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A Novel Variant of ARID1B-Related CSS in a Rwandan patient: A Case Report

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ABSTRACT

INTRODUCTION: CSS (CSS) is a rare neurodevelopmental disorder characterized by developmental delay, intellectual disability, hypotonia, distinctive craniofacial dysmorphism, and hypoplasia or aplasia of the distal phalanges or nails, particularly of the fifth digits. Pathogenic variants involving genes encoding components of the Switch/Sucrose Non-Fermentable chromatin-remodeling complex especially ARID1B gene critical for embryonic development and gene regulation represent the most common molecular cause of the syndrome. Although advances in genomic technologies have improved recognition of CSS worldwide over the past 3 decades, reports from sub-Saharan Africa remain limited.

CASE PRESENTATION: We report a male patient referred to Rwanda Military Teaching Hospital, Pediatric Department in Medical genetic unit for global developmental delay and feeding difficulties. Clinical examination revealed, hypotonia, developmental milestone delay, coarse facial appearance, sparse scalp hair, thick eyebrows, long eyelashes, broad nasal bridge, anteverted nostrils, low-set ears, micrognathia, and hypoplastic toenails.

Results: Conventional cytogenetic analysis demonstrated a male karyotype (46, XY). Whole exome sequencing-based copy number variants analysis identified a 7.3 Mb interstitial deletion involving chromosome 6q25.3–q25.1 encompassing the ARID1B gene. The finding was confirmed by multiplex ligation-dependent probe amplification, establishing the diagnosis of CSS type 1. The patient was managed in multidisciplinary team approach including physiotherapy and speech therapy and he demonstrated clinical improvement.

CONCLUSION: This report describes the first genetically confirmed case of CSS in Rwanda. It highlights the diagnostic utility of advanced molecular genetic testing in children with developmental delay and dysmorphic features and underscores the importance of expanding access to clinical genetic services in resource-limited settings to reduce diagnostic odyssey and timely patient management.

Keywords: CSS, ARID1B, Developmental delay, Copy number variation

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INTRODUCTION

Coffin-Siris syndrome (CSS) is a rare congenital neurodevelopmental disorder with an estimated prevalence of fewer than Less than 1 per 100,000 live births worldwide [1]. although the true frequency remains uncertain because of underdiagnosis and phenotypic variability, It was first described by Coffin and Siris in 1970 [1,2]. It is characterized by developmental delay or intellectual disability, hypotonia, feeding difficulties, distinctive craniofacial dysmorphism, and hypoplasia or aplasia of the distal phalanges and nails, particularly affecting the fifth digits [1–3]. The syndrome exhibits considerable clinical variability, ranging from mild developmental impairment to severe multisystem involvement.

Advances in molecular genetics have established CSS as a member of a group of disorders resulting from dysfunction of the BRG1/BRM-associated factor (BAF) [4], also known as the Switch/ Sucrose Non- Fermentable (SWI/SNF) chromatin-remodeling complex. This complex plays a fundamental role in transcriptional regulation, embryonic development, cellular differentiation, and neurodevelopment [3,5]. Pathogenic variants affecting several genes encoding components of the BAF complex have been associated with CSS, including ARID1A, ARID1B, SMARCB1, SMARCA4, SMARCE1, ARID2, and SOX11 [1–3].

Among these genes, ARID1B is the most frequently implicated, accounting for a substantial proportion of molecularly confirmed cases [6–8]. ARID1B haploinsufficiency has been associated with a broad phenotypic spectrum ranging from isolated intellectual disability to the classic presentation of CSS [7–9].

Affected individuals commonly present with global developmental delay, hypotonia, feeding difficulties, growth impairment, characteristic facial features, and digital anomalies. Additional manifestations involving the cardiovascular, neurological, gastrointestinal, genitourinary, auditory, and musculoskeletal systems have also been reported, contributing to marked phenotypic heterogeneity [1,2,10]. Because many of these findings overlap with those observed in other syndromic causes of developmental delay, molecular testing has become essential for establishing an accurate diagnosis and providing appropriate genetic counseling [11].

Although the recognition of CSS has increased considerably following the widespread implementation of genomic technologies, reports from Africa remain scarce. Expanding access to genomic medicine is increasingly recognized as a priority for improving diagnosis and management of rare genetic disorders across the continent [12,13]. To our knowledge, no genetically confirmed case of CSS has previously been reported in Rwanda.

Here, we describe a Rwandan patient with classical clinical manifestations of CSS associated with a large deletion involving ARID1B. We discuss the clinical presentation, molecular findings, management, and broader implications of this case for the development of genomic medicine in resource-limited settings.

