

## Review

## Dystonia genes and their biological pathways

H.A. Jinnah<sup>a,\*</sup>, Yan V. Sun<sup>b</sup><sup>a</sup> Departments of Neurology, Human Genetics and Pediatrics, Emory University School of Medicine, Atlanta, GA, United States of America<sup>b</sup> Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, United States of America

## ARTICLE INFO

## Keywords:

Dystonia  
Neurobiology  
Gene  
Genetics  
Mutation  
Genetic variant  
Biological pathways  
Calcium homeostasis  
Mitochondrial disease  
NBIA  
Dopamine

## ABSTRACT

The dystonias are a group of disorders characterized by excessive contraction of muscles leading to abnormal involuntary movements. The clinical manifestations are very heterogeneous, with numerous distinct syndromes. The etiologies for dystonia are also heterogeneous with idiopathic, acquired, and inherited forms. Technological advances in genetics over the past two decades have led to a rapid growth in the number of genes associated with dystonia. These genes encode proteins with very diverse biological functions. This review focusses on genes that have contributed to understanding shared biological pathways relevant to specific subgroups of dystonia syndromes. Although many potential shared biological pathways have been proposed, the ones addressed here include defects in dopamine signaling, mitochondrial dysfunction and energy maintenance, toxic accumulation of heavy metals in the brain, and calcium channels and abnormal calcium homeostasis. Elucidation of these and other shared pathways is important for understanding the biological basis for dystonia and for designing novel experimental therapeutics that have the broadest potential for multiple types of dystonia.

## 1. What is dystonia?

Dystonia is not a single disorder, but a family of related disorders. It is defined by its clinical manifestations, rather than a specific gene defect or biological pathway. Excessive contraction of muscles is the core biological problem that underlies its clinical manifestations, which vary according to the muscles that are involved and the severity of their contractions (Albanese et al., 2013). In its most severe form (generalized dystonia) many muscles throughout the body are affected. Movements have a quality that is stiff, often with slow twisting and writhing, rapid repetitive jerking, or fixed abnormal postures. Fortunately, generalized dystonia is rare, and it is more common to see involvement of smaller groups of muscles in a restricted distribution in the body (focal dystonia). The most commonly recognized focal dystonia syndromes involve neck muscles (cervical dystonia or torticollis), the face (blepharospasm or Meige syndrome), the larynx (laryngeal dystonia or spasmodic dysphonia), or a limb (e.g. writer's cramp or other task-specific hand dystonias) (Jinnah et al., 2013).

Dystonia may arise at any age, and the age at onset is important because childhood-onset cases are more likely to have a discoverable cause than adult-onset cases. Dystonia also varies over time. Some subtypes are slowly progressive, others advance in a stepwise fashion over weeks or years, and some are relatively static for decades.

Dystonia may occur in a relatively pure form, without other clinical problems (isolated dystonia, previously known as primary dystonia). Alternatively, it may be part of a broader clinical syndrome that includes other neurological or medical problems (combined dystonia).

Unlike some disorders such as Huntington's disease where there is a single gene and associated biological pathway for pathogenesis, for dystonia there are many genes and biological pathways, and even non-genetic causes (Balint et al., 2018). Dystonia often is compared with Parkinson's disease, but this comparison is misleading. While Parkinson's disease also may be caused by multiple different genes and non-genetic factors, all of them converge to a single biological pathway that involves degeneration of nigrostriatal dopamine neurons. Most types of dystonia are not associated with degenerative changes in a single neural pathway. Instead, dystonia is considered a network disorder, which can result from degenerative or non-degenerative disturbances in several different regions of the nervous system (Jinnah et al., 2017b; Neychev et al., 2011; Prudente et al., 2014). This etiological heterogeneity is important to keep in mind when considering dystonia genes and its biological pathways.

## 2. What genes should be considered?

Technological advances in genetics over the past two decades have

\* Corresponding author at: Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322, Woodruff Memorial Research Building, Suite 6300, 101 Woodruff Circle, United States of America.

E-mail address: [hjinnah@emory.edu](mailto:hjinnah@emory.edu) (H.A. Jinnah).

<https://doi.org/10.1016/j.nbd.2019.05.014>

Received 27 March 2019; Received in revised form 5 May 2019; Accepted 17 May 2019

Available online 18 May 2019

0969-9961/ © 2019 Elsevier Inc. All rights reserved.

led to a rapid growth in the number of dystonia genes, many of which have been summarized in recent reviews (Balint et al., 2018; Domingo et al., 2016; LeDoux, 2012; Weisheit et al., 2018). It has become challenging to define a consistent list of dystonia genes for several reasons. Criteria for what constitutes a “dystonia gene” have changed in the past decade, and some of the earliest genes described have since been questioned because of lack of confirmation or failure to demonstrate any functional abnormality in the gene product (Domingo et al., 2016).

Because of the large number of genes, many prior reviews covered only a small subset of relevant genes. Some reviews have focused only on genes associated with isolated dystonia, with little or no coverage of the much larger group of genes associated with combined dystonia. Others have focused only on the most recently described genes, or specific genes of particular interest to the authors. Many prior reviews of dystonia genetics have been organized according to the Human Genome Organization's nomenclature system for genetic loci, which has now reached DYT29. Unfortunately, this approach for reviewing dystonia genes is misleading, because the DYT naming convention is incomplete (Marras et al., 2016; Marras et al., 2012). This list implies 29 dystonia genes, but it neglects numerous disorders in which dystonia is a consistent or dominant clinical feature. For example, one review on the diagnosis of dystonia included more than 100 different inherited disorders, organized into 18 different tables according to specific phenotypic features of the clinical syndromes (Fung et al., 2013). A more recently published article described a next generation sequencing panel with 94 different dystonia genes (van Egmond et al., 2017). Other sources list even greater numbers of dystonia genes. For example, some commercially available gene panels include 192 dystonia genes (e.g. MNG Laboratories, Atlanta GA). While these larger lists are more comprehensive, they may include genes where dystonia is a minor component in a much more complex phenotype, genes where dystonia is a relatively rare manifestation of the disease, and even genes with unproven associations with dystonia.

Table 1 includes a list of genes typically said to be associated with isolated dystonia syndromes. This list has only 6 genes, one of which has not been independently confirmed (CIZ1) and two others where distinguishing pathological from non-pathological genetic variants has proven challenging (ANO3 and COL6A3) (Lohmann et al., 2016; Olschewski et al., 2019). The biological processes for these 6 genes are quite diverse, so finding shared biological pathways is challenging. Some studies have suggested biological connections between THAP1 and TOR1A, although the evidence is limited and indirect (Gavarini et al., 2010; Kaiser et al., 2010). A similar list of genes associated with combined dystonia syndromes is challenging to construct because of the huge number.

The focus of the current review is on selected genes that have contributed to elucidating shared biological pathways. It spans both old and new genes, associated with either isolated or combined dystonia, regardless of their inclusion in the DYT nomenclature system.

### 3. Are there shared biological pathways that lead to dystonia?

#### 3.1. Biological pathways for dystonia

*Divergent or convergent?* An important initial question to consider is whether the many different subtypes of dystonia merely share a superficial phenotypic resemblance with entirely unrelated etiologies, or whether they may have shared biological substrates. At first glance, the functions of the dystonia genes appear quite divergent since they span a wide variety of biological processes. These processes include basic metabolic processes (amino acids, carbohydrates, organic acids, lipids and purines), cellular handling of ions (sodium, potassium, calcium, copper, and manganese), DNA transcription and repair, various aspects of mitochondrial function, protein folding and trafficking, and others (Fung et al., 2013). Despite this very divergent list of biological

**Table 1**  
Genes associated with isolated dystonia.

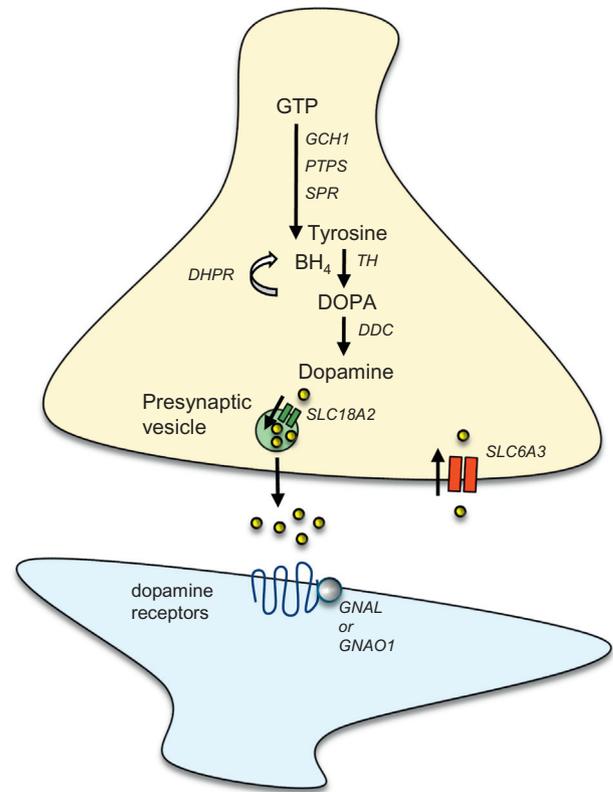
Gene	Protein	Function	Inheritance	Typical phenotype
ANO3	Anoctamin-3	Related to family of calcium-activated chloride channels	AD (~50% penetrant)	Adult-onset craniocervical dystonia with prominent tremor
CIZ1	Cip1-interacting zinc finger protein 1	DNA binding and replication	AD (reduced penetrance)	Adult-onset cervical dystonia
COL6A3	α3 subunit of type VI collagen	Major component of collagen in most connective tissues	AR	Childhood-onset cervical and upper body
GNAL	G-protein subunit alpha L	Cell surface guanine-nucleotide binding protein involved in signal transduction	AD (~50% penetrance)	Adult-onset focal or segmental involving neck
THAP1	Thanatos-associated domain-containing apoptosis protein 1	DNA binding and transcription	AD (~60% penetrance)	Adolescent-onset craniocervical and upper body
TOR1A	Torsin family 1 member A	Endoplasmic reticulum protein chaperone	AD (~30% penetrance)	Childhood-onset limb or generalized

Abbreviations: AD, autosomal dominant.

