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Letter to the Editor

A *SLC20A2* mutation identified in an asymptomatic patient with brain calcification☆

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Dear Editor-in-Chief,

Primary familial brain calcification (PFBC) also known as Fahr's disease is a clinically heterogeneous neurodegenerative disorder characterized by progressive neuropsychiatric and movement disorders. This clinical heterogeneity is caused by symmetric and bilateral calcification in basal ganglia but often involving the thalami, cerebellum and subcortical white matter. PFBC occurs after the age of 40 years and it is usually inherited in an autosomal dominant manner [1]. On conventional brain MR imaging, calcium deposits determine loss of signal intensity (hypointensities) in T2 and GRE-T2* weighted sequences. However, iron may also appears hypointense on T2-weighted sequences, mimicking the appearance of calcium. Calcifications are typically detected by a non-contrast head computer tomography (CT) scan because calcium appears hyperdense to the surrounding brain parenchyma while iron is isodense. Recent evidence suggests that variants in *SLC20A2* gene are responsible for most cases identified in Primary familial brain calcification. *SLC20A2*, localized on chromosome 8p.11.21, encodes for the sodium-dependent inorganic phosphate transporter 2 (PiT2) [2]. PiT-2 belongs to a cotransporter family (NaPi), which also includes PiT-1. These transporters are involved in phosphate homeostasis in various tissues, including the brain [3]. When *SLC20A2* gene is mutated, uptake of Pi is severely impaired likely causing buildup of calcium phosphate. Recently, we reported a new mutation in *SLC20A2* gene identified in southern Italy family with PFBC [4]. Sanger sequencing analysis of the entire gene detected a novel heterozygous deletion c.21_21delG, which as predicted by Mutation Taster and Sift, causes a highly disruptive frameshift, then generates a truncated protein. We observed this variant, p.Leu7Phefs*10, in the proband and his affected mother. We also evaluated asymptomatic daughters of the proband. Their brain MRI revealed diffuse hypointensities in the basal ganglia and subcortical white matter. Moreover, the analysis of mutations in the asymptomatic daughters and the affected brother of the proband was not possible because the DNA was unavailable. In this letter we reported a new case carrying the p.Leu7Phefs*10 variant in heterozygous form. This variant was not found in 150 unrelated controls subjects.

A 55-year-old woman was subjected to neurological assessment for accidental fall. She reported no previous neurological or psychiatric disorders. The patients did not report any symptoms. Her neurological examination was normal. However, a head CT scan showed as incidental finding extensive and diffuse calcifications in the basal ganglia and dentate nuclei. A brain MRI examination revealed extensive and bilateral loss of signal intensities in the basal ganglia and dentate nuclei (Fig. 1). Laboratory serologic tests found that calcium, phosphorus, magnesium, calcitonin and PTH were all within the normal range. According to family anamnesis, the patient documented that her mother had reported a slight cognitive decline during her last years of life. Analysis of mutations in her mother was not possible because the DNA was unavailable.

Interestingly, Fahr's disease is clinically heterogeneous, some mutation carriers show neurologic and/or psychiatric symptoms whereas others do not exhibit any clinical presentations throughout their life despite the presence of severe cerebral calcifications. Some studies showed that no difference in the extent and severity of brain calcifications was observed between affected individuals and those with positive CT scans but without clinical symptoms [5].

Another hypothesis is the variable age of onset which is typically reported between 30 and 60 years, with gradual progression [6]. Therefore, we cannot exclude that our case develops many symptoms afterwards.

Furthermore, the identification of *SLC20A2* mutations in asymptomatic cases and apparently sporadic patients may suggest reduced penetrance and that genetic forms of brain calcification are underestimated [7]. In order to clarify the relationship between the appearance of calcifications and the onset of neurologic signs, a systematic neurological examination of PFBC mouse models at various ages is warranted.

