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GENETICS (V. BONIFATI, SECTION EDITOR)

MYORG Mutations: a Major Cause of Recessive Primary Familial Brain Calcification

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Abstract

Purpose of Review Until recently, the gene associated with the recessive form of familial brain calcification (PFBC, Fahr disease) was unknown. *MYORG*, a gene that causes recessive PFBC was only recently discovered and is currently the only gene associated with a recessive form of this disease. Here, we review the radiological and clinical findings in adult *MYORG* mutation homozygous and heterozygous individuals.

Recent Findings *MYORG* was shown to be the cause of a large fraction of recessive cases of PFBC in patients of different ethnic populations. Pathogenic mutations include inframe insertions and deletions in addition to nonsense and missense mutations that are distributed throughout the entire *MYORG* coding region. Homozygotes have extensive brain calcification in all known cases, whereas in some carriers of heterozygous mutation, punctuated calcification of the globus pallidus is demonstrated. The clinical spectrum in homozygotes ranges from the lack of neurological symptoms to severe progressive neurological syndrome with bulbar and cerebellar signs, parkinsonism and other movement disorders, and cognitive impairments. Heterozygotes are clinically asymptomatic.

MYORG is a transmembrane protein localized to the endoplasmic reticulum and is mainly expressed in astrocytes. While the biochemical pathways of the protein are still unknown, information from its evolution profile across hundreds of species (phylogenetic profiling) suggests a role for MYORG in regulating ion homeostasis via its glycosidase domain.

Summary *MYORG* mutations are a major cause for recessive PFBC in different world populations. Future studies are required in order to reveal the cellular role of the MYORG protein.

Keywords Primary familial brain calcification · Fahr disease · *MYORG* · Phylogenetic profiling

Introduction

Primary familial brain calcification (PFBC), also known as Fahr disease, is a progressive neurological disorder with extensive brain calcification, lacking known metabolic causes such as calcium or phosphorus homeostasis disorders [1]. Earlier studies identified only dominantly inherited forms of the disease, including those associated with mutations in the *SCL20A2* [2], *PDGFRB* [3], *PDGFB* [4], and *XPR1* [5] genes. While adult-onset, apparently recessive forms of PFBC were previously described [6], only in 2018 *MYORG* (myogenesis-regulating glycosidase, HGNC: 19918), the first gene associated with a recessive form of the disease was reported [7••]. At the time of writing this review, the *MYORG* gene (also known as *KIAA1161*, *NET37*, or IBGC7) is the only known gene associated with a recessive form of the disease.

The *MYORG* gene association with PFBC (MYORG-PFBC) was first reported in families of Chinese origin, but has since been confirmed in recessive PFBC cases from other ethnicities [8•, 9, 10•, 11]. These data indicate that mutations in the gene are responsible for a large fraction of recessive PFBC. In the largest set of cases examined so far, 11/29 probands with PFBC, which showed no other known genetic cause, had biallelic *MYORG* mutations [10•]. *MYORG* mutations explained PFBC in 6/13 families of Chinese ancestry

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[7••] and in 2/2 of families of Palestinian origin where a recessive mode of inheritance was most likely [8•].

Clinical Features of *MYORG*-PFBC

In *MYORG*-PFBC, as with other forms of PFBC, some subjects with extensive brain calcification show apparently normal neurological examinations [8•]. The most common presenting sign in symptomatic individuals is dysarthria, usually reported in the 3rd to 6th decades of life, but which can also occur from an age as early as 15 years. Hyperkinetic movement disorders are also frequent in symptomatic individuals, documented in all cases in one study and less frequently in another [10•]. These can range from mild facial grimacing to chorea of the limbs and severe general dystonia. These abnormalities are not necessarily symmetrical as is the case with other metabolic diseases (e.g., Wilson's disease). Other frequently observed neurological signs of *MYORG*-PFBC include parkinsonism, appendicular and truncal cerebellar signs, and cognitive impairments. Additional infrequently reported symptoms include migraine-like headaches [7••], urinary incontinence, hallucinations, seizures [12], and central pain syndrome [13].

It is yet unclear what factors can affect the severity of symptoms in individuals with this recessive form of PFBC. It has been suggested that homozygous truncating mutations in the *MYORG* gene may be associated with a more severe phenotype [7••]. This observation, however, is based on only two patients, whereas it could not be confirmed in the cohort of another study [8•]. Since the cellular function of *MYORG* is still unknown, it is not yet possible to correlate between the residual activity of the protein and the severity of the phenotype.

