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Primary familial brain calcification caused by *MYORG* mutations in an Italian family

1. Introduction

Primary familial brain calcification (PFBC) is characterized by symmetrical brain calcifications, mainly located in the basal ganglia, thalami, cerebellum and subcortical white matter, with negative etiological assessment [1]. Clinical phenotype includes variable combinations of movement disorders, psychiatric signs, cognitive impairment and, more rarely, seizures and headache. Pathogenic variants in four genes (*SLC20A2,PDGFRB,PDGFB,XPR1)* cause autosomal dominant PFBC [1]. Recently, biallelic pathogenic variants in the *Myogenesis Regulating Glycosidase (MYORG)* gene were identified to cause the first autosomal recessive form of PFBC [2]. Here, we report an Italian family with autosomal recessive PFBC carrying compound heterozygous *MYORG* variants.

The study was approved by the appropriate institutional review boards and all participants provided written informed consent. We studied a family with two siblings (SIE-33/SIE-34) (Fig. 1A) clinically diagnosed with PFBC [3] by: (i)the evidence of bilateral, symmetrical brain calcium deposits in CT scans; (ii)the absence of other causes of brain calcification; (iii)normal serum levels of calcium, phosphorous, vitamin D, thyroid and parathyroid hormones. Pathogenic variants in the known genes for dominant PFBC were not detected by us in this family (*SLC20A2, PDGFRB,PDGFB* data reported in Ref. [3], *XPR1* data unpublished). Protocols for the genetic analysis of *MYORG* gene are reported in the Supplementary file and identified variants are annotated according to the 714 amino acids protein transcript NM_020702.5/ENST00000297625.

By Sanger sequencing of *MYORG* coding region and exon-intron boundaries, we detected two extremely rare variants co-segregating with PFBC in the two affected siblings (SIE-33/SIE-34) (Fig. 1A). The proband is a 71-year-old man with a twenty-year history of depression, who developed gait impairment in the last ten years, and repeated episodes of loss of consciousness interpreted and treated as epileptic crises. Neurological examination revealed ataxic gait, postural instability, global bradykinesia and dysarthria. CT images showed severe bilateral calcifications involving the basal ganglia, cerebellum, thalami, occipital cortex and the subcortical and periventricular white matter (Fig. 1B and C; Fig. 1 i,l,m from Ref. [3]). His younger sister is a 69 year-old woman with a parkinsonian syndrome characterized by hypokinesia, resting and action hand tremor, and head tremor. She also suffered from depression and anxiety since the adolescence, and later developed apathy and insomnia. The CT scan revealed marked bilateral calcifications in the basal ganglia, thalami, cerebellum, periventricular and subcortical white matter, and brainstem (Fig. 1D and E; Fig. 1 n,o,p from Ref. [3]).

The first variant c.940C > T (GRCh38/hg38:chr9:34372004) is predicted to lead to a premature stop codon (p.Arg314*) through the only coding exon, likely resulting in a truncated protein product. The second variant c.373_394delinsG (GRCh38/hg38:chr9:34372550-34372571) is predicted to cause the deletion of eight amino acids and the insertion of a Valine residue (p.Cys125_Leu132delinsVal), likewise expected to have an effect on stability or function of the protein (Fig. 1F and G). The c.940C > T variant is present with an extremely low frequency in the dbSNP database (0.002%, from the TOPMed study,rs769496749), but it is absent in gnomAD. The variant c.373_394delinsG is absent in both dbSNP and gnomAD.

Eight relatives with normal neurological examination were available for DNA testing, and none carried both *MYORG* variants, in keeping with an autosomal recessive mode of PFBC inheritance. Three relatives (aged 19,43,60 years) were heterozygous carriers of the p.Cys125_Leu132delinsVal variant; another two (37,45 years) were heterozygous for p.Arg314*; the remaining three (32,61,62 years) did not carry any of the two variants (Fig. 1A). The CT scan in these eight subjects revealed no evidence of brain calcifications.

Biallelic *MYORG* pathogenic variants have been reported in about twenty families so far. None of the two variants identified in our study were previously associated with PFBC [2,4,5]. *MYORG* encodes a member of the glycosyl hydrolase 31 family, expressed in S100β$^+$ brain astrocytes and *MYORG* pathogenic variants may affect the glycosidase activity in astrocytes [2]. The impairment of astrocyte function may lead to neurovascular unit (NVU) dysfunction and subsequent disruption of the blood brain barrier (BBB) [2]. NVU dysfunction has indeed been proposed as a potential mechanism also in PFBC forms caused by *PDGFB* and *PDGFRB* pathogenic variants [2].

In our two patients, the neuroimaging findings were consistently remarkable for the widespread and abundant calcifications, also including the pons in one patient(SIE-34). Brainstem calcifications might be characteristic of patients with this genetic form [5]. As reported by Grangeon et al. [5], patients with *MYORG* mutations display a homogeneous clinical pattern, usually showing dysarthria at disease onset and at least four out of five of the following clinical manifestations: dysarthria, cerebellar syndrome, gait disorder, akinetic-hypertonic and pyramidal signs [5]. Our proband (SIE-33) showed a clinical picture consistent with this description, while the sister displayed an extrapyramidal syndrome with cerebellar signs (hypokinesia, resting and action tremor). Together with the recessive pattern of inheritance, the clinical and neuroimaging picture might help clinicians in orienting genetic testing. In conclusion, we report an Italian family with PFBC due to *MYORG* variants, expanding the mutational and phenotypic spectrum of this disease.

