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Short communication

Anticipation in a family with primary familial brain calcification caused by an *SLC20A2* variant

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ABSTRACT

Aim of the study: To describe a family with primary familial brain calcification (PFBC) due to *SLC20A2* variant showing possible genetic anticipation.

Materials and methods: We conducted historical, genealogical, clinical, and radiologic studies of a family with PFBC. Clinical evaluations including neurological examination and head computed tomography (CT) scans of a proband and her father were performed. They provided additional information regarding other family members. To identify a causative gene variant, we performed whole-exome sequencing for the proband followed by segregation analysis in other affected members using direct sequencing.

Results: In this family, nine affected members were identified over four generations. The proband suffered from chronic daily headache including thunderclap headache. We identified an *SLC20A2* (c.509delT, p.(Leu170*)) variant in three affected members over three generations. Interestingly, the age of onset became younger as the disease passed through successive generations, suggestive of genetic anticipation.

Conclusions and clinical implications: For clinical purpose, it is important to consider thunderclap headache and genetic anticipation in PFBC caused by *SLC20A2* variants. Further investigation is required to validate our observation.

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1. Introduction

Primary familial brain calcification (PFBC) is a heritable neurodegenerative disorder characterized by prominent brain calcifications. Four causative genes have been discovered: SLC20A2, PDGFRB, PDGFB, and XPR1 [1]. Of these, *SLC20A2* is the most common, accounting for 55% of patients with PFBC-related variants [2]. Cognitive impairment, neuropsychiatric symptoms, headache, seizures, and movement disorders including parkinsonism, dystonia, and chorea are all have been observed in patients with PFBC [2]. The brain calcifications occur in the basal ganglia, thalamus, cerebellum (dentate nucleus), subcortical white matter, and cortices (particularly in the occipital cortex). Pathogenic variants in *SLC20A2* cause loss-of-function of the encoded type III sodium-dependent phosphate transporter 2 (PiT2), thereby disrupting phosphate homeostasis and leading to the formation of calcifications [3]. We report a PFBC family with an *SLC20A2* variant in which possible anticipation was observed.

2. Materials and methods

We conducted historical, genealogical, clinical, and radiologic studies of a family with PFBC. Neurological examination of a proband and her father were performed. They both provided genealogical information for creation of a family pedigree. We reviewed head computed tomography (CT) scans of the proband, her father, and her son. Only radiologic report of head CT was available for the proband's grandmother. We performed whole-exome sequencing for the proband in order to find causative gene variants. For segregation analysis, we tested *SLC20A2* gene in the proband's parents and son by direct sequencing. This study was approved by our institutional review board and all participants provided written informed consent for genetic testing.

3. Results

3.1. *Family description*

As shown in Fig. 1, symptomatic members were identified in each generation, indicating autosomal dominant inheritance. Two siblings and 3 cousins of the proband developed neurologic symptoms including headache, seizure, and tremor. Head CT has not been performed on these individuals and the presence of brain calcifications could not be confirmed. Of note, the age of symptom onset in individuals with CT confirmed brain calcifications decreased in successive generations ranging from 34 to 13 years.

3.2. *Clinical presentations*

A 37-year-old woman presented with a one-year history of severe headache and hand tremor, which were noticed after a head injury the previous year (Pedigree, Fig. 1A). She had postural and kinetic hand tremor in both hands with slightly left-sided predominance. She suffered from chronic daily headache superimposed on recurrent thunderclap headaches that partially responded to nimodipine. Neuropsychiatric assessment demonstrated mild frontal-subcortical dysfunction. Otherwise, her neurological examination revealed no abnormal findings.

Her 59-year-old father had bilateral hand tremor for 10 years, which mostly consisted of postural and kinetic components with right-sided predominance. He also had headache, frontal-subcortical dysfunction, depression, and personality changes. He walked independently but had trouble with balance and experienced many falls. On balance testing, he had difficulties in recuperating. No bradykinesia or rigidity was observed. His deep tendon reflexes were brisk particularly in the lower extremities with a tendency to ankle clonus. Babinski signs were absent bilaterally.

The proband's paternal grandmother suffered from headache and tremor since her 1970s. She died of an accidental trauma at the age of 84 years. The proband's 11-year-old son had headache and tremor. He also experienced seizures at the age of 2 years.

3.3. *Head CT findings*

Brain calcifications in the bilateral globus pallidus, thalamic pulvinar, right caudate, and left frontal-subcortical white matter were evident in the proband (Fig. 1B). Head CT of the proband's father showed more widely-distributed calcifications compared to the proband including bilateral dentate nuclei of the cerebellum, globus pallidus, caudate heads, thalami, posterior cortices, frontal-subcortical white matter, and left parietal subcortical white matter (Fig. 1C). We received a radiologic report on the proband's paternal grandmother that described extensive basal ganglia calcifications. Brain calcifications were also evident in the bilateral globus pallidus and frontal-subcortical white matter in the proband's son (Fig. 1D).

3.4. *Genetic analyses*

The prominent brain calcifications were evident through four generations, suggesting an underlying genetic etiology. We conducted whole exome sequencing for the proband and identified a heterozygous *SLC20A2* variant (Chr8(GRCh37): g.42320530del, NM_001257180.1:c.509delT, NP_001244109.1:p.(Leu170*)). We confirmed that the proband's father and son carried the variant but her mother did not. This variant has not been reported in ExAC [4]. *In silico* analysis using MutationTaster2 predicted that p.(Leu170*) was disease causing [5].

4. Discussion

We identified an SLC20A2 p.(Leu170*) variant in three affected members over three generations in a family with PFBC. In the variant carriers, clinical symptoms were characterized by tremor and headache in addition to brain calcifications. Both of tremor and headache have been observed in 25% of patients with *SLC20A2* variant [6]. Of note, the proband had obvious episodes of thunderclap headache. To our knowledge, the thunderclap headache has never been reported in PFBC due to

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