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Adams-Oliver Syndrome – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: Aplasia Cutis Congenita with Terminal Transverse Limb Defects

Anna Lehman, MD,[1] Wim Wuyts, PhD,[2] and Millan S Patel, MD[1]

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Adams-Oliver syndrome (AOS) is characterized by aplasia cutis congenita (ACC) of the scalp and terminal transverse limb defects (TTLD). ACC lesions usually occur in the midline of the parietal or occipital regions, but can also occur on the abdomen or limbs. At birth, an ACC lesion may already have the appearance of a healed scar. ACC lesions less than 5 cm often involve only the skin and almost always heal over a period of months; larger lesions are more likely to involve the skull and possibly the dura, and are at greater risk for complications, which can include infection, hemorrhage, or thrombosis, and can result in death. The limb defects range from mild (unilateral or bilateral short distal phalanges) to severe (complete absence of all toes or fingers, feet or hands, or more, often resembling an amputation). The lower extremities are almost always more severely affected than the upper extremities. Additional major features frequently include cardiovascular malformations/dysfunction (23%), brain anomalies, and less frequently renal, liver, and eye anomalies.

Diagnosis/testing

The diagnosis of AOS can be established in a proband with one of the following:

- Clinical findings of ACC of the scalp and TTLD
- ACC or TTLD and a first-degree relative with findings consistent with AOS
- ACC or TTLD and either a pathogenic variant in an autosomal dominant AOS-related gene (*ARHGAP31*, *DLL4*, *NOTCH1*, or *RBPJ*) or two pathogenic variants in an autosomal recessive AOS-related gene (*DOCK6* or *EOGT*)

Author Affiliations: 1 Department of Medical Genetics, University of British Columbia, Vancouver, Canada; Email: alehman@cw.bc.ca; Email: mpatel@cw.bc.ca. 2 Department of Medical Genetics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; Email: wim.wuyts@uantwerpen.be.

Management

Treatment of manifestations:

- ACC. Care by a pediatric dermatologist and/or plastic surgeon depending on severity. Goals of non-operative therapy are to prevent infection and promote healing. Large and/or deep lesions with calvarial involvement require acute care and may eventually also require reconstruction by a neurosurgeon.
- Limb. Many AOS limb anomalies are not severe enough to require surgical or prosthetic intervention. Occupational therapy and/or physical therapy are used as needed to assist with limb functioning. Rarely, surgical intervention for hand malformations is indicated.

Surveillance:

- Cardiovascular. Echocardiography annually until age three years for signs of pulmonary hypertension.
- Neurologic. Annual pediatric care, including neurologic examination and ongoing assessment of psychomotor development.
- Ocular. Annual assessment by pediatric ophthalmologist until age three years for evidence of abnormal retinal vascular development.

Evaluation of relatives at risk: Presymptomatic diagnosis to identify as early as possible those who would benefit from initiation of treatment and/or surveillance for cardiovascular, neurologic, and/or ocular manifestations.

Genetic counseling

ARHGAP31-, *DLL4*-, *NOTCH1*-, and *RBPJ*-related Adams-Oliver syndrome (AOS) are inherited in an autosomal dominant manner. Intrafamilial variability in the extent and severity of cutaneous and limb defects is often striking. The proportion of AOS caused by *de novo* pathogenic variants is unknown. Each child of an individual with autosomal dominant AOS has a 50% chance of inheriting the pathogenic variant.

DOCK6- and *EOGT*-related AOS are inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Once the *AOS*-related pathogenic variant(s) have been identified in an affected family member, molecular genetic prenatal testing and preimplantation genetic testing for a pregnancy at increased risk for AOS are possible.

Diagnosis

Suggestive Findings

Adams-Oliver syndrome (AOS) **should be suspected** in individuals with the following clinical findings:

- **Aplasia cutis congenita (ACC).** ACC of the scalp (most often over the posterior sagittal suture) is the classic finding; it may range from the most severe finding of total absence of an area of skull and dura to the mildest finding: hairless patches of varying size at the vertex of the scalp detected on a focused examination of the scalp.

  Of note, when a scalp lesion is not obviously cutis aplasia (e.g., a simple hairless lesion may appear similar to nevus psiloliparus or nevus sebaceous), a skin biopsy can confirm the characteristic features of absent epidermis, dermal atrophy, and lack of adnexal structures and elastic fibers. Generally, a skin biopsy is not necessary because a nevus sebaceous has a yellowish waxy appearance versus the eroded or scarred appearance of ACC.

- **Terminal transverse limb defects (TTLD) spectrum,** which can include small distal phalanges, short distal phalanges, brachysyndactyly, or ectrodactyly. Note: Many unaffected infants have small toenails at birth.
- **Cardiovascular defects** with ACC or TTLD [Digilio et al 2008]
  - Almost any type of heart malformation can occur in AOS.
  - Vascular defects include incomplete retinal vascularization, CNS microbleeds that on imaging may mimic – and later result in – intracranial calcifications, hepatoportal sclerosis (i.e., non-cirrhotic or idiopathic portal hypertension), pulmonary vein stenosis, deficient gut vasculature, and aberrant vessels of placental chorionic villi.
  - Widespread cutis marmorata telangiectatica congenita is common (19%).
- **Neurologic findings with ACC or TTLD.** Although most individuals with AOS do not have neurologic involvement, frequent neurologic findings in a subset of people include intellectual disability, seizures, or cerebral palsy. Of note, intellectual disability is rare in the absence of a structural brain anomaly or microcephaly.

Establishing the Diagnosis

The diagnosis of Adams-Oliver syndrome (AOS) **is established** in a proband with one of the following:

- The clinical findings of both aplasia cutis congenita (ACC) of the scalp and terminal transverse limb defects (TTLD)
- Either ACC or TTLD and a first-degree relative with findings consistent with AOS
- Either ACC or TTLD and either a pathogenic (or likely pathogenic) variant in an autosomal dominant AOS-related gene or biallelic pathogenic (or likely pathogenic) variants in an autosomal recessive AOS-related gene identified on molecular genetic testing (Table 1)

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include 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 considered if mutation of a particular gene accounts for a significant proportion of Adams-Oliver syndrome (AOS) in which the mode of inheritance is known (Table 1) and/or certain clinical findings (such as neurologic involvement) are present.

Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found; however, it is unknown at present what proportion of individuals with AOS have intragenic deletions or duplications that cannot be detected by sequence analysis.

