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Abstracts

Articles appearing in the April 2019 issue

Homozygous *TRPV4* mutation causes congenital distal spinal muscular atrophy and arthrogryposis

Objective To identify the genetic cause of disease in a form of congenital spinal muscular atrophy and arthrogryposis (CSMAA).

Methods A 2-year-old boy was diagnosed with arthrogryposis multiplex congenita, severe skeletal abnormalities, torticollis, vocal cord paralysis, and diminished lower limb movement. Whole-exome sequencing (WES) was performed on the proband and family members. In silico modeling of protein structure and heterologous protein expression and cytotoxicity assays were performed to validate pathogenicity of the identified variant.

Results WES revealed a homozygous mutation in the *TRPV4* gene (c.281C>T; p.S94L). The identification of a recessive mutation in *TRPV4* extends the spectrum of mutations in recessive forms of TRPV4-associated disease. p.S94L and other previously identified TRPV4 variants in different protein domains were compared in structural modeling and functional studies. In silico structural modeling suggests that the p.S94L mutation is in the disordered N-terminal region proximal to important regulatory binding sites for phosphoinositides and for PACSIN3, which could lead to alterations in trafficking or channel sensitivity. Functional studies by Western blot and immunohistochemical analysis show that p.S94L increased TRPV4 activity-based cytotoxicity and decreased TRPV4 expression levels, therefore involving a gain-of-function mechanism.

Conclusions This study identifies a novel homozygous mutation in *TRPV4* as a cause of the recessive form of CSMAA.

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Clinical, genetic, and pathologic characterization of *FKRP* Mexican founder mutation c.1387A>G

Objective To characterize the clinical phenotype, genetic origin, and muscle pathology of patients with the *FKRP* c.1387A>G mutation.

Methods Standardized clinical data were collected for all patients known to the authors with c.1387A>G mutations in *FKRP*. Muscle biopsies were reviewed and used for histopathology, immunostaining, Western blotting, and DNA extraction. Genetic analysis was performed on extracted DNA.

Results We report the clinical phenotypes of 6 patients homozygous for the c.1387A>G mutation in *FKRP*. Onset of symptoms was <2 years, and 5 of the 6 patients never learned to walk. Brain MRIs were normal. Cognition was normal to mildly impaired. Microarray analysis of 5 homozygous *FKRP* c.1387A>G patients revealed a 500-kb region of shared homozygosity at 19q13.32, including *FKRP*. All 4 muscle biopsies available for review showed end-stage dystrophic pathology, near absence of glycosylated α-dystroglycan (α-DG) by immunofluorescence, and reduced molecular weight of α-DG compared with controls and patients with homozygous *FKRP* c.826C>A limb-girdle muscular dystrophy.

Conclusions The clinical features and muscle pathology in these newly reported patients homozygous for *FKRP*c.1387A>G confirm that this mutation causes congenital muscular dystrophy. The clinical severity might be explained by the greater reduction in α-DG glycosylation compared with that seen with the c.826C>A mutation. The shared region of homozygosity at 19q13.32 indicates that *FKRP* c.1387A>G is a founder mutation with an estimated age of 60 generations (~1,200–1,500 years).

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H. Mitsumoto, P.L. Nagy, C. Gennings, et al. 2015;1:e3. doi.org/10.1212/01.NXG.0000464294.88607.dd