The many faces of *SCN1A*

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Abstract:

Clinical presentations of *SCN1A*-related disorders can be highly variable, which can prove challenging for diagnostic test selection. We describe several different testing pathways to an *SCN1A* diagnosis and highlight the benefit of having multiple phenotypic-based approaches available.

A total of 105 cases from next generation (panel-based) sequencing and 180 cases from exome sequencing with a referral indication of epilepsy, intellectual disability, and/or autism spectrum disorder were reported by our laboratory from October 2015-May 2016. Five cases were positive for an *SCN1A* mutation. We reviewed the clinical phenotypes and testing strategies employed for these five cases.

Among the five *SCN1A*-positive cases, four different testing pathways were represented. Case 1 is a toddler with febrile seizures and intractable epilepsy. A nonsense mutation was identified on a targeted 13-gene febrile seizures panel. Case 2 is a toddler with febrile seizures and suspected Dravet syndrome, and case 3 is an adult with intractable epilepsy and intellectual disability. A comprehensive 100-gene epilepsy panel was ordered for both, revealing a nonsense mutation and a missense mutation, respectively. Case 4 is an adult with unspecified seizures and an autism spectrum disorder. A missense mutation was revealed on a broad 196-gene neurodevelopment panel. Whole exome sequencing (~20,000 genes targeted) identified a *de novo* nonsense mutation in case 5, an adult with unspecified seizure disorder, intellectual disability, dysmorphic features, and positive family history.

Four different testing pathways were employed, all resulting in a diagnosis of an *SCN1A*-related disorder. Cases 1 and 2 presented as toddlers with febrile seizures, but clinicians opted for different test strategies. Case 2 may have benefitted from a targeted fever panel, resulting in more timely and cost-effective diagnosis. Cases 3 and 4 both presented as adults with somewhat non-specific phenotypes; however, individual features (intractable epilepsy vs. unspecified seizures plus autism) warranted testing via different broad panels. Case 5 presented with the most complex phenotype involving multiple organ systems, and utilized the broadest testing option. Although variability in clinical presentation may be challenging for diagnosis, the availability of a variety of phenotypic-based testing options allows clinicians the opportunity to tailor testing to each patient while not missing an important diagnosis.