Encephalopathies with KCNC1 variants: genotype-phenotype-functional correlations

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Abstract

Objective: To analyze clinical phenotypes associated with KCNC1 variants other than the Progressive Myoclonus Epilepsy-causing variant p.Arg320His, determine the electrophysiological functional impact of identified variants and explore genotype-phenotype-physiological correlations. Methods: Ten cases with putative pathogenic variants in KCNC1 were studied. Variants had been identified via whole-exome sequencing or gene panel testing. Clinical phenotypic data were analyzed. To determine functional impact of variants detected in the K3.1 channel encoded by KCNC1, Xenopus laevis oocyte expression system and automated two-electrode voltage clamping were used. Results: Six unrelated patients had a Developmental and Epileptic Encephalopathy and a recurrent de novo variant p.Ala421Val (c.1262C>T). Functional analysis of p.Ala421Val revealed loss of function through a significant reduction in whole-cell current, but no dominant-negative effect. Three patients had a contrasting phenotype of Developmental Encephalopathy without seizures and different KCNC1 variants, all of which caused loss of function with reduced whole-cell currents. Evaluation of the variant p.Ala513Val (c.1538C>T) in the tenth case, suggested it was a variant of uncertain significance. Interpretation: These are the first reported cases of Developmental and Epileptic Encephalopathy due to KCNC1 mutation. The spectrum of phenotypes associated with KCNC1 is now broadened to include not only a Progressive Myoclonus Epilepsy, but an infantile onset Developmental and Epileptic Encephalopathy, as well as Developmental Encephalopathy without seizures. Loss of function is a key feature, but definitive electrophysiological separation of these phenotypes has not yet emerged.
Introduction

Humans have over 70 genes encoding for different potassium channel subunits. Pathogenic variants in many of these genes have been associated with a variety of neurological, cardiac, and other diseases. Voltage-gated potassium channels are important in setting membrane resting potential, regulating firing patterns and modifying action potential duration and neurotransmitter release.\(^1^\)\(^2^\) Mutations in genes encoding voltage-gated potassium channels have been implicated in several conditions including spinocerebellar ataxia, paroxysmal movement disorders, and various epilepsies.\(^3^\)\(^5^\)

**KCNC1**, which encodes the K\(_{\text{v}3.1}\) subunit, was not known to be associated with human disease until the recent description of Myoclonus Epilepsy and Ataxia due to KCNC1 mutation (MEAK).\(^6^\)\(^7^\) MEAK is a type of Progressive Myoclonus Epilepsy (PME) due to a specific recurrent heterozygous missense mutation, p.Arg320His. K\(_{\text{v}3.1}\) expression is largely restricted to the central nervous system, with predominant expression in GABAergic interneurons.\(^8^\) When analyzed *in vitro*, the PME causing mutation was shown to have a dominant-negative loss of function effect.\(^6^\) Subsequently, a truncating variant in **KCNC1**, p.Arg339X, was described in three related individuals with intellectual disability (ID) and dysmorphic features without epilepsy.\(^9^\) This raises the possibility of a wider spectrum of phenotypes associated with pathogenic **KCNC1** variants. We thus sought cases with other variants in **KCNC1** and analyzed the clinical, electrographic, and radiological features.

Here, we describe an emerging genotype-phenotype correlation with pathogenic variants in **KCNC1**. Analysis of ten patients with putative pathogenic variants in **KCNC1** facilitated identification of nine patients with novel pathogenic **KCNC1** variants. Six of these patients carry a recurrent **KCNC1** variant and present with a developmental and epileptic encephalopathy (DEE).\(^10^\) Three patients had a contrasting phenotype of developmental encephalopathy without seizures and different **KCNC1** variants. The cellular electrophysiological impact of these variants is also presented.

Methods

Ascertainment

We studied 10 cases with putative pathogenic variants in **KCNC1**. Eight cases were referred to the University of Melbourne by direct personal correspondence given our previously published work. Two cases were identified employing the web-based matching platform DECI-PHER.\(^11^\)

Variant identification

Variants were identified via clinical whole-exome sequencing (WES) or gene panel testing via the subjects’ home institution. The variant in one patient (patient 1) was identified through research WES testing as part of the Deciphering Developmental Disorders study.\(^12^\) Consent for genetic testing was obtained through treating institutions using local protocols.

