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Primary dystonia: molecules and mechanisms

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Abstract

Primary dystonia is characterized by abnormal, involuntary twisting and turning movements that reflect impaired motor system function. The dystonic brain seems normal, in that it contains no overt lesions or evidence of neurodegeneration, but functional brain imaging has uncovered abnormalities involving the cortex, striatum and cerebellum, and diffusion tensor imaging suggests the presence of microstructural defects in white matter tracts of the cerebellothalamocortical circuit. Clinical electrophysiological studies show that the dystonic CNS exhibits hyperactive plasticity—perhaps related to deficient inhibitory neurotransmission—in a range of brain structures, as well as the spinal cord. Dystonia is, therefore, best conceptualized as a motor circuit disorder, rather than an abnormalcy of a particular brain structure. None of the aforementioned abnormalities can be strictly causal, as they are not limited to regions of the CNS subserving clinically affected body parts, and are found in seemingly healthy patients with dystonia-related mutations. The study of dystonia-related genes will, hopefully, help researchers to unravel the chain of events from molecular to cellular to system abnormalities. *DYT1* mutations, for example, cause abnormalities within the endoplasmic reticulum–nuclear envelope endomembrane system. Other dystonia-related gene products traffic through the endoplasmic reticulum, suggesting a potential cell biological theme underlying primary dystonia.

Introduction

Primary dystonia is a neurological disorder characterized by disabling, abnormal, involuntary movements, which can have devastating consequences for the patient. Interestingly, primary dystonia exhibits features of both neurological and psychiatric disease. Like psychiatric disease, the condition is characterized by abnormal functioning of a structurally normal-appearing brain, and can disrupt processes of normal development or neuronal plasticity. Like other neurological diseases, primary dystonia is a motor system disorder that can be caused by several different single-gene mutations. These features suggest that an improved understanding of this illness could provide valuable insights into clinically important aspects of nervous system function.

The CNS abnormalcy underlying dystonia is poorly understood, creating substantial challenges for disease classification and scientific study. Here, after reviewing essential clinical aspects of primary dystonia, we reconsider the classification of primary dystonia from a basic research—as opposed to a clinical—perspective, and discuss why different

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schemes are required depending on the needs of the particular investigator. We then consider the systems-level and electrophysiological abnormalities that have been detected in primary dystonia, highlighting the challenges and potential pitfalls that exist in trying to synthesize these studies into an integrated and coherent picture. We largely limit our discussion to studies of patients with primary dystonia, since the presence of additional neurological abnormalities in patients with secondary dystonia further complicates interpretation. We then turn to an overview of the inherited forms of primary dystonia, summarizing the cell biological data that are emerging from the study of dystonia-related genes. In this section, we highlight instances where molecular findings can provide insight into the identified electrophysiological abnormalities, and speculate about the potential functional connections between dystonia-related genes.

Clinical features and classification

Motor features

Dystonia is a neurological sign characterized by involuntary, prolonged twisting and turning movements that are frequently stereotyped and repetitive, and produce characteristic abnormal postures (Figure 1). Dystonic movements manifest in a wide variety of ways, and can affect practically all voluntary muscles. Prolonged (lasting up to many seconds) co-contraction of agonist and antagonist muscles causes the affected body part to twist. The stereotypic patterns of movement arise from repeated involvement of the same groups of muscles, and additional muscles not normally recruited for a motor task are often engaged. Strikingly, dystonia can be task specific, occurring only during particular actions such as writing. Dystonic movements are also frequently exacerbated by voluntary action—even by unaffected body parts (a phenomenon known as ‘overflow’)—and, when severe, can lead to fixed abnormal postures at rest. Early in the course of the illness, dystonic movements can often be ameliorated through the use of a sensory trick, or ‘geste antagoniste’, whereby touching a nearby body part reduces the dystonic movements.

Key points

- Primary dystonia is defined as an illness in which dystonic movements occur as an isolated sign in the absence of an identifiable neuropathological lesions or exogenous cause
- Secondary dystonia refers to dystonic movements that result from a lesion to the motor system, and is typically accompanied by additional neurological signs
- Dystonia seems to be a motor system or motor circuit disorder rather than representing an abnormality of a particular motor structure
- Abnormalities of inhibition, sensory processing and plasticity have been identified in patients with dystonia, but might not be sufficient for the development of dystonic movements
- The genetic basis of many inherited forms of dystonia is now known, and the study of dystonia-related genes should provide important mechanistic insights leading to novel therapeutic strategies

Primary versus secondary dystonia

Dystonic movements can be symptomatic of virtually any pathological process that affects the motor system, particularly the basal ganglia. Movements that are caused by a known motor system insult, such as trauma, neurodegenerative disease, cerebral palsy or exposure to dopamine receptor antagonists, are termed ‘secondary dystonia’. Primary dystonia, by

contrast, is classified clinically as a disease in which dystonic movements occur as an isolated symptom (although some patients might have an associated tremor), in the absence of recognizable brain damage or an exogenous cause. The term ‘dystonia’, therefore, refers to both a neurological symptom and a specific group of diseases.

Primary dystonia is typically categorized according to age at onset. This feature is tightly correlated with the body part initially affected, as well as the underlying cause and likelihood of spread. Early-onset (childhood) dystonia is typically dominantly inherited, often begins in the arm or leg, and can spread widely, resulting in severe motor disability. By contrast, late-onset (adult) dystonia is usually idiopathic, begins in the face or neck, and is less likely to spread to surrounding body parts. Whether the genetic and idiopathic forms of primary dystonia share common cellular or neural system abnormalities is unknown, but recent reports suggest that polymorphisms of the *DYT1* locus, the site of the gene mutated in the most common cause of childhood-onset dystonia, can predispose patients to—or alter the severity of—adult-onset primary dystonia.^{1,2} The distinction between primary and secondary dystonia is of great clinical utility because different forms of dystonia require distinct medication regimens.

