Primary Familial Brain Calcification Caused by a Novel Compound Heterozygous Mutation in the *MYORG* Gene

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Abstract

Purpose: To demonstrate a novel compound heterozygous mutation in MYORG-related recessive primary familial brain calcification.

Case report: We report a case of primary familial brain calcification with newly-discovered compound heterozygous mutation in the MYORG gene presenting with progressive parkinsonism, cerebellar signs, and typical diffuse brain calcifications.

Conclusion: Clinicians should consider MYORG testing in patients who have primary brain calcifications with either a negative or recessive family history.

Keywords: primary familial brain calcification, MYORG, autosomal recessive.

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INTRODUCTION

Primary familial brain calcification (PFBC) is a neurodegenerative disorder characterized by abnormal bilateral calcifications in the brain, and is caused by genetic mutations that can be inherited in an autosomal dominant or recessive manner. The majority of patients have dominantly inherited PFBC, and there are four causative genes: *SLC20A2, XPR1, PDGFRB*, and *PDGFB*[(1)]. Recessively inherited PFBC is less common and less well understood. The causative genes, *MYORG* and *JAM2*, were identified relatively recently in 2018 and 2020, respectively[(1,2)]. Here, we report a case of a newly discovered pathogenic compound heterozygous mutation in *MYORG*.

CASE REPORT

A 67-year-old otherwise healthy woman presented with progressive dysarthria, dysphagia, ataxia, and bradykinesia for 2 years. Her symptoms caused impairment of her activities of daily living, including eating, communication, and working. She reported that her younger brother had a history of progressive dysarthria and ataxia since he was 50 years old and began to require wheelchair assistance when he was 57 years old. Computed tomography (CT) of his brain revealed diffuse symmetrical brain calcifications (Figure 1A). The parents were healthy.

Neurological examination revealed dysarthria, dysphagia, resting tremor, bradykinesia, reduced arm

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swing, brisk bilateral deep tendon reflexes, dysmetric finger-nose-finger tests, and ataxic wide-based gait. A cranial CT revealed symmetric calcifications in the centrum semiovale, corona radiata, basal ganglia, thalami, occipital lobe, central pons, and cerebellum (Figure 1B). Laboratory test results were unremarkable, and secondary causes of brain calcification were excluded. Genetic analysis revealed two variants in *MYORG*, c.225G>A (p.W75*) and c.1727G>C (p.R576P) (Figure 2), and PFBC was diagnosed. We contacted her younger brother and other family members for further genetic testing. However, they refused for personal reasons.

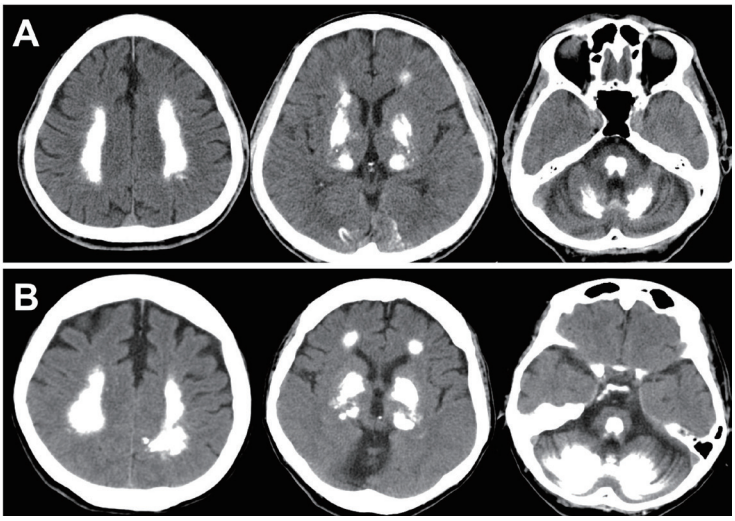

Fig. 1. Brain CT of the patient's younger brother (A) and the patient (B) showing diffuse brain calcifications in the centrum semiovale, corona radiata, basal ganglia, thalami, occipital lobe, central pons, and cerebellum.

