Dystonia and Genetics

Shih-Fen Chen¹ and Yu-Chih Shen²,³

¹Department of Life Science and Graduate Institute of Biotechnology, Dong-Hwa University
²Department of Psychiatry, Tzu-Chi General Hospital
³School of Medicine and Department of Human Development, Tzu-Chi University, Taiwan

1. Introduction

In recent years, the identification of several new dystonia genes has provided important insights into the nature of this clinically and genetically heterogeneous disorder. Currently, about twenty different forms of monogenic dystonia are distinguished genetically and have been designated DYT 1–13; DYT 14, which has been redefined as DYT 5; and DYT 15–21 (Ozelius et al., 2011; Wider et al., 2008). Among these DYTs, ten genes have been identified using linkage analysis in families: DYT 1, 3, 5/14, 6, 8, 11, 12, 16, and 18 (See Table 1 and Figure 1) (Ozelius et al., 2011).

A DYT is designated based on phenotype or chromosomal location. Therefore, it represents a clinically heterogeneous group of disorders that include primary dystonia, where dystonia is the only phenotype (DYT 1, 2, 4, 6, 7, 13, 17, and 21); dystonia plus syndromes, where other phenotypes in addition to dystonia, such as parkinsonism or myoclonus, are seen (DYT 3, 5/14, 11, 12, 15, and 16); and paroxysmal forms of dystonia/dyskinesia (DYT 8, 9, 10, 18, 19, and 20) (Table 1) (Ozelius et al., 2011).

2. Primary dystonia

The clinical phenotype of primary dystonia is broad, ranging from early-onset generalized to late onset focal. Early-onset dystonia is rare, often starts in a limb, tends to generalize, and frequently has a monogenic origin. Late-onset dystonia is relatively common, rarely involves the lower extremities, has a tendency to remain focal, and appears to be sporadic in most cases (Schmidt & Klein, 2010). Six of the primary dystonia are associated with an early-onset generalized phenotype (DYT 1, 2, 4, 6, 13, and 17), whereas two of them are characterized by a late-onset focal phenotype (DYT 7 and 21) (Ozelius et al., 2011). Genes have been identified for DYT 1 and 6 (See Table 1).

2.1 Early-onset primary dystonia

2.1.1 DYT1

DYT1 dystonia is the most common and severe form of hereditary dystonia, with an estimated frequency of 1/9000 in the Ashkenazi Jewish and 1/160000 in the non-Jewish
population. The onset age of affected members ranges from 6 to 42 years, and the severity of the disease varies considerably. In very early-onset cases, symptoms typically begin in a lower limb and progress up the body over the following years. In contrast, later-onset cases are usually limited to upper-body parts, correlating with a somatotopic gradient in the basal ganglia (Bressman et al., 2000).

