Evaluating the Epidemiological Burden of KCNQ2 Epilepsy

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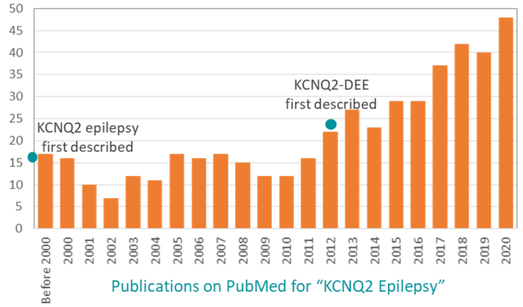
BACKGROUND

About KCNQ2 Epilepsy

- Loss-of-function variants in the *KCNQ2* gene account for a significant proportion of neonatal-onset genetic epilepsy.
- KCNQ2 epilepsy typically presents during the first week of life, with multiple, daily seizures, caused by loss of Kv7.2 mediated potassium current.
- The spectrum of severity ranges from self-limiting epilepsy to severe developmental and epileptic encephalopathy (KCNQ2-DEE).
- Clinical features of KCNQ2-DEE include:
  - Frequent, daily refractory focal tonic seizures, status epilepticus is common;
  - Most often associated with severe developmental delay and motor disabilities;
  - Seizure activity can decrease with age, however severe impairments persist; and
  - Large proportion of patients are dependent for mobility, feeding, hand use and communication (Berg *et al*. 2021).
- Heterozygous causal variants are most often *de novo*. However, they can also be inherited (autosomal dominant). Mosaicism has also been reported in some patients.
- Minority of patients have Kv7.2 gain-of-function variants and a different phenotype.
- No treatments are specifically approved for KCNQ2 epilepsy.
- The Kv7 channel potentiator, XEN496, is currently in development as a precision medicine for KCNQ2 epilepsy.

METHODS



- We conducted a detailed literature review of epidemiological data for KCNQ2 epilepsy, along with a review of cases identified by genetic testing providers and patient registry data.
- PubMed was advanced searched using a combination of search terms around the key concepts of "KCNQ2," "Epilepsy," "Encephalopathy", "Incidence", "Prevalence" and "Epidemiology". Additional records were identified by conducting targeted searches of the grey literature including Google, Google Scholar and conference proceedings. Last date to collect data was March 1, 2021.

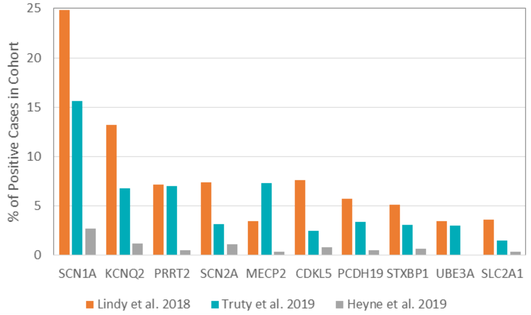
RESULTS

- One publication provided a prospective population-based incidence for KCNQ2 epilepsy (Symonds *et al.* 2019). Additional publications provided the frequency of *KCNQ2* variants for consecutive newborns in the Neonatal Seizure Registry, and for two prospective cohorts, including newborns at high risk for genetic epilepsy.
- Of the cases of KCNQ2 epilepsy identified in these cohorts, approximately 30-77% were KCNQ2-DEE.

Study	Study Cohort (Country)	Frequency of KCNQ2 Epilepsy	Frequency of SCN1A Epilepsy
Symonds et al. 2019	• Prospective population based cohort of patients presenting with epilepsy <**36 months of age** • Collected 05/2014 – 05/2017 (Scotland) • Genetic testing performed in 97% (333/343) of cohort	• 1 per 17,000 live births • 10/343 (2.9% of cohort) • Most commonly identified genetic etiology in patients <6 months with afebrile seizures	• 1 per 12,200 live births • 14/343 (4.1% of cohort)
Berg et al. 2017	• Prospective cohort, presenting with epilepsy **<36 months of age** • Collected 03/2012 – 04/2015 (USA) • Genetic testing performed in 40% (n=180) of patients with no known etiology (n=446)	• 2/775 (0.3% of cohort) • 2/446 (0.4% of patients with no known etiology)	• 12/775 (1.5% of cohort) • 12/446 (2.7% of patients with no known etiology)
Shellhaas et al. 2017	• Consecutive **newborns** with clinical or EEG diagnosis of seizures • Collected 01/2013 – 11/2015 (USA) • Genetic testing performed in 83% (n=29) of patients with DEE (n=35)	• 13/611 (2.1%) of all newborns • 10/35 (28.6%) of those with DEE • Most commonly identified genetic etiology in patients with DEE or self-limiting epilepsy	• Not applicable due to age, however 1/35 (2.9%) of those with DEE had an *SCN1A* variant
Tsuchida et al. 2019	• Prospective, observational cohort of **neonates <14 days post term** with EEG-confirmed seizures and negative standard of care diagnostics • Collected 08/2018 – 08/2019 (USA) • Genetic testing performed in 86% (n=18) of patients enrolled in study (n=21)	• 9/18 (50% of patients with genetic test performed) • Most commonly identified genetic etiology in patients with DEE or self-limiting epilepsy	• Not applicable due to age

