A Rare Cause of Paroxysmal Movement Disorder Associated with *TBC1D24 Gene* Mutation in Two Siblings

Dear Editor,

TBC1D24 (TBC1 domain family member 24) gene mutation is inherited as autosomal recessive or compound heterozygous. The *TBC1D24* gene encodes the protein, which is the 24th member of the Tre2-Bub2-Cdc16 (TBC) domain subgroup that interacts with the guanosine triphosphatase (GTPase). TBC group proteins activate some GTPase proteins that regulate synaptic vesicle transport, cellular oxidative stress response, and proteins that activate Rab (Ras-related protein in the brain) molecules. It has been reported that the *TBC1D24* gene plays a role in cerebral cortex development and presynaptic neurotransmission.[1,2] In the literature, *TBC1D24* gene mutation-related disorders are mostly associated with epileptic encephalopathies such as familial infantile myoclonic epilepsy (FIME), early infantile epileptic encephalopathy 16 (EIEE16), partial migratory seizures, autosomal dominant/autosomal recessive non-syndromic familial hearing losses, and DOORS syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation).[3]

However, studies, which have reported the relationship between paroxysmal movement disorder and *TBC1D24* gene mutation, are insufficient. In this article, we would like to describe two siblings with c.457G>A (p. Glu153Lys) pathogenic variant in the *TBC1D24* (NM_001199107.2) gene who presented with paroxysmal polymyoclonus and were followed up with epileptic encephalopathy since neonatal period.

Two siblings who were born at 38 gestational weeks, had no problems in the prenatal, natal, and postnatal period, and had first-degree consanguinity between mother and father were presented. Written consent was obtained from the parents.

The first patient is a 6-year-old male who was referred with dysarthria and involuntary polymyoclonus in the arms, hands, head, and neck (resembling whole-body tremor). It was learned that he had myoclonic jerks and twitching attacks in the mouth, eyes, arms, and feet from the first week of birth and the myoclonus was triggered by fever, fatigue, infection, and hunger. He was followed up as epilepsy from the neonatal period, so levetiracetam, sodium valproate, and clobazam were started. On physical examination, he was conscious, oriented, and cooperative, his intelligence level was low compared to his peers, patellar deep tendon reflexes (DTR) were normoactive, muscle strength was 5/5, and intentional tremor was observed. He had hypermetropia and hearing loss. There was no dystonia, spasticity, or hypertonicity during the myoclonus period. There were no epileptiform discharges except for background abnormality on the electroencephalogram (EEG) when the patient had active myoclonus. In addition, there were no epileptiform abnormalities in all EEGs obtained from the neonatal period [Figure 1]. He experienced myoclonus attacks 3–4 times a year, lasting 48–72 h, triggered by hunger, fever, and fatigue. He was admitted to the pediatric intensive care unit as status epilepticus many times and a midazolam infusion was started.

The second patient is a 12-year-old girl who was referred with status epilepticus due to fever during the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (COVID-19) infection. She had preserved consciousness polymyoclonus for 72 h in the hand, arm, head, and neck (resembling whole-body tremor). She was followed up with the diagnosis of epilepsy from the neonatal period and used phenobarbital and levetiracetam. There were no epileptiform discharges except background abnormality in all EEGs obtained from the neonatal period. On physical examination, she had an intentional tremor and generalized myoclonus, and other physical examinations were completely similar to her brother's. She had hypermetropia and hearing loss. Also, there was no onychodystrophy or osteodystrophy. The patient's complaints were triggered by insomnia, fatigue, and fever, and lasted 24 h. When the patient presented with these complaints, midazolam infusion was started in the pediatric intensive care unit as status epilepticus.

Complete blood tests, routine biochemistry tests (creatinine, urea, AST/ALT, creatine kinase, B12, TSH, f-T4, f-T3), basal metabolic tests (Tandem-mass, urinary organic acid (UOA), serum amino acids, very-long-chain fatty acids, biotinidase activity, homocysteine) were all normal in both patients. Both of the two siblings' electrocardiography (ECG) and electromyography (EMG) were normal, but P100 wave latency could not be obtained bilaterally in both eyes in the visual evoked potential (VEP) test. There was no mutation detected in both *SCN1A* and *SLC2A1* genes. Brain magnetic resonance imaging (MRI) of the two siblings demonstrated cerebellar atrophy accompanied by mild cortical atrophy [Figure 2]. Carbamazepine was started, and other medications were