- For autosomal dominant or simplex (i.e., a single occurrence in a family) AOS: *NOTCH1* and *DLL4* are the most frequently mutated AOS-related genes.
- For autosomal recessive AOS with neurologic and ocular abnormalities: *DOCK6* analysis may be particularly indicated.

A multigene panel that includes *ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, *RBPJ*, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene 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 and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes *ARHGAP31*, *DLL4*, *DOCK6*, *EOGT*, *NOTCH1*, and *RBPJ*) fails to confirm a diagnosis in an individual with features of AOS. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene 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 Adams-Oliver Syndrome (AOS)

Gene [1]	Proportion of AOS Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
ARHGAP31	<5% (2/47) [5]	AD	≥99%	Unknown [6]
DLL4	~9.9% (9/91) [7]	AD	≥99%	Unknown [6]
DOCK6	~17% (13/78) [8]	AR	≥99%	Unknown [9]
EOGT	<10% [10]	AR	≥99%	Unknown [6]
NOTCH1	~23% (17/74) [11, 12]	AD	≥99%	Unknown [13]
RBPJ	<10% [10, 14]	AD	≥99%	Unknown [6]

Table 1. continued from previous page.

Gene [1]	Proportion of AOS Attributed to Pathogenic Variants in Gene	MOI	Proportion of Pathogenic Variants [2] Detected by Method	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
Unknown	40%-50% [5, 7, 10, 11, 12, 14, 15]	?	NA	

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Southgate et al [2011]
6. No data on detection rate of this gene using gene-targeted deletion/duplication analysis are available.
7. Meester et al [2015]
8. Sukalo et al [2015]
9. No data on detection rate of *DOCK6* gene-targeted deletion/duplication analysis are available; however, one person with a deletion of exons 42-47 has been described [Sukalo et al 2015].
10. Wim Wuyts, unpublished data
11. Stittrich et al [2014]
12. Southgate et al [2015]
13. No data on detection rate of *NOTCH1* gene-targeted deletion/duplication analysis are available; however, one person with a heterozygous deletion has been described [Stittrich et al 2014].
14. Hassed et al [2012]
15. The genetic cause has not been found in individuals with AOS and severe or lethal pulmonary hypertension [Author, personal observation; including in 2 such individuals in whom testing of the 6 known genes revealed no pathogenic variants].

Clinical Characteristics

Clinical Description

Adams-Oliver syndrome (AOS) is characterized by aplasia cutis congenita (ACC) of the scalp and terminal transverse limb defects (TTLD). Additional major features frequently include cardiovascular malformations/ dysfunction and less frequently, renal and brain anomalies (Table 2) [Snape et al 2009].

Table 2. Frequency of Clinical Features Associated with Adams-Oliver Syndrome in Probands and Family Members

Finding	Frequency [1]
Cutis aplasia	~80%
Transverse terminal limb defects	~85%
Cardiac malformations	~23%
Cutis marmorata telangiectatica congenita	~20%
Neurologic abnormalities	Uncommon in AD & simplex AOS; ~30% in AR kindreds
Ophthalmologic abnormalities	<10%
Prenatal complications (intrauterine growth restriction or oligohydramnios)	<10%

Table 2. continued from previous page.

Finding	Frequency [1]
Renal abnormalities	<5%

Adapted from Snape et al [2009] and the literature thereafter
1. As reported in the literature

The severity of malformations ranges from subtle to disabling or life threatening; variability among family members is common. Although rare, severe morbidity and mortality in AOS usually results from hemorrhage or infection involving large and deep calvarial lesions, or from cardiovascular anomalies including severe heart malformations. At least five children with AOS have died from refractory pulmonary hypertension (~1% risk), all in the first three years of life.

Cutaneous/Cranial

Aplasia cutis congenita lesions usually occur in the midline of the parietal or occipital regions of the scalp, but can also occur on the abdomen or limbs, particularly in the setting of cutis marmorata telangiectatica congenita (CMTC). At birth, a lesion may already have the appearance of a healed scar (i.e., the absence of hair follicles).

Cutis aplasia lesions less than 5 cm often involve only the skin and almost always heal over a period of months into hairless, fibrotic patches with wound care measures only [Brzezinski et al 2015]. Scars may be either atrophic or hypertrophic.

Larger lesions are more likely to involve the skull and possibly the dura, and are at greater risk for complications, which can include infection, hemorrhage or thrombosis (especially of the sagittal sinus), brain herniation, CSF leakage, and seizures, and can result in death [Bernbeck et al 2005, Peralta-Calvo et al 2012, Udayakumaran et al 2013].

AOS-related ACC lesions – of the scalp and elsewhere – are generally non-membranous. Membranous ACC (appearing like a bulla) is hypothesized to arise from a different mechanism and may be associated with ectopic neural tissue and other findings such as a hair collar [Browning 2013].

Cutis aplasia lesions histologically show variable absence of epidermis, dermis, subcutaneous tissue, muscle, or bone.

Calvarial bone is affected in about half of reported individuals, which may reflect ascertainment and reporting biases toward more severely affected persons.

Cutis marmorata telangiectatica congenita (CMTC), one of the more clinically obvious findings, affects approximately 20% of individuals. CMTC is a network of superficial, persistently dilated small blood vessels, which creates a marbled or lattice-like appearance, also known as livedo reticularis. It usually becomes more prominent with strong emotions.

CMTC typically includes areas of phlebectasia, skin atrophy, or ulceration; when severe, CMTC is often associated with hypoplasia of the underlying structures (e.g., a smaller limb). Despite its name, telangiectasiae are only found in a minority of those with CMTC.

Cutis marmorata (CM), a milder vascular skin marbling phenomenon, is a normal physiologic finding in infants that shows marked enhancement with cold exposure or strong emotions and usually fades by age four months. Children with AOS may have more prominent CM than usual, but not have CMTC. A key distinction between CM and CMTC is that the vascular dilatation of CMTC does not fade markedly with local warming.

Limb

The term transverse terminal limb defect (TTLD), which is used to describe the types of anomalies seen in AOS, indicates involvement of all elements distal to a certain point. (In contrast, longitudinal defects [e.g., isolated radial or fibular aplasia] are not observed in AOS.) Although a few individuals with AOS have strictly transverse limb reduction defects, most have mild medial to lateral gradients in severity (or less commonly, the reverse) and others have a medial ray defect in the form of ectrodactyly.

The limb defects of AOS range from mild to severe. The mild end of the spectrum is unilateral or bilateral short distal phalanges, which may or may not affect all fingers or toes. Toes are almost always more severely affected than fingers. The nails may be dystrophic, shortened, or absent. Rarely, the distal phalanx may be present when the middle phalanx is absent [Isrie et al 2014].

