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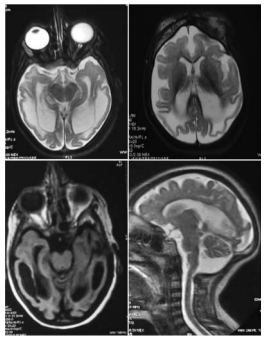
Abstracts

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 polynucleotide 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.

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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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Most-Read Articles

March 30, 2019

CHCHD10 variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1. doi.org/10.1212/NXG.0000000000000003

The Clinical Outcome Study for dysferlinopathy: An international multicenter study

E. Harris, C.L. Bladen, A. Mayhew, et al. 2016;2:e89. doi.org/10.1212/NXG.0000000000000089

KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients

J.J. Millichap, K.L. Park, T. Tsuchida, et al. 2016;2:e96. doi.org/10.1212/NXG.0000000000000096

Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk

B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016;2:e97. doi.org/10.1212/NXG.0000000000000097

Phenotypic and molecular analyses of primary lateral sclerosis

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

