Same Gene, Different Journeys : Four Faces of Coffin-Siris Syndrome

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Abstract

Background: Coffin–Siris syndrome (CSS) is a rare neurodevelopmental disorder caused by pathogenic variants in genes of the BAF chromatin-remodelling complex, most commonly ARID1B. It is characterized by developmental delay, dysmorphic features, seizures, feeding difficulties, and variable fifth-digit anomalies. Marked phenotypic heterogeneity often leads to delayed recognition, particularly in resource-limited settings.

Methods: We report a case series of four genetically confirmed children with 6q25.3–q27 deletions involving ARID1B, evaluated at a tertiary care centre. Clinical, neurological, radiological, audiological, and molecular findings were analyzed.

Results: All four children presented in infancy with global developmental delay, recurrent seizures, and significant feeding difficulties requiring nutritional support. Dysmorphic facial features were present in all cases; however, classical fifth-digit hypoplasia was observed in only one child. Neuroimaging revealed structural brain abnormalities in all patients, including corpus callosum thinning, cerebellar vermis hypoplasia, hydrocephalus, and periventricular leukomalacia. Electroencephalography showed generalized background slowing in each case. Hearing impairment was identified in three children. Muscle tone varied, with hypotonia in three cases and hypertonia in one, highlighting phenotypic diversity despite a shared molecular basis. Whole-exome sequencing confirmed de novo deletions involving ARID1B in all patients.

Conclusion: This case series underscores the broad clinical spectrum of ARID1B-related CSS and demonstrates significant genotype–phenotype variability even among patients with similar chromosomal deletions. Limb anomalies may be absent, and neurological manifestations predominate. Early genetic evaluation in infants with unexplained developmental delay and dysmorphism facilitates timely diagnosis, multidisciplinary management, and genetic counselling. Increased awareness and integration of molecular testing are essential to improve recognition of CSS in developing countries.

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- Coffin–Siris syndrome
- ARID1B
- Developmental delay
- Phenotypic variability
- Genetic diagnosis

Introduction:

Coffin–Siris syndrome (CSS) is a rare, genetically mediated congenital disorder characterized by intellectual disability, developmental delay, distinctive facial dysmorphism, and hypoplasia or aplasia of the fifth fingernails and terminal phalanges. It was first described by Coffin and Siris in 1970 as a syndrome of mental retardation with absent fifth fingernails and terminal phalanges[1].CSS is now recognized as a disorder caused by pathogenic variants in genes encoding components of the BRG1/BRM-associated factor (BAF) chromatin remodelling complex, which plays a critical role in regulating gene expression during embryonic development[2,3].Among these genes, *ARID1B* is the most frequently implicated and accounts for a substantial proportion of reported cases[4].Variants in *ARID1B* commonly arise de novo and are associated with a broad phenotypic spectrum, ranging from mild intellectual disability to severe multisystem involvement[5].

Clinically, individuals with CSS typically present with global developmental delay, hypotonia, feeding difficulties, seizures, hearing impairment, and characteristic facial features[6].In addition, structural brain abnormalities, including corpus callosum hypoplasia, vermian anomalies, and ventriculomegaly, have been frequently reported[7].

Despite advances in molecular diagnostic techniques, CSS remains underrecognized, particularly in low- and middle-income countries where access to genetic testing is limited. The marked clinical heterogeneity and overlap with other neurodevelopmental disorders often lead to delayed diagnosis or misclassification. Reports from India and similar resource-constrained settings are scarce and largely limited to isolated case reports[9]. Consequently, region-specific data on phenotypic variability, neuroimaging findings, and molecular characteristics remain insufficient, emphasizing the need for additional systematic documentation.

The present study describes four children with Coffin–Siris syndrome associated with deletions involving the 6q25.3–q27 region encompassing the *ARID1B* gene. The rationale of this case series is to highlight the wide clinical spectrum of CSS, particularly with respect to neurological manifestations, muscle tone variability, feeding problems, and structural brain abnormalities, and to reinforce the importance of early genetic evaluation in infants presenting with unexplained developmental delay and dysmorphic features. Early identification facilitates appropriate multidisciplinary intervention and genetic counselling.

The novelty of this study lies in the presentation of four genetically confirmed cases from a single tertiary care centre, demonstrating striking phenotypic diversity despite a shared molecular basis. The coexistence of hypotonia and hypertonia, varied neuroimaging patterns, and differing limb anomalies within this cohort underscores the complexity of genotype–phenotype correlations in ARID1B-related disorders. Furthermore, this series contributes to the limited Indian literature on CSS and supports the integration of early whole-exome sequencing into routine pediatric evaluation for syndromic developmental delay.

