We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Dystonia and Genetics

Shih-Fen Chen¹ and Yu-Chih Shen^{2,3}

¹*Department of Life Science and Graduate
Institute of Biotechnology, Dong-Hwa University*

²*Department of Psychiatry, Tzu-Chi General Hospital*

³*School 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 DYT, 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).

Dystonia type	Designation	Mode of inheritance	Gene locus	Protein (Gene)
Primary dystonia				
Early-onset primary dystonia	DYT1	Autosomal dominant	9q34	TorsinA (TOR1A)
	DYT2	Autosomal recessive	Unknown	Unknown
	DYT4	Autosomal dominant	Unknown	Unknown
	DYT6	Autosomal dominant	8p21-22	Thanatos-Associated Protein 1 (THAP1)
	DYT13	Autosomal dominant	1p36	Unknown
	DYT17	Autosomal recessive	20p11-q13	Unknown
Late-onset primary dystonia	DYT7	Autosomal dominant	18p	Unknown
	DYT21	Autosomal dominant	2q14-21	Unknown
Dystonia plus syndrome				
Dystonia plus parkinsonism	DYT3	X-chromosomal recessive	Xq13	Gene transcription factor (TAF1)
	DYT5/14	Autosomal dominant	14q22	GTP cyclohydrolase I (GCH1)
		Autosomal recessive	11p15	Tyrosine hydroxylase (TH)
	DYT12	Autosomal dominant	19q12-13	Na ⁺ /K ⁺ ATPase α 3 subunit (ATP1A3)
	DYT16	Autosomal recessive	2q31	Stress-response protein (PRKRA)
Dystonia plus myoclonus	DYT11	Autosomal dominant	7q21	ϵ -sarcoglycan (SCGE)
	DYT15	Autosomal dominant	18p11	Unknown
Paroxysmal dystonia/dyskinesia				
Non-kinesigenic form	DYT8	Autosomal dominant	2q33-36	Myofibrillogenesis regulator 1 (MR1)
	DYT20	Autosomal dominant	2q31	Unknown
Kinesigenic form	DYT10	Autosomal dominant	16p11-q12	Unknown
	DYT19	Autosomal dominant	16q13-22	Unknown
Exercise-induced forms	DYT9	Autosomal dominant	1p21-13	Unknown
	DYT18	Autosomal dominant	1p35-31	Glucose transporter (SLC2A1)

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

Fig. 1. Ideogram showing major chromosomal regions implicated by linkage studies of dystonia. Red circles indicate areas for which DYT genes have been found. Blue circles indicate areas for which there is suggestive evidence of linkage to different DYT loci.

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 endoplasmic 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 TFIID 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 biopterins, 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 $\alpha 3$ 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 $\alpha 3$ 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-1 (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 MR1 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 MR1L 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

DYT 19 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

- Ahmad, F.; Davis, M. B.; Waddy, H. M.; Oley, C. A.; Marsden, C. D. & Harding, A. E. (1993). Evidence for locus heterogeneity in autosomal dominant torsion dystonia. *Genomics*, Vol. 15, No. 1, pp. 9-12, ISSN 0888-7543
- Asmus, F. & Gasser, T. (2010). Dystonia-plus syndromes. *European Journal of Neurology*, Vol. 17, Suppl 1, pp. 37-45, ISSN 1468-1331
- Auburger, G.; Ratzlaff, T.; Lunkes, A.; Nelles, H. W.; Leube, B.; Binkofski, F.; Kugel, H.; Heindel, W.; Seitz, R.; Benecke, R.; Witte, O. W. & Voit, T. (1996). A gene for