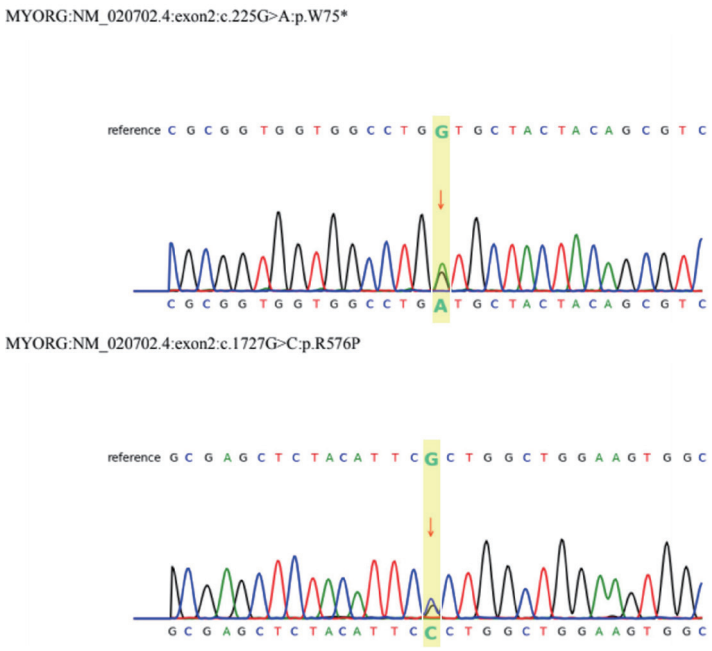

Fig. 2. Whole exome sequencing analysis showed two variants in the MYORG with c.225G > A (p.W75*) and c.1727G > C (p.R576P).

DISCUSSION

The pattern of autosomal recessive inheritance in PFBC was first proposed by Smits et al. in 1983 [3]. However, the first causative gene, *MYORG*, was not identified until 2018, by Yao et al. [4]. Being highly expressed in astrocytes, mutations in *MYORG* are hypothesized to lead to astrocyte dysfunction, resulting in the interruption of neurovascular unit function and formation of calcified nodules [4]. Chen et al. [5] reported that two patients with *MYORG*-related PFBC presented with decreased cerebral perfusion and dysfunction of the nigrostriatal dopamine pathway. Cerebral ischemia may be due to varying calcifications in the affected vessels, while the impairment of the nigrostriatal dopamine pathway may be caused by calcifications between neural circuits. Brain calcifications are extensive in homozygotes and compound heterozygotes and can cause severe disabilities, including movement disorders and neuropsychiatric symptoms [6].

A large, multicenter study[7] described the characteristics of *MYORG*-related PFBC in nine patients. The average age at disease onset was 59 years. Symptoms at onset included parkinsonism, ataxia, dysarthria, cognitive decline, and headache. Of note, "central pontine calcification" on brain CT was observed in three patients, which was distinct from other genetic PFBC cases, and was thought to be an indication of MYORG-related PFBC. Compared to the cases mentioned above, our patient had a later onset age (67 years old), which might have been influenced by the compound heterozygous status. Her clinical presentations of progressive parkinsonism and cerebellar signs on neurological examinations and the characteristic "central pontine calcification" on brain CT (Figure 1 B) were similar to those of the *MYORG*-related PFBC cases described by Chelban et al. [7].

To the best of our knowledge, this case demonstrates a newly discovered pathogenic compound heterozygous mutation, c.225G>A and c.1727G>C (p.R576P) in the MYORG gene. The c.225 G>A (p.W75*) mutation is known to be pathogenic. However, the variant c.1727 G>C (p.R576P) has not been previously reported, and is possibly pathogenic in this case. Modern molecular biology techniques have expanded our understanding of recessive PFBC. Since the exact function of the *MYORG* gene is currently unclear, further studies are warranted to elucidate the pathogenic mechanisms. Clinicians should be aware that in patients presenting with primary brain calcifications, especially in cases involving the central pons and recessive or negative family histories, screening for *MYORG* mutations is recommended.

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