abnormal iron deposition in basal ganglia, substantia nigra and adjacent areas, and cerebellar atrophy. It is caused by *PLA2G6* mutations and comprises three phenotypes. We aimed to investigate genetic mutations in patients with predominantly extrapyramidal symptoms.

Methods: Eighteen Chinese patients with early onset of extrapyramidal symptoms were identified and underwent targeted next-generation sequencing, followed by Sanger sequencing. Detailed clinical and radiological features are presented. Prediction software was used to evaluate the pathogenicity of the identified variants.

Results: We identified 7 *PLA2G6* variants including five known variants (c.668C>T, c.991G>T, c.1117G>A, c.1982C>T, and c.2218G>A) and two novel variants (c.1511C>T, and c.1915G>A) in four index cases. Among them, three cases had initial symptoms of difficulty walking or gait disturbance around the age of 30, and one case and his sibling developed mental handicap at age 7. Two cases exhibited a phenotype of “early parkinsonism” and the other two cases mimicked a phenotype of “hereditary spastic paraplegia (HSP)”. Iron deposition in globus pallidus and substantia nigra was seen in three cases. Cerebellar atrophy was present in all four cases.

Conclusions: Our study expands the mutation spectrum of the *PLA2G6* gene and further supports the hypothesis that *PLA2G6* mutations are associated with a continuous clinical spectrum from PLAN to HSP.

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1. Introduction

Phospholipase A2-associated neurodegeneration (PLAN) is a major subgroup of neurodegeneration with brain iron accumulation (NBIA), which is characterized by abnormal iron accumulation in the basal ganglia, substantia nigra, thalamus, and cerebellum [1].

It is inherited in an autosomal recessive manner and caused by mutations within *PLA2G6* [2]. Clinically, PLAN comprises three phenotypes which overlap clinically and radiologically: infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (aNAD), and *PLA2G6*-related dystonia-parkinsonism [3]. Classic INAD is a devastating syndrome with neurodevelopmental regression, hypotonia, optic atrophy, and progressive spastic tetraparesis. Age at onset is usually from six months to three years and many cases do not survive beyond their first decade. However, aNAD is less aggressive than INAD and has variable presentations. Onset is usually in early childhood. Affected children may present with ataxia, hypotonia, dystonia, optic atrophy, and features of autism. *PLA2G6*-related dystonia-parkinsonism has onset in childhood or young adulthood and predominantly shows features of parkinsonism, dystonia, cognitive decline, and psychiatric dysfunction. Brain MRI may demonstrate abnormal iron accumulation in the globus pallidus, substantia nigra, striatum, in addition

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to cerebellar atrophy. Compared to INAD and aNAD, early diagnosis of *PLA2G6*-related dystonia-parkinsonism is more difficult. Most of the patients are likely to be diagnosed with Parkinson's disease (PD), Wilson's disease (WD), dystonia, or psychosis. Although brain imaging provides important clues for diagnosis, not all patients present with typical iron accumulation on brain MRI, especially in the early stage of the disease. Detecting causative mutations of *PLA2G6* is crucial to the diagnosis.

In the Chinese population, cases affected with PLAN have only been rarely documented. To our knowledge, no more than 50 PLAN patients of Chinese ancestry have been reported so far and the vast majority of these cases were INAD (Supplemental Table 1) [4–8]. The other two phenotypes were described in a small number of cases. Only a few patients had adult onset and exhibited features of early-onset Parkinsonism or PD [9–13]. Moreover, obvious iron deposition in basal ganglia or substantia nigra was not described in Chinese patients with *PLA2G6*-related dystonia-parkinsonism. In this study, we collected 18 unrelated Chinese patients who exhibited primary extrapyramidal symptoms, with or without cognitive impairment and cerebellar ataxia. We performed genetic investigations in these cases using targeted next-generation sequencing (NGS). After verification by Sanger sequencing, we found 7 *PLA2G6* variants including five previously reported variants and two novel variants in four index patients. Detailed clinical features and MRI imaging are presented.

2. Methods

2.1. Study subjects

This study was approved by the Ethics Committee of Second Affiliated Hospital, Zhejiang University School of Medicine. Eighteen unrelated patients with predominantly extrapyramidal symptoms were recruited from Department of Neurology between March 2015 and August 2016. The age at onset of these patients was younger than 40 years old. The neurological examination and clinical evaluations were performed by at least two senior neurologists. Routine blood tests and radiological examination were performed. In addition, 200 matched control individuals of Chinese ancestry were recruited. Written informed consent was obtained from all the participants. For cases younger than 18 years, informed consent was obtained from their parents.