Like primary dystonia, dopa-responsive dystonia and myoclonus dystonia feature dystonic movements and are not associated with neuropathological lesions, but are categorized as ‘dystonia-plus’ diseases rather than primary dystonia because of the presence of additional clinical signs.³ Given that this clinical classification scheme might separate diseases that share basic neurobiological mechanisms, we propose a scientific definition of primary dystonia that includes all diseases that cause dystonia without producing neuropathological lesions, including the dystonia-plus diseases (Table 1). We note, however, that classification systems based on the presence or absence of neuropathological lesions are likely to evolve as rapidly advancing brain imaging technologies enable the visualization of subtle brain abnormalities. Eidelberg and colleagues, for example, have reported diffusion tensor imaging (DTI) signals that are consistent with microstructural abnormalities of cerebellothalamocortical white matter tracts in patients harboring the *DYT1* or *DYT6* primary dystonia mutations (see below).⁴ These issues highlight the critical need for a better understanding of the underlying molecular and cellular mechanisms underlying different forms of dystonia. Such knowledge should yield a more durable classification system that will benefit researchers studying basic mechanisms of dystonia and clinicians testing novel therapeutics (for example, by enabling patients with mechanistically related dystonias to be grouped together in clinical trials).

Motor circuit abnormalities

Secondary dystonia is most commonly associated with lesions of the putamen or globus pallidus, so a common assumption prevails that striatal dysfunction is the principal cause of primary dystonia. Dystonia can, however, also result from lesions of the caudate, thalamus and brainstem (and possibly the cerebellum and frontal or parietal cortex). In fact, in primary dystonia, abnormal CNS function has been documented in nearly every region of the CNS that is relevant for motor control and sensorimotor integration, including the spinal cord, brainstem, cerebellum, basal ganglia and cerebral cortex. Physiological abnormalities can even be present in brain regions that do not correspond to the involved body parts (for example, abnormalities in the ipsilateral cortex, or spinal cord reflex abnormalities in patients with cervical dystonia). The fact that lesions of diverse brain structures can cause secondary dystonia, and the finding that physiological abnormalities in multiple areas of the nervous system are associated with primary dystonia, support the idea that dystonia should be thought of as a motor system or motor circuit disorder, rather than as an abnormality of a particular motor structure.

The characteristics of dystonic movements have been used to formulate hypotheses about the nature of the neural processing abnormalities that cause dystonia. The fact that dystonia can be highly task specific has led some to suggest that specific motor programs are disrupted, although this concept remains incompletely understood. Dystonia does not typically spread to body parts corresponding to the well-known somatotopic organization of the nervous system; that is, it does not typically spread from leg to arm to face. In fact, it is not uncommon for dystonia to spread from one limb to the contralateral limb, leading to so-called bibrachial (arms) or bicrural (legs) patterns of involvement. These patterns of spread and the task specificity that can characterize dystonic movements hint at an undefined functional organization of the motor system that could be affected by the disease. Others have hypothesized that co-contraction of agonists and antagonists and spread of activation to muscles not normally involved in a task raise the possibility that the basal ganglia are normally involved in the selection of competing movement representations, a notion that is consistent with some aspects of basal ganglia organization.⁵

The circuit abnormalities underlying dystonia have been explored using widely varying techniques, including clinical electrophysiological methods (for example, transcranial magnetic stimulation [TMS]), PET and DTI. Two issues confound the interpretation of these studies. First, these methods measure different properties of neural circuits and are performed in a variety of clinical settings, making it difficult to compare the various studies and reconcile them into an integrated view of circuit dysfunction. Second, distinguishing the network abnormalities that cause dystonia from compensatory changes or internal representations of persistent movement or posture is a challenging task. A related complication that arises when studying secondary dystonia is that of determining whether the physiological alterations identified are relevant to dystonia or to the associated neurological abnormalities that exist in these patients.

Eidelberg and colleagues have begun to unravel some of these issues in a series of studies on patients with defined genetic forms of primary dystonia.^{6–9} They took advantage of the fact that the dominantly inherited mutation that causes DYT1 dystonia (Table 1 and discussed below) is only ~30% penetrant, allowing the effects of the mutation to be compared in patients with and without dystonic movements. By performing ¹⁸F-fluorodeoxyglucose PET imaging on non-manifesting *DYT1* mutation carriers, as well as on patients with clinically manifesting DYT1 dystonia, both while awake and during sleep (when no dystonic movements are evident), the investigators identified two independent regional metabolic covariance patterns, termed ‘movement-related’ and ‘movement-free’. The movement-related pattern was characterized by increased metabolic activity in the midbrain, cerebellum and thalamus. This pattern of activity decreased with sleep and was not present in non-manifesting *DYT1* mutation carriers. By contrast, the movement-free pattern was characterized by elevated metabolic activity in the lentiform nuclei (putamen and globus pallidus), supplementary motor area and cerebellum, and was present in the brains of both manifesting and non-manifesting *DYT1* mutation carriers, including during sleep in the affected patients. These findings indicate the existence of an abnormal motor circuit, represented by the movement-free pattern that is tightly linked to the disease mutation, regardless of the penetrance of dystonia. Interestingly, the abnormalities that are common to manifesting and non-manifesting patients could explain reports that non-manifesting carriers show impairments in motor sequence learning¹⁰ or the ability to envision rotation of body parts.¹¹

One cause of the *DYT1*-linked aberrant metabolic activity could be abnormalities of white matter micro-structure (that is, an abnormal number, density or morphology of white matter axons). Through use of probabilistic tractography, an imaging method based on DTI scans, Eidelberg and colleagues reported abnormalities of the cerebellothalamocortical axon tracts

in manifesting and non-manifesting carriers of the *DYT1* or *DYT6* mutations.⁴ All individuals with dystonia-linked genotypes exhibited reductions of the cerebellothalamic tract, but only non-manifesting patients had additional reductions of the thalamocortical tract. These findings give rise to an updated view of the abnormal motor circuitry underlying primary dystonia (Figure 2).

