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Genetic and clinical features of primary torsion dystonia

Laurie J. Ozelius[a] and **Susan B. Bressman**[b]

Laurie J. Ozelius: laurie.ozelius@mssm.edu; Susan B. Bressman: SBressma@chpnet.org

[a] Departments of Genetics and Genomic Sciences and Neurology, Mount Sinai School of Medicine, One Gustave L Levy Pl, Box 1498 New York, NY, 10029, USA

[b] Department of Neurology, Beth Israel Medical Center, 10 Union Square East, Suite 5J, New York, NY, 10003, USA

Abstract

Primary torsion dystonia (PTD) is defined as a syndrome in which dystonia is the only clinical sign (except for tremor), and there is no evidence of neuronal degeneration or an acquired cause by history or routine laboratory assessment. Seven different loci have been recognized for PTD but only two of the genes have been identified. In this review we will described the phenotypes associated with these loci and discuss the responsible gene.

Keywords

Primary torsion dystonia; early onset dystonia; focal dystonia; *TOR1A*; *THAP1*; *DYT7*; *DYT13*; *DYT17*

Definition of Dystonia

Dystonia refers to muscle contractions that cause sustained twisting and repetitive movements and postures, which are usually directional in nature (Fahn 1988). There are many causes for dystonia and various classification schemes have been employed to help organize the diverse etiologies. One classification proposes two main etiologic categories (Bressman 2003; Elia et al., 2010): primary torsion dystonia (PTD) (previously named idiopathic torsion dystonia), and non-primary dystonia. PTD is defined as a syndrome in which dystonia is the only (except for hand tremor) clinical manifestation, and there is no evidence of neuronal degeneration or an acquired cause. Non-primary dystonia including non-degenerative “dystonia-plus” syndromes which are inherited disorders that produce clinical signs in addition to dystonia; heredodegenerative disorders which also typically include signs other than dystonia; and acquired causes. This review will focus on the PTDs.

Primary Torsion Dystonia (PTD)

The clinical spectrum of PTD is remarkably broad. Symptoms may begin at any age from early childhood to senescence; similarly, there is a range in the degree of muscle involvement from contractions that are limited to a single body region, such as the neck, to

Corresponding Author: Laurie Ozelius, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1498, New York, NY 10029, phone:212 659-6753, fax: 212 849-2508, laurie.ozelius@mssm.edu.

widespread involvement of limb, axial, and cranial muscles. Age at onset distribution for PTD is bimodal, with modes at age 9 (early-onset) and 45 (late-onset) (Bressman et al., 1989). Moreover, there is a relationship between the age at onset of symptoms, body region first affected, and clinical progression of signs (Greene et al., 1995; O'Dwyer et al., 2005). When PTD begins in childhood or adolescence, it often starts in a leg or arm, and then progresses over 5-10 years to involve multiple body regions. When PTD begins in adult years, symptoms first involve the arm (writer's cramp), neck (cervical dystonia or torticollis), laryngeal (spasmodic dysphonia) or other cranial muscles (e.g. blepharospasm). Unlike early-onset, adult or late-onset dystonia tends to remain localized with a focal or segmental anatomic distribution. A rarer clinical phenotype, denoted in families as “mixed”, starts early in life and tends to spread but cervical and cranial muscles including speech are more frequently affected compared to most early-onset primary dystonia (Tables 1 and 2).

PTD is the third most common movement disorder after Parkinson's disease and essential tremor. In Rochester, Minnesota, prevalence was 330 per million, with late-onset focal disease being 9 times more common than early-onset generalized (Nutt et al., 1988). A more recent analysis of European cases found a lower frequency of about 152 per million, and again focal cases constituted the majority (117 per million) (ESDE Collaborative Group 2000). Both of these clinically based studies are likely underestimates of the true frequency of PTD, because a significant proportion of disease is not diagnosed (Risch et al., 1995; Muller et al., 2002).

Seven genes have been mapped for primary dystonia including *DYT1*, *2*, *4*, *6*, *7*, *13* and *17*, however only two of these *DYT1* (*TOR1A*), and *DYT6* (*THAP1*) have been identified. *DYT1*, *2*, *6*, *13* and *17* are associated with an early onset phenotype whereas *DYT4* and *7* are more focal in distribution (de Carvalho Aguiar and Ozelius, 2002; Chouery et al., 2008) (Table 2).

