Genotype & Phenotype of Ohtahara Syndrome—What’s SCN2A Got to Do With It? A Clinician’s Read

Clinical Spectrum of SCN2A Mutations Expanding to Ohtahara Syndrome.

OBJECTIVE: We aimed to investigate the possible association between SCN2A mutations and early onset epileptic encephalopathies (EOEEs). METHODS: We recruited a total of 328 patients with EOEE, including 67 patients with Ohtahara syndrome (OS) and 150 with West syndrome. SCN2A mutations were examined using high resolution melt analysis or whole exome sequencing. RESULTS: We found 14 novel SCN2A missense mutations in 15 patients: 9 of 67 OS cases (13.4%), 1 of 150 West syndrome cases (0.67%), and 5 of 111 with unclassified EOEEs (4.5%). Twelve of the 14 mutations were confirmed as de novo, and all mutations were absent in 212 control exomes. A de novo mosaic mutation (c.3976G>C) with a mutant allele frequency of 18% was detected in one patient. One mutation (c.634A>G) was found in transcript variant 3, which is a neonatal isoform. All 9 mutations in patients with OS were located in linker regions between 2 transmembrane segments. In 7 of the 9 patients with OS, EEG findings transitioned from suppression-burst pattern to hypsarrhythmia. All 15 of the patients with novel SCN2A missense mutations had intractable seizures; 3 of them were seizure-free at the last medical examination. All patients showed severe developmental delay. CONCLUSIONS: Our study confirmed that SCN2A mutations are an important genetic cause of OS. Given the wide clinical spectrum associated with SCN2A mutations, genetic testing for SCN2A should be considered for children with different epileptic conditions.

Commentary
The title of this article cannot help but to catch the eye of every practitioner of pediatric epilepsy. It contains words (“clinical, spectrum, SCN2A”) that imply improved understanding and hopefully treatment of Ohtahara syndrome (OS), a severe pediatric epilepsy syndrome of infancy. This is how the read went for this clinician who is not an expert (or even very knowledgeable) regarding the language and technologies of epilepsy genetics.

The introductory paragraphs appropriately put the syndrome and its possible molecular genetic basis in the context of what is known. We are reminded that OS is one of the early onset epileptic encephalopathies (EOEEs) that include West syndrome and Dravet as well as the seizure semiology, EEG findings, and prognoses of each. A list of five mutations (STXBP1, KCNQ2, CDKL5, ARX, SPTAN1), that have been reported for OS and spasms is then provided. An early take home message for the practitioner is that multiple de novo mutations can give rise to different clinical and EEG phenotypes. This is followed by a primer on voltage-gated sodium channel subunits of which the gene that is being reported, SCN2A coding the α subunit Na\textsubscript{1.2}, is detailed. The thought that this information may relate to medication that putatively works on the sodium channel comes to mind, but as we know, this level of targeting a specific channel, much less subunit to direct therapy has not been realized as yet. The introduction ends with a brief paragraph informing the reader that mutations in the SCN2A gene have been associated with several pediatric epilepsy syndromes, and that severity may be related to whether the mutation was familial or de novo.

The core of any scientific publication is the Methods by which the data was obtained and interpreted. The reader who is not knowledgeable regarding the technology of mutation screening, whole exome sequencing, and parentage testing must rely on the expert peer review provided by the journal for assurance that the methodology is sound. This is not a trivial issue as illustrated by the recent “sting operation” that revealed that not all scientific journals provide a high level of scrutiny to submitted articles (1). Fortunately, we are reassured by the very high standard for review in the journal that published this article.

Moving on to the Results, the reader is confronted by text the meaning of which is not immediately accessible to the average clinician for example, “… 2 de novo nonsynonymous
From the authors, it is suggested (and I agree) that pursuing genotype–phenotype correlations is a worthwhile endeavor. As knowledge of the mutations grows with regard to developmental expression, location in the subunits and physiological consequences, it is conceivable that innovative treatment strategies will be developed in the future. This is in the domain of research and development.

What is the value of genetic testing for the patient/family in the syndromes that comprise the EOEEs? With very few exceptions in which this knowledge will lead to a specific therapy (e.g., GLUT1), the practical implications are extremely limited. So much so that one of the pioneers of gene discovery for the epilepsies indicated that “at present, whilst very exciting at a research and neurobiological level, these technologies are not useful in clinical practice,” (9) even when taking into account the ever-falling cost of testing. This is not to say that there isn’t value in having a specific diagnosis to obviate the need for potentially invasive and expensive testing, provide genetic counseling, identify carrier status, and provide closure for the family as to “what is wrong” with their child (10). Thus, although the immediate return is small and reading challenging, the clinician charged with the care of children with epilepsy should make the effort to extract as much understanding as possible from articles such as this one that provide a window into understanding in the present and hope for better therapies in the future.

by Jeffrey Buchhalter, MD, PhD, FAAN

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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5. Journal Issue you are submitting for: 14.5

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<th>Money to Your Institution*</th>
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