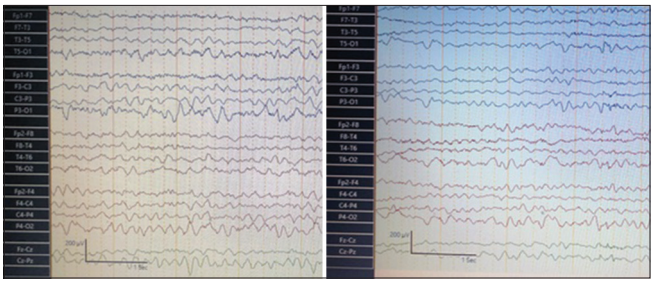

Figure 1: Patient one and two. The EEGs are wakefulness EEGs and show us 5–6 Hz theta waves. Therefore, there are only background abnormalities without epileptiform discharges

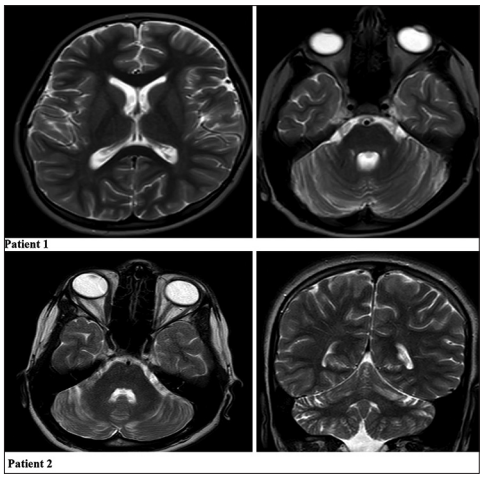

Figure 2: Cerebellar and mildly cortical atrophy are noticed in the brain MRI

discontinued for both siblings. No new attacks have been seen in the patients after carbamazepine during the first year.

Next-generation sequencing test was performed using a custom QIAGEN- QIAseqTM Targeted DNA Panel (QIAGEN, Hilden) that includes 34 genes named *SCN1A, SCN2A, SCN9A, SCN1B, GABRG2, SCN3A, TAP1, BRD2, EFHC1, GABRA1, EPM2A, KCTD7, KCNQ3, KCNJ10, SLC2A1, KCNK9, GABRB3, LGI1, TBC1D24, DEPDC5, TBC1D22A, ATP1A2, GRIN2A, CACNA1A, CHRNA2, CHRNA4, CHRNB2, KCNT1, KCNA1, KCNMA1, KCNMB3, KCNQ2, KCNQ3,* and *STXBP1*. As a result of mutation analyses, we found homozygous c.457G>A (p. Glu153Lys) pathogenic mutation in the *TBC1D24* (NM_001199107.2) gene. The mutation was confirmed by Sanger sequencing as homozygous in the probands and heterozygous in both the healthy parents [Figures 3 and 4].

Figure 3: The mutation analysis revealed a homozygous *amino* acid change at codon 153 in the second exon of the *TBC1D24* gene in two patients

