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Aicardi Syndrome

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Summary

Clinical characteristics

Aicardi syndrome is a neurodevelopmental disorder that affects primarily females. Initially it was characterized by a typical triad of agenesis of the corpus callosum, central chorioretinal lacunae, and infantile spasms. As more affected individuals have been ascertained, it has become clear that not all affected girls have all three features of the classic triad and that other neurologic and systemic defects are common, including other brain malformations, optic nerve abnormalities, other seizure types, intellectual disability of varying severity, and scoliosis.

Diagnosis/testing

The diagnosis of Aicardi syndrome is based exclusively on clinical findings. Modified diagnostic criteria include either presence of the classic triad or the presence of two of the classic triad plus at least two other major or supporting features. A gene for Aicardi syndrome has not been identified, but several observations support a hypothesis that Aicardi syndrome is caused by *de novo* pathogenic variants in a gene on the X chromosome that is subject to X-chromosome inactivation.

Management

Treatment of manifestations: Treatment is individualized and long-term management by a pediatric neurologist with expertise in management of infantile spasms and medically refractory epilepsy is essential. Physical therapy, occupational therapy, and speech therapy should begin at the time of diagnosis. Appropriate musculoskeletal support and treatment for prevention of scoliosis-related complications is indicated.

Surveillance: Includes routine monitoring of growth, nutritional status and safety of oral intake, seizure control, developmental progress and educational needs, respiratory function and aspiration risk, and the spine and degree of scoliosis.

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Genetic counseling

With the exception of affected monozygotic twin girls, all individuals with Aicardi syndrome reported to date have represented simplex cases (i.e., a single affected family member). Parent-to-child transmission of Aicardi syndrome has not been reported, and the recurrence risk to sibs is thought to be less than 1%. While prenatal ultrasound or intrauterine MRI findings of corpus callosum agenesis and neuronal migration abnormalities may be suggestive of Aicardi syndrome, no findings are diagnostic.

Diagnosis

No consensus clinical diagnostic criteria for Aicardi syndrome have been published.

The diagnosis of Aicardi syndrome is based exclusively on clinical findings. Modified diagnostic criteria have been proposed [Sutton et al 2005, adapted from Aicardi 1999]:

- The presence of the classic triad is diagnostic for Aicardi syndrome.
- The presence of two of the classic triad plus at least two other major or supporting features is strongly suggestive of the diagnosis of Aicardi syndrome.

Classic triad

- Agenesis of the corpus callosum
- Distinctive chorioretinal lacunae
- Infantile spasms

Major features

- Cortical malformations (mostly polymicrogyria)
- Periventricular and subcortical heterotopia
- Cysts around third cerebral ventricle and/or choroid plexus
- Optic disc/nerve coloboma or hypoplasia

Supporting features

- Vertebral and rib abnormalities
- Microphthalmia
- "Split-brain" EEG
- Gross cerebral hemispheric asymmetry
- Vascular malformations or vascular malignancy

Note: Aicardi syndrome appears to be an X-linked dominant disorder with lethality in males; however, no gene or candidate region on the X chromosome has been identified (see Molecular Pathogenesis).

Clinical Characteristics

Clinical Description

Aicardi syndrome, first described by Aicardi et al [1965], is a neurodevelopmental disorder that affects primarily females [Aicardi 1999, Van den Veyver 2002, Aicardi 2005]. Initially it was characterized by a typical triad of agenesis of the corpus callosum, typical chorioretinal lacunae, and infantile spasms; however, as more affected individuals have been ascertained, it has become clear that other neurologic and systemic defects are common. Indeed, not all affected girls have all three features of the classic triad (see Table 1).

Table 1. Select Features of Aicardi Syndrome

Feature		% of Persons w/Feature	Comment
Neurologic	Seizures	>95%	Nearly all present w/infantile spasms in 1st mos of life; various other seizure types develop over time.
	ID/DD	100%	Many have severe-profound ID & do not develop language or ability to walk or sit independently; however, the degree of developmental impairment varies.
	Structural brain malformations	100%	While agenesis of the corpus callosum is part of the classic triad, virtually all have other brain malformations (e.g., heterotopias, cysts).
Ocular	Chorioretinal lacunae	100%	Typically in central part of retina (not periphery); may cause visual impairment if they involve the macula; may be bilateral or unilateral
	Optic nerve abnormalities	>90%	Colobomas & hypoplasia of optic nerves are common & → visual impairment.
Other	Costovertebral abnormalities	~50%	Fusion of vertebrae & ribs can be seen, often (along w/severe hypotonia) → scoliosis.

Based on Wong & Sutton [2018]
DD = developmental delay; ID = intellectual disability

Neurologic. The neurologic examination can reveal microcephaly, axial hypotonia, and appendicular hypertonia with spasticity often affecting one side and brisk deep tendon reflexes as well as hemiparesis [Aicardi 2005; Author, unpublished data]. Moderate-to-severe developmental delay and intellectual disability are typical, although individuals with only mild or no learning disabilities or developmental delay have been reported (reviewed in Wong & Sutton [2018]).

Many girls with Aicardi syndrome develop seizures before age three months, and most before age one year. Infantile spasms are seen early on; ongoing medically refractory epilepsy with a variety of seizure types develops over time. Common EEG findings include asynchronous multifocal epileptiform abnormalities with burst suppression and dissociation between the two hemispheres.

Brain MRI reveals dysgenesis of the corpus callosum, which is most often complete but can be partial. Polymicrogyria or pachygyria, which are predominantly frontal and perisylvian and associated with underopercularization, are typical. Periventricular and intracortical gray matter heterotopia are very common. Gross cerebral asymmetry, choroid plexus papillomas, ventriculomegaly, and intracerebral cysts, often at the third ventricle and in the choroid plexus, are frequently present [Aicardi 2005, Hopkins et al 2008]. Recently, posterior fossa and cerebellar abnormalities are increasingly recognized as important components of the phenotype [Hopkins et al 2008, Steffensen et al 2009].

Ophthalmologic. The pathognomonic chorioretinal lacunae of Aicardi syndrome are white or yellow-white, well-circumscribed, round, depigmented areas of the retinal pigment epithelium and underlying choroid with variably dense pigmentation at their borders (Figure 1) [Fruhman et al 2012] that can cluster in the posterior pole of the globe around the optic nerve. The sensory retina overlying the lacunae is usually intact but may be disorganized or entirely absent.

Almost all individuals have some ocular abnormalities. Fruhman et al [2012] described data on 40 females with Aicardi syndrome examined by a single expert ophthalmologist and retinal specialist. Of the 75 eyes that could be evaluated, all had chorioretinal lacunae. Other common optic nerve findings included:

- Coloboma (39% of eyes)
- Glial proliferation (19% of eyes)
- Severe dysplasia (17% of eyes)

- Pseudoadenomatous proliferation of the retinal pigment epithelium (14% of eyes)

All eye findings can be unilateral or bilateral and asymmetric.

Craniofacial. Characteristic facial features reported in Aicardi syndrome include a short philtrum, prominent premaxilla with resultant upturned nasal tip and decreased angle of the nasal bridge, large ears, and sparse lateral eyebrows [Sutton et al 2005].

Plagiocephaly and facial asymmetry, occasionally with cleft lip and palate (3%), have been reported. Pierre Robin sequence has been reported in a single case [Jensen & Christiansen 2004].

Skeletal. Costovertebral defects, such as hemivertebrae, block vertebrae, fused vertebrae, and missing ribs, are common and can lead to marked scoliosis in up to one third of affected individuals [Donnenfeld et al 1989]. Hip dysplasia has been reported.

Gastrointestinal. Constipation, gastroesophageal reflux, diarrhea, and feeding difficulties are perceived by parents to be the second most difficult problem to manage (after seizures) [Glasmacher et al 2007].

Extremities. Small hands, along with an increased incidence of hand malformations, have been reported [Sutton et al 2005].

Dermatologic. An increased incidence of vascular malformations and pigmentary lesions has been observed [Sutton et al 2005].

