KMT2B-Related Dystonia in Indian Patients With Literature Review and Emphasis on Asian Cohort

Debjyoti Dhar,1* Vikram V Holla,1* Riyanka Kumari,2,3* Neenarika Sriram,1 Jitender Saini,4 Ravi Yadav,1 Akhilesh Pandey,5,6 Nitish Kamble,1 Babylakshmi Muthusamy,2,3,4,5 Pramod Kumar Pal1,6

1Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India
2Institute of Bioinformatics, International Technology Park, Bengaluru, Karnataka, India
3Manipal Academy of Higher Education, Manipal, Karnataka, India
4Department of Neuroimaging and Intervention Radiology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India
5Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
6Center for Individualized Medicine, Mayo Clinic, Rochester, MN, USA

ABSTRACT

Objective Mutations in the KMT2B gene have been identified in patients previously diagnosed with idiopathic dystonia. Literature on KMT2B-related dystonia is sparse in the Indian and Asian populations.

Methods We report seven patients with KMT2B-related dystonia studied prospectively from May 2021 to September 2022. Patients underwent deep clinical phenotyping and genetic testing by whole-exome sequencing (WES). A systematic literature search was performed to identify the spectrum of previously published KMT2B-related disorders in the Asian subcontinent.

Results The seven identified patients with KMT2B-related dystonia had a median age at onset of four years. The majority experienced onset in the lower limbs (n = 5, 71.4%), with generalization at a median duration of 2 years. All patients except one had complex phenotypes manifesting as facial dysmorphism (n = 4), microcephaly (n = 3), developmental delay (n = 3), and short stature (n = 1). Magnetic resonance imaging (MRI) abnormalities were present in four cases. WES revealed novel mutations in the KMT2B gene in all patients except one. Compared to the largest cohort of patients with KMT2B-related disorders, the Asian cohort, comprising 42 patients, had a lower prevalence of female patients, facial dysmorphism, microcephaly, intellectual disability, and MRI abnormalities. Protein-truncating variants were more prevalent than missense variants. While microcephaly and short stature were more common in patients with missense mutations, facial dysmorphism was more common in patients with truncating variants. Deep brain stimulation, performed in 17 patients, had satisfactory outcomes.

Conclusion This is the largest series of patients with KMT2B-related disorders from India, further expanding the clinico-genotypic spectrum. The extended Asian cohort emphasizes the unique attributes of this part of the world.

Keywords Asia; Dystonia; Genetics; India; KMT2B.

Dystonia is one of the common presentations in movement disorder clinics.1 The consensus 2013 update segregated dystonia into two axes. While the first axis deals with the unique clinical characteristics, the second is based on etiology.1 With the advent of neurogenetics, the etiologic spectrum of primary dystonia has expanded manifold. In 2016, the KMT2B gene on chromo-
some 19q13.12 was discovered as a causative gene in a subset of patients with genetically determined early-onset generalized dystonia (OMIM 606834 or DYT28) by two different research groups. This gene encodes a histone lysine methyltransferase enzyme, which is involved in the epigenetic modification associated with active gene transcription. The protein plays an important role in the transfer of a methyl group to the fourth lysine of histone H3 (H3K4 pathway).

Patients with loss-of-function mutations in the KMT2B gene typically manifest in the first decade of life with generalized dystonia. They usually exhibit limb onset presentation, particularly in the lower limbs. Involvement of the neck, trunk and larynx at onset has also been reported in the literature. Many of these patients develop laryngeal dystonia leading to dysphonia. Although classically described under the category of isolated dystonia, associated movement disorders in the form of myoclonus, parkinsonism and cerebellar ataxia have also been observed. KMT2B-related disorders are frequently associated with complex phenotypes, including facial dysmorphism, microcephaly, delayed development, intellectual disability, cognitive impairment, and short stature. The disease has an autosomal dominant inheritance, with the majority of mutations appearing de novo. Many variants of this gene have been discovered to date, including frameshift mutations; whole gene deletions; and nonsense, splice-site, missense and in-frame deletion mutations. Synonymous variants have also been identified as mediators of the disease.

Recent studies have shown a high prevalence of KMT2B mutations among patients previously diagnosed with idiopathic dystonia. Often, these patients have medically refractory and disabling dystonia. The applicability of deep brain stimulation (DBS) and its efficacy in this subset of patients have shown significant promise. In this study, we aimed to delineate the phenotypic spectrum of KMT2B-related dystonia patients from National Institute of Mental Health and Neurosciences.

