GFAP Gene Analysis in Alexander Disease

Mendelian Inheritance in Man Number: 203450 (Alexander Disease); 137780 (Glial Fibrillary Acidic Protein; GFAP)

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 mutations in the GFAP gene. The recurrence risk, even when both parents are negative for GFAP mutations, 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 mutations in the NDUFV1 gene.

Inheritance pattern:
Autosomal dominant, most cases sporadic

Reasons for referral:
1. Confirmation of a clinical diagnosis
2. Differentiation of Alexander disease from Canavan disease
3. Genetic counseling
4. Prenatal diagnosis in at-risk pregnancies

Test method:
Using genomic DNA obtained from the submitted biological material, all 9 exons of the GFAP gene are tested using bi-directional sequence analysis. Mutations 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 mutations. Sequence analysis as performed by GeneDx is expected to identify all of the published mutations occurring in the GFAP gene, making the sensitivity of this test very high.

Mutation spectrum:
The vast majority of mutations identified in AD have been heterozygous missense mutations that are suspected to cause a gain in GFAP function. Many of these point mutations affect an arginine residue. There are mutation hot spots in exons 1 and 4, although mutations have been
identified in other regions of the gene. Mutations found in infantile AD have also been seen in juvenile and adult forms of AD, suggesting that other factors contribute to the expression of the disease.

**Specimen Requirements and Shipping/Handling:**

- **Blood**: A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes**: As an alternative to blood, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children less than 6 months of age.
- **Prenatal Diagnosis**: For prenatal testing for a known mutation in the GFAP gene, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Alexander Disease” page on our website: [www.genedx.com](http://www.genedx.com)