Early Onset DYT1 PTD

A 3 bp (GAG) deletion in the coding region of the *TOR1A* (*DYT1*) gene located on chromosome 9, is a major cause of early onset, generalized dystonia, the most common and severe form of hereditary dystonia (Ozelius et al., 1997). The delGAG mutation removes a single in-frame amino acid (glutamic acid) from the C-terminal region (position 302 or 303) of the encoded protein, torsinA. Despite extensive screening (Ozelius et al., 1999; Leung et al., 2001; Tuffery–Giraud et al., 2001), this deletion is the only one that is clearly associated with primary dystonia to date although two other missense variations have been described involving dystonia including a p.R288Q identified in a single patient with severe fixed dystonia, facial palsy, and long tract signs, with first symptoms in infancy (Zirn et al., 2008) and a p.F205I reported in a man with orobulbar dystonia beginning in his forties with bipolar disease treated with lithium, a remote history of neuroleptic exposure and cogwheeling and action but not rest tremor in his arms (Calakos et al., 2010). Both mutations when over-expressed in cells, produced intracellular inclusions similar to those seen with the delGAG mutation (see below).

The clinical expression of DYT1 dystonia is quite variable, even within families; 70% of gene carriers have no definite signs of dystonia and among the remaining 30% dystonia ranges from mild focal dystonia, e.g. writer's cramp (Gasser et al., 1998) to life-threatening generalized dystonia (“dystonic storm”) (Opal et al., 2002). There are however common DYT1 clinical characteristics that have been described across ethnic groups (Valente et al., 1998; Bressman et al., 2000; Im et al., 2004; Yeung et al., 2005; Gambarin et al., 2006; Lin et al., 2006). In the great majority of people with dystonia due to the delGAG mutation symptoms begin early with a mean age onset at 13 years (range 3 to 64 years) and all but a few cases beginning by the age of 26 years. In 90% of cases, an arm or leg is affected first.

About 65% progress to a generalized or multifocal distribution, the rest having segmental (10%) or only focal (25%) involvement. Often those with focal dystonia have late–onset writer's cramp (Opal et al., 2002), and are identified through family studies. When viewed in terms of body regions ultimately involved, one or more limbs are almost always affected (over 95% have an affected arm). The trunk and neck may also be affected (about 25-35%) and they may be the regions producing the greatest disability (Chinnery et al., 2002); spread to cranial muscles is less common (< 15-20%).

DYT1 dystonia is inherited in an autosomal dominant manner with reduced penetrance (30%) (Risch et al., 1990). If symptoms do not occur prior to 26 years of age in carriers, they usually remain unaffected for the rest of their life. However, with the identification of the disease gene, we now know that unaffected *TOR1A* mutant gene carriers have endophenotypes in the absences of overt motor signs of dystonia expanding the notion of penetrance and phenotype. Comparing non-manifesting family members, to their non-carrier family members as well as those manifesting dystonia, it was found that both manifesting and non-manifesting gene carriers had the same increased risk for early onset recurrent major depression when compared to their non-carrier related family members (Heiman et al., 2004) but no differences in OCD frequency (Heiman et al., 2007).

Other DYT1 endophenotypes have been investigated using various imaging and neurophysiological approaches with the goal of illuminating pathophysiologic mechanisms that take a gene carrier from “non- manifesting” to manifesting. Non-manifesting gene carriers show deficits in specific motor sequence learning paradigms (Ghilardi et al., 2003) with molecular imaging studies revealing microstructural changes involving cerebellothalamocortical fiber tracts (Carbon et al., 2004a; Argyelan et al., 2009) and volume changes in the basal ganglia (Draganski et al., 2009), decreased striatal D2 receptor availability (Asanuma et al., 2005; Carbon et al., 2009), and altered metabolism in specific brain regions (Eidelberg et al., 1998). Electrophysiological analyses have also identified genotype associated abnormalities, namely reduced intracortical inhibition and a shortened cortical silent period (Edwards et al., 2003a) as well as higher tactile and visuo-tactile temporal discrimination thresholds (TDT) and temporal order judgments (Fiorio et al., 2007). TDT abnormalities have also been identified in adult-onset focal PTD patients and their healthy relatives and correlate with a bilateral increase in putaminal grey matter (Bradley et al., 2009) suggesting shared mechanisms among PTD forms. The subtle abnormalities in brain physiology, together with findings of no apparent neurodegeneration in the brains of affected DYT1 patients (Hedreen et al., 1988; Rostasy et al., 2003; McNaught et al., 2004), suggest that neurodevelopmental differences in brain circuitry in *TOR1A* mutant gene carriers may underlie susceptibility to the dystonic phenotype. Factors contributing to penetrance are presumed to involve co-inheritance of genetic variants or environmental insults including drug exposure, peripheral injury and viral infection (Edwards et al., 2003b; Saunders-Pullman et al., 2004). Although none of these environmental causes have been proven, a variant in the *TOR1A* gene has been associated with penetrance (Risch et al., 2007, see below).

The delGAG mutation is preserved across ethnicities, readily allowing for screening, regardless of genetic background. However, because of a founder mutation, it accounts for about 80% of early onset cases in the Ashkenazi Jewish population (Bressman et al., 1994; 2000); this compares with 16-53% in early-onset non-Jewish populations (Valente et al., 1998; Lebre et al., 1999; Slominsky et al., 1999; Brassat et al., 2000; Bressman et al., 2000; Zorzi et al., 2002). The frequency of the delGAG mutation has been estimated at 1/2000 – 1/6000 (giving a carrier frequency of 1/1000-1/3000) among Ashkenazi Jews (Risch et al., 1995); translating into a disease frequency of 1/3,000-1/9,000 (based on a penetrance of 30%). A study analyzing dried blood spots from 12,000 newborns in France, identified one

disease allele (Frederic et al., 2007); a carrier incidence consistent with the approximate 5 fold increased frequency of early-onset dystonia in Ashkenazim compared to non-Jews advanced in older studies, prior to gene identification (Zeman and Dyken, 1967). These studies suggest that a significant proportion of early-onset cases, especially among non-Jews, are not due to *TOR1A*; other causes, including proposed genes, have been implicated (Moretti et al., 2005; Fuchs et al., 2009).

TOR1A and TorsinA

TOR1A is a member of a gene family with three other highly homologous genes in the human genome; *TOR1B*, *TOR2A* and *TOR3A* (Ozelius et al., 1999). At both the DNA and protein level, TOR1B is 70% identical to *TOR1A. TOR 2A* and *TOR3A* share about 50% homology with *TOR1A* at the amino acid level (Ozelius et al., 1999; Dron et al., 2002). By northern blot analysis *TOR1B*, *TOR2A* and *TOR3A* are all ubiquitously expressed.

The *TOR1A* gene encodes a 332 amino acid protein, torsinA, which is a member of the AAA + superfamily (ATPases associated with a variety of cellular activities) (Neuwald et al., 1999). These proteins are characterized by Mg++-dependent ATPase activity and typically form six-membered, homomeric ring structures. Many serve as chaperones that mediate conformational changes in target proteins. They are associated with a variety of functions including protein folding and degradation, cytoskeletal dynamics, vesicle recycling and membrane trafficking (Vale, 2000). TorsinA is widely distributed in the brain but restricted to neurons. Although most pathological studies of DYT1 brains have not detected specific neuronal loss, one study of four DYT1 brains found perinuclear inclusion bodies in the midbrain reticular formation and periaqueductal grey (McNaught et al., 2004) however, these changes were not noted in brains from adult-onset PTD cases (Holton et al., 2008; Simonyan et al., 2010).

Most of the wild-type torsinA protein appears to be located in the lumen of the endoplasmic reticulum (ER) and shuttles between the ER and the nuclear envelope (NE) while the mutant protein is more often associated with the NE (Naismith et al., 2004; Goodchild and Dauer, 2004; Hewett et al., 2006). This aberrant localization as well as impaired interactions of mutant torsinA may result in stress - induced abnormalities and defects in synaptic vesicle recycling, including impaired dopamine release (Torres et al., 2004; Misbahuddin et al., 2005; Esapa et al., 2007; Granata et al., 2008). It has also been shown that mutant torsinA interferes with the linkage between the NE/ER membranes and the cytoskeleton which may be important in neurite extension during brain development (Kamm et al., 2004; Hewett et al., 2006; 2007; Nery et al., 2008). Other cellular effects of the mutation include impaired interactions with major binding partners (Naismith et al., 2009) and, in neuronal models, altered tyrosine hydroxylase activity and sequestration of tyrosine hydroxylase in inclusions (O'Farrell et al., 2009). How all these cellular effects relate ultimately to human disease expression is unclear. However, it does seem clear that mutant torsinA results in a loss of function. This is suggested by cellular studies that demonstrate that mutant torsinA inhibits the wild-type protein (Torres et al., 2004; Hewett et al., 2006) and further, that mutant torsinA destabilizes the wild-type protein causing premature degradation through not only the macroautophagy pathway but also by the proteasome (Giles et al., 2008; 2009), as well as in mice where torsinA null mice and torsinA homozygous knock-in (delGAG) mice display similar phenotypes (Goodchild et al., 2005).

