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

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

**Mendelian Inheritance in Man Number:** 606609 (TREX1 gene), 606034 (RNASEH2A gene), 610326 (RNASEH2B gene), 610330 (RNASEH2C gene), 225750 (Aicardi-Goutieres Syndrome 1), 610181 (Aicardi-Goutieres Syndrome 2), 610329 (Aicardi-Goutieres Syndrome 3), 610333 (Aicardi-Goutieres Syndrome 4)

**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 (ref 1-5) with no detectable infectious etiology. 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 (ref 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 (ref 7) skin and joint manifestations, progressive intracranial calcifications, and chronically elevated CSF lymphocytes (ref 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.

**Inheritance pattern:**
Primarily autosomal recessive inheritance; rare cases of autosomal dominant de novo mutations in the TREX1 gene have been reported.

**Reasons for referral:**
1. Confirmation of a clinical diagnosis
2. Development of an appropriate management plan
3. Genetic counseling
4. Prenatal diagnosis in families with a defined mutation
5. Carrier testing
**Test method:**
Analysis of the TREX1, RNASEH2A, RNASEH2B, and RNASEH2C genes is offered as one complete panel. The panel includes concurrent sequence analysis of all coding exons of TREX1, RNASEH2A, RNASEH2B, and RNASEH2C. 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:**
Approximately 83% of patients with characteristic clinical findings of AGS are expected to have mutations in TREX1, RNASEH2A, RNASEH2B, or RNASEH2C (ref 9). In those individuals with identifiable molecular changes, 65% had disease-causing mutations either in TREX1 or RNASEH2B. Moreover, almost all individuals with RNASEH2B mutations had at least one mutation in exon 2, 6, or 7. In one study, thirteen patients of Pakistani origin were found to harbor a common homozygous mutation, R69W, on a common haplotype, suggestive of a founder mutation (ref 9).

**Mutation spectrum:**
Approximately 60% of mutations identified in the TREX1 are missense mutations, with the remaining 40% of mutations being nonsense and frameshift mutations. For the RNASEH2A, RNASEH2B and RNASEH2C genes, almost all mutations are missense changes, with few small duplications or insertions.

**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:** Can be used as an alternative to blood. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.

**Prenatal Diagnosis:** For prenatal testing for a known mutation in the TREX1, RNASEH2A, RNASEH2B, or RNASEH2C genes, 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 “Aicardi-Goutieres Syndrome” page on our website: www.genedx.com

**References Cited:**