

# Molecular Diagnosis of Sexual Differentiation Disorders in Burkina Faso

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## Abstract

Sex development anomalies represent a group of congenital pathologies in which chromosomal, gonadal and anatomical sex differentiation is atypical. The aim of our study was to use molecular biology techniques to elucidate sex in cases of anomalies of sexual differentiation in Burkina Faso. This cross-sectional study took place from March 2023 to June 2023. Oral and blood samples were collected respectively using sterile swabs and stored on Swab Kits and NUCLEIcard™

(<https://www.copangroup.com/product-ranges/nucleic-card/>) were used to determine gonosome profiles. Extraction was carried out using the DNA Swap solution Kit and the DNA IQ System Kit, and a PowerPlex® 21 kit (Promega) for amplification. The Applied Biosystems 9700 thermal cycler was used for PCR followed by 36 cm capillary electrophoresis in the Applied Biosystems 3130 prism sequencer. Sequence files were analyzed using GeneMapper IDX v. 3.2 software. Seven (07) patients were registered during the study period. There were 4 cases of XX DSD or 46, XX DSD and 3 cases of XY DSD or 46, XY DSD. The median age of our patients was 16 years. Civilian sex was male in 4 cases and female in 3. The most frequent reason for consultation was micropenis in 3 cases, followed by primary amenorrhea and sex ambiguity. There

were 03 cases of discrepancy between genetic sex and civil sex. The accessibility of molecular diagnosis is little known to clinicians. XX DSDs or 46, XX DSDs were the most frequent (4/7) in our study. The problem facing this situation is early diagnosis to help prevent complications in Burkina Faso.

## Keywords

Gonosome, DSD, Abnormal Sexual Development, Burkina Faso

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## 1. Introduction

Sexuality is the set of functions of sexual differentiation and reproduction [1]. Sexual differentiation can be defined as a process that ensures the development of the appropriate genital tract and external genitalia in response to hormonal signals constituting phenotypic sex [2]. Although sexual differentiation is operational in the vast majority of cases, some individuals are confronted with anomalies of sexual development (ADS) or disorders of sexual development (DSD). These anomalies encompass all congenital pathologies in which chromosomal, gonadal and anatomical sex differentiation is atypical and non-harmonious [3] [4]. Various pathologies such as chromosomal abnormalities can contribute significantly to morbidity, disordered sexual development and human mortality. We have cases of Turner syndrome (45, X0), Klinefelter syndrome or Noonan syndrome (47, XXY) [5], Mixed gonadal dysgenesis (45, X0/46, XY) [3] which are responsible for functional disorders in humans. Statistics on cases of sexual differentiation disorders are still patchy and variable around the world. According to experts, between 0.05 and 1.7% of the world's population is born with intersex characteristics [6]. In India, the figure is between 2.5% and 12% [7]. In the USA, it is estimated at 1 per 2000 births [8]. In West Africa, a prevalence of 5.4% of sexual ambiguity was reported in Mali from a study of 12 cases [9]. The management of these cases, complex as they are, requires several multidisciplinary approaches, including genetic determination, which should enable an early diagnosis to be made so that the subject concerned can live better with this problem in his or her family and social environment in general. The aim of this study is to propose a molecular biology approach to genetic sex determination in Burkina Faso.

## 2. Materials and Methods

### 2.1. Population and Type of Study

The present study was cross-sectional with accidental sampling. It took place at Hôpital Saint Camille de Ouagadougou (HOSCO) and Centre de Recherche Biomoléculaire Pietro Annigoni (CERBA) between March and June 2023. The study population consisted of adults and/or minors in whom gender ambiguity or abnormal sexual differentiation had been observed and confirmed by a physician.

All participants and/or legal guardians had given their free and informed consent.

## 2.2. Biological Sample

Sampling involved the population of Ouagadougou (Burkina Faso). A sample size has not been clearly defined. This is accidental sampling. This is due to the rarity of the cases. Samples consisted of buccal (02) and blood (05) swabs taken from adults and/or minors with sex ambiguity or sex differentiation disorder (SDD) clinically confirmed by a specialist. After obtaining informed consent from patients and/or their parents in the presence of a witness, samples were taken at the Hôpital Saint Camille de Ouagadougou (HOSCO) and at the Centre de Recherche Biomoléculaire Pietro Annigoni (CERBA) respecting good laboratory practices for extracting and purifying DNA for biological analysis. Oral samples were taken using sterile swabs, and blood samples using FTA NUCLEIcard™ copan Flock Technologies SARL

(<https://www.copangroup.com/product-ranges/nucleic-card/>). All samples were stored at  $-20^{\circ}\text{C}$  pending molecular biology analysis.