Variants in the genes encoding torsinA interacting proteins could confer risk to other forms of PTD or influence penetrance of DYT1 dystonia.

Role of *TOR1A* Variations in Penetrance of DYT1 Dystonia

When mutant torsinA is over-expressed in cells, it forms membrane inclusions that are thought to derive from the ER/NE (Bragg et al., 2004; Gonzalez-Alegre and Paulson, 2004; Goodchild and Dauer, 2004; Naismith et al., 2004). Aside from the GAG deletion, there is a SNP in the coding sequence at residue 216 that encodes aspartic acid (D) in 88% and histidine (H) in 12% of control-population alleles (Ozelius et al., 1997). The functional significance of this SNP has been demonstrated in cell culture. Cells over-expressing torsinA with the H allele developed inclusions similar to those observed in cells over-expressing GAG-deleted torsinA. Further, when the H allele is co-overexpressed with a construct carrying the GAG deleted torsinA, fewer inclusions are formed suggesting that the two alleles interact and may have a canceling effect on each other, resulting in less pathology (Kock et al., 2006). These findings suggest that the D216H polymorphism could play a role in human dystonia, possibly influencing susceptibility to non-DYT1 dystonia (see Association Studies in Late-onset PTD); they also implicate the D216H polymorphism as a potential modifier of DYT1 penetrance, as described below.

When the relationship of this SNP to penetrance of DYT1 dystonia was examined, a significant increase in the frequency of the 216H allele was noted in non-manifesting carriers of the GAG deletion relative to manifesting carriers (Risch et al., 2007). Analysis of haplotypes demonstrated a highly protective effect of the H allele in *trans* with the GAG deletion (*trans* refers to the fact that two genetic variants are located on different alleles); there was also suggestive evidence that the D216 allele in *cis* is required for the disease to be penetrant. These results which, have been confirmed in one study (Kamm et al., 2008), support this variant as a potent intragenic modifier; however, it has a relatively small role in explaining reduced penetrance because the H allele is not common (about 12%) in the population. In fact, in a French cohort of DYT1 patients and family members, no H alleles were found and thus this modifier is not a factor in this population (Frédéric et al., 2009). Functional confirmation of this genetic association has been provided by imaging studies that reveal that the altered metabolism seen in specific brain regions in DYT1 non-manifesting carriers is regulated by the D216H SNP (Carbon and Eidelberg, 2009).

Early-Onset non-DYT1 PTD

There remains a large group of early-onset PTD, especially among non-Jewish populations, that is not due to the GAG deletion in *TOR1A*. Five other dystonia loci have been posited for families having an early to adolescent onset phenotype including *DYT2* and *DYT4*, both unmapped, *DYT13* and *DYT17* located on chromosomes 1 and 20 respectively and *DYT6* for which the gene, *THAP1*, has been identified.

DYT2 PTD

An autosomal recessive form of dystonia, *DYT2*, with a phenotype resembling DYT1 dystonia has been reported in five consanguineous families including three Spanish gypsy families (Gimenez-Roldan et al., 1988), a Sephardic Jewish family (Khan et al., 2003), and a family of Arab decent (Moretti et al., 2005). All of the cases in these families have an early age of onset and most have symptoms starting in the limbs followed by rapid generalization. To date, no genetic linkage studies or homozygosity mapping have been performed in any of these families.

DYT4 PTD

A single large Australian family with dystonia symptoms ranging from focal to generalized but with prominent whispering dysphonia has been designated as *DYT4* (Parker, 1985; Ahmad et al., 1993). The disease is inherited as an autosomal dominant trait with reduced

penetrance and has a wide range of age at onset (13-37 yrs) though most cases begin in their 20s. Linkage to a chromosomal location has not been established for this locus although; the *DYT6* locus was excluded as a cause in this family (Djarmati et al., 2009).

Mixed PTD

Two loci, *DYT*6 (Almasy et al., 1997) and *DYT*13 (Valente et al., 2001), have been mapped in families with adolescence-onset, autosomal dominant transmission and reduced penetrance; while a third locus, *DYT17*, also displays adolescence-onset but is inherited as an autosomal recessive trait (Chouery et al., 2008). Overall clinical features in these families differ somewhat from DYT1 dystonia (although there are individuals within these families that show phenotypic overlap with DYT1 PTD) and produce what has been coined a "mixed" phenotype. This term was chosen because most, but not all, affected family members expressed clinical features that were intermediate (or mixed) yet distinct from 1) early-onset limb predominant dystonia associated with mutations in the *TOR1A* gene and 2) late–onset localized cervical and cranial dystonia, which constitutes the majority of primary dystonia. Like DYT1 dystonia, onset is often early and dystonia tends to spread (although gait is usually not severely affected); however unlike DYT1 dystonia, and similar to adult onset PTD, dystonia more frequently affects cranial and cervical muscles.