Mechanisms of brain dysfunction

Ongoing research has identified several electro-physiological, neurochemical and cell biological phenotypes that are characteristic of the dystonic brain. Substantial support exists for each of these abnormalities, but their interrelationships, and the nature of the higher-order circuit disruption to which they contribute, remain unclear. For example, studies of patients with dystonia consistently document deficient inhibition and abnormal plasticity, but no direct experimental evidence exists to clearly establish a relationship between these processes, or to indicate which of the neurochemical or cell biological features of the disease underlie these abnormalities. The lack of an animal model that exhibits dystonic movements and bears a clear etiological relationship to a human form of the disease has precluded the *in vivo* studies that would be needed to address such issues in a mechanistic fashion.

The discovery of genetic mutations underlying inherited forms of dystonia (Table 1) is a relatively recent development that holds great promise for contributing to our understanding of the pathogenesis of primary dystonia. These discoveries have already provided some exciting insights into the molecular basis of primary dystonia, although no convincing relationship between the different dystonia-related genes has been demonstrated. Consequently, no common molecular pathway that is critical for development of the disease has yet emerged. Nevertheless, the identification of these dystonia-related genes has provided some interesting clues into potential relationships between different forms of dystonia, and the cell biological mechanisms that could underlie the abnormal CNS function or development that is believed to cause primary dystonia. For example, torsin-1A (encoded by the *TOR1A* gene at the *DYT1* locus) and ϵ -sarcoglycan (encoded by *SGCE* at the *DYT11* locus) may be involved in the proper trafficking and localization of neuronal membrane proteins, and Na⁺-K⁺-ATPase (α 3 subunit encoded by *ATP1A3* at the *DYT12* locus) and GTP cyclohydrolase 1 (encoded by *GCH1* at the *DYT5* locus) are clearly essential for normal neurotransmission. Moreover, these proteins could all plausibly contribute to the electrophysiological and neurochemical abnormalities identified in primary dystonia.

Neurophysiological mechanisms

Beradelli and colleagues have reviewed in detail the neurophysiological abnormalities associated with dystonia.¹² Here, we will summarize the main themes, highlight new findings, and indicate areas of convergence with neurochemical and molecular data. A broad consensus exists in the literature that deficient inhibition is a general feature of the dystonic CNS. Deficient inhibition has been demonstrated in the cortex, brain-stem and spinal cord of patients with dystonia, and the co-contraction of agonist and antagonist muscles that is a hallmark of dystonia is accompanied by loss of reciprocal spinal inhibition between opposing muscles. TMS studies demonstrate increased excitation in the primary motor cortex in patients with dystonia, a finding that is believed to reflect deficient cortical inhibition. In 'double-pulse' TMS studies, a small electrical subthreshold 'conditioning' pulse precedes a suprathreshold pulse over the motor cortex. Normally, this 'prepulse' suppresses the electromyographic response that would otherwise have been evoked by the suprathreshold shock and detected in the corresponding muscle. In patients with dystonia, however, the electromyographic response is not suppressed to a normal extent. This abnormality is thought to reflect cortical dysfunction, as the prepulse is not strong enough to activate subcortical structures. γ -Aminobutyric acid (GABA) is the primary inhibitory

neurotransmitter in the CNS, so many have argued that this deficient inhibition is attributable to malfunctioning cortical GABA interneurons. Moreover, as discussed below, neurochemical and molecular studies provide additional support for the potential importance of deficient inhibition in dystonia (see, for example, sections on GABA and DYT11 dystonia). Studies in other types of dystonia (for example, blepharospasm) show reduced inhibitory function with respect to the blink or perioral reflex^{13,14} that are believed to reflect deficient brainstem inhibition, and assessment of subcortical regions by means of functional imaging and PET indicates that dystonia is associated with impaired inhibition in both cortical and subcortical regions.^{15–18} Importantly, deficient inhibition is not limited to CNS regions subserving clinically affected body parts (see, for example Chen *et al.*¹⁹ and Deuschlet *et al.*²⁰), and is, therefore, not a ‘cause’ of dystonia *per se*. Rather, deficient inhibition seems to be a widespread feature of the dystonic CNS, and could be a necessary but not sufficient feature of disease pathogenesis (a so-called ‘endophenotype’ of the disease).

Abnormalities of sensory processing represent another endophenotype of the dystonic brain.^{21–22} The idea that sensory dysfunction contributes to dystonia comes from longstanding observations that trauma to a limb or the neck can cause dystonia in these body parts, and that a sensory trick (discussed in section on clinical phenomenology above) can suppress the symptoms. Several reports document that patients with dystonia show marked impairments in discriminating between two close-interval sensory stimuli,^{22–24} a phenomenon known as deficient temporal discrimination threshold (TDT). Patients with blepharospasm show TDT impairments for stimuli presented on their face or hands, and *DYT1* mutation carriers have abnormal TDT regardless of the presence or absence of dystonic symptoms. The primary somatosensory cortex, which processes temporal discrimination, seems to be the anatomical region responsible for the observed TDT deficiency in dystonic patients.²⁵ Deficient cortical inhibitory mechanisms could also underlie this form of sensory dysfunction, but this issue requires additional study.

