RESEARCH REVIEW

AMERICAN JOURNAL OF medical genetics PART A

Adams–Oliver Syndrome Review of the Literature: Refining the Diagnostic Phenotype

Susan Hassed,* Shibo Li, John Mulvihill, Christopher Aston, and Susan Palmer

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

Manuscript Received: 4 June 2015; Manuscript Accepted: 31 July 2016

The Adams–Oliver syndrome (AOS) is defined as aplasia cutis congenita (ACC) with transverse terminal limb defects (TTLD). Frequencies of associated anomalies are not well characterized. Six causative genes have been identified: *ARHGAP31, DOCK6, EOGT, RBPJ, NOTCH1*, and *DLL4*. We review 385 previously described individuals (139 non-familial and 246 familial probands and family members) and add clinical data on 13 previously unreported individuals with AOS. In addition to ACC and TTLD, the most commonly associated anomalies included a wide variety of central nervous system (CNS) anomalies and congenital heart defects each seen in 23%. CNS anomalies included structural anomalies, microcephaly, vascular defects, and vascular sequelae. CNS migration defects were common. Cutis marmorata telangiectasia congenita (CMTC) was found in 19% of the study population and other vascular anomalies were seen in 14%. Hemorrhage was listed as the cause of death for five of 25 deaths reported. A relatively large number of non-familial probands were reported to have hepatoportal sclerosis with portal hypertension and esophageal varices. Non-familial probands were more likely to have additional anomalies than were familial probands. The data reported herein provide a basis for refining the diagnostic features of AOS and suggest management recommendations for probands newly diagnosed with AOS. © 2017 Wiley Periodicals, Inc.

Key words: Adams–Oliver syndrome; aplasia cutis congenita; transverse terminal limb defects; *DOCK6*; *RBPJ*; *EOGT*; *NOTCH1*; *DLL4*

How to Cite this Article:
Hassed S, Li S, Mulvihill J, Aston C, Palmer S. 2017. Adams–Oliver syndrome review of the literature: Refining the diagnostic phenotype.
Am J Med Genet Part A 173A:790–800.

INTRODUCTION

The Adams–Oliver syndrome [AOS (MIM#100300)] is a rare inherited multiple malformation syndrome characterized by aplasia cutis congenita (ACC) and transverse terminal limb reduction defects (TTLD) and was initially described in a three generation family [Adams and Oliver, 1945]. Since then, numerous other anomalies have been reported including cutis marmorata telangectasia congenita (CMTC), microcephaly without associated brain anomalies, microphthalmia, cleft lip and/or palate, accessory nipple, and imperforate vaginal hymen. Other anomalies of the limbs have also been described including Poland anomaly, small nails, cutaneous syndactyly, bony syndactyly, split hand or foot, polydactyly, and brachydactyly. Rare complex as well as more common cardiac anomalies and other vascular anomalies have been reported, as have intellectual deficits in the absence of brain anomalies and rare CNS anomalies. The phenotype within families may range from no obvious clinical manifestations in obligate mutation carriers to severe anomalies in multiple systems that result in miscarriage or stillbirth (Supplementary Table SI).

In 2011, two of several genes associated with AOS were identified. These were autosomal dominant gain-of-function mutations of *ARHGAP31* (MIM#610911) in two families [Southgate et al., 2011] and homozygous loss of function mutations in *DOCK6* (MIM#614194) in two consanguineous families [Shaheen et al., 2011]. Both proteins interact with ras-related C3 botulinum toxin substrate 1(RAC1); ARHGAP31 is a GTPase-activating protein (GAP) that controls activation of RAC1 cycling between active GTP-bound protein and inactive GDP-bound protein and leads to a reduction of activated RAC1, whereas DOCK6 functions as a switch between the conformational states of GDP-bound (inactive) and GTP-bound (active) RAC1 [Shaheen et al., 2011]. Isrie later reported another large family harboring an *ARHGAP31* mutation and having TTLD as the only anomaly [Isrie et al., 2014].

Hassed et al. [2012] identified mutations in *RBPJ* (recombination signal binding protein for immunoglobulin kappa J region) (MIM#147183) through exome sequencing in two independent kindreds with autosomal dominant AOS. RBPJ is of central importance in the Notch signaling pathway.

Conflicts of interest: none.

*Correspondence to:
Susan Hassed, PhD, LCGC, Children's Hospital of Oklahoma, 1200 Children's Ave, Suite 12100, Oklahoma City, OK 73104.
E-mail: susan-hassed@OUHSC.edu

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 4 February 2017
DOI 10.1002/ajmg.a.37889

Homozygous mutations in *EOGT* (MIM#314789) were identified in three consanguineous families with AOS [Shaheen et al., 2013]. EOGT glycosylates NOTCH1 in mammals and is considered to be the cause of AOS in those three families.

In 2014, mutations in *NOTCH1* (MIM#190198) were identified in a father and daughter with AOS, three additional non-familial probands (one was previously described by Silva et al. [2012]) and the proband from a fifth family previously described by Vandersteen and Dixon [2011] whose sister and father were not tested because they are no longer living [Stittrich et al., 2014].

