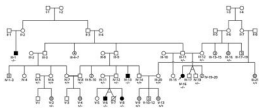
WHAT'S HAPPENING IN Neurology® Genetics

Neurology.org/NG

Abstracts

Articles appearing in the June 2018 issue

Chorea-acanthocytosis: Homozygous 1-kb deletion in *VPS13A* detected by whole-genome sequencing



Objective To determine a molecular diagnosis for a large multigenerational family of South Asian ancestry with seizures, hyperactivity, and episodes of tongue biting.

Methods Two affected individuals from the family were analyzed by whole-genome sequencing on the Illumina HiSeq X platform, and rare variants were prioritized for interpretation with respect to the phenotype.

Results A previously undescribed, 1-kb homozygous deletion was identified in both individuals sequenced, which spanned 2 exons of the *VPS13A* gene, and was found to segregate in other family members.

Conclusions *VPS13A* is associated with autosomal recessive chorea-acanthocytosis, a diagnosis consistent with the phenotype observed in this family. Whole-genome sequencing presents a comprehensive and agnostic approach for detecting diagnostic mutations in families with rare neurologic disorders.

NPub.org/NG/9106a

Absence of NEFL in patient-specific neurons in early-onset Charcot-Marie-Tooth neuropathy

Objective We used patient-specific neuronal cultures to characterize the molecular genetic mechanism of recessive nonsense mutations in neurofilament light (NEFL) underlying early-onset Charcot-Marie-Tooth (CMT) disease.

Methods Motor neurons were differentiated from induced pluripotent stem cells of a patient with early-onset CMT carrying a novel homozygous nonsense mutation in NEFL. Quantitative PCR, protein analytics, immunocytochemistry, electron microscopy, and single-cell transcriptomics were used to investigate patient and control neurons.

Results We show that the recessive nonsense mutation causes a nearly total loss of NEFL messenger RNA (mRNA), leading to the absence of NEFL protein in the patient's cultured neurons. Yet the cultured neurons were able to differentiate and form neuronal networks and neurofilaments. Single-neuron gene expression fingerprinting pinpointed NEFL as the most downregulated gene in the patient neurons and provided data of intermediate filament transcript abundancy and dynamics in cultured neurons. Blocking of nonsense-mediated decay partially rescued the loss of NEFL mRNA.

Conclusions The strict neuronal specificity of neurofilament has hindered the mechanistic studies of recessive NEFL nonsense mutations. Here, we show that such mutation leads to the absence of NEFL, causing childhood-onset neuropathy through a loss-of-function mechanism. We propose that the neurofilament accumulation, a common feature of many neurodegenerative diseases, mimics the absence of NEFL seen in recessive CMT if aggregation prevents the proper localization of wild-type NEFL in neurons. Our results suggest that the removal of NEFL as a proposed treatment option is harmful in humans.

NPub.org/NG/9106b

Most-Read Articles

As of June 6, 2018

Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk

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

A novel *DYNC1H1* mutation causing spinal muscular atrophy with lower extremity predominance

Q. Niu, X. Wang, M. Shi, Q. Jin. 2015;1:e20. doi.org/10.1212/NXG.0000000000000017

The Clinical Outcome Study for dysferlinopathy: An international multicenter study

E. Harris, C.L. Bladen, A. Mayhew, et al. 2016;2:e89. doi.org/10.1212/NXG.0000000000000089

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to AMPD2 loss

A.P.L. Marsh, V. Lukic, K. Pope, et al. 2015;1:e16. doi.org/10.1212/NXG.0000000000000014