GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

# Aicardi-Goutières Syndrome

[*Includes: RNASEH2A-Related Aicardi-Goutières Syndrome, RNASEH2B-Related Aicardi-Goutières Syndrome, RNASEH2C-Related Aicardi-Goutières Syndrome, TREX1-Related Aicardi-Goutières Syndrome*]

**Jean Aicardi, MD, FRCP**
*Department of Child Neurology and Metabolic Diseases*
*Hospital Robert-Debre*
*Paris*

**Yanick J Crow, MRCP, PhD**
*Leeds Institute of Molecular Medicine*
*St James's University Hospital*
*Leeds*
*Bradford Institute for Health Research*
*Bradford Royal Infirmary*
*Bradford*

**John BP Stephenson, DM, FRCP, HonFRCPCH**
*Fraser of Allander Neurosciences Unit*
*Royal Hospital for Sick Children*
*Glasgow*

Initial Posting: June 29, 2005.
Last Update: April 17, 2008.

## Summary

**Disease characteristics.** Aicardi-Goutières syndrome (AGS) is an early-onset encephalopathy that usually results in severe mental and physical handicap. A subgroup of infants with AGS present at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, a picture highly reminiscent of congenital infection. Otherwise, affected infants present at variable times after the first few days of life, frequently after a period of apparently normal development. Typically, they demonstrate the subacute onset of a severe encephalopathy characterized by extreme irritability, intermittent sterile pyrexias, loss of skills, and slowing of head growth. Between 20% and 50% of affected individuals have generalized tonic-clonic or focal tonic seizures. As many as 40% have chilblain skin lesions on the fingers, toes, and ears.

**Diagnosis/testing.** The diagnosis can be made with confidence in individuals with typical clinical findings, characteristic abnormalities on cranial CT (calcification of the basal ganglia and white matter) and MRI (leukodystrophic changes), and identifiable mutations in one of the four known causative genes. Mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* are identified in approximately 80% of individuals with characteristic clinical and MRI findings of AGS; such testing is clinically available. At least one other disease-causing gene is postulated but remains unknown.

**Management.** *Treatment of manifestations:* chest physiotherapy and treatment of respiratory complications; attention to diet and feeding methods to assure adequate caloric intake and avoid aspiration; management of seizures using standard protocols. *Surveillance:* repeat ophthalmologic examinations in the first few months of life for evidence of glaucoma; monitoring older children for evidence of scoliosis, insulin-dependent diabetes mellitus (IDDM), and hypothyroidism (although the risks of such complications are apparently low).

**Genetic counseling.** Most AGS is inherited in an autosomal recessive manner; in a few instances, it can be caused by *de novo* autosomal dominant mutations in *TREX1*. At conception, each sib of an affected individual with autosomal recessive AGS has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once a sib at risk for autosomal recessive AGS is known to be unaffected, the risk of his/her being a carrier is 2/3. Most individuals with AGS do not reproduce. Prenatal testing is possible for pregnancies at increased risk if the disease-causing mutation(s) in the family has/have been identified.

## Diagnosis

### Clinical Diagnosis

Aicardi-Goutières syndrome (AGS) is an early-onset encephalopathy usually associated with significant mental and physical handicap. The diagnosis can be made with confidence in individuals with typical clinical findings, characteristic abnormalities on cranial CT and MRI, and identifiable mutations in one of the four known causative genes.

The following features are seen in the majority of affected individuals [Goutières et al 1998; Lanzi et al 2002; Rice, Patrick et al 2007]:

- Calcification of the basal ganglia, particularly the putamen, globus pallidus, and thalamus but also extending into the white matter, sometimes in a periventricular distribution
- White matter changes, particularly affecting the frontotemporal regions with (in severe cases) cyst-like formation
- Cerebral atrophy
- Chronic cerebrospinal fluid (CSF) leukocytosis
- Increased concentration of interferon-alpha (IFN-α) in the CSF
- Increased concentration of neopterin in the CSF [Rice, Patrick et al 2007]

The following additional features can be regarded as supportive of the diagnosis:

- Chilblain lesions on the digits, ears, and pressure points
- Appearance of microcephaly during the first year of life
- Dystonia
- Sterile pyrexias

Exclusion criteria include the following:

- Evidence of prenatal/perinatal infection including CMV, toxoplasmosis, rubella, herpes simplex, and HIV
- Evidence of a known metabolic disorder or neurodegenerative disorder

**Neuroimaging—Calcification.** Intracranial calcifications are best visualized on CT scan. The following are noted:

- Calcifications frequently involve the globus pallidus, putamen, caudate nucleus, thalamus, and dentate nucleus [Lanzi et al 2002] (Figure 1A, 1B).
- They frequently extend into the white matter, in particular the periventricular area (Figure 1C).

- They are often punctate but may be large and extensive.
- Those identified at diagnosis tend to remain stable, although progression can be observed [Lanzi et al 2002, Lanzi et al 2005].
- Extent of calcification is not correlated with the severity of neurologic outcome; cases without intracranial calcification have been documented [Aicardi & Goutières 1984].

**Leukodystrophy.** Hypodensity of the white matter is present in 75% to 100% of affected individuals [Lanzi et al 2002]. On MRI hypodensity appears on T2-weighted images as a hyperintense signal most commonly located around the horns of the ventricles (Figure 1). White matter changes can be particularly prominent frontally [Crow, Massey et al 2004].

Of note, intracranial calcification is not always recognized on MRI, the initial imaging modality employed in most units.

**Cerebral atrophy**

- Progressive atrophy of the periventricular white matter and sulci is an almost constant feature.
- Cerebellar atrophy and brain stem atrophy may be prominent (Figure 2D) [Crow, Massey et al 2004; Sanchis et al 2005].

**Magnetic resonance spectroscopy** (MRS) demonstrates a reduced N-acetylaspartate/creatine ratio reflecting decreased neuronal/axonal density or viability, increased myo-inositol/creatine ratio reflecting gliosis or osmotic stress, and a persisting brain lactic alkalosis similar to that seen in infants surviving perinatal hypoxia-ischemia [Robertson et al 2004]. These changes are not particularly helpful from a diagnostic perspective.

## Testing

The most important clinical laboratory tests contributing to the diagnosis of AGS involve an assessment of the CSF for numbers of white cells and concentrations of interferon alpha and neopterin. These tests are most likely to be informative early on in the disease process and are frequently normal after the first few years of life [Rice, Patrick et al 2007].

**Interferon-alpha (IFN-α).** CSF IFN-α concentration is greater than 2 IU/mL (normal: <2 IU/mL) [Goutières et al 1998, Lebon et al 2002].

- Levels are highest in the early stages of the disease. The IFN-α CSF concentration tends to normalize over the first three to four years of life [Rice, Patrick et al 2007].
- The concentration of IFN-α is usually higher in CSF than in blood, where it may be normal.
- High levels of IFN-α have been identified in fetal blood at 26 weeks' gestation [Desanges et al 2006].

**CSF lymphocytosis.** Lymphocytosis is defined as more than five lymphocytes/$mm^3$ CSF. Typical values range from five to 100 lymphocytes/$mm^3$ [Goutières et al 1998; Rice, Patrick et al 2007].

- A decrease in the number of lymphocytes occurs with time, although high cell counts may persist for several years.
- A normal cell count can be observed in the presence of elevated concentrations of IFN-α in the CSF even at an early stage of the disease [Crow et al 2003; Rice, Patrick et al 2007].

**CSF neopterin.** CSF concentrations of neopterin (and less so biopterin) are frequently raised in molecularly proven AGS [Rice, Patrick et al 2007], so it appears that this is a good marker of the disease:

- Levels are highest in the early stages of the disease and tend to normalize over time.
- Levels of the neurotransmitter metabolites 5HIAA, HVA, and 5MTHF are normal.

Note: Levels of CSF protein can also be raised without oligoclonal bands [Lanzi et al 2002].

