WHAT'S HAPPENING IN Neurology® Genetics

Neurology.org/NG

Abstracts

Papers appearing in the August 2020 issue

Expanded genetic insight and clinical experience of DNMT1-complex disorder

Objective To report novel causal mutations, expanded clinical phenotypes, and clinical management of DNA methyltransferase 1 (DNMT1)-complex disorder.

Methods Neurophysiologic testing, imaging, and genetic findings were summarized in clinical context for 5 cases with DNMT1-complex disorder.

Results We identified 2 novel DNMT1 mutations (p.E510K and p.P1546A) by whole-exome sequencing (WES). Case 1 (p.E510K) presented with childhood ataxia, treatment-refractory seizures and rapid cognitive decline in his 50s. Case 2 also had childhood onset and presented with seizures, language regression, hearing loss, narcolepsy with cataplexy symptoms, optic atrophy, sensory neuropathy, and hypogammaglobulinemia requiring IV immunoglobulin. Case 2 (p.P1546A) was identified with a de novo and the first mutation residing outside the targeting sequence domain. Case 3 (p.A570V) had paralytic asymmetric onset attacks triggered by emotionality and lasting sometimes for weeks. Neuropsychological testing showed executive dysfunction localizing to frontosubcortical and frontoparietal structures. He gradually developed left predominant brain atrophy. MRI showed T2 hyperintense lesions that enhanced on T1 postgadolinium images, and brain PET showed hypometabolism in atrophied regions. Case 4 (p.T497P) underwent left cochlear implant, resulting in significant hearing improvements at all tested frequencies (250–6,000 Hz). Case 5 (p.Y511H) had profound gait ataxia with posterior column atrophy of the spinal cord and abnormal evoked potentials primarily affecting the fasciculus gracilis.

Conclusions Broader application of WES further expands genotype-phenotype correlations of DNMT1-complex disorder. Two mutations are identified with early childhood onsets. The expanded new phenotypes include asymmetric brain hemiatrophy with parenchymal gadolinium enhancement, spinal cord atrophy, prolonged cataplectic spells, and hypogammaglobulinemia. Hearing loss treatment by cochlear implantation is helpful and should be considered.

NPub.org/NG/9511a

Somatic *SLC35A2* mosaicism correlates with clinical findings in epilepsy brain tissue

Objective Many genetic studies of intractable epilepsy in pediatric patients primarily focus on inherited, constitutional genetic deficiencies identified in patient blood. Recently, studies have revealed somatic mosaicism associated with epilepsy in which genetic variants are present only in a subset of brain cells. We hypothesize that tissue-specific, somatic mosaicism represents an important genetic etiology in epilepsy and aim to discover somatic alterations in epilepsy-affected brain tissue.

Methods We have pursued a research study to identify brain somatic mosaicism, using next-generation sequencing (NGS) technologies, in patients with treatment refractory epilepsy who have undergone surgical resection of affected brain tissue.

Results We used an integrated combination of NGS techniques and conventional approaches (radiology, histopathology, and electrophysiology) to comprehensively characterize multiple brain regions from a single patient with intractable epilepsy. We present a 3-year-old male patient with West syndrome and intractable tonic seizures in whom we identified a pathogenic frameshift somatic variant in *SLC35A2*, present at a range of variant allele fractions (4.2%–19.5%) in 12 different brain tissues detected by targeted sequencing. The proportion of the *SLC35A2* variant correlated with severity and location of neurophysiology and neuroimaging abnormalities for each tissue.

Conclusions Our findings support the importance of tissue-based sequencing and highlight a correlation in our patient between *SLC35A2* variant allele fractions and the severity of epileptogenic phenotypes in different brain tissues obtained from a grid-based resection of clinically defined epileptogenic regions.

NPub.org/NG/9511b

Most-Read Articles

As of July 14, 2020

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

***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

Homozygous deletion in MICU1 presenting with fatigue and lethargy in childhood

D. Lewis-Smith, K.J. Kamer, H. Griffin, et al. 2016;2e59. doi.org/10.1212/NXG.0000000000000059