ORIGINAL RESEARCH ARTICLE

Spectrum and determinants of disorders of sex development in Sudan

DOI: 10.29063/ajrh2026/v30i10.7

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Abstract

This study characterizes disorders of sex development (DSD) in 60 Sudanese patients recruited from Khartoum (2021 – 2022), revealing a high rate of late presentation (63.3% post-puberty), consanguinity, and female genital mutilation (FGM) in 75% of cases with genotype – phenotype discordance. Karyotyping showed 61.7% had a 46,XY karyotype and 31.7% a 46,XX karyotype, with 33.3% exhibiting discordance between chromosomal sex and sex of rearing. SRY gene analysis by PCR was negative in 10% of patients, and Sanger sequencing in a subset of 46,XY individuals identified five novel SRY mutations in seven patients. The findings underscore the influence of sociocultural practices such as female genital mutilation, and consanguinity on the expression and management of disorders of sex development in Sudan. The study offers critical insights from an underrepresented African population and addressing a gap in global literature on disorders of sex development. *(Afr J Reprod Health 2026; 30 [10]:85-94).*

Keywords: Disorder of Sex Development, SRY gene mutation, chromosomal analysis, Sudan

Résumé

Cette étude caractérise les troubles du développement sexuel (TDS) chez 60 patients soudanais recrutés à Khartoum (2021-2022). Elle révèle un taux élevé de diagnostic tardif (63,3 % après la puberté), de consanguinité et de mutilations génitales féminines (MGF) dans 75 % des cas présentant une discordance génotype-phénotype. Le caryotype a montré que 61,7 % des patients présentaient un caryotype 46,XY et 31,7 % un caryotype 46,XX, tandis que 33,3 % présentaient une discordance entre le sexe chromosomique et le sexe d'éducation. L'analyse du gène SRY par PCR était négative chez 10 % des patients, et le séquençage Sanger chez un sous-groupe d'individus 46,XY a permis d'identifier cinq nouvelles mutations du gène SRY chez sept patients. Ces résultats soulignent l'influence de pratiques socioculturelles telles que les mutilations génitales féminines et la consanguinité sur l'expression et la prise en charge des troubles du développement sexuel au Soudan. Cette étude apporte un éclairage essentiel sur une population africaine sous-représentée et comble une lacune dans la littérature mondiale sur les troubles du développement sexuel.. *(Afr J Reprod Health 2026; 30 [10]: 85-94).*

Mots-clés: Trouble du développement sexuel, mutation du gène SRY, analyse chromosomique, Soudan

Introduction

Disorders of Sex Development (DSD) are regarded as an umbrella term, referring to a group of congenital conditions in which the development of the chromosomal, gonadal, or anatomical sex are atypical.[1] The 2006 Chicago Consensus introduced a standardized classification system that replaced outdated and stigmatizing terms such as "intersex" and "pseudohermaphroditism" with a more precise, evidence-based framework dividing DSD into three main categories: 46,XY DSD, 46,XX DSD, and Sex Chromosome DSD. [2,3]This classification emphasizes a multidisciplinary approach that integrates clinical, hormonal, imaging, genetic, and molecular tests to guide diagnosis, gender assignment, and long-term care.

The estimated global incidence of DSD is approximately 1 in 4,500 to 1 in 5,000 live births. [4] The overall prevalence varies depending on the specific subtype and population studied. For instance, 46,XY DSD occurs in about 1 in 20,000 newborns, while 46,XX testicular DSD has an incidence of 1 in 20,000–25,000 male births. [4,5] Complete gonadal dysgenesis affects approximately 1 in 150,000 individuals, and ovotesticular DSD, though rare in Western countries, appears to be more common in parts of Africa.[4]

Various factors predispose persons to DSD, but the identification of the SRY (Sex-determining Region Y) mapped to chromosome Yp11.3 by Sinclair et al. (1990) was a true landmark discovery in the field.[6] The SRY gene encodes a transcription factor that contains a high-mobility-group (HMG) box domain, which initiates testis differentiation during embryogenesis. Functional SRY gene expression triggers a cascade of downstream genes, including SOX9, AMH, and WT1, which promote Sertoli cell differentiation and result in normal male development.[7] Thus, mutations, e.g., deletions or translocations involving the SRY gene, are well-established causes of 46,XY complete gonadal dysgenesis (Swyer syndrome) or 46,XX testicular DSD (sex reversal). Less than 20 Cases of SRY mutations have been reported, reflecting an evident disparity between a few studies from African countries and what has been reported from developed countries.[8] The disparity is even sharper when it comes to full-gene sequencing, which is often skipped in African studies due to high costs and infrastructural constraints.