## 2.3. DNA Extraction

DNA extraction from sterile swabs was performed using the DNA Swap solution extraction Kit DC8271. The choice of this kit is due to its specificity on STRs, and particularly the extraction of DNA from buccal swabs. The cottony ends of the stem were cut off in a 1.5 mL Eppendorf tube before the addition of 1 mL of Swap solution for DNA extraction at  $70^{\circ}\text{C}$  according to the manufacturer's protocol. Extracted DNA is stored at  $-80^{\circ}\text{C}$  for further analysis.

DNA extraction from blood samples on FTA paper was performed using the DNA IQ System Kit (ref: DC6701). The choice of this kit is due to its specificity for the extraction of DNA from blood, particularly with STRs. Two or three FTA paper pellets cut with the "Harry punch" instrument were inserted into a 1.5 mL Eppendorf tube before the addition of 75  $\mu\text{L}$  of lysis buffer. The assembly was vortexed for 5 seconds and centrifuged briefly to return the FTA paper pellets to the bottom of the tube. Eppendorf tubes containing the mixture were then incubated at  $56^{\circ}\text{C}$  on a hot plate for 2 hours to potentiate proteinase K digestion. Following digestion, 150  $\mu\text{L}$  of lysis solution was added to each tube, along with 7  $\mu\text{L}$  of DNA IQ resin for DNA binding. The whole set was vortexed and placed on magnetic separation support for 10 minutes. A further 100  $\mu\text{L}$  of lysis solution was added after carefully removing the previous solution without disturbing the resin pellet. The next steps consisted of a series of three consecutive rinses followed by a drying step before the addition of 75  $\mu\text{L}$  of elution solution to elute the DNA. The eluted DNA was carefully transferred to another labelled tube and stored at  $-80^{\circ}\text{C}$  for further analysis.

## 2.4. DNA Amplification

DNA amplification was carried out in a total reaction volume of 12.5  $\mu\text{L}$  using

the PowerPlex® 21 kit (Ref DC8902). PowerPlex® 21 kit (Ref DC8902), is a reference kit for the amplification of STRs. Indeed, the reliability of this kit has been proven in several studies. The amplification mix consisted of 2.5 µl of master mix, 2.5 µl of primers and 5.5 µl of molecular biology grade water. A volume of 2 µl of extracted DNA was added to 10.5 µL of PCR mix for amplification. For the positive control DNA (2800 M) 3 µL is added to the PCR mix. Amplification was performed using the Applied Biosystems 9700 PCR System thermal cycler. The amplification program included an initial denaturation step at 96°C for 1 minute; followed by 24 cycles of (denaturation at 94°C for 10 seconds, primer hybridization at 59°C for 1 minute and extension at 72°C for 30 seconds) and a final extension step at 60°C for 20 minutes. All amplified samples were stored at -20°C protected from light until capillary electrophoresis.

### 2.5. Capillary DNA Electrophoresis

Capillary electrophoresis was performed using the 3130 AB prism DNA analyzer. The capillary length used was 36 cm with type 4 polymer (POP4). The reaction medium consisted of 9.5 µL Hi Di formamide and 0.5 µL of internal lane standard (WEN ILS 500). A 96-well plate was used for electrophoresis migration in the DNA analyzer. Per well, a volume of 1 µL of PCR product or allelic marker was added to 10 µL of reaction medium. The 3130 ABI DNA analyzer had 4 capillaries, so only 3 samples per run could be analyzed simultaneously with the allelic marker in the fourth well. A DNA denaturation step was performed just before the start of capillary electrophoresis. This involved heating the plate to 96°C for 3 minutes on the 9700 applied biosystem, before inducing thermal shock by immediately placing the plate on ice. Electrophoresis conditions were 5 seconds for injection time and 15 kVolts for voltage. The chosen injection time is suitable for the contact time with the sequence products in order to prevent saturation of the camera during reading of the electropherogram profile. Electrophoresis data were collected using Data Collection v3.0 software in fsa format. DNA amplification and capillary electrophoresis were carried out at CERBA (Pietro Annigoni Biomolecular Research Center).

