Published in final edited form as:
Exp Neurol. 2008 August ; 212(2): 242–246. doi:10.1016/j.expneurol.2008.04.020.

Commentary: Dopaminergic dysfunction in DYT1 dystonia

Thomas Wichmann*
Department of Neurology/School of Medicine and Yerkes National Primate Research Center, Emory University, 954 Gatewood Road NE, Atlanta, GA 30329, USA

Abstract

A three-base-pair deletion in the torsinA gene leads to generalized torsion dystonia (DYT1) in humans, an often devastating movement disorder in which voluntary movements are disrupted by sustained muscle spasms and abnormal limb posturing. In a recent issue of *Experimental Neurology*, Zhao et al. (2008) have provided a thorough behavioral, anatomic, and biochemical characterization of a mouse line that over-expresses human mutant torsinA, with particular emphasis on the possible role of dopaminergic dysfunction in these animals. This commentary provides an overview of the clinical and genetic features of the human disease and of the available transgenic mouse models for DYT1 dystonia, and discusses the evidence favoring the role of dopamine in the clinical manifestations of the disease.

Clinical and genetic characteristics of dystonia

The term ‘dystonia’ refers to pathological sustained muscle contractions, twisting movements, and abnormal postures, which are frequently exacerbated by attempted movement. Dystonia often presents with co-contractions of agonist and antagonist muscles, and with ‘overflow’ phenomena, where muscle activation spreads beyond that intended.

Dystonia is present in a heterogeneous group of disorders with diverse etiologies. While most dystonias are non-genetic in origin, an important subset of them is inherited. The most common of these genetic forms is generalized torsion dystonia (DYT1 dystonia). This disease usually starts in childhood (mean age of onset 12.5 years), with almost all cases starting before the age of 28 years (Berardelli et al., 1998; Bressman, 2004). The onset of the disease is often focal, in an individual limb, with subsequent generalization.

The overall prevalence of DYT1 dystonia is 3–4 per 100,000, with an annual incidence of 0.2 per 100,000 (Nutt et al., 1988). The prevalence is substantially higher in the Ashkenazi Jewish population, due to a founder effect (1:2000 to 1:6000, Bressman et al., 1989; Risch et al., 1990). DYT1 dystonia is an autosomal dominant disease with a low phenotypical penetrance of only 30% (Bressman et al., 1989; Risch et al., 1990; Ozelius et al., 1992).

DYT1 dystonia is caused by a 3-basepair deletion in the TOR1A gene on chromosome 9 (9q32–34, see Ozelius et al., 1989, 1997; Kramer et al., 1990). The gene codes for torsinA, a

*Fax: +1 404 727 9294., twichma@emory.edu.

332 amino-acid protein (Ozelius et al., 1997) that belongs to the AAA family of proteins (ATPases associated with diverse cellular activities), and has structural homology to heat shock and chaperone proteins (Hewett et al., 2003). AAA proteins are involved in many cellular functions, such as membrane trafficking, protein chaperone functions and others. The specific function of torsinA remains unknown, but it is thought that it plays a prominent role in development, supported by the fact that DYT1 dystonia starts during a discrete period of time in human patients (see above), and by the observation that homozygous TOR1A knock-out mice, or mice with homozygous expression of the mutant torsinA gene do not survive more than a few days after birth (Goodchild et al., 2005).

TorsinA is widely distributed throughout the central nervous system, and has been detected specifically in the cerebral cortex, striatum, substantia nigra pars compacta, thalamus, hippocampus, cerebellum, midbrain, pons and spinal cord (Augood et al., 1998, 1999; Shashidharan et al., 2000; Konakova et al., 2001; Rostasy et al., 2003). Within neurons, wild-type torsinA localizes to the endoplasmic reticulum (Liu et al., 2003; Naismith et al., 2004; Hewett et al., 2007), while mutant torsinA protein is found in the perinuclear space (Hewett et al., 2000; Gonzalez-Alegre and Paulson, 2004; Goodchild and Dauer, 2004). Perhaps relevant to the topic of dopaminergic dysfunction to DYT1 dystonia, associations of mutant torsinA with the vesicular monoamine transporter (VMAT2) and with alpha-synuclein have been described (Sharma et al., 2001; Misbahuddin et al., 2005).

Animal models for DYT1 dystonia

A variety of genetically modified mouse strains have been described that either over-express human mutant torsinA (Sharma et al., 2005; Shashidharan et al., 2005; Grundmann et al., 2007), are heterozygous for mouse mutant torsinA (Dang et al., 2005), or in which expression of endogenous torsinA is reduced (Goodchild et al., 2005; Dang et al., 2006). The recent paper by Zhao et al. in *Experimental Neurology* (Zhao et al., 2008) characterizes anatomical, behavioral and biochemical features of one of the strains that over-express mutant human torsinA, hMT1 mice, which were generated by Sharma et al. (Sharma et al., 2005). Other animals from the series generated by Sharma et al. (Sharma et al., 2005), including animals over-expressing human wild-type torsinA (hWT) and a second (different) line of animals over-expressing human mutant torsinA (hMT2), were also initially examined in the study by Zhao et al. (2008) but were then not further considered, because expression levels of human torsinA in these animals were found to be low.