Cutaneous or osseous syndactyly is often present. Occasionally, oligodactyly (entirely missing fingers or toes) or camptodactyly (fixed contracture of phalangeal joints) is observed.

The severe end of the spectrum can involve complete absence of all toes or fingers, feet or hands, or more. The appearance of a TTLD can often resemble an amputation.

Constriction rings and necrotic lesions have been observed [Keymolen et al 1999, Pereira-Da-Silva et al 2000].

Most individuals with AOS retain prehension of the thumb and fingers. Milder involvement, with fully preserved function, is much more common than severe involvement [Authors, personal observation].

Poland syndrome, the combination of unilateral aplasia of part of the pectoralis muscle and ipsilateral upper limb anomalies, has been reported convincingly in one family [Der Kaloustian et al 1991]. Of note, family 2 of this report most likely had scalp-ear-nipple syndrome (see Differential Diagnosis).

Radiographs can be helpful in delineating which bones are short; one would expect distal phalanges to be more severely affected than proximal phalanges, which in turn would be more affected than metacarpals.

Cardiovascular

Twenty-three percent of individuals with AOS have a major congenital cardiac malformation which can include left-sided obstructive lesions (bicuspid aortic valve, hypoplastic left ventricle, Shone's complex), septal defects, and conotruncal defects (tetralogy of Fallot, truncus arteriosus) [Snape et al 2009]. Although in some families the recurrences of a cardiac defect are very similar (e.g., tetralogy of Fallot or aortic valvulopathy), variability is more the norm.

Non-cirrhotic or idiopathic portal hypertension (also known as hepatoportal sclerosis), which is likely secondary to hepatic venulopathy or thrombosis, occurs in fewer than 10% of affected individuals [Swartz et al 1999]. Non-cirrhotic portal hypertension can initially be asymptomatic and only associated with mild thrombocytopenia, splenomegaly, or portal vein enlargement. However, eventually gastroesophageal varices can develop and affected individuals may experience variceal hemorrhage [Garcia-Tsao 2015]. Liver synthetic function would be expected to be normal. Liver fibrosis may be seen additionally or in isolation and massive steatosis has been reported in one individual.

Pulmonary hypertension occurs in fewer than 5% of individuals with AOS, but when present is associated with high mortality [Patel et al 2004]. It appears to be caused in most instances by primary abnormalities of the pulmonary vasculature, often on the venous side.

Other cardiovascular problems that may be present:

- Pulmonary vein stenosis, hypoplastic pulmonary and cerebral arteries [Fryns et al 1996, Swartz et al 1999]

- Pulmonary or intracranial arteriovenous and hemangiomatous malformations [Maniscalco et al 2005, Gómez et al 2015]
- Cerebral microbleeds that can mimic intracerebral calcifications on neuroimaging studies [Patel et al 2004]
- Dilated, tortuous scalp veins (common)
- Absent intrahepatic portal vein [Snape et al 2009]
- Abnormal hepatic microvasculature
- Abnormal renal microvasculature [Fayol et al 2006]
- Vascular anomalies of the limbs (such as femoral artery duplication) [Digilio et al 2008]
- Small bowel infarction [Lehman et al 2014] or deficient stomach and gut vasculature associated with chronic nausea or anorexia
- Dilated, tortuous placental blood vessels [Lehman et al 2014]

Neurologic

Although the majority of individuals with AOS have no neurologic deficits, a significant minority have a range of clinical and neuroimaging findings including the following [Sukalo et al 2015].

Possible clinical findings:

- Cognitive disability, dyslexia, autism spectrum disorders
- Spastic hemiplegia or diplegia
- Seizures

Possible imaging findings:

- Brain malformations and migration defects: microcephaly, cortical dysplasia, polymicrogyria, pachygyria, dysgenetic corpus callosum
- Cortical atrophy with ventriculomegaly, cerebral hemorrhage, intracranial calcifications (often periventricular)
- Delayed myelination

Brain involvement appears to associate with more severe vascular phenotypes, suggesting that impaired vascular supply to the developing brain may be a key component of pathogenesis for neurologic findings.

Although most individuals with brain involvement do not have an affected parent (suggesting either autosomal recessive inheritance or a *de novo* heterozygous pathogenic variant consistent with autosomal dominant inheritance), exceptions occur.

The severity of neurologic impairment can be such that central respiratory insufficiency can cause early death [Mempel et al 1999].

One individual has been reported with Tourette syndrome, which was not noted in two other sibs with AOS [Hassiem & Cavanna 2015].

Renal

Renal anomalies are rare and usually consist of small kidneys, hydronephrosis, or renal cortical vascular anomalies.

Ocular

The ophthalmologic complications of AOS can include the following [Fayol et al 2006, Temtamy et al 2007, Peralta-Calvo et al 2012]:

- Microphthalmos
- Peters anomaly-like findings
- Cataracts
- Retinal folds
- Incomplete or abnormal retinal vasculature (including persistent fetal vasculature)
- Esotropia
- Optic nerve hypoplasia / optic atrophy
- Rod dystrophy

Incomplete vascularization and fibrovascular proliferative ischemic retinopathy can appear similar to retinopathy of prematurity or certain cases of Norrie disease or Coats disease, and can lead to retinal hemorrhages or tractional retinal detachment, resulting in visual impairment [Lehman et al 2014].

Other

Other rarely reported, not necessarily associated findings include:

- Midline frontonasal cysts (a single family only [Rodrigues 2007])
- Cleft lip/palate
- Supernumerary nipples
- Dilated cardiomyopathy (may be secondary to CHD [Atasoy et al 2013])
- Gastroschisis
- Umbilical hernia
- Diastasis recti
- Cryptorchidism
- Prenatal growth restriction or postnatal impaired growth in severe forms of AOS

Possible Phenotype Correlations by Gene

While subtypes of AOS have not been established, emerging data suggest:

- High risk for severe brain involvement in *DOCK6*-AOS (autosomal recessive inheritance) and less risk in *ARHGAP31*-AOS (autosomal dominant inheritance).
- Increased risk for cardiac defects in *NOTCH1-, DOCK6-*, *DLL4-,* and *EOGT*-AOS and lower risk in *RBPJ-* and *ARHGAP31*-AOS.

ARHGAP31. The risk for cerebral involvement with this autosomal dominant form of AOS appears to be less than for the autosomal recessive forms, as to date neurologic abnormalities have not been reported in individuals with *ARHGAP31*-AOS.

