

A novel *SLC20A2* mutation in a family with primary familial brain calcification

G. Peppoloni, I. Taglia, C. Battisti, S. Bianchi and A. Federico

Department of Medicine, Surgery and Neurosciences. University of Siena, Siena, Italy

Background

Primary Familial Brain Calcification (PFBC), also known as Fahr's disease, is a rare neurodegenerative disorder characterized by bilateral and symmetric calcifications, mainly in the basal ganglia, but also in dentate nuclei of the cerebellum, thalami, brainstem and subcortical white matter. The main manifestations include movement disorders as parkinsonism (57%) or hyperkinetic movements (43%), cerebellar symptoms, and neuropsychiatric features, with prevalence of cognitive impairment and mood disorders. Four genes have been linked to PFBC, with an autosomal dominant transmission: *SLC20A2*, *PDGFRB*, *PDGFB* and *XPR1*. *SLC20A2* encodes the inorganic phosphate transporter PiT-2, involved in phosphate homeostasis; the disease mechanism is a loss of function of PiT-2 that leads to an accumulation of inorganic phosphate in the brain and, consequently, to calcium phosphate deposits.

Case report

A 70-year-old man with a slowly progressive extrapyramidal syndrome, started six years before with fatigability, limb weakness, global bradykinesia and hypophonic voice. The patient also suffered from stuttering, sleep disorders, mild anxiety and depression. He had no cognitive impairment.

- MRI images: little calcium deposits in the globus pallidus bilaterally and in the right caudate nucleus (fig. 1).
- Phospho-calcium metabolism and serum parathormone: normal.

The patient carried a **novel duplication of twelve nucleotides, TGGTTCGTGACC, from position 1876 to 1887 of cDNA, located in the exon 11 of *SLC20A2* gene (fig. 2)**. This variant causes an in-frame duplication of four aminoacids, Tryptophan-Phenylalanine-Valine-Tyrosine (WFVT), at the position 626-629, which results in an extension of the protein.

The variant is carried also by the younger son and the brother of the patient, both without neurological disturbances (fig.3).