Deficient inhibition and abnormal sensory processing could contribute to the abnormal plasticity that has been documented in the CNS of patients with dystonia. A large body of literature details how, through sensorimotor feedback loops, sensory input normally leads to functional modifications throughout the motor system. Altered perception of sensory input would, therefore, be expected to contribute to motor system reorganization as a compensatory mechanism, ultimately resulting in abnormal motor output. Studies employing numerous paradigms have repeatedly documented abnormal CNS plasticity in patients with dystonia (reviewed by Quartarone *et al.*²⁶). Interestingly, patients with dystonia can require weeks to respond to deep brain stimulation therapy, in contrast to the near-immediate response of patients with Parkinson disease. Such observations further support a key concept addressed earlier in this review, namely, that dystonia is probably not driven by the activity of a single nucleus, but, rather, might arise from a broadly dysfunctional motor system that requires time to reorganize and accommodate changes occurring in multiple areas along the motor circuit. The best proof-of-concept experiment demonstrating how sensory input can both alter motor system organization and drive abnormal motor output are the owl monkey studies of Byl and colleagues.²⁷ This group showed that the frequent simultaneous stimulation of multiple digits in one hand, experienced through performance of highly repetitive and stressful hand movements, led not only to abnormal hand movements reminiscent of dystonia, but also to degradation of the receptive fields corresponding to the hands in the primary sensory cortex. Only those monkeys that developed abnormal movements showed this degraded cortical representation, potentially linking these phenomena. Whether and how such cortical changes propagate to other brain areas, such as the basal ganglia, and how they affect the interplay between critical motor areas, will need to be addressed in the future.

Neurochemical abnormalities

γ -Aminobutyric acid—In addition to its general role in CNS inhibition, GABAergic neurotransmission is important in shaping plastic responses of the CNS to somatosensory and other stimuli, including the maintenance and plasticity of cortical receptive fields. GABA is, therefore, the neurotransmitter most plausibly linked to the electrophysiological mechanisms identified in primary dystonia. In 2007, Levy and Hallett used new technology to measure levels of GABA in the cortex and striatum of patients with adult-onset primary dystonia.¹⁸ By means of J-resolved proton multi-metabolite spectroscopy, both contralateral and ipsilateral motor cortices and lentiform nuclei were examined in patients with right-sided, focal, task-specific dystonia. The investigators found decreased GABA levels selectively in cortical and subcortical regions contralateral to the dystonic limb. Potentially consistent with a role for deficient GABAergic activity in primary dystonia, drugs that potentiate GABA neurotransmission, such as benzodiazepines and baclofen, are modestly effective against dystonic movements. Moreover, application of the GABA antagonist bicuculline to the motor cortex of monkeys causes abnormal co-contraction of agonist and antagonist muscle groups during activities requiring fine motor skills, and produces abnormal movements reminiscent of task-specific dystonia.²⁸ Amelioration of dystonic symptoms by GABAergic drugs is, however, by no means complete or universally effective, and abnormalities of dopamine and acetylcholine have also been implicated in dystonia, consistent with the idea that neurochemical defects at multiple points along the motor circuit might be required for dystonia to manifest. Indeed, Levy and Hallett¹⁸ speculated that deficient GABA levels could be consistent with reduced dopaminergic neurotransmission in the putamen, since D₂ dopamine receptors mostly inhibit the GABAergic striatal medium spiny neurons. As we examine dopamine and its role in dystonia, therefore, the fact that these neurotransmitters are part of a plastic network and are both effectors and receptors of change should be borne in mind.

Dopamine—Dopamine is the neurotransmitter most clearly linked to causes of human dystonia. Dystonias related to dopaminergic dysfunction are characterized clinically as forms of secondary dystonia (tardive dystonia) or dystonia-plus (dopa-responsive dystonia). These conditions do, however, feature dystonia in the absence of structural brain lesions, pointing to circuit disorders that could hold clues to the pathogenesis of traditional forms of primary dystonia (see section ‘Primary versus secondary dystonia’ above).

A central role for dopaminergic systems in the maintenance of traditional forms of primary dystonia seems unlikely, as patients with primary dystonia cannot be treated effectively with dopaminergic drugs. By contrast, the onset and maintenance of tardive dystonia and dopa-responsive dystonia are both clearly linked to dopamine. For example, antipsychotic and antiemetic medications that block dopamine receptors (especially D₂ receptors) can cause acute dystonic reactions or tardive dystonia—a permanent form of dystonia. The symptoms of tardive dystonia are blocked by drugs that prevent storage and synthesis of dopamine (for example, reserpine, tetra-benazine or α -methylparatyrosine), demonstrating that dopaminergic systems are required for the maintenance of dystonia in this particular clinical setting. Dystonia also occurs in the context of other dopamine related diseases, such as Parkinson disease, and can be a complication of levodopa therapy for this condition. Dopa-responsive dystonia (DYT5, reviewed in the next section), in which dramatic amelioration of symptoms occurs with the administration of levodopa, further highlights a connection with dopamine.

Multiple imaging studies in patients have identified D₂ receptor abnormalities in patients with primary dystonia. Reduced binding of ¹⁸F-spiperone, a D₂ dopaminergic antagonist, was found in the putamen of patients with primary dystonia,²⁹ and similar findings were

observed through use of another agent that binds to D₂ receptors.³⁰ Interestingly, a study of patients with non-manifesting DYT1 dystonia also showed ~15% decreased D₂ binding (assessed by use of ¹¹C-raclopride) in the caudate and putamen.³¹ Importantly, these findings do not necessarily reflect receptor levels; altered concentrations of synaptic dopamine can also lead to tracer displacement. Similarly, evidence for possible presynaptic dysfunction was found in an ¹⁸F-dopa study of familial idiopathic dystonia,³² and a number of postmortem studies have also shown modest abnormalities in dopamine and its metabolites in patients with primary dystonia.^{33–36} Importantly, the observation that similar abnormalities are seen in patients with dystonia and non-manifesting *DYT1* mutation carriers indicates that dopaminergic alterations do not directly cause dystonia. Rather, these observations could indicate a compensatory response, or might represent another dystonia endophenotype.

