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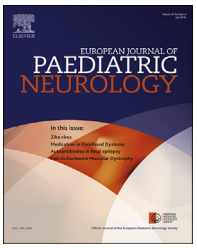

Review article

Review of the phenotype of early-onset generalised progressive dystonia due to mutations in *KMT2B*

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ABSTRACT

In 2016, two research groups independently identified microdeletions and pathogenic variants in the lysine-specific histone methyltransferase 2B gene, *KMT2B* in patients with early-onset progressive dystonia. *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 *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.

Contents

abbreviations: 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.

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1. 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, *KMT2B* in patients with early onset progressive dystonia.[5,6] *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, *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 *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.

2. Clinical characteristics

To date, 43 patients with *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 endoscopic 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-existing 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 26b,[5] Patient 3[7]), paroxysmal cervical dystonia only (Patient 26a[5]), oromandibular dystonia with no lower limb dystonia (Patient 18[5]), or only dystonia of lower limbs (Patient 10[5]).

3. 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 (Fig. 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]

4. 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.[5–7] Published data therefore suggests that GPI-DBS should be considered early in the disease course of *KMT2B*-dystonia.

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