DLL4. A significant minority of individuals have cardiovascular anomalies.

DOCK6. Approximately 15 families/probands with *DOCK6*-AOS have been reported. A cohort-based study yielded likely pathogenic *DOCK6* variants in 29% (9/31) of families with suspected autosomal-recessive inheritance versus 2% (1/47) of simplex cases [Sukalo et al 2015]. To date, severe intellectual and neurologic impairments appear to be consistent findings in *DOCK6*-AOS, with findings in keeping with disturbed intracranial vasculogenesis. Ocular malformations and retinal issues are also seen more common in this subgroup; cardiac malformations have been reported as well.

EOGT. Periventricular calcifications and cardiovascular anomalies occurred in a significant minority [Shaheen et al 2013].

NOTCH1. *NOTCH1*-AOS appears to show a particularly high rate of cardiac malformations and vasculopathy, occurring in at least half of affected individuals [Stittrich et al 2014, Southgate et al 2015]. Thrombotic occlusive

or sclerotic portal venopathy leading to portal hypertension has been seen in several individuals, more commonly in simplex cases. Two children with *NOTCH1*-AOS have had pulmonary hypertension, which was mild in one [Southgate et al 2015] and transient in the other [Stittrich et al 2014]. At least one individual had neurologic deficits (spastic diplegia and intellectual disability) in the context of intracranial vascular lesions.

RBPJ. Intellectual impairment was a variable feature in both families reported with *RPBJ*-AOS [Hassed et al 2012].

Genotype-Phenotype Correlations

For the genes known to be associated with Adams-Oliver syndrome, no genotype-phenotype correlations (either with a class of pathogenic variants or with any specific pathogenic variants) have been identified.

Penetrance

Familial autosomal dominant AOS typically shows decreased penetrance.

- ***NOTCH1* and *DLL4***. Incomplete penetrance was observed in at least 2/9 families with a *NOTCH1* pathogenic variant and 3/16 families with a *DLL4* pathogenic variant (and likely more) [Stittrich et al 2014, Meester et al 2015, Southgate et al 2015].
- ***RBPJ***. Incomplete penetrance has not been reported to date.
- ***ARHGAP31***. In one large pedigree with limb anomalies, but no cutis aplasia, 3/16 (19%) heterozygotes had no clinical manifestations of AOS [Isrie et al 2014]. In two other large pedigrees, only one individual was noted to have no clinical manifestations of AOS [Southgate et al 2011].

Nomenclature

A sporadic co-occurrence of ACC and TTLD was first reported by Pincherle [1938], seven years before the description of a large family with several affected family members [Adams & Oliver 1945].

Prevalence

An estimate of the incidence for AOS is 0.44 per 100,000 live births [Martínez-Frías et al 1996].

The authors' experience in a tertiary pediatric care center supports a somewhat higher incidence, and further recognition of milder phenotypes within the spectrum of AOS may yet reveal a significantly higher incidence.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *DOCK6, EOGT*, and *RBPJ*.

Other phenotypes observed in *ARHGAP31*, *DLL4*, and *NOTCH1* include the following:

ARHGAP31. A germline variant in *ARHGAP31* has been associated with familial isolated terminal transverse limb defects in 15 affected members of one family [Isrie et al 2014].

DLL4. Several families with isolated ACC and a *DLL4* pathogenic variant were described; the number of family members is too small to conclude that these pathogenic variants cause only ACC and not other aspects of AOS.

NOTCH1. Germline *NOTCH1* variants affecting diverse domains of the protein can be associated with cardiac defects. Many of these variants were present also in unaffected parents or controls, yet statistically overrepresented in an affected cohort and associated with reduced signaling in vitro, suggesting decreased penetrance [Riley et al 2011].

- Several variants have been associated with autosomal dominant congenital heart defects affecting the left ventricular outflow tract (LVOT), most commonly bicuspid aortic valve (BAV), with an additional frequent feature of adult-onset precocious aortic valve calcification [Garg et al 2005, Foffa et al 2013].
- Rare *NOTCH1* variants have also been identified in 4.2% of individuals with sporadically occurring BAV and much less frequently with other LVOT malformations [Mohamed et al 2006, McBride et al 2008].

Sporadic tumors (including hematologic and solid) occurring as single tumors in the absence of any other findings of this syndrome may contain a somatic variant in *NOTCH1* or *RBPJ* that is not present in the germline. In these circumstances predisposition to these tumors is not heritable. For more details see Molecular Genetics, *NOTCH1* and *RBPJ*, **Cancer and benign tumors**.

Differential Diagnosis

Syndromic Aplasia Cutis Congenita (ACC)

Scalp-ear-nipple (SEN) syndrome (Finlay-Marks syndrome; OMIM 181270). Clinical findings include the following:

- Variable combinations of ACC of the scalp (usually in the vertex or occipital region), hypothelia/athelia, mammary hypoplasia, ear anomalies (either cupped, overfolded, or hypoplastic)
- Variable digital anomalies including distal hypoplasia, syndactyly and camptodactyly
- Occasional hypodontia, renal hypoplasia/malformations or ocular anomalies (colobomata or cataracts)
- Normal intellectual development; however, affected sibs in one family presented with severe hypotonia and developmental delay, and a severe autosomal recessive form of the condition was suspected [Al-Gazali et al 2007].

SEN syndrome is caused by mutation of *KCTD1* and is inherited in an autosomal dominant manner. (Reported *KCTD1* pathogenic variants were predicted to disrupt the domain responsible for repressing TFAP2A transcriptional activity. *TFAP2A* pathogenic variants are the cause of branchiooculofacial syndrome which can often feature scarred branchial and auricular skin lesions in keeping with healed cutis aplasia.)

Focal dermal hypoplasia (Goltz syndrome)

- Multisystem disorder characterized primarily by involvement of the skin, skeletal system, eyes, and face
- Can feature both cutis aplasia and limb anomalies (syndactyly, polydactyly, camptodactyly or oligodactyly).
- A distinguishing feature from AOS is that the dermal hypoplasia usually follows lines of Blaschko.
- Other distinguishing features include ectodermal dysplasia, subepidermal deposits of subcutaneous fat, metaphyseal striations, and papillomas of the skin and mucous membranes.

Focal dermal hypoplasia is inherited in an X-linked manner. Females (90% of affected individuals) are heterozygous or mosaic for a *PORCN* pathogenic variant. Live-born affected males (10% of affected individuals) are mosaic for a *PORCN* pathogenic variant.