Tumors/malignancies. The incidence of tumors may be increased. A variety of rare tumor types have been reported: benign tumors such as choroid plexus papillomas [Taggard & Menezes 2000, Pianetti Filho et al 2002] and lipomas, as well as malignant tumors including angiosarcomas, hepatoblastomas, meduloblastoma, embryonal carcinomas, and teratomas [Sutton et al 2005, Wharton et al 2018].

Growth. The average heights and weights of girls with Aicardi syndrome closely follow those of the general population up to ages seven and nine years, respectively, after which the growth rate for both height and weight is lower. Growth curves for Aicardi syndrome based on parent survey data have been published [Glasmacher et al 2007]. The weight-versus-height ratio remains similar to the general population.

Endocrine. Either precocious puberty or delayed puberty may be present [Glasmacher et al 2007].

Survival. Survival in Aicardi syndrome is highly variable and likely depends on the severity of seizures. In a survey by Glasmacher et al [2007], the mean age at death was 8.3 years, although the median age of death was 18.5 years. The ages of death were distributed from before age one year to older than 23 years. The oldest surviving individual reported in this survey was age 32 years. Another paper also indicated that the survival is longer than previously reported, especially in more mildly affected individuals, with the highest risk of death at age 16 years and a probability of survival at age 27 years of 0.62 [Kroner et al 2008].

Nomenclature

Note: Aicardi syndrome is NOT related to Aicardi-Goutières syndrome, an early-onset encephalopathy.

Prevalence

Aicardi syndrome is very rare and appears to affect all ethnicities equally. Its incidence has been estimated at between 1:105,000 and 1:167,000 in the United States and between 1:93,000 and 1:99,000 in some European countries [Kroner et al 2008].

The exact prevalence of Aicardi syndrome is unknown; it has been estimated to be at least 853 in the US and over 4,000 worldwide [Kroner et al 2008].

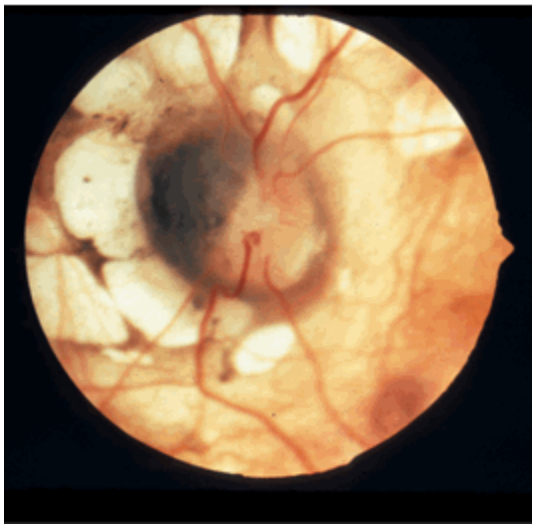

Figure 1. Classic lacunae surround the modestly dysplastic left optic disc. Note the nasal "papilla nigra" appearance and the anomalous branching patterns of the central vasculature.

Image courtesy of Dr Richard A Lewis

Differential Diagnosis

Agenesis of the corpus callosum may occur in isolation, in conjunction with other brain malformations, or as part of a larger syndrome. It has been suggested that agenesis of the corpus callosum in association with cysts that do not communicate with the ventricles and presence of subependymal heterotopia and polymicrogyria is relatively specific for Aicardi syndrome [Barkovich et al 2001].

Neuronal migration disorders, including polymicrogyria (see also Polymicrogyria Overview), pachygyria, and heterotopia, may occur as isolated malformations or as part of the phenotype associated with other syndromes or chromosome abnormalities.

Infantile spasms are observed in most girls with Aicardi syndrome, but this type of seizure is not specific for Aicardi syndrome. Infantile spasms may occur in isolation or as part of the phenotype of other syndromes, inborn errors of metabolism, or chromosome disorders.

Hereditary disorders. See Table 2.

