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Dystonia – new advances in classification, genetics, pathophysiology and treatment

Skogseid IM. Dystonia – new advances in classification, genetics, pathophysiology and treatment.
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Dystonia is a heterogeneous movement disorder and has been defined as 'a syndrome of sustained muscle contractions, frequently causing twisted and repetitive movements, or abnormal postures'. The classification of dystonia has developed along with increasing knowledge, and different schemes have been suggested, including age at onset, body distribution, and etiology as the main differentiating factors. A revised definition and a new classification of dystonia have now been proposed by a group of leading dystonia experts and will be referred here. The discovery of the first two gene mutations causing primary generalized dystonia (DYT1-TOR1A and DYT6-THAP1) has facilitated studies on pathogenesis and pathophysiology of primary dystonias, by comparing neurophysiology between manifesting and non-manifesting carriers, and by studying the molecular biology of the mutant gene products. During recent years, several other gene mutations causing primary dystonia, dystonia-plus, and paroxysmal dystonia disorders have been discovered. Only during the last year, by the use of whole-exome sequencing techniques, mutations in three different genes in families with predominantly cervical dystonia were found, which may lead to improved insight into the pathogenesis also of the more frequent focal dystonias. Botulinum neurotoxin (BoNT) and deep brain stimulation (DBS) have revolutionized the symptomatic treatment for dystonia during the last two decades and continue to be refined to improve efficacy and expand their indications. Unfortunately, no progress has been made in the oral medication of dystonia. Current and future new insights into pathogenetic and pathophysiological mechanisms of dystonia will hopefully lead to improvement also in this area soon.

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Introduction

The term 'dystonia' was introduced 102 years ago by Oppenheim, who described four patients with 'dystonia musculorum deformans', in whom 'muscle tone was hypotonic at one occasion, and in tonic muscle spasm at another, usually, but not exclusively, elicited upon voluntary movements' (1). The first descriptions in the medical literature of writer′s cramp, which is a focal dystonia, were published some decades earlier (2, 3). During the first seven decades of the 20th century, focal dystonias were regarded by many neurologists to be psychogenic, but this began to change after C. David Marsden published his comprehensive paper on adult–onset torsion dystonias in 1976 (4). This was a very important contribution to the current view of dystonia as a neurological hyperkinetic movement disorder.

In 1984, a committee assembled by the Dystonia Medical Research Foundation provided the first consensus definition of dystonia as 'a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures' (5). This definition has been used by most clinicians and researchers since, but with the rapidly expanding spectrum of defined diseases featuring dystonia and/or dystonic tremor as the only or the main clinical sign, it has become clear that this definition has some limitations (6).

The classification of dystonia has developed along with increasing knowledge, and different schemes have been suggested, including age at onset, body distribution, and etiology as the main factors to differentiate between different dystonia syndromes. A group of leading experts in dystonia has now proposed both a revised definition of dystonia and a new classification (6), which may become even more widely accepted as a common definition and classification for all involved in the care of people with dystonia in the future.

The discovery in 1997 of the first gene mutation causing primary generalized dystonia (DYT1-TOR1A) (7) has facilitated studies on pathogenesis and pathophysiology of DYT1-dystonia, comparing neurophysiology between manifesting and non-manifesting carriers (8), and on the molecular biology of the mutant gene product torsinA in various animal models (9). Several other pathogenic gene mutations causing generalized forms of dystonia, including primary dystonia, dystonia-plus, and paroxysmal dystonia disorders, have been discovered since. Autosomal dominant inheritance and reduced penetrance are typical for many of these genetic dystonias, although a few recessive and X-linked disorders have also been identified (10). Although about 15–25% of patients with focal and segmental dystonia have first-degree relatives with dystonia, the search for genes or susceptibility factors explaining this has been disappointing (10). However, using the new whole-exome sequencing techniques, mutations in three different genes in families with predominantly cervical dystonia were found during the last year and may be the start of a new era of improved insight into the pathogenesis of focal dystonias, and thus of more targeted medical treatment (11). The genetic basis of metabolic or heredodegenerative disorders that often lead to dystonia has been elucidated, and neuroimaging and other laboratory techniques for diagnosing causes of secondary dystonia have improved and become more widely available. Thus, as the last two decades brought us the two revolutions in dystonia treatment, this decade may bring to light the pathogenetic basis for many of the dystonia disorders.

