Title: Review of the phenotype of early-onset generalised progressive dystonia due to mutations in \textit{KMT2B}

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\textbf{Key-words}
\textit{KTM2B}; dystonia; microdeletions; genetic and inherited disorders

\textbf{Abbreviations}
\begin{tabular}{ll}
CNV & Copy number variants \\
GPI-DBS & Globus pallidus interna-deep brain stimulation \\
ID & Intellectual disability \\
MLPA & Multiplex ligation-dependent probe amplification \\
MRI & Magnetic resonance imaging \\
NGS & Next generation sequencing \\
PEG & Percutaneous endoscopic gastrostomy \\
PPTV & Predicted protein-truncating variants \\
WES & Whole exome sequencing \\
WGS & Whole genome sequencing \\
\end{tabular}

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Highlights

- Microdeletions and intragenic variants in \( KMT2B \) are associated with early onset progressive dystonia, with predominant cervical and oromandibular involvement.
- GPI-DBS should be considered early in the disease course, as medical therapy is of limited benefit.
- Microarray should be included in first tier genetic testing in children and adults with dystonia.
Abstract

In 2016, two research groups independently identified microdeletions and pathogenic variants in the lysine-specific histone methyltransferase 2B gene, \textit{KMT2B} in patients with early-onset progressive dystonia. \textit{KMT2B}-dystonia (DYT28) is emerging as an important and frequent cause of childhood-onset progressive generalised dystonia and is estimated to potentially account for up to 10\% of early-onset generalised dystonia. Herein, we review variants in \textit{KMT2B} associated with dystonia, as well as the clinical phenotype, treatment and underlying disease mechanisms. Furthermore, in context of this newly identified condition, we summarise our approach to the genetic investigation of paediatric dystonia.
Introduction

Dystonia is a hyperkinetic movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive movements and postures affecting the limbs, trunk, neck and face. Dystonic movements are typically patterned, twisting, and may be tremulous, and they are often initiated or worsened by voluntary action and associated with overflow muscle activation.\(^1\) Childhood-onset dystonia may be acquired or genetic in origin, and can occur in isolation or in association with other movement disorders, neurological or systemic manifestations.\(^1\)

With the advent of next generation sequencing (NGS), new genetic causes of childhood-onset movement disorders have been identified, as well as phenotypic expansion of known dystonia genes.\(^2\)\(^-\)\(^4\) Despite these advances, a significant number of children and adults remain without a genetic diagnosis. It is likely that gene discovery in dystonia is complicated by reduced penetrance and intrafamilial variability, which make the interpretation of new variants more challenging. The identification of a genetic diagnosis is key to optimising clinical care, as it enables informed genetic counselling, disease prognostication and targeted disease-specific treatments.

In 2016, two groups independently identified microdeletions and pathogenic variants in the lysine-specific histone methyltransferase 2B gene, \textit{KMT2B} in patients with early onset progressive dystonia.\(^5\)\(^,\)\(^6\) \textit{KMT2B} (Chr. 19:35,717,817-35,738,879, hg38, OMIM 606834) has a key role in gene expression and transcription activation. Though only recently reported, \textit{KMT2B}\(^-\)dystonia (DYT28) is emerging as an important and frequent cause of childhood-onset progressive generalised dystonia and may account for up to 10% of early-onset generalised dystonia.\(^2\) Herein, we review variants in \textit{KMT2B} associated with dystonia, as well as the clinical phenotype, treatment and underlying disease mechanisms. Furthermore, in context of this newly identified condition, we summarise our approach to the genetic investigation of paediatric dystonia.

Clinical characteristics

To date, 43 patients with \textit{KMT2B} variants are published including cases with microdeletions encompassing the gene (n=14), as well as intragenic predicted protein-truncating variants (PPTV) (n=17) and nonsynonymous missense variants (n=12).\(^5\)\(^,\)\(^9\) The clinical phenotype is of an early onset progressive dystonia, which typically begins in the lower limbs. The dystonia becomes generalised over time (range 1-9 years, mean 4.4 years) with cervical (retrocollis
and torticollis), oromandibular (facial dystonia, and bulbar-oromandibular) and laryngeal
dysphonia and spasmodic laryngeal spasm) involvement. Bulbar features are often
predominant and present in the majority; some patients develop disabling dysarthria
progressing to anarthria as well as swallowing difficulties necessitating percutaneous
gastrostomy (PEG) tube for nutrition. Bulbar symptoms may be present at the
onset of dystonia or develop over time. The clinical phenotype of previously described cases
is summarised in Table 1.

Early phenotype-genotype correlation studies indicate that, chromosomal microdeletions and
PPTV present at a statistically significant younger age, when compared to intragenic missense
variants (mean age of 4.82 years compared to 11.75 years). In addition, patients with
nonsynonymous variants have fewer co-existing systemic and neurological findings or pre-
exisiting development delay (Table 1) when compared to those with microdeletions or
PPTVs. Dysmorphic features of an elongated face, broad nasal base, bulbous nasal tip, fifth-
finger clinodactyly or second and third syndactyly has been identified in some patients, and
more frequently in those with microdeletions and PPTV. Other reported systemic features
include preceding developmental delay (38%), intellectual disability (ID) (57%, mild to
severe), microcephaly (21% of cohort, only reported in PPTV and microdeletions) and short
stature (21%). Dermatological (cutis aplasia, abnormal scarring) systemic (renal and
respiratory), ophthalmological (oculomotor apraxia, strabismus) and psychiatric symptoms
are also reported in some individuals (Table 1). As with other dystonia genes, atypical
phenotypes are reported including, dystonia presenting later in adulthood (Patient 26b5,
Patient 37), paroxysmal cervical dystonia only (Patient 26a3), oromandibular dystonia with no
lower limb dystonia (Patient 185), or only dystonia of lower limbs (Patient 105).

**Neuroimaging features**

Meyer and colleagues noted subtle, symmetrical hypointensity of the globus pallidi
-especially the lateral aspect of the globus pallidus externa) on T2, diffusion and susceptibility
weighted magnetic resonance imaging (MRI) images in 17 of 22 reviewed scans (Figure 1).5
The significance of this hypointensity is unclear and may be an age-dependent finding.
Patient age at the time of scan appears to influence MRI findings, as globus pallidus externa
hypointensity was more prevalent in individuals who had neuroimaging performed at a
younger age (average age of patients with abnormal imaging, 11.7 years; average age of
patients with normal imaging 19 years) and in one patient was seen to diminish with
increasing age.5
Treatment
Dystonia-specific medications and levodopa trials have had minimal or no clinical benefit in patients with KMT2B-dystonia. To date, 13 patients have had globus pallidus interna-deep brain stimulation (GPI-DBS, mean age of insertion 21.7 years, range 6-53 years) with a clinical response evident in all patients. In some patients after GPI-DBS, there was a remarkable improvement in motor function and return of independent ambulation. Published data therefore suggests that GPI-DBS should be considered early in the disease course of KMT2B-dystonia.

KMT2B Variants reported to date
To date, 40 different variants are reported including heterozygous interstitial microdeletions (n=14), PPTV (frameshift, splice-site and stop-gain variants) (n=15) and nonsynonymous variants of KMT2B (n=11) (Table 1). There are no recurring variants or mutation hotspots, though described variants are frequently located in key protein domains, including the catalytic SET domain. The majority of the variants in KMT2B occurred de novo, but rarely autosomal dominant inheritance with reduced penetrance is reported. Symptomatic relatives (patient 26b, F4-II-4 and F4-I-3) and asymptomatic carriers [mothers of patient 22 and 27, adult daughters (aged 32 and 34 years) of patient 3] are described. Symptomatic parents appear to have a milder phenotype than their children, often with later onset dystonia and fewer systemic features. Incomplete penetrance is not unique to KMT2B-dystonia and reported in many other genetic dystonia (DYT1, DYT2).

Disease Mechanisms in KMT2B dystonia
KMT2B encodes lysine methyltransferase 2B, specifically involved in the methylation of histone H3 at lysine 4 (H3K4). This is an important epigenetic regulator involved in gene expression and transcription activation, considered essential for normal development and to maintain proper neural function. The underlying mechanism of how KMT2B causes dystonia is not fully elucidated. KMT2B is ubiquitously expressed during brain development and in the adult brain, with the highest expression in areas of motor control and cerebellum. KMT2B gene expression on qRT-PCR analysis was significantly reduced for microdeletion and PPTV variants compared to control fibroblasts. Preliminary work has also shown that KMT2B variants are associated with reduced transcript levels of both THAP1 and TOR1A in fibroblasts. It is proposed that variants in KMT2B affect the expression (including transcriptional stability and consistency) of a specific set of genes crucial to normal motor control.
How to approach the investigation of a child with dystonia

The discovery of KMT2B-related disease further highlights the clinical need for a systematic approach to the genetic investigation of early-onset dystonia. Dystonia may occur in isolation or associated with other neurological and systemic features. Careful clinical history and detailed examination can aid diagnosis and direct further diagnostic testing.

