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DYT16: the original cases

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Abstract

Objective—DYT16 is an autosomal recessive dystonia-parkinsonism due to putative mutations at PRKRA gene. The aim of this study was to describe clinical features providing video documentation of patients with DYT16 dystonia.

Methods—We examined and videotaped all homozygous carriers of the DYT16 gene.

Results—We identified two phenotypes, generalised dystonia and dystonia-parkinsonism non-responsive to levo-dopa, with three patients belonging to each of the groups. There was inter-individual and intra-family phenotypic heterogeneity.

Conclusions—DYT16 is a rare autosomal recessive dystonia characterised by generalised dystonia or dystonia-parkinsonism. Patients are refractory to pharmacological therapy.

Dystonia is the third most common movement disorder after parkinsonism and tremor, with a prevalence ranging from 2 to 50 cases per million for early onset, and from 30 to 7320 cases per million for late-onset forms.¹ To date, 20 genetic loci have been linked to familial primary dystonias, and the gene has been cloned in 10 of these. We have recently described DYT16, a novel young-onset dystonia-parkinsonism (OMIM, 612067) in three apparently non-related Brazilian families.² Subsequently, another patient with early-onset generalised dystonia has been reported to have a frameshift mutation in the DYT16 gene, although because this is a heterozygous change, its role in disease remains unclear.³ We now present the first detailed clinical description, with video documentation, of the original patients with the DYT16 mutation (figure 1). This study was approved by the local ethics committee, and all patients provided informed written consent.

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Case reports

Phenotype 1: generalised dystonia

Patient 1—This 32-year-old man presented at the age of 11 years with painful foot inversion on walking. Two years later, he developed abnormal pronation of his left arm with involuntary wrist and finger flexion. He then developed difficulties with phonation and articulation, and difficulties swallowing. He was noted to have left shoulder and arm elevation, and contortions of the right upper limb. One year later, he developed involuntary neck extension, and opisthotonic posturing and facial grimacing also emerged over the next 3 years. By this time, his speech was unintelligible and he could no longer walk without assistance. Treatment with high doses of anticholinergic drugs (biperiden 24 mg daily), levodopa-carbidopa (375–37.5 mg daily) and botulinum toxin (500 units at splenii capitis) failed to provide benefit (Family 1, supplementary video 1).

Patient 2—This 34-year-old man had had a slight developmental delay in motor milestones in infancy (gait and speech at age 2.5 years). At the age of 11 years, he presented with involuntary closure of the left hand. In the same year, he noticed an abnormal posterior-inferior deviation of the left shoulder. Two years later, right foot inversion, left elbow and wrist extension, left fingers flexion and a strangulated speech occurred. At the age of 16 years, his neck started to extend involuntarily, and he developed tongue protrusion and a sardonic smile, right arm flexion, right wrist extension with finger abduction, forward flexion of the trunk, twisting of the hip and left foot inversion. There was no response to baclofen (60 mg daily), anticholinergic drugs (biperiden, 24 mg daily) and botulinum toxin (600 U of Botox per section in spleni capitis). He now uses a sensory trick (touch of the occiput) to correct his neck posture and allow him to walk (Family 2, supplementary video 2).

Patient 3—This 42-year-old woman developed writer's cramp at the age of 7 years. Five years later, she was found to have left leg extension with flexion of the fingers, left scoliosis, slurred speech and a sardonic smile. At the age of 17 years, involuntary bilateral wrist extension, bilateral knee flexion with foot inversion, and swallowing difficulties appeared. Two years later, she developed orolingual dystonia with lip and tongue protrusion, and she lost her voice completely. There were no parkinsonian signs. Reflexes were brisk, but the plantar responses were downgoing. Levodopa-carbidopa (375–37.5 mg daily), baclofen (30 mg daily) and trihexyphenidyl (20 mg daily) did not improve her symptoms. Botulinum toxin injection at submentonian muscles caused a moderate improvement of dysphagia. She died at the age of 44 years from bronchopneumonia (Family 3, supplementary video 3).

Phenotype 2: dystonia-parkinsonism non-responsive to Levo-Dopa

Patient 4—This 64-year-old man developed involuntary left leg extension when walking, at the age of 18 years. Over the next 10 years his condition worsened with the development of involuntary right hip flexion, dystonic posturing of the right arm with shoulder elevation, involuntary flexion of left arm with thumb abduction, a right laterocollis, axial dystonia to the right, and a marked dysarthrophonia. On examination, he was noted to have a segmental dystonia involving the neck, trunk and arms; mild bradykinesia and hypomimia. Modest

improvement has been noticed with biperiden (12 mg daily) and baclofen (30 mg daily) (Family 2, supplementary video 4).