**Table 2**  
Selected dystonia genes associated with dopamine signaling.

Gene	Protein	Function	Inheritance	Typical phenotype
<i>ADCY5</i>	Adenylate cyclase 5	Couples dopamine receptors to cAMP messenger systems	AR	Childhood-onset mixed motor dystonia with chorea and dystonia
<i>DDC</i>	Aromatic amino acid decarboxylase	Enzyme involved in dopamine synthesis	AR	Infantile encephalopathy, oculogyric crises, dysautonomia, dystonia
<i>GCHI</i>	GTP-cyclohydrolase 1	Rate-limiting step in tetrahydropterin synthesis	AD (partial penetrance)	DRD
<i>GNAL</i>	G-protein subunit alpha L	Cell surface guanine-nucleotide binding protein involved in dopamine receptor signal transduction	AD (partial penetrance)	Adult-onset focal or segmental involving neck
<i>GNAO1</i>	G-protein subunit alpha O1	Cell surface guanine-nucleotide binding protein involved in dopamine-receptor signal transduction	AR	Childhood-onset mixed motor dystonia with chorea and dystonia
<i>HPRT1</i>	Hypoxanthine-guanine phosphoribosyl transferase	Purine metabolism enzyme that results in marked dopamine deficiency without neurodegeneration	XL	Lesch-Nyhan disease
<i>LRRK2</i>	Leucine-rich repeat kinase 2	Protein kinase associated with dopamine neuron degeneration	AD	Parkinson's disease, often with dystonia
<i>POLG</i>	Polymerase gamma 1	Mitochondrial enzyme that results in loss of dopamine neurons	AR	Markedly varied from infancy to later adulthood
<i>PINK1</i>	PTEN-induced putative kinase 1	Protein kinase associated with dopamine neuron degeneration	AR	Parkinson's disease, often with dystonia
<i>PRKN</i>	Parkin	Ubiquitin-ligase protein associated with dopamine neuron degeneration	AR	Parkinson's disease, often with dystonia
<i>PTPS</i>	6-pyruvoyl-tetrahydropterin synthase	Enzyme involved in tetrahydropterin synthesis	AR	DRD or infantile encephalopathy
<i>SLC18A2</i>	Vesicular monoamine transporter 2	Presynaptic storage of dopamine in vesicles	AR	Infantile-onset parkinsonism, dystonia, dysautonomia
<i>SLC6A3</i>	Dopamine transporter	Presynaptic uptake of dopamine from the synaptic cleft	AR	Infantile to adult onset parkinsonism and dystonia
<i>SNCA</i>	$\alpha$ -synuclein	Presynaptic protein associated with dopamine neuron degeneration	AD	Parkinson's disease, often with dystonia
<i>SPR</i>	Sepiapterin reductase	Enzyme involved in tetrahydropterin synthesis	AR	DRD or infantile encephalopathy
<i>TH</i>	Tyrosine hydroxylase	Enzyme involved in rate-limiting step in dopamine synthesis	AR	DRD or infantile encephalopathy

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DRD, dopa-responsive dystonia.



**Fig. 1.** Dopaminergic signaling in dystonia. The presynaptic dopamine neurons is shown at the top, with the postsynaptic target at the bottom. Abbreviations: BH<sub>4</sub>, tetrahydropterin, *DDC*, gene symbol for aromatic amino acid decarboxylase; DOPA, levodopa; *GCHI*, gene symbol for GTP cyclohydrolase; GTP, guanosine triphosphate; *GNAL*, gene symbol for G<sub>olf</sub> protein; *PTPS*, gene symbol for pyruvoyl-tetrahydropterin synthase; *SLC18A2*, gene symbol for vesicular dopamine uptake transporter or VMAT2; *SLC6A3*, gene symbol for dopamine transporter *SPR*, gene symbol for sepiapterin reductase; *TH*, gene symbol for tyrosine hydroxylase.

processes, some common themes can be recognized.

### 3.2. Dopamine signaling

One of the most widely recognized themes that is shared across multiple inherited forms of dystonia involves dopamine signaling (Table 2 and Fig. 1) (Karimi and Perlmuter, 2015; Thompson et al., 2011). Dopa-responsive dystonia is a childhood-onset focal or generalized dystonia that is sometimes combined with parkinsonism. The first gene to be associated with this phenotype was *GCHI*, which encodes the enzyme GTP-cyclohydrolase (Kurian et al., 2011; Wijemanne and Jankovic, 2015). This enzyme is involved in the synthesis of tetrahydropterin, a cofactor that is required by the enzyme tyrosine hydroxylase for the synthesis of dopamine. In patients with pathological variants in *GCHI*, dystonia can be treated effectively with levodopa, the precursor to dopamine. This observation provides strong evidence linking dopamine with dystonic movements.

The dopa-responsive dystonia phenotype may also occur in association with genes involved in other steps in tetrahydropterin synthesis including *SPR* (sepiapterin reductase) and *PTPS* (pyruvoyl-tetrahydropterin synthase). The phenotype also occurs with defects involving *TH* (tyrosine hydroxylase), the rate-limiting step in dopamine synthesis. Dystonia can also be a prominent feature associated with defects in genes involved in other steps of dopamine synthesis or handling including *DDC* (aromatic amino acid decarboxylase) (Wassenberg et al., 2017), *SLC18A2* (intracellular vesicular monoamine transporter 2) (Rilstone et al., 2013), and *SLC6A3* (cell surface

monoamine transporter) (Ng et al., 2014). In these disorders, dystonia is typically combined with other neurological features, presumably resulting from abnormalities that affect additional monoamine pathways; norepinephrine, epinephrine, and serotonin. All together, these disorders provide strong convergent evidence for a shared molecular pathway involving dopamine synthesis and metabolism for at least some types of dystonia.

In addition to functional disturbances in dopamine synthesis or metabolism, dystonia occurs in association with genes that result in degenerative changes of dopamine neurons. The *POLG* gene encodes a mitochondrial enzyme (polymerase gamma 1) associated with varied phenotypes that often include dystonia, along with prominent loss of nigrostriatal dopamine neurons (Tzoulis et al., 2013). In fact, many of the genes that cause degeneration of nigrostriatal dopamine neurons in parkinsonian disorders (*LRRK2*, *PARKIN*, *PINK1*, *SNCA*) can also cause dystonia (Kasten et al., 2018). In these disorders, focal dystonia of one arm or leg may precede development of the parkinsonian phenotype by many years.

Defects in dopamine pathways in dystonia are not limited to dopamine neurons themselves, but can also involve post-synaptic mechanisms (Abela and Kurian, 2018). The *GNAL* gene has been linked with isolated adult-onset dystonia that may be focal, segmental or generalized (Fuchs et al., 2013; Vemula et al., 2013). This gene encodes the  $\alpha$ -subunit of a G-protein ( $G_{\alpha i p}$ ), a GTP-binding protein involved in coupling dopamine receptors (and other receptors) on the post-synaptic membrane of striatal neurons to the adenylate-cyclase second messenger system. The *GNAO1* gene encodes the  $\alpha$ -subunit of another G-protein ( $G_i$ ), which also is involved coupling dopamine receptors (and other receptors) to the adenylate-cyclase second messenger system. Early reports emphasized childhood-onset of chorea and epilepsy as prominent aspects of the clinical phenotypes associated with *GNAO1*. However, a more recent review suggested that dystonia is one of the commonest features included in the phenotype (Schirrinzi et al., 2019). Finally, pathological genetic variants in the *ADCY5* gene have also been linked with a variety of clinical phenotypes in children and adolescents, where dystonia may be a prominent feature (Carecchio et al., 2017; Chen et al., 2015). This gene encodes adenylate cyclase type 5, which is highly expressed in the basal ganglia.

In addition to genes with direct connections to dopamine pathways, there are other genes that appear to affect dopamine signaling, although the mechanisms are not clear. The *HPRT1* gene is associated with Lesch-Nyhan disease (Fu et al., 2013), where generalized dystonia is universal and commonly part of a more complex neurobehavioral syndrome (Jinnah et al., 2006), but may occasionally appear as isolated or even focal dystonia (Jinnah et al., 2010). This gene encodes an enzyme involved in purine metabolism, but dystonia has been linked to dysfunction of nigrostriatal dopamine pathways (Goettle et al., 2014). In this disorder, nigrostriatal dopamine neurons do not degenerate, but they do not appear to synthesize and metabolize dopamine properly.

The *TOR1A* gene is associated with childhood-onset generalized dystonia, and sometimes focal or adult-onset phenotypes (Ozelius et al., 1997). It encodes torsinA, a ubiquitously expressed enzyme that is thought to play a role as a chaperone in the endoplasmic reticulum (Gonzalez-Alegre, 2019; Weisheit et al., 2018). Although there are no obvious links between *TOR1A* and dopamine pathways, there are two independent reports suggesting that dopamine neurons are unusually large in autopsy materials from subjects with this disorder (Iacono et al., 2019; Rostasy et al., 2003). Genetically engineered mouse models have revealed a similar morphological change among dopamine neurons, along with prominent deficits in dopamine release (Balcioglu et al., 2007; Page et al., 2010; Song et al., 2012). The mechanisms linking defects in *TOR1A* to dopamine neuron dysfunction remain unclear, although several recent studies have provided some novel insights to explain the association (Bonsi et al., 2019; Scarduzio et al., 2017).

Although all of these inherited disorders are rare, collectively they

provide strong convergent evidence that abnormalities of dopamine signaling are associated with dystonia. There is some evidence that abnormal dopamine signaling may be relevant for more common sporadic adult-onset focal dystonias too. Human positron emission tomography (PET) studies have revealed reductions in striatal dopamine receptors in blepharospasm or focal hand dystonia (Karimi et al., 2011; Perlmutter et al., 1997). PET studies have also implied reduced dopamine signaling among individuals with laryngeal dystonia (Simonyan et al., 2013) and writer's cramp (Berman et al., 2013). Among individuals with dystonia acquired from brain lesions, the severity of dystonia correlates with loss of nigrostriatal dopamine fibers to the basal ganglia (Vidailhet et al., 1999).

The mechanisms relating dopamine to dystonia appear to vary among the different subtypes (Fan et al., 2018). For *GCHI*, the mechanism appears to involve dopamine deficiency, since dystonia can be reversed by levodopa. However, dopamine deficiency alone may not be a sufficient explanation, because dopamine deficiency in adults usually causes parkinsonism, not dystonia. Thus dopamine deficiency in the developing brain may be important for dopa-responsive dystonia. Levodopa is only partly effective in other inherited disorders (e.g. *TH*, *SPR*, *PTPS*), or it is not effective (e.g. *HPRT1*, *TOR1A*, adult-onset idiopathic dystonias). Therefore, alternative mechanisms must be considered for these other disorders. For example, abnormal dopamine signaling may trigger maladaptive plastic changes during development that are not readily reversible with levodopa. Alternatively, these other disorders may involve some additional pathological process, and correction of the dopamine problem alone may be insufficient (Bonsi et al., 2019; Scarduzio et al., 2017).

### 3.3. Mitochondrial dysfunction or energy homeostasis

One of the earliest themes to be recognized across different types of dystonia involves mitochondrial dysfunction (Nemeth, 2002). Dystonia is a very frequent manifestation of Leigh's syndrome, an acute or sub-acute necrotizing encephalopathy with prominent involvement of the basal ganglia. Leigh's syndrome can be caused by more than 75 different genes, both mitochondrial and nuclear, predominantly involved in oxidative phosphorylation (Lake et al., 2016). Leber's hereditary optic neuropathy syndrome is caused by mutations in the genes encoding the subunits of the enzyme NADH dehydrogenase. It is characterized by progressive visual loss often combined with other neurological features including dystonia (Leber's Plus syndrome). Defects in *TIMM8A*, which encodes the translocase of inner mitochondrial membrane type 8a, cause the dystonia-deafness syndrome (Mohr-Tranebjaerg syndrome), sometimes without deafness (Swerdlow et al., 2004). Another gene which is associated with a wide variety of clinical phenotypes that may include dystonia is *POLG*, which encodes mitochondrial polymerase gamma type 1.

Mitochondria play a key role in energy homeostasis, and recent observations have suggested that the mitochondrial theme might be more broadly expanded to include defects in non-mitochondrial genes that affect energy homeostasis (Ghaoui and Sue, 2018; Martikainen et al., 2016; Moustris et al., 2011). There are several non-mitochondrial genes involved with energy homeostasis that are also associated with dystonia. These include *SLC2A1* (brain glucose transporter, GLUT1), *GCDH* (glutaryl CoA dehydrogenase, glutaric aciduria type 1), *MUT* (methylmalonyl CoA mutase, methylmalonic aciduria) *PCCA* or *PCCB* (propionyl CoA carboxylase, propionic acidemia), and multiple genes associated with the pyruvate decarboxylase complex. For most of the disorders directly or indirectly affecting mitochondrial function, dystonia is generalized and is part of a more complex syndrome that includes other clinical problems (Fung et al., 2013). However, for some patients with mitochondrial disease dystonia may be focal (Kim et al., 2007; Muller-Vahl et al., 2000; Simon et al., 2003; Swerdlow and Wooten, 2001), the presenting problem (Head et al., 2004; Sudarsky et al., 1999), or the biggest problem (McFarland et al., 2007; Simon

et al., 2003).

Although all of these disorders are rare, they collectively provide strong support for the concept that certain subtypes of dystonia may share defects in mitochondrial function or energy homeostasis as an etiological mechanism. This theme may also be relevant to more common idiopathic isolated adult-onset focal dystonias. There are reports of functional abnormalities in mitochondrial complex I among adult-onset isolated focal dystonias (Benecke et al., 1992; Schapira et al., 1997), although these have not been confirmed recently. Some mitochondrial genes have been reported to be associated with atypical phenotypes including adult-onset focal dystonia, rather than the more complex syndromes more typical of childhood-onset cases (Kim et al., 2007; Muller-Vahl et al., 2000; Simon et al., 2003; Swerdlow and Wooten, 2001; Tuladhar et al., 2013). However, the extent of mitochondrial gene defects among the more common sporadic cases is unknown, because of the lack of methodical studies of mitochondrial genes in large dystonia cohorts.

The mechanisms by which mitochondrial dysfunction or energy homeostasis may cause dystonia are not entirely clear. For several of these disorders (e.g. Leigh's syndrome), dystonia is accompanied by overt damage to the basal ganglia. For other disorders, there is no obvious damage, and the mechanism may involve functional changes due to energy shortage. For example, dystonia associated with *SLC2A1* is transient and triggered by prolonged exercise, presumably because serum glucose levels fall below the range of the GLUT1 glucose transporter to maintain brain glucose (Pearson et al., 2013). In this disorder, attacks of dystonia can be prevented by simple measures aimed at maintaining blood glucose levels, such as avoidance of prolonged fasting or avoidance of prolonged exercise. Dystonia can also be mitigated via the ketogenic diet (which provides ketones as an alternative brain energy fuel that does not require the GLUT1 transporter) or triheptanoin (a carbohydrate that also serves as an alternative brain fuel that can bypass the GLUT1 transporter) (Jinnah et al., 2018). Thus even transient energy shortage can cause dystonia, without overt histopathological damage to the brain.

### 3.4. Heavy metal accumulation

Another theme shared by several inherited dystonias involves the cellular transport or storage of heavy metals. The *ATP7B* gene is associated with Wilson's disease, a multisystem disease that affects the brain, liver, kidneys and other organs. The neurological manifestations commonly include dystonia, which may be focal or generalized (Bandmann et al., 2015; Machado et al., 2006). This gene encodes a copper transporter, with marked accumulation of copper in the liver and brain. Most recently, genes involved in manganese transport and storage similarly have been linked with dystonia including *SLC30A10*, *SLC39A14* and *SLC39A8* (Quadri et al., 2012; Riley et al., 2017; Tuschl et al., 2012; Tuschl et al., 2016). For these disorders of manganese handling, dystonia typically emerges during childhood, often accompanied by parkinsonism and other neurological problems.

The mechanism responsible for dystonia in disorders of copper and manganese transport is thought to involve toxic accumulation of heavy metals. For reasons that are not entirely clear, the basal ganglia seem to be particularly vulnerable to this process. Treatments that reduce the stores of these metals can prevent symptoms from developing or worsening (Jinnah et al., 2018). Often, these treatments can reverse symptoms at least partly.

Dystonia also is very common in the group of disorders known as neurodegeneration with brain iron accumulation (NBIA) (Di Meo and Tiranti, 2018; Tello et al., 2018; Wiethoff and Houlden, 2017). The NBIA disorders are associated with at least 12 different genes (Table 3 and Fig. 2). Two of these are directly involved with iron homeostasis, *FTL* (ferritin light chain) and *CP* (ceruloplasmin). Four are involved in lipid biology, *FA2H* (fatty acid hydroxylase 2), *PLA2G6* (phospholipase A2), *SCP2* (sterol carrier proteins X and 2), and *C19orf12* (which

encodes a protein of the outer mitochondrial membrane). Two more are involved in coenzyme A (CoA) synthesis, *COASY* (CoA synthase) and *PANK2* (pantothenate kinase type 2). Two are involved in degradation of intracellular proteins and other cellular debris via the autophagosome, *ATP13A2* (P-type cation pump of lysosomes) and *WDR45* (a member of the WD scaffold protein family). One is suspected to be involved with mRNA metabolism (*GTPBP2*) and the last is a protein with unknown function that localizes to nucleoli (*DCAF17*).

