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Aicardi-Goutières Syndrome

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Summary

Clinical characteristics

Most characteristically, Aicardi-Goutières syndrome (AGS) manifests as an early-onset encephalopathy that usually, but not always, results in severe intellectual and physical disability. A subgroup of infants with AGS present at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, a picture highly suggestive of congenital infection. Otherwise, most affected infants present at variable times after the first few weeks 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. Over time, as many as 40% develop chilblain skin lesions on the fingers, toes, and ears. It is becoming apparent that atypical, sometimes milder, cases of AGS exist, and thus the true extent of the phenotype associated with pathogenic variants in the AGS-related genes is not yet known.

Diagnosis/testing

The diagnosis of AGS is established in a proband with typical clinical findings and characteristic abnormalities on cranial CT (calcification of the basal ganglia and white matter) and MRI (leukodystrophic changes); AND/OR by identification of one of the following:

- Biallelic pathogenic variants in *ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, or *TREX1*
- Specific heterozygous autosomal dominant pathogenic variants in *TREX1* and *ADAR*
- A variety of heterozygous autosomal dominant pathogenic variants in *IFIH1*

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.

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Surveillance: Monitoring for signs of diabetes insipidus in the neonatal period; repeat ophthalmologic examinations at least for the first few years of life to evaluate for evidence of glaucoma; monitoring for evidence of scoliosis, insulin-dependent diabetes mellitus, and hypothyroidism.

Genetic counseling

AGS is most frequently inherited in an autosomal recessive manner; in a few instances the disease can result from specific *de novo* or inherited autosomal dominant pathogenic variants in *ADAR* or *TREX1*, and a variety of heterozygous autosomal dominant pathogenic variants in *IFIH1*. 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. Individuals with AGS do not typically reproduce. Once the pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk for AGS, and preimplantation genetic testing are possible.

Diagnosis

In its most characteristic form, Aicardi-Goutières syndrome (AGS) can be considered an early-onset encephalopathy associated with significant intellectual and physical disability.

Suggestive Findings

Aicardi-Goutières syndrome (AGS) **should be suspected** in individuals with the following clinical, neuroimaging, and supportive laboratory findings [Goutières et al 1998, Lanzi et al 2002, Rice et al 2007b, Livingston et al 2013].

Clinical features

- Encephalopathy and/or significant intellectual disability
- Acquired microcephaly during the first year of life
- Dystonia and spasticity
- Sterile pyrexias
- Hepatosplenomegaly
- Chilblain lesions on the feet, hands, ears, and sometimes more generalized mottling of the skin. See Figure 1.

Exclusion criteria include the following:

- Evidence of prenatal/perinatal infection including, but not limited to, CMV, toxoplasmosis, rubella, herpes simplex, Zika, and HIV
- Evidence of a known other metabolic disorder or neurodegenerative disorder

Neuroimaging

- Calcification (best visualized on CT scan) of the basal ganglia, particularly the putamen, globus pallidus and thalamus but also extending into the white matter, sometimes in a para- (rather than true peri-) ventricular distribution [Lanzi et al 2002, Uggetti et al 2009, Livingston et al 2013]. See Figure 2.

  Note: Intracranial calcification is not always recognized on MRI, the initial imaging modality employed in most units.

- White matter changes, particularly affecting the frontotemporal regions with (in severe cases) temporal lobe cyst-like formation. See Figure 3.

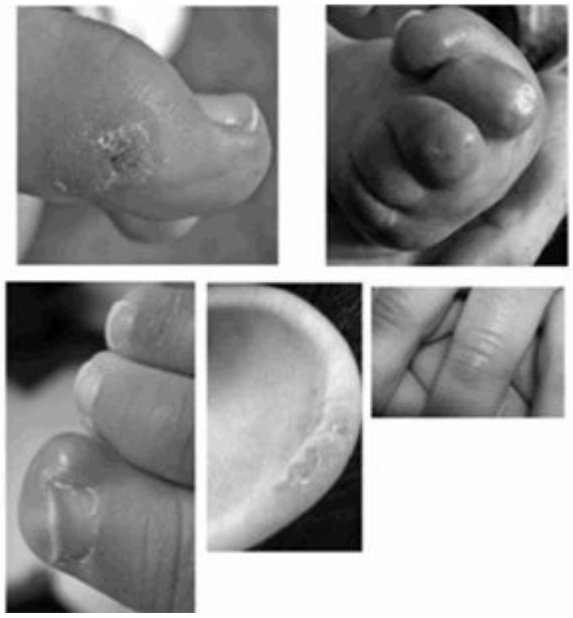

Figure 1. Examples of chilblains seen in AGS

Rice et al [2007b]; reprinted with permission of *The American Journal of Human Genetics*, University of Chicago Press.