Table 2. Genes of Interest in the Differential Diagnosis of Aicardi Syndrome

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder			
			Neurologic	Ophthalmologic	Other	Distinguishing from AIC
COX7B *HCCS* *NDUFB11*	Microphthalmia w/ linear skin defects syndrome	XL	Corpus callosum agenesis, seizures, ID	Microphthalmia, cataract, coloboma	Linear skin defects	Characteristic linear skin defects
FLNA	X-linked periventricular heterotopia	XL	Neuronal migration defects, seizures, ID	None	–	No ophthalmic abnormalities

Table 2. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features of DiffDx Disorder			
			Neurologic	Ophthalmologic	Other	Distinguishing from AIC
KIF11	MCLMR (OMIM 152950)	AD	Severe microcephaly, ID	Peripheral retinal defects	Lymphedema	Microcephaly is severe, neuronal migration defects uncommon, chorioretinal changes peripheral, & optic nerves normal. [1]
PLK4	MCCRP2 (OMIM 616171)	AR	Severe microcephaly, ID	Cataract, microcornea	Short stature	Microcephaly is severe.
PORCN	Focal dermal hypoplasia (Goltz syndrome)	XL	Normal & ID	Microphthalmia, coloboma	Cutis aplasia, telangectasias & other dermatologic abnormalities	Characteristic skin defects
TSC1 *TSC2*	Tuberous sclerosis complex	AD	Infantile spasms, cortical tubers	Achromic retinal patches	Renal cysts	Absence of characteristic eye findings of Aicardi syndrome
TUBGCP4	MCCRP3 (OMIM 616335)	AR	Severe microcephaly, ID	Peripheral retinal defects, microphthalmia	–	Microcephaly is severe, chorioretinal changes peripheral, & optic nerves normal. [1]
TUBGCP6	MCCRP1 (OMIM 251270)	AR	Severe microcephaly, ID	Peripheral retinal defects, microphthalmia	Short stature	Microcephaly is severe, chorioretinal changes peripheral, & optic nerves normal. [1]

AD = autosomal dominant; AIC = Aicardi syndrome; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; MCCRP = microcephaly and chorioretinopathy, autosomal recessive; MCLMR = microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability; MOI = mode of inheritance; XL = X-linked

1. In contrast to AIC, in which chorioretinal lacunae are central & optic nerves almost always involved

Syndromes of unknown cause

- **Orofaciodigital syndrome type IX** (OFD9; OMIM 258865). Although chorioretinal lacunae are virtually pathognomonic for Aicardi syndrome, they have also been reported in OFD .
- **Oculocerebrocutaneous syndrome** (OMIM 164180) characterized by orbital cysts and anophthalmia or microphthalmia, focal skin defects, brain malformations that include polymicrogyria, periventricular nodular heterotopias, enlarged lateral ventricles, and agenesis of the corpus callosum, is predominant in males and has a pathognomonic mid-hindbrain malformation [Moog et al 2005].

Management

No clinical practice guidelines for Aicardi syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Aicardi syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Aicardi Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, head circumference.	
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD
Costovertebral abnormalities	Spine radiographs	• To evaluate for hemivertebrae, block vertebrae, fused vertebrae; missing, malformed, fused ribs • Orthopedics consultation if costovertebral abnormalities are significant
Musculoskeletal / Activities of daily living	Physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology/nutrition/ feeding team eval	To incl: • History of constipation, diarrhea, GERD • Eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in patients w/ dysphagia &/or aspiration risk.
Eyes/Vision	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, strabismus
Endocrine	Physical exam for evidence of precocious or delayed puberty	
Skin	Dermatologic eval	For vascular malformations & pigmentary lesions at risk for malignant transformation
Risk of malignancy	No regular screening recommended, given variety of tumors seen. Treating clinicians should be alert to risk of malignancy.	Angiosarcoma, hepatoblastoma, medulloblastoma, embryonal carcinoma, & teratoma have been reported.
Genetic counseling	By genetics professionals [1]	To date, no gene has been identified as causative of Aicardi syndrome. Genetic testing may be warranted to rule out aforementioned differential diagnoses, esp if presentation is not classic for Aicardi syndrome.
Family support & resources		Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Aicardi Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist; recent studies have shown ≤50% ↓ in median number of seizures w/cannabidiol. [1]	• Most persons require multiple medications for mgmt of seizures, & seizure types may change over time, requiring changes in medications. • Education of parents/caregivers [2]
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Mobility / Activities of daily living	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, hygiene, disability parking placard.
Abnormal vision &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	Community vision services through early intervention or school district
Costovertebral abnormalities	Per treating orthopedist	Can incl musculoskeletal support & treatment for prevention of scoliosis-related complications
Bowel dysfunction	Monitor for constipation.	Stool softeners, prokinetics, osmotic agents, or laxatives as needed