Acetylcholine—The symptoms of DYT1 dystonia and other forms of primary dystonia can often be treated effectively with anticholinergic medications. Response to anticholinergic drugs does not necessarily reflect a primary role for acetylcholine in primary dystonia, but it does indicate that dissecting the role of acetylcholine in symptom modification could provide important insights into the nature of the dystonic circuit. Acetylcholine is deeply intertwined with dopaminergic function and dysfunction. Abnormal cholinergic function can result intrinsically from abnormal cholinergic physiology or collaterally from altered dopaminergic inputs. Cholinergic interneurons are found in regions with dense dopaminergic innervation, such as the dorsal and ventral striatum, where dopaminergic afferents exert strong control over cholinergic synaptic transmission.³⁷ Cholinergic interneurons are tonically active, and, although they constitute only ~2% of the cell population in the neostriatum, they branch extensively onto GABAergic medium spiny neurons and have been shown to modulate subthreshold and suprathreshold responses of these neurons to cortical and thalamic excitation.³⁸ Modulation of cholinergic interneurons is thought to occur through D₂ dopamine receptors and M₂ and M₄ muscarinic autoreceptors.^{39,40}

Molecular mechanisms

As discussed above, considerable uncertainty remains as to the relative importance of the various neuro-physiological and neurochemical mechanisms linked to dystonia, and to how they relate to one another (that is, which mechanisms are primary and which are secondary). Although inherited forms of primary dystonia are far less common than sporadic disease, the discovery of genetic forms of dystonia is exciting because these conditions are expected to share important pathogenic mechanisms with idiopathic dystonia, leading to mechanistic insights that suggest novel therapeutic strategies.

The effort to characterize the genetic forms of dystonia is still in its infancy, but the genes discovered to date suggest some potential themes related to previously identified mechanisms and clinical features of dystonia. For example, two proteins, Na⁺–K⁺–ATPase and ε-sarcoglycan have both been implicated in the control of neuronal excitability, and torsin-1A, by virtue of its localization in the endoplasmic reticulum, could conceivably control the ability of these and other membrane proteins to traffic normally from the endoplasmic reticulum to the plasma membrane.

DYT1 dystonia

DYT1 dystonia (also known as Oppenheim dystonia) is a childhood-onset disease with a mean age of onset of 12 years (although rare instances of onset in adulthood have been reported^{41,42}). DYT1 dystonia typically affects the legs, arms and trunk, and much less frequently affects cranial structures. The disease is caused by an in-frame deletion in the

TOR1A gene that removes a single glutamic acid residue (the ΔE deletion).⁴³ As discussed above, the mutation only shows ~30% penetrance, but all mutation carriers exhibit abnormal brain metabolism, independent of clinical status.^{8,10} Mutation carriers who do not develop dystonia by their early twenties typically remain free of dystonia for life, suggesting that a developmental window of susceptibility exists during which torsin-1A function is critical for brain function.

Torsin-1A is widely expressed in neuronal and non-neuronal tissues,^{43,44–46} and it belongs to the AAA+ (ATPases associated with various cellular activities) family of proteins, which use energy from ATP hydrolysis to unfold proteins or disassemble protein complexes. Torsin-1A is localized in the lumen of the endoplasmic reticulum–nuclear envelope endomembrane system. Wild-type torsin-1A is predominantly found in the endoplasmic reticulum, but several observations indicate that the nuclear envelope lumen is also a site of torsin-1A activity that has particular relevance to disease pathogenesis.^{47–50} Multiple laboratories have observed that an artificially engineered ‘substrate trap’ mutant of torsin-1A, which prevents it from dissociating from its protein partners, causes the protein to accumulate abnormally in the nuclear envelope,^{47–49} leading to morphological abnormalities of this structure and a potentially anomalous distribution of nuclear pores.⁴⁹ ΔE -torsin-1A also accumulates at the nuclear membrane,^{47–49,51,52} suggesting that the *DYT1* mutation could lead to an abnormal interaction with a nuclear envelope partner—possibly lamina-associated polypeptide 1 (LAP1), a torsin-1A-interacting protein that is localized to the inner nuclear membrane.⁵³

Further support for the importance of nuclear-envelope-localized torsin-1A function in the pathogenesis of DYT1 dystonia comes from genetic studies in mice. Neurons from *Tor1a* null mice or ‘knock-in’ mice homozygous for the ΔE deletion of *Tor1a* exhibit abnormal nuclear envelope membranes, whereas the nuclei from all non-neuronal cell types seem normal.⁴⁶ Fibroblasts from patients with DYT1 dystonia and tissue from heterozygous *Tor1a* ΔE knock-in mice also have reduced steady-state torsin-1A levels.⁴⁶ These studies suggest that the *DYT1* mutation impairs normal torsin-1A function. AAA+ proteins typically function as hexamers and DYT1 dystonia is a dominantly inherited disease, so ΔE -torsin-1A might also exert dominant-negative effects on wild-type torsin-1A in patients with this condition.^{47,54}

What might be the role of torsin-1A at the nuclear envelope? One possibility is that torsin-1A acts within the nuclear envelope lumen to regulate connections between proteins that tether the nucleus to the cytoskeletal network.^{50,55} Nucleocytoskeletal connections coordinate nuclear movements that are crucial for various developmental events in the CNS, including neurogenesis, neural tube closure, and neural migration.^{56,57} Nesprins, a family of outer nuclear membrane proteins, form the nucleocytoskeletal link by binding to the cytoskeletal network in the cytosol. Nesprins are anchored within the nuclear envelope through interaction with SUN protein family members, which are inner nuclear membrane proteins. Torsin-1A has been reported to interact with nesprin-3, and this protein is mislocalized in mouse *Tor1A* null fibroblasts and fibroblasts from patients with DYT1 dystonia.⁵⁸ Other studies have shown that overexpression of torsin-1A in a neuronal cell line inhibits neurite outgrowth.^{59,60} Torsin-1A could conceivably mediate such effects via nesprin-3, which projects into the cytosol.