**c. 1875_1887DupTGGTTCGTGACC
p.625_629dupTrpPheValThr**

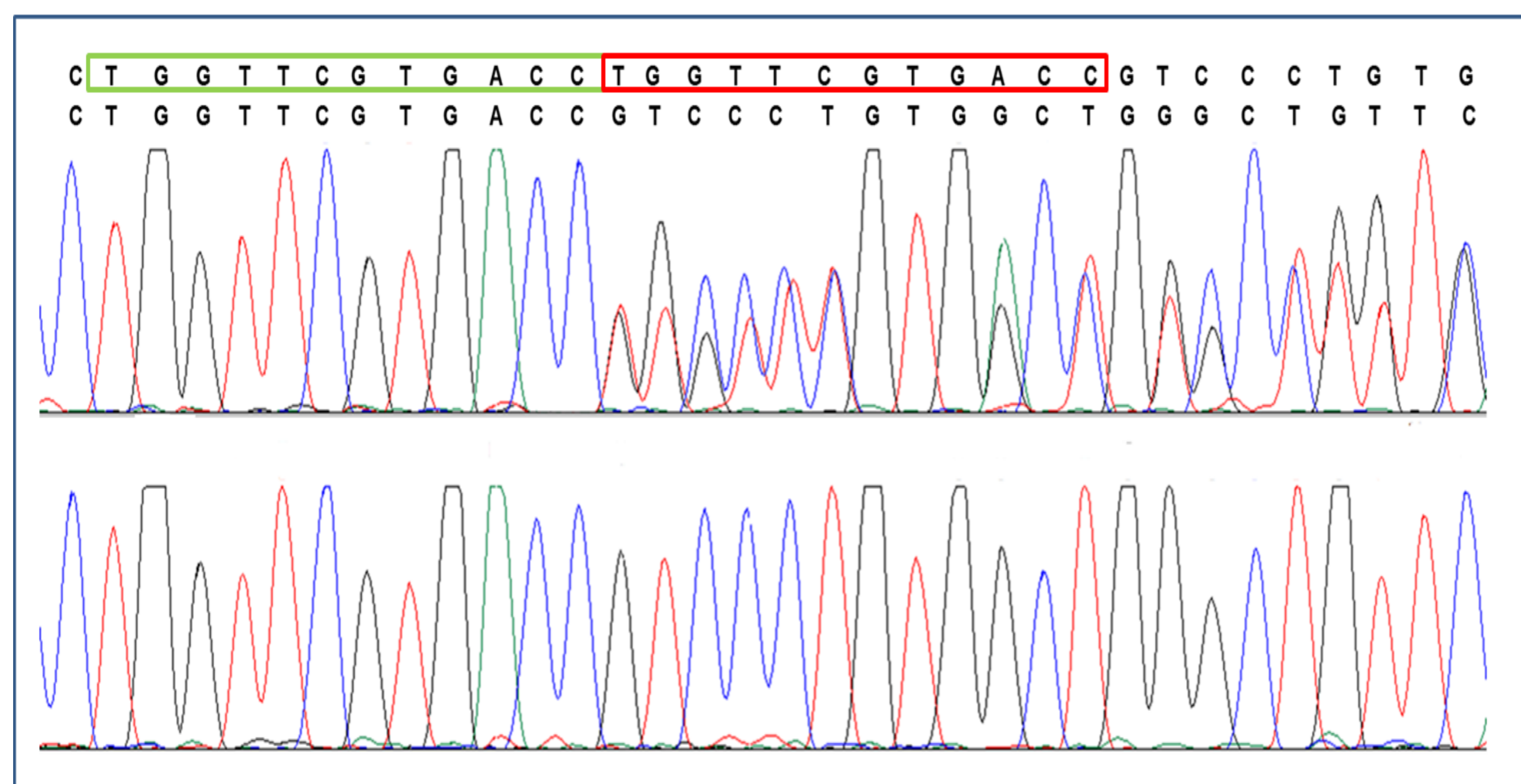


Fig.2. Novel duplication of twelve nucleotides, TGGTTCGTGACC, from position 1876 to 1887 of cDNA located in the exon 11 of *SLC20A2* gene

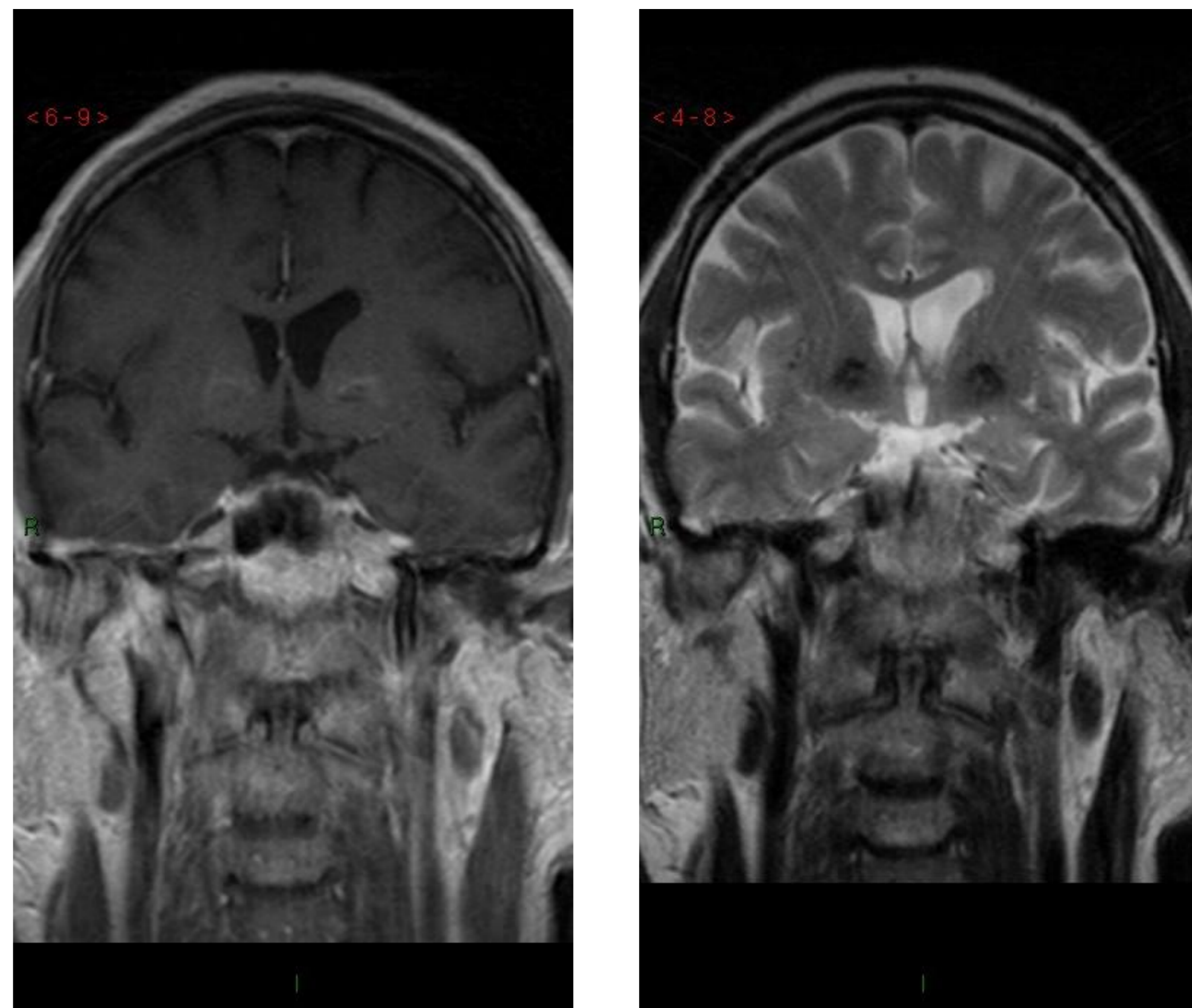


Fig.1. Brain MRI images: little calcium deposits in the globus pallidus bilaterally and in the right caudate nucleus.

