A CASE REPORT ON SCN2A-RELATED DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY WITH APPARENT GAIN-OF-FUNCTION EFFECTS

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Introduction: SCN2A has emerged in recent years as a key causative gene for pediatric epilepsy (1). In addition to epilepsy, SCN2A is also a well-established disease gene associated with other neurological and neurodevelopmental disorders including dystonia and ataxia, autism spectrum disorder, and intellectual disability (ID).

The function of $Na_V1.2$ has been well characterized. Along with other sodium channel paralogs, $Na_V1.2$ is involved in the generation and propagation of action potentials in predominantly excitatory neurons. Alterations of single amino acid residues in the protein sequence of $Na_V1.2$ are known to induce significant alterations in channel function, contributing to disease phenotypes. Although pathogenic *SCN2A* variants are most often present in the germline state, mosaicism has been reported at a rate of 6.4% in a cohort of *SCN2A*-related epilepsy cases.

Genotype-phenotype correlations have been observed recently for pathogenic *SCN2A* variants. Loss-of-function (LoF) variants are typically associated with later-onset seizures, and gain-of-function (GoF) variants are more closely associated with early-onset epilepsy in the neonatal or infantile period. *SCN2A* GoF potentiates $Na_V1.2$ activity and is most closely associated with early infantile epileptic encephalopathy (EIEE) and self-limited familial and nonfamilial infantile epilepsy (formerly benign familial infantile seizures).

Published data indicates that SCN2A is being more widely acknowledged as a cause of epileptic encephalopathy. Loss-of-function variants are generally linked to neurodevelopmental delay and later-onset seizures, while gain-of-function variants tend to lead to early infantile-onset epilepsy. These correlations indicate genotype-phenotype relationships.

Objective: We report an infant who presented with migrating focal seizures in the neonatal period. She was found to have a mosaic c.4534C>Gp.Pro1512Ala variant in SCN2A. Functional studies on this variant revealed a mixture of gain-

and loss-of-function effects. This was unexpected in the context of her severe infantile-onset epilepsy, as previous reports on genotype-phenotype correlations and EIMFS would have suggested a pure GoF effect. This study demonstrates that our current understanding of genotype-phenotype correlations for SCN2A-related epilepsy and neurodevelopmental disorders is still evolving.

Materials and Methods:

Genetic Testing. A Whole Exome Sequencing was performed through a commercial diagnostic laboratory (SmartGene, Tashkent, Uzbekistan). Whole exome sequencing (WES) as a trio was also performed by SmartGene.

Clinical Description. The proband was delivered at term after an uncomplicated pregnancy to a 23-yr-old mother. Parents were nonconsanguineous with no family history of epilepsy. The patient presented with hypotonia and tonic seizures (bilateral independent focal and sequential) on day 5 of life. Her head circumference (HC) at birth was at the 25th percentile. Continuous video electroencephalography (EEG) monitoring confirmed multiple electroclinical tonic seizures of asymmetric clinical semiology but likely symmetric EEG onset, in addition to frequent multifocal epileptiform potentials. Background activity was seemingly normal during the awake state, with trace alternant during quiet sleep with up to 9 s of interburst intervals. By 10 days of life, focal seizures with rapid contralateral hemispheric involvement were observed, suggesting EIMFS

A 6-week-old girl was hospitalized in our department due to experiencing daily seizures in multiple areas, which started on the 5th day after birth. She had no notable personal history. Prior to her admission to our clinic, she had been given levetiracetam within the recommended therapeutic levels but it did not effectively control her seizures. Upon undergoing electroencephalography, bilateral and multifocal epileptiform discharges were observed. Prompt seizure management was achieved using phenytoin, in accordance with recent literature suggesting the use of sodium channel blockers for SCN2A-related epileptic encephalopathies. Following treatment, the child remained free from seizures but experienced delayed development in motor and cognitive skills. She is now 8 months old and has a DQ of ~ 55. No other family members are known to have similar issues.

Results: Genetic testing revealed a new *de novo*, missense mutation in the SCN2A gene, c.4534C>A, in a heterozygote state, not previously reported by our knowledge, in both, patient and his mother. This variant was confirmed with

Sanger sequencing. This variant is absent in gnomAD (date of access 02/12/2023) and has only been reported once in the literature in an individual with early infantile epileptic encephalopathy but otherwise limited available phenotypic information. Trio-based exome sequencing was subsequently performed to rule out other potential contributing variants and was negative for other rare variants in epilepsy-associated genes and for other de novo coding variants.

Conclusion: This case illustrates that our understanding of genotype-phenotype correlations is still limited and highlights the complexity of the underlying electrophysiological effects of SCN2A variants. Also of note in our patient is her favorable response to phenytoin, a known sodium channel blocker.

Additional studies will be extremely important in helping to further clarify genotype-phenotype correlations, as well as in identifying reasons behind exceptions and nuances. With an improved understanding of the functional and clinical consequences of various disease-related *SCN2A* variants, the possibility for the development of specific, individualized therapies for different variant types will become increasingly tangible.

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