Clinical Features:
Aicardi Goutières Syndrome (OMIM number(s) for the disorder: 225750 (AGS1), 610181 (AGS2), 610329 (AGS3), and 610333 (AGS4) is a heritable disorder of the central nervous system, characterized by calcifications of the basal ganglia and white matter, and elevated CSF alpha interferon [1-6] 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 cytomegalovirus, rubella or HIV infection[7]. 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 [8] skin and joint manifestations, progressive intracranial calcifications, chronically elevated CSF lymphocytes[9] and elevated CSF pterins.

AGS has been described as a neurodegenerative disorder, but does not truly fit that characterization, as children may remain clinically stable for long periods of time, and may more readily be understood as a heritable disorder of cell intrinsic immunity. 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.

Disorders previously thought of as distinct, such as Cree encephalitis[10], pseudo-TOUCH and familial systemic lupus erythematosus, with significant immunologic phenotypes, are now thought to be a within the AGS spectrum[10]. In addition, other disorders, with dissimilar phenotypes but predominant autoimmune and or neurologic manifestations, such as familial chilblain lupus (FCL) [11] and autosomal dominant retinal vasculopathy with cerebral leukodystrophy (RVCL) [12, 13], are now known to be allelic with AGS. Familial chilblain lupus (FCL) [OMIM 610448] is a rare cutaneous form of systemic lupus erythematosus (SLE). FCL has autosomal dominant inheritance with heterozygous mutations in TREX1 [11] [14]; Autosomal dominant retinal vasculopathy with cerebral leukodystrophy (RVCL) [OMIM 192315] is a rare disorder with retinal vasculopathy, migraine, Raynaud's phenomenon, stroke, and dementia with onset in middle age. RVCL has autosomal dominant inheritance with heterozygous mutations in TREX1[13]. Finally heterozygous mutations in TREX1 have been found in a subset of patients with Systemic Lupus Erythmatosa (SLE)[15].

Suggested minimal criteria for diagnosis are intracranial calcifications with abnormal central nervous system white matter with no infectious explanation, characteristic clinical findings such as chilblains, and/or CSF findings of leukocytes, pterins or alpha interferon.

Molecular Genetics:
Approximately 83% of patients with characteristic clinical findings have mutations in TREX1(OMIM 606609), RNASEH2A(OMIM 606034), RNASEH2B(OMIM 610326), or RNASEH2C(OMIM 610330)[6]. In those individuals with identified molecular changes, 65% had disease caused by TREX1 or RNASEH2B mutations. Moreover, almost all individuals with RNASEH2B mutations had at least one mutation in exon 2, 6, or 7. These observations allow for a targeted initial screening strategy.

The early-onset neonatal form of AGS described above is most frequently seen in association with TREX1, RNASEH2A, and RNASEH2C mutations while the later-onset presentation is most frequently seen in association with RNASEH2B mutations [6]. Mortality is
correlated with genotype: 34% of individuals with TREX1, RNASEH2A, and RNASEH2C mutations were known to have died compared to 8% with RNASEH2B mutations (p=0.001)[6].

Certain genotypes are more common and may be associated with specific ethnic groups: a missense change in TREX1 (c.341G>A) is common in people from Northern Europe; a missense change in RNASEH2B (c.529G>A) is seen in 62% of RNASEH2B disease alleles from all ethnic groups; a missense change in RNASEH2C mutation c.205C>T (p.Arg69Trp) is seen in Pakistani families and represents an ancient founder mutation[6]. For TREX1, approximately 60% of mutations are missense (including the R114H recurrent mutation). The remaining 40% of mutations are stops/insertions/deletions. For RNASEH2A, RNASEH2B and RNASEH2C almost all are missense changes, with few small duplications or insertions.

Inheritance:
Mode of inheritance of the disorder: Autosomal recessive in most cases. Rare cases of AGS presentation with TREX1 de novo heterozygous mutations have been described [6]. Heterozygous mutations of TREX1 have also been associated with other phenotypes, including FCL, RVCL and SLE.

Additional Resources:
Please see www.genetests.org for the GeneReview on AGS.

Test Methods:
We offer full sequencing of TREX1, RNASEH2A, RNASEH2B and RNASEH2C in a tiered fashion (see below). Patients with negative results or variants of unknown significance can enroll in Dr Adeline Vanderver and Dr Yanick Crow’s collaborative research study (Children’s National Medical Center, Washington DC, and University of Manchester, Manchester UK).

Tier 1 (TREX1, RNASEH2B exons 2, 6-7, RNASEH2C founder mutation if indicated)
Sample specifications: 1-5 cc of blood in a purple top (EDTA) tube
Cost: $1100
CPT codes: 83891 x 11, 83898 x 11, 83894 x 11, 83904 x 20, 83892 x 2, 83912 x 2
Turn around time: 6-8 weeks

Tier 2 (RNASEH2C full gene, RNASEH2A full gene, RNASEH2B remaining exons)
Sample specifications: 1-5 cc of blood in a purple top (EDTA) tube
Cost: $2400
CPT codes: 83891 x 20, 83898 x 20, 83894 x 20, 83904 x 40, 83892 x 2, 83912 x 2
Turn around time: 10 weeks

Testing for a known mutation in additional family members
Sample specifications: 1-5 cc of blood in a purple top (EDTA) tube
Cost: $500 for two mutations (compound heterozygotes) and $350 for one mutation (homozygous mutations and single heterozygotes).
CPT codes: 83891, 83898 x 2, 83894, 83904, 83892 x 2, 83912 x 2
Turn around time: 2-3 weeks
Prenatal testing for a known mutation

Sample specifications: 2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid or 20mg Chorionic villi

Cost: $2,000

CPT codes: 83891, 83898 x 2, 83894, 83904, 83892 x 2, 83912 x 2

Turn around time: 2 weeks

Results

You will be informed of the results for the submitted specimen as soon as testing has been completed. Results, along with an interpretative report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested.

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References: