Abstract Preview

- Titles should follow this form: Human genetics is great: Analysis of the *ASHG* gene confirms enormous potential of the field
- Do not use all caps
- Human gene names and loci should be written in italicized capital letters and Arabic numerals. Protein product names should not be italicized.
- Abstracts are printed as submitted. Please check for accuracy before submitting.

Print

De novo **missense variants in the alternative exon 5 of *SCN2A* are a rare cause of neurodevelopmental disorders with or without seizures**

D.N. Shinde[1], L. Rohena[2,3], S. Weatherspoon[4], K.L. Helbig[5], C. Antolik[1], D.R. Hamlin[2], J.M. Berg[2], C. Schultz[1], Z. Powis[1], S. Tang[1], K. Radtke[1]. 1) Ambry Genetics, Aliso Viejo, CA; 2) Department of Pediatrics, Division of Medical Genetics, San Antonio Military Medical Center, San Antonio, TX; 3) Department of Pediatrics, Division of Medical Genetics, University of Texas Health Science Center at San Antonio, San Antonio, TX; 4) Department of Pediatric Neurology, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, TN; 5) Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA.

SCN2A encodes $Na_v1.2$, the alpha subunit of the neuronal voltage-gated sodium channel that is responsible for generation and propagation of action potentials. Heterozygous mutations in *SCN2A* cause a spectrum of neurodevelopmental disorders including benign familial infantile seizures and early infantile epileptic encephalopathy, with or without autism spectrum disorders and intellectual disability. $Na_v1.2$ has two developmentally regulated isoforms (neonatal [N] and adult [A]) that use alternatively spliced coding exons 5N and 5A, respectively. During early brain development, the N isoform is more abundantly expressed than the A isoform, but its relative proportion decreases as it is replaced by the A isoform during postnatal development. N channels are less excitable than A channels, and mutations in *SCN2A* that increase neuronal excitability of the N channels to the level of the A channels, are thought to increase susceptibility to seizures in the neonatal period. Although most mutations in *SCN2A* are found in both the isoforms, to date, there is only one report of a likely pathogenic variant, c.634A>G (p.N212D), found exclusively in the N isoform in an infant with Ohtahara syndrome. Here, we report two additional unrelated affected individuals with *de novo* missense variants in exon 5N of *SCN2A*, c.647T>A (p.L216H) and c.668G>T (p.R223I), that were identified using trio-based whole exome sequencing. Both the affected individuals presented with global developmental delay and abnormal brain MRI findings. Additionally, infantile spasms were observed in one of the affected individuals, while the other presented with intellectual disability and autistic behaviors. Both altered amino acids are located in the voltage-sensor S4 transmembrane helix of $Na_v1.2$, and structural analysis indicates that the alterations impact channel function by disrupting charge gating. Functional studies to determine impact on channel activity are ongoing, and identification of additional affected individuals may help to elucidate the phenotypic spectrum of variants in exon 5N of *SCN2A*. Our results highlight the clinical utility of reporting variants in alternative isoforms of genes with clinically well-characterized primary isoforms.

Close Window