A de novo mutation in the Sodium-Activated Potassium channel KCNT2 changes channel function and causes epileptic encephalopathy

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Early infantile epileptic encephalopathy (EIEE)
- Estimated to affect 4.3 of 10,000 live births per year (Hino-Fukuyo et al., 2005).
- Characterized by intractable seizures and severe cognitive impairment and/or developmental delay (Berg et al., 2010).

Patient Clinical Characteristics
- From 3 months, he had multiple daily isolated seizures.
- At 4 months, he developed daily epileptic spasms lasting up to 8 minutes, and there was further regression in his development.
- Currently at 4 years, he has multiple daily seizures that have remained resistant to U105 trial, a ketogenic diet and the following anti-epileptic medication: topiramate, nitrazepam, levetiracetam, lamotrigine, vigabatrin, ethosuximide, pyridoxal phosphate.

Clinical presentation of the epileptic encephalopathy patient

Fig. 1. Clinical presentation. Representative whole-cell current traces recorded in Xenopus oocytes expressing WT, F240L, and 1:1 WT:F240L Slick constructs. (A) Currents evoked by depolarizing steps. (B) Currents evoked by hyperpolarizing steps. (C) Records superimposed showing that the peak current amplitude and duration of F240L is reduced compared to WT and 1:1 WT:F240L constructs. Representative current traces are shown for each condition. The difference in current amplitudes and durations is significant (p<0.05).

SUMMARY
- Early onset epileptic encephalopathies (EIEEs) are a debilitating spectrum of disorders associated with cognitive impairments.
- We present the first clinical report of a KCNT2 mutation in an EIEE patient. The de novo heterozygous variant Phex240Leu SLICK was identified by exome sequencing and confirmed by Sanger sequencing.
- Phex240Leu rSlick and hSLICK channels were electrophysiologically characterized in CHO cells and Xenopus laevis oocytes, respectively, to reveal three significant alterations to channel function.
- Phex240Leu channels displayed constitutive activity.
- [Cl−]-sensitivity of WT channels was reduced in Phex240Leu channels.
- KCNT2 selective WT channels were made non-selective by Phex240Leu.
- Further, rSlick channels induced membrane hyperexcitability when expressed in primary neurons, resembling the cellular seizure phenotype.
- Our results confirm that Phex240Leu is a change-of-function KCNT2 mutation, the first description of altered selectivity in KCNT2, and indeed, K+ channels.
- Overall, the results establish pathogenicity of the Phex240Leu KCNT2 mutation in the reported EIEE patient.

Phe240Leu alters [Cl−] sensitivity and K+ selectivity of rSlick channels in CHO Cells

Fig. 3. Phe240Leu causes constitutive activity and 'change-in-function' of rSlick and hSLICK in Xenopus Oocytes.

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