## Molecular Genetic Testing

*GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the* GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

**Molecular Genetic Testing—Genes.** Mutations in the following genes are associated with AGS:

- *TREX1* (AGS1 locus) [Crow, Hayward et al 2006]
- *RNASEH2B* (AGS2 locus), the gene encoding subunit B of ribonuclease H2 [Crow, Leitch et al 2006]
- *RNASEH2C* (AGS3 locus), the gene encoding subunit C of ribonuclease H2 [Crow, Leitch et al 2006]
- *RNASEH2A* (AGS4 locus), the gene encoding subunit A of ribonuclease H2 [Crow, Leitch et al 2006]

**Other loci.** In a recent study, 17% of individuals with clinically typical AGS had no mutations identifiable in *TREX1*, *RNASEH2A*, *RNASEH2B*, or *RNASEH2C*, suggesting that disease-causing mutations in at least one other gene remain to be identified [Rice, Patrick et al 2007].

### Clinical testing

- **Sequence analysis.** Mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* have been found in approximately 83% of individuals with clinical and MRI presentation of AGS, by use of sequence analysis of the coding regions and splice sites [Rice, Patrick et al 2007]. (See Figure 3)

  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.

  In addition, a founder homozygous mutation in *RNASEH2C* was seen recurrently in 13 families of Pakistani descent.

  Thus, initial screening of *TREX1* and exons 2, 6, and 7 of *RNASEH2B*, plus an analysis for the common *RNASEH2C* Pakistani mutation where appropriate, will identify the majority of all individuals with mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, or *RNASEH2C*. See, however, Other loci.

  Affected individuals are almost always homozygotes or compound heterozygotes for mutations within the same gene. However, a single child with clinically typical AGS has been described with disease resulting from a *de novo* heterozygous mutation in *TREX1* [Rice, Newman et al 2007].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Aicardi-Goutières Syndrome

| Gene Symbol | Proportion of AGS Attributed to Mutations in This Gene | Test Method | Mutation Detection Frequency by Test Method [1] | Test Availability |
|---|---|---|---|---|
| *TREX1* | 25% | Sequence analysis | >95% | Clinical Testing |
| *RNASEH2B* | 40% | | >90% [2] | Clinical Testing |
| *RNASEH2C* | 14% | | >95% | Clinical Testing |
| *RNASEH2A* | 4% | | >95% | Clinical Testing |

1. In individuals with a firm clinical diagnosis of AGS
2. In a small number of affected individuals, only a single mutation has been identified in the *RNASEH2B* gene. This may reflect a failure to detect a second mutation by current sequencing methods, but this has not yet been determined.

**Interpretation of test results.** For issues to consider in interpretation of sequence analysis results, click here.

## Testing Strategy

**To confirm the diagnosis in a proband.** AGS is usually considered following the identification of calcification on cranial CT in a child with clinical features described in Clinical Diagnosis. The finding on MRI of white matter changes with frontotemporal cysts is highly suggestive of the diagnosis, as are chilblains.

Note: With the advent of molecular testing, CSF analysis is not always undertaken: (1) After the first few years of life, assay of CSF white cells/IFN-α/pterins is likely to be non-contributory; and (2) assay of CSF white cells/IFN-α/pterins is still of value in the younger child because it can provide further evidence in favor of the diagnosis before pursuing molecular genetic testing, an important consideration given that the molecular basis of AGS has not yet been clarified in all cases.

**Carrier testing for at-risk relatives** requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

**Prenatal diagnosis** for at-risk pregnancies requires prior identification of the disease-causing mutations in the family.

## Genetically Related (Allelic) Disorders

**Cree encephalitis** is characterized by severe psychomotor retardation, progressive microcephaly, cerebral atrophy, white matter attenuation, intracerebral calcification, a CSF lymphocytosis, and systemic immune abnormalities, features similar to AGS. Linkage analysis and measurement of CSF concentration of IFN-α suggested that the two disorders were allelic [Crow et al 2003]; this was confirmed when molecular genetic testing revealed that all children with Cree encephalitis are homozygous for the c.490C>T mutation in *TREX1*. Inheritance is autosomal recessive.

Note: Cree encephalitis should be distinguished from another neurologic condition, Cree leukoencephalopathy, a form of vanishing white matter disease caused by *EIF2B5* mutations, occurring at high frequency in the same population [Fogli et al 2002]. (See Childhood Ataxia with Central Nervous System Hypomyelination/Vanishing White Matter.)

**Familial chilblain lupus (FCL)** [OMIM 610448] is a rare cutaneous form of systemic lupus erythematosus (SLE) characterized by painful bluish-red papular or nodular skin lesions in acral locations (including the dorsal aspects of fingers and toes, heels, nose, cheeks, ears, and in some cases knees), which are most frequently precipitated by cold [Lee-Kirsch et al 2006]. Rice, Newman et al (2007) described a heterozygous *TREX1* mutation in affected members of a family with chilblain lupus; a second distinct mutation was subsequently described by Lee-Kirsch, Chowdury et al (2007). Inheritance is autosomal dominant.

Note: OMIM designates autosomal dominant AGS as AGS5; this *GeneReview* does not use that nomenclature.

**Autosomal dominant retinal vasculopathy with cerebral leukodystrophy (RVCL)** [OMIM 192315]. Richards et al (2007) have shown that C terminus mutations in *TREX1* cause RVCL, an autosomal dominant microvascular endotheliopathy variably associated with a retinal vasculopathy, migraine, Raynaud's phenomenon, stroke, and dementia with onset in middle age. This finding raises the possibility that the heterozygous parents of children with AGS caused by *TREX1* mutations, at least those with mutations in the C terminus of the gene, may be at risk of developing RVCL.

**Systemic lupus erythematosus (SLE).** Lee-Kirsch, Gong et al (2007) have found heterozygous mutations in *TREX1* in nine of 417 individuals with SLE. This finding raises the possibility that individuals with AGS caused by *TREX1* mutations (as well as their heterozygous parents) may be at risk of developing SLE.

## Clinical Description

### Natural History

Pregnancy, delivery, and the neonatal period are normal in approximately 80% of infants with Aicardi-Goutières syndrome (AGS) [Rice, Patrick et al 2007]. However, brain calcifications can be identified in utero [Le Garrec et al 2005] and 20% of cases, mainly those caused by *TREX1* mutations, present at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, a picture reminiscent of congenital infection.

All other affected infants present at variable times after the first few days of life, frequently after a period of apparently normal development. The majority of these later-presenting infants exhibit subacute onset of a severe encephalopathy characterized by extreme irritability, intermittent sterile pyrexias, loss of skills, and slowing of head growth. The encephalopathic phase usually lasts several months. The opinion of most pediatricians caring for such children is that the disease does not progress beyond the encephalopathic period. Death is usually considered to be secondary to the neurologic damage incurred during the initial disease episode, not to further regression.

*RNASEH2B* mutations are associated with a significantly later age at presentation (in a number of cases after age 12 months) and a lower childhood mortality, with several individuals known to be alive beyond age 18 years with no signs of disease progression. Some individuals with *RNASEH2B* mutations have relatively preserved intellectual function, with one individual having a completely normal IQ and head circumference documented at age 19 years, his only feature of AGS being spastic cerebral palsy [McEntagart et al 1998].

Typically, affected individuals have peripheral spasticity, dystonic posturing particularly of the upper limbs, truncal hypotonia, and poor head control. Seizures have been reported in 53% of individuals with AGS [Rice, Patrick et al 2007]. A number of children demonstrate a marked startle reaction to sudden noise, and the differentiation from epilepsy can be difficult. Almost

all affected individuals have severe intellectual and physical impairment. Variability in the severity of the neurologic outcome can be observed among siblings. Most affected children exhibit a severe acquired microcephaly; however, in those children with preserved intellect, head circumference is normal.

Hearing is almost always normal.

Visual function varies from normal to cortical blindness. Ocular structures are almost invariably normal on examination.

