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Genetics and Pathogenesis of Dystonia

Mirja Thomsen,[1] Lara M. Lange,[1] Michael Zech,[2,3] and Katja Lohmann[1]

[1]Institute of Neurogenetics, University of Lübeck, Lübeck, Germany; email: katja.lohmann@uni-luebeck.de

[2]Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany

[3]Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany

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Abstract

Dystonia is a clinically and genetically highly heterogeneous neurological disorder characterized by abnormal movements and postures caused by involuntary sustained or intermittent muscle contractions. A number of groundbreaking genetic and molecular insights have recently been gained. While they enable genetic testing and counseling, their translation into new therapies is still limited. However, we are beginning to understand shared pathophysiological pathways and molecular mechanisms. It has become clear that dystonia results from a dysfunctional network involving the basal ganglia, cerebellum, thalamus, and cortex. On the molecular level, more than a handful of, often intertwined, pathways have been linked to pathogenic variants in dystonia genes, including gene transcription during neurodevelopment (e.g., *KMT2B*, *THAP1*), calcium homeostasis (e.g., *ANO3*, *HPCA*), striatal dopamine signaling (e.g., *GNAL*), endoplasmic reticulum stress response (e.g., *EIF2AK2*, *PRKRA*, *TOR1A*), autophagy (e.g., *VPS16*), and others. Thus, different forms of dystonia can be molecularly grouped, which may facilitate treatment development in the future.

INTRODUCTION

Dystonia is a clinically and genetically highly heterogeneous neurological movement disorder for which a number of groundbreaking genetic and molecular insights have recently been gained, but their translation into new therapies is still limited. Early reports of patients with detailed descriptions of dystonic features date back to the seventeenth century but may have already been noticed in the ancient world more than 2,000 years ago (1). For a long time, dystonia was viewed as a psychiatric disorder caused by an unidentifiable anatomical, physiological, or biochemical abnormality. It took until 1911, when the German neurologist Hermann Oppenheim coined the term dystonia musculorum deformans to describe adolescents suffering from muscular hypotonia on one occasion and tonic muscle spasms on another (2, 3), for dystonia to be recognized as an organic disease with a potentially inherited origin (2, 3). However, his work was partly forgotten until ~50 years ago, when there was a paradigm shift and subspecialization in movement disorders took place (1). Nowadays, the term dystonia refers to abnormal, often repetitive movements or postures (or both) caused by sustained or intermittent muscle contractions (4).

Within the past decades, our understanding of genetic causes and the underlying pathophysiology has dramatically improved. For the first time, pathogenic variants leading to dystonia were discovered in 1994, when pathogenic variants in the GTP cyclohydrolase 1 (*GCH1*) gene were found after screening this gene as a strong functional candidate on the basis of its role in the biosynthesis of tetrahydrobiopterin, located within the linked region for dopa-responsive dystonia (DRD) (5). Nowadays, pathogenic variants in more than 400 genes have been linked to dystonia or dystonic symptoms. However, we are still lacking better treatments and meaningful biomarkers. Within this article, we summarize current knowledge of the genetic forms and related pathology on the molecular and neuropathophysiological levels.

CLINICAL CONTEXT

Dystonia can be used to describe either a single sign as part of a different disease or a disease itself in which dystonia is the prominent or sole clinical feature. The etiology is variable, including a range of acquired, inherited, or idiopathic causes.

While the clinical presentation of dystonia is highly heterogeneous, it also shows certain common features. Dystonic movements typically follow a pattern and may involve twisting movements. They are often initiated or exacerbated by voluntary action and associated with overflow muscle activation (4). Dystonia may also be associated with a dystonic tremor, an inconsistent feature that can be difficult to distinguish from essential tremor. While dystonic movements and postures remain the main characteristics of dystonia, there are a few additional secondary signs that may or may not be present and hint at the clinical diagnosis of dystonia. These include the geste antagoniste, mirror dystonia, and overflow dystonia (6). The geste antagoniste (also known as the sensory trick) describes a voluntary action by the patient that can reduce or even completely suppress abnormal postures or dystonic movements, for example, touching the chin in cervical dystonia. Mirror dystonia describes movements or postures that are triggered by the performance of contralateral actions and movements, showing similar or even the same characteristics as the dystonia. Overflow dystonia refers to involuntary muscle contractions that accompany the most prominent dystonic movement but extend beyond the usually anatomically affected body region or may even involve a different, nonadjacent region.

Dystonia was considered a rare disease (defined by the European Union as affecting less than 1 in 2,000 individuals). According to recent epidemiological studies, the prevalence of isolated dystonia may be a bit higher and was estimated as 52.7/100,000 (7) or 30.9/100,000 (8). However, the true prevalence may be even higher since many cases may remain un- or misdiagnosed. Notably, for most subforms, there is a higher prevalence in females (7).

General Classification of Dystonia

The classification of dystonia evolved over time, and numerous attempts have been made to classify the heterogeneous group of dystonias. With an increased understanding of the disease and its various clinical manifestations and etiologies, it became clear that the majority of the available classifications had several shortcomings and only limited clinical usefulness. Therefore, an international expert panel was formed, and the most recent and well-established classification system to date was developed (4).

This classification includes two distinct axes: clinical characteristics (axis I) and etiology (axis II). The items of the clinical characteristics axis are used to describe the specific phenomenology of dystonia in a given patient. These characteristics include age at onset, body distribution, temporal pattern, and associated features. The subcategories and respective explanations are listed in **Table 1**. The second axis, addressing etiology, is still evolving and should be updated regularly as new causes of dystonia are identified. It comprises two complementary characteristics, anatomical changes and pattern of inheritance, both of which should not be considered mutually exclusive. The assignment of these characteristics is based on different diagnostic tests, for example, brain imaging, genetic, metabolic, or other tests.

Classification and Nomenclature of Hereditary Forms of Dystonia

Not only the general classification system for dystonia but also the (sub)classification and nomenclature for hereditary forms of the disease have evolved over time. Originally, locus symbols (e.g., DYT1) were used to specify chromosomal regions that had been linked to a familial disorder with an as-yet-unknown gene (9). With our knowledge growing and new sequencing techniques leading to the rapid identification of numerous novel and potentially disease-causing (dystonia) genes in recent years, this system soon proved to be unsuitable as a reference (9). Therefore, in 2013, the Movement Disorder Society initiated the Task Force for the Nomenclature of Genetic Movement Disorders to revise the system. The new nomenclature, published in 2016, introduced a number of rules and recommendations (10). First, only disorders for which pathogenic variants, as a monogenic cause, have been identified were included. Further, the new nomenclature assigned a movement disorder prefix representing the disease's prominent phenotype (e.g., DYT for dystonia). In addition, the term includes the name of the causal gene, for example, DYT-TOR1A for dystonia caused by pathogenic variants in the *TOR1A* gene. If there is a link to two different movement disorders, a double prefix was assigned (e.g., DYT/PARK-ATP1A3 for pathogenic variants in the *ATP1A3* gene linked to a dystonia-parkinsonism syndrome). Notably, a certain level of evidence for a genotype-phenotype relationship is required to become included into the system and respective disease lists. To reflect the continuous identification of novel genes causing dystonia and other diseases, the lists of confirmed genetic forms are updated biyearly, with the last update occurring in 2022 (11, 12).

According to the 2022 update, 52 genes are currently listed for monogenic forms of dystonia that were described in patients with frequent or predominant dystonia, excluding only anecdotal gene-dystonia links. This list includes 9 genes causing isolated, 10 genes causing combined, and 33 genes causing complex forms of dystonia (**Figure 1**). Additionally, the task force listed seven conditions that usually present with other phenotypes but can have prominent dystonia in a subset of patients and six genes related to predominant neurodevelopmental disorders or epileptic encephalopathies in which, frequently, less prominent dystonia can be encountered.

Detailed reviews on the clinical presentation of patients with genetic forms of isolated dystonia (13, 14) or DRD (15) have been recently published or are in preparation within the Movement Disorder Society genetic mutation database (MDSGene) framework. An overview of genetic

Table 1 Consensus classification of dystonia

I. Clinical characteristics		
Category	**Subcategory**	**Description**
Age at onset	Infancy	Birth to 2 years
	Childhood	3–12 years
	Adolescence	13–20 years
	Early adulthood	21–40 years
	Late adulthood	>40 years
Body distribution	Focal	Only one affected body region
	Segmental	Two or more contiguous body regions
	Multifocal	Two or more noncontiguous body regions
	Hemidystonia	More body regions restricted to one body site
	Generalized (with or without leg involvement)	Involvement of the trunk and at least two other body regions with or without leg involvement
Temporal pattern: disease course	Static	No progression over the course of the disease
	Progressive	Progression over the course of the disease
Temporal pattern: variability	Persistent	Persistent to approximately the same extent throughout the day
	Action-specific	Occurring only during a particular activity or task
	Diurnal	Fluctuations during the day with recognizable variations in occurrence, severity, and phenomenology
	Paroxysmal	Sudden self-limited episodes usually induced by a trigger with return to preexisting state
Associated features	Isolated dystonia	Dystonia as the only motor feature, except for a possible tremor
	Combined dystonia	Dystonia combined with another movement disorder (e.g., myoclonus, parkinsonism, etc.)
	Complex dystonia (10)	Occurrence of other neurological or systemic manifestations; dystonia may be less prominent
II. Etiology		
Nervous system pathology		Evidence of degeneration Evidence of structural (often static) lesions No evidence of degeneration or structural lesions
Inherited, acquired, or idiopathic		Inherited: autosomal dominant, autosomal recessive, X-linked, mitochondrial Acquired: perinatal brain injury, infection, drug, toxic, vascular, neoplastic, brain injury, psychogenic Idiopathic: dystonia without identifiable cause, sporadic or familial

Table adapted from Reference 4.

variants and corresponding phenotypes from the English literature can be found on the MDSGene website (**https://www.mdsgene.org**) and is beyond the scope of this review article.