- 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
- Bennett, L. B.; Roach, E. S. & Bowcock, A. M. (2000). A locus for paroxysmal kinesigenic dyskinesia maps to human chromosome 16. *Neurology*, Vol. 54, No. 1, pp. 125-130, ISSN 0028-3878
- Bentivoglio, A. R.; Del Grosso, N.; Albanese, A.; Cassetta, E.; Tonali, P. & Frontali, M. (1997). Non-DYT1 dystonia in a large Italian family. *Journal of Neurology, Neurosurgery, and Psychiatry*, Vol. 62, No. 4, pp. 357-360, ISSN 0022-3050
- Brashear, A.; Dobyns, W. B.; de Carvalho Aguiar, P.; Borg, M.; Frijns, C. J.; Gollamudi, S.; Green, A.; Guimaraes, J.; Haake, B. C.; Klein, C.; Linazasoro, G.; Munchau, A.; Raymond, D.; Riley, D.; Saunders-Pullman, R.; Tijssen, M. A.; Webb, D.; Zaremba, J.; Bressman, S. B. & Ozelius, L. J. (2007). The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. *Brain*, Vol. 130, No. Pt 3, pp. 828-835, ISSN 1460-2156
- Breakefield, X. O.; Blood, A. J.; Li, Y.; Hallett, M.; Hanson, P. I. & Standaert, D. G. (2008). The pathophysiological basis of dystonias. *Nature Reviews Neuroscience*, Vol. 9, No. 3, pp. 222-234, ISSN 1471-0048
- Bressman, S. B.; Sabatti, C.; Raymond, D.; de Leon, D.; Klein, C.; Kramer, P. L.; Brin, M. F.; Fahn, S.; Breakefield, X.; Ozelius, L. J. & Risch, N. J. (2000). The DYT1 phenotype and guidelines for diagnostic testing. *Neurology*, Vol. 54, No. 9, pp. 1746-1752, ISSN 0028-3878
- Camargos, S.; Scholz, S.; Simon-Sanchez, J.; Paisan-Ruiz, C.; Lewis, P.; Hernandez, D.; Ding, J.; Gibbs, J. R.; Cookson, M. R.; Bras, J.; Guerreiro, R.; Oliveira, C. R.; Lees, A.; Hardy, J.; Cardoso, F. & Singleton, A. B. (2008). DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. *Lancet Neurology*, Vol. 7, No. 3, pp. 207-215, ISSN 1474-4422
- Cannon, S. C. (2006). Pathomechanisms in channelopathies of skeletal muscle and brain. *Annual Review of Neuroscience*, Vol. 29, pp. 387-415, ISSN 0147-006X
- Caraballo, R.; Pavsek, S.; Lemainque, A.; Gastaldi, M.; Echenne, B.; Motte, J.; Genton, P.; Cersosimo, R.; Humbertclaude, V.; Fejerman, N.; Monaco, A. P.; Lathrop, M. G.; Rochette, J. & Szepietowski, P. (2001). Linkage of benign familial infantile convulsions to chromosome 16p12-q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. *American Journal of Human Genetics*, Vol. 68, No. 3, pp. 788-794, ISSN 0002-9297
- Chan, P.; Gonzalez-Maeso, J.; Ruf, F.; Bishop, D. F.; Hof, P. R. & Sealfon, S. C. (2005). Epsilon-sarcoglycan immunoreactivity and mRNA expression in mouse brain. *The Journal of Comparative Neurology*, Vol. 482, No. 1, pp. 50-73, ISSN 0021-9967
- Chen, J.; Shi, W.; Zhang, Y.; Sokol, R.; Cai, H.; Lun, M.; Moore, B. F.; Farber, M. J.; Stepanchick, J. S.; Bonnemann, C. G. & Chan, Y. M. (2006). Identification of functional domains in sarcoglycans essential for their interaction and plasma membrane targeting. *Experimental Cell Research*, Vol. 312, No. 9, pp. 1610-1625, ISSN 0014-4827

