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BRIEF REPORT

Coffin-Siris syndrome and cancer susceptibility

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ABSTRACT

Coffin-Siris syndrome (CSS) is a rare neurodevelopmental disorder that is associated with multiple congenital anomalies and caused by de novo monoallelic germline pathogenic variants in BAF-complex genes. Despite their function as tumor suppressors, the cancer risk in patients with CSS remains unclear. We analyzed cancer sequencing data sets, conducted a comprehensive literature review of patients with CSS diagnosed with malignancies, and examined a cohort of 376 CSS registry patients to estimate cancer frequency. A review of the literature identified several reports of patients with CSS diagnosed with a malignancy, with *ARID1A* being the most frequent causative gene and associated with hepatoblastoma in 3 cases. Although no cases of malignancy were reported among the patients in the CSS registry, only 26 patients with *ARID1A*-CSS were available for analysis. Combining these patients with all cases reported in the literature led to the estimate of hepatoblastoma prevalence in *ARID1A*-CSS of 3.6% (95% CI 0.79%-10.4%). Our findings suggest the hepatoblastoma risk among patients with *ARID1A*-CSS may exceed the established 1% risk threshold and therefore warrant surveillance. There remains insufficient evidence to support any other CSS gene-cancer association, emphasizing the need for further systematic study.

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Introduction

Coffin-Siris syndrome (CSS) is a neurodevelopmental disorder characterized by variable intellectual disability, growth restriction, hypertrichosis, sparse scalp hair, coarse facial features, hypoplasia of the fifth digit nails or phalanges, and other congenital anomalies involving the cardiac, gastrointestinal, genitourinary, and/or central nervous systems.[1] CSS has been attributed to monoallelic pathogenic variants in *ARID1A*, *ARID1B*, *ARID2*, *SMARCB1*, *SMARCA4*, *SMARCE1*, *SMARCC2*, *SOX11*, *SOX4, PHF6*, and *DPF2*, which encode subunits of the BAF complex. This complex mediates the opening and closing of chromatin to facilitate processes such as transcription and DNA repair.[2] BAF-complex genes also function as tumor suppressors, whose loss has been linked to carcinogenesis.[3] For most CSS-associated genes, the syndrome is produced through a loss-of-function mechanism, though in the case of *SMARCA4*, *SMARCB1*, and *SMARCE1*, dominant-negative or gain-of-function variants cause CSS, whereas germline loss-of-

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function variants in these genes cause tumor predisposition syndromes, illustrating the dual role of BAF-complex genes.[4]

Despite the rarity of the CSS, multiple case reports have documented malignancies among affected individuals. Most recently, hepatoblastoma in infants with pathogenic variants in *ARID1A* has been reported.[5,6] However, an updated analysis of cancer risk in CSS has not been undertaken, leaving the need for surveillance unclear. In this study, we analyze cancer sequencing data sets, conduct a comprehensive literature review, and examine a CSS registry to better characterize the cancer risk among affected individuals and provide valuable insights for health care providers and families of individuals with CSS.

Materials and Methods

Obtaining frequency of somatic alterations in Coffin-Siris genes across cancer

Deidentified cancer genomic sequencing data were accessed and queried online through the cBioPortal for Cancer Genomics (https://www.cbioportal.org/).[7] Somatic alterations included all loss-of-function single-nucleotide variants, indels, and copy number variants classified as pathogenic or likely pathogenic. Single-gene alteration frequency by cancer type was obtained through the cancer type summary. The total and altered cases for overlapping cancer types were combined when appropriate. Statistical analysis comparing deleterious alteration counts was performed with Microsoft Excel version 16.64 (Microsoft) using the Z-test for independent proportions. A P value equal to or less than .05 was considered significant.

Literature search for reports of cancer associated with CSS

A comprehensive review of the peer-reviewed literature through MEDLINE was conducted using PubMed for articles published between 1970 and November 2022. Search keywords included "Coffin-Siris syndrome," "tumor," "malignancy," and "cancer." Keywords were connected by the Boolean functions AND OR. Studies providing data on the presence of cancer in a patient clinically or molecularly diagnosed with CSS were included. Patient characteristics and the CSS-associated variant were collected when available.

Review of CSS/BAF complex registry data

Deidentified patient data from a CSS/BAF complex registry were stratified into groups based on the causative gene. Demographic characteristics and malignancy history were analyzed for each group.

Calculating hepatoblastoma prevalence among patients with *ARID1A*-CSS

The prevalence of hepatoblastoma in our CSS registry and across all published cases of CSS in which patients survived the perinatal period was determined by dividing cases of hepatoblastoma over total cases of patients with *ARID1A*-CSS. CIs were calculated by the modified Wald method using GraphPad Prism version 8.4.3 (GraphPad Software).