Treatment and Management of Dystonia

Despite considerable research and first insights, the whole picture of the pathophysiology of dystonia is still largely unknown. Thus, to date, there is no targeted causal treatment for most forms of dystonia. The management of dystonia predominantly includes symptomatic treatment options. Treatment has several different pillars, including chemo-denervation with botulinum toxin injections, pharmacological therapies, physical therapies, and surgery (16). The suitable treatment option largely depends on clinical features, such as distribution and severity of symptoms, but also on etiology. If possible, the treatment should be directed against the specific etiology, for

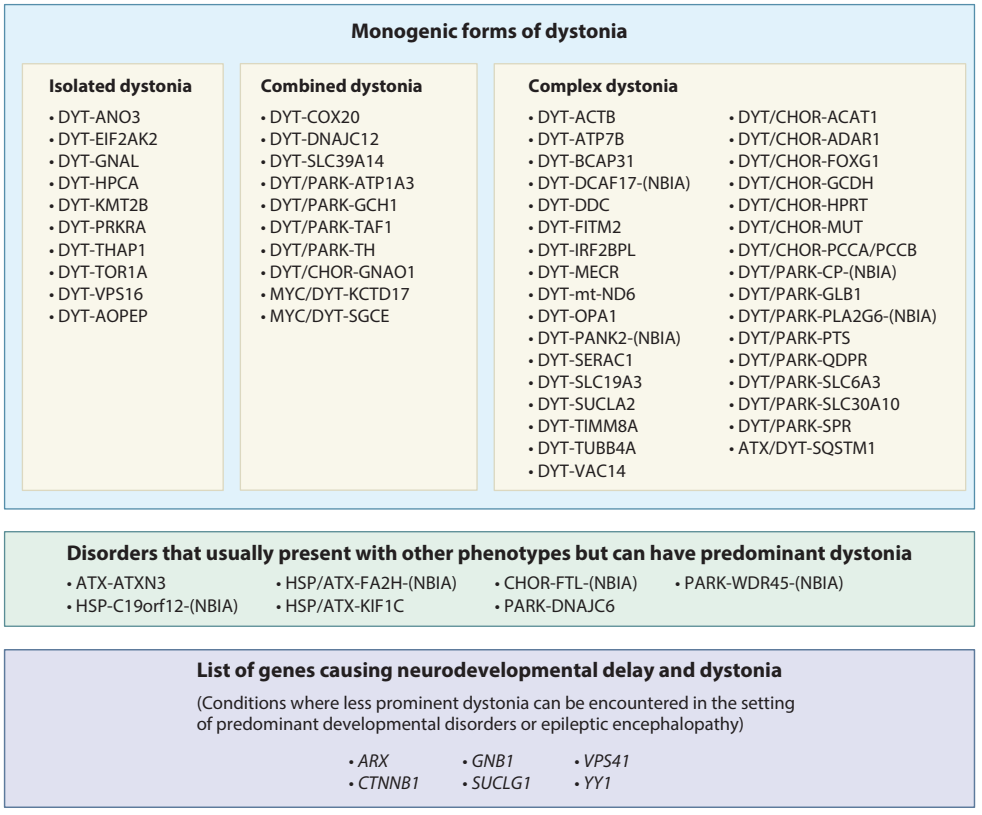


Figure 1

Overview of confirmed monogenic forms of dystonia based on the most recent update of the Task Force for the Nomenclature of Genetic Movement Disorders (11). One condition, DYT-AOPEP, was added to the list because it was identified after the publication of the most recent update. For genes causing neurodevelopmental delay and dystonia, the figure shows selected examples. Additional genes in this large group can be found on the OMIM® webpage (**https://www.omim.org**). Abbreviations: ATX, ataxia; CHOR, chorea; DYT, dystonia; HSP, hereditary spastic paraplegia; NBIA, neurodegeneration with brain iron accumulation; PARK, Parkinson's disease.

example, in metabolic or autoimmune forms of dystonia (17). Chemo-denervation with the neurotoxin botulinum toxin injected directly into the affected muscle groups is commonly used for focal and segmental dystonia (18). It prevents muscle contraction by inhibiting acetylcholine release, and targeted injections can thereby reduce tone in specific muscles, relieving dystonic symptoms. Generalized dystonia is typically treated pharmacologically or by surgery. Pharmacological treatment includes dopaminergic treatments in so-called DRDs with levodopa (15). However, for other (hereditary) forms of dystonia, the overall response to dopaminergic therapy is often poor (13, 16). Anticholinergics are an alternative (19, 20), although high-dose anticholinergic therapy is often associated with serious side effects such as cognitive impairment or hallucinations, particularly in adults (21). Other pharmacological options include baclofen (oral or intrathecal administration), tetrabenazine, benzodiazepines, or even neuroleptics, all, however, with a variable response and often dominant side effects (16).

Deep brain stimulation (DBS) is a successful alternative for drug therapy–refractory severe dystonia. The DBS targets in dystonia are the globus pallidus internus (GPi-DBS) and, more

recently and less commonly, the subthalamic nucleus (STN-DBS) (22). Interestingly, for hereditary forms of dystonia, the response to DBS varies depending on the gene causing the disease; for example, there is usually a particularly favorable response in DYT-KMT2B, DYT-TOR1A, and MYC/DYT-SGCE, whereas the effects in DYT-THAP1 and DYT-GNAL are more variable (23). Lastly, physical therapies, such as physiotherapy, should always be part of the treatment (16).

Genetic Causes of Dystonia

As indicated, the genetic causes of dystonia are manifold. While pathogenic variants in many different genes have been found in a small subset of patients with dystonia and many different syndromes with dystonic features, no genetic cause can yet be identified in the vast majority of patients, especially the ones with late-onset focal dystonia, the most common dystonia form. Instead, it is hypothesized that genetic risk variants play a significant role. To date, three large-scale genome-wide association studies (GWASs) have been reported that aimed to identify such risk factors in rather homogeneous groups of dystonia patients, namely those with cervical dystonia (24, 25) and musicians' dystonia (26). While all of these studies reported candidate variants [*NALCN* (24), *ARSG* (26), and *COL8A1* and *DENND1A* (25), respectively], replication was rarely promising (27, 28) and often negative (25, 29). A systematic meta-analysis of genetic risk factors in dystonia, including GWASs and candidate gene approaches, highlighted interesting association signals in *TOR1A*, *DRD1*, and *ARSG*. However, no variant displayed a compelling association with dystonia in the available data (30), indicating that there are no common variants with an at least moderate effect size contributing to the risk of dystonia. It remains to be seen if larger sample sizes (currently up to only ~1,000 patients were included) will shed further light on genetic risk factors in dystonia. However, it might be possible, if the risk per common variant is low and if rare variants contribute with little effect size, that hundreds of thousands of patients and controls are required for the identification of risk variants by GWASs and burden analyses to elucidate possibly oligogenic inheritances. Currently, our limited knowledge in this field does not allow any conclusions about the underlying pathophysiology. Therefore, we focus in the next section on monogenic forms for which pathogenic variants in genes linked to diverse pathways have been implicated in dystonia.

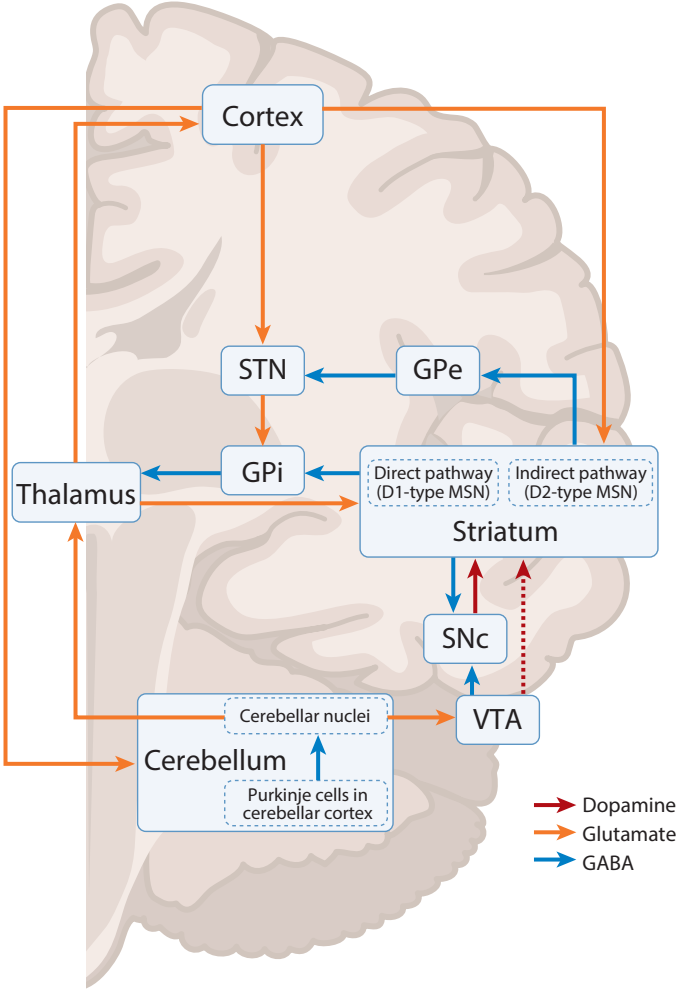
COMMON THEMES: SHARED PATHOPHYSIOLOGY AND DISEASE MECHANISMS

Pathophysiology

The planning, coordination, and execution of movement involve a complex interaction of different brain areas (**Figure 2**). In this interaction, the motor cortex is the final output area that integrates incoming signals and sends information to the spinal cord and muscles. While in other movement disorders, specific brain regions could be linked to disease pathogenesis, for example, the basal ganglia in Parkinson's disease or the cerebellum in cerebellar ataxias, the anatomical basis of dystonia is still debated, as several brain regions have been implicated in the disease (31).

Neuropathological studies can be a powerful tool to elucidate the underlying mechanism of disease; however, in dystonia research, they have had minimal impact on our understanding because they have not shown any consistent structural brain abnormalities (31). This may be due to several reasons, including the small number of studies, a lack of systematic quantitative assessments, and, maybe most importantly, the substantial phenotypic and pathological heterogeneity in dystonia. While combined and complex dystonia forms often show neurodegeneration or developmental alterations in the cerebellum or basal ganglia, most studies on isolated dystonia have not revealed evidence of neuronal loss or overt neuroanatomical changes.