Definition and classification

The new definition of dystonia, which was recently published in the journal Movement Disorders, is: 'Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned, twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation' (6). The motor phenomenology with special relevance for dystonia is further defined, including its aggravation by voluntary action and maintenance by antigravity postures, dystonic tremor, mirror dystonia, overflow, and alleviating maneuvers such as sensory tricks and gestes antagonistes. One aim of the new definition has been to exclude several conditions that also result in abnormal movements, postures or spasms, and thus mimic dystonia, the so-called pseudodystonias.

Whereas dystonia until now has been classified according to age at onset, body distribution, and etiology (primary, dystonia-plus, heredodegenerative, and secondary), the expert group now proposes to classify dystonia on the basis of *two distinct axes: clinical features and etiology* (6). Five descriptors are utilized to specify the *clinical features* axis: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and coexistence of other neurological or systemic manifestations. Age at onset is divided into infancy (0–2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40), and late adulthood (>40 years). Body distribution is, as in earlier classifications, divided into focal, segmental, multifocal, generalized, and hemidystonia. The definition of generalized dystonia emphasizes that the trunk and two other body regions must be involved, but leg involvement is not obligatory according to this new classification. Temporal pattern distinguishes between static or progressive disease course and variability of symptoms, which could be persistent, action-specific, diurnal, or paroxysmal. Regarding the coexistence of other movement disorders, the term 'isolated dystonia' is used when these are not present, and the term 'combined dystonia' if they are. Finally, other neurological manifestations (than movement disorders) or systemic manifestations are denoted if present. The *etiology* axis is described by whether nervous system pathology is present or not, and whether it is inherited, acquired, or idiopathic. Under the subheading 'nervous system pathology', patients may have evidence of degeneration, evidence of a structural (often static) lesion, or no evidence of either of these. Inherited dystonia forms may be autosomal dominant, autosomal recessive, X-linked recessive or mitochondrial. Acquired causes may include perinatal brain injuries, infections, drugs, toxins, vascular lesions, neoplastic diseases, brain injuries (head trauma, brain surgery), or psychogenic cause.

Finally, idiopathic cases can be subdivided into sporadic or familial (6).

Genetics and pathophysiology

Until last year, only two primary/isolated forms of familial dystonia (DYT1 and DYT6), both with early or young adult onset had been shown to be unequivocally associated with gene mutations (7, 12). Since then, mutations in four more genes have been implicated as causes of familial, primary dystonia, of which three are segmental or focal cervical dystonia forms with adolescent to adult onset (Table 1). During recent years, several gene mutations have also been identified to explain dystonia-plus syndromes and paroxysmal dyskinesia syndromes, and those included in the DYT-designation system are shown in Table 1. In addition, five loci have been identified in single families (primary dystonia: DYT13, 17, 21, and paroxysmal dyskinesia: DYT19, 20), for which the genes have not been found. It is important to be aware, however, that there are several other inherited diseases with known genetic defects that may be clinically dominated by dystonia (with or without parkinsonism, ataxia or other cerebellar signs, myoclonus or other neurological or systemic signs), but are not included in the DYT-designation system. Examples include six disorders of dopamine synthesis (13) in addition to the DYT5a and DYT5b variants of levodopa-responsive dystonia-parkinsonism, among them sepiapterin-reductase deficiency (see paper by Koht JA et al. in this supplement). Other examples are Wilson's disease, panthothenate-kinase-associated neurodegeneration and Lesch-Nyhan's disease, just to name a few.

Although the estimated frequency of DYT1-dystonia is only 1/160000 worldwide, it is the most common form of early-onset primary/isolated dystonia (14). Nearly all cases carry the same mutation, a recurrent GAG deletion in exon 5 of the TOR1A (TorsinA) gene (7), inherited as an AD trait. But clinical dystonia develops in only 20–30% of mutation carriers, and this low penetrance is associated with the presence of the p.D216H polymorphism (15). In the typical DYT1-phenotype, dystonia starts in a limb during childhood and often spreads within a few years to the other limbs and trunk to become generalized, with the cranial-cervical region usually spared. Interestingly, the dystonia may, however, remain segmental or be purely focal and show adult onset (16), and clinical manifestations can show a variable phenotype within the same family (17, 18). Mutant TorsinA has been found to be abnormally located within cell compartments and to exhibit aberrant interaction with other proteins. The results are thought to be synaptic vesicle recycling defects and altered development of neuronal connections (9).

