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A Novel Pattern of Dystonia in DYT-*VPS16*

"Speaking in Tongues"

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Abstract

Objectives

To expand the phenotype and genotype of *VPS16*-related dystonia (DYT-*VPS16*).

Methods

We report 2 patients with previously unreported *VPS16* truncating variants and highlight some distinctive phenomenological characteristics of DYT-*VPS16*.

Results

The 2 patients, who were unrelated, presented with early-onset orofacial dystonia with prominent tongue involvement. Case 1, a 37-year-old woman, developed disabling orofacial dystonia, with tongue protrusion (lingual dystonia), orofacial gesticulations, and hyperkinetic dysarthria, responsible for an odd "foreign language" quality. Case 2, a 36-year-old woman, exhibited orofacial dystonia with prominent lingual involvement and orofacial gesticulations. In both patients, orofacial dystonia led to predominant speech impairment with no or discrete swallowing difficulties.

Discussion

Substantial tongue dystonia may be a distinctive feature of DYT-*VPS16*. Our cases widen the phenotypic spectrum of DYT-*VPS16* and may provide physicians with a new clinical clue for this disease.

Introduction

Monoallelic variants in *VPS16* (vacuolar protein sorting 16 homolog) have been recently identified as a cause of early-onset dystonia[1,2] (DYT-*VPS16*) (OMIM ID: 619291) with a prevalence estimated to be between 0.9 and 4% of genetic dystonias.[3] To date, 44 patients from 31 families with DYT-*VPS16* and 14 different monoallelic mutations have been reported. Onset of dystonia was classically in childhood or young adulthood (mean age 14 years, range 3–50) with a focal onset (cervical or limb).[2,4] Initial localization was cranial/bulbar (20%), limbs (54%), and axial (36%) with progressive expansion to other body parts.[2,4,5] Most of the patients (35/44) had isolated dystonia while some had dystonia with a myoclonic component (2/44).[6,7] A more complex phenotype was found in few patients (7/44) with associated neurologic features: peripheral neuropathy, intellectual disability, or neuropsychiatric manifestations including mood disorders and impulsivity.[1] Biallelic variants have also been described leading to a similar, although more severe, dystonia phenotype.[4]

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In this report, we describe in detail 2 unrelated patients with genetically confirmed DYT-*VPS16* and highlight a novel clinical feature: orofacial dystonia with prominent lingual involvement leading to a peculiar hyperkinetic dysarthria with an indefinite "foreign language" quality.

Methods

We report the clinical history and phenomenological characterization of 2 additional patients with DYT-*VPS16*. We retrospectively collected data from the medical charts of the patients. Trio-based and duo-based genome sequencing were performed at SeqOIA laboratory in case 1 and her asymptomatic parents and in case 2 and a distant affected relative, respectively (eFigure 1).

Standard Protocol Approvals, Registrations, and Patient Consents

The patients gave their written informed consent for publication.

Authorization has been obtained for disclosure of any recognizable persons in photographs, videos, or other information that may be published in the journal.

Data Access

Clément Desjardins (first author) takes full responsibility for the data and the analyses and interpretation; he has full access to all the data, and he has the right to publish any and all the data, separate and apart from the guidance of any sponsor.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