On MRI, appears on T_2-weighted images as a hyperintense signal most commonly located around the horns of the ventricles (Figure 3B)

- Cerebral atrophy, which may be progressive and involve the periventricular white matter and sulci

  Cerebellar atrophy and brain stem atrophy may also be prominent (Figure 3D) [Crow et al 2004a, Sanchis et al 2005].
- Bilateral striatal necrosis
- Intracerebral vasculopathy including intracranial stenosis, moyamoya, and aneurysms

Supportive Laboratory Findings

Peripheral blood

- Positive interferon signature identified using quantitative PCR analysis of RNA/cDNA [Rice et al 2013a, Crow et al 2015]
- Elevated liver enzymes
- Thrombocytopenia

Cerebrospinal fluid (CSF)

- Chronic CSF leukocytosis, defined as more than five lymphocytes/mm^3 CSF.
  - Typical values range from five to 100 lymphocytes/mm^3 [Goutières et al 1998, Rice et al 2007b, Rice et al 2013a].
  - 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 et al 2007b].
- Increased interferon-alpha (IFN-α) activity in the CSF (normal: <2 IU/mL)

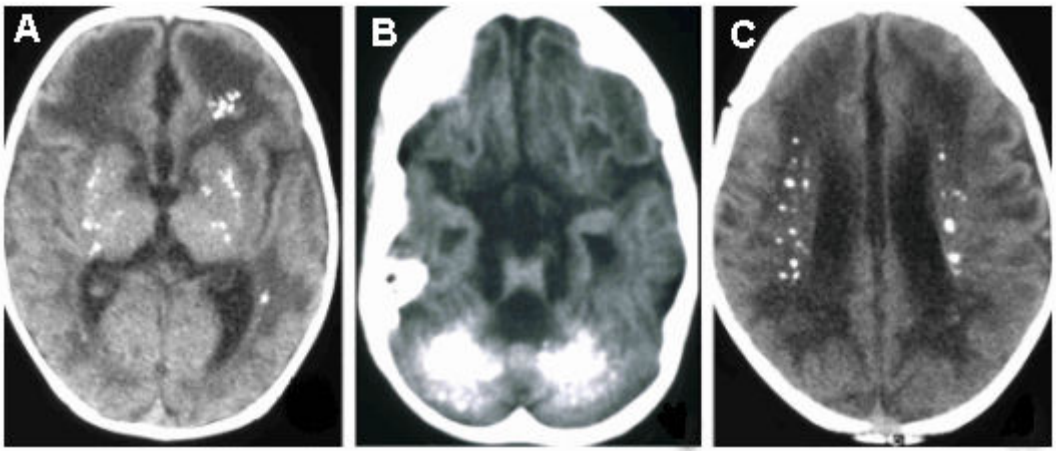

Figure 2. Examples of intracranial calcification on CT scan in individuals with AGS. Calcification is seen:

A. In the basal ganglia;

B. In the dentate nuclei of the cerebellum;

C. In a periventricular distribution.

Rice et al [2007b]; reprinted with permission of *The American Journal of Human Genetics*, University of Chicago Press.

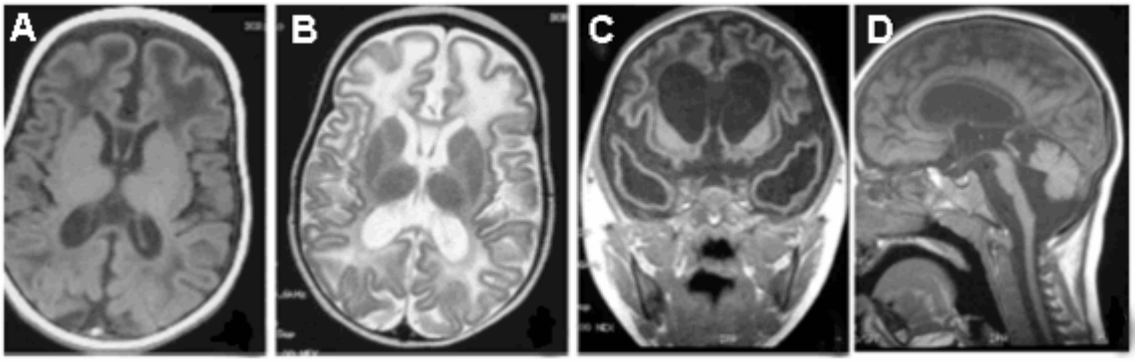

Figure 3. The spectrum of brain changes seen on MRI in AGS

A. Hypointensity on T_1-weighted imaging of the white matter

B. Hyperintensity on T_2-weighted imaging of the white matter

C. Extensive bitemporal cystic lesions

D. Significant thinning of the brain stem and cerebellar atrophy

Rice et al [2007b]; reprinted with permission of *The American Journal of Human Genetics*, University of Chicago Press.

- Recorded IFN-α activity is usually highest in the early stages of the disease. The IFN-α CSF activity can normalize over the first three to four years of life [Rice et al 2007b, Rice et al 2013a].
- Recorded IFN-α activity is usually higher in CSF than in blood, where it may be normal.
- High IFN-α activity has been identified in fetal blood at 26 weeks' gestation [Desanges et al 2006].

- Increased concentration of neopterin in the CSF [Rice et al 2007b]
  - Levels are highest in the early stages of the disease and can normalize over time.
  - Levels of the neurotransmitter metabolites 5HIAA, HVA, and 5MTHF are normal.

Establishing the Diagnosis

The diagnosis of AGS **is established** in a proband with typical clinical findings and characteristic abnormalities on cranial CT (calcification of the basal ganglia and white matter) and MRI (leukodystrophic changes) and/or by the identification of biallelic pathogenic (or likely pathogenic) variants in *ADAR*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, or *TREX1*; specific heterozygous autosomal dominant pathogenic (or likely pathogenic) variants in *TREX1* and *ADAR*; or a variety of heterozygous autosomal dominant pathogenic (or likely pathogenic) variants in *IFIH1*.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing can be pursued based on the individual's ethnicity and/or in the order in which pathogenic variants most commonly occur (see Table 1).

