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The Apparent Paradox of Phenotypic Diversity and Shared Mechanisms Across Dystonia Syndromes

Alessio Di Fonzo[1], **Alberto Albanese**[2], **Hyder H. Jinnah**[3]

[1)]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neurology Unit, Milan, Italy

[2)]Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milano, Italy

[3)]Departments of Neurology, Human Genetics, and Pediatrics, Emory University School of Medicine, Atlanta GA, 30322, USA

Abstract

Recent findings: The continuing discoveries of genetic causes for dystonia syndromes are transforming our view of these disorders. They share unexpectedly common underlying mechanisms, including dysregulation in neurotransmitter signaling, gene transcription, and quality control machinery. The field has further expanded to include forms recently associated with endolysosomal dysfunction.

Purpose of review: We describe here how such mechanisms shared by different genetic forms can give rise to motor performance dysfunctions with a clinical aspect of dystonia.

Summary: The discovery of biological pathways shared between different monogenic dystonias is an important conceptual advance in the understanding of the underlying mechanisms, with a significant impact on the pathophysiological understanding of clinical phenomenology. The functional relationship between dystonia genes could revolutionize current dystonia classification systems, classifying patients with different monogenic forms based on common pathways. The most promising effect of these advances is on future mechanism-based therapeutic approaches.

Keywords

dystonia; genetics; environment; molecular mechanisms; movement disorders

Introduction

Dystonia is a collection of physical signs that are variably aggregated in different syndromes (1). The current definition and classification of dystonia provide a common language that is used to describe and classify these diverse syndromes (2,3). Dystonia is characterized by hyperkinetic features, such as involuntary postures and movements, including tremor; but at the same time displays hypokinetic features, particularly a slowing of voluntary movement (4,5).

Corresponding Author: Hyder H. Jinnah, hjinnah@emory.edu Departments of Neurology, Human Genetics, and Pediatrics, Emory University School of Medicine, Atlanta GA, 30322, USA.

The complexity of clinical presentations have been ordered by the current classification scheme (2). This two-axis system has been well received and widely adopted (6). According to axis 1, dystonia can occur in isolation (isolated dystonia), or in combination with another movement disorder, or with additional neurological and medical problems. Etiology of dystonia (axis 2) can be idiopathic (unknown), inherited (of genetic origin) or acquired (environmental) (2). Many genes are known to cause dystonia; a gene list aggregated by phenotype has been recently published (1), but the listing is far from complete. Whole-genome sequencing of an unselected patient population with dystonia showed that approximately 12% of non-acquired dystonia patients carried a pathogenic gene mutation (7). This suggests that dystonia is idiopathic in the vast majority of patients, with a minority of cases being inherited. There is a high degree of phenotypic overlap in patients with inherited dystonia and their phenotypic differences are of limited use for guessing any specific genetic etiology (8*). Performing wide gene panels or whole exome/genome sequencing is warranted for cases where an inherited etiology is considered (9).

The complex derangement of voluntary movement observed in dystonia is currently interpreted as due to the disorganization of an anatomical network including widespread motor and sensory brain regions (10). Network derangement can occur in patients who suffer from discrete brain lesions and have a relatively homogeneous dystonia phenotype (11) as well as in patients with inherited disorders (12).

As the number of genes associated with dystonia and the phenotypic heterogeneity of cases sharing the same genetic cause increase, the correlation between clinical and molecular findings seems to lead to apparent paradoxes. We here try to shed light on these paradoxes, unraveling how shared molecular mechanisms explain similar phenotypes in different monogenic forms, and on the other hand how heterogeneity in dystonia can be attributable to a common underlying mechanism.

How can so many different genes cause the same disorder?

