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7

Other primary generalized dystonias

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INTRODUCTION

Dystonia is the only clinical sign of primary torsion dystonias (PTDs) and there is no identifiable exogenous cause or other inherited or degenerative disease.¹ The best-known PTD is DYT1 dystonia,² but PTDs encompass several other genetically determined forms, none of which has been characterized. DYT1 dystonia was first identified among Ashkenazi Jews^{3,4} and was then recognized as a possible cause of early-onset generalized PTD in populations of any ethnic origin.⁵⁻⁷ Clinical observations have reported that DYT1 dystonia can have heterogeneous phenotypic expressions,⁸⁻¹⁰ making it difficult to differentiate DYT1 and non-DYT1 patients on clinical grounds.¹¹

This chapter revises the evidence collected during the last decade, in order to report the phenotype of non-DYT1 generalized PTD families either linked or unlinked to known loci, and to characterize the clinical features of non-DYT1 early-onset dystonia in sporadic and familial PTD patients.

EPIDEMIOLOGY

The available evidence suggests that non-DYT1 PTDs are by far more prevalent in the general population than DYT1 cases. In a large series of Italian PTD patients, it has been observed that DYT1 cases accounted for 41% of the patients with generalized dystonia and for only 5.4% of all PTD cases.¹² A large Italian study on early-onset (<21 years) PTD showed that non-DYT1 cases account for 75% of all early-onset cases.¹¹ This finding is consistent with previous data showing that DYT1 cases account for only 7.9% of total PTDs in Serbia,¹³ for 15% in Denmark,¹⁴ and for 16% in Italy.¹⁵

There are no published data on the prevalence of generalized (or early-onset) non-DYT1 dystonia in the

general population, because most epidemiologic studies were service-based rather than community-based and were performed before DYT1 testing became available.^{16,17} Early-onset cases account for about 15% of all PTDs, the majority of which are represented by non-DYT1 late-onset (focal or segmental) cases.¹⁸

CLINICAL FEATURES

Familial dystonias have been listed with progressive numbering preceded by the DYT code (meaning 'dystonia'; Table 7.1). This list was originally supposed to include only primary dystonias, but currently encompasses several heterogeneous conditions, such as unmapped PTD familial loci (e.g. *DYT2* and *DYT4*), hereditodegenerative dystonias (e.g. *DYT3*), dystonia-plus syndromes (*DYT5* and *DYT11*, *DYT12*, *DYT14*), and paroxysmal dyskinesias or choreoathetosis (*DYT8*, *DYT9*, *DYT10*). Therefore, of the 15 DYT loci, only six refer to PTDs, namely those marked as *DYT1*, *DYT2*, *DYT4*, *DYT6*, *DYT7*, and *DYT13*. With the exception of *DYT2*, all PTDs are inherited as a dominant trait with reduced penetrance.

Monogenic primary torsion dystonias

Four PTD genotypes have been identified, three of which present with generalized phenotypes.

DYT1 phenotype

A common cause of generalized PTD is the GAG deletion in the *DYT1* gene encoding the protein Torsin A.⁴ The disease was originally described among Ashkenazi Jews with a relatively homogeneous phenotype characterized by early limb-onset generalized dystonia.^{3,19}

66 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

Table 7.1 Genetic classification of primary dystonias							
Locus	Prevalent presentation	Phenotype	Onset	Inheritance	Chromosome location	Gene	Genetic testing
<i>DYT1</i>	Generalized early-onset AD Oppenheim's PTD	Limb early onset, often rapidly progressive to generalization; less frequent: focal/segmental adult onset. Infrequently cranial-cervical	Early onset (<30 years in most cases)	AD, reduced penetrance	9q34	Torsin A	GAG deletion
<i>DYT2</i>		Early-onset generalized dystonia with prominent cranial-cervical involvement	?	AR	?	NA	NA
<i>DYT4</i>	Focal (cervical) Whispering dysphonia	Described only in a large Australian kindred with laryngeal and cervical PTD	13–37 years	AD	?	NA	NA
<i>DYT6</i>	Variable Young adult-onset PTD of mixed type	In two German Mennonite families, focal or generalized PTD; cervical, cranial, and limb involvement	5–38 years; average: 18.9 and 18.3 years	AD	8p21-p22	NA	NA
<i>DYT7</i>	Focal (cervical) Adult-onset cervical PTD	In one German family, cervical (laryngeal) adult-onset dystonia	28–70 years	AD, incomplete penetrance	18p	NA	NA
<i>DYT13</i>	Segmental Variable onset, cranial-cervical dystonia	In one Italian family, young-onset, cranial-cervical PTD, occasional generalization	5–40 years	AD, incomplete penetrance	1p36.13-36.32	NA	NA

AD autosomal dominant; AR autosomal recessive; NA not available; OMIM Online Mendelian Inheritance in Man.

