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Discovering a new part of the phenotypic spectrum of Coffin-Siris syndrome in a fetal cohort

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ABSTRACT

Purpose: Genome-wide sequencing is increasingly being performed during pregnancy to identify the genetic cause of congenital anomalies. The interpretation of prenatally identified variants can be challenging and is hampered by our often limited knowledge of prenatal phenotypes. To better delineate the prenatal phenotype of Coffin-Siris syndrome (CSS), we collected clinical data from patients with a prenatal phenotype and a pathogenic variant in one of the CSS-associated genes.

Methods: Clinical data was collected through an extensive web-based survey.

Results: We included 44 patients with a variant in a CSS-associated gene and a prenatal phenotype; 9 of these patients have been reported before. Prenatal anomalies that were frequently observed in our cohort include hydrocephalus, agenesis of the corpus callosum, hypoplastic left heart syndrome, persistent left vena cava, diaphragmatic hernia, renal agenesis, and intrauterine growth restriction. Anal anomalies were frequently identified after birth in patients with *ARID1A* variants (6/14, 43%). Interestingly, pathogenic *ARID1A* variants were much more frequently identified in the current prenatal cohort (16/44, 36%) than in postnatal CSS cohorts (5%-9%).

Conclusion: Our data shed new light on the prenatal phenotype of patients with pathogenic variants in CSS genes.

Introduction

Coffin-Siris syndrome (CSS) (OMIM 135900 and others) is characterized by neurodevelopmental delay and may be accompanied by hypoplasia of the fifth digit and/or nail, distinct facial features, hypertrichosis, and a varying degree of congenital anomalies.[1-6] In the current literature, most patients present with no prenatal ultrasound (US) anomalies. Congenital diaphragmatic hernia,[7] hypoplastic left heart syndrome (HLHS),[8] and intrauterine growth restriction (IUGR)[9] have been occasionally described, whereas agenesis of the corpus callosum (ACC)[10] is observed more frequently.

Application of prenatal genome-wide sequencing is rapidly becoming standard care.[11-15] The interpretation of prenatally identified variants can be challenging because of the limited knowledge of prenatal phenotypes, because most genome-wide sequencing in diagnostics and research has focused on postnatal phenotypes. CSS is no exception to this rule. For example, we recently detected a novel de novo missense variant in *SMARCA4* (OMIM 614609) in a fetus with HLHS. HLHS had been described in 1 patient with *ARID1A*-CSS[8] before. With this little information, it was difficult to be certain about the pathogenicity of the variant, showing a typical difficulty encountered in current genetic practice.

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This study aimed to increase knowledge of the prenatal phenotype of CSS by presenting a detailed description of the prenatal features in a cohort of patients with 1 or more prenatal US anomalies and a pathogenic variant in one of the CSS-related genes.

Materials and Methods

Patient collection

Patients were collected through our outpatient CSS expertise center in the Leiden University Medical Center, Leiden, the Netherlands. Additional patients were included through international contacts, from physicians contacting us for second opinions, through contacts with the Baylor Genetics Laboratory, and through laboratories who reported pathogenic variants in LOVD[16] and ClinVar.[17] We also included patients who were presented at conferences and via the fetal sequencing consortium, which consists of an international group of medical professionals who discuss results of prenatal diagnostics in a biweekly case meeting.

Patient selection

Inclusion criteria were (1) the presence of any anomaly that was mentioned in US reports, excluding so called soft-markers (eg, echogenic focus in the left ventricle) and (2) a pathogenic or likely pathogenic genetic variant in a CSS-associated gene (*ARID1A*, *ARID1B*, *ARID2*, *BICRA*, *DPF2*, *SMARCA2* duplication, *SMARCA4*, *SMARCB1*, *SMARCC2*, *SMARCD1*, *SMARCE1*, *SOX11*, *SOX4*). The exclusion criterium was the ACC as the sole prenatal US anomaly in combination with a pathogenic *ARID1B* variant, because the association between the ACC and pathogenic *ARID1B* variants is well established.[10,18]

Timing of the identification of the genetic variant could be prenatal, postnatal, or postmortem.

Data collection

Data were collected through an online questionnaire. If required, genetic data were completed using Alamut version 2.11.

A patient was considered to have IUGR if it was reported as such by the contributing clinician.

Results

Genetic variants

In total, 44 patients with variants in *ARID1A* (n = 16, 36%), *ARID1B* (n = 19, 43%), *SMARCA4* (n = 3, 7%), and *SMARCB1* (n = 6, 14%) and a prenatal phenotype detected by US were identified (Supplemental Table 1). Variants were classified using the American College of Medical Genetics and Genomics/Association for Molecular Pathology criteria.

