

# Advances in the genetics of primary torsion dystonia

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## Abstract

Knowledge about the genetics of primary torsion dystonia (PTD) has been progressing at a very slow pace compared with other movement disorders. For many years, only one causative gene was known, *DYT1/TOR1A*, yet the recent identification of a second PTD causative gene (*DYT6/THAP1*), the detection of subclinical alterations caused by mutations in PTD genes in some healthy non-penetrant individuals, and functional studies on *TOR1A* and *THAP1* protein products have significantly improved mutation detection, genotype-phenotype correlates, and our understanding of the cellular mechanisms underlying the development of dystonia.

## Introduction and context

Torsion dystonias are characterized by involuntary muscle contractions that result in repetitive movements and abnormal postures. The term 'primary torsion dystonia' (PTD) usually refers to pure primary forms characterized by dystonia alone [1] (Table 1), yet this term has also been employed with a more extensive meaning to describe all forms of primary dystonias, although such usage is discouraged [2]. Pure PTD (hereafter referred to simply as PTD) can be further divided based on the age of onset (early onset being variably defined as beginning between the ages of 20 and 30 years) and distribution of dystonia (which can be focal, segmental, or generalized). Familial aggregation is more common in early-onset forms, which also present a higher propensity to generalize, whereas late-onset PTD is often sporadic and tends to remain focal or segmental in distribution [1,3].

For several years, only one gene causative of autosomal dominant PTD has been known: the *DYT1/TOR1A* gene [4]. *DYT1* dystonia is caused in nearly all cases by a GAG deletion in exon 5 of *TOR1A* and is typically characterized by early onset in a limb, generalization, and a tendency to spare the cranial-cervical muscles [5,6]. There is markedly reduced penetrance (only 30%

of mutation carriers actually develop the disease in their life) and wide phenotypic variability even within families; atypical phenotypes, including late-onset, focal, or segmental dystonia phenotypes with cranial-cervical involvement, have been reported [7,8].

## Major recent advances

### The *DYT6/THAP1* gene

In 2009, Fuchs and colleagues [9] identified *THAP1* (thanatos-associated protein domain-containing apoptosis-associated protein 1) as the second gene causative of autosomal dominant PTD. The *THAP1* gene encodes a protein characterized by a conserved putative DNA-binding motif, a proline-rich region, and a large coiled-coil region that includes a nuclear localization domain. Deleterious mutations were first identified in four ancestrally related Amish-Mennonite families and in a fifth, unrelated family of German ancestry. Subsequently, *THAP1* heterozygous mutations were identified in 9 out of 36 (25%) *DYT1*-negative families with early-onset non-focal PTD [10]. This high mutation frequency was not confirmed by other studies that reported an overall prevalence of about 1.0-2.5% in PTD cohorts variably selected on the basis of family history, early onset, generalization, or involvement of

**Table 1. Primary pure dystonia genes/loci according to the DYT nomenclature**

Disease (OMIM)	Gene/locus	Phenotype	Transmission
DYT1 (128100)	<i>TOR1A</i>	Generalized early-limb-onset dystonia	AD
DYT2 (224500)	Unknown	Early-onset generalized dystonia with prominent cranial-cervical involvement	AR
DYT4 (128101)	Unknown	Whispering dysphonia	AD
DYT6 (602629)	<i>THAP1</i>	Generalized cervical and upper-limb-onset dystonia	AD
DYT7 (602124)	18p	Adult-onset cervical dystonia	AD
DYT13 (607671)	1p36.13-36.32	Cervical and upper-limb dystonia	AD
DYT17 (612406)	20p11.2-q13.12	Segmental or generalized dystonia with prominent dysphonia	AR

AD, autosomal dominant; AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man [32].

the laryngeal or cervical regions (or both) [11-14]. The *THAP1* phenotype typically presents with early-onset dystonia that differs from DYT1 dystonia in the frequent involvement of the cranial-cervical district. In particular, speech is commonly affected because of oro-mandibular dystonia or laryngeal dystonia (or both). Interestingly, *THAP1* was recently found mutated also in sporadic cases with focal or segmental dystonia involving the cervical or laryngeal district that started in the patients' fifth or sixth decade, suggesting that this gene may also play a role in the pathogenesis of late-onset, focal/segmental PTD [14,15]. As for DYT1/*TOR1A*, *THAP1* mutations are also associated with reduced penetrance, with healthy mutation carriers identified in several families.

#### **Tackling PTD complexity: in pursuit of penetrance modifiers and endophenotypes**

The low penetrance and variable phenotypic expression associated with mutations in DYT1 and DYT6 genes represent the complexity of PTD genetics well, calling for the identification of genetic modifiers even in these monogenic forms. Among the most common forms of late-onset focal or segmental dystonia, clinical examination of first-degree relatives detected a positive family history in up to 25% of patients [16]. These findings support the hypothesis that PTD represents a truly complex disorder in which several genetic variants of low penetrance variably co-occur with environmental factors that affect the development and phenotypic manifestation of the disease.