- Chouery, E.; Kfoury, J.; Delague, V.; Jalkh, N.; Bejjani, P.; Serre, J. L. & Megarbane, A. (2008). A novel locus for autosomal recessive primary torsion dystonia (DYT17) maps to 20p11.22-q13.12. *Neurogenetics*, Vol. 9, No. 4, pp. 287-293, ISSN 1364-6753
- de Carvalho Aguiar, P.; Sweadner, K. J.; Penniston, J. T.; Zaremba, J.; Liu, L.; Caton, M.; Linazasoro, G.; Borg, M.; Tijssen, M. A.; Bressman, S. B.; Dobyns, W. B.; Brashear, A. & Ozelius, L. J. (2004). Mutations in the Na⁺/K⁺ ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. *Neuron*, Vol. 43, No. 2, pp. 169-175, ISSN 0896-6273
- Djarmati, A.; Schneider, S. A.; Lohmann, K.; Winkler, S.; Pawlack, H.; Hagenah, J.; Bruggemann, N.; Zittel, S.; Fuchs, T.; Rakovic, A.; Schmidt, A.; Jabusch, H. C.; Wilcox, R.; Kostic, V. S.; Siebner, H.; Altenmuller, E.; Munchau, A.; Ozelius, L. J. & Klein, C. (2009). Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. *Lancet Neurology*, Vol. 8, No. 5, pp. 447-452, ISSN 1474-4422
- Duan, W.; Zhang, Z.; Gash, D. M. & Mattson, M. P. (1999). Participation of prostate apoptosis response-4 in degeneration of dopaminergic neurons in models of Parkinson's disease. *Annals of Neurology*, Vol. 46, No. 4, pp. 587-597, ISSN 0364-5134
- Esapa, C. T.; Waite, A.; Locke, M.; Benson, M. A.; Kraus, M.; McIlhinney, R. A.; Sillitoe, R. V.; Beesley, P. W. & Blake, D. J. (2007). SGCE missense mutations that cause myoclonus-dystonia syndrome impair epsilon-sarcoglycan trafficking to the plasma membrane: modulation by ubiquitination and torsinA. *Human Molecular Genetics*, Vol. 16, No. 3, pp. 327-342, ISSN 0964-6906
- Gavarini, S.; Cayrol, C.; Fuchs, T.; Lyons, N.; Ehrlich, M. E.; Girard, J. P. & Ozelius, L. J. (2010). Direct interaction between causative genes of DYT1 and DYT6 primary dystonia. *Annals of Neurology*, Vol. 68, No. 4, pp. 549-553, ISSN 1531-8249
- Gesierich, A.; Niroomand, F. & Tiefenbacher, C. P. (2003). Role of human GTP cyclohydrolase I and its regulatory protein in tetrahydrobiopterin metabolism. *Basic Research in Cardiology*, Vol. 98, No. 2, pp. 69-75, ISSN 0300-8428
- Ghezzi, D.; Viscomi, C.; Ferlini, A.; Gualandi, F.; Mereghetti, P.; DeGrandis, D. & Zeviani, M. (2009). Paroxysmal non-kinesigenic dyskinesia is caused by mutations of the MR-1 mitochondrial targeting sequence. *Human Molecular Genetics*, Vol. 18, No. 6, pp. 1058-1064, ISSN 1460-2083
- Goodchild, R. E. & Dauer, W. T. (2004). Mislocalization to the nuclear envelope: an effect of the dystonia-causing torsinA mutation, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 101, No. 3, pp. 847-852, ISSN 0027-8424
- Gorke, W. & Bartholome, K. (1990). Biochemical and neurophysiological investigations in two forms of Segawa's disease. *Neuropediatrics*, Vol. 21, No. 1, pp. 3-8, ISSN 0174-304X
- Grimes, D. A.; Bulman, D.; George-Hyslop, P. S. & Lang, A. E. (2001). Inherited myoclonus-dystonia: evidence supporting genetic heterogeneity. *Movement Disorders*, Vol. 16, No. 1, pp. 106-110, ISSN 0885-3185
- Grotzsch, H.; Pizzolato, G. P.; Ghika, J.; Schorderet, D.; Vingerhoets, F. J.; Landis, T. & Burkhard, P. R. (2002). Neuropathology of a case of dopa-responsive dystonia associated with a new genetic locus, DYT14. *Neurology*, Vol. 58, No. 12, pp. 1839-1842, ISSN 0028-3878