Results

We first examined cancer sequencing data to assess the relative degree to which the genes associated with CSS may influence carcinogenesis. A pan-cancer analysis combining data from 8 studies queried a total of 51,439 adult patients and found the mean somatic pathogenic alteration in *ARID1A* to be 7.9%, which was significantly more than any other Coffin-Siris gene, $P < .00001$ (Supplemental Figure 1A). The next most frequently altered Coffin-Siris genes were *ARID2* in 2.7% of cases and *SMARCA4* in 2.2% of cases. We then investigated whether pathogenic alterations in the Coffin-Siris genes were seen in pediatric malignancies by querying 4 pediatric pan-cancer studies that included 1427 patients (Supplemental Figure 1B). In this cohort, pathogenic alterations were less frequently seen than in adult cancers, with *SMARCB1* (2.2%), *SMARCA4* (1.4%), and *ARID1A* (1.4%) having significantly greater mean alteration frequencies than the other Coffin-Siris genes ($P = .04$).

Examination of which adult cancer types were enriched for pathogenic variants in Coffin-Siris genes revealed that *ARID1A* was frequently altered in endometrial cancers (599 cases, 37.0%), urothelial cancers (438 cases, 23.3%), and esophagogastric malignancies (352 cases, 14.7%), among others (Supplemental Table 1). Among the pediatric cancers, pathogenic variants in *SMARCB1* were highly enriched in rhabdoid tumors (19 cases, 61.3%), whereas pathogenic variants in *SMARCA4* were only seen in a single case of this tumor type, representing 7.7% of profiled samples. *ARID1A* alterations were enriched in 2 cases of both non-Hodgkin lymphoma and Ewing sarcoma, comprising 13.3% of these samples. No *ARID1A* alterations were detected in the 10 cases of hepatoblastoma sequenced in this cohort; however, a recent analysis of 154 hepatoblastoma cases found that *ARID1A* is one of the most common drivers of carcinogenesis, with somatic variants occurring in 6.0% of cases.[8] These data reflected the established function of Coffin-Siris genes, principally *ARID1A*, *SMARCB1*, and *SMARCA4,* as tumor suppressors capable of influencing carcinogenesis.

We therefore sought to determine how closely the pathogenic variants observed in cancer mirrored those associated with CSS because this would indicate that de novo pathogenic variants causing Coffin-Siris may simultaneously

Table 1 Review of all published cases of malignancy associated with Coffin-Siris syndrome

Malignancy	Patient Characteristics	Germline Variant	Variant Type	Reference
Medulloblastoma	8-year-old female	NR	NR	Rogers et al, 1988[9]
Neuroblastoma	8-year-old male	NR	NR	Pollono et al, 2009[10]
Schwannomatosis	27-year-old male	NR	NR	Wong et al, 2009[11]
Hepatoblastoma	22 months old	*ARID1A* NM_006015.6: c.31_56del (p.Ser11Alafs*91)	Frameshift	Tsurusaki et al, 2012[12]
Hepatoblastoma	15-month-old female	*ARID1A* NM_006015.6: c.6182T>C (p.Leu2061Ser)	Missense	Cárcamo et al, 2022[5]
Hepatoblastoma	12-month-old male	*ARID1A* NM_006015.6: c.2144C>A (p.Ser715*)	Nonsense	van der Sluijs et al, 2023[6]
Acute lymphoblastic leukemia	16 years old	*ARID1A* NM_006015.6: c.4993+1G>A	Splice-site	Diets et al, 2018[14]
Sertoli-Leydig cell tumor, temporal glioneuronal tumor	3 years old, 12-year-old male	*ARID1B*	NR	van der Sluijs et al, 2019[13]
Papillary thyroid carcinoma	15-year-old male	*ARID1B* NC_000006.11: g.(155538131_158756793)del	Deletion	Vengoechea et al, 2014[15]
Small-cell carcinoma of the ovary, hypercalcemic type	13-year-old female	*SMARCA4* NM_003072.5: c.2935C>T (p.Arg979*)	Nonsense	Errichiello et al, 2017[16]
Schwannomatosis	33-year-old male	*SMARCB1* NM_003073.5: c.1121G>A (p.Arg374Gln)	Missense	Gossai et al, 2015[17]
Anaplastic astrocytoma	18-month-old female	*SMARCE1* NM_003079.5: c.227A>G (p.Tyr76Cys)	Missense	Lin et al, 2018[18]

NR, not reported.

