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WHITE MATTER INVOLVEMENT IN A FAMILY WITH A NOVEL *PDGFB* MUTATION

OPEN

Primary familial brain calcification (PFBC) (formerly idiopathic basal ganglia calcification; Fahr disease) is an autosomal dominant cerebral microvascular calcifying disorder with variable clinical and imaging features.[1] Four causative genes have been identified: *SLC20A2*,[2] *PDGFRB*,[3] *PDGFB*,[4] and *XPR1*.[5]

We describe a family with 5 members carrying a novel mutation c.3G>C of the *PDGFB* gene highlighting the white matter involvement observed at neuroimaging (figure 1A).

Case descriptions. ***Patient IV-2.*** A 5-year-old girl presented with her second unprovoked tonic-clonic seizure. The first episode occurred at age 2 years. She was born at term after an uneventful pregnancy and a normal delivery by healthy nonconsanguineous parents. Her psychomotor development and neurologic examination were unremarkable. The blood investigations and EEG were normal. Brain MRI revealed multifocal confluent white matter lesions and small cysts in the frontoparietal lobes (figure 1B). Head CT showed calcifications in the globi pallidi (figure e-1 at Neurology.org/ng). No treatment was given and the patient remained seizure-free over the years. However, she began to have attacks of sporadic migraine without aura at age 12 years. At age 14 years, brain MRI was unchanged. At age 17 years, cognitive functions and neurologic examination were persistently normal.

Patient IV-1. This 22-year-old university student presented with migraine since adolescence. He was cognitively and neurologically normal. Brain MRI showed confluent white matter lesions and small cysts in the frontal lobes (figure 1C), associated with calcifications in the globi pallidi (figure e-1).

Patient III-2. This patient reported rare migraine without aura attacks since age 30 years. Neurologic examination and cognitive functions were normal. Brain MRI showed multiple periventricular and subcortical white matter lesions associated with basal ganglia calcifications (figure 1D). Areas of perivascular contrast enhancement were observed after gadolinium administration (figure e-2).

Patient II-2. This 72-year-old woman complained of migraine without aura in adulthood. Brain MRI showed scattered subcortical white matter lesions in the frontal lobes (figure 1E) and calcifications in the globi pallidi (figure e-1).

Patient III-5. This patient presented with occasional episodic migraine without aura since age 30 years. Neurologic examination and cognitive functions were normal. Brain MRI revealed diffuse and scattered white matter lesions in the frontoparietal lobes (figure 1F). Calcifications of the basal ganglia, pulvinar, dentate nuclei, and white matter were noted on CT (figure e-1). Electron microscopy of skin biopsy showed capillary basal membrane abnormalities consistent with microangiopathy (figure 1, G and H).

Genetic study. We performed exome sequencing in patients III-2 and IV-2 and selected rare nonsynonymous coding variants shared by the two affected relatives (figure 1A). We initially focused our analysis on the genes underlying autosomal dominant brain calcification (*SLC20A2*, *XPR1*, *PDGFB*, and *PDGFRB*) and vascular leukoencephalopathy (*CADASIL*, *COL4A1*, and *COL4A2*) and identified a G to C substitution affecting the first codon of the *PDGFB* gene (c.3G>C), which is expected to impair protein translation (table e-1). Segregation analysis of c.3G>C mutation was performed in 9 family members (figure 1A).

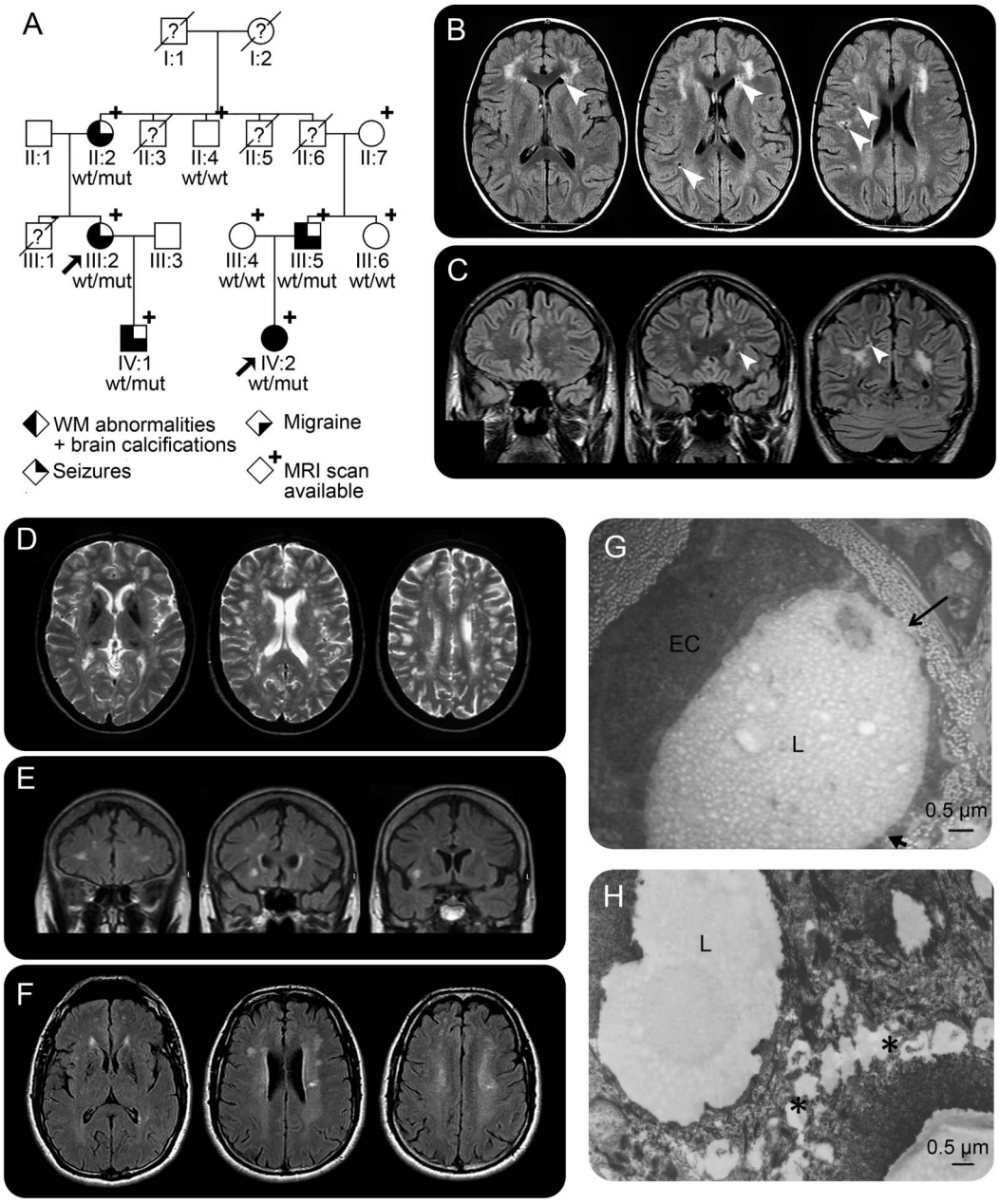
Discussion. Twelve *PDGFB* mutations have been reported so far (table e-2). Brain calcifications are the main imaging findings.[1] We showed that white matter abnormalities may be an early and prominent imaging presentation. The c.3G>C mutation affects the first codon of *PDGFB*, similarly to a previously reported family, in whom, however, only CT scan data were available.[4]

Our patients had migraine without aura, which is often reported in PFBC, even in the absence of white matter abnormalities.[1] Although migraine may be associated with white matter hyperintensities cross-sectionally,[6] at least in subject IV-2, migraine appeared several years after the finding of white matter abnormalities without evidence of progression over time.

PDGFRB and *PDGFB* mutations result in pericyte dysfunction and blood-brain barrier (BBB) impairment contributing to the development of brain

Supplemental data at Neurology.org/ng

Figure 1 Overview of the genetic and MRI data of the family and skin biopsy findings of individual III-5



(A) Pedigree and segregation analysis of PDGFB mutation. Individuals who underwent exome sequencing are indicated by arrows. PDGFB genotypes are reported under the symbols (wt, normal allele; mut, c.3G>C). (B) Case IV-2 (age 5 years): axial FLAIR brain MRI images demonstrate focal confluent areas of white matter hyperintensity in the frontal and parietal lobes associated with small cystic lesions (arrowheads). (C) Case IV-1 (age 22 years): coronal FLAIR images reveal similar focal confluent areas of white matter hyperintensity associated with small cystic lesions in the frontoparietal regions (arrowheads). (D) Case III-2 (age 44 years): axial T2-weighted images show confluent calcifications of lenticular, caudate, and pulvinar nuclei associated with multiple patchy hyperintensities of the periventricular and subcortical supratentorial white matter. (E) Case II-2 (age 73 years): coronal FLAIR images reveal scattered foci of white matter hyperintensity in the frontal and insular regions. (F) Case III-5 (age 42 years): axial FLAIR images reveal diffuse and patchy hyperintensities of the periventricular white matter with prevalent involvement of the frontal regions. (G) Electron microscopy of skin biopsy of individual III-5 showing an endothelial cell with areas of membrane fragmentation (arrowhead) and focal interruption (arrow) (magnification ×3,000). (H) High-resolution electron microscopy image of skin biopsy of individual III-5 showing basement membrane with thickened and fragmented areas (asterisks) (magnification ×7,000); EC = endothelial cell; FLAIR = fluid-attenuated inversion recovery; L = lumen.

calcifications and clinical manifestations, including migraine.[1] The perivascular contrast enhancement identified in 1 patient supports the pathogenic role of BBB dysfunction in this condition.

Small cysts were identified in the affected white matter of patients IV-2 and IV-1, similarly to genetic leukoencephalopathies, such as "*COL4A1* mutation-related disorders." It is interesting that the ultrastructural

abnormalities reported in patients with COL4A1 mutation are similar to those depicted by skin biopsy electron microscopy of patient III-5.

The most recent classification of leukodystrophies and leukoencephalopathies lists 6 different conditions under the term genetic leukoencephalopathies related to vascular disorders, including *COL4A1* mutation–related disorders.[7]

We suggest including white matter abnormalities related to PFBC mutations in the differential diagnosis of genetic leukoencephalopathies due to vascular disorders. The magnetic resonance finding of calcifications and small cysts may support the clinical suspect, especially in families with incomplete penetrance.

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