

# Idiopathic torsion dystonia

**Author: Doctor Christoph Kamm<sup>1</sup>**

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**Scientific Editor: Professor Thomas Gasser**

<sup>1</sup>Department of Neurology and Hertie Institute for Clinical Brain Research, University of Tuebingen, Hoppe-Seyler Str. 3, 72076 Tübingen, Germany. <mailto:christoph.kamm@med.uni-tuebingen.de>

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## Abstract

*Idiopathic torsion dystonia (ITD) is characterized by involuntary, repetitive, sustained muscle contractions or postures involving one or more sites of the body. Symptoms typically develop first in an arm or leg in middle to late childhood and progress in approximately 30% of patients to other body regions (generalized dystonia) within about five years. Distribution and severity of symptoms vary widely between affected individuals. The majority of cases from various ethnic groups are caused by an autosomal dominantly inherited deletion of 3 bp (GAG) in the DYT1 gene on chromosome 9q34. This gene encodes a protein named torsinA, which is presumed to act as a chaperone protein associated with the endoplasmic reticulum, although its precise function within the cell remains to be determined. ITD is a rare disease, with an estimated prevalence of approximately 3.4:100,000. The prevalence in the Ashkenazi Jewish population is approximately five to ten times higher, due to a founder mutation. Treatment options include botulinum toxin injections for focal symptoms, pharmacological therapy such as anticholinergics (most commonly trihexyphenidil) for generalized dystonia and surgical approaches such as deep brain stimulation of the internal globus pallidus in severe cases.*

## Keywords

DYT1, torsinA, idiopathic torsion dystonia, genetics

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## Disease name and synonyms

- Idiopathic torsion dystonia
- Primary torsion dystonia
- Oppenheim's dystonia
- Dystonia musculorum deformans
- Early onset (generalized) dystonia

## Definition / diagnostic criteria

Idiopathic torsion dystonia (ITD) is characterized by involuntary, repetitive, sustained muscle contractions or postures, typically of the limbs, which may spread to other body parts, in the absence of other neurological abnormalities. It is inherited in an autosomal dominant fashion with a reduced penetrance of 30-40% (Bressman *et al.* 1989), suggesting that various genetic and/or

environmental factors contribute to development of the disease. The majority of cases are caused by a deletion of 3 bp (GAG) in the *DYT1* gene on chromosome 9q34.

The following diagnostic criteria have been established for ITD (Bressman *et al.* 1989; Cassetta *et al.* 1999; Bressman *et al.* 2002):

- **Definite dystonia:**

Characteristic overt twisting or directional movements and postures that are consistently present.

- **Probable dystonia:**

Postures or movements suggestive of dystonia that are insufficient in intensity or consistency to merit classification as definite (e.g. excessively tense and labored writing with minimal posturing, flurries of blinking but no episodes of sustained closure, etc.)

- **Possible dystonia:**

Muscle contractions not considered abnormal but remotely suggestive of dystonia (e.g. unusual hand grip with mild excess hand tension but normal flowing handwriting, increased blinking with no flurries or sustained contractions, etc.)

Only the category of "definite dystonia" was shown to be 100% specific in *DYT1* families (Bressman *et al.* 2002).

### Differential diagnosis

Differential diagnosis includes disorders in which dystonia is one of several neurological conditions present. This large and diverse group includes the dystonia-plus syndromes, the hereditary dystonias and the secondary ("symptomatic") dystonias.

### Dystonia-plus

Dystonia-plus refers to conditions in which dystonia is one of only two neurological abnormalities present, the other usually being either parkinsonism or myoclonus. This group includes X-linked Dystonia-Parkinsonism ("Lubag", *DYT3*), [Dopa-responsive dystonia](#) (DRD, *DYT5*), [Myoclonus-Dystonia](#) (*DYT11*), Rapid Onset Dystonia-Parkinsonism (*DYT13*), and the paroxysmal dystonias (*DYT8*, *DYT9*, *DYT10*).