Similar to disorders of copper and manganese described above, dystonia in the NBIA disorders typically emerges early during development and is accompanied by parkinsonism and other neurological and medical problems. Also similar to disorders of copper and manganese, the basal ganglia appear to be particularly vulnerable in NBIA. However, the mechanism responsible for dystonia in NBIA is not entirely clear. At first glance these NBIA-causing genes harbor little in common. The mechanism of iron accumulation is not always clear, since only two of the NBIA genes (*FTL* and *CP*) are directly involved in iron homeostasis. However, several pieces of evidence point to mitochondrial dysfunction as a potentially unifying theme. Several mitochondrial enzymes are critically dependent on iron as a cofactor for activity, and the mitochondria serve as a major storage depot for intracellular iron. It is widely known that unhealthy or degenerating neurons accumulate heavy metals, so accumulation of iron may only be an indirect biomarker of the pathological process. Four of the genes express proteins that are physically linked to the mitochondrial membranes (*C19orf12*, *COASY*, *PANK3*, and *PLA2G6*), and several others are involved in lipid biology or metabolism of lipids via CoA-dependent pathways, a critical source of energy. Whether or not strategies aimed at reducing iron stores in these disorders will have therapeutic value is currently being investigated.

### 3.5. Calcium channels and calcium homeostasis

Defects in calcium channels as a potential shared theme for dystonia were first proposed following observations in animal models. A drug that activates L-type calcium channels was shown to provoke generalized dystonia in young mice (Jinnah et al., 2000), and a series of spontaneous mouse mutants with defects in the *Cacna1a* gene affecting the P/Q-type calcium channels were shown to have phenotypes of generalized, focal, or paroxysmal dystonia (Shirley et al., 2008).

Since then, inherited defects in multiple genes affecting calcium handling have since been linked with dystonia in humans. The *CACNA1A* gene encodes the pore-forming subunit of the P/Q-type voltage-regulated calcium channel. Numerous pathological genetic variants have been described, along with numerous different clinical phenotypes. The classic phenotypes include episodic ataxia type 2, progressive spinocerebellar ataxia type 6, hemiplegic migraine, and epilepsy (Rajakulendran et al., 2012). Dystonic movements may be an accompanying feature for all of these phenotypes (Ikeuchi et al., 1997; Muzaimi et al., 2003; Spacey et al., 2005). In some cases, dystonia may be the most prominent problem. For example, the *CACNA1A* gene has been associated with paroxysmal torticollis of infancy (Giffin et al., 2002; Roubertie et al., 2008; Shin et al., 2016; Vila-Pueyo et al., 2014), as well as adult-onset phenotypes of cervical dystonia, blepharospasm, and hand dystonia (Arpa et al., 1999; Cuenca-Leon et al., 2009; Hess et al., 2010; Mantuano et al., 2010). Recently, a whole exome sequencing study of 31 subjects with blepharospasm from 21 families revealed a novel co-segregating deleterious genetic variant in the *CACNA1A* gene (Tian et al., 2018). Although reports of dystonia associated with the *CACNA1A* gene are rare and some findings have yet to be confirmed, there seems to be convergent evidence to suggest that defects in this gene can cause dystonia. Unfortunately, *CACNA1A* has never been the target of candidate gene studies in large dystonia cohorts, because the size and structure of the gene makes it difficult to evaluate.

More recently, other genes related to calcium have been linked with dystonia. Numerous reports have linked the *ANO3* gene with dystonia,

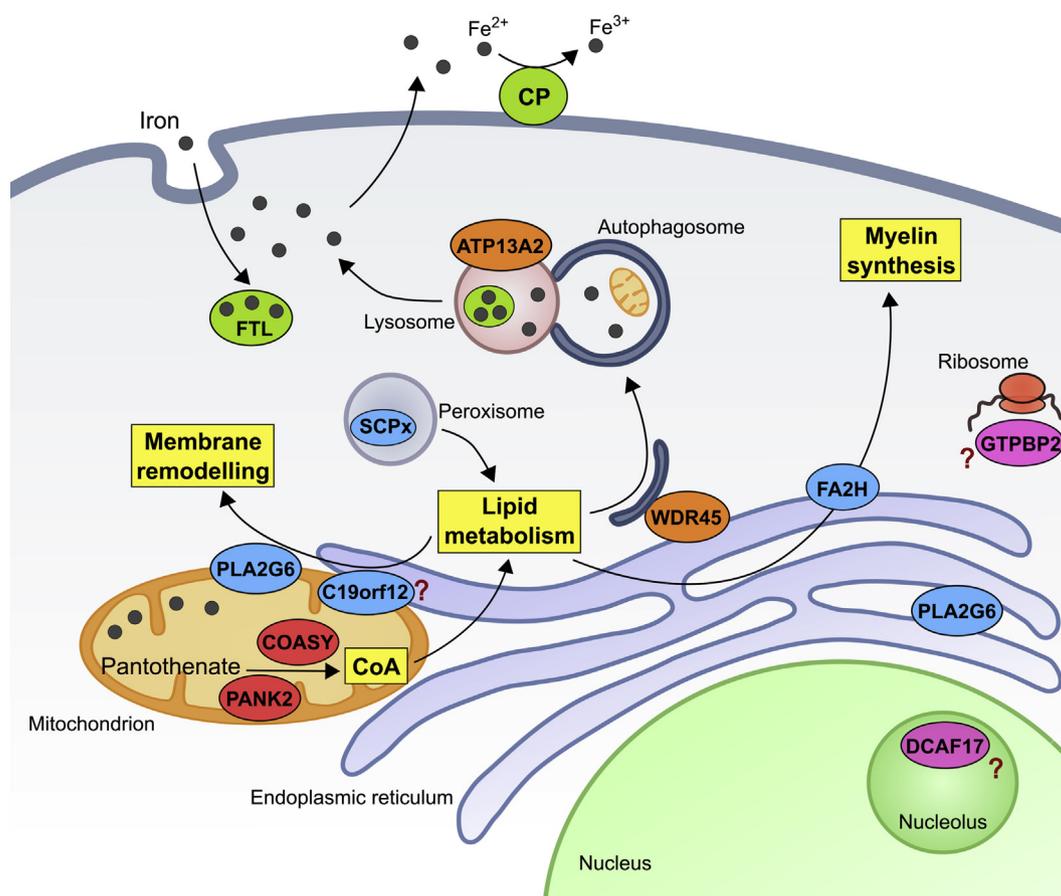
**Table 3**  
Genes associated with NBIA disorders.

Gene	Protein	Function	Inheritance	Disorder
<i>ATP13A2</i>	P-type ATPase 13A2	Lysosomal cation pump	AR	Kufor-Rakeb disease
<i>C19orf12</i>	Unknown	Mitochondrial membrane protein	AR	Mitochondrial membrane protein associated neurodegeneration (MPAN)
<i>COASY</i>	CoA synthase	CoA synthesis	AR	COASY protein associated neurodegeneration (CoPAN)
<i>CP</i>	Ceruloplasmin	Heavy metal transport	AR	Aceruloplasminemia
<i>DCAF17</i>	DDB1 and CUL4 associated factor 17	Nucleolar protein	AR	Woodhouse-Sakati disease
<i>FA2H</i>	Fatty acid hydroxylase type 2	Fatty acid metabolism	AR	Fatty acid hydroxylase associated neurodegeneration
<i>FTL</i>	Ferritin light chain	Heavy metal transport	AD	Hereditary neuroferritinopathy
<i>GTPBP2</i>	GTP binding protein	Suspected mRNA metabolism	AR	NA
<i>PANK2</i>	Pantothenate kinase type 2	CoA synthesis	AR	Pantothenate-kinase associated neurodegeneration (PKAN)
<i>PLA2G6</i>	Phospholipase A2	Phospholipid metabolism	AR	PLA2G6 associated neurodegeneration (PLAN)
<i>SCP2</i>	Sterol carrier proteins X and 2	Metabolism of fatty acids	AR	Leukoencephalopathy with dystonia and motor neuropathy
<i>WDR45</i>	$\beta$ -propeller protein	Autophagosome protein	XL	$\beta$ -propeller associated neurodegeneration (BPAN)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive, CoA, coenzyme A; XL, X-linked.

with a phenotype that often involves the neck and upper body, often combined with tremor (Blackburn et al., 2016; Charlesworth et al., 2012; Kuo et al., 2019; Ma et al., 2018; Ma et al., 2015; Miltgen et al., 2016; Nelin et al., 2018; Stamelou et al., 2014; Tunc et al., 2019; Yoo et al., 2018a; Yoo et al., 2018b; Zech et al., 2016; Zech et al., 2014). This gene encodes anoctamin-3, a protein that falls in the family of calcium-gated chloride channels, although its precise function is not yet firmly established. Because genetic variants in this gene are common among normal individuals, it has been difficult to know which of the reported variants are pathogenic and which are benign variants (Olschewski et al., 2019).