Although ΔE -torsin-1A shows enhanced accumulation in the nuclear envelope, much of this protein remains within the main endoplasmic reticulum. Dysfunction of endoplasmic reticulum-related functions might, therefore, also contribute to the pathogenesis of DYT1 dystonia. Torsin-1A is reported to inhibit trafficking of polytopic membrane-bound proteins, including the dopa mine transporter.⁵⁴ Moreover, fibroblasts from patients with DYT1

dystonia show defective protein processing through the secretory pathway—an anomaly that can be rescued by downregulating the mutant protein.^{61,62} Potentially relevant to this observation, torsin-1A has also been reported to interact with proteins that are involved in synaptic vesicle maturation and exocytosis.^{63,64}

In summary, current evidence indicates that the *DYT1* mutation impairs torsin-1A function, which could lead to abnormalities in nucleocytoplasmic connections and/or protein processing through the secretory pathway. Importantly, however, many of the phenotypes observed have been in fibroblasts, whereas in patients the *DYT1* mutation seems to exert its effects predominantly on neurons. Future work must, therefore, focus on whether the abnormalities observed in fibroblasts extend to neurons, and, if so, what makes these cells particularly susceptible to torsin-1A dysfunction.

DTY6 dystonia

DTY6 (generalized) dystonia, another dominantly inherited dystonia, is clinically similar to DYT1 dystonia. In contrast with the latter condition, however, the areas of the body initially affected include the cranial muscles, neck and arms, but rarely the legs, and the degree of progression to other regions varies. Fuchs *et al.* initially reported that two mutations in the *THAP1* gene caused DYT6 dystonia in five separate families.⁶⁵ These findings were followed by reports identifying 11 additional mutations in *THAP1* through large genetic screening studies.⁶⁶⁻⁶⁷ THAP1 is a member of the THAP family of proteins, which contain an evolutionarily conserved zinc-dependent DNA-binding domain.⁶⁸ Of the 13 mutations identified, nine are within the DNA-binding domain, three are predicted to disrupt the nuclear localization signal (thereby preventing the protein product from entering the nucleus), and one removes the start codon.⁶⁵⁻⁶⁷ These findings suggest that reduced THAP1 function in the nucleus, and consequent transcriptional dysregulation, contributes to the pathogenesis of DYT6 dystonia. The nuclear localization of THAP1 indicates that it could potentially interact with torsin-1A-related pathways. THAP1 interacts with retinoblastoma-associated protein,⁶⁹⁻⁷⁰ which is known to localize to the inner nuclear membrane by binding A-type lamins. Torsin-1A interacts with LAP1,⁵³ which crosses the inner nuclear membrane and also interacts with A-type lamins. By binding to THAP1, LAP1 could potentially represent a molecular link between DYT1 and DYT6 dystonia.

DTY5 dystonia

Unlike other DYT categories, the DYT5 (dopa-responsive) dystonia classification represents a dystonia syndrome (also known as Segawa syndrome) that encompasses a variety of genetic causes. The classic form of dopa-responsive dystonia is caused by dominantly inherited mutations in the *GCH1* gene, and presents as a childhood illness with a diurnal pattern. Affected children are relatively normal early in the day, but develop a dystonic gait in the afternoon. These children can also have features of parkinsonism, including rigidity, postural instability and an abnormally flexed posture. This form of Segawa syndrome is virtually cured by small amounts of daily levodopa. GCH1 is required for the biosynthesis of tetrahydrobiopterin (BH₄), an essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme controlling dopamine synthesis. Over 100 different *GCH1* mutations have been identified worldwide,⁷¹ but ~40–50% of patients with dopa-responsive dystonia do not harbor any known *GCH1* mutations.⁷² DYT14 dystonia was originally believed to be a novel form of dopa-responsive dystonia, but is now known to result from a multi-exonic deletion in *GCH1*, meaning that it is now classed as a form of DYT5 dystonia.⁷³ Recessive mutations in the tyrosine hydroxylase gene (*TH*) also cause dystonia that is responsive to levodopa, but loss of *TH* function causes a complex syndrome that begins in infancy, and, in addition to dystonia, features ptosis, hypotonia, hypokinesia and psychomotor delay.^{74–78}

GCH1 normally functions as a homodecamer, and many of the mutant forms of the protein seem to exert dominant-negative effects. The mutant protein could form a heterodecamer with wild-type GCH1, which would result in a nonfunctional or dysfunctional oligomer. Interestingly, BH₄ levels, which reflect GCH1 activity, are reduced in the cerebrospinal fluid of patients with DYT5 dystonia, but are normal in the plasma and urine,⁷⁹ suggesting that the CNS is uniquely susceptible to this molecular defect. The enzymatic activity of tyrosine hydroxylase peaks in dopaminergic neurons during early childhood,⁸⁰ a factor that could account for the age-dependent symptoms of DYT5 dystonia. The presence of wild-type GCH1 does allow BH₄ synthesis to occur in dopa-responsive dystonia, but the diurnal fluctuations that characterize this condition seem to result from an inability to synthesize sufficient quantities to last throughout the day.⁸¹

DYT11 and DYT15 dystonia

Myoclonus–dystonia is a clinical syndrome dominated by the co-occurrence of dystonic and myoclonic (rapid lightning-like jerking) movements, usually affecting the arms and neck. In addition, the disorder can be accompanied by a variety of psychiatric features, including obsessive–compulsive disorder, alcoholism, and drug abuse. Disease onset is from childhood to early adulthood. Like many other primary dystonias, such as DYT1 and DYT6, the symptoms tend to progress over a period of time, and eventually reach a plateau. The disease is caused by dominantly inherited mutations in *SGCE* (DYT11 dystonia),⁸² or an as yet unidentified gene linked to chromosomal location 18p11 (DYT15 dystonia).