In contrast to DYT1-dystonia, DYT6-dystonia is characterized by onset in cranial-cervical and laryngeal areas, but also tends to generalize and most often has a juvenile onset. Penetrance is about 60%. Mutations in the THAP1 (thanatos-associated-protein-1) gene were initially identified in Amish–Mennonite families (12), but by 2011, about 60 familial and sporadic cases had been reported worldwide (19). Concomitantly, a more

Table 1 Dystonia syndromes with known gene mutations included in the DYT designation system

Subgroup	DYT no.	Inheritance pattern	Clinical description	Chromosome	Mutated gene
Primary/Isolated dystonia	DYT1	AD	EO, extremities > Frequent generalization	9q34	TOR1A
	DYT4	AD	YO, larynx > Occasional generalization	19p.13.12-13	TUBB4a
	DYT6	AD	YO/AO > Gen./Seg. Larynx	8p11.21	THAP1
	DYT23	AD	AO, Cervical dystonia (CD)	9q34	CIZ1
	DYT24	AD	AO, Tremulous CD, +/− brachial, larynx	11p14.2	ANO3
	DYT25	AD	AO, CD, +/− face, larynx, legs	18p11	GNAL
Dystonia-Plus/Dystonia combined with other movement disorders	DYT5a	AD	Dopa-responsive dystonia	14q22.1-2	GTPCH1
	DYT5b	AR	Dopa-responsive dystonia	11p15.5	TH
	DYT11	AD	Myoclonus-dystonia	7p21.3	SGCE
	DYT12	AD	Rapid-onset dystonia-parkinsonism	19q13.2	ATP1A3
	DYT16	AR	Early-onset dystonia-parkinsonism	2q31.2	PRKRA
	DYT3	X-linked	Dystonia-parkinsonism	Xq13.1	TAF1
Paroxysmal (P) Dyskinetic syndromes	DYT8	AD	P Non-Kinesiogenic Dyskinesia	2q35	MR1
	DYT9/	AD	P Dyskinesia w/episodic ataxia + spasticity	1p34.2	SLC2A1
	DYT18	AD	P Exercise-induced Dyskinesia	1p34.2	SLC2A1
	DYT10	AD	P Kinesiogenic Dyskinesia (PKD)	16p11.2	PRRT2

AD, autosomal dominant; AR, autosomal recessive; EO, early onset; YO, young onset; AO, adult onset.

heterogenic phenotype was described, including onset in adults or in a limb, and lack of generalization (20). In sharp contrast to DYT1-dystonia, almost every case of DYT6-dystonia bears a unique mutation, requiring direct sequencing of the entire THAP1 coding region for molecular diagnosis.

Recently, through the use of whole-exome sequencing in combination with linkage analysis, four new genes have been found that are strongly implicated as causative of primary/isolated segmental/focal dystonia, mainly affecting the upper body, particularly the cervical and laryngeal region, and with very little tendency to generalize. Mutations in the TUBB4a gene were found in a large English–Australian family that has the fully penetrant adductor spasmodic dysphonia (DYT4-dystonia) with juvenile to adult onset, occasional generalization, and sometimes alcohol benefit (21, 22). Three different genes have been found in families with mainly adolescent to adult onset of cervical focal or segmental dystonia (involvement of larynx or arm, Table 1). First, a missense mutation in the CIZ1 gene was reported in a large family with adult onset CD, but in only 2 of 308 sporadic cases (23). The protein encoded by CIZ1 is a nuclear protein involved in DNA synthesis and cell-cycle control. Mutations in a second gene, ANO3, were identified as the cause of an autosomal dominant cranio-cervical-brachial dystonia (24), and five novel variants were found when the whole gene was screened in a cohort of 188 individuals with cervical dystonia. Interestingly, patients with mutations in ANO3 often had dystonic tremor, affecting the head, voice or upper limbs, and some patients with isolated upper limb tremor had been misdiagnosed as having essential tremor. Age at onset ranged from early childhood to 40 years of age (24). As with CIZ1, the dystonia never became generalized. ANO3 is most highly expressed in the striatum and is thought to encode a calcium-activated chloride channel (24) that is believed to be involved in modulating neuronal excitability. Finally, in 2013, two groups reported that mutations in the GNAL gene could cause adult onset primary dystonia (25, 26) with a strong predilection for the cervical region. Cervical dystonia was observed in 93% and spread to other sites in half of cases (25). According to the report of the first group, six of 39 families screened (15%) had mutations in this gene, but the second group found only three patients with mutations among 760 persons screened (26). GNAL encodes the stimulatory subunit of a G-protein that is involved in dopamine signaling (27) and is expressed in medium spiny neurons in the striatum. Here, it is thought to link D1 and adenosine A2 receptors, and thus may interfere with postsynaptic dopamine and/or adenosine signaling.