Variants in *KCNQ2* are a Leading Cause of Epilepsy in Large Cohorts

- Epilepsy genetic testing capabilities have rapidly expanded in recent years due to improvements in sequencing technologies and the identification of new genes.
- Genetic testing companies recently reported on the diagnostic yield of their epilepsy genetic testing platforms in large cohorts of patients with epilepsy.



- *KCNQ2* was one of the highest yielding genes in these large cohorts, with a causal variant frequency of approximately 50% of that observed for *SCN1A* variants.

Study	Sponsor (Country)	Study Cohort	Age of Patients	*KCNQ2* Diagnostic Yield*	*SCN1A* Diagnostic Yield*
Lindy et al. 2018	GeneDx (USA)	Consecutive, unselected patients with epilepsy and/or neurodevelopmental disorders (n=8565)	• Mean age of diagnosis 5 years, 8 months (range 1 week – 47 years)	• 159/1207 (13%) of P/LP cases • 159/8565 (1.9%) of cohort	• 322/1299 (25%) of P/LP cases • 322/8565 (3.8%) of cohort
Heyne et al. 2019	CeGaT (Germany); Courtagen (USA)	Patients with neurodevelopmental disorders with epilepsy (n=6994)	• Onset 0-3 years in majority of patients	• 1.2% of ultra-rare and *de novo* variants (variants not assessed for pathogenicity)	• 2.7% of ultra-rare and *de novo* variants (variants not assessed for pathogenicity)
Truty et al. 2019	Invitae (USA)	Consecutive, unselected, patients with various forms of epilepsy (n=9769)	• Most 0–5 years • Mean 8.6 years (range 0–82 years)	• 103/1502 (6.9%) of P/LP cases • 103/9413 (1.1%) of cohort tested • 53% of all *KCNQ2* variants were VUS	• 236/1502 (15.7%) of P/LP cases • 236/9413 (2.5%) of cohort tested • 50% of all *SCN1A* variants were VUS

*P/LP = Pathogenic or Likely Pathogenic Variant; VUS = Variant of Uncertain Significance

- 75% of cases without a molecular diagnosis had a VUS in a potentially causal gene in one cohort (Truty *et al.* 2019). Parental testing of 846 patients led to reclassification of VUS in 54% of patients, including to P/LP for *SCN1A*, *KCNQ2* and others.
- KCNQ2 Cure Alliance is the largest KCNQ2 epilepsy support group, and report approximately 1,000 patients with KCNQ2-DEE internationally. 74% of cases in their registry are in children <12 years of age as many adults and older children have not been tested, suggesting that the condition is underdiagnosed.
- There are limitations to this study due differences in the ascertainment of patients including the collection of limited clinical data, differing diagnostic practices and access to genetic testing, variable age ranges and possible geographical biases.

CONCLUSIONS

- Cases of KCNQ2 epilepsy are often undiagnosed or misdiagnosed, particularly in adults with epilepsy, making it challenging to determine the true frequency in the population.
- 50% of newborns seizing within the first 14-days post term who were negative for standard of care diagnostic evaluation for acute causes of seizures were KCNQ2 epilepsy positive.
- With increased awareness, diagnostic rates of KCNQ2 epilepsy are growing.
- Broader access to genetic testing, including sponsored testing programs, such as "Behind the Seizure" (Invitae), improved variant interpretation and further prospective studies with detailed clinical information will help to improve our understanding of the epidemiological burden of KCNQ2 epilepsy.

Phase 3 Clinical Study

- Phase 3 clinical trial of XEN496 as a precision medicine for KCNQ2-DEE (EPIK Study) is currently recruiting patients **www.epikstudy.com** (ClinicalTrials.gov NCT04639310)