The different published DYT1 transgenic mouse lines have been characterized to varying degrees in terms of their behavior and anatomy. None of them shows overt spontaneously occurring dystonia, although the strains generated by Shashidharan et al. show self-clasping behavior (suggestive of dystonic movements; seen in 40% of animals) when hung by their tails (Shashidharan et al., 2005). However, the available strains show abnormalities in behavioral tests. For instance, open field activity is increased in most of the published reports (Dang et al., 2005, 2006; Shashidharan et al., 2005; Grundmann et al., 2007). Increased latencies or slip counts in tests of beam walking, combined with normal Rotarod performance have also been documented in some studies (Dang et al., 2005, 2006), while the reverse constellation of findings was seen in others (Grundmann et al., 2007). The

published studies did not find abnormalities on footprint analyses (Dang et al., 2005; Grundmann et al., 2007), or vertical rope climbing (Dang et al., 2005, 2006).

In their studies of hMT1 mice, Zhao et al. (2008) observed increases in hind-base width measured by footprint analysis, and traversal times and slip counts on raised beam running tasks, while performance on an accelerating Rotarod paradigm was normal. This pattern of behavioral abnormalities differs in some respects from that documented in the other studies, specifically those reported with a similar panel of tests by Grundmann et al. in one of the other DYT1-over-expressing mouse lines (see above, Grundmann et al., 2007).

At this point, noclear pattern of a bnormalities has emerged from the literature that would neatly separate animals with abnormal torsinA expression from wild-type animals. More importantly, these animalsdo not display an easily quantifiable behavioral phenotype that would reliably correspond to dystonia in patients. The absence of such a phenotype obviously hampers efforts to use these animal models to develop new clinically relevant (i.e., anti-dystonic) treatments.

The different transgenic mouse lines also differ anatomically. TorsinA-containing aggregates in neurons, perinuclear inclusion bodies or blebbing of the nuclear membrane were seen in some of the previous studies in transgenic animals, specifically in brain stem nuclei (Dang et al., 2005; Goodchild et al., 2005; Shashidharan et al., 2005; Grundmann et al., 2007), but, in agreement with other studies (e.g., Sharma et al., 2005), Zhao et al. (2008) found no such abnormalities in the hMT1 mice. The question of whether inclusion body pathology is specific to the transgenic mouse models, or whether it is also part of human DYT1 disease remains somewhat controversial. Most histopathological studies of brains from patients with DYT1 failed to find evidence of protein accumulation or inclusion bodies (Walker et al., 2002; Rostasy et al., 2003), but a recent study of postmortem material from DYT1 patients has reported that perinuclear inclusion bodies are present in neurons in various brain stem areas (McNaught et al., 2004).

The role of dopamine in dystonia

A large number of inherited or acquired insults to the nervous system are associated with the development of dystonia (see, e.g., Nemeth, 2002). The identification of the genetic mutation in DYT1 dystonia brought with it the hope that the search for the causes and treatments for dystonia would accelerate. Frustratingly, more than ten years later, the brain mechanisms that result in DYT1 or other types of dystonia remain unclear. In search for a potential target for therapeutic interventions, a specific focus of the study by Zhao et al. (2008) and, in fact, of many earlier studies of dystonia, is the question of whether dystonia arises from dopaminergic dysfunction in the brain.

There are several lines of evidence that link dopaminergic dysfunction to the development of dystonia in general (Augood et al., 2002, 2004; Casey, 2004; Perlmutter and Mink, 2004). For example, dystonia is a prominent feature of ‘DOPA-responsive dystonia’, a disease in which patients have a genetic defect of dopamine synthesis, caused by reduced GTP-cyclohydrolase activity (Ichinose et al., 1994; Nagatsu and Ichinose, 1997; Nygaard, 1995; Patel et al., 1995). These patients respond dramatically to treatment with low doses of the

dopamine precursor L-DOPA. Another inherited disease in which dystonia is possibly due to a disturbance of dopamine synthesis is Lesch-Nyhan disease (Ernst et al., 1996; Wong et al., 1996; Visser et al., 2004), a condition in which a defect in purine synthesis gives rise to numerous medical problems, as well as neurologic symptoms including dystonia. Positron-emission tomography (PET) studies in Lesch-Nyhan disease show reductions in [^{18}F]-DOPA uptake, and in labeling with WIN-35,428, a marker of dopamine transporter, in the basal ganglia and other regions of the brain (Ernst et al., 1996; Wong et al., 1996). Mutations in the gene that codes for the rate-limiting enzyme in dopamine metabolism, tyrosine hydroxylase, also give rise to dystonias (Knappskog et al., 1995), as do mutations within the dopamine D2 receptor gene (myoclonus-dystonia, DYT11, Klein et al., 1999), or polymorphisms within the dopamine D5 receptor gene (Placzek et al., 2001).

In addition to these genetic conditions, dystonia also occurs in the context of other dopamine-related diseases or treatments. Thus, dystonia is frequently a feature of Parkinsonism, sometimes occurring early in the course of the disease, even prior to drug treatments (Purves-Stewart, 1898; Duvoisin et al., 1974; Nausieda et al., 1980; Katzenschlager et al., 2002; Bruno et al., 2004), or later in the disease, as “off”-period dystonia (e.g., Fabbrini et al., 2007). Interestingly, dystonia can also be a complication of antiparkinsonian therapy (Hallett, 1981; Fabbrini et al., 2007; Suzuki et al., 2008). Finally, dystonia may also be an acute or chronic complication of treatment with dopamine receptor blocking agents in patients with psychiatric or gastrointestinal disorders (e.g., Burke et al., 1982; Bateman et al., 1985; Burke et al., 1985; Rupniak et al., 1986; Kang et al., 1988; Factor and Matthews, 1991; Casey, 2004; Pinninti et al., 2006).