Between 20% and 50% of affected individuals [Goutieres et al 1998; Rice, Patrick et al 2007] have seizures that are usually generalized tonic-clonic or focal tonic. Massive myoclonic jerks have been reported [Lanzi et al 2002].

As many as 40% of affected individuals [Rice, Patrick et al 2007] have skin lesions with chilblain puffy swelling on the fingers and toes and sometimes the ear and other pressure points (e.g., elbows) [Tolmie et al 1995, Stephenson 2002] (see Figure 4). The cutaneous lesions may be complicated by periungual infection and necrosis. Chilblains are associated with mutations in all four genes.

Infrequently observed features of AGS are summarized in Table 2.

Table 2. Infrequent Features Seen in a Cohort of 123 Individuals with Mutation-Positive AGS

| Feature | Mutated Gene | | | |
|---|---|---|---|---|
| | *TREX1* | *RNASEH2B* | *RNASEH2C* | *RNASEH2A* |
| Scoliosis | 0 | 9 | 0 | 0 |
| Cardiomegaly | 4 | 0 | 1 | 1 |
| Abnormal antibody profile | 2 | 3 | 1 | 0 |
| Preserved language | 0 | 6 | 0 | 0 |
| Demyelinating peripheral neuropathy | 1 | 2 | 1 | 0 |
| Congenital glaucoma | 2 | 0 | 1 | 0 |
| Micropenis | 1 | 0 | 1 | 0 |
| Hypothyroidism | 1 | 1 | 0 | 0 |
| Insulin-dependent diabetes mellitus | 1 | 1 | 0 | 0 |
| Transitory deficiency of antidiuretic hormone | 1 | 0 | 0 | 0 |

Rice, Patrick et al 2007

**Pathology—Neuropathologic findings.** The main neuropathologic findings [Kumar et al 1998, Barth 2002]:

- Severe microcephaly
- Diffuse but non-homogeneous demyelination with astrocytosis; absence of signs of storage or myelin breakdown
- Multiple wedge-shaped microinfarcts in the neocortex and cerebellar cortex, suggestive of a microangiopathy
- Calcific deposits in the white matter, thalami, basal ganglia, and dentate nuclei
- Calcification in the media, adventitia, and perivascular spaces of small vessels

- Inflammation in the leptomeninges and areas of necrosis

**Skin biopsy.** Tubuloreticular inclusions in endothelial cells are observed in some individuals, particularly those with high circulating levels of IFN-α [Rich 1981, Goutières et al 1998]. On direct immunofluorescence, fine, granular staining for IgM may be seen in the basement membrane [Stephenson 2002].

### Genotype-Phenotype Correlations

The phenotypes associated with mutations in each of the four genes known to cause AGS overlap, but the early-onset neonatal form of AGS is most frequently seen in association with *TREX1*, *RNASEH2A*, and *RNASEH2C* mutations while the later-onset presentation (sometimes occurring after several months of normal development and occasionally associated with remarkably preserved neurologic function) is most frequently seen in association with *RNASEH2B* mutations [Rice, Patrick et al 2007].

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) [Rice, Patrick et al 2007].

### Nomenclature

The microcephaly-intracranial calcification syndrome (MICS, also known as "pseudo-TORCH syndrome" or "Baraitser-Reardon syndrome") was previously differentiated from AGS on the basis of congenital microcephaly and the presence of non-neurologic abnormalities, including elevation of liver enzymes, hepatomegaly, and thrombocytopenia at birth [Reardon et al 1994]. However, recent studies have shown that these same features can be seen in mutation-positive persons with AGS [Rice, Patrick, et al 2007]. Of note, in the majority of MICS cases reported no information is available on CSF cell count and IFN-α concentration; thus it is probable that most cases of MICS are in fact AGS.

**"Familial systemic lupus erythematosus."** Dale et al (2000) described two children of consanguineous parents with early-onset encephalopathy, intracranial calcifications, chilblain skin lesions, and the progressive production of high levels of autoantibodies. CSF was not analyzed. These cases most likely represent AGS [Aicardi & Goutieres 2000].

### Prevalence

The actual frequency of AGS is unknown.

Mutations have been found in affected individuals of all ethnic origins [Crow, Hayward et al 2006; Crow, Leitch et al 2006; Rice, Patrick et al 2007]:

- The most prevalent *TREX1* mutation in AGS is a missense change (c.341G>A) that is particularly common in people from Northern Europe.
- The most prevalent *RNASEH2B* mutation is a missense change (c.529G>A) that was seen in 62% of *RNASEH2B* mutated alleles.
- The *RNASEH2C* mutation c.205C>T (p.Arg69Trp) is seen particularly frequently in Pakistani families and represents an ancient founder mutation [Rice, Patrick et al 2007].

## Differential Diagnosis

*For current information on availability of genetic testing for disorders included in this section, see* GeneTests Laboratory Directory. —ED.

Calcification of the basal ganglia is a nonspecific finding seen in many diseases. However, in the context of an early-onset encephalopathy, conditions to consider include the following:

- **TORCH congenital infections** are the most common conditions in the differential and the most important to rule out because misdiagnosis would result in erroneous counseling as to risk of recurrence.
- **The microcephaly-intracranial calcification syndrome** (MICS, also known as "pseudo-TORCH syndrome" or "Baraitser-Reardon syndrome"). Considering the phenotype of early-onset Aicardi-Goutière syndrome (AGS) cases (see Clinical Description) [Reardon et al 1994], it seems likely that most cases of MICS are in fact AGS (see Nomenclature). However, a number of other phenotypes are associated with neonatal intracranial calcification [Knoblauch et al 2003, Gardner et al 2005]; thus this phenotype undoubtedly represents a heterogeneous group of diseases.

  Superficially, at least, the MRI scan findings in AGS with frontotemporal white matter changes and cysts can cause confusion with Alexander disease, megalencephalic leukoencephalopathy with subcortical cysts, and childhood ataxia with central nervous system hypomyelination/vanishing white matter disease. The degree of white matter loss at an early age has also prompted consideration of Pelizeaus-Merzbacher disease in some individuals. In general terms, AGS should be considered in the differential diagnosis of an unexplained leukoencephalopathy. This clinical point is of particular importance because intracranial calcification is not always recognized on MRI, the initial imaging modality employed in most medical facilities.
- **Familial hemophagocytic lymphohistiocytosis** (FHL) is also an inherited autoimmune disorder with sterile pyrexias, cerebrospinal fluid lymphocytosis, and occasional cerebral calcification; but serious confusion with AGS has not been reported. Inheritance is autosomal recessive.
- **Cockayne syndrome,** a leukodystrophy with striocerebellar calcifications characterized by its distinctive facial features, dwarfism, nerve deafness, cataracts, retinal dystrophy, and skin photosensitivity. Inheritance is autosomal recessive.
- **Pontocerebellar atrophy type II** can be suggested by the combination of brain stem and cerebellar atrophy with marked dystonia in individuals with early-onset AGS.
- **Neonatal lupus erythematous.** Prendiville et al (2003) described basal ganglia calcifications and patchy white matter attenuation in infants with neonatal lupus erythematosus reminiscent of the imaging findings seen in AGS. These children demonstrated extensive erythematous skin lesions distinct from the chilblain lesions seen in AGS. The authors reported normal neurologic outcome in these cases.
- **Hoyeraal-Hreidarsson syndrome.** This X-linked disorder caused by mutations in the *DKC1* gene presents in the first months of life with microcephaly, cerebellar hypoplasia, and intracerebral calcifications. Affected males develop a pancytopenia that persists (in contrast to the thrombocytopenia seen in some individuals with AGS, which usually resolves in the first few weeks of life).
- **Mitochondrial cytopathies,** including Leigh syndrome and the familial mitochondrial encephalopathy with intracerebral calcifications described by Samson et al (1994). See Mitochondrial Disorders Overview.
- **3-hydroxyisobutyric aciduria.** Chitayat et al (1992) described monozygotic male twins, born to nonconsanguineous parents, who had dysmorphic facial features, microcephaly, migrational brain disorder, and congenital intracerebral calcification.

