HHS Public Access

Author manuscript

Clin Dysmorphol. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Clin Dysmorphol. 2023 October 01; 32(4): 147–150. doi:10.1097/MCD.0000000000000463.

Further Evidence of Biallelic Variants in *KCNK18* as a cause of Intellectual Disability and Epilepsy with Febrile Seizure Plus

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Abstract

Introduction: *KCNK18*, a potassium channel subfamily K member 18 (MIM*613655), encodes for TWIK-related spinal cord K+ channel (TRESK) and is important for maintaining neuronal excitability. Monoallelic variants in *KCNK18* are known to cause autosomal dominant migraine, with or without aura, susceptibility to, 13 (MIM#613656). Recently, biallelic missense variants in *KCNK18* have been reported in three individuals from a non-consanguineous family with intellectual disability (ID), developmental delay, autism spectrum disorder (ASD), and seizure.

Methods: Singleton exome sequencing was performed for the proband after detailed clinical evaluation to identify the disease-causing variants in concordance with the phenotype.

Results: We herein report an individual with ID, developmental delay, ASD, and epilepsy with febrile seizure plus with a novel homozygous stopgain variant, c.499C>T p.(Arg167Ter) in *KCNK18*.

Conclusion: This report further validates *KCNK18* as a cause of autosomal recessive ID, epilepsy, and ASD.

Keywords

Autism spectrum disorder; TRESK; intellectual disability; epilepsy; exome sequencing

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Conflict of interests: The authors declare no conflict of interest. All the authors have read and approved the manuscript.

Introduction

Potassium channel subfamily K member 18, *KCNK18* (MIM*613655) belongs to a newly described, calcium-dependent, two-pore domain potassium channel encoding TWIK-related spinal cord K^+ channel (TRESK). It functions as a background K^+ channel to maintain the K^+ equilibrium potential and regulate the resting membrane potential (Czirják et al., 2004). Until recently, heterozygous disease-causing variants in *KCNK18* were typically known to cause autosomal dominant migraine, with or without aura, susceptibility to, 13 (MIM #613656) (Lafrenière et al., 2010). Lately, a study by Pavinato et al (2021) have reported three individuals from a non-consanguineous family harbouring biallelic missense variants in *KCNK18* with intellectual disability (ID), autism spectrum disorder (ASD), and seizures (Pavinato et al., 2021). We hereby report a six-year-old male from an Indian family with mild motor delay, speech delay, moderate ID, ASD, and epilepsy with febrile seizure plus (EFS+), harboring a novel homozygous stopgain variant, p.(Arg167Ter), in *KCNK18*.

Methods:

Ethical approval and consenting

Individual in the study was clinically evaluated at the Department of Medical Genetics, Kasturba Hospital, Manipal. Informed consent, approved by the institutional ethics committee, Kasturba Medical College and Kasturba Hospital, was obtained from the family for genetic testing, and publication of data. Genomic DNA was extracted from the proband, elder sibling and their parents from peripheral blood using the QIAamp DNA Blood Mini Kit (Cat #51106).

Molecular testing

Singleton ES (Illumina, Inc., San Diego, California, USA) was performed for the proband using the Medgenome TWIST comprehensive capture kit (Twist Bioscience). Variants were filtered and prioritized as per our in-house variant filtering strategy. Variants with minor allele frequency <1% were filtered against population database gnomAD and in-house variant database of 2533 exomes. Exonic and splice site variants were then prioritized based on their concordance to the observed phenotype and multiple in-silico pathogenicity tools.

Results:

Clinical details

A six-year-old male, second born to a non-consanguineously married couple (Supp Fig. 1A), presented with developmental delay and multiple episodes of febrile seizures. He was born by normal vaginal delivery at term and weighed 3kg (−0.9SD) at birth. He attained social smile by three months, neck control by five months, rolling-over by five months, sitting without support by ten months, standing independently by 1 year, walking by 2 years, and bi-syllables by 2 years. The first episode of febrile seizure was noted at 18 months with uprolling of eyes and generalized tonic posturing, associated with post ictal drowsiness lasting for two minutes. The second and third episodes of febrile seizures were observed at 2 years and 4 years of age respectively, with similar semiology. The last episode of seizure

was noted at 6 years of age, which lasted for about 30 minutes. He was admitted to the pediatric care for further treatment. He was initially started on levetiracetam from 18 months to three years, and then was changed to sodium valproate.