In a relatively small cohort of Arkadir et al. [8•], individuals with milder radiological involvement of the brain stem exhibited a less severe neurological phenotype. The extensive calcifications of the basal ganglia and the cerebellum did not distinguish between individuals at different degrees of clinical severity. Like in other progressive syndromes, severity of symptoms increases with the patient age. The oldest individual in our cohort, however, was asymptomatic, while his younger 5 siblings (who were homozygous for the same mutation) had symptoms [8•]. This observation implies for other genetic or environmental modifiers that affect the phenotypic severity.

It seems that *MYORG*-PFBC cannot be reliably distinguished from other types of PFBC based solely on clinical findings. In *MYORG*-PFBC, dysarthria was shown to be a prominent feature (and the most common presenting sign) in the majority of symptomatic cases. In contrast, the frequency of dysarthria is far lower in PFBC cases associated with mutations in the dominant genes [10•, 14]. Seizures, on the other hand, are less prevalent in *MYORG*-PFBC [10•].

Radiological Features of *MYORG*-PFBC

Recessive mutations in the *MYORG* gene cause extensive brain calcification (Fig. 1a). All diagnosed individuals had calcifications involving the cerebellum and basal ganglia [8•, 10•, 12]. It was suggested in some studies that brain calcifications are more widespread in *MYORG*-PFBC relative to PFBC cases associated with dominant genes [10•, 12] where calcification of the cerebellum and basal ganglia is not always present (34% and 70%, respectively) [15]. It seems, therefore, that the absence of calcification of the cerebellum or basal ganglia almost rules out *MYORG*-PFBC. In addition, a propensity for calcification in the posterior fossa, and more specifically in the pons, can distinguish *MYORG*-PFBC from the known autosomal dominant forms of the disease [10•]. Additional calcifications of the thalami, brainstem, deep midbrain nuclei, and cortical areas were variably demonstrated. It seems that once cortical areas are involved, the occipital lobes are the most vulnerable.

Clinical and Radiological Features of *MYORG* Single Heterozygous Mutation Carriers

Extensive brain calcification is associated with homozygous and compound heterozygous mutations in the *MYORG* gene [7••, 8•, 10•, 11]. It seems, however, that a mutation in only a single allele can lead to a radiological phenotype of punctuated calcification that is limited to the internal part of the globus pallidus (Fig. 1b). This radiological sign was demonstrated in 3/5 (60%) of *MYORG* mutation carriers in the study by Arkadir et al. [8•]. Two of these three individuals were younger than 40 years at the time that their scans were carried out. All carriers in this study, including the ones with punctuated calcifications, were asymptomatic. Punctuated calcification was also reported by others in elderly obligatory carriers of the *MYORG* pathogenic mutation [10•].

A single case of a 68-year-old male carrier with postural tremor was reported in another study as showing calcifications [9] that were more than minimal in the cerebellum, globus pallidus, and centrum semiovale. These calcifications were shown to be less prominent than those of his homozygote son. In this particular case, however, the *MYORG* gene was not fully sequenced and it was impossible to rule out a compound heterozygous state.

In elderly patients, punctuated calcification that is limited to the internal part of the globus pallidus was shown in 20% of individuals [16], and its presence is not considered to be clinically meaningful. The high prevalence of punctuated calcification in a young cohort in the Arkadir et al. study [8•] is unexpected. This observation raises a question regarding the role of *MYORG* mutations in causing this radiological sign in the general population.