Children with dystonia may often be labelled early in their disease course as having “dyskinetic” or “dystonic cerebral palsy”. However, a number of inherited conditions can mimic cerebral palsy and should be suspected, especially in the presence of “clinical red flags” which are rarely seen in acquired forms of cerebral palsy. Indeed, absence of a perinatal hypoxic ischemic insult, similarly affected family members, normal MRI brain (or neuroimaging features atypical for acquired cerebral palsy) and a progressive disease course would all increase clinical suspicion of an underlying genetic or neurometabolic condition (Yellow box, Figure 2). If neuroimaging and first-line neurometabolic investigations are negative, then genetic testing is the next step in the diagnostic algorithm (Figure 2).

Chromosomal microarray should be considered as a first-line genetic evaluation in children and adults presenting with dystonia, especially in the presence of additional features such as dysmorphism or ID. In a single centre review of children and adults with movement disorders, 28% had a significant copy number variant (CNV) detected on routine diagnostic microarray. Pathogenic microdeletions encompassing causative genes have been described in individuals with dystonia (KMT2B), myoclonus-dystonia (SGCE) and benign hereditary chorea (TTTF1). CNVs and are not usually detected on gene-panels or whole exome sequencing (WES), and pathogenic deletions and duplications could be potentially missed. However, over time, the increased availability of whole genome sequencing (WGS) will facilitate future CNV analysis. Chromosomal microarray should therefore be performed in all individuals presenting with dystonia associated with additional features. CNVs should also be excluded in those with a very distinct phenotype (e.g. myoclonus-dystonia) when direct Sanger sequencing is negative, either via microarray or targeted gene multiplex ligation-dependent probe amplification (MLPA).

In recent years, single gene testing has been generally surpassed by gene panels, a cost-effective route by which to analyse multiple genes associated with a specific disorder. However, single gene testing may still have some clinical utility for distinct phenotypes (e.g. movement disorder with a low CSF:plasma glucose ratio – SLC2A1). A number of diagnostic targeted next-generation gene panels are now available, which sequence genes
associated with movement disorders. Genes included in a gene panel will vary depending on
the laboratory, and may not include newly identified dystonia genes. A retrospective review
in a single tertiary centre estimated the diagnostic yield of a panel at 14.8% compared to 7.4%
if the traditional route of consecutive single gene testing was undertaken. Some diagnostic
gene panels will also offer MLPA to identify CNVs.

At present, WES is becoming increasingly available in a clinical setting with a number of
diagnostic laboratories undertaking clinical exomes for targeted gene analysis. The ability to
interrogate WES data for recently identified genes is an added advantage, many of which are
not always available immediately on established gene panels. However differential coverage
of individual genes can be an issue. Research WES and WGS has certainly aided the
identification of new disease-causing dystonia genes, as well as expanding the genotype and
phenotype of known dystonia genes. Next generation sequencing should, therefore, be
considered in patients with negative first tier investigations or atypical phenotypes. The
diagnostic rate of WES in a single publication was 37.5%, with the yield likely to be higher in
early onset generalised dystonia cohorts, where genetic dystonia is highly suspected.

Conclusion
In conclusion, microdeletions and intragenic variants of KMT2B are an important cause of
childhood-onset progressive dystonia. Clues to diagnosis include early onset dystonia
(usually of the lower limbs) with generalisation, and predominant cervical, oromandibular
and laryngeal involvement. Additional clinical features include neurological, dermatological,
psychiatric and systemic features. The identification of KMT2B should prompt early referral
for GPI-DBS. For childhood dystonia suspected to be genetic in origin, microarray should be
considered as a first-tier genetic investigation before performing gene panels and
diagnostic/research WES and WGS.
References