Dominant dystrophic epidermolysis bullosa (DDEB)

- Typically, ACC lesions are restricted to the limbs and the clinical diagnosis is clear from persistent skin fragility and blistering postnatally.
- Limb anomalies are generally limited to absence of the nails.
- DDEB is caused by mutation of *COL7A1*.

Other causes of syndromic aplasia cutis congenita (ACC)

- Chromosome disorders

- Trisomy 13 (Patau syndrome)
- Wolf-Hirschhorn syndrome (4p- syndrome; OMIM 194190)

- Setleis syndrome (focal facial dermal dysplasia 3; OMIM 227260), with bitemporal or preauricular skin lesions resembling ACC
- Johanson-Blizzard syndrome (See Pancreatitis Overview.)
- Oculocerebrocutaneous (Delleman) syndrome (OMIM 164180)
- Kabuki syndrome
- Limb body wall complex
- Knobloch syndrome (OMIM 267750), with high myopia, neuronal elements in scalp defects, occipital encephalocele
- Various ectodermal dysplasias

Isolated aplasia cutis congenita (ACC)

- Estimated to occur in one in 3,000 live births, most often as an isolated, sporadic malformation [Marneros 2015].
- Familial recurrence is rarely observed, and can be caused by a heterozygous pathogenic variant in *BMS1* (OMIM 107600), a ribosomal GTPase that recruits Rcl1 to preribosomes and promotes ribosomal subunit maturation [Karbstein & Doudna 2006].
- Hypoproliferation and/or impaired differentiation at a location of rapid growth (the cranium) have been hypothesized as part of the pathogenesis for this condition [Marneros 2015].

Non-genetic causes of aplasia cutis congenita (ACC)

- Birth trauma (e.g., scalp electrode avulsion)
- Amniotic bands
- Intrauterine vascular disruption (e.g., secondary to embolism from co-twin loss)
- Teratogens (misoprostol, cocaine, methotrexate, angiotensin-converting enzyme inhibitors, methimazole, benzodiazepines, valproic acid) [Brzezinski et al 2015].

Terminal Transverse Limb Defects (TTLD)

Amniotic band sequence (OMIM 217100). Considering that the concurrence of transverse distal limb anomalies with cutis aplasia is diagnostic of AOS, there is not an immediate differential diagnosis for this particular combination of features with the notable exception of amniotic band sequence, which can present as a complete phenocopy, particularly if bands have not been observed on prenatal ultrasonography or at delivery. Since constriction rings of the limbs or toes have been described with AOS, this feature does not fully distinguish these two conditions. It is somewhat unusual for amniotic bands to cause focal scalp defects; in contrast, defects at the vertex of the scalp are most consistent with AOS (but may occur elsewhere). Some clinicians do not diagnose amniotic band sequence unless band tissue is physically present or is seen on prenatal ultrasound examination, or the amnion is torn or knotted on placental analysis. In the absence of physical evidence for amnion disruption, constriction rings may be interpreted as evidence of vascular disruption.

Congenital dyserythropoietic anemia type I

- Toes and fingers show limb reductions with absent or hypoplastic nails, often involving partial syndactyly.
- Duplicated metacarpals or metatarsals may be seen.
- Other features are mild to moderate macrocytic anemia and evidence of ineffective erythropoiesis on bone marrow aspirates.
- Jaundice, early onset gallstone formation, and splenomegaly may also be seen.
- CBC with blood smear should be performed in individuals with TTLD to assess for the macrocytic anemia of congenital dyserythropoietic anemia.

- Congenital dyserythropoietic anemia type I is caused by mutation of *CDAN1* or *CDIN1* (*C15ORF41*) and is inherited in an autosomal recessive manner.

Poland syndrome (OMIM 173800). Key features are unilateral hypoplasia or aplasia of part or all of the pectoralis major, ipsilateral axillary hypohidrosis, and ipsilateral upper limb reduction defects, often with syndactyly.

Hypoglossia-hypodactylia anomaly (Hanhart "syndrome"; OMIM 103300). Key features are small or absent mandibular structures (variably involving mandible, lower incisors, and tongue) and symmetric or asymmetric limb defects.

Non-genetic causes of TTLD

- **Teratogens** (e.g., phenytoin, misoprostol, and ergotamine) [Holmes 2002].
- **Vascular disruption** of any cause, including thrombosis, which may be primary due to fetal thrombophilia or may be secondary to other causes such as embolism from co-twin loss
- **Chorionic villus sampling** (CVS), particularly when performed prior to ten weeks' gestation

Other

Use of exome sequencing. The following are examples in which the use of exome sequencing (in clinical practice) facilitated the diagnosis of Adams-Oliver syndrome when other syndromes initially had been suspected and vice versa:

One individual with retinopathy of prematurity, small toes, VSD, but no cutis aplasia, was diagnosed initially with Coffin-Siris syndrome. Exome sequencing, however, identified biallelic *DOCK6* pathogenic variants causing the diagnosis to be revised to Adams-Oliver syndrome [Bramswig et al 2015]. Close examination of her scalp showed three small hairless scars.

Another individual was suspected to have a variant of AOS on the basis of cutis marmorata, arterial hypertension, dilated aorta, cerebral calcifications, mild hypotrichosis, and dystrophic nails [Wünnemann et al 2016]. Exome sequencing, however, demonstrated a *de novo SOX18* pathogenic variant, which causes hypotrichosis-lymphedema-telangiectasia syndrome (OMIM 607823). Of note, the protein encoded by *SOX18* acts upstream of Notch signaling. In most individuals with a *SOX18* pathogenic variant, progressive alopecia and lymphedema should be distinguishing features.

Other. Rodrigues [2007] reported a unique family who met the diagnostic criteria for AOS but had the additional features of midline frontal cysts, cardiac lesions, prominent nasal bridge, and gingival cleft that were consistent across multiple affected family members. This constellation of malformations likely represents a distinct syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Adams-Oliver syndrome (AOS), the following evaluations are recommended.

Cutaneous/cranial

- Consultation with a plastic surgeon regarding aplasia cutis congenita (ACC) or any significant cutis aplasia on the body
- Consultation with a dermatologist, which may be especially useful in those with extensive cutis marmorata telangiectatica congenita (CMTC)

- Consideration of skull x-ray; on occasion a bony defect may be present even in the absence of ACC, which may require use of a protective helmet. Ultrasonography and CT can also help assess skull involvement.
- Consultation with a neurosurgeon in children with a significant calvarial defect

Cardiovascular

- Consultation with a pediatric cardiologist. Echocardiography should be performed even when clinical signs of congenital heart disease are absent.
- Any evidence for pulmonary hypertension should be sought.
- Systemic blood pressure should be checked.
- Abdominal ultrasound examination should be performed to check for splenomegaly and patency of the portal vein.