Further evidence that altered dopaminergic transmission plays a role in dystonia comes from PET imaging studies, which have demonstrated abnormalities of dopaminergic transmission in many dystonia patients (Ernst et al., 1996; Wong et al., 1996; Black et al., 1997; Perlmutter et al., 1997a,b; Brashear et al., 1999; Perlmutter and Mink, 2004). Specifically, reduced striatal dopamine receptor binding (Perlmutter et al., 1997a,b; Naumann et al., 1998), or [^{18}F]-DOPA uptake, suggestive of reduced DOPA decarboxylase activity (Playford et al., 1993), have been observed.

A link between striatal dopamine depletion and the development of dystonia is also suggested by the observation that dystonia can occur as a transient phenomenon in MPTP-treated monkeys before the animals develop overt Parkinsonism (Perlmutter et al., 1997a,b; Tabbal et al., 2006). PET measurements of [^{18}F]-DOPA uptake have directly demonstrated that striatal dopaminergic activity was reduced at the time at which dystonia was present in these animals (Tabbal et al., 2006).

Given the evidence for dopaminergic dysfunction, it is instructive to consider the similarities and differences between dystonia and Parkinson’s disease. The similarity between the two disorders is underscored by several observations. For instance, it is well known that dystonia occurs in many patients with Parkinson’s disease (Tolosa and Compta, 2006), and that the gene defect causing ‘DOPA-responsive dystonia’ results in prominent Parkinsonism in some individuals (e.g., Van Hove et al., 2006). In addition, electrophysiologic recording studies in dystonic and Parkinsonian patients undergoing neurosurgical procedures have demonstrated

similar abnormalities of neuronal firing patterns in the basal ganglia in both dystonia and Parkinsonism (Vitek et al., 1998; Starr et al., 2005), giving rise to the speculation that dystonia, like Parkinsonism, may result from changes in striatal dopaminergic transmission.

The question of why such disturbances result in Parkinsonism in some cases, and in dystonia in others remains unanswered. One obvious difference between the two conditions is the type of the underlying dopaminergic dysfunction. Parkinsonism is associated with substantial striatal dopamine loss, while striatal dopamine levels in dystonia are, at most, only modestly reduced. However, other differences between the two diseases are also worth considering. Thus, striatal dopamine depletion in Parkinsonism is associated with long-term (and probably irreversible) anatomic changes, such as the loss of dendritic spines of striatal neurons (Ingham et al., 1998; Arbuthnott et al., 2000; Day et al., 2006). The available evidence suggests that the striatal micro-anatomy is less affected in dystonia, although further study of this topic is needed. Other anatomical and biochemical differences between Parkinson's disease and dystonia, such as the possibility of (partial) degeneration of specific cell types in thalamus, cortex, brainstem or cerebellum, differential changes in dopamine receptor expression or dopamine uptake sites in the basal ganglia may contribute to the differences in phenotype.

Developmental factors may also be important. The age at which a disturbance in dopaminergic metabolism occurs appears to influence the resulting behavioral phenotype (Visser et al., 2000). Spontaneous dystonia in Parkinson's disease occurs predominantly in patients with early-onset disease (Jankovic, 2005; Tolosa and Compta, 2006), and acute dystonic reactions and tardive dystonia in response to neuroleptic medications are more common in children and young adults than in the elderly (Gershanik, 1998). Likewise, among individuals carrying the gene mutation for DOPA-responsive dystonia, childhoodonset disease tends to produce dystonia, while patients with adultonset disease more commonly express Parkinsonism (Bandmann et al., 1996; Uncini et al., 2004). The influence of age on the type of movement disorder associated with dopamine dysfunction has been studied extensively in rodents (Goldstein et al., 1989; Joyce et al., 1996; Bruno et al., 1998). Adult rodents with >90% destruction of nigrostriatal dopamine pathways exhibit Parkinsonism with L-DOPA-responsive akinesia and bradykinesia. In contrast, in juvenile animals, the same lesions lead to marked hyperkinesis that is worsened by L-DOPA.

Dopaminergic dysfunction in DYT1 dystonia

The contribution of dopaminergic dysfunction specifically to DYT1 dystonia has been explored bothinDYT1 patients, and in the transgenic mouse models of the disease. Autopsy studies have demonstrated that, unlike the situation in Parkinsonian patients, there is no obvious change in the number of SNc cells in DYT1 dystonia patients (Zweig et al., 1988; Furukawa et al., 2000), although SNc cells in dystonia patients may be somewhat larger than normal (Rostasy et al., 2003). In line with the anatomic findings, striatal dopamine levels in postmortem brain material from dystonia patients were found to be either normal or show only mild decreases in the rostral putamen and caudate nucleus (Furukawa et al., 2000; Augood et al., 2002; Augood et al., 2004). However, several authors have reported functional changes in dopaminergic transmission, specifically an increase in dopamine

turnover, along with trends towards reductions in dopamine D1-like and D2-like receptor binding (Augood et al., 2002,2004; Asanuma et al., 2005). The available studies suggest that the function of the dopamine transporter, however, is not compromised (Naumann et al., 1998; Augood et al., 2002; Augood et al., 2004). It is worth bearing in mind that such biochemical studies are very difficult to conduct in humans because of the limited availability of suitable autopsy material, and because factors such as postmortem delay and differences in processing methods greatly influence biochemical and other measurements of dopamine metabolism (Spokes, 1979; Kontur et al., 1994; Hornykiewicz, 2001; Augood et al., 2004).

Dopaminergic dysfunction has also been examined in several of the genetic animal models of DYT1 dystonia, using measurements of tissue levels of dopamine, and of its metabolites, 3,4-dihydroxy-phenylacetic acid (DOPAC) and homovanillic acid (HVA). DYT1 knockdown mice, a mouse strain in which endogenous torsinA levels are reduced, were shown to have normal striatal dopamine levels, but reduced DOPAC levels (Dang et al., 2006). DYT1 knock-in mice appear to have normal striatal dopamine level, but reduced HVA levels (Dang et al., 2005). In published studies on mouse lines that over-express human mutant torsinA, striatal dopamine levels and DOPAC or HVA levels were either found to be normal (Grundmann et al., 2007), or reduced (in behaviorally affected animals only, Shashidharan et al., 2005). Previous studies in hMT1 mice showed that the overall striatal levels of dopamine or its metabolites, and the levels of the dopamine transporter, vesicular transporter, and dopamine receptors did not differ from those found in wild-type animals (Balcioglu et al., 2007). In agreement with these previous studies, Zhao et al. (Zhao et al., 2008) did not find a significant change in the overall striatal level of dopamine. However, they demonstrated a significant increase in dopamine turnover (with elevated DOPAC and HVA levels).

Beyond the changes in dopamine metabolism, changes may also occur in the functional regulation of striatal dopamine release in hMT1 mice. Thus, dopamine release triggered by amphetamine in hMT1 mice was found to be less than in controls (Balcioglu et al., 2007), and electrophysiologic studies have suggested that the function of D2-receptor coupled N-type calcium channels may be altered in these animals, resulting in secondary alterations of cholinergic signaling in the striatum (Pisani et al., 2006), which may in turn explain some of the previously identified changes in motor learning (Sharma et al., 2005).

These studies provide evidence that dopamine signaling is altered in DYT1 dystonia. In most studies, the levels of striatal dopamine are not altered, but there is evidence for changes in the regulation of dopamine release. Overall, the changes in dopaminergic function are relatively modest in magnitude, and the link between them and the movement disorder is not clear.

Conclusion

The detailed characterizations by Zhao et al. of the behavioral, morphological, and biochemical changes in hMT1 mice (Zhao et al., 2008) allow the reader to better compare this strain of mice with other DYT1 mouse models, so that their suitability for studies of

specific aspects of human DYT1 dystoniamay be better evaluated. The available mouse lines clearly differ from one another. Zhao et al. (2008) point out that some of the apparent differences may reflect technical constraints, such as the choice of specific promoters, construct designs, insertion sites chosen to generate the different DYT1 over-expressing animal models, strain differences between mice, and probably also the exact behavioral and other tests used to assess them.

Despite much effort to generate and study transgenic mouse strains that model dystonia, there is a growing realization that the translation of insights gained from studies in these animals into pathophysiologic schemes describing the human disease, or into new treatments for DYT1 dystonia may not be as straightforward as researcher and patients might wish it to be. Transgenic animal models may prove valuable for evaluating some of the biochemical and electrophysiologic consequences of over-expression of mutant torsinA, and may eventually be useful for developing and testing treatments aimed at normalizing torsinA expression or function. An obvious limitation of these models is that the behavioral phenotype does not replicate DYT1 dystonia. The fact that even non-dystonic motor problems in these animals are only unmasked in behavioral (stress-) tests, that they differ among transgenic animal lines, and that the tests themselves are relatively non-specific and may not correspond to dystonia *per se*, makes the available transgenic DYT1-models less attractive as test beds for the development of new symptomatic treatments for dystonia.

The comprehensive characterization of hMT1 mice by Zhao et al. (2008) like earlier work, reminds us that we know much more about the genetics of DYT1 dystonia than about the pathophysiology of the movement disorder. It may be important to consider whether many of the identified abnormalities associated with dystonia are actually not primary, but instead reflect compensatory or secondary changes. If so, it would be worthwhile to expand the search for cause(s) and treatments of DYT1 dystonia to include non-dopaminergic changes, subtle anatomic alterations, neuronal network changes, and other functional abnormalities. This research will most likely require not only animal models such as the mice characterized by Zhao et al. (2008) but also further studies of patients with DYT1 dystonia.

Acknowledgments

Work on this review was supported by a grant from the Bachmann-Strauss foundation, and by an NIH/NCRR grant to the Yerkes National Primate Research Center (RR-000165).

References

Arbuthnott GW, Ingham CA, Wickens JR. Dopamine and synaptic plasticity in the neostriatum. J Anat. 2000; 196(Pt 4):587–596. [PubMed: 10923989]

Asanuma K, Ma Y, Okulski J, Dhawan V, Chaly T, Carbon M, Bressman SB, Eidelberg D. Decreased striatal D2 receptor binding in non-manifesting carriers of the DYT1 dystonia mutation. Neurology. 2005; 64:347–349. [PubMed: 15668438]

Augood SJ, Hollingsworth Z, Albers DS, Yang L, Leung J, Breakefield XO, Standaert DG. Dopamine transmission in DYT1 dystonia. Adv Neurol. 2004; 94:53–60. [PubMed: 14509654]

Augood SJ, Hollingsworth Z, Albers DS, Yang L, Leung JC, Muller B, Klein C, 0Breakefield XO, Standaert DG. Dopamine transmission in DYT1 dystonia: a biochemical and autoradiographical study. Neurology. 2002; 59:445–448. [PubMed: 12177384]