Meester et al. in 2015 screened 91 families with AOS and identified mutations in *DLL4* (MIM#605185) in nine of those families [Meester et al., 2015]. There were four non-familial probands, five familial probands, and 13 family members reported with clinical findings, a mutation in *DLL4*, or both. DLL4 is a member of the delta family of membrane-bound ligands containing extracellular epidermal growth factor (EGF)-like domains and is expressed in arterial endothelium [Shutter et al., 2000], supporting the thesis that AOS is due to an error in vascularization in a subset of affected individuals.

There are now six genes found to be causally related to AOS; two function in the CDC42/RAC1 pathway and four are important in Notch signaling.

MATERIALS AND METHODS

The dataset evaluated herein is comprised of information obtained through a comprehensive review of the literature and included publications in English, Spanish, Portuguese, and French. The initial search used the terms Adams–Oliver syndrome, aplasia cutis congenita, cutis marmorata telangiectasia congenita, and transverse terminal limb defects. The bibliography of each paper was examined for additional sources not identified in the original search.

Reported in addition to those from the literature are unpublished probands and family members from seven geneticists who provided specific information using a form provided by the author (Supplementary Form I) and previously unreported participants from the University of Oklahoma (OU) study population (Table I); the group is comprised of seven non-familial probands and two families (one proband and two family members in each family). The primary data set is restricted to those with both ACC and TTLD; in those where only one feature is present in the proband, a family member must have had the other feature for the family to be included in the analysis.

Those probands from the literature, contributed probands, or the OU study group where the proband was identified as having Adams–Oliver syndrome but ACC and TTLD were not both present in the proband or among family members are not included in the analysis. However, one family with a frameshift mutation in *ARHGAP31* reported by Isrie et al. [2014] that has TTLD in the absence of other anomalies has been included in the analysis due to the fact that there is a proven mutation in a gene known to cause AOS.

The frequency of probands with specific anomalies, in addition to ACC and TTLD, was compared using Pearson chi-square tests to determine if non-familial probands were more likely than familial probands to have additional anomalies. The average number of additional anomalies per proband was compared using Student *t*-tests to determine if non-familial probands tend to have more anomalies in multiple body systems as compared to familial probands. Correlation (denoted as r) in occurrence of pairs of anomalies was calculated and tested to be different from zero ($r = 0$) (Supplementary Table SII). Analyses used Excel (MS Office 2013) and IBM SPSS for Windows (Version 20.0. Armonk, NY: IBM Corp). *P*-values <0.05 were treated as significant for the purposes of discussion.

Current Clinical Reports

Family Cu. Cu-Pt1 is a female with a very large ACC of the scalp and an underlying bony defect through the dura. There was reduction of all four limbs consisting of absent hands and feet with a few vestigial nubbins. She had an atrial septal defect (ASD) and no other anomalies. Cu-Pt2, her brother, was identified to have AOS on prenatal ultrasound examination and the pregnancy was terminated. The boy had a very large scalp ACC with bony defect and herniating brain. The four limb reduction consisted of absent wrists and hands with right forearm showing tiny nubbins, the ankles and feet were absent. There were no other anomalies. Cu-Pt3, the mother of Cu-pt1 and Cu-pt2, had normal scalp and mild four limb reduction consisting of short 4th metacarpal, short 2nd fingers on hands, and indistinct 5th finger flexion creases. Both feet showed mild shortening of toes.

Fry-pt1. The proband is a female with small scalp ACC and mild two limb reduction consisting of loss of middle and terminal phalanges of 3rd, 4th, and 5th fingers and 3/4/5 syndactyly of the right hand. The left hand showed similar defects but affected the 2nd and 3rd fingers with minimal syndactyly. The feet were normal. There were no other anomalies.

Hd-pt1. The proband is a female with scalp ACC and underlying thinning of the calvarium with a mild three limb defect including both feet with the left foot affected more than right, cutaneous syndactyly of 4th and 5th toes, and small nails. The left hand had a small 5th finger with short nail. Her CHD was reported to be tetralogy of Fallot, ventricular septal defect (VSD), SVC to coronary sinus. An abnormal head magnetic resonance imaging (MRI) showing multiple foci of T1 signal hyperintensity within the subependymal and periventricular regions of the lateral ventricles, ischemia, periventricular leukomalacia, hypoplastic corpus callosum, and microcephaly. Developmental delay was present. Physical examination was positive for esotropia.

Hs2-pt1. The proband is a female with ACC of the scalp and three-limb reduction described on bone survey as follows: (i) right "mitten hand" with absent distal phalanges; (ii) left hand with the thumb terminating at mid-proximal phalanx, 2nd finger terminating at the base of the proximal phalanx, 3rd finger terminating at the base of the middle phalanx, 4th finger terminating at the proximal interphalangeal joint, and intact 5th finger; and (iii) right foot missing all but the base of the proximal phalanx of the hallux, the middle and distal phalanges of the second toe and some soft tissue from the third toe. No other anomalies were present.