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy

1. Devinsky et al [2018]

2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

    - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
    - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication Issues

Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 5. Recommended Surveillance for Individuals with Aicardi Syndrome

System/Concern	Evaluation	Frequency
Feeding	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	At each visit
Gastrointestinal	Monitor for constipation & other bowel problems; stool softeners or pro-motility agents as needed.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone (e.g., spasticity), movement disorders.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Costovertebral abnormalities	Monitor spine for progression of scoliosis (by exam; perform radiographs as needed).	
Precocious or delayed puberty	Pediatric endocrinologist w/hormonal testing & supplementation as needed	If symptomatic
Malignancy	Treating physicians should be aware of possible ↑ risk of rare malignancies; if there are symptoms concerning for a malignancy, consider screening.	
Family / Care givers	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

The gene(s) in which pathogenic variants are causative of Aicardi syndrome are not known. While autosomal inheritance cannot be fully excluded in the absence of a known genetic cause, several observations support a hypothesis that Aicardi syndrome is caused by a *de novo* pathogenic variant in a gene on the X chromosome that is subject to X-chromosome inactivation (see Molecular Genetics).

Aicardi syndrome is typically seen in females but has also been reported in males with a 47,XXY karyotype and, very rarely, in 46,XY males.

Risk to Family Members

Parents of a proband. With the exception of affected monozygotic twin girls, all individuals with Aicardi syndrome reported to date have represented simplex cases (i.e., a single affected family member). Parent-to-child transmission of Aicardi syndrome has not been reported.

Sibs of a proband. The recurrence risk to sibs is thought to be less than 1%.

Offspring of a proband

- No instances of mother-to-daughter transmission have been documented, despite the presence of rare adult women with Aicardi syndrome who do not have a degree of intellectual disability that would result in decreased reproductive fitness. This raises the question of whether fertility may be reduced in women with Aicardi syndrome. The hypothesis that fertility in Aicardi syndrome is reduced could also be supported by reports of precocious puberty in individuals with Aicardi syndrome [Glasmacher et al 2007], which reflect an underlying reproductive hormone dysregulation that could lead to both precocious puberty and inability to sustain a pregnancy successfully.
- While the genetic cause is currently unknown, theoretically, if a female with Aicardi syndrome conceives, the risk that the causative variant will be transmitted could be as high as 50%.

Other family members. Given that almost all probands with Aicardi syndrome reported to date have represented simplex cases, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, 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 pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing

Molecular genetic testing. Prenatal testing by molecular genetic testing is not possible as the gene(s) in which pathogenic variants are causative of Aicardi syndrome are not known.

Other

- Some features detected on prenatal ultrasound examination, such as agenesis of the corpus callosum with intracranial cysts in a female fetus, may raise suspicion for Aicardi syndrome and a number of other developmental brain abnormalities.
- Findings of corpus callosum agenesis and neuronal migration abnormalities on intrauterine MRI may be suggestive but not diagnostic [Masnada et al 2020].
- Other features, such as costovertebral defects and microphthalmia, are more difficult to detect prenatally and are not present in all cases.
- Definitive prenatal diagnosis of Aicardi syndrome has not been reported in a low-risk pregnancy; furthermore, definitive diagnosis of Aicardi syndrome relies on neonatal confirmation of suspected findings and detection of additional features including chorioretinal lacunae and seizures.

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.