CASE PRESENTATION

An 18-month-old male patient was referred to Rwanda Military Teaching Hospital, Pediatrics Department for evaluation of global developmental delay and feeding difficulties, He was born at term by cesarean delivery with a birth weight of 3.0 kg. The neonatal period was uneventful, no history of birth asphyxia or Postnatal Hospitalization. There

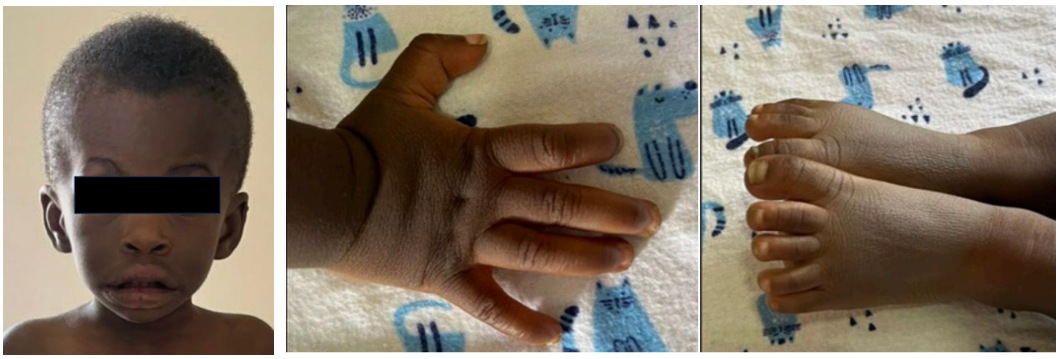

Figure 1: Face profile with coarse facial appearance (Left) and shortened digits affecting both the hands (Middle) and feet (Right)

was no known family history of genetic disorders, developmental delay, intellectual disability, congenital anomalies, or parental consanguinity. At the initial genetic evaluation, the child exhibited significant global developmental delay. He was unable to sit independently, crawl, or produce meaningful words. Feeding difficulties were reported by the mother, including poor oral intake and prolonged feeding times. Physical examination revealed growth impairment, the weight was 8.2 kg, height 74 cm (-2 SD) and head circumference of 42 cm, all below the expected range for age. Generalized hypotonia was noted. Dysmorphic features included a coarse facial appearance (Figure 1), sparse scalp hair, thick eyebrows, long eyelashes, broad nasal bridge, anteverted nostrils, wide mouth with thick lips, low-set ears, and micrognathia.

Examination of the extremities revealed hypoplastic nails involving the first and fifth toes of the left foot and the fifth toe of the right foot. Shortened digits affecting both the hands and feet were also observed (Figure 2).

Cardiovascular examination demonstrated normal heart sounds without audible murmurs. Abdominal examination identified a small umbilical hernia. Neurological assessment confirmed generalized hypotonia without focal neurological deficits. Further investigations were undertaken to evaluate possible syndromic causes of developmental delay. Echocardiography demonstrated normal cardiac anatomy and function. Abdominal ultrasonography was unremarkable. Electroencephalography performed at six months of age, showed normal heart. Brain computed tomography scan showed no structural abnormalities as well as Audiological assessment.

Routine laboratory investigations, including renal and liver function tests were within normal range. Conventional cytogenetic analysis revealed a normal male karyotype (46, XY). Given the strong clinical suspicion of an underlying genetic syndrome, further genomic testing was performed. Whole Exome sequencing (WES) was done after obtaining the parental consent form. WES was performed using the CentoDysmorph panel. Genomic DNA was enzymatically fragmented and enriched via DNA capture probes, followed by indexed library sequencing on an Illumina platform. The assay design targeted all coding exons of the panel genes alongside 10 bp of flanking intronic sequences, as well as any previously identified pathogenic and likely pathogenic variants. The main findings of exome sequencing are summarized in Table 1.

The deleted interval encompassed 31 genes, including ARID1B, a dosage-sensitive gene known to cause CSS type 1 through haploinsufficiency. The identified deletion was classified as pathogenic according to ACMG criteria.

Whole exome Sequencing based copy number variation analysis identified a 7.3 Mb interstitial deletion involving chromosome 6q25.3–q25.1, encompassing the ARID1B gene. The finding was subsequently confirmed by multiplex ligation-dependent probe amplification (MLPA), establishing the genetic diagnosis of autosomal dominant CSS type 1.

Following diagnosis, the patient was enrolled in a multidisciplinary rehabilitation program consisting of physiotherapy focused on neuromotor stimulation and functional rehabilitation, as well as speech therapy sessions conducted three times weekly. During follow-up, significant developmental progress was observed. The child achieved independent sitting and standing, began taking assisted steps, and developed the ability to produce several meaningful words.

Written informed consent was obtained from the

Table 1: Whole Exome Sequencing Findings of Copy Number Variations and Genes Dtected

CNV Description	Size	Gene count	Interpretation	Related Disorder
seq[GRCh37]del(chr6)(q25.3q25.1) chr6:g.(151004879 158331058)x1	7326	31	Pathogenic	C

CNV Description	RefSeq GENES
seq[GRCh37]del(chr6)(q25.3q25.1) chr6:g.(151004879 158331058)x1	AKAP12, ARID1B, ARMT1, CCDC170, CLDN20, CNKSR3, ESR1, FBXO5, IPCEF1, MIR1202, MIR1273C, MIR3692, MIR4466, MTHFD1L, MTRF1L, MYCT1, NOX3, OPRM1, PLEKHG1, RGS17, RMND1, SCAFB, SNX9, SYNE1, SYNE1-AS1, TFB1M, TIAM2, TMEM242, VIP, ZBTB2, ZDHHC14

patient's mother for publication of the clinical information, genetic findings, and accompanying images. All identifying information was removed to protect patient confidentiality.

