

KMT2B-Related Dystonia: Challenges in Diagnosis and Treatment

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Established Facts

- Mutations of *KMT2B* cause a progressive and severe complex hereditary movement disorder, which has onset in childhood.
- The main clinical key feature of the disease is progressive dystonia, which interferes with activities of daily living in a progressive manner.

Novel Insights

- An undescribed de novo nonsense mutation in the *KMT2B* gene is reported in a Turkish boy with progressive dystonia.
- Deep brain stimulation appears to be a unique treatment solution for complex movement disorders resistant to aggressive medical therapy.

Keywords

KMT2B · Childhood dystonia · Movement disorder · Exome sequencing · Novel mutation

Abstract

In this study, we report the first known Turkish case of a novel nonsense mutation c.2453dupT (p.M818fs*28) in the *KMT2B* (NM_014727.2) gene diagnosed in a male patient with *KMT2B*-related dystonia (*DYT-KMT2B*, *DYT-28*, *Dystonia*28*), which is a complex, childhood-onset, progressive, hereditary dystonia. The patient, who is followed up from 9 to 13 years of age, had dysmorphic features, developmental

delay, short stature, and microcephaly, in addition to focal dystonia and hemichorea (in the right and left lower extremities). Generalized dystonia involving bulbar and cervical muscles, in addition to dystonic cramps, myoclonus, and hemiballismus, were also observed during the course of the follow-up. While he was able to perform basic functions like eating, climbing stairs, walking, and writing with the aid of levodopa and trihexyphenidyl treatment, his clinical status gradually deteriorated secondary to progressive generalized dystonia in the 4-year follow-up. Deep brain stimulation has been shown to be effective in several patients which could be the next preferred treatment for the patient.

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Introduction

KMT2B-related dystonia, which is also known as DYT-28, DYT-*KMT2B*, Dystonia 28, and OMIM 617284, gained its place in the literature following the first reports concerning the phenotype-genotype relationship in 2016, and since then, approximately 80 cases have been reported [Abela and Kurian, 2018]. *KMT2B*, which is located in 19q13.12, plays a role in neuronal differentiation, the activation of neuronal maturation gene programs. Dystonia candidate genes are expressed in all tissues, including the brain, with the highest rate of expression in the cerebellum [Barbagiovanni et al., 2018]. Mutations in *KMT2B* cause a progressive and severe complex hereditary movement disorder with onset in childhood [Abela and Kurian, 2018; Kawarai et al., 2018; Carecchio et al., 2019; Zech et al., 2019]. Dystonia is severe and interferes with activities of daily living. Although the disorder is called *KMT2B*-related dystonia, clinical features include other abnormal movements like dyskinesia, myoclonus, chorea, and ballismus, and as such, it is a complex movement disorder [Abela and Kurian, 2018; Kawarai et al., 2018; Carecchio et al., 2019; Zech et al., 2019]. Dysmorphic features such as microcephaly, short stature and mild dysmorphic findings, such as epicanthus, an elongated face, and bulbous nasal tip, developmental delay, short stature, microcephaly, spasticity, hyperreflexia, eye movement abnormalities, dermatologic features, seizures, and psychiatric comorbidities have also been described as phenotypic features in a few cases [Abela and Kurian, 2018; Kawarai et al., 2018; Carecchio et al., 2019; Zech et al., 2019]. To contribute to the phenotype-genotype relationship in *KMT2B*-related dystonia, herein, we describe the clinical and genetic features of an 8-year-old boy of Turkish origin, who presented with a complex, progressive movement disorder accompanied by multisystem involvement, where whole-exome sequencing (WES) revealed a previously unreported de novo nonsense mutation c.2453dupT (p.M818fs*28) in the *KMT2B* (NM_014727.2) gene.

Case Presentation

The patient, 8 years and 9 months old, was admitted with difficulty in using his right leg and foot while walking and climbing up the stairs, tic-like movements in his left shoulder and arm for the 4–5 months prior, and difficulty using his left hand for a month. He was born via normal vaginal delivery, weighing 2,400 g, as a healthy second child to a nonconsanguineous Turkish couple. His medical history revealed feeding problems since newborn period,

and later with solid food. He was able to walk at 13 months before talking at 3 years of age with difficulty pronouncing some sounds and had normal gross motor skills until 3 months prior. Physical examination revealed indistinct facial features, such as epicanthus and an elongated face with a bulbous nasal tip. Height, head circumference, and weight were below 3 SD (17 kg, 49 cm, and 118 cm, respectively), right nasolabial fold was mildly flattened, mimetic lines in his right forehead were less pronounced and his speech pattern was dysarthric. Involuntary motor movement (hemichorea?) was observed in the left hand, arm, and shoulder accompanied by a low-amplitude high-frequency intentional tremor. His left hand exhibited milkmaid's grip, in addition to intermittent loss of tonus during consecutive motor movement, and writing cramps. He had a waddling gait in his right leg and thus, had trouble walking on non-smooth surfaces and needed support while climbing stairs. The family noticed worsening of symptoms near the end of the day. Electromyography revealed dystonia in the distal right lower extremity and proximal left upper extremity, in addition to a less-pronounced myoclonus, which were compatible with myoclonic dystonia or dystonic myoclonus. Workup for hereditary movement disorders and neurometabolic diseases was performed due to a syndromic presentation including dysmorphic facial features (epicanthus, an elongated face with a bulbous nasal tip), retardation in expressive language and dysarthria, growth retardation, chorea and tremors in upper extremities, and focal dystonia in the lower extremities. Metabolic evaluation including vitamin D, vitamin E, vitamin B12, methylmalonic acid, iron, ferritin, transferrin, ceruloplasmin and copper, lysosomal enzymes, urea, uric acid, lactate, TSH, fT3, fT4, parathyroid hormone, creatinine kinase and liver function tests, total cholesterol, LDL, HDL, triglycerides, ammonia, lactate, pyruvate, and cranial MRI were normal. The patient was given 1 mg/kg/day of levodopa (L-DOPA) and 5 mg/day of domperidone for symptomatic treatment and referred to the endocrinology department for growth retardation, and was followed up for precocious puberty and short stature (bone age: 7, calendar age: 9 years 9 months). There was no attenuation of abnormal movements at the end of 6 months, even though the L-DOPA was escalated to 8 mg/kg/day. On the contrary, nasal speech due to laryngeal and cervical dystonia, and increased dystonia in his left arm and leg, with dystonic cramps in the lower extremities were new features at the follow-up. Added to the treatment was 1 mg/day of trihexyphenidyl, which was titrated up to 10 mg/day at the end of the 2 years since the patient was responsive. L-DOPA was titrated down during this period, but had to be continued at 3 doses of 100 mg/day due to worsening of the symptoms (for details, see Fig. 1). During the follow-up from 9 to 13 years of age, speech deterioration due to increased cervical, laryngeal, and bulbar dystonia, difficulty in jaw opening and closing, orofacial dyskinesia, difficulty in tongue control, dystonic cramps in the upper extremities, and hemiballistic jerks in both arms were observed. Symptoms were aggravated by emotional stressors such as speaking in front of a group and answering questions in classroom. During the follow-up, although the patient was able to perform basic life functions independently with the aid of appropriate medical treatment, there was a marked exacerbation in progressive gait disturbances, an inability to climb up the stairs without support, and difficulty in walking on non-smooth surfaces. A positive response to the trihexyphenidyl dose adjustments was obtained throughout the follow-up; however, the family was given the option of deep brain stimulation (DBS) due the lack of complete re-

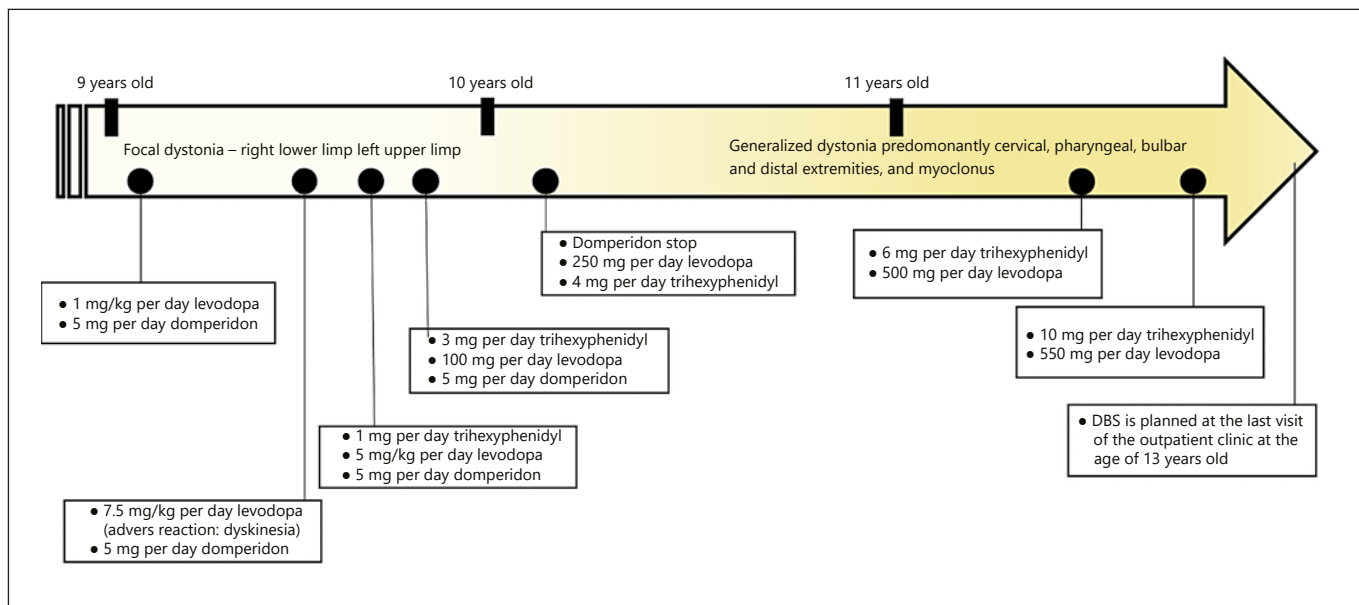


Fig. 1. Timeline of the treatments and progression of the disease.

sponse to the high-dose oral medical therapies and progressive worsening of life quality. An increase in anxiety was observed in the patient, who did not have psychiatric comorbidity at onset.

Genetic Study

DNA was extracted from peripheral blood samples using the QIASymphony DNA Mini Kit (QIAGEN GmbH, Hilden, Germany). Chromosomal microarray analysis was normal. The WES analysis of the patient was performed at the Medical Genetics Department of Ankara City Hospital using xGen Exome Research Panel v2 (Integrated DNA Technologies, Inc., Coralville, IA, USA). VCF files were annotated using Qiagen Ingenuity Variant Analysis and Clinical Insight Interpret (QIAGEN GmbH). A novel variant of the *KMT2B* (NM_014727.2) gene was identified at exon 3, c.2453dupT (p.M818fs*28). Thus far, this variant has not been reported in any of the databases. Segregation analysis was performed by sequencing the mutation, and the parents carried the wild-type variant.

Discussion

About 50 different mutations of *KMT2B* have been reported in the literature (Table 1). Dystonia 28, childhood-onset (OMIM 617284) was associated with it in the OMIM database. Nonsense and frameshift mutations that seriously alter protein structure have been reported to be causes of dystonia [Abela and Kurian, 2018; Kawarai et al., 2018; Carecchio et al., 2019; Zech et al., 2019]. Herein, an affected individual with *KMT2B*-re-

lated dystonia who had a novel nonsense *KMT2B* mutation was presented. As in *KMT2B* dystonia, WES was proven to be beneficial in the diagnosis of complex movement disorders and diseases with multisystem involvement and helped in the diagnosis of our patient. Because a large number of genes associated with dystonia have been reported, WES was performed for molecular diagnosis. We identified a novel mutation in *KMT2B* (NM_014727.2):c.2453dupT (p.M818fs*28). The frameshift mutation alters the protein structure seriously and in silico databases report it as “disease causing.” Sanger sequencing was done and confirmed that the mutation was de novo.

At present, no data exist regarding the clinical features, prediction of outcome, genotype-phenotype relationship, or severity of the *KMT2B* variants [Kawarai et al., 2018; Carecchio et al., 2019; Abela and Kurian, 2018]. Moreover, cases exhibiting neurodevelopmental disorders without movement disorders have been reported in the literature, which were named *KMT2B*-related neurodevelopmental diseases [Carecchio et al., 2019]. However, *KMT2B*-related dystonia and other hereditary movement disorders or mitochondrial and inborn errors of metabolism with systemic involvement are clinically difficult to distinguish from each other [Abela and Kurian, 2018; Kawarai et al., 2018; Carecchio et al., 2019; Zech et al., 2019]. With this report, we described the first reported Turkish patient carrying a

Table 1. Summary of clinical features and mutations of reported patients with *KMT2B*-related dystonia

| Age of onset, years | Onset site of dystonia | Distribution of dystonia | Additional abnormal movement disorders | Clinical features | Intellectual disability and psychiatric disorders | Type of mutations | DBS (age at surgery, years) |
|-------------------------------|------------------------|--------------------------|--|--|---|---|-----------------------------|
| <i>Kawarai et al., 2018</i> | | | | | | | |
| P1 | 7 | UL, LL | Face, trunk UL, LL, neck, larynx; generalized | Chorea Microcephaly, elongated face Bulbous nasal tip | Normal/IQ: 90 | c.309delG | 16 |
| P2 | 7 | Right hand | Trunk, UL, LL, neck, larynx; generalized | NR Microcephaly, short stature | Normal/IQ: 84 | c.1656dupC | 17 |
| P3 | 5 | Right toe | Trunk, UL, LL, neck, larynx; generalized | Myoclonus Microcephaly, short stature | Mild/IQ <69 | c.3325_3326insC | 13 |
| P4 | 6 | Legs | Trunk, UL, LL, neck; generalized | Myoclonus Microcephaly, short stature, hypotonia | Borderline/IQ: 75 | c.5636delG | ND |
| <i>Carecchio et al., 2019</i> | | | | | | | |
| P5 | 6 | LL | LL, larynx; generalized | NR Brisk LL reflexes | Mild/IQ: 69 | c.6210_6213delTGAG; p.Ser2070AArgfs*20 | 8 |
| P6 | 4 | LL, larengeal | Face, OM, LL, axial; generalized | NR Bulbous nasal tip, mild eyelid ptosis, absent LL reflexes | Mild/IQ-NR | c.1656dupC; p.Lys553Glnfs*46 | ND |
| P7 | 5 | LL | UL, larynx, OM; generalized | NR Brisk LL reflexes | Normal/IQ: 91 | c.6413dupC; p.Ala2139Glyfs*6 | ND |
| P8 | 4 | LL | Trunk, cervical; generalized | Myoclonus Elongated face | Borderline/IQ: 77 | c.5405_5429del; p.Gln1802_ Ala1808del | 14 |
| P9 | 6 | LL | Trunk, OM | NR Broad nasal bridge, low-set ears, epicanthal fold, thin upper lip, right hemiparesis following intraoperative lenticular hemorrhage | Borderline/IQ: 75 | c.5114G>A; p.Arg1705Gln | 10 |
| P10 | 9.5 | Neck | Trunk, OM; generalized | NR NR | Normal/IQ-NR | c.2240A>G; p.Gln747Arg | 16 |
| P11 | 3.5 | LL | OM; generalized | NR Brisk LL reflexes | Normal/IQ: 96 | c.5330G>C; p.Arg1777Pro | 10 |
| P12 | 4 | LL | OM, larynx; generalized | NR Microcephaly, bulbous nasal tip, thin upper lip, prognathism, parkinsonism | NR | c.5258T>C; p.Leu1753Pro | 11 |
| P13 | 7 | LL | Larynx; generalized | NR Bulbous nasal tip, brisk LL reflexes | Borderline/IQ: 75 | c.4844C>T; p.Ser1615Leu | 38 |
| P14 | 13 | Neck | Cervical | NR NR | NR | c.3431A>T; p.Asp1144Val | ND |
| P15 | 10 | LL | OM, larynx; generalized | NR Bulbous nasal tip | Mild/IQ-NR | c.7292T>C; p.Leu2431Ser | ND |
| P16 | 7 | LL | Larynx; generalized | NR Microcephaly, elongated face, low-set ears, mild eyelid ptosis, brisk LL reflexes | Mild/IQ: 57 | c.3008G>A; p.Arg1003Gln | ND |
| P17 | 3 | LL | Generalized | NR Thin upper lip, bulbous nasal tip, right hemiparesis following intraoperative lenticular hemorrhage | Mild/IQ: 68 | c.4895C>T; p.Ala1632Val | 8 |
| P18 | 6 | Neck, UL | Generalized | NR Brisk LL reflexes | Mild/IQ: 74 | Del: chr19:35,608,696–36,869,486 | ND |

Table 1 (continued)

| | Age of onset, years | Onset site of dystonia | Distribution of dystonia | Additional abnormal movement disorders | Clinical features | Intellectual disability and psychiatric disorders | Type of mutations | DBS (age at surgery, years) |
|--------------------------|---------------------|------------------------|--------------------------|--|--|---|--------------------------------|-----------------------------|
| <i>Zech et al., 2016</i> | | | | | | | | |
| P19 | 7 | LL | Generalized | NR | NR | Normal | c.6406delC; p.Leu2136Serfs*17 | Unknown |
| P20 | 3 | LL | Generalized | NR | Microcephaly, short stature, strabismus, VUR | Normal | c.1633C>T; p.Arg545* | ND |
| P21 | 11 | LL | Generalized | NR | Microcephaly, syndactyly, delayed speech, astigmatism | Mild | c.7050-2A>G; p.Phe2321Serfs*93 | ND |
| P22 | 4 | LL | Generalized | NR | Microcephaly, short stature, delayed speech, astigmatism | Mild | c.2428C>T; p.Gln810* | ND |
| P23 | 9 | UL | Focal | NR | Microcephaly, short stature, delayed speech, astigmatism | Mild | c.2428C>T; p.Gln810* | |
| P24 | 11 | LL | Focal | Tremor | Delayed speech | Mild | c.2428C>T; p.Gln810* | |

NR, not reported; UL, upper limbs; LL, lower limbs; OM, oro-mandibular; IQ, intelligence quotient; DBS, deep brain stimulation; ND, not done; VUR, vesicourethral reflux.

heterozygous, previously unreported variant in *KMT2B*, who was followed up for 5 years, and had progressive dystonia, which began focally in the upper and lower extremities but became generalized with the involvement of laryngopharyngeal muscles within 6 months. Dystonia usually begins in the lower extremities; however, onset in upper extremities has also been reported [Kawaraki et al., 2018; Carecchio et al., 2019]. Causes of pure dystonia were ruled out due to accompanying hemichorea and tremors, along with the addition of myoclonus and hemiballismus during the follow-up period. As reported by Kawaraki et al. [2018], the coexistence of myoclonus and dystonia supports the notion that *KMT2B*-related dystonia could be a candidate for myoclonus-dystonia genes.

Cranial MRI anomalies (findings in the globus pallidus), spasticity, eye movement abnormalities, dermatologic involvement, seizures, and hearing loss, which have been reported in the literature, were not present in this patient [Abela and Kurian, 2018; Kawaraki et al., 2018; Carecchio et al., 2019; Zech et al., 2019].

Physical therapy and rehabilitation, including swallowing and speech rehabilitation, ergotherapy, and oral therapy directed towards movement disorders, did not prevent progression and were partially helpful in facilitating daily activities. We observed an increase in anxiety in our patient who did not have psychiatric comorbidity at onset. In such patients, psychiatric comorbidities could stem from progressive deterioration of daily activities and drop in quality of life, rather than the primary effect of the disease. It has been shown that DBS is beneficial in controlling symptoms and halting the progression of the disease in patients with *KMT2B*-related movement disorder [Zech et al., 2019]. Patients with *KMT2B*-related dystonia who had been treated using DBS showed significant clinical improvement in 2 different studies [Li et al., 2020; Cif et al., 2020]. One of these studies reported less improvement in the laryngeal dystonia, but truncal and cervical dystonia showed a better response [Cif et al., 2020]. DBS has not been applied to the patient in this case report, but it is planned. In addition, DBS appears to be a unique treatment solution for complex movement disorders resistant to aggressive medical therapy.

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Statement of Ethics

Written informed consent was obtained from the parents for publication of this case report, including the publication of images, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Concept and Design – A.A., Ö.Y.K., A.C.C., Ö.T.D.; Supervision-Genetic study – A.C.C.; Literature Review – A.A., Ö.Y.K.; Writer – A.C.C., Ö.Y.K.; Critical Review – A.A., Ö.Y.K., A.C.C., Ö.T.D.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.