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Infantile-Onset Paroxysmal Movement Disorder and Episodic Ataxia Associated with a *TBC1D24* Mutation

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Abstract

Mutations that disrupt the *TBC1D24* presynaptic protein have been implicated in various neurological disorders including epilepsy, chronic encephalopathy, DOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures) syndrome, nonsyndromic hearing loss, and myoclonus. We present the case of a 22-month-old male with infantile-onset paroxysmal episodes of facial and limb myoclonus. The episodes were linked to biallelic variants in exon 2 of the *TBC1D24* gene that lead to amino acid changes (c.304C >T/p.Pro102Ser and c.410T > C/p.Val137Ala), each variant being inherited from a parent. Follow-up imaging in adolescence revealed widened right cerebellar sulci. We discuss the evolving landscape of *TBC1D24* associated phenotypes; this case adds to a growing body of evidence linking this gene to movement disorders in children.

Keywords

- *TBC1D24*
- genetics
- infancy
- cerebellum
- episodic ataxia
- myoclonus

Introduction

TBC1D24 encodes a member of the family of Tre2-Bub2-Cdc16 (TBC) domain-containing proteins.[1] This family helps to coordinate proteins of the Ras superfamily, including Rab proteins and GTP (guanosine triphosphate) ases, in the regulation of exo- and endocytosis. Mutations in *TBC1D24* are associated with an expanding list of neurological disorders.[2] This list includes various epilepsies and epileptic encephalopathies, DOORS (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures) syndrome, several nonsyndromic deafness syndromes, and several newly-described conditions involving myoclonus with and without seizure activity. This report focuses on an unusual neurological presentation associated with new *TBC1D24* variants.

Case Study

This healthy and developmentally normal boy was born after an uneventful pregnancy and term birth. Family history was positive for childhood seizures or paroxysmal events of unknown significance in his maternal cousin, grandfather,

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and great-grandfather, none of which lasted into adulthood. The child's maternal great-grandparents were consanguineous.

The patient first presented at our institution at the age of 22 months with a 2-month history of paroxysmal movements, mostly precipitated by fever or fatigue. These movements were characterized by facial myoclonus involving a single eyelid and generalizing to the entire face (►**Video 1**), occasionally accompanied by alternating upper and lower limb tremors. These episodes could last up to 45 minutes and responded rapidly to 5 mg intrarectal diazepam. Repeated electroencephalograms (EEGs) and a brain magnetic resonance imaging (MRI) performed at 21 months were normal. No episodes were captured during the initial EEGs; however, by 30 months, these paroxysmal episodes had evolved into left sided ataxic episodes involving sudden flexion of the left wrist, tremor of the left upper limb, confusion, and diminished speech. The diminished speech was difficult to assess given the patient's age and was thought to be a form of aphasia, but could not be clearly distinguished from mutism or anarthria. One of these events was recorded on EEG and correlated to a physiological mu rhythm in the right central–parietal region that was present prior to, during, and shortly after the episode. The episodes could not be provoked in the patient.

Video 1

Video of upper and lower limb tremors during clinic visit around 22 months of age. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0039-1688410.

An extensive neurometabolic workup (►**Table 1**) including blood, urine, and cerebrospinal fluid (CSF) analyses revealed no abnormalities (►**Table 2**). The patient was started on a regimen of gabapentin and clobazam as maintenance therapy, along with clonazepam or rectal diazepam as rescue treatment. He responded well initially with a significant decrease in the frequency of episodes. Over the following 2 years, however, the abnormal movements resumed, occurring up to multiple times per week. The introduction of acetazolamide at 6.25 mg/kg/day administered twice a day led to a substantial improvement in the frequency of the attacks.