Early imaging studies based on computed tomography and magnetic resonance imaging (MRI) suggested a basal ganglia origin of dystonia. These studies investigated patients with acquired dystonia and revealed that focal lesions in the putamen (a part of the striatum) or GPi most commonly caused dystonia (32). This first model proposed that dystonia develops due to a hyperfunction of the direct pathway and a hypofunction of the indirect pathway, leading to reduced inhibition of the thalamus by the GPi and, ultimately, increased excitation of the motor cortex (33). However, additional lesion studies revealed that the thalamus, cortex, cerebellum, and brain stem are also frequently affected in acquired dystonia (34). Furthermore, imaging studies in patients with genetic and idiopathic dystonia have highlighted subtle abnormalities in all these brain regions even in the absence of apparent structural lesions (35). Even though the implicated areas are similar across studies, the results are inconsistent even for specific dystonia subtypes, and most studies do



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Schematic representation of brain circuits involved in dystonia. Dystonia is considered to arise from a dysfunctional brain network involving the cortico-cerebello-thalamo-cortical and cortico-striato-thalamo-cortical loops, which interact with each other in producing and modulating movement. The basal ganglia pathways have a well-established role in motor control: The striatum receives modulatory dopaminergic input from the substantia nigra pars compacta (SNc), which can stimulate direct or indirect pathway medium spiny neurons (MSNs). The indirect pathway [dopamine receptor 2 (D2)-type MSN] relays through the globus pallidus externus (GPe) and subthalamic nucleus (STN), leading to the excitation of globus pallidus internus (GPi) neurons (by the excitatory neurotransmitter glutamate), which inhibit thalamic neurons [by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA)] and reduce movement. In contrast, stimulation of the direct pathway [dopamine receptor 1 (D1)-type MSN] inhibits GPi neurons, consequently removing inhibitory input into the thalamus and facilitating movement through excitatory stimulation of the cortex. In addition, the so-called hyperdirect pathway includes excitatory projection directly from the cortex to STN, but its role in dystonia is less clear. Moreover, the involvement of the cerebellum in dystonia has been increasingly considered. GABAergic Purkinje cells of the cerebellar cortex project on downstream deep cerebellar nuclei, which, in turn, have direct connections to the basal ganglia via the thalamus, which is considered the primary hub structure of the two pathways. Moreover, GABAergic neurons in the ventral tegmental area (VTA) send inhibitory input to SNc dopaminergic neurons and thereby alter dopaminergic input into the striatum. Additionally, the VTA contains dopaminergic neurons that project directly to the striatum but are believed to play a more minor role in motor function (*dashed red line*). Importantly, no consensus exists on how exactly the different circuits are altered in dystonic versus healthy conditions. Dystonic movements may be caused by both pathological activation and suppression of the same pathway, and the relevance of each network component remains to be elucidated and may be distinct for different disease subtypes. For clarity reasons, the structures belonging to the basal ganglia (STN, GPe, GPi, striatum, and SNc) and the VTA are not located at the correct anatomical positions with respect to the coronal brain section in the background. Figure adapted from images created with BioRender.com.

not detect any abnormalities in discrete anatomical regions. However, the spatial and temporal patterns of brain activity (determined by fluorodeoxyglucose positron emission tomography) in the putamen, GPi, cerebellum, and motor cortex were shown to differ in dystonia patients compared with controls (36), suggesting that these structures are linked together in a network, and their abnormal connectivity underlies dystonia.

Generally, interventional studies have a greater potential to establish a causal link, so much of the research has also focused on animal models. In rodents, selective lesions in the striatum can cause dystonia (37, 38). Moreover, activation of excitatory glutamate receptors in the cerebellum can induce dystonia (39), and DBS of deep cerebellar nuclei or activation of inhibitory gamma-aminobutyric acid (GABA) receptors in the cerebellum alleviates dystonia (40, 41). Besides these phenotypic models, many genetic animal models have been developed to study the disease mechanism and have provided evidence that dystonia may be caused by abnormal cerebellar Purkinje cell or striatal neuron firing (35). However, a considerable limitation of the available genetic models is that most do not replicate the overt motor features found in human patients, impeding the establishment of cause and effect. Nevertheless, they have substantially contributed to our understanding of the molecular pathogenesis of many inherited dystonia forms (see the next section), demonstrating that the utility of a specific model largely depends on the research question. In humans, interventional studies are problematic for obvious reasons; however, the effectiveness of GPi-DBS in many dystonia forms (but not in others) has provided evidence for the involvement of the basal ganglia in at least certain subtypes.

The body of evidence suggests that dystonia does not result from the dysfunction of a single brain area but from a dysfunctional network involving the cortico-striato-thalamo-cortical and cortico-cerebello-thalamo-cortical loops (**Figure 2**) (16, 35, 42, 43). Traditionally, these two brain circuits were considered to be separated from each other, but currently, a more direct interaction is considered to play a critical role in dystonia (43). Direct connections between the cerebellum and

basal ganglia have increasingly been demonstrated (44). While the network model proposes that all dystonia subtypes arise from a dysfunctional interplay of basal ganglia, cerebellum, thalamus, and cortex, the exact relevance of each component remains to be elucidated and might be distinct for each dystonia subtype.

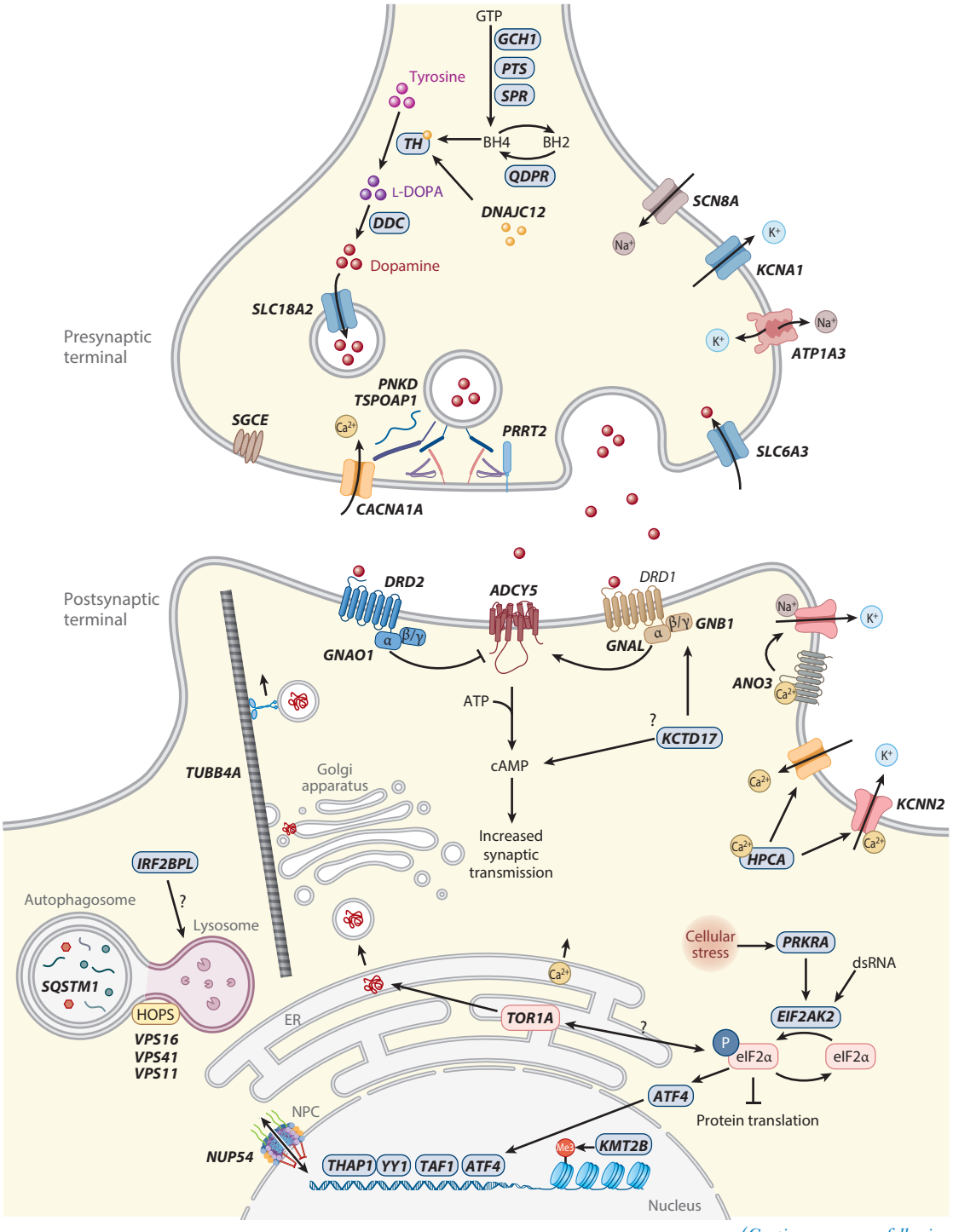
Molecular Mechanisms

While the discovery of genetic causes has led to a better understanding of dystonia pathogenesis, the relationships between the respective proteins and pathways often remain unclear. A central goal is to identify pathways and therapeutic targets shared by genetically distinct forms of dystonia, as apparently unrelated genetic forms could converge on shared downstream pathophysiological processes. Treatments targeting pathophysiological clusters would overcome the need to develop individualized therapeutics for each individual, and often extremely rare, dystonia subtype. Here, we address in detail seven pathways affected by monogenic forms of dystonia, including striatal dopamine signaling, gene transcription and neurodevelopment, calcium signaling and synaptic transmission, cellular stress response, endoplasmic reticulum (ER) and nuclear envelope (NE) function, cytoskeleton, and autophagy and lysosomal function. Other pathways such as mitochondrial dysfunction (other than that related to calcium homeostasis) and metal accumulation such as in Wilson's disease (copper) or neurodegeneration with brain iron accumulation (NBIA) are not discussed in detail here.

Striatal dopamine signaling. There has been much evidence indicating that defects in dopamine signaling in striatal neurons play a central role in dystonia pathogenesis. For instance, dystonia is often observed in patients with Parkinson's disease (45), which is associated with a loss of dopaminergic neurons in the substantia nigra (SNc), and dystonia is a frequent side effect in patients treated with antidopaminergic agents (46).

The striatum is the main input station of the basal ganglia and is mainly made up of medium spiny neurons (MSNs). MSNs receive excitatory glutamatergic input from the cortex and thalamus and modulatory dopaminergic input from the midbrain, especially the SNc (**Figure 2**). They are classified into D1-type dopamine receptor (D1R)-expressing (part of the direct pathway) and D2-type dopamine receptor (D2R)-expressing (part of the indirect pathway) neurons that are generally believed to exert opposite effects on movement control. The abovementioned traditional model of the imbalance between the direct and indirect pathway resulting in dystonia has been reassessed, and it is now believed that the spatial and temporal patterns of pathway activity (and, therefore, GPi activity) are more important (16).