- Blau et al (2003) described three individuals with microcephaly, severe mental and motor retardation, dyskinesia, spasticity, and occasional seizures with extremely high CSF concentrations of neopterin and biopterin and low CSF concentration of 5-methyltetrahydrofolate. Although reported as having AGS, they did not demonstrate a CSF lymphocytosis or elevation of IFN-α concentration. Thus, these individuals may have an undefined syndrome within the group of infants with encephalopathy and intracranial calcifications. However, molecular genetic testing of the four genes known to be associated with AGS has not yet been undertaken in this group and it is now known that a similar pterin profile can be observed in individuals who are mutation positive for AGS [Rice, Patrick et al 2007].
- **Cerebroretinal microangiopathy with calcifications and cysts** (CRMCC, also known as Coats plus, Labrune syndrome, and leukoencephalopathy with cysts/LCC) [Crow, McMenamin et al 2004; Linnankivi et al 2006]. A number of children with this condition have been misdiagnosed as having a later-onset form of AGS; however, Briggs et al (2008) have also presented evidence of very early onset of this condition. CRMCC is not associated with raised CSF white cells, IFN-α, or pterins; affected individuals do not have mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, or *RNASEH2C*.

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Aicardi-Goutières syndrome (AGS), the following evaluations are recommended:

- Developmental assessment
- Assessment of feeding and nutritional status
- Ophthalmologic examination
- EEG to evaluate for seizures if suspected

### Treatment of Manifestations

The following are appropriate:

- Chest physiotherapy and vigorous treatment of respiratory complications
- Attention to diet and method of feeding to assure adequate caloric intake
- Management of seizures using standard protocols

### Surveillance

Surveillance includes the following:

- Assessment for glaucoma in the first few months of life
- Monitoring of the spine for the development of scoliosis
- Monitoring for signs of insulin-dependent diabetes mellitus (IDDM) and hypothyroidism

### Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

### Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

### Other

Corticosteroids can lower the CSF concentration of interferon [PG Barth 2003, personal communication]; the clinical benefit of such treatment is unproven.

**Genetics clinics** are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

**Support groups** have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the* GeneTests Clinic Directory.

### Mode of Inheritance

*RNASEH2A*-related Aicardi-Goutières syndrome (AGS), *RNASEH2B*-related AGS, *RNASEH2C*-related AGS, and most cases of *TREX1*-related AGS are inherited in an autosomal recessive manner.

Rarely, *TREX1*-related AGS is the result of a *de novo* dominant mutation.

### Risk to Family Members — Autosomal Recessive Inheritance

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic; however, the findings of Lee-Kirsch, Gong et al (2007) and Richards et al (2007) suggest that heterozygotes may be at increased risk of developing later-onset SLE or RVCL.

**Sibs of a proband**

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

**Offspring of a proband.** Most individuals with AGS do not reproduce.

**Other family members of a proband.** Each sib of the proband's parents is at a 50% risk of being a carrier.

### Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis, once the disease-causing mutations have been identified in the family.

### Risk to Family Members — *De Novo* Dominant Mutation

**Parents of a proband**

- To date, the three probands with AGS who had a heterozygous *TREX1* mutation had the disorder as the result of a *de novo* mutation [Rice, Patrick et al 2007; Crow, personal communication].
- Parents of a proband are not affected.

**Sibs of a proband**

- Because heterozygous *TREX1* mutations resulting in AGS occur *de novo*, the risk to the sibs of a proband is small.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

**Offspring of a proband.** Most individuals with AGS do not reproduce.

**Other family members of a proband.** Because heterozygous *TREX1* mutations resulting in AGS occur *de novo*, other family members of a proband are not at increased risk.

### Related Genetic Counseling Issues

**Family planning.** The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy. It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are at risk of being carriers.

**DNA banking.** DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

### Prenatal Testing

**Molecular genetic testing.** Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele(s) must be identified in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

**Percutaneous umbilical blood sampling (PUBS).** Among families without a molecular diagnosis in which the clinical diagnosis has otherwise been established, sampling of fetal

blood in the third trimester of at-risk pregnancies has in some cases been used to measure serum concentration of IFN-α [Le Garrec 2005, Desanges et al 2006]. The false positive and negative rates associated with such testing are unknown [P Lebon, personal communication].

**Preimplantation genetic diagnosis (PGD)** may be available for families in which the disease-causing mutation(s) has/have been identified. For laboratories offering PGD, see Testing.

## Molecular Genetics

*Information in the Molecular Genetics tables is current as of initial posting or most recent update.* —ED.

Table A. Molecular Genetics of Aicardi-Goutieres Syndrome

| Locus Name | Gene Symbol | Chromosomal Locus | Protein Name |
|---|---|---|---|
| AGS1 | *TREX1* | 3p21.3-p21.2 | Three prime repair exonuclease 1 |
| AGS2 | *RNASEH2B* | 13q14.3 | Ribonuclease H2 subunit B |
| AGS3 | *RNASEH2C* | 11q13.2 | Ribonuclease H2 subunit C |
| AGS4 | *RNASEH2A* | 19p13.13 | Ribonuclease H2 subunit A |

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Aicardi-Goutieres Syndrome

| | |
|---|---|
| 225750 | AICARDI-GOUTIERES SYNDROME 1; AGS1 |
| 606034 | RIBONUCLEASE H2, SUBUNIT A; RNASEH2A |
| 610181 | AICARDI-GOUTIERES SYNDROME 2; AGS2 |
| 610326 | RIBONUCLEASE H2, SUBUNIT B; RNASEH2B |
| 610329 | AICARDI-GOUTIERES SYNDROME 3; AGS3 |
| 610330 | RIBONUCLEASE H2, SUBUNIT C; RNASEH2C |
| 610333 | AICARDI-GOUTIERES SYNDROME 4; AGS4 |

Table C. Genomic Databases for Aicardi-Goutieres Syndrome

| Gene Symbol | Entrez Gene | HGMD |
|---|---|---|
| *TREX1* | 84126 (MIM No. 606605) | TREX1 |
| *RNASEH2B* | 79621 (MIM No. 610326) | RNASEH2B |
| *RNASEH2C* | 84153 (MIM No. 610330) | RNASEH2C |
| *RNASEH2A* | 10535 (MIM No. 606034) | RNASEH2A |

For a description of the genomic databases listed, click here.

**Note:** HGMD requires registration.

### *TREX1(AGS1)*

**Normal allelic variants:** *TREX1* has one exon. GenBank accession numbers: AAK07616, AF319569.

Note: A great deal of confusion re *TREX1* and the overlapping *ATRIP* gene exists in the databases. *TREX1* and *ATRIP* are distinct genes that encode distinct proteins; they are not known to be relevant to one another [Yang et al 2007].

**Pathologic allelic variants:** Stop mutations, deletions, and insertions are common in *TREX1*, but the most prevalent mutation is a missense change (c.341G>A) that affects the dimerization of the TREX1 protein (three prime repair exonuclease 1) and is likely to be a functional null allele. The c.341G>A mutation is particularly common in people from Northern Europe.

Affected individuals are almost always homozygotes or compound heterozygotes for mutations within the same gene. However, one child with clinically typical AGS had a *de novo* heterozygous mutation in *TREX1* [Rice, Newman et al 2007], which changed an amino acid that is one of four residues essential for coordinating two magnesium ions involved in *TREX1* DNA binding and catalysis; thus it seems likely that the mutation represents a gain of function (see Table 3).