The continuous progress in identifying genetic causes of dystonias represents a huge opportunity to understand the biological complexity underlying pathogenesis. The more dystonia genes emerge in different forms, the more we are beginning to discern the existence of previously unexplored biological convergences among the underlying molecular mechanisms. Many pathways of convergence have been described. The main ones include dopamine transmission, gene transcription machinery, endoplasmic reticulum (ER) -mediated cellular stress response, and more recently also vesicular/endolysosomal trafficking. It is therefore possible that the pathology underlying the spectrum of individual monogenic dystonias may ultimately be attributed to abnormalities in a few convergent pathways. There are several prior reviews of some of these pathways (13–16), so only the most important and recent ones are highlighted here.

Dopamine Transmission

Defects in nigrostriatal dopamine transmission have been firmly implicated in dystonia pathogenesis. Based on the nature of enzymatic defects they can be grouped in: a) enzymatic

defects in BH4 metabolism: GTP cyclohydrolase 1 (*GCH1*), sepiapterin reductase (*SPR*), dihydropteridine reductase (*DHPR*), 6-pyruvoyl tetrahydropterin synthase (*PTS*), pterin-4a-carbinolamine dehydratase (*PCD*) deficiencies b) Primary neurotransmitter synthesis defects: tyrosine hydroxylase (*TH*), aromatic amino acid decarboxylase deficiency (*DDC*) c) Monoamine transportopathies (*SLC6A3* and *SLC18A2*) (17,18*)

Genetic variants in *GCH1*, *SPR*, and *PTS* lead to dystonias by altering the biosynthetic pathway of tetrahydrobiopterin (BH4). BH_4 deficiency is characterized by insufficient synthesis of the monoamine neurotransmitters dopamine and serotonin due to a disturbance of BH_4 biosynthesis or recycling. Recently, guidelines according to the SIGN (Scottish Intercollegiate Guidelines Network) methodology were proposed by evaluating all available evidence for the diagnosis and treatment of BH4 deficiencies (19). Beyond the dysfunction linked to dopamine transport and signaling in the striatum, other potential mechanisms are emerging. A proteomic analysis on TH knock in mice revealed that nearly 20% of the differentially regulated striatal proteins are encoded by genes reported to be involved in inherited disorders characterized by dystonic features, suggesting shared mechanisms across many different forms of dystonia (20*).

More hints on the mechanisms underlying these disorders come from the discovery of new genes. DNAJC12, a gene encoding a heat shock protein that likely increases TH stability in nigrostriatal dopaminergic neurons, was found to be causative in cases with intellectual disability, developmental delay, often in combination with prominent dystonia and parkinsonism (21,22). More recently, independent reports associated mutations of the *NR4A2* gene, previously implicated in a neurodevelopmental disorder with autism, intellectual disability, and epilepsy (23), to cases presenting with early-onset dystonia and dopa-responsive dystonia-parkinsonism (24–26). Finally, new achievements from experimental models suggest interesting links between other monogenic forms of isolated dystonia and impaired transmission and dopaminergic signaling (27,28*). Altogether, these observations provide strong support for abnormal dopamine transmission as a shared mechanism for multiple different types of dystonia.

Gene transcription/regulation

Abnormal regulation of gene transcription for dystonia is supported by the identification of dystonia-causing mutations in *THAP1* and *KMT2B* (29,30). *KMT2B*, encoding a histone H3 methyltransferase, is involved in chromatin plasticity and epigenetic control during early development (31). A recent study demonstrated that *KMT2B* loss of function leads to a non-random DNA hypermethylation selectively involving promoters and other regulatory regions that control gene expression (32**). Importantly, this study proved the feasibility of validating childhood-onset associated pathogenic *KMT2B* variants by methylation analysis on peripheral blood DNA.

Recent observations associated pathogenic variants within the *YY1* gene with dystonia (33–35). *YY1* encodes yin and yang 1, a zinc-finger transcription factor involved in neurodevelopment, which is known to have an established role in oligodendrocyte lineage progression. An interplay between *THAP1* and *YY1* has been suggested from several

lines of evidence. *THAP1* loss may alter brain myelination by significantly reducing DNA binding of *YY1* (36*). Also, alterations in various neurotransmitter release cycle pathways, extracellular matrix organization, deoxyribonucleic acid methylation, and differential expression of transcription factors, including *YY1* and *THAP1* itself emerged from a transcriptome analysis in induced pluripotent stem cells (iPSCs)-derived neurons of *THAP1* manifesting versus non-manifesting patients (37*).