### 2.6. Data Analysis and Interpretation

Sequence files (.fsa) collected with the Data Collection software were analyzed using GeneMapper IDX v. 3.2. This software assembles the sequences obtained and compares them on an allelic scale to generate profiles of the alleles present by loci in each sample analyzed. Each individual's genetic profile includes one allele from the father and one from the mother at each locus analyzed. Inclusion of amelogenin in the PowerPlex® 21 kit (Promega) thus enables gonosome profiling and identification of the genetic sex of the individual in question.

## 3. Results

The socio-demographic characteristics of the subjects are mainly age, sex, school-

ing, marital status and place of origin. The gender status corresponds to that declared at birth or in the civil register (**Table 1**).

Analysis of **Table 1** provides us with socio-demographic information and the gender declared at birth or at civil status. According to this table, we obtained 3 single cases, 3 cases whose marital status was not applicable (NA) to minors of this age, and one divorced case. According to the origin of the cases, 4 came from the provinces and 3 from the capital. With regard to sex declared at birth or at civil status, 4 were male and 3 were female. By level of education, 4 were in school and 3 were out of school.

**Table 2** briefly describes the ADS cases with the reasons for consultation and the elements of sexuation. According to the reason for consultation, we observed 3 cases of micropenis, 1 case of gender ambiguity, 2 cases of primary amenorrhea and 2 cases of gynecomastia. For elements of sexuation, we noted 3 cases of micropenis, 1 case of clitoral hypertrophy, 1 case of clitoral hypertrophy or micropenis and 1 unspecified case (**Table 2**).

The genetic profile is obtained with the powerplex21 kit, which includes 21 markers. In our study, amelogenin was our marker of interest. For amelogenin, in the case of male sex, allele 1 is “X” and allele 2 is “Y”. In the case of the female sex, the “X” allele being double, it will optionally be represented once (**Figure 1**).

**Figures 2(a)-(g)** show the gonosome electrophoregrams of the various ADS cases. A male individual shows two distinct peaks, the X chromosome peak and the Y chromosome peak. A female case shows a single peak, that of the X chromosome only.

The comparative analysis of the synthesis of civil and genetically determined sex and the age of the subjects is shown in **Table 3**. We observed a discrepancy between the civil sex and the genetic sex. The civil sex of our cases was male in 4 cases and female in the other 3. Genetically, we observed 3 male cases and 4 female cases (**Table 3**).

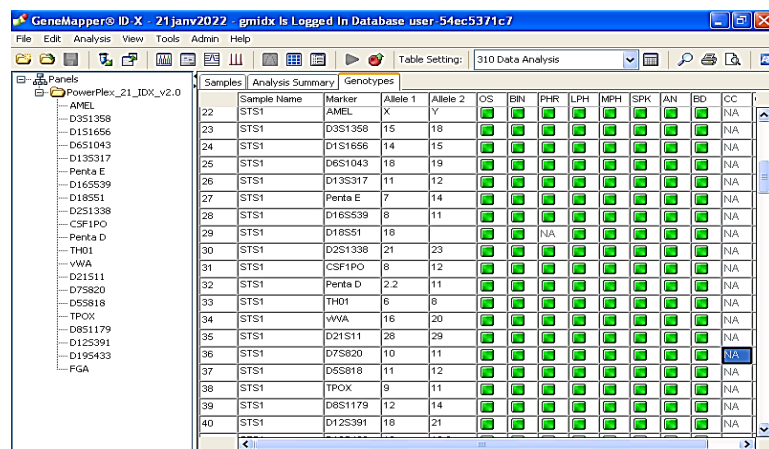
**Table 1.** Socio-demographic data (M: male, F: female).

