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.

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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 centrotemporal spikes on EEG.

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

Results Biochemical characterization of the variant suggested normal protein expression and trafficking. Functional characterization reveals 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 centrotemporal 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. Severity of 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.

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