MATERIALS & METHODS
Patients and methods
Seven patients with KMT2B-related dystonia from a cohort of patients with primary dystonia were studied prospectively in a National Institute of Mental Health and Neurosciences in India from May 2021 to September 2022. Patients presenting with primary dystonia of any age group who were identified to have a pathogenic or likely pathogenic mutation involving the KMT2B gene by whole-exome sequencing (WES) were included. Detailed clinical phenotyping based on the standard motor and disability scores was performed. Patients were assessed using standard clinical rating scales, including the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), Global Dystonia Rating Scale (GDS) and Unified Dystonia Rating Scale (UDRS). The results were then compared to those of previously published studies. This study was approved by the National Institute of Mental Health and Neurosciences (NIMHANS) ethics committee (No. NIMH/DO/IEC (BS & NS DIV)/2020-21). All patients were recruited after an informed written consent form was signed. Parental consent was obtained in the case of minors.

Genetic analyses
Blood samples were subjected to genomic DNA extraction using a QIAamp DNA blood minikit (QIAGEN, Valencia, CA, USA, #51104) according to the manufacturer’s instructions. Following a quality check, the raw reads were then aligned to the human reference genome (GRCh37) using the BMA-mem algorithm. Removal of polymerase chain reaction duplicates was facilitated using the Picard toolkit (https://broadinstitute.github.io/picard/). Variants were identified using the framework of the Genome Analysis Toolkit (GATK) (Broad Institute, Cambridge, MA, USA). Base quality score recalibration was performed for filtration of the variants. The variants were annotated utilizing the freely available platform ANNOVAR (https://www.openbioinformatics.org/annovar/). Variants that were common and had a minor allele frequency > 0.01 were not considered after comparison with the 1000 Genomes Project, Exome Aggregation Consortium (ExAC), and gnomAD databases (https://gnomad.broadinstitute.org/). The individual sequence variants were interpreted using various software tools, including PolyPhen-2, Sorting Intolerant from Tolerant (SIFT), and MutationTaster. The mutation effects of the variants on the clinical phenotypes were classified in accordance with American College of Medical Genetics and Genomics (ACMG) standards and guidelines into benign, likely pathogenic or pathogenic. In addition, the variants were also checked for their novelty by analysis of mutation databases (ClinVar; https://www.ncbi.nlm.nih.gov/clinvar/?term=KMT2B) and literature curation.

Systematic review of literature
We performed an exhaustive literature search in the publicly available medical databases of PubMed using the medical subject headings (MeSH) “KMT2B”, “dystonia” and “disorder” to identify appropriate studies published through January 31, 2023. The studies were subjected to title and abstract screening, after which studies pertaining to the Asian population were included. Data extraction was performed, including demographic parameters, clinical phenotype and variant details. All identified studies published after the largest systematic review by Cif et al. in 2020 were assessed separately to provide completeness.
KMT2B-Related Dystonia in Indian Patients
Dhar D, et al.

RESULTS

Demographic data

We identified seven patients with likely pathogenic or pathogenic mutations involving the KMT2B gene. All participants in the study were of Indian descent. Males constituted 57.1% (n = 4) of the study group. The median age at assessment was 18 years (interquartile range [IQR] 14.5 to 19.5 years). The median age at onset was 4 years (IQR: 4.5 months to 7.5 years), with a range varying from 2 months to 10 years. As per Axis 1 classification, three patients had onset in the infantile period (up to 2 years), and the remaining four patients had childhood onset (3 to 12 years). None of these patients had a positive family history. Consanguinity was present in 28.6% (n = 2) of patients.

Clinical profile

All the patients identified with KMT2B mutations developed generalized dystonia during their disease course. The most common site of onset was the lower limbs (n = 5, 71.4%). The other two patients had onset in the neck (Patient 3) and larynx (Patient 2). Lower limb involvement was observed in all cases. Oro-mandibular involvement was present in 2 cases (28.6%) (Patients 2 and 5), while laryngeal involvement was observed in three patients (42.9%) (Patients 2, 3 and 5). The median duration to generalization was 2 (IQR: 1.8 to 2.5) years. Patients had high motor and clinical severity scores on the standard clinical scales.