The actual burden of DSD in many African countries, including Sudan, remains underreported due to limited diagnostic resources, cultural stigma, and lack of national registries. This under-ascertainment likely masks the actual prevalence, particularly in regions with high rates of consanguinity, which may increase the risk of recessive forms of DSD.[9]

Despite these challenges, there has been growing recognition of DSD in Sudan, reflected in increased referrals to specialized centers and the establishment of collaborative networks such as the Sudanese Intersex Working Group (SIWG).[10] However, comprehensive genetic studies on Sudanese DSD populations are scarce, and the mutational spectrum of key genes, such as SRY, is largely unexplored in this population.

This study aimed to characterize the clinical, cytogenetic, and molecular profiles of Sudanese patients with DSD and to characterize the SRY gene mutations using the gene sequence of the SRY gene for a better understanding of the spectrum of SRY gene mutations in the Sudanese population.

Methods

Patients

This cross-sectional study was conducted between January 2020 and May 2022 at the Elite Medical Center, which provides genetic services in Khartoum, Sudan. A total of 60 patients referred with a provisional diagnosis of DSD were enrolled in the study. Patients were referred from various regions across Sudan, reflecting a diverse ethnic and geographic distribution.

A detailed medical history was collected through face-to-face interviews using structured questionnaire administered by trained clinicians, which included demographic data, family history, with an emphasis on consanguinity, age at presentation, sex of rearing, and clinical complaints. A thorough physical examination was performed, focusing on external genitalia, secondary sexual characteristics, and the presence of gonads. Phenotypic classification was based on external genital appearance using the Prader scale for virilization and standardized clinical criteria for DSD evaluation.[2] Hormonal profiles including follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone levels, and response to human chorionic gonadotropin (hCG) stimulation test, were assessed using Enzyme-Linked Immunosorbent Assay (ELISA) at Elite Medical Center Laboratory. Ultrasound imaging was performed when indicated to assess internal reproductive structures.

Cytogenetic analysis

Peripheral blood samples (5 mL) were collected in sodium heparin tubes under aseptic conditions and processed within 2 hours of collection. Lymphocyte cultures were established using McCoy's 5A medium supplemented with 25% fetal bovine serum (FBS), 3.4% phytohemagglutinin (PHA), and 1% penicillin/streptomycin. Cultures were incubated at 37°C in a 5% CO_2 atmosphere for 72 hours.

Chromosome harvesting was performed after metaphase arrest using colchicine (0.1 mL of 10 μg/mL), which was added 30 minutes before termination. Cells were subjected to hypotonic treatment with 0.075 M KCl, followed by fixation in methanol: acetic acid (3:1 v/v) through multiple changes. Metaphase spreads were prepared on clean glass slides and aged at 65°C overnight.

Chromosomes were banded using Wright's staining technique following Sorensen buffer pretreatment. At least 25 metaphases per patient were analyzed under light microscopy. The karyotype description was according to the International System for Human Cytogenetic Nomenclature (ISCN, 2021). [11] Digital karyotyping was performed using the CytoVision system (Applied Imaging, UK).

Molecular genetic analysis

Genomic DNA was extracted from 2–5 mL of whole blood collected in EDTA tubes using a modified guanidine thiocyanate-chloroform method. Briefly, red blood cells were lysed, followed by proteinase K digestion of white blood cells. DNA was precipitated with isopropanol, washed with 70% ethanol, air-dried, and resuspended in nuclease-free water. DNA concentration and purity were assessed using a spectrophotometer.

The SRY gene was amplified via polymerase chain reaction (PCR) using primers XES10 [with DNA sequences (5' to 3'): GAGCTCGAGAATTCGGTGTTGAGGGCGGAG AAATGC] and XES11 [with DNA sequences (5' to 3'):GAGCTCGAGAATTCGTAGCCAATGTTAC CCGATTGTC], flanking the open reading frame of the SRY gene (GenBank: L10102), yielding a 778 bp product.