The *HPCA* gene encodes an intracellular calcium sensor that is highly expressed in the striatum and couples intracellular calcium levels to cell surface calcium channels and neuronal excitability. It has been associated with early-onset autosomal recessive generalized dystonia (Atasu et al., 2018; Charlesworth et al., 2015). Disease-associated genetic variants in this gene result in exaggerated calcium influx via N-type calcium channels (Helassa et al., 2017). The myoclonus dystonia syndrome has also been linked with the *CACNA1B* gene, which encodes the  $\alpha 1B$  subunit of N-type calcium channels (Groen et al., 2015). This association has been questioned because only one family has been so far described. However, it is interesting to note that this gene affects N-type



**Fig. 2.** Schematic representation of biological processes for disorders of neurodegeneration with brain iron accumulation (NBIA). This figure was reproduced from a recent comprehensive review of NBIA (Di Meo and Tiranti, 2018). Abbreviations: *ATP13A2*, gene symbol for lysosomal cation pump protein; CoA, coenzyme A; *COASY*, gene symbol for CoA synthase; *CP*, gene symbol for ceruloplasmin; *DCAF17*, gene symbol for nucleolar-localized protein with unknown function; *FA2H*, gene symbol for fatty acid hydroxylase 2; *GTPBP2*, gene symbol for GTP-binding protein with unknown function; *FTL*, gene symbol for ferritin light chain; *PANK2*, pantothenate kinase type 2; *PLA2G6*, phospholipase A2; *WDR45*, gene symbol for  $\beta$ -propeller protein.

calcium channels, the same channel that is indirectly affected by the *HPCA* gene (Helassa et al., 2017). Another relevant gene is *KCTD17*, which encodes the potassium channel tetramerization domain-containing protein 17. This channel is regulated by intracellular calcium levels, and it has been linked with the myoclonus-dystonia syndrome (Graziola et al., 2018; Marce-Grau et al., 2019; Mencacci et al., 2015). Dystonia is a frequent problem in human paroxysmal dyskinesias, which are sometimes caused by defects in the *KCNMA1* gene. This gene encodes the  $\alpha$ -subunit of a calcium-activated potassium channel, also known as the BK channel (Erro and Bhatia, 2019). Dystonia is common in a group of disorders known as familial basal ganglia calcification, or Fahr's disease. Some cases have been linked with the *SLC20A2* gene, which encodes a sodium-dependent phosphate transporter. The mechanism responsible for brain calcification is not clear, but likely involves abnormal calcium-phosphate interactions. A recent study has linked a complex phenotype that includes generalized dystonia with the *CAMK4* gene, which encodes a calcium-calmodulin-dependent kinase (Zech et al., 2018).

Although all of these genes associated with the biology of calcium are rare causes of dystonia and some have not been confirmed, the collective data from both humans and animals establish disorders of calcium homeostasis as a shared cause for dystonia. The mechanisms responsible for dystonia have not been determined. However, intracellular calcium levels are intimately linked with neuronal excitability and neuronal plasticity. They therefore provide an intriguing link with many human physiological studies that have shown abnormalities in neuronal excitability and neural plasticity (Quartarone and Hallett, 2013; Quartarone and Pisani, 2011). The biological theme involving calcium channels and perhaps calcium homeostasis may more broadly extend to other ions that affect neuronal excitability and function. For instance, the *ATPIA3* gene causes rapid-onset dystonia-parkinsonism (de Carvalho Aguiar et al., 2004). It encodes the  $\alpha_3$  subunit of the  $\text{Na}^+/\text{K}^+$  ATPase, a cell surface ion transporter that is critical for maintaining the ionic gradients responsible for neuronal signaling.

### 3.6. Other shared biological pathways

Other shared pathways have also been recognized for smaller numbers of genes. These include defects in synaptic functions, regulation of gene transcription, changes in the endoplasmic reticulum or nuclear envelope, responsiveness to intracellular stress, abnormalities of cell cycling, eIF2 $\alpha$  signaling, and others (Bragg et al., 2011; Gonzalez-Alegre, 2019; LeDoux et al., 2013; Nibbeling et al., 2017; Rittiner et al., 2016; Weisheit et al., 2018).

It is important to recognize that many of the shared pathways may not be mutually exclusive. For example, nigrostriatal dopamine neurons are among the most energetically demanding neurons in the brain, due to their huge dendritic arbors and unique aspects of dopamine metabolism and release (Bolam and Pissadaki, 2012). Their excitability is regulated by intracellular calcium. Furthermore, mitochondria play a key role in calcium storage and homeostasis. Thus there could be links between dopamine signaling, mitochondrial function, and/or maintenance of intracellular energy or calcium levels.

Most of the shared biological themes described above focus on molecular processes encoded by specific genes. However, it is important to recognize that there are additional shared themes that occur at the anatomical level. For example, there are numerous genes that point to dysfunction of the basal ganglia as a cause for dystonia (Balint et al., 2018). Many of these genes are associated with a combination of dystonia and parkinsonism, so the biological pathways for these two disorders may overlap for some genes. On the other hand, there are also numerous genes that point to dysfunction of the cerebellum and an overlap between mechanisms causing dystonia and ataxia too (Nibbeling et al., 2017). Thus some genes may not intersect at the molecular level, but at the anatomical level, by affecting common brain

regions that result in dystonia.

Other genes may intersect at processes related to development or aging of the brain. Several investigators have called attention to dystonia as a developmental disorder, because many of the genes involved appear to affect biological processes in developing children without causing any obvious degenerative changes (Domingo et al., 2016; Niethammer et al., 2010; Weisheit et al., 2018). On the other hand, there are also numerous dystonia genes associated with overt degenerative changes. Some of these are associated with degenerative changes during early development, while others are associated with degenerative changes in aged adults. Thus one subgroup of dystonias may reflect developmental mechanisms, while another subgroup may involve degenerative processes.

## 4. Why are shared biological pathways relevant?

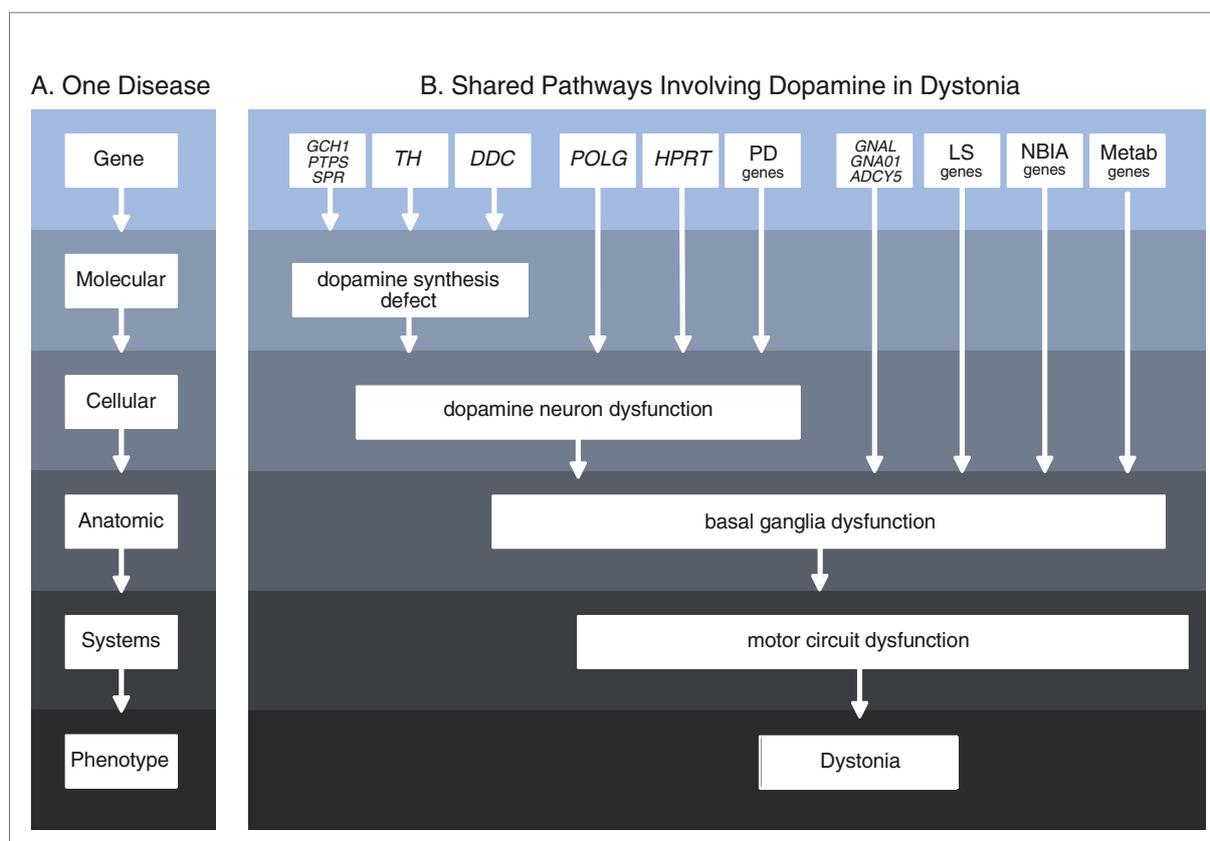
Elucidating the genes responsible for dystonia and particularly their shared biological pathways is important for basic neuroscientific understanding of a peculiar defect in motor control that involves matching the strength and distribution of muscles recruited to perform a specific task. Understanding the biology provides fundamental knowledge regarding how the brain controls movement.