Dystonia-linked genes affect striatal dopamine signaling at three stages: dopamine synthesis, cycling, and signaling (**Figure 3**). Pathogenic variants in *GCH1*, *SPR*, *PTS*, *TH*, and *QDPR* are linked to DRD (15). These genes are highly expressed in SNc dopaminergic neurons and are involved in dopamine synthesis or metabolism. Additionally, dopa decarboxylase deficiency (due to biallelic variants in *DDC*) causes complex dystonia, and biallelic variants in *DNAJC12*, encoding a heat shock protein that increases TH stability, have been linked to a neurodevelopmental syndrome with prominent dystonia and parkinsonism (11). Furthermore, loss-of-function (LOF) variants in *SLC18A2* (47), encoding a transporter for dopamine packing in synaptic vesicles, and *SLC6A3* (10), encoding a transporter for reuptake of synaptic dopamine, have been associated with autosomal recessive dystonia-parkinsonism. Importantly, the abovementioned genetic defects leading to reduced dopamine synthesis and release are treatable with pharmacotherapy (levodopa or dopamine agonists) or even viral vector–based gene therapy that has yielded promising results in DYT-DDC patients and a knockout (KO) mouse model for DYT/PARK-SLC6A3 that replicates the human phenotype (48).



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Molecular mechanism of dystonia genes. Genes implicated in dystonia (boldface) are involved in several neuronal cell functions, and many are functionally connected through mutual regulation. Molecular functions include dopamine synthesis and processing (*GCH1*, *PTS*, *SPR*, *QDPR*, *TH*, *DNAJC12*, *DDC*, *SLC18A2*, and *SLC6A3*), ion channels or pumps regulating neuronal excitability (*SCN8A*, *KCNA1*, *ATP1A3*, *CACNA1A*, and *KCNN2*), synaptic vesicle release (*TSPOAP1*, *PNKD*, and *PRRT2*), G protein–coupled receptor signaling (*ADCY5*, *DRD2*, *GNAL*, *GNB1*, and *GNAO1*), cellular stress response (*PRKRA*, *EIF2AK2*, *TOR1A*, and *ATF4*), calcium homeostasis (*ANO3*, *HPCA*, and *TOR1A*), autophagy and lysosomal function (*VPS16*, *VPS41*, *VPS11*, *SQSTM1*, and *IRF2BPL*), regulation of gene transcription (*KMT2B*, *THAP1*, *YY1*, *TAF1*, and *ATF4*), protein processing and trafficking (*TOR1A*, *TUBB4A*, and *NUP54*), and synapse assembly and structure (*SGCE* and *TUBB4A*). The figure shows a presynaptic dopaminergic neuron and postsynaptic medium spiny neuron (expressing D1-type or D2-type dopamine receptors) as an example, but dystonia genes may also primarily function in other brain cells, for instance, in the cerebellum. Details about the function of the represented genes and biological consequences due to dystonia-causing genetic variants can be found in the main text. Abbreviations: ER, endoplasmic reticulum; HOPS, homotypic fusion and protein sorting complex; NPC, nuclear pore complex. Figure adapted from images created with BioRender.com.

The first clue of an important link between dopamine signaling and non-DRD came from the discovery of heterozygous pathogenic variants in *GNAL* [encoding G protein G(olf) subunit alpha (Gαolf)]. Gαolf is coupled to D1R. Upon dopamine binding, Gαolf dissociates from the beta-gamma subunit and activates adenylate cyclase type 5 (AC5), resulting in the production of the second messenger cAMP (cyclic adenosine monophosphate) and increased neuronal activity (49). Thus, pathogenic variants in *GNAL*, which are mostly LOF alleles (50, 51), are expected to lead to an uncoupling of D1R activation and cAMP production, resulting in reduced direct pathway activity. Notably, Gαolf is also coupled to adenosine receptor 2A, which has a less-defined role in motor function but is evidenced to colocalize with D2R and modulate indirect pathway activity (52). Interestingly, pathogenic variants in *ADCY5*, the gene encoding AC5, are also associated with mixed movement disorders, including dystonia (11). In contrast to *GNAL*, variants in *ADCY5* were shown to be gain-of-function (GOF) alleles, leading to increased cAMP production in cell-based assays (53). Therefore, dystonic movements may be caused by both pathological activation and suppression of the direct pathway, further supporting the idea that the simple model of decreased thalamus inhibition is not suitable.

Additional components of dopamine receptor signaling have been implicated in dystonia: Patients with heterozygous *GNAO1* variants [encoding G protein G(o) subunit alpha (Gαo)] can present with predominant or isolated dystonia (11, 54). Gαo is coupled to D2R and, upon dopamine binding, inhibits AC5 activity and cAMP production, influencing the excitability of indirect pathway neurons. Phenotypic outcomes likely depend on the specific pathogenic variant (54). Additionally, heterozygous variants in *GNB1*, a gene linked to neurodevelopmental delay and dystonia, may impact striatal dopamine signaling. The gene encodes the β1 subunit of G protein G(olf) that interacts with the *GNAL* gene product Gαolf. Pathogenic *GNB1* variants may reduce the association with Gαolf and reduce coupling to D1R (55). Furthermore, the beta-gamma subunit also signals to various downstream effectors, for example, inhibiting presynaptic voltage-gated calcium and potassium channels, thereby affecting neurotransmitter release (56). Additionally, variants in dopamine receptors were directly linked to movement disorders when, for instance, a variant in *DRD2* (encoding D2R) was reported to cause childhood-onset chorea with prominent dystonia in a large pedigree (57).

Pathogenic variants in other DYT genes, although without obvious functional connection, were also shown to be associated with altered striatal dopaminergic neurotransmission. For DYT-TOR1A, the most prevalent genetic form of isolated dystonia, knock-in rodent models carrying the recurrent trinucleotide GAG deletion demonstrated alterations in both pre- and postsynaptic dopamine signaling, namely impaired dopamine release (58) and deficient D2R signaling (59). For DYT-THAP1, mice with conditional knockout (cKO) of *THAP1* in the central nervous

system (CNS) displayed impaired D2R signaling and differential expression of genes involved in dopamine signaling, including *DRD2*, *ADCY5*, *GNAL*, and *SLC6A3* (60). Additionally, functional work in *Drosophila* has revealed that the homologs of *KCTD17* and *HPCA* disrupt dopaminergic postsynaptic pathways (61–63).

A recent systems biology approach (64) further supported the central role of dopaminergic signaling in dystonia. The study aimed to identify the cellular specificity of all currently known DYT genes and predict their functional relationships in the adult brain. Dystonia genes were overall enriched in striatal MSNs (in particular *ADCY5*, *GNAL*, *ANO3*, *KCTD17*, and *HPCA*), and these genes were associated with synaptic transmission, especially with postsynaptic structures. These findings suggest that especially the postsynaptic function of MSNs may be critical in dystonia pathogenesis. Remarkably, none of the non-DRD genes were specific to dopaminergic neurons or coclustered with the DRD genes, supporting the view of DRDs as a distinct subgroup from both a clinical and a biological perspective.

Gene transcription and neurodevelopment. Pathogenic variants in *THAP1* and *KMT2B* are frequent causes of isolated dystonia (13), and the gene products are involved in the regulation of gene expression as transcription factors or histone methyltransferases, indicating that aberrant transcriptional regulation is a molecular mechanism in dystonia pathogenesis. *THAP1* encodes the THAP domain–containing protein 1, a zinc-finger transcription factor that regulates gene transcription. Most dystonia-causing missense variants are located within the DNA binding domain (13) and alter the sequence-specific DNA binding ability of the protein (65), leading to reduced transcriptional activity (66). Other variants hinder the protein from being localized to the nucleus (67) or disrupt the dimerization of THAP1 with itself or cofactors (68, 69)—in any case resulting in LOF and altered gene transcription of target genes, some of which have been identified in transcriptome studies and may include other dystonia-related genes (70–72). A recent study in induced pluripotent stem cell (iPSC)-derived MSNs from DYT-THAP1 patients further registered a reduced expression of $GABA_A$ receptor alpha-2 subunit, suggesting that loss of THAP1 leads to reduced GABAergic synaptic transmission in the basal ganglia (73).

Insights from rodent models have shed further light on the consequences of loss of THAP1 function. *THAP1* cKO in the murine CNS provided evidence that the protein is essential for myelination and CNS maturation, as its conditional deletion delays maturation of the oligodendrocyte lineage and leads to persistent motor deficits (74). Transcriptional alterations consequential to the loss of THAP1 function were greater at younger ages, further indicating that *THAP1* is particularly important during neurodevelopment (75). In the striatum and cerebellum, significant changes in gene expression particularly affected genes involved in regulating neuronal growth, synaptic transmission, gliosis, cytokine signaling, and myelination. Intriguingly, among the differentially expressed genes were other dystonia-causing genes, including *GCH1*, *TH*, *SGCE*, *ANO3*, *GNAL*, and *TUBB4A* in the striatum and *KMT2B* in the cerebellum (70), linking several DYT genes on the molecular level. An interaction of *THAP1* and *TOR1A* was already reported in earlier studies: THAP1 targets the *TOR1A* promotor in vitro to suppress its transcription, and this suppression is decreased in *THAP1*-mutated cells (76, 77).

KMT2B (histone-lysine *N*-methyltransferase 2B) encodes an epigenetic writer involved in transcriptional regulation through methylation of a lysine residue (K4) of the histone 3 (H3) protein, a component of the DNA-packing chromatin. H3K4 methylation is associated with active transcription, specifically important for transcriptional consistency and stability during cell division (78, 79). Like *THAP1*, *KMT2B* has the highest brain regional expression in the cerebellum and plays an essential role in normal development and maturation of brain circuits involved in motor control. It is involved in the differentiation of embryonic stem cells (80) and regulates only

a specific set of genes rather than being responsible for the overall levels of H3K4 methylation in the genome (81). Very recently, this specificity was further elucidated with the discovery of a unique DNA methylation pattern in peripheral blood from DYT-KMT2B patients that has been described by three independent studies (82–84) and differed from epigenetic alterations made by other KMT2 methyltransferases. This so-called episignature is based on CpG methylation, an epigenetic mechanism known to be inversely correlated to H3K4 methylation (85). Loss of KMT2B function was associated with hypermethylation of these CpG sites, consequential to loss of H3K4 methylation, indicating that haploinsufficiency is likely the disease mechanism underlying DYT-KMT2B. This is in line with the observation that most mutations found in patients are truncating LOF variants, but some missense variants also have been shown to affect enzyme activity with the same molecular consequence (84).