Hs9-pt1. The proband is a female born with large ACC of the scalp, underlying skull defect, and small nail of the left hallux. There was hemorrhage from the scalp defect. CMTC was widespread. An

TABLE I. Reported Probands and Family Members This Review

Reference	Identifier	Female	Male	ACC scalp	Severity scalp defect*	Bleeding from lesion	Bony defect	Limb reduction	Small nails	Syndactyly or brachydactyly	Location	Poland anomaly	CHD	CMTC
Abbott	Su-pt1		+	+	3		+	+	+					
	Su-pt1 brother		+											+
	Su-pt1 pat grandmother	+		+										
Curry	Cu-pt1	+		+	4		+	+					+	
	Cu-pt2 brother		+	+	4		+	+						
	Cu-pt3 mother	+						+						
Fryer	Fry-pt1	+		+	1			+		Cutaneous	hands			
Haldeman-Englert	Hd-pt1	+		+				+	+	Cutaneous	4/5 R toes		+	
Seaver	Sr-pt1		+	+	3	+	+	+	+					+
Toutain	Tu-pt1	+		+				+	+				+	+
Hassed study	Hs2-pt1	+		+				+		Cutaneous	R hand			
	Hs10-pt1		+	+				+					+	
	Hs9-pt1	+		+	3	+	+	+					+	+

Reports part 2												
Identifier	Microcephaly	CNS anomaly	Seizures	Age at inception (Years)	Eye anomaly	GI anomaly	Other cutaneous	Short stature	Dev. delay	Vascular anomaly	Other	
Su-pt1												
Su-pt1 brother												
Su-pt1 pat grandmother												
Cu-pt1												
Cu-pt2 brother												
Cu-pt3 mother												
Fry-pt1												
Hd-pt1	+	+							+			
Sr-pt1	+		+	0.2		+		+				
Tu-pt1		+							+	+		
Hs2-pt1												
Hs10-pt1												
Hs9-pt1		+	+	0.01		+			+	+	46,XX CGH + SNP array normal, death at 17 mo due to pulmonary hypertension	

Contributors: Mary Alice Abbott, MD, PhD, Chief, Medical Genetics, Baystate Children's Hospital, Springfield, MA. Cynthia Curry, MD, Valley Children's Hospital, Fresno, CA. AE Fryer, MD, FRCP, Liverpool Women's Hospital and Alder Hey Children's Hospital, Liverpool, England. Chad Haldeman-Englert, MD, FACMG, Wake Forest School of Medicine, Winston-Salem, NC. Laurie Seaver, MD, University of Hawaii John A. Burns School of Medicine, Honolulu, HI. Dr. Annick Toutain, Service de Genetique, Centre Hospitalo-Universitaire, Tours, France.

*1 = <3 cm, 2 = 3 to <5 cm, 3 = 5 to <10 cm, and 4 = > = 10 cm.

echocardiogram revealed a small patent ductus arteriosis (PDA), bicuspid aortic valve, pulmonary hypertension, and right ventricular hypertrophy. Head MRI identified a periventricular splinter hemorrhage with echogenic foci in the periventricular white matter and medullary vein thrombosis. She had a seizure disorder and developmental delay. The child died at 17 months of age due to pulmonary hypertension. Hepatic fibrosis versus cirrhosis was identified at autopsy. A second pregnancy of a full sibling was terminated following identification of hypoplastic left heart. Because fetal autopsy was unavailable, the sibling was not included in this data set.

Hs10-pt1. The proband is a male with scalp ACC without cranial defect and three limb reduction described on bone survey as follows: (i) small proximal phalanx and absence of the middle and distal phalanges of the first finger of the left hand; (ii) small middle and distal phalanges of the 2nd, 3rd, and 4th toes, absent middle phalanx of the little toe, and small distal phalanx of the hallux of the left foot; and (iii) small distal phalanx of the 3rd toe and small proximal phalanx and absent distal phalanx of the hallux, of the right foot. Head MRI revealed no anomalies.

Family Su. Su-pt1 is a male with a large scalp ACC, underlying bony defect without hemorrhage from the defect. There was mild two limb reduction defect described as bilateral hypoplastic toes. There were small nails on the hands. Echocardiogram, brain MRI, and renal ultrasonogram showed no abnormality. The older brother of the proband had normal limbs and scalp, but exhibited CMTC over his left knee and lower leg. The paternal grandmother was reported to have a bald spot, but was not examined.

Sv-pt1. The proband is a male with a large scalp ACC, underlying bony defect, and hemorrhage from the defect. There was mild two limb reduction defect described as generalized brachydactyly of both feet, the right hallux was small, all toes showed small nails, and the feet were short. He had microcephaly and developed seizures at 2 months of age. He had widespread CMTC and short stature. At 4 months of age he developed a large bowel obstruction and was determined to have congenital bands or adhesions in the absence of previous surgery.

Tu-pt1. The proband is a female with scalp ACC. Radiographs of the extremities showed an ossification defect of the middle and distal phalanges of the 2nd to 5th toes and mild hypoplasia of the distal phalanges of the fingers, mainly of the 2nd and 5th fingers. There were prominent veins on the face and diffuse CMTC. A heart defect was present that consisted of VSD, right pulmonary artery stenosis, hypoplastic aortic arch, hypoplastic vena cava, and absent left superior vena cava. She developed pulmonary hypertension. Head ultrasonography revealed right subependymal cyst. She exhibited developmental delay.