DYT13 PTD

The *DYT13* locus was reported in a single large Italian family (Valente et al., 2001) and shares several clinical features with DYT6 dystonia (see below). Most cases show juvenile onset (mean 16 yrs, range 5-43 yrs) while distribution remains segmental with prominent craniocervical involvement and only occasional generalization (Bentivoglio et al., 2004). Only 2 of 11 individuals developed leg dystonia, and like DYT6 PTD, the disability from leg dystonia was mild. There is less speech involvement in DYT13 PTD. The locus was mapped to chromosome 1p36 and at present, no other families have been linked to this locus.

DYT17 PTD

In 2008, *DYT17* was mapped to chromosome 20 in a consanguineous Lebanese family. Onset in three siblings was in adolescence (14-19 years), cervical muscles were affected first, and like DYT6 PTD (see below) there was progression to segmental (in two sibs) or generalized dystonia with severe dysphonia and dysarthria (Chouery et al., 2008).

DYT6 PTD

The *DYT6* gene was mapped to chromosome 8p21-q22 in three Amish-Mennonite families that share a common haplotype and ancestor (Almasy et al., 1997; Saunders-Pullman et al., 2007). The disease is inherited as an autosomal dominant trait, and there is reduced penetrance of about 60% in the Amish-Mennonite kindred. A heterozygous insertion/deletion mutation was identified in these families in the *THAP1* gene, resulting in a truncation of the encoded protein (Fuchs et al., 2009).

Although this gene was initially thought to have a limited role, restricted to related Amish Mennonite families, more than 45 distinct *THAP1* mutations have been identified among PTD patients of mainly European Caucasian ancestry (Bonetti et al., 2009; Bressman et al., 2009; Djarmati et al., 2009; Fuchs et al., 2009; Paisán-Ruiz et al., 2009; Clot et al., 2010; Groen et al., 2010; Houlden et al., 2010; Sohn et al., 2010; Xiao et al., 2010; Zittel et al., 2010) but also in Brazilian (de Carvalho Aguiar et al., 2010) and Chinese (Cheng et al., 2010) patients. The frequency of *THAP1* mutations ranges from around 1% when screening all types of PTD (Bonetti et al., 2010; Sohn et al., 2010; Xiao et al., 2010) to as high as 25%

when a very specific clinical phenotype is selected (multiplex families in which at least one individual has non-focal involvement and onset <22 years) (Bressman et al., 2009). A careful study taking into account age and site onset, distribution of dystonia, and family history is needed in order to better estimate the proportion due to *THAP1* mutations.

Despite the diversity of ancestries, a typical phenotype has emerged. DYT6 dystonia is characterized by an average early age at onset, although there is a broad range (mean of 16 years, with range of 5 to 62 years) (Bressman et al., 2009; Xiao et al., 2010). Approximately one quarter of cases start in the cranial muscles (larynx, tongue, and facial muscles) one-quarter in the neck and one-half in the arm, and in contrast to DYT1 cases rarely start in the leg (4%). Most spread to at least a segmental distribution with over half having generalized or multifocal involvement. Despite the relatively high proportion generalizing, the need for assistive devices for mobility is much less than in DYT1 dystonia (Almasy et al., 1997; Saunders-Pullman et al., 2007; Bressman et al., 2009). Speech involvement is a prominent feature (Bressman et al., 2009; Djarmati et al., 2009; Fuchs et al., 2009; Paisán-Ruiz et al., 2009; Cheng et al., 2010; Clot et al., 2010; de Carvalho Aguiar et al., 2010; Groen et al., 2010; Houlden et al., 2010; Sohn et al., 2010; Xiao et al., 2010; Zittel et al., 2010). In addition to this typical phenotype, about 10% have only focal dystonia and in screens of adult onset focal cases a low frequency (about 1%) have been reported with mutations in the *THAP1* gene (Houlden et al., 2010; Sohn et al., 2010; Xiao et al., 2010). Psychiatric features were reported in one study (Houlden et al., 2010) but were not found in two others (Groen et al., 2010; Zittel et al., 2010), further investigation is necessary to determine if this is a consistent feature. Two studies have also reported substantia nigra hyperechogenicity using transcranial sonography in both manifesting and non-manifesting mutation carriers suggesting this may be an endophenotype (Saunders-Pullman et al., 2010; Zittel et al., 2010). The significance of this finding is elusive but may be related to the reduced striatal D2 receptor availability reported in PET studies (Carbon et al., 2009).