Remarkably, a recent study in mouse embryonic stem cells revealed that it is not the methylation of H3K4 itself that underlies KMT2B's transcriptional regulation. Instead, while binding to the target gene's promotor region, KMT2B functions as a repellent for other histone methyltransferases and the DNA methylation machinery that is associated with silent transcription (86). In other words, KMT2B prevents active suppression. This raises the possibility that *KMT2B*-dependent transcription, which is reduced in DYT-KMT2B patients, could potentially be rescued by inhibition of other epigenetic enzymes.

Intriguingly, an interaction between *KMT2B*, *THAP1*, and *TOR1A* has been suggested. In fibroblasts from *KMT2B* mutation carriers, reduced levels of *TOR1A* and *THAP1* mRNA were detected, indicating that KMT2B may be an upstream regulator of other DYT genes (81).

Another link between transcriptional regulation and dystonia pathogenesis was made with the discovery of *YY1* (yin and yang 1) as a cause of complex neurological syndromes with dystonic features (87, 88). *YY1* encodes a zinc-finger transcription factor with the highest brain regional expression in the cerebellum. Like THAP1, the protein has a known key role in neurodevelopment and myelination, and it is particularly important for maturation of the oligodendrocyte lineage. In fact, it has been suggested that the proteins encoded by *YY1* and *THAP1* interact as coregulators of the same genes, as loss of THAP1 function also reduces the DNA occupancy of YY1 (74, 89).

Aberrant transcriptional regulation is also likely the molecular basis of *TAF1*-related X-linked dystonia-parkinsonism (XDP) (90). Downregulation of *TAF1* in XDP patients compared with controls has been shown in postmortem striatum tissue (91) and in iPSC-derived neural stem cells at early stages (92). Transcriptional changes following *TAF1* KO particularly affect genes involved in neurodevelopment and synaptic transmission and histone genes (93). *TAF1* (TATA-box binding protein–associated factor 1) encodes a transcription factor that is part of the transcription factor IID complex involved in RNA polymerase II–mediated transcription. It is ubiquitously expressed but also has the highest brain regional expression in the cerebellum, and brain-specific isoforms exist. During normal development in mice, *TAF1* expression is extremely elevated in the embryonic stage and decreased and maintained at stable levels from postnatal week three onward (94), suggesting an essential function of TAF1 during embryogenesis. Notably, while coding variants in *TAF1* lead to a severe neurodevelopmental disorder (95), an intronic SVA insertion is the cause of XDP (96), which may have a milder impact on the protein's level and function and thus downstream transcriptional changes.

These findings reveal that transcriptional alterations occurring during early development underlie certain subtypes of hereditary dystonia, supporting the view of dystonia as a neurodevelopmental circuit disorder. Even though these alterations bring about multiple different effects, they seem to converge in aberrant signal transmission in striatal and cerebellar neurons, with several different DYT genes being connected on the molecular level through mutual regulation.

Calcium signaling and synaptic transmission. Calcium (Ca^{2+}) ions are considered key signaling molecules in the cell (97). In neurons, they regulate neurotransmitter release, neuronal excitability, and synapse formation (98). The precise temporal and spatial regulation of responses to even subtle changes in intracellular Ca^{2+} levels is of high importance in modulating synaptic vesicle release and neuronal activity. These changes arise from either Ca^{2+} influx from the extracellular space or the release of Ca^{2+} from the ER (99), the primary Ca^{2+} storage site in the cell. Further, a functional interaction between the ER and mitochondria modulates cell bioenergetics and functionality since Ca^{2+} released by the ER is taken up by mitochondria, where it regulates the activity of transporters, enzymes, and proteins involved in organelles' metabolism (100). Notably, several forms of complex dystonia are associated with genes linked to mitochondrial function (e.g., *COX20*, *SERAC1*, *SUCLA2*, and *TIMM8A*; see **Figure 1**) and result from defects in energy homeostasis, but these are reviewed elsewhere (101). Furthermore, several proteins involved in synaptic transmission—specifically, membrane depolarization and repolarization by ion currents, vesicle release, and calcium homeostasis—have been implicated in dystonia (**Figure 3**).

Pathogenic variants in *ATP1A3* underlie rapid-onset dystonia-parkinsonism (RDP). The gene encodes the neuron-specific α3 subunit of the Na^+/K^+-ATPase (NKA α3) pump, which generates electrochemical ion gradients essential for maintaining and restoring resting membrane potentials, initiating action potentials, and neurotransmitter release. Heterozygous *ATP1A3* variants may result in reduced catalytic activity and a failure to generate the pump currents (102). In rodents, simultaneous pharmacological blockage of the pump in both the cerebellum and basal ganglia replicated the features of RDP (41), whereby blocking in the basal ganglia alone resulted in parkinsonism and, on the other hand, cerebellar blockage resulted in dystonic movements. Furthermore, the authors observed cerebellar hyperactivity during dystonic movements that could be alleviated by acute perfusion of GABA into the cerebellum. This aberrant cerebellar activity was found to adversely affect basal ganglia function, supporting earlier findings that cerebellar output nuclei alter the neuronal firing rates and dopamine levels in the basal ganglia. Recently, the first human in vivo evidence in RDP patients showed that Na^+ predominantly accumulated inside cerebellar cells due to pump deficiency (103). Another hint implicating the cerebellum as the primary instigator in this disease is that while other neurons can upregulate other NKA isoforms to compensate for dysfunctional NKA α3, cerebellar Purkinje cells lack this option due to exclusive expression of this specific isoform (104). Additionally, NKA α3 plays a vital role in regulating intracellular Ca^{2+} levels since any alterations in Na^+ also affect Ca^{2+}. Blockage of NKA α3 leads to an increase in both Na^+ and Ca^{2+} (98), which is believed to result in abnormally high neuronal firing rates.

Moreover, ion channels influencing neuronal excitability and implicated in movement disorders including dystonic features are encoded by *KCNN2* (small conductance calcium-activated potassium channel, SK2) (105) and *KCNA1* (voltage-gated potassium channel, Kv1.1) (106). As potassium channels, they contribute to repolarization after action potentials by generating an efflux of K^+ ions, thereby dampening neuronal firing rates. For *KCNN2*, this is coupled to changes in intracellular Ca^{2+} levels. Disease-related LOF variants lead to increased neuronal excitability, affecting primarily cerebellar neurons (105, 107).

Very recently, biallelic LOF and missense variants in *TSPOAP1* have been linked to complex and isolated dystonia, respectively (108). The gene encodes RIMBP1, a central component of the presynaptic active zone that determines the precise localization of presynaptic voltage-gated calcium channels (VGCCs), thus ensuring tight coupling between incoming action potentials and Ca^{2+}-dependent vesicle release. Missense variants were shown to lead to abnormally increased synaptic transmission in cerebellar Purkinje cells, likely due to the recruitment of more VGCCs to the active zone. In contrast, LOF variants are expected to reduce the density of VGCCs in

the active zone, suggesting that both decreased and increased cerebellar synaptic transmission can underlie dystonia. Interestingly, variants in *CACNA1A*, encoding a VGCC, have recently been linked to prominent dystonia (47, 109). As with *TSPOAP1*, both LOF and GOF were identified in patients, leading to irregular firing of cerebellar Purkinje cells. Moreover, *CACNA1A* null mice develop dystonia associated with cerebellar atrophy (110).

Other hints for aberrant vesicle release underlying dystonic phenotypes are pathogenic variants in *PNKD* and *PRRT2*, both associated with paroxysmal dyskinesias with prominent dystonia in a subset of patients. Both genes encode proteins that negatively regulate presynaptic vesicle release, and disease-related LOF variants lead to increased synaptic transmission, especially within cerebellar Purkinje cells (111, 112). In *PRRT2*-related disease, defective coupling of presynaptic Ca^{2+} influx and vesicle release was suggested to lie at the core of the disease (113). Additionally, PRRT2 was shown to negatively regulate SCN8A (114)—pathogenic variants in this gene cause a similar phenotype including dystonia. *SCN8A* encodes a voltage-gated sodium channel essential for rapid membrane depolarization as part of action potentials, and mice harboring *SCN8A* pathogenic variants exhibit abnormal sodium currents in cerebellar Purkinje cells and cortical pyramidal neurons (115).

HPCA, a gene linked to isolated dystonia (13), encodes the neuron-specific calcium-binding protein hippocalcin, mainly expressed in striatal MSNs. Upon cytosolic Ca^{2+} binding, the protein undergoes a conformational change leading to translocation from the cytosol to the plasma membrane. This translocation was shown to result in K^+ currents that control neuronal spike frequency by slow afterhyperpolarization (116). Also, hippocalcin is evidenced to directly interact with VGCCs (117), and loss of this interaction in *HPCA* knockdown neurons led to an uncoupling of depolarization and Ca^{2+} influx (118). Consequently, Ca^{2+} influx through N-type calcium channels increases, resulting in increased vesicle release. Different pathogenic variants either prevent hippocalcin's translocation and the accompanied K^+ currents or lead to increased Ca^{2+} influx and vesicle release. Either way, the result is hyperexcitability of striatal neurons (119).