It was later reported that, particularly in Caucasian patients,⁵ the *DYT1* phenotype is broader than originally thought. The 'classical' *DYT1* phenotype is characterized by early onset in a limb, generalization without spread to the craniocervical region.⁵ In a series of patients with early-onset PTD it has been confirmed that dystonia never starts in the craniocervical region in *DYT1* carriers, but it has been shown that craniocervical sites can be involved in later stages.¹¹ It is remarkable that *DYT1* patients who develop severe generalized involvement may carry out their daily activities with significant adaptation in many cases. Extreme cases have also been observed, ranging from asymptomatic status to craniocervical involvement or even to status dystonicus.^{9,20-22}

Atypical *DYT1* phenotypes can be grouped in five main types.²³

1. Generalized dystonia with cranial-cervical involvement, more frequent in Europe than in North America, with a record prevalence of 80% in *DYT1* patients of a French series.⁷
2. The generalized myoclonus-dystonia phenotype that is more severe than that observed in *DYT11* myoclonus-dystonia.¹⁰
3. Focal dystonia with slow progression; in these cases spread may occasionally occur several years after onset.^{24,25}
4. Late-onset.⁹
5. Non-limb (cervical, laryngeal, or trunk) onset^{6,26} are rarer forms of *DYT1* dystonia.

Regardless of onset, position emission tomography (PET) studies have shown that *DYT1* dystonia is associated with abnormal movement preparation due to defective sensorimotor integration. These features are genotype-specific, as putaminal metabolism is increased in *DYT1* patients, but decreased, for example, in *DYT6* patients.²⁷ Since clinical criteria can hardly distinguish *DYT1* from non-*DYT1* patients, the identification of endophenotypes associated with *DYT1* carriers (either affected or non-affected) provides a new potential diagnostic tool. Striatal D₂ receptor binding is reduced in manifesting as well as in non-manifesting *DYT1* carriers.²⁸ Another possible endophenotype of *DYT1* carriers is the finding of higher tactile and visuotactile temporal discrimination thresholds or temporal order judgments.²⁹

DYT6 phenotype

The *DYT6* locus has been mapped in two Mennonite families, where dystonia was inherited as an autosomal dominant trait with an estimated penetrance of 30%.³⁰ The locus was mapped to 8p21-q22 and a founder effect

was supported by the observation that haplotypes across the candidate region were identical in the affected members of the two families, suggesting a common underlying mutation. A total of 15 definitely affected individuals were identified among 220 family members.

The *DYT6* phenotype has been described as 'mixed type', characterized by early or adult onset and prevalent segmental (craniocervical) distribution, with presentation at onset equally involving limb, cervical, and cranial muscles. Four patients presented generalized dystonia, and some had a classical *DYT1* phenotype. *DYT6* patients with generalized phenotype had (on average) an older age at disease onset than *DYT1* patients (18.9 ± 11.9 years; range: 5–38 years); in addition, they commonly had craniocervical involvement either at onset or later during disease progression. Many *DYT6* patients were remarkably disabled in their living activities by this craniocervical involvement. It has been shown that manifesting *DYT6* gene carriers have bilateral hypermetabolism in the supplementary motor area and the temporoparietal cortex, and bilateral hypometabolism in the putamen.²⁷

DYT7 phenotype

The *DYT7* locus mapping to the short arm of chromosome 18 was identified in a large German family with autosomal dominant focal dystonia.³¹ The mean age of disease onset was 40 years and no patient had generalized dystonia.

DYT13 phenotype

The *DYT13* locus was mapped in a family with prominent upper body involvement (craniocervical and upper limb), the majority of whom had onset in infancy or adolescence.^{32,33} Disease progression was evaluated for 6 years in this family.³⁴ There were 11 definitely affected individuals, two of whom had generalized dystonia with early onset in the upper limb or in the cervical region. The peculiar features of the *DYT13* phenotype are prominent cervical or upper limb involvement; disability is mild, even in generalized cases.