Table 3. *TREX1(AGS1* ) Pathologic Allelic Variants Discussed in This *GeneReview*

| DNA Nucleotide Change [1] | Protein Amino Acid Change | Reference Sequence [2] |
|---|---|---|
| c.58_59insG [1] | p.Glu20GlyfsX81 | AAK07616<br>AF319569 |
| c.212_213dupTG | p.Ala72TrpfsX16 | |
| c.341G>A [1] | p.Arg114His | |
| c.365T>C | p.Val122Ala | |
| c.366_368dupGGC | p.Ala123dup | |
| c.397delC | p.Leu133CysfsX26 | |
| c.393_408dup | p.Glu137ProfsX23 | |
| c.490C>T | p.Arg164X | |
| c.500delG | p.Ser166ThrfsX12 | |
| c.598G>T | p.Asp200Asn | |
| c.600_601insGAT | p.Asp200dup | |
| c.602t>A | p.Val201Asp | |
| c.609_662dup | p.Leu204_Ala221dup | |
| c.625_628dupCAGT | p.Trp210SerfsX31 | |
| c.868_885del | p.Pro289_Ala294del | |
| c.907A>C | p.Thr303Pro | |

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Frequency of alleles for this gene: c.341G>A (50%); c.58_59insG (1%); remaining alleles (<1%) [Rice, Patrick et al 2007]
2. www.ncbi.nlm.nih.gov/Genbank

**Normal gene product:** *TREX1* is a single-exon gene encoding a 314-amino acid residue protein.

*TREX1* represents the major 3'↓5' DNA exonuclease activity measured in mammalian cells. The protein has three conserved sequence motifs known as Exo I, II, and III. These motifs contain four conserved acidic residues that participate in coordination of divalent metal ions required for catalysis. In addition, the protein contains a C-terminal domain of about 75 amino acids, which is probably involved in subcellular localization of the protein, and a polyproline motif that may be involved in the interaction with other proteins. *TREX1* appears to have a role in the disposal of ssDNA produced as a normal replication intermediate during S phase [Yang et al 2007].

**Abnormal gene product:** The most prevalent mutation in *TREX1* is a missense change (c. 341G>A) that affects the dimerization of the TREX1 protein (3' repair exonuclease 1) and is likely to be a functional null allele.

***RNASEH2B***

**Normal allelic variants:** The *RNASEH2B* gene has 11 exons and codes for a 308-amino acid protein.

**Pathologic allelic variants:** Almost all mutations so far identified in *RNASEH2B* are missense [Crow, Leitch et al 2006; Rice, Patrick et al 2007] (see Table 4).

Table 4. *RNASEH2B* Pathologic Allelic Variants Discussed in This *GeneReview*

| DNA Nucleotide Change [1] | Protein Amino Acid Change | Reference Sequence [2] |
|---|---|---|
| c.64+1G>A | -- | NM_024570.1 NP_078846.1 |
| c.136+1delG [1] | -- | |
| c.244+1G>T | -- | |
| c.436+1G>T | -- | |
| c.510+1G>A | -- | |
| c.128C>A | p.Pro43His | |
| c.132T>A | p.Cys44X | |
| c.172C>T | p.Gln58X | |
| c.179T>G | p.Leu60Arg | |
| c.218G>T | p.Trp73Leu | |
| c.247G>A | p.Gly83Ser | |
| c.257A>G | p.His86Arg | |
| c.412C>T | p.Leu138Phe | |
| c.476G>T | p.Ser159Ile | |
| c.485A>C | p.Lys162Thr | |
| c.488C>T [1] | p.Thr163Ile | |
| c.529G>A [1] | p.Ala177Thr | |
| c.547C>A | p.Val183Met | |
| c.554T>G [1] | p.Val185Gly | |
| c.655T>C | p.Tyr219His | |

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Frequency of alleles for this gene: c.529G>A (62%); c.488C>T (7%); c.554T>G (7%); c.136+1 delG (4%); remaining alleles (<2%) [Rice, Patrick et al 2007].
2. www.ncbi.nlm.nih.gov/Genbank

**Normal gene product:** The precise function of the ribonuclease H2 subunit B protein within the human RNASEH2 complex is unknown.

**Abnormal gene product:** Mutations in genes encoding any of the three subunits of the ribonuclease H2 complex are thought to cause AGS resulting from a loss of enzymatic function.

***RNASEH2C***

**Normal allelic variants:** *RNASEH2C* is a four-exon gene encoding a 164-amino acid protein.

**Pathologic allelic variants:** All mutations so far identified in *RNASEH2C* are missense [Crow, Leitch et al 2006; Rice, Patrick et al 2007] (see Table 5).

Table 5. *RNASEH2C* Pathologic Allelic Variants Discussed in This *GeneReview*

| DNA Nucleotide Change [1] | Protein Amino Acid Change | Reference Sequence [2] |
|---|---|---|
| c.38G>A | p.Arg13His | NM_032193.3<br>NP_115569.2 |
| c.205C>T [1] | p.Arg69Trp | |
| c.227C>T | p.Pro76Leu | |
| c.412C>T | p.Pro138Leu | |
| c.428A>T | p.Lys143Ile | |
| c.451C>T | p.Pro151Ser | |

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Frequency of alleles: c.205C>T (72%); all other alleles seen only in single families
2. www.ncbi.nlm.nih.gov/Genbank

**Normal gene product:** The function of ribonuclease H2 subunit C (RNASEH2C) within the RNASEH2 complex is unknown.

**Abnormal gene product:** See *RNASEH2B* Abnormal gene product.

***RNASEH2A***

**Normal allelic variants:** *RNASEH2A* has eight exons.

**Pathologic allelic variants:** Almost all mutations in *RNASEH2A* are missense [Crow, Leitch et al 2006; Rice, Patrick et al 2007] (see Table 6).

Table 6. *RNASEH2A* Pathologic Allelic Variants Discussed in This *GeneReview*

| DNA Nucleotide Change [1] | Protein Amino Acid Change | Reference Sequence [2] |
|---|---|---|
| c.109G>A | p.Gly37Ser | NM_006397.2<br>NP_006388.2 |
| c.207_208insG | p.Thr69AspfsX50 | |
| c.322C>T | p.Arg108Trp | |
| c.556C>T | p.Arg186Trp | |
| c.690C>A | p.Phe231Leu | |
| c.704G>A | p.Arg236Gln | |
| c.716_717dupGC | p.Thr239AlafsX77 | |
| c.719C>T | p.Thr241Met | |
| c.872G>A | p.Arg292His | |

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Frequency of each allele is less than 1%.
2. www.ncbi.nlm.nih.gov/Genbank

**Normal gene product:** The *RNASEH2A* gene encodes the ribonuclease H2 subunit A, which comprises 299 amino acids. Ribonuclease H (RNASEH) enzymes endonucleolytically cleave ribonucleotides from RNA:DNA duplexes. RNASEH2 has been proposed to function in the

removal of lagging strand Okazaki fragment RNA primers during DNA replication, as well as in the excision of single ribonucleotides from DNA:DNA duplexes. However, the precise biologic function of the human RNASEH2 complex is uncertain.