Augood SJ, Martin DM, Ozelius LJ, Breakefield XO, Penney JB Jr, Standaert DG. Distribution of the mRNAs encoding torsinA and torsinB in the normal adult human brain. Ann Neurol. 1999; 46:761–769. [PubMed: 10553994]

Augood SJ, Penney JB Jr, Friberg IK, Breakefield XO, Young AB, Ozelius LJ, Standaert DG. Expression of the early-onset torsion dystonia gene (DYT1) in human brain. Ann Neurol. 1998; 43:669–673. [PubMed: 9585364]

Balcioglu A, Kim MO, Sharma N, Cha JH, Breakefield XO, Standaert DG. Dopamine release is impaired in a mouse model of DYT1 dystonia. J Neurochem. 2007; 102:783–788. [PubMed: 17550429]

Bandmann O, Daniel S, Marsden CD, Wood NW, Harding AE. The GTP-cyclohydrolase I gene in atypical parkinsonian patients: a clinico-genetic study. J Neurol Sci. 1996; 141:27–32. [PubMed: 8880688]

Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. Br Med J (Clin Res Ed). 1985; 291:930–932.

Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. Brain. 1998; 121:1195–1212. [PubMed: 9679773]

Black KJ, Gado MH, Perlmutter JS. PET measurement of dopamine D2 receptor-mediated changes in striatopallidal function. J Neurosci. 1997; 17:3168–3177. [PubMed: 9096151]

Brashear A, Mulholland GK, Zheng QH, Farlow MR, Siemers ER, Hutchins GD. PET imaging of the pre-synaptic dopamine uptake sites in rapid-onset dystonia-parkinsonism (RDP). Mov Disord. 1999; 14:132–137. [PubMed: 9918356]

Bressman SB. Dystonia genotypes, phenotypes, and classification. Adv Neurol. 2004; 94:101–107. [PubMed: 14509661]

Bressman SB, de Leon D, Brin MF, Risch N, Burke RE, Greene PE, Shale H, Fahn S. Idiopathic dystonia among Ashkenazi Jews: evidence for autosomal dominant inheritance. Ann Neurol. 1989; 26:612–620. [PubMed: 2817837]

Bruno JP, Sandstrom MI, Arnold HM, Nelson CL. Age-dependent neurobehavioral plasticity following forebrain dopamine depletions. Dev Neurosci. 1998; 20:164–179. [PubMed: 9691191]

Bruno MK, Ravina B, Garraux G, Hallett M, Ptacek L, Singleton A, Johnson J, Hanson M, Considine E, Gwinn-Hardy K. Exercise-induced dystonia as a preceding symptom of familial Parkinson's disease. Mov Disord. 2004; 19:228–230. [PubMed: 14978684]

Burke RE, Fahn S, Jankovic J, Marsden CD, Lang AE, Gollomp S, Ilson J. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. Neurology. 1982; 32:1335–1346. [PubMed: 6128697]

Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. Ann Neurol. 1985; 17:200–202. [PubMed: 3977303]

Casey DE. Pathophysiology of antipsychotic drug-induced movement disorders. J Clin Psychiatry. 2004; 65(Suppl 9):25–28. [PubMed: 15189109]

Dang MT, Yokoi F, McNaught KS, Jengelley TA, Jackson T, Li J, Li Y. Generation and characterization of Dyt1 DeltaGAG knock-in mouse as a model for early-onset dystonia. Exp Neurol. 2005; 196:452–463. [PubMed: 16242683]

Dang MT, Yokoi F, Pence MA, Li Y. Motor deficits and hyperactivity in Dyt1 knockdown mice. Neurosci Res. 2006; 56:470–474. [PubMed: 17046090]

Day M, Wang Z, Ding J, An X, Ingham CA, Shering AF, Wokosin D, Ilijic E, Sun Z, Sampson AR, Mugnaini E, Deutch AY, Sesack SR, Arbuthnott GW, Surmeier DJ. Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. Nat Neurosci. 2006; 9:251–259. [PubMed: 16415865]

Duvoisin RC, Yahr MD, Lieberman J, Antunes J, Rhee S. The striatal foot. Trans Am Neurol Assoc. 1974; 97:267.

Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Hardy K, Hankerson JG, Doudet DJ, Cohen RM. Presynaptic dopaminergic deficits in Lesch–Nyhan disease. N Engl J Med. 1996; 334:1568–1572. [PubMed: 8628337]

Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. Mov Disord. 2007; 22:1379–1389. quiz 1523. [PubMed: 17427940]

Factor SA, Matthews MK. Persistent extrapyramidal syndrome with dystonia and rigidity caused by combined metoclopramide and prochlorperazine therapy. South Med J. 1991; 84:626–628. [PubMed: 2035085]

Furukawa Y, Hornykiewicz O, Fahn S, Kish SJ. Striatal dopamine in early-onset primary torsion dystonia with the DYT1 mutation. Neurology. 2000; 54:1193–1195. [PubMed: 10720299]

Gershanik, OS. Drug-induced dyskinesias. In: Jankovic, J.; Tolosa, E., editors. Parkinson's Disease and Movement Disorders. 3. Williams & Wilkins; Baltimore: 1998. p. 579-600.

Goldstein SR, Matsumoto RR, Thompson TL, Patrick RL, Bowen WD, Walker JM. Motor effects of two sigma ligands mediated by nigrostriatal dopamine neurons. Synapse. 1989; 4:254–258. [PubMed: 2558420]

Gonzalez-Alegre P, Paulson HL. Aberrant cellular behavior of mutant torsinA implicates nuclear envelope dysfunction in DYT1 dystonia. J Neurosci. 2004; 24:2593–2601. [PubMed: 15028751]

Goodchild RE, Dauer WT. Mislocalization to the nuclear envelope: an effect of the dystonia-causing torsinA mutation. Proc Natl Acad Sci U S A. 2004; 101:847–852. [PubMed: 14711988]

Goodchild RE, Kim CE, Dauer WT. Loss of the dystonia-associated protein torsinA selectively disrupts the neuronal nuclear envelope. Neuron. 2005; 48:923–932. [PubMed: 16364897]

Grundmann K, Reischmann B, Vanhoutte G, Hubener J, Teismann P, Hauser TK, Bonin M, Wilbertz J, Horn S, Nguyen HP, Kuhn M, Chanarat S, Wolburg H, Van der Linden A, Riess O. Overexpression of human wildtype torsinA and human DeltaGAG torsinA in a transgenic mouse model causes phenotypic abnormalities. Neurobiol Dis. 2007; 27:190–206. [PubMed: 17601741]

Hallett M. Bromocriptine for levodopa-induced end-of-dose dystonia. Lancet. 1981; 1:616. [PubMed: 6110850]

Hewett J, Gonzalez-Agosti C, Slater D, Ziefer P, Li S, Bergeron D, Jacoby DJ, Ozelius LJ, Ramesh V, Breakefield XO. Mutant torsinA, responsible for early-onset torsion dystonia, forms membrane inclusions in cultured neural cells. Hum Mol Genet. 2000; 9:1403–1413. [PubMed: 10814722]

Hewett J, Ziefer P, Bergeron D, Naismith T, Boston H, Slater D, Wilbur J, Schuback D, Kamm C, Smith N, Camp S, Ozelius LJ, Ramesh V, Hanson PI, Breakefield XO. TorsinA in PC12 cells: localization in the endoplasmic reticulum and response to stress. J Neurosci Res. 2003; 72:158–168. [PubMed: 12671990]

Hewett JW, Tannous B, Niland BP, Nery FC, Zeng J, Li Y, Breakefield XO. Mutant torsinA interferes with protein processing through the secretory pathway in DYT1 dystonia cells. Proc Natl Acad Sci U S A. 2007; 104:7271–7276. [PubMed: 17428918]

Hornykiewicz O. Chemical neuroanatomy of the basal ganglia–normal and in Parkinson's disease. J Chem Neuroanat. 2001; 22:3–12. [PubMed: 11470551]

Ichinose H, Ohye T, Takayashi E, Seki N, Hori T, Segawa M, Nomura Y, Endo K, Tanaka H, Tsuji S. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet. 1994; 8:236–242. [PubMed: 7874165]

Ingham CA, Hood SH, Taggart P, Arbuthnott GW. Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway. J Neurosci. 1998; 18:4732–4743. [PubMed: 9614247]

Jankovic J. Dystonia and other deformities in Parkinson's disease. J Neurol Sci. 2005; 239:1–3. [PubMed: 16199057]

Joyce JN, Frohna PA, Neal-Beliveau BS. Functional and molecular differentiation of the dopamine system induced by neonatal denervation. Neurosci Biobehav Rev. 1996; 20:453–486. [PubMed: 8880735]

Kang UJ, Burke RE, Fahn S. Tardive dystonia. Adv Neurol. 1988; 50:415–429. [PubMed: 3400500]

Katzenschlager R, Costa D, Gacinovic S, Lees AJ. [(123)I]-FP-CIT-SPECT in the early diagnosis of PD presenting as exercise-induced dystonia. Neurology. 2002; 59:1974–1976. [PubMed: 12499495]

Klein C, Brin MF, Kramer P, Sena-Esteves M, de Leon D, Doheny D, Bressman S, Fahn S, Breakefield XO, Ozelius LJ. Association of a missense change in the D2 dopamine receptor with myoclonus dystonia. Proc Natl Acad Sci U S A. 1999; 96:5173–5176. [PubMed: 10220438]

Knappskog PM, Flatmark T, Mallet J, Ludecke B, Bartholome K. Recessively inherited L-DOPA-responsive dystonia caused by a point mutation (Q381K) in the tyrosine hydroxylase gene. Hum Mol Genet. 1995; 4:1209–1212. [PubMed: 8528210]

Konakova M, Huynh DP, Yong W, Pulst SM. Cellular distribution of torsin A and torsin B in normal human brain. Arch Neurol. 2001; 58:921–927. [PubMed: 11405807]

Kontur PJ, al-Tikriti M, Innis RB, Roth RH. Postmortem stability of monoamines, their metabolites, and receptor bindinginrat brain regions. J Neurochem. 1994; 62:282–290. [PubMed: 7505313]

Kramer PL, de Leon D, Ozelius L, Risch N, Bressman SB, Brin MF, Schuback DE, Burke RE, Kwiatkowski DJ, Shale H, et al. Dystonia gene in Ashkenazi Jewish population is located on chromosome 9q32–34. Ann Neurol. 1990; 27:114–120. [PubMed: 2317008]

Liu Z, Zolkiewska A, Zolkiewski M. Characterization of human torsinA and its dystonia-associated mutant form. Biochem J. 2003; 374:117–122. [PubMed: 12780349]

