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Expanding the Phenotype of Homozygous *KCNMA1* Mutations; Dyskinesia, Epilepsy, Intellectual Disability, Cerebellar and Corticospinal Tract Atrophy

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Background: The *KCNMA1* gene encodes the α-subunit of the large conductance, voltage, and calcium-sensitive potassium channel (BK channels) that plays a critical role in neuronal excitability. Heterozygous mutations in *KCNMA1* were first illustrated in a large family with generalized epilepsy and paroxysmal nonkinesigenic dyskinesia. Recent research has established homozygous *KCNMA1* mutations accountable for the phenotype of cerebellar atrophy, developmental delay, and seizures.

Case Report: Here, we report the case of a patient with a novel homozygous truncating mutation in *KCNMA1* (p.Arg458Ter) presenting with both the loss- and gain-of-function phenotype with paroxysmal dyskinesia, epilepsy, intellectual delay, and corticospinal–cerebellar tract atrophy.

Conclusion: This report extends the *KNCMA1* mutation phenotype with a patient who carries a novel frameshift variant, presenting with both the gain- and loss-of-function phenotypes along with spinal tract involvement as a novel characteristic.

Keywords: Cerebellar atrophy, dyskinesia, epilepsy, *KCNMA1*, spinal tract atrophy

The *KCNMA1* gene encodes the α-subunit of the large conductance, voltage, and calcium-sensitive potassium channel (BK channels), which is also activated by the concentration of cytosolic Mg^{2+} and is known to be predominantly expressed in the amygdala, caudate nucleus, cerebral cortex, hippocampus, hypothalamus, spinal cord, and Purkinje cells in the cerebellum (1,2). Initially, the *KCNMA1* mutations were illustrated in a large family with generalized epilepsy and paroxysmal nonkinesigenic dyskinesia (3). A recent study established a correlation of the homozygous *KCNMA1* mutation with cerebellar ataxia, developmental delay, and seizures. In addition, both the gain- and loss-of-function have been proposed as the underlying molecular mechanism in this channelopathy resulting in increased excitability (4). Here, we report the case of a patient with a novel homozygous truncating mutation in *KCNMA1* (p.Arg458Ter) presenting with both the loss- and gain-of-function phenotype with paroxysmal dyskinesia, epilepsy, intellectual delay, and corticospinal–cerebellar tract atrophy.

CASE PRESENTATION

A 15-year and 11-month-old male patient was referred to our genetics unit at the age of 15 years. He was born at term to a third-degree consanguineous healthy parents with a healthy birth weight (3250 g), height (53 cm), and occipitofrontal circumference (34 cm). There was a prolonged labour, and the APGAR score was 7-8. His motor milestones were delayed, and he never walked alone. In addition, he had a social smile and could talk approximately 10 simple words. His seizures, although mostly absent, started at the age of 18 months and were well-controlled by valproic acid. Meanwhile, he also experienced clonic and generalized tonic–clonic (GTCS) and atonic seizures and had spasticity predominant in the lower extremities with no pathological reflexes. While electroencephalography revealed generalized spike-wave activities, electromyography and metabolic tests were normal. Furthermore, the brain magnetic resonance imaging (MRI) performed at the age of 3 years revealed moderate atrophy with prominent folia in the upper parts of the supratentorial cerebellar vermian region.

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Moreover, symmetric T2 hyperintensities were observed at the retroatrial periventricular deep white matter. Diffusion tensor imaging images obtained at the age 14 years revealed the involvement of tegmental to corticospinal atrophy (Figure 1). Besides, the atrophy of the cerebellum had progressed compared to previous MRI studies (Figure 2). The patient's last examination determined contractures on the large joints, dyskinetic tremor, and dystonia. Of note, this study was reported per the tenets of the Declaration of Helsinki and was approved by the institutional review board and ethical committee of our university. We obtained written informed consent from the patient.

The exome sequencing revealed a homozygous nonsense change in the *KCNMA1* gene NM_001161352.1:c.1372[C>T];[C>T] NP_001154824.1:p.[(Arg458*)];[(Arg458*)]. The variant was not observed in any publicly available database (e.g., EXAC, EVS, and 1000 genomes) or in our internal database. In addition, we identified another variant, rs60734921, in the *CACNAH1* gene, which has been described in a study as a risk factor for generalized

