DYT30 due to *VPS16* Mutation: An Etiology of Childhood-Onset Generalized Dystonia

Sir,

The mutation in the *VPS16* gene is associated with early-onset generalized dystonia with prominent oromandibular, bulbar, cervical, and upper-limb involvement and is labeled as DYT30 (OMIM ID: 619291). Apart from the dystonia, patients may have intellectual disability and neuropsychiatric signs. The inheritance in majority of patients is autosomal dominant. There is no report of DYT30 from India. Hereby, we report on a 36-year-old male patient who had limb-onset dystonia at 10 years of age that generalized involving cranial, cervical, and truncal musculature. Whole exome sequencing (WES) showed a novel mutation in the *VPS16* gene (p.Arg525Ter variant).

A 36-year-old male patient, born out of non-consanguineous parentage, is the fourth born out of five siblings with a normal perinatal and development history. He developed dystonic posturing of the right foot at the age of 10 years, followed by right upper limb dystonia, initially during action, followed by rest by 2 years of the onset of symptoms. At the age of 15 years, he developed dystonic posturing of the left foot and left upper limb. Subsequently, at the age of 18 years, he developed facial dystonia involving the lips and tongue, causing speech and swallowing difficulties. There was no tongue, lips, or cheek bite. At the age of 20 years, the patient had cervical and truncal dystonia, causing difficulty in ambulation, but he was still independent. At the age of 36 years, he presented to us in dystonic crisis following a febrile illness and became bed-bound. There was no history of jaundice, seizures, and myoclonus. There was no diurnal fluctuation. His mother had one spontaneous abortion at 8 weeks, and two siblings had died in the early infantile period from an unknown cause [Figure 1]. There was no similar complaint in parents. His cognition was normal, with no behavioral abnormalities. The systemic examination was unremarkable. Neurological examination showed normal cognition, anarthric speech, pes cavus with hammer toes,

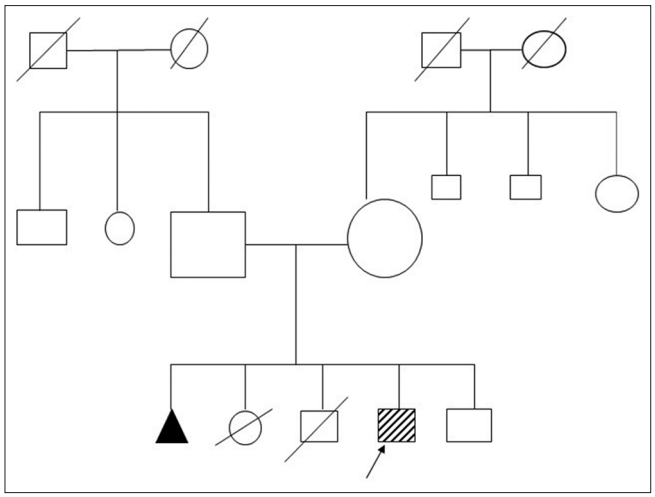

Figure 1: Shows pedigree chart

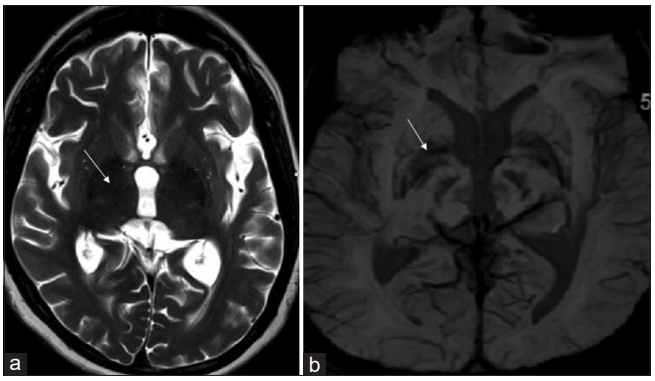

Figure 2: Brain MRI axial T2-weighted image (a) showing mineralization in the globus pallidus (white arrow) and (b) susceptibility-weighted imaging showing mineralization in the globus pallidus (white arrow)

cranial dystonia, perioral dystonic movement, and dystonic movement of the neck, upper, and lower limbs [Video 1]. There were no pyramidal or cerebellar signs. Patient had severe retrocollis on ambulation when he recovered from the dystonic crisis [Video 2]. A clinical possibility of early childhood-onset primary persistent generalized dystonia like DYT 1, 6, 5a, and 28 was considered. Complete hemogram, renal, hepatic, and thyroid functions were normal. Serum copper, ceruloplasmin, and ferritin levels were normal. Saline dilution test for acanthocytes was negative. Nerve conduction studies were normal. Brain magnetic resonance imaging (MRI) showed mild diffuse cerebral atrophy with bilateral globus pallidus mineralization [Figure 2]. WES showed a novel heterozygous mutation in the *VPS16* gene (p.Arg525Ter variant). The p.Arg525Ter variant is observed in 1/21,836 (0.0046%) alleles from individuals of gnomAD European Finnish background in gnomAD. This variant is predicted to cause loss of normal protein function through protein truncation. This variant is a stop-gain variant that occurs in an exon of VPS16 upstream of where nonsense-mediated decay is predicted to occur. There are two downstream pathogenic loss-of-function variants, with the furthest variant being 122 residues downstream of this variant. This indicates that the region is critical to protein function. The p.Arg525Ter variant is a loss-of-function variant in the gene *VPS16*, which is intolerant of loss-of-function variants, as indicated by the presence of an existing pathogenic loss-of-function variant NP_072097.2:p.G241Sfs*47 and three others. The clinical phenotype of the proband matches with that of the disorder caused by pathogenic variants in the gene. For these reasons, this variant was classified as likely pathogenic as per the American College of Medical Genetics guidelines. Patient was treated with levodopa 300mg/day, oral baclofen 50 mg/day, trihexyphenidyl 14 mg/day, and tetrabenazine 50mg/day. He was able to ambulate with support within 2 weeks of the acute dystonic crisis.