Elucidating genes and pathways is also important for experimental therapeutics (Jinnah and Hess, 2008; Thompson et al., 2011). The basic pathogenesis of many inherited disorders can be viewed as a multi-step process that begins with a specific genetic defect, and triggers downstream molecular, cellular, physiological and anatomic events (Fig. 3). Elucidating each step provides different targets for experimental therapeutics. Interventions focusing on individual dystonia genes or their immediate “upstream” molecular consequences may provide useful therapeutics for individual disorders. However, interventions focusing on shared biological pathways “downstream” have greater potential as therapeutics for a larger group of disorders. These therapeutic interventions may not be relevant for all types of dystonia, but rather specific clusters of disorders. For example, some defects in dopamine synthesis provide a shared mechanism for a group of inherited disorders that can be treated with levodopa supplementation. However, this treatment is not effective for all dystonias associated with dopaminergic defects, so there are additional targets for therapeutic development. Molecular defects involving accumulation of heavy metals or calcium homeostasis provide novel targets for other groups of disorders, where treatments targeted at dopamine pathways may not be successful.

Shared biological pathways for dystonia are not limited molecular mechanisms (Fig. 3). For example, some inherited disorders have unrelated molecular pathways, yet they converge on a specific cellular process, such as mitochondrial function. Alternatively, they may converge on a specific cell type, such as nigrostriatal dopamine neurons, or on anatomical pathways, such as basal ganglia circuitry. Identifying shared anatomical pathways also provides targets for therapeutic interventions. Deep brain stimulation surgery targeting the outflow pathways of the basal ganglia provides one of the best examples. Targeting a single brain region with this approach can be remarkably successful in numerous types of dystonia with very diverse molecular mechanisms such as *TOR1A* (DYT1 dystonia) and *SGCE* (myoclonus-dystonia syndrome) (Jinnah et al., 2017a). However, this strategy does not work for other subtypes of dystonia involving different molecular mechanisms, such as *ATPIA3* (rapid onset dystonia-parkinsonism). These observations suggest that the dystonias with different molecular mechanisms may group into shared anatomical pathways, but these anatomical pathways are not the same for all (Jinnah et al., 2017b; Prudente et al., 2014).

## 5. Conclusions

Technological advances in genetics have led to a rapid growth in the number of dystonia genes. This growing number of genes is important



**Fig. 3.** Schematic representation of the pathogenesis of dystonia. The left side of the figure shows the classical pathway for pathogenesis of an inherited disease, with a gene defect triggering multiple downstream changes leading to the clinical phenotype. The right side of the figure shows this concept applied to the pathogenesis of dystonia, where shared pathways may be identified at multiple levels. Several genes contribute to defects in dopamine signaling at the molecular/biochemical level by affecting the synthesis of dopamine (*GCH1*, *SPR*, *PTPS*, *TH*, *DDC*). Several others contribute to dopamine neuron dysfunction, such as *HPRT1*, *POLG* or genes responsible for degeneration of dopamine neurons in Parkinson's disease (PD genes). Others lead to dysfunction of post-synaptic neurons in the basal ganglia, such as *GNAL*, *GNAO1*, *ADCY5*, neurodegeneration with brain iron accumulation (NBIA genes), Leigh's syndrome genes (LS genes), or metabolic disorders of amino acid or organic acids (Metab genes). The final common pathway is a circuit involved in motor control that may include other brain regions.

because it helps to understand the causes for inherited forms of dystonia, and it helps to begin to link them into shared biological pathways. It seems unlikely that there will be one final common pathway that explains all types of dystonia, but rather multiple pathways that can account for specific clusters of dystonia. Several such clusters can be recognized already. Shared pathways may occur the cellular level, the anatomical level. It is likely that more pathways will soon be elucidated.

#### Acknowledgements

This work was supported in part by NIH Grants NS096455 and the Dystonia Coalition, a part of the Rare Diseases Clinical Research Network of the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences (grants TR001456 and NS065701).

#### Disclosures

H. A. Jinnah has active or recent grant support from the US government (National Institutes of Health), private philanthropic organizations (the Benign Essential Blepharospasm Research Foundation, Cure Dystonia Now), academically-oriented institutions (the Dystonia Study Group), and industry (Cavion Therapeutics, Ipsen Pharmaceuticals, Retrophin Inc.). Dr. Jinnah has also served on advisory boards or as a consultant for Abide Therapeutics, Allergan Inc., CoA Therapeutics, Medtronic Inc., Psyadon Pharmaceuticals, Retrophin

Inc., and Saol Therapeutics. He has received honoraria or stipends for lectures or administrative work from the American Academy of Neurology, the American Neurological Association, the Dystonia Medical Research Foundation, the International Neurotoxin Society, the International Parkinson's Disease and Movement Disorders Society, The Parkinson's Disease Foundation, and Tyler's Hope for a Cure. Dr. Jinnah serves on the Scientific Advisory Boards for several private foundations including the Benign Essential Blepharospasm Research Foundation, Cure Dystonia Now, the Dystonia Medical Research Foundation, and Tyler's Hope for a Cure. He also is principle investigator for the Dystonia Coalition, which receives the majority of its support through NIH grant TR001456 from the Office of Rare Diseases Research at the National Center for Advancing Translational Sciences, and previously NS065701 from the National Institutes of Neurological Disorders and Stroke. The Dystonia Coalition has received additional material or administrative support from industry sponsors (Allergan Inc. and Merz Pharmaceuticals) as well as private foundations (The American Dystonia Society, Beat Dystonia, The Benign Essential Blepharospasm Foundation, Cure Dystonia Now, Dystonia Europe, Dystonia Inc., Dystonia Ireland, The Dystonia Medical Research Foundation, The Foundation for Dystonia Research, The National Spasmodic Dysphonia Association, and The National Spasmodic Torticollis Association).

#### References

- Abela, L., Kurian, M.A., 2018. Postsynaptic movement disorders: clinical phenotypes, genotypes, and disease mechanisms. *J. Inherit. Metab. Dis.* 41, 1077–1091.
- Albanese, A., et al., 2013. Phenomenology and classification of dystonia: a consensus