Moreover, involvement of impaired calcium homeostasis and synaptic transmission in dystonia is supported by pathogenic variants in *ANO3* and *KCTD17*, although the gene products have less defined functions. *ANO3* encodes anoctamin-3, belongs to a family of calcium-activated chloride channels, and is most highly expressed in striatal neurons (120). While the name suggests the involvement of chloride channels in dystonia pathogenesis, it has now been demonstrated that ANO3 does not have ion channel activity (121). Instead, evidenced functions of the protein include direct interaction with sodium-activated potassium channels, which are involved in resting membrane potential maintenance and, therefore, neuronal excitability (121). ANO3 dampens excitability by increasing the sodium sensitivity of the channel. In line with this finding, *ANO3* KO rats show a significant reduction of K(Na) currents accompanied by a decreased threshold for action potential firing leading to increased neuronal firing (122). A second function of ANO3 is that of a lipid scramblase that dissipates the asymmetrical distribution of phospholipids in the plasma membrane in response to small increases in intracellular Ca^{2+} levels—a critical process in apoptosis and modifying synaptic connections (121). However, how this function is linked to dystonia remains unclear. Lastly, ANO3 may act as a Ca^{2+} sensor that regulates Ca^{2+} homeostasis in neurons. Cell studies have demonstrated clear abnormalities in ER-dependent Ca^{2+} signaling in *ANO3*-mutated cells. It is suggested that ANO3 influences Ca^{2+} signaling by reducing the Ca^{2+} pool inside the ER (120). While it remains to be investigated how mutant ANO3 impairs signal transduction, it is conceivable that it leads to abnormal striatal neuron excitability.

KCTD17 encodes a member of the potassium channel tetramerization domain proteins. However, unlike what the name suggests, the protein is not predicted to form transmembrane domains but was shown to be distributed in the cytosol, dendritic projections, and synapses (62).

Expression studies showed that *KCTD17*, *ANO3*, and *HPCA* belong to the same putaminal coexpression network (see above), suggesting that all three proteins function mainly in the striatum and are functionally interconnected. It was recently demonstrated that KCTD17 may modulate neuronal excitability by regulating cAMP production and G protein β-subunit levels (123). In addition, fibroblasts carrying pathogenic *KCTD17* variants displayed abnormalities in Ca^{2+} release from the ER in response to different stimuli (124). Similar to ANO3, this is believed to be due to a reduced Ca^{2+} pool in the ER.

Finally, other dystonia forms have been linked to perturbed Ca^{2+} homeostasis. *TOR1A* knock-in mice displayed increased amplitudes of Ca^{2+} currents after depolarization in striatal neurons (125), and iPSC-derived MSNs from *SGCE*-mutation carriers displayed elevated basal intracellular Ca^{2+} levels compared with controls (126).

The exact cellular mechanism by which abnormalities in Ca^{2+} homeostasis can lead to dystonia, or whether they are instead a consequence, is poorly understood. However, it can be inferred that impaired Ca^{2+} handling leads to altered cellular sensitivity to Ca^{2+}, which in turn induces rapid neuronal repolarization after action potentials. This would enable faster firing rates and manifest in hyperexcitability of the affected brain regions—as stated above, affecting primarily cerebellar (*ATP1A3*, *KCNA1*, *CACNA1A*, *TSPOAP1*, *PNKD*, *PRRT2*, *SCN8A*, and *KCNN2*) or striatal (*HPCA*, *ANO3*, and *KCTD17*) neurons. Regarding treatment, the involvement of dysregulated Ca^{2+} responses raises exciting possibilities, as selective calcium channel blockers and modulators are abundant in the drug market.

Cellular stress response. Another major area of functional convergence among DYT genes is the regulation of the cellular stress response. The eIF2α (eukaryotic initiation factor 2 alpha) pathway is an essential and conserved component of the integrated stress response (ISR). It is activated by various types of stress stimuli, for example, viral infections, unfolded proteins in the ER, hypoxia, and nutrient deprivation, to restore cellular homeostasis (127). The core event of the pathway is the phosphorylation of eIF2α by one of four members of the eIF2α kinase family, leading to a decrease in global protein synthesis and induction of selected genes that either promote cellular recovery and restore homeostasis or induce apoptosis (**Figure 3**). Accordingly, transient eIF2α phosphorylation is generally favorable for cellular survival, while prolonged phosphorylation due to exposure to severe stress is proapoptotic (128).

Pathogenic variants in two key players of this process, namely *PRKRA* and *EIF2AK2*, have been linked, although rarely, to isolated dystonia (13, 14). *EIF2AK2* (eukaryotic translation initiation factor 2 alpha kinase, also referred to as PKA or PKR) is one of the kinases responsible for eIF2α phosphorylation. It is activated either by double-stranded RNA (due to viral infections) or through the binding of PRKRA (interferon-inducible double-stranded RNA–dependent protein kinase activator A) in response to cellular stress (129). All pathogenic *EIF2AK2* variants reported thus far are located within one of the double-stranded RNA binding motifs of the protein, which is also the site of interaction with PRKRA (14). Functional studies in DYT-EIF2AK2 patients' fibroblasts revealed that the mutated protein led to prolonged phosphorylation of eIF2α in response to stress and, therefore, to persistent activation of the eIF2α pathway (130). It is suggested that this might lead to a failure to activate survival mechanisms, resulting in enhanced cellular death or consistent cellular abnormalities.

As introduced above, PRKRA is an important regulator of EIF2AK2. The most common dystonia-causing *PRKRA* variant (p.P222L) was shown to lead to prolonged and enhanced activation of EIF2AK2 in response to ER stress in patient cells, pointing to a GOF mechanism (131). The intensified activation was due to altered binding kinetics of the mutated PRKRA protein, reflected by an increased affinity of the PRKRA-EIF2AK2 interaction. A subsequent study

confirmed the same effect for other dystonia-associated *PRKRA* variants (132). Therefore, mutated PRKRA seems to increase cellular susceptibility to ER stress, disabling the cells from coping with cellular stress and restoring homeostasis. Furthermore, brain imaging findings in DYT-PRKRA patients suggested nigrostriatal neurodegeneration (133, 134), indicative of enhanced cellular death consequential to the intensified stress response. Nevertheless, because neurodegeneration is usually not observed in dystonia, future studies are needed to investigate whether apoptosis is indeed a cellular consequence in DYT-EIF2AK2 and DYT-PRKRA.

Pathogenic variants in a third gene that is part of the eIF2α pathway, *ATF4*, were reported in patients with cervical dystonia (135); however, this report is pending confirmation by additional studies. ATF4 is a transcription factor and an effector of EIF2AK2.

In addition, stress-induced eIF2α signaling has been reported to be significantly dysregulated in other forms of dystonia, namely DYT-TOR1A (135, 136), DYT-THAP1 (137), and XDP (96). Furthermore, cellular stress response is tightly linked to Ca^{2+} signaling, as Ca^{2+} ions released from the ER are involved in integrating and regulating cellular stress–coping mechanisms in response to various stress stimuli (97).

The discovery of aberrant eIF2α signaling underlying certain forms of dystonia brings about exciting therapeutic possibilities. A recent study discovered that the flavonoid luteolin was sufficient to disrupt the PRKRA-EIF2AK2 interaction. Consequently, the increased sensitivity of patient cells to ER stress was rescued, and the cells were protected from ER stress–induced apoptosis (132). Hence, a pharmacological inhibitor that disrupts this interaction in the brain could benefit DYT-EIF2AK2 and DYT-PRKRA patients. Furthermore, the implication of eIF2α signaling in dystonia pathogenesis suggests that response to viral infections (which trigger the ISR) may be a potential risk factor for disease development in patients harboring genetic variants associated with reduced penetrance. An important future question will be to determine where in the brain selective vulnerability to altered eIF2α signaling occurs and how pathogenic variants in the abovementioned ubiquitously expressed genes manifest in dystonia.

Endoplasmic reticulum and nuclear envelope function. The function and stress response of the ER is also tightly linked to *TOR1A*—the main dystonia gene (13), in which a 3-base-pair deletion leading to the deletion of a glutamate residue (ΔE) is the most frequent pathogenic variant. *TOR1A* encodes torsinA, a protein belonging to the AAA+ family that uses ATP hydrolysis for several cellular functions, including protein trafficking, refolding, and degradation (138). Studies have demonstrated that expression of ΔE torsinA is associated with abnormalities in protein folding and trafficking (139), affecting, for example, D2R processing in striatal neurons (see above). Additionally, a role for torsinA in the maintenance of ER protein homeostasis and, thus, prevention of ER stress has been demonstrated. In line with this finding, ΔE torsinA has been linked to increased ER stress (140) and sensitivity to ER stress (141). TorsinA is ubiquitously expressed in all tissues, while the DYT-TOR1A phenotype is restricted to the nervous system. This may be due to the homologous protein TOR1B, whose expression rescues phenotypes caused by TOR1A dysfunction in cells, except in neurons where *TOR1B* is not expressed (142).

Wild-type torsinA cycles between the ER and the contiguous NE, with the bulk of protein detected in the ER (143). In contrast, ΔE torsinA predominantly colocalizes with NE markers and disrupts the normal NE membrane structure, resulting in the formation of NE-derived bleb-like structures and trafficking defects (144, 145). In the heterozygous state, ΔE torsinA also recruits wild-type torsinA to the NE, causing a dominant-negative effect (143). This mislocalization of ΔE torsinA was utilized to study which cellular pathways are modifiers of the pathologic phenotype observed in DYT-TOR1A. Interestingly, the eIF2α signaling pathway was the top hit (135), and knockdown of each of the four eIF2α kinases (including EIF2AK2) was shown to worsen the

mislocalization significantly. This suggests that decreased eIF2α signaling might play a central role in the disease mechanism of DYT-TOR1A (in contrast to DYT-EIF2AK2 and DYT-PRKRA, where increased eIF2α signaling is the underlying pathomechanism).

Very recently, the role of the nuclear pore complex (NPC) and a subset of its components, the phenylalanine-glycine-rich region–containing nucleoporins (FG-NUPs), has been highlighted in the etiology of DYT-TOR1A (146). NPCs form channels in the NE that control the bidirectional transport of proteins, mRNA, and other macromolecules between the cytoplasm and nucleus. The abnormal bleb-like structures observed in *TOR1A*-mutated cells were shown to result in NPC biogenesis deficits and, therefore, deficient nuclear transport. Furthermore, these structures contain nonfunctional FG-NUP condensates that lead to the sequestration of protein quality-control network components, ultimately triggering ER stress. The vulnerability window associated with penetrance of *TOR1A*-related dystonia may be explained by the transient nature of blebs and depends on the effectiveness of cells in coping with nuclear-transport defects and proteotoxicity. Additionally, biallelic variants in one of the nucleoporin genes itself, *NUP54*, were recently linked to early-onset complex dystonia with striatal lesions (147). Intriguingly, abnormal NEs were also a reported feature of cerebellar Purkinje cells of *SGCE* KO mice (148), suggesting that nucleoporins may have broader mechanistic implications across different dystonia subtypes.

