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Case Report

ARID1A-Associated Coffin-Siris Syndrome: A Rare Case Report with Steroid-Resistant Nephrotic Syndrome and Single Kidney

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Abstract

Coffin-Siris syndrome (CSS), a rare BAFopathy, is characterized by developmental delay, dysmorphic features, and variable anomalies. We report a 12-year-old boy with a novel ARID1A truncating mutation presenting with global developmental delay, facial dysmorphism, single kidney, and steroid-resistant nephrotic syndrome (SRNS). Genetic analysis confirmed a heterozygous p.Glu1017Ter mutation in ARID1A. This report expands the phenotypic spectrum of CSS by highlighting its association with glomerular disease, a previously unreported feature.

Introduction

Coffin-Siris syndrome (CSS), a notable BAFopathy, features intellectual disability, microcephaly, coarse facial traits, short stature, cleft palate, hypoplastic fifth digits, and ectodermal defects (e.g., hypertrichosis, sparse hair). Associated issues include motor and speech delays, hearing loss, heart defects, respiratory infections, feeding difficulties, and scoliosis.[1] Since its initial description, approximately 200 cases of CSS have been reported globally.[2] However, its prevalence and features remain incompletely understood.[3] Mutations in genes encoding components of the BRG1-associated factor (BAF) chromatin-remodeling complex - such as SMARCB1, SMARCA2, SMARCE1, DPF2, ARID1A, ARID1B, and SOX11- are identified in 60% to 90% of cases. The phenotypic variability of CSS makes diagnosis challenging.[4] Fleck et al proposed minimal diagnostic criteria, including developmental delay, hirsutism, coarse facial features, and underdeveloped terminal phalanges or fifth-digit nails.[5] We report the clinical and molecular findings of a boy with CSS with steroid-resistant nephrotic syndrome (SRNS), caused by a novel de novo truncating mutation in the ARID1A gene.

Case Report

A 12-year-old boy presented to our Nephrology OPD with anasarca, accompanied by periorbital and scrotal swelling. He was subsequently diagnosed with childhood-onset nephrotic syndrome and initiated on prednisolone at a dose of 2 mg / kg / day. Due to his older age at presentation, a renal biopsy was considered but was deferred after NCCT KUB revealed a single kidney (Figure 1). After six weeks of full-dose steroids without achieving remission, he was diagnosed with SRNS. The patient also exhibited speech difficulties and slow motor activity. There was no history of parental consanguinity, and he was the older of the couple's two children. He was born via Caesarean section with a history of delayed cry. His infancy was marked by recurrent seizures and global developmental delay. Brain imaging revealed agenesis

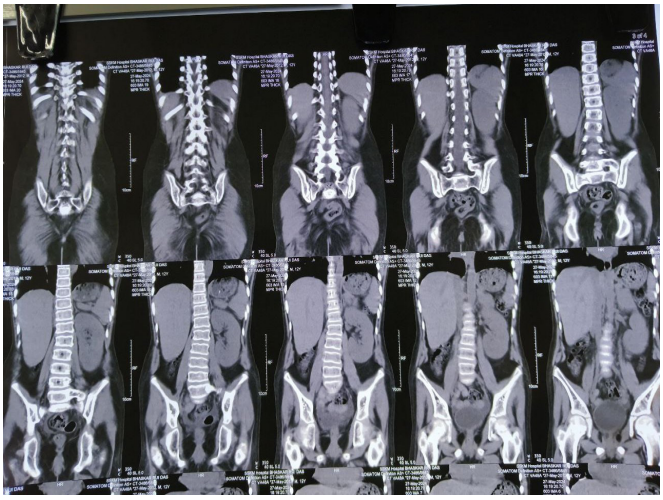

Figure 1: (NCCT KUB): Non visualization of right kidney in renal fossa or else where

of the corpus callosum (Figure 2).