PCR reactions (25 µL volume) contained 50–100 ng of genomic DNA, 0.3 µL (1.5 U) of Taq DNA polymerase, 0.5 µL of each primer, 2.0 µL dNTPs (100 mM), 1.5 µL $MgCl_2$ (1.5 mM), 2.5 µL 10× PCR buffer, and nuclease-free water. Amplification was carried out in a thermal cycler (Techne TC-3000) with initial denaturation at 94°C for 2 minutes, followed by 32 cycles of 94°C (80 s), 60°C (1.5 min), and 71°C (2.5 min), with a final extension at 71°C for 10 minutes.

PCR products were electrophoresed on a 1% agarose gel containing 0.5 µg/mL ethidium bromide in 1×TBE buffer, visualized under UV light, and documented using a gel documentation system (Syngene). Fertile 46,XX females and 46,XY males served as negative and positive controls, respectively.

DNA sequencing and mutation analysis

Given the primary clinical and phenotypic characteristics of the cohort, *SRY* gene analysis was prioritized in a subset of 16 patients who exhibited specific features suggestive of *SRY*-related pathogenesis. These included individuals with 46, XY complete or partial gonadal dysgenesis, suspected cases of 46,XX testicular or ovotesticular DSD, or those with a family history consistent with Y-chromosome-linked inheritance. Samples were submitted for bidirectional Sanger sequencing at Macrogen Inc. (Seoul, South Korea). After purification, sequencing was performed using the same primers (XES10 and XES11). High-quality sequence data were obtained and analyzed using BioEdit Sequence Alignment Editor (v7.0.5.3). Sequences were compared to the reference SRY gene (NM_003140.3) to identify nucleotide variations.

Detected variants were classified according to ACMG/AMP guidelines,[12] and assessed for conservation, predicted functional impact, and novelty by comparison with public databases (dbSNP, ClinVar, HGMD).

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0. Descriptive statistics (frequencies and percentages) were used to summarize categorical variables. Continuous variables were expressed as mean ± SD or median and range where appropriate.

Ethical considerations

The study was approved by the Research and Ethics Committee of Assafa college (Approval ID: DSR-ACEC NO 19-6-3). Written informed consent was obtained from all participants or their legal guardians in the case of minors. All procedures adhered to the principles of the Declaration of Helsinki, ensuring confidentiality and voluntary participation

Results

Of the 60 patients, 38 (63.3%) presented after pubertal age (14 years for boys and 12 years for girls), while 22 (36.7%) were accessible before puberty (Table 1).

Table 1: Demographic, clinical, cytogenetic, and molecular profile of 60 DSD patients from Sudan

Category	Sub-category	Number	Percentage (%)
Sex of Rearing	Female	39	65.0
	Male	21	35.0
Age at Presentation	Before puberty	22	36.7
	After puberty	38	63.3
Primary Reason for Referral	Ambiguous genitalia	36	60.0
	Primary amenorrhea	18	30.0
	Other	6	10.0
Ethnic Background	Afro-Asiatic	42	70.0
	Nilo-Saharan	17	28.3
	Niger-Congo	1	1.7
Consanguinity	Yes	51	85.0
	No	9	15.0
Karyotype	46,XY	37	61.7
	46,XX	19	31.7
	Abnormal Karyotype	4	6.7
SRY Gene status (PCR)	Positive	36	60.0
	Negative	24	40.0
Genotype–Sex of Rearing	Matched	37	61.7
Concordance	Discordant	23	38.3
46,XY Patients Raised as Females	Total	20	33.3
	Underwent FGM	15	75.0
	Did not undergo FGM	5	25.0
Phenotype–Genotype Concordance	Concordant	11	18.4
(Adults, n=42)	Discordant	31	81.6

The ages of the presentation ranged from one month to 45 years. According to their assigned sex, 39 (65%) of the patients grew up as females, and 21 (35%) grew up as males.Regarding the tribal origin of the patients, the results revealed that 42 (70%) were of Afro-Asiatic descent, 17 (28.3%) were Nilo-Saharan, and 1 (1.7%) was of Niger-Congo origin.