Vacuolar protein sorting-associated proteins 16 (VPS16) is a key component of the homotypic fusion and vacuole protein sorting (HOPS) complex, and the gene encodes a core subunit of the VPS-C complex that is required for vesicle transport and fusion processes in the late endosomes/lysosome pathway. The mutation in the *VPS16 gene* is associated with early-onset generalized dystonia. Other manifestation of the *VPS16* mutation is mucopolysaccharidosis-plus syndrome. The inheritance of the *VPS16* mutation is autosomal dominant, though autosomal recessive has been reported. Around 14 distinct *VPS16* mutations have been reported in generalized dystonia cases, with loss-of-function variants in all these mutations.[1,2] Cai *et al.*[3] (2016) reported a novel homozygous missense mutation, c.156 C>A in *VPS16,* in a Chinese consanguineous family with adolescent-onset primary dystonia by WES and homozygosity mapping. The phenotypic presentation was the onset of dystonia symptoms from the cervical region with an onset age of 11–14 years and getting generalized to cause severe motor disability. Steel *et al.*[4] (2020) conducted WES in 138 individuals with generalized dystonia and reported 18 individuals harboring heterozygous loss-of-function *VPS16* variants and one with a microdeletion. The age at onset of dystonia ranged from 3 to 30 years, with cervical onset in three patients, oromandibular onset in four, limb-onset in eight, craniocervical in three, and cervico-brachial in one patient. Generalized dystonia occurred in 16 patients, segmental in two and focal in one patient. All, except three patients, were still ambulant. Five patients had undergone deep brain stimulation, with two having significant improvement, one partial improvement, and two no improvement. Li *et al.*[1] (2021) reported three rare heterozygous variants of *VPS16* (NM_022575.4) in three unrelated subjects. The patient with the pathogenic novel frameshift variant (c. 1929_1930del, p.R643fs*) had early-onset lower limb onset focal dystonia at 8 years of age, followed by cervical dystonia, oromandibular, and bulbar dystonia by 28 years of age. The dystonia was slowly progressive. Petry-Schmelzer *et al.*[5] (2022) reported a 43-year-old patient with cervicobrachial dystonia who had a heterozygous predicted loss-of-function variant of *VPS16* (c.1903C>T, p.Arg635Ter). Our patient had limb-onset dystonia during the first decade, followed by craniocervical and truncal dystonia by 20 years of age [Table 1]. WES showed a novel stop-gain variant (p.Arg525Ter).

Table 1: Phenotypic features of reported cases of DYT30

Author	Clinical features	Response to deep brain stimulation
Cai *et al*. (2016) (*n*=5)	Cervical onset dystonia with generalization with age of onset at 11–14 years	-
Steel *et al*. (2020) (*n*=18)	Age at onset of dystonia ranged from 3-30 years; cranio-cervical and limb onset dystonia with generalization with retained ambulation in majority	Response to deep brain stimulation was noted
Li *et al*. (2021) (*n*=3)	Early-onset lower limb focal dystonia at 8 years of age followed by cervical dystonia, oromandibular and bulbar dystonia by 28 years of age	-
Petry-Schmelzer *et al*. (2022) (*n*=1)	Cervicobrachial dystonia with onset at the fourth decade with no generalization	Response to pallidal deep brain stimulation was noted
Present study (*n*=1)	Limb-onset dystonia during the first decade followed by craniocervical and truncal dystonia by 20 years of age	-

DYT 30 should be considered in patients with early childhood onset, progressive generalized dystonia. The differential diagnosis for childhood-onset isolated generalized dystonia is DYT 1, 6, and 5a. DYT 1 presents typically as limb-onset dystonia with progressive generalization that spares cranial muscles in early childhood. DYT 6 has childhood, adolescence, or early adulthood (4–20 years) onset, with dystonia onset at the craniocervical region and spread to the limbs. DYT 5 has an onset at the first decade with lower limb onset and subsequent trunk dystonia and diurnal variation. DYT 28 or DYT-KMT2B is a close differential diagnosis of autosomal-dominant early childhood, limb-onset generalized dystonia with associated intellectual disability and short stature. This is the first report of DYT 30 from India.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Sridhar Shashi, Saraswati Nashi, Gautham Arunachal[1], Venkatachalam N, Hansashree Padmanabha, Pooja Mailankody, Deepak Menon, Faheem Arshad, Suvarna Alladi, Pavagada Mathuranath, Rohan R. Mahale

Departments of Neurology, and [1]Human Genetics, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Address for correspondence: Dr. Rohan R. Mahale, Department of Neurology, NIMHANS, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru - 560 029, Karnataka, India.
E-mail: rohanmahale83@gmail.com

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