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A Novel XPR1 Variant Cause of Idiopathic Basal Ganglia Calcification Presented with Parkinsonism: Case Report

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ABSTRACT

Primary familial brain calcification (PFBC) also known as Fahr's disease, is a rare inherited disorder characterized by bilateral calcification in the basal ganglia according to neuroimaging. We reported a case of novel XPR1 variant cause of idiopathic basal ganglia calcification presented with left predominant parkinsonism clinical conditions. A 54-year-old male presented with a history of early onset of Parkinson's disease with symptoms of left predominant diminished arm movements, mild rigidity, and bradykinesia. His serum parathyroid hormone levels are normal. CT brain shows diffused symmetric calcifications in bilateral basal ganglia, thalamus, dentate nucleus, pons, and cerebral and cerebellar hemispheres. Ultrasound of the Kidneys, Ureters, and Bladder (USG KUB) revealed right renal calculus. He has been taking medications for Type-2 Diabetes mellitus. Other routine blood test results were normal. Patient has no definitive history of familial genetic inheritance of bilateral calcification of the basal ganglia. Patient was referred for whole exome sequencing. The whole exome sequencing test identified the homozygous missense variant "c.1233A>T p.(Glu411Asp)" detected in the XPR1 gene on chromosomal position Chr1:180834972:A>T. This variant has been located in exon 10 of the transcript NM_004736 and it leads to change in amino acid from Glutamic acid to Aspartic acid at codon 411. The detected XPR1 gene variant "c.1233A>T p.(Glu411Asp)" in our case of 54-year old male has not been reported in the previously published literature. In conclusion, detected novel XPR1 gene variant "c.1233A>T p.(Glu411Asp)" in the chromosomal position Chr1:180834972:A>T led to change in amino acid from Glutamic acid to Aspartic acid at codon 411, and caused to idiopathic basal ganglia calcification in a 54-year old male presented with left predominant parkinsonism clinical conditions.

Keywords: *Parkinsonism Idiopathic basal ganglia calcification; XPR1 gene; Glutamic acid; Aspartic acid.*

Introduction

Basal ganglia calcification is a common incidental finding in brain imaging being reported in 20%–30% of the elderly [1]. More than 50 clinical diagnoses have been reported to be associated with calcium accumulation in the basal ganglia [2]. This condition was previously called familial idiopathic basal ganglia calcification, Fahr syndrome, Fahr's disease, and striopallidodentate calcinosis, but primary familial brain calcification (PFBC) was coined to imply that there is a genetic component [3]. The prevalence of

PFBC is estimated to be 2.1–6.6 per 1000 persons [4], although it may be underestimated due to incomplete clinical penetrance and heterogenous presentations [5].

PFBC symptoms typically occur after the age of 40 with progressive neuropsychiatric and movement disorders, although some individuals may remain asymptomatic [6]. However, the penetrance of PFBC is considered to be full by the age of 50 years if the presence of abnormal calcifications on computed tomography (CT) scan is used as the major diagnostic criterion; virtually all pathogenic variant carriers reaching the age of 50 years have abnormal calcifications on CT scan [7].

Clinically, patients with PFBC experience a variable combination of neuropsychiatric and motor symptoms, including parkinsonism, dystonia, seizures, ataxia, chorea, dementia, psychosis, and frontal-subcortical cognitive dysfunction. Radiologically, abnormal calcification is present within the bilateral basal ganglia, but also the subcortical white matter, cerebellum, thalamus, and brainstem [8]. Bilateral calcifications of the basal ganglia are visualized on CT scans [9].

To date, two inheritance patterns have been found in PFBC patients. Heterozygous variants in *SLC20A2*, *PDGFRB*, *PDGFB*, and *XPR1* are responsible for autosomal dominant PFBC. While biallelic changes in *MYORG*, *JAM2*, and *CMPK2* are associated with autosomal recessive forms of the PFBC disease. At present, around 50% of patients with PFBC do not have a pathogenic variant in the seven currently known genes, which indicates a more diverse genetic heterogeneity [5]. Herein we presented a novel *XPR1* variant cause of PFBC in a 54-year-old male presented with parkinsonism secondary to bilateral calcifications of the basal ganglia.

Case Presentation

A 54-year-old male presented with a history of early onset of Parkinson's disease with symptoms of left predominant diminished arm movements, mild rigidity, and bradykinesia (Video 1). Mild rigidity was noticed on the right side also. Patients has five-year history of slowness in walking, and performing day-to-day's activities. Since in the past 2-3 years behavioural changes such as anger outburst and irregular talking at times were noticed. No family history of similar loss or seizure. He was suspected to have Fahr's disease. His serum parathyroid hormone levels are normal. CT brain shows diffused symmetric calcifications in bilateral basal ganglia, thalamus, dentate nucleus, pons, and cerebral and cerebellar hemispheres (Figure 1). Ultrasound of the Kidneys, Ureters, and Bladder (USG KUB) revealed right renal calculus. He has been taking medications for Type-2 Diabetes mellitus. Other routine blood test results were normal.