<table>
<thead>
<tr>
<th>Dystonia type</th>
<th>Designation</th>
<th>Mode of inheritance</th>
<th>Gene locus</th>
<th>Protein (Gene)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary dystonia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early-onset primary dystonia</td>
<td>DYT1</td>
<td>Autosomal dominant</td>
<td>9q34</td>
<td>Torsin A (TOR1A)</td>
</tr>
<tr>
<td></td>
<td>DYT2</td>
<td>Autosomal recessive</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>DYT4</td>
<td>Autosomal dominant</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>DYT6</td>
<td>Autosomal dominant</td>
<td>8p21-22</td>
<td>Thanatos-Associated Protein 1 (THAP1)</td>
</tr>
<tr>
<td></td>
<td>DYT13</td>
<td>Autosomal dominant</td>
<td>1p36</td>
<td>Unknown</td>
</tr>
<tr>
<td>Late-onset primary dystonia</td>
<td>DYT7</td>
<td>Autosomal dominant</td>
<td>18p</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Dystonia plus syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia plus parkinsonism</td>
<td>DYT3</td>
<td>X-chromosomal recessive</td>
<td>Xq13</td>
<td>Gene transcription factor (TAF1)</td>
</tr>
<tr>
<td></td>
<td>DYT5/14</td>
<td>Autosomal dominant</td>
<td>14q22</td>
<td>GTP cyclohydrolase I (GCH1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autosomal recessive</td>
<td>11p15</td>
<td>Tyrosine hydroxylase (TH)</td>
</tr>
<tr>
<td></td>
<td>DYT12</td>
<td>Autosomal dominant</td>
<td>19q12-13</td>
<td>Na+/K+ ATPase ß3 subunit (ATP1A3)</td>
</tr>
<tr>
<td></td>
<td>DYT16</td>
<td>Autosomal recessive</td>
<td>2q31</td>
<td>Stress-response protein (PRKRA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>e-sarcoglycan (SCGE)</td>
</tr>
<tr>
<td>Dystonia plus myoclonus</td>
<td>DYT11</td>
<td>Autosomal dominant</td>
<td>7q21</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Paroxysmal dystonia/dyskinesia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-kinesigenic form</td>
<td>DYT8</td>
<td>Autosomal dominant</td>
<td>2q33-36</td>
<td>Myofibrillogenesis regulator 1 (MR1)</td>
</tr>
<tr>
<td></td>
<td>DYT20</td>
<td>Autosomal dominant</td>
<td>2q31</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kinesigenic form</td>
<td>DYT10</td>
<td>Autosomal dominant</td>
<td>16p11-q12</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>DYT19</td>
<td>Autosomal dominant</td>
<td>16q13-22</td>
<td>Unknown</td>
</tr>
<tr>
<td>Exercise-induced forms</td>
<td>DYT9</td>
<td>Autosomal dominant</td>
<td>1p21-13</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>DYT18</td>
<td>Autosomal dominant</td>
<td>1p35-31</td>
<td>Glucose transporter (SLC2A1)</td>
</tr>
</tbody>
</table>

Table 1. Twenty forms of monogenic dystonia are distinguished genetically and have been designated DYT 1–13; DYT 14, which is redefined as DYT 5; and DYT 15–21.
DYT1 dystonia is inherited in an autosomal dominant pattern with 30% penetrance (Bressman et al., 2000). Regardless of ethnic background, most cases are caused by a three base pair (GAG) deletion in the coding region of the TOR1A gene on chromosome 9q34, leading to the loss of a glutamic acid in the carboxy terminal region of the encoded protein TorsinA (Ozelius et al., 1997). The Asparagine to Histidine substitution at position 216 moderates the effects of the DYT1 GAG deletion. Haplotype analysis demonstrates Asp216 in cis is required for the disease to be penetrant (Risch et al., 2007).

TorsinA is a member of the AAA family (ATPases Associated with diverse cellular Activities), which has many different functions, including cytoskeletal dynamics, protein processing and degradation, vesicle recycling, and intracellular trafficking (Neuwald et al., 1999). TorsinA is predominantly located within the lumen of the endoplasmatic reticulum. The mutant form relocates to the nuclear envelope, where it alters connections between the inner and outer nuclear membranes, suggesting DYT1 dystonia may be one of a group of diseases associated with defects in nuclear membrane structure and function (Goodchild & Dauer, 2004; Naismith et al., 2004). In addition, loss of TorsinA activity would lead to a dysfunction of protein processing through the secretory pathway and defective degradation of mutant proteins in the cell (Hewett et al., 2007). Furthermore, TorsinA is expressed prominently in the substantia nigra, and its staining pattern is granular and present in the neuronal processes, suggesting that DYT1 dystonia may be associated with a dysfunction of dopamine transmission (Konakova et al., 2001; Shashidharan et al., 2005).
2.1.2 DYT2

DYT2 dystonia is clinically similar to DYT1 dystonia, but it is inherited in an autosomal recessive manner (Schmidt & Klein, 2010). Nevertheless, some experts posit that DYT2 dystonia is unlikely for recessive inheritance but is consistent with dominant inheritance with low penetrance (Zlotogora, 2004). Until now, no gene locus has been identified.

2.1.3 DYT4

DYT4 dystonia has been described in a large Australian family containing members of at least five generations distributed in an autosomal dominant pedigree pattern. Onset age ranges from 13 to 37 years. Dystonia first involves speech, then torticollis, and later develops dysphonia. Some patients have been identified with Wilson disease (Ahmad et al., 1993). Until now, no gene locus has been identified. Linkage studies exclude location of the responsible locus on 9q (see DYT1) (Ahmad et al., 1993). Investigation for linkage using markers flanking the Wilson disease locus likewise also yields negative results (Ahmad et al., 1993).

2.1.4 DYT6

DYT6 dystonia is characterized by early involvement of craniofacial muscles with secondary generalization often involving the arms and is characterized by laryngeal dystonia that causes speech difficulties. The mean age at onset is 16 years, with more than half of the patients developing symptoms before age 16 years. It is inherited in an autosomal dominant pattern with 60% penetrance (Djarmati et al., 2009).

DYT6 dystonia is caused by mutations in the THAP1 gene, which encodes the Thanatos-Associated Protein 1 on chromosome 8p21-22 (Schmidt & Klein, 2010). The protein belongs to the family of sequence-specific DNA-binding cellular factors that functions as a nuclear proapoptotic protein and regulates endothelial cell proliferation (Kaiser et al., 2010). THAP1 interacts with prostate apoptosis response 4 protein (Par-4) (Roussigne et al., 2003), an effector of cell death linked to neurodegenerative diseases, including Parkinson’s disease (Duan et al., 1999). Additionally, THAP1 has been shown to bind to the TorsinA promoter and repress its expression. DNA binding is disrupted and expression decreased by pathogenic THAP1 mutations (Kaiser et al., 2010). These data link the molecular pathways underlying DYT1 and DYT6 dystonia and highlight transcriptional dysregulation as a cause of primary dystonia (Gavarini et al., 2010).

2.1.5 DYT13

DYT13 dystonia is reported in a large non-Jewish Italian family with autosomal dominant idiopathic torsion dystonia spanning three generations. Eight members have definite torsion dystonia characterized by average onset at 15 years of age, symptoms beginning in the cervical or craniocervical region or in the upper limbs, and slow progression to other body regions (more than 18 years). Two treated patients are unresponsive to dopaminergic medication (Bentivoglio et al., 1997). Linkage analysis on this family identifies a locus within a 22-cM interval on chromosome 1p36 (Valente et al., 2001).
2.1.6 DYT17

DYT17 dystonia is reported in a large, consanguineous Lebanese family, in which three sisters have primary focal torsion dystonia beginning with torticollis at ages 17, 19, and 14 years, respectively. Two years after onset, the symptoms spread, causing segmental dystonia for two patients and generalized dystonia for the third. At the time of examination, when the sisters were in their thirties, all had severe dysphonia and dysarthria (Chouery et al., 2008). DYT17 dystonia is inherited in an autosomal recessive manner. The responsible gene locus is linked to a 20.5-Mb interval on chromosome 20p11-q13 (Chouery et al., 2008).

2.2 Late-onset primary dystonia

2.2.1 DYT7

DYT7 dystonia was first described in a German family. Family members are primarily affected with cervical dystonia beginning in mid-adulthood (mean age of onset: 43). The dystonic symptoms remain focal in all cases of over 9 years of disease duration (Leube et al., 1996). The mode of inheritance is autosomal dominant with reduced penetrance. The family shows linkage to chromosome 18p (Leube et al., 1996). Following the above study, eighteen nuclear adult-onset focal dystonia families from central Europe were studied by genotyping with 18p microsatellites. In three families, the affected relatives do not share an 18p haplotype, suggesting locus heterogeneity in this disorder (Leube et al., 1997).