<table>
<thead>
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<th>Pat *</th>
<th>KMT2B variant inheritance</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Presenting dystonia and other features</th>
<th>Current pattern of dystonia</th>
<th>ID</th>
<th>Dysmorphic features</th>
<th>Other features</th>
<th>Treatment- Benefit</th>
<th>DBS (age)- response</th>
<th>MRI pattern * Age</th>
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<td>M</td>
<td>Bill, BiUL</td>
<td>Cervical</td>
<td>Oromandibular</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>24( ) (20)</td>
<td>c.4966_4968TCCdel p.Ser1656del De novo</td>
<td>10</td>
<td>F</td>
<td>Bill, BiUL</td>
<td>R hand dystonic tremor</td>
<td>4</td>
<td>BILL, BiUL</td>
<td>Cervical</td>
<td>Oromandibular</td>
<td>Dysarthria</td>
<td>Action induced myoclonus</td>
</tr>
<tr>
<td>25( ) (20)</td>
<td>c.3528+2T&gt;A Unknown</td>
<td>40</td>
<td>M</td>
<td>Bill, BiUL</td>
<td>Cervical</td>
<td>Oromandibular</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>26( ) (21)</td>
<td>c.6406delC p.Leu2136Serfs*17 De novo</td>
<td>31</td>
<td>F</td>
<td>Bill, BiUL</td>
<td>Cervical</td>
<td>Oromandibular</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pat</td>
<td>AMF2B variant</td>
<td>Inheritance</td>
<td>Age (y)</td>
<td>Sex</td>
<td>Presenting dystonia and other features</td>
<td>Age (y)</td>
<td>Current pattern of dystonia</td>
<td>ID</td>
<td>Dysmorphic features</td>
<td>Other features</td>
<td>Treatment-Benefit</td>
</tr>
<tr>
<td>------</td>
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<td>----------------------------------------</td>
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<td>--------------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>27*</td>
<td>c.1633C&gt;T</td>
<td>F2-II-1</td>
<td>11</td>
<td>F</td>
<td>BILL</td>
<td>3</td>
<td>BILL, BiUL</td>
<td>No</td>
<td>NR</td>
<td>Neurological (microcephaly and strabismus) Systemic (short stature, VUR) Moderate motor delay</td>
<td>L-dopa- no benefit Anticholinergics –NR</td>
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<tr>
<td>29*</td>
<td>c.2482C&gt;T</td>
<td>F4-III-2</td>
<td>6</td>
<td>F</td>
<td>L. foot</td>
<td>4</td>
<td>BiLL</td>
<td>Mild</td>
<td>NR</td>
<td>Neurological (microcephaly, astigmatism) Systemic (short stature) Global DD</td>
<td>L-dopa- NR</td>
</tr>
<tr>
<td>30*</td>
<td>c.2482C&gt;T</td>
<td>F4-II-4</td>
<td>36</td>
<td>M</td>
<td>Hand cluminess</td>
<td>9</td>
<td>Hand- writer cramp</td>
<td>Mild</td>
<td>NR</td>
<td>Neurological (microcephaly, astigmatism) Systemic (short stature) Speech delay</td>
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<tr>
<td>31*</td>
<td>c.2482C&gt;T</td>
<td>F4-I-3</td>
<td>61</td>
<td>M</td>
<td>Hand cluminess</td>
<td>11</td>
<td>Limb (writer-cramp)</td>
<td>Mild</td>
<td>NR</td>
<td>Speech delay</td>
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<tr>
<td>32*</td>
<td>c.4955G&gt;A</td>
<td>F1-II-2</td>
<td>18</td>
<td>M</td>
<td>RLL</td>
<td>6</td>
<td>BiLL, BiUL</td>
<td>Mild</td>
<td>Elongated face</td>
<td>Systemic (short stature) Dermatological (hypertichosis)</td>
<td>Yes (15y)- Clinical response</td>
</tr>
<tr>
<td>33*</td>
<td>c.4986C&gt;A</td>
<td>F1-II-3</td>
<td>20</td>
<td>F</td>
<td>RLL</td>
<td>5</td>
<td>BiLL, BiUL</td>
<td>No</td>
<td>Elongated face</td>
<td>Bulbous nasal tip</td>
<td>L-dopa trial- no benefit THP- not tolerated</td>
</tr>
<tr>
<td>34*</td>
<td>c.5114G&gt;A</td>
<td>F1-II-4</td>
<td>8</td>
<td>M</td>
<td>BiLL</td>
<td>3</td>
<td>BiLL, BiUL</td>
<td>Mild</td>
<td>Elongated face</td>
<td>Bulbous nasal tip Broad phaltrum Up-slanted eyes Low-set ears Periorbital fullness Gap between front teeth</td>
<td>L-dopa trial- no benefit CLZ, THP, IT</td>
</tr>
<tr>
<td>35*</td>
<td>c.5284C&gt;T</td>
<td>F1-II-5</td>
<td>27</td>
<td>F</td>
<td>LLL</td>
<td>6</td>
<td>BiLL, BiUL</td>
<td>No</td>
<td>No</td>
<td>Neurological (ocularmotor apraxia with difficulty initiating saccades) Systemic (short stature)</td>
<td>L-dopa trial- no benefit THP- no benefit</td>
</tr>
</tbody>
</table>