Whole Exome Sequencing

Patient was referred for whole exome sequencing. Nucleic acid (DNA) was extracted from peripheral blood using standard Qiagen nucleic acid isolation kit. Library was prepared as per instruction manual of SOPHiA Whole Exome Solution v2 kit and sequencing was performed using Illumina NovaSeq 6000 platform as per user manual. The sequencing reads, quality control, mapping on hg38 human reference genome, variant calling (SNVs, Small InDels) and variant annotation was carried out using SOPHIA DDM. It used different databases like OMIM, ClinVar (v20220416), dbSNP (v155), 1000 Genomes (v5.20130502), ExAC (r0.3.1), and genomAD (v2.1.1). Prediction of implication of coding non-synonymous SNVs on the structure and function of protein, and relevant variants were reported based on The American College of Medical Genetics and Genomics (ACMG) guidelines.

The whole exome sequencing test identified the homozygous missense variant "c.1233A>T p.(Glu411Asp)" detected in the *XPR1* gene on chromosomal position Chr1:180834972:A>T. This variant is noted to have a total depth of 151X. It is located in exon 10 of the transcript NM_004736 and it leads to change in amino acid from Glutamic acid to Aspartic acid at codon 411 (Table 1). This variant has not been reported in ClinVar. This variant has not been reported in population frequency databases such as gnomAD and ExAC. This variant is predicted to be deleterious by In silico prediction tools such as AlphaMissense, Mutation Taster, and DANN. As per ACMG classification the variant can be classified as variant of uncertain significant (VUS) with criteria PM2, PP2.

Figure 1. CT image showing diffused symmetric calcifications in bilateral basal ganglia, thalamus, dentate nucleus, pons, and cerebral and cerebellar hemispheres.

Table 1: Sequence variants related to phenotype

Gene (Transcript)	Location	DNA/Protein Change	Zygosity	Inheritance	Classification	Associated Disease/OMIM
XPR1 (+) NM_004736	Exon 10	c.1233A>T p.(Glu411Asp)	Homozygous	Autosomal Dominant	Uncertain Significance	Basal ganglia calcification, idiopathic, 6 (#616413)

He was prescribed with Tab. Levodopa 100mg + Carbidopa 25mg thrice daily for 8 weeks; Tab. Pramipexole 0.25mg thrice daily for 8 weeks; Tab. Trihexyphenidyl 2mg thrice daily for 8 weeks; Tab. Betahistine 24mg twice daily for 8 weeks; Tab. Clozapine 12.5mg once daily SOS. Upon follow-up after 8-weeks patient's condition improved and doing okay.

Discussion

Parkinsonism was reported in 16.7%–80% of PFBC cases, with a prevalence of 28.6% in *XPR1* mutation carriers [10]. *XPR1* mutations are known to be inherited in an autosomal dominant manner [11]. Contrastingly, no family history of familial idiopathic basal ganglia calcification was observed in our case. The observed prominent clinical symptoms of parkinsonism such as left predominant diminished arm movements, mild rigidity, and bradykinesia secondary to bilateral calcifications of the basal ganglia in our case may be due to sporadic mutations of *XPR1* gene. Literature reports evidenced that pre-synaptic dopamine loss was observed in carriers of *XPR1* mutations [3]. Whereas, in our case showed neither presynaptic dopamine transporter (DAT) loss nor striatal hypometabolism indicating that parkinsonism is not always related to dopaminergic dysfunction in *XPR1*-mutation carriers.

The *xenotropic and polytropic retrovirus receptor 1 (XPR1)* gene was identified in 2015 [12], and it is located on chromosome 1 and encodes for xenotropic and polytropic retrovirus receptor 1 (*XPR1*). *XPR* contains eight transmembrane domains and an amino-terminal SPX domain [13]. This protein mediates Pi efflux from cells. *XPR1* variants may cause haploinsufficiency, leading to the intracellular accumulation of Pi and formation of calcium phosphate [14]. Corroborated to this mechanism reported in the literature, detected variant in our case "c.1233A>T p.(Glu411Asp)" in the *XPR1* gene on chromosomal position Chr1:180834972:A>T leading to change in amino acid from Glutamic acid to Aspartic acid at codon 411 would cause phenotypic left predominant parkinsonism symptoms secondary to bilateral calcifications of the basal ganglia on CT findings could be due to haploinsufficiency caused by detected *XPR1* variant "c.1233A>T p.(Glu411Asp)", and which might led to the intracellular accumulation of Pi and formation of calcium phosphate [14]. Furthermore, to the best our literature knowledge, the detected *XPR1* gene "c.1233A>T p.(Glu411Asp)" variant in our case of 54-year old male has not been reported in the previously published literature.

Conclusion

In conclusion, we are reporting a novel *XPR1* gene variant ""c.1233A>T p.(Glu411Asp)" in the chromosomal position Chr1:180834972:A>T leading to change in amino acid from Glutamic acid to Aspartic acid at codon 411 cause idiopathic basal ganglia calcification in a 54-year old male presented with left predominant parkinsonism clinical conditions.

Patient Consent Declaration

Authors hereby declare that they have obtained patient consent.

Conflict of Interest

None

Funding

None to declare.

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