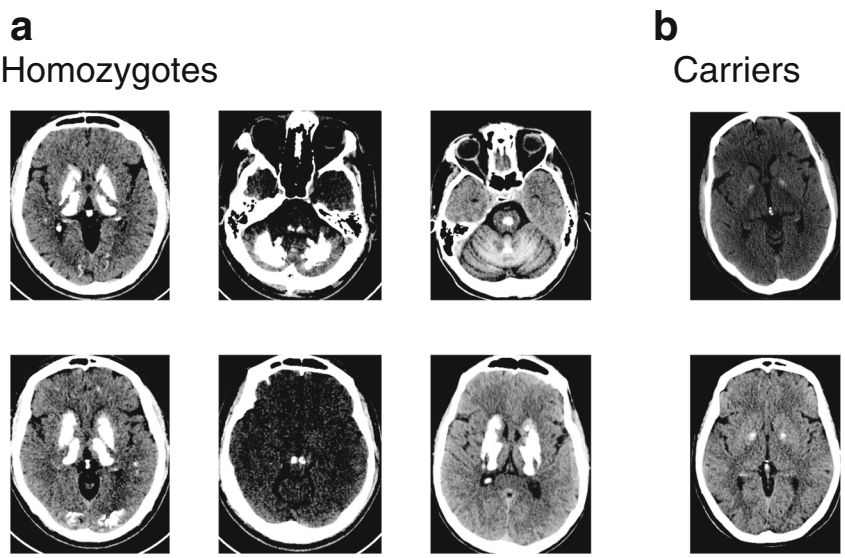

Fig. 1 Findings in computerized tomography (CT) scans associated with pathogenic mutations in the *MYORG* gene. **a** In all cases, homozygotes demonstrate extensive calcification of the basal ganglia and cerebellum. Calcifications in additional brain regions (cortical and subcortical, brain stem, and midbrain nuclei) are variable. **b** Carriers often demonstrate punctuated calcification of the globus pallidus. CT scans are reproduced with permission from [8•]. (Reproduced from Arkadir D, Lossos A, Rahat D, Snineh A, Schueler-Furman O, Nitschke S, et al. MYORG is associated with recessive primary familial brain calcification. Annals of Clinical and Translational Neurology. 2019;6 [1]:106–13; with permission from John Wiley & Sons, Inc.)

Genomic and Cellular Characterization of the *MYORG* Gene

The *MYORG* gene is localized to chromosome 9. The canonical transcript (NM_020702.5/ENST00000297625.7) comprises 6744 bases encompassing two exons. The first exon is comprised entirely of a 5′ untranslated region (5′UTR), and the second exon includes a part of the 5′UTR, together with the protein-coding sequence and the 3′UTR. Expression studies reveal that the gene is expressed in the skeletal muscle, colon, small intestine and liver, and in all regions of the brain, including the cerebellum and basal ganglia (striatum and substantia nigra), as well as other regions [17, 18]. Real-time PCR and fluorescence in situ hybridization studies in mice further confirm that *Myorg* (the mouse homolog of *MYORG*) is highly expressed in the cerebellum, specifically in the astrocytes and to a lesser degree in oligodendrocytes [7••]. The protein is mainly localized to the endoplasmic reticulum [7••]. RNAseq data from human brains suggest that MYORG is expressed almost exclusively in astrocytes with almost undetectable expression in oligodendrocytes [19].

The MYORG protein is composed of 714 amino acids and traverses the endoplasmic reticulum envelope. Datta and colleagues [20] suggested, based on proteinase studies, that the 56-amino acid long N-terminal region faces the lumen. This region is followed by a transmembrane domain (residues 57–80), which is followed by an additional region (residues 81–300) whose function is unclear. The C-terminal region is a glycoside hydrolase domain of the GH31 family facing the endoplasmic reticulum.

Little is known about the function of the MYORG gene in healthy tissues. Other members of the GH31 family are known to remove sugar moieties from glycosylated proteins but, up to now, no substrates of the MYORG glycosidase have been recognized. The protein was shown to play a role in muscle cell differentiation by regulating the phosphorylation of Erk and Akt and secretion of IGF-II [20]. In *Myorg* homozygous knockout mice, brain calcifications are first observed at the age of 9 months, initially in the thalamus [7••]. As in human PFBC, these deposits were shown to contain mainly calcium phosphate [7••].

A phylogenetic profile is a comparative genomics approach that predicts gene function based on its co-evolution with other genes in the tree of life [21–23]. Co-evolution analysis aimed at MYORG uncovered a large number of genes encoding for calcium channels and other genes related to ion transport [8•]. This analysis also suggested that MYORG is co-evolved with several genes that possibly interact with PDGFRB (a protein associated with PFBC), including PDCD6IP/ALIX that inhibits PDGFRB internalization and degradation [24]. These findings have not been experimentally validated, and the existence of a functional relationship between MYORG and PDGFRB is yet to be tested. It should also be noted that Yao and colleagues [7••] did not find any evidence for co-localization of MYORG and PDGFRB in mouse brains. In addition, it has been suggested that PDGFB/PGDFRB-related PFBC is caused by impaired pericyte organization [19], although MYORG expression was not detected in pericytes or other endothelial cells.

Table 1 *MYORG* pathogenic mutations

Ref	genomic position(GRCh38)	cDNA alteration (NM_020702.5)	Amino acid alteration
[7••]	9:34372841-T-C	c.103A>G	p.M35 V
[10•]	9:34372753-C-T	c.191G>A	p.G64E
[7••]	9:34372719-C-A	c.225G>A	p.W75*
[10•]	9:34372606-A-C	c.338T>G	p.L113R
[7••, 10•, 12]	9:34372595-AGCGGAAGGCCAins	c.348_349ins CTGGCCTTCCGC	p.116_117insLAFR
[12]	9:34372502-GGATGAAGAAGTGCAdel	c.428_442delTGCACTTCTTCATCC	p.143_147delLHFFI
[7••]	9:34372337-G-A	c.607C>T	p.Q203*
[12]	9:34372257-C-A	c.687G>T	p.W229C
[7••]	9:34372249-G-A	c.695C>T	p.S232 L
[10•]	9:34372236-GGCins	c.706_708dupGCC	p.A236dup
[10•]	9:34372197-C-G	c.747G>C	p.W249C
[7••]	9:34372161-GC-AA	c.782_783GC>TT	p.R261L
[8•]	9:34371882-GTCdel	c.1060_1062delGAC	p.D354del
[10•]	9:34371866-Adel	c.1078delT	p.Y360fs
[7••]	9:34371847-TCGAAGdel	c.1092_1097delCTTCGA	p.365_366delFD
[10•]	9:34371826-G-T	c.1118C>A	p.A373D
[8•]	9:34371711-Gdel	c.1233delC	p.F411Lfs*
[10•]	9:34371644-C-G	c.1300G>C	p.D434H
[7••]	9:34371623-G-C	c.1321C>G	p.R441G
[7••]	9:34371616-C-T	c.1328G>A	p.W443*
[10•, 13]	9:34371611-G-A	c.1333C>T	p.Q445del
[10•]	9:34371550-Cdup	c.1394dupG	p.E466fs
[10•]	9:34371517-G-T	c.1427C>A	p.T476 N
[12]	9:34371513-G-T	c.1431C>A	p.Y477*
[9]	9:34371414-Cdel	c.1530delG	p.N511Tfs
[10•]	9:34371404-AGGdel	c.1538_1540delCCT	p.S513del
[10•]	9:34371113-G-A	c.1831C>T	p.R611W
[10•]	9:34371079-A-G	c.1865T>C	p.L622P
[10•, 11]	9:34370977-A-G	c.1967A>G	p.I656T
[10•]	9:34370965-A-T	c.1979T>A	p.L660Q

Further phylogenetic profile analysis using more refined methods [25••] also showed that MYORG is co-evolved with alpha Klotho (KL), a protein involved in ion regulation which is also active in astrocytes [26]. Similar to MYORG, Klotho regulates Erk and Akt by modulating their phosphorylation [26]. In the kidney, it also regulates Ca^{2+} and phosphate serum levels by regulating the localization and activation of ion transporters [27]. In particular, Klotho hydrolyses *N*-glycan moieties on TRPV5 calcium channels, leading to the channel's localization to the plasma membrane [27]. To the best of our knowledge, Klotho has never been investigated in relation to brain calcifications. However, the combination of these functional similarities between Klotho and MYORG, as well as the fact that MYORG is co-evolved with multiple proteins involved in ion transport, may suggest that MYORG modulates the activity of ion channels via its glycosidase activity.

Pathogenic Mutations in the *MYORG* Gene

To date, 30 pathogenic mutations causing recessive PFBC have been reported in *MYORG* (Table 1). Pathogenic mutations are distributed throughout the entire coding regions of the *MYORG* gene (Fig. 2) and include nonsense and missense mutations and inframe insertions and deletions. The frequency of specific mutations in different ethnic populations is not yet clear. One mutation (c.348_349insCTGGCCTTCCGC) was suggested to be a founder mutation among Han Chinese [10•]. The rarity of the mutations, as reported in pubic databases such as GnomAD, was one of the criteria used to recognize the mutations as pathogenic. The allele frequency as reported in databases, however, may be lower than the true allele frequency in certain sub-populations that are underrepresented in these databases [28]. Additional studies are required to improve our knowledge regarding the frequency