We are only starting to understand the DNA regulatory mechanism complex linked to transcription factors genes associated with dystonia. Recently, *THAP1*, *YY1*, and *HCF1* were found to bind directly to the promoter of *SHLD1*, a component of the Shieldin complex, which shields double-strand DNA breaks from nucleolytic resection (38*). Altogether, these observations suggest that another shared mechanism for many types of dystonia may involve abnormal neural development. A critical role for developmental processes has been recognized before, including specific time windows in which the abnormality may occur (39).

Quality Control Machinery and Trafficking

A recent area of mechanistic convergence among different dystonia genes is the quality control machinery. ER-associated degradation (ERAD) is the major pathway by which folding of proteins is continuously monitored and misfolded polypeptides are transferred from the ER to the cytosol to be degraded by the proteasome (40). The ER undergoes continuous dynamic remodeling, especially in response to specific stimuli, as in the unfolded protein response (UPR). Downstream UPR, the cytosolic signaling cascades mediate restoration of ER status by arresting protein translation, via PERK-mediated phosphorylation of the translation factor eIF2α (eukaryotic initiation factor 2 alpha), and by transcriptional upregulation of lumenal oxidoreductases and chaperones, and ERAD (41). Substrates of ERAD are limited to proteins. On the other hand, the autophagy-lysosome system is able to degrade parts of the ER, including membranes. Proteins, membranes and organelles are delivered to the lysosomes via different routes including ER-phagy, ERES-microautophagy, or vesicular transport (Fig. 1). Interestingly, newly discovered monogenic forms of dystonia are linked at different level to the quality control machinery (42).

The *TOR1A* gene encodes for torsinA, a protein embedded in the lumen of the endoplasmic reticulum and the endomembrane space of nuclear envelope (43,44). Different functional roles have been attributed to torsinA, including being a component of the cytoskeleton and the nuclear envelope, and involvement in the secretory pathway and synaptic vesicle machinery. Experimental models using transgenic rodents, and more recently iPSCs-derived neurons from patients carrying the common *TOR1A* ΔGAG deletion support the impairment of nuclear envelope and impaired nucleocytoplasmic transport eventually leading to mislocalization of mRNAs and proteins (45). In addition, torsinA associates with proteins implicated in ERAD, where fibroblasts from *TOR1A*-associated dystonia patients are more sensitive to ER stress and less able to degrade proteins that have to undergo ERAD-degradation (46). Several reports linked expression of this gene with dysregulation of eIF2α (47).

A new actor recently implicated the pathogenesis of dystonia is the eukaryotic translation initiation factor 2 alpha kinase 2 (*EIF2AK2*) (48**). *EIF2AK2* phosphorylates eIF2α in the presence of ER stress. Of note, *EIF2AK2* activity is regulated by the interferon-inducible double-stranded RNA-dependent Protein Kinase Activator A (*PRKRA*), whose mutations cause a rare form of young onset parkinsonism-dystonia (49,50). To further support the molecular link with stress response, fever-induced decompensation has recently been described in a patient carrying an *EIF2AK2* novel variant (51,52).

The autophagy-lysosomal system has been implicated in the pathogenesis of dystonia at different levels. The homotypic fusion and protein sorting (HOPS) complex physiologically facilitates the fusion of autophagosomes with lysosomes, which is a critical step in the process of cellular clearing and protein homeostasis. Recent publications reported genetic variants in genes encoding central parts of the HOPS complex to cause dystonia of various degrees, which were grouped under the term HOPS-associated neurological disorders (53–56**). Three of the six vacuolar protein sorting-C proteins, forming the HOPS complex, have been identified to cause autosomal-dominant (*VPS16*) or autosomal-recessive (*VPS11*, *VPS16*, and *VPS41*) dystonia. In most cases, dystonic features first presented in infancy (*VPS41*) or adolescence (*VPS11*), whereas onset in *VPS11*-mutated patients was in adulthood with progressive generalization. Additional symptoms, including epilepsy, polyneuropathy, optic neuropathy and spasticity, have been described for manifestations in infancy. Functional studies on patient's cells documented impairment of the autophagolysosome for all three gene mutations (57**).