- If only one pathogenic variant is identified in *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, or *SAMHD1*, gene-targeted deletion/duplication analysis can be considered next.
- Gene-targeted deletion/duplication analysis may also be considered if a heterozygous pathogenic variant that is not known to be associated with autosomal dominant AGS is identified in *TREX1* or *ADAR*.

A multigene panel that includes *ADAR*, *IFIH1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *TREX1*, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *ADAR*, *IFIH1, RNASEH2A*, *RNASEH2B*, *RNASEH2C, SAMHD1,* and *TREX1*) fails to confirm a diagnosis in an individual with features of AGS. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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

Gene [1]	Proportion of AGS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method	
		Sequence analysis [3, 4]	Gene-targeted deletion/ duplication analysis [5]
ADAR	7%	32/32 alleles [6]	Unknown [7]
IFIH1	3%	17/17 alleles [8]	Unknown [7]
RNASEH2A	5%	34/34 alleles [9]	Unknown [7]
RNASEH2B	36%	~99% [10]	Unknown [11]
RNASEH2C	12%	~99% [12, 13]	Unknown [7]
SAMHD1	13%	Up to 95% [14]	Up to 30% [14, 15]
TREX1	23%	~99% [16]	Unknown [7]
Unknown	1%	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sequence analysis of the coding regions and splice sites of *ADAR*, *IFIH1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, and *TREX1* has identified pathogenic variants in approximately 90%-95% of individuals with clinical and MRI presentation of AGS [Rice et al 2007b, Rice et al 2009, Crow et al 2015].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques including quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. 32/32 alleles were detectable by sequence analysis [Crow et al 2015]. A dominant p.Gly1007Arg variant in *ADAR* has been reported [Rice et al 2012, Livingston et al 2014a]. A recurrent *ADAR* variant, p.Pro193Ala, is seen in affected persons of European origin.
7. No deletions or duplications involving *ADAR, IFIH1, RNASEH2A*, *RNASEH2C*, or *TREX1* have been reported to cause Aicardi-Goutières syndrome.
8. Rice et al [2014], Crow et al [2015]
9. Rice et al [2007b], Crow et al [2015]
10. 90% of individuals with biallelic pathogenic variants in *RNASEH2B* are either homozygous or compound heterozygous for the missense change (p.Ala177Thr).
11. A deletion of *RNASEH2B* exons two through five has been reported [Crow et al 2015].
12. Rice et al [2007b], Crow et al [2015]
13. The *RNASEH2C* variant p.Arg69Trp is seen particularly frequently in Asian (most commonly Pakistani) families and represents an ancient founder variant [Rice et al 2007b].
14. 25/26 alleles [Rice et al 2009] and 47/67 alleles [Crow et al 2015] were detected by sequence analysis. Note: Rice et al [2009] did not perform deletion/duplication analysis and in some families in the study no pathogenic variants were detected.
15. A recurrent deletion including exon 1 has been observed in several affected individuals of Ashkenazi Jewish ancestry and very likely represents a founder variant [Ramesh et al 2010]. 20/67 alleles in Crow et al [2015] were detectable by deletion/duplication analysis; however, this study included persons of Ashkenazi Jewish descent. Note: A homozygous deletion of ≥1 exons can be suspected by the failure of exons to amplify by PCR. A recurrent splice acceptor site pathogenic variant (c.1411-2A>G) in intron 12 is seen in persons of Amish ancestry and represents an ancient founder variant [Xin et al 2011].
16. In approximately 100 individuals with *TREX1*-related AGS, all pathogenic variants were detectable by sequence analysis [Rice et al 2007b, Crow et al 2015]. A recurrent p.Arg164Ter founder variant in *TREX1* is seen in individuals of Cree ancestry. The most prevalent *TREX1* variant in AGS is a missense change (p.Arg114His) that is particularly common in people from northern Europe.

Clinical Characteristics

Clinical Description

In its most characteristic form, Aicardi-Goutières syndrome (AGS) can be considered an early-onset encephalopathy associated with significant intellectual and physical disability.

Pregnancy, delivery, and the neonatal period are normal in approximately 80% of infants with Aicardi-Goutières syndrome (AGS) [Rice et al 2007b]. However, brain calcifications can be identified in utero [Le Garrec et al 2005] and 20% of cases, mainly those caused by biallelic pathogenic variants in *TREX1*, 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 weeks 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; occasionally, however, affected individuals do appear to show progression and/or episodes of regression. Death is usually considered to be secondary to the neurologic damage incurred during the initial disease episode, not to further regression. Several affected individuals older than age 30 years show no obvious signs of disease progression.

Neurologic features. Typically, affected individuals have peripheral spasticity, dystonic posturing (particularly of the upper limbs), truncal hypotonia, and poor head control. Seizures are reported in up to half of affected children, but are usually relatively easily controlled [Goutières et al 1998, Rice et al 2007b]. A number of children demonstrate a marked startle reaction to sudden noise, and the differentiation from epilepsy can be difficult. Most affected individuals have severe intellectual and physical impairment. Variability in the severity of the neurologic outcome can be observed among sibs. Most affected children exhibit a severe acquired microcephaly; in children with preserved intellect head circumference can be normal.