The first patient with generalized PTD was a woman who presented postural tremor of the upper limbs at age 5. The tremor rapidly diffused to involve the whole body and did not aggravate. Upon observation in her sixties, the patient had generalized dystonia with prominent action tremor affecting the larynx, limbs, and trunk. Despite this widespread involvement, her disability was mild. Being a housekeeper, she could run her daily duties without help. The second patient with generalized dystonia was a man, who had cervical onset at age 20. He did not progress for the following 30 years. In his fifties,

68 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

dystonia spread to the right hand, then to both upper limbs, and to the head. He was last examined at age 56, when he had a generalized dystonia involving the neck and all the limbs. Similar to the other patient, his disability was mild: he could still work on a farm and was engaged in full-time labor.

PTD pedigrees

Two familial PTD phenotypes with occasional generalisation have been coded. In addition, several other pedigrees, many of which with generalisation, have also been described.

DYT2 phenotype

This is a recessive dystonia locus originally described in three consanguineous pedigrees of Spanish Gypsies. The disease was named 'autosomal recessive dystonia in Gypsies' and listed as DYT2.^{35,36} In two of the families, the phenotype was similar to that of DYT1 dystonia, consisting in early limb onset and progression to generalization; in the third family, dystonia presented with prominent oromandibular and cervical dystonia.³⁶

A Sephardic Jewish Iranian family with a similar phenotype and autosomal recessive inheritance has been described more recently.³⁷ Three siblings in this family had PTD with limb onset in childhood, and slow progression to generalized dystonia with predominant craniocervical involvement. Two patients first developed in-turning of the foot with gait abnormalities, and all had cervical involvement, facial grimacing, blepharospasm, and involvement of the upper and lower limbs. Two patients also had dystonic dysphagia. It was hypothesized that this Sephardic family originating from Spain could be related to the DYT2 Gypsy family, but this possibility appears unlikely, also because most Iranian Jews do not originate from Spain or Portugal.³⁸

A third family with childhood-onset, generalized dystonia, and autosomal recessive inheritance was also classified as DYT2.³⁹

Overall, the *DYT2* phenotype is consistent in the three families described and is characterized by early onset, generalization, and autosomal recessive transmission. DYT2 dystonia should be considered in every family with such features, particularly if there is prominent craniocervical involvement. Unfortunately, DYT2 dystonia has not been mapped to a genetic locus yet.

DYT4 phenotype

A large Australian pedigree had 20 members affected by dystonia in at least five consecutive generations and autosomal dominant inheritance.⁴⁰ This PTD pedigree

was classified as DYT4. Penetrance was complete in all the examined obligate gene carriers; age at onset varied from 13 to 37 years. Many of the patients presented with 'whispering dysphonia', others had cervical dystonia; most eventually developed generalized dystonia. Wilson's disease coexisted in the same pedigree, but was excluded as a cause of dystonia in the affected individuals.⁴¹ The *DYT4* phenotype has not been observed in other families or individual cases.

Non-coded pedigrees

In some PTD families not carrying the *DYT1* mutation, the phenotype has been described in the affected individuals. Linkage studies have not been performed in these small pedigrees, which have remained unclassified.

A non-Jewish American family presented with adult-onset *DYT1*-negative PTD.⁴² The disease started in the neck in six cases and in a leg in one. All patients developed cervical dystonia, and language impairment (dysarthria or dysphonia) occurred in five patients. Four patients developed generalization of symptoms. In another Swedish family, transmission was autosomal dominant with variable phenotype.⁴³ There was involvement of the face and larynx, and generalization occurred in three of the 10 patients. A family from South Tyrol had six affected individuals, four of whom developed generalization approximately 5 years after onset.⁴⁴ Limbs were involved at onset in all but one patient, who started with cervical dystonia. Upper body involvement was observed in three of the four generalized cases. An Italian family had six affected individuals, one of whom had severe segmental dystonia.⁴⁵ The prevalent phenotype was with adult-onset craniocervical dystonia with occasional axial involvement but no generalization.

Table 7.2 provides a synopsis of unclassified PTD pedigrees with a generalized phenotype.

Non-DYT1 early-onset PTD cases

The observation that early-onset dystonia cases progress to severe forms was reported since the first descriptions of dystonia.^{46,47} In their seminal description of the natural history of PTD, Marsden et al⁴⁸ identified age at onset as one of the most important features in determining outcome. A consensus meeting later identified three age groups for PTD onset: childhood (0–12 years), adolescent (13–20 years), and adult (>20 years).⁴⁹ Based on this consensus, cases with early onset (encompassing onset in childhood or in adolescence) were distinguished from those with adult onset by the threshold age of 21 years. Later retrospective series have confirmed that patients with early onset were more likely to have

Table 7.2 Clinical features of unclassified PTD pedigrees with generalized dystonia; cases without generalization are not listed

