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A familial case of *CAMK2B* mutation with variable expressivity

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Abstract

Variants in CAMK2-associated genes have recently been implicated in neurodevelopmental disorders and intellectual disability. The clinical manifestations reported in patients with mutations in these genes include intellectual disability (ranging from mild to severe), global developmental delay, seizures, delayed speech, behavioral abnormalities, hypotonia, episodic ataxia, progressive cerebellar atrophy, visual impairments, and gastrointestinal issues. Phenotypic heterogeneity has been postulated. We present a child with neurodevelopmental disorder caused by a pathogenic *CAMK2B* variant inherited from a healthy mother. A more mildly affected sib was determined to have the same variant. Monoallelic mutations in *CAMK2B* in patients have previously only been reported as de novo mutations. This report adds to the clinical phenotypic spectrum of the disease and demonstrates intrafamilial variability of expression of a *CAMK2B* mutation.

Keywords

CAMK2B, variable expression, familial mutation, neurodevelopmental disease, seizures

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Introduction

Calcium/calmodulin-dependent protein kinase II (CAMK2) has been shown to be important in neuronal synaptic plasticity and learning processes, particularly for regulation of the glutamatergic signaling pathway.[1] Variants in CAMK2-associated genes have recently been implicated in neurodevelopmental disorders and intellectual disability.[1–3] CAMK2 has four subunits (α, β, γ, and δ) encoded by different genes (*CAMK2A, CAMK2B, CAMK2G*, and *CAMK2D*, respectively).[2,3] De novo heterozygous variants have been identified in patients in three of these genes: *CAMK2A, CAMK2B*, and *CAMK2G*, with clinical manifestations ranging from mild to severe intellectual disability, global developmental delay, seizures, delayed speech, behavioral anomalies, hypotonia, episodic ataxia, progressive cerebellar atrophy, visual impairments, and gastrointestinal (GI) issues.[1,2] Defects in *CAMK2D* have not yet been definitively linked to disease. A possible pathogenic variant in *CAMK2D* has been reported in a patient with congenital hyperinsulinism—a very different phenotype from that seen in patients with defects in the other three subunits.[4] In addition, a patient with homozygous nonsense variant (c.85C>T;p.Arg29Ter) in *CAMK2A* inherited from consanguineous parents has been reported in two siblings with severe neurodevelopmental symptoms.[5]

The pathophysiology related to CAMK2 deficiency has been suggested to be a result of disruption of CAMK2 autophosphorylation and impairment of neuronal migration.[1,2] In addition, phenotypic heterogeneity of these genes has been postulated from mouse studies in which the brains of animals expressing different variants in *CAMK2B* displayed disrupted neuronal migration in variable degree.[1] Here, we present a child with a neurodevelopmental disorder associated with a maternally inherited, monoallelic *CAMK2B* variant born to a phenotypically normal mother. This report expands the clinical phenotype and inheritance pattern associated with *CAMK2B* variants and underscores the potential impact of intrafamilial variability in the expression of a pathogenetic variant in this gene.

Case report

A 3-year-old female of European descent presented for evaluation of complex focal seizures and global developmental

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Table 1. Phenotypic comparisons of known cases of heterozygous c.85C>T CAMK2B mutation.

Clinical feature	Patient (proband)	Sister	Mother	Individual 15[a]
Age of symptom onset	11 months	ND	NA	Unknown
Gender	Female	Female	Female	Female
Ethnicity	European	European	European	Unknown
Mutation	Heterozygous c.85C>T p.Arg29Ter Maternally inherited	Heterozygous c.85C>T p.Arg29Ter Maternally inherited	Heterozygous c.85C>T p.Arg29Ter Uncertain inheritance	Heterozygous c.85C>T p.Arg29Ter De novo
Other genetic findings	None	ND	ND	Parentally inherited heterozygous VUS in *ALOXE3, RAG1*, and *TLR1*
Global developmental delay	+Severe	−	−	+Mild
Seizures	+	−	−	+
EEG abnormality	+	ND	ND	ND
Visual impairments	−	+	−	−
Speech delay	+	+	−	+
Abnormal affect/emotion regulation	+	−	−	−
Gross motor problems	−	+	−	−
Gastrointestinal abnormalities	−	−	−	−

ND: not described; NA: not applicable; VUS: variant of unknown significance; EEG: electroencephalography.
[a]Individual 15 as described in Kury et al.[1]

delay, with a prominent delay in expressive speech. She displayed poor impulse control, behavioral outbursts, and general difficulty with regulating emotions. The patient is the second child of non-consanguineous, healthy parents, born at 40 weeks gestation to a 27-year-old, gravida 2, para 1 mother. No prenatal or delivery complications were noted. Birth weight was 2.8 kg (~15th centile), and birth length was 46.4 cm (~6th centile). Family history was significant for a maternal first cousin with a history of febrile seizures, now resolved, and a 6-year-old sister with a history of speech delay and learning difficulties, but no seizures.