Almost 51(85%) of the patients had a consanguineous marriage history, while the remaining 9 (15%) did not. The analysis of clinical presentation was heterogeneous, with 36 (60%) of the patients presenting due to ambiguous genitalia, 18(30%) due to primary amenorrhea, and the remaining 6(10%) were due to other various complaints such as impotence, infertility, and undescended testicles (Table 1).Karyotype analysis identified a 46,XY result in 37 (61.7%) of patients, 46,XX in 19 (31.7%), and sex chromosome mosaicism or aneuploidy in 4 (6.7%). The abnormal karyotypes included 46,XX/46,XY and 45,XO/46,XX in two patients each (3.3%) (Table 1, Figure 1).There was a notable discordance between sex of rearing and karyotype results. Among the 39 patients raised as females, 20 (33.3%) had a 46,XY karyotype. Of these, 15(75%) had undergone FGM. In contrast, among the 21 patients raised as males, 4(6.7%) had non-46,XY karyotypes: 2 with 46,XX and 2 with 46,XX/46,XY.

Phenotypic-genotypic concordance was observed in only 11 (18.4%) of the 42 adult patients, indicating a widespread mismatch between the clinical presentation and the underlying genetic sex. Physical examination revealed absent secondary sexual characteristics in 23(42.6%) of adult patients.

The results of the PCR of the SRY gene

PCR-based detection of the SRY gene demonstrated its presence in 36 (60%) of all patients (Table 1). Among these, 31(51.7%) had a 46,XY karyotype, 3 (5.0%) were 46,XX, and 2 (3.3%) were mosaic (46,XX/46,XY). The SRY gene was absent in 24 (40%) of patients, 16 (26.6%) had 46, XX, 6 (10.0%) had 46, XY, and 2 (3.3%) had an abnormal karyotype (45,XO/46,XX) (Figure 2).

Based on integrated clinical, cytogenetic, and molecular findings, the final diagnoses were categorized into 46,XY DSD in 37 (61.7%) patients, 46,XX DSD in 20 (33.3%), and Ovotesticular DSD in only one (1.7%) patient.

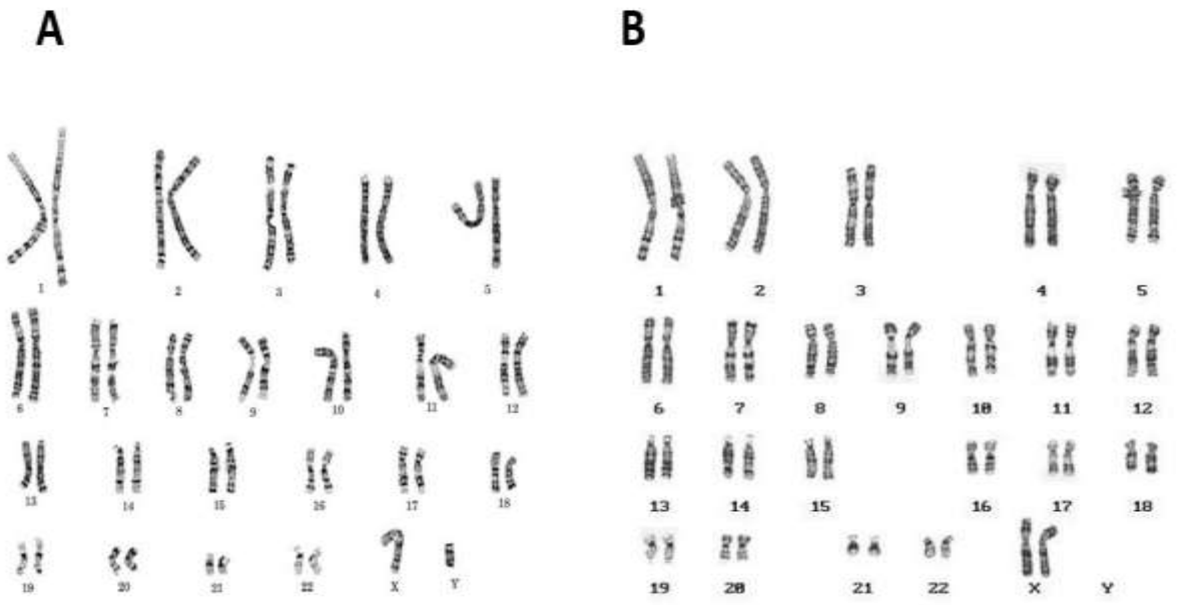

Figure 1: chromosomal analysis showing A: Normal male karyotype (46,XY), B: Normal female karyotype (46,XX)