Furthermore, lysosomal storage disorders have been reported to cause combined dystonia, which has been particularly recognized in cases of Niemann-Pick type C, fucosidosis, GM1, and GM2 gangliosidosis, and Gaucher's disease type 3. Recently, GM3 deficiency has been linked with dystonic phenotypes (58). The I1061T *NPC1* mutant accumulates in the ER lumen and is degraded by two independent pathways functioning in a complementary fashion, in part by ER-phagy in a FAM134B- and autophagy-dependent process; in part, it is triaged through ERAD by the proteasome (59). Dystonic phenotypes have been associated with other endo-lysosomal and autophagy related genes — *WDR45*, *VAC14* and *ATP13A2* — further establishes the growing link between lysosomal dysfunction and dystonia (57). In addition, biallelic loss-of-function *SQSTM1* variants were associated with progressive dystonia, chorea, ataxia, and vertical gaze palsy in several patients (60), and pathogenic *IRF2BPL* variants were identified in cases featuring dystonia as part of a complex neurodevelopmental syndrome (61,62). Intriguingly, enlarged lysosomes filled with an osmiophilic material were reported in a skin biopsy from a patient with a pathogenic *IRF2BPL* variant, suggesting a possible crucial role in lysosomal function (63).

How much the dysfunction of the autophagy-lysosomal system will contribute to the pathogenesis of isolated dystonias, rather than more complex forms, remains to be understood. Of course, the discovery of these forms opens a window to future possible treatments targeting the lysosome in different forms of dystonia.

How can a single gene cause multiple different phenotypes?

Most dystonia genes are associated with significant heterogeneity of clinical phenotypes. For example, a common GAG deletion in *TOR1A* is typically associated with dominantly inherited childhood-onset dystonia that begins in one leg and then spreads to a generalized pattern (8). However, the same gene deletion can also begin elsewhere before spreading to generalized dystonia, or cause focal dystonia that does not spread, and remains limited to the neck, the larynx, or to another region. Sometimes, onset is delayed until adulthood. The same deletion has also been reported to cause a tremor without overt dystonia. Finally, the deletion is only 30% penetrant, which means it causes no apparent clinical phenotype in 70% of carriers.

The same type of clinical heterogeneity can be seen with genes responsible for other isolated dystonias, such as *THAP1* (8). Genetic variants in *THAP1* are typically associated with segmental craniocervical dystonia with onset in adolescence or early adulthood. However, genetic variants may also be associated with onset in other age groups, focal dystonia affecting different body parts, generalized dystonia, and tremor without overt dystonia. About half of the carriers of a pathogenic variant in *THAP1* are non-penetrant. Significant clinical heterogeneity also occurs for other genes associated with isolated dystonia such as *ANO3* or *GNAL*. These observations for the isolated dystonias raise questions regarding the mechanisms responsible for so much phenotypic heterogeneity from a single gene. Phenotypic heterogeneity can express as quantitative or qualitative differences, whereby genetic variations influence the clinical severity or the clinical expression.