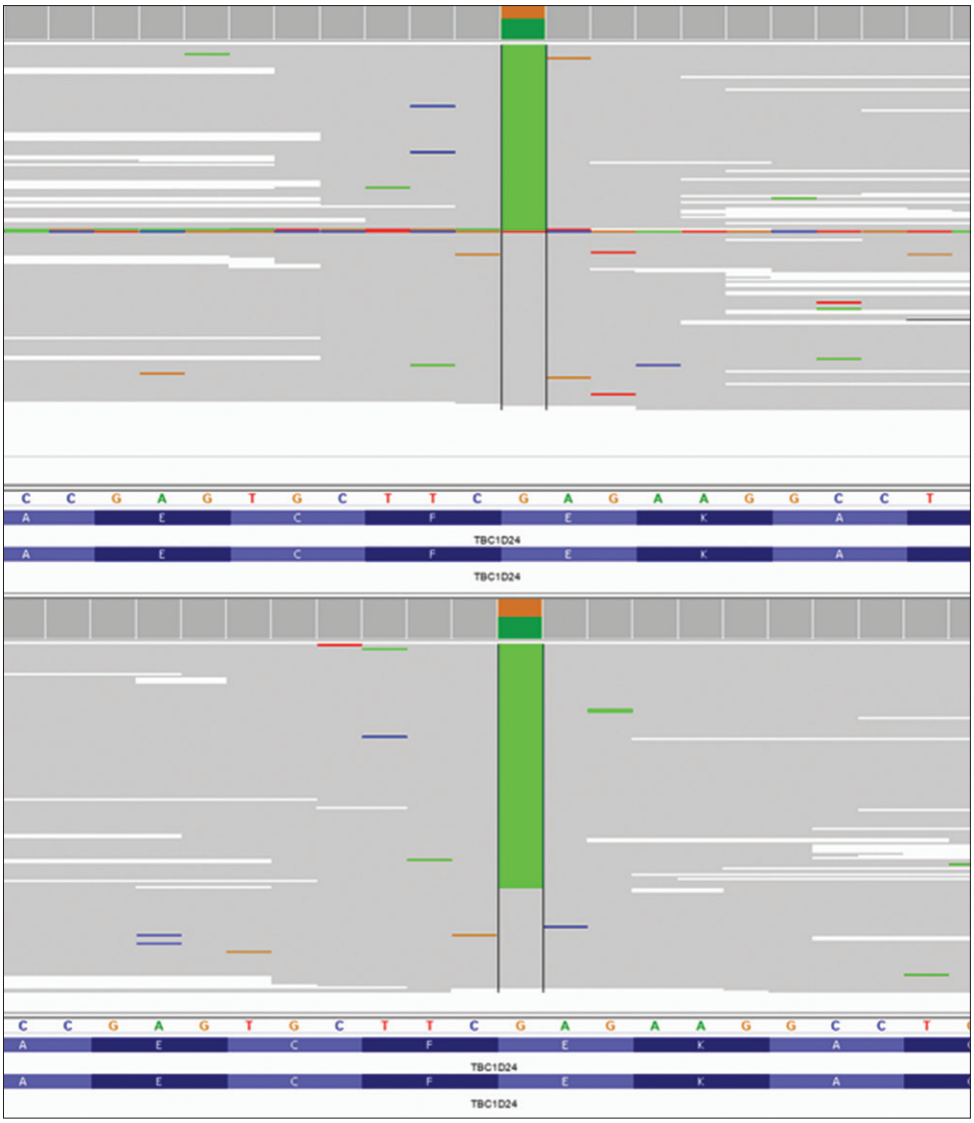

Figure 4: The parents were both heterozygous for the p.Glu153Lys mutation in the *TBC1D24* gene

In this article, two siblings who had a pathogenic variant in the *TBC1D24* gene and presented with polymyoclonus in the whole body with preserved consciousness, which appeared after the first week of birth were reported. It was detected as a homozygous c.457G>A (p. Glu153Lys) pathogenic variant in the exon two regions of the *TBC1D24* gene in the two siblings, and the parents were heterozygous and healthy. In previously published articles, it was emphasized that *TBC1D24*-related clinical disorders are associated with myoclonic epilepsies, epileptic encephalopathies, generalized epilepsies, or DOORS syndrome. However, similar to our patients, the cases presented with preserved consciousness polymyoclonus with normal EEG and cerebellar atrophy on the brain MRI have been reported in the literature. Zhang *et al*.[4] presented two patients who had been detected with a pathogenic variant in the *TBC1D24* gene, were followed up with epileptic encephalopathy from early infancy with normal EEG, and used multiple epileptic drugs, but whose seizures were still not under the control. We consider that many of these conditions might be paroxysmal movement disorders. Cordani *et al*.[5] reported a case evaluated as epileptic encephalopathy at five months of age and treated with multiple epileptic drugs but later it was considered as alternating hemiplegia. Zimmern *et al*.[6] presented a case similar to our patient, who presented with polymyoclonus in which consciousness was preserved from the early infancy period, had normal EEGs, accompanied by cerebellar atrophy in brain MRI, and later was evaluated as paroxysmal myoclonus and episodic ataxia. Duru *et al*. and Guven and Tolun[7,8] presented a case with dystonic attacks that was detected as a pathogenic variant in the *TBC1D24* gene, considered as a movement disorder. Similar to our patients, Ngoh *et al*.[9] reported a patient with a *TBC1D24* gene mutation who had multifocal polymyoclonus including his eyes, lips, and face, and cerebellar atrophy in the brain MRI. Harvey *et al*.[10] reported that *TBC1D24* gene-related disorders are included in the paroxysmal exercise-induced dystonia group. In recent

studies, disorders related to the *TBC1D24* gene mutation were included in the group of epilepsy and paroxysmal movement disorders, along with other mutations of *CACNA1A, SCN1A, ATP1A2 CHRNA4, KCNA1,* and *SLC16A2*.[11]

As a result, a paroxysmal movement disorder caused by the *TBC1D24* gene mutation should be considered in the etiology of patients with prolonged polymyoclonus, including eyes, face, or lips during the neonatal period, who have polymyoclonus with preserved consciousness, normal EEG, and cerebellar atrophy in the brain MRI.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 25-May-2022 **Revised:** 20-Feb-2023 **Accepted:** 27-Feb-2023
Published: 24-Apr-2023

DOI: 10.4103/aian.aian_465_22