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HYPOTHESIS

Reevaluating the pathogenicity of the variations c.439 G>A and c.2132 C>T in the *PLA2G6* gene

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Abstract. The phospholipase A2 group VI (*PLA2G6*) gene encodes for a Ca^{2+}-independent PLA_2, which is localized in the cytosol, in the endoplasmic reticulum and in the mitochondrial membrane, plays a major role in phospholipid remodelling. Mutations within this gene have been reported to cause different phenotypes: infantile-onset neuroaxonal dystrophy associated with brain iron accumulation and adult-onset parkinsonian syndrome. In the present study, we analysed the *PLA2G6* gene sequence in an asymptomatic young woman that was referred to our laboratory by a geneticist for an history of infantile neuroaxonal dystrophy in her little maternal cousin in whom the results of the genetical analysis were not available. We found two variants in the *PLA2G6* gene (NM_003560.4, c.439 G>A and c.2132 C>T, p.Ala147Thr and p.Pro711Leu) previously reported as pathogenic. These results prompted us to perform a segregation analysis in the parents of this woman and we only found the presence of both variants in the asymptomatic 56-year-old patient's mother. Our molecular genetic testing clearly indicates that the c.439 G>A and c.2132 C>T variations identified in the *PLA2G6* gene are positioned in *cis* and are not responsible for infantile neuroaxonal dystrophy which is an autosomal recessive disease.

Keywords. *PLA2G6* gene; infantile neuroaxonal dystrophy; mitochondria.

The phospholipase A2 superfamily is constituted by enzymes which catalyze the hydrolysis of glycerophospholipids at the sn-2 position to produce free fatty acids and lysophospholipids. Among the different family members, the *PLA2G6* is characterized by an enzymatic activity which does not require Ca^{2+} and is located in the cytosol, endoplasmic reticulum and mitochondria (see review of Smani *et al.* 2016). Mutations in the *PLA2G6* gene have been associated with neurodegeneration of brain iron accumulation (NBIA) disorders (Gregory and Hayflick 2013). Four different subtypes, including infantile neuroaxonal dystrophy (INAD), can be differentiated based on the clinical symptoms and the age at the onset (Guo *et al.* 2018). INAD is an autosomal recessive disorder with an early age of onset and is characterized by a progressive psychomotor deterioration, hypotonia, cerebellar ataxia, extrapyramidal signs and visual abnormality. During the progression of the disease, iron accumulation can be detected by MRI affecting the basal ganglia, especially the globus pallidus and the substantia nigra. In 2008, Gregory and collaborators reported *PLA2G6* mutations in 56 patients clinically diagnosed with INAD (Gregory *et al.* 2008). Among those mutations, they found compound heterozygous missense (c.439 G>A and c.2132 C>T; p.Ala147Thr and p.Pro711Leu) variants in the patient N°188. The alanine at the position 147 is localized in the first ankyrin repeat domain (see https://www.uniprot.org/uniprot/O60733) and is reported as a variant of uncertain significance in the ClinVar database. The proline residue at position 711 is located between the two calmodulin-binding domains and is outside the catalytic patatin-like phospholipase (PNPLA) domain. While this latter variation is not reported in the ClinVar database, several softwares for the prediction of sequence variations (including Polyphen-2, mutation tasting, Sift and align GVGD) indicated that the c.2132 C>T change would have a deleterious impact on the protein function.

Recently, we analysed the *PLA2G6* gene in our laboratory by Sanger sequencing in a 28-year-old pregnant woman for genetic counselling since her little maternal cousin died of *PLA2G6*-associated INAD (*PLA2G6*

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mutation(s) not available due to the absence of communication between the patient and her cousin). We found that this asymptomatic woman harboured both the c.439 G>A and c.2132 C>T variations as previously reported (Gregory *et al.* 2008). We thus performed segregation analysis in her parents and showed that those variants were inherited only from her mother. In their study, Gregory *et al.* could not have tested the parents of the affected children to evaluate the segregation of the mutations (personal communication with Pr Susan J. Hayflick). In conclusions, our molecular genetic testing clearly indicates that the c.439 G>A and c.2132 C>T variations are positioned in *cis* and are not responsible for INAD which is an autosomal recessive disease.

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