- Hancks, D. C. & Kazazian, H. H. Jr. (2010). SVA retrotransposons: Evolution and genetic instability. *Seminars in Cancer Biology*, Vol. 20, No. 4, pp. 234-245, ISSN 1096-3650
- Hewett, J. W.; Tannous, B.; Niland, B. P.; Nery, F. C.; Zeng, J.; Li, Y. & Breakefield, X. O. (2007). Mutant torsinA interferes with protein processing through the secretory pathway in DYT1 dystonia cells, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 104, No. 17, pp. 7271-7276, ISSN 0027-8424
- Hilgenberg, L. G.; Su, H.; Gu, H.; O'Dowd, D. K. & Smith, M. A. (2006). Alpha3Na⁺/K⁺-ATPase is a neuronal receptor for agrin. *Cell*, Vol. 125, No. 2, pp. 359-369, ISSN 0092-8674
- Ichinose, H.; Ohye, T.; Takahashi, E.; Seki, N.; Hori, T.; Segawa, M.; Nomura, Y.; Endo, K.; Tanaka, H.; Tsuji, S. (1994). Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nature Genetics*, Vol. 8, No. 3, pp. 236-242, ISSN 1061-4036
- Kaiser, F. J.; Osmanoric, A.; Rakovic, A.; Erogullari, A.; Uflacker, N.; Braunholz, D.; Lohnau, T.; Orolicki, S.; Albrecht, M.; Gillesen-Kaesbach, G.; Klein, C. & Lohmann, K. (2010). The dystonia gene DYT1 is repressed by the transcription factor THAP1 (DYT6). *Annals of Neurology*, Vol. 68, No. 4, pp. 554-559, ISSN 1531-8249
- Kamm, C.; Mayer, P.; Sharma, M.; Niemann, G. & Gasser, T. (2007). New family with paroxysmal exercise-induced dystonia and epilepsy. *Movement Disorders*, Vol. 22, No. 6, pp. 873-877, ISSN 0885-3185
- Konakova, M.; Huynh, D. P.; Yong, W. & Pulst, S. M. (2001). Cellular distribution of torsin A and torsin B in normal human brain. *Archives of Neurology*, Vol. 58, No. 6, pp. 921-927, ISSN 0003-9942
- Kupke, K. G.; Lee, L. V. & Muller, U. (1990a). Assignment of the X-linked torsion dystonia gene to Xq21 by linkage analysis. *Neurology*, Vol. 40, No. 9, pp. 1438-1442, ISSN 0028-3878
- Kupke, K. G.; Lee, L. V.; Viterbo, G. H.; Arancillo, J.; Donlon, T. & Muller, U. (1990b). X-linked recessive torsion dystonia in the Philippines. *American Journal of Medical Genetics*, Vol. 36, No. 2, pp. 237-242, ISSN 0148-7299
- Lee, H. Y.; Xu, Y.; Huang, Y.; Ahn, A. H.; Auburger, G. W.; Pandolfo, M.; Kwiecinski, H.; Grimes, D. A.; Lang, A. E.; Nielsen, J. E.; Averyanov, Y.; Servidei, S.; Friedman, A.; Van Bogaert, P.; Abramowicz, M. J.; Bruno, M. K.; Sorensen, B. F.; Tang, L.; Fu, Y. H. & Ptacek, L. J. (2004). The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. *Human Molecular Genetics*, Vol. 13, No. 24, pp. 3161-3170, ISSN 0964-6906
- Lee, L. V.; Pascasio, F. M.; Fuentes, F. D. & Viterbo, G. H. (1976). Torsion dystonia in Panay, Philippines. *Advances in Neurology*, Vol. 14, pp. 137-151, ISSN 0091-3952
- Lee, L. V.; Rivera, C.; Teleg, R. A.; Dantes, M. B.; Pasco, P. M.; Jamora, R. D.; Arancillo, J.; Villareal-Jordan, R. F.; Rosales, R. L.; Demaisip, C.; Maranon, E.; Peralta, O.; Borres, R.; Tolentino, C.; Monding, M. J. & Sarcia, S. (2011). The unique phenomenology of sex-linked dystonia parkinsonism (XDP, DYT3, "Lubag"). *International Journal of Neuroscience*, Vol. 121, Suppl 1, pp. 3-11, ISSN 1563-5279.
- Leube, B.; Hendgen, T.; Kessler, K. R.; Knapp, M.; Benecke, R. & Auburger, G. (1997). Evidence for DYT7 being a common cause of cervical dystonia (torticollis) in Central Europe. *American Journal of Medical Genetics*, Vol. 74, No. 5, pp. 529-532, ISSN 0148-7299