In search of penetrance modifiers in DYT1 dystonia, a large study on a cohort of American subjects carrying the pathogenic GAG deletion showed that the frequency of the *TOR1A* coding variant D216H in *trans* with the deletion (e.g., on the other allele) was increased in healthy mutation carriers and decreased in affected subjects compared with controls, suggesting a relevant role for this variant in regulating penetrance of DYT1-PTD [17]. Two subsequent studies on German-Italian and French DYT1 mutation carriers, respectively,

gave rise to contrasting results, the first one supporting and the second arguing against the original findings [18,19]. At present, the role of this variant requires confirmation, and the mechanisms underlying reduced penetrance of DYT1 and DYT6 mutations remain to be understood.

In this scenario, the identification of novel disease-associated genes is hampered by the scarcity of large families with several affected members and the difficulty to pool homogeneous families for linkage purposes or groups of patients for association studies.

An interesting approach to overcome these limitations is the identification of endophenotypes, which are subclinical traits related to a specific genetic background (i.e., a pathogenetic mutation in a PTD gene) detectable also in healthy individuals who are non-penetrant carriers of the mutation. Indeed, several studies have reported the presence of subclinical abnormalities in healthy carriers of DYT1 or DYT6 mutations by neuroimaging (positron emission tomography, voxel-based morphometry, diffusion tensor magnetic resonance imaging) [20,21], neurophysiological (cortical and spinal inhibition, temporal discrimination, body movement representation) [22-24], and expression profiling approaches [25]. In light of these findings, similar approaches have been employed to detect possible endophenotypes among healthy relatives of patients with familiar forms of focal dystonia, in which the major causative gene is still unknown. In particular, a recent study correlated an altered temporal discrimination threshold detected in some healthy family members of dystonic patients with structural putaminal abnormalities detected by voxel-based morphometry, supporting the usefulness of this endophenotypic trait and its potential relevance in genetic studies [26].

#### **Future directions**

Given that the first PTD gene was discovered in 1997 [4], the identification of new dystonia genes has

progressed at a very slow pace compared with advancements in the field of non-primary dystonias and other movement disorders (such as Parkinson disease). The TOR1A protein product, TorsinA, is a member of the AAA1 superfamily of ATPases associated with a variety of cellular activities. This superfamily of chaperone proteins performs critical functions related to protein degradation, membrane trafficking, vesicle fusion and organelle movement, cytoskeletal dynamics, and correct folding of proteins [27,28]. TorsinA is almost ubiquitously expressed, and its expression in the brain is restricted to neurons, where it is associated with the endoplasmic reticulum (ER). In cellular models expressing the pathogenic GAG deletion, mutant TorsinA is redistributed from the ER lumen to the nuclear envelope (NE) [29]. These cells also display abnormal morphology and thickening of the NE, including altered connections between the inner and outer membranes, and generation of whorled membrane inclusions that appear to 'spin off' the ER and NE. These inclusions are associated with the vesicular monoamine transporter VMAT2, a finding that might functionally relate TorsinA to the dopaminergic system [30]. In addition, TorsinA has been found to regulate cellular trafficking of the dopamine transporter and other membrane-bound proteins. It has also been shown that the mutant TorsinA interferes with cytoskeletal events that may affect the development of neuronal pathways in the brain and that it is prematurely degraded by both the proteasome and macroautophagy pathways [31].

THAP1, instead, is a member of a family of cellular factors sharing a highly conserved DNA-binding THAP domain, which is an atypical zinc finger, and can regulate endothelial cell proliferation. A proposed disease mechanism is that DYT6 mutations may disrupt THAP1 binding to DNA and produce transcriptional dysregulation. Although the mechanism underlying dysfunction of the THAP1 protein in DYT6 dystonia is not known in the same detail as that of TorsinA, these two genetic disorders are capable of producing comparable motor abnormalities that likely underlie a similar disruption of communication within the basal ganglia. The availability of a second PTD gene will provide new insights into the pathophysiology of this very peculiar movement disorder and allow investigators to perform comparative functional studies to identify shared pathways leading to the development of dystonia. In particular, we expect that functional imaging studies will be able to further identify shared as well as different patterns of activation/deactivation of brain areas in patients with DYT1 and DYT6 dystonia, highlighting their specific role in

the pathogenesis of these forms of PTD. There is great need for specific molecular models which could explain the underlying pathogenetic mechanisms shared by different genetic forms.

### Abbreviations

ER, endoplasmic reticulum; NE, nuclear envelope; PTD, primary torsion dystonia; THAP1, thanatos-associated protein domain-containing apoptosis-associated protein 1.

### Competing interests

The authors declare that they have no competing interests.

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