- update. *Mov. Disord.* 28, 863–873.
- Arpa, J., et al., 1999. Clinical features and genetic analysis of a Spanish family with spinocerebellar ataxia 6. *Acta Neurol. Scand.* 99, 43–47.
- Atasu, B., et al., 2018. HPCA confirmed as a genetic cause of DYT2-like dystonia phenotype. *Mov. Disord.* 33, 1354–1358.
- Balcioglu, A., et al., 2007. Dopamine release is impaired in a mouse model of DYT1 dystonia. *J. Neurochem.* 102, 783–788.
- Balint, B., et al., 2018. Dystonia. *Nat Rev Dis Primers.* vol. 4, pp. 25.
- Bandmann, O., et al., 2015. Wilson's disease and other neurological copper disorders. *Lancet Neurol.* 14, 103–113.
- Benecke, R., et al., 1992. Electron transfer complex I defect in idiopathic dystonia. *Ann. Neurol.* 32, 683–686.
- Berman, B.D., et al., 2013. Striatal dopaminergic dysfunction at rest and during task performance in writer's cramp. *Brain* 136, 3645–3658.
- Blackburn, P.R., et al., 2016. A novel ANO3 variant identified in a 53-year-old woman presenting with hyperkinetic dysarthria, blepharospasm, hyperkinesias, and complex motor tics. *BMC Med. Genet.* 17, 93.
- Bolam, J.P., Pissadaki, E.K., 2012. Living on the edge with too many mouths to feed: why dopamine neurons die. *Mov. Disord.* 27, 1478–1483.
- Bonsi, P., et al., 2019. RGS9-2 rescues dopamine D2 receptor levels and signaling in DYT1 dystonia mouse models. *EMBO Mol Med* 11.
- Bragg, D.C., et al., 2011. Molecular pathways in dystonia. *Neurobiol. Dis.* 42, 136–147.
- Carecchio, M., et al., 2017. ADCY5-related movement disorders: frequency, disease course and phenotypic variability in a cohort of paediatric patients. *Parkinsonism Relat. Disord.* 41, 37–43.
- Charlesworth, G., et al., 2012. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am. J. Hum. Genet.* 91, 1041–1050.
- Charlesworth, G., et al., 2015. Mutations in HPCA cause autosomal-recessive primary isolated dystonia. *Am. J. Hum. Genet.* 96, 657–665.
- Chen, D.H., et al., 2015. ADCY5-related dyskinesia: broader spectrum and genotype-phenotype correlations. *Neurology* 85, 2026–2035.
- Cuenca-Leon, E., et al., 2009. Late-onset episodic ataxia type 2 associated with a novel loss-of-function mutation in the CACNA1A gene. *J. Neurol. Sci.* 280, 10–14.
- de Carvalho Aguiar, P., et al., 2004. Mutations in the Na<sup>+</sup>/K<sup>+</sup> -ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. *Neuron* 43, 169–175.
- Di Meo, I., Tiranti, V., 2018. Classification and molecular pathogenesis of NBIA syndromes. *Eur. J. Paediatr. Neurol.* 22, 272–284.
- Domingo, A., et al., 2016. Novel dystonia genes: clues on disease mechanisms and the complexities of high-throughput sequencing. *Mov. Disord.* 31, 471–477.
- Erro, R., Bhatia, K.P., 2019. Unravelling of the paroxysmal dyskinesias. *J. Neurol. Neurosurg. Psychiatry* 90, 227–234.
- Fan, X., et al., 2018. Dopamine receptor agonist treatment of idiopathic dystonia: a re-appraisal in humans and mice. *J. Pharmacol. Exp. Ther.* 365, 20–26.
- Fu, R., et al., 2013. Genotype-phenotype correlations in neurogenetics: Lesch-Nyhan disease as a model disorder. *Brain* 137, 1282–1303.
- Fuchs, T., et al., 2013. Mutations in GNAL cause primary torsion dystonia. *Nat. Genet.* 45, 88–92.
- Fung, V.S., et al., 2013. Assessment of the patient with dystonia: an update on dystonia syndromes. *Mov. Disord.* 28, 889–898.
- Gavarini, S., et al., 2010. Direct interaction between causative genes of DYT1 and DYT6 primary dystonia. *Ann. Neurol.* 68, 549–553.
- Ghaoui, R., Sue, C.M., 2018. Movement disorders in mitochondrial disease. *J. Neurol.* 265, 1230–1240.
- Giffin, N.J., et al., 2002. Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation. *Dev. Med. Child Neurol.* 44, 490–493.
- Goettle, M., et al., 2014. Loss of neurotransmitter phenotype among midbrain dopamine neurons in Lesch-Nyhan disease. *Ann. Neurol.* 76, 95–107.
- Gonzalez-Alegre, P., 2019. Advances in molecular and cell biology of dystonia: focus on torsinA. *Neurobiol. Dis.* 127, 233–241.
- Graziola, F., et al., 2019. A novel KCTD17 mutation is associated with childhood early-onset hyperkinetic movement disorder. *Parkinsonism Relat. Disord.* 61, 4–6.
- Groen, J.L., et al., 2015. CACNA1B mutation is linked to unique myoclonus-dystonia syndrome. *Hum. Mol. Genet.* 24, 987–993.
- Head, R.A., et al., 2004. Pyruvate dehydrogenase deficiency presenting as dystonia in childhood. *Dev. Med. Child Neurol.* 46, 710–712.
- Helassa, N., et al., 2017. Biophysical and functional characterization of hippocalcin mutants responsible for human dystonia. *Hum. Mol. Genet.* 26, 2426–2435.
- Hess, E.J., et al., 2010. Neuronal voltage-gated calcium channels: brief overview of their function and clinical implications in neurology. *Neurology* 75, 937–938.
- Iacono, D., et al., 2019. Hypertrophy of nigral neurons in Torsin1A deletion (DYT1) carriers manifesting dystonia. *Parkinsonism Relat. Disord.* 58, 63–69.
- Ikeuchi, T., et al., 1997. Spinocerebellar ataxia type 6: CAG repeat expansion in alpha1A voltage-dependent calcium channel gene and clinical variations in Japanese population. *Ann. Neurol.* 42, 879–884.
- Jinnah, H.A., Hess, E.J., 2008. Experimental therapeutics for dystonia. *Neurotherapeutics* 5, 198–209.
- Jinnah, H.A., et al., 2000. Calcium channel agonists and dystonia in the mouse. *Mov. Disord.* 15, 542–551.
- Jinnah, H.A., et al., 2006. Delineation of the motor disorder of Lesch-Nyhan disease. *Brain* 129, 1201–1217.
- Jinnah, H.A., et al., 2010. Attenuated variants of Lesch-Nyhan disease. *Brain* 133, 671–689.
- Jinnah, H.A., et al., 2013. The focal dystonias: current views and challenges for future research. *Mov. Disord.* (7), 926–943.
- Jinnah, H.A., et al., 2017a. Deep brain stimulation for dystonia: a novel perspective on the value of genetic testing. *J. Neural Transm. (Vienna)* 124, 417–430.
- Jinnah, H.A., et al., 2017b. The anatomical basis for dystonia: The motor network model. In: *Tremor Other Hyperkinet Mov (N Y)*. vol. 7, pp. 506.
- Jinnah, H.A., et al., 2018. Treatable inherited rare movement disorders. *Mov. Disord.* 33, 21–35.
- Kaiser, F.J., et al., 2010. The dystonia gene DYT1 is repressed by the transcription factor THAP1 (DYT6). *Ann. Neurol.* 68, 554–559.
- Karimi, M., Perlmuter, J.S., 2015. The role of dopamine and dopaminergic pathways in dystonia: insights from neuroimaging. *Tremor Other Hyperkinet Mov (N Y)* 5, 280.
- Karimi, M., et al., 2011. Decreased striatal dopamine receptor binding in primary focal dystonia: a D2 or D3 defect? *Mov. Disord.* 26, 100–106.
- Kasten, M., et al., 2018. Genotype-phenotype relations for the Parkinson's disease genes parkin, PINK1, DJ1: MDSGene systematic review. *Mov. Disord.* 33, 730–741.
- Kim, H.T., et al., 2007. Blepharospasm and limb dystonia caused by Mohr-Tranebjaerg syndrome with a novel splice site mutation in the deafness/dystonia peptide gene. *Mov. Disord.* 22, 1328–1331.
- Kuo, M.C., et al., 2019. Craniocervical dystonia with levodopa-responsive parkinsonism co-segregating with a pathogenic ANO3 mutation in a Taiwanese family. *Parkinsonism Relat. Disord.* (in press).
- Kurian, M.A., et al., 2011. The monoamine neurotransmitter disorders: an expanding range of neurological syndromes. *Lancet Neurol.* 10, 721–733.
- Lake, N.J., et al., 2016. Leigh syndrome: one disorder, more than 75 monogenic causes. *Ann. Neurol.* 79, 190–203.
- LeDoux, M.S., 2012. The genetics of dystonias. *Adv. Genet.* 79, 35–85.
- LeDoux, M.S., et al., 2013. Emerging molecular pathways for dystonia. *Mov. Disord.* 15, 968–981.
- Lohmann, K., et al., 2016. The role of mutations in COL6A3 in isolated dystonia. *J. Neurol.* 263, 730–734.
- Ma, L.Y., et al., 2015. Mutations in ANO3 and GNAL gene in thirty-three isolated dystonia families. *Mov. Disord.* 30, 743–744.
- Ma, J., et al., 2018. Targeted gene capture sequencing in diagnosis of dystonia patients. *J. Neurol. Sci.* 390, 36–41.
- Machado, A., et al., 2006. Neurological manifestations in Wilson's disease: report of 119 cases. *Mov. Disord.* 21, 2192–2196.
- Mantuano, E., et al., 2010. Identification of novel and recurrent CACNA1A gene mutations in fifteen patients with episodic ataxia type 2. *J. Neurol. Sci.* 291, 30–36.
- Marce-Grau, A., et al., 2019. Childhood onset progressive myoclonic dystonia due to a de novo KCTD17 splicing mutation. *Parkinsonism Relat. Disord.* 61, 7–9.
- Marras, C., et al., 2012. Fixing the broken system of genetic locus symbols: Parkinson disease and dystonia as examples. *Neurology* 78, 1016–1024.
- Marras, C., et al., 2016. Nomenclature of genetic movement disorders: recommendations of the international Parkinson and movement disorder society task force. *Mov. Disord.* 31, 436–457.
- Martikainen, M.H., et al., 2016. Clinical, genetic, and radiological features of extra-pyramidal movement disorders in mitochondrial disease. *JAMA Neurol.* 73, 668–674.
- McFarland, R., et al., 2007. Homoplasmy, heteroplasmy, and mitochondrial dystonia. *Neurology* 69, 911–916.
- Mencacci, N.E., et al., 2015. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. *Am. J. Hum. Genet.* 96, 938–947.
- Miltgen, M., et al., 2016. Novel heterozygous mutation in ANO3 responsible for craniocervical dystonia. *Mov. Disord.* 31, 1251–1252.
- Moustris, A., et al., 2011. Movement disorders and mitochondrial disease. *Handb. Clin. Neurol.* 100, 173–192.
- Muller-Vahl, K.R., et al., 2000. Mitochondriopathy, blepharospasm, and treatment with botulinum toxin. *Muscle Nerve* 23, 647–648.
- Muzaimi, M.B., et al., 2003. Task specific focal dystonia: a presentation of spinocerebellar ataxia type 6. *J. Neurol. Neurosurg. Psychiatry* 74, 1444–1445.
- Nelin, S., et al., 2018. Youngest presenting patient with dystonia 24 and review of the literature. *Clin Case Rep* 6, 2070–2074.
- Nemeth, A.H., 2002. The genetics of primary dystonias and related disorders. *Brain* 125, 695–721.
- Neychev, V.K., et al., 2011. The functional neuroanatomy of dystonia. *Neurobiol. Dis.* 42, 185–201.
- Ng, J., et al., 2014. Dopamine transporter deficiency syndrome: phenotypic spectrum from infancy to adulthood. *Brain* 137, 1107–1119.
- Nibbeling, E.A., et al., 2017. Using the shared genetics of dystonia and ataxia to unravel their pathogenesis. *Neurosci. Biobehav. Rev.* 75, 22–39.
- Niethammer, M., et al., 2010. Hereditary dystonia as a neurodevelopmental circuit disorder: evidence from neuroimaging. *Neurobiol. Dis.* 42, 202–209.
- Olschewski, L., et al., 2019. Role of ANO3 mutations in dystonia: a large-scale mutational screening study. *Parkinsonism Relat. Disord.* (in press).
- Ozelius, L.J., et al., 1997. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat. Genet.* 17, 40–48.
- Page, M.E., et al., 2010. Cell-autonomous alteration of dopaminergic transmission by wild type and mutant (DeltaE) TorsinA in transgenic mice. *Neurobiol. Dis.* 39, 318–326.
- Pearson, T.S., et al., 2013. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). *Curr Neurol Neurosci Rep* 13, 342.
- Perlmuter, J.S., et al., 1997. Decreased [18F]spiperone binding in putamen in idiopathic focal dystonia. *J. Neurosci.* 17, 843–850.
- Prudente, C.N., et al., 2014. Dystonia as a network disorder: what is the role of the cerebellum? *Neuroscience* 260, 23–35.
- Quadri, M., et al., 2012. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease. *Am. J. Hum. Genet.* 90, 467–477.
- Quartarone, A., Hallett, M., 2013. Emerging concepts in the physiological basis of dystonia. *Mov. Disord.* 28, 958–967.
- Quartarone, A., Pisani, A., 2011. Abnormal plasticity in dystonia: disruption of synaptic