A comprehensive account of the pathophysiology of dystonia is far beyond the scope of this review. A general overview of the mechanisms that have been implicated is illustrated in Fig. 1. As can be seen, the pathophysiological picture appears multifaceted and impacts a broad spectrum of neurophysiological processes. Extensive structural and functional imaging studies have been performed on manifesting and non-manifesting carriers of DYT1- and DYT6-mutations, and were recently reviewed. The results suggest that primary dystonia can be viewed as a neurodevelopmental circuit disorder, involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways (28). Aberrant plasticity in various forms of primary dystonia has been reported from several groups. One of them recently reported an interesting comparison between primary and secondary dystonia regarding this and found normal motor cortex plasticity in secondary dystonia as opposed to primary dystonia (29), thus demonstrating that abnormally enhanced cortical plasticity is not required for clinical expression of dystonia.

Treatment

Firstly, it is important not to overlook treatable causes of dystonia, such as monoamine transmitter deficiency disorders and Wilson's disease. In the various subtypes of monoamine transmitter

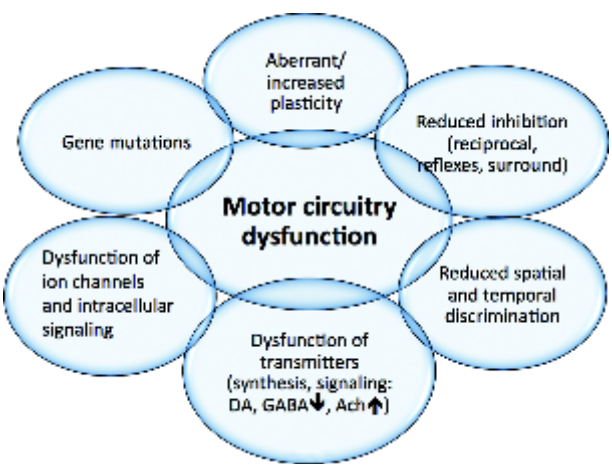

Figure 1. Schematic illustration of factors implicated in the pathogenesis of dystonia. (The figure does not intend to explain the possible relationship between the different factors shown).

deficiency disorders, therapeutic agents may now not only include levodopa and dopamine agonists, but also tetrahydrobiopterin or 5-hydroxytryptophan (13). Copper-chelating agents such as penicillamine and trientine remain to be the most important treatment options in Wilson's disease. In paroxysmal exercise-induced dyskinesia caused by Glut-1-deficiency, a ketogenic diet is a therapeutic option in addition to acetazolamide, whereas in paroxysmal kinesiogenic dyskinesia, carbamazepine can be effective.

The two modalities that revolutionized the symptomatic treatment for dystonia, namely injections of botulinum neurotoxin (BoNT) and deep brain stimulation (DBS), were introduced about 25 and 15 years ago, respectively, but continue to be refined by clinicians and researchers to improve their efficacy and safety. Fortunately, they are also becoming more and more available for people suffering from dystonia worldwide. However, it is a fact that in many less developed countries, neither of these very effective treatments to relieve dystonia is yet available, at least not for the poorer segment of the population.

Four BoNT products are now available for use in humans: three BoNTA products (ona-BoNT/Botox®; Allergan, Irvine, CA, USA, abo-BoNT/Dysport®; Ipsen, Paris, France, and inco-BoNT Xeomin®; Merz Pharma, Frankfurt, Germany) and one BoNTB product (rima-BoNT/Neurobloc®; Eisai, Tokyo, Japan). All have cervical dystonia (CD) as indication, and the three BoNTAs also have blepharospasm as indication. In inco-BoNTA, the complexing proteins that are part of the natural BoNTs were removed to reduce the protein load of the injected product and thus to reduce the risk of antibody formation. A recent review of the immunogenicity of the four BoNTA products (30) concluded that immunogenicity is at a low and comparable level (about 1–3%) for all three commercially available BoNTA products, whereas it is higher for BoNTB, and that no published clinical data support the hypothesis that non-toxic accessory proteins (NAPs) increase the immune response. The shortcomings of many of the reviewed studies are, however, that they include relatively few injection cycles and some of them also too few patients to be conclusive. In a study of 37 CD patients, who had developed secondary non-response and neutralizing antibodies (NABTs) after treatment with abo- or ona-BoNTA, and who were switched to treatment with inco-BoNTA (200 Mouse Units every 3 months or even higher doses after 1 year), NABTs declined well below the initial titer in 31 patients (84%), and in 23 patients, (62%) test assay results were even negative or below the lower detection limit, after 48 months of inco-BoNTA treatment (31). The slopes of decline in NABTs were similar to a control group of 24 patients in whom BoNTA treatment was completely stopped. If confirmed by other and larger studies, this may indicate that inco-BoNTA has a clinically significant lower immunogenicity than abo- or ona-BoNTA and that dystonia patients that develop NABTs to either of the latter should be switched to inco-BoNTA rather than to rima-BoNTB. So far, all the BoNT-producing companies still recommend no less than 12 weeks interval between treatments, but this may change if any of the companies provide studies showing that more frequent injections of their drug do not increase immunogenicity. Long-term treatment with BoNT in CD is associated with a good health-related quality of life in the majority of patients (32, 33), and the proportion of patients that experiences this might be even higher if shorter intervals between treatments could be recommended. EMG or ultrasound guidance can also improve efficacy of BoNT injections in selected cases, particularly in hand dystonias.

Deep brain stimulation (DBS) in the postero-ventro-lateral part of the internal globus pallidus (GPi-DBS) has been established as an effective treatment for primary generalized dystonia, through the pioneer open Montpellier study (34), the first single-blinded French study (35), and the randomized, sham-stimulation-controlled German study, in which our center participated (36). This study showed significant improvement in quality of life already after 3–6 months of GPi-DBS (36, 37). All of these groups have during recent years also published long-term outcomes in their patients. At 3 years follow-up, mean improvement in the motor part of the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) was 58% in the French study (38) and 61% in the German study (39), thus a further significant improvement compared with results at the 6 months follow-up. In the German study, 5 years follow-up data were also available and showed a sustained efficacy, both in the generalized and segmental dystonia group (39). The Montpellier group have observed worsening of dystonia after many years of very effective bilateral GPi-stimulation in some of their primary generalized dystonia patients and have shown that implanting a second pair of electrodes (on average 4.5 years after the first pair) can improve outcome in some of these patients (40).

Several open and a few blindedly evaluated patient series of GPi-DBS in primary focal or

segmental cervical dystonia have shown that this treatment can be very effective also in this dystonia subgroup. In our own patient series (41), median improvement in the severity score of the TWSTRS (Toronto Western Spasmodic Torticollis Rating Scale) showed a median improvement of 70% at median follow-up of 21 (12–48) months ($n = 8$), and the Toronto group (42) have recently reported blinded evaluations at mean 7.7 years showing a 54% (SD 27%) improvement ($n = 10$). Thus, severe and medically intractable primary CD should be evaluated for GPi-DBS.

GPi-DBS has also been used with good benefit in myoclonus–dystonia and in patients with drug (neuroleptic)-induced tardive dystonia. Functionally important benefit from GPi-DBS has also been observed in other forms of secondary dystonia, such as dyskinetic cerebral palsy (43), PKAN, Lesch–Nyhan syndrome, and in some other secondary dystonia syndromes. Beneficial effect for dystonia has also been reported for DBS in other targets, such as the subthalamic nucleus, the zona incerta (for dystonic tremor), and ventral thalamic nuclei, such as the ventral-oralis nuclei for task-specific hand dystonia. These targets have much less robust scientific basis than GPi-DBS in dystonia, however.