Dystonic spasms were reported in two cases (Patients 4 and 6). None of the patients had status dystonicus during the follow-up period. The mean BFMDRS motor and disability scores were 77.4 ± 19.0 and 19.9 ± 6.6, respectively. In one of the patients, the onset of dystonia was precipitated by febrile illness (Patient 3).

Complex phenotypes included microcephaly (n = 3; Patients 4, 5 and 7), developmental delay with subsequent intellectual disability (n = 3; Patients 2, 5 and 6), facial dysmorphism (n = 4; Patients 1, 2, 5 and 6) and short stature (n = 1; Patient 4). Facial dysmorphism manifested as bulbous nose tip (n = 5; Patients 2, 4–7), elongated faces (n = 1; Patient 5), dolichocephaly (n = 1; Patient 6), everted ears with high-arched palate (n = 1; Patient 5), thick lips (n = 1; Patient 1) and coarse facial features (n = 1; Patient 1). Additional manifestations included skeletal deformities in the form of genu varum (n = 2; Patients 2 and 5), genu valgum (n = 1; Patient 5), hammer toes (n = 1; Patient 2) and kyphoscoliosis (n = 1; Patient 1).

The clinical diagnosis was dopa-responsive dystonia (DRD) in three cases (Patients 4, 6 and 7), neurodegeneration with iron accumulation (NBIA) spectrum in two cases (Patients 1 and 2), and postencephalitis (Patient 3) and hypoxic ischemic encephalopathy (HIE) sequela (Patient 6) in a single case each. Brain MRI, performed at variable ages and durations of illness, showed abnormalities in four cases (Patients 1–4), which included symmetric hypointensity of the bilateral globus pallidus (n = 3; Patients 1, 2, and 4) and nonspecific white matter signal changes with cerebellar atrophy (n = 1; Patient 3) (Figure 1). All the patients were on medical management, which comprised trihexyphenidyl, tetrabenazine, levodopa-carbidopa and clonazepam in various combinations. Levodopa was prescribed based on the clinical possibility of DRD in five cases, with modest subjective benefits. None of the patients were treated surgically (Supplementary Table 1 in the online-only Data Supplement). Compared to the extended cohort of Cif et al., Indian patients had a lower female preponderance (40% vs. 57.6%); older age of onset (median 6.5 years, IQR [1.4 to 9.8] vs. 5 years, IQR [3.9 to 7]); and slightly lower prevalence of complex phenotypes, such as intellectual disability (30% vs. 57%), developmental delay (20% vs. 46.7%), facial dysmorphism (50% vs. 66.1%), microcephaly (20% vs. 55.1%), short stature (10% vs. 30.7%), and psychiatric manifestations (10% vs. 27.4%). Interestingly, none of the patients in our study population had a positive family history of dystonia.

Genetic analysis results

The WES panel found missense variants in 5 patients (Patients 1, 2, and 5–7) and a single base pair (1-bp) deletion resulting in a frameshift and premature truncation in 2 patients.

Statistical methods

Categorical variables are expressed as frequencies, while continuous variables are expressed as means with standard deviations. Descriptive statistics were performed as a first step for the analysis of demographic and clinical parameters. The Asian cohort was divided into two groups, the missense variant group and the truncating variant group, based on the type of genetic variant identified. Internal comparisons were performed between these groups with respect to demographic and clinical parameters. Normality tests were performed using the Shapiro-Wilk test. Qualitative data were subjected to χ² tests for comparison. Comparisons of normally distributed data were performed using independent samples t tests, while nonnormally distributed data were analyzed using the Mann-Whitney U test. SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for all statistical computations.
Patients 3 and 4) in the KMT2B gene. All the variants were heterozygous. Based on the current ACMG guidelines, five of these variants were classified as likely pathogenic (p.Tyr2488Cys in Patient 1, p.Leu1753Pro in Patient 2, p.Leu161fs in Patient 3, p.His2413Arg in Patient 5 and p.Cys1341Ser in Patient 7), one was classified as pathogenic (p.Glu1065ArgTer117 in Patient 4), and one was classified as a variant of uncertain significance (VUS) (Patient 6). These variants were not detected in the population-based databases of the 1000 Genomes Project, gnomAD and ExAC. The variants were predicted to be deleterious by the standard tools SIFT, PolyPhen2, and MutationTaster. Further details are provided in the clinical vignettes below, and the complete list of genomic KMT2B mutations is presented in Supplementary Table 2 in the online-only Data Supplement.