Phenotype

The clinical features are summarized in Tables 1 and 2. The median time in weeks of gestation at which the first US anomalies were detected tends to be lowest among patients with *ARID1A* variants (14+5 weeks), followed by *ARID1B* (20+0 weeks), *SMARCA4* (20+0 weeks), and *SMARCB1* (24+0 weeks) (Supplemental Figure 1). Unless stated otherwise, frequencies in the text refer to anomalies that were detected prenatally. The total prevalence of features (detected prenatally or by postnatal assessment) in this cohort is shown in Table 1.

Genotype-phenotype correlation

ARID1A

Of the 16 *ARID1A* pregnancies, 11 (69%) were terminated on request of the parents because the anomalies diagnosed by US carried a poor prognosis. One pregnancy led to an intrauterine fetal death, and one resulted in a child who died shortly after birth. Brain anomalies were most frequently present (10/15, 73%), especially hydrocephalus (n = 7) and ACC (n = 5). Cardiac anomalies were reported in 60% (9/15). HLHS was detected in 2 fetuses and hypoplastic right heart in 1 fetus. Persistent left vena cava (n = 3) and double outlet right ventricle (n = 3) were cardiovascular anomalies reported in a subset of fetuses. In one case, the ventricular septal defect and patent ductus arteriosus spontaneously resolved at 4 months of age. Renal anomalies were observed in 27% (4/15) of cases, including 1 case with unilateral renal agenesis who received a peritoneal dialysis catheter at the age of 1 year and a renal transplant 6 years later. Diaphragmatic hernia was detected in 13% (2/15) of fetuses, and in 3 cases, a diaphragmatic hernia was identified during postnatal investigation (34%, 5/15). Postnatal investigation also revealed supernumerary ribs in 2 patients and anal anomalies in 43% (6/14); 4 patients had anal atresia and 2 patients had an anteriorly placed anus.

ARID1B

Despite excluding isolated ACC cases for *ARID1B*, brain anomalies were detected in 76% (13/17) of *ARID1B* cases, but only in a subset during pregnancy (29.4%, 5/17). Most often, ACC was not detected prenatally. Cardiac anomalies were present in 19% (3/16), including 1 fetus with HLHS. Fetus 18 with a complex cardiac defect also had a 22q11 deletion. This patient died during her first day of life because of respiratory insufficiency. Another fetus had unilateral renal agenesis.

SMARCA4

Of the 3 fetuses with a *SMARCA4* variant, 2 had a severe cardiac anomaly (ie, HLHS). One of these patients died