### Hereditary dystonias

In hereditary dystonias, dystonia is part of a more widespread neurodegenerative syndrome, often with known inheritance. This includes [Idiopathic Parkinson's Disease \(IPD\)](#), [multiple system atrophy \(MSA\)](#), [progressive supranuclear palsy \(PSP\)](#), [Hallervorden-Spatz Disease](#), [Wilson's disease](#), [Rett syndrome](#), Neuroacanthocytosis, and others.

### Secondary dystonia

Secondary (symptomatic) dystonias are caused by environmental insults such as stroke, tumours, infections, drugs and toxins or by metabolic disorders (e.g. homocystinuria, [metachromatic leukodystrophy](#), [Lesch-Nyhan syndrome](#), and others).

### Etiology

Neuropathologically, ITD is characterized by a lack of neurodegeneration, suggesting that neuronal dysfunction, rather than loss of neurons, underlies disease symptoms. However, cell bodies of dopaminergic neurons appear to be enlarged in brains from dystonia patients (Rostasy *et al.* 2003). Despite the reduced penetrance of 30-40% for clinical symptoms, functional imaging studies found metabolic hyperactivity in the lentiform nuclei, cerebellum and supplemental motor areas and impaired sequence learning in both manifesting and non-manifesting carriers of the *DYT1* GAG deletion, indicating that penetrance of the GAG deletion is greater than assumed based on clinical grounds (Eidelberg *et al.* 1998; Ghilardi *et al.* 2003).

Several lines of evidence suggest that the disease is caused by a dysfunction of the basal ganglia: (1) Although torsinA is ubiquitously expressed, expression levels within the human brain are highest within dopaminergic neurons of the substantia nigra (Augood *et al.* 1999); (2) Striatal [<sup>18</sup>F]dopa uptake is mildly reduced in manifesting *DYT1* GAG deletion carriers (Playford *et al.* 1993); (3) An increase in the ratio of dopamine metabolites to dopamine was found in the postmortem striatum of *DYT1* dystonia brains as compared to controls (Augood *et al.* 2002); (4) A phenotypically similar form of inherited dystonia, dopa-responsive dystonia (DRD), is caused by insufficient synthesis of dopamine, and symptomatic dystonia frequently affects patients with acquired lesions of the basal ganglia (e.g. stroke).

Initial studies suggest that torsinA is an endoplasmic reticulum/nuclear envelope protein which is involved in chaperone functions [reviewed in (Breakefield *et al.* 2001)] and participates in intracellular trafficking (Kamm *et al.* 2004).

### Clinical description

ITD is characterized by involuntary, repetitive, sustained muscle contractions or postures involving one or more sites of the body. Typically, symptoms develop first in an arm or leg in middle to late childhood (mean age of onset: 12.5 years) (Bressman *et al.* 2000) and progress in approximately 30% of patients to other body regions (generalized dystonia) within about five years (Greene *et al.* 1995). "Torsion" refers to the twisting nature of body movements

observed in ITD, often affecting the trunk. Patients may be severely physically incapacitated, but are normal intellectually and show no other neurological symptoms. Distribution and severity of symptoms vary widely between affected individuals, ranging from mild focal dystonia, e.g. writer's cramp (Gasser *et al.* 1998) to severe generalized dystonia, even within families (Opal *et al.* 2002). Earlier age of onset and onset in the legs predict a more severe clinical course, i.e. development of generalized dystonia (Burke *et al.* 1986; Marsden 1988).

The *DYT1* GAG deletion is responsible for the majority of typical early onset dystonia cases of diverse ethnic origins, whether inherited or caused by a *de novo* mutation, whereas only a small minority of patients with atypical, e.g. focal dystonia, harbor this mutation (Ozelius *et al.* 1997; Valente *et al.* 1998; Kamm *et al.* 1999; Klein *et al.* 1999; Bressman *et al.* 2000; Kamm *et al.* 2000; Grundmann *et al.* 2003). If mutant gene carriers pass the age of approximately 28 years without developing symptoms, they usually escape the disease for their lifetime.

