Abstracts

Articles appearing in the December 2017 issue.

Clinical features and outcome of 6 new patients carrying de novo *KCNB1* gene mutations

Objective To describe electroclinical features and outcome of 6 patients harboring *KCNB1* mutations.

Methods Clinical, EEG, neuropsychological, and brain MRI data analysis. Targeted next-generation sequencing of a 95 epilepsy gene panel.

Results The mean age at seizure onset was 11 months. The mean follow-up of 11.3 years documented that 4 patients following an infantile phase of frequent seizures became seizure-free; the mean age at seizure offset was 4.25 years. Epilepsy phenotypes comprised West syndrome in 2 patients, infantile-onset unspecified generalized epilepsy, myoclonic and photosensitive eyelid myoclonic epilepsy resembling Jeavons syndrome, Lennox-Gastaut syndrome, and focal epilepsy with prolonged occipital or clonic seizures in every one. Five patients had developmental delay prior to seizure onset evolving into severe intellectual disability with absent speech and autistic traits in one and stereotypic hand movements with impulse control disorder in another. The patient with Jeavons syndrome evolved to moderate intellectual disability. Mutations were de novo, 4 missense, and 2 nonsense, 5 were novel, and 1 resulted from somatic mosaicism.

Conclusions *KCNB1*-related manifestations include a spectrum of infantile-onset generalized or focal seizures whose combination leads to early infantile epileptic encephalopathy including West, Lennox-Gastaut, and Jeavons syndromes. Long-term follow-up highlights that following a stormy phase, seizures subside or cease and treatment may be eased or withdrawn. Cognitive and motor functions are almost always delayed prior to seizure onset and evolve into severe, persistent impairment. Thus, *KCNB1* mutations are associated with diffuse brain dysfunction combining seizures, motor, and cognitive impairment.

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Copy number variation analysis increases the diagnostic yield in muscle diseases

Objective Copy number variants (CNVs) were analyzed from next-generation sequencing data, with the aim of improving diagnostic yield in skeletal muscle disorder cases.

Methods Four publicly available bioinformatic analytic tools were used to analyze CNVs from sequencing data from patients with muscle diseases. The patients were previously analyzed with a targeted gene panel for single nucleotide variants and small insertions and deletions, without achieving final diagnosis. Variants detected by multiple CNV analysis tools were verified with either array comparative genomic hybridization or PCR. The clinical significance of the verified CNVs was interpreted, considering previously identified variants, segregation studies, and clinical information of the patient cases.

Results Combining analysis of all different mutation types enabled integration of results and identified the final cause of the disease in 9 myopathy cases. Complex effects like compound heterozygosity of different mutation types and compound disease arising from variants of different genes were unraveled. We identified the first large intragenic deletion of the titin (*TTN*) gene implicated in the pathogenesis of a severe form of myopathy. Our work also revealed a double-trouble effect in a patient carrying a single heterozygous insertion/deletion mutation in the *TTN* gene and a Becker muscular dystrophy causing deletion in the dystrophin gene.

Conclusions Causative CNVs were identified proving that analysis of CNVs is essential for increasing the diagnostic yield in muscle diseases. Complex severe muscular dystrophy phenotypes can be the result of different mutation types but also of the compound effect of 2 different genetic diseases.

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