Functional analysis

Mutagenesis and RNA preparation

Mutations were introduced into human **KCNC1** cDNA encoding transcript 1 (NM_001112741; Kv3.1b) or transcript 2 (NM_004976; Kv3.1a) cloned into a pCMV-Entry vector that were obtained from OriGene Technologies using QuikChange Lightning Site-Directed Mutagenesis Kit (Agilent Technologies) according to the manufacturer’s instructions. Insertion of mutation was confirmed and additional mutations excluded by Sanger sequencing. cRNA was prepared using the T7 mMessage mMachine kit from Ambion (Austin, TX).

Oocyte preparation and injection

*Xenopus* oocytes (Dumont stage V or VI) were surgically removed from *Xenopus laevis* and prepared as described previously.\(^13^\) Oocytes were kept in ND96 solution and stored at 17°C. Equal volumes (50 nL) of cRNAs with the concentrations adjusted to 0.2–0.5 μg/μL were injected using Robooinject® (Multi Channel Systems) in the same batch of oocytes plated in 96 well-plates. Recordings were performed in parallel two days after injection. Amplitudes of interest for all currents recorded on the same day were normalized to the mean value obtained for the K\(_{\text{v}3.1}\) wild-type on that day, so that the normalized data from different experiments could be pooled.

Automated oocyte two-microelectrode voltage clamp

Potassium currents in oocytes were recorded at room temperature (20–22°C) on Roboocyte2® (Multi Channel Systems) using prepulled and prepositioned intracellular glass microelectrodes with a resistance of 0.3–1 MΩ when filled with 0.5 mol/L KCl/1.5 mol/L KAc. Oocytes were held at –90 mV and perfused with bath solution containing (in mmol/L) 96 NaCl, 2 KCl, 1.8 CaCl\(_2\), 1 MgCl\(_2\) and 5 HEPES, pH 7.5. Currents were sampled at 5 kHz. For the analysis of channel activation, we used 0.5-s long depolarizing steps applied at 10 mV increments,
from $-60 \text{ mV}$ to $+60 \text{ mV}$, followed by a step to $-90 \text{ mV}$ for 0.5 sec to analyze tail currents.

**Data analysis**

Electrophysiological recordings from the Roboocyte2® were extracted using Roboocyte2+ (Multi Channel Systems) and analyzed using AxoGraph (AxoGraph Scientific, Sydney, Australia). Plotting of graphs and statistical analysis was performed using GraphPad Prism 7 (GraphPad Software, La Jolla, CA). Maximum current amplitudes were compared at the end of a 0.5-s test pulse to $+60 \text{ mV}$. The voltage-dependence of channel activation was derived from tail current amplitudes recorded at $90 \text{ mV}$ for 0.5 sec to analyze tail currents.6

**Results**

**KCNC1 variants associated with developmental and epileptic encephalopathy (DEE)**

We identified six unrelated patients with DEE and a recurrent missense variant p.Ala421Val (c.1262C $> T$). All were confirmed de novo variants. The variant p.Ala421Val is absent from the gnomAD database and predicted as deleterious using in silico methods. The six patients were from the United Kingdom, Germany, France, and North America. Patient 1 had a family history of epilepsy on both maternal and paternal sides; the remaining five patients had no significant family history. All presented between birth and 10 months with predominantly generalized seizure types (Table 1); myoclonic seizures were reported in all but one case (patient 2).

Developmental delay without regression was seen in all patients, however, they were able to walk and achieved intelligible speech. Associated neurological features included mild non-progressive ataxia ($n=4$), as well as hypotonia ($n=4$). Three patients (3, 4, and 6) exhibited similar dysmorphic features including a large mouth, smooth philtrum, up-slanting palpebral fissure and dental enlargement (Fig. 1). Three patients were noted to have a combination of respiratory co-morbidities (central sleep apnoea, sleep disturbance) and musculoskeletal abnormalities (pectus excavatum, hypermobile joints). Two of these patients also had gastrointestinal co-morbidities.