THAP1 is a member of a family of cellular factors sharing a highly conserved THAP (Thanatos-associated protein) DNA binding domain, which is an atypical zinc finger (Clouaire et al., 2005; Roussigne et al., 2003). In addition to the THAP domain at the N-terminus, *THAP1* possesses a low complexity-proline rich region, a coiled-coil domain and nuclear localization signal (NLS) at its C-terminus. Associated with its DNA binding function, *THAP1* regulates endothelial cell proliferation via modulation of pRb/E2F cell cycle target genes (Cayrol et al., 2007). *THAP1* has also been described to function as a nuclear proapoptotic factor that associates with promyelocytic leukemia nuclear bodies (PML NB) and potentates both serum withdrawal and TNF-alpha induced apoptosis (Roussigne et al., 2003). *In vitro*, the C-terminal region of *THAP1* has been shown to interact with prostate apoptosis response 4 protein (Par-4) (Roussigne et al., 2003), a well characterized effector of cell death linked to prostate cancer and neurodegenerative diseases, including Parkinson's diseases (Duan et al., 1999). Very recently, two studies have reported an interaction between *THAP1* and *TOR1A*. Thap1 protein binds directly to the *TOR1A* promoter in cell lines, primary cells and mouse brain tissue and this interaction is disrupted by pathogenic *THAP1* mutations (Gavarini et al., 2010). Additionally, using *in-vitro* assays, wild-type *THAP1* was shown to repress the expression of *TOR1A*, whereas dystonia-associated mutant *THAP1* results in decreased repression of *TOR1A* (Kaiser et al., 2010). This data establish transcriptional dysregulation as a cause of PTD and links the molecular pathways underlying DYT1 and DYT6 dystonia. Interestingly, *THAP1* may also be physically associated with a second form of dystonia involving a transcription factor, namely *DYT3* (Mazars et al., 2010). There is no data on *THAP1* function in the brain.

The majority of mutations identified to date in PTD patients are thought to eliminate the DNA binding function of the protein. These include missense mutations within the DNA

binding domain itself, several of which have been shown to be functional by gel shift assays (Fuchs et al., 2009; Gavarini et al., 2010), substitution mutations that disrupt the NLS or nonsense and frameshift mutations that truncate the protein within the DNA binding domain or before the NLS (Bressman et al., 2009; Djarmati et al., 2009; Fuchs et al., 2009; Paisán-Ruiz et al., 2009; Cheng et al., 2010; Clot et al., 2010; de Carvalho Aguiar et al., 2010; Groen et al., 2010; Houlden et al., 2010; Sohn et al., 2010; Xiao et al., 2010; Zittel et al., 2010). A smaller number of missense mutations have also been identified in the C-terminal end of the protein in and near the coiled-coil domain (Bonetti et al., 2009; Groen et al., 2010; Houlden et al., 2010; Sohn et al., 2010; Xiao et al., 2010) a region known to participate in interactions with other proteins (Roussigne et al., 2003). Two recent reports propose that *THAP1* binds DNA as a homodimer (Sabogal et al., 2010; Campagne et al., 2010). Bonetti et al. (2009) suggests that the coiled-coil domain is important for dimerization, and mutations in this region could disrupt this process thus indirectly interfere with the DNA binding function of *THAP1*. No consistent relationship between mutation type or position and phenotype has been found. In fact, a homozygous missense mutation in the C-terminal region was reported in an individual with onset at age 57 with segmental dystonia (Houlden et al., 2010). Mutations in the 5′ untranslated region (Xiao et al., 2010), within introns (Houlden et al., 2010; Xiao et al., 2010) and heterozygous synonymous amino acid substitutions (Paisán-Ruiz et al., 2009; Groen et al., 2010; Xiao et al., 2010) have also been reported in PTD cases but are of unknown significance. Finally, unlike the recurrent delGAG mutation in the *TOR1A* gene, because almost every individual/family has a distinct *THAP1* mutation, genetic screening is more involved, requiring sequencing of the three exons of this gene.

