Abstracts

Articles appearing in the December 2017 issue

c.207C>G Mutation in sepiapterin reductase causes autosomal dominant dopa-responsive dystonia

Objective To elucidate the genetic cause of an Egyptian family with dopa-responsive dystonia (DRD), a childhood-onset dystonia, responding therapeutically to levodopa, which is caused by mutations in various genes.

Methods Rare variants in all coding exons of *GCH1* were excluded by Sanger sequencing. Exome sequencing was applied for 1 unaffected and 2 affected family members. To investigate the functional consequences of detected genetic variants, urinary sepiapterin concentrations were determined by high-performance liquid chromatography.

Results A heterozygous rare nonsynonymous variant in exon 1 of sepiapterin reductase (*SPR*, c.207C>G, p. Asp69Glu) was found in all affected family members. Urinary concentrations of sepiapterin were above the standard of normal controls in most *SPR* mutation carriers, suggesting functional biochemical consequences of the mutation. Variant filtering of all genes involved in the tetrahydrobiopterin pathway, required for levodopa synthesis, revealed an additional common variant in dihydrofolate reductase (*DHFR*, rs70991108). The presence of both variants was significantly more strongly associated with the biochemical abnormality and the clinical disease state as opposed to 1 variant only.

Conclusions The rare *SPR* mutation can cause autosomal dominant DRD with incomplete penetrance. The common *DHFR* variant might have synergistic effects on production of tetrahydrobiopterin and levodopa, thereby increasing penetrance.

NPub.org/NG/9010a

Characterization of a *KCNB1* variant associated with autism, intellectual disability, and epilepsy

Objective To perform functional characterization of a potentially pathogenic *KCNB1* variant identified by clinical exome sequencing of a proband with a neurodevelopmental disorder that included epilepsy and centrottemporal spikes on EEG.

Methods Whole exome sequencing identified the *KCNB1* variant c.595A>T (p.Ile199Phe). Biochemical and electrophysiologic experiments were performed to determine whether this variant affected protein expression, trafficking, and channel functional properties.

Results Biochemical characterization of the variant suggested normal protein expression and trafficking. Functional characterization revealed biophysical channel defects in assembled homotetrameric and heterotetrameric channels.

Conclusions The identification of the *KCNB1* variant c.595A>T (p.Ile199Phe) in a neurodevelopmental disorder that included epilepsy with centrottemporal spikes expands the phenotypic spectrum of epilepsies associated with *KCNB1* variants. The *KCNB1*-I199F variant exhibited partial loss of function relative to the wild-type channel. This defect is arguably less severe than previously reported *KCNB1* variants, suggesting the possibility that the degree of *KCNB1* protein dysfunction may influence disease severity.

NPub.org/NG/9010b

Most-Read Articles

As of January 11, 2018

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

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1.

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.

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

Q. Niu, X. Wang, M. Shi, Q. Jin. 2015;1:e20.

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.

Expanding genotype/phenotype of neuromuscular diseases by comprehensive target capture/NGS

X. Tian, W.-C. Liang, Y. Feng, et al. 2015;1:e14.

Neurology[®]

What's Happening In *Neurology*[®] Genetics
Neurology 2018;90;461
DOI 10.1212/WNL.0000000000005098

This information is current as of March 5, 2018

Updated Information & Services

including high resolution figures, can be found at:
<http://n.neurology.org/content/90/10/461.full>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints

Information about ordering reprints can be found online:
<http://n.neurology.org/subscribers/advertise>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2018 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.