Lysosomal Disorders Panel

Panel Gene List: *ABHD5, ADAMTSL2, AGA, ARSA, ARSB, ASAH1, ATP6AP1, CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSF, DNAJC5, FUCA1, GAA, GALC, GALNS, GBA, GLA, GLB1, GNE, GNPTAB, GNPTG, GNS, GPC3, GRN, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, LAMP2, LIPA, LYST, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PNPLA2, PPT1, PSAP, SCARB2, SGSH, SLC17A5, SMPD1, SUMF1, TPP1, VPS33A*

Clinical Features:

Lysosomal disorders are a clinically and genetically heterogeneous group of disorders caused by deficiency of lysosomal enzymes, or non-enzymatic proteins involved in lysosomal biogenesis, transport, or maturation. Deficiency of these enzymes or proteins leads to the accumulation of partially degraded products resulting in progressive cellular dysfunction and clinical abnormalities. Most lysosomal disorders can be classified by the nature of the stored material: mucopolysaccharidoses, mucolipidoses, glycoproteinoses, sphingolipidoses, oligosaccharidosis and glycogen storage diseases.[1] Lysosomal disorders may affect a single organ system or multiple organ systems. The disease course of these conditions is generally progressive, but the age of onset, nature and severity of symptoms can be variable between the disorders. Common symptoms of lysosomal disorders include hepatosplenomegaly, coarsening of facial features, short stature, corneal clouding, dysostosis multiplex, and neurological regression.[2] Due to the overlap in clinical findings between these disorders, the diagnosis of lysosomal storage is challenging and requires specific enzymatic analysis or molecular studies or both.[3]

The GeneDx Lysosomal Disorder Panel includes genes known to be associated with mucopolysaccharidoses, mucolipidoses, glycoproteinoses, sphingolipidoses, oligosaccharidosis, and lysosomal glycogen storage diseases. The diagnosis of these disorders can help direct treatment and medical management and allow for accurate recurrence risks and genetic counseling.

Genetics:

Most lysosomal storage diseases are associated with autosomal recessive inheritance. The *ATP6AP1, GLA, GPC3, IDS,* and *LAMP2* genes are associated with X-linked inheritance, the *DNAJC5* gene is associated with autosomal dominant inheritance, and the *GNE* and *GRN* genes are associated with both autosomal dominant and recessive inheritance

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. Recombinations involving the *IDS* gene and its pseudogene that do not involve exon-level deletions will not be detected by this test. For the *GUSB* genes deletion/duplication analysis is limited, and will only detect large (multi-exon) events. This test does not include exon-level deletion/duplication analysis for the *ADAMTSL2, GBA*, and *GRN* genes. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Sanger sequencing is also used to evaluate the *GBA* gene and to compensate for regions of low coverage. 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.

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. In a study of 66 unrelated patients from Spain who were suspected to have an a lysosomal disorder, a next generation sequencing panel of 57 genes identified a diagnosis in thirty eight percent (25/66) of patients.[4]

References:

1. Penati et al. (2017) J. Inherit. Metab. Dis. 40 (4):543-554 (PMID: 28560469)
2. James et al. (2016) J Paediatr Child Health 52 (3):262-71 (PMID: 27124840)
3. Giugliani et al. (2016) Expert Rev. Mol. Diagn. 16 (1):113-23 (PMID: 26567866)
4. Fernández-Marmiesse et al. (2014) Orphanet J Rare Dis 9 :59 (PMID: 24767253)