Different genetic variants may have different consequences. The mechanisms responsible for this remarkable clinical heterogeneity among the isolated dystonias are not known. However, multiple clues have been obtained from other disorders where dystonia is combined with additional neurological or medical problems. The first potential mechanism involves how severely the genetic variant impacts the function of the associated protein. Some variants cause complete loss of protein function, while others produce only partial loss of function. Variants causing complete loss of function often produce a severe or earlier onset phenotype, while those causing partial loss of function often produce less severe or later-onset phenotypes. One well known example involves the *HPRT1* gene, which encodes for the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt) (64). Genetic variants in *HPRT1* that result in complete loss of HGprt function result in Lesch-Nyhan disease, characterized by infantile-onset severe generalized dystonia, along with cognitive and behavioral problems. Genetic variants in *HPRT1* that permit a very small amount of residual enzyme function may result in less severe generalized dystonia, with little or no cognitive or behavioral problems. Genetic variants in *HPRT1* that permit even more residual enzyme function may produce very mild dystonia or even focal dystonia (65).

This mechanism of variable loss of protein function has been established for numerous other genes as well, and could explain clinical heterogeneity for genes where there are numerous different genetic variants that could have different effects on their protein products, such as *THAP1, ANO3* or *GNAL*.

Dystonia genes interact with other genes, a mechanism that could account for clinical heterogeneity associated with a single dystonia gene. An interaction with other genes could exaggerate the pathological effects of the dystonia gene, or could compensate for its defects. There is no evidence supporting this potential mechanism for any of the isolated dystonia genes; but there are data supporting this mechanism for combined dystonia syndromes. One example involves the *GCH1* gene, which causes dopa-responsive dystonia that is often combined with parkinsonism (18). This disease is also associated with considerable variation in the clinical phenotype, with onset in children or adults, focal and generalized forms, and varying requirements for levodopa. Pathogenic variants in *GCH1* are only partly penetrant, with symptomatic females outnumbering males approximately 4:1, even for the same genetic variant in the same family (66). These observations provide evidence that genes on the sex chromosomes have a sizable influence on the expression of dystonia. What genes are responsible for sex differences associated with *GCH1* variants is unknown. There could be genes on the X-chromosome that make females more vulnerable, or there could be genes on the Y-chromosome that protect males. It is interesting to note that there is a significant female predominance for most other types isolated dystonia as well (67*).

Dystonia genes interact with environmental influences, providing a third mechanism that might account for clinical heterogeneity associated with a single dystonia gene. There are numerous epidemiological studies that have disclosed these potential influences on the incidence and severity of different types of isolated dystonias, although the mechanisms are not well understood. Some of the best illustrations of the gene-environment interaction come from other types of dystonia that are combined with additional problems. One particularly well-studied example is glutaric aciduria type 1, associated with the *GCDH* gene (68). Individuals with pathogenic defects in *GCDH* may remain virtually symptom-free for their entire lives. However, if they experience a high fever during a specific developmental window (usually less than 2 years of age), they may suffer an acute encephalopathic crisis with striatal necrosis and permanently disabling severe generalized dystonia with parkinsonism. This fever is typically caused by a common infectious disease, such as a respiratory virus or a gastrointestinal bacterium. Fortunately, the mechanisms responsible for fever-induced striatal necrosis have been sufficiently well characterized and effective treatments have been developed (68).

Another well-established gene-environment relationship involves *GLUT1*, where some genetic variants cause paroxysmal dystonia (69). Symptoms occur in children or young adults, and they are reliably triggered by fasting. This gene encodes a transporter that is essential for moving glucose from the blood into the brain. Genetic variants that produce a weak transporter are adequate for maintaining brain glucose when serum glucose levels are high, but they are unable to maintain brain glucose when blood glucose levels drop during fasting (70). Useful treatments involve avoidance of fasting, administration of triheptanoin as an alternative energy source that does not require the glucose transporter, or a ketogenic diet, where ketones replace glucose as energy source.

Another interesting gene-environment interaction involves the *ATP1A3* gene, which is associated with rapid-onset dystonia-parkinsonism (71). Pathogenic variants in this gene may again remain silent for life, but symptoms can be triggered by psychological or physical

stress. Similar to variants associated with *GCDH*, symptoms associated with *ATP1A3* begin rapidly, over a period of hours or days, and they often become permanent. However, symptoms associated with *ATP1A3* typically first emerge in teenagers or young adults, not in children less than 2 years old. Another difference between *GCDH* and *ATP1A3* is that there is no evidence for striatal necrosis associated with *ATP1A3*. The biological mechanisms responsible for stress-induced dystonia associated with *ATP1A3* are not known. However, it is interesting to note that stress transiently exaggerates symptoms in many different types of dystonia, both inherited and idiopathic.

