Pathogenic and Likely Pathogenic Variants in KCNQ2 Underlie a Large Majority of Genetic Epilepsy in Neonates and Infants <6 Months of Age

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RATIONALE

About *KCNQ2*-related Epilepsy

- Variants in the *KCNQ2* gene underlie a spectrum of neonatal-onset epilepsies with varying severity, from severe developmental and epileptic encephalopathy (DEE) to a milder self-limited form
- *KCNQ2*-related epilepsy typically presents during the first week of life, with multiple, daily seizures, caused by loss of Kv7.2 mediated potassium current
- Heterozygous pathogenic variants are typically *de novo*; however, they can also be inherited (autosomal dominant). Mosaicism has also been reported in some patients
- In order to provide improved access to genetic testing for children with epilepsy, a targeted, no-cost sponsored testing program was launched in the United States, Canada and Australia

Objective

- The objective of this analysis was to determine the molecular diagnostic yield and age of diagnosis of patients with *KCNQ2*-related epilepsy, identified through a sponsored pediatric genetic testing program

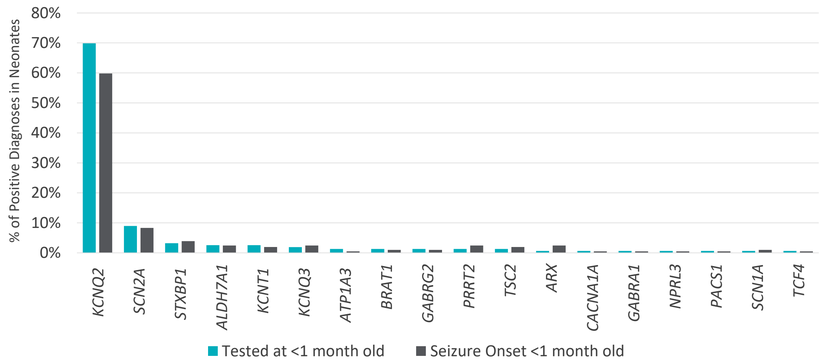
METHODS

- The sponsored testing program uses a next-generation sequencing panel with simultaneous sequence and exonic copy number variant detection in up to 186 genes previously associated with epilepsy
- Patients were eligible for sponsored testing if they had at least 1 unprovoked seizure and were 0-48 (Feb 2019-Jan 2020) or 0-96 months of age (Jan 2020-present)
- The tests were accompanied by a brief clinical history including age of seizure onset, seizure type, family history, developmental delays and use of antiseizure medications, which was provided by the ordering clinician
- Observed variants in epilepsy genes were analyzed and interpreted. Clinical reports included variants classified as pathogenic or likely pathogenic or variants of uncertain significance (VUS)
- The results of 14,813 tests ordered through the program between February 2019 and May 2021 are presented

RESULTS

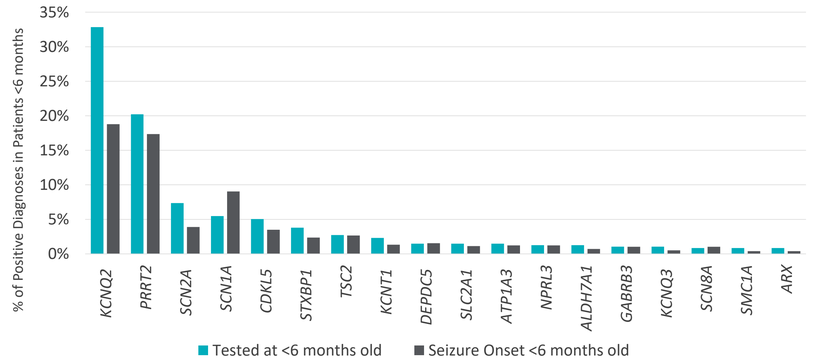
- Overall, 1.3% (196/14,813) of tests ordered in patients <96 months of age had a definitive positive molecular diagnosis (PosMD) for variants in *KCNQ2*. This accounted for 9.9% (196/1,968) of all PosMD in any gene in the cohort
- As *KCNQ2*-related epilepsy presents early in life, we analyzed the available data in children <24 months at the time of testing or with a reported age of seizure onset of <24 months