**Case vignettes**

**Patient 1**

A 12-year-old boy presented with abnormal posturing of all limbs that started in the right lower limb two years earlier, followed by sequential involvement of the right upper limb, trunk, neck, and finally left upper and lower limbs. Examination revealed facial dysmorphism, including thick lips, coarse facial features, chalky-white dentition, and thoracic kyphoscoliosis with generalized dystonia. Brain MRI showed a hypointensity of the bilateral globus pallidus internus on susceptibility-weighted imaging (SWI), inappropriate for the patient's age, and posterior putaminal atrophy. A clinical possibility of NBIA was considered. Secondary work-up, including a metabolic panel, spot urine for mucopolysaccharides, and screening for inborn errors of metabolism, were negative. WES revealed a previously reported heterozygous missense variant (Chr19:g.36228077A>G;NM_014727.3;c.7463A>G;p.Tyr2488Cys) in exon 33 of the KMT2B gene. Sanger sequencing for this variant in the parents was negative. According to the ACMG guidelines, the variant was identified as likely pathogenic (PM2, PM6, PP2, PP3, PP4, and PP5). This variant has been reported previously and proposed to alter interactions with other proteins due to its location on the FYRC domain. The patient was treated with a multitude of symptomatic measures, including levodopa, with no significant benefits. Surgical intervention with DBS was discussed with family members (Supplementary Video 1 in the online-only Data Supplement).

**Patient 2**

An 18-year-old male presented with drooling, jaw-opening...
dystonia, lingual dystonia, anarthria, and dysphagia from the age of 5 years. Subsequently, he developed torticollis and mild truncal involvement. General physical examination revealed a bulbous nose tip and skeletal deformities, including hammer toes, genu varum and facial dysmorphism in the form of a high-arched palate. Brain MRI showed bilateral symmetric globus pallidus (GP) hypointensities. WES revealed a heterozygous missense variant ([Chr19:g.36227669A>G;(NM_014727.3);c.7238A>G;p. His2413Arg]) in exon 31 of the KMT2B gene. This variant was identified as pathogenic (PM1, PM2, PP2, PP3, PP4, and PP6). There was mild initial improvement in his symptoms with symptomatic measures and levodopa therapy. Sialorrhea partially improved with botulinum toxin therapy (Supplementary Video 2 in the online-only Data Supplement).

Patient 3
A 43-year-old woman presented with generalized dystonia with oromandibular and laryngeal involvement. Her symptoms began as cervical dystonia at the age of 3 months, which generalized over a period of 3 years. Brain MRI showed nonspecific white matter hyperintensities and mild cerebellar atrophy. WES revealed a novel heterozygous frameshift mutation caused by a 1-bp deletion ([Chr19:g.36210725delC;(NM_014727.3);c.481delC;p.Leu161fs]) in exon 3 of the KMT2B gene of chromosome 19 (g.36210725delC). According to the ACMG guidelines, the variant was identified as likely pathogenic (PM1, PM2, PP2, PP3, PP4, and PP6). There was mild initial improvement in his symptoms with symptomatic measures and levodopa therapy. Sialorrhea partially improved with botulinum toxin therapy (Supplementary Video 2 in the online-only Data Supplement).

Patient 4
A 16-year boy presented with generalized dystonia with onset in the right foot. The interval to generalization was 3 years. Thereafter, he went on to develop laryngeal dystonia with subsequent anarthria 4 years later. He also had associated choreiform movements, which had a relatively recent onset of approximately 2 months earlier. Facial dysmorphism was observed in the form of a bulbous nose tip, microcephaly and short stature. His BFMDRS, UDRS, and GDS motor scores were 106, 86, and 121, respectively. He was severely disabled, with a BFMDRS disability score of 23. Brain MRI showed streaks of mineralization in the bilateral globus pallidus. WES revealed a novel de novo heterozygous frameshift mutation caused by a 1-bp deletion ([Chr19:g.36214765delC;(NM_014727.3);c.3192delC;p.Glu1065Arg-Ter117]) in exon 8 of the KMT2B gene. According to the ACMG guidelines, the variant was identified as pathogenic (PVS1, PM2, PM6, and PP4). The patient was treated with medical management. The parents were informed about the option of DBS (Supplementary Video 4 in the online-only Data Supplement).

