Reducing the time to diagnosis and increasing the detection of individuals with *SCN1A*-related disease through a sponsored epilepsy genetic testing program

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Early *SCN1A*-related disease identification can be facilitated by a sponsored epilepsy genetic testing program.

Background

- The *SCN1A* gene is associated with a spectrum of disorders, including Dravet syndrome, generalized epilepsy with febrile seizures+ (GEFS+), and early infantile epileptic encephalopathy (EEIE).
- Dravet syndrome is a treatment-resistant developmental and epileptic encephalopathy characterized by seizure onset in the first year of life, severe neurodevelopmental decline and behavioral problems.
- Between 2011 and 2015, the reported average age at molecular diagnosis for patients with *SCN1A*-related disorders was 6.2 years of age (Lindy et. al 2018).
- To reduce the age at molecular diagnosis, we launched a targeted testing program for children in the United States (US), Canada, and Australia suspected to have genetic epilepsy.
- The results of 6874 tests through this program and the clinical characteristics of 152 patients from the US and Canada diagnosed with *SCN1A*-related disorders are presented.

Methods

- Eligible participants had a single unprovoked seizure and were 0-48 (Feb/19-Jan/20) and 0-96 months of age (Jan/20-present).
- Physicians ordering genetic testing provided brief clinical information for each patient, including seizure type (generalized, febrile, focal), family history, language delay, and motor disturbances (ataxia, clumsiness, and/or frequent falls).
- The sponsored testing program uses a next-generation sequencing panel with simultaneous sequence and exonic copy number variant detection in up to 186 epilepsy-related genes.

Results

- Of 6874 patients, 152 had a positive molecular diagnosis (PosMD) related to the *SCN1A* gene, accounting for 2.2% of all patients tested.
- The average age at molecular diagnosis was 23 months for patients identified with a *SCN1A* PosMD and the average age of the first seizure was 9.8 months (range 73 months).
- Most patients presented with generalized seizures (76.3%, n=116) and febrile seizures (65.8%, n=100).
- Approximately 30% of patients had focal seizures (n=49) and motor disturbances (n=45), while 15% had language delays (n=23).
- Approximately 6% (n=9) of patients had a family history of epilepsy.

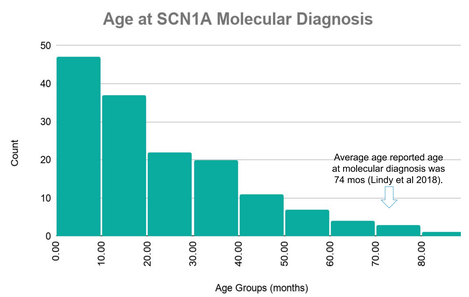

Figure 1: The average age at *SCN1A* molecular diagnosis was 23 months, significantly younger than the age at diagnosis previously reported in the literature (Lindy et al 2018).

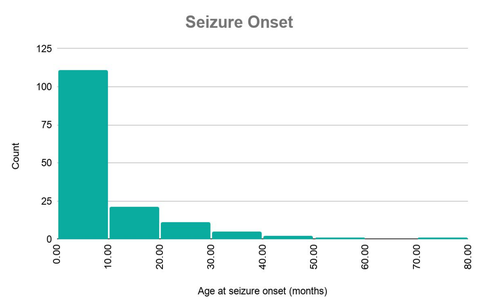

Figure 2: The average at first seizure was 9.8 months.

Results

Table 1: Clinical features reported in 152 *SCN1A*-positive patients.

	Number	Percent
History of Generalized Seizures	116	76.3
History of Febrile Seizures	100	65.8
History of Focal Seizures	49	32.2
Family History of Epilepsy	9	5.9
History of Language Developmental Delay	23	15.1
History of Motor Disturbance	45	29.6
History of Abnormal EEG	42	27.6
History of Abnormal MRI	11	7.2

Conclusion

- By providing a targeted epilepsy gene panel sponsored testing program, a large cohort of *SCN1A*+ patients has been identified.
- Results demonstrated a substantial decrease in the average age at molecular diagnosis from >6 years of age (2011-2015) to <2 years of age (2019-2020).
- Based on the reported clinical findings, we expect most patients to be diagnosed with GEFS+ or Dravet syndrome.
- As precision medicine therapies emerge, an early molecular diagnosis is vital to enable early intervention, to ensure transformative outcomes in patients with *SCN1A*-related disorders.

Reference: Lindy et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. *Epilepsia.* 2018 May;59(5):1062-1071.