A role for torsinA in NPC-independent transport across the NE has also been demonstrated. In contrast to the canonical mRNA export through NPCs, mRNAs can be part of large ribonucleoprotein complexes that exit the nucleus via NE budding and are transported to specific cellular locations. This process, in which torsinA is a vital mediator, is particularly essential for synapse formation and plasticity. In the absence of torsinA, ribonucleoproteins are sequestered in the perinuclear space of the NE and do not reach their synaptic target, impairing proper synaptic protein synthesis and, thus, synaptic terminal development (144).

In summary, the diverse functions attributed to torsinA (and to the ER/NE system), including protein processing, trafficking of biomolecules, and regulation of stress response, seem to be vital for neurodevelopment and synaptic plasticity and function. Pathogenic *TOR1A* variants, in particular the recurrent GAG deletion, impair these functions, resulting in multiple downstream consequences such as abnormal receptor composition and defective synaptic physiology. It is proposed that the basal ganglia are the brain structure most affected by torsinA dysfunction (139). Further studies are required to explore which mechanisms cause dystonia and which are merely subclinical consequences. As eIF2α signaling and nuclear transport dysfunction are also implicated in other dystonia subtypes, they are likely relevant in the disease pathogenesis.

Autophagy and lysosomal function. Evidence suggests an involvement of the endolysosomal and autophagic systems in dystonia pathogenesis. For instance, many lysosomal storage disorders, in which lysosomal dysfunction leads to the accumulation of various substrates in cells, can present with prominent complex dystonia (e.g., Niemann-Pick type C and GM1 gangliosidosis). Patients affected by these diseases often display characteristic pathologic imaging findings affecting the striatum (149).

The first clue to an important link between autophagy and lysosomal function and isolated dystonia came from the discovery of mutations in the *VPS16* gene (150). This gene encodes vacuolar protein sorting–associated protein 16 homolog, a part of the homotypic fusion and protein sorting (HOPS) complex comprising six proteins (VPS11, VPS16, VPS18, VPS33A, VPS39, and VPS41). The HOPS complex mediates the fusion of late endosomes and autophagosomes with lysosomes and, therefore, plays a fundamental role in removing misfolded or aggregated proteins and damaged cellular organelles (151). *VPS16* has the highest brain regional expression in the cerebellum but is also expressed in many other brain regions. Almost all identified disease-causing

variants lead to a loss of protein function (14). Electron microscopy studies in cultured patients' fibroblasts revealed vacuolar changes consistent with lysosomal dysfunction and indicative of an impaired function of the HOPS complex (152). This observation also confirmed two earlier studies: Abnormal accumulation of vacuoles was demonstrated in a *Drosophila VPS16* knockdown model (153), and depletion of *VPS16* in a human cell line study resulted in an impairment of endosomal-lysosomal function (154).

Biallelic variants in two additional HOPS complex components, namely *VPS11* and *VPS41*, have been linked to complex neurodevelopmental disorders with dystonia (152, 155, 156). Functional studies in patient-derived fibroblasts carrying variants in *VPS16*, *VPS11*, and *VPS41* display comparable abnormalities of the lysosomal and autophagic compartments (152, 157). It is postulated that this may hinder key cellular processes within the neural networks involved in motor control, ultimately manifesting in dystonic movements (152). While disease-related variants in *VPS16*, *VPS11*, and *VPS41* display overlapping abnormalities on the cellular level, imaging findings suggest some differences in the pathophysiology of the disorders. For example, brain MRI of all investigated patients with VPS41-related disease demonstrated progressive cerebellar atrophy. On the other hand, patients with VPS11-associated dystonia, as well as some DYT-VPS16 patients, showed subtle basal ganglia changes (157). Hence, the brain structures primarily affected by the disorders may be distinct, supporting the view that dystonia is a network disorder without one unifying causative mechanism or brain area.

Interestingly, for some patients with *VPS16* and *VPS41* variants, imaging findings were indicative of brain iron accumulation (157). Complex dystonia is one of the most frequent clinical presentations of NBIA, a group of genetic disorders displaying iron accumulation in the basal ganglia (e.g., linked to *DCAF17*, *PANK2*, and *CP*; see **Figure 1**) that is also tightly linked to lysosomal dysfunction (reviewed in 158).

In addition to the discussed HOPS-associated disorders, other dystonias have been linked to pathogenic variants in endolysosomal and autophagic pathways. These include *IRF2BPL*, linked to complex dystonia and encoding a zinc-finger transcription factor that may also function as a ubiquitin ligase (159). Electron microscopy studies in cultured patients' fibroblasts confirmed extensive abnormalities consistent with lysosomal dysfunction (160). Additionally, it is suggested from imaging findings that nigrostriatal degeneration may contribute to the disorder (161).

Another example is *SQSTM1*, which encodes an autophagy receptor (sequestosome 1/p62) that targets ubiquitinated cargos to the autophagosome and, therefore, plays a vital role in autophagy regulation. Biallelic LOF variants were reported in several unrelated cases with childhood-onset neurodegeneration presenting with dystonia, ataxia, cognitive decline, and gaze palsy (162–164). Functional work in cultured patients' fibroblasts demonstrated clear abnormalities in autophagy flux and mitophagy (autophagy of mitochondria). Intriguingly, *SQSTM1* is known to be part of an autophagy gene transcription program that is induced in response to ER stress via the eIF2α-signaling pathway (165). It has been suggested that the eIF2α-ATF4 pathway is the major regulatory pathway that induces the transcriptional activation of a large number of autophagy genes in response to cellular stress. Thus, these findings link two cellular pathways involved in dystonia pathogenesis, integrated stress response and autophagy, on the molecular level.

Given the substantial relationship between the discussed dystonia forms and lysosome-associated disorders, possible therapeutic approaches may be deduced from lysosome-associated disorders, including autophagy inducers, small-molecule chaperones, or substrate-reducing molecules, which are already under study (166, 167).

Cytoskeleton. Some forms of dystonia indicate that abnormalities in the cytoskeleton can underlie dystonic phenotypes. A relevant example is the ε-sarcoglycan gene (*SGCE*), linked to

myoclonus-dystonia (MD). The protein belongs to the sarcoglycan family comprising six different transmembrane glycoproteins (α, β, γ, δ, ε, and ζ), which are best known for their function in muscular tissue, where they form part of the dystrophin-glycoprotein complex (DGC) that links the cytoskeleton to the extracellular matrix (168).

Two major hypotheses of the disease mechanism of MYC/DYT-SGCE have been proposed. First, since *SGCE* belongs to the imprinted genes, which are generally known to be involved in multiple developmental processes, it is believed to be crucial during brain development. In line with this hypothesis, *SGCE* was shown to be ubiquitously and highly expressed during embryonic development in rodents. Thereafter, the expression dramatically declined but was preserved in neurons, with high levels in cerebellar Purkinje cells (169). In the human brain, the major brain-specific isoform (11b) is also mainly expressed in the cerebellum and moderately expressed in the striatum (170). Hence, the expression pattern of the gene suggests that the disease has at least a neurodevelopmental component (like, e.g., DYT-THAP1 and DYT-KMT2B).

Second, abnormal synaptic transmission and Ca^{2+} homeostasis have been implicated in SGCE-related disease. The brain-specific isoform was shown to be enriched in presynaptic structures (171) and to interact with postsynaptic scaffolding proteins, suggesting that ε-sarcoglycan plays an essential role in synapse assembly and function (172). Furthermore, ε-sarcoglycan may be part of DGC-like complexes in the brain. As loss of dystrophin is known to cause increased activity of Ca^{2+} channels in neurons, it is hypothesized that loss of ε-sarcoglycan could likewise result in neuronal membrane damage and Ca^{2+} accumulation (173). A recent study in iPSC-MSNs confirmed elevated basal intracellular Ca^{2+} levels in patient-derived cells compared with controls (126). Even though it is tempting to speculate that the pathophysiological changes in *SGCE*-related MD arise from a DGC dysfunction in the brain, it remains to be investigated whether ε-sarcoglycan is genuinely a part of DGC-like complexes in the brain and how the whole DGC function would be affected by a loss of this protein. ε-Sarcoglycan might also have independent and brain-specific functions (172).

Animal models have provided evidence for the involvement of both the basal ganglia and the cerebellum in MYC/DYT-SGCE. For instance, *SGCE* KO mice showed increased striatal dopamine levels and reduced pre- and postsynaptic striatal D2R levels, suggesting a possible role of ε-sarcoglycan in stabilizing synaptic membranes of dopaminergic neurons (174). On the other hand, mice with cerebellar *SGCE* cKO demonstrated aberrant firing of cerebellar Purkinje cells and deep cerebellar nuclei neurons (175). Interestingly, the authors observed that cerebellar KO produced dystonia and myoclonus, whereas KO in the basal ganglia resulted in only subtle motor defects, suggesting that the cerebellum may be the primary instigator. Furthermore, a recent mouse model carrying a heterozygous LOF allele and mimicking the MD phenotype has provided evidence that ε-sarcoglycan may act as an inhibitor of synaptogenesis, as the protein loss resulted in excessive formation of excitatory synapses. This is also supported by the fact that pharmacologically enhancing GABA transmission alleviated symptoms (176).

Another example where pathogenic changes in cytoskeletal proteins underlie dystonia is TUBB4A-related disease. *TUBB4A* encodes the brain-specific β-tubulin isotype β-tubulin 4A with high cerebellar expression, and pathogenic variants can cause a broad spectrum of diseases, including whispering dystonia (also known as DYT4) (177, 178). β-Tubulins form heterodimers with α-tubulins that are arranged into microtubules—the largest cytoskeletal filament in cells. Microtubules are essential for maintaining and changing cell morphology, axon extension, and assembly of mitotic spindles during cell division and serve as tracks for intracellular transport. Notably, TUBB4A depletion did not cause a phenotype in mice, pointing to dominant-acting mutant tubulin (179). Moreover, it was shown that mutant TUBB4A proteins are integrated into the microtubule network (180).