2.2. Genetic investigations

Genomic DNA was extracted from peripheral EDTA-treated blood using Blood Genomic Extraction Kit (Qiagen, Hilden, Germany). A customized panel was designed to cover 9 genes of NBIA, 23 genes of PD, and 55 genes of hereditary spastic paraplegia (HSP) (Supplemental Table 2). A detailed protocol of NGS was reported in our previous study [14,15]. Sanger sequencing was performed to verify the filtered potential variants. Co-segregation analysis was carried out in families with genetic mutations. SIFT, PolyPhen-2, Mutation Taster, PROVEAN, and SNAP were used to predict the pathogenicity of the identified variants.

3. Results

3.1. Identification of variants by targeted NGS and Sanger sequencing

Targeted NGS was performed in 18 unrelated patients. After verification by Sanger sequencing, we found 7 variants within *PLA2G6* (NM 003560) in four index cases, all of whom harbored compound heterozygous variants (Fig. 1A). Among these missense

variants, four variants (c.991G > T, c.1117G > A, c.1982C > T, and c.2218G > A) have been documented as pathogenic variants in PLAN patients and have been included in HGMD [8,13,16,17]. The variant c.668C > T was for the first time associated with PLAN and two variants (c.1511C > T, and c.1915G > A) were novel (Fig. 1B). These three variants (c.668C > T, c.1511C > T, and c.1915G > A) are much conserved in different species (Fig. 1B). The frequency of c.668C > T (p.P223L) was 0.000008320 (1/120186) in ExAC, but absent in 1000G, dbSNP, and 200 matched controls. It was predicted to be deleterious by SIFT, PolyPhen-2, Mutation Taster, PROVEAN, and SNAP. According to American College of Medical Genetics and Genomics (ACMG) standards, this variant was classified as a likely pathogenic variant. The other two variants c.1511C > T (p.S504L) and c.1915G > A (p.A639T) were absent in ExAC, 1000G, dbSNP, and 200 control individuals. Variant c.1915G > A was predicted to be deleterious by all prediction software mentioned above. According to ACMG, this variant was classified as a likely pathogenic variant. Variant c.1511C > T was predicted to be deleterious by the Mutation Taster, but benign by SIFT and PolyPhen-2, neutral by PROVEAN and SNAP. To evaluate the potential pathogenicity of variant c.1511C > T, further functional studies are needed.

3.2. Clinical features of patients carrying *PLA2G6* variants

The detailed clinical features of patients carrying *PLA2G6* variants are summarized in Table 1. Among these four index cases, three cases were possible sporadic and one case had a positive family history. All the patients were males except Case 4. Three cases had initial symptoms of walking difficulty or gait disturbance around the age of 30, while one case developed mental handicap and psychiatric symptoms at the age of 7. Two cases (Case 2 and 3) had a phenotype suggestive of early PD, while the other two cases (Case 1 and 4) mimicked a phenotype of HSP.

Case 1 was a 27-year-old male with mental handicap for 20 years and gait disturbance for 4 years. His birth history was normal with full-term delivery. In childhood, he began to exhibit a decline in intellectual ability. At the age of 13, he developed agitation and irritability and had to discontinue his studies. Risperidone was prescribed, but the symptoms were not alleviated. At the age of 23, he had gait disturbance and slurred speech. His lower limbs became very rigid and he often fell. Difficulty with walking gradually worsened over the following two years and the patient became wheelchair-bound at the age of 25. Neurological examination showed obvious dysarthria, reduced facial expression, increased muscle tone, and hyperreflexia in all limbs, with intact strength. The plantar responses were extensor bilaterally. No nystagmus was observed. Laboratory tests revealed slightly decreased ceruloplasmin of 185 (200–600 mg/dL), and the full blood count, serum lipids, vitamin B12, and serum ferritin were normal. Brain MRI revealed hypointensity in the globus pallidus on T2-weighted (Fig. 2A) and T2-Flair images (Fig. 2B) as well as atrophy of cerebellum (Fig. 2C). Cervical and thoracic MRI were normal. The patient's 13-year-old brother also had a two year history of mental handicap, although his symptoms were much milder. His neurological examination showed globally brisk reflexes and bilateral extensor plantar responses. Brain MRI revealed iron deposition in the globus pallidus bilaterally (Fig. 2D) and substantia nigra (Fig. 2E). Mild cerebellar atrophy was observed as well (Fig. 2F).

Case 2 was a 28-year-old male who had eight months of walking difficulty and hand tremor. He was an office clerk without exposure to any toxins. His birth and developmental milestones were unremarkable. Initially, he noticed stiffness of his lower limbs and difficulty walking. He tended to trip and fall easily when turning quickly. There was no muscle weakness and no atrophy in his limbs.

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