### Diagnostic methods

Molecular genetic diagnostic in conjunction with genetic counseling is recommended for individuals with age of onset below 26 years, and may also be considered in those with onset after 26 years having a relative with typical early onset dystonia (Bressman *et al.* 2000).

### Epidemiology

ITD is a rare disease, with an estimated prevalence of 3.4:100,000 and annual incidence of 0.2:100,000 in Rochester, Minnesota (Nutt *et al.* 1988). The prevalence in the Ashkenazi Jewish (AJ) population is estimated to be five to ten times higher (Zeman and Dyken 1967), due to a founder mutation which appears to have arisen approximately 350 years ago in Byelorussia/Lithuania (Risch *et al.* 1995). The frequency of the *DYT1* GAG deletion in the AJ population is high, between 1:2000 and 1:6000.

### Genetic counseling

Based on a study of 100 British families containing 107 index cases of generalized, multifocal or segmental dystonia and 79 secondary cases prior to the availability of *DYT1* testing, the estimated recurrence risk for a child or sibling in familial cases has been calculated to be 21% (given a penetrance of 42%), whereas in an isolated case it is approximately 14% (Fletcher *et al.* 1990). However, due to the low penetrance and marked variability in clinical severity, the actual observed risk for both familial and isolated cases is rather lower.

## Management including treatment

### Drug therapy

Because DRD (*DYT5*) is phenotypically very similar to ITD, but its symptoms, in contrast to ITD, typically respond very well to dopaminergic therapy, it is recommended that every patient with early onset focal dystonia (onset below 26 years) be given a trial of L-Dopa/decarboxylase inhibitor with a slowly increasing daily dose of up to 300-400 mg.

In general, drug therapy in ITD is not very effective. Anticholinergics, especially in a high dosage (e.g. trihexyphenidyl up to 30-60 mg/day), are the only substance class for which controlled studies are available (Burke *et al.* 1986). Dosage should be increased very slowly to prevent side effects such as cognitive or memory deficits, which are frequently dose-limiting, although children can generally tolerate much higher doses than adults. Other substances, which may or may not be effective include baclofen, benzodiazepines such as diazepam or clonazepam, pimizid or tetrabenazin.

### Botulinum toxin injections

Independent of genetic background, local botulinum toxin injections directly into affected muscles now represents the first line treatment of focal dystonias (reviewed in Jankovic 2004). Therefore, botulinum toxin injections by trained movement disorder specialists may be a useful therapy for selected muscle groups in ITD, such as neck muscles for torticollis, facial muscles for blepharospasm or hand/arm muscles for writer's cramp. If successful, the injections need to be repeated on a regular basis (usually every 3-6 months).

### Surgical approaches

Due to technical advances in recent years, interest in functional surgical approaches in dystonia has been renewed, in particular deep brain stimulation (DBS) of the globus pallidus and pallidotomy [reviewed in (Vercueil *et al.* 2002)]. Although experience with this approach is still limited, preliminary results in patients with primary generalized dystonia, especially *DYT1* GAG deletion carriers, are very promising. Therefore, DBS may be helpful in selected ITD patients with severe generalized dystonia.

### Unresolved questions

Very little is known yet about the normal cellular function of the torsinA protein. Further studies are required to address how mutant torsinA causes neuronal dysfunction, and how this mutation leads to a dominantly inherited disease with markedly reduced penetrance and a very selective neurological phenotype. Since the age

of onset is associated with a period of motor learning and high synaptic plasticity, a possible role of torsinA in coordinated neuronal development merits further investigation. In addition, further evidence for or against direct involvement of the dopaminergic system in ITD is warranted.

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