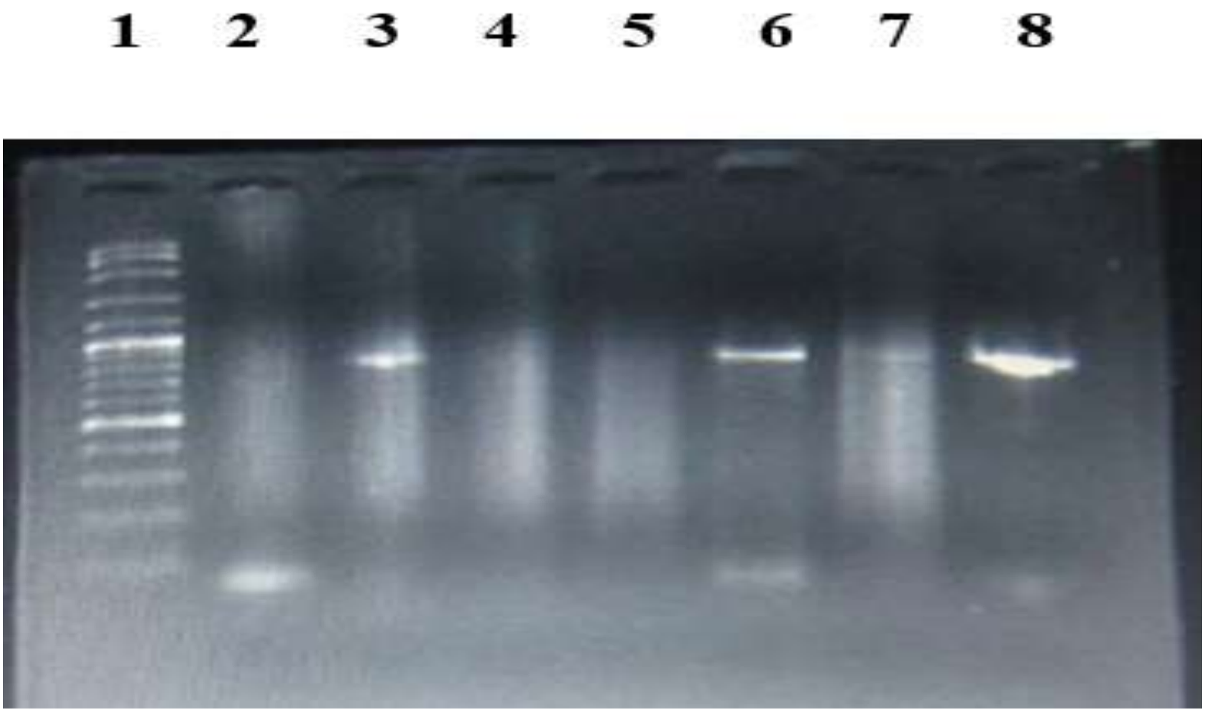

Figure 2: shows PCR amplification of the SRY gene from left to right: (1)100bp ladder, (2) -ve control (Fertile female), (3) +ve control (Fertile male), and (lanes 4-8) patients

SRY gene sequence results

Based on the clinical presentation and previous investigation results, SRY gene sequencing was performed on PCR products from 16 patients. Of these, 7 revealed pathogenic variants, while 9 showed no detectable mutations. Five novel missense mutations were identified, all of which were previously unreported in public databases (dbSNP, ClinVar, HGMD) (Table 2, Figure 3).