During subsequent years, genetic investigations were performed. After sequencing of *KCNA1, SLC2A1, CACNA1A*, *CACNB4*, *SLC1A3*, *FGF14*, *ADCY5*, *PRRT2*, *ATP1A3*, *NOL3*, *P2RX7*, and *PNKD* all returned negative, the patient was found to have biallelic variants in exon 2 of the *TBC1D24* gene that lead to amino acid changes (c.304C > T/p.Pro102Ser inherited from the mother; c.410T > C/p.Val137Ala inherited from the father). These variants were confirmed using Sanger's sequencing. The p.Pro102Ser variant is extremely rare in the ExAC database (1 out of 118,938 individuals), while the p. Val137Ala variant is entirely absent from polymorphism databases (including ExAC, 1,000 Genomes, Exome variant server [EVS]). The p.Pro102Ser variant was not found in the maternal grandfather who was known to have had childhood seizures. Other family members with childhood seizures were not available for DNA sequencing.

On the same drug regimen, the patient who was 1- year-old at the time of the discovery of these variants continued to experience these paroxysmal episodes once a month. A year later, he was briefly hospitalized at an outside institution for a prolonged myoclonic episode involving the left upper limb. An MRI at the time revealed a widening of the right-sided cerebellar sulci with gliosis seen as a hypersignal on T2-weighted imaging, along with enlarged Virchow–Robin spaces bilaterally (►**Fig. 1**). After renewed discussions with the family, the patient was started on carbamazepine. On a regimen of 300 mg twice a day (13.2 mg/kg/day), he remained episode-free for 11 months. Shortly after the onset of a viral upper respiratory infection, he presented a breakthrough focal clonic seizure of the left arm evolving to a bilateral seizure, and, shortly thereafter, a similar event involving the right arm without generalization. Blood levels of carbamazepine were within normal ranges (6.8 mg/L, norm: 4–12). The doses of carbamazepine were left unchanged, and the patient has not presented further episodes since. He is currently a cognitively normal and socially well-adapted 14-year-old.

Discussion

Our patient's clinical presentation involves a complex movement disorder associated with compound heterozygous variants of *TBC1D24*. These variants both occur in functional domains, near clusters of other known pathogenic variants, and involve changes in conserved amino acid sequences. While it is difficult to definitely ascertain that these variants are pathogenic, evidence from bioinformatic analyses suggest that these variants are likely not benign. The p.Pro102-Ser variant was predicted to be damaging by Polyphen-2[3] and MutationTaster[4] but not by SIFT[5] and PROVEAN.[6] The p. Val137Ala variant was predicted to be damaging by Polyphen-2, MutationTaster, and PROVEAN but not by SIFT. Using CADD,[7] both variants were found to be among the top 1% of most deleterious substitutions possible in the human genome. Combining these insights from bioinformatics with the clinical insight that many compound heterozygous variants in *TBC1D24* have been associated with a clinical picture of infantile-onset paroxysmal myoclonus similar to that seen in our patient, we consider these variants as likely pathogenic.[8] Nerve conduction studies and electromyography (EMG) with back-averaging, which could have further characterized the movement disorder, were discussed but could not be performed due to logistical difficulties.

Thanks to advances in genetic sequencing, there has been a remarkable increase in the number of symptoms and phenotypes associated with *TBC1D24* mutations. These include an important number of epilepsies and epileptic encephalopathies, DOORS syndrome, several nonsyndromic deafness syndromes, and clinical syndromes involving multifocal myoclonus as a central feature.[2] Epileptic syndromes in the setting of *TBC1D24* mutations are phenotypically