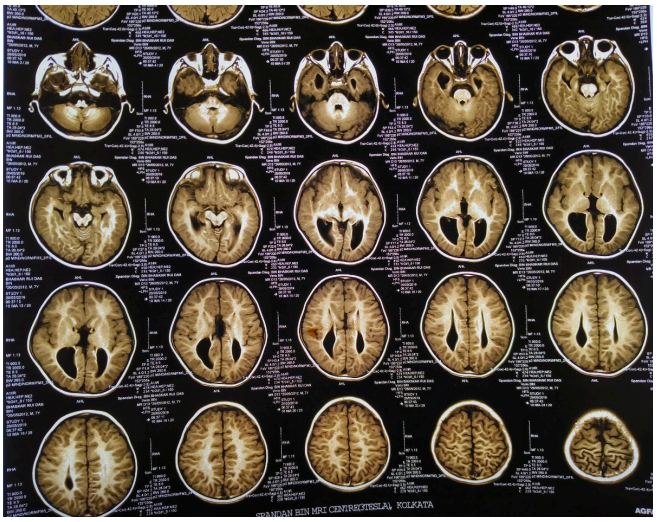

Figure 2: (MRI Brain): Complete agenesis of corpus callosum

On physical examination, his height was 143 cm (Z score -0.71, IAP Growth chart), weight was 32 kg (Z score -0.84, IAP Growth chart) and his head circumference was 52 cm. He had hypospadias and facial dysmorphism, including low-set ears and down-slanting palpebral fissures, but lacked other classic features commonly reported, such as a high-arched palate, thick eyebrows, hypertrichosis, and hypoplastic fifth digits (Figure 3). He also had global hypotonia without any visual or hearing impairments, and cardiac evaluation showed no congenital heart defects.

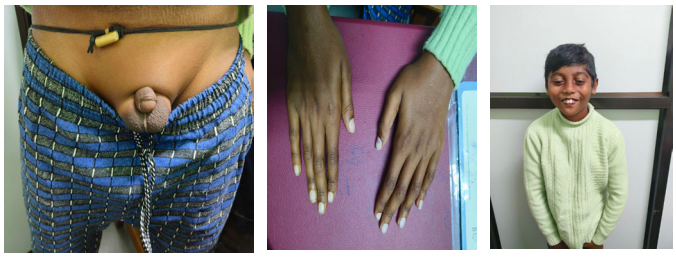

Figure 3: Photograph showing hypospadias and facial dysmorphism, including low-set ears and down-slanting palpebral fissures, but lacked classic feature commonly reported, such as a hypoplastic fifth digits

(Written informed consent was obtained from the patient's parents for the publication of this case report and accompanying photographs. Efforts have been made to ensure the patient's anonymity.)

WES was conducted using the SureSelect Human All Exon V6 kit (Agilent, USA) on the NovaSeq platform (Illumina, USA). Sequence reads were aligned to the reference genome (UCSC hg19) using BWA (v0.7.12, MEM algorithm), achieving a mean coverage depth of 100×, with over 99.2% of bases covered at a depth greater than 10×. Genetic evaluation was conducted which revealed a novel heterozygous variant in Exon 11 of the ARID1A gene (chr1: g.26767850G>T), leading to a "stop-gained" mutation (G>T) at nucleotide position 3049. This p.Glu1017Ter variant is predicted to cause protein truncation and loss of normal function and is classified as "likely pathogenic" per American College of Medical Genetics guidelines, confirming the diagnosis of Coffin-Siris syndrome.[6]

Discussion

CSS is caused by mutations in genes encoding subunits of the SWI / SNF (BAF) chromatin remodelling complex.[1,2,7] The syndrome is associated with an expanding genomic region and a wide phenotypic spectrum, characterized by intellectual disability, developmental delay, coarse facial features, hypertrichosis, sparse scalp hair, and hypoplastic or absent fifth fingernails or toenails. Other variable features include growth failure, craniofacial abnormalities, spinal anomalies, and congenital heart defects. Unlike the classical presentation, our case lacked some typical features such as hypertrichosis and hypoplastic fifth digits, but demonstrated unique findings like steroid-resistant nephrotic syndrome and a single kidney, expanding the phenotypic spectrum of CSS.

Among the genes implicated in CSS, ARID1B mutations are the most common, accounting for 51 – 75% of cases. Variants in ARID1A are less frequent, reported in 7 – 8% of cases.[8] Other genes, such as SMARCB1, SMARCA2, SMARCE1, DPF2, and SOX11, are implicated in smaller subsets of patients. Despite these genetic associations, genotype-phenotype correlations in CSS remain poorly understood. For instance,

while ARID1B variants are linked to more severe intellectual disability and developmental delay, ARID1A mutations are relatively understudied, with limited data on their phenotypic presentations.

