Dystonia and Parkinsonism Panel
Sequence Analysis and Exon-Level Deletion/Duplication Testing of 73 Genes

Panel Gene List:

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ADAR, ADCY5, AFG3L2, ANO3, APTX, ARSA, ATM, ATP13A2, ATP1A3, ATP6AP2, ATP7B, C10orf2, C19orf12, CACNA1A, COASY, CP, CYP27A1, DCAF17, DLAT, DNAJC5, DNAJC6, FA2H, FBXO7, FTL, GBA, GCDH, GCH1, GLRA1, GNAL, KCNMA1, KMT2B, LRRK2, MARS2, MCOLN1, MRE11A, NKX2-1*, NPC1, NPC2, PANK2, PARK2, PARK7, PDGFB, PINK1, PLA2G6, PNKD, PNKP, POLG, POLR3B, PRKRA, PRRT2, SCP2, SGCE, SLC16A2 , SLC20A2, SLC2A1, SLC30A10, SLC6A3, SMPD1, SNCA, SPR, SYNJ1, TH, THAP1, TIMM8A, TOR1A, TOR1AIP1, TPK1, TRAPPC11, TUBB4A**, VPS13A, VPS35, WDR45, XPR1*

*This panel does not include deletion/duplication testing of the GBA and NKX2-1 genes.

** Only whole gene deletions or duplications of TUBB4A may be detected.

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*This panel does not include deletion/duplication testing of the NKX2-1 gene.

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Parkinson Disease Panel Gene List:

AFG3L2, ATP13A2, ATP6AP2, C10orf2, C19orf12, COASY, CP, CYP27A1, DNAJC5, DNAJC6, FBXO7, GBA, LRRK2, PARK2, PARK7, PINK1, PLA2G6, POLG, PRKRA, SLC16A2, SLC20A2, SLC6A3, SMPD1, SNCA, SYNJ1, VPS13A, VPS35, WDR45, XPR1*

*This panel does not include deletion/duplication testing of the GBA gene

Clinical Features:

Dystonia and parkinsonism describe movement disorders that result in abnormal, uncontrolled, movements often caused by inappropriate muscle contractions or nerve signals.[1,2] Some neurodegenerative disorders can have symptoms of both dystonia and parkinsonism. Overlapping features of dystonia and parkinsonism include postural and gait instability, tremor, and speech problems. Treatment is available for some causes of dystonia and parkinsonism.

Dystonia:

Dystonia is characterized by patterned or twisting movements and postures.[1] Dystonias are highly variable and clinically classified by age of onset, affected body part, temporal pattern, or associated features.[1,3] Age of onset ranges from infancy to late adulthood, and almost all parts

of the body can be affected. The number and location of affected body parts determine if the dystonia is focal, segmental, multifocal, hemidystonia, or generalized. Although some dystonias are isolated and occur independent of other neurological features, combined and complex forms have been described. Combined dystonias occur when dystonia is observed with other movement disorders including parkinsonism, myoclonus, and paroxysmal dyskinesia, whereas complex dystonias include those that are associated with neurodegenerative or metabolic disorders. Often times, dystonia can be triggered or worsened by nonspecific factors, such as stress, or fatigue.[1] The prevalence of isolated dystonia is estimated to be 16.4:100,000.[4]

Parkinsonism:

Parkinsonism describes all motor dysfunctions that manifest as resting tremor, muscle rigidity, bradykinesia, and postural instability.[5,6] Additional features of Parkinson disease include action or postural tremor, sleep disturbance, mood disorders, dysautonomia, psychosis, and dementia.[5] The neuropathology of Parkinson disease involves the selective loss of dopaminergic neurons and accumulation of inclusions (Lewy bodies) in the brain.[5] The age of onset for disease is generally 60-70 years of age; however, onset can be earlier, especially for monogenic forms.[5,6] Parkinson disease is the second most common neurodegenerative disease and has an age-dependent prevalence that is estimated to be 13.4:100,000, with a prevalence of approximately 1% of individuals over 60 years of age and 4% of individuals over 85 years of age.[2,5]

Inheritance Pattern/Genetics:

Movement disorders such as dystonia and parkinsonism can be either genetic or acquired in nature. Acquired causes include, but are not limited to, brain lesions (resulting from trauma or infection), hypoxic insults, drugs, psychological disorders, and other environmental insults.[1,5] Multifactorial inheritance may also be responsible for some forms of dystonia and parkinsonism.[2,5,6] Genetic forms of dystonia and parkinsonism can be associated with autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance.[1,5] Approximately 20% of patients with dystonia are reported to have a positive family history, whereas ~15% of patients with Parkinson disease have a family history and 5-10% have a monogenic form.[2,7] Unfortunately, the etiology of most parkinsonism is unknown.[2,5]

Pathogenic variants in a single gene may be associated with a wide range of phenotypes (clinical heterogeneity), and conversely, pathogenic variants in different genes can cause the same phenotype (genetic heterogeneity). Clinical evaluation alone may not be sufficient to distinguish the various genetic causes of dystonia and parkinsonism given their phenotypic and genetic heterogeneity. The Dystonia and Parkinsonism panel at GeneDx can assist in confirming a clinical diagnosis or aid in the development of a comprehensive medical plan including symptom management and recurrence risk assessment. In some instances,

molecular confirmation of a clinical diagnosis of dystonia and/or parkinsonism may have implications for treatment and management of the specific form of disease.

The Dystonia and Parkinsonism Panel at GeneDx includes sequencing and deletion/duplication analysis of genes associated with Mendelian forms of dystonia and parkinsonism. The complete list of genes and associated disorders is included in the table below.

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Sanger sequencing is also used to evaluate the GBA gene and to compensate for regions of low coverage. Reported clinically significant variants are confirmed by an appropriate orthogonal method. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Test Sensitivity:
The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: GBA gene, no copy number testing; NKX2-1 gene, no copy number testing; TUBB4A gene only whole gene

deletions or duplications may be detected. The repeat expansion in the CACNA1A gene that is associated with SCA6 is not performed as part of this Dystonia and Parkinsonism Panel.

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Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
ADAR	Aicardi-Goutières syndrome (AGS); dyschromatosis symmetrica hereditaria 1 (DSH)	AD/AR	7% of AGS, AGS is a rare contribution to dystonia[1]
ADCY5	Familial dyskinesia with facial myokymia (FDFM)	AD/AR	Rare contribution to dystonia[2]
AFG3L2	Spinocerebellar ataxia, type 28 (SCA28); spastic ataxia 5 (SPAX5)	AD/AR	~1.5% of autosomal dominant cerebellar ataxia, rare contribution to dystonia[3,4]
ANO3	Dystonia 24 (adult-onset focal or segmental dystonia)	AD	1% of dystonia[5,6]
APTX	Ataxia with oculomotor apraxia type I (AOA1)	AR	3.6-9.1% of autosomal recessive ataxias, rare contribution to dystonia[7]
ARSA	Metachromatic leukodystrophy (MLD); also known as arylsulfatase A deficiency	AR	Rare contribution to dystonia[8]
ATM	Ataxia-telangiectasia	AD/AR	Rare contribution to dystonia[9]
ATP13A2	Kufor-Rakeb syndrome (NBIA subtype)	AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10]
ATP1A3	Rapid-onset dystonia-parkinsonism; alternating hemiplegia of childhood; CAPOS syndrome	AD	Rare overall[11]
ATP6AP2	X-linked parkinsonism with spasticity (XPDS); X-linked intellectual disability and epilepsy	XL	Rare overall[12,13]
ATP7B	Wilson disease	AR	Commonly associated with dystonia and parkinsonism[14]

Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
C10orf2 (AKA TWNK)	Chronic progressive external ophthalmoplegia (CPEO)	AD/AR	Rare contribution to dystonia[15]
C19orf12	Mitochondrial membrane protein-associated neurodegeneration (MPAN, AKA NBIA4)	AR	6-10% of NBIA, NBIA is commonly associated with dystonia[10,16,17]
*CACNA1A**	Episodic ataxia type 2 (EA2); familial hemiplegic migraine (FHM); spinocerebellar ataxia type 6 (SCA6)*	AD	EA2 is rare[18] 7% of FHM[19,20]
COASY	COASY protein-associated neurodegeneration (CoPAN) (AKA NBIA6)	AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10,21]
CP	Aceruloplasminemia (NBIA subtype)	AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10]
CYP27A1	Cerebrotendinous xanthomatosis (CTX)	AR	~98% of CTX, rare contribution to dystonia[22]
DCAF17	Woodhouse-Sakati syndrome (WSS) (NBIA subtype)	AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10]
DLAT	Pyruvate dehydrogenase E2 deficiency	AR	Rare association with dystonia[23]
DNAJC5	Kufs disease	AD	25% of Kufs disease (adult neuronal ceroid lipofuscinoses)[24,25]
DNAJC6	Juvenile-onset Parkinson disease	AR	Rare cause of parkinsonism[26,27]
FA2H	Fatty acid hydroxylase-associated neurodegeneration (FAHN) (NBIA subtype) or spastic paraplegia type 35 (SPG35)	AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10]
FBXO7	Parkinsonian-pyramidal syndrome (PSS)	AR	Rare contribution to parkinsonism[28,29]
FTL	Neuroferritinopathy (NBIA subtype)	AD/AR	Rare contribution to NBIA, NBIA is commonly associated with dystonia[10]
*GBA***	Gaucher disease	AR	Rare association with parkinsonism[30]
GCDH	Glutaric aciduria type I (GA I)	AR	Rare association with parkinsonism[31]
GCH1	Dopa-responsive dystonia (DRD); tetrahydrobiopterin (BH4)-deficient hyperhphenylalaninemia type B	AD/AR	Common cause of dystonia[32]
GLRA1	Hereditary hyperekplexia 1 (HKPX1)	AD/AR	80% of hyperekplexia, rare contribution to dystonia[33]
GNAL	Dystonia-25	AD	Rare cause of dystonia[34]
KCNMA1	Paroxysmal dyskinesia (PKD)	AD/AR	Rare cause of dystonia[35]
KMT2B	Dystonia-28	AD	Rare cause of dystonia[36]
LRRK2	Parkinson disease	AD	1-2% of Parkinson disease[28,37]
MARS2	Autosomal recessive spastic ataxia with leukoencephalopathy (ARSAL)	AR	Rare rare contribution to dystonia[38]
MCOLN1	Mucolipidosis type IV	AR	Rare overall; founder mutations in the Ashkenazi Jewish population[39]
MRE11A	Ataxia-telangiectasia-like disorder (ATLD)	AR	Rare rare contribution to dystonia[40]
*NKX2-1***	Benign hereditary chorea (BHC); brain-lung-thyroid syndrome	AD	Rare contribution to dystonia[41,42]
NPC1	Niemann-Pick disease type C (NPC)	AR	Rare contribution to dystonia[43]
NPC2	Niemann-Pick disease type C (NPC)	AR	Rare contribution to dystonia[43]

Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
PANK2	Pantothenate kinase-associated neurodegeneration (PKAN) (NBIA subtype)	AR	35-50% of NBIA, NBIA is commonly associated with dystonia[10,44,45]
PARK2	Juvenile Parkinson disease	AR	~1% of Parkinson disease; up to 50% of early-onset Parkinson disease[28,46,47]
PARK7	Early-onset Parkinson disease	AR	Rare in Parkinson disease; 1-2% of early-onset Parkinson disease[28,47]
PDGFB	Idiopathic basal ganglia calcification (IBGC)	AD	Rare overall; ~11% of primary familial brain calcification[48,49]
PINK1	Early-onset Parkinson disease	AR	Rare in Parkinson disease; 1-8% of early-onset Parkinson disease[28,47]
PLA2G6	PLA2G6-associated neurodegeneration (PLAN): (NBIA subtype)	AR	20% of NBIA, NBIA is commonly associated with dystonia[10,50]
PNKD	Familial paroxysmal nonkinesigenic dyskinesia (PNKD)	AD	Rare contribution to parkinsonism[51]
PNKP	Microcephaly, seizures, and developmental delay (MCSZ)	AR	Rare contribution to parkinsonism[52]
POLG	POLG-related disorders	AD/AR	Rare in parkinsonism[53,54]
POLR3B	4H leukodystrophy: hypomyelination, hypodontia, and hypogonadotropic hypogonadism	AD/AR	Rare association with dystonia[55]
PRKRA	Dystonia 16	AD/AR	Rare contribution to dystonia[56]
PRRT2	paroxysmal kinesigenic dyskinesia (PKD); PKD with infantile convulsions (PKD/IC); benign familial infantile seizures (BFIS); hemiplegic migraine	AD	62-96% of familial PKD/IC; 36% sporadic PKD/IC[57,58] 83% familial and 30% sporadic BFIS[57,59,60]
SCP2	Leukoencephalopathy with dystonia and motor neuropathy	AR	Rare in NBIA, NBIA is commonly associated with dystonia[61]
SGCE	Myoclonus-dystonia (DYT11)	AD	~40-65% of myoclonus-dystonia[62]
SLC16A2	MCT8-specific thyroid hormone cell-membrane transporter deficiency (Allan-Herndon-Dudley syndrome)	XL	Rare contribution to dystonia[63]
SLC20A2	Idiopathic basal ganglia calcification (IBGC)	AD	~40% of primary familial brain calcification (PFBC), PFBC is commonly associated with dystonia[64,65]
SLC2A1	Glucose transporter type 1 deficiency syndrome (Glut1-DS)	AD	91% of GLUT1 deficiency commonly associated with dystonia[66,67]
SLC30A10	Hypermanganesemia with dystonia	AR	Rare[68]
SLC6A3	Hereditary dopamine transporter deficiency syndrome	AR	Rare in parkinsonism and dystonia[28,69]
SMPD1	Acid sphingomyelinase (ASM) deficiency (Niemann-Pick disease types A and B)	AR	>95% of ASM deficiency, rare contribution to dystonia[70]
SNCA	Parkinson disease; lewy body dementia	AD	Rare cause of Parkinson disease[28]
SPR	Dopa responsive dystonia due to sepiapterin reductase deficiency	AR	Rare contribution to dystonia[71]
SYNJ1	Early-onset parkinsonism	AR	Rare cause of Parkinson disease[72,73,74]
TH	Tyrosine hydroxylase deficiency	AR	Rare contribution to dystonia[75]

Gene	Disease Associations	Inheritance	Diagnostic Yield in Selected Population(s)
THAP1	Torsion dystonia type 6	AD	Founder mutation in the Amish-Mennonite population[76]; ~1-4% of isolated dystonia[77]
TIMM8A	Deafness-dystonia-optic neuronopathy (DDON) syndrome (Mohr-Tranebjaerg syndrome)	XR	Rare contribution to dystonia[78]
TOR1A	Early-onset isolated dystonia	AD	Founder mutation accounts for 80-90% of cases of early-onset dystonia in the Ashkenazi Jewish population and 16-53% of cases in non-Jewish population[79]
TOR1AIP1	Early-onset dystonia; limb-girdle muscular dystrophy; and cardiomyopathy	AR	Rare contribution to dystonia[80,81]
TPK1	Thiamine pyrophosphokinase deficiency	AR	Rare contribution to dystonia[82]
TRAPPC11	Limb-girdle muscular dystrophy type 2S (LGMD2S)	AR	Rare contribution to dystonia[83,84]
*TUBB4A***	Torsion dystonia-4 (DYT4); hypomyelinating leukodystrophy-6 (HLD6)	AD	Rare cause of dystonia[85,86]
VPS13A	Choreoacanthocytosis	AR	Rare contribution to dystonia[87,88]
VPS35	Late-onset levodopa-responsive Parkinson disease	AD	Rare cause of Parkinson Disease[28,89]
WDR45	Beta-propeller protein-associated neurodegeneration (BPAN) (NBIA subtype)	XL	1-2% of NBIA, NBIA is commonly associated with dystonia[10,90]
XPR1	Primary familial brain calcification (PFBC)	AD	8% of cases negative for other forms of PFBC, PFBC is a rare cause of dystonia[91,92]

*The CAG repeat expansion in CACNA1A that causes SCA6 may not be detectable by this test.
**Does not include deletion/duplication testing of GBA and NKX2-1.
*** Only whole gene deletions or duplications of TUBB4A may be detected.

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