Table 1 Neurometabolic workup

Specimen	Test	Result	Reference range
Blood			
	Chemistry	Within normal limits	
	Lactate	1.4 mmol/L	1.0–1.9
	Pyruvate	94 mol/L	50–105
	Lactate: pyruvate ratio	14.9	12–18
	Ammonium	40 mol/L	11–35
	Zinc	20.9 mol/L	10–23
	Ceruloplasmin	0.55 g/L	0.22–0.61
	Copper	21.7 mol/L	12.5–23.6
	Lipid panel	Within normal limits	
	Erythrocytes	4.9 T/L	3.9–5.3
	Hemoglobin	133 g/L	115–135
	Platelets	506 G/L	168–392
	Leucocytes	11.4 G/L	5–14.5
	TSH	1.9 mU/L	0.4–4
	Nonesterified fatty acids (NEFA)	0.7 mmol/L	0.3–0.8
	Acylcarinitine profile	Unremarkable	
	Complete amino acid profile	Glutamine at the upper limit of normal, otherwise unremarkable	
	Antivoltage gated K+ channel antibody (anti-VGKC)	Negative	
	Borrelia burgdorferi serologies (IgM, IgG)	Negative	
CSF			
	Appearance	Clear	
	Erythrocytes	16 M/L	
	Leucocytes	< 1 M/L	
	Glucose	2.9 mmol/L	2.8–4.0
	Sodium	144 mmol/L	142–154
	Potassium	2.9 mmol/L	2.5–3.5
	Proteins	0.22 g/L	0.15–0.45
	Lactate	1.3 mmol/L	0.0–2.8
	Pyruvate	97 mol/L	
	Biogenic amines	Biopterin at lower limit of normal, otherwise unremarkable	
Urine			
	Organic aciduria	negative	
	Urinalysis	Normal	

Abbreviations: CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M; TSH, thyroid stimulating hormone.

Table 2 Results of variant prediction software

Prediction technique	Pro102Ser variant (maternal)	Val137Ala variant (paternal)
Polyphen-2	Probably damaging, score 1.00 (sensitivity = 0.0, specificity = 1.0)	Probably damaging, score 0.960 (sensitivity = 0.75, specificity = 0.95)
SIFT	Tolerated (score = 0.086, cut-off = 0.05)	Tolerated (score = 0.187, cut-off = 0.05)
PROVEAN	Neutral (score = 2.05, cut-off = 2.5)	Deleterious (score = 2.5, cut-off = 2.5
MutationTaster	Disease-causing	Disease-causing
CADD (PHRED-like, scaled) score	24.1	22.6

Abbreviations: CADD, Combined Annotation Dependent Depletion; PROVEAN, Protein Variant Effect Analyzer; SIFT, Sorting Intolerant from Tolerant.

