Published in final edited form as:
Pediatr Neurol. 2014 January ; 50(1): 112–114. doi:10.1016/j.pediatrneurol.2013.06.024.

Identification of a novel *de novo* p.Phe932Ile KCNT1 mutation in a patient with leukoencephalopathy and severe epilepsy

Adeline Vanderver, MD[1,*], **Cas Simons, PhD**[2], **Johanna L. Schmidt, MPH, MGC**[1], **Philip L. Pearl, MD**[1], **Miriam Bloom, MD**[3], **Bennett Lavenstein, MD**[1], **David Miller**[4], **Sean M. Grimmond, PhD**[4], and **Ryan J. Taft, PhD**[2,*]

[1] Department of Neurology, Children's National Medical Center, Washington, DC, USA.

[2] Institute for Molecular Bioscience, University of Queensland, St Lucia, Queensland 4072, Australia

[3] Department of Pediatrics, Children's National Medical Center, Washington, DC, USA.

[4] Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, University of Queensland, St Lucia, Queensland 4072, Australia

Abstract

We present a male with early infantile epileptic encephalopathy (EIEE) and a leukoencephalopathy in whom whole exome family trio sequencing identified a heterozygous *de novo* mutation in *KCNT1*, a sodium gated potassium channel gene. Severely delayed myelination was anecdotally reported in previous cases with *KCNT1* mutations. This case reinforces that *KCNT1* sequencing should be included in an investigation of patients with severely delayed myelination and epilepsy.

Keywords

Leukoencephalopathy; Myoclonic; KCNT1; Delayed myelination

Introduction

Recent advances in MRI analysis have led to significant improvements in the diagnosis of pediatric leukoencephalopathy patients. At least 50% of these patients, however, remain

[*] To whom correspondence should be addressed: Adeline Vanderver: avanderv@childrensnational.org 111 Michigan Ave, NW, Washington DC, 20010, USA; telephone: (1) 202 476 6230; facsimile: (1) 202 476 5226 Ryan J Taft: r.taft@uq.edu.au Queensland Bioscience Precinct, Bldg 80. St Lucia, QLD 4072.

Author Contributions: Dr Adeline Vanderver: corresponding author, designed this study and performed clinical analyses. Dr Cas Simons: created the bioinformatics exome pipeline and performed data analyses. Johanna L. Schmidt, MPH, MGC: participated in study design, participant consent, and research genetic counseling. Dr. Philip Pearl: provided review of neurophysiology. Dr Miriam Bloom: participated in study design and provided the clinical description. David Miller: performed the family exome sequencing. Dr Sean M Grimmond: supervised the exome sequencing. Dr. Ryan J Taft: corresponding author, supervised the exome sequencing and data analysis, and designed this study.

without an ultimate diagnosis[1] – which, in part, may be due to the fact that the clinical and MRI presentation of leukencephalopathies can be highly variable. The advent of whole genome and exome sequencing provides an agnostic platform by which to assess individual leukoencephalopathy cases (ideally within the context of their familial genetics) for known and novel disease-associated mutations.

Case Study

The proband first came to medical attention at one month of age when, after an uneventful gestation and delivery, he was noted to have abnormal movements characterized as myoclonic seizures. Over the ensuing months, seizures evolved to consist of both generalized tonic clonic and myoclonic events, with frequent status epilepticus, which was exacerbated by febrile events, resulting in several dozen hospitalizations. Seizures are now better controlled, but on a regimen of Oxcarbazepine, Topiramate, Levetiracetam and Zonisamide. At approximately two years of age, the patient developed truncal and head titubation and adventitious movements characterized as choreathetoid, which intruded on sleep and residual neurologic function. Upon initial observation and subsequently, the patient showed no evidence of dysmorphic facies, though he was microcephalic (orbitofrontal head circumference >2 standard deviations below the mean). The patient has also suffered from severe developmental stagnation and now, at age 10 years, is able to only minimally communicate with his care providers, is unable to sit or walk and does not have any self-help skills. Neuroimaging, first obtained at several months of age, and repeated serially over the course of his care, showed an initial severe deficit in the development of age appropriate myelination that has never normalized. Indeed, the most recent MRI, performed at 7 years of age, has shown evidence of progression of myelination but at levels that are still severely reduced (Figure 1A-C), consistent with severely delayed myelination.

Electroencephalogram telemetry done at age two years was characterized by high voltage background slowing (delta range, 0.5-2.5 Hz) and superimposed multifocal interictal sharp discharges with occasional periods of burst-suppression. Habitual clinical events were recorded as myoclonias involving the extremities with associated oral dyskinesias followed by a motionless appearance, without changes in the electrographic background, most consistent with subcortical events. Subsequent EEGs have continued to show an absence of normal background organization with multifocal epileptiform discharges during wakefulness and with activation in sleep, although without ictal events (Figure 1D).