2.2.2 DYT21

DYT21 dystonia was first described in a family from northern Sweden. The phenotype in this family is characterized by later onset (mean: 27 years; range, 13-50 years) and mainly multifocal dystonia, with onset in the cranial/cervical muscles in most and the hands in about 25% (Norgren et al., 2011). The disease is inherited in an autosomal dominant manner with a penetrance that may be as high as 90%. The DYT21 locus in this family is mapped to chromosome 2q14-21 (Norgren et al., 2011).

3. Dystonia plus syndrome

Dystonia associated with but not secondary to other movement disorders, such as parkinsonism or myoclonus, are classified as dystonia plus syndrome (Schmidt & Klein, 2010). Within the dystonia plus classification there are four forms that include parkinsonism as part of their phenotype (DYT 3, 5/14, 12, and 16), and two that have myoclonus in addition to dystonia (DYT 11 and 15). Genes have been identified for all these forms except DYT 15 (Ozelius et al., 2011).

3.1 Dystonia plus parkinsonism

3.1.1 DYT3

DYT3 dystonia was first identified in an island of the Philippines (Lee et al., 1976). First manifestations are noted in the head and neck in 39%, in the lower limbs in 33%, in the upper limbs in 24%, and in the trunk in 9%. At least one “parkinsonian symptom” (bradykinesia, rigidity, loss of postural reflexes, and resting tremor) is found in 36% of the...
cases. The mean age of onset is 34.8 years, which is similar to that in the adult-onset autosomal dominant form. Nevertheless, DYT3 dystonia tends to generalize in most patients within 7 years of onset (Kupke et al., 1990b; Lee et al., 2011).

DYT3 dystonia is inherited in an X-linked recessive pattern (Kupke et al., 1990a). It is caused by an SVA (short interspersed nuclear element, variable number of tandem repeats, and Alu composite) retrotransposon insertion in intron 32 of the TAF1 gene (TATA box binding protein associated factor) on Xq13, which encodes the largest component of the TFII D complex (Makino et al., 2007; Pasco et al., 2011). The insertion is 2,627 bp in length. SVA retrotransposon insertions are thought to be active in the human genome and are thought to alter the expression level of adjacent genes that cause diseases. The insertion has a high GC content (approximately 70%) and a large number of CpG sites (more than 150) in its nucleotide sequence, so it is frequently hypermethylated in its insertion site (Hancks & Kazazian, 2010). In DYT3 dystonia, the decreased expression of the neuron-specific TA14-391 isoform, and probably other TAF1 isoforms, results in transcriptional dysregulation of many neuronal genes, including that which encodes the dopamine receptor (Makino et al., 2007; Pasco et al., 2011).

### 3.1.2 DYT5/14

The symptom presentation of DYT5 dystonia ranges from spasticity in early childhood to dystonia in mid-childhood, and finally becomes parkinsonism in later life. It is characterized by a dramatic response to L-dopa therapy and by diurnal fluctuation in the severity of symptoms (Ozelius et al., 2011).

DYT5 dystonia is inherited in either an autosomal dominant or recessive manner. The autosomal dominant form is mostly caused by mutations in the gene encoding GTP cyclohydrolase I (GCH1) on chromosome 14q22 (Ichinose et al., 1994). GCH1 is rate-limiting in the conversion of GTP to tetrahydrobiopterin (BH4), the cofactor for tyrosine hydroxylase (TH), which is the rate-limiting enzyme for dopamine synthesis (Gesierich et al., 2003). An autosomal recessive form of DYT5 dystonia that is associated with infantile parkinsonism is caused by mutations in the TH gene on chromosome 11p15 (Gorke & Bartholome, 1990). Other forms of DYT5 dystonia result from a deficiency of other enzymes in the biosynthetic pathway for bioperins, such as sepiapterin reductase (Asmus & Gasser, 2010). All of these defects diminish the activity of TH, which explains the molecular basis for the efficacy of L-dopa treatment, as this drug bypasses the enzymatic defect (Breakefield et al., 2008). The diurnal variation of symptoms, which typically are worse during the course of the day and improve overnight with sleep, is thought to derive from use-dependent depletion of BH4 in dopamine-producing neurons (Breakefield et al., 2008).