No. of patients	Mean age at onset (years, range)	Site of onset: number	Progression: number	Cranial involvement: number	Additional features	Reference
7	28.4 (7–50)	Neck: 6 Leg: 1	Generalized: 4 Segmental: 3	Yes: 7	Tongue involvement in 4 patients Family with AD inheritance	42
7	27.3 (17–50)	Face: 4 Arm: 2 Unknown: 1	Generalized: 3 Multifocal: 3 Focal: 1	Yes: 4	Prominent cranial involvement Family with AD inheritance	43
6	23.3 (4–50)	Cervical: 1 Arm: 3 Leg: 2	Generalized: 4 Segmental: 2	Yes: 2	Prominent cervical involvement Family with AD inheritance	44
16 probands	The proband with generalized dystonia was early onset	NA	Generalized: 1 Segmental: 7 Focal: 8	NA	At least one early-onset patient in each family	13
25 patients	7.7 (1.5–15)	Cranial: 1 Neck: 1 Arm: 12 Trunk: 2 Leg: 9	Generalized: 22 Segmental: 3	Yes: 16	Series of both sporadic and familial patients	15
1	2	Leg: 1	Generalized: 1	No	Myoclonus dystonia-like phenotype with familial occurrence. AD inheritance	54
7 probands	13.9 (1–17)	Cervical: 3 Arm: 2 Leg: 2	Generalized: 3 Multifocal: 1 Segmental: 2 Focal: 1	Yes: 2	The proband of DYT 13 family is included	11

AD autosomal dominant; NA not available.

70 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

a generalized form than those with older age at onset and that there is a bimodal curve representing the frequency distribution of age at disease onset, with a nadir separating two clusters of patients.^{50,51}

Later series described the frequency distribution of ages at onset and attempted to identify the predictive value of early vs adult age at disease onset for the probability of developing a generalized form of dystonia.^{3,51} In North American series (characterized by a predominance of Ashkenazi Jewish patients), a threshold age at disease onset of more than 26 years indicated a low probability of being carrier of a *DYT1* mutation,²⁶ but this was not confirmed in other series based on different populations.⁵² Thus, while all retrospective series confirm a bimodal distribution of age at onset for PTD, with a higher likelihood of generalization for the early age group, the measured predictive value of the age thresholds vary based on the populations considered.

In a large Italian series, encompassing a majority of non-*DYT1* patients, the frequency distribution of the ages at onset was a bimodal curve with modes at 9 and 57 years and a nadir at 21 years.¹² The sensitivity and specificity of age at onset to predict generalization were calculated for all patients with a follow-up observation of at least 5 years. Receiver operating characteristic (ROC) curves were plotted and the best trade-off threshold predicting generalization was found at 32 years, yielding sensitivity and specificity of 83% (Figure 7.1). The negative predictive value was 99%, indicating a negligible probability that patients with age at onset higher than 32 years would progress to generalization.

The phenotype of non-*DYT1* early-onset PTD cases is not completely characterized, but several series remarked differences from the *DYT1* phenotype that may be

unapparent in individual cases. In a French Study of 100 patients with sporadic PTD,⁷ 10 were affected by generalized dystonia, and five of them carried the *DYT1* mutation. The phenotype of generalized dystonia in non-carriers was not described in detail, but it was reported that age at onset was higher in non-carriers. In a series of 30 Italian patients with early-onset sporadic PTD, 25 were not *DYT1* carriers: 22 of them had generalized dystonia, and 16 presented oromandibular or laryngeal involvement.¹⁵

A series of 57 consecutive genetically characterized patients with early-onset PTD was recently reported.¹¹ The majority of these patients (43 (75%), 27 men, 16 women; ratio, 1.7: 1) did not carry the *DYT1* mutation. Twenty-nine non-*DYT1* patients eventually developed generalized dystonia, with notable oromandibular involvement in 17 and laryngeal involvement in four. The remaining 14 non-*DYT1* patients developed segmental (eight), multifocal (one), or focal (five) forms. Non-*DYT1* patients with generalized dystonia had earlier onset than those without generalization.

