**AP4S1 splice-site mutation in a case of spastic paraplegia type 52 with polymicrogyria**

Susana Carmona, PhD, Clara Marecos, MD, Marta Amorim, MD, Ana C. Ferreira, MD, Carla Conceição, MD, José Brás, PhD, Sofia T. Duarte, MD, PhD,* and Rita Guerreiro, PhD*

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Hereditary spastic paraplegias (HSPs) are a group of rare inherited neurodegenerative disorders that result from primary retrograde dysfunction of the long descending fibers of the corticospinal tract, causing lower limb spasticity and muscular weakness. This group of diseases has a heterogeneous clinical presentation. An extensive list of associated genes, different inheritance patterns, and ages at onset have been reported in HSPs.1 Spastic paraplegia type 52 (SPG52) is an autosomal recessive disease caused by AP4S1 mutations. The disease is characterized by neonatal hypotonia that progresses to hypertonia and spasticity in early childhood, developmental delay, mental retardation, and poor or absent speech. Febrile or afebrile seizures may also occur.2–4

**Clinical case presentation**

We report the case of a Portuguese 2-year-old boy born to healthy nonconsanguineous parents after a full-term gestation with intrauterine growth restriction after week 37. During the first months of life, the patient presented poor weight gain, hyperammonemia with elevation of glutamine and ornithine, low citrulline, and negative orotic acid. Weight recovery and normalization of amino acid profile were observed after protein restriction and remained normal after reintroduction of normal diet. Genetic study of urea cycle disorders (NAGS, CPS, and OTC) was negative. Around 9 months of age, global developmental delay, hypotonia, and strabismus were evident. Brain MRI with spectroscopy (performed at 10 months) showed delayed myelination/hypomyelination associated with a posterior perisylvian polymicrogyria, thinning of the corpus callosum, dilation and dysmorphia of the ventricles, and enlargement of the subarachnoid frontotemporal space (figure A). Spectroscopy suggested a possible discrete reduction of N-acetylaspartate. EEG showed a slight intermittent lentinification in the left temporal region. At 15 months of age, the patient had 1 afebrile episode of status epilepticus. Two previous shorter episodes with fever had also occurred. Levetiracetam was started. No regression of psychomotor development after seizure was observed, and the patient has been evolving gradually with improvement of axial hypotonia. He says a few simple words, responds to his name, and has some nonverbal communication. The most recent neurologic evaluation revealed an alteration of the muscle tone (hypertonia) in the left lower limb and pyramidal signs in both legs.

Exome sequencing of the proband and parents was performed as described in Supplementary Material (links.lww.com/NXG/A86) and revealed the homozygous AP4S1 splice site NM_001128126.2:c.294+1G>T r.619_687del variant in the proband, present in the heterozygous state in the parents (figure B). The variant was located in a 2.4-Mb homozygous region
of chromosome 14. This variant is extremely rare in the population, with only 1 heterozygous individual present in the Genome Aggregation Database. In silico analysis predicted the loss of the donor splice site of exon 4. A transcript size analysis and Sanger sequencing of cDNA confirmed the presence of a shorter transcript skipping exon 4 associated with the variant (figure C). As a consequence, the polypeptide of 23 amino acids (76 a.a.–98 a.a.) encoded by exon 4 is lost (figure D).

**Discussion**

*AP4S1* encodes the small subunit of the adaptor protein complex-4 (AP4 complex). This complex is recruited to the trans-Golgi network, where it mediates vesicle trafficking to endosomes or basolateral plasma membrane in a clathrin-independent manner. Mutations in the 4 subunits of the complex have been associated with similar autosomal recessive phenotypes mainly characterized by spastic tetraplegia. The mutation found in our patient leads to the loss of exon 4, with predicted important consequences to the protein structure and the AP4 complex function. Anatomical changes similar to those observed in patients have been reported in an AP-4 complex knockout mouse model: enlargement of the lateral ventricles and thinning of the corpus callosum. Similar changes have also been seen in the patient described here, together with febrile and afebrile seizures. When exome sequencing was performed and analyzed, the patient did not show hypertonia in the lower limbs. However, as reported in other patients, this clinical entity may progress from hypotonic to hypertonic status. The most recent neurologic evaluation revealed the presence of hypertonia in the left leg, associated with pyramidal signs, suggesting the possibility of future development of a spastic paraparesis, typical of this disease.

*Author contributions*

S. Carmona: study concept and design; acquisition, analysis and interpretation of data; and writing of the manuscript. C. Marecos, M. Amorim, A.C. Ferreira, and C. Conceição: acquisition of patient data and critical revision of the manuscript. J. Brás: study concept and design; analysis and interpretation of data; and critical revision of the manuscript for intellectual content. S.T. Duarte:
acquisition of patient data; analysis and interpretation of data; and writing and critical revision of the manuscript for intellectual content. R. Guerreiro: study concept and design; analysis and interpretation of data; study supervision; and writing and critical revision of the manuscript for important intellectual content.

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