A dopa-responsive dystonia in the family reported by Grotzsch et al. was originally thought to be at a locus on chromosome 14, separate from the DYT5 locus, and was designated DYT14 (Grotzsch et al., 2002). Wider et al. restudied the same family and determined that the disorder is indeed DYT5 caused by mutation in the GCH1 gene (Wider et al., 2008).

### 3.1.3 DYT12

DYT12 dystonia is characterized by abrupt onset of dystonia with parkinsonism over a few minutes to 30 days, a clear rostrocaudal (face, arm, leg) gradient of involvement, and
prominent bulbar findings, and it is triggered by stress. Onset age is usually in late adolescence or early adulthood (range 15 to 45 years). Treatment with dopaminergic medications is usually not effective (Brashear et al., 2007).

DYT12 dystonia is inherited in an autosomal dominant pattern with reduced penetrance. It is caused by heterozygous mutations in the ATP1A3 gene encoding the α3 subunit of the Na+/K+ATPase on chromosome 19q12-13 (de Carvalho Aguiar et al., 2004). Na+/K+ATPase maintains an electrochemical gradient across the plasma membrane. It consists of α, β, and γ subunits, with the human α3 subunit only expressed in the brain and heart, indicating a specialized role in excitable tissues (Hilgenberg et al., 2006). DYT12 dystonia could result from reduced function of this ion transporter and could appear to exacerbate the physiologic response to stress, as in stress-induced channelopathies (Cannon, 2006).

3.1.4 DYT16

DYT16 dystonia is characterized by early-onset (2-18 years) gait abnormalities and leg pain, followed by dysphagia, spasmodic dysphonia, generalized dystonia, torticollis, upper limb dystonia, and opisthotonic posturing. Orofacial dystonia and facial grimacing are prominent features. Possible parkinsonian signs are reported in a minority of patients, are limited to bradykinesia in the presence of severe generalized dystonia, and are not responsive to dopaminergic medication (Camargos et al., 2008).

DYT16 dystonia is inherited in an autosomal recessive pattern. It is caused by mutations in the PRKRA gene on chromosome 2q31, which encodes the protein kinase, interferon-inducible double-stranded RNA-dependent activator (Camargos et al., 2008; Seibler et al., 2008). The function of the protein remains largely unknown.

3.2 Dystonia plus myoclonus

3.2.1 DYT11

DYT11 dystonia is characterized by myoclonic jerks affecting mostly proximal muscles, occurring at rest and increasing with activity or changes in posture. Onset age is in childhood or adolescence. Symptoms often respond to alcohol, and patients may have psychiatric abnormalities (Saunders-Pullman et al., 2002).

DYT11 dystonia is inherited in an autosomal dominant pattern. It is caused by loss-of-function mutations in the SGCE gene encoding ε-sarcoglycan on chromosome 7q21. Maternal imprinting of SGCE results in reduced penetrance of the disorder when the mutation is inherited from the mother (Zimprich et al., 2001). ε-sarcoglycan is highly expressed during brain development and is highly expressed in dopaminergic neurons, as well as in other neuronal subtypes (Chan et al., 2005). The mutant proteins are unable to reach the cell surface and are retained intracellular and degraded (Esapa et al., 2007). The exact pathophysiology is thought to be similar to the sarcoglycans that are mutated in limb girdle muscular dystrophies (Chen et al., 2006). More studies are needed to determine whether ε-sarcoglycan participates in the formation of dystrophin-glycoprotein complexes in the brain like it does in muscles.
3.2.2 DYT15

DYT15 dystonia is reported in a large Canadian family, in which twelve members over four generations have alcohol-responsive myoclonic dystonia characterized by jerky movements of the upper limbs, hands, and axial muscles. Four members also have dystonia of the upper limbs, and one has dystonia of the leg (Grimes et al., 2001). Mutation in the SGCE gene is excluded (DYT11), and linkage of the disorder to a 17-cM region on chromosome 18p11 is seen. Two unaffected obligate carriers and all affected members carried the same haplotype. Five other unaffected members also carried at least part of the haplotype, suggesting reduced penetrance of the disorder in this family (Grimes et al., 2001).