Patient 5
A 19-year-old girl, born to second-degree consanguineous parents with a background of globally delayed developmental milestones, presented with limb onset and generalized dystonia from the age of 2 months. She had severe intellectual disability and sparing of oro-bucco-lingual parts. Facial dysmorphism was observed in the form of a bulbous nose tip, elongated facies and high-arched palate. Skeletal deformities included left genu valgum and right genu varum. Her BFMDRS motor and disability severity scores were 87.5 and 29, respectively. Brain MRI was normal. WES revealed a novel heterozygous missense variant ([Chr19:g.36227669A>G;(NM_014727.3);c.7238A>G;p.His2413Arg]) in exon 31 of the KMT2B gene. This variant is located in a highly conserved FYR C-terminal domain. According to the ACMG standards, the variant was classified as likely pathogenic (PM1, PM2, PP2, and PP4) (Supplementary Video 5 in the online-only Data Supplement).

Patient 6
A 20-year-old male, born to nonconsanguineous parents, with unexplained developmental delay presented with generalized dystonia of lower-limb onset from the age of 6 months. Additional manifestations included a bulbous nose tip, dolichocephaly of the skull and recent-onset psychosis. Brain MRI and metabolic work-ups were normal. The patient had an initial modest response to the levodopa trial. The clinical differentials considered were DRD and sequelae of HIE. WES revealed a novel heterozygous missense variant ([Chr19:g.36223433G>A;(NM_014727.3);c.5983G>A;p.Ala1995Thr]) in exon 28 of the KMT2B gene. Although the variant was identified as a VUS (PM2, PP2, PP3, PP4, and PP6) according to the ACMG guidelines, the recent guidelines for further classification of VUSs show that this variant carries a score of 4, which implies that the variant is more likely to be pathogenic than benign. Following an initial few months of modest response to levodopa, the patient’s response plateaued. Mild improvement occurred with symptomatic measures. Botulinum toxin led to minimal improvement of his cervical dystonia. The option of DBS was discussed, but the patient did not consent to the procedure (Supplementary Video 6 in the online-only Data Supplement).

Patient 7
A 13-year-old girl, born to third-degree consanguineous parents, presented with generalized dystonia, which initiated in the left foot at the age of 4 years. Generalization occurred over a period of 2 years, with maximal severity in the trunk. Truncal posturing was used to improve touching the torso to the wall,
suggestive of sensory tricks. Her facial features revealed a bulbous nose tip. Brain MRI and secondary work-up were normal. WES showed a novel heterozygous missense variant (Chr 19g.36218074T>A;NM_014727.3:c.4021T>A;p.Cys1341Ser) in exon 15 of the KMT2B gene. According to the ACMG guidelines, the variant was identified as likely pathogenic (PM2, PP2, PP3-S, and PP4) (Supplementary Video 7 in the online-only Data Supplement).

**KMT2B: Asian cohort**

Our search strategy identified 221 publications, of which 169 were subjected to abstract and title screening. Finally, 42 articles were identified, of which 16 articles involved patients of Asian descent. These 16 articles included a total of 35 cases of KMT2B-related dystonia and neurodevelopmental disorder (Supplementary Figure 1 in the online-only Data Supplement). Our current cohort of 7 cases from this study further extends the total number of cases to 42. Compared with the global data, the Asian cohort of KMT2B-related disorders had a lower female prevalence (38.1% vs. 57.6%). The proposed core clinical features of facial dysmorphism (54.8% vs. 66.1%), microcephaly (38.1% vs. 55.1%) and intellectual disability (40.4% vs. 57%) had comparatively lower prevalence in this subgroup. The additional manifestations of psychiatric symptoms (7.1% vs. 27.4%), ophthalmological involvement (2.4% vs. 30.7%), and dermatological features (2.4% vs. 10.3%) were also less prevalent. There were no reported cases of autism spectrum disorders in this cohort. The typically described brain MRI finding of hypointensity of the GP and associated hypointensity in the lateral streak of the GP on SWI sequences were less common in the Asian subpopulation (16.7% vs. 41.4%). Genetic analysis showed that protein-truncating variants (PTVs) were more common than missense variants in the Asian subgroup (n = 28, 66.8%), which is consistent with the global literature. Patients with missense variants had a greater prevalence of facial dysmorphism (n = 13, 92.9% vs. n = 10, 35.7%, p = 0.001), while microcephaly (n = 14, 50.0% vs. n = 2, 14.3%, p = 0.025) and short stature (n = 18, 64.3% vs. n = 2, 14.3%, p = 0.003) were more prevalent in the PTV subgroup (Table 1). A favorable response to DBS was observed in both the global and Asian patient cohorts with KMT2B dystonia, indicating a promising management approach (Table 2, Supplementary Tables 3 and 4 in the online-only Data Supplement).7

**DISCUSSION**

Our current study identified 7 unique variants in the KMT2B gene among patients with primary dystonia. The largest study thus far in the literature, published by Cif et al.7 in 2020, comprised 53 patients with confirmed KMT2B-related dystonia. They compared their cohort with 80 previously reported patients and summarized their findings of 133 patients with KMT2B-related dystonia and neurodevelopmental disorders. The most common causative mutations were protein-truncating variants (n = 103, 61.3%), followed by missense variants (n = 46, 27.4%) and chromosomal deletions (n = 18, 10.7%). Since that publication, there has been a further expansion of the literature with 18 scientific papers, comprising 60 additional patients with pathogenic, likely pathogenic or VUSs.5,20-36 A single report of a synonymous variant leading to the generation of a premature stop codon resulting in early-onset dystonia has also been published.4 In contrast to the world literature, the most common mutations

### Table 1. Comparison of clinicopathological parameters in the Asian cohort based on the type of mutation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Protein-truncating variants (n = 28)</th>
<th>Missense variants (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>16.4 ± 12.0</td>
<td>15.6 ± 5.8</td>
<td>0.766</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>6.0 (5–9.9)</td>
<td>9.0 (6.5–19.0)</td>
<td>0.063</td>
</tr>
<tr>
<td>Sex, male</td>
<td>18 (64.3)</td>
<td>8 (57.1)</td>
<td>0.742</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized dystonia</td>
<td>24 (85.7)</td>
<td>13 (92.9)</td>
<td>0.650</td>
</tr>
<tr>
<td>Multifocal dystonia</td>
<td>2 (7.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Segmental dystonia</td>
<td>-</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Dystonia absent</td>
<td>2 (7.1)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>First site involved*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb</td>
<td>14 (50.0)</td>
<td>9 (64.3)</td>
<td>0.515</td>
</tr>
<tr>
<td>Upper limb</td>
<td>7 (25.0)</td>
<td>3 (21.4)</td>
<td>0.560</td>
</tr>
<tr>
<td>Neck</td>
<td>3 (10.7)</td>
<td>1 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Larynx</td>
<td>2 (7.1)</td>
<td>1 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Trunk</td>
<td>2 (7.1)</td>
<td>1 (7.1)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Complex phenotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td>13 (46.4)</td>
<td>4 (28.6)</td>
<td>0.331</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>13 (46.4)</td>
<td>4 (28.6)</td>
<td>0.331</td>
</tr>
<tr>
<td>Facial dysmorphism</td>
<td>10 (35.7)</td>
<td>13 (92.9)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>14 (50.0)</td>
<td>2 (14.3)</td>
<td>0.025†</td>
</tr>
<tr>
<td>Short stature</td>
<td>18 (64.3)</td>
<td>2 (14.3)</td>
<td>0.003†</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td>-</td>
<td>3 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>4 (14.3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ophthalmologic symptoms</td>
<td>-</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Dermatologic symptoms</td>
<td>-</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>MRI abnormality</td>
<td>4 (14.3)</td>
<td>2 (14.3)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent DBS</td>
<td>14 (50.0)</td>
<td>3 (21.4)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation, n (%) or median (interquartile range) unless otherwise indicated. *Five patients had simultaneous onset involving more than one site; †p-value is significant. MRI, magnetic resonance imaging; DBS, deep brain stimulation.
in the KMT2B gene in our study cohort were missense mutations (n = 5), followed by two PTVs (Table 2, Supplementary Tables 3 and 4 in the online-only Data Supplement).