Disclosures

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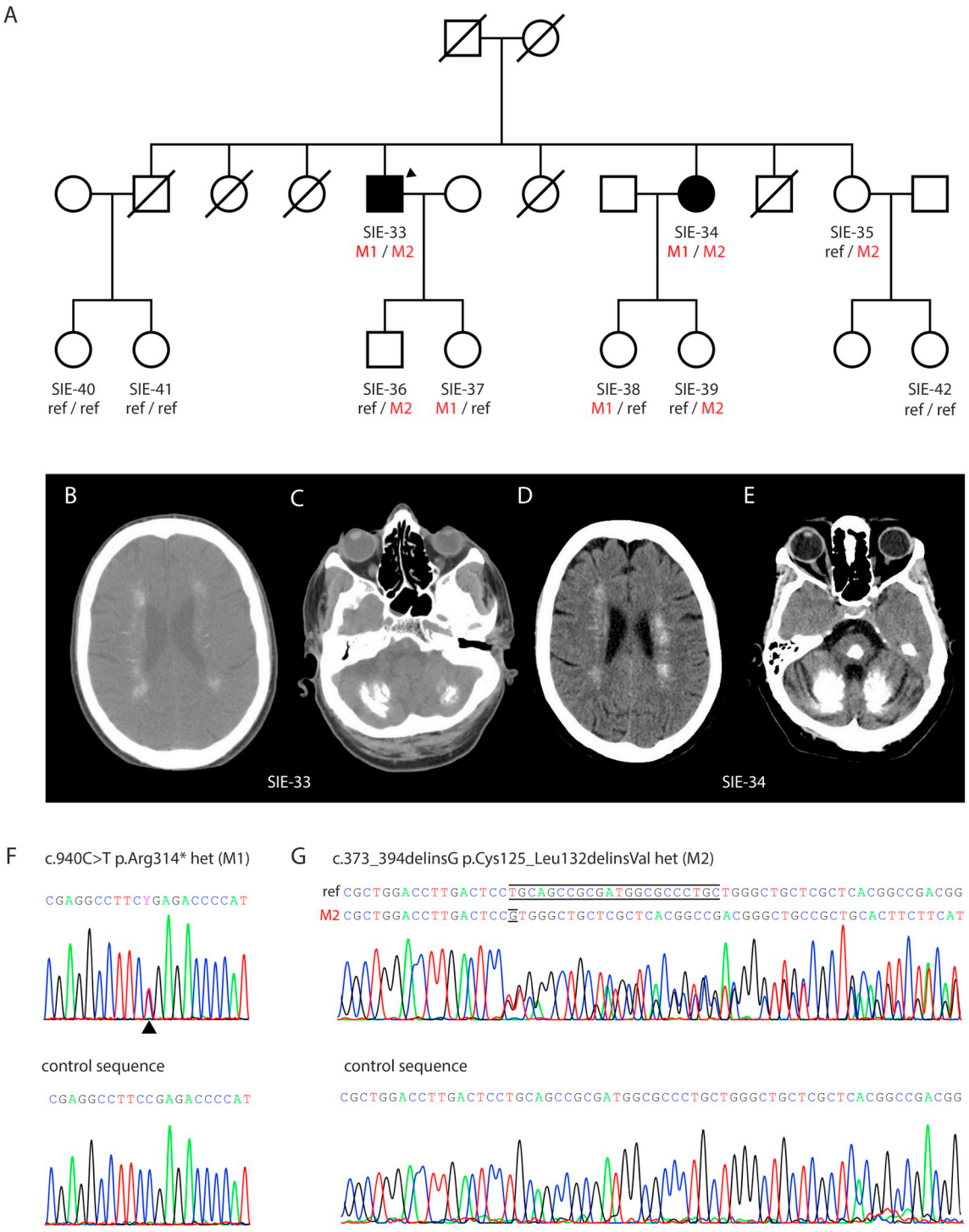

Fig. 1. Pedigree of the PFBC family, CT scans and *MYORG* variants.
(A) Pedigree of the PFBC family. Filled symbols represent affected individuals; empty symbols indicate individuals free from clinical symptoms and with no evidence of brain calcifications in brain CT. The proband is indicated by an arrowhead. Subjects with individual codes (SIE-) were examined clinically and by brain CT. *MYORG* variants in available family members are reported. M1, p.Arg314*; M2, p.Cys125_Leu132delinsVal; ref, reference (wild-type sequence).
(B-E) CT scans of patients SIE-33 (B-C) and SIE-34 (D-E) show calcifications in the periventricular white matter (B, D), cerebellum (C, E), and brainstem (E).
(F-G) Electropherograms of the *MYORG* variants and corresponding wild-type sequences.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.021.

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