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 abnormalitities, 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 fucosidosis have 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:
Variant analysis of the *FUCA1* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *FUCA1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

Test Sensitivity:

Variant analysis of the *FUCA1* gene identified all but one variant in 40 patients with fucosidosis.[2] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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 : Ejhg 7 (1):60-7 (PMID: 10094192)
3. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)