TREX1, RNASEH2A, RNASEH2B, and RNASEH2C Genes Analysis in Aicardi-Goutieres Syndrome

Disorder also known as: AGS, encephalopathy, familial infantile, with intracranial calcification and chronic cerebrospinal fluid lymphocytosis, Cree encephalitis, pseudotoxoplasmosis syndrome

Clinical Features:
Aicardi-Goutieres syndrome is a heritable disorder of the central nervous system, characterized by calcifications of the basal ganglia and white matter, and elevated CSF alpha interferon with no detectable infectious etiology.[1-5] These patients may present in the neonatal period with a syndrome that mimics *in utero* viral infections, including coombs positive hemolytic anemia and autoimmune thrombocytopenia, elevated transaminases, microcephaly, seizures, vasculitic skin lesions, and cerebral calcifications. Often, these patients are initially suspected of having a congenital cytomegalus virus, rubella or HIV infection.[6] A genetic cause may be suspected only after the birth of a second affected child. This condition may also present in older infants with progressive microcephaly, dystonia, seizures and developmental delay as well as sterile pyrexias, lupus like skin and joint manifestations, progressive intracranial calcifications, and chronically elevated CSF lymphocytes. [7,8] Some children diagnosed with Aicardi-Goutieres syndrome may remain clinically stable for long periods of time. Developmental regression associated with painful skin lesions and systemic manifestations, often in an episodic manner, occur in the early years of life, followed in many cases by years of stability. Progressive cerebral atrophy and cerebral calcifications are seen. Many children succumb later in life to medical complications, but children living into their teens and later are known.

Genetics:
Primarily autosomal recessive inheritance; rare cases of autosomal dominant de novo variant in the TREX1 gene have been reported.

Test Methods:
Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested genes were PCR amplified and capillary sequencing was performed. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing or another appropriate method was used to confirm all potentially pathogenic variants. If present, apparently homozygous variants were confirmed using alternate primer pairs to significantly reduce the possibility of allele drop-out. Sequence alterations were reported according to the Human Genome Variation Society (HGVS)

nomenclature guidelines. Benign and likely benign variants, if present, are not included in this report but are available upon request. The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing.

Test Sensitivity:

Approximately 83% of patients with characteristic clinical findings of AGS are expected to have variants in TREX1, RNASEH2A, RNASEH2B, or RNASEH2C.[9] In those individuals with identifiable molecular changes, 65% had pathogenic variants either in TREX1 or RNASEH2B. Moreover, almost all individuals with RNASEH2B variants had at least one variant in exon 2, 6, or 7. In one study, thirteen patients of Pakistani origin were found to harbor a common homozygous variant, R69W, on a common haplotype, suggestive of a founder mutation[9].

References:

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