Discussion

Disorders of Sex Development (DSD) constitute a complex and heterogeneous group of congenital conditions characterized by discordance among chromosomal, gonadal, and anatomical sex. This study provides a comprehensive overview of DSD cases among Sudanese patients, underscoring the high incidence of late presentation, genotype–phenotype discordance, and misgendering, particularly in individuals with a 46,XY DSD who are frequently raised as females and fall victims to female genital Mutilation (FGM) during their first years of life.[13]

The most striking finding was the late age of patients' presentation, with almost half of our patients presenting between 20 and 45 years old. This finding contrasts sharply with the developed countries, where over 95% of DSD cases are diagnosed neonatally.[14] In Sudan, the absence of a structured DSD referral system and the cultural sensitivity surrounding genital ambiguity often result in delayed evaluation, misdiagnosis, and inappropriate gender assignment. These findings highlight the primary, interrelated factors that contribute to the notable incidence of late presentations. These factors include the challenges within the healthcare system, socioeconomic influences, and the cultural dynamics of the Sudanese society.[15]

Female Genital Mutilation (FGM) involves the surgical removal of female external genitalia for non-medical reasons and remains prevalent in Sudan, despite being illegal since 1940.[16] It affects 86% of Sudanese females aged 5 to 15 and poses significant social ritual challenges, especially for children with undiagnosed DSD.[17] This inhumane practice complicates the assessment of genitalia, leading to delays or misdiagnoses, often surfacing during puberty. Our study found that 75% of patients with a 46,XY karyotype raised as females had undergone FGM, with 33% showing genotype-sex discordance, resulting in identity confusion and stigma. Previous studies highlighted that DSD cases diagnosed at puberty often had FGM.[18] Societal change cannot be solely enforced by legislation; effective eradication of FGM requires focused interventions by health professionals and community leaders. A recent study in Sudan supports this notion by reporting up to a 50% reduction in FGM in areas where intensive anti-FGM campaigns took place.[19]The genotype–phenotype discordance observed in this study is alarming; 38.3% of patients had a mismatch between their sex of rearing and karyotype, with 33.3% of all patients being 46,XY individuals raised as females. This highlights a critical gap in clinical evaluation and the dire consequences of relying solely on phenotypic appearance for gender assignment in the absence of genetic confirmation. Moreover, most of the rural areas' deliveries are attended by unsafe birth assistants like Traditional Birth Attendants (TBAs), or untrained family members (old relatives), both of whom are unable to recognize the ambiguity of the DSD genitalia.[20]

The molecular analyses in this study revealed that the SRY gene was absent in 10% of 46,XY patients, confirming SRY deletions as a cause of 46,XY complete gonadal dysgenesis (Swyer syndrome). Conversely, SRY was present in 5% of 46,XX patients, indicating translocation and 46,XX testicular DSD.[21] Of the 36 patients with 46,XY DSD, 19 were selected for SRY gene sequencing. This selection was based on strict inclusion criteria, mainly focusing on patients with a 46,XY karyotype, absence of secondary sexual characteristics, and no evidence of androgen insensitivity or adrenal disorders. This targeted approach ensured that sequencing efforts were focused on cases most likely to harbor SRY-related defects, maximizing diagnostic yield and scientific relevance. It also reflects the pragmatic challenges of resource-limited settings, where prioritization is essential in the face of limited access to advanced technologies. Among the 16 sequenced cases, seven (43.8%) harbored novel missense mutations in the SRY gene, five of which have not been previously reported in global databases (dbSNP, ClinVar, HGMD).

Table 2: Five novel SRY gene mutations identified in 5 DSD patients

Mutation	Nucleotide Change (cDNA)	Amino Acid Change (Protein)	Codon position	Location	Mutation Type	conservation	Zygosity
1	c.211 A>G	p.Ser71Ala	71	HMG box	Missense	Non-conservative	Heterozygous
2	c.394G>A	p.Ala132Val	132	HMG box	Missense	Conservative	Heterozygous
3	c.19G>C	p.Ser7Trp	7	HMG box	Missense	Non-conservative	Heterozygous
4	c.539_540 insA	p.Ser180Argfs	180	Outside HMG box	Frameshift	Non-conservative	Heterozygous
5	c.93A>C	p.Asn31Thr	31	Outside ORF	Missense	Conservative	Heterozygous

Notably, three patients harbored more than one mutation. One patient had two mutations (c.211A>G and c.539_540insA). One had three mutations (c.394G>A, c.19G>C, and c.539_540insA). Two mutations (c.394G>A and c.539_540insA) were recurrent across multiple unrelated patients. Familial clustering was observed in two families: Two sisters with 46,XY DSD, and three cousins with 46,XY DSD, one of whom carried the c.211A>G and c.539_540insA mutations

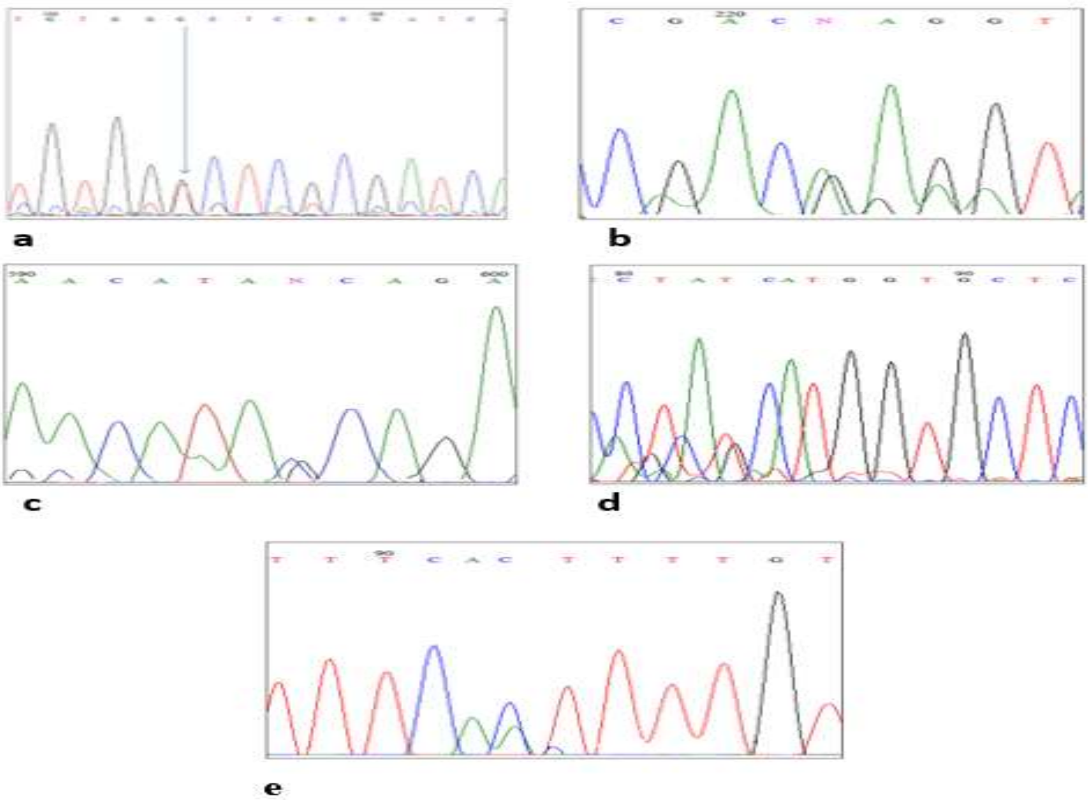

Figure 3: Chromatograms of 5 novel SRY gene mutations identified in Sudanese DSD patients
(a) c.211A>G (p.Ser71Ala): Missense mutation within the HMG box domain.
(b) c.394G>A (p.Ala132Val): Missense mutation within the HMG box domain.
(c) c.19G>C (p.Ser7Trp): Missense mutation near the N-terminal region of the HMG box domain.
(d) c.539_540insA (p.Ser180Argfs): Frameshift mutation outside the HMG box domain.
(e) c.93A>C (p.Asn31Thr): Missense mutation outside the open reading frame (ORF).

Three of these mutations were located within the HMG box (p.Ser71Ala, p.Ala132Val, p.Ser7Trp), a highly conserved domain critical for DNA binding and testis determination. The identification of non-conservative and frameshift mutations in functionally significant regions supports their pathogenic role in disrupting male gonadal development.

