Nystagmus Xpanded Panel

A targeted test for genetic causes of nystagmus using a trio approach

Overview:

Nystagmus is an involuntary, rapid, and repetitive movement of the eyes most often accompanied by some degree of visual impairment, and is typically congenital or early onset (Gottlob et al., 2014; Richards et al., 2015). Nystagmus is a relatively common and nonspecific clinical feature that can be associated with many genetic conditions, including both ophthalmic disorders where clinical features are limited to eye findings, and syndromic disorders with additional extra-ocular features involving other organ systems. Due to the genetically and phenotypically heterogeneous nature of genetic conditions that include nystagmus as a clinical feature, as well as the potential lack of additional clinical features in infancy or early childhood, it can be challenging to determine the underlying cause of nystagmus or predict the disease-causing gene based on early clinical features or ancillary testing alone. Moreover, new genes associated with genetic conditions that include nystagmus as a clinical feature are being discovered regularly, making it challenging for clinical laboratories to keep traditional testing panels up-to-date. 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 identified variants.

The Nystagmus Xpanded panel uses a trio approach that includes concurrent analysis of the affected proband and both parents, which increases the likelihood of identifying a definitive genetic explanation for nystagmus in an individual. Depending on the family structure, family history of nystagmus or other clinical features, and the availability of both parents, other family members of the affected individual may be evaluated in conjunction with the proband. Please contact GeneDx for prior approval when both parents are not available to submit samples for the Nystagmus Xpanded panel. The Nystagmus Xpanded panel is based on exome capture (EC), NextGeneration sequencing (NGS), and targeted analysis of a comprehensive list of approximately 800 genes currently associated with nystagmus. The design of the panel allows for a comprehensive, dynamic gene list that is updated regularly to ensure inclusion of genes recently associated with nystagmus.

Genetics of Nystagmus:

The inheritance pattern of the genetic conditions for which nystagmus is a presenting clinical feature can be autosomal dominant, autosomal recessive, X-linked, mitochondrial, or digenic (Richards et al., 2015; Thorburn et al., 2014; Parisi et al., 2017). The incidence of infantile nystagmus, also known as congenital nystagmus, is estimated to be 1:1000 to 1:1500 (Richards et al., 2015), while the overall incidence of nystagmus is difficult to quantify given the wide variety of underlying etiologies. Pathogenic variants in a certain 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). Incomplete penetrance and/or variable expressivity have been reported in some genetic conditions associated with nystagmus. In some instances, molecular confirmation of a specific genetic etiology, in some cases before additional symptoms present, may have implications for treatment and management of the individual with nystagmus.

Test Method:

Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are captured 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 individual and relative samples, if submitted. Sequence and copy number alterations are reported according to the Human Genome Variation Society (HGVS) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively.

Please note that while the Nystagmus Xpanded panel captures and sequences the exome, analysis is targeted to the specific phenotype-driven gene list for this panel. The Nystagmus Xpanded Panel gene list includes approximately 800 genes. The list was developed by searching for genes associated with nystagmus in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) terms. The gene list is systematically updated at least quarterly. The current gene list is available on our website.

Result Reporting:

The Nystagmus Xpanded 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 nystagmus in the published or emerging literature. The report will include pathogenic or likely pathogenic variants in genes associated or likely associated with the patient's phenotype. In some instances, the report may also include specific variants of uncertain significance (VUS) in genes that are possibly associated with the patient's phenotype. Variants that are considered to be benign or likely benign will not be reported. As the Nystagmus Xpanded Panel includes approximately 800 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.

Test Sensitivity:

The clinical sensitivity of the Nystagmus Xpanded Panel depends in part on the patient's clinical phenotype. Previous exome sequencing performed at GeneDx evaluating individuals with nystagmus has demonstrated an overall diagnostic rate of 34.6%, with trio-based testing demonstrating a 38.1% diagnostic rate and singleton testing demonstrating a 26.3% diagnostic rate. 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 known to be associated with nystagmus. The clinical sensitivity is expected to be significantly lower for singleton testing when only the affected proband is tested (Retterer et al., 2015).

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 94% of the genes on the panel have an average coverage of greater than 99.0% coverage at 10X. Several genes with a high clinical sensitivity have an average coverage of less than 90% at 10X, including

GRK1 (85.6%), *KCNC3* (88.4%), *OCLN* (87.4%), *OPN1LW* (85.6%), *POMGNT1* (66.9%), *POMT2* (56.9%), *PROM1* (87.7%), *PRPH2* (79.5%), *RAB18* (89.2%), *RAB3GAP2* (84.9%), and *RASA2* (82.5%). Note that these numbers represent the average coverage for the genes on the panel, derived by combining data from a large number of patients. 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 may not be detectable with this test. Small sections of a few individual genes have inherent sequence properties that yield suboptimal data and pathogenic variants in those regions may not be reliably detected. In addition, mitochondrial genome sequencing and sequencing of noncoding RNA molecules (microRNA) is not performed as part of the Nystagmus Xpanded Panel.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the Nystagmus Xpanded 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 Nystagmus Xpanded 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.

Specimen Requirements and Shipping/Handling:

- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Swabs:** A single complimentary GeneDx buccal swab is sufficient. Specimens may be held at room temperature before overnight shipping for up to 1 week.
- **Purified DNA:** High quality extracted DNA can be accepted. At least 15ug is requested (with a minimum concentration of 50ng/µl).
- **Other Specimens:** Contact GeneDx for specific inquiries and specimen requests.

Required Information:

- Sample Submission (Requisition) Form – complete all pages, including consent for testing
- Detailed clinical records and prior genetic testing results for the affected individual as well as family history information should be submitted prior to or at the same time as the biological specimens.
- Payment Options Form or Institutional Billing Instructions

For test codes, CPT codes, and turn-around-times, please refer to the "Nystagmus Xpanded Panel" page on our website: www.genedx.com

References:

Gottlob et al. (2014) Curr. Opin. Neurol. 27 (1):83-91 (PMID: 24346039); Richards et al. (2015) Can. J. Ophthalmol. 50 (6):400-8 (PMID: 26651297); Thorburn DR, Rahman S. Mitochondrial DNA-Associated Leigh Syndrome and NARP. 2003 Oct 30 [Updated 2014 Apr 17]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1173/; Parisi M, Glass I. Joubert Syndrome. 2003 Jul 9 [Updated 2017 Jun 29]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1325/; Retterer et al. (2015) Genet. Med.: (PMID: 26633542).

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