KCNT1 EPILEPSY

HOPE IS ON THE HORIZON

Accelerating Research and Drug Discovery for KCNT1-Related Disorders

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CLINICAL CHARACTERISTICS OF KCNT1-RELATED EPILEPSY

KCNT1-related epilepsy is associated with intractable seizures (40-100 per day), and severe developmental delay and impairment.
Many patients never learn to walk or speak.
The two most common phenotypes are epilepsy of infancy with migrating focal seizures (EIMFS, reclassified from MMPSI/MPSI) and Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE, formerly known as ADNFLE). Other phenotypes include Early-Onset Epileptic Encephalopathy (EOEE), West syndrome, Ohtahara syndrome, early myoclonic encephalopathy, leukodystrophy, focal epilepsy and multifocal epilepsy.

Common consequences include respiratory and gut issues, global developmental impairment and regression, intellectual disability, inconsolable crying and irritability, cortical visual impairment, psychiatric disorders, behavioral and emotional problems, hypotonia, dystonia, dyskinesia, and constipation. Some children develop pulmonary collateral arteries which burst, filling their lungs with blood. Children are at risk for sudden unexpected death in epilepsy (SUDEP).

HIGH MORTALITY RATE

A child dies almost every month. Based on our data, approximately 12% of affected individuals die before reaching the age of 20, with an average age of 6. Many of these deaths result from complications such as respiratory failure, seizures, and SUDEP. Because infants in the EOEE group die quickly, it is likely that there are both more uncatalogued individuals and deaths.

MOLECULAR GENETICS AND TISSUE EXPRESSION

KCNT1-related disorders are caused by gain of function mutations in the KCNT1 gene (also known as Slack, Slo2.2; chromosome locus 9q34.3) which codes for the sodium-activated potassium channel $K_{Na}1.1$ in both excitatory and inhibitory neurons, which function in ion conductance and developmental signaling pathways. This channel is expressed in the brain (olfactory bulb, brainstem, and hippocampus) and in several peripheral tissues.

PREVALENCE AND DIAGNOSIS

We are aware of ~500 families around the world who include an individual with KCNT1-related epilepsy, out of an estimated 3,000 diagnosed. Estimated incidence is ≤1.121 per 100,000 live births. KCNT1 accounts for 39% of EIMFS, 3% of EOEE, and 1% of ADSHE cases. Diagnosis is established in patients with intractable epilepsy and a heterozygous pathogenic variant in KCNTl by genetic testing.

We are seeking interested researchers, clinicians, and life science companies to help us understand this disorder, treat our patients, and cure KCNT1. Contact us at info@kcnt1epilepsy.org to let us know how you can help us solve the KCNT1 puzzle.

KCNT1 EPILEPSY FOUNDATION

Founded in 2019, our mission is to accelerate research and drug development efforts focused on finding a cure for KCNT1-related epilepsy. The KCNT1 Epilepsy Foundation supports the KCNT1 community with educational resources, the latest research, and serves as the central point of contact for families impacted by this disorder and for clinicians and scientists who care for patients and study KCNT1. We maintain a family contact database and are establishing a registry. We also coordinate scientific research projects, maintain a biobank of patient tissues, host KCNT1 conferences, and more.
See our activities and assets at www.kcnt1epilepsy.org.

RESEARCH ASSETS

- Mouse models
- Zebrafish models
- Drosophila models
- Stable wild type and mutant cell lines
- iPSC lines
- Natural history data
- Biobank of patient samples, including plasma, whole blood, PBMCs, urine
- Post-mortem brain and other tissues

CHALLENGES OF ULTRA-RARE DISEASE

Diagnosis and management: Most physicians, including pediatric epilepsy specialists, lack experience with rare, complex cases leading to delayed diagnosis and lack of appropriate care.
Novel therapeutic development: ultra-rare disease typically attracts less attention from researchers and drug developers, with fewer patients to recruit to clinical trials and smaller economic incentives. **Travel:** Due to the profound impairment of individuals with KCNT1, travel is challenging and decentralized clinical trials will be needed.

OVERLAPPING RESEARCH AREAS

KCNT1 has been implicated in autism, intellectual development, hearing impairment, traumatic brain injury (TBI)-induced seizure, and is linked to other channelopathies such as SCN8A and SCN1A.

THERAPIES ARE CRITICALLY NEEDED

EXISTING THERAPIES ARE NOT ADEQUATE

No specific treatments exist. Seizures are treated with conventional anticonvulsants but most patients show minimal improvement. Ketogenic diet is occasionally helpful in reducing seizure burden. Various therapies and medical management are utilized for symptom control, including physical therapy, speech and swallowing therapy, and vision therapy, but do little to help children achieve normal developmental milestones.

This patient population has high unmet need. *Our goals are to bring novel therapies to patients and repurposed therapeutics that help ameliorate symptoms while novel, KCNT1-specific therapies are in development.*

There are currently several groups developing KCNT1-specific Antisense Oligonucleotides (ASOs), small molecules, and siRNA approaches. No groups have progressed to clinical trial as of 2024. The KCNT1 Epilepsy Foundation is working to identify teams to collaborate with on gene editing to cure this disorder, and to identify repurposed drugs for immediate use. Carvedilol, an FDA approved drug identified in repurposing screens, shows mild efficacy and we have initiated an observational trial of its use.