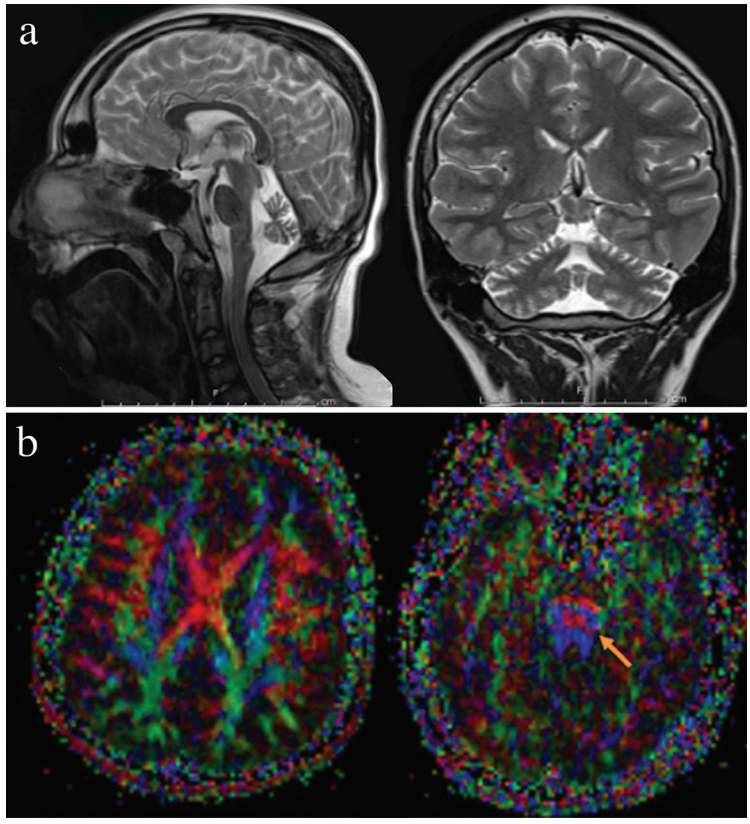

FIG. 1. a, b. Sagittal and coronal brain magnetic resonance images of a 14-year-old boy revealed cerebellar vermian volume loss with normal pons and spinal canal (a). Diffusion tensor imaging images displayed thinning of the tegmental extending through corticospinal tracts (b).

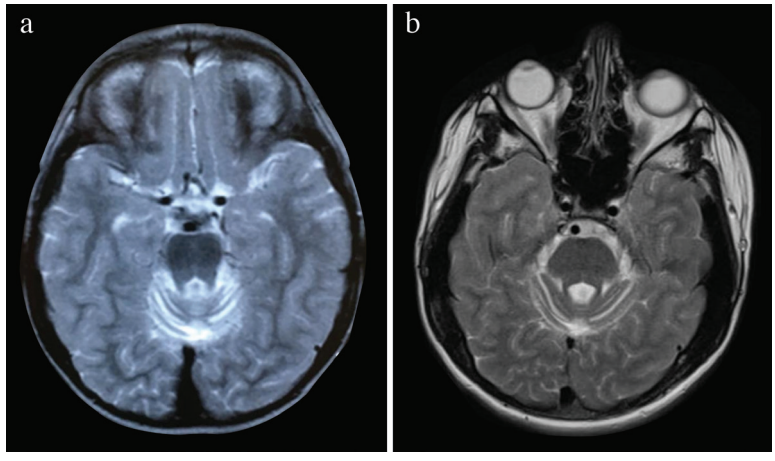

FIG. 2. a, b. Compared to previous magnetic resonance imaging, the atrophy of the cerebellum progressed; (a) performed when he was of 3 years and (b) performed 12 years after the initial magnetic resonance imaging.

TABLE 1. The clinical and characteristic phenotype of patients with the *KCNMA1* gene mutation

Clinical features	Current study	Tabarki et al. (4) (2016)	Tabarki et al. (4) (2016)	Khosravani et al. (5) (2015)	Khosravani et al. (5) (2015)	Du et al. (3) (2005)
Sex	Male	Female	Female	Male	Male	10 males, 6 females
Age of onset	1.5 years	8 months	8 months	20 days	7 months	6 months to 15 years
Perinatal history	Unremarkable	Unremarkable	Unremarkable	Unremarkable	Unremarkable	Unremarkable
Family history	Negative	Positive	Positive	Negative	Negative	Positive
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Not specified	Not specified	Autosomal dominant
Seizures	Absence, Atonic to GTCS	Myoclonic seizures evolving to tonic and GTCS	Myoclonic seizures	Yes (not specified)	Yes (not specified)	Absence, GTCS
EEG	Focal and generalized spike waves	Lennox–Gastaut pattern	Mild background slowing	Normal	Normal	Generalized spike-wave complexes
Paroxysmal nonkinesigenic dyskinesia	+	–	–	+	+	+
MRI	Cerebellar and spinal tract atrophy	Cerebellar atrophy	Cerebellar atrophy	Normal	Normal	Normal
KCNMA1 mutation	c.1372C>T (homozygous)	c.2026dupT (homozygous)	c.2026dupT (homozygous)	c.2650G>A (heterozygous)	c.3158A>G (heterozygous)	c.1301A>G (heterozygous)
Protein	p.Arg458Ter	p.(Try676Leufs*7)	p.(Try676Leufs*7)	p.Glu884Lys	p.Asn1053Ser	p.Asp434Gly
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	*de novo*	*de novo*	Autosomal dominant