The same series showed that sporadic non-*DYT1* patients had cranial involvement and earlier generalization more often than *DYT1* patients. By contrast, familial non-*DYT1* cases had older age at onset and older age at generalization, more frequent cervical involvement, and less common limb onset. Progression was more rapid in sporadic non-*DYT1* patients than in familial non-*DYT1* patients, suggesting that the latter may belong to a different phenotype (Figure 7.2). In keeping with this, familial non-*DYT1* cases of this Italian series had a relatively homogeneous phenotype, similar to the so-called 'mixed phenotype',^{30,34} with cervical involvement, frequent non-limb onset, relatively benign disease

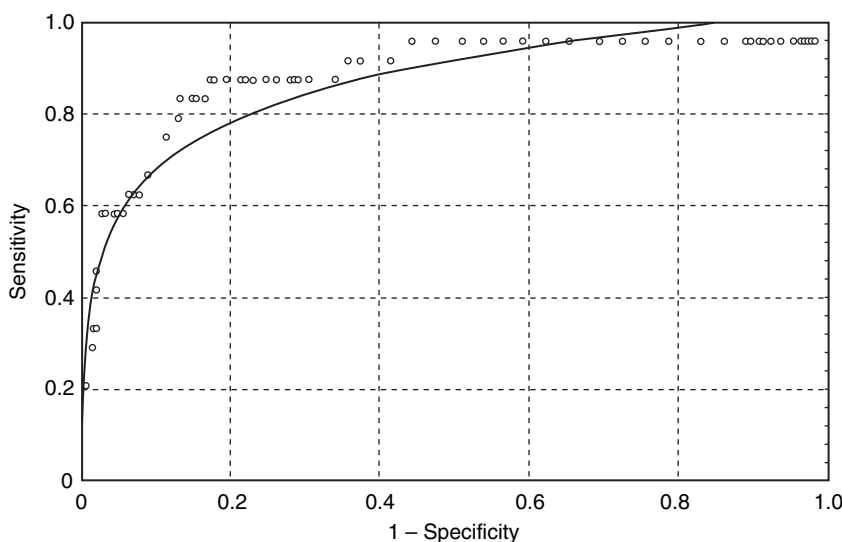


Figure 7.1 ROC curve plotting sensitivity and specificity for the prediction of dystonia generalisation in 443 patients followed-up for more than 5 years.¹² Age at disease onset predicts generalization with sensitivity and specificity of 83%.

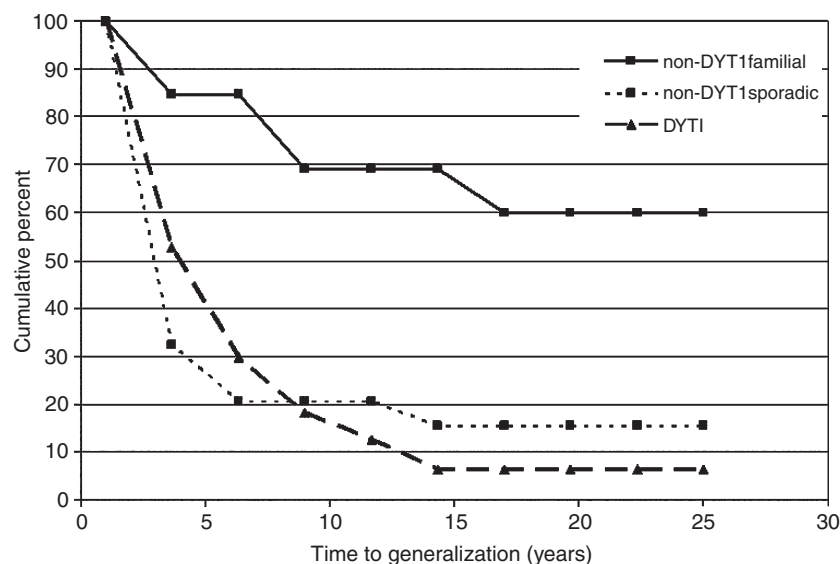


Figure 7.2 Survival curves for the progression of dystonia measured by the time to generalization. DYT1 patients are compared to familial and sporadic non-DYT1 cases. It is shown that familial non-DYT1 cases have less severe progression than DYT1 or sporadic non-DYT1 patients. (Reproduced from Fasano et al,¹¹ with permission.)

course, and uncommon generalization. This finding suggests that these non-DYT1 Italian families may share a common genetic defect.

CONCLUSIONS AND OUTLOOK

Generalized dystonias represent a heterogeneous group encompassing sporadic and familial cases with overlapping clinical features. A certain number of still unmapped genes are certainly responsible for these cases. Since large families suitable for linkage analysis are rare, it is useful to classify patients into homogeneous phenotypic groups and to look for endophenotypic markers before planning new linkage studies. The available data on familial PTD cases suggest that the traditional classification of 'predominantly generalized' and 'predominantly focal' forms⁵³ may be reductive. Indeed, regardless of the predominant familial phenotype, generalized and focal PTDs often coexist in the same pedigree, making clinical heterogeneity a cardinal feature of inherited dystonias.

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72 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

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