SUMMARY DATA—ALL REPORTS

There were a total of 398 individuals included in this report. Probands who had no family members reported were grouped as non-familial and probands with family members with features of AOS were considered as familial. Of probands and family members with confirmed AOS, 252 (63%) had no anomalies in other body systems. Non-familial probands were significantly more likely to have anomalies in addition to those required to make the diagnosis of AOS than were probands with affected family members (60% vs. 38%, respectively, $P = 0.0026$). The frequency of anomalies in various body systems was compared between non-familial probands and familial probands (Table II). Non-familial probands had a greater number of anomalies per individual ($P = 0.0012$), were much more likely to have CNS anomalies ($P = 0.0010$), were more likely to have both CNS and cardiac anomalies ($P = 0.049$), and more likely to have anomalies of the liver, most resulting in esophageal varices ($P = 0.031$) than were familial probands. Of all those with no anomalies in other systems (n = 252), 24 (10 non-familial, six familial, eight family members) had CMTC, 16 (seven non-familial, five familial, four family members) exhibited vascular anomalies, largely prominent or tortuous vessels on the scalp or face, and 11 (five non-familial, three familial, three family members) had both CMTC and other vascular anomalies for a total of 51 (20%) with some type of vascular finding in the absence of an anomaly in another body system.

TABLE II. Comparison of Isolated and Familial Probands

Feature	Non-familial probands	Familial probands	Significance
Average number of other malformations	0.98	0.54	0.0012
CNS anomalies	63	17	0.0010
Non-vascular	7	3	0.70
Vascular or secondary effects	22	12	0.0075
Isolated microcephaly	10	4	0.56
Developmental disability	21	12	0.82
Structural anomaly of the eye	10	5	0.70
Cleft lip w/without cleft palate	6	1	0.23
Congenital heart defect (CHD)	50	21	0.16
Both CNS and CHD	27	9	0.049
Liver anomalies	9	0	0.031
Renal anomalies	4	1	0.46
CMTC	44	17	0.16

ACC and Underlying Calvarial Involvement

All but 1% of ACC was found on the scalp; 49% of probands (74 non-familial, 38 familial) and 20% of family members with a scalp defect had underlying bone hypoplasia.

Limb Anomalies

The spectrum of limb anomalies previously reported in addition to reduction defects include syndactyly, split hand or foot, and polydactyly. Cutaneous syndactyly, bony syndactyly, or both were reported in 29% of probands (45 non-familial, 21 familial), and 16% of family members. Small nails were reported in 51% of probands (84 non-familial, 31 familial), and 11% of family members.

Poland anomaly was first reported by Der Kaloustian et al. [1991] in two families; the mother of a proband with AOS in Family 1 and the proband and his mother, both with AOS, in Family 2. Hoyme et al. [1992] later reported an additional two male family members in Family 2, a male, who was a first cousin to the mother of the proband and his son for a total 2% of the study group.

Central Nervous System (CNS) Involvement

A common finding was brain anomalies in 35% of probands (63 non-familial, 17 familial), and 8% of family members, which is higher than previously reported. Brain anomalies were grouped based on etiology: isolated microcephaly, non-vascular cause, possible vascular component, and secondary to vascular sequelae (Table III).

Microcephaly without underlying brain anomalies was reported in 7% of probands (11 non-familial, four familial), and 1.2% of family members. Of all those with reported isolated microcephaly (n = 17), seven had some type of negative evaluation of the brain (CT, MRI, EEG, or autopsy), and the remaining 10 had no evaluation reported.

Structural anomalies were varied, and many could not be attributed to vascular events; encephalocele, microcephaly with a brain anomaly, and neuronal migration anomalies were included in that group. Most unexpected was a high rate of CNS migration defects: pachygyria, polymicrogyria, dysplasia, heterotopia, schizencephaly, and colpocephaly, at 40% of all those with a structural anomaly and 10% of all reported brain anomalies.

Anomalies of brain do not appear to be dependent upon a communicating anomaly between brain and skull as 48% of those with brain anomalies had intact crania and 55% of probands with a bony defect had no identified brain anomaly. However, dilated or abnormally shaped ventricles were more than three times as common in probands with calvarial defects.

CNS anomalies with a possible vascular component or sequelae of vascular dysfunction (ischemia, infarct, periventricular leukomalacia and/or calcifications) were reported in 22% of probands (42 non-familial, nine familial), and 5% of family members. Many individuals had greater than one anomaly with a vascular component (Table III).

Comparisons were made among isolated microcephaly, the occurrence of structural brain anomalies, and vascular anomalies or their effects. Individuals with vascular anomalies or their effects were significantly more likely to have anomalies in other systems ($P = 0.0002$), and that group of defects was significantly associated with developmental delay (correlation $r = 0.79$, $P < 0.0001$), far higher than in individuals with other structural anomalies or isolated microcephaly.

