Leukodystrophy Xpanded Panel

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

Disorder also known as
white matter disorders; leukoencephalopathy

Overview
Leukodystrophies are a clinically and genetically heterogeneous group of myelin disorders caused by abnormal development or destruction of the white matter of the central nervous system with or without peripheral nervous system involvement (Vanderver et al., 2014). Characteristic features include: hypotonia, spasticity, motor impairment/dysfunction, and variable MRI abnormalities. Other features can include: seizures, dystonia, dyskinesia, ataxia, developmental delay or regression, changes in cognition, endocrine dysfunction, and abnormalities of vision or hearing (Vanderver et al., 2014).

Due to the heterogeneous nature of leukodystrophies, it can be challenging to determine a specific diagnosis or predict the disease-causing gene based on clinical features alone. It is often necessary to perform testing of multiple genes to identify the underlying genetic cause of leukodystrophy in an individual. Moreover, new genes associated with leukodystrophy 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 suspicious variants.

The Leukodystrophy 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 leukodystrophy. Depending on the family structure, family history of leukodystrophy, 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 Leukodystrophy Xpanded Panel. The Leukodystrophy Xpanded Panel is based on exome capture (EC), NextGeneration sequencing (NGS), and targeted analysis of a comprehensive list of genes currently associated with leukodystrophy. The design of the panel allows for a comprehensive, dynamic gene list that will be updated regularly to ensure inclusion of genes newly associated with leukodystrophy.

Genetics of Leukodystrophy
Leukodystrophy can be caused by genetic disorders, metabolic diseases, trauma, infection, and in up to 50% of cases, the etiology is unknown (Vanderver et al., 2014; Bonkowsky et al., 2010). The inheritance pattern can be autosomal dominant, autosomal recessive, or X-linked; however, autosomal recessive inheritance is most common (Vanderver et al., 2014). While the overall incidence of this group of disorders is difficult to estimate, historic studies have reported an overall prevalence ranging from 1 in 5,000 to 1 in 50,000 (Bonkowsky et al., 2010; Heim et al., 1997). In some cases, confirmation of the molecular genetic cause of leukodystrophy may have implications for treatment and management of the specific disorder.

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 customdeveloped analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to

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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) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. A list of additional variants not included in the report is available upon request.

Please note that while the Leukodystrophy Xpanded panel captures and sequences the whole exome, analysis is targeted to a phenotype-specific gene list for leukodystrophy. The gene list includes more than 300 genes. The list was developed by searching for genes associated with the phenotype “leukodystrophy,” “leukoencephalopathy,” “dysmyelination,” “demyelination,” “myelin disorder,” “white matter disease,” and “white matter abnormalities” in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) terms categorized within the “leukodystrophy” branch. Additionally, genes were added to the list using GeneDx data from clinical whole exome sequencing done on patients with leukodystrophy and from emerging literature about new genes causing leukodystrophy. The gene list is systematically updated at least quarterly. The current gene list is available on our website (https://www.genedx.com/testcatalog/genetic-testing-for-neurological-disorders/).

Results Reporting

The Leukodystrophy Xpanded Panel is performed on the proband and the parental samples (and/or additional relatives) when submitted together for analysis. A single Leukodystrophy Xpanded 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, additional fees will apply.

As the Leukodystrophy Xpanded Panel includes over 300 genes, the report that is issued for the affected individual will not include a comprehensive list of all observed variants. Specifically, the report includes any pathogenic/likely pathogenic variants in genes responsible for the phenotype of the patient, while variants of uncertain significance (VUS) are not routinely reported, only at our discretion. If desired, clinicians can request a separate file containing a list of identified variants, which 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. The absence of reportable incidental findings for any particular gene does not rule out the possibility of pathogenic variants in that gene.

Test Sensitivity

The clinical sensitivity of the Leukodystrophy Xpanded test depends in part on the patient’s clinical phenotype. Overall, patients with a clinical indication that includes leukodystrophy have a 33% positive rate by exome sequencing (ES) (Zou et al., 2017). When parents are sequenced and analyzed concurrently (trio-based testing), the positive rate increases to 34%, whereas the positive rate is significantly lower (23%) for cases where only the proband is tested (singleton testing) (Zou et al., 2017). The sensitivity of this test is expected to be comparable to exome sequencing since it uses a trio approach to test a comprehensive list of genes previously associated with leukodystrophy. The clinical sensitivity is expected to be significantly lower for singleton testing when only the affected proband is tested.

The average coverage of all genes on the panel is greater than 98% at 10X (with a depth of 10 or more reads), and approximately 85% of the genes on the panel have an average coverage of greater than 99% at 10X. 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.

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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 mutations in those regions may not be reliably detected.

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

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