It is postulated that different cell types are differentially susceptible to tubulin perturbations, depending on the expression ratio of other β-tubulin isoforms and, therefore, the degree of the dominant-negative effect of mutant TUBB4A. In line with this idea, oligodendrocytes seem to be particularly affected. Dystonia-causing variants were shown to be associated with aberrant microtubule growth dynamics in oligodendrocytes, supporting a GOF mechanism (181). It is postulated that this may disrupt cell proliferation, resulting in impaired arborization and myelination of neurons, ultimately leading to reduced signal transduction. Notably, impaired oligodendrocyte maturation with the consequence of myelination deficits seems to be a convergent mechanism, as this is also an observed feature in THAP1- and YY1-related dystonia (see above). Additionally, an iPSC study demonstrated functional impairment of microtubule-associated transport in iPSC-derived neurons from DYT-TUBB4A patients (180), which could affect essential cargos, deliveries of mitochondria, and lysosomal function.

Another hereditary dystonia form involving a cytoskeletal protein is *ACTB*-associated complex dystonia-deafness. *ACTB* encodes the ubiquitously expressed and highly conserved β-actin that forms cytoskeletal filaments essential for cell migration, cell morphology, mitosis, and intracellular transport. Dystonia-causing variants were shown to destabilize actin filaments, which may lead to various cellular defects (182). Notably, imaging findings were indicative of striatal neuron dysfunction, and GPi-DBS successfully improved dystonia in patients (183, 184).

Even though the exact mechanism by which abnormalities in cytoskeletal proteins induce dystonic phenotypes is poorly understood, it is becoming increasingly evident that they may be accompanied by cellular changes frequently observed across dystonia forms. These include impaired calcium homeostasis, synapse assembly and function, and myelination deficits, resulting in aberrant neuronal firing.

GENETIC TESTING

An important aspect of establishing a diagnosis, appropriate care, and therapeutic options lies in genetic testing. This is specifically challenging in a heterogeneous disorder such as dystonia.

Methods Applied in Genetic Testing

However, the increasing availability of different next-generation sequencing (NGS) techniques dramatically improves the diagnostic yield since the whole genome can be tested in parallel, shortening the time until diagnosis if there is a monogenic cause in a known dystonia-linked gene. From a technical point of view, NGS can target selected previously known disease genes (a gene panel), all annotated exons (exome sequencing, mainly comprising the coding regions of all genes), or even the whole genome (genome sequencing). Since variant interpretation in exome data, but especially in genome data, is highly challenging (with approximately four million variants, it is like looking for a needle in a haystack), a further level of genetic information, for example, derived from RNA sequencing (RNAseq), could guide variant interpretation. This, for instance, would be the case for deep intronic variants that activate a cryptic exon and thus can lead to a frameshift. While gene panel sequencing is the cheapest method, it is highly customized and cannot easily be adjusted for novel discoveries. Exome sequencing is ideal for the detection of coding variants but has limitations in GC-rich regions due to the enrichment step and for structural variants. Currently, the diagnostic yield highly depends on the characteristics of the given patient. A large study using exome sequencing in 708 patients revealed a genetic cause in ~20%. Notably, the diagnostic yield reached almost 50% in patients with early-onset (<20 years), generalized, nonisolated dystonia, while it was as low as 1% in patients with late-onset, isolated, focal dystonia (185). On the basis of these observations, a scheme for prioritizing patients for exome sequencing, which

is necessary given limited resources, has recently been proposed (185). As we learned from other diseases (186), genome sequencing may add another 5–10% to the diagnostic yield, which is probably also the case for dystonia (28). Currently, diagnostic exome sequencing or gene panel testing may be the most efficient method to arrive at a definite diagnosis.

Nevertheless, in certain populations, specific genetic testing may still be the method of choice due to the high prevalence of certain founder mutations; for example, in a Filipino male patient with dystonia and/or parkinsonism, testing for the SVA insertion in the *TAF1* gene might reveal the genetic cause (96). Another example of variant-specific testing would be the 3-base-pair GAG deletion in the *TOR1A* gene in an Ashkenazi Jewish patient with early-onset generalized dystonia (187). The advantage of variant-specific testing lies in the broader availability (in terms of equipment and expertise), the lower costs, and the usually faster processing time due to simplified interpretation.

Notably, in the case of a negative sequencing-based test, the possibility of a missed copy number variant (CNV), which is a considerable cause in *SGCE*-linked MD (188) or *GCH1*-linked dystonia (189), needs to be considered. While such variants are typically detectable by genome sequencing, they are still often missed by exome sequencing, especially if they affect only one to two exons. Currently, the method of choice for detecting CNVs is multiplex ligation-dependent probe amplification (MLPA). However, CNVs have also rarely been detected in other dystonia genes such as *GNAL* (190). Since no MLPA kit is available for this gene, quantitative polymerase chain reaction or genome sequencing has to be applied for its detection.

Distinguishing Benign from Pathogenic Variants

A major challenge in genetic testing, especially upon exome or genome sequencing application, is the interpretation of variants. According to the recommendations from the American College of Medical Genetics and Genomics (191), variants can be classified as pathogenic or likely pathogenic if there is clear evidence for a disease-causing role or as benign/likely benign if there is evidence against such a role, for instance, because the variant in question has a higher frequency in the general population than the disease itself (191, 192). The remaining variants, unfortunately often the majority of detected variants, need to be treated as variants of uncertain significance (VUS), which is quite unsatisfactory. As mentioned above, RNAseq might help in cases where the variant has a direct and pronounced effect on the transcription level, which, for example, is the case for frameshift variants that undergo nonsense-mediated mRNA decay. For variants that act on a functional level, such as protein-protein or protein-DNA interactions, specific assays have to be established. A few such gene-specific readouts were developed, including luciferase assay for *THAP1* to assess the transcription factor activity (66), bioluminescence resonance energy transfer assays to test *GNAL* variants for their capability to form functional G protein–coupled receptors (50, 193), and, more recently, a DNA methylation pattern (episignature) for variants in *KMT2B* (84). Levodopa responsiveness and the level of metabolites from levodopa biosynthesis in cerebrospinal fluid or blood can guide the interpretation of variants in genes linked to DRD, though with limitations (15, 194). Further, for instance, for the interpretation of missense variants in *TOR1A* or *SGCE*, two major genes for isolated and combined dystonia, respectively, no tests have yet been proposed.

The situation becomes even more challenging when a variant is found in a novel dystonia candidate gene. In a small or moderately sized pedigree, NGS analyses may identify variants in biologically plausible genes without the statistical corroboration of linkage analysis or extensive segregation analysis. The most convincing evidence for validating a novel dystonia gene will always derive from the replication of the initial finding by independent research groups in unrelated samples. For ultrarare diseases such as *HPCA*-related dystonia, this can take several years and expand the phenotypic spectrum (195). The dystonia relation of some other genes is still pending

or has been seriously questioned by replication studies, including variants in *COL6A3* (196) and *CACNA1B* (197).

REDUCED PENETRANCE

Luckily, not all carriers of a pathogenic variant develop the disease, a phenomenon called reduced penetrance. A related topic is variable expressivity, that is, when the same genetic cause leads to different phenotypic expressions, for instance, in terms of age at onset, severity, or additional features. An intriguing example is the phenotypic spectrum in carriers of the same pathogenic 3-base-pair deletion in *TOR1A*. In fact, most carriers (up to 70%) remain unaffected, others develop focal dystonia, and others are bedridden due to severe generalized dystonia since childhood (13). The observation of reduced penetrance and variable expressivity suggests that additional genetic, epigenetic, and/or environmental factors are likely to play an essential role in disease manifestation. Several attempts have been made to identify the underlying molecular mechanisms, and for some of the genetic forms, we have begun to understand them. For *TOR1A*, a cell culture model first suggested that a relatively common coding polymorphism (p.Asp216His, rs1801968) in this gene can decrease the formation of intracellular inclusions triggered by the 3-base-pair deletion (198). Shortly thereafter, it was shown that if this variant is present in *trans* to the pathogenic variant, the penetrance is decreased to 3%; thus, it protects the individual (199). For *SGCE*, penetrance is nearly 0% upon maternal transmission, which has been explained by maternal imprinting, mediated via epigenetic DNA modification (methylation) leading to silencing of the maternal allele and expression only of the paternal allele (200). In *THAP1*-linked dystonia, disease expression may be related to alterations in the transcriptional regulation, and the *DRD4* gene has been suggested to play a role (71). Finally, the homogeneous group of XDP patients (all carry the same haplotype and have the same ethnicity due to a founder event) has enabled the identification of several genetic modifiers of XDP in a relatively small group of patients, including the number of hexanucleotide repeats within the SVA insertion (96, 201) and common variants in genes linked to repeat instability [*MSH3* and *PMS2* (202)].

Identifying factors that influence penetrance may also have value for therapeutic strategies. If these factors are modifiable, they could help prevent the development of dystonia in the respective carriers. This is currently a hot topic in the field.

CONCLUSIONS

We gain the most mechanistic insight into the pathogenesis of dystonia by understanding the action of genes and their encoded products mutated in monogenic forms of dystonia—a list that is constantly growing. Considering the currently known isolated dystonia genes, disease mechanisms are diverse and affect gene transcription during neurodevelopment (*KMT2B* and *THAP1*), calcium homeostasis (*HPCA*, *TOR1A*, and *ANO3*), striatal dopamine signaling (*GNAL*), ER stress response (*PRKRA*, *EIF2AK2*, and *TOR1A*), and autophagy (*VPS16*). Relationships between the associated disease pathways remain difficult to understand, but as demonstrated, several connections have been identified that link the distinct molecular pathways implicated in dystonia. For instance, transcription factors regulate other dystonia genes, and impaired ER function and calcium homeostasis may induce a stress response, autophagy, and aberrant synaptic function.

Intriguingly, even though the molecular origin of pathogenesis might differ between dystonia subtypes, convergence on the cellular and anatomical level has become increasingly evident. Several different molecular defects eventually lead to aberrant activity of striatal or cerebellar neurons, disturbing the brain circuits involved in motor control. The current state of research suggests that it is unlikely that one driver molecule or mechanism exists. Instead, the distinct mechanisms

trigger the same downstream effects, eventually leading to the clinical phenotype of dystonia. As a consequence, different forms of dystonia can be categorized into molecular groups, which will assist with treatment development and application.

An important future question will be whether the same molecular pathways are also affected in idiopathic dystonia patients, especially the ones with late-onset focal dystonia, the most common subtype. Therefore, large genomic efforts are warranted to further elucidate the genetic basis of this patient group.

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