EEG: electroencephalography; GTCS: generalized tonic–clonic; MRI: magnetic resonance imaging

idiopathic epilepsy (5). While the population frequency of the variant in the *CACNAH1* gene was 0.0012/39 according to the EXAC, it was classified as a variant of unknown significance in the dbSNP database (Table 2).

TABLE 2. Annotations, frequency, and bioinformatic prediction scores of variants in select candidate genes

Gene	*KCNMA1*	*CACNA1H*
Position [hg19]	10:78846314	16:1252303
Nukleotit change	c.1372C>T	c.1853C>T
Protein change	p.Arg458Ter	p.Pro618Leu
Zygosity	Hom	Het
EXAC frequency	–	0.001201
PhyloP score	2.672	4.985
PhyloP prediction	Conserved	Conserved
SIFT score	–	(0.01)
SIFT prediction	–	Deleterious
Polyphen2 score	–	(0.991)
PolyPhen prediction	–	Probably_damaging
Mutation taster score	1	0.999
Mutation taster prediction	Disease causing	Disease causing
dbSNP ID	–	rs60734921
Read depth	170	47
Transkript	NM_001161353	NM_021098.2
Exon	11/28	9/35

DISCUSSION

Large-conductance calcium-sensitive BK channels are one of the potassium channels that hyperpolarize the neurons and are encoded by *KCNMA1* (6,7). Reportedly, mutations in *KCNMA1* have been identified in clinical cases of epilepsy and paroxysmal nonkinesic dyskinesia (3,8). In addition, a study functionally investigated the *D434G* mutation of *KCNMA1* by the patch clamp method and was found to be associated with the gain of function (3). Some studies have suggested that the gain of function at BK channels resulted in the faster and rapid repolarization of the action potential in the syndrome mechanism, accounting for an increase in the excitability of the brain (3,9). Moreover, Sausbier et al. (2,10) reported that *KCNMA1*$^{-/-}$ mice exhibited abnormal eye-blink reflex, abnormal locomotion, and abnormal motor coordination. Thus, either gain- or loss-of-function mutations might result in the disease phenotype. Furthermore, both the gain- and loss-of-function phenotype can be observed in other channelopathies such as *KCNA2*, *GRIN1*, and *DEAF1* gene mutations.

Recently, Tabarki et al. (4) reported a different phenotype of the same gene. In their study, the siblings were homozygous for a frameshift variant in *KCNMA1* and had tractable myoclonic seizures starting around the age 1, which later evolved into tonic and GTCS type. In addition, they had a severe developmental delay, but no dyskinesia, and their brain MRI revealed cerebellar atrophy that was not a feature of previously reported heterozygous mutations (4). Table 1 summarizes the clinical and characteristic features of patients with *KCNMA1* mutations. Unlike previous reports, our case had corticospinal and tegmental tract involvement

besides cerebellar atrophy, which could be attributed to the possible progressive course of the disease attributive to the advanced age of our patient. In addition, our patient had dyskinesia and dystonic movements, which were not known for biallelic mutations. Reportedly, the variant found in the *CACNA1H* gene could also contribute the proband's phenotype; however, the variant is a known single nucleotide polymorphism that was considered a risk factor for generalized epilepsy but not the dyskinesia phenotype (5). In conclusion, this report presents a unique case of a patient who manifested both phenotypes of the gain- and loss-of-function mutations of *KCNMA1* (dyskinesia, epilepsy, and cerebellar atrophy) and had tegmental and spinal tract atrophy that has not been reported to date. Thus, electrophysiological analyses and expression studies are warranted to gain an insight into functional consequences of biallelic mutations of the *KCNMA1* gene. Overall, this study highlights the importance of using exome sequencing techniques for expanding the disease phenotypes to reveal the disease pathogenesis.

Conflict of Interest: No conflict of interest was declared by the authors.

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