Late-onset focal and segmental PTD

Late or adult-onset PTD is about 9-10 times more frequent than early-onset PTD with a prevalence estimated at 30/100,000 in the general population (Nutt et al., 1988; ESDE Collaborative Group, 2000). The disease usually begins in mid-adulthood and usually starts with focal onset in cervical, cranial muscles with a limited tendency to spread widely and generalize. Focal forms include torticollis, writer's cramp, blepharospasm and spasmodic dysphonia. Although phenotypically different, these forms are thought to be related complex diseases that share common susceptibility genes as well as additional individual genetic and environmental risk factors that occur in different combinations resulting in specific disease (DeFazio et al., 2007). One clue that genetic factors are involved, is that a family history of dystonia has been reported in up to 25% of first-degree relatives of late-onset PTD cases (Waddy et al., 1991) Martino et al., (2004) clearly show that in order to obtain accurate family history information, neurologic exams of at-risk subjects is the best method although more recently several screening based tools have been developed to identify cases among family members (Saunders-Pullman et al., 2005; Aniello et al., 2006). Genetic studies to determine the mode of inheritance using segregation analyses conclude that focal dystonia is inherited as an autosomal dominant trait but with very low penetrance (about 12%-15% compared to 30% for early-onset) (Waddy et al., 1991; Defazio et al., 1993); an alternative explanation is that penetrance may be higher in a subset with the remainder sporadic. Consistent with the notion of increased penetrance in a subset of late-onset PTD, are descriptions of large families with more highly penetrant autosomal dominant disease (Uitti et al., 1993; Bressman et al., 1996; Munchau et al., 2000).

DYT7 PTD

Linkage studies in a large family with seven affected members from northwest Germany, resulted in the mapping of the *DYT7* locus to chromosome 18p (Leube et al., 1996). All members had adult-onset cervical dystonia (mean 43 yrs; range 28 to 70 yrs), although some also had brachial and cranial involvement. Other clinically similar families have been

excluded from *DYT7* (Jarman et al., 1999) suggesting yet other loci for adult onset focal PTD.

Association Studies in Late-onset PTD

The great majority of cases of focal PTD appear to be sporadic or occur in small families that by themselves are not informative for traditional linkage studies. An alternative approach for determining genetic susceptibility is association studies, in which allele frequencies at genetic variations are compared between cases and controls. Two types of association studies can be performed, candidate gene studies where variants in genes implicated in disease pathophysiology are examined or genome wide association studies (GWAS) where variants across the entire genome are examined in an unbiased manner. At present there are no published GWAS for PTD; instead, association studies have focused on particular candidate genes implicated in PTD including genes related to dopaminergic transmission, brain plasticity and genes that underlie Mendelian forms of dystonia.

A variety of data support a role for dysfunction of the dopamine system in the pathophysiology of dystonia (Wichmann et al., 2008). A polymorphism in the dopamine D5 receptor (*DRD5*) gene has been associated with adult-onset torticollis (Placzek et al., 2001; Brancati et al., 2003) and blepharospasm (Misbahuddin et al., 2002) from Britain and Germany. This result could not however, be replicated in an independent cohort of Italian and North American blepharospasm patients or in a cohort of focal PTD patients from France and Germany (Sibbing et al., 2003; Clarimon et al., 2007).

A functional SNP, V66M, in brain-derived neurotrophic factor (*BDNF*) has also been examined for associations with focal PTD. This SNP has been shown to modulate human cortical plasticity (Cheeran et al., 2008) and abnormalities in synaptic plasticity have been implicated in dystonia (Quartarone et al., 2008). Contradictory findings have been reported for V66M, with one group finding no association in a cohort of 156 Italian patients with cranial and cervical dystonia compared to 170 control subjects (Martino et al., 2009) and a second team finding a two fold increase in the V66M heterozygotes among 34 cervical dystonia patients compared to 54 controls and 53 with Parkinson's disease; all subjects in the study were Caucasian from the US (Cramer et al., 2009).

Finally, a number of studies have examined the influence of various SNPs in the Mendelian PTD genes *TOR1A* and more recently *THAP1*, for their involvement in adult-onset PTD. As several of the reported mutation screening studies for *THAP1* included focal/segmental PTD patients, non-coding SNPs identified through these studies were examined for associations. Several of these studies suggested that variants in *THAP1* might contribute to risk of focal dystonia (Djarmati et al., 2009; Houlden et al., 2010; Xiao et al., 2010) but the associated variants were not consistent.