The high frequency of novel mutations suggests a unique genetic landscape in the Sudanese population, possibly shaped by founder effects, consanguinity, and ethnic diversity. This underscores the importance of population-specific genetic studies, as global mutation databases may not fully represent the variants present in underrepresented populations, such as Sudan. Despite the detection of SRY mutations in 7 patients, 9 out of 16 (56.2%) had no identifiable SRY defect, reinforcing the well-established fact that SRY mutations account for only 15–20% of 46,XY DSD cases.[22, 23] This high rate of undiagnosed cases is not due to methodological limitations. Still, it reflects the genetic heterogeneity of DSD, where defects in autosomal genes (e.g., NR5A1, DHH, MAP3K1, WT1) or X-linked regulators play a significant role.[24, 25] Studies from North Africa, including Sudan and Egypt, have shown that high consanguinity increases the likelihood of recessive mutations in the NR5A1 and SOX9 genes.[25] Studies from Sri Lanka also show novel variants in these genes that may act as disease modifiers. The studies showed that Mutations in NR5A1 can cause both 46,XY DSD, such as gonadal dysgenesis, micropenis, and cryptorchidism, and 46,XX DSD, including premature ovarian failure and amenorrhea.[26] The absence of SRY mutations in a majority of cases justifies the need for broader genetic screening, including whole-exome sequencing, to uncover non-SRY causes of DSD in future studies.

The high percentage of consanguineous marriages in our patients' families (85%), along with the familial clustering observed in two pedigrees, two sisters, and three cousins with 46,XY DSD, further supports the role of inherited genetic factors, possibly autosomal recessive or X-linked, since SRY mutations are usually de novo. Consanguineous marriage significantly contributes to the increased prevalence of certain DSDs, such as 5-alpha reductase two deficiency, which is inherited in an autosomal recessive manner in specific populations.[27] This highlights the importance of family-based genetic studies and cascade screening in high-risk families.

The spectrum of the DSD in this study underscores the crucial need for a multidisciplinary approach to DSD management, which integrates clinical evaluation, cytogenetics, molecular genetics, endocrinology, psychology, and ethics, as outlined by SIWG over the past 20 years.[10] In low-resource settings, such as Sudan, where expert health personnel are scarce and advanced technologies are often costly and unavailable, a non-profitable network can significantly enhance early and accurate diagnosis, provide evidence-based counseling for gender assignment, and facilitate long-term follow-up.

The social and religious context in Sudan adds profound complexity to DSD care. In Islamic societies, gender identity is deeply tied to legal, familial, and spiritual roles. Misgendering can lead to social exclusion, marital breakdown, and even suicide.[28] Therefore, early and accurate diagnosis is not only a medical imperative but a cultural and ethical necessity

Study strengths and limitations

This study provides one of the most detailed clinical and molecular characterizations of DSD in Sudan to date, integrating phenotypic, cytogenetic, and SRY sequencing data from a nationally referred cohort. Its major strength lies in documenting five novel SRY mutations, including three within the functionally critical HMG box, and linking genetic findings with sociocultural factors such as consanguinity and FGM, which contribute to delayed diagnosis. These insights address a significant gap in DSD literature from underrepresented African populations.

The study is limited by its single-center design and modest sample size (n = 60), reflecting the realities of specialized genetic services in resource-constrained settings. The absence of whole-gene or exome sequencing restricted detection to SRY-related variants, while many cases likely involve mutations in other DSD-associated genes. Nevertheless, the findings underscore the need for national guidelines that promote early diagnosis, multidisciplinary care, ethical gender assignment, and community-based efforts to prevent harmful practices like FGM, key priorities advocated by SIWG.

Conclusion

The clinical spectrum of DSD in Sudan presents a distinctive profile when compared to that of developed countries. Late presentations are characteristic of this profile, as the majority of patients seek medical attention after puberty. It is often linked to consanguineous marriages, instances of misgendering at birth, and occurrences of mutilated external genitalia. Furthermore, the molecular characteristics are diverse, primarily reflecting autosomal inherited mutations, as well as a notable frequency of novel mutations in the SRY gene.

Competing interest

None

Funding

None

Data availability

All data are available upon request.

Acknowledgement

The authors would like to acknowledge the staff of the Elite Clinic for their technical support.

Contribution of authors

Manal M.E.A Elkareem and Imad Fadl-Elmula conceived the project. At the same time, clinical and genetic data were collected by Manal M.E.A Elkareem, Samia M. Ahmed, and Rayan Khalid Analysis and interpretation of the data were performed by Manal M.E.A Elkareem, Rayan Khalid, and Samia Mahdi. Manal M.E.A Elkareem and Samia M. Ahmed wrote the initial manuscript draft, with input and revisions from Rayan Khalid and Imad Fadl-Elmula. All authors have approved the final draft of the manuscript.

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