Table 1 Clinical characteristics of included patients

	ARID1A					*ARID1B*					*SMARCA4*					*SMARCB1*				
Clinical Features	(n = 16[a])	Detected by US[b]	Detected by Postnatal Investigation	Total Affected	% Total	(n = 19)	Detected by US[b]	Detected by Postnatal Investigation	Total Affected	% Total	(n = 3)	Detected by US[b]	Detected by Postnatal Investigation	Total Affected	% Total	(n = 6)	Detected by US[b]	Detected by Postnatal Investigation	Total Affected	% Total
Sex, female	15	—	—	9	60%	19	—	—	5	26%	3	—	—	2	67%	6	—	—	4	67%
First US anomaly, time of AD in days, n (min-max, median)	12	—	—	(84-224, 103)		14	—	—	(60-259, 140)		3	—	—	(82-145, 140)		6	—	—	(140-231, 168)	
Anomalies																				
Placenta anomaly	15	1	—	1	7%	19	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Single umbilical artery	15	7	—	7	47%	19	3	1	4	21%	3	—	—	—	—	6	—	—	—	—
Oligohydramnios	15	3	—	3	20%	19	3	—	3	16%	3	—	—	—	—	6	—	—	—	—
Polyhydramnios	15	—	—	—	—	19	3	—	3	16%	3	—	—	—	—	6	1	—	1	17%
IUGR	15	2	—	2	13%	19	4	—	4	21%	3	—	—	—	—	6	3	—	3	50%
Short femur	15	2	—	2	13%	19	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Brain anomaly	15	1-	1	11	73%	17	5	8	13	76%	3	—	—	—	—	6	3	1	4	67%
Hydrocephalus	15	7	—	7	47%	17	1	—	1	6%	3	—	—	—	—	6	—	—	—	—
ACC	14	5	1	6	43%	17	—	7	7	41%	3	—	—	—	—	5	2	—	2	40%
Ventriculomegaly	14	4	—	4	29%	17	2	—	2	12%	3	—	—	—	—	5	1	1	2	40%
Dandy Walker malformation	14	1	2	3	21%	17	—	—	—	—	3	—	—	—	—	5	—	—	—	—
intracranial cysts	14	2	2	4	29%	17	1	—	1	6%	3	—	—	—	—	5	1	—	—	—
Enlarged cisterna magna	14	—	1	1	7%	17	2	—	2	12%	3	—	—	—	—	5	1	1	2	40%
Cerebellar vermis atrophy or hypoplasia	14	2	3	5	36%	17	1	1	2	12%	3	—	—	—	—	5	—	1	1	20%
Increased NT	15	7	—	7	47%	19	3	—	3	16%	3	1	—	1	33%	6	—	—	—	—
Cardiovascular anomaly	15	9	3	12	80%	16	3	3	6	38%	3	2	—	2	67%	6	1	1	2	33%
Vascular anomaly	15	—	—	8	53%	15	2	2	4	27%	3	1	—	1	33%	6	1	—	1	17%
Aortic arch anomaly	15	2	1	3	20%	14	2	—	2	14%	3	1	—	1	33%	6	1	—	1	17%
Involving the vena cava	15	3	1	4	27%	14	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Patent ductus arteriosus[c]	15	n.a.	1	1	7%	14	1	—	1	7%	3	n.a.	—	—	—	6	n.a.	—	—	—
Cardiac anomaly	15	9	1	10	67%	15	3	—	3	20%	3	2	—	2	67%	6	1	1	2	33%
Hypoplastic left heart	15	2	—	2	13%	16	1	—	1	6%	3	2	—	2	67%	6	—	—	—	—
Hypoplastic right heart	15	1	—	1	7%	16	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Atrioventricular canal	15	1	1	2	13%	14	—	—	—	—	3	—	—	—	—	6	—	—	—	—
DORV	15	3	—	3	20%	14	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Septal defect (isolated or in combination with other structural cardiac anomalies)	15	4	5	9	60%	14	—	2	2	14%	3	1	—	1	33%	6	—	1	1	17%
Valve defect	15	—	—	3	20%	14	—	—	—	—	3	2	—	2	67%	6	—	—	—	—
Cardiac position/Dextrocardia	15	1	—	1	7%	14	—	—	—	—	3	—	—	—	—	6	1	—	1	17%
Cardiovascular intervention	4	—	—	—	—	14	—	—	1	7%	3	—	—	1	33%	6	—	—	—	—
Diaphragmatic hernia	15	2	3	5	33%	16	1	—	1	6%	3	2	—	2	67%	6	—	—	—	—
Anal anomaly	14	n.a.	6	6	43%	15	n.a.	—	—	—	3	n.a.	—	—	—	6	n.a.	—	—	—
Renal anomaly	15	4	3	7	47%	16	1	1	2	13%	3	1	—	1	33%	6	3	—	1	17%
Renal dysplasia	14	—	3	3	21%	15	—	1	1	7%	3	—	—	—	—	6	—	—	—	—
Renal agenesis	14	3	—	2-3	13-20%	15	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Hydronephrosis[c]	4	—	—	—	—	15	1	—	1	7%	3	—	—	—	—	6	2	—	1	17%
Genitourinary anomaly	12	—	5	5	42%	15	—	8	8	53%	3	—	—	—	—	6	—	3	3	50%
Urinary anomaly	14	—	2	2	14%	15	—	3	3	20%	3	—	—	—	—	6	—	1	1	17%
Genital anomaly	14	—	2	2	14%	15	—	3	3	20%	3	—	—	—	—	3	—	2	2	67%
Cryptorchidism[c]	6	n.a.	—	—	—	14	n.a.	10	10	71%	1	n.a.	n.a.	n.a.	—	2	n.a.	2	2	100%
Hypospadia	6	n.a.	1	1	17%	14	—	—	—	—	1	n.a.	n.a.	n.a.	—	2	n.a.	1	1	50%
Digit anomaly	14	n.a.	10	10	71%	11	—	4	4	36%	2	—	2	2	100%	4	—	3	3	75%
Nail anomaly	11	n.a.	6	6	55%	11	n.a.	5	5	45%	2	n.a.	2	2	100%	2	n.a.	1	1	50%
TOP	11[I]					—			—	—	—			—	—	—			—	—
Mean time AD, days	10	—	—	(101-161, 132.1)	67%	1	—	—	(144)	5%	—	—	—	—	—	1	—	—	(159)	17%
IUFD																				
Mean time AD, days	1	1	—	(126-126, 126)	7%	19	—	—	—	—	3	—	—	—	—	6	—	—	—	—
Died	17	—	—	13	87%	19		—	2	11%	3	—	—	1	33%	6	—	—	1	17%

ACC, agenesis of the corpus callosum; *AD*, amenorrhea duration; *DORV*, double outlet right ventricle; *IUFD*, intrauterine fetal death; *IUGR*, intrauterine growth restriction; *n.a.*, not applicable, *NT*, nuchal translucency; *TOP*, termination of pregnancy; *US*, ultrasound.