Case 1:

Case 1 was a 6-month-old female infant born at term with antenatal history of significant decreased foetal movements, with admission to the neonatal intensive care unit for respiratory distress syndrome at birth. She presented with delayed attainment of gross motor and speech milestones. On examination, she exhibited distinctive dysmorphic features, including coarse facial features with thick eyebrows and hypoplastic fifth fingernails, which are characteristic of Coffin–Siris syndrome. Neurological evaluation revealed generalized hypotonia and recurrent tonic–clonic seizures. Hearing assessment showed conductive hearing loss. Magnetic resonance imaging of the brain demonstrated thinning of the corpus callosum. Electroencephalography revealed generalized slowing of background activity. She also had significant feeding difficulties with poor sucking reflex, necessitating nasogastric feeding

support. Genetic evaluation using whole-exome sequencing identified a heterozygous 6q25.3–q27 deletion involving the *ARID1B* gene. Parental karyotyping was normal, indicating a de novo mutation. Based on the clinical, radiological, and molecular findings, a diagnosis of Coffin–Siris syndrome was established (Figure 1).

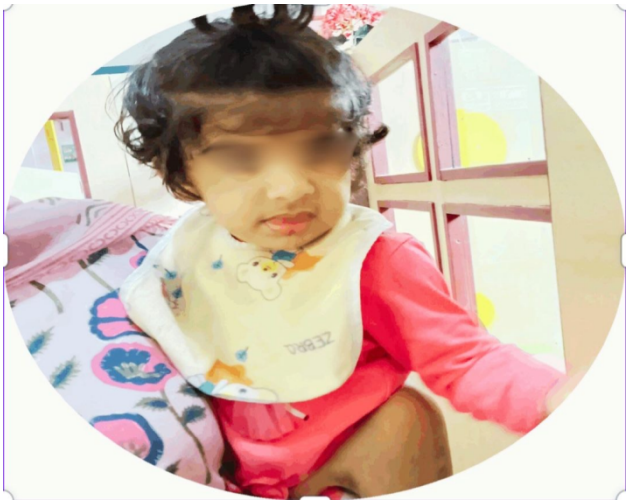

Figure 1: Clinical photograph showing coarse facial features with thick eyebrows characteristic of Coffin–Siris syndrome.

Case 2:

Case 2 was a 2-month-old male infant born preterm normal vaginal delivery at 34 weeks of gestation with history of pregnancy-induced hypertension and respiratory distress syndrome, at birth. He presented with global developmental delay and poor feeding. Clinical examination revealed generalized hypotonia and dysmorphic facial features, including a wide mouth, flat nasal bridge, and low-set ears. He had recurrent tonic–clonic seizures. Audiological evaluation demonstrated bilateral sensorineural hearing loss. Cardiological assessment revealed a small atrial septal defect on echocardiography. Neuroimaging showed hypoplasia of the cerebellar vermis on magnetic resonance imaging of the brain, and electroencephalography revealed generalized background slowing. He required nasogastric tube feeding due to persistent feeding difficulties. Genetic analysis by whole-exome sequencing identified a 6q25.2–q27 deletion involving the *ARID1B* gene. Parental karyotyping was normal, suggesting a de novo chromosomal abnormality. In view of the characteristic clinical features, neurological involvement, and confirmatory molecular findings, a diagnosis of Coffin–Siris syndrome was made (Figure 2).

Figure 2: Clinical features including wide mouth, flat nasal bridge, and low-set ears associated with ARID1B-related Coffin-Siris syndrome

Case 3:

A 1-year-old male child born at term to a mother with gestational diabetes mellitus, with a history of perinatal birth asphyxia. She presented with global developmental delay and recurrent myoclonic seizures. In contrast to the other cases in this series, neurological examination revealed hypertonia. He also had nystagmus and left-sided hearing loss. Dysmorphic features included sparse scalp hair and a flat midface. Neuroimaging revealed periventricular leukomalacia with global cerebral atrophy on magnetic resonance imaging of the brain, and electroencephalography showed generalized background slowing. She had significant feeding difficulties requiring nasogastric tube support. Genetic evaluation using whole-exome sequencing identified a 6q25.3–q27 microdeletion involving the *ARID1B* gene. Parental karyotyping was normal, indicating a de novo mutation. The presence of developmental delay, epilepsy, characteristic dysmorphism, and confirmatory molecular findings supported the diagnosis of Coffin–Siris syndrome (Figure 3).

Figure 3: Clinical photograph demonstrating sparse scalp hair and flat midface.