All patients had abnormal EEGs. Five patients demonstrated slowing of background rhythms. Four patients demonstrated interictal generalized spike-and-wave discharges, and EEG in the other two patients captured electroclinical seizures with bi-frontal onset. Myoclonus without electrographic correlate was noted in two patients, and normalization of electrographic abnormalities over a period of years was noted in two patients. MRI brain imaging showed no specific abnormalities.

All patients had moderate-severe intellectual disability. Long-term seizure frequency and response to treatment was variable. Two patients achieved improved seizure control in late childhood (at 9 and 15 years of age, respectively) with combination antiepileptic therapy, and one patient had a good clinical response to vagal nerve stimulator insertion. The remaining three patients had ongoing refractory seizures despite multiple antiepileptic medications.

A single patient with DEE and KCNC1 missense variant p.Ala513Val (c.1538C $> T$) was also identified. The electro-clinical phenotype was of Epilepsy of Infancy with Focal Migrating Seizures (EIFMS), and the patient died at 6 months of age from cardiorespiratory arrest. Recognized genetic causes of EIFMS were not detected on a 77 gene panel testing. The KCNC1 variant was confirmed de novo but it appears once in gnomAD, and thus was considered a variant of uncertain significance.

**KCNC1 variants associated with developmental encephalopathy (DE) without seizures**

Three patients, including a mother-son pair, presented with a developmental encephalopathy without seizures (Table 2). The mother-son pair with a truncating variant p.Gln492X (c.1474C $> T$) had mild-moderate intellectual disability, no dysmorphic features and the son developed a nephroblastoma at four years of age. No other causative variants were identified on WES, The third case had missense variant p.Arg317His (c.950G $> A$), and presented with mild intellectual disability and autism. The patient had never been noted to have a seizure. A 23-hour EEG video to investigate episodes of staring revealed rare irregular generalized spike wave discharges, with no clinical seizures. Brain MRI revealed cerebellar and posterior pontine atrophy. Trio WES also revealed a maternally inherited MAOA variant.

**Functional analysis**

To determine functional impact of variants detected in the K$_3$3.1 channel (Fig. 2A), encoded by KCNC1, we used
Table 1. Clinical features of patients with Developmental and Epileptic Encephalopathy and recurrent KCNC1 missense variant p.Ala421Val.

| Patient | Inheritance | Gender | Age at onset | Seizure types | Response to treatment | Age at walking | Intelligible speech | Cognitive Function | Neurological Features | Co-morbidities | Clinical course |
|---------|-------------|--------|--------------|---------------|-----------------------|----------------|---------------------|-------------------|---------------------|----------------|----------------|
| 1       | De novo     | F      | Birth        | Myoclonic     | Refractory            | 2.5 years      | Yes                 | Moderate-severe ID | Ataxia1             | Behavioural disturbance | Refractory seizures age 16 |
| 2       | De novo     | M      | 3 months     | Atypical absence | Response to LMT and VPA | 3 years        | Yes                 | Severe ID          | Nil                 | Sleeping disturbance  | Monthly seizures at 3 years |
| 3       | De novo     |        | 10 months    | Focal to bilateral tonic clonic | Refractory then response to VPA Clobazam | 2.5 years      | Yes                 | Moderate-severe ID | Nil                 | Failure to thrive | Seizure control improved age 15 |
| 4       | De novo     | F      | 9 months     | Myoclonic     | Refractory to medication, response to VNS | 2.5 years      | Yes                 | Moderate-severe ID | Hypotonia           | GERD, Chronic diarrhoea, | <1 seizure every 3 months post VNS |
| 5       | De novo     | M      | 9.5 months   | Myoclonic     | Response to LEV and LMT | 3 years        | Yes                 | Ataxia1, mild decreased power, hypotonia | Sleep disturbance | Fibromyalgia | Seizures every 2-3 months |
| 6       | De novo     | M      | 5 months     | Myoclonic     | Response to VPA       | 3 years        | Yes                 | Moderate ID         | Hypermobile joints | Stereotypies |

Abbreviations: GERD, gastro-esophageal reflux disease; ID, intellectual disability; GTCS, generalized tonic clonic seizures; LEV, levetiracetam; LMT, lamotrigine; VNS, vagal nerve stimulator; VPA, sodium valproate.