[a]One fetal case/TOP no additional information available.

[b]Separately reported as US anomaly.

[c]Only data of non-TOP and IUFD cases.

Table 2 Distribution of genetic variants per gene within our cohort and within published CSS cohorts

Gene	Total	%	CSS cohort Santen et al[a,b]		CSS cohort Wieczorek et al[a,b]		CSS cohort Tsurusaki/ Sekiguchi et al[a,b]		Cumulative Frequency of CSS Cohorts Combined[a,b]		*P*-value Fisher's exact
ARID1A	16/44	36.4%	4/45	8.9%	1/21	4.8%	6/78	7.7%	11/144	7.6%	<.01
ARID1B	19/44	43.2%	28/45	62.2%	14/21	76.2%	48/78	61.5%	90/144	62.5%	.04
SMARCA4	3/44	6.8%	4/45	8.9%	0/21	0.0%	7/78	9.0%	11/144	7.6%	1.00
SMARCB1	6/44	13.6%	4/45	8.9%	1/21	4.8%	8/78	10.3%	13/144	9.0%	.40

CSS, Coffin-Siris syndrome.
[a]Only patients with pathogenic variants in a CSS-associated gene were taken into account.
[b]Numbers may not add up to 100%, because pathogenic variants in other CSS-associated genes were detected.

postnatally as a result of her congenital anomalies. The fetus without a severe cardiac anomaly had hydrops, diaphragmatic hernia, double renal collecting system, and abnormal feet position. Parents decided to continue this pregnancy after they received the genetic results at 19+4 weeks of gestation.

SMARCB1

IUGR was reported for 50% (3/6) of fetuses with a *SMARCB1* variant. Brain anomalies were reported for 2 fetuses. One fetus had an abnormal cardiac position (ie, ventricular axis and apex to the right of the midline) with biventricular hypertrophy and a minor size discrepancy of the great arteries, and 1 fetus had a cardiac septal defect that was detected postnatally. Two fetuses had hydronephrosis on prenatal US, of which 1 case resolved postnatally. During postnatal assessment, it appeared that both males with *SMARCB1* variants had cryptorchidism.

Discussion

Genotype

In total, we identified 44 CSS cases with prenatal US anomalies, making this the largest case series to date. *ARID1A* ($n = 16$) or *ARID1B* ($n = 19$) variants were most frequent in this prenatal cohort. The frequency of *ARID1A* variants in particular was remarkable. *ARID1A* variants were overrepresented among the cases that did not survive into the neonatal period (76.5%, $n = 13$ for *ARID1A* vs 23.5%, $n = 4$ for the non-*ARID1A* group, $P < .001$). Furthermore, the median gestational age at which the anomalies were detected was earlier (14+5 weeks for *ARID1A* vs 20+0 weeks for the non-*ARID1A* group) (Supplemental Figure 1), although the difference was not significant ($P = .17$). This may fit with our previous finding that *ARID1A* variants in postnatal cases are frequently present in a mosaic state,[1] which suggests that nonmosaic pathogenic *ARID1A* variants may lead to an embryonically severe or lethal phenotype. The likely explanation for the relative lack of postnatal *ARID1A* variants (Table 2) is that most fetuses with full pathogenic variants display severe congenital anomalies, leading to a large proportion of pregnancy terminations as well as fetal and neonatal demise. Thus far, such cases were less likely to undergo extensive diagnostic sequencing. Contrary to our previous findings where all 4 patients with *ARID1A* variants appeared mosaic in lymphocytes,[1] all patients in this cohort appear to have the pathogenic variant in 50% of sequence reads.

Phenotype

Frequent findings in fetal cases with pathogenic *ARID1A* variants, such as hydrocephalus, hypoplastic left or right heart syndrome, renal agenesis, diaphragmatic hernia, and postnatally detected anal anomalies, have not been previously recognized as part of the CSS phenotypic spectrum. Sporadically, patients have been reported with one of these anomalies and a pathogenic variant in a CSS-associated gene.[6,7,18-20] Unilateral renal agenesis was reported among patients with clinically diagnosed CSS in the era before identification of CSS genes.[21,22]

Pregnancies were terminated in 68.8% (11/16) of the *ARID1A* cases, which makes it impossible to assess severity of developmental delay or treatment response postnatally. Compared with reported congenital and/or structural anomalies among *ARID1A* patients,[1-4,23] the severity of the congenital anomalies in our *ARID1A* cases appears to be more severe (Table 1).