On examination at 6 years, his height was 118cm (+0.19SD), weight was 17kg (−1.8SD) and head circumference was 50cm (−1.2SD). No other characteristic dysmorphic features were noted. He had normal vision and hearing. His genitalia and extremities were normal. He had normal muscle tone and his deep tendon reflexes were normal.

On follow-up at 7 years, he was able to run, speak sentences, recite the alphabet in his native language, sing kindergarten-taught poems, count to 10 and interacts well with his peers. However, he was unable to climb stairs, write neatly, had difficulty in calculation, and had poor memory. Seizures were not observed after 6 years of age, as he was on anti-epileptics such as sodium valproate. An electroencephalogram (EEG) done at 18 months, 5 years and 7 years, showed no abnormalities. Brain magnetic resonance imaging (MRI) done at 4 years revealed normal results. During a subsequent clinical psychology consultation at 7 years, Seguin Form Board Test (SFBT) showed mental age of 5 years, and intelligence quotient of 74, indicative of borderline deficits in intellectual functioning. According to the Conners' Teacher Rating Scale (CTRS), he showed significant attention deficit hyperactivity disorder (ADHD) features. Psychiatry consultation at 7 years showed poor eye contact, hyperactivity, self-talk, temper tantrums, inattention and stereotypes like staring at hands, and inward movements of hands.

His nine-year-old elder sister, with normal development and intellect, has a history of a single episode of febrile seizure at 3 years of age.

Molecular testing

A novel homozygous stopgain variant c.499C>T p.(Arg167Ter) in exon 3 of *KCNK18* (NM_181840.1) was identified in concordance with the observed phenotype. Validation and segregation of this variant by Sanger sequencing confirmed the presence of this variant in homozygous state in the proband and heterozygous state in his elder sibling and parents (Supp Fig. 1B). This variant is present in 17 individuals in heterozygous state in the population database gnomAD, however, it is not present in homozygous state in gnomAD and our in-house database of 2533 exomes.

Discussion

Two pore domain potassium channels (K2P) are encoded by fifteen different potassium channel subfamily K member (KCNK) genes, categorized into six protein subfamilies: TWIK, TREK, TASK, TALK, THIK, and TRESK, based on the sequence similarity and functional resemblance. The TRESK channel, encoded by *KCNK18,* is composed of 384 amino acids (Enyedi and Czirják, 2015) and is highly expressed in brain [www.gtexportal.org (accessed on 04 December 2022)]. Human TRESK consists of four transmembrane helices, two pore-forming domains, and intracellular N- and C-termini (Czirják et al., 2004). TRESK channel is different from the other K2P channels by the presence of a long intracellular loop between the second and third transmembrane segments

(TMS), and a relatively short C-terminal tail. It plays a significant role in regulation of neuronal excitability and maintaining resting membrane potential (Ter et al., 2010). It is unique from the other K2P channels in that it is activated by calcineurin, a calcium-dependent phosphatase (Czirják et al., 2004).

Heterozygous variants in *KCNK18* are known to cause autosomal dominant susceptibility to migraine, with or without aura. This association was first established by candidate gene approach in a large multigenerational family affected with typical migraine with aura and a heterozygous frameshift variant p.(Phe139fs) in *KCNK18*. Functional characterization of this variant showed loss of TRESK channel activation by dominant-negative mechanism (Lafrenière et al., 2010).

Notably, a study by Han et al (2018) reported a twelve-year-old boy with speech impairment, ID, disorientation, and migraine with a heterozygous missense variant, p.(Trp101Arg) in *KCNK18* inherited from a symptomatic mother with migraine, mild ID and visual impairment (Han et al., 2018). This report further expanded the phenotypic spectrum to include neurodevelopmental phenotypes. Imbrici et al (2020) further carried out functional validation of the p.(Trp101Arg) heterozygous missense variant, which also showed reduction in the TRESK channel activity by dominant-negative mechanism (Imbrici et al., 2020).