Neurologic

- Brain MRI to delineate any brain malformations and identify lesions suggestive of micro-hemorrhage or ischemia. Infants with brain anomalies are at increased risk for seizures, developmental delay, or motor deficits and warrant evaluation and close follow up by developmental specialists.
- MR angiography and venography to show the vascular anatomy. Surgical procedures may result in unexpected complications if anomalous vasculature is unrecognized. MRI and MRV are also important to guide wound care when the ACC lesion is large and to determine whether protection of the superior sagittal sinus is sufficient.

Ocular. Pediatric ophthalmology assessment of the retina should be obtained within a short time frame so that lesions at high risk can be treated prior to retinal detachment and/or visual loss.

Other

- Abdominal ultrasound to look for liver or renal anomalies
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Cutaneous/Cranial

Consultation with a pediatric dermatologist or plastic surgeon provides individualized management. The goals of non-operative therapy are to prevent infection and promote healing.

Wounds without calvarial involvement. The most preferred dressing currently is a silver-coated, low-adherent primary wound dressing (e.g., Acticoat®), plus a barrier of a flexible polyamide net coated with soft silicone (e.g., Mepitel®) if there is any bone defect. Plastic wrap (e.g., Saran®) can be used to prevent desiccation. Once the wound begins to granulate, the frequency of dressing changes can be decreased. Non-infected, partial thickness skin wounds may be adequately dressed with a hydrocolloid (e.g., DuoDerm®).

Other less preferred, less costly dressings are:

- Sterile saline-soaked gauze/compresses (wet-to-wet), which should be changed every four hours. Although this labor-intensive option is effective, it is not frequently used anymore.
- Silver sulfadiazine dressings changed twice daily work well in older children, but these cannot be used in infants younger than age two months (corrected for prematurity) because of the risk of accompanying electrolyte disturbance.

Wounds with calvarial defects: acute care. As soon as possible a plastic surgeon should be consulted for any large and/or deep lesion and imaging performed (see Evaluations Following Initial Diagnosis, **Neurologic**). Operative management of large lesions involving the calvarium requires involvement of a neurosurgeon.

It is critically important to avoid drying of the wound and eschar separation, which can lead to catastrophic, terminal hemorrhage from the sagittal sinus or from a dilated vein.

One option is a dermal regeneration plate (a porous matrix of bovine tendon collagen and glycosaminoglycan) and a semipermeable silicone layer (which provides a framework for cell migration) which is applied in the operating room to a meticulously debrided wound and then monitored for infection [Khashab et al 2009].

In one child with a CSF leak, a biocellulose membrane provided a barrier and supported eventual healing [Frantz et al 2015].

It has been suggested that debridement over the midline be avoided (if possible) to decrease the risk of fatal hemorrhage from the sagittal sinus [Udayakumaran et al 2013].

A surgical procedure may be necessary for more severe defects (e.g., large areas of aplasia cutis congenita on the scalp or skull abnormalities) or wounds complicated by hemorrhage, infection, or CSF leakage.

- Although some infants have received skin grafts [Swartz et al 1999, Cohen et al 2014], including allogenic grafts [Swartz et al 1999, Udayakumaran et al 2013], difficulties in infants can include limited donor sites and possible interference with growth of the calvarium as well as the usual risks of graft loss and donor-site morbidity. A reason for the high complication rate specific to AOS may be the presence of an anomalous vascular supply.
- Use of abdominal muscle fascia to cover exposed dura has been reported [Peralta-Calvo et al 2012].

Wounds with calvarial defects: late calvarial reconstruction. Although many skull defects (especially small ones) show spontaneous closure over a period of months, some remain at least partially open and require reconstruction by a neurosurgeon. As some lesions can also involve the dura, it is important to consider the role of the dura in promoting osteogenesis.

Cranioplasty, if needed, is usually considered around age three to four years [Beekmans & Wiebe 2001]. Because cranioplasty requires good quality skin coverage over the bone graft, scalp reconstruction must be done at the same time or earlier.

- Bone grafting in the neonatal period using unaffected skull, with coverage of the sampled site with vascularized peri-osteum, has been reported [Steinbok 2000].
- Use of a split rib graft with a latissimus dorsi muscle flap has also been reported.

After healing is complete, scar revision with tissue expansion for cosmesis can be discussed. When the defect is severe the hair-bearing scalp may not be able to completely restore hair to the entire scalp even with tissue expansion.

Limb

Limb malformations may warrant consultation with specialists in orthopedics, plastic surgery, and/or rehabilitation medicine. X-rays of limbs are often performed immediately after birth but are most informative, in terms of delineating the extent of involvement, after age one year.

Many AOS limb anomalies are not severe enough to require surgical or prosthetic intervention.

Occupational therapy and/or physical therapy is used as needed to assist with limb functioning, such as to improve walking and running stability in those with abnormal toes.

Analysis in a gait laboratory may help identify those who would benefit from prosthetic rehabilitation.

Distraction lengthening is problematic at the phalangeal level because of limited covering soft tissue, skeletal stock, and vascularity, but could be an option for metacarpals or the forearm bones in certain circumstances [Sivakumar & Smith 2015].

"On-top" plasty is another, quite complex, surgical strategy to achieve prehension when necessary; a digital tip can be transposed onto a proximal phalanx and neurovascular pedicle.

Cardiovascular

Many congenital heart malformations and certain vascular malformations can be ameliorated with a range of standard surgical procedures.

Treatment of pulmonary hypertension with a variety of standard therapies is often found to be ineffective.

Neurologic

If developmental delays or disabilities are suspected, a full assessment with recommendations for supportive therapies should be obtained.

Routine pediatric care should include periodic neurologic examination for signs of spasticity, particularly if neonatal brain imaging showed evidence of periventricular calcifications.

Early physiotherapy can maximize motor function and range of motion.

The risk for epilepsy is increased, particularly when neuroimaging and/or neurologic examination are abnormal. Management of seizures is per routine.

Ocular

Early prophylactic laser photocoagulation may help preserve vision of those with retinal vasculopathy [Peralta-Calvo et al 2012]. Such treatment can decrease the progression from ischemia to neovascularization, gliosis, and retinal detachment.