Code	Age*	Gender	Educated*	Marital Status*	Origin
GS01	1 day	F	NA	NA	Ouagadougou
GS07	16 months	M	No	NA	Ouagadougou
GS06	7 years	M	Yes	NA	Ouagadougou
GS04	16 years	F	Yes	Single	Province
GS03	20 years	M	No	Single	Province
GS05	20 years	F	Yes	Single	Province
GS02	30 years	M	Yes	Divorced	Province

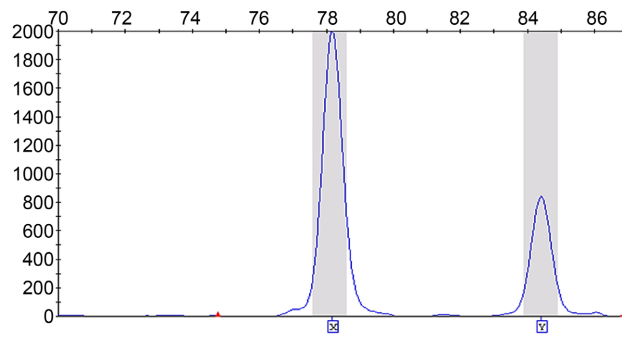
(\*) Schooling and marital status are not applicable (NA) to minors of this age.

**Table 2.** Clinical profile of observed cases of sexual differentiation disorders.

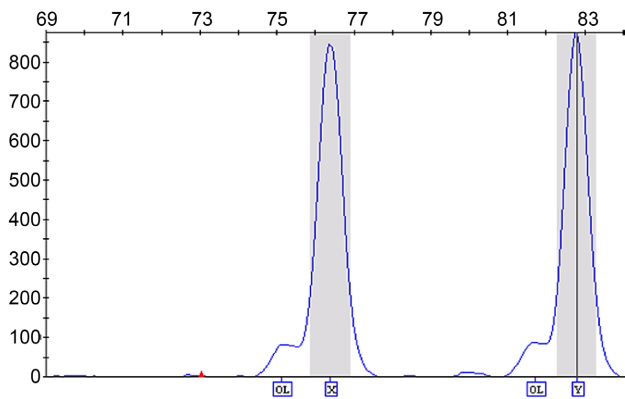
Case	Sex declared at birth or civil status	Reason for consultation	Elements of sexuation
GS01	female	Sexual ambiguity	Not specified
GS02	male	Presence of micropenis with absence of erection – breast development – absence of beard and moustache	Adolescence: – presence of a micropenis about 4 cm long and a scrotum containing microtesticles about 10 mm in diameter – No vaginal orifice  At puberty: – development of clitoral hypertrophy or micropenis with urinary meatus – absence of vaginal orifice – fusion of labia majora
GS03	male	Gynecomastia	– presence of micropenis or a clitoral hypertrophy of about 2 cm with a urinary meatus below – presence of a vaginal orifice below the urinary meatus – fusion of labia majora
GS04	female	Primary amenorrhea	– presence of an enlarged and excised clitoris. – Presence of labia majora and minora, as well as a urinary meatus and vaginal orifice
GS05	female	primary amenorrhea; absence of menses accompanied by absence of breast development in adolescence	Presence of a micropenis or an enlarged clitoris whose size does not allow it to urinate as men do (while standing) – presence of a micropenis about 2 cm long, with a urinary meatus underneath (an opening in the penis on the underside of the organ) – presence of skin folds—no visible glans. – No glans visible
GS06	male	Presence of micropenis	
GS07	male	the presence of a micropenis with a thickening of the penis	



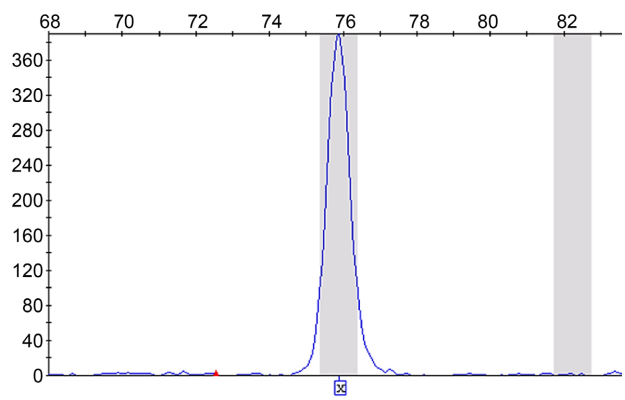
**Figure 1.** Genetic analysis profile with quality criteria.