4. Paroxysmal dystonia/dyskinesia

This is a heterogeneous group of disorders characterized by sudden transient attacks of involuntary movements. They are subdivided into non-kinesigenic (DYT 8 and 20), kinesigenic (DYT 10 and 19), and exercise-induced forms (DYT 9 and 18). The genes for DYT 8 and 18 have been identified (Ozelius et al., 2011).

4.1 Non-kinesigenic form

4.1.1 DYT8

DYT8 dystonia is characterized by attacks of uncontrollable dystonic choreoathetosis and onset in infancy or childhood. The attacks last only a few minutes, occur a few times a day, and are not accompanied by unconsciousness. Alcohol, coffee, hunger, fatigue, and tobacco are precipitating factors. Between attacks, affected individuals are phenotypically normal (Ozelius et al., 2011).

DYT8 dystonia is inherited in an autosomal dominant pattern with incomplete penetrance. It is caused by mutations in the gene for the myofibrillogenesis regulator-I (MR1) on chromosome 2q33-36, which lead to valine-to-alanine substitutions at positions 7 and 9 and also are predicted to disrupt α-helix structures of MRI proteins (Rainier et al., 2004). MR1 long isoform (MR1L) is likely to have similar enzymatic activity to hydroxyl-acyl glutathione hydrolase (HAGH), which functions in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a byproduct of oxidative stress (Lee et al., 2004). Thus, in this form of dystonia, toxins and stress could combine with abnormal MR-1 activity to exacerbate neuronal toxicity. Recently, a mutation in the N-terminal mitochondrial targeting sequence (MTS) of the MR1 gene has been reported in a three-generation family (Ghezzi et al., 2009). Their results differ from the above findings with regard to localization of the MRIL and suggest a novel disease mechanism based on a deleterious action of the MTS.

4.1.2 DYT20

DYT20 dystonia was reported in a Canadian family of European descent, in which 10 members spanning 4 generations have PNKD. This disorder is characterized by episodic dystonia primarily affecting the hands and feet symmetrically. Age at onset ranged from childhood to age 50 years. Episodes last 2 to 5 minutes (up to 10 minutes in 1 patient) and
occur daily or several times per month. Alcohol, caffeine, and excitement are not obvious triggers (Spacey et al., 2006).

DYT20 dystonia is inherited in an autosomal dominant manner. The gene locus is linked to chromosome 2q31, which is distinct from the DYT8 locus on chromosome 2q33-36 (Spacey et al., 2006).

### 4.2 Kinesigenic form

#### 4.2.1 DYT10

DYT10 dystonia is characterized by recurrent and brief attacks of involuntary movement precipitated by sudden unexpected movements. Onset age is in childhood or adolescence. It differs from the DYT8 dystonia by later onset in many cases; by briefer duration of attacks (seconds to minutes), which usually occur daily; and by good response to anticonvulsants. About 40% of patients have afebrile, general convulsions in infancy (Bennett et al., 2000).

Both autosomal dominant and autosomal recessive inheritance of this disorder is proposed. The cases interpreted as autosomal recessive may have been instances of reduced penetrance in an affected parent or new mutation. The gene locus maps to chromosome 16p11-q12 (Tomita et al., 1999). DYT10 dystonia shares some clinical features with benign familial infantile convulsions (BFIC2) and with infantile convulsions and paroxysmal choreoathetosis (ICCA). The three disorders overlap across a pericentromeric region of chromosome 16, suggesting that they may be allelic disorders (Caraballo et al., 2001).

#### 4.2.2 DYT19

DYT19 dystonia is reported in a large Indian clan in which thirteen individuals have received a definite diagnosis. The onset age ranges from 7 to 13 years. It is characterized by brief attacks of up to 2 minutes consisting of dystonic or choreic movements precipitated by sudden movements, with a frequency of 1 to 20 episodes per day. None of the affected patients have a history of benign infantile convulsions. Some of them, however, have sporadic episodes of generalized tonic-clonic seizures in their teenage years that spontaneously resolve (Valente et al., 2000).

DYT19 dystonia is inherited in an autosomal dominant manner with incomplete penetrance (75%). The gene locus is linked to chromosome 16q13-22, which is distinct from the DYT10 locus (16p11-q12) (Valente et al., 2000).

### 4.3 Exercise-induced form

#### 4.3.1 DYT9

DYT9 dystonia is characterized by paroxysmal choreoathetosis, ataxia, and spasticity. Onset age ranges from 2 to 15 years, with most patients presenting clear symptoms before attending school. The episodes last approximately 20 minutes and occur at frequencies ranging from twice a day to twice a year. The involuntary movements and dystonia are similar to those in DYT8 dystonia. In both disorders, episodes can be induced by alcohol, fatigue, and emotional stress; nevertheless, in DYT9 dystonia, physical exercise can precipitate the episodes (Auburger et al., 1996).
Inheritance is clearly autosomal dominant. By linkage analysis, the gene for this disorder probably lies in a 2-cM region on chromosome 1p21-13, where a cluster of potassium channel genes is located. Until now, the precise gene locus has not been identified (Auburger et al., 1996).

4.3.2 DYT18

DYT18 dystonia is characterized primarily by onset in childhood of paroxysmal exercise-induced dyskinesia. The dyskinesia involves transient abnormal involuntary movements, such as dystonia and choreoathetosis, induced by exercise or exertion, and affecting the exercised limbs. Some patients may also have epilepsy, most commonly childhood absence epilepsy, with an average onset of about 2 to 3 years. Mild mental retardation may also occur (Margari et al., 2000).

DYT18 dystonia is inherited in an autosomal dominant manner. It is caused by heterozygous mutations in the SLC2A1 gene, which encodes the GLUT1 transporter, on chromosome 1p35-31 (Schneider et al., 2009; Weber et al., 2008). A defect in the GLUT1 glucose transporter causing decreased glucose concentration in the central nervous system is part of a spectrum of neurologic phenotypes resulting from GLUT1 deficiency. A ketogenic diet often results in marked clinical improvement of the motor and seizure symptoms (Kamm et al., 2007; Pascual et al., 2004)

5. Conclusion

Currently, the dystonias represent a clinically and genetically heterogeneous set of movement disorders. Although the identified dystonia genes are diverse and the underlying mechanisms of how they cause dystonia remain wanting, their identification has led basic research to understand the pathophysiology of dystonia. For example, DYT6 THAP1 has been shown to bind to the DYT 1 TorsinA promoter and repress its expression (Kaiser et al., 2010), suggesting that common pathways may be involved in dystonia, and novel treatments targeting these common pathways may be effective for the treatment of different forms of dystonia. Next, better understanding of the underlying mechanisms of these dystonia genes and their interactions would allow researchers to compare and reclassify the dystonia subtypes that would help direct therapies and define endophenotypes. Finally, new genetic technologies, including SNP based genome-wide association study, microarray comparative genomic hybridization study, next-generation exomic and whole-genome sequencing, should accelerate gene discovery for dystonias that should further elucidate the underlying pathways.

6. References


autosomal dominant paroxysmal choreoathetosis/spasticity (CSE) maps to the vicinity of a potassium channel gene cluster on chromosome 1p, probably within 2 cM between D1S443 and D1S197. Genomics, Vol. 31, No. 1, pp. 90-94, ISSN 0888-7543


Dystonia and Genetics


Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following: