



Abstracts

Papers appearing in the December 2020 issue

New Recessive Mutations in *SYT2* Causing Severe Presynaptic Congenital Myasthenic Syndromes

Objective To report the identification of 2 new homozygous recessive mutations in the synaptotagmin 2 (*SYT2*) gene as the genetic cause of severe and early presynaptic forms of congenital myasthenic syndromes (CMSs).

Methods Next-generation sequencing identified new homozygous intronic and frameshift mutations in the *SYT2* gene as a likely cause of presynaptic CMS. We describe the clinical and electromyographic patient phenotypes, perform ex vivo splicing analyses to characterize the effect of the intronic mutation on exon splicing, and analyze the functional impact of this variation at the neuromuscular junction (NMJ).

Results The 2 infants presented a similar clinical phenotype evoking first a congenital myopathy characterized by muscle weakness and hypotonia. Next-generation sequencing allowed to the identification of 1 homozygous intronic mutation c.465+1G>A in patient 1 and another homozygous frameshift mutation c.328_331dup in patient 2, located, respectively, in the 5' splice donor site of *SYT2* intron 4 and in exon 3. Functional studies of the intronic mutation validated the abolition of the splice donor site of exon 4 leading to its skipping. In-frame skipping of exon 4 that encodes part of the C2A calcium-binding domain of *SYT2* is associated with a loss-of-function effect resulting in a decrease of neurotransmitter release and severe presynaptic and postsynaptic NMJ defects.

Conclusions This study identifies new homozygous recessive *SYT2* mutations as the underlying cause of severe and early presynaptic form of CMS expanding the genetic spectrum of recessive *SYT2*-related CMS associated with defects in neurotransmitter release.

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Genotype-Phenotype Correlations in Patients With De Novo *KCNQ2* Pathogenic Variants

Objective Early identification of de novo *KCNQ2* variants in patients with epilepsy raises prognostic issues toward optimal management. We analyzed the clinical and genetic information from a cohort of patients with de novo *KCNQ2* pathogenic variants to dissect genotype-phenotype correlations.

Methods Patients with de novo *KCNQ2* pathogenic variants were identified from Italy, Denmark, and Belgium. Atomic resolution Kv7.2 structures were also generated using homology modeling to map the variants.

Results We included 34 patients with a mean age of 4.7 years. Median seizure onset was 2 days, mainly with focal seizures with autonomic signs. Twenty-two patients (65%) were seizure free at the mean age of 1.2 years. More than half of the patients (17/32) displayed severe/profound intellectual disability; however, 4 (13%) of them had a normal cognitive outcome.

A total of 28 de novo pathogenic variants were identified, most missense (25/28) and clustered in conserved regions of the protein; 6 variants recurred, and 7 were novel. We did not identify a relationship between variant position and seizure offset or cognitive outcome in patients harboring missense variants. Besides, recurrent variants were associated with overlapping epilepsy features but also variable evolution regarding the intellectual outcome.

Conclusions We highlight the complexity of variant interpretation to assess the impact of a class of de novo *KCNQ2* mutations. Genetic modifiers could be implicated, but the study paradigms to successfully address the impact of each single mutation need to be developed.

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