Intellectual deficits of varying degree were reported in 15% of probands (21 non-familial, 12 familial), and 2% of family members. Of those 37 probands and family members with intellectual deficits reported, 9% of probands (one non-familial, two familial), and 50% of family members had isolated microcephaly, 39% of probands (11 non-familial, two familial) had microcephaly in association with other brain anomalies, 33% of probands (seven non-familial, four familial), and 25% of family members had a brain anomaly without microcephaly, and 18% of probands (two non-familial, four familial), and 25% of family members had developmental disability in the absence of reported brain anomalies or microcephaly. Thus, intellectual deficits are unusual in probands or family members of probands in the absence of microcephaly or underlying brain anomaly.

Congenital Heart Defects (CHD)

Congenital heart defects (CHD) were present in 23% of the study group, 31% of probands (50 non-familial, 21 familial), and 12% of family members. Pulmonary hypertension was reported in 4% of probands (seven non-familial, one familial), and 2% of family members. Of those reported to have had echocardiography, catheterization, autopsy, or other study, 23 non-familial, 10 familial, and six family members were reported to have no cardiac anomalies (Table IV).

Vascular Anomalies Other Than CHD

CMTC was reported in 26% of probands (43 non-familial, 17 familial), and 9% of family members, occurring in 19% of all affected. Of those with CMTC, 11% of probands (19 non-familial, six familial), and 4% of family members had additional vascular anomalies (cardiac defects are considered separately) and of those with CMTC and other extra-cardiac vascular anomalies, 4% of probands (six non-familial, two familial), and 2% of family members had no anomalies in other systems. Tortuous or prominent vessels occurred in 15% of probands (24 non-familial, nine familial), and 6% of family members, most being located on the scalp or face; other vascular anomalies were reported in 8% of probands (14 non-familial, four familial), and 2% of family members, and two of those individuals had both tortuous or prominent vessels and another vascular anomaly. A total of 26% of individuals from this review had some vascular anomaly: CMTC, another vascular anomaly, or both.

Anomalies of vascular origin were compared, with CMTC showing a significant correlation with skull defect ($r = 0.14$, $P = 0.035$) and heart defects ($r = 0.14$, $P = 0.030$), but not with vascular brain anomaly ($r = 0.02$, $P = 0.80$). CHD showed a significant correlation with vascular brain anomaly ($r = 0.19$, $P = 0.0044$), but not with non-vascular brain anomalies ($r = 0.04$, $P = 0.59$) or isolated microcephaly ($r = -0.02$, $P = 0.79$).

In the study group, hemorrhage, generally from a scalp defect, occurred in 13% of probands (25 non-familial, 4 familial), 3% of

TABLE III. Brain Anomalies

	All probands total n = 227		Family members total n = 171		Study total n = 398		Calvarial defect present	
Feature	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Isolated microcephaly[a]	14	6	2	1.2	16	4	5	31
Non-vascular etiology								
Encephalocele	3	1.3			3	0.8	2	67
Microcephaly with other anomalies	20	9	2	1.2	22	6	9	41
Neuronal migration anomalies								
Pachygyria or polymicrogyria	5	2	1	0.6	6	1.5	2	33
Cortex dysplasia	6	3	1	0.6	7	1.8	3	43
Heteropia	1	0.4			1	0.3	1	100
Schizencephaly or cleft	2	0.9			2	0.5	1	50
Colpocephaly	1	0.4			1	0.3	1	100
Possible vascular component								
Hemimegalencephaly	2	0.9			2	0.5	2	100
Hemihypoplasia	1	0.4			1	0.3	1	100
Hypoplasia cerebrum	1	0.4			1	0.3	1	100
Small cerebellum/DWM/Chiari	4	1.8	2	1.2	6	1.5	1	17
Diencephalon/pitutary hypoplasia	3	1.3	1	0.6	4	1.0	2	50
Brainstem hypoplasia	2	0.9	1	0.6	3	0.8	1	33
Thin or absent corpus callosum	13	6	3	2	16	4	7	44
Hydrocephalus	6	3	1	0.6	7	1.8	5	71
Enlarged ventricles	16	7	3	2	19	5	8	42
Abnormal ventricle shape	5	2	2	1.2	7	1.8	5	71
Extra-axial CSF/subdural cyst	10	4	1	0.6	11	3	7	64
Secondary to vascular sequlae								
Vascular hypoplasia	2	0.9			2	0.5	2	100
Venous sinus aplasia	1	0.4			1	0.3	1	100
Thrombosis	3	1.3			3	0.8	1	33
Stroke/ischemia	7	3	1	0.6	8	2	5	63
Calcifications	16	7	4	2	20	5	11	55
Periventricular leukomalacia	8	4	2	1.2	10	3	3	30
Subdural hematoma			1	0.6	1	0.3	1	100
Intraventricular hemorrhage	3	1.3			3	0.8	1	33
White matter foci of unclear etiology	3	1.3			3	0.8	1	33
Abnormal brain vasculature	1	0.4			1	0.3	1	100
No anomalies-shown by imaging or autopsy	24	11	2	1.2	26	7	14	54
Calvarial defect with brain anomaly	40	18	5	3	45	11		
Calvarial defect without brain anomaly	73	32	28	16	101	25		

[a]In reports where measurements were reported, the assessment of microcephaly was accurate.

family members, and 9% in total. The occurrence of hemorrhage did not correlate with the size of the scalp defect in those where size was reported (Table V). A total of 24 deaths were reported and five were due to hemorrhage; in one the defect was >9 cm and the size of the defect was not reported in the others.

