New Study in Journal, Brain, Reveals Expanded Clinical Phenotype Spectrum in SCN2A-related disorders

GETTYSBURG, PA, UNITED STATES, April 26, 2024 /EINPresswire.com/ -- A groundbreaking study newly published in Brain, "Expanded clinical phenotype spectrum correlates with variant function in SCN2A-related disorders," sheds a deeper light on how the different genetic variants that occur in the SCN2A gene are correlated with changes in the sodium channel function and how this relates to the diverse clinical presentations of SCN2A-related disorders. The study is a result of a partnered effort between the SCN2A Clinical Trial Readiness Study, an endpoint discovery study fully funded by The FamilieSCN2A Foundation, and the Channelopathy-associated Epilepsy Research Center without Walls (CWoW), funded by the National Institute of Neurological Diseases and Stroke (NINDS).

The FamilieSCN2A Foundation - learn the difference 'families' make.

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> *Dr. Alfred George*

The research, led by Drs. Anne Berg (CTRS) and Alfred George (CWoW) from Northwestern University, sheds light on one of the reasons that different genetic variants are associated with markedly different clinical presentations in individuals with SCN2A-related disorders. A key to this puzzle is the specific impact that each genetic variant has on sodium channel function. This impact can range from causing the channel to be hyperactive (more open than normal) to being completely inactive (entirely closed). By systematically analyzing the effect each variant had on the function of its corresponding sodium channel and combining those data with the CTRS data on clinical phenotype, the study provides crucial insights into the underlying factors driving the diverse manifestations of these disorders.

"Our findings provide important insights into the relation between ion channel function and the clinical condition of the SCN2A-affected individual. Until this study and based on a limited

number of individuals, we associated hyperactive channels with onset of seizures in the first few months of life and channels with decreased or no activity with later-onset epilepsy or autism without epilepsy. It turns out to be more complicated than that. There is a spectrum of channel effects from hyperactivity to moderate, severe, and complete inactivity. This correlates well with the primary phenotype reflected by onset of seizures in the first week of life and underscores the importance of understanding variant function in SCN2A-related disorders. By elucidating the relationship between variant function and clinical phenotype spectrum, we can better tailor treatments and interventions for affected individuals."

CTRS

Both, Dr. Berg and Dr. George are recipients of a FamilieSCN2A Foundation's Core Value Award

“The study's findings have significant implications for diagnosis, prognosis, and the development of targeted therapies for individuals with SCN2A-related disorders. Additionally, this work has significant implications in effectively designing optimal clinical trials for the entire SCN2A patient population.” said co-corresponding author Dr. Alfred George, chair of pharmacology at Northwestern University Feinberg School of Medicine.

About The FamilieSCN2A Foundation:
The FamilieSCN2A Foundation, a 501(c)3 organization committed to advancing research and support for individuals and families affected by SCN2A-related disorders, is proud to have fully funded this critical study and are committed to making the data accessible. The Foundation remains dedicated to driving progress in understanding, treating, and ultimately finding cures for SCN2A-related disorders.

About the SCN2A Clinical Trial Readiness Study (CTRS):
The SCN2A Clinical Trial Readiness Study, led by Dr. Anne Berg, is a longitudinal study designed to assess the suitability of available clinical outcome assessment measures for use in clinical

trials of novel therapies of SCN2A-affected individuals. These are measures needed to demonstrate whether a new therapy provides meaningful clinical benefit. The study recruited a total of 81 families of children affected by SCN2A-RD living in countries around the world. The clinical findings highlighted the severe to profound impairments in young people with SCN2A-RD. This included inability to walk, use hands, communicate, and eat safely. Other conditions frequently reported by parents included dystonia, hypotonia, scoliosis, autonomic dysfunction (such as temperature dysregulation), and vision problems. Autism was the most common behavioral diagnosis. The study helped to achieve a more refined understanding of the relation between primary (seizure) phenotype, markers of encephalopathy, and the impact of the variant on NaV1.2 function. Future analyses are focusing on the suitability of the various clinical outcome assessment measures in the SCN2A-RD population.

About the Northwestern CWoW study:
The Northwestern team extensively analyzed the functional effects of each SCN2A variant on the sodium channels and found a spectrum of effects of the SCN2A variants on sodium channel function from hyperactive channels to completely inactive channels. Importantly, the clinical condition of the child varied with the functional impact on the channel. Hyperactive channels were generally associated with seizure onset in the first week of life. More impaired channel function was more common when the age of seizure onset was older. In fact, almost all of those without seizures had completely inactive sodium channels. The severity of other disease-related features also followed this gradient with those most severely impaired (unable to walk, communicate, eat, use their hands) had the youngest age at seizure onset and hyperactive channels. As age at seizures-onset increased and channels became less active, severe neurological impairments in the child tended to be less severe.

Clinical assessment outcome measures provided quantitative evidence of the severe and pervasive impairments in the cohort members. The Vineland-3 revealed function that, on average, was 4 to 5 standard deviations below the test normative mean. Use of alternative scoring, particularly the Growth Scale Values (GSV) of the Vineland, provided a much richer understanding of the strengths and weaknesses of individuals in the group, which were not reflected in the standardized scores, and supports the use of the GSV approach as being a psychometrically suitable way – in terms of range and lack of floor effects - to measure specific outcomes (e.g. expressive or receptive communication) in young people with SCN2A-RD. Separate analyses are all demonstrating excellent internal consistency, test-retest reliability, and inter-rater reliability of the Vineland subscales. This again supports their suitability as outcome measures for SCN2A-related disorders.

Finally, in collaboration with the Channelopathy Research Center, we are achieving a more refined understanding of the relation between primary (seizure) phenotype, markers of encephalopathy, and the impact of the variant on NaV1.2 function.

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