- Leube, B.; Rudnicki, D.; Ratzlaff, T.; Kessler, K. R.; Benecke, R. & Auburger, G. (1996). Idiopathic torsion dystonia: assignment of a gene to chromosome 18p in a German family with adult onset, autosomal dominant inheritance and purely focal distribution. *Human Molecular Genetics*, Vol. 5, No. 10, pp. 1673-1677, ISSN 0964-6906
- Makino, S.; Kaji, R.; Ando, S.; Tomizawa, M.; Yasuno, K.; Goto, S.; Matsumoto, S.; Tabuena, M. D.; Maranon, E.; Dantes, M.; Lee, L. V.; Ogasawara, K.; Tooyama, I.; Akatsu, H.; Nishimura, M. & Tamiya, G. (2007). Reduced neuron-specific expression of the TAF1 gene is associated with X-linked dystonia-parkinsonism. *American Journal of Human Genetics*, Vol. 80, No. 3, pp. 393-406, ISSN 0002-9297
- Margari, L.; Perniola, T.; Illiceto, G.; Ferrannini, E.; De Iaco, M. G.; Presicci, A.; Santostasi, R. & Ventura, P. (2000). Familial paroxysmal exercise-induced dyskinesia and benign epilepsy: a clinical and neurophysiological study of an uncommon disorder. *Neurological Sciences*, Vol. 21, No. 3, pp. 165-172, ISSN 1590-1874
- Naismith, T. V.; Heuser, J. E.; Breakefield, X. O. & Hanson, P. I. (2004). TorsinA in the nuclear envelope, *Proceedings of the National Academy of Sciences of the United States of America*, Vol. 101, No. 20, pp. 7612-7617, ISSN 0027-8424
- Neuwald, A. F.; Aravind, L.; Spouge, J. L. & Koonin, E. V. (1999). AAA+: A class of chaperone-like ATPases associated with the assembly, operation, and disassembly of protein complexes. *Genome Research*, Vol. 9, No. 1, pp. 27-43, ISSN 1088-9051
- Norgren, N.; Mattson, E.; Forsgren, L. & Holmberg, M. (2011). A high-penetrance form of late-onset torsion dystonia maps to a novel locus (DYT21) on chromosome 2q14.3-q21.3. *Neurogenetics*, Vol. 12, No. 2, pp. 137-143, ISSN 1364-6753
- Ozelius, L. J.; Hewett, J. W.; Page, C. E.; Bressman, S. B.; Kramer, P. L.; Shalish, C.; de Leon, D.; Brin, M. F.; Raymond, D.; Corey, D. P.; Fahn, S.; Risch, N. J.; Buckler, A. J.; Gusella, J. F. & Breakefield, X. O. (1997). The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nature Genetics*, Vol. 17, No. 1, pp. 40-48, ISSN 1061-4036
- Ozelius, L. J.; Lubarr, N. & Bressman, S. B. (2011). Milestones in dystonia. *Movement Disorders*, Vol. 26, No. 6, pp. 1106-1126, ISSN 1531-8257
- Pasco, P. M.; Ison, C. V.; Munoz, E. L.; Magpusao, N. S.; Cheng, A. E.; Tan, K. T.; Lo, R. W.; Teleg, R. A.; Dantes, M. B.; Borres, R.; Maranon, E.; Demaisip, C.; Reyes, M. V. & Lee, L. V. (2011). Understanding XDP through imaging, pathology, and genetics. *International Journal of Neuroscience*, Vol. 121, Suppl 1, pp. 12-17, ISSN 1563-5279
- Pascual, J. M.; Wang, D.; Lecumberri, B.; Yang, H.; Mao, X.; Yang, R. & De Vivo, D. C. (2004). GLUT1 deficiency and other glucose transporter diseases. *European Journal of Endocrinology*, Vol. 150, No. 5, pp. 627-633, ISSN 0804-4643
- Rainier, S.; Thomas, D.; Tokarz, D.; Ming, L.; Bui, M.; Plein, E.; Zhao, X.; Lemons, R.; Albin, R.; Delaney, C.; Alvarado, D. & Fink, J. K. (2004). Myofibrillogenesis regulator 1 gene mutations cause paroxysmal dystonic choreoathetosis. *Archives of Neurology*, Vol. 61, No. 7, pp. 1025-1029, ISSN 0003-9942
- Risch, N. J.; Bressman, S. B.; Senthil, G. & Ozelius, L. J. (2007). Intragenic Cis and Trans modification of genetic susceptibility in DYT1 torsion dystonia. *American Journal of Human Genetics*, Vol. 80, No. 6, pp. 1188-1193, ISSN 0002-9297