Unfortunately, no progress has been made in the oral medication of dystonia during the last decades. It is hoped that current and future insights into pathogenetic and pathophysiological mechanisms will lead to more progress in this area within the near future, as well-tolerated oral medications that provide a significant benefit to dystonia patients are desperately needed.

Future dystonia research should aim to define the causal links between underlying genetic defects and the different pathophysiological processes implicated in dystonia, with the ultimate aim to develop treatments that target selectively the most pivotal mechanisms in each case. In current clinical practice, however, diagnosing dystonia and selecting the right treatment still relies heavily on the clinical knowledge and skills of the doctor who encounter the patient. Although the treatment options for most patients are still symptomatic, they can be very effective in experienced hands, and thanks to this, many patients can enjoy a good quality of life living with their dystonia.

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References

1. Oppenheim H. About a rare spasm disease of childhood and young age (Dysbasia lordotica progressiva, dystonia musculorum deformans). Neurologische Centralblatt 1911;**30**:1090–107.
2. Duchenne GBA. L'électrisation localisée, 2nd edn. Paris: J.-B. Baillière, 1861;298.
3. Gowers WR. A manual of diseases of the nervous system, 2nd edn. London: Churchill, 1888.
4. Marsden CD. The problem of adult-onset idiopathic torsion dystonia and other isolated dyskinesias in adult life (including blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis, or axial dystonias. In: Eldridge R, Fahn S, eds. Advances in neurology, Vol. 14. New York: Raven Press, 1976;259–76.
5. Fahn S, Marsden CD, Calne DB. Classification and investigation of dystonia. In: CD Marsden, S Fahn, eds. Movement disorders 2. London: Butterworths, 1987; 332–58.
6. Albanese A, Bhatia K, Bressmann SB et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;**28**:863–73.
7. Ozelius L, Hewett JW, Page C et al. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat Genet 1997;**17**:40–8.
8. Carbon M, Su S, Dhawan V, Raymond D, Bressman S, Eidelberg D. Regional metabolism in primary torsion dystonia: effects of penetrance and genotype. Neurology 2004;**62**:1384–90.
9. Granata A, Warner TT. The role of torsinA in dystonia. Eur J Neurol 2010;**17** (Suppl. 1):81–7.
10. Petrucci S, Valente EM. Genetic issues in the diagnosis of dystonias. Front Neurol 2013;**4**:34.
11. Petrucci S, Valente EM. Novel genes and novel pathogenetic mechanisms in adult-onset primary dystonia. Mov Disord 2013;**28**:440.
12. Fuchs T, Gavarini S, Saunders-Pullman R et al. Mutations in the THAP1gene are responsible for DYT6 primary torsion dystonia. Nat Genet 2009;**41**:286–8.
13. Kurian MA, Gissen P, Smith M, Heales SJR, Clayton PT. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. Lancet Neurol 2011;**10**:721–33.
14. Bressman SB, Sabatti C, Raymond D et al. The DYT1 phenotype and guidelines for diagnostic testing. Neurology 2000;**54**:1746–52.
15. Kamm C, Fischer H, Garavaglia B et al. Susceptibility to DYT1 dystonia in European patients is modified by the D216H polymorphism. Neurology 2008;**70**:2261–2.
16. Ozelius LJ, Bressman SB. Genetic and clinical features of primary torsion dystonia. Neurobiol Dis 2011;**42**:127–35.

