

XPR1 Mutations: Another Cause of Primary Familial Brain Calcification

With the discovery of the genetic causes of brain calcifications, the term idiopathic basal ganglia calcifications (formerly known as Fahr disease) does not seem to be appropriate anymore and recent reports suggested it would be better replaced by the term primary familial brain calcification (PFBC), also owing to the fact that imaging abnormalities extend beyond the basal ganglia to the cerebellum, thalamus, brainstem, and subcortical white matter.^{1,2} PFBC is a genetically heterogeneous disorder typically transmitted in an autosomal-dominant fashion and variably characterized by a combination of dystonia, parkinsonism, ataxia, cognitive impairment, and behavioral changes.¹ An intriguing feature of PFBC is the phenomenon that the penetrance of the clinical phenotype is reduced, resulting in approximately 35% of the mutation carriers having calcifications visible on CT scans, but none of the above-mentioned symptoms.² Thus far, three different genes have been associated with PFBC (i.e., *SLC20A2*, *PDGFB*, and *PDGFRB*; Table 1), accounting for around half of the cases.^{3,4} This leaves a substantial number of families with PFBC genetically unexplained, suggesting that other genes are yet to be identified.

TABLE 1 Known genes and loci associated with PFBC

Locus	Gene	Chromosomal Area	Reference
IBGC1/ IBGC3	<i>SLC20A2</i>	8p11	Hsu et al. ⁴
IBGC2	<i>Unknown</i>	2q37	Volpato et al. ⁸
IBGC4	<i>PDGFRB</i>	5q32	Nicolas et al. ⁹
IBGC5	<i>PDGFB</i>	22q12	Keller et al. ¹⁰
IBGC6	<i>XPR1</i>	1q25	Legati et al. (highlighted in this commentary) ³

IBGC = idiopathic basal ganglia calcification; however, this term does not account for the fact that imaging abnormalities often extend beyond the basal ganglia.

By performing exome sequencing in a family of Swedish ancestry lacking mutations in *SLC20A2*, *PDGFB*, and *PDGFRB*, and with a clinical phenotype that consisted of progressive cognitive impairment, speech impairment (slurred speech and palilalia), chorea, and ataxia, Legati et al. now identified a c.434T>C transition in the mammalian *XPR1* gene as an additional genetic cause of PFBC.³ Further sequencing of *XPR1* in 86 sporadic and familial cases identi-

fied the same c.434T>C mutation in two affected individuals from a family of French descent (claimed to be unrelated to the first family on the basis of segregation patterns of variants surrounding *XPR1*).³ Three additional, probably damaging, variants were identified in this cohort of cases affected by brain calcifications.³

The *XPR1* gene encodes a cell-surface multipass membrane protein initially identified as the mammalian receptor for xenotropic murine leukemia viruses.⁵ It also mediates phosphate export across the membrane, a function that is highly conserved across evolution.⁶ Thus, *XPR1* is the second gene encoding a phosphate transporter to be implicated in PFBC, after *SLC20A2*. *XPR1* is highly expressed in neuronal stem cells and human brain, and its role in phosphate homeostasis supports its pathogenic role in PFBC.

Legati et al. tested the identified *XPR1* variants in a complementation assay for phosphate efflux in human cells, finding that inhibition of phosphate export led to increase of intracellular phosphate concentration. The investigators therefore suggested that *XPR1* mutation-mediated calcium phosphate precipitation is likely to occur intracellularly.³ This would differentiate *XPR1*- from *SLC20A2*-associated PFBC. In fact, the presence of mutations in *SLC20A2* (encoding PiT2, a phosphate importer) inhibits phosphate uptake, thus leading to deposition of calcium phosphate in the vascular extracellular matrix. Although phosphate import and export are mediated by different mechanisms, it is currently unknown whether *XPR1* and PiT2 interact or are regulated by other common factors. The other two genes accounting for PFBC also interact in this pathway: The encoded proteins, PDGF-B and PRGFR β , modulate phosphate transport⁷ and may also regulate *XPR1* and PiT2 levels in brain.³

Further studies will clarify whether this pathway could be targeted to identify potential treatments for this yet untreatable disorder.

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