Dystonia and Parkinsonism Panel

Panel Gene List:

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ADAR, ADCY5, AFG3L2, ANO3, APTX, ARSA, ATM, ATP13A2, ATP1A2, ATP1A3, ATP6AP2, ATP7B, CAP31**, C19ORF12, CACNA1A***, CACNA1B, CHCHD2, COASY, CP, CYP27A1, DCAF17, DCTN1, DDC*, DLAT, DNAJC12*, DNAJC5, DNAJC6, ECHS1*, FA2H, FBXO7, FITM2*, FTL, FUCA1*, GBA*, GCDH, GCH1, GLRA1, GNAL, GNAO1*, HEXA, HPCA, HPRT1, KCNJ6*, KCNMA1, KCTD17, KMT2B, LRRK2, MAPT, MARS2, MCOLN1, MECR, MRE11, NKX2-1, NPC1, NPC2, NUBPL*, NUS1*, PANK2, PARK7, PDGFB, PDGFRB, PINK1, PLA2G6, PNKD, PNKP, POLG, POLR3B, PRKN, PRKRA, PRRT2, PTS, RAB39B*, SCP2, SERAC1*, SGCE, SLC16A2, SLC19A3, SLC20A2, SLC2A1, SLC30A10, SLC6A3, SMPD1, SNCA, SPAST, SPR, SQSTM1, SUCLA2*, SYNJ1, TH, THAP1, TIMM8A, TOR1A, TOR1AIP1, TPK1, TPP1*, TRAPPC11, TUBB4A**, TWNK*, VPS13A, VPS35, WDR45, XPR1, ZFYVE26*

* Sequence analysis only of the *ATP1A2, DDC, DNAJC12, ECHS1, FITM2, FUCA1, GBA, GNAO1, KCNJ6, NUBPL, NUS1, RAB39B, SERAC1, SUCLA2, TPP1,* and *TWNK* genes.

**Only whole gene deletions or duplications of *BCAP31* and *TUBB4A* may be detected.

*** The CAG repeat expansion in *CACNA1A* that causes SCA6 may not be detectable by this test.

Dystonia Panel Gene List:

ADAR, ADCY5, AFG3L2, ANO3, APTX, ARSA, ATM, ATP13A2, ATP1A2, ATP1A3, ATP7B, BCAP31**, C19ORF12, CACNA1A, CACNA1B, COASY, CP, CYP27A1, DCAF17, DDC*, DLAT, DNAJC12*, ECHS1*, FA2H, FITM2*, FTL, FUCA1*, GCDH, GCH1, GLRA1, GNAL, GNAO1*, HEXA, HPCA, HPRT1, KCNJ6*, KCNMA1, KCTD17, KMT2B, MARS2, MCOLN1, MECR, MRE11, NKX2-1, NPC1, NPC2, NUBPL*, PANK2, PDGFB, PDGFRB, PLA2G6, PNKD, PNKP, POLR3B, PRKRA, PRRT2, PTS, SCP2, SERAC1*, SGCE, SLC16A2, SLC19A3, SLC20A2, SLC2A1, SLC30A10, SLC6A3, SPAST, SPR, SQSTM1, SUCLA2*, SYNJ1, TH, THAP1, TIMM8A, TOR1A, TOR1AIP1, TPK1, TPP1*, TRAPPC11, TUBB4A**, VPS13A, WDR45, XPR1*

* Sequence analysis only of the *ATP1A2, DDC, DNAJC12, ECHS1, FITM2, FUCA1, GNAO1, KCNJ6, NUBPL, SERAC1, SUCLA2,* and *TPP1* genes.

**Only whole gene deletions or duplications of *BCAP31* and *TUBB4A* may be detected.

Parkinson Disease Panel Gene List:

AFG3L2, ATP13A2, ATP6AP2, C19ORF12, CHCHD2, COASY, CP, CYP27A1, DCTN1, DNAJC5, DNAJC6, FBXO7, FTL, GBA, GCH1, LRRK2, MAPT, NPC1, NPC2, NUS1*, PANK2, PARK7, PDGFB, PDGFRB, PINK1, PLA2G6, POLG, PRKN, PRKRA, PTS, RAB39B*, SLC20A2, SLC30A10, SLC6A3, SMPD1, SNCA, SYNJ1, TH, TWNK*, VPS13A, VPS35, WDR45, XPR1, ZFYVE26*

* Sequence analysis only of the *GBA, NUS1, RAB39B,* and *TWNK* genes.

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.

Neurodegeneration with brain iron accumulation (NBIA) is a group of inherited neurologic disorders characterized by abnormal accumulation of iron in the basal ganglia with clinical features including progressive dystonia and dysarthria, spasticity, parkinsonism, neuropsychiatric abnormalities, and optic atrophy or retinal degeneration.[3] Primary familial brain calcification (PFBC) is a neurodegenerative disorder with characteristic calcium deposits in the basal ganglia and other brain areas visualized on neuroimaging, which typically presents in the fourth to fifth decade with a gradually progressive movement disorder and neuropsychiatric symptoms.[4]

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.[1,5] 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.[6]

Parkinsonism:

Parkinsonism describes all motor dysfunctions that manifest as resting tremor, muscle rigidity, bradykinesia, and postural instability.[7,8] Additional features of Parkinson disease include action or postural tremor, sleep disturbance, mood disorders, dysautonomia, psychosis, and dementia.[7] The neuropathology of Parkinson disease involves the selective loss of dopaminergic neurons and accumulation of inclusions (Lewy bodies) in the brain.[7] The age of onset for disease is generally 6070 years of age; however, onset can be earlier, especially for monogenic forms.[7,8] 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.[2,7]

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.[1,7] Multifactorial inheritance may also be responsible for some forms of dystonia and parkinsonism.[2,7,8] Genetic forms of dystonia and parkinsonism can be associated with autosomal dominant, autosomal recessive, X linked, or mitochondrial inheritance.[1,7] 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.[2,9] Unfortunately, the etiology of most parkinsonism is unknown.[2,7]

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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data and to evaluate the GBA gene. 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.

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: *ATP1A2, DDC, DNAJC12, ECHS1, FITM2, FUCA1, GBA, GNAO1, KCNJ6, NUBPL, NUS1, RAB39B, SERAC1, SUCLA2, TPP1,* and *TWNK* genes, no copy number testing; *BCAP31* and *TUBB4A* genes, only whole gene deletions or duplications may be detected.

Clinical 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.

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