The postnatal *ARID1B* phenotype has been extensively reported on by our group and others.[10,18,24,25] Although we excluded patients with ACC as the sole prenatal presenting feature, 29.4% (5/17) had 1 or more brain anomalies. IUGR was detected more frequently in our cohort compared with previously reported frequencies in patients[18] (Fisher's exact, $P = .04$), which might indicate that it is more common in the subset of patients with congenital anomalies. The frequency of cardiac anomalies in the fetal series does not differ significantly from previously reported frequencies in patients[18] (Fisher's exact, $P = 1.00$).

It is remarkable that all *SMARCA4* fetuses had severe congenital anomalies, which have not previously been reported among patients with *SMARCA4* variants. Li et al[9] do

report other prenatal findings in 6 of 13 patients with *SMARCA4* variants (ie, IUGR [$n = 4$], cardiac anomaly [$n = 2$], and ACC [$n = 1$]).

The most frequent US anomaly in *SMARCB1* variants was IUGR, which is a frequent, nonspecific prenatal US finding. Where the postnatal *SMARCB1* patient group usually presents with a phenotype considered at the severe end of the CSS spectrum,[1,6,25] there does not to appear to be a more severe prenatal presentation for this gene compared with patients with *ARID1A*, *ARID1B,* or *SMARCA4* variants. However, we show here that growth delay,[1,4] which is a prevalent feature among reported patients with CSS and is often more extreme in *SMARCB1* patients, is detected prenatally as IUGR in several patients.

We did not identify patients with a prenatal presentation and a pathogenic variant in the other CSS-related genes (*ARID2*, *BICRA*, *DPF2*, *SMARCA2* duplication, *SMARCC2*, *SMARCD1*, *SMARCE1*, *SOX11*, *SOX4*) during this study. It is possible that prenatal US anomalies are less prevalent among these patients. The number of patients known with pathogenic variants in these genes is, however, still relatively small, so a prenatal phenotype may be identified in the future.

Not all cases in this cohort underwent a similar US examination, which is reflected by the fact that not all anomalies were detected prenatally. Table 1, however, gives an overview of the potential for prenatal detection if every fetus would have been examined on the level of a tertiary referral center. Because not every case underwent extensive US examination, this may be an underestimation.

Conclusion

This study highlights the prenatal phenotypic spectrum of CSS in a prenatal cohort with a molecularly confirmed pathogenic variant in a CSS-associated gene. Pathogenic variants in *ARID1A* were identified much more frequently in this group than in cohorts of postnatal patients with CSS. Frequently observed prenatal anomalies include hydrocephalus, ACC, HLHS, double outlet right ventricle, persistent left vena cava, congenital diaphragmatic hernia, renal agenesis, and IUGR, indicating that the prenatal phenotype of CSS significantly differs from the postnatal phenotype. This difference may be explained by an increased rate of pregnancy termination for fetuses at the severe end of the spectrum and in increased chance of fetal or postnatal demise. Genome-wide sequencing has been less frequently applied in such cases until now, leaving this part of the CSS spectrum undiscovered.

Data Availability

De-identified patient data will be made available on request to the corresponding author.

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Ethics Declaration

The Institutional Review Board of Leiden University Medical Center, Leiden, The Netherlands provided approval waivers for using de-identified data and publishing aggregated data (no: G18.098 and G21.129) without obtaining specific informed consent. Clinical data was de-identified by allocating patient numbers. Where possible, informed consent was obtained by the referring clinician.

Conflict of Interest

All authors declare no conflicts of interest.

Additional Information

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Update

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CORRECTION

Discovering a new part of the phenotypic spectrum of Coffin-Siris syndrome in a fetal cohort

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In the article "Discovering a new part of the phenotypic spectrum of Coffin-Siris syndrome in a fetal cohort" by van der Sluijs PJ et al (*Genet Med* 2022;24:1753-1760), the author listing was updated in the Supplementary Material from "H. Scott" to "H. S. Scott" and in Supplemental Figure 1 the labels in the figure caption for A, B, C, and D have been updated to match the figure artwork. The revised supplement file has been published with this correction.

Supplementary Material

Supplementary data association with this article can be found in the online version at https://doi.org/10.1016/j.gim.2022.100004.

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