predispose to cancer by fulfilling the role of the first hit as described by Knudson's two-hit hypothesis. Comparisons were performed between the germline pathogenic variants associated with Coffin-Siris as reported in ClinVar to the somatic pathogenic alterations reported in cBioPortal. Among the CSS genes with sufficient entries to be analyzed in ClinVar, we observed that predominantly truncating pathogenic variants in *ARID1A*, *ARID1B*, and *ARID2* were associated with both CSS and cancer (Supplemental Figure 2). In the case of *SMARCA4* and *SMARCB1*, pathogenic missense variants and splice-site variants were predominantly responsible for CSS, whereas truncating variants were significantly more associated with hereditary cancer risk, particularly rhabdoid tumor predisposition syndrome.

We then conducted a comprehensive review to identify all reported cases of individuals with CSS and a history of malignancy. Twelve cases were identified, with 9 cases of cancer occurring in children and 3 in adults.[5,6,9-18] *ARID1A* was the CSS gene most frequently associated with malignancy because it has been implicated in 3 cases of hepatoblastoma and 1 case of acute lymphoblastic leukemia among individuals with CSS (Table 1). Two individuals with CSS due to *ARID1B* pathogenic variants were also reported to have a history of malignancy. Finally, a pathogenic variant in *SMARCA4* was associated with CSS and small-cell carcinoma of the ovary, whereas pathogenic variants in *SMARCB1* and *SMARCE1* were associated with schwannomatosis in an adult with CSS and anaplastic astrocytoma in an infant with CSS, respectively.

To contextualize these reports of malignancy in patients with CSS, we examined our own CSS cohort of 376 patients whose demographic characteristics and clinical data have been maintained in a dedicated registry since 2015 (Supplemental Table 2). As expected, pathogenic variants in *ARID1B* were found in 218 cases, whereas *ARID1A* variants were seen in 26 participants (6.3%). Of note, 54 participants (13.2%) had *SMARCA4* variants, and 24 participants (5.9%) had *SMARCB1* variants. Patients were between 1 and 46 years old, with a median age of 9 years. We found that across all individuals enrolled in the registry, no pediatric malignancies were reported, nor have any adult-onset malignancies been documented among the 42 adults with CSS.

Nevertheless, the 3 existing reports of hepatoblastoma in patients with *ARID1A*-CSS, along with the findings that loss-of-function variants in *ARID1A* cause both CSS and frequently drive hepatoblastoma carcinogenesis, prompted us to estimate the overall prevalence of hepatoblastoma in this patient population. We found 31 patients confirmed to harbor a causative *ARID1A* variant across several CSS cohort studies, whereas an additional 26 *ARID1A*-CSS cases were noted in exome/genome sequencing studies (Supplemental Tables 3 and 4). We further identified an additional 15 patients with *ARID1A*-CSS described in case reports (Supplemental Table 5). After combining all of these patients with the 26 *ARID1A* cases in our registry, we had a total of 98 patients with *ARID1A-CSS*, which was then reduced to 84 patients after excluding cases that did not survive the perinatal period (Supplemental Table 6). Thus,

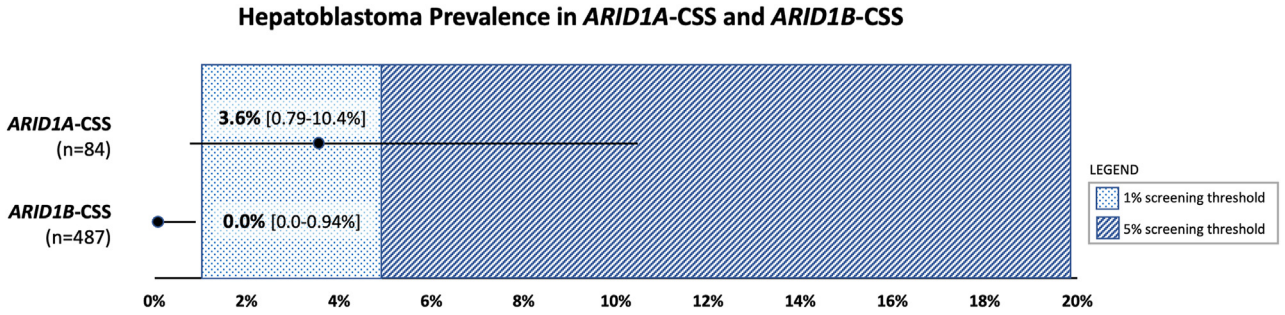

Figure 1 Forest plot representing the prevalence of hepatoblastoma in patients with *ARID1A*-CSS and *ARID1B*-CSS among all reported cases who survived the perinatal period, inclusive of those in our CSS registry. The solid circle with a horizontal bar represents the point prevalence and 95% CI, calculated using the modified Wald method. Surveillance screening thresholds of 1% and 5% are depicted for reference.

we found the prevalence of hepatoblastoma in *ARID1A*-CSS is 3.6% with 95% CIs that extend from 0.79% to 10.4% (Figure 1). For comparison, the prevalence of hepatoblastoma in the similarly pooled 487 cases of *ARID1B*-CSS is 0.0% with the upper CI extending to 0.94%, confirming a <1% risk in this group.