Recently, Pavinato et al (2021) described three siblings from a family with biallelic missense variants in *KCNK18* with ID, ASD, and seizure (Pavinato et al., 2021). Autism spectrum disorder, mild to moderate ID, motor delay, and speech delay were the characteristic features observed in individuals with biallelic *KCNK18* variants. The proband of in the present study presented with recurrent febrile seizures, persisting beyond five years of age, consistent with the phenotype of febrile seizure plus, and also had febrile status epilepticus. This severity in the seizure phenotype of the proband can be attributed to the deleterious loss-of-function variant (Pavinato et al., 2021). A detailed comparison of the clinical and molecular features observed in all the individuals with autosomal recessive *KCNK18*-related disorder is described in Table 1.

The two previously reported missense variants, p.(Tyr163Asp) and p.(Ser252Leu) in *KCNK18* in compound heterozygous state, significantly impair the ability of the TRESK channel to respond to calcineurin-dependent activation, leading to loss-of-function of the channel in Xenopus oocytes (Pavinato et al., 2021). The stopgain variant p.(Arg167Ter) identified in the present study can either lead to the formation of an abnormal protein product or can trigger the transcript to undergo nonsense-mediated mRNA decay. The variant would lead to truncation of half of the TRESK protein after the second TMS, containing important downstream regulatory motifs such as phosphorylation, dephosphorylation, and calcineurin binding sites present in the intracellular loop of the TRESK protein (Czirják et al., 2004; Enyedi and Czirják, 2015). This is predicted to cause a significant loss of TRESK channel activity, further impacting the neuronal membrane excitability. The consequences would probably mimic the increase in cellular excitability observed in dorsal root ganglia (DRG) neurons of TRESK functional knockout mice (Dobler et al., 2007). Based on these evidences, the variant is classified as ‘pathogenic’ using

the American College of Medical Genetics and Genomics (ACMG) sequence variants interpretation guidelines criteria, PVS1, PM2, and PP3, and is submitted to ClinVar (ID: SCV002769814.1) (Richards et al., 2015).

In conclusion, we further validate *KCNK18* as a cause of autosomal recessive ID, epilepsy, and ASD. Reports of additional families will further help in understanding the disease spectrum and establish a genotype-phenotype correlation for this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the patient and his family for participating in the study. We also thank the National Institutes of Health, USA, for funding the project titled ‘Genetic Diagnosis of Neurodevelopmental Disorders in India’ (1R01HD093570-01A1).

Funding:

National Institutes of Health, USA (1R01HD093570-01A1)

Data availability

The data can be shared upon a reasonable request to the corresponding author.

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Table 1:

Clinical features and molecular details of individuals with biallelic *KCNK18* variants

Clinical and molecular details	**Present study**		**Pavinato, L et al (2021)**	
Family	**Family 1**		**Family 2**	
Proband	**P1**	**P2**	**P3**	**P4**
Gender	**Male**	**Female**	**Female**	**Male**
Consanguinity	**Non-consanguineous**	**Non-consanguineous**	**Non-consanguineous**	**Non-consanguineous**
Variants in *KCNK18* (NM_181840.1)	c.499C>T p.(Arg167Ter)	c.487T>G p.(Tyr163Asp)/ c.755C>T p.(Ser252Leu)	c.487T>G p.(Tyr163Asp)/ c.755C>T p.(Ser252Leu)	c.487T>G p.(Tyr163Asp)/ c.755C>T p.(Ser252Leu)
Type of variant	Stopgain	Missense	Missense	Missense
Zygosity	Homozygous	Compound heterozygous	Compound heterozygous	Compound heterozygous
Age at last exam	7 years	26 years	19 years	16 years
Age at presentation	18 months	18 months	NA	NA
Symptoms at presentation	Seizures	Speech delay	Mild ID	Developmental delay
Motor delay	+	+	NA	NA
Intellectual disability	+	+	+	+
Intelligence quotient (IQ)	74	64	56	NA
Speech delay	+	+	NA	NA
Seizures	+	-	+	-
Autistic features	+	+	+	+
Miscellaneous features	-	Partial temporal–spatial disorientation, frontal cephalalgy, dyslexia, dysarthria	-	Dyslexia
Magnetic resonance imaging	Normal	NA	NA	NA
Electroencephalogram	Normal	NA	Comitiality	NA

NA: Not available; +: present; -:absent; ID: Intellectual disability