The patient's seizures were refractory to medical management until approximately 7 years of age when the patient was placed on multiple anticonvulsants, at which point they became infrequent. The underlying cause of the seizures and delayed myelination, however, remained enigmatic. Extensive biochemical and genetic testing[2] revealed no abnormalities other than mildly increased levels of sialic acid in the CSF and urine, and subsequent fibroblast and genetic studies of sialic acid metabolism were unremarkable.

The patient's presentation and severely delayed myelination were consistent with an inherited leukoencephalopathy, and he was therefore enrolled prospectively in a Myelin Disorders Bioregistry Project study on unclassified leukoencephalopathies at Children's

National Medical Center (CNMC). To investigate the possible genetic origin of the patient's disease we performed whole exome sequencing on DNA collected from the proband and the unaffected parents. We produced > 19 Gb of sequence for each individual, yielding a mean depth of 57 fold coverage with an average 90.4% of target bases sequenced at least 18 times. Using a custom-developed pipeline that integrates parental variant calls into the analysis of the affected child[3,4], a heterozygous *de novo* mutation in *KCNT1* (MIM 608167; NM_020822.2) was identified in the proband (NM_020822: c.2794T>A, p.F932I; Figure 1E). Sanger sequencing of the trio confirmed that this mutation was specific to the patient, and further analysis showed that it is not present in dbSNP135, the 1000 Genomes Project database or the NHLBI Exome Sequencing Project database. This was the only de novo mutation identified in this screen that passed our filtering criteria. KCNT1 p.F932 is highly conserved (phyloP score of 0.989744), and the p.F932I change is, in principle, the most damaging non-synonymous change found in our screen, with a PolyPhen2 score of 0.998, a SIFT score of 0.99, and MutationTaster score of 0.78.

Discussion

Three recent reports have shown that mutations in *KCNT1*, a sodium-gated potassium channel,cause at least two forms of severe epilepsy.[5-7] A set of missense *KCNT1* mutations were recently described in four families with nocturnal frontal lobe epilepsy (NFLE), including a *de novo* mutation associated with a sporadic case[6] (Figure 1E). Additionally, and a total of eight subjects from two studies investigating malignant migrating partial seizures of infancy (MMPSI), one subtype of early infantile epileptic encephalopathy (EIEE), were shown to have five additional *KCNT1* mutations, three of which were *de novo*[5,7] (Figure 1E). Although our patient did not demonstrate the features of MMPSI, he does have features consistent with the broader symptomatic description of EIEE, including refractory myoclonic seizures with onset at 1 month.

KCNT1 encodes the largest potassium channel subunit, and is thought to regulate the hyperpolarization that follows repetitive firing. Functional studies have shown that mutations in the cytoplasmic C-terminal domain lead to constitutive activation of the channel[3], which is predicted to disrupt normal neuronal firing and directly lead to epileptogenesis. The novel *KCNT1* mutation described here sits immediately adjacent to two of those recently described (Figure 1E), and we therefore conclude that it is the underlying disease-causing change in this case. KCNT1 related epilepsies fall within a broader group of potassium channel related epilepsies that may be amendable to channel specific therapies, and the findings made here will thus direct future epilepsy therapy in this patient.

Previously reported patients with KCNT1 mutations include subjects with malignant migrating partial seizures of infancy who demonstrated delayed myelination. Severely delayed myelination is a non-specific feature of primary disorders of neuronal function, and KCNT1 mutations should be included in an investigation of patients with severely delayed myelination and epilepsy.

Acknowledgments

Study Funding: AV is supported by a grant from the National Institutes of Health, National Institute of Neurologic Disorders and Stroke (1K08NS060695) and the Myelin Disorders Bioregistry Project. RJT is supported by an ARC Discovery Early Career Research Award, Institute for Molecular Bioscience core funds, and a University of Queensland Foundation Research Excellence Award. We acknowledge the Genomics Virtual Lab (GVL) project and the use of computing resources from the NeCTAR Research Cloud.

References

1. van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology. 1999; 213:121–33. [PubMed: 10540652]
2. Mastrangelo M, Celato A, Leuzzi V. A diagnostic algorithm for the evaluation of early onset genetic-metabolic epileptic encephalopathies. Eur J Paediatr Neurol. 2012; 16:179–91. [PubMed: 21940184]
3. Taft RJ, Vanderver A, Leventer RJ, et al. Mutations in DARS Cause Hypomyelination with Brain Stem and Spinal Cord Involvement and Leg Spasticity. Amer. J. Hum. Gen. 2013; 92:774–80.
4. Simons C, Wolf NI, McNeil N, et al. A De Novo Mutation in the β-Tubulin Gene TUBB4A Results in the Leukoencephalopathy Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum. Amer. J. Hum. Gen. 2013; 92:767–73.
5. Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012; 44:1255–9. [PubMed: 23086397]
6. Heron SE, Smith KR, Bahlo M, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 2012; 44:1188–90. [PubMed: 23086396]
7. McTague A, Appleton R, Avula S, et al. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. Brain. 2013; 136:1578–91. [PubMed: 23599387]

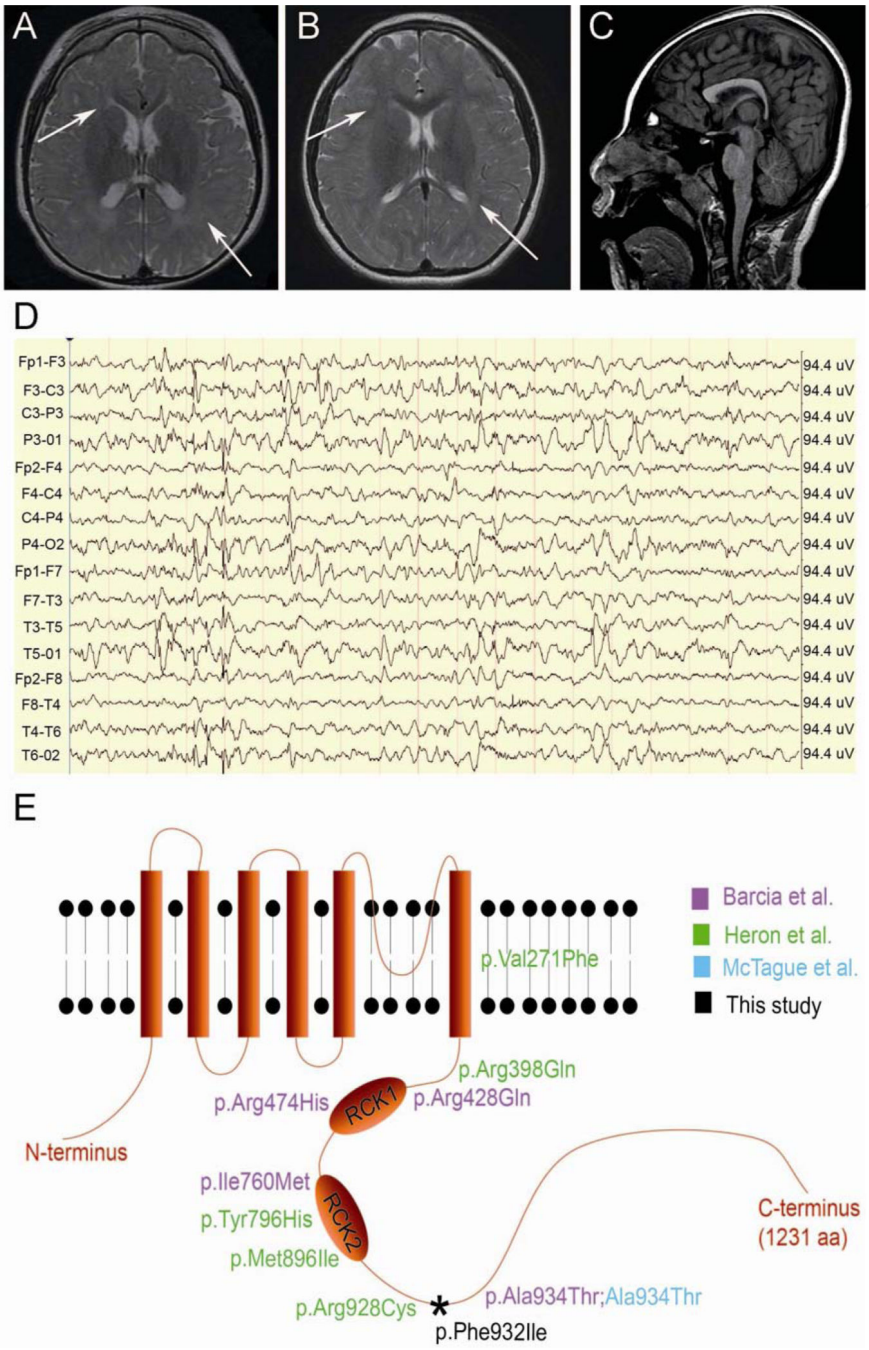

Figure 1.

Patient MRI, EEG and KCNT1 mutation information. (**A-C**) Initial studies demonstrated a severe delay in acquisition of normal myelination demonstrated on T2 weighted images (**A**, T2 axial image obtained at 3 years of age). However over time there was slow gradual progression of myelination (**B**, T2 axial image obtained at 7 years of age), demonstrated in the deep white matter (white arrows). Sagittal images (**C**, T1 weighted, 7 years of age) show microcephaly, and a shorted corpus callosum with a thin splenium. (**D**) EEG showing multifocal spike-wave discharges (bipolar longitudinal montage, epoch length 15 s,

sensitivity 7 mcv/mm, tc 0.16 s, HFF 70 Hz). (**E**) A schematic of KCNT1 and the mutations recently described by Barcia *et al.* (purple text), Heron *et al.* (green text), McTague *et al.* (blue text) or in this study (black text and asterisk). Domain annotation is per Barcia et al. and Interpro. Note that nearly all amino acid changes are found in the cytoplasmic C-terminal protein domain.