GFAP Gene Analysis in Alexander Disease

Clinical Features:
Alexander disease (AD) is a progressive disorder of the white matter of the central nervous system (CNS). The three types of AD are categorized by age of onset: infantile, juvenile, and adult. Affected infants develop a megalencephalic leukodystrophy, seizures, spasticity, ataxia, and psychomotor retardation. Infantile AD frequently leads to death within a decade after the diagnosis. Juvenile and adult forms of AD have a more slowly progressive course and are characterized by ataxia, bulbar signs and spasticity. Rosenthal fibers, observed in the astrocytes of affected individuals upon autopsy, are a hallmark feature of AD. These cytoplasmic inclusions are made up of glial acidic fibrillary protein (GFAP) and small heat-shock proteins. MRI has proven to be a useful tool for diagnosing AD, and often shows high signal intensity of white matter in the frontal area and basal ganglia. Alexander disease is usually sporadic and is most often caused by *de novo* heterozygous variants in the GFAP gene. The recurrence risk, even when both parents are negative for GFAP variants, is unknown and may thus warrant consideration of prenatal diagnosis for couples who have had an affected child. There is one report of a clinically-diagnosed Alexander disease patient with apparent autosomal recessive variants in the NDUFV1 gene.

Genetics:
Autosomal dominant, most cases sporadic.

Test Methods:
Using genomic DNA obtained from the submitted biological material, all 9 exons of the GFAP gene are tested using bi-directional sequence analysis. 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:
A number of studies have found that 90-95% of individuals diagnosed with Alexander disease have GFAP variants. Sequence analysis as performed by GeneDx is expected to identify all of the published variants occurring in the GFAP gene, making the sensitivity of this test very high.

References:

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