McNaught KS, Kapustin A, Jackson T, Jengelley TA, Jnobaptiste R, Shashidharan P, Perl DP, Pasik P, Olanow CW. Brainstem pathology in DYT1 primary torsion dystonia. Ann Neurol. 2004; 56:540–547. [PubMed: 15455404]

Misbahuddin A, Placzek MR, Taanman JW, Gschmeissner S, Schiavo G, Cooper JM, Warner TT. Mutant torsinA, which causes early-onset primary torsion dystonia, is redistributed to membranous structures enriched in vesicular monoamine transporter in cultured human SH-SY5Y cells. Mov Disord. 2005; 20:432–440. [PubMed: 15593317]

Nagatsu T, Ichinose H. GTP cyclohydrolase I gene, dystonia, juvenile parkinsonism, and Parkinson's disease. J Neural Transm Suppl. 1997; 49:203–209. [PubMed: 9266429]

Naismith TV, Heuser JE, Breakefield XO, Hanson PI. TorsinA in the nuclear envelope. Proc Natl Acad Sci U S A. 2004; 101:7612–7617. [PubMed: 15136718]

Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. Mov Disord. 1998; 13:319–323. [PubMed: 9539347]

Nausieda PA, Weiner WJ, Klawans HL. Dystonic foot response of Parkinsonism. Arch Neurol. 1980; 37:132–136. [PubMed: 7356417]

Nemeth AH. The genetics of primary dystonias and related disorders. Brain. 2002; 125:695–721. [PubMed: 11912106]

Nutt JG, Muenter MD, Aronson A, Kurland LT, Melton LJ III. Epidemiology of focal and generalized dystonia in Rochester, Minnesota. Mov Disord. 1988; 3:188–194. [PubMed: 3264051]

Nygaard TG. Dopa-responsive dystonia. Curr Opin Neurol. 1995; 8:310–313. [PubMed: 7582048]

Ozelius L, Kramer PL, Moskowitz CB, Kwiatkowski DJ, Brin MF, Bressman SB, Schuback DE, Falk CT, Risch N, de Leon D, et al. Human gene for torsion dystonia located on chromosome 9q32–q34. Neuron. 1989; 2:1427–1434. [PubMed: 2576373]

Ozelius LJ, Hewett JW, Page CE, Bressman SB, Kramer PL, Shalish C, de Leon D, Brin MF, Raymond D, Corey DP, Fahn S, Risch NJ, Buckler AJ, Gusella JF, Breakefield XO. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet. 1997; 17:40–48. [PubMed: 9288096]

Ozelius LJ, Kramer PL, de Leon D, Risch N, Bressman SB, Schuback DE, Brin MF, Kwiatkowski DJ, Burke RE, Gusella JF, et al. Strong allelic association between the torsion dystonia gene (DYT1) andloci on chromosome 9q34 in Ashkenazi Jews. Am J Hum Genet. 1992; 50:619–628. [PubMed: 1347197]

Patel K, Roskrow T, Davis JS, Heckmatt JZ. Dopa responsive dystonia. Arch Dis Child. 1995; 73:256–257. [PubMed: 7492170]

Perlmutter JS, Mink JW. Dysfunction of dopaminergic pathways in dystonia. Adv Neurol. 2004; 94:163–170. [PubMed: 14509670]

Perlmutter JS, Stambuk MK, Markham JM, Black KJ, McGee-Minnich L, Jankovic J, Moerlein SM. Decreased [^{18}F]spiperone binding in putamen in idiopathic focal dystonia. J Neurosci. 1997a; 17:843–850. [PubMed: 8987805]

Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD. MPTP induces dystonia and parkinsonism. Clues to the pathophysiology of dystonia. Neurology. 1997b; 49:1432–1438. [PubMed: 9371934]

Pinninti NR, Mago R, Adityanjee. Tardive dystonia-associated prescription of aripiprazole. J Neuropsychiatry Clin Neurosci. 2006; 18:426–427. [PubMed: 16963598]

Pisani A, Martella G, Tscherter A, Bonsi P, Sharma N, Bernardi G, Standaert DG. Altered responses to dopaminergic D2 receptor activation and N-type calcium currents in striatal cholinergic interneurons in a mouse model of DYT1 dystonia. Neurobiol Dis. 2006; 24:318–325. [PubMed: 16934985]

Placzek MR, Misbahuddin A, Chaudhuri KR, Wood NW, Bhatia KP, Warner TT. Cervical dystonia is associated with a polymorphism in the dopamine (D5) receptor gene. J Neurol Neurosurg Psychiatry. 2001; 71:262–264. [PubMed: 11459908]

Playford ED, Fletcher NA, Sawle GV, Marsden CD, Brooks DJ. Striatal [18F] dopa uptake in familial idiopathic dystonia. Brain. 1993; 116:1191–1199. [PubMed: 8221055]

Purves-Stewart J. Paralysis agitans with an account of a new symptom. Lancet. 1898; 2:1258–1260.

