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Zeroing in on Phenotypes While Also Broadening Our Understanding of KCNT1-Related Epilepsy

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KCNT1-Related Epilepsies and Epileptic Encephalopathies: Phenotypic and Mutational Spectrum

Bonardi CM, Heyne HO, Fiannacca M, et al. *Brain*. 2021;144(12): 3635-3650. doi:10.1093/brain/awab219.

Variants in KCNT1, encoding a sodium-gated potassium channel (subfamily T member 1), have been associated with a spectrum of epilepsies and neurodevelopmental disorders. These range from familial autosomal dominant or sporadic sleep-related hypermotor epilepsy to epilepsy of infancy with migrating focal seizures (EIMFS) and include developmental and epileptic encephalopathies. This study aims to provide a comprehensive overview of the phenotypic and genotypic spectrum of KCNT1 mutation-related epileptic disorders in 248 individuals, including 66 previously unpublished and 182 published cases, the largest cohort reported so far. Four phenotypic groups emerged from our analysis: (i) EIMFS (152 individuals, 33 previously unpublished); (ii) developmental and epileptic encephalopathies other than EIMFS (non-EIMFS developmental and epileptic encephalopathies) (37 individuals, 17 unpublished); (iii) autosomal dominant or sporadic sleep-related hypermotor epilepsy (53 patients, 14 unpublished); and (iv) other phenotypes (6 individuals, 2 unpublished). In our cohort of 66 new cases, the most common phenotypic features were: (i) in EIMFS, heterogeneity of seizure types, including epileptic spasms, epilepsy improvement over time, no epilepsy-related deaths; (ii) in non-EIMFS developmental and epileptic encephalopathies, possible onset with West syndrome, occurrence of atypical absences, possible evolution to developmental and epileptic encephalopathies with sleep-related hypermotor epilepsy features; one case of sudden unexplained death in epilepsy; (iii) in autosomal dominant or sporadic sleep-related hypermotor epilepsy, we observed a high prevalence of drug-resistance, although seizure frequency improved with age in some individuals, appearance of cognitive regression after seizure onset in all patients, no reported severe psychiatric disorders, although behavioral/psychiatric comorbidities were reported in ~50% of the patients, sudden unexplained death in epilepsy in one individual; and (iv) other phenotypes in individuals with mutation of KCNT1 included temporal lobe epilepsy, and epilepsy with tonic–clonic seizures and cognitive regression. Genotypic analysis of the whole cohort of 248 individuals showed only missense mutations and one inframe deletion in KCNT1. Although the KCNT1 mutations in affected individuals were seen to be distributed among the different domains of the KCNT1 protein, genotype–phenotype considerations showed many of the autosomal dominant or sporadic sleep-related hypermotor epilepsy-associated mutations to be clustered around the RCK2 domain in the C terminus, distal to the NADP domain. Mutations associated with EIMFS/non-EIMFS developmental and epileptic encephalopathies did not show a particular pattern of distribution in the KCNT1 protein. Recurrent KCNT1 mutations were seen to be associated with both severe and less severe phenotypes. Our study further defines and broadens the phenotypic and genotypic spectrums of KCNT1-related epileptic conditions and emphasizes the increasingly important role of this gene in the pathogenesis of early onset developmental and epileptic encephalopathies as well as of focal epilepsies, namely autosomal dominant or sporadic sleep-related hypermotor epilepsy.

Commentary

After an initial detailed description of any epilepsy syndrome, finding an etiology for a child's epilepsy is the most crucial step necessary to move away from a population-based treatment where standard antiseizure medications (ASMs) are used—towards personalized treatment of the child's epilepsy based on etiology.

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When available, genetic testing using next generation sequencing has now become a cornerstone for investigation of developmental and epileptic encephalopathy (DEE). Testing of epilepsy panels is more cost effective that individual gene sequencing. This approach not only allows a wider net to be cast but many times we are surprised by finding "a" genetic variant not previously known to be associated with "the" DEE being investigated instead of finding "the" genetic variant that is known to cause "that particular DEE." Pathogenicity of a new variant is typically determined based on guidelines like those published by the American College of Genetics and Clinical Genomics.[1] Additionally, disease gene validity is established through the periodic updating of clinical phenotypes associated with new pathogenic variants (in a gene thought to be causative for epilepsy). As an example, the syndrome of Malignant Migrating Partial Seizures of Infancy (MMPSI) was initially described due to gain of function mutations in the C terminus at various positions in KCNT1 but later also described in a Canadian family with different heterozygous variants where affected individuals had both an early onset DEE and a milder phenotype.[2,3]

Thus, we are constantly widening the borders of the "known and initially described" phenotype associated with mutations in a particular gene as new pathogenic variants are discovered. A cursory Pubmed search with the phrase "expanding the phenotype of . . ." yielded close to 200 hits with quite a few large-scale studies published within the last couple years on various DEEs including CHD2, PURA, KCNB1, etc.[4-6] Such publications enrich genotype–phenotype associations, help with timely initiation of appropriate therapies, could guide genetic counseling, and improve interpretation of new variants. To complicate matters further, for the syndrome of MMPSI also called Epilepsy of infancy with Migrating Focal Seizures (EIMFS), more than 30 genes are now implicated.[7] However, most cases are caused by mutations in KCNT1. In DEE that are multigenic and rare, large cohorts of patients described through multicenter, national, and international collaborative efforts are necessary for widening the clinical phenotype.

Through an international collaboration, Bonardi et al[8] publish the largest cohort yet of patients with KCNT1-associated epilepsy. How does their paper add to other publications on DEE associated with KCNT1 variants in the last several years[7,9,10]? The authors embarked on a monumental task of cataloguing heterogeneous, retrospectively obtained information into a uniform cataloguing system of phenotypic characteristics, seizure and EEG characteristics, treatment effects and lastly; phenotype–genotype correlations for 66 newly described and 182 previously published cases.

Expansion of the Genotype and Phenotype by Including 248 Patients With KCNT1 Variants in the Present Cohort

Salient Take Away Message From the Phenotypic Analyses. Although these and previous authors classified patients into 4 clinical categories: (i) EIMFS, (ii) other early onset epileptic encephalopathy (EOEE) without EIMFS, (iii) autosomal dominant/sporadic Sleep-related Hypermotor Epilepsy (ADSHE), and (iv) other seizure types; in the end—there remain 2 major phenotypes of epilepsy associated with KCNT1 mutations—(i) EOEE with or without migrating focal seizures and (ii) ADSHE.

The EOEE phenotype with or without migrating focal seizures accounts for most patients with mutations in KCNT1. Authors report that most patients are developmentally normal at onset with subsequent regression once epilepsy is established. This is however very difficult to judge when seizure onset is within the first couple months after birth. Most patients start with focal seizures 1-1.6 months after birth, seizures are very difficult to treat, patients report multiple daily or at least daily seizures, median of 9 ASMs are used in treatment. Severe developmental delay is common with most patients being non ambulatory at last follow-up. However, despite the treatment challenges, most patients report reduced seizure frequencies over time. Medication combinations associated with better seizure control include phenobarbital, quinidine, vigabatrin, clobazam, ketogenic diet. Varying presentations of seizure types and epilepsy syndromes can be reported including epileptic spasms, West syndrome, and Ohtahara syndrome. EEG is typically suggestive of a severe DEE with multifocal epileptiform activity, decremental pattern, hypsarrhythmia. MRIs can be nonspecifically abnormal with atrophy, white matter abnormalities, leukoencephalopathy. Comorbid microcephaly is noted in close to 50% patients, scoliosis and cortical visual loss is also noted. Overall, a higher mortality is noted in the EOEE phenotype than ADSHE phenotype.

The ADSHE patients are older with a median age of 5 years at onset, have less propensity to daily seizures, also tend to have medically intractable epilepsy with most patients being treated with a median of 6 ASMs. Medications noted to help included clobazam, oxcarbazepine and valproic acid. Although patients are developmentally normal at onset, they may show developmental regression. Behavioral comorbidity is noted in up to half the patients. EEG interictally is typically normal at onset. SUDEP has been reported.

Although authors report that some patients with EOEE/ADSHE are seizure free, they fail to mention the ASM that led to seizure freedom.

Other phenotypes: a handful of patients with KCNT1 variants have shown either bitemporal epilepsy, epilepsy with myoclonic atonic seizures (EMAS), or no syndrome. Whether functional studies were performed of these variants was not clear.

Salient Take Away Message From the Genotypic Analyses of These 248 Patients

All mutations except one were due to missense mutations in KCNT1. Early onset syndromes are almost always due to de novo mutations and not inherited although this is not a guarantee.

Late onset syndromes could be inherited from an asymptomatic parent (either due to poor penetrance or parental mosaicism). When more than one child is affected in a family with epilepsy always look for mosaicism in the proband if a KCNT1 mutation is not detected on first pass. Several recurrent mutations were identified by authors; however, the phenotypic effects of these mutations were pleiotropic with early onset/late

onset presentations of the same defect. Additionally, within one family, several affected individuals could have varying clinical presentations ranging from EIFMS/EOEE to ADSHE. Thus, genetic counseling regarding prognosis must be cautionary.

ADSHE syndrome is highly likely to be associated with variants in the RCK2 arm of the gene.

Questions Not Addressed by This Comprehensive Review

Explanation of how a given KCNT1 variant causes varying phenotype in this devastating epilepsy remains to be elucidated. Much work remains to be done on the path towards precision medicine that might be beneficial to a particular infant with EOEE.

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