WHAT'S HAPPENING IN

Neurology® Genetics

Neurology.org/NG

Abstracts

Papers appearing in the February 2019 issue

Analysis of *FUS*, *PFN2*, *TDP-43*, and *PLS3* as potential disease severity modifiers in spinal muscular atrophy

Objective To investigate mutations in genes that are potential modifiers of spinal muscular atrophy (SMA) severity.

Methods We performed a hypothesis-based search into the presence of variants in fused in sarcoma (*FUS*), transactive response DNA-binding protein 43 (*TDP-43*), plastin 3 (*PLS3*), and profilin 2 (*PFN2*) in a cohort of 153 patients with SMA types 1–4, including 19 families. Variants were detected with targeted next-generation sequencing and confirmed with Sanger sequencing. Functional effects of the identified variants were analyzed in silico and for PLS3, by analyzing expression levels in peripheral blood.

Results We identified 2 exonic variants in *FUS* exons 5 and 6 (p.R216C and p.S135N) in 2 unrelated patients, but clinical effects were not evident. We identified 8 intronic variants in *PLS3* in 33 patients. Five *PLS3* variants (c.1511+82T>C; c.748+130 G>A; c.367+182C>T; c.891-25T>C (rs145269469); c.1355+17A>G (rs150802596)) potentially alter exonic splice silencer or exonic splice enhancer sites. The variant c.367+182C>T, but not RNA expression levels, corresponded with a more severe phenotype in 1 family. However, this variant or level of PLS3 expression did not consistently correspond with a milder or more severe phenotype in other families or the overall cohort. We found 3 heterozygous, intronic variants in *PFN2* and *TDP-43* with no correlation with clinical phenotype or effects on splicing.

Conclusions *PLS3* and *FUS* sequence variants do not modify SMA severity at the population level. Specific variants in individual patients or families do not consistently correlate with disease severity.

NPub.org/NG/9411a

Expanding the molecular and phenotypic spectrum of truncating *MT-ATP6* mutations

Objective To describe the clinical and functional consequences of 1 novel and 1 previously reported truncating *MT-ATP6* mutation.

Methods Three unrelated probands with mitochondrial encephalomyopathy harboring truncating *MT-ATP6* mutations are reported. Transmitochondrial cybrid cell studies were used to confirm pathogenicity of 1 novel variant, and the effects of all 3 mutations on *ATPase 6* and complex V structure and function were investigated.

Results Patient 1 presented with adult-onset cerebellar ataxia, chronic kidney disease, and diabetes, whereas patient 2 had myoclonic epilepsy and cerebellar ataxia; both harbored the novel m.8782G>A; p.(Gly86*) mutation. Patient 3 exhibited cognitive decline, with posterior white matter abnormalities on brain MRI, and severely impaired renal function requiring transplantation. The m.8618dup; p.(Thr33Hisfs*32) mutation, previously associated with neurogenic muscle weakness, ataxia, and retinitis pigmentosa, was identified. All 3 probands demonstrated a broad range of heteroplasmy across different tissue types. Blue-native gel electrophoresis of cultured fibroblasts and skeletal muscle tissue confirmed multiple bands, suggestive of impaired complex V assembly. Microscale oxygraphy showed reduced basal respiration and adenosine triphosphate synthesis, while reactive oxygen species generation was increased. Transmitochondrial cybrid cell lines studies confirmed the deleterious effects of the novel m.8782 G>A; p.(Gly86*) mutation.

Conclusions We expand the clinical and molecular spectrum of *MT-ATP6*-related mitochondrial disorders to include leukodystrophy, renal disease, and myoclonic epilepsy with cerebellar ataxia. Truncating *MT-ATP6* mutations may exhibit highly variable mutant levels across different tissue types, an important consideration during genetic counseling.

NPub.org/NG/9411b

Most-Read Articles

As of January 13, 2020

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

***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

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

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

The Alzheimer's Disease Sequencing Project: Study design and sample selection

G.W. Beecham, J.C. Bis, E.R. Martin, et al. 2017;3:e194. doi.org/10.1212/NXG.0000000000000194