**Indian cohort of patients with KMT2B-related disorders**

To the best of our knowledge, this is the largest series of patients with KMT2B-related dystonia from India. There have been three previously reported cases from India.28,30,31 The prevalent mutations detected in the Indian cohort diverge from the global data, as missense variants in the KMT2B gene were identified as the most frequent occurrence instead of PTVs (Table 2).7 The overwhelming predominance of missense variants in the Indian cohort (80%) can explain the overall lower prevalence of systemic features and the relatively older age of onset when compared to the global data.7 Some neurodevelopmental attributes, such as intellectual disability, short stature, microcephaly and lack of family history, predispose patients with KMT2B-related disorders to the misdiagnosis of dyskinetic cerebral palsy, as has been described with several other genetically mediated hyperkinetic movement disorders, such as monoamine neurotransmitter disorders and ADCY5-, NKX2-1-, PDE10A-, GPR88-, GNBI- and PDE2A-related dyskinesia.37 The absence of a positive family history is an important factor because history is not often truly revealed due to the prevalent social stigma associated with genetic disorders in this part of the world.

Table 2. Comparison of clinical, neuroimaging and genotype data of patients with KMT2B-related disorders in different subgroups

<table>
<thead>
<tr>
<th></th>
<th>Indian cohort*</th>
<th>Asian cohort</th>
<th>Cif et al.’2020 (extended cohort)</th>
<th>Analysis of all cases after Cif et al.’2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>10</td>
<td>42†</td>
<td>133</td>
<td>67†</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>40</td>
<td>38.1</td>
<td>57.6</td>
<td>43.1</td>
</tr>
<tr>
<td>Median AAO in years (IQR [range])</td>
<td>6.5 (1.4–9.8) [2–20]</td>
<td>7 (5–11.5) [1 month–43]</td>
<td>5 (3.9–7) [0.2–43]</td>
<td>8 (5–14) [0–69]</td>
</tr>
<tr>
<td>Median duration to generalization in years (IQR [range])</td>
<td>2 (1.5–3) [2 months–6]</td>
<td>2 (1–7) [1 month–22]</td>
<td>2 (1–5) [0–10.5]</td>
<td>3 (1–9) [1 month–22]</td>
</tr>
<tr>
<td>Dystonia</td>
<td>10 (100)</td>
<td>40 (95.2)</td>
<td>123 (92.5)</td>
<td>59/67 (88.1)</td>
</tr>
<tr>
<td>Complex phenotypes††</td>
<td>Developmental delay</td>
<td>2 (20)</td>
<td>17 (40.4)</td>
<td>46.7</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
<td>3 (30)</td>
<td>17 (40.4)</td>
<td>57.0</td>
</tr>
<tr>
<td></td>
<td>Autism spectrum disorder</td>
<td>-</td>
<td>-</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>Short stature</td>
<td>1 (10)</td>
<td>20 (48.0)</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>Microcephaly</td>
<td>2 (20)</td>
<td>16 (38.1)</td>
<td>55.1</td>
</tr>
<tr>
<td></td>
<td>Facial dysmorphism</td>
<td>5 (50)</td>
<td>23 (54.8)</td>
<td>66.1</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathies</td>
<td>-</td>
<td>4 (9.5)</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>Ophthalmological manifestations</td>
<td>1 (10)</td>
<td>1 (2.4)</td>
<td>30.7</td>
</tr>
<tr>
<td></td>
<td>Psychiatric symptoms</td>
<td>1 (10)</td>
<td>3 (7.1)</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>Dermatological features</td>
<td>1 (10)</td>
<td>1 (2.4)</td>
<td>10.3</td>
</tr>
<tr>
<td>MRI abnormality††</td>
<td>4 (40)</td>
<td>7 (16.7)</td>
<td>41.4</td>
<td>7/46 (15.2)</td>
</tr>
<tr>
<td>Genetetic mutations</td>
<td>Missense</td>
<td>8 (80)</td>
<td>14 (33.3)</td>
<td>35 (26.3)</td>
</tr>
<tr>
<td></td>
<td>PTV§</td>
<td>2 (20)</td>
<td>28 (66.8)</td>
<td>80 (60.2)</td>
</tr>
<tr>
<td></td>
<td>Chromosomal deletion</td>
<td>0 (0)</td>
<td>-</td>
<td>18 (13.5)</td>
</tr>
<tr>
<td>Management††</td>
<td>DBS</td>
<td>1 (10)</td>
<td>17 (40.5)</td>
<td>44.8</td>
</tr>
<tr>
<td></td>
<td>Positive response to DBS</td>
<td>1/1 (100)</td>
<td>17/17 (100)</td>
<td>100</td>
</tr>
</tbody>
</table>