Retinal detachments should be treated promptly with appropriate interventions, such as bilateral lensectomies, pars plana vitrectomies, or silicone oil tamponade.

Surveillance

Cardiovascular

- Echocardiography annually until age three years for signs of pulmonary hypertension
- Consideration of abdominal ultrasound examination for signs of portal hypertension in those with failure to thrive, persistent nausea, abdominal swelling, or black stools

Neurologic. Annual pediatric care, including neurologic examination and ongoing assessment of psychomotor development

Ocular. Annual assessment by pediatric ophthalmologist until age three years to identify those with abnormal retinal vascular development

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic relatives of an affected individual in order to identify as early as possible those who would benefit from initiation of treatment and/or surveillance for cardiovascular and/or neurologic manifestations.

Evaluations can include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Examination by a clinical geneticist if the pathogenic variant(s) in the family are not known.

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

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

ARHGAP31-, *DLL4*-, *NOTCH1*-, and *RBPJ*-related Adams-Oliver syndrome (AOS) are inherited in an autosomal dominant manner.

DOCK6- and *EOGT*-related AOS are inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant AOS have an affected parent. Intrafamilial variability in the extent and severity of cutaneous and limb defects is often striking.
- A proband with autosomal dominant AOS may have the disorder as the result of a *de novo* *ARHGAP31*, *DLL4*, *NOTCH1*, or *RBPJ* pathogenic variant. The proportion of AOS caused by *de novo* pathogenic variants is unknown.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations are (1) a *de novo* pathogenic variant in the proband or (2) germline mosaicism in a parent. No instances of germline mosaicism have been reported to date and the number of described families is too few to determine the frequency of somatic mosaicism.
- The family history of individuals may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, even when there is an apparently negative family history, focused clinical evaluation of the scalp and limbs of the parents of a proband (possibly including hand and foot x-rays) and/or molecular genetic testing should be performed.
- Note: If the parent is the individual in whom the *ARHGAP31*, *DLL4*, *NOTCH1*, or *RBPJ* pathogenic variant first occurred, the parent may have somatic (and germline) mosaicism for the variant and may be mildly/minimally affected, although this phenomenon has not 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%.
- The sibs of a proband with clinically unaffected parents are still at increased risk for AOS because of the possibility of reduced penetrance in a parent.

- If the *ARHGAP31*, *DLL4*, *NOTCH1*, or *RBPJ* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband

- Each child of an individual with autosomal dominant AOS has a 50% chance of inheriting the pathogenic variant.
- Clinical outcome in offspring who inherit a pathogenic variant cannot be accurately predicted because of reduced penetrance and variable expressivity.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child diagnosed with autosomal recessive AOS are obligate heterozygotes (i.e., carriers of one *DOCK6* or *EOGT* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive AOS are obligate heterozygotes (carriers) for a pathogenic variant in *DOCK6* or *EOGT*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *DOCK6* or *EOGT* pathogenic variant.

Carrier (heterozygote) detection. Carrier testing for at-risk relatives requires prior identification of the *DOCK6* or *EOGT* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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, 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 and Preimplantation Genetic Testing

Once the *AOS*-related pathogenic variant(s) have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for AOS are possible.

Other issues:

- Routine prenatal ultrasound examination frequently misses minor limb anomalies, but directed assessment may be able to identify and estimate the extent of any defects.
- Intrauterine growth restriction, while not at all specific, may be present in a minority of severely affected infants.
- While there is very little literature on the detection of scalp or calvarial defects with targeted 3D ultrasound or fetal MRI, it is certainly theoretically possible.
- Calvarial defects may lead to elevated maternal serum α-fetoprotein level and positive amniotic fluid acetylcholinesterase [Dror et al 1994].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **MedlinePlus**

  Adams-Oliver syndrome

- **Children's Craniofacial Association**

  Phone: 800-535-3643

  Email: contactCCA@ccakids.com

  www.ccakids.org

- **REACH**

  Helping children with upper limb differences live life without limits.

  United Kingdom

  Phone: 0845 1306 225; 020 3478 0100

  www.reach.org.uk

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. Adams-Oliver Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ARHGAP31	3q13.32-q13.33	Rho GTPase-activating protein 31		ARHGAP31	ARHGAP31
DLL4	15q15.1	Delta-like protein 4		DLL4	DLL4
DOCK6	19p13.2	Dedicator of cytokinesis protein 6		DOCK6	DOCK6
EOGT	3p14.1	EGF domain-specific O-linked N-acetylglucosamine transferase		EOGT	EOGT
NOTCH1	9q34.3	Neurogenic locus notch homolog protein 1	NOTCH1 database	NOTCH1	NOTCH1
RBPJ	4p15.2	Recombining binding protein suppressor of hairless		RBPJ	RBPJ

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 Adams-Oliver Syndrome (View All in OMIM)

100300	ADAMS-OLIVER SYNDROME 1; AOS1
147183	RECOMBINATION SIGNAL-BINDING PROTEIN FOR IMMUNOGLOBULIN KAPPA J REGION; RBPJ
190198	NOTCH RECEPTOR 1; NOTCH1
605185	DELTA-LIKE CANONICAL NOTCH LIGAND 4; DLL4
610911	RHO GTPase-ACTIVATING PROTEIN 31; ARHGAP31
614194	DEDICATOR OF CYTOKINESIS 6; DOCK6
614219	ADAMS-OLIVER SYNDROME 2; AOS2
614789	EGF DOMAIN-SPECIFIC O-LINKED N-ACETYLGLUCOSAMINE TRANSFERASE; EOGT
614814	ADAMS-OLIVER SYNDROME 3; AOS3
615297	ADAMS-OLIVER SYNDROME 4; AOS4
616028	ADAMS-OLIVER SYNDROME 5; AOS5
616589	ADAMS-OLIVER SYNDROME 6; AOS6

Molecular Pathogenesis

Adams-Oliver syndrome (AOS) results from disturbance of the Notch signaling pathway or genes that regulate GTPases involved in actin cytoskeleton organization:

- EOGT glycosylates NOTCH1; DLL4 is a ligand for NOTCH1; and RBPJ is a binding partner for activated NOTCH1.
- DOCK6 and ARHGAP31 are known regulators of CDC42, a focal point for regulation of the actin cytoskeleton.

Although AOS is currently thought of as a multi-pathway disorder, the several known points of linkage between Notch signaling and CDC42 suggest that the pathogenic mechanisms may be unified in the future.

