V374A KCND3 Pathogenic Variant Associated With Paroxysmal Ataxia Exacerbations

**Objective** Ataxia channelopathies share common features such as slow motor progression and variable degrees of cognitive dysfunction. Mutations in potassium voltage-gated channel subfamily D member 3 (KCND3), encoding the K+ channel, Kv4.3, are associated with spinocerebellar ataxia (SCA) 19, allelic with SCA22. Mutations in potassium voltage-gated channel subfamily C member 3 (KCNC3), encoding another K+ channel, Kv3.3, cause SCA13. First, a comprehensive phenotype assessment was carried out in a family with autosomal dominant ataxia harboring 2 genetic variants in KCNC3 and KCND3. To evaluate the physiological impact of these variants on channel currents, in vitro studies were performed.

**Methods** Clinical and psychometric evaluations, neuroimaging, and genotyping of a family (mother and son) affected by ataxia were carried out. Heterozygous and homozygous Kv3.3 A671V and Kv4.3 V374A variants were evaluated in Xenopus laevis oocytes using 2-electrode voltage-clamp. The influence of Kv4 conductance on neuronal activity was investigated computationally using a Purkinje neuron model.

**Results** The main clinical findings were consistent with adult-onset ataxia with cognitive dysfunction and acetazolamide-responsive paroxysmal motor exacerbations in the index case. Despite cognitive deficits, fluoro-deoxyglucose (FDG)-PET displayed hypometabolism mainly in the severely atrophic cerebellum. Genetic analyses revealed the new variant c.1121T > C (V374A) in KCND3 and c.2012T > C (A671V) in KCNC3. In vitro electrophysiology experiments on Xenopus oocytes demonstrated that the V374A mutant was nonfunctional when expressed on its own. Upon equal co-expression of wild-type (WT) and V374A channel subunits, Kv4.3 currents were significantly reduced in a dominant negative manner, without alterations of the gating properties of the channel. By contrast, Kv3.3 A671V, when expressed alone, exhibited moderately reduced currents compared with WT, with no effects on channel activation or inactivation. Immunohistochemistry demonstrated adequate cell membrane translocation of the Kv4.3 V374A variant, thus suggesting an impairment of channel function, rather than of expression. Computational modeling predicted an increased Purkinje neuron firing frequency upon reduced Kv4.3 conductance.

**Conclusions** Our findings suggest that Kv4.3 V374A is likely pathogenic and associated with paroxysmal ataxia exacerbations, a new trait for SCA19/22. The present FDG PET findings contrast with a previous study demonstrating widespread brain hypometabolism in SCA19/22.