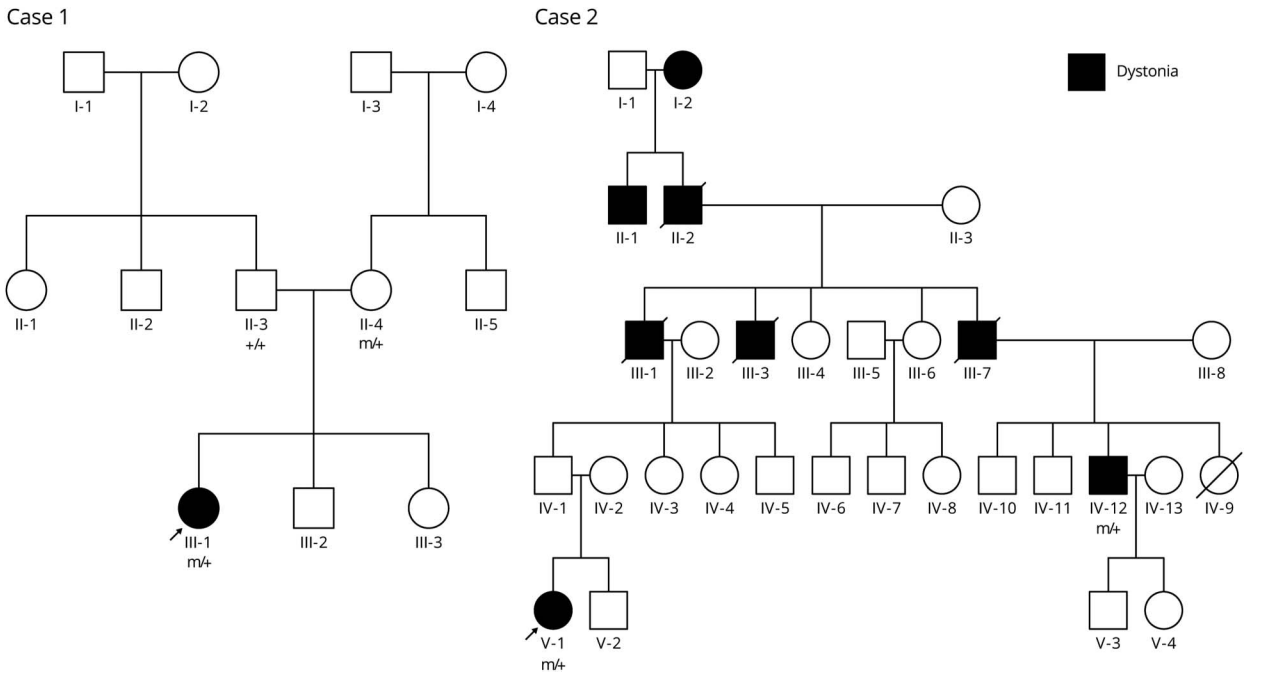
Results

Case 1

A 37-year-old White woman developed progressive speech impairment since the age of 17. She had no familial history of neurologic disease (Figure) nor history of any current or previous exposure to dopamine receptor antagonists. Birth delivery and psychomotor development were normal. Owing to her odd speech disorder, she underwent extensive investigations (brain MRI, EMG, and biological tests including Rach antibody, all normal), and the diagnosis of functional neurologic disorder was considered.

At age 27, she gradually developed motor impairment in the right upper limb with postural tremor and difficulty performing skilled motor tasks such as applying makeup or buttoning up her clothes. These abnormal movements were improved by alcohol. Her speech impairment progressively worsened, with mild difficulty chewing and drinking and a tendency for the tongue to protrude. There was no tongue biting. Clinical examination confirmed the diagnosis of orofacial dystonia: it was mainly triggered by speech with prominent involvement of the tongue evoking a foreign unknown language that lacked any readily understandable content (Video 1).

Figure Family Pedigrees of the 2 Cases



Black fillings indicate affected status by dystonia. The following symbols indicate the patients who underwent whole-genome sequencing: m/+ and +/+ for variant carriers and nonvariant carriers, respectively.

She also had postural tremor with dystonic posture of the right arm, overflow phenomenon, and mirror dystonia of the upper limbs.

Brain MRI was normal. Trio genome sequencing revealed a heterozygous frameshift variant in *VPS16*, NM_022575.4: c.444_445del/p.(Ala150Profs*11), classified as probably pathogen according to ACMG/ACP criteria[8] and which was also found in her asymptomatic mother (Figure).

Case 2

The second patient was a 36-year-old White woman, suffering from multiple sclerosis from the age of 20, treated with rituximab, and relapse free for 2 years, which was seen for a generalized myoclonic dystonia. Her paternal grandfather and several other family members had generalized dystonia, with autosomic dominant transmission and incomplete penetrance. Birth delivery and psychomotor development were normal. She had no history of any current or previous exposure to dopamine receptor antagonists.