Although these example disorders of gene-environment interaction are all quite rare, they show how disease associated with a single gene can be markedly influenced by common environmental factors such as infectious diseases, diet, brain stimulation, or even psychological stress.

Conclusion

Dystonia is a complex and intriguing movement disorder both for the clinician and the neuroscientist. Inherited dystonias provide the opportunity to understand the complexity of mechanisms that cause these clinical features.

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Conflicts of Interest

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Key Points

- New genetic discoveries reveal common mechanisms underlying the pathogenesis of dystonia
- Endolysosomal trafficking defect is emerging as a new pathogenetic mechanism in dystonia
- Dystonia genes interaction with environmental factors account for clinical heterogeneity

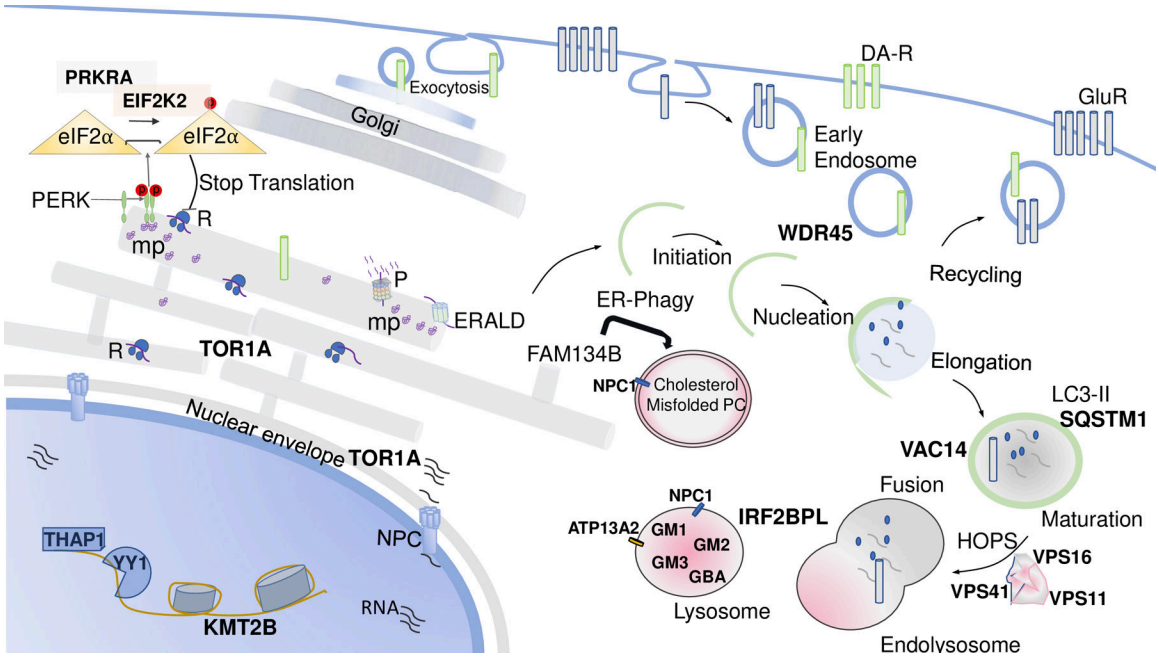

Figure 1.

Schematic representation of converging biological processes associated to dystonia syndromes. Abbreviations: DA-R, Dopamine Transporters; GluR, Glutamate Transportes; HOPS, homotypic fusion and vacuole protein sorting; mp, misfolded proteins; NPC, nuclear pore complex; R, ribosome; P, proteasome; PERK, PKR-like ER kinase; PC, procollagen.