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Movement Disorder Genetics for the Clinician

Aloysius Domingo, MD, PhD

ABSTRACT

The contribution of genes to etiology is variable for different movement disorders. Some diseases are by definition genetic, such as Huntington's disease. Other disorders such as Parkinson's disease may have monogenic causes but are largely the result of nongenetic factors. Dystonia and the atypical parkinsonisms have high genetic burdens in their etiologies, with reduced penetrance being a common feature. I review the clinical and molecular features and genotype-phenotype correlations in monogenic causes of autosomal dominant (*SNCA*, *LRRK2*, *VPS35*) and recessive (*PARKIN*, *PINK1*, *DJ-1*) Parkinson disease, and of isolated (*TOR1A*, *THAP1*, *GNAL*) and combined (*GCH1*, *TH*, *ATP1A3*, *PRKRA*, *TAF1*, *SGCE*) dystonia. Because the genetics of movement disorders is complex, genetic testing in aid of clinical diagnosis can only be recommended for genes that are unequivocally disease causing. However, gene panel testing is slowly transitioning into clinical utility, heralding the transition of movement disorder genetics from bench to bedside. This is a shortened version of a book chapter on movement disorder genetics.

INTRODUCTION

Genetics have revolutionized the field of movement disorders in the past 25 years. We now know that Parkinson disease (PD), for example, previously a textbook example of a non-hereditary condition, has a genetic etiology in as much as 3% of cases. Although we are still far from a complete understanding of the disease mechanisms underlying hereditary movement disorders, we have garnered insights into pathophysiology by studying genes, proteins, and pathways.

The degree of genetic contribution to the etiology of movement disorders is highly variable, ranging from fully penetrant causative mutations to low-penetrant mutations and risk factor alleles. Some disorders, such as Huntington disease (HD) are by definition genetic and caused by a mutation in a single gene. Other movement disorders, such as Parkinson disease or the dystonias, can be caused by mutations in several different genes but appear largely sporadic in the overwhelming majority of cases. For common movement disorders with reported frequencies of up to 10% in the general population, such as restless legs syndrome (RLS) and essential tremor (ET), no clearly causative gene has yet been identified and independently confirmed.

An important concept in genetic movement disorders is the phenomenon of reduced penetrance (absence of disease in a mutation carrier, which is found in many dominant disorders) and highly variable disease expression. The latter can sometimes be extreme, with the same gene being involved in distinct phenotypes, referred to as pleiotropy. An illustrative example are mutations in the *ATP1A3* gene – first described to cause rapid-onset dystonia-parkinsonism and now also found as the underlying cause of alternating hemiplegia in childhood and CAPOS (cerebellar ataxia, pes cavus, optic atrophy, sensorineural hearing loss) syndrome.

From the Center for Genomic Medicine and Collaborative Center for XDP, Massachusetts General Hospital, Boston, MA, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, Health Program, Philippine Genome Center, University of the Philippines, Quezon City.

DISCUSSION

GENETICS OF PARKINSON'S DISEASE AND PARKINSONISM

'Parkinsonism' encompasses the etiologically heterogeneous clinical syndromes that present with bradykinesia, rest tremor, rigidity, and postural instability (Williams & Litvan, 2013). The prototype is idiopathic Parkinson disease, which is typically late-onset and progressive and has a good response to dopamine replacement therapy. Although largely not inherited in a Mendelian fashion, in early-onset, familial, and ethnic cases, the probability of an underlying genetic cause is higher (Alcalay et al., 2010).

Genes that are confirmed to be linked with monogenic PD include: *SNCA, LRRK2, VPS35, PARKIN, PINK1,* and *DJ1*. The first three cause dominantly inherited or sporadic disease that closely resembles idiopathic disease; the recessive genes *PARKIN, PINK1,* and *DJ1* meanwhile cause early-onset PD (EOPD).

Dominantly inherited monogenic PD

Single-nucleotide missense mutations and multiplications in the alpha-synuclein (*SNCA*) gene cause monogenic PD that is generally younger at onset (Polymeropoulos et al., 1997). The decline of levodopa-responsive motor symptoms is also faster, and the development of motor fluctuations is typically earlier than in sporadic PD.

LRRK2 (Leucine-rich repeat kinase 2) is the most frequently mutated gene in idiopathic PD. The most common mutation, G2019S, represents 4% of familial and 1% of sporadic PD across all populations (Healy et al., 2008); thus, PARK-*LRRK2* is the most important differential diagnosis when considering genetic PD, given also that the phenotype is often indistinguishable from non-genetic disease (Zimprich et al., 2004).*VPS35* (vacuolar sorting protein 35) was the first PD-causing gene identified via next generation sequencing (Vilariño-Güell et al., 2011; Zimprich et al., 2011). PARK-*VPS35* is dominantly inherited with reduced penetrance, and has a phenotype that is very similar to idiopathic PD (Bonifati, 2014).

Early-onset, recessively inherited monogenic PD

PARKIN mutation carriers have an earlier age at onset but less aggressive disease (Klein & Schlossmacher, 2007). It is the most common form of EOPD across all ethnic groups, representing about 10-20% of cases of PD with age at onset within the fourth decade. Dystonia is a common presenting sign and may even sometimes be seen as an isolated finding (Lohmann et al., 2003;

TABLE 1. Monogenic causes of Parkinson disease

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Typical PD			
PARK-*SNCA*	More aggressive, prominent non-motor features	AD	PARK1 and 4
PARK-*LRRK2*	Sporadic, tremor-dominant PD	AD	PARK8
PARK-*VPS35*	May be sporadic, late-onset PD	AD	PARK17
PARK-*GBA*	Highly reduced penetrance	AD	none
Early-onset PD			
PARK-*PARKIN*	EOPD with dystonia as initial sign	AR	PARK2
PARK-*PINK1*	EOPD with non-motor features	AR	PARK6
PARK-*DJ1*	Rare cause of EOPD	AR	PARK7

AD – autosomal dominant; AR – autosomal recessive

Grünewald et al., 2013).

Mutations in PINK1 were first identified in three EOPD families with homozygous mutations (Valente et al., 2004). It now represents 1-9% of all genetic PD across all ethnicities (Klein & Schlossmacher, 2006). The usual phenotype is indistinguishable from PARK-PARKIN, only with a higher rate of psychiatric symptoms and cognitive impairment (Kasten et al., 2010).

PARK-DJ1 is significantly less common than either PARK-PARKIN or PARK-PINK1, and accounts for only 1-2% of cases (Klein & Schlossmacher, 2006). Clinical and neuroimaging features are similar to the other two recessive PD syndromes (Bonifati et al., 2003).

GENETICS OF DYSTONIA

While Hermann Oppenheim probably described the first cases of genetic dystonia in 1911 (i.e., DYT1), and coined the term 'dystonia musculorum deformans' (Oppenheim, 1911; Klein & Fahn, 2013), the modern history of dystonia genetics dates back to 1994 when mutations in the *GCH1* (GTP cyclohydrolase I) gene were discovered as the cause of dopa-responsive dystonia. Today, confirmed genes for isolated dystonias are *TOR1A*, *THAP1,* and *GNAL*. In the combined forms, dystonia can be accompanied by parkinsonism (*GCH1, TH, ATP1A3, PRKRA, TAF1*) or myoclonus (*SGCE*).

Monogenic isolated dystonia

In DYT-*TOR1A,* the mean age of onset is at 13 years with twisting of an arm or leg, and progression to involve other limbs and the torso, but usually sparing the face and neck (Bressman et al., 2000). Almost all cases are caused by the same 3-base pair deletion (GAG) in the coding region of the torsin (*TOR1A*) gene, which occurs in 90% of patients of Ashkenazi Jewish origin due to a founder effect (Ozelius et al., 1997). If symptoms do not occur prior to 28 years of age in mutation carriers, they usually remain unaffected for the rest of their life.

THAP1-associated dystonia combines features of focal and generalized primary dystonia and is also inherited in an autosomal dominant manner with penetrance estimated at 40%. The onset is later (mean 19 years) than in *TOR1A*-associated dystonia and there is more prominent cranial involvement with dysphonia being a predominant feature (Fuchs et al., 2009).

Mutations in the *GNAL* gene cause cervical or cranial dystonia with onset most commonly in the thirties (Vemula et al., 2013). *GNAL* mutations probably account for about 1% of all cases of focal or segmental dystonia involving the cranio-cervical region (Kumar et al., 2013).

Monogenic combined dystonias

Dopa-responsive dystonia (DRD) is characterized by childhood onset of dystonia, diurnal fluctuation of symptoms, and a dramatic response to L-dopa therapy (Segawa et al., 1976). Later in the course of the disease, parkinsonian features may occur and may, in rare cases, be the only sign of the condition (Mencacci et al., 2014). The more frequent form of DRD (DYT5a) is caused by dominant mutations in the GTP cyclohydrolase 1 (*GCH1*)

TABLE 2. Selected monogenic causes of atypical parkinsonism

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Kufor-Rakeb Syndrome, PARK-*ATP13A2*	Juvenile parkinsonism with supranuclear gaze palsy, brain iron accumulation	AR	PARK9
Parkinsonian-pyramidal Syndrome, PARK-*FBXO7*	Juvenile parkinsonism with pyramidal signs	AR	PARK15
EOPD with atypical features, PARK-*DNAJC6*	Also with mental retardation and seizures	AR	PARK19
EOPD with atypical features, PARK-*SYNJ1*	With seizures, cognitive decline, dystonia	AR	PARK20