1Ataxia, where noted, was mild and non-progressive.

2Child too young for grading of intellectual disability.
Xenopus laevis oocyte expression system and automated two-electrode voltage clamping. Current traces obtained from a set of depolarizing pulses from $-60$ to $+60$ mV (Fig. 2B) revealed a clear loss of function for all but the Ala513Val variant, being the variant observed once in gnomAD.

Current amplitudes analyzed at the end of the current trace were obtained at maximum voltage (+60 mV) and normalized for all variants to the corresponding wild type (Kv3.1a for p.Ala421Val, p.Arg317His, p.Gln492X and p.Arg339X and Kv3.1b for p.Ala513Val) recorded on the same day, therefore providing the relative current amplitude (Fig. 2C and D). Voltage dependence of activation determined from tail current amplitudes recorded at $-90$ mV for the variants showing current amplitudes above the background level (p.Gln492X and p.Ala513Val) showed no significant difference compared to the corresponding WT channels (Fig. 2E).

To determine potential dominant-negative effect, we performed coexpression experiments, where both WT and mutant cRNA of the same concentration were injected at a 1:1 ratio. Two variants that showed very small or no

Table 2. Clinical features of patients with KCNC1 variants and Developmental Encephalopathy without seizures.

| Patient | 1 | 2 | 3 |
|---------|---|---|---|
| KCNC1 variant | p.Arg317His | p.Gln492X | p.Gln492X |
| Gender | M | F | M |
| Cognitive Function | Mild ID | Mild-Moderate ID | Mild-moderate ID |
| Seizures | No | No | No |
| Dysmorphic Features | Nil | Nil | Nil |
| Neurological Features | Autism | Nil | Nil |
| MRI | Cerebellar and posterior pontine atrophy | Not performed | Not performed |
| EEG | Rare generalized spike-wave | Not performed | Not performed |

Figure 1. Facial features of patient 3 showing a large mouth, smooth philtrum, up-slanting palpebral fissure, and dental enlargement.
currents, (Arg317His and Arg339X) caused a significant reduction compared to the WT current amplitude indicating a dominant-negative effect (Fig. 3A and 3). For the coexpression of the Gln492X with the WT, the normalized current amplitudes were as follows: WT + H2O \(1.00 \pm 0.03\) (\(n = 111\)) and WT + Gln492X \(-1.02 \pm 0.12\) (\(n = 21\)). In both cases, the injected amount of WT cRNA was the same, so that the resulting current amplitude of the coexpression should be the sum of the expressed WT + H2O \((1.00 \pm 0.03)\) and half of the amplitude recorded for the Gln492X alone \((0.7 \pm 0.1;\) Fig. 2C), that is, with a value of about 1.3. Since this predicted value is larger than the recorded one this might suggest the dominant-negative effect of the Gln492X.

The conductance-voltage relationships for Ala421Val + WT, Arg317His + WT, Gln492X + WT, and Arg339X + WT did not differ from the wild type alone (Fig. 3C). With no changes seen in the voltage dependence of activation, the observed reduction in current amplitudes may be explained by other mechanisms such as reduced number of mutant channels reaching the membrane or reduced open probability of these channels.

**Discussion**

We describe the phenotypic features of 10 patients with putative pathogenic variants in KCNC1, and also present the electrophysiological impact of these variants. These are summarized in Table 3 and compared to the previously described recurrent p.Arg320His variant that causes progressive myoclonus epilepsy.6,7

Six patients carry the recurrent KCNC1 missense variant p.Ala421Val and present with a DEE. These are the first reported cases of DEE due to KCNC1 mutation, and...
thus broaden the spectrum of phenotypes associated with KCNC1 missense variants to include infantile onset DEE. The Kv3 subfamily exhibits very fast activation and deactivation kinetics, enabling the generation of very high frequency action potentials.1 Kv3.1 expression is largely restricted to the central nervous system, predominantly in inhibitory GABAergic interneurons.8 An impact of KCNC1 variants on early development is supported by the fact that embryonic expression of Kv3.1 channels in animal models is well-established, 14–16 with gradual increases in transcript levels noted after birth in murine models, especially postnatal days 8–14.17 Embryonic expression when the fast spiking phenotype is not present suggests that these channels may also have other critical roles in early development, including in cell proliferation, migration, and regulation of neuronal and glial properties.17,18