DISCUSSION

CSS is a rare neurodevelopmental disorder caused by pathogenic variants affecting genes encoding components of the BRG1/BRM-associated factor (BAF), also known as the SWI/SNF (Switch/sucrose Non-Fermantible) chromatin-remodeling complex [14]. These proteins play essential roles in transcriptional regulation, embryonic development, and neuronal differentiation. Among the genes associated with CSS, ARID1B is the most frequently implicated and is responsible for the majority of molecularly confirmed cases of CSS type 1 [1–3,6,7]. The diagnosis was established through the combination of clinical findings and identification of an approximately 7.3 Mb interstitial deletion involving chromosome 6q25.3–q25.1 encompassing ARID1B after performing whole exome sequencing. This finding is consistent with previous studies demonstrating that ARID1B haploinsufficiency is a major cause of both CSS and a broader spectrum of neurodevelopmental disorders [6–8]. The molecular diagnosis was particularly important in this case because conventional cytogenetic analysis revealed a normal male karyotype. This highlights the limitations of standard karyotyping in detecting submicroscopic chromosomal abnormalities and emphasizes the additional diagnostic value of genomic technologies such as next-generation sequencing-based copy number variation analysis and MLPA confirmation. Furthermore, large deletions involving ARID1B have been associated with classical CSS phenotypes and, in some instances, more severe developmental manifestations, likely due to the involvement of adjacent genomic regions [8,10]. Clinically, our patient demonstrated many of the characteristic manifestations of CSS. Global developmental delay, generalized hypotonia, feeding difficulties, growth impairment, and distinctive craniofacial dysmorphism were evident from early childhood. These findings are among the most frequently reported features in individuals with ARID1B-related CSS and reflect the critical role of the BAF complex in normal neurodevelopment [1,2,10]. The patient's inability to sit independently, crawl, or produce meaningful speech at the time of initial evaluation illustrates the significant developmental impact associated with ARID1B haploinsufficiency. The craniofacial and skeletal findings observed in this case further support the diagnosis. Coarse facial appearance, sparse scalp hair, thick eyebrows, long eyelashes, broad nasal bridge, anteverted nostrils, low-set ears, micrognathia, and thick lips closely resemble the phenotype described in previous reports [2,9,15]. In addition, hypoplastic nails affecting multiple toes and shortening of the digits represent classic diagnostic features of CSS. These abnormalities of the distal phalanges and nails, particularly involving the fifth digits, remain among the most recognizable clinical hallmarks of the syndrome and may provide important diagnostic clues in settings where molecular testing is not readily available [1,2,10].

Despite the presence of significant neurodevelopmental impairment, no major cardiac, renal, auditory, or structural neurological abnormalities were identified in this patient. Previous studies have documented considerable phenotypic variability among individuals with CSS, with congenital anomalies affecting multiple organ systems occurring in only a subset of cases [2,10]. The absence of major extracranial malformations in our patient therefore reflects the variable expressivity commonly observed in ARID1B-related disorders and highlights the importance of maintaining clinical suspicion even in the absence of multisystem involvement. Table 1 summarizing the Phenotypic features observed in the patient compared with commonly reported manifestations of CSS. Will be attached in the appendix for reference

An important aspect of this case is the favorable developmental response observed following multidisciplinary intervention. After enrollment in physiotherapy and speech therapy programs, the patient achieved significant improvements in motor and language development, including independent sitting and standing, assisted ambulation, and the acquisition of meaningful speech. Although no curative treatment currently exists for CSS, early developmental interventions have been shown to improve functional outcomes and quality of life in children with neurodevelopmental disorders [16,17]. This observation reinforces the importance of early diagnosis, allowing timely implementation of supportive therapies and individualized follow-up.

To our knowledge, this is the first genetically confirmed case of CSS reported from Rwanda.

The report contributes to the limited literature on rare genetic disorders in sub-Saharan Africa and underscores the growing importance of genomic medicine across the continent [12,13]. Beyond documenting a rare condition, this case illustrates the clinical value of advanced genomic testing in children presenting with unexplained developmental delay and dysmorphic features, particularly when conventional investigations are inconclusive. Expanding access to genetic services and molecular diagnostics in resource-limited settings may facilitate earlier diagnosis, improve patient management, and strengthen genetic counseling for affected families.

CONCLUSION

This case involving a 18 months-old male patient diagnosed with CSS associated with global developmental delay. It highlights the role of maintaining a heightened level of suspicion by healthcare professionals for rare diseases patients who present with developmental delays and dysmorphic features. Timely clinical genetic evaluation can facilitate prompt diagnosis and all-encompassing treatment plans. Additionally, knowing the inheritance pattern facilitate proper genetic counseling. This case report provides insightful information on a rare genetic disease; disseminating this information health care providers could help to identify the syndrome earlier in the future and proper patient management.

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