*Pat: Patient

**AMF2B variant:** Genetic variation in the AMF2B gene

**Inheritance:** Genetic mode of inheritance

**Age (y):** Age in years

**Sex:** Gender

**Presenting dystonia and other features:** Symptoms and associated conditions

**Current pattern of dystonia:** Type and severity

**ID:** Identification

**Dysmorphic features:** Physical anomalies

**Other features:** Additional medical conditions

**Treatment-Benefit:** Medical treatments and their benefits

**DBS (age)-response:** Deep brain stimulation response at specified age

**MRI pattern + Age:** MRI pattern and associated age

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* indicates cases with specific genetic or inheritance type.
<table>
<thead>
<tr>
<th>Pat</th>
<th>KM72B variant</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Presenting dystonia and other features Age (y)</th>
<th>Current pattern of dystonia</th>
<th>ID</th>
<th>Dysmorphic features</th>
<th>Other features</th>
<th>Treatment</th>
<th>DBS (age)- response</th>
<th>MRI pattern</th>
<th>Age</th>
</tr>
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<tbody>
<tr>
<td>36</td>
<td>c.5342T&gt;C p. Leu1781Pro De novo</td>
<td>19</td>
<td>F</td>
<td>R.L. foot posturing Gait disturbance 8</td>
<td>BLL, BiUL Cervical (torticollis) Oromandibular (dysarthria, swallowing difficulties Laryngeal (dysphonia)</td>
<td>No</td>
<td>Eliminated face Bulbous nasal tip</td>
<td>NR</td>
<td>L-dopa trial – no benefit LVT – mild benefit</td>
<td>Yes (19y)</td>
<td>Clinical response Improved walking</td>
<td>Yes</td>
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<tr>
<td>37</td>
<td>c.7549C&gt;T p. Arg2517Tnp Maternal</td>
<td>8</td>
<td>M</td>
<td>Delayed motor and speech development 8</td>
<td>Cervical (severe panaxymal retricollis) Oromandibular (jaw dystonia)</td>
<td>No</td>
<td>Bulbous nasal tip</td>
<td>Psychiatric (ADHD)</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>38</td>
<td>c.7549C&gt;T p. Arg2517Tnp De novo</td>
<td>46</td>
<td>F</td>
<td>BiUL Posturing Torticollis Inability to walk long distances or run 23</td>
<td>BLL, BiUL Cervical (torticollis) Laryngeal (dysphonia)</td>
<td>No</td>
<td>Bulbous nasal tip</td>
<td>Neurological (Idiopathic intracranial hypertension)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>39</td>
<td>c.8021T&gt;C p. Ile2674Thr Maternal</td>
<td>19</td>
<td>F</td>
<td>RUL Posturing Tremor Poor handwriting Myoclonic jerks 9</td>
<td>BILL, BiUL Oromandibular Laryngeal (dysphonia)</td>
<td>Mild</td>
<td>Bulbous nasal tip</td>
<td>Psychiatric (anxiety, self-harm, OCD)</td>
<td>L-dopa trial- no benefit THP-no benefit LVT-no benefit CBZ-initial benefit, not sustained CLZ- not tolerated</td>
<td>No</td>
<td>NA</td>
<td>10y</td>
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<td>40</td>
<td>c.3700G&gt;A p. Glu1234Lys De novo</td>
<td>21</td>
<td>M</td>
<td>L LL dystonia-exercise induced 17</td>
<td>BLL, BiUL Cervical Oromandibular Laryngeal (spasmodic dysphonia)</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>L-dopa trial – no benefit Anticholinergics- partial benefit</td>
<td>No</td>
<td>No^</td>
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<td>41</td>
<td>c.4622C&gt;T p. Ala1541Val^ Unknown</td>
<td>60</td>
<td>M</td>
<td>Generalised 43</td>
<td>BiUL Cervical Oromandibular (dysarthria) Laryngeal (dysphonia)</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>L-dopa trial</td>
<td>Yes (53y)- clinical response</td>
<td>No^</td>
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<tr>
<td>42</td>
<td>c.5336G&gt;A p. Arg1779Gln^ Unknown</td>
<td>52</td>
<td>F</td>
<td>LL posturing 7</td>
<td>BiUL, BiUL, trunk Cervical (retro-torticollis) Oromandibular (lingual, dysarthria)</td>
<td>No</td>
<td>NR</td>
<td>L-dopa trial</td>
<td>Yes (43y)- clinical response</td>
<td>No^</td>
<td></td>
<td></td>
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<tr>
<td>43</td>
<td>c.4847C&gt;T p. Ala1616Val De novo</td>
<td>13</td>
<td>F</td>
<td>Trunk 6</td>
<td>BiUL, BiUL, trunk Cervical</td>
<td>Mod</td>
<td>Bulbous nasal tip</td>
<td>Neurological (strabismus) Other (SNHL)</td>
<td>NR</td>
<td>NR</td>
<td>No^</td>
<td></td>
</tr>
</tbody>
</table>