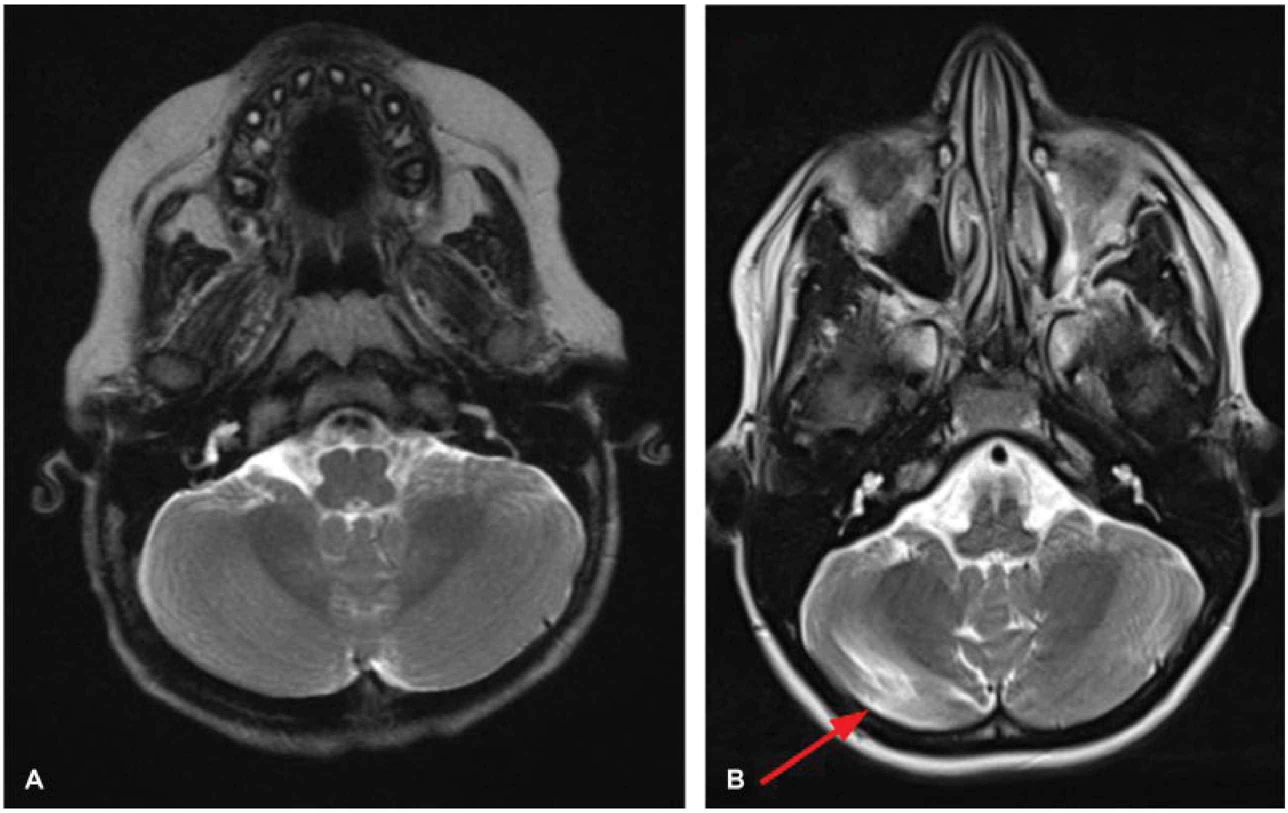

Fig. 1 Axial T2-weighted MRI at **(A)** 21 months and **(B)** 11 years of age. The latter MRI shows a widening of the sulci of the right cerebellum, with gliosis, indicated by the arrow. MRI, magnetic resonance imaging.

heterogeneous and, according to a recent review, no clear genotype–phenotype correlation has yet emerged.[2] In addition to phenotypic pleiotropy in unrelated patients with the same *TBC1D24* mutations, most patients studied to date are compound heterozygotes, which makes the study of individual mutations difficult.[2] Several distinct clinical entities featuring epilepsy have been reported. The spectrum ranges from infantile epilepsy without long-term neurodevelopmental sequelae, to severe forms of infantile encephalopathy with epilepsy, resulting in profound intellectual disability and early death. The most common clinical profile of *TBC1D24*-related epilepsy seems to be that of treatment-refractory infantile-onset myoclonic epilepsy.[2]

Multifocal myoclonus with and without EEG correlation has been reported in patients with *TBC1D24* mutations. Myoclonic attacks were described in two families with *TBC1D24*-related epilepsy.[9,10] Doummar et al found novel *TBC1D24* mutations in a patient with cortical multifocal myoclonus, gait ataxia, and mild intellectual disability. Their patient was also found to have a cerebellar sequela on T2-weighted imaging, similar to that observed in our patient.[11] Another report described new *TBC1D24* mutations in siblings with multifocal myoclonus, cerebellar atrophy, and signaling abnormalities yet without EEG correlation.[12] Finally, a Chinese boy was reported to have paroxysmal episodes of focal myoclonus affecting eyelids and limbs, without EEG correlation, and was found to have novel compound heterozygous mutations of *TBC1D24*.[13] These episodes were precipitated by fever or fatigue and were associated with ataxia and mild intellectual disability.

Our case adds to the understanding of the myoclonus phenotype associated with *TBC1D24* variants by presenting a unique association of myoclonus, tremors, and possible aphasia without intellectual disability or EEG abnormalities. It also adds to a list of cases involving cerebellar involvement with or without clinically significant ataxia and cerebellar syndromes.[11,12,14,15] While the exact clinical significance of these cerebellar findings remains unclear, the increasing number of reports of cerebellar anomalies on imaging in patients with *TBC1D24*-related disorders is certainly worth noting.

In summary, our case report expands the spectrum of manifestations associated with *TBC1D24* mutations. The complex movement disorder described in our otherwise healthy patient could represent a suggestive feature. Further and larger studies, both clinical and biological, are needed to confirm the role of *TBC1D24* in childhood-onset movement disorders and seizures.

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Conflict of Interest
None.

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