Hearing is almost always normal.

Ophthalmology. Visual function varies from normal to cortical blindness. Ocular structures are almost invariably normal on examination. However, there is a risk of congenital glaucoma or later-onset glaucoma [Crow et al 2004a, Crow et al 2015].

Skin lesions. As many as 40% of affected individuals [Rice et al 2007b] have skin lesions with chilblains on the fingers and toes and sometimes the ears and other pressure points (e.g., elbows) [Tolmie et al 1995, Stephenson 2002] (see Figure 1). The cutaneous lesions may be complicated by periungual infection and necrosis.

Other

- **Intracranial large-vessel disease.** An additional previously undescribed feature of AGS, which so far appears to be almost exclusively related to biallelic pathogenic variants in *SAMHD1*, is intracranial large-vessel disease causing both intracranial stenoses (in some cases reminiscent of moyamoya disease) and aneurysms (see Phenotype Correlations by Gene) [Ramesh et al 2010, Thiele et al 2010, du Moulin et al 2011, Xin et al 2011].
- **Refractory four-limb dystonia.** Several individuals with *ADAR* pathogenic variants have been reported to demonstrate an acute or subacute onset of refractory four-limb dystonia starting between age eight months and five years [Livingston et al 2014a, Crow et al 2015] (see Phenotype Correlations by Gene).
    - Individuals can be developmentally normal at initial presentation.

- This phenotype can occur due to either biallelic pathogenic variants in *ADAR* or the autosomal dominant pathogenic variant p.Gly1007Arg in *ADAR*.
- Like other AGS-related phenotypes, bilateral striatal necrosis due to biallelic pathogenic variants in *ADAR* or the recurrent dominant pathogenic p.Gly1007Arg variant in *ADAR* are typically associated with an upregulation of ISGs.

Additional infrequently observed features of AGS are summarized in Table 2.

Table 2. Infrequent Features Seen in a Cohort of 123 Individuals with Molecularly Confirmed AGS

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

Rice et al [2007b]. Note: This paper was published before it was determined that pathogenic variants in *ADAR, IFIH1,* and *SAMHD1* can cause AGS.

Neuroimaging/neuropathologic findings

- Calcifications on neuroimaging:
  - Are often punctate but may be dense and rock-like;
  - When identified at diagnosis tend to remain stable, although progression can be observed [Lanzi et al 2002, Lanzi et al 2005];
  - Are not correlated with the severity of neurologic outcome; in rare cases, calcifications may be absent and may or may not be seen on repeat scans. Therefore, their absence does not rule out the diagnosis [Aicardi & Goutières 1984].
- The main neuropathologic findings identified in severely affected individuals include [Kumar et al 1998, Barth 2002]:
  - Diffuse but nonhomogeneous 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.

Phenotype Correlations by Gene

In general, the early-onset neonatal form of AGS is most frequently seen in association with biallelic pathogenic variants in *RNASEH2A*, *RNASEH2C*, *or TREX1*. 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 biallelic pathogenic variants in *RNASEH2B*, *SAMHD1*, or *ADAR* but may also be seen in individuals who have an autosomal dominant heterozygous pathogenic variant in *ADAR* or *IFIH1* [Crow et al 2015].

Mortality is correlated with genotype: 34% of individuals with *RNASEH2A*, *RNASEH2C*, and *TREX1* pathogenic variants were known to have died compared to 8% with *RNASEH2B* pathogenic variants (p=0.001) [Rice et al 2007b]. The mortality associated with other genotypes is less clear.

ADAR. Pathogenic variants in *ADAR* have been associated with a clinical presentation of acute bilateral striatal necrosis.

A subgroup of individuals with *ADAR* pathogenic variants can present with symmetric signal changes in the caudate and putamen, often associated with swelling and later shrinkage in the context of an acute or subacute onset of refractory four-limb dystonia. Cases have been identified with onset as late as age four years on a background of completely normal development [La Piana et al 2014, Livingston et al 2014a].

ADAR-related disease should be considered in the differential diagnosis of apparently nonsyndromic bilateral striatal necrosis (BSN) with severe dystonia of varying evolution. The finding of an interferon signature provides a useful screening test for the presence of *ADAR* pathogenic variants in this context.

RNASEH2B. Some individuals with biallelic pathogenic variants in *RNASEH2B* have relatively preserved intellectual function, with a few having a completely normal IQ and head circumference [McEntagart et al 1998].

RNASEH2C. A family with a recurrent Asian founder variant in *RNASEH2C* and striking intrafamilial variability has been described [Crow et al 2015].

SAMHD1

- Intracerebral vasculopathy, including intracranial stenosis and aneurysms, is observed more frequently in individuals who have biallelic pathogenic variants in *SAMHD1*.
- Dale et al [2010] reported two sibs who had biallelic null variants in *SAMHD1*. The older girl showed mild intellectual disability with microcephaly. Her younger brother had significant spastic paraparesis with normal intellect and head size. Both children had an unclassified chronic inflammatory skin condition with chilblains and recurrent mouth ulcers. One of the sibs had a chronic progressive deforming arthropathy of the small and large joints with secondary contractures. Similar joint involvement was described by Ramantani et al [2010] (see also Crow et al [2015]).
- Biallelic pathogenic variants in *SAMHD1* are most frequently associated with chilblains and glaucoma [Crow et al 2015].

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 persons with AGS in whom pathogenic variants in one of the associated genes have been identified [Rice et al 2007b]. 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 & Goutières 2000]. Additional individuals with AGS who have signs and symptoms similar to systemic lupus erythematosus have also been described.

Prevalence

The actual frequency of AGS is unknown.

Pathogenic variants have been found in affected individuals of all ethnic origins [Crow et al 2006a, Crow et al 2006b, Rice et al 2007b, Rice et al 2013b] (see Table 1).

Genetically Related (Allelic) Disorders

Other phenotypes caused by pathogenic variants in *ADAR*, *IFIH1*, *RNASEH2B*, and *TREX1* are listed in Table 3.

Table 3. Allelic Disorders

Disorder	*ADAR*	*IFIH1*	*RNASEH2B*	*SAMHD1*	*TREX1* [1]
Dyschromatosis symmetrica hereditaria 1 (DSH) [2]	X				
"Pure" spastic paraparesis [3] or childhood-onset paraparesis with normal intellect [4]	X	X	X		
Autosomal dominant retinal vasculopathy with cerebral leukodystrophy (RVCL) [5]					X
Systemic lupus erythematosus (SLE) [6]	X	X			X
Cree encephalitis [7]					X

Table 3. continued from previous page.

Disorder	*ADAR*	*IFIH1*	*RNASEH2B*	*SAMHD1*	*TREX1* [1]
Familial chilblain lupus (FLE) [8]				X	X

1. Mutation of *TREX1* can be associated with additional phenotypes not included in this table [Rice et al 2015].
2. The heterozygous *ADAR* p.Gly1007Arg variant, which has been shown to cause autosomal dominant AGS [Rice et al 2012], was previously described in two individuals with DSH demonstrating neurodegeneration with dystonia and intracranial calcification [Tojo et al 2006, Kondo et al 2008].
3. Crow et al [2014a], Crow et al [2015]
4. Rice et al [2014]
5. Richards et al [2007] have shown that C terminus mutation of *TREX1* causes 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, unproven, that the heterozygous parents of children with AGS caused by *TREX1* pathogenic variants, at least those with variants in the C terminus of the gene, may be at risk of developing RVCL.
6. Lee-Kirsch et al [2007b] found heterozygous pathogenic variants in *TREX1* in nine of 417 individuals with SLE. This finding raises the possibility that individuals with AGS caused by mutation of *TREX1* (as well as their heterozygous parents) may be at risk of developing signs and symptoms similar to SLE.
7. Linkage analysis and measurement of CSF concentration of IFN-α suggested that AGS and Cree encephalitis were allelic [Crow et al 2003]; this was confirmed when molecular genetic testing revealed that all children with Cree encephalitis are homozygous for the p.Arg164Ter pathogenic variant in *TREX1*.
8. Rice et al [2007a] described a heterozygous *TREX1* pathogenic variant in affected members of a family with chilblain lupus; a second distinct pathogenic variant was subsequently described by Lee-Kirsch et al [2007a]. Additional pathogenic variants have been described. FLE may also be caused by a heterozygous pathogenic variant in *SAMHD1* [Ravenscroft et al 2011].

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *RNASEH2A* or *RNASEH2C*.

Differential Diagnosis

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.

  Note: Other congenital infections, such as those associated with Zika and HIV, should also be considered in the differential diagnosis.

- **The microcephaly-intracranial calcification syndrome (MICS).** Given the phenotype of early-onset Aicardi-Goutières syndrome (AGS) cases (see Clinical Characteristics) [Reardon et al 1994], it is 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 (see Nomenclature).

- **Band-like calcification polymicrogyria (BLC-PMG; pseudo-TORCH syndrome)** (OMIM 251290) [Abdel-Salam et al 2008, Briggs et al 2008] shows radiologic and clinical overlap with AGS, demonstrating intracranial calcification and significant psychomotor retardation with microcephaly and epilepsy. The condition can be differentiated by the observation of polymicrogyria (which has never been reported in AGS) and the identification of biallelic pathogenic variants in *OCLN* [O'Driscoll et al 2010].

- Superficially, at least, the MRI scan findings in AGS with frontotemporal white matter changes and cysts can be confused 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 hypomyelination 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.

- **Classic Cockayne syndrome (CS type 1),** a leukodystrophy with striocerebellar calcifications, is variably characterized by its distinctive facial features, dwarfism, nerve deafness, cataracts, retinal dystrophy, and skin photosensitivity. Inheritance is autosomal recessive.
- **Neonatal lupus erythematosus.** 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,** a severe form of dyskeratosis congenita, is caused by mutation in *DKC1* (X-linked) or *TINF2* (autosomal dominant). Hoyeraal Hreidarsson syndrome 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 also Mitochondrial Disorders Overview.
- **3-hydroxyisobutyric aciduria** (OMIM 236795). 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 intellectual disability 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, it is now known that a similar pterin profile can be observed in individuals with molecularly confirmed AGS [Rice et al 2007b].
- **Cerebroretinal microangiopathy with calcifications and cysts (CRMCC; Coats plus)** (OMIM 612199) is caused by biallelic pathogenic variants in *CTC1* [Crow et al 2004b, Linnankivi et al 2006, Anderson et al 2012, Livingston et al 2014b].
- **Leukoencephalopathy, brain calcifications, and cysts (Labrune syndrome)** (OMIM 614561)