The patient developed focal afebrile seizures with alteration of awareness with or without secondary generalization beginning at 11 months of age. They usually started with deviation of upward gaze followed by cyanosis and rhythmic facial and body jerks lasting less than 3 min and occurring 1 to 2 times per week. Seizures lasting over a minute left the patient fatigued and sometimes with right-sided weakness. Current therapy includes levetiracetam 350 mg twice a day, vitamin B6 50 mg daily, and topiramate 30 mg twice a day with much lower frequency of her seizures. She has previously failed therapy with oxcarbazepine and lacosamide, which were discontinued due to side effects and lack of efficacy. An electroencephalogram showed scattered single sharp waves that occurred from the left temporal area with occasional spread of these into the left central region. Brain magnetic resonance imaging (MRI) was normal. Early developmental milestones were slightly delayed, including crawling at 9 to 10 months, walking at 16 to 17 months, and first word at 1 year of age. Subsequent speech was significantly delayed, mainly in expressive speech. Physical examination was notable for bilateral epicanthal folds but no other dysmorphic features. She had no visual or GI abnormalities, and muscle tone was normal. A hearing evaluation was unremarkable.

Combined comparative genomic hybridization and single nucleotide polymorphism (CGH + SNP) array analysis, and a comprehensive epilepsy gene panel containing 87 genes (GeneDx, Test code #523) were all normal; therefore, whole exome sequencing (WES) was performed (GeneDx, Gaithersburg, MD, USA). WES identified a maternally inherited, heterozygous, pathogenic variant in the *CAMK2B* gene (NM_001220.4; c.85C>T;p.Arg29Ter). No other clinically relevant gene variants were identified. Following this discovery, the patient's 8-year-old sister underwent targeted variant testing and was found to be heterozygous for the same pathogenic variant in the *CAMK2B* gene. The sister's clinical history was significant for speech difficulties for which she attends speech therapy once per week, minimal balance issues, and mild myopia.

Discussion

CAMK2B-related disorder (MIM: 607707) is a non-dysmorphic neurodevelopmental condition that has been reported previously in several patients with de novo heterozygous mutations in the *CAMK2B* gene. Phenotypic heterogeneity has been reported in patients from different families, including variable speech delay, learning disability, abnormal behavior, gross motor delay, hypotonia, mild dysmorphic

facial features, visual problems, GI abnormalities, microcephaly, seizures, and abnormal brain MRI.[1,2] Studies with mouse models have shown that both *Camk2a* and *Camk2b* have distinct but partial overlapping function in the brain and are important for learning and synaptic plasticity.[6–10] In utero shRNA knockdown studies of endogenous *Camk2b* and overexpression of mutant *Camk2b* constructs in mouse embryos have demonstrated variable disturbance of neuronal migration. Thus, both adequate dosage of CAMK2B and normal function are crucial for normal neurodevelopment and migration.[1]

Previously reported *CAMK2B* mutations have been de novo and monoallelic, consistent with autosomal dominant inheritance with decreased reproductive fitness. The c.85C>T;p.Arg29Ter nonsense mutation observed in our patient has previously been reported as a de novo mutation in a patient with similar symptoms to our patient, including mild intellectual disability, delayed speech and language development, and seizures (see Table 1 for a comparison of symptoms).[1] However, inheritance from an apparently healthy parent is unique to our patient whose mother is intellectually normal, having attended 2 years of college, works independently, and reports no neurological symptoms. In addition, our patient's sister has relatively mild phenotype, further highlighting the intrafamilial variability of expression in this pedigree and the need for functional studies of mutations in this gene.

Conclusion

In summary, this case adds to the phenotypic spectrum associated with *CAMK2B* mutations and provides evidence of intrafamilial variable expression of disease symptoms. While previous pathogenic mutations in this gene have been reported to be de novo and monoallelic, our patient had a maternally inherited c.85C>T;p.Arg29Ter mutation from an apparently healthy mother. In addition, a sister with the same variant had only mild symptoms. Thus, testing parents of children with this defect, even if healthy, is important in order to assess genetic risk and diagnosis for other family members. In addition, it is important to note that, as of this writing, the *CAMK2A* and *CAMK2B* genes are not included in available comprehensive epilepsy gene panels, and thus a reflex to exome sequencing is justified if diagnosis is not made on evaluation of the more focused number of genes.

Authors' note

The contents of this case report are solely the responsibility of the authors and do not necessarily represent the official views of National Human Genome Research Institute (NHGRI) or National Institutes of Health (NIH).

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Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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