FUCA1 Gene Analysis in Fucosidosis

CLINICAL FEATURES

Fucosidosis is a very rare lysosomal storage disorder that is characterized by accumulation of alpha-linked fucose-containing glycolipids and oliogaccharides. The clinical features include intellectual disability, growth retardation, progressive neurodegeneration with loss of mental and motor skills, coarse facies, recurrent infections, skeletal abnormalities, joint contractures, angiokeratoma corporis diffusum, visceromegaly, seizures, ocular abnormalities and hearing loss. Historically, two types of fucosidosis were described, based on severity and age of onset. However, current interpretation is that there is a continuum of phenotypes, and individuals within the same family have been reported with phenotypes on both ends of the clinical spectrum.[1] A minority of patients have rapidly progressive neurologic deterioration leading to death before age 5 years, while the majority have slower neurologic deterioration and survive into the second or third decade. Patients with fucosidosis have been described worldwide with Italians and Mexican-Indian populations of New Mexico and Colorado having a higher incidence.[1]

GENETICS

Fucosidosis is caused by pathogenic variants in the *FUCA1* gene that encodes the lysosomal enzyme α-1-fucosidase, which hydrolyzes fucose from fucose-containing glycoconjugates. In patients with fucosidosis, α-1-fucosidase deficiency results in the accumulation of fucosyl-glycolipids, glycopeptides and oligosaccharides in various tissues and urinary excretion of fucosyl-glycolipids, glycopeptides and other degradation products. All patients with fucosidosishave nearly absent α-1-fucosidase enzyme activity.[2] The *FUCA1* gene is located on chromosome 1p34.1 and has 8 exons.

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the FUCA1gene 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.

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VARIANT SPECTRUM

More than 30 variants have been identified in the *FUCA1* gene that are spread throughout the gene and include mostly inactivating variants: nonsense, small deletions/insertions, splice-site, and large deletions. Missense variants have also been described.[1-3] Most families are homozygous for a single variant.[2] Genotype/phenotype correlations have not been established.[1]

REFERENCES:

1. Willems et al. (1991) American Journal Of Medical Genetics 38 (1):111-31 (PMID: 2012122)
2.Willems et al. (1999) European Journal Of Human Genetics 7 (1):60-7 (PMID: 10094192)
3.Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)

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