Most *SGCE* mutations are deletions or nonsense mutations that eliminate gene function.⁸² The *SGCE* gene is maternally imprinted, so individuals depend on expression from the paternal allele. Nearly all patients with myoclonus–dystonia inherit a loss-of-function allele from their father and, therefore, lack functional ε-sarcoglycan protein. Consequently, although the disease is dominantly inherited, maternal imprinting seems to cause a recessive-like loss of function. A few patients with myoclonus–dystonia have, however, inherited a mutant maternal allele, a situation that is difficult to explain on the basis of the currently understood biology of the gene.⁸³

SGCE is one of five known members of the sarcoglycan gene family. These genes encode transmembrane proteins that are components of the dystrophin–glycoprotein complex (DGC), a membrane-spanning complex that makes connections with both the extracellular matrix and the intracellular actin cytoskeleton.^{84,85} Mutations in multiple protein components of the DGC, including other sarcoglycan family members, cause various forms of muscular dystrophy,^{84,85} but none of these other illnesses include dystonia. Interestingly, *SGCE* is the only sarcoglycan family member to be expressed in the CNS,^{86–88} and it is also expressed in striated and smooth muscle.^{86,87} Despite this expression pattern, patients with myoclonus–dystonia do not develop muscular dystrophy, perhaps because other sarcoglycan family members are able to compensate in these tissues. Studies have tended to focus on the function of the DGC in striated muscle, but this complex is also expressed in the CNS, where it has roles in brain development and function. DGC components (including ε-sarcoglycan) are concentrated at postsynaptic sites, particularly in association with GABAergic inhibitory synapses.^{89,90} This finding is especially interesting given the probable role of deficient inhibition in dystonia, and the documented abnormalities of GABA neurotransmission. A potential link with torsin-1A is suggested by an *in vitro* study, which demonstrated that torsin-1A can interact with and promote the degradation of mutant ε-sarcoglycan in the endoplasmic reticulum.⁹¹

DYT12 dystonia

DYT12 dystonia, also known as rapid-onset dystonia–parkinsonism, is characterized by the precipitous onset of dystonic and parkinsonian symptoms, often leading to marked disability in a matter of days to weeks, followed by stabilization. Some patients, however, can progress more slowly (over a period of months). The illness is caused by dominant mutations in the gene encoding the $\alpha 3$ subunit of the Na^+/K^+ -ATPase (*ATP1A3*).⁹² Six missense mutations have been identified in this gene, and structural modeling and cell biological studies indicate that they are loss-of-function mutations that impair enzyme activity or stability.⁹²

The Na^+/K^+ -ATPase is a hetero-oligomeric complex consisting of a catalytic α subunit and an associated β modulatory subunit in a 1:1 stoichiometry. The complex harnesses the energy from ATP hydrolysis to generate and maintain the plasma membrane electrochemical gradient. Four α subunits (encoded by the genes *ATP1A1–4*) have been identified, and these isoforms display differential substrate affinity, kinetics and tissue distribution. *ATP1A3* is predominantly expressed in neural tissues,⁹³ potentially explaining the neural specificity of DYT12 dystonia. Mutations that impair activity but not protein stability could act as dominant-negative alleles, disrupting the function of an otherwise wild-type complex. Previous work has linked abnormal inhibition of Na^+/K^+ -ATPase function to CNS hyperexcitability and epileptiform bursts.⁹⁴ Loss of $\alpha 2$ subunit function causes neural hyperactivity and impairs reuptake of glutamic acid and GABA at nerve terminals,⁹⁵ potentially linking Na^+/K^+ -ATPase to the dysregulated inhibition that is thought to be important for dystonia pathogenesis. Furthermore, the neuronally expressed $\alpha 3$ isoform could have a key role during the repeated firing of action potentials.⁹⁶ How the CNS is able to function normally for many years before the catastrophic events that result from Na^+/K^+ -ATPase mutations remains unclear.

Conclusions and future perspectives

The features that make primary dystonia fascinating—disruption of the motor circuit without associated neuropathological lesions—also make this condition extraordinarily challenging to study. Numerous questions abound: what aspect of neuronal dysfunction is fundamental to dystonia? Is the relevant motor circuit selectively targeted by the condition or, rather, selectively vulnerable to a general abnormality of neural transmission? Which dystonias share underlying molecular mechanisms, and might, therefore, require a similar therapeutic approach?

Two major advances over the past decade have changed these questions from subjects of largely theoretical interest to tractable—albeit challenging—scientific problems. First, advances in both functional and structural brain imaging are making the identification of circuit abnormalities in human patients possible. Second, the discovery of dystonia-related genes has enabled investigators to focus on novel cell biological mechanisms that could underlie circuit function, and could suggest novel therapeutic approaches. These twin advances are particularly fortuitous because they should allow investigators to begin to bridge the different levels of brain organization—systems and molecular—that must be synthesized to dissect the mechanisms of dystonia. Moreover, these fields are synergistic: animal models designed to elucidate the functions of human dystonia-related genes can be imaged, and imaged patients with dystonia can now be screened for polymorphisms and mutations in dystonia-related genes.

One key to realizing the potential of these advances will be the creation of an animal model based on a human dystonia-related gene that recapitulates key features of the disease. Such a model has not yet emerged from the known genetic causes of primary dystonia.

Considerable effort should continue to be applied to this research goal, both through the use of novel strategies (for example, the Cre-loxP recombination system or bacterial artificial chromosome transgenesis) and by attempting animal model building based on all discovered genes. We must move beyond studies in non-neuronal cells to explore whether the identified mechanisms are also operative in neurons, and, if so, whether the neurons most relevant to motor function are particularly susceptible to such mechanisms. Identifying whether different dystonia-related genes function in common molecular pathways is another important research goal. Such approaches should greatly enhance our understanding of the mechanisms that give rise to dystonia, and finally allow us to translate recent advances into novel therapeutic strategies.

Review criteria

Information for this Review was obtained by searching the PubMed database using the search terms “primary dystonia” or “dystonia” alone or in combination with the search terms “pathophysiology”, “genetics”, “pathogenesis” or “basal ganglia”. Separate searches were also performed for each specific genetic form of dystonia (for example, “torsinA” and “DYT1”). No time limits were placed on the search results returned. Only full-text articles, not abstracts, were used.