Discussion

Our results indicate that patients with *ARID1A*-CSS may have an increased cancer risk, particularly hepatoblastoma. This is supported by the relatively high somatic alteration rate in *ARID1A* across adult and pediatric malignancies compared with other BAF-complex genes, as well as the finding that *ARID1A* loss-of-function variants cause CSS and are enriched in cancer. Additionally, a comprehensive review of the literature led us to identify several cases in which CSS has been associated with malignancies, with *ARID1A* being the most frequent causative gene. Data from a large CSS registry demonstrated no cases of malignancy in the cohort, indicating a low absolute risk of pediatric malignancy among individuals with *ARID1B*-associated CSS. For other CSS-associated genes, particularly *ARID1A*, we could not accurately determine the absolute cancer risk because of the limited representation. Combining all reported cases of *ARID1A*-CSS resulted in an estimated hepatoblastoma prevalence of 3.6% with CIs spanning from 0.79% to 10.4%. Thus, we cannot definitively conclude that patients with *ARID1A*-CSS have a hepatoblastoma risk exceeding 1%, which has been established as the threshold for surveillance by the American Association for Cancer Research international panel of experts, though we acknowledge that in the United Kingdom and Europe, the cancer risk surveillance threshold is typically greater than 5%.[19,20]

Nonetheless, our prevalence estimate indicates that health care providers and family members should engage in shared decision making to determine whether hepatoblastoma surveillance is appropriate for patients with *ARID1A*-CSS. It should be noted that hepatoblastoma screening recommendations have traditionally involved abdominal ultrasounds and serum alpha-fetoprotein (AFP) measurements every 3 months until the fourth birthday; however, updated international consensus guidelines for hepatoblastoma screening in Beckwith-Wiedemann now recommend ultrasound surveillance alone, without serum AFP measurements, because of the drawbacks of frequent venipuncture and challenges in interpreting AFP elevations.[19,20]

We anticipate that pediatric cancer risk estimates and surveillance recommendations will be more precisely defined over time as more patients are diagnosed with CSS. For instance, mosaicism for *ARID1A* in CSS has been well described, presumably because of the lethality of pathogenic variants in the gene, and we expect these individuals to have a lower risk for malignancy because of the lower burden of cells with a monoallelic loss of *ARID1A*.[2] Nevertheless, substantiating this genotype-phenotype correlation and others will require increasing patient enrollment in registries and participation in clinical studies.

Our study faces limitations because of the incomplete demographic and clinical data available for all individuals in the analysis. We acknowledge the potential for ascertainment bias because CSS cases with associated malignancies may be reported more frequently than those without. Furthermore, underreporting of pediatric malignancies in patients with CSS could result because of early-life mortality. Overall, the data herein do not support an increased pediatric cancer risk in CSS, except for those with *ARID1A* variants. Additionally, a lack of adult patients with CSS in our registry and other studies hinders our ability to draw conclusions about cancer risk in adulthood for patients with CSS.

Despite these limitations, our study provides multiple lines of evidence for cancer risk in a rare syndrome in which causative genes are implicated in oncogenesis. It offers updated recommendations on hepatoblastoma surveillance for patients with *ARID1A*-CSS based on its prevalence that emphasizes informed provider-family decision making. This work also highlights the importance of systematic patient recruitment and follow-up to refine cancer risk estimates for patients with CSS over time.

Data Availability

The data used in this study were deidentified and are freely accessible through public databases. They do not require institutional review board approval or new data deposition.

cBioPortal adult cancer accession link: https://bit.ly/3TZKrYL

cBioPortal pediatric cancer accession link: https://bit.ly/3gLIKzs

https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=672[ARID1A]

https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=672[ARID1B]

https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=672[ARID2]

https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=672[SMARCA4]

https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=672[SMARCB1]

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Ethics Declaration

The use of deidentified patient data was approved by the Eastern Virginia Medical School Institutional Review Board under protocol 15-03-EX-0058, and all participants in the Coffin-Siris syndrome registry provided their informed consent.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2023.100818) contains supplemental material, which is available to authorized users.

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