# A pediatric case with primary familial brain calcification due to a homozygous variant on the *JAM2* gene

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## INTRODUCTION

Primary familial brain calcification (PFBC), also known as Fahr disease, is a genetic neurodegenerative disorder characterized by bilateral extensive calcifications in the basal ganglia and other brain regions in the absence of known metabolic-endocrinologic causes. PFBC is inherited in an autosomal-dominant or autosomal-recessive manner or caused by de novo genetic changes. Although four gene mutations have been reported to be associated with autosomal-dominant PFBC the genetic cause of autosomal-recessive PFBC (AR-PFBC) was not known until recently.

JAM2 gene (junctional adhesion molecule 2), encoding a tight-junction protein responsible for cell-to-cell adhesion in endothelial cells, is recently reported as the second genetic cause underlying AR-PFBC. So far, very limited patients with JAM2 mutation in AR-PFBC cases have been published, and only one of them was a child.

## OBJECTIVES

Herein we present a case who is the youngest patient with homozygous JAM2 variant-associated AR-PFBC in the literature.

## CASE

**Case:**A 6-year-old girl was referred to our pediatric neurology department with a generalized-tonic clonic seizure lasting 10 minutes accompanied by fever during a new-onset common cold.

She is the fourth child of consanguineous parents. Family history was non-contributory. Her physical and neurological examination was normal. Her electroencephalography and neurodevelopmental tests were compatible with her age.

Cranial MRI revealed heterogeneous hyperintense signal changes in the basal ganglia, dentate nucleus and subcortical white matter on T1-weighted imaging (Fig 1).

She was evaluated in detail for the potential etiology of calcification and all tests including metabolic, endocrinologic, infectious, and vasculitic screening were normal. Therefore, she was diagnosed with idiopathic brain calcification and was examined for the most common gene for AD-PFBC including SLC20A2 and PDGFB which were normal. However whole-exome analysis (WES) revealed a homozygous variant (c.177_180del (p.R60fs*) on the JAM2 gene consistent with AR- PFBC. Parents were also found to have a heterozygous mutation in the JAM2 gene. Her neurologic and psychiatric examinations were all normal at the final visit.

## DISCUSSION

The genetic cause of AR-PFBC was not known until recently. In 2018, biallelic mutations in the myogenesis-regulating glycosidase (MYORG) gene was reported as the first AR gene that has been associated with intracranial calcification. In 2021, we reported the first pediatric patient in the literature who had a novel homozygous variant in the MYORG gene with mild clinical findings. In 2021, Cen et all reported that biallelic loss-of-function mutations in JAM2 gene were a cause of the autosomal recessive form of PFBC (AR- PFBC) in four patients.

Eleven patients between 7 and 50 years of age with primary familial brain calcification related to a mutation on the JAM2 gene have been reported so far. It is reported that most of the patients with JAM2 gene mutation (10/11) were symptomatic and the onset of symptoms changed early childhood period to the late 30s.

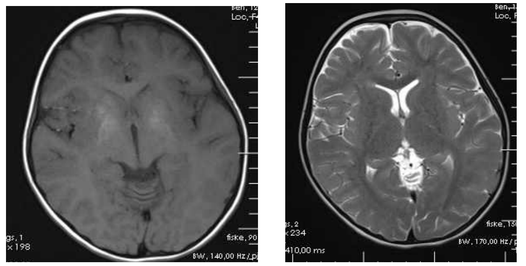

**Fig 1**. Brain MRI: Heterogeneous hyperintense signal changes on the basal ganglia, dentate nucleus and subcortical white matter.

## CONCLUSIONS

In conclusion, the JAM2 gene is recently reported as the second genetic cause underlying autosomal-recessive PFBC. To the best of our knowledge, the present case is the youngest patient with homozygous JAM2 variant-associated AR-PFBC in the literature.

## REFERENCES

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