- Roussigne, M.; Cayrol, C.; Clouaire, T.; Amalric, F. & Girard, J. P. (2003). THAP1 is a nuclear proapoptotic factor that links prostate-apoptosis-response-4 (Par-4) to PML nuclear bodies. *Oncogene*, Vol. 22, No. 16, pp. 2432-2442, ISSN 0950-9232
- Saunders-Pullman, R.; Ozelius, L. & Bressman, S. B. (2002). Inherited myoclonus- dystonia. *Advances in Neurology*, Vol. 89, pp. 185-191, ISSN 0091-3952
- Schmidt, A. & Klein, C. (2010). The role of genes in causing dystonia. *European Journal of Neurology*, Vol. 17 Suppl 1, pp. 65-70, ISSN 1468-1331
- Schneider, S. A.; Paisan-Ruiz, C.; Garcia-Gorostiaga, I.; Quinn, N. P.; Weber, Y. G.; Lerche, H.; Hardy, J. & Bhatia, K. P. (2009). GLUT1 gene mutations cause sporadic paroxysmal exercise-induced dyskinesias. *Movement Disorders*, Vol. 24, No. 11, pp. 1684-1688, ISSN 1531-8257
- Seibler, P.; Djarmati, A.; Langpap, B.; Hagenah, J.; Schmidt, A.; Bruggemann, N.; Siebner, H.; Jabusch, H. C.; Altenmuller, E.; Munchau, A.; Lohmann, K. & Klein, C. (2008). A heterozygous frameshift mutation in PRKRA (DYT16) associated with generalised dystonia in a German patient. *Lancet Neurology*, Vol. 7, No. 5, pp. 380-381, ISSN 1474-4422
- Shashidharan, P.; Sandu, D.; Potla, U.; Armata, I. A.; Walker, R. H.; McNaught, K. S.; Weisz, D.; Sreenath, T.; Brin, M. F. & Olanow, C. W. (2005). Transgenic mouse model of early-onset DYT1 dystonia. *Human Molecular Genetics*, Vol. 14, No. 1, pp. 125-133, ISSN 0964-6906
- Spacey, S. D.; Adams, P. J.; Lam, P. C.; Materek, L. A.; Stoessl, A. J.; Snutch, T. P. & Hsiung, G. Y. (2006). Genetic heterogeneity in paroxysmal nonkinesigenic dyskinesia. *Neurology*, Vol. 66, No. 10, pp. 1588-1590, ISSN 1526-632X
- Tomita, H.; Nagamitsu, S.; Wakui, K.; Fukushima, Y.; Yamada, K.; Sadamatsu, M.; Masui, A.; Konishi, T.; Matsuishi, T.; Aihara, M.; Shimizu, K.; Hashimoto, K.; Mineta, M.; Matsushima, M.; Tsujita, T.; Saito, M.; Tanaka, H.; Tsuji, S.; Takagi, T.; Nakamura, Y.; Nanko, S.; Kato, N.; Nakane, Y. & Niikawa, N. (1999). Paroxysmal kinesigenic choreoathetosis locus maps to chromosome 16p11.2-q12.1. *American Journal of Human Genetics*, Vol. 65, No. 6, pp. 1688-1697, ISSN 0002-9297
- Valente, E. M.; Bentivoglio, A. R.; Cassetta, E.; Dixon, P. H.; Davis, M. B.; Ferraris, A.; Ialongo, T.; Frontali, M.; Wood, N. W. & Albanese, A. (2001). DYT13, a novel primary torsion dystonia locus, maps to chromosome 1p36.13--36.32 in an Italian family with cranial-cervical or upper limb onset. *Annals of Neurology*, Vol. 49, No. 3, pp. 362-366, ISSN 0364-5134
- Valente, E. M.; Spacey, S. D.; Wali, G. M.; Bhatia, K. P.; Dixon, P. H.; Wood, N. W. & Davis, M. B. (2000). A second paroxysmal kinesigenic choreoathetosis locus (EKD2) mapping on 16q13-q22.1 indicates a family of genes which give rise to paroxysmal disorders on human chromosome 16. *Brain*, Vol. 123 (Pt 10), pp. 2040-2045, ISSN 0006-8950
- Weber, Y. G.; Storch, A.; Wuttke, T. V.; Brockmann, K.; Kempfle, J.; Maljevic, S.; Margari, L.; Kamm, C.; Schneider, S. A.; Huber, S. M.; Pekrun, A.; Roebeling, R.; Seeböhm, G.; Koka, S.; Lang, C.; Kraft, E.; Blazevic, D.; Salvo-Vargas, A.; Fauler, M.; Mottaghy, F. M.; Munchau, A.; Edwards, M. J.; Presicci, A.; Margari, F.; Gasser, T.; Lang, F.; Bhatia, K. P.; Lehmann-Horn, F. & Lerche, H. (2008). GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a