Case 4:

A 1-year-old male child with a positive family history of developmental delay in a sibling was evaluated for delayed developmental milestones and recurrent seizures. She was born at term following an antenatal period complicated by oligohydramnios. Since early infancy, she had exhibited feeding difficulties with marked oral aversion and poor weight gain. On clinical examination, she was noted to have generalized hypotonia and dysmorphic features, including a depressed nasal bridge, low anterior hairline, and hypertrichosis. Limb examination revealed broad halluces. She experienced recurrent tonic–clonic seizures and showed evidence of conductive hearing loss on audiological assessment. Neuroimaging demonstrated hydrocephalus with thinning of the corpus callosum on magnetic resonance imaging, while electroencephalography revealed mild background slowing. Cardiac evaluation was unremarkable. Genetic testing by whole-exome sequencing confirmed a 6q25.3–q27 deletion involving the *ARID1B* gene, and parental karyotyping was normal, consistent with a de novo mutation. In view of the characteristic clinical features, neurological involvement, and molecular findings, a diagnosis of Coffin–Siris syndrome was established (Figure 4).

Figure 4: Clinical features including hypertrichosis, depressed nasal bridge, and low anterior hairline

Discussion:

This case series demonstrates considerable phenotypic variability in Coffin–Siris syndrome (CSS), despite a shared molecular basis involving ARID1B deletions. All four patients exhibited global developmental delay, seizures, feeding difficulties, and characteristic dysmorphic features, which are consistent with the classical descriptions of CSS in earlier reports. Similar core manifestations, including intellectual disability, growth retardation, coarse facial features, and fifth-digit anomalies, were documented in the early radiological and clinical review by Lucaya et al[11].Our findings therefore reaffirm the persistence of these hallmark features across decades and across different populations.

Neurological involvement was prominent in our cohort, with all patients demonstrating seizures, abnormal electroencephalographic findings, and

structural brain abnormalities on neuroimaging. These observations are comparable to those reported by Jain et al., who described seizures, hypotonia, and global developmental delay in their paediatriccase[12].Similarly, Schrier et al. emphasized that cognitive or developmental delay and fifth-digit abnormalities are the two most consistent features of CSS and proposed that their absence should prompt reconsideration of the diagnosis[7]. In our series, although the classical hypoplastic fifth digit was present only in one patient, all cases fulfilled the major neurological and developmental criteria, supporting the concept that limb anomalies, while suggestive, are not mandatory for diagnosis.

Feeding difficulties were universal in our patients, necessitating nasogastric tube feeding or specialized nutritional support. This finding parallels previous observations by Lucaya et al., who reported feeding problems in the majority of affected infants[11]. Schrier et al. also categorized feeding difficulties as an important systemic feature contributing to diagnostic certainty[7].The high prevalence of feeding problems in our cohort highlights the need for early nutritional intervention and multidisciplinary management in children with CSS.

A notable finding in the present study was the variability in muscle tone. While hypotonia, as seen in three of our cases, is commonly reported in CSS, one patient exhibited hypertonia. This contrasts with most published case reports, including that of Jain et al., where hypotoniapredominated[12].Such variability supports the observations of Schrier et al., who described a spectrum of "classic" and "variant" phenotypes and emphasized that clinical features exist along a continuum rather than as fixed entities[7].

All patients in our series were found to have deletions involving the 6q25.3–q27 region encompassing the ARID1B gene, confirming a de novo molecular etiology. This finding aligns with the growing body of evidence identifying ARID1B as the most frequently mutated gene in CSS. Studies on BAF-complex–related disorders, including those involving ARID2 mutations, have demonstrated consistent developmental delay and dysmorphic features with marked phenotypic variability[13].Our results further support this genotype–phenotype heterogeneity, as significant clinical differences were observed despite similar genetic deletions.

Structural brain abnormalities, including hydrocephalus, corpus callosum thinning, cerebellar vermis hypoplasia, and periventricular leukomalacia, were identified in all four cases. Such findings are in agreement with previous studies reporting frequent central nervous system malformations among affected individuals[7,11]. The consistent presence of neuroimaging abnormalities in our series suggests that early magnetic resonance imaging may play an important role in supporting clinical suspicion of CSS.

Compared with previously published case reports and reviews, the early age at diagnosis in our patients is noteworthy. Most earlier studies reported diagnosis later in infancy or early childhood, often after developmental delay became evident[11,12].In our cohort, antenatal and perinatal complications, early feeding problems, and early-onset seizures prompted prompt evaluation and genetic testing, facilitating earlier diagnosis. This emphasizes the importance of heightened clinical awareness and early molecular investigations.

The novelty of this study lies in the presentation of four genetically confirmed cases from a single tertiary care centre, demonstrating striking phenotypic diversity despite a shared molecular basis. The coexistence of hypotonia and hypertonia, varied neuroimaging patterns, and differing limb anomalies within this cohort underscores the complexity of genotype–phenotype correlations in ARID1B-related disorders. Furthermore, this series contributes to the limited Indian literature on CSS and supports the integration of early whole-exome sequencing into routine pediatric evaluation for syndromic developmental delay.

In summary, the findings of the present study are largely concordant with previously published literature regarding the core clinical features

of CSS, including developmental delay, seizures, feeding difficulties, and dysmorphism[11-13].However, our series highlights substantial phenotypic variability, particularly in limb anomalies and muscle tone, reinforcing the spectrum nature of the disorder. The consistent identification of ARID1B deletions further strengthens the role of molecular testing in confirming diagnosis. Early recognition and multidisciplinary management remain essential to optimize outcomes and provide appropriate genetic counselling (Table 1).

Conclusion:

This case series highlights the wide phenotypic spectrum of Coffin–Siris syndrome associated with ARID1B deletions, even among patients with similar genetic abnormalities. In conclusion, Coffin–Siris syndrome remains an under-recognized but important cause of paediatric neurodevelopmental disorders. Comprehensive clinical assessment supported by early genetic testing is essential for accurate diagnosis, individualized care, and improved long-term outcomes. Further multicentric studies with larger cohorts are required to better elucidate genotype–phenotype correlations and to develop standardized management guidelines for affected children.

Table 1: Summary of all cases

Parameter	Case 1	Case 2	Case 3	Case 4
Age at Diagnosis	6 months	2 months	1 year	1 year
Sex	Female	Male	Male	Male
Delivery Mode	LSCS for CPD	NVD	NVD	NVD
Gestational Age	Term	Preterm (34 weeks)	Term	Term
Birth Weight	2.6 kg	1.9 kg	2.8 kg	2.7 kg
Antenatal Findings	Decreased fetal movements	PIH	GDM mother	Oligohydramnios
Perinatal Complications	RDS	RDS	Birth asphyxia	Feeding difficulty
Dysmorphic Features	Thick eyebrows, coarse facies, hypoplastic 5th fingernails	Wide mouth, flat nasal bridge, low set ears	Sparse scalp hair, flat midface	Hypertrichosis, depressed nasal bridge, low anterior hairline
Growth Parameters	Weight <3rd percentile, HC normal	Weight and HC <3rd percentile	Weight normal, microcephaly	Weight and HC at 10th percentile
Developmental Delay	Gross motor and speech delay	Global delay	Global delay	Global delay
Tone	Hypotonia	Hypotonia	Hypertonia	Hypotonia
Seizures	Tonic-clonic	Tonic-clonic	Myoclonic	Tonic-clonic
MRI Brain	Thin corpus callosum	Vermis hypoplasia	PVL, global atrophy	Hydrocephalus, thin corpus callosum
EEG	Generalized slowing	Generalized slowing	Generalized slowing	Mild background slowing
Ophthalmic	Strabismus	Nystagmus	Nystagmus	Esotropia
ENT/Hearing	Conductive hearing loss	Bilateral SNHL	Left-sided loss	Conductive hearing loss
Cardiac Findings	Normal	Small ASD	PDA	Normal
Feeding Problems	Poor suck, NG feeds	NG feeds	NG feeds	Oral aversion
Limb Abnormalities	Hypoplastic 5th digit	None	Short fingers	Broad halluces

Parameter	Case 1	Case 2	Case 3	Case 4
WES Findings	6q25.3-q27 deletion	6q25.2-q27 deletion	6q25.3-q27 microdeletion	6q25.3-q27 deletion
Karyotype (Parental)	Normal	Normal	Normal	Normal
Family History	Negative	Negative	Negative	Sibling with developmental delay

Genetic Test Reports

Case 1:

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
ARID1B (NM_020732.3)	Exon 5	c.1335del (p.Ala446ArgfsTer6)	Heterozygous	Coffin–Siris syndrome 1 (OMIM #135900)	Autosomal dominant	Likely Pathogenic

Case 2:

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
ARID1B (CNV)	6q25.3q27	Heterozygous deletion (Copy number = 1)	Heterozygous	Coffin–Siris syndrome 1 (OMIM #135900)	Autosomal dominant	Pathogenic

Case 3:

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
SMARCC2	Exon 10	c.877G>T (p.Gly293Trp)	Heterozygous	Coffin–Siris syndrome 8	Autosomal dominant	VUS
KANSL1	Exon 6	c.1799A>G (p.Lys600Arg)	Heterozygous	Koolen–de Vries syndrome	Autosomal dominant	VUS

Case 4:

Gene (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
ARID1B (CNV)	6q25.3q27	Partial gene deletion (Copy number = 1)	Heterozygous	Coffin–Siris syndrome 1 (OMIM #135900)	Autosomal dominant	Pathogenic

Conflict of Interest : Nil

Funding : Nil

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