Renal involvement in CSS is rare and primarily reported as structural anomalies such as horseshoe kidney, vesicoureteral reflux, and hydronephrosis, with an estimated prevalence of 1 – 5% in affected individuals.[9,10] To date we could not find the published literature, the association of CSS with nephrotic syndrome or SRNS has not been reported, making this case unique and significant. The identification of nephrotic syndrome in our patient expands the phenotypic spectrum of CSS and raises the possibility that renal manifestations, including glomerular disease, may be underrecognized components of the syndrome. The novel heterozygous truncating variant (p.Glu1017Ter) in ARID1A identified in this patient is classified as "likely pathogenic" as per ACMG guidelines. This variant is predicted to cause a loss of function by truncating the ARID1A protein, a critical subunit of the SWI / SNF complex. Functional impairment of ARID1A may disrupt chromatin remodeling, leading to the observed developmental, neurological, and renal abnormalities. The identification of this variant not only confirms the diagnosis of CSS but also underscores the importance of genetic evaluation in patients with atypical presentations. The patient has achieved remission with tacrolimus and is also receiving levetiracetam and valproate for seizure management.

Conclusions

This report presents a novel case of CSS with a single kidney and SRNS, expanding the phenotypic spectrum of ARID1A-associated CSS. It emphasizes the need to consider CSS in patients with global developmental delay, dysmorphic features, and renal abnormalities.

Conflict of Interest: None

Funding Source: None

References

1. Vergano SS, Deardorff MA. Clinical features, diagnostic criteria, and management of Coffin-Siris syndrome. Am J Med Genet C Semin Med Genet. 2014 Sep;166C(3):252-6
DOI: 10.1002/ajmg.c.31411
PMID: 25169447

2. Mannino EA, Miyawaki H, Santen G, Schrier Vergano SA. First data from a parent-reported registry of 81 individuals with Coffin-Siris syndrome: Natural history and management recommendations. Am J Med Genet A. 2018 Nov;176(11):2250-2258
DOI: 10.1002/ajmg.a.40471
PMID: 30276971

3. Curcio MR, Ferranti S, Lotti F, Grosso S. Coffin-Siris syndrome and epilepsy. Neurol Sci. 2021 Feb;42(2):727-729
DOI: 10.1007/s10072-020-04782-y
PMID: 33006724

4. Kosho T, Miyake N, Carey JC. Coffin-Siris syndrome and related disorders involving components of the BAF (mSWI/SNF) complex: historical review and recent advances using next generation sequencing. Am J Med Genet C Semin Med Genet. 2014 Sep;166C(3):241-51
DOI: 10.1002/ajmg.c.31415
PMID: 25169878

5. Fleck BJ, Pandya A, Vanner L, Kerkering K, Bodurtha J. Coffin-Siris syndrome: review and presentation of new cases from a questionnaire study. Am J Med Genet. 2001 Feb 15;99(1):1-7
DOI:10.1002/1096-8628(20010215)99:1<1::aid-ajmg1127>3.0.co;2-a
PMID: 11170086

6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24
DOI: 10.1038/gim.2015.30
PMID: 25741868 PMCID: PMC4544753

7. Vasileiou G, Vergarajauregui S, Endele S, Popp B, Büttner C, Ekici AB, et al. Deciphering Developmental Disorders Study; Thiel CT, Lüdecke HJ, Strom TM, Calpena E, Wilkie AOM, Wieczorek D, Engel FB, Reis A. Mutations in the BAF-Complex Subunit DPF2 Are Associated with Coffin-Siris Syndrome. Am J Hum Genet. 2018 Mar 1;102(3):468-479
DOI: 10.1016/j.ajhg.2018.01.014
PMID: 29429572; PMCID: PMC5985265

8. Cárcamo B, Masotto B, Baquero-Vaquer A, Ceballos-Saenz D, Zapata-Aldana E. "Cancer in ARID1A-Coffin-Siris syndrome: Review and report of a child with hepatoblastoma." Eur J Med Genet. 2022;65(11):104600
DOI: 10.1016/j.ejmg.2022.104600

9. Wakim V, Mazzola S, Dell K, Wang X. P366: Kidney cysts: Potential underrecognized phenotype of Coffin-Siris syndrome. Genet Med. Open. 2024;2:101260
DOI:10.1016/j.gimo.2024.101260

10. Project details. Accessed January 11, 2025. https://www.erknet.org/research/research-projects/project-details?uid=241