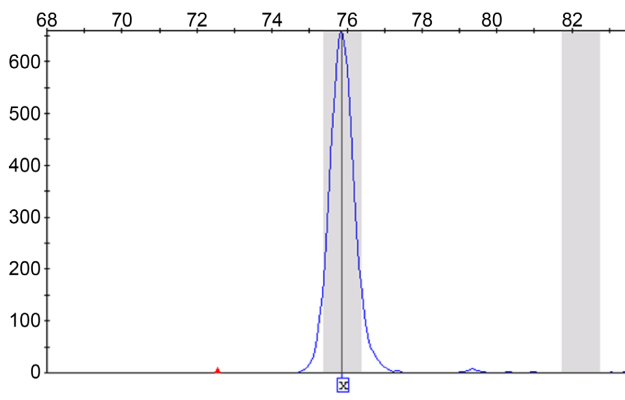
(a)



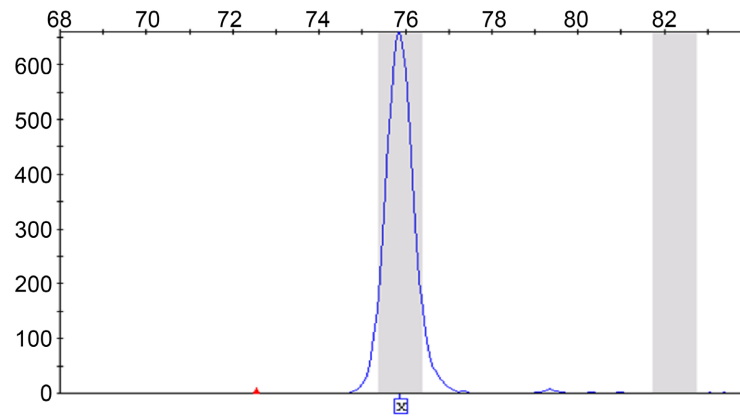
(b)



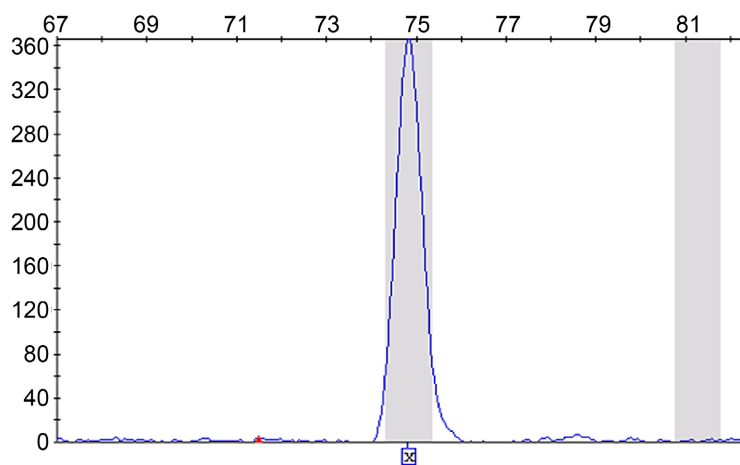
(c)



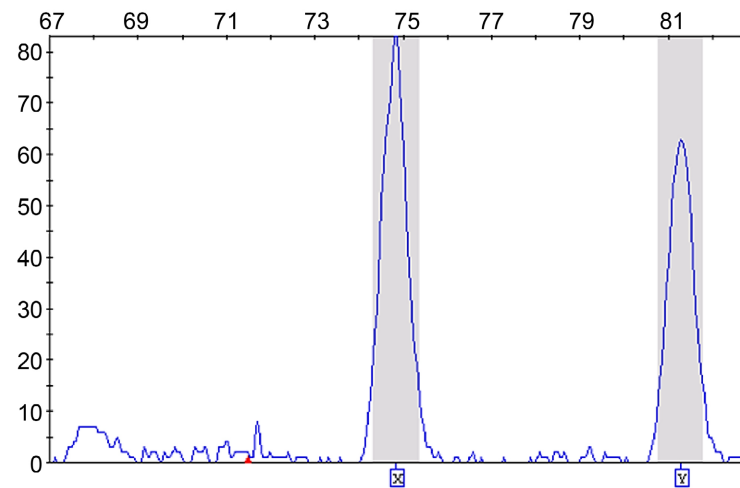
(d)



(e)



(f)



(g)

**Figure 2.** (a): GS01 electropherogram of chromosomes XY profiles; (b): GS02 electropherogram of chromosomes XY profiles; (c): GS03 electropherogram of chromosomes XX profiles; (d): GS04 electropherogram of chromosomes XX profiles; (e): GS05 electropherogram of chromosomes XX profiles; (f): GS06 electropherogram of chromosomes XX profiles; (g): GS07 electropherogram of chromosomes XY profiles.