**Abnormal gene product:** See *RNASEH2B* Abnormal gene product.

## Resources

*GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search* GeneTests *for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

**International Aicardi-Goutieres Syndrome Association (IAGSA)**
Via Vittadini 1
27100 Pavia
Italy
**Phone:** 39 0382 33342
**Email:** iagsa@libero.it
www.aicardi-goutieres.com

**United Leukodystrophy Foundation (ULF)**
2304 Highland Drive
Sycamore IL 60178
**Phone:** 800-728-5483; 815-895-3211
**Email:** office@ulf.org
Aicardi-Goutieres Syndrome

## References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

### Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

### Literature Cited

Aicardi J, Goutieres F. A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. Ann Neurol. 1984;15:49–54. [PubMed: 6712192]

Aicardi J, Goutieres F. Systemic lupus erythematosus or Aicardi-Goutieres syndrome? Neuropediatrics. 2000;31:113. [PubMed: 10963096]

Barth PG. The neuropathology of Aicardi-Goutieres syndrome. Eur J Paediatr Neurol 6 Suppl A:A27-31. 2002 [PubMed: 12365358]

Blau N, Bonafe L, Krageloh-Mann I, Thony B, Kierat L, Hausler M, Ramaekers V. Cerebrospinal fluid pterins and folates in Aicardi-Goutieres syndrome: a new phenotype. Neurology. 2003;61:642–7. [PubMed: 12963755]

Briggs TA, Abdel-Salam GM, Balicki M, Baxter P, Bertini E, Bishop N, Browne BH, Chitayat D, Chong WK, Eid MM, Halliday W, Hughes I, Klusmann-Koy A, Kurian M, Nischal KK, Rice GI, Stephenson JB, Surtees R, Talbot JF, Tehrani NN, Tolmie JL, Toomes C, van der Knaap MS, Crow YJ. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC). Am J Med Genet A. 2008;146:182–90. [PubMed: 18076099]

Chitayat D, Meagher-Villemure K, Mamer OA, O'Gorman A, Hoar DI, Silver K, Scriver CR. Brain dysgenesis and congenital intracerebral calcification associated with 3-hydroxyisobutyric aciduria. J Pediatr. 1992;121:86–9. [PubMed: 1625099]

Crow YJ, Black DN, Ali M, Bond J, Jackson AP, Lefson M, Michaud J, Roberts E, Stephenson JB, Woods CG, Lebon P. Cree encephalitis is allelic with Aicardi-Goutieres syndrome: implications for the pathogenesis of disorders of interferon alpha metabolism. J Med Genet. 2003;40:183–7. [PubMed: 12624136]

Crow YJ, Hayward BE, Parmar R, Robins P, Leitch A, Ali M, Black DN, van Bokhoven H, Brunner HG, Hamel BC, Corry PC, Cowan FM, Frints SG, Klepper J, Livingston JH, Lynch SA, Massey RF, Meritet JF, Michaud JL, Ponsot G, Voit T, Lebon P, Bonthron DT, Jackson AP, Barnes DE, Lindahl T. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. Nat Genet. 2006;38:917–20. [PubMed: 16845398]

Crow YJ, Leitch A, Hayward BE, Garner A, Parmar R, Griffith E, Ali M, Semple C, Aicardi J, Babul-Hirji R, Baumann C, Baxter P, Bertini E, Chandler KE, Chitayat D, Cau D, Dery C, Fazzi E, Goizet C, King MD, Klepper J, Lacombe D, Lanzi G, Lyall H, Martinez-Frias ML, Mathieu M, McKeown C, Monier A, Oade Y, Quarrell OW, Rittey CD, Rogers RC, Sanchis A, Stephenson JB, Tacke U, Till M, Tolmie JL, Tomlin P, Voit T, Weschke B, Woods CG, Lebon P, Bonthron DT, Ponting CP, Jackson AP. Mutations in genes encoding ribonuclease H2 subunits cause Aicardi-Goutieres syndrome and mimic congenital viral brain infection. Nat Genet. 2006;38:910–6. [PubMed: 16845400]

Crow YJ, Massey RF, Innes JR, Pairaudeau PW, Rowland Hill CA, Woods CG, Ali M, Livingston JH, Lebon P, Nischall K, McEntagart M, Hindocha N, Winter RM. Congenital glaucoma and brain stem atrophy as features of Aicardi-Goutieres syndrome. Am J Med Genet. 2004;129A:303–7. [PubMed: 15326633]

Crow YJ, McMenamin J, Haenggeli CA, Hadley DM, Tirupathi S, Treacy EP, Zuberi SM, Browne BH, Tolmie JL, Stephenson JB. Coats' plus: a progressive familial syndrome of bilateral Coats' disease, characteristic cerebral calcification, leukoencephalopathy, slow Neuropediatrics. 2004;35:10–9. [PubMed: 15002047]

Dale RC, Tang SP, Heckmatt JZ, Tatnall FM. Familial systemic lupus erythematosus and congenital infection-like syndrome. Neuropediatrics. 2000;31:155–8. [PubMed: 10963105]

Desanges C, Lebon P, Bauman C, Vuillard E, Garel C, Cordesse A, Oury JF, Crow Y, Luton D. Elevated interferon-alpha in fetal blood in the prenatal diagnosis of Aicardi-Goutieres syndrome. Fetal Diagn Ther. 2006;21:153–5. [PubMed: 16354995]

Fogli A, Wong K, Eymard-Pierre E, Wenger J, Bouffard JP, Goldin E, Black DN, Boespflug-Tanguy O, Schiffmann R. Cree leukoencephalopathy and CACH/VWM disease are allelic at the EIF2B5 locus. Ann Neurol. 2002;52:506–10. [PubMed: 12325082]

Gardner RJ, Chow CW, Simpson I, Fink AM, Meagher SE, White SM. Severe fetal brain dysgenesis with focal calcification. Prenat Diagn. 2005;25:362–4. [PubMed: 15906425]

Goutieres F, Aicardi J, Barth PG, Lebon P. Aicardi-Goutieres syndrome: an update and results of interferon-alpha studies. Ann Neurol. 1998;44:900–7. [PubMed: 9851434]

Knoblauch H, Tennstedt C, Brueck W, Hammer H, Vulliamy T, Dokal I, Lehmann R, Hanefeld F, Tinschert S. Two brothers with findings resembling congenital intrauterine infection-like syndrome (pseudo-TORCH syndrome). Am J Med Genet A. 2003;120:261–5. [PubMed: 12833411]

Kumar D, Rittey C, Cameron AH, Variend S. Recognizable inherited syndrome of progressive central nervous system degeneration and generalized intracranial calcification with overlapping phenotype of the syndrome of Aicardi and Goutieres. Am J Med Genet. 1998;75:508–15. [PubMed: 9489795]

Lanzi G, Fazzi E, D'Arrigo S. Aicardi-Goutieres syndrome: a description of 21 new cases and a comparison with the literature. Europ J Paediatr Neurol 6(Suppl A):9-A22. 2002 [PubMed: 12365365]

Lanzi G, Fazzi E, D'Arrigo S, Orcesi S, Maraucci I, Uggetti C, Bertini E, Lebon P. The natural history of Aicardi-Goutieres syndrome: follow-up of 11 Italian patients. Neurology. 2005;64:1621–4. [PubMed: 15883328]

Le Garrec M, Doret M, Pasquier JC, Till M, Lebon P, Buenerd A, Escalon J, Gaucherand P. Prenatal diagnosis of Aicardi-Goutieres syndrome. Prenat Diagn. 2005;25:28–30. [PubMed: 15662687]

Lebon P, Meritet JF, Krivine A, Rozenberg F. Interferon and Aicardi-Goutieres syndrome. Europ J Paediatr Neurol 6 Suppl A:47-53. 2002 [PubMed: 12365361]

Lee-Kirsch MA, Gong M, Schulz H, Ruschendorf F, Stein A, Pfeiffer C, Ballarini A, Gahr M, Hubner N, Linne M. Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. Am J Hum Genet. 2006;79:731–7. [PubMed: 16960810]

Lee-Kirsch MA, Chowdhury D, Harvey S, Gong M, Senenko L, Engel K, Pfeiffer C, Hollis T, Gahr M, Perrino FW, Lieberman J, Hubner N. A mutation in TREX1 that impairs susceptibility to granzyme A-mediated cell death underlies familial chilblain lupus. J Mol Med. 2007;85:531–7. [PubMed: 17440703]

Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, de Silva U, Bailey SL, Witte T, Vyse TJ, Kere J, Pfeiffer C, Harvey S, Wong A, Koskenmies S, Hummel O, Rohde K, Schmidt RE, Dominiczak AF, Gahr M, Hollis T, Perrino FW, Lieberman J, Hubner N. Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet. 2007;39:1065–7. [PubMed: 17660818]