- **Aicardi Syndrome Foundation**
  PO Box 3202
  St. Charles IL 60174
  Phone: 800-374-8518 (toll-free)
  Email: web@aicardisyndrome.org
  www.aicardisyndrome.org
- **MedlinePlus**
  Aicardi syndrome
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Aicardi Syndrome Information Page
- **Aicardi Syndrome International Registry**
  Phone: 301-230-4674
  Email: byk@rti.org
  aicardisyndromefoundation.org/register/register-your-child/

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

304050	AICARDI SYNDROME; AIC

Molecular Pathogenesis

A gene for Aicardi syndrome has not been identified, but several observations support a hypothesis that Aicardi syndrome is caused by *de novo* pathogenic variants in a gene on the X chromosome that is subject to X-chromosome inactivation [Van den Veyver 2002].

- Nearly all affected individuals are female and, except for one pair of sisters and a pair of concordant monozygotic twins, all reported cases are simplex (i.e., a single occurrence in a family).
- At least six pairs of twins who are discordant for Aicardi syndrome are known, five of whom are confirmed dizygotic, excluding the possibility that the etiology is a prenatal toxin or other disruptive event [Taggard & Menezes 2000].
- Rare known males with a confirmed diagnosis of Aicardi syndrome have a 47,XXY karyotype [Aicardi 1999, Chen et al 2009, Zubairi et al 2009, Shetty et al 2014]. The presence of Aicardi syndrome in males with a 46,XY karyotype has been disputed, but new cases have been reported. It is possible that these are caused by mosaic pathogenic variants in the putative Aicardi syndrome gene [Chappelow et al 2008, Anderson et al 2009]

- The variable severity and asymmetry of the Aicardi syndrome phenotype could be explained if the putative mutated gene undergoes X-chromosome inactivation. Earlier limited studies, some using older methods, had conflicting results, showing either random or skewed X-chromosome inactivation patterns. The most recent study on 35 individuals with Aicardi syndrome, the largest series examined thus far, demonstrated non-random X-chromosome inactivation in leukocyte-derived DNA in 11 of 33 informative individuals, with six (18%) having extremely skewed patterns. This is significantly increased compared to the general population [Eble et al 2009].
- Because a subset of the clinical findings of Aicardi syndrome (including colobomas, agenesis of the corpus callosum, microphthalmia, and seizures) overlaps with those of microphthalmia with linear skin defects (MLS) syndrome and with Goltz syndrome (focal dermal hypoplasia), it was hypothesized that these three conditions were allelic and that the gene for Aicardi syndrome was located on Xp22. However, sequencing and deletion studies now indicate that Aicardi syndrome is likely not allelic to MLS syndrome [Van den Veyver 2002] or to Goltz syndrome [Wang et al 2007].
- Until the genetic basis of Aicardi syndrome is known, the possibility remains that Aicardi syndrome is caused by a *de novo* pathogenic variant on an autosome with sex-limited expression in females. Interestingly, while one report described a girl with an 11-Mb deletion of 1p36 with an Aicardi syndrome phenocopy [Bursztejn et al 2009], it is important to note that she did not have the chorioretinal lacunae typical of Aicardi syndrome and did have facial features and cardiac defects characteristic of the 1p36 deletion syndrome (OMIM 607872).

Efforts to identify the mutated gene using array comparative hybridization with genome-wide DNA microarrays [Wang et al 2009] and X-chromosome DNA microarrays [Yilmaz et al 2007] have not been successful to date. Exome and X-chromosome genome sequencing by at least three separate groups have also been unsuccessful [Author, unpublished data].

Chapter Notes

Author Notes

Dr Sutton's website

Dr Van den Veyver's website

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The retina photo and legend were provided by Dr Richard A Lewis.

Revision History

- 12 November 2020 (bp) Comprehensive update posted live
- 6 November 2014 (me) Comprehensive update posted live
- 20 September 2012 (vrs) Revision: microcephaly with or without chorioretinopathy, lymphedema, or intellectual disability added to differential diagnosis
- 27 April 2010 (me) Comprehensive update posted live
- 30 June 2006 (ca) Review posted live
- 2 August 2005 (ivv) Original submission

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