**Table 3.** Summary of comparison between declared civil sex and genetic sex (M: male, F: female).

Code	Age	Civil gender	Genetic gender		Discordance
			Genotype	phenotype	
GS01	1 day	F	XY	M	Yes
GS07	16 months	M	XY	M	No
GS06	7 years	M	XX	F	Yes
GS04	16 years	F	XX	F	No
GS03	20 years	M	XX	F	Yes
GS05	20 years	F	XX	F	No
GS02	30 years	M	XY	M	No

#### 4. Discussion

Our study enrolled seven (07) participants with a clinically confirmed anomaly of sexual differentiation. The median age of our patients was 16 years, corresponding to adolescence, with extremes of 1 day and 30 years. This observation had been made by other authors who also found a comparable mean of  $14.3 \pm 8.9$  years [9]. This could mean that the average age at which ADS was diagnosed was around adolescence, whereas such diagnoses should be made at birth [10]. According to this author, the diagnosis of DSD was made late in life, making early management difficult. The proportion of cases of pure gonadal dysgenesis could explain this situation, as this diagnosis is generally only evoked in the face of pubertal disorders [10].

The majority of participants had attended school, and all had been registered as either male or female. Observation of the data showed a high frequency of ADS in large cities. Indeed, 03 out of 07 patients came from the capital (Ouagadougou) and the other 04 from other regions. This proportion could be explained by the fact that urban dwellers have greater access to health centers, which would enable them to be more sensitized than rural dwellers [9]. What's more, given that people living in big cities are supposed to be more exposed to chemical pollutants, we might think that this frequency would be due to pollution, as some authors have pointed out [9].

According to the level of schooling, 03 of our patients had secondary education, 01 had primary education, 02 were not old enough to go to school and 01 had no schooling. The relatively high frequency of students and the high school level of our patients could be explained by the fact that students are more aware and had the courage to explain their anomalies. It could also be assumed that the high school level is an advantage for these patients, motivating them to consult us. With regard to marital status, 03 of our patients were single, with 02 children, one newborn and one divorced. Moreover, the high frequency of single patients could be explained by the fact that the majority of these patients were schoolchildren. In some cases, it could be assumed that their anomaly was the

reason for their marital status, as they did not want to be discovered by others. The case of the divorced man, for example, can be explained by the fact that this patient had a micropenis and an absence of erection. The rest of our patients had not reached marriageable age.

Generally speaking, the main reasons for medical consultation among all patients were essentially linked to sexual differentiation disorders, namely the presence of a micro-penis, primary amenorrhea, breast development and absence of erection (Table 2). In some participants, there was a discrepancy between external genitalia and secondary sexual characteristics. Similar cases had been reported in Mali from 1995 to 2002, *i.e.* over a period of 7 years, in 12 patients where this discordance had been observed [9] [11]. According to the authors, this discrepancy could be due to the young age of the patients, which did not allow them to have sufficient hormonal secretion to significantly influence the development of secondary sexual characteristics [9] [11]. The majority of cases were quite rare, and it was generally noted that long periods of time were needed to observe an average of ten cases. Other cases were reported in other African countries, namely Côte d'Ivoire, where 25 patients were recorded over a period of 18 years, 7 of whom had been able to perform karyotyping [3]. In Nigeria and Zambia 39 and 19 cases of ADS respectively have been reported over a period of 09 years [12] [13]. Furthermore, according to Hue *et al.* (2019), 24 cases of ADS were reported over a 10-year period in Senegal; and 04 cases of ADS in Congo over a 05-year period [3]. In Africa, although ADS cases are exotic and quite rare, this does not reflect reality [3] [14]. Patients with DSA are said to suffer from numerous taboos and myths that fuel their experiences. Indeed, they are said to face a referral problem for their care, which makes it difficult to obtain a national register of ADS cases in African countries [14]. What's more, in some African countries, the birth of a child with a congenital malformation is considered a curse and a disgrace for the family. The mothers of these children are often considered to be primarily responsible [3]. Indirect factors characterize the social and societal problems experienced by patients with ASD. These include the consideration of gender when choosing a name for religious or traditional baptism, and how to dress and educate them [3]. To avoid these family and societal problems, some countries, such as Germany, have found as an alternative the implementation of an indeterminate gender status until the age of puberty.