Risch NJ, Bressman SB, deLeon D, Brin MF, Burke RE, Greene PE, Shale H, Claus EB, Cupples LA, Fahn S. Segregation analysis of idiopathic torsion dystonia in Ashkenazi Jews suggests autosomal dominant inheritance. Am J Hum Genet. 1990; 46:533–538. [PubMed: 2309703]

Rostasy K, Augood SJ, Hewett JW, Leung JC, Sasaki H, Ozelius LJ, Ramesh V, Standaert DG, Breakefield XO, Hedreen JC. TorsinA protein and neuropathology in early onset generalized dystonia with GAG deletion. Neurobiol Dis. 2003; 12:11–24. [PubMed: 12609485]

Rupniak NM, Jenner P, Marsden CD. Acute dystonia induced by neuroleptic drugs. Psychopharmacology (Berl). 1986; 88:403–419. [PubMed: 2871578]

Sharma N, Baxter MG, Petravicz J, Bragg DC, Schienda A, Standaert DG, Breakefield XO. Impaired motor learning in mice expressing torsinA with the DYT1 dystonia mutation. J Neurosci. 2005; 25:5351–5355. [PubMed: 15930383]

Sharma N, Hewett J, Ozelius LJ, Ramesh V, McLean PJ, Breakefield XO, Hyman BT. A close association of torsinA and alpha-synuclein in Lewy bodies: a fluorescence resonance energy transfer study. Am J Pathol. 2001; 159:339–344. [PubMed: 11438481]

Shashidharan P, Kramer BC, Walker RH, Olanow CW, Brin MF. Immunohistochemical localization and distribution of torsinA in normal human and rat brain. Brain Res. 2000; 853:197–206. [PubMed: 10640617]

Shashidharan P, Sandu D, Potla U, Armata IA, Walker RH, McNaught KS, Weisz D, Sreenath T, Brin MF, Olanow CW. Transgenic mouse model of early-onset DYT1 dystonia. Hum Mol Genet. 2005; 14:125–133. [PubMed: 15548549]

Spokes EG. An analysis of factors influencing measurements of dopamine, noradrenaline, glutamate decarboxylase and choline acetylase in human postmortem brain tissue. Brain. 1979; 102:333–346. [PubMed: 455043]

Starr PA, Rau GM, Davis V, Marks WJ Jr, Ostrem JL, Simmons D, Lindsey N, Turner RS. Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson's disease and normal macaque. J Neurophysiol. 2005; 93:3165–3176. [PubMed: 15703229]

Suzuki M, Hirai T, Ito Y, Sakamoto T, Oka H, Kurita A, Inoue K. Pramipexole-induced antecollis in Parkinson's disease. J Neurol Sci. 2008; 264:195–197. [PubMed: 17826796]

Tabbal SD, Mink JW, Antenor JA, Carl JL, Moerlein SM, Perlmutter JS. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced acute transient dystonia in monkeys associated with low striatal dopamine. Neuroscience. 2006; 141:1281–1287. [PubMed: 16766129]

Tolosa E, Compta Y. Dystonia in Parkinson's disease. J Neurol. 2006; 253(Suppl 7):VII7–VII13. [PubMed: 17131231]

Uncini A, De Angelis MV, Di Fulvio P, Ragno M, Annesi G, Filla A, Stuppia L, Gambi D. Wide expressivity variation and high but no gender-related penetrance in two dopa-responsive dystonia families with a novel GCH-I mutation. Mov Disord. 2004; 19:1139–1145. [PubMed: 15390021]

Van Hove JL, Steyaert J, Matthijs G, Legius E, Theys P, Wevers R, Romstad A, Moller LB, Hedrich K, Goriounov D, Blau N, Klein C, Casaer P. Expanded motor and psychiatric phenotype in autosomal dominant Segawa syndrome due to GTP cyclohydrolase deficiency. J Neurol Neurosurg Psychiatry. 2006; 77:18–23. [PubMed: 16361586]

Visser JE, Bar PR, Jinnah HA. Lesch–Nyhan disease and the basal ganglia. Brain Res Brain Res Rev. 2000; 32:449–475. [PubMed: 10760551]

Visser JE, Harris JC, Barabas G, Eddey GE, Jinnah HA. The motor disorder of classic Lesch–Nyhan disease. Nucleosides Nucleotides Nucleic Acids. 2004; 23:1161–1164. [PubMed: 15571221]

Vitek, JL.; Zhang, J.; Evatt, M.; Mewes, K.; DeLong, MR.; Hashimoto, T.; Triche, S.; Bakay, RAE. GPi pallidotomy for dystonia: clinical outcome and neuronal activity. In: Fahn, S.; Marsden, CD.; DeLong, MR., editors. Dystonia 3. Lippincott-Raven; Philadelphia: 1998. p. 211-220.

Walker RH, Brin MF, Sandu D, Good PF, Shashidharan P. TorsinA immunoreactivity in brains of patients with DYT1 and non-DYT1 dystonia. Neurology. 2002; 58:120–124. [PubMed: 11781416]

Wong DF, Harris JC, Naidu S, Yokoi F, Marenco S, Dannals RF, Ravert HT, Yaster M, Evans A, Rousset O, Bryan RN, Gjedde A, Kuhar MJ, Breese GR. Dopamine transporters are markedly reduced in Lesch–Nyhan disease in vivo. Proc Natl Acad Sci U S A. 1996; 93:5539–5543. [PubMed: 8643611]

Zhao Y, DeCuypere M, LeDoux MS. Abnormal motor function and dopamine neurotransmission in DYT1 ΔGAG transgenic mice. Exp Neurol. 2008; 210:719–730. [PubMed: 18299128]

Zweig RM, Hedreen JC, Jankel WR, Casanova MF, Whitehouse PJ, Price DL. Pathology in brainstem regions of individuals with primary dystonia. Neurology. 1988; 38:702–706. [PubMed: 3362365]