Linnankivi T, Valanne L, Paetau A, Alafuzoff I, Hakumaki JM, Kivela T, Lonnqvist T, Makitie O, Paakkonen L, Vainionpaa L, Vanninen R, Herva R, Pihko H. Cerebroretinal microangiopathy with calcifications and cysts. Neurology. 2006;67:1437–43. [PubMed: 16943371]

McEntagart M, Kamel H, Lebon P, King MD. Aicardi-Goutieres syndrome: an expanding phenotype. Neuropediatrics. 1998;29:163–7. [PubMed: 9706629]

Prendiville JS, Cabral DA, Poskitt KJ, Au S, Sargent MA. Central nervous system involvement in neonatal lupus erythematosus. Pediatr Dermatol. 2003;20:60–7. [PubMed: 12558850]

Reardon W, Hockey A, Silberstein P, Kendall B, Farag TI, Swash M, Stevenson R, Baraitser M. Autosomal recessive congenital intrauterine infection-like syndrome of microcephaly, intracranial calcification, and CNS disease. Am J Med Genet. 1994;52:58–65. [PubMed: 7977464]

Rice G, Newman WG, Dean J, Patrick T, Parmar R, Flintoff K, Robins P, Harvey S, Hollis T, O'Hara A, Herrick AL, Bowden AP, Perrino FW, Lindahl T, Barnes DE, Crow YJ. Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi-Goutieres syndrome. Am J Hum Genet. 2007;80:811–5. [PubMed: 17357087]

Rice G, Patrick T, Parmar R, Taylor CF, Aeby A, Aicardi J, Artuch R, Montalto SA, Bacino CA, Barroso B, Baxter P, Benko WS, Bergmann C, Bertini E, Biancheri R, Blair EM, Blau N, Bonthron DT, Briggs T, Brueton LA, Brunner HG, Burke CJ, Carr IM, Carvalho DR, Chandler KE, Christen HJ, Corry PC, Cowan FM, Cox H, D'Arrigo S, Dean J, De Laet C, De Praeter C, Dery C, Ferrie CD, Flintoff K, Frints SG, Garcia-Cazorla A, Gener B, Goizet C, Goutieres F, Green AJ, Guet A, Hamel BC, Hayward BE, Heiberg A, Hennekam RC, Husson M, Jackson AP, Jayatunga R, Jiang YH, Kant SG, Kao A, King MD, Kingston HM, Klepper J, van der Knaap MS, Kornberg AJ, Kotzot D, Kratzer W, Lacombe D, Lagae L, Landrieu PG, Lanzi G, Leitch A, Lim MJ, Livingston JH, Lourenco CM, Lyall EG, Lynch SA, Lyons MJ, Marom D, McClure JP, McWilliam R, Melancon SB, Mewasingh LD, Moutard ML, Nischal KK, Ostergaard JR, Prendiville J, Rasmussen M, Rogers RC, Roland D, Rosser EM, Rostasy K, Roubertie A, Sanchis A, Schiffmann R, Scholl-Burgi S, Seal S, Shalev SA, Corcoles CS, Sinha GP, Soler D, Spiegel R, Stephenson JB, Tacke U, Tan TY, Till M, Tolmie JL, Tomlin P, Vagnarelli F, Valente EM, Van Coster RN, Van der Aa N, Vanderver A, Vles JS, Voit T, Wassmer E, Weschke B, Whiteford ML, Willemsen MA, Zankl A, Zuberi SM, Orcesi S, Fazzi E, Lebon P, Crow YJ. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. Am J Hum Genet. 2007;81:713–25. [PubMed: 17846997]

Rich SA. Human lupus inclusions and interferon. Science. 1981;213:772–5. [PubMed: 6166984]

Richards A, van den Maagdenberg AM, Jen JC, Kavanagh D, Bertram P, Spitzer D, Liszewski MK, Barilla-Labarca ML, Terwindt GM, Kasai Y, McLellan M, Grand MG, Vanmolkot KR, de Vries B, Wan J, Kane MJ, Mamsa H, Schafer R, Stam AH, Haan J, de Jong PT, Storimans CW, van Schooneveld MJ, Oosterhuis JA, Gschwendter A, Dichgans M, Kotschet KE, Hodgkinson S, Hardy TA, Delatycki MB, Hajj-Ali RA, Kothari PH, Nelson SF, Frants RR, Baloh RW, Ferrari MD, Atkinson JP. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. Nat Genet. 2007;39:1068–70. [PubMed: 17660820]

Robertson NJ, Stafler P, Battini R, Cheong J, Tosetti M, Bianchi MC, Cox IJ, Cowan FM, Cioni G. Brain lactic alkalosis in Aicardi-Goutieres syndrome. Neuropediatrics. 2004;35:20–6. [PubMed: 15002048]

Samson JF, Barth PG, de Vries JI, Menko FH, Ruitenbeek W, van Oost BA, Jakobs C. Familial mitochondrial encephalopathy with fetal ultrasonographic ventriculomegaly and intracerebral calcifications. Eur J Pediatr. 1994;153:510–6. [PubMed: 7957369]

Sanchis A, Cervero L, Bataller A, Tortajada JL, Huguet J, Crow YJ, Ali M, Higuet LJ, Martinez-Frias ML. Genetic syndromes mimic congenital infections. J Pediatr. 2005;146:701–5. [PubMed: 15870678]

Stephenson JB. Aicardi-Goutieres syndrome - observations of the Glasgow school. Eur J Paediatr Neurol 6 Suppl A:67-70. 2002 [PubMed: 12365363]

Tolmie JL, Shillito P, Hughes-Benzie R, Stephenson JB. The Aicardi-Goutieres syndrome (familial, early onset encephalopathy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis). J Med Genet. 1995;32:881–4. [PubMed: 8592332]

Yang YG, Lindahl T, Barnes DE. Trex1 exonuclease degrades ssDNA to prevent chronic checkpoint activation and autoimmune disease. Cell. 2007;131:873–86. [PubMed: 18045533]

## Chapter Notes

### Acknowledgments

We would like to thank Dr Gillian Rice for her help in compiling the gene mutation data.

### Revision History

- 17 April 2008 (me) Comprehensive update posted to live Web site
- 29 June 2005 (me) Review posted to live Web site
- 1 September 2004 (ja) Original submission

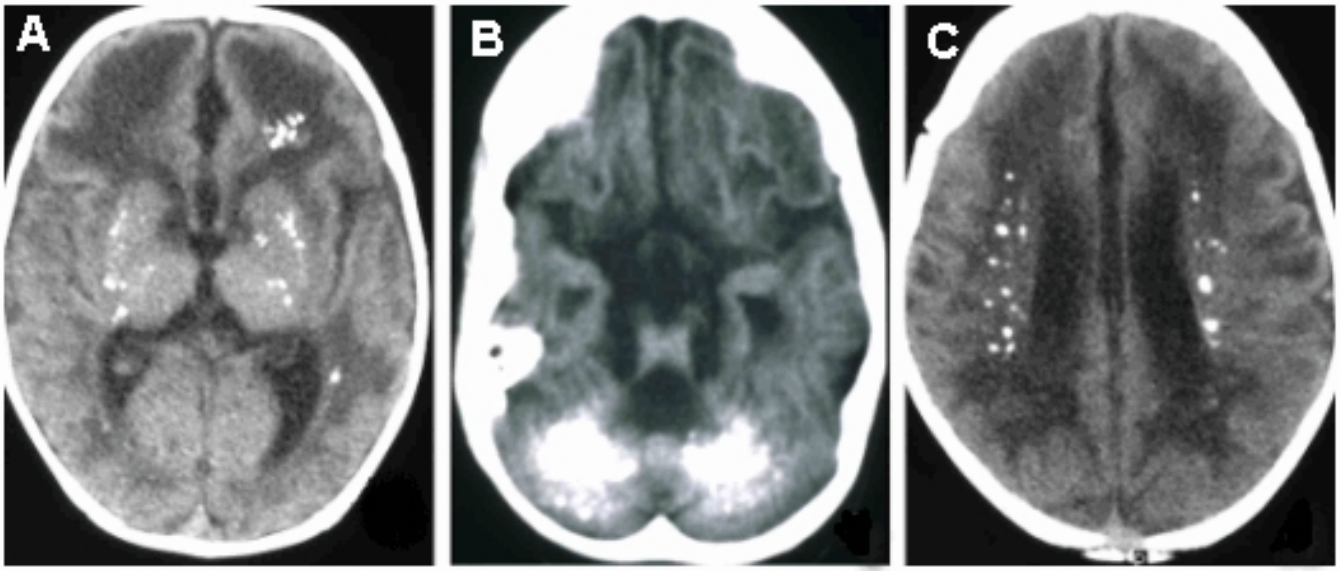


**Figure 1.** Examples of intracranial calcification on CT scan in individuals with AGS. Calcification is seen in the basal ganglia (panel A), in the dentate nuclei of the cerebellum (panel B), and in a periventricular distribution (panel C).
Figure originally published in *The American Journal of Human Genetics*, University of Chicago Press, October 2007.