- homeostasis. *Neurobiol. Dis.* 42, 162–170.
- Rajakulendran, S., et al., 2012. Neuronal P/Q-type calcium channel dysfunction in inherited disorders of the CNS. *Nat. Rev. Neurol.* 8, 86–96.
- Riley, L.G., et al., 2017. A SLC39A8 variant causes manganese deficiency, and glycosylation and mitochondrial disorders. *J. Inherit. Metab. Dis.* 40, 261–269.
- Rilstone, J.J., et al., 2013. Brain dopamine-serotonin vesicular transport disease and its treatment. *N. Engl. J. Med.* 368, 543–550.
- Rittiner, J.E., et al., 2016. Functional genomic analyses of Mendelian and sporadic disease identify impaired eIF2 $\alpha$  signaling as a generalizable mechanism for dystonia. *Neuron* 92, 1238–1251.
- Rostasy, K., et al., 2003. TorsinA protein and neuropathology in early onset generalized dystonia with GAG deletion. *Neurobiol. Dis.* 12, 11–24.
- Roubertie, A., et al., 2008. Benign paroxysmal tonic upgaze, benign paroxysmal torticollis, episodic ataxia and CACNA1A mutation in a family. *J. Neurol.* 255, 1600–1602.
- Scarduzio, M., et al., 2017. Strength of cholinergic tone dictates the polarity of dopamine D2 receptor modulation of striatal cholinergic interneuron excitability in DYT1 dystonia. *Exp. Neurol.* 295, 162–175.
- Schapira, A.H., et al., 1997. Complex I function in familial and sporadic dystonia. *Ann. Neurol.* 41, 556–559.
- Schirinzi, T., et al., 2019. Phenomenology and clinical course of movement disorder in GNAO1 variants: results from an analytical review. *Parkinsonism Relat. Disord.* 61, 19–25.
- Shin, M., et al., 2016. The genetics of benign paroxysmal torticollis of infancy: is there an association with mutations in the CACNA1A gene? *J. Child Neurol.* 31, 1057–1061.
- Shirley, T.L., et al., 2008. Paroxysmal dyskinesias in mice. *Mov. Disord.* 23, 259–264.
- Simon, D.K., et al., 2003. A heteroplasmic mitochondrial complex I gene mutation in adult-onset dystonia. *Neurogenetics* 4, 199–205.
- Simonyan, K., et al., 2013. Abnormal striatal dopaminergic neurotransmission during rest and task production in spasmodic dysphonia. *J. Neurosci.* 33, 14705–14714.
- Song, C.H., et al., 2012. Functional analysis of dopaminergic systems in a DYT1 knock-in mouse model of dystonia. *Neurobiol. Dis.* 48, 66–78.
- Spacey, S.D., et al., 2005. Two novel CACNA1A gene mutations associated with episodic ataxia type 2 and interictal dystonia. *Arch. Neurol.* 62, 314–316.
- Stamelou, M., et al., 2014. The phenotypic spectrum of DYT24 due to ANO3 mutations. *Mov. Disord.* 29, 928–934.
- Sudarsky, L.R., et al., 1999. Dystonia as a presenting feature of the 3243 mitochondrial DNA mutation. *Mov. Disord.* 14, 488–491.
- Swerdlow, R.H., Wooten, G.F., 2001. A novel deafness/dystonia peptide gene mutation that causes dystonia in female carriers of Mohr-Tranebjaerg syndrome. *Ann. Neurol.* 50, 537–540.
- Swerdlow, N.R., et al., 2004. Dystonia with and without deafness is caused by TIMM8A mutation. *Adv. Neurol.* 94, 147–153.
- Tello, C., et al., 2018. On the complexity of clinical and molecular bases of neurodegeneration with brain iron accumulation. *Clin. Genet.* 93, 731–740.
- Thompson, V.B., et al., 2011. Convergent mechanisms in etiologically-diverse dystonias. *Expert Opin. Ther. Targets* 15, 1387–1403.
- Tian, J., et al., 2018. Whole-exome sequencing for variant discovery in blepharospasm. *Mol Genet Genomic Med* (in press).
- Tuladhar, A.M., et al., 2013. POLG mutation presenting with late-onset jerky torticollis. *J. Neurol.* 260, 903–905.
- Tunc, S., et al., 2019. A recurrent de-novo ANO3 mutation causes early-onset generalized dystonia. *J. Neurol. Sci.* 396, 199–201.
- Tuschl, K., et al., 2012. Syndrome of hepatic cirrhosis, dystonia, polycythemia, and hypermanganesemia caused by mutations in SLC30A10, a manganese transporter in man. *Am. J. Hum. Genet.* 90, 457–466.
- Tuschl, K., et al., 2016. Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. *Nat. Commun.* 7, 11601.
- Tzoulis, C., et al., 2013. Severe nigrostriatal degeneration without clinical parkinsonism in patients with polymerase gamma mutations. *Brain* 136, 2393–2404.
- van Egmond, M.E., et al., 2017. A post hoc study on gene panel analysis for the diagnosis of dystonia. *Mov. Disord.* 32, 569–575.
- Vemula, S.R., et al., 2013. Role of G $\alpha$ (olf) in familial and sporadic adult-onset primary dystonia. *Hum. Mol. Genet.* 22, 2510–2519.
- Vidailhet, M., et al., 1999. Dopaminergic dysfunction in midbrain dystonia. *Arch. Neurol.* 56, 982–989.
- Vila-Pueyo, M., et al., 2014. A loss-of-function CACNA1A mutation causing benign paroxysmal torticollis of infancy. *Eur. J. Paediatr. Neurol.* 18, 430–433.
- Wassenberg, T., et al., 2017. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. *Orphanet J Rare Dis* 12, 12.
- Weisheit, C.E., et al., 2018. Inherited dystonias: clinical features and molecular pathways. *Handb. Clin. Neurol.* 147, 241–254.
- Wiethoff, S., Houlden, H., 2017. Neurodegeneration with brain iron accumulation. *Handb. Clin. Neurol.* 145, 157–166.
- Wijemanne, S., Jankovic, J., 2015. Dopa-responsive dystonia—clinical and genetic heterogeneity. *Nat. Rev. Neurol.* 11, 414–424.
- Yoo, D., et al., 2018a. Early-onset generalized dystonia starting in the lower extremities in a patient with a novel ANO3 variant. *Parkinsonism Relat. Disord.* 50, 124–125.
- Yoo, H.S., et al., 2018b. A novel heterozygous ANO3 mutation with basal ganglia dysfunction in a patient with adult-onset isolated segmental dystonia. *J Clin Neurol* 14, 596–597.
- Zech, M., et al., 2014. Rare sequence variants in ANO3 and GNAL in a primary torsion dystonia series and controls. *Mov. Disord.* 29, 143–147.
- Zech, M., et al., 2016. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. *Mov. Disord.* 32, 549–559.
- Zech, M., et al., 2018. A unique de novo gain-of-function variant in CAMK4 associated with intellectual disability and hyperkinetic movement disorder. *Cold Spring Harb Mol Case Stud* 4.