- cation leak. *The Journal of Clinical Investigation*, Vol. 118, No. 6, pp. 2157-2168, ISSN 0021-9738
- Wider, C.; Melquist, S.; Hauf, M.; Solida, A.; Cobb, S. A.; Kachergus, J. M.; Gass, J.; Coon, K. D.; Baker, M.; Cannon, A.; Stephan, D. A.; Schorderet, D. F.; Ghika, J.; Burkhard, P. R.; Kapatos, G.; Hutton, M.; Farrer, M. J.; Wszolek, Z. K. & Vingerhoets, F. J. (2008). Study of a Swiss dopa-responsive dystonia family with a deletion in GCH1: redefining DYT14 as DYT5. *Neurology*, Vol. 70, No. 16 Pt 2, pp. 1377-1383, ISSN 1526-632X
- Zimprich, A.; Grabowski, M.; Asmus, F.; Naumann, M.; Berg, D.; Bertram, M.; Scheidtmann, K.; Kern, P.; Winkelmann, J.; Muller-Myhsok, B.; Riedel, L.; Bauer, M.; Muller, T.; Castro, M.; Meitinger, T.; Strom, T. M. & Gasser, T. (2001). Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus-dystonia syndrome. *Nature Genetics*, Vol. 29, No. 1, pp. 66-69, ISSN 1061-4036
- Zlotogora, J. (2004). Autosomal recessive, DYT2-like primary torsion dystonia: a new family. *Neurology*, Vol. 63, No. 7, pp. 1340, ISSN 1526-632X

IntechOpen

Dystonia - The Many Facets

Edited by Prof. Raymond Rosales

ISBN 978-953-51-0329-5

Hard cover, 220 pages

Publisher InTech

Published online 14, March, 2012

Published in print edition March, 2012

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:

Shih-Fen Chen and Yu-Chih Shen (2012). Dystonia and Genetics, Dystonia - The Many Facets, Prof. Raymond Rosales (Ed.), ISBN: 978-953-51-0329-5, InTech, Available from:
<http://www.intechopen.com/books/dystonia-the-many-facets/dystonia-and-genetics>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen