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CASE REPORT

A *KMT2B* Frameshift Variant Causing Focal Dystonia Restricted to the Oromandibular Region After Long-Term Follow-up

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ABSTRACT

KMT2B-linked dystonia (DYT-*KMT2B*) is a childhood-onset dystonia syndrome typically beginning in the lower limbs and progressing caudocranially to affect the upper limbs with eventual prominent craniocervical involvement. Despite its recent recognition, it now appears to be one of the more common monogenic causes of dystonia syndromes. Here, we present an atypical case of DYT-*KMT2B* with oromandibular dystonia as the presenting feature, which remained restricted to this region three decades after symptom onset. This appears to be the first reported case of DYT-*KMT2B* from Southeast Asia and provides further supporting evidence for the pathogenic impact of the *KMT2B* c.6210_6213delTGAG variant.

Keywords DYT-*KMT2B*; *KMT2B*; Monogenic dystonia; Oromandibular dystonia.

Mutations in the lysine-specific histone methyltransferase 2B (*KMT2B*) gene were recently recognized as a cause of early-onset generalized dystonia, failure to thrive, microcephaly, intellectual disability, and facial dysmorphism.[1-3] This condition now appears to be one of the more common monogenic causes of dystonia syndromes and, from a clinical management perspective, seems particularly responsive to deep brain stimulation (DBS) surgery.[3,4]

In a recent review of patients with *KMT2B*-associated dystonia (DYT-*KMT2B*), the median age of onset was 6.0 years, with dystonia typically involving the legs initially and becoming generalized over a median of 2.0 years (range: 0–10.5 years).[2] Cranial involvement occurred at a median age of 9.0 years.[4] However, cervical and craniofacial (including oromandibular) dystonia are not invariably seen in DYT-*KMT2B* (being present in 35%, 28%, and 25% of cases, respectively).[2]

We report an atypical case of *KMT2B*-associated isolated oromandibular dystonia (OMD). To our knowledge, this phenotype—presenting as OMD and remaining as such three decades after initial onset—has not been reported in DYT-*KMT2B*. This also appears to be the first account of DYT-*KMT2B* from Southeast Asia, a region with 700 million people of diverse ethnicities that has been underrepresented in neurogenetics research.[5,6]

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CASE REPORT

Clinical characterization

This patient of mixed descent (Indian father, Chinese mother) started having slurred speech at 12 years of age, which gradually worsened over the years to include occasional choking and was associated with involuntary jaw opening and tongue movements. There were no involuntary movements elsewhere in the body. Upon initial evaluation at our center at age 28 years, involuntary jaw opening and tongue protrusion were observed, with Burke-Fahn-Marsden Dystonia Rating Scale-Movement (BFMDRS-M) and Unified Dystonia Rating Scale (UDRS) scores of 15/120 and 7.5/112, respectively (Supplementary Video 1 and Supplementary Table 1 in the online-only Data Supplement). There was no parkinsonism, myoclonus, or ataxia, and the Montreal Cognitive Assessment (MoCA) score was normal (29/30). Brain MRI, blood tests (full blood count; blood film; liver, kidney, and thyroid function; and caeruloplasmin), 24-hour urinary copper, and slit-lamp ophthalmic examination results were normal. Tetrabenazine 25 mg bid, sublingual atropine, and botulinum toxin injections into the parotid glands (Dysport® 200 units each side) produced minimal benefit. DBS surgery was discussed, but since cranial dystonia was a relatively less proven indication for this treatment, the patient and family decided against it.

The patient's speech gradually became less intelligible, and he had increasing difficulty eating, needing to manually push food to the back of the mouth. At the age of 38 years, a video fluoroscopic swallowing study showed moderate-to-severe oropharyngeal dysphagia; he weighed only 35.7 kg (body mass index [BMI] = 14.9 kg/m^2). Advice was given regarding dietary modification and swallowing techniques; placement of a percutaneous feeding tube was discussed but declined by the patient. Glycopyrrolate 2 mg/d for drooling and zolpidem 5 mg/d for dystonia were prescribed, with minimal benefit. The patient was reluctant to undergo repeat botulinum toxin treatment.

The patient had chronic hepatitis B but no other medical history, including psychiatric disorder or neuroleptic treatment. Birth and developmental history were unremarkable, as was family history. The patient's younger brother and sister were healthy.

At his last visit with us, at age 41 years, he had severe drooling such that he carried around a bagful of cloth pieces to pack into his mouth. His weight had stabilized around 39 kg (BMI = 16.2 kg/m^2). Jaw-opening dystonia was constantly present, with tongue protrusion and very effortful speech (BFMDRS-M = 20/120; UDRS = 16/112) (Supplementary Video 2 in the online-only Data Supplement). There was no abnormal posturing in the neck, trunk, or limbs. Cognition remained intact (MoCA = 28/30). Despite his physical limitations, he remained independent for personal care, had managed to complete a computer science degree, and continued to work for an international health agency. He was taking trihexyphenidyl 4 mg/d and clonazepam 0.5 mg/d with modest benefit. Given the reports of improvement of *KMT2B*-related dystonia with DBS, this therapeutic option was discussed again, with the patient's decision pending at the time of reporting.

Genetic testing

At the age of 40 years, the patient's DNA obtained from peripheral blood was sent for whole-exome sequencing (WES) as part of collaborative research between the University of Malaya and the University of Luebeck (approved by the Ethics Committees of both institutions). At approximately the same time, an Invitae Dystonia Comprehensive Panel involving full gene sequencing and deletion/duplication analysis of 38 target genes and variants (https://www.invitae.com/en/providers/test-catalog/test-03351) was ordered in another center (by Prof. NMI). These analyses identified a heterozygous variant in *KMT2B* (c.6210_6213delTGAG [p.Ser2070Argfs*20]), which was pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines (PVS1, PM2, PP3; CADD score 34). Polymerase chain reaction testing excluded a SINE-VNTR-Alu (SVA) insertion in the *TAF1* gene.

Targeted sequencing of the *KMT2B* variant excluded the presence of the mutation in the patient's father (Figure 1); the mother was already deceased (from an unrelated illness).

DISCUSSION

To our knowledge, dystonia restricted to the oromandibular region after long-term follow-up has not been reported in DYT-*KMT2B*. Most DYT-*KMT2B* cases described to date became generalized during the disease course, with only eight cases remaining focal or multifocal/segmental,[2] primarily involving the limbs.[1,4] This report therefore expands the phenotypic spectrum of DYT-*KMT2B*. The condition should now be considered in the differential diagnosis of patients with OMD at onset or patients where OMD is prominent or even isolated later during the disease course in addition to other genetic disorders, such as Wilson's disease, DYT-*THAP1*, DYT-*ANO3*, DYT-*GNAL*, X-linked dystonia parkinsonism, brain iron accumulation syndromes, spinocerebellar ataxia (SCA), Lesch-Nyhan disease, and tardive syndromes (detailed list of references provided in the Supplementary Material in the online-only Data Supplement).[2,7,8] Genetic testing for the above disorders was negative in this case, although SCA-related mutations are not covered in WES and complex rearrangement mutations in *HPRT1* causing Lesch-Nyhan disease may have been missed.

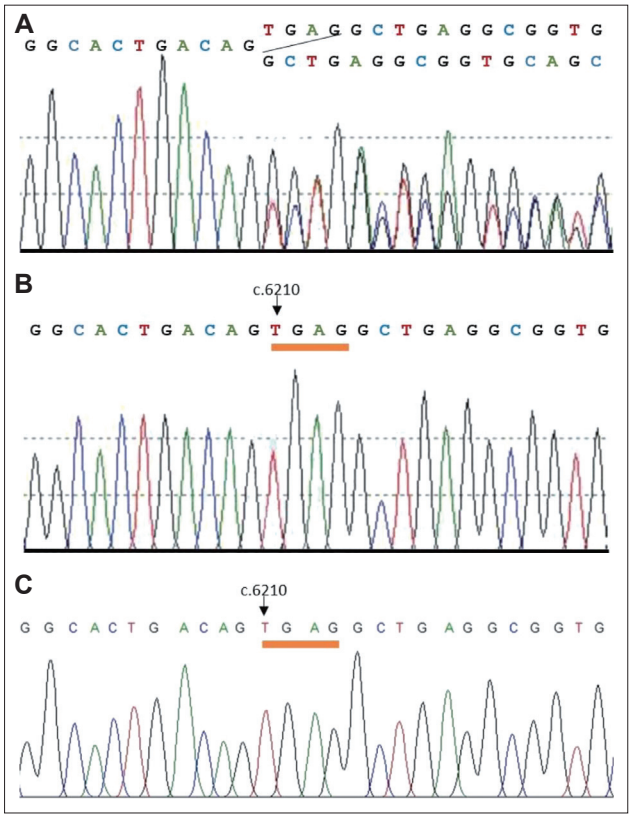

Figure 1. DNA sequence electropherograms indicating a heterozygous four base-pair deletion in *KMT2B* in the patient (A). The wild type allele is indicated above and the allele with the deletion below. For comparison, a healthy control is shown in (B) and the sequence of the patient's father in (C).

The reason for our patient's dystonia being confined to the oromandibular region (and the absence of cognitive or systemic involvement apart from the weight loss attributed to severe OMD) is unknown and may relate to environmental or genetic/epigenetic modifiers. The specific variant in our patient involved a 4-base pair deletion in exon 28, leading to a presumed frameshift causing a premature stop codon and truncation of the *KMT2B* protein. This variant has not been reported in the ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), gnomAD (https://gnomad.broadinstitute.org/) or Variome (https://www.humanvariomeproject.org/) databases but has been described in one (de novo) case,[9] an intellectually disabled Italian girl who had leg dystonia at the age of 6 years, which later became generalized with prominent laryngeal involvement. She underwent DBS at age 8 years (outcome unreported). A high rate of de novo mutations in *KMT2B* is thought to be responsible for DYT-*KMT2B* occurring mostly in a sporadic manner,[1,3] and this seems likely in our patient's case, although we could only confirm the absence of the mutation in the father. In addition, reduced penetrance may account for a few reported familial cases where the *KMT2B* mutation was inherited from unaffected parents.[9]

Our patient was of Asian race and appears to be the first case of DYT-*KMT2B* reported from Southeast Asia. A total of 28 cases have been reported from Asia, primarily China (20 cases), as well as three cases from India, two from Japan, and one each from South Korea, Bangladesh, and Afghanistan (detailed list of references provided in the Supplementary Material in the online-only Data Supplement). The number of identified cases will likely increase substantially in the future, with improved awareness and availability of molecular genetic testing (although this testing is still costly and out of reach for many patients in this part of the world). Despite the likely underdiagnosis of cases, a recent MDS-Gene systematic review reported that Asians comprised the second most frequently affected ethnic group overall for isolated dystonias (13.6% of total cases) and for a number of specific dystonia genes, including *TOR1A* (14.1%), *ANO3* (26.4%), *GNAL* (13.2%), and *KMT2B* (14.7%).[2]

Even with treatment, dystonia often remains symptomatic, and medications are often unsatisfactory due to suboptimal efficacy and/or adverse reactions. Botulinum toxin has been successfully deployed for OMD and drooling, with jaw-closing dystonia typically more straightforward to treat than jaw-opening dystonia (associated with higher rates of dysphagia).[10] DBS of the globus pallidus internus has been successfully performed, particularly in DYT-*TOR1A* and to some extent in DYT-*THAP1* and DYT-*SCGE*.[3] Favorable short- and long-term outcomes, in terms of reduced BFMDRS scores and improved function and quality of life, have been reported in DYT-*KMT2B*.[1,4,9] In a recent meta-analysis[3] that included 42 patients undergoing DBS for *KMT2B*-associated dystonia, 41% experienced > 50% clinical improvement in BFMDRS scores. Most literature on outcomes of DBS in DYT-*KMT2B*, however, concerned generalized dystonia, and it remains to be seen if OMD is consistently improved. Only a handful of cases have specifically noted OMD improvement after DBS.[4] Considering the troublesome nature of our patient's symptoms, it may be reasonable to consider DBS in this case.

In conclusion, our case with an atypical presentation of OMD that has remained restricted to the oromandibular region after three decades adds to the heterogeneity of *KMT2B*-associated dystonia phenotypes. It also underscores the role of comprehensive genetic testing in childhood-onset dystonia and provides further support for the pathogenic impact of the *KMT2B* c.6210_6213delTGAG variant.

Ethics Statement

Written informed consent from the patient and the father was obtained for the study, including publication of the report and video, and the genetics research was approved by the Ethics Committees of the University of Malaya (20191010-7917) and the University of Lübeck (19-254).

Supplementary Video Legends

Video 1. (Taken in 2010) With the patient seated, there are oromandibular

dystonic movements of moderate severity (including jaw opening [50%−75% of possible range], tongue protrusion, contraction of superficial anterior neck muscles [accessory muscles for jaw opening]), that worsen when talking and are present most of the time (50%−75% of the time; predominantly submaximal), even at rest. There is marked difficulty in understanding his speech (occurring frequently [> 75% of the time]). The patient is able to arise from a chair quickly and walk independently, with normal posture, base, cadence, and stride length. There is no ataxia, parkinsonism, tremor, myoclonus, or other hyperkinesias. He reports frequent choking during the interview (not shown).

Video 2. (Taken in 2022) With the patient seated, there are severe oromandibular dystonic movements (including forced jaw opening [> 75% of possible range], tongue protrusion, contraction of superficial anterior neck muscles) occurring almost constantly (> 75% of the time; predominantly maximal), even at rest. There is marked difficulty in understanding his speech (occurring frequently [> 75% of the time]). There is obvious drooling of saliva (with the patient inserting towels into the mouth to counteract this), and marked difficulty in swallowing food and fluids (with the patient manually pushing food into the mouth and extending the neck to facilitate feeding; not shown). In comparison to the earlier video, he has undergone substantial weight loss. There is no blepharospasm or abnormal neck, truncal or limb posturing, and no abnormal posturing when writing. The patient is able to arise from a chair quickly and walk independently, with normal posture, base, cadence, and stride length. There is no ataxia, parkinsonism, tremor, myoclonus, or other hyperkinesias.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22109.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Shen-Yang Lim. Data curation: all authors. Funding acquisition: Shen-Yang Lim, Ai Huey Tan, Christine Klein, Katja Lohmann. Writing—original draft: Alfand Marl F. Dy Closas, Shen-Yang Lim. Writing—review & editing: all authors.

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Supplementary Table 1. Comparison of BFMDRS and UDRS for years 2010 and 2022

RATING SCALE	2010	2022
BFMDRS	15	20
Eyes	0	0
Mouth	6	8
Speech and Swallowing	9	12
Neck	0	0
Arm	0	0
Trunk	0	0
Leg	0	0
UDRS	7.5	16
Eyes and upper face	0	0
Lower face	0	0
Jaw and Tongue	7.5	16
Larynx	0	0
Neck	0	0
Shoulder and proximal arm (right and left)	0	0
Distal arm and hand including elbow (right and left)	0	0
Pelvis and proximal leg (right and left)	0	0
Distal leg and foot including knee (right and left)	0	0
Trunk	0	0

BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale-Movement; UDRS, Unified Dystonia Rating Scale.