Xpanded® Adult Movement Disorders Panel
A Targeted Test for Monogenic Causes of Movement Disorders in Adults Using a Trio Approach

CLINICAL FEATURES

Adult onset movement disorders cover a vast array of phenotypes and known disorders. Phenotypes commonly observed in adult onset disease include ataxia, akathisia, abnormal gait, chorea, dystonia, dysarthria, spasticity, tremor, among others.[1,2] A large number of the disorders for which these phenotypes are a prominent feature have a genetic etiology that can guide future testing, treatment, and medical management.[1,3] The etiology of a specific phenotype can be difficult to discern as these features are common to many heterogeneous disorders.[1,4,5] It is often necessary to perform testing of multiple genes to identify an underlying genetic cause in an individual. Moreover, new genes reported to cause disorders that present with one or more movement abnormalities are being discovered regularly, making it challenging to keep traditional multi-gene panels current. Additionally, interpretation of the clinical significance of variants in these newly discovered genes is often difficult in the absence of parental testing to clarify the inheritance of the variants.

The Xpanded® Adult Movement Disorders Panel uses a trio approach that includes concurrent analysis of the affected proband and both parents, when available, which increases the likelihood of identifying a definitive genetic explanation for disease. Depending on the family structure, family history, and availability of both parents, other family members of the affected individual may be evaluated in conjunction with the proband. Please contact GeneDx to determine which family members will be most informative, when both parents are not available for testing. The Xpanded Adult Movement Disorders Panel is based on exome capture, Next Generation sequencing (NGS), and targeted analysis of a comprehensive list of ~500 genes currently associated with adult onset movement disorders. The design of the panel allows for a comprehensive, dynamic gene list that is updated regularly to ensure inclusion of genes recently associated with movement disorders.

INHERITANCE PATTERN/GENETICS

Movement disorders can result from a wide variety of clinical or environmental risk factors including, but not limited to, drug or environmental exposures, drug interactions, vitamin deficiencies, autoimmune disorders, alcoholism, trauma (including stroke), psychiatric disorders, infection, or genetic defects.[4,6,7] In a review of individuals with onset of ataxia after age 40, 36% had multiple system atrophy cerebellar type, 18% had acquired ataxia, 9% had a genetic etiology and 35% had an unknown etiology.[7] A study of adults meeting criteria for primary brain calcification, which is known to cause a wide spectrum of movement disorders, found that 25.4% of participants were suspected to have a genetic etiology.[8] Lastly, analysis of a panel of genes associated with movement disorders reported a positive rate of 22% in unselected individuals.[5] The majority of adult-onset movement disorders are inherited in an autosomal dominant manner, but autosomal recessive, X-linked, and mitochondrial inheritance patterns have been documented.[4,7-9] Confirmation of the molecular genetic cause of the disorders may have implications for medical management, surveillance for associated complications or other organ systems involvement, eligibility for needed services, and treatment.[1,4]

TEST METHODS

Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are captured using a proprietary system developed by GeneDx and sequenced by massively parallel (NextGen) sequencing on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants in targeted genes using a custom-developed analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants identified in the proband and relative samples, if submitted. Sequence

and copy number alterations are reported according to the Human Genome Variation Society (HGVS) guidelines. A list of additional variants not included in the report is available upon request.

Please note that while the Xpanded Adult Movement Disorders Panel captures and sequences the whole exome, analysis is targeted to the specific phenotype-driven gene list for this panel. The Xpanded Adult Movement Disorders Panel gene list includes ~500 genes. The list was developed by searching for genes associated with movement disorders in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) terms. This list undergoes continual review and curation by GeneDx experts. During this review, genes are added to the list using GeneDx data from clinical exome sequencing (ES) done on patients with adult-onset movement disorders. Additionally, genes may be removed from the panel if they are found to be weakly or questionably associated with movement disorders. In rare situations, genes are removed from the panel if they are expected to be low yield for this phenotype, but contain an inherent high risk for incidental findings. Xpanded panel gene lists are regularly updated/improved using evidence from the literature and from GeneDx data from clinical ESdone on patients with adult onset movement disorders.

RESULTS REPORTING

The Xpanded Adult Movement Disorders Panel is performed on the proband and the parental samples (and/or additional relatives) when submitted together for analysis. A single report will be issued on the affected proband in the family. A separate report will not be issued for unaffected parents or other family members who may also have submitted a specimen for the purpose of allowing better interpretation of the results from the affected individual. If additional reports are requested for other affected family members, extra fees will apply.

The report that is issued for the affected individual will include reportable variants in genes that have been previously associated with adult onset of movement disorders in the published or emerging literature. Pathogenic/likely pathogenic variants in genes responsible for the phenotype of the patient will be reported; however, because this is a phenotype-driven test of a large number of genes, variants of uncertain significance (VUS) are not routinely reported, only at our discretion. Variants that are considered to be benign or likely benign will not be reported. As the Xpanded Adult Movement Disorders Panel includes ~500 genes, the report will not include a comprehensive list of all observed variants. If desired, clinicians can request a separate file containing a list of identified variants that will be provided upon completion of testing.

In rare instances, this test may reveal a pathogenic variant that is not directly related to the test indication. For example, pathogenic variants in genes associated with an increased risk for cancer, cardiac abnormalities, or metabolic defects could be identified. In the event that an incidental finding is identified, this information will be disclosed to the ordering health care provider if it is likely to impact medical care.[10] The absence of reportable incidental findings for any particular gene does not rule out the possibility of pathogenic variants in that gene.