Clinically, 02 of our patients presented with primary amenorrhea in adolescence and absence of breast development as a reason for consultation, and 01 had breast development. These 02 patients presented with primary amenorrhea in adolescence and an absence of breast development as the reason for consultation. The latter were declared girls at birth and registered as women. The one with breast development was declared a boy at birth and registered as male. These patients therefore present with a disorder of breast development, the girls having passed the age of puberty and the boy having reached the age of onset of secondary sexual characteristics. These disorders can be explained by disturbances

in estrogen and testosterone secretion, which are linked to gonadal abnormalities in these 03 patients. Hormones are involved in breast development in women (estrogen) and in the arrest of breast growth in men (testosterone) [15]. With regard to menstruation, all women of menstruating age had primary amenorrhea, *i.e.* 02 patients in our study. This could be explained by the fact that these patients had few or no ovaries or uterus. Indeed, according to Hanoune *et al.* (1996), Harry *et al.* (2016) these organs play a very important role in the menstruation process [15] [16]. Micropenis was the reason for consultation in 03 patients, one of whom also had an absence of erection. The presence of micropenis could be due to hormonal imbalance. Thus, the reasons for consultation of our patients were dominated by micropenis (03 cases), *i.e.* 42.9%, followed by primary amenorrhea (02 cases), *i.e.* 28.57%, then sexual ambiguity and gynecomastia, *i.e.* 14.28% of cases each. According to some authors, the most frequent reasons for consultation were sexual ambiguity, primary amenorrhea, gynecomastia or periodic urethrorrhagia [3], pubertal anomalies such as virilization of a girl, absence of mammary thrust or primary amenorrhea [17], external genital anomalies [18], cryptorchidism, inguinal hernia or hypospadias [19].

In terms of etiology, we determined the genetic sex of all our patients. This would enable us to make a proposal for the classification of our ADS. The genetic sex of our patients was determined on the basis of electrophoregram analysis of the amelogenin marker. This gave us ADS XX and ADS XY. This classification does not necessarily fit in with the new classification, which classifies ADS according to their karyotype (46, XY DSD or 46, XX DSD). Our study does not determine the number of autosomes, but does provide a profile of the gonosomes. In addition, we genetically observed 03 male patients (XY) and 04 female patients (XX). Although the patients were declared and registered at civil status as girls or boys, certain discrepancies were observed between the genetic sex of these patients and that assigned at birth. Thus, we have 03 cases of discordance between genetic sex and civil sex or breeding sex. According to these discrepancies, there was one case (GS01) of female breeding sex whose genetic sex turned out to be male (XY) and two cases (GS03 and GS06) of male breeding sex with which the genetic sex turned out to be female (XX). The breeding sex was male in (04) cases out of seven and the genetic sex was female in (04) cases out of seven. Hué *et al.* in Côte d'Ivoire reported that (05) out of seven cases were male and (03) out of seven were male genetically (according to karyotype), (02) cases as sex chromosome anomalies, which was not observed in our study. The discrepancy between these two sexes could be explained by the fact that the child's sex was determined at birth by the parents [3]. According to the African conception, in front of an ADS, the attribution of a sex was preferentially that of masculine. Indeed, according to this conception, a boy in a family is considered an extra arm or heir [3]. Concerning the classification of patients according to sex 46, XY or XY and 46, XX or XX our patients presented a developmental defect of the external genitalia. In the XY group, there was one case of hypospadias and

one case of micropenis with absence of erection. In XXs, a penoclitral organ with the presence of a fusion of labia majora and a urinary meatus in two cases, one of which had significant gynecomastia, and the presence of labia majora and labia minora, as well as a urinary meatus and a vaginal orifice in one case. Our results differ from those found by Hué *et al.* (2019) in Côte d'Ivoire according to this classification of sex 46, XY, including unilateral gonadal ectopy in one patient and bilateral in the other two. A penoclitral organ with a masculine-type bulge whose presence of labia majora without labia minora was observable. Two cases of micropenis, one case of significant gynecomastia. In addition, cases of DSD have also been reported elsewhere, Ganie *et al.* (2017) in South Africa reported that 96% of 46, XY DSD were due to abnormalities in androgen synthesis and action [20]. This parameter was not taken into account in our study. Concerning the sex declared at birth, we found two cases of XX male sex and one case of XY female sex. This type of discrepancy between the two sexes has been reported elsewhere: in their study, Hué *et al.* found two cases of male breeding sex 46, XX DSD and one case of female breeding sex 46, XY DSD. It should be noted, however, that female 46, XY DSD is not uncommon. Di *et al.* (2013) reported 7 cases of female 46, XY DSD out of 128 cases, Agustino Utari *et al.* (2013) reported 12 cases of female 46, XY DSD reared as a girl [18] [21]. Ekenze *et al.* reported 16 cases of female 46, XY DSD out of 39 cases [12]. Also Öcal *et al.* (2010) found 52.4% female 46, XY DSD, Marzuki *et al.* (2013) reported 22 cases of female 46, XY DSD raised as girl over 70 years [22] [23]. Like female 46, XY DSD, male 46, XX DSD cases have also been reported elsewhere. Ekenze *et al.* (2015) found 17 cases of male 46, XX DSD or 43.6% in a study of 39 patients, Öcal *et al.* (2010) found 34.6% male 46, XX DSD in 208 cases [12] [22].

It should be noted that sex reversals can have a genetic origin. Indeed, some 46, XY DSD individuals with a mutation or deletion of the SRY gene present a sexual inversion leading to sterility, as an anomaly in this gene blocks male differentiation. Also a deletion or mutation of the SOX9 gene could cause sex reversal [24]. A deletion of the DMRT1 gene would also lead to sex reversion in XY patients, giving them a female phenotype. The management of these complex cases requires several multidisciplinary approaches. These include sex determination methods, the main ones being anatomical, hormonal and genetic. Genetic methods, however, enable genetic sex to be established at birth and/or on request, and this can be done within a short period of time. Genetic sex is the basis; its analysis may be requested in the first instance in cases of abnormal sexual differentiation. Genetic sex can be determined once and only once during an individual's lifetime, and could prove relatively beneficial in terms of saving time. What's more, anatomical and hormonal methods give results that can evolve over time, whereas genetic methods, once determined, remain identical regardless of the period. It is therefore essential to carry out a molecular sex diagnosis when faced with a case of sexual differentiation disorder. In such cases, molecular genetics should be the first recourse, enabling the clinician to deter-

mine the child's genetic sex prior to surgery. We invite clinicians to refer to molecular genetics in these situations.

## 5. Conclusion

DSDs are a rare entity. These DSDs in our study present as XX and XY. Clinical data identified seven (07) cases of abnormal sexual development in our study. These cases were dominated by XX DSD or 46, XX DSD in 57.1% of cases and XY DSD or 46, XY DSD in 42.9% of cases. Among the latter, we note a discrepancy between civil, phenotypic and genetic sex. This was observed in two (02) male patients whose genetic sex turned out to be female, and in one (01) female patient whose genetic sex turned out to be male. This situation may call into question or reinforce the current classification of DSDs. The problem with this situation is early diagnosis to help prevent complications. Thus, training health-care personnel, raising public awareness of the need to use health centers in the event of ADS, and international collaboration can help improve diagnosis and minimize psychological morbidity. The promotion of a multidisciplinary approach is also necessary to enable the establishment of databases on ADS in Burkina Faso, and to facilitate the management of these patients. This approach will also facilitate the creation of a national or regional reference center for the management of ADS. Institutional capacity-building is also necessary, as this will raise the technical level of reference structures for neo-natal ADS diagnosis.

## Conflicts of Interest and Funding Sources

The authors declare that they have no known competing financial interests or personal relationships that might have appeared to influence the work reported in this article. The authors report no other sources of funding.

## Ethical Considerations

Participants and/or legal guardians have given their free and informed consent. The study was approved by the institutional ethics committee of Hôpital Saint Camille de Ouagadougou (HOSCO), deliberation N°2023-07-017 of July 17, 2023.

## Authors' Contributions

BBVEJT, SS, ZTM and JS developed the study protocol and initiated the manuscript plan with the collaboration of all co-authors. BBVEJT and SS coordinated the manuscript writing activities. TA handled the clinical aspects. OM, BP, KI and SA contributed to the molecular analyses. STS, DF and YA contributed to the drafting of the manuscript.

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