Variants in *KCNQ2* are the Leading Cause of Epilepsy in Neonates



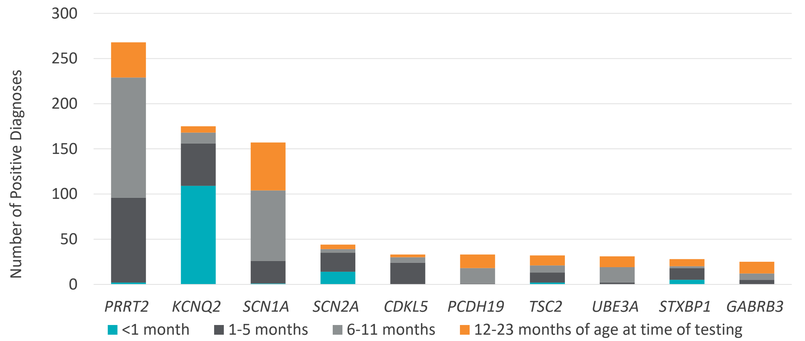
- In patients tested at <1 month of age (neonates), variants in *KCNQ2* accounted for 69.9% (n=109/156) of the PosMD, and 19% (n=109/573) of all neonates tested
- In patients tested at <96 months of age with a reported age of seizure onset of <1 month of age (neonates), variants in *KCNQ2* accounted for 59.8% (n=122/204) of PosMD and 13.4% of tests ordered (n=122/909)

Variants in *KCNQ2* are also the Most Frequent PosMD in Infants <6 Months Old



- In the cohort of infants <6 months of age at testing, *KCNQ2* variants were still the most frequent molecular diagnosis in patients, accounting for 32.8% (n=156/475) of the PosMD, and 8.6% of the infants tested <6 months of age (n=156/1820)
- In patients tested <96 months of age with a reported seizure onset of <6 months of age, variants in *KCNQ2* accounted for the majority of the PosMD 18.8% (n=183/974) and 5.7% (183/3193) of the tests ordered

Overall Diagnostic Yield of Top 10 Epilepsy Genes in Patients Aged <24 months



- In patients tested <24 months of age, the most frequent PosMD were for *PRRT2* (23.7%), *KCNQ2* (15.5%), *SCN1A* (13.9%), *SCN2A* (3.9%), *CDKL5* and *PCDH19* (both 2.9%)
- The mean age of PosMD in *KCNQ2* in patients tested at <24 months of age (n=176) was 1.9 months. The mean time to a *KCNQ2* PosMD was 1 month between onset of seizures and time of testing in 189 patients with seizure onset <24 months

Family Testing Increases *KCNQ2* Diagnostic Yield

- 211 patients aged <96 months with a VUS in *KCNQ2* had no other PosMD identified
- Genetic testing of family members was offered to help clarify the interpretation of the VUS. 105 (50%) patients with a VUS provided family samples for testing

Reclassification	Unique Variants Reclassified	Number of Patients Impacted
VUS > Likely Benign	2	6
VUS > Likely Pathogenic	9	11
VUS > Pathogenic	10	15

- 30% (32/105) had a VUS in *KCNQ2* reclassified. 19 unique VUS were upgraded to a PosMD, reclassifying 26 patients overall
- 79% of reclassifications were due to family testing. Majority were *de novo*

CONCLUSIONS

- Pathogenic variants in *KCNQ2* are the most common cause of genetic epilepsy during early infancy and diagnostic yield for *KCNQ2* is high in patients with seizure onset <6 months of age
- The proportion of neonatal epilepsy patients with a PosMD for variants in *KCNQ2* is much higher than previously reported in a prospective US cohort (Shellhaas et al. 2017)
- By 24 months of age, the number of cases of *KCNQ2*-related epilepsy identified in the cohort is similar to *SCN1A*-related disorders
- Conducting family testing for patients with a VUS in *KCNQ2* will lead to significantly increased rates of PosMD, further enhancing the value of genetic testing
- Early diagnosis has important implications in informing prognosis and treatment strategies including access to potential precision therapies in clinical development, such as XEN496 for *KCNQ2*-DEE in the Phase 3 "EPIK" study. **www.epikstudy.com** (ClinicalTrials.gov NCT04639310)