TABLE 3. Monogenic causes of dystonia

Designation and clinical subgroup	Additional phenotypic notes	Mode of transmission	Previous locus symbol
Isolated dystonias			
DYT-*TOR1A*	Early-onset generalized dystonia	AD	DYT1
DYT-*THAP1*	Adolescent-onset dystonia of mixed type	AD	DYT6
DYT-*GNAL*	Adult-onset cranial-cervical dystonia	AD	DYT25
Combined dystonias			
Dystonia plus parkinsonism			
DYT-*GCH1*	Dopa-responsive dystonia	AD	DYT5a
DYT-*TH*	Dopa-responsive dystonia	AR	DYT5b
DYT-*ATP1A3*	Rapid-onset dystonia-parkinsonism	AD	DYT12
DYT-*PRKRA*	Dystonia-parkinsonism	AR	DYT16
DYT-*TAF1*	Dystonia-parkinsonism	X-linked	DYT3
Dystonia plus myoclonus			
DYT-SGCE	Myoclonus-dystonia	AD	*DYT11*

gene. Penetrance is lower among men than women.

ATP1A3-associated rapid-onset dystonia has a sudden onset within hours to weeks, typically in adolescence or young adulthood, in response to physical or mental stress. It is inherited in an autosomal dominant fashion with reduced penetrance. Typical features include dystonic spasms predominantly in the upper limbs, orofacial dystonia, dysarthria, and dysphagia, along with symptoms of parkinsonism (de Carvalho Aguiar et al., 2004).

PRKRA-linked dystonia-parkinsonism is a rare, recessively inherited form of early-onset generalized dystonia, which is accompanied by parkinsonism and caused by mutations in the *PRKRA* gene (Camargos et al., 2008).

X-linked dystonia-parkinsonism (XDP) is endemic to the Philippines and inherited in an X-linked recessive fashion (Lee et al., 2012, Domingo et al., 2015). Patients present in adulthood with dystonia, most pronounced in the craniofacial region. The dystonia subsequently generalizes and patients develop parkinsonian features, which predominate in late disease stages. XDP is the only condition among the isolated and combined dystonias with overt neurodegeneration of the striatum. The underlying genetic cause is an in intronic SVA insertion in the *TAF1* gene (Aneichyk et al., 2018), which has been observed in individuals of Filipino descent.

Myoclonus-dystonia (M-D) is characterized by a combination of myoclonus and dystonia with onset usually in childhood or early adolescence. In most affected individuals, myoclonic jerks are dramatically but transiently ameliorated by intake of alcohol. The disease is inherited as an autosomal dominant trait with reduced penetrance and caused by loss-of-function mutations in the *SGCE* gene (Zimprich et al., 2001).

GENETIC TESTING IN MOVEMENT DISORDERS

This review attempted to simplify the genetic causes of PD and dystonia, however, it is nonetheless obvious that the nuances of inheritable neurologic disorders are complex. Thus, consultation with a geneticist is recommended prior to embarking on "gene hunting" for a suspected case. The decision to undergo genetic testing involves many different factors, including the indication for the test, the implication of the results based on the stage of disease, the feasibility, sensitivity-specificity, and accuracy of the

test, and the general lack of neuroprotection in PD and other movement disorders, among others (Klein & Schlossmacher, 2006). Furthermore, several cases of false positive findings exist in the literature (MacArthur et al., 2014), and so a careful assessment of the diagnostic value of any variant discovered by genetic testing cannot be overemphasized.

At least for PD, dystonia, and Huntington's disease, guidelines on molecular diagnosis and clinical genetic testing have been established by the European Federation of Neurological Societies (EFNS) (Harbo et al., 2009). In PD, the guidelines recommend testing for *LRRK2* in familial cases with dominantly inherited PD, and for *PARKIN, PINK1*, and *DJ1* in EOPD and in those suggestive of recessive inheritance, emphasizing the role of history-taking and careful assessment of the family history and inheritance pattern prior to the genetic test. In dystonia, genetic testing for the GAG deletion in *TOR1A*, and for *GCH1* and *SGCE* in clinically compatible cases, is recommended.

Lastly, while genetic etiologies are likely only rare causes of movement disorders such as PD and dystonia, gene panel testing via next generation sequencing technology has recently become available as an option that allows for accurate and final diagnosis in patients facing a long and expensive 'diagnostic odyssey' (Lohmann & Klein, 2014).

ADDITIONAL READING

For a more detailed review of the genetics of movement disorders, Parkinson disease, and dystonia, the following book chapters are recommended reading:

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3. Domingo A, Klein C. Genetics of Parkinson disease. In: Handbook of Clinical Neurology Volume 147 and 148: Neurogenetics (Eds.: Aminoff MJ, Boller F, Swaab DF). 2018 (Elsevier).

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