17. Opal P, Tintner R, Jankovic J et al. Intrafamilial phenotypic variability of the DYT1 dystonia: from asymptomatic TOR1A gene carrier status to dystonic storm. Mov Disord 2002;**17**:339–45.
18. Edwards M, Wood N, Bhatia K. Unusual phenotypes in DYT1 dystonia: a report of five cases and a review of the literature. Mov Disord 2003;**18**:706–11.
19. Blanchard A, Ea V, Roubertie A et al. DYT6 dystonia: review of the literature and creation of the UMD Locus-Specific Database (LSDB) for mutations in the THAP1 gene. Hum Mutat 2011;**32**:1213–24.
20. LeDoux MS, Xiao J, Rudzinska M et al. Genotype-phenotype correlations in THAP1 dystonia: molecular foundations and description of new cases. Parkinsonism Relat Disord 2012;**18**:414–25.
21. Hersheson J, Mencacci NE, Davis M et al. Mutations in the autoregulatory domain of β-tubulin 4a cause hereditary dystonia. Ann Neurol 2013;**73**:546–553
22. Lohmann K, Wilcox RA, Winkler S et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the *TUBB4* gene. Ann Neurol 2012;**73**:537–45.
23. Xiao J, Uitti RJ, Zhao Y et al. Mutations in CIZ1 cause adult onset primary cervical dystonia. Ann Neurol 2012;**71**:458–69.
24. Charlesworth G, Plagnol V, Holmstrom KM et al. Mutations in ANO3 cause dominant cranio cervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet 2012;**91**:1041–50.
25. Fuchs T, Saunders-Pullman R, Masuho I et al. Mutations in GNAL cause primary torsion dystonia. Nat Genet 2013;**45**:88–92.
26. Vemula SR, Puschmann A, Xiao J et al. Role of Galpha (olf) in familial and sporadic adult-onset primary dystonia. Hum Mol Genet 2013;**22**:2510–9.
27. Zhuang X, Belluscio L, Hen R. G(olf)alpha mediates dopamine D1 receptor signaling. J Neurosci 2000;**20**: RC91.
28. Niethammer M, Carbon M, Argyelan M, Eidelberg D. Hereditary dystonia as a neurodevelopmental circuit disorder: evidence from neuroimaging. Neurobiol Dis 2011;**42**:202–9.
29. Kojovic M, Pareés I, Kassavetis P et al. Secondary and primary dystonia: pathophysiological differences. Brain 2013;**136**:2038–49.
30. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. J Neural Transm 2013;**120**:275–90.
31. Hefter H, Hartmann C, Kahlen U, Moll M, Bigalke H. Prospective analysis of neutralising antibody titres in secondary non-responders under continuous treatment with a botulinumtoxin type A preparation free of complexing proteins—a single cohort 4-year follow-up study. BMJ Open 2012;**2**:1–7.
32. Skogseid IM, Malt UF, Røislien J, Kerty E. Determinants and status of quality of life after long-term botulinum toxin therapy for cervical dystonia. Eur J Neurol 2007;**14**:1129–37.
33. Zetterberg L, Aquilonius SM, Lindmark B. Impact of dystonia on quality of life and health in a Swedish population. Acta Neurol Scand 2009;**119**:376–82.
34. Coubes P, Cif L, El Fertit H et al. Electrical stimulation of the internal globus pallidus in generalized dystonia: long-term results. J Neurosurg 2004;**101**:189–94.
35. Vidailhet M, Vercueil L, Houeto JL et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 2005;**352**:459–67.
36. Kupsch A, Benecke R, Mueller J et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;**355**:1978–90.
37. Skogseid IM. Pallidal deep brain stimulation is effective, and improves quality of life in primary segmental and generalized dystonia. Acta Neurol Scand Suppl 2008;**188**:51–5.
38. Vidailhet M, Vercueil L, Houeto JL et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. Lancet Neurol 2007;**6**:223–9.
39. Volkmann J, Wolters A, Kupsch A et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012;**11**:1029–38.
40. Cif L, Gonzalez-Martinez V, Vasques X et al. Staged implantation of multiple electrodes in the internal globus pallidus in the treatment of primary generalized dystonia. J Neurosurg 2012;**116**:1144–52.
41. Skogseid IM, Ramm-Pettersen J, Volkmann J, Kerty E, Dietrichs E, Røste GK. Good long-term efficacy of pallidal stimulation in cervical dystonia: a prospective, observer-blinded study. Eur J Neurol 2012;**19**:610–5.
42. Walsh RA, Sidiropoulos C, Lozano AM et al. Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years. Brain 2013;**136**:761–9.
43. Vidailhet M, Yelnik J, Lagrange C et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. Lancet Neurol 2009;**8**:709–17.