



Abstracts

Papers appearing in the February 2021 issue

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, fluorodeoxyglucose (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.

[NPub.org/NG/9618a](https://pubmed.ncbi.nlm.nih.gov/34818181/)

Detailed Clinical and Psychological Phenotype of the X-Linked *HNRNPH2*-Related Neurodevelopmental Disorder

Objective To expand the clinical phenotype of the X-linked *HNRNPH2*-related neurodevelopmental disorder in 33 individuals.

Methods Participants were diagnosed with pathogenic or likely pathogenic variants in *HNRNPH2* using American College of Medical Genetics and Genomics/Association of Molecular Pathology criteria, largely identified via clinical exome sequencing. Genetic reports were reviewed. Clinical data were collected by retrospective chart review and caregiver report including standardized parent report measures.

Results We expand our clinical characterization of *HNRNPH2*-related disorders to include 33 individuals, aged 2–38 years, both females and males, with 11 different *de novo* missense variants, most within the nuclear localization signal. The major features of the phenotype include developmental delay/intellectual disability, severe language impairment, motor problems, growth, and musculoskeletal disturbances. Minor features include dysmorphic features, epilepsy, neuropsychiatric diagnoses such as autism spectrum disorder, and cortical visual impairment. Although rare, we report early stroke and premature death with this condition.

Conclusions The spectrum of X-linked *HNRNPH2*-related disorders continues to expand as the allelic spectrum and identification of affected males increases.

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