CLINICAL SENSITIVITY

The clinical sensitivity of the Xpanded Adult Movement Disorders Panel depends in part on the patient's clinical phenotype. Previous ES studies have reported identification of a definitive pathogenic variant in 16% of individuals with spastic paraplegia, 32% of individuals with cerebellar ataxia, and 11% of individuals with Parkinson's disease.[11,12] It has been demonstrated that the yield of ES testing is higher with a Trio approach compared to a Proband-only approach, although most of these studies focused on early-onset disorders.[13]The sensitivity of this test is expected to be comparable to trio-based exome sequencing since it uses a trio approach to test a comprehensive list of genes previously associated with adult onset movement disorders. The clinical sensitivity is expected to be lower for singleton testing when only the affected proband is tested.

The average coverage of all genes on the panel is greater than 99% at 10X (with a depth of 10 or more reads), and approximately 95% of the genes on the panel have an average coverage of greater than 99% at 10X. Some

genes with a relatively high clinical sensitivity have an average coverage of less than 90% at 10X, including *CEP152*(88.4%), *CHRNA7* (80.7%), *OCLN* (82.5%), and *KIF5C* (10.1%). The coverage of each gene on the panel for a specific patient may vary, and the actual coverage for each gene is included in the final report.

LIMITATIONS

Some types of genetic disorders, such as those due to nucleotide repeat expansion/contraction, abnormal DNA methylation, and other mechanisms may not be detectable with this test. Additionally, small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be reliably detected. For example, repeat expansions in the genes associated with fragile X tremor ataxia syndrome and spinocerebellar ataxia would not be detectable by the XpandedAdult Movement Disorders Panel. Additionally, this test includes screening for homozygous loss of exon 8 (formerly exon 7) of the *SMN1* gene. If a high clinical suspicion of adult-onset *SMN1*-related SMA is present, diagnostic testing for *SMN1/2* should be completed.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the Xpanded Adult Movement Disorders Panel may identify the presence of a variant in the sequence of an affected individual, but that we will not recognize it as the cause of their disease due to insufficient knowledge about the gene and its function. Even if the Xpanded Adult Movement Disorders Panel identifies the underlying genetic cause of a disorder in an affected individual, it is possible that such a diagnosis will not permit an accurate prediction of the prognosis or severity of the disease. While there is a possibility that identifying the genetic cause may help direct management and treatment of the disease, it is also possible that this knowledge will not change management or treatment.

REFERENCES:

1. Jinnah HA et al. Treatable inherited rare movement disorders. Movement Disorders: Official Journal Of The Movement Disorder Society. 2018 01 33(1):21-35.28861905
2. Lynch DS et al. Practical approach to the diagnosis of adult-onset leuko dystrophies: an updated guide in the genomic era. Journal Of Neurology, Neurosurgery, And Psychiatry. 2018 Nov 22.30467211
3. Marras C et al. Nomenclature of genetic movement disorders: Recommendations of the international Parkinson and movement disorder society task force. Movement Disorders: Official Journal Of The Movement Disorder Society. 2016 Apr 31(4):436-57.27079681
4. Barsottini OG et al. Adult onset sporadic ataxias: a diagnostic challenge. Arquivos De Neuro Psiquiatria. 2014 Mar 72(3):232-40.24676442
5. Montaut S et al. Assessment of a Targeted Gene Panel for Identification of Genes Associated With Movement Disorders. Jama Neurology. 2018 Oct 01 75(10):1234-1245.29913018
6. Park JE. Clinical characteristics of functional movement disorders: A Clinic-based Study. Tremor And Other Hyperkinetic Movements (New York, N.Y.). 2018 8:504.30191082
7. Lieto M et al. Degenerative and acquired sporadic adult onset ataxia. Neurological Sciences: Official Journal Of The Italian Neurological Society And Of The Italian Society Of Clinical Neurophysiology. 2019 Jul 40(7):1335-1342.30927137
8. Ramos EM et al. Primary brain calcification: an international study reporting novel variants and associated phenotypes. European Journal Of Human Genetics: EJHG. 2018 Oct 26(10):1462-1477.29955172
9. Klockgether T. Sporadic ataxia with adult onset: classification and diagnostic criteria. The Lancet. Neurology. 2010 Jan 9(1):94-104.20083040
10. Kalia SS et al. Recommendations for reporting of secondary findings in clinical exo me and ge nome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genetics In Medicine: Official Journal Of The American College Of Medical Genetics. 2017 Feb 19(2):249- 255.27854360
11. van de Warrenburg BP et al. Clinical exome sequencing for cerebellar ataxia and spastic paraplegia uncovers novel gene-disease associations and una nticipated rare disorders. European Journal Of Human Genetics: EJHG. 2016 10 24(10):1460-6.27165006
12. Schormair B et al. Diagnostic exome sequencing in early-onset Parkinson's disease confirms VPS13C as a rare cause of autosomal-recessive Parkinson's disease. Clinical Genetics. 2018 Mar 93(3):603-612.28862745
13. Retterer K et al. Clinical application of who le-exome sequencing across clinical indications. Genetics In Medicine: Official Journal Of The American College Of Medical Genetics. 2016 Jul 18(7):696-704.2663354