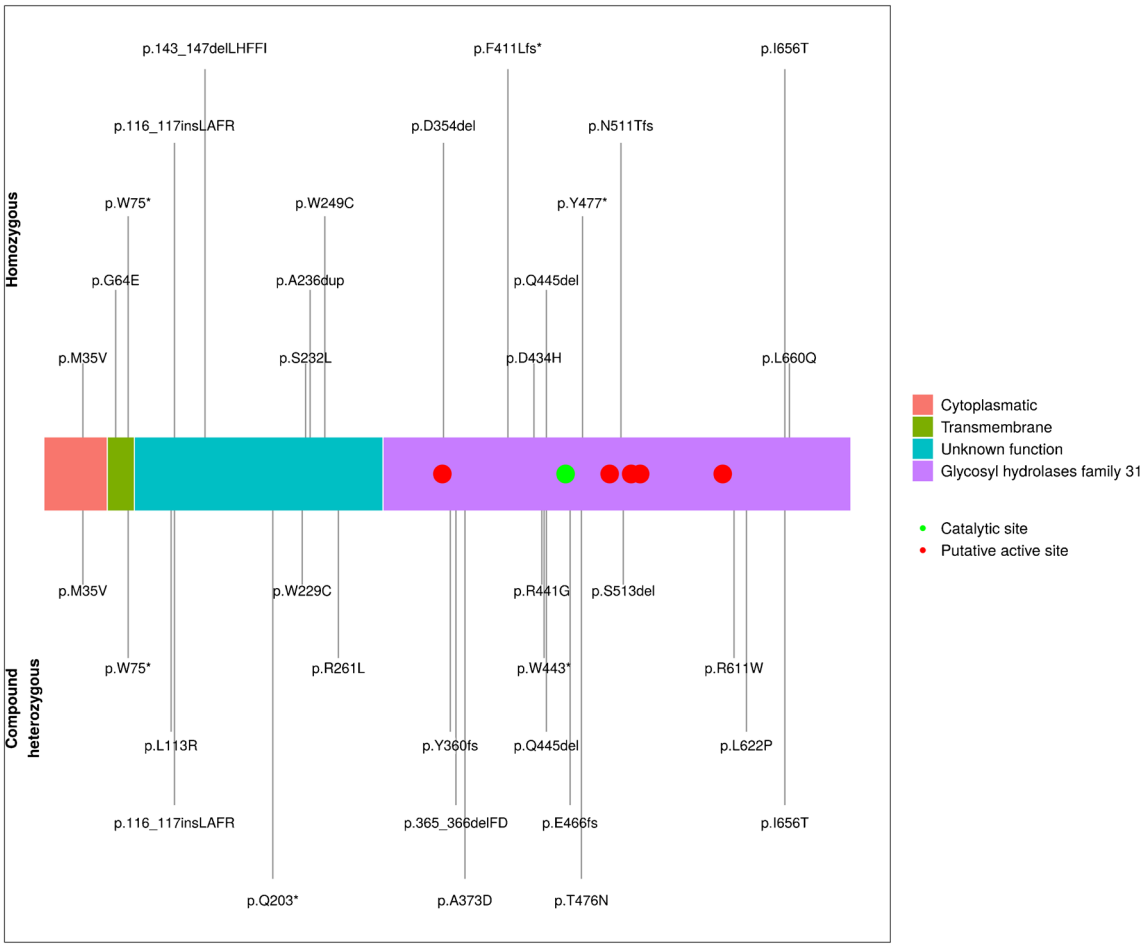

Fig. 2 Distribution of known *MYORG* pathogenic mutations in PFBC along the protein sequence. The colored bar represents the four regions of the protein. Homozygous mutations are indicated above the bar, and compound heterozygous mutations below the bar. Red points represent residues that are predicted to be part of the active/substrate binding site based on homology with other GH31 family proteins. Green points represent the position of the catalytic site. Information regarding active and catalytic sites was obtained from the NCBI conserved domains web-server [31]

of pathogenic *MYORG* mutations, especially since the true prevalence of PFBC in the population may be greater than present estimations indicate [29, 30].

Conclusions

Mutations in the *MYORG* gene are a major cause for recessive PFBC in different world populations. Common features of MYORG-PFBC such as dysarthria and propensity for calcification in the posterior fossa are helpful clinical clues that may assist in distinguishing this type of PFBC from other types caused by dominant genes. Future studies are required in order to reveal the cellular role of the MYORG protein.

Compliance with Ethical Standards

Conflict of Interest Max Bauer, Dolev Rahat, Elad Zisman, Yuval Tabach, Alexander Lossos, Vardiella Meiner, and David Arkadir each declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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