Hepatoportal disease was reported in 4% of probands (nine non-familial, one familial) and a single family member. Of those with hepatoportal disease, five showed hepatoportal sclerosis on histology, three with fibrosis, one with sinusoidal dilatation, one with massive steatosis, and one with biliary atresia. Esophageal varices were noted in seven, absent in two, and unknown in two; portal hypertension was reported in all those with esophageal varices and in one with unknown presence of varices. Three of the group were reported to lack portal hypertension, esophageal varices, or portal anomalies, and two of them were reported to have CMTC and other organ system anomalies. One familial proband had biliary atresia that was successfully repaired in infancy and he had no other anomalies (Table VI).

Ocular Anomalies

Esotropia, previously suggested as a feature of AOS, was reported in one male proband and his sister as well as one other unrelated female proband (1%) and may well be considered a secondary effect of an underlying brain abnormality.

TABLE IV. Congenital Heart Defects

	All probands total n = 227		Family members total n = 171		Study total n = 398	
	n	%	n	%	n	%
Valvular anomalies						
Aortic valve (bicuspid or parachute)	12	5	10	6	22	6
Mitral valve (prolapse or parachute)	1	0.4	1	0.5	2	0.5
Pulmonary valve (prolapse, stenosis)	2	0.9	1	0.5	3	0.8
Tricuspid valve atresia or incompetence	3	1.3	1	0.5	4	1.0
Vascular anomalies						
Patent ductus arteriosus	8	4	2	1.2	10	3
Pulmonary stenosis, obstruction, atresia	12	5			12	3
Coarctation of the aorta or stenosis	3	1.3	2	1.2	5	1.3
Hypoplastic transverse aortic arch	3	1.3			3	0.8
Right aortic arch	1	0.4			2	0.5
Totally anomalous venous return	2	0.9			2	0.5
Truncus arteriosis	3	1.3			4	1.0
Transposition great vessels	1	0.4			1	0.3
Ventricular anomalies						
Ventricular septal defect	21	9	1	0.5	22	6
Double-outlet left ventricle	1	0.4			1	0.3
Left ventricular hypertrophy	2	0.9	1	0.5	3	0.8
Hypoplastic right ventricle	1	0.4			1	0.3
Double-outlet right ventricle	3	1.3			3	0.8
Right ventricular hypertrophy	3	1.3			3	0.8
Atrial anomalies						
Atrial septal defect (including secundum)	17	7	1	0.5	18	5
Patent foramen ovale	6	3			6	1.5
Small left atrium	1	0.4			1	0.3
Other anomalies						
Dextrocardia	1	0.4			1	0.3
Pulmonary hypertension	8	4	3	2	11	3
Tetralogy of Fallot	7	3	4	2	11	3
Ischemic cardiomyopathy			1	0.5	1	0.3
Left coronary artery stenosis			1	0.5	1	0.3
No anomalies-shown by imaging or autopsy	33	15	7	4	40	10
Non-cardiac vascular anomalies						
Cutis marmorata telangiectasia congenita	61	27	15	9	76	19
Prominent vessels	22	10	8	5	30	8
Tortuous vessels	17	7	3	2	20	5

Microphthalmia has been suggested as a feature in AOS, and was reported as a mild feature in a single proband (0.3%).

Multiple other ocular anomalies have been reported in 7% of probands (10 non-familial, 5 familial) and 2% of family members. Reported anomalies were retinal bleeding, retinal folds and detachment (7), avascular retina (1), optic nerve hypoplasia (1) or atrophy (1), rod dystrophy (1), hypoplastic disc (1), unusual choroidal architecture (1), Peters anomaly (1), partial exophthalmos (1), upper eyelid anomaly (1), and cataract (2). All but two of those with ocular anomalies also have anomalies in other systems.

Other Anomalies

Cleft lip and/or palate was reported in 2% of probands (six non-familial, one familial) and no family members.

Imperforate vaginal hymen was reported in a single familial proband (0.3%).

Accessory nipple was reported in 1% of probands (two familial) and 0.8% of family members.

Anomalies Associated With Mutations in Specific Genes

When looking at genotype-phenotype correlations for the genes identified to date, it is interesting to note that, other than one individual with a communicating skull defect and two with syndactyly, individuals with *ARHGAP31* mutations have no anomalies other than those required for diagnosis (n = 25). Those with *RBPJ* associated AOS include two individuals with microcephaly, a proband and her father, and one other with a communicating

TABLE V. Risk of Hemorrhage Compared to Size of Scalp Defect

Defect size	Literature reports # of hemorrhage (total scalp defect)	Current report # of hemorrhage (total scalp defect)	Total # of hemorrhage (total scalp defect)	Total % of hemorrhage with scalp defect
Less than 3 cm	1 (45)	0 (1)	1 (46)	2
>3–5 cm	4 (33)	0 (0)	4 (33)	12
>5–9 cm	8 (69)	2 (2)	8 (71)	11
>9 cm	14 (53)	0 (2)	14 (55)	25
Not stated	5 (108)	0 (9)	5 (117)	4

skull defect, but no additional anomalies (n = 6). Individuals with *DOCK6* mutations have the broadest range of anomalies reported, followed by those with *NOTCH1* mutations. Structural brain anomalies or microcephaly are reported for all genes other than *ARHGAP31* (Table VII). Of the six genes identified to date as causally related to AOS, *NOTCH1* is the only gene that has been identified as a cause of another condition, aortic valve disease, and six of the 10 probands with *NOTCH1* mutations who had a cardiac defect had aortic valve disease alone or in conjunction with other cardiac anomalies.