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Figure 1.

Clinical examples of primary dystonia. **a** | Writer's cramp. Abnormal clenching of fingers occurs selectively during writing; patient is otherwise normal. **b** | Dystonia of arm, neck and face, exacerbated during writing. Patient first developed writer's cramp, but subsequently developed dystonia of the neck (torticollis) and face. **c** | Fixed dystonic foot posture. **d** | Involuntary dystonic flexion of trunk and extension of neck (retrocollis) during gait.

Figure 2.

Motor circuit abnormalities associated with DYT1 genotype and clinical symptom manifestation. Left column shows simplified motor circuit diagrams and right column shows cerebellothalamocortical tract reconstructions from fiber tractography data.⁴ The *DYT1*-mutation-positive state is characterized by reduced dopamine D₂ receptor availability^{29,97} and abnormalities of the cerebellothalamocortical tract, regardless of the presence or absence of symptoms. The site and consequences of decreased D₂ receptor availability are not understood, as striatal D₂ receptors are expressed on cortical, dopaminergic and cholinergic axons, as well as on medium spiny output neurons. Manifesting and non-manifesting DYT1 carriers exhibit similar abnormalities of cerebellothalamic tract

microstructure (indicated by broken arrows connecting these structures). Non-manifesting DYT1 carriers show greater abnormalities of thalamocortical microstructure than do symptomatic patients, which could counteract the motor consequences of the cerebellothalamic abnormalcy. The loss of cerebellothalamocortical connectivity is associated with changes in movement-related cerebral blood flow (indicated by coloring of cortex, thalamus and cerebellum). Basal ganglia output (from GPi to thalamus) is reduced or abnormal in hyperkinetic disorders, which is believed to result in disinhibition of the ventral anterior–ventral lateral thalamocortical output.⁹⁸ Abbreviations: GPe, globus pallidus externa; GPi, globus pallidus interna; SNpC, substantia nigra pars compacta; STN, subthalamic nucleus.

Table 1

Genetic causes of primary dystonia

Locus and designation	OMIM® number	Age of onset	Chromosomal location	Gene	Mode of inheritance	Clinical characteristics	References
<i>DYT1</i> : early-onset primary dystonia (Oppenheim dystonia)	128,100	Childhood (mean 12 years, <25 years in most cases)	9q34	Torsin-1A (<i>TOR1A</i>)	Autosomal dominant	Early-onset, usually starts in a limb, can generalize to other body parts as disease progresses	Ozelius <i>et al.</i> (1997) ⁹⁹
<i>DYT5</i> : dopa-Responsive dystonia (Segawa syndrome)	128,230 605,407	variable, often childhood Infancy	14q22.1-q22.2 11p	GTP cyclohydrolase 1 (<i>GCH1</i>) Tyrosine hydroxylase (<i>TH</i>)	Autosomal Dominant Autosomal recessive	Dystonia with concurrent or subsequent parkinsonism, diurnal worsening of symptoms and a dramatic response to levodopa Dystonia, ptosis, hypotonia, hypokinesia and psychomotor delay	Ichinose <i>et al.</i> (1994) ¹⁰⁰ Lüdtke <i>et al.</i> (1995) ¹⁰¹
<i>DYT6</i> : dystonia 6	602,629	variable, often childhood	8p21-q22	THAP domain-containing protein 1 (<i>THAP1</i>)	Autosomal dominant	Frequently starts in craniocervical muscles, often generalizes	Almasy <i>et al.</i> (1997) ¹⁰² Fuchs <i>et al.</i> (2009) ⁶⁵ Bressman <i>et al.</i> (2009) ⁶⁶
<i>DYT7</i> : dystonia 7	602,124	Adulthood	18p	Unknown	Autosomal dominant	Focal torsion dystonia, often remains cervical; torticollis	Leube <i>et al.</i> (1996) ¹⁰³ Waddy <i>et al.</i> (1991) ¹⁰⁴
<i>DYT11</i> : Myoclonus-dystonia	159,900	variable, often early childhood	7q21, 11q23.1	ε-sarcoglycan (<i>SGCE</i>)	Autosomal dominant	Rapid, jerk-like movements, responsive to alcohol; combined with variable degrees of dystonia	Zimprich <i>et al.</i> (2001) ⁸²
<i>DYT12</i> : rapid-onset dystonia-parkinsonism	128,235	Childhood, adolescence or adulthood	19q12-q13.2	α3 subunit of Na ⁺ -K ⁺ -ATPase (<i>ATP1A3</i>)	Autosomal dominant	Dystonia or parkinsonism developing over hours or weeks	Kramer <i>et al.</i> (1999) ¹⁰⁵ de Carvalho Aguiar <i>et al.</i> (2004) ⁹²
<i>DYT13</i> : dystonia 13	607,671	Average onset 15 years of age	1p36.32-p36.13	Unknown	Autosomal dominant	Torsion dystonia, begins in the cervical or craniocervical region or upper limbs, slow progression to other body regions	Bentivoglio <i>et al.</i> (1997) ¹⁰⁶ valente <i>et al.</i> (2001) ¹⁰⁷
<i>DYT15</i> : alcohol-Responsive myoclonic dystonia	607,488	variable, often childhood	18p11	Unknown	Autosomal dominant	Alcohol-responsive myoclonic dystonia characterized mainly by jerky movements of the upper limbs, hands, and axial	Grimes <i>et al.</i> (2002) ¹⁰⁸

Locus and designation	OMIM® number	Age of onset	Chromosomal location	Gene	Mode of inheritance	Clinical characteristics	References
muscles							

Abbreviation: OMIM®, Online Mendelian Inheritance in Man® (Johns Hopkins University, Baltimore, MD, USA) References