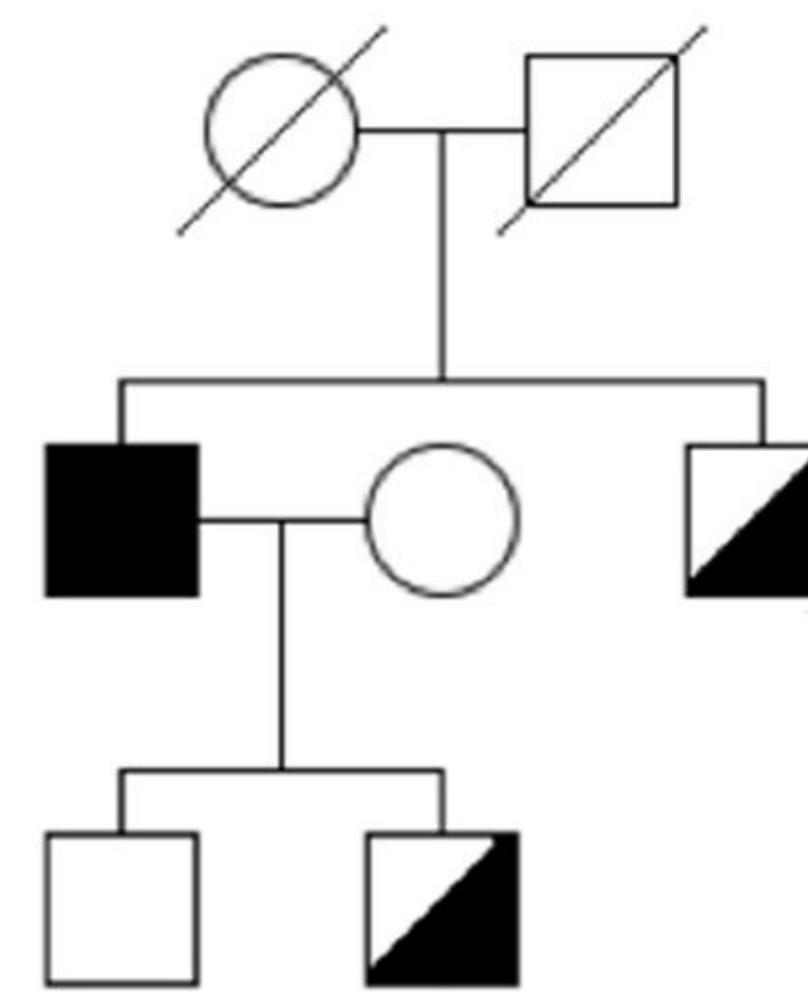


Fig. 3 Pedigree of PFBC family: filled black symbol represents our proband; black lower half-symbols indicate asymptomatic subjects carrying *SLC20A2* mutation.

Conclusion

SLC20A2 gene harbours the highest number of causal variants. We identified a family affected by a novel *SLC20A2* mutation, responsible for clinical signs only in the proband, as a proof of the high frequency of asymptomatic cases. Although genotype-phenotype correlation studies showed a prevalence of cognitive impairment linked to *SLC20A2* mutations (compared to *PDGFRB* and *PDGFB*), our proband presented only with parkinsonism and mood disorder. In conclusion, PFBC is an autosomal dominant disease with a very heterogeneous clinical presentation; only 50% of cases are linked to a specific gene, suggesting that other genes are yet to be described.

References

1. Lemos R. R., Ramos EM, Legati A, Nicolas G, Jenkinson EM, Livingston JH, Crow YJ, Campion D, Coppola D, Oliveira JRM *Update and Mutational Analysis of SLC20A2: A major cause of Primary Familial Brain Calcification*, Hum Mutat. 2015 May;36(5):489-95.
2. Tadic V, Westenberger A, Domingo A, Alvarez-Fischer D, Klein C, Kasten M *Primary Familial Brain Calcification with known gene mutations: A systematic review and challenges of phenotypic characterization*, JAMA Neurol. 2015;72(4):460-467
3. Taglia I, Bonifati V, Mignarri A, Dotti MT, Federico A, *Primary Familial Brain Calcification: update on molecular genetics*, Neurol Sci. 2015 May;36(5):787-94.