GLA Gene Testing in Fabry Disease

Clinical Features:
Males with Fabry disease often present in childhood with attacks of abdominal pain and angocarparasthesia. Vascular skin lesions (angiokeratoma) are frequent, and vascular lesions may also occur elsewhere, including ocular fundi and kidney. Whorl-like corneal dystrophy is not uncommon. Neurological symptoms include autonomic dysfunction, orthostatic hypotension, and stroke. Angina, exercise intolerance and EKG changes occur, often with normal coronary arteries, heart size and hemodynamics, although left ventricular wall and septal hypertrophy are not infrequent. Respiratory complications include chronic airflow obstruction. Progressive kidney disease leads to end-stage renal disease, typically in the third to fifth decade in untreated males who also at risk for developing cardiac and cerebrovascular disease.\(^1\,^2\) Approximately 60-70% of females with a single pathogenic GLA variant have some disease manifestations, and 10% of these individuals present with a disease severity that is similar to that of affected males.\(^3\)

Genetics:
Fabry disease is caused by pathogenic variants in the GLA gene resulting in deficiency of the enzyme alpha-galactosidase A. Enzyme deficiency leads to lysosomal accumulation of globotriaosylceramide in various tissue types. The GLA gene is located on the X chromosome and contains 7 exons.

Inheritance Pattern:
X-linked

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions, as well as an additional region in intron 4 encompassing the c.640-801 (IVS4-801) variant, of the GLA gene 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 the reference sequence 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. 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.

**Variant Spectrum:**
A variety of variants occur in Fabry disease, including missense, nonsense, splice-site, partial gene rearrangements, and small and large deletions and insertions with partial and whole gene deletions accounting for approximately 2% of GLA variants. Although, most variants are “private”, occurring only in a single family, the A143P pathogenic variant is a founder mutation in the Nova Scotian population and has been identified in approximately 28% of individuals with Fabry disease in Canada.

**References:**