Much more extensive studies have been carried out with the *TOR1A* gene. The D216H SNP described above as being associated with decreased penetrance in DYT1 dystonia patients, has also been examined in adult-onset PTD patients. An association with increased risk of dystonia has been found in German patients with various forms of focal/segmental dystonia and a positive family history (Bruggemann et al., 2009) but no associations with D216H were noted in three other studies; however, the focal/segmental cases in these studies were primarily sporadic (Sibbing et al., 2003; Kamm et al., 2006) or contained a small proportion of familial cases (Sharma et al., 2010). Several SNPs from the 3′ untranslated region of *TOR1A* have been implicated in risk of focal dystonia in an Icelandic population and Italian blepharospasm patients (Clarimon et al., 2005; 2007) as well as the risk of spread of blepharospasm in Italian and US cohorts (Defazio et al., 2009). Two other studies, one in a focal Austrian/German population (Kamm et al., 2006) and the other in focal/segmental

patients of mixed European descent (Sharma et al., 2010), also showed an association with 3′ SNPs but in both cases, rather than being a risk haplotype, the SNPs showed a strong protective effect. Sharma et al. (2010) explored this association further and found that when they stratified their population based on family history, the association was stronger in cases with a negative family history of dystonia; when they divided the sample based on site of dystonia, cervical dystonia showed a statistically significant association and laryngeal dystonia showed a trend toward a significant association. Finally, two studies from Germany failed to show any association with SNPs in the *TOR1A* gene (Sibbing et al., 2003; Hague et al., 2006).

Overall, these candidate gene association studies are inconclusive. The contradictory data reported for all of these genes is most likely due to several confounding factors including small number of SNPs tested, limited sample size, clinical heterogeneity and the use of different ethnic groups. The samples used for the studies described above, included segmental cases, subjects with all different subtypes of focal PTD, both familial and sporadic cases as well as cases from more isolated populations like Iceland, northern Germany and Italy as compared to US cohorts. As the majority of late-onset PTD is most likely a complex disorder in which multiple factors act together to cause disease, studying single or a few SNPs within one gene in a limited number of heterogeneous cases is unlikely to elucidate associations. Rather, a genome-wide association or next-generation sequencing approach is critical for identifying the genetic risk factors contributing to late-onset PTD. However, the large number of uniformly phenotyped late-onset cases needed for this approach will only be achieved through a world-wide collaborative effort. Further, assessment of potential environmental risk factors in this population, would allow for the examination of gene:environment interactions that might also contribute to risk of developing PTD.

Conclusions

The well described clinical diversity of PTD is reflected, not surprisingly, in genetic heterogeneity. The majority of DYT1 dystonia is characterized by an early limb onset phenotype whereas DYT6 dystonia is more likely to involve cranial facial muscles and speech. However, within these two genetic subtypes, there is clinical overlap not only with each other but also with the more common focal/segmental forms of PTD. On the molecular side, the potential association of variants in *TOR1A* and *THAP1* with susceptibility to focal/segmental PTD as well as the recent discovery that Thap1 binds to the *TOR1A* promoter (Gavarini et al., 2010; Kaiser et al., 2010) suggests that common pathways may be involved in PTD. Imaging studies (Carbon et al., 2004b Carbon et al., 2008) also point to common pathway dysfunction. These findings raise the possibility that novel therapeutics, targeting common pathways could be effective for the treatment of different forms of PTD. Identification of additional PTD genes and genetic risk factors should aid in the elucidation of the mechanisms underlying PTD.

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Table 1

Classification of Dystonia

By Age At Onset	
Early	
	Childhood
	Adolescence
Late/Adult	
By Distribution	
focal - single body region (e.g., writer's cramp, blepharospasm, torticollis, spasmodic dysphonia)	
segmental - contiguous body regions (e.g., face + jaw or Meige syndrome, torticollis + writer's cramp)	
multifocal - non-contiguous body regions (e.g. arm + leg which is hemidystonia if ipsilateral, blepharospasm +writer's cramp)	
generalized - both legs (or one leg and the trunk) + at least one other body region-usually one or both arms	
By Cause	
Primary (previously idiopathic)	
Non - Primary	

Table 2
Causes of Primary Torsion Dystonia (PTD)

Child or adolescent onset, usually involving limbs > cervical > cranial muscles
*DYT*1 /TORIA (coding for torsinA), recurring heterozygous GAG deletion
Other genes (e.g. *DYT*2, *DYT4*), not yet localized
"Mixed", primarily early onset and frequent involvement of brachial, cranial and cervical muscles
*DYT*6 (coding *THAP1*), different heterozygous mutations
*DYT*13 on Chr 1p (gene not identified) in an Italian family and apparent autosomal domimant in heritance
*DYT*17 on Chr 20 (gene not identified) in a Lebanese sibship (autosomal recessive)
Adult and cervical, cranial, or brachial-onset, usually remaining focal or segmental
*DYT*7 on Chr 18 (gene not identified) in a German torticollis family
Other genes/causes not yet localized