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs 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
- Consultation with a clinical geneticist and/or genetic counselor

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:

- Monitoring for signs of diabetes insipidus in the neonatal period
- Assessment for glaucoma at least for the first few years of life
- Monitoring of the spine for the development of scoliosis
- Monitoring for signs of insulin-dependent diabetes mellitus and hypothyroidism

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Research into the role of immunosuppressive agents in the treatment of AGS is ongoing [Crow & Rehwinkel 2009, Crow et al 2014].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

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

Note: The description of intracranial large-vessel disease in association with biallelic pathogenic variants in *SAMHD1* raises important questions about the management of such individuals. The occlusive and aneurysmal arteriopathies described could be amenable to treatment (revascularization for the former and coiling or clipping for the latter). Moreover, the likely inflammatory basis of the arteriopathy suggests that immunosuppression may play a role in management. A key question is whether inflammatory disease is active at the time of clinical presentation, or whether the arterial abnormalities observed represent the end result of a now-quiescent inflammatory process.

Given the lack of evidence, no definitive statement about these issues can be made at present. However, the potential for intervention exists, and it could be argued that some individuals (e.g., those with lesser psychomotor problems) warrant such intervention and should be actively screened for intracranial arteriopathy, if only by close inspection of the vasculature at the base of the brain seen on routine MRI. Chilblains were present in all the affected individuals described by Ramesh et al [2010], and it may be that their presence predicts an increased risk for intracranial vasculopathy.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

RNASEH2A, *RNASEH2B*, *RNASEH2C*, and *SAMHD1*-related Aicardi-Goutières syndrome (AGS) is inherited in an autosomal recessive manner.

TREX1 and *ADAR*-related AGS can be inherited in an autosomal recessive or autosomal dominant manner depending on the specific pathogenic variant.

IFIH1-related Aicardi-Goutières syndrome (AGS) is inherited in an autosomal dominant manner.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one AGS-related pathogenic variant).
- Heterozygotes (carriers) are not at risk of developing AGS; however, the findings of Lee-Kirsch et al [2007b] and Richards et al [2007] suggest that heterozygotes may be at increased risk of developing later-onset systemic lupus erythematosus (SLE) or retinal vasculopathy with cerebral leukodystrophy (RVCL), depending on the specific gene and pathogenic variant involved (see Genetically Related Disorders).

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.
- Heterozygotes (carriers) are not at risk of developing AGS; however, heterozygotes may be at increased risk of developing later-onset systemic lupus erythematosus (SLE) or retinal vasculopathy with cerebral leukodystrophy (RVCL), depending on the specific gene and pathogenic variant involved (see Genetically Related Disorders).

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

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an AGS-related pathogenic variant.

Carrier (heterozygote) detection. Carrier testing for at-risk relatives requires prior identification of the AGS-related pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- To date, most probands with autosomal dominant AGS have had the disorder as a result of a *de novo* *TREX1*, *ADAR*, or *IFIH1* pathogenic variant [Rice et al 2007b, Haaxma et al 2010, Rice et al 2012, Abe et al 2014].

Vertical transmission of pathogenic variants in *TREX1* (p.Asp18Asn; Abe et al [2013]) and *ADAR* (p.Gly1007Arg; Rice et al [2012], Livingston et al [2014a]) has been reported.

- Molecular genetic testing is recommended for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant. Another possible explanation is germline mosaicism in a parent (though theoretically possible, no instances of germline mosaicism have been reported).

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected, the risk to the sibs is 50%.
- If the *TREX1*, *ADAR*, or *IFIH1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant AGS has a 50% chance of inheriting the AGS-related pathogenic variant; however, most individuals with AGS do not reproduce.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at 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 affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing for AGS are possible.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **International Aicardi-Goutières Syndrome Association (IAGSA)**
  Italy
  Email: associazione.iagsa@tiscali.it; iagsa@libero.it
  www.aicardi-goutieres.org

- **MedlinePlus**
  Aicardi-Goutieres syndrome
- **United Leukodystrophy Foundation (ULF)**
  224 North Second Street
  Suite 2
  DeKalb IL 60115
  Phone: 800-728-5483 (toll-free); 815-748-3211
  Fax: 815-748-0844
  Email: office@ulf.org
  Aicardi-Goutieres Syndrome
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Aicardi-Goutieres Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ADAR	1q21.3	Double-stranded RNA-specific adenosine deaminase	ADAR database	ADAR	ADAR
IFIH1	2q24.2	Interferon-induced helicase C domain-containing protein 1	IFIH1 database	IFIH1	IFIH1
RNASEH2A	19p13.13	Ribonuclease H2 subunit A	RNASEH2A @ LOVD	RNASEH2A	RNASEH2A
RNASEH2B	13q14.3	Ribonuclease H2 subunit B	RNASEH2B @ LOVD	RNASEH2B	RNASEH2B
RNASEH2C	11q13.1	Ribonuclease H2 subunit C	RNASEH2C @ LOVD	RNASEH2C	RNASEH2C
SAMHD1	20q11.23	Deoxynucleoside triphosphate triphosphohydrolase SAMHD1		SAMHD1	SAMHD1
TREX1	3p21.31	Three prime repair exonuclease 1	Three prime repair exonuclease 1 (TREX1) @ LOVD	TREX1	TREX1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Aicardi-Goutieres Syndrome (View All in OMIM)

146920	ADENOSINE DEAMINASE, RNA-SPECIFIC; ADAR
225750	AICARDI-GOUTIERES SYNDROME 1; AGS1
606034	RIBONUCLEASE H2, SUBUNIT A; RNASEH2A

Table B. continued from previous page.