Patient 5—This 35-year-old patient had a slight delay of developmental milestones (he was not able to speak until the age of 2 years). Symptoms began when he was 12 years old, with a tendency for his left leg to turn in when walking. After 1 year, there was adductor spasmodic dysphonia, oromandibular dystonia, and dystonic protrusion of the tongue. Three years later, he developed left laterocolis, elevation of left shoulder, left arm extension with wrist flexion, and right flexion of fingers. At last examination, 23 years after the onset of dystonia, the patient also had a *risus sardonicus*, marked bradykinesia, enhanced deep reflexes, and bilateral ankle clonus. A slight improvement of parkinsonism, but not of dystonia, was noticed with levodopa-carbidopa 375, 37.5 mg daily. Dystonic features did not ameliorate with anticholinergic drugs (biperiden 24 mg daily) (Family 1, supplementary video 5).

Patient 6—This 48-year-old woman had had difficulty speaking since early childhood. At 10 years of age, her mother had noticed hand slowness and awkwardness. Ten years later, the patient had noticed bilateral rest tremor of her hands, and an equinovarus posture of the left foot, wrist extension, and hyperflexion of the fingers when writing. She then developed freezing of gait, dysphagia, a hoarse strangulated dysphonia, *risus sardonicus*, and oromandibular and tongue dystonia. On examination, she had moderate parkinsonism with hypomimia, postural tremor of the hands, mild generalised bradykinesia and rigidity. There was no response to both levodopa (375–37.5 mg daily) and biperiden (12 mg daily) (Family 2, supplementary video 6).

Discussion

Most of the identifiable loci for hereditary dystonia have an autosomal dominant pattern of inheritance (DYT1, DYT4, DYT5a (GTP-cyclohydrolase 1), DYT6, DYT7, DYT8, DYT9, DYT10, DYT11, DYT12, DYT13, DYT15, DYT18, DYT19, DYT20 and DYT21), while only one has an autosomal recessive pattern (DYT5b), and one has been linked to X chromosome (Lubag).⁴ We now describe the clinical features associated with the second autosomal recessive locus, linked to mutations in *PRKRA*.² We describe marked phenotypic heterogeneity associated with *PRKRA* mutations even within members of the same family. The patients presented with either a pure generalised dystonia or with a dystonia-parkinsonism that was relatively unresponsive to L-dopa. In these cases, we observe a gradual onset of dystonia in childhood, affecting the limbs with prominent, relatively rapid onset, bulbar cranial-cervical, and striking axial dystonia, opisthotonus, hyperextension of the trunk and tortipelvis. Laryngeal dystonia, rendering the voice barely intelligible or leading to anarthria, is an important clinical feature of these patients. Parkinsonism appears as a feature later than dystonia in all cases where both are present and rest tremor has not been seen. It can be distinguished from other dystonia-plus syndromes by mode of inheritance (Lubag is X linked), absence of levodopa responsiveness (Segawa or DYT5 responds dramatically to low doses of L-dopa), absence of response to alcohol and clonazepam with the presence of jerky upper limb and neck movements (typical features of DYT11), and a more gradual onset than rapid-onset dystonia-parkinsonism or DYT12,

which has an acute presentation. The phenomenology of DYT16 resembles other forms of dystonia-parkinsonism: neurodegeneration with brain iron accumulation, Kufor-Rakeb and Wilson's disease. However, the absence of cognitive decline and normal brain MRI rule out such diagnoses.

DYT16 cases that present with pure dystonia are an important differential diagnosis of DYT1 and DYT6. The former has a childhood or adolescent onset, often beginning in a limb. Later, it may spread to other limbs and axial muscles becoming generalised, but typically sparing laryngeal and cranial muscles. The latter feature helps to distinguish it from DYT16. DYT6 is phenotypically similar to DYT1, although a great proportion of DYT6 cases have onset in cranial or cervical muscles. Patients with initial limb involvement almost invariably develop cranial or cervical dystonia later in the course of the disease. Of note, most DYT6 patients have involvement of laryngeal muscles, which makes the distinction from DYT16 difficult. Features that may help to distinguish DYT16 from DYT1 are laryngeal dystonia, which are invariably present in the latter, whereas, not all patients with DYT6 have this form of dystonia; the severity of laryngeal involvement is greater in DYT16; and the latter is recessive, while DYT6 is autosomal dominant, although incomplete penetrance may lead to misinterpretation as a recessive or even sporadic condition. In some instances, definitive diagnosis can be made only with the use of molecular tools.

PKR is an interferon-inducible, double-stranded RNA-activated protein kinase. This protein seems to have an important role in apoptosis pathway from neurons exposed to cell stress, and it is well known that it plays an important role in control of cell death.⁵ *Drosophila* lacking functional PKR have a severe defect in nervous system coordination or neuromuscular function resulting in significantly reduced locomotion; and it has been suggested that PKR may be required for *drosophila* neuronal development and mouse embryogenesis.⁶ There are recent studies suggesting that PKR is implicated in Alzheimer's disease,⁷ extrastriatal degeneration in Parkinson's and Huntington disease.⁸ It has also been shown that PKR may also be implicated in neuronal death in prion diseases since phosphorylated PKR-positive neurons have a straight correlation with neuronal apoptosis and neuronal degeneration in prion disease.⁹ Further studies are needed to determine whether mutant protein in patients with DYT16 results in loss or gain of function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Pedigree of the affected patients.