The identification of the same mutation (p.Leu7Phefs*10) in an PFBC family previously described with a clear phenotype [4] and in a new asymptomatic patient with CT scans positive, confirm the phenotypic variability and the reduced penetrance highlighting the necessity of the genetic analysis. The identification of genetic mutations in SLC20A2 gene allow specific treatments that limit progression of calcification in the basal ganglia in Fahr's disease. However, there are not specific treatments, except for a theoretically unconfirmed report of using chelators with an antioxidant and calcium antagonist [8].

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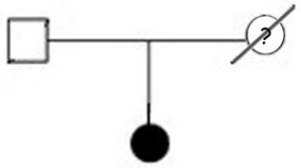

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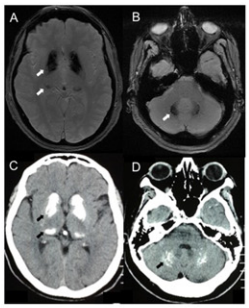

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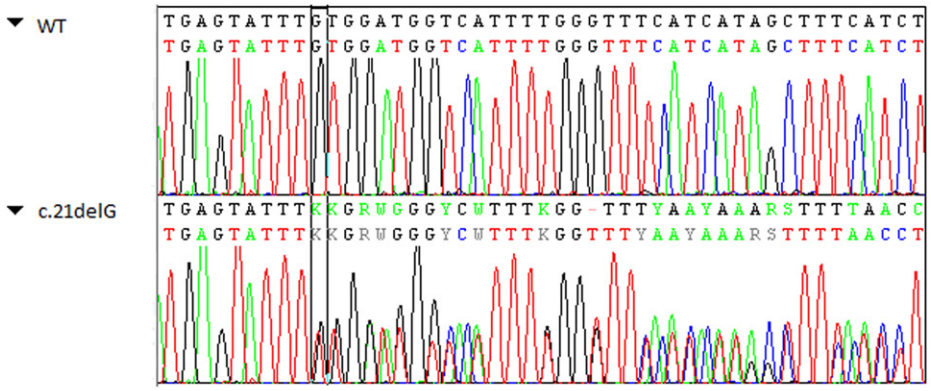

conservation nucleotide level for all changes - no scoring up to now	species	match	gene	aa	alignment
	Human			67182	GATGAGTATTTGTGGATGGTCATT
	mutated	not conserved		67182	gatgagtattt-tggatggtcat
	Ptroglodytes	all identical	ENSPTRG00000020206	73008	gatgagtatttgtggatggtcat
	Mmulatta	all identical	ENSMMUG00000020186	72766	gatgagtatttgtggatggtcat
	Fcatus	all identical	ENSFCAG00000010077	2021	gatgagtatttgtggatggtcat
	Mmusculus	all identical	ENSMUSG00000037656	60605	gacgggtatctgtggatggtcat
	Ggallus	all identical	ENSGALG00000010159	28881	gaggagtacctgtggatggtcat
	Trubripes	no alignment	ENSTRUG00000016698	n/a	
	Drerio	no alignment	ENSDARG00000060796	n/a	
	Dmelanogaster	no alignment	FBgn0260795	n/a	
	Celegans	no alignment	C48A7.2	n/a	
	Xtropicalis	all identical	ENSXETG00000009532	4327	gagtacttgtggatggtaat

Fig. 1. 1. Pedigree of the family with SLC20A2 mutation. The black filled-in symbols represent the affected individuals. The question mark represents the unclear phenotype of the mother's proband. Empty symbols indicate unaffected individuals. 2. Axial T2*-weighted gradient echo MR images of the proband showing (white arrows) bilateral loss of signal intensity in the head of the caudate nuclei, putamen, globus pallidus and thalami (A) and bilateral loss of signal intensities in the dentate nuclei (B). Non-contrast head CT slice detects (black arrows) extensive and bilateral calcifications in the head of the caudate nuclei, putamina and thalami (C) and bilateral calcifications in the dentate nuclei (D). 3. Sequence Electropherogram of the novel heterozygous deletion mutation (c.21_21delG, p.Leu7Phefs*10); Alignment of the region surrounding the mutation (indicated in black) in orthologous and paralogous proteins, showing the high conservation of each affected amino acid in vertebrates and in the paralogous genes.

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