At age 6, she developed focal right hand dystonia while learning how to write. Dystonia secondarily spread to both upper limbs and the left lower limb. Dystonia was associated with myoclonus and led to motor impairment performing skilled motor tasks such as makeup application or buttoning up her clothes. At age 23, she developed speech impairment that remained stable thereafter.

Clinical examination confirmed the diagnosis of orofacial dystonia with prominent lingual involvement and tongue protrusion (Video 2), which was mainly triggered by speech. The protrusion of the tongue interfered with articulation and distorted both lingual and labial phonemes. She presented an unstable voice, likely due to laryngeal dystonia. She also had dystonia with myoclonus of the upper limbs, trunk, and lower limbs.

Brain MRI was normal apart from typical multiple sclerosis lesions with periventricular, juxtacortical, and optic nerve locations. Duo genome sequencing revealed a heterozygous frameshift variant in *VPS16*, NM_022575.4:c.1394del/p.(Leu465Argfs*89), probably pathogen according to ACMG/AMP criteria,[8] which was also found in her only living affected relative, a distant cousin (Figure). Her father, an asymptomatic obligatory carrier, was not tested.

Discussion

We describe in detail 2 new cases with novel variants in *VPS16*, which expand the phenotypic spectrum of *VPS16*-related dystonia. We highlight a new clinical feature: orofacial dystonia with prominent tongue involvement.

Some clinical and genetic features of our 2 patients are in line with previous reports. The DYT-*VPS16* phenotype seems to be one of early-onset generalized dystonia, with focal onset and gradual spread of dystonia, in isolation or in combination with other features, especially myoclonus. The clinical spectrum seems to be broad and heterogenous in presentation and severity, even within the same family, with incomplete penetrance. This could be explained by additional genetic or environmental modifying factors.[1]

Our cases also highlight a previously unreported clinical feature of DYT-*VPS16*. Both cases exhibited prominent lingual dystonia disrupting the production of speech and impairing their intelligibility. In the first case, the phenotype was dominated by orofacial dystonia with prominent lingual involvement leading to a particular hyperkinetic dysarthria with a "foreign language" quality. In the second case, the phenotype was also dominated by orofacial dystonia leading to hyperkinetic dysarthria with lingual dystonia at the forefront, although milder than patient 1. Only one case of DYT-*VPS16* with orofacial dystonia and prominent tongue involvement has been described, but in the setting of a more severe and complex phenotype.[9]

Orofacial dystonia as a main clinical feature of early-onset dystonia is rare and mostly seen in *THAP1*[10], *ATP1A3*,[11] and *KMT2B*[12] variants, in neurodegeneration with brain iron accumulation[13] or in some metabolic disorders.[14] In orofacial dystonia, the main pathophysiologic hypothesis suggests an involvement of multiple brain regions, including mostly hyperexcitability of mesencephalic trigeminal circuits and a central generator pattern located in the brainstem.[15] This is also consistent with reports of bilateral and symmetrical T2 and T2* hypointensities in the midbrain (red nucleus and cerebral peduncle) in some cases of *VPS16* mutation carriers suggesting iron deposition,[1,2] which was not seen in our patients.

In both families, unaffected heterozygous individuals are present, emphasizing the incomplete penetrance of VPS16 monoallelic truncating variants. This is consistent with the occurrence of heterozygous individuals in gnomAD and with the fact that both variants NM_022575.4(*VPS16*):c.444_445del and NM_022575.4(*VPS16*):c.1394del are now reported in 3 and 8 individuals of the gnomADv4 population database, respectively.[16]

The clinical description of our 2 patients expands the growing phenotypic spectrum of DYT-*VPS16* and reinforces the idea that *VPS16* pathogenic variants should be looked for more systematically in early-onset dystonia, especially when there is orofacial involvement. We hypothesize that the prominence of tongue dystonia, inducing a "foreign language" quality, may be a hallmark of orofacial dystonia in DYT-*VPS16*.

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