DISCUSSION

Since first reported seven decades ago, AOS has broadened from the original pair of features, cutis aplasia and asymmetric limb reduction defects, to include anomalies in multiple body systems.

It is clear that there is no single type of brain anomaly reported in those with AOS or their family members, but reported brain anomalies are likely to be a result of the underlying genetic defect. There may be some number of probands with brain anomalies that have not been investigated, although there were 24 (11%) probands and two (1.2%) family members reported to be negative for brain anomalies following evaluation. Brain anomalies are variable and consist of structural anomalies and those caused by neuronal migration defects as well as vascular anomalies. The pattern of abnormalities is not consistent within families and individuals frequently have anomalies of more than one type, suggesting that the underlying genetic defect does not determine whether anomalies are more likely to be due to vascular cause or a neuronal migration defect. Not all individuals with brain anomalies are reported to have intellectual deficits and those with intellectual disability do not all have an identified brain anomaly (Table III). Isolated microcephaly also appears to be a manifestation of AOS. It

TABLE VI. Probands and Family Members With Liver Pathology

Liver pathology	Liver histology	Portal hypertension/esophageal varices/portal anomalies	Non-hepatic MICRO vascular anomalies
Po-pt1 [Pouessel et al., 2006]	Hepatoportal sclerosis	+/+/—	CMTC
Gi-pt1 [Girard et al., 2005]	Hepatoportal sclerosis	+/+/Extra-hepatic portal vein obstruction	CMTC
Gi-pt2 [Girard et al., 2005]	Hepatoportal sclerosis	+/+/Extra-hepatic portal vein obstruction	None known
Sz-pt1 [Swartz et al., 1999]	Hepatoportal sclerosis	+/+/abnormal portal branches	Extensive CMTC; lung plexigenic arteriopathy
Shi-pt1 [Snape et al., 2009]	Hepatoportal sclerosis	+/?/?	(unknown)
Sp-pt2 [Snape et al., 2009]	Fibrosis	+/+/Absent & hypo- plastic portal branches	CMTC
Si-pt1 [Silva et al., 2012]	Sinusoidal dilatation	+ /+/Hypoplastic portal branches; late obstruction	CMTC; distal watershed stokes
Fy-pt1 [Fayol et al., 2006]	Massive steatosis	—/—/—	extensive CMTC; heart, kidney, brain (autopsy)
Mee-pt5 first cousin [Meester et al., 2015]	Fibrosis	+/+/?	None known
Hs9-pt1	Fibrosis	—/—/—	CMTC, heart defect, periventricular splinter hemorrhage, medullary vein thrombosis
RD-pt1 [Renfree and Dell 2016]	Biliary atresia	—/—/—	None known

is not possible at this time to determine the etiology and that may indeed depend on the underlying genetic cause. However, not all individuals with "isolated" microcephaly have had imaging of the brain reported.

Congenital heart defects (CHD) are frequent in those with AOS and should be considered to be a part of AOS.

Hemorrhage from a scalp defect was reported in a large number of probands, but was not significantly associated with the size of the scalp defect and may be due to an inherent defect in vascular development (Table V). This review also supports the inclusion of CMTC as an occasional manifestation of AOS, since it occurs in 27% of probands and 10% of family members. Additionally, pulmonary hypertension, which is often due to vascular narrowing, was seen in eight probands and three family members, and is likely due to AOS.

Liver anomalies were surprisingly common, occurring in 11 (3%) individuals in the study population: nine non-familial probands, one familial proband, and one cousin. Most (7 of 11) were reported to have CMTC which supports a vascular etiology (Table VI).

It has been suggested that the Poland anomaly is a result of a vascular anomaly in the subclavian artery [Fraser et al., 1989] and may be a severe expression of asymmetrical limb reduction defects; therefore, a feature of AOS.

Small nails should be considered a part of AOS, not necessarily secondary to the limb reduction, as it is seen on digits that show no other abnormality. However, clinical judgement should be employed when determining if the finding in a particular proband is indicative of an anomaly or within the normal range of development. Cutaneous syndactyly has been suggested as the result of a vascular anomaly [Fraser et al., 1989] and occurred in 29% of probands and 22% of family members, supporting inclusion as a feature of AOS. Surprisingly, split hand or foot was reported once in this study group, although it is possible to postulate that, like the Poland anomaly, it may be a severe presentation of an underlying vascular anomaly. Polydactyly was reported in three probands and no family members, and may be due to some other cause.

Although facial clefting has not frequently been reported with AOS, cleft lip and/or palate may be a part of AOS in a subset of affected individuals, depending upon the specific genetic etiology.

Though not previously suggested as a part of AOS, many of the reported ophthalmologic anomalies have a vascular cause, so it is reasonable to consider retinal vascular anomalies a part of AOS. Interestingly to date, where the gene mutation is known, ocular anomalies are reported only in those with *DOCK6* mutations and of all ocular anomalies, 28% were in non-familial probands with *DOCK6* mutations. Nohata et al. [2016] demonstrated that Rac1, which is activated through phosphorylation by DOCK6 of bound GDP, is necessary in the mouse for endothelial sprouting in the retinal vasculature.

In support of the hypothesis that AOS is primarily a vascular disruption defect, four of the genes with mutations causative for AOS are involved in the Notch signaling pathway. Mutations in those four genes could well be expected to lead to disruption of the pathway leading to errors in transcriptional regulation of a variety of other genes [Aminkeng, 2015]. Mutations in the two other genes

TABLE VII. Gene Mutations With Reported Anomalies

	ARHGAP31	*DOCK6*	*RBPJ*	*EOGT*	*NOTCH1*	*DLL4*
	AD	AR	AD	AR	AD	AD
Feature	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number with gene mutation	25 (7)	16 (4)	6 (2)	19 (5)	23 (6)	18 (5)
Percentage of all reports						
Vertical transmission demonstrated	+	−	+	−	+	+
ACC	6 (24)	15 (94)	6 (100)	18 (95)	18 (78)	16 (89)
Hemorrhage from lesion					3 (13)	
Skull defect	1 (4)		1 (17)	5 (26)	7 (30)	3 (17)
TTLD	25 (100)	16 (100)	6 (100)	5 (26)	19 (83)	6 (33)
Syndactyly	2 (8)	2 (12)		11 (58)	5 (22)	1 (6)
Small nails		4 (25)		5 (26)	6 (26)	1 (6)
Congenital heart defect		5 (31)		3 (16)	10 (43)	2 (11)
Pulmonary stenosis					1 (4)	1 (6)
Pulmonary hypertension					1 (4)	2 (11)
Brain anomaly		11 (69)		2 (11)	3 (13)	1 (6)
Isolated microcephaly		3 (19)	1 (17)			
Eye anomaly		5 (31)				
GI—esophageal varicies					3 (13)	
Vascular anomalies						
CMTC		2 (12)		1 (6)	3 (13)	5 (28)
Prominent vessels				6 (32)		
Tortuous vessels		1 (6)				
Lymphedema					1 (4)	

identified to date, *DOCK6* and *ARHGAP31*, result in loss-of-function and gain-of-function, respectively, of the resulting proteins both of which interact with RAC1 to activate (DOCK6) through phosphorylation of bound GDP or inactivate (ARHGAP31) through conversion of bound GTP to GDP. Nohata et al. [2016] recently reported that Rac1 excision in E10.5 mouse embryo resulted in severe hemorrhage at E15.5. They also noted that vascular network formation of the back skin was significantly reduced and postulated that it was due to abnormal angiogenesis.

The severity of the disorder covers a wide range, though non-familial probands are significantly more likely to have anomalies in additional systems than are probands with affected family members ($P = 0.0026$). While the difference between non-familial and familial probands may be due to a variety of causes it is tempting to consider that non-familial probands have mutations in genes with autosomal recessive inheritance or new mutations in genes with dominant inheritance that result in severe phenotypes as has been the case with many disorders that were considered to be "sporadic" prior to determination of their molecular basis. To determine the etiology and specific features of the many types of AOS, the molecular cause of the disorder will need to be determined in a broader group of affected individuals.

Features that have previously been suggested as a part of AOS that now appear to be unrelated to the underlying diagnosis include esotropia, microphthalmia, accessory nipple, imperforate vaginal hymen, and polydactyly.

In light of the fact that newly diagnosed probands with AOS may have anomalies not apparent on physical examination, we suggest that those who are considered to have AOS be evaluated via echocardiogram, abdominal ultrasonography for liver anomalies, and detailed ophthalmological exam to identify the presence of retinal anomalies. A brain MRI may be considered, but could be deferred depending upon development.

In summary we suggest that, in view of the now six genes found to have mutations as a cause of AOS, it is not surprising that our review suggests a wide range of natural history, morbidity, and mortality for individuals with a clinical diagnosis of AOS. However, to date, all reported genes function in the Notch signaling cascade or the CDC42/RAC1 pathway. It will be important to determine the specific genetic cause of AOS in individuals with a clinical diagnosis to identify the anomalies typical for each mutation or pathway, and determine the underlying developmental pathogenesis of each genetic variant.

Future study is needed to follow individuals diagnosed during childhood to delineate the clinical history of the disorder and determine if there are any late effects of the underlying genetic cause that are not directly related to congenital anomalies. As more genes are identified to be associated with the phenotype that is referred to as AOS, the greater will be our understanding of the complex pathways involved in proliferation, differentiation, cell-to-cell signaling, and cell movement as drivers of fetal development.

ACKNOWLEDGMENTS

The authors wish to acknowledge Astrid Rasmussen, MD, PhD and Sanjay Bidichandani, MBBS, PhD for their assistance translating articles in Portuguese, Spanish, and French.

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