In this cohort of patients with DEE and KCNC1 variant p.Ala421Val, onset was within the first 10 months of life, with predominantly generalized seizure types seen. Myoclonus was a prominent feature in many patients but the pattern was not that of a PME. Seizures were generally refractory to treatment, persistent developmental delay without regression and moderate-severe intellectual disability were seen. Mild non-progressive ataxia was a common associated neurological feature. No consistent associated co-morbidities were noted in this cohort, however musculoskeletal, respiratory, and gastrointestinal features were seen in several patients. Functional analysis of KCNC1 variant p.Ala421Val revealed loss of function through a significant reduction for R317H and R339X but not for the A421V coexpression, ***P < 0.001, **P < 0.01 using one-way ANOVA with Dunnett’s multiple comparisons test; WT + H2O (n = 111), WT + A421V (n = 62); WT + R317H (n = 11); WT + Q492X (n = 21); WT + R339X (n = 17). (C) Conductance-voltage relationships of the WT and its coexpressions with A421V, R317H and R339X. V0.5 and slope factor (k) values were as follows: for WT + H2O 18.2 ± 1.4 mV, 12.4 ± 0.4 (n = 27), for WT + A421V 16.6 ± 1.8, 15.2 ± 0.4 (n = 36), for WT + R317H 21.1 ± 4.5 mV, 17.8 ± 1.9 (n = 8), for WT + Q492X 25 ± 3 mV, 13.9 ± 0.5 (n = 12), and for WT + R339X 15.8 ± 3.1 mV, 12.2 ± 1.1 (n = 15).
Table 3. Phenotypes and electrophysiological changes associated with KCNC1 variants.

| Phenotype                        | KCNC1 variant | Seizure types               | Cognitive function                                      | Electrophysiological characteristics | Developmental and epileptic encephalopathy | Developmental encephalopathy without seizures |
|----------------------------------|---------------|-----------------------------|--------------------------------------------------------|--------------------------------------|------------------------------------------|---------------------------------------------|
|                                  | p.Arg320His   | Myoclonic tonic-clonic      | Normal with mild late decline in some                  | Marked reduction                     | p.Ala421Val                              | p.Arg339X                                   |
|                                  | (infrequent)  | (infrequent)                |                                                        |                                      | p.Gln492X                                | p.Arg317His                                 |
|                                  |               |                             |                                                        |                                      | Nil                                      | Nil                                         |
|                                  |               |                             |                                                        |                                      | Moderately ID                            | Mild ID                                     |
|                                  |               |                             |                                                        |                                      | No change                                | No change                                   |
|                                  |               |                             |                                                        |                                      | Yes                                      | Unknown¹                                   |
|                                  |               |                             |                                                        |                                      |                                        | Yes                                         |

¹Not assessed as current with mutant was not markedly reduced (see Methods).

changes, suggests that it is unlikely to be pathogenic even though it occurred de novo and other known causes of EIMFS (e.g., SCN2A and KCNT1 variants) were not detected. Although de novo mutation is the usual mechanism in DEEs, this highlights caution is necessary in attributing pathogenesis to a novel de novo variant in an otherwise persuasive clinico-molecular context.

The other three patients with novel variants in KCNC1 presented with a different phenotype of developmental encephalopathy (DE) without seizures. These cases add to the published literature of three related patients from one family with a different KCNC1 truncation variant p.Arg339X, with DE but without epilepsy.⁹ Of note, the previously reported cases also had dysmorphic features (including prognathism, dysplastic ears, protruding tongue), which our patients did not.

