Abstracts

Articles appearing in the April 2019 issue

Novel PNKP mutations causing defective DNA strand break repair and PARP1 hyperactivity in MCSZ

**Objective** To address the relationship between novel mutations in poly-nucleotide 5’-kinase 3’-phosphatase (PNKP), DNA strand break repair, and neurologic disease.

**Methods** We employed whole-exome sequencing, Sanger sequencing, and molecular/cellular biology.

**Results** We describe a patient with microcephaly with early-onset seizures (MCSZ) from the Indian subcontinent harboring 2 novel mutations in PNKP, including a pathogenic mutation in the fork-head associated domain. In addition, we confirm that MCSZ is associated with hyperactivation of the single-strand break sensor protein poly (ADP-ribose) polymerase 1 (PARP1) following the induction of abortive topoisomerase I activity, a source of DNA strand breakage associated previously with neurologic disease.

**Conclusions** These data expand the spectrum of PNKP mutations associated with MCSZ and show that PARP1 hyperactivation at unrepaired topoisomerase-induced DNA breaks is a molecular feature of this disease. 

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 resultant decreased TRPV4 expression levels therefore involves 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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H. Mitsumoto, PL. Nagy, C. Gennings, et al. 2015;1:e3. doi.org/10.1212/01.NXG.0000464294.88607.dd