Values are presented as n (%) or median (IQR [range]) unless otherwise indicated. *comprises seven patients from the current study (7 patients) and one patient each from Rajan et al.28 2021, Pandey et al.30 2020 and Padmanabha et al.31 2021; †includes 7 patients from the current study; ‡comprises frameshift, premature stop codons and splice-site variants; §comprises deletions and insertions; ¶psychosis in one patient; **acne vulgaris and premature graying in one patient; ††values in ‘Cif et al.’2020 (extended cohort) column represent only percentage; †‡this value represents only percentage. IQR, interquartile range; AAO, age at onset; MRI, magnetic resonance imaging; PTV, protein-truncating variant; DBS, deep brain stimulation.
Asian cohort of patients with KMT2B-related disorders

Previous studies have shed light on the differences in the phenotypic profile of dystonia across various ethnicities.\(^3\) The study by Almasy et al.\(^3\) in the mid-nineties expanded the outlook on ethnic differences beyond the conventional knowledge of greater affliction of idiopathic torsion dystonia among the Ashkenazi Jews. Their important observation of the phenotypic difference between the Jewish and non-Jewish dystonia cohorts paved the way for further research. As revealed in previous studies, patients with PTVs have a greater prevalence of systemic manifestations, such as microcephaly and short stature.\(^7\) This serves to highlight the fact that genotype rather than ethnicity plays a major role in determining the phenotype. It has been postulated that KMT2B haploinsufficiency or dysfunction may impact the expression of key genes that regulate neurodevelopment and motor control. Studies in mice have shown that knockout of KMT2B in the forebrain leads to altered expression of several dystonia-causing genes, leading to the motor phenotype.\(^2\) However, it is important to note that KMT2B-related phenotypes may also be influenced by other factors, such as epigenetic modifications and environmental variables.\(^7\) Further research is necessary to determine the precise mechanisms by which KMT2B mutations affect downstream gene expression and the role of other factors in the manifestation of KMT2B-related phenotypes (Table 2, Figure 2, Supplementary Table 3 in the online-only Data Supplement).

Limitations

One of the major limitations of this study is that functional investigations to understand pathogenicity were not performed, and parental genetic testing and familial segregation analysis were not performed for all patients. Formal assessment of intellectual disability was not available in our patients, which was attributed to severe motor disability that interfered with detailed neuropsychological testing. The therapeutic options were severely constrained due to a lack of financial support for DBS.

Conclusions

This study elucidates the clinical profile of six novel mutations in the KMT2B gene that have been identified as potentially pathogenic and linked to the causation of early-onset dystonia. It expands the literature on genetic dystonia with respect to the Indian population with the largest sample size from the country thus far. In addition, the extended Asian cohort emphasizes the key phenotypic and genotypic attributes of KMT2B-related dystonia and neurodevelopmental disorders in this part of the world.

Supplementary Video Legends

Video 1. Video of Patient 1 showing facial dysmorphism, scoliosis, and severe disabling generalized dystonia.

Video 2. Video of Patient 2 showing facial dysmorphism, bulbous nose tip, and prominent cranio cervical and perioral dystonia with mild truncal involvement.
Video 3. Video of Patient 3 showing generalized dystonia.
Video 4. Video of Patient 4 showing facial dysmorphism, bulbous nose tip, microcephaly, and severely disabling generalized dystonia.
Video 5. Video of Patient 5 showing elongated faces, bulbous nose tip, and generalized dystonia.
Video 6. Video of Patient 6 showing facial dysmorphism, elongated faces, bulbous nose tip, and generalized dystonia.
Video 7. Video of Patient 7 demonstrating generalized dystonia.

Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.23035.

Conflicts of Interest
The authors have no financial conflicts of interest.

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Author Contributions

ORCID IDs
Debjyoti Dhar https://orcid.org/0000-0002-4835-4698
Vikram V Holla https://orcid.org/0000-0002-3634-2219
Riyanka Kumari https://orcid.org/0000-0002-6550-8305
Neerharika Sriram https://orcid.org/0000-0002-7736-8597
Jitender Saini https://orcid.org/0000-0002-5218-0264
Ravi Yadav https://orcid.org/0000-0002-8016-9089
Akhilesh Pandey https://orcid.org/0000-0001-9943-6127
Nitish Kamble https://orcid.org/0000-0002-7933-8826
Babylakshmi Muthusamy https://orcid.org/0000-0002-2257-3630
Pramod Kumar Pal https://orcid.org/0000-0002-4085-2377

References