For a detailed summary of gene and protein information for the genes listed below, see Table A, **Gene**.

ARHGAP31

Gene structure. *ARHGAP31* comprises 12 exons encoding an 8-kb transcript with a 4332-bp open reading frame (NM_020754.3).

Pathogenic variants. All AOS-related *ARHGAP31* variants identified to date are dominant pathogenic truncating variants resulting in a gain of function. All are located in exon 12, the terminal exon.

Normal gene product. The ARGHAP31 protein has 1444 amino acids and is an inhibitor of CDC42/RAC1 GTPases. It contains a RhoGAP domain at its N terminus, potential protein kinase C phosphorylation sites, and five proline-rich SH3-binding motifs at its C terminus.

Abnormal gene product. The mutated ARGHAP31 protein causing AOS shows increased activity (gain of function), resulting in loss of available active CDC42, an important GTPase involved in cytoskeletal organization. As a result, the actin cytoskeletal structure is disrupted.

DLL4

Gene structure. *DLL4* comprises 11 exons (NM_019074.3).

Pathogenic variants. Dominant loss-of-function *DLL4* pathogenic variants, including nonsense, frameshift, and missense variants, cause AOS. Missense variants often change or create cysteine residues which are crucial for domain structure by forming disulfide bonds.

Normal gene product. The DLL4 protein contains a MNNL (N-terminal) domain, a DSL (Delta/Serrate/Lag-2) domain, and multiple EGF domains. It is a membrane-bound ligand for multiple NOTCH receptors and may compete for binding with JAG1, another Notch ligand [Luca et al 2015].

Abnormal gene product. *DLL4* pathogenic variants disrupt DLL4 integrity leading to loss of DLL4 function. As DLL4 is a NOTCH ligand this disrupts the Notch signaling pathway.

DOCK6

Gene structure. *DOCK6* comprises 48 exons (NM_020812.3).

Pathogenic variants. *DOCK6* pathogenic variants causing AOS are recessive loss-of-function variants, including nonsense variants, splice site variants, and large deletions.

Normal gene product. *DOCK6* encodes a 2047-amino acid protein containing two DOCK homology regions (DHR-1 and DHR-2). The DOCK6 protein belongs to the dedicator of cytokinesis family acting as a guanine nucleotide exchange factor for the Rho GTPases CDC42 and RAC1, which are involved in actin-cytoskeleton organization [Miyamoto et al 2007].

Abnormal gene product. AOS-causing *DOCK6* pathogenic variants lead to inactivation of CDC42 and RAC1, resulting in impaired actin-cytoskeleton organization.

EOGT

Gene structure. *EOGT* comprises 18 exons (NM_001278689.1).

Pathogenic variants. *EOGT* variants causing AOS are recessive loss-of-function variants.

Normal gene product. The EOGT protein is an EGF-domain-specific O-linked N-acetylglucosamine (O-GlcNAc) transferase involved in glycosylation of the EGF-repeat domain of Notch, allowing binding of the Notch ligands, which initiates the Notch signaling cascade [Sakaidani et al 2012].

Abnormal gene product. *EOGT* pathogenic variants cause impaired glycosyltransferase activity of EOGT, resulting in defective O-GlcNAcetylation of the target proteins.

NOTCH1

Gene structure. *NOTCH1* comprises 34 exons (NM_017617.3).

Pathogenic variants. *NOTCH1* variants causing AOS are dominant loss of function variants. AOS-causing missense variants are mostly located in the ligand binding domains of *NOTCH1* and often change or create cysteine residues, which are crucial for domain structure by forming disulfide bonds. Pathogenic frameshift, splice site, and deletion variants are also seen.

Normal gene product. The NOTCH1 protein contains 2555 amino acids. The ectodomain of NOTCH1 contains a series of epidermal growth factor (EGF)-like repeats that are responsible for ligand binding, a cysteine-rich region in close proximity with the heterodimerization domains, and a negative regulatory region (NRR) that blocks ADAM10/17 protease access to their cleavage sites. Intracellular NOTCH1 contains a RAM (RBPjk associate molecule) region, ankyrin repeats, a transactivation domain, and a PEST domain.

Binding of NOTCH ligands initiates internalization of the ligand by the presenting cell, which is thought to stretch the extracellular domain of the NOTCH receptor, removing the inhibition of the NRR and allowing ADAM10/17 protease cleavage to liberate the extracellular domain. This exposes a gamma-secretase cleavage site, with cleavage catalyzing release of the NOTCH intracellular domain (NICD). NICD translocates to the nucleus where it acts as a co-activator within a transcription factor complex to regulate gene expression [Andersson et al 2011].

Abnormal gene product. Most *NOTCH1* pathogenic variants causing AOS appear to be loss-of-function variants resulting in deregulation of the Notch signalling pathway, influencing levels of downstream regulated genes.

Cancer and benign tumors. Somatic *NOTCH1* pathogenic variants, most often activating, have been identified in hematologic cancers, and occur in 4%-12% of chronic lymphocytic leukemia and 60% of T-cell leukemia [Puente et al 2011, Quesada et al 2011, Wang et al 2011, Witkowski et al 2015], making it one of the more frequently mutated genes in hematologic malignancy.

Conversely, pathogenic variants of *NOTCH1* that likely inactivate the protein are found with notable frequency in squamous cell carcinomas of the skin, lung, and head and neck, as well as several types of brain tumors including low-grade glioma, anaplastic astrocytoma, and oligodendroglioma [Agrawal et al 2011, Bettegowda et al 2011, Killela et al 2014, Kim et al 2014, South et al 2014, Brat et al 2015].

RBPJ

Gene structure. *RBPJ* comprises 12 exons, of which 11 are coding (NM_005349.3).

Pathogenic variants. All *RBPJ* variants described to date are dominant loss-of-function variants resulting in loss of the DNA binding properties of RBP-J.

Normal gene product. The RBP-J protein is a DNA binding protein of 500 amino acids that acts as part of the Notch signaling pathway by controlling the expression of cascades of genes involved in cellular differentiation and function.

Abnormal gene product. AOS-related pathogenic variants in *RBPJ* result in decreased DNA binding capacity of the mutated protein, leading to deregulation of the Notch signaling pathway.

Cancer and benign tumors. Sporadic breast tumors and numerous other human cancers occurring as single tumors in the absence of any other findings of AOS frequently contain a somatic variant in *RBPJ* that is not present in the germline; thus, predisposition to these tumors is not heritable [Kulic et al 2015].

Chapter Notes

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