^, Not analyzed by Meyer and Colleagues; +, number in brackets refers to patient number in original paper; *, typical pattern of bilateral subtle hypointensity of the globus pallidi (especially the lateral aspect of the globus pallidus externa) on T2, diffusion and susceptibility weighted MRI images; BiLL, Bilateral lower limbs; BiUL, Bilateral upper limbs; BLF, baclofen; BTX, botulinum toxin; CLZ, clonazepam; CHD, congenital heart disease; CLZ, clonazepam; DD, developmental delay; F, female; GD, generalised dystonia; GBP, gabapentin; IT, intrathecal; IUGR, intra-uterine growth retardation; L, left; LL, lower limb; LVT, levetiracetam; M, male; m, months; mod, moderate; NA, not analysed; NR, not recorded; Pat, Patient; PEG, percutaneous endoscopic gastrostomy; Sev, severe; SNHL, sensorineural hearing loss; SUL, sulpiride; R, right; TBZ, tetrabenazine; THP, trihexyphenidyl; UL, upper limbs; y, years
Figure 1: Radiological features of KMT2B variants. MR imaging (Patient 1, age 9 years, 5 months) T2-weighted (A), echo-planar technique diffusion image with b value of zero (B) and susceptibility-weighted sequences (C). Abnormal findings are indicated by yellow arrows with evidence of bilateral subtle hypointensity of the globus pallidus with hypointense lateral streak of globus pallidus externa. Figure is modified with permission from Meyer et al., 2017. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet 2017;49(2):223–37.

Figure 2 Diagnostic algorithm for the investigation of a child presenting with dystonia
*Neurometabolic investigations of dystonia
Blood: Amino acids, lactate, creatine kinase, biotinidase, renal and liver profile, glucose, copper, caeruloplasmin, urate, thyroid function tests, ammonia, acylcarnitine profile
Urine: Organic acids, copper, guanidinoacetate
CSF: Neurotransmitters, glucose and lactate (paired with serum samples)
^Sheffield Dystonia and Parkinson Panel (28 genes)
AFG3L2, ANO3, ATP1A3, ATP7B, CYP27A1, FA2H, FTL, GBA, GCH1, GNAL, LRRK2, MAPT, PANK2, PARK2, PARK7, PINK1, PNKD, PRKCG, PRRT2, SGCE, SLC16A2, SLC2A1, SNCA, SPG11, SPR, TH, THAP1, WDR45
CNV, Copy number variants; EBV, Epstein Barr Virus; ID, Intellectual disability; MLPA, Multiplex ligation-dependent probe amplification; MRI, Magnetic resonance imaging; WES, Whole exome sequencing; WGS, Whole genome sequencing

Table 1: Table of KMT2B variants, dystonia phenotype, response to treatment and additional clinical features
^, Not analyzed by Meyer and Colleagues; +, number in brackets refers to number in original paper; *, typical pattern of bilateral subtle hypointensity of the globus pallidus (especially the lateral aspect of the globus pallidus externa) on T2, diffusion and susceptibility weighted MRI images; BiLL, bilateral lower limbs; BiUL, bilateral upper limbs; BLF, baclofen; BTX, botulinum toxin; CLZ, clonazepam; CHD, congenital heart disease; CLZ, clonazepam; F, female; GD, generalised dystonia; GBP, gabapentin; IT, intrathecal; IUGR, intra-uterine growth retardation; L, left; LL, lower limb; LVT, levetiracetam; M, male; m, months; mod, moderate, NA, not analysed; NR, not recorded; Pat, patient; PEG, percutaneous endoscopic gastrostomy; Sev, severe; SNHL, sensorineural hearing loss; SUL, sulpiride; R, right; TBZ, tetrabenazine; THP, trihexyphenidyl; UL, upper limbs; y, years
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