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Abstracts

Papers appearing in the October 2020 issue

Isoform-specific loss of dystonin causes hereditary motor and sensory neuropathy

Objective To determine the genetic cause of axonal Charcot-Marie-Tooth disease in a small family with 2 affected siblings, one of whom had cerebellar features on examination.

Methods Whole-exome sequencing of genomic DNA and analysis for recessively inherited mutations; PCR-based messenger RNA/complementary DNA analysis of transcripts to characterize the effects of variants identified by exome sequencing.

Results We identified compound heterozygous mutations in dystonin (DST), which is alternatively spliced to create many plakin family linker proteins (named the bullous pemphigoid antigen 1 [BPAG1] proteins) that function to bridge cytoskeletal filament networks. One mutation (c.250C>T) is predicted to cause a nonsense mutation (p.R84X) that only affects isoform 2 variants, which have an N-terminal transmembrane domain; the other (c.8283+1G>A) mutates a consensus splice donor site and results in a 22 amino acid in-frame deletion in the spectrin repeat domain of all BPAG1a and BPAG1b isoforms.

Conclusions These findings introduce a novel human phenotype, axonal Charcot-Marie-Tooth, of recessive *DST* mutations, and provide further evidence that BPAG1 plays an essential role in axonal health

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LINS1-associated neurodevelopmental disorder: Family with novel mutation expands the phenotypic spectrum

Objective Clinical, neuroimaging, and genetic characterization of 3 patients with *LINS1*-associated developmental regression, intellectual disability, dysmorphism, and further neurologic deficits.

Methods Three affected brothers from a consanguineous family from Afghanistan, their 2 healthy siblings, and both parents were all assessed in the clinic. General and neurologic examination, expert dysmorphology examination, and 3T brain MRI were performed. Whole-exome sequencing was performed for the 3 affected brothers, followed by Sanger sequencing in all available family members.

Results The index patient and his 2 affected brothers presented a complex neurologic syndrome with similar features but marked intrafamilial phenotypical variability, including varying degrees of cognitive impairment, speech impairment, dystonia, abnormal eye movements, and dysmorphic features. All 3 affected brothers are homozygous for a novel, pathogenic frameshift mutation in *LINS1*, c.1672_1679del, and p.Gly558Profs*22, whereas both parents and healthy siblings are heterozygous for the mutation. No major brain malformations were evident in 3T brain MRI of the affected brothers.

Conclusions This consanguineous family with a novel mutation expands the spectrum of *LINS1*-associated disorder to include developmental regression, oculomotor signs, and dystonia, previously not described in the published 9 cases of this rare disorder. The 3T-MRI data from our 3 patients and review of the neuroimaging data in the literature showed unspecific brain MRI changes. LINS1 protein is a known modulating factor of the Wnt signaling pathway, with important roles in organogenesis including of the cerebral cortex. More research is warranted to disentangle the underlying pathophysiologic mechanisms, leading to cognitive impairment and the complex phenotype of *LINS1*-associated disorder.

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D. Lewis-Smith, K. J. Kamer, H. Griffin, et al. 2016;2e59. doi.org/10.1212/NXG.0000000000000059

***KCNQ2* encephalopathy Features, mutational hot spots, and ezogabine treatment of 11 patients**

J.J. Millichap, K.L. Park, T. Tsuchida, et al. 2016;2:e96. doi.org/10.1212/NXG.0000000000000096

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B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016;2:e97. doi.org/10.1212/NXG.0000000000000097

***CHCHD10* variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease**

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1. doi.org/10.1212/NXG.0000000000000003