Interestingly, quantification of mRNA in fibroblasts from a patient with Arg339X variant showed > 50% reduction of KCNC1 transcript compared to the control data, possibly due to nonsense mediated decay (NMD).⁹ This effect may explain why the observed dominant-negative effect for this mutant was not more pronounced in our experiments. The pathogenicity of this variant may thus be a consequence of both reduced expression of KCNC1 and a damaging effect of the mutant protein that escaped NMD and interacted with the WT subunits. We were not able to obtain fibroblasts from Gln492X variant carriers. However, given that this variant produces a longer channel protein yielding potassium currents reaching about 70% of the WT, we do not expect the NMD effect would be the critical mechanism. Our functional analysis of the three different KCNC1 variants associated with this phenotype of DE without seizures reveals that again all variants cause a loss of function, all with reduced whole-cell currents. Moreover, two of the three variants caused a dominant-negative effect, which was not seen for the DEE-causing variant p.Ala421Val. However, p.Gln492X showed a milder effect so that it is difficult to make conclusions about the electrophysiological features which distinguish these variants from the DEE-causing variant.

Of note, the p.Arg317His variant resulted in functional changes similar to the PME-causing p.Arg320His variant but the phenotype seen in this patient is a DE without epilepsy. The proximity of this variant to the PME-causing one is noted, (Arg317 is the third arginine in the S4 segment of K₃.1.1), and somewhat challenging to reconcile. However, we did observe that the loss of function and the dominant negative effect were not as prominent as seen for p.Arg320His. Moreover, no shift in the voltage-dependence of activation was found for the Arg317His expressed with the WT. This is consistent with the findings reported for two S4 segment disease variants at the same position in the related K₃.3. Both of these variants caused a dominant negative effect but only the alteration of the fourth arginine lead to a hyperpolarizing shift of the activation curve.¹⁹ The third and fourth arginine have been shown critical for the voltage sensor domain conformation. Analogous arginines in the crystal structure of the K₃.1.2 channel are shown to face S1 and S2 helices, and establish salt bridge interactions with the acidic amino acids.²⁰ Interestingly, removal of the positive charge within the S4 segment also affects protein turnover and surface expression of K₃.3.²¹ We may thus propose that a similar mechanism may underlie the pathogenicity of Arg317His. This patient was also noted to have a maternally inherited MAOA variant. Mutation in MAOA has been implicated in DE, autism, and behavioral disturbances,²² with no reports of EEG abnormalities. The patient’s mother was unaffected.

A lack of clear distinguishing electrophysiological features between the DEE-causing variants and those associated with DE without epilepsy may, at least in part, be a
reflection of the fact that we have not examined the variants’ impact in the context of co-expression of other Kv3 subunits. Kv3 subunits assemble either as homomers or heteromers to form voltage-gated tetrameric potassium ion channels. In vitro, Kv3.1 can assemble with Kv3.3 and Kv3.4, and Kv3.1 and Kv3.2 co-immunoprecipitate in vivo.23,24 Kv3.1 and Kv3.3 have areas of overlapping expression, especially in the cerebellum, and a degree of functional redundancy is thought to explain why KCNC1 and KCNC3 knockout mice have relatively mild phenotypes, but double knockout mice exhibit myoclonus, tremor, and ataxia.25–27 Clearly there is significant interaction between subunits, and it is feasible that this may be relevant when considering an emerging spectrum of disease seen with different mutations in KCNC1.

The description of these cases expands the phenotypic spectrum seen with mutation in KCNC1 to now not only include a type of Progressive Myoclonus Epilepsy, but to also include an infantile onset DEE, as well as a DE without seizures. A genotype-phenotype correlation is emerging with respect to pathogenic variants in KCNC1, whereby the recurrent missense mutation p.Arg320His causes MEAK, the recurrent missense variant p.Ala421Val gives rise to the infantile onset DEE, and truncation variants result in a developmental encephalopathy without seizures. At this stage, definitive electrophysiological functional correlations for these phenotypes have not emerged, which is a target for future investigation.

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Author Contributions

J.C, S.M, S.P, and S.B were involved in conception and design of the study, acquisition and analysis of data and manuscript drafting and completion. All remaining authors were involved in acquisition and analysis of data and manuscript review.

Conflict of interest

The authors declare no conflicts of interest.

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