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# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **Novel mutation of *SLC20A2* in an Italian patient presenting with migraine**

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Dear Sirs,

Idiopathic basal ganglia calcifications (IBGC), also known as Fahr's disease, are rare neurological diseases characterized by symmetric calcium deposits in the basal ganglia and other brain regions. Clinically, IBGC patients show high phenotypic heterogeneity, both in the neuradiological findings and in clinical manifestations. Recently, *PDGFRB*, *PDGFB* and *SLC20A2* have been identified as causative genes for IBGC [2].

We report the case of an Italian patient with IBGC associated with a novel mutation in the *SLC20A2* gene, who presented with episodic migraine. In September 2013, a 48-year-old woman presented to our outpatient clinic with a 29-years history of headache. The recurrent attacks were characterized by pulsating pain of moderate intensity in frontotemporal location, associated with severe nausea and photo/phonophobia, lasting up to 72 hours, with six-eight episodes a month. The reported symptoms fulfilled ICHD-III beta version criteria for episodic migraine without aura (code 1.1) [2]. The medical history of the patient was unremarkable. A positive family history for migraine (mother and maternal aunt) and psychosis (another maternal aunt) was reported. Neurological examination showed hyperreflexia and slightly neck rigidity, while no cerebellar signs were identified. A computed tomography scan showed severe calcifications at the bilateral globus pallidus, caudate nuclei, putamen, and dentate nuclei (Figure 1A). Laboratory tests were normal (including serum 25-hydroxyvitamin D and calcium concentrations) and excluded any parathyroid dysfunction. Neuropsychological screening showed a mild impairment in verbal fluency and mild attention deficit. The remaining neuropsychological tests had normal scores, also in those for visuospatial functions. STAIx-1 and STAIx-2 tests showed high level of anxiety.

The patient received genetic counselling and on the basis of the neuroradiological findings with calcifications both in basal ganglia and cerebellum, *SLC20A2* was sequenced. We analyzed the

candidate gene by direct genomic sequencing of the coding exons, performed on an ABI Prism 3130 XL platform. We identified a novel frameshift mutation p.Val507Glufs\*2 in the isoform 1 (c.1520\_1521delTG, exon 8, NM\_006749) (Figure 1B,C). This genetic change was predicted to change an aminoacid and insert a stop codon, likely leading to a degradation of the mutated messenger RNA due to nonsense mediated decay [3]. No other relative was available for segregation analysis.

*SCL20A2* encodes the type III sodium dependent phosphate transporter 2, broadly expressed and with high levels in brain. *SLC20A2* gene mutations have been reported in China, Brazil, Japan, and Spain [3-12], and all are predicted to give a loss-of-function, causing gene haploinsufficiency [3]. The mechanisms leading to calcifications remain to be elucidated, although a role for increased inorganic phosphate can be supposed [4].

The clinical manifestations in patients with IBGC range widely from neurological and/or psychiatric symptoms to asymptomatic status. Because migraine is a common disorder in general population (mainly in women), the coexistence of IBGC and migraine may be coincidental in our patient. On the other way, migraine has frequently been reported as symptom in a large series of IBGC patients with *SLC20A2* mutations [13].

The basal ganglia are involved in the integration of information between cortical and thalamic regions and in particular in domains involved in pain processing. Brain imaging studies of migraineurs have shown altered activation in the basal ganglia in comparison with controls [14]. In addition, migraine is reportedly more frequent in patients with other known basal ganglia disorders [15]. Our report might further support that basal ganglia may be involved in central pain processing and migraine pathophysiology.

We suggest that migraine should be considered when evaluating patients with IBGC and their first-degree relatives, in particular in young age, when other neurological symptoms are absent. The

identification of new genetic variants further enlarge the spectrum of mutations in *SLC20A2*, helping to better elucidate the worldwide distribution and the different clinical features.

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### **Conflicts of interest**

The authors declare no financial or other conflicts of interest.

### **Ethical standards**

This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the patient.

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**Figure 1.** A) Brain CT scans showing the locations of calcification in basal ganglia and cerebellum. B) Sequencing chromatogram showing the wild-type sequence and the heterozygous c.1520\_1521delTG mutation in the *SLC20A2* gene. The TG deleted nucleotides are boxed. C) Model of the PiT2 protein. Mutations described in the literature are reported (1-30): see legend for mutation types. The new mutation causes a Val 507 to Glu aminoacid change, and a frameshift with a stop codon at the next aminoacid. The C-terminal protein region lost in the p.Val507Glufs\*2 mutant is highlighted. Mutations nomenclature was revised accordingly to Human Genome Variation society (HGVS) (<http://www.hgvs.org/mutnomen/>; version September 13, 2013), and in [7, 8, 13, 14, 18, 26] is different from those reported in the original paper.