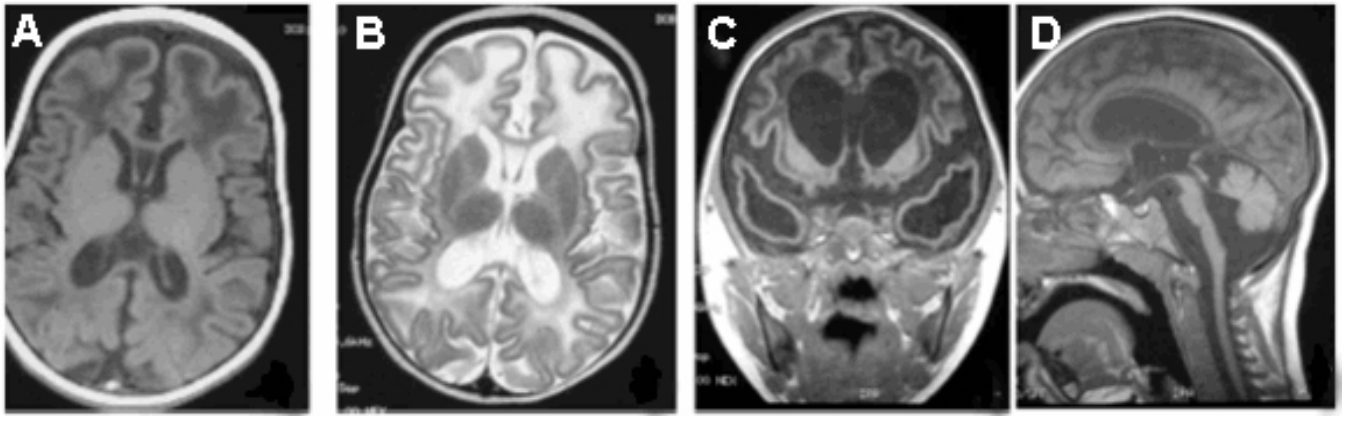


**Figure 2.** The spectrum of brain changes seen on MRI in AGS. Hypointensity on T1-weighted imaging (panel A) and hyperintensity on T2-weighted imaging (panel B) of the white matter, extensive bitemporal cystic lesions (panel C), and significant thinning of the brain stem and cerebellar atrophy (panel D).
Figure originally published in *The American Journal of Human Genetics*, University of Chicago Press, October 2007.

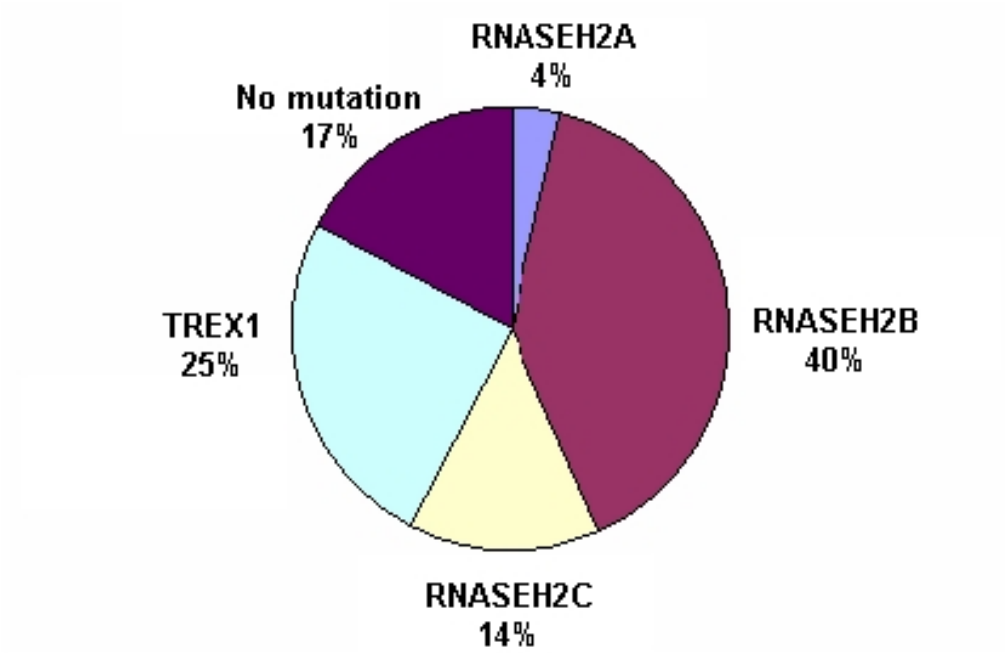


**Figure 3.** Percentages of 127 families with AGS with biallelic mutations in *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, and *TREX1*, as well as those with no identifiable mutation(s)

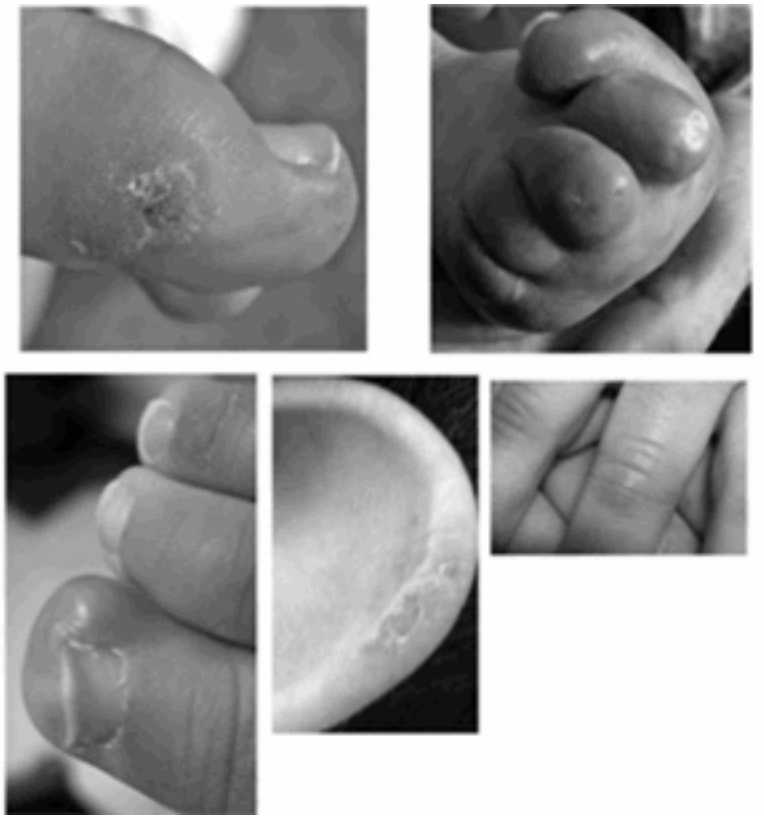

**Figure 4.** Examples of chilblains seen in AGS.
Figure originally published in *The American Journal of Human Genetics*, University of Chicago Press, October 2007