606609	3-PRIME @REPAIR EXONUCLEASE 1; TREX1
606754	SAM DOMAIN- AND HD DOMAIN-CONTAINING PROTEIN 1; SAMHD1
606951	INTERFERON-INDUCED HELICASE C DOMAIN-CONTAINING PROTEIN 1; IFIH1
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
612952	AICARDI-GOUTIERES SYNDROME 5; AGS5
615010	AICARDI-GOUTIERES SYNDROME 6; AGS6
615846	AICARDI-GOUTIERES SYNDROME 7; AGS7

ADAR

Gene structure. *ADAR* is a single-copy 16-exon gene that encodes two main isoforms constitutively expressed in mammalian cells: a truncated protein (p110 NP_001020278.1) encoded by a transcript variant of 15 exons (NM_001025107.2) and an IFN inducible full-length protein (p150 NP_001102.2) induced isoform encoded by transcript variant NM_001111.4. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The majority of pathogenic variants in *ADAR* result in autosomal recessive disease. Missense, nonsense, frameshift, and splice site pathogenic variants have been reported. One missense variant, p.Pro193Ala, is common in individuals of European origin. One dominant variant, p.Gly1007Arg, has been reported [Rice et al 2012, Livingston et al 2014a].

Table 4. Selected *ADAR* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.577C>G	p.Pro193Ala	NM_001111.4 NP_001102.2
c.3019G>A	p.Gly1007Arg	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. DRADA, double-stranded RNA-specific adenosine deaminase, is a modular protein with a C-terminal deaminase catalytic domain, three centrally located dsRNA-binding domains (dsRBDs) and one or two N-terminal Z-DNA–binding domains; compared with p110, the p150 isoform of human DRADA possesses an additional 295 N-terminal amino acids containing a nuclear export signal and an extra Z-DNA/Z-RNA-binding domain.

Abnormal gene product. Pathogenic variants in *ADAR* are believed to cause AGS as a result of loss of protein activity; the precise mechanism leading to disease is unclear.

IFIH1

Gene structure. *IFIH1* has 16 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. All *IFIH1* pathogenic variants associated with AGS to date have been missense variants that cause dominant disease.

Normal gene product. *IFIH1* encodes the interferon-induced helicase C domain-containing protein 1, a cytosolic double-stranded RNA receptor.

Abnormal gene product. Pathogenic variants in *IHIF1* associated with AGS encode missense variants that cause up-regulation of type I interferon signaling [Rice et al 2014].

RNASEH2A

Gene structure. *RNASEH2A* has eight exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The majority of pathogenic variants in *RNASEH2A* are missense; splicing and frameshift pathogenic variants have also been reported [Crow et al 2006b, Rice et al 2007b] (see Table 5).

Table 5. Selected *RNASEH2A* Pathogenic Variants

DNA Nucleotide Change [1]	Predicted Protein Change	Reference Sequences
c.69G>A [2]	p.Val23=	NM_006397.2 NP_006388.2
c.75C>T [2]	p.Arg25=	
c.109G>A	p.Gly37Ser	
c.207_208insG	p.Thr69AspfsTer50	
c.322C>T	p.Arg108Trp	
c.556C>T	p.Arg186Trp	
c.690C>A	p.Phe231Leu	
c.704G>A	p.Arg236Gln	
c.716_717dupGC	p.Thr239AlafsTer77	
c.719C>T	p.Thr241Met	
c.872G>A	p.Arg292His	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Frequency of each allele is less than 1%.
2. Two synonymous variants (c.69G>A and c.75C>T) in *RNASEH2A* are pathogenic due to an alteration in RNA splicing [Rice et al 2013b].

Normal gene product. *RNASEH2A* 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 in the context of AGS is uncertain.

Abnormal gene product. See ***RNASEH2B*, Abnormal gene product**.

RNASEH2B

Gene structure. *RNASEH2B* has 11 exons and codes for a 308-amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Almost all pathogenic variants so far identified in *RNASEH2B* are missense [Crow et al 2006b, Rice et al 2007b] (see Table 6).

The frequency of alleles identified in affected individuals is:

- p.Ala177Thr (62%)
- p.Thr163Ile (7%)
- p.Val185Gly (7%)
- c.136+1delG (4%)
- Remaining alleles (<2%) [Rice et al 2007b]

Table 6. Selected *RNASEH2B* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.64+1G>A	--	NM_024570.1
c.136+1delG	--	
c.244+1G>T	--	
c.436+1G>T	--	
c.510+1G>A	--	
c.128C>A	p.Pro43His	NM_024570.1 NP_078846.1
c.132T>A	p.Cys44Ter	
c.172C>T	p.Gln58Ter	
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	p.Thr163Ile	
c.529G>A	p.Ala177Thr	
c.547C>A	p.Val183Met	
c.554T>G	p.Val185Gly	
c.655T>C	p.Tyr219His	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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

Abnormal gene product. Pathogenic variants 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

Gene structure. *RNASEH2C* is a four-exon gene encoding a 164-amino acid protein. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. All pathogenic variants so far identified in *RNASEH2C* are missense [Crow et al 2006b, Rice et al 2007b] (see Table 7).

The frequency of alleles identified in affected individuals is:

- p.Arg69Trp (72%)
- Remaining alleles (seen only in single families)

Table 7. Selected *RNASEH2C* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.38G>A	p.Arg13His	NM_032193.3 NP_115569.2
c.205C>T	p.Arg69Trp	
c.227C>T	p.Pro76Leu	
c.412C>T	p.Pro138Leu	
c.428A>T	p.Lys143Ile	
c.451C>T	p.Pro151Ser	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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**.

SAMHD1

Gene structure. *SAMHD1* has 16 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The majority of pathogenic variants are missense, splice site, nonsense, or frameshift variants [Rice et al 2009].

Three large deletions plus a small deletion have also been identified. A large deletion of exon 1 is common among individuals of Ashkenazi Jewish descent [Crow et al 2015].

Table 8. Selected *SAMHD1* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.359_370del12	p.Asp120_His123del	NM_015474.3 NP_056289.2
c.368A>C	p.His123Pro	
c.427C>T	p.Arg143Cys	
c.428G>A	p.Arg143His	
c.433C>T	p.Arg145Ter	
c.434G>A	p.Arg145Gln	

Table 8. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.445C>T	p.Gln149Ter	
c.602T>A	p.Ile201Asn	
c.625G>A	p.Gly209Ser	
c.649_650insG	p.Phe217CysTer2	
c.760A>G	p.Met254Val	
c.1106T>C	p.Leu369Ser	
c.1153A>G	p.Met385Val	
c.1324C>T	p.Arg442Ter	
c.1411-2A>G	(splice acceptor)	
c.1503+1G>T	(splice donor)	
c.1642C>T	p.Gln548Ter	
c.1609-1G>C	(splice acceptor)	
(exons 12-16del)	--	
(8984bp promoter+ex1del)	--	NM_015474.3
(exons 1-13del)	--	

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GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. SAMHD1 is a 626-amino acid protein that consists of a SAM domain and an HD domain; the protein acts as a dNTP triphosphohydrolase [Goldstone et al 2011].

Abnormal gene product. Pathogenic variants in *SAMHD1* are believed to cause AGS as a result of mislocalization of the protein or loss of protein function.

TREX1 (*AGS1*)

Gene structure. *TREX1* has one exon. For a detailed summary of gene and protein information, see Table A, **Gene**.

Note: A great deal of confusion regarding *TREX1* and the overlapping gene *ATRIP* 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].

Pathogenic variants. Stop variants, deletions, and insertions are common in *TREX1*, but the most prevalent pathogenic variant is a missense variant (p.Arg114His) that affects the dimerization of the TREX1 protein (3' repair exonuclease 1) and is likely to be a functional null allele. The pathogenic variant p.Arg114His is particularly common in people from northern Europe.

Affected individuals are almost always homozygotes or compound heterozygotes for pathogenic variants within the same gene. However, children with clinically typical AGS had a *de novo* heterozygous pathogenic variant in *TREX1* [Rice et al 2007a, Haaxma et al 2010, Abe et al 2014] (see Table 9).

The frequency of alleles identified in affected individuals is [Rice et al 2007b]:

- p.Arg114His (50%)
- c.58_59insG (1%)
- Remaining alleles (<1%)

Table 9. Selected *TREX1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.52G>A	p.Asp18Asn	AAK07616.1 AF319569.1
c.58_59insG	p.Glu20GlyfsTer81	
c.212_213dupTG	p.Ala72Trpfster16	
c.341G>A	p.Arg114His	
c.365T>C	p.Val122Ala	
c.366_368dupGGC	p.Ala123dup	
c.397delC	p.Leu133CysfsTer26	
c.393_408dup16	p.Glu137ProfsTer23	
c.490C>T	p.Arg164Ter	
c.500delG	p.Ser166ThrfsTer12	
c.598G>T	p.Asp200Asn	
c.600_601insGAT	p.Asp200dup	
c.602T>A	p.Val201Asp	
c.609_662dup54	p.Leu204_Ala221dup	
c.625_628dupCAGT	p.Trp210SerfsTer31	
c.868_885del18	p.Pro289_Ala294del	
c.907A>C	p.Thr303Pro	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

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

TREX1 protein 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 play a role in the disposal of single-stranded DNA possibly produced as a normal replication intermediate during S phase [Yang et al 2007], or derived from retro-elements [Stetson et al 2008].

Abnormal gene product. The most prevalent pathogenic variant in *TREX1* is a missense change (p.Arg114His) that affects the dimerization of the TREX1 protein (3' repair exonuclease 1) and is likely to be a functional null allele, as are other reported frameshift variants.

Chapter Notes

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Revision History

- 22 November 2016 (ma) Comprehensive update posted live
- 13 March 2014 (me) Comprehensive update posted live
- 1 March 2012 (cd) Revision: targeted mutation analysis for the c.490C>T mutation in *TREX1* available clinically
- 19 January 2012 (cd) Revision: deletion/duplication analysis available clinically for *SAMHD1*, *TREX1*, *RNASEH2A*, and *RNASEH2B*; multigene panels available
- 4 November 2010 (me) Comprehensive update posted live
- 17 April 2008 (me) Comprehensive update posted live
- 29 June 2005 (me) Review posted live
- 1 September 2004 (ja) Original submission

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