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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 seventies. 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

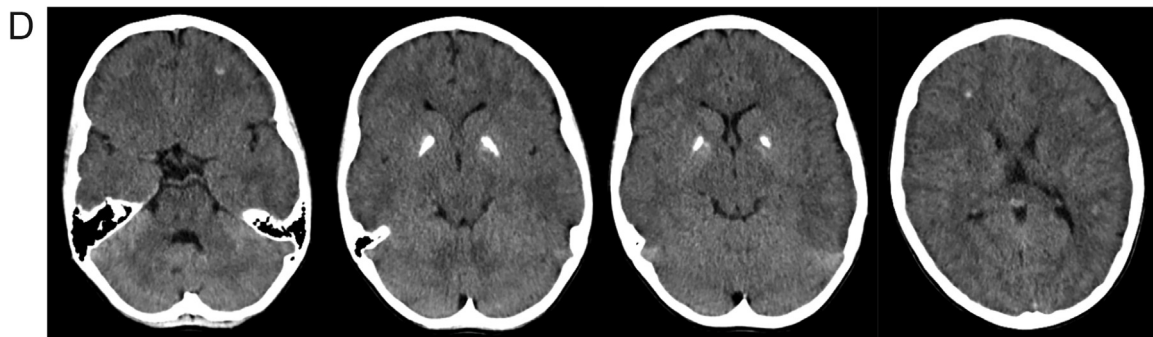
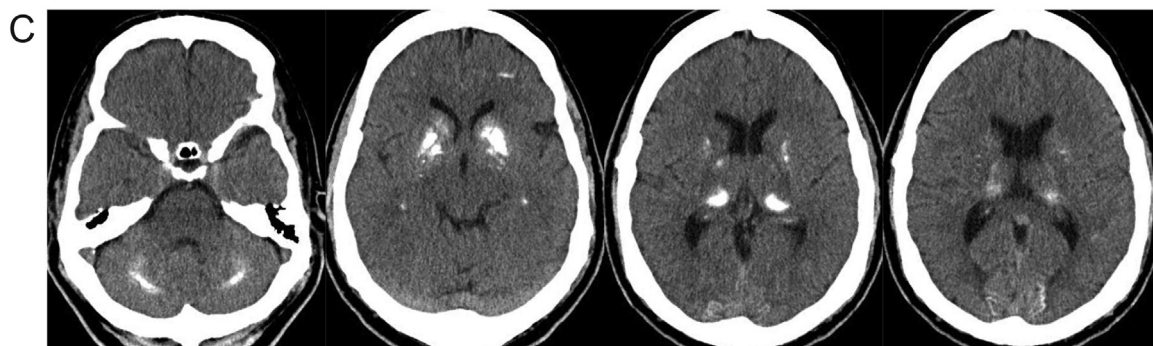
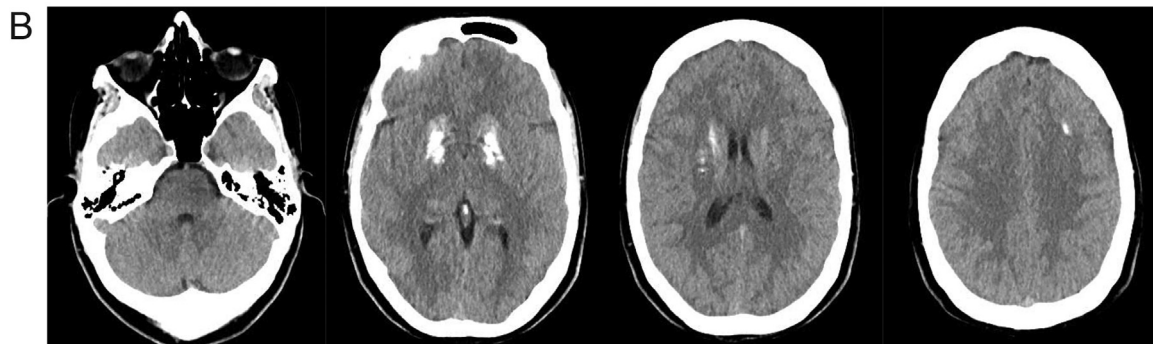
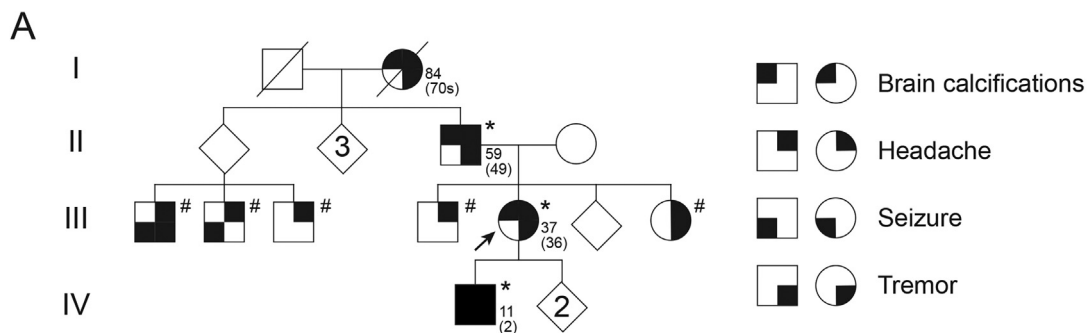


Fig. 1 – (A) A pedigree of the family with *SLC20A2* p.(Leu170*). Standard pedigree symbols are used; squares, male; circles, female; diamonds, obscured gender to protect privacy; slush through symbols, deceased individuals. An arrow indicates the proband. The numbers inside the symbols represent a number of family members; the numbers at the right lower side of the symbols, current age or age at death of the individuals; the numbers in parentheses, age of symptom onset; the hash signs, symptomatic members without radiological evidence of brain calcifications; and the asterisks, mutation carriers. **B**, head CT scans of the proband showed brain calcifications in bilateral globus pallidus, right caudate head, and left frontal-subcortical white matter. **C**, head CT scans of the proband's father showed brain calcifications in bilateral cerebellum, globus pallidus, caudate heads, thalami, posterior cortices, frontal-subcortical white matter, and left parietal subcortical white matter. **D**, head CT scans of the proband's son showed brain calcifications in bilateral globus pallidus and frontal-subcortical white matter.

SLC20A2 variant. Her brain MR angiography and venography in a remission period were normal. While it remains unclear whether this type of headache is intrinsically associated with the SLC20A2 variant, the proband described similar severe headache episodes in both her father and son.

p.(Leu170*) was previously reported and segregated in a large family with PFBC [7,8]. This variant is predicted to cause loss-of-function of PiT2 through haploinsufficiency and is likely pathogenic. In our family, the neurologic symptoms developed 13–34 years earlier as the disease passed through generations, suggestive of genetic anticipation. Anticipation was also observed in the family with p.(Leu170*) [8] and others [9,10]. In the previous family with p.(Leu170*) [8], the average decrease in age at onset was 20 years (range 12–40 years). Our observation remains preliminary due to possible ascertainment bias. Nevertheless, it is important to be aware of possible anticipation in PFBC. Although the mechanism of genetic anticipation in PFBC is unknown, it is possible that there are genetic modifiers such as repeat expansions that may co-exist with the reported variant. It may be of interest to look for genetic links between these two families carrying the p.(Leu170*) variant.

5. Clinical implications/future directions

Thunderclap headache and genetic anticipation could be observed in PFBC with SLC20A2 variant. Further investigation is needed to confirm our observations.

Conflict of interest

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