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Gender Identity and Phenotypic Variation of Sex Chromosome Disorders: A Study at Center for Disorder of Sex Development in Indonesia

Putri Azalia,[1] Tri Indah Winarni,[2] Achmad Zulfa Juniarto[2]*

[1]Faculty of Medicine Diponegoro University Semarang, Indonesia

[2]Division of Human Genetics Center for Biomedical Research (CEBIOR) Faculty of Medicine Diponegoro University Semarang, Indonesia

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*) Correspondence to:
achmadzulfajuniarto@lecturer.undip.ac.id

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ABSTRACT

Background: Sex chromosome DSD (Disorder of Sex Development) can be caused by numerical or structural abnormality in sex chromosome, which will lead to the atypical development in phenotype and also psychosexual. Gender assignment often become the primary problem in management of individual with DSD.

Objective: To describe gender identity and phenotype variability based on karyotype classification among sex chromosome DSD cases in Indonesia.

Methods: This study is a descriptive retrospective study. Analyzing gender identity, karyotype classification and phenotype data from medical record of patients with cytogenetic analysis results classified as sex chromosome DSD in CEBIOR over 18 years period from 2004 to 2022.

Results: Data showed the sex chromosome DSD classification with karyotype 45,X and variant (without Y chromosome), constituted 43.7% (42/96) cases, 100 % (42/42) patients have female gender identity; 19.8% (19/96) cases had karyotype 45,X/46,XY or Turner variant mosaicism with Y chromosome, majority of patients have male gender identity 73.7% (14/19); 18.7% (18/96) cases had 47,XXY (Klinefelter syndrome) and variant, majority of patients have male gender identity in 88.9 % (16/18) cases; 11.4% (11/96) cases had 46,XX/46,XY karyotype, majority have male gender identity in 81.8 %(9/11) cases ; and 6 cases (6.25%) classified as others, 66.67% (4/6) cases all of which contain Y chromosome, have male gender identity.

Conclusion: This study shows the presence of Y chromosome in the karyotype support a male gender identity. Sex chromosome DSD constitute high karyotype diversity and wide phenotypic abnormalities that necessitates careful clinical and cytogenetic evaluation.

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1. Introduction

Disorder of Sex Development (DSD) is a recent nomenclature that have been used since a consensus was made by the Lawson Wilkins Pediatric Endocrine Society and European Society of Pediatric Endocrinology to replace intersex / ambiguous genitalia in the year of 2006. DSD is defined as a congenital condition in which the development of chromosomal, gonadal or anatomic sex is atypical. DSD generally classified as 46 XY, DSD; 46 XX, DSD; and sex chromosome DSD.[1] Sex Chromosome DSD were then also classified as 45,X (Turner Syndrome and variant), 45X/46XY Mixed Gonadal Disgenesis (MGD), 47 XXY (Klinefelter syndrome and variant), and 46 XY/46 XX (chimeric or ovotesticular DSD). [2] Sex chromosome DSD can be caused by numerical or structural abnormality in sex chromosome, which will lead to the atypical development in phenotype and also psychosexual. [3,4] Sex Chromosome Aneuploidi /SCA has an estimate cases of 1 in 500 births, but can be more common in the conception period.[5] Incidence and prevalence of SCA in the general population cannot still be determind until recently.[6] In a recent publication in Indonesia the prevalence of sex chromosome DSD is in third place after 46,XY DSD which is the most prevalent and 46,XX DSD. [7]

DSD can be known since birth from the ambiguity of external genitalia, but many also diagnosed in puberty or adult with the complaint of delayed or absence of puberty or infertility.[8] Sex of rearing depends on the genetic sex, degree of virilization of external genitalia, prospects of restoring normal appearance of external genitalia and fertility and parent's/patient's preferences. [9] On every case of DSD to reach the best prognosis, phenotype is one of determining factor , which include internal and external genitalia, hormonal characteristic and also reproduction function.[10] Gender assignment is often become the primary problem in management of individual with DSD, the difficulty arise related with upbringing pattern, parents and patient education, and also medical operation that need to

be done. [11] DSD management in Indonesia still have a lot of downfall, for instance the influence of culture and religion, involvement of genetic counsellor still not much acknowledged in the health care services, and also less support from the national health insurance in the treatment and diagnosis of DSD cases.[7] It is hoped that this study can be used to increase the knowledge and also awareness of health related worker and Indonesia society as a whole about the gender identity and also phenotype variance of sex chromosome DSD, which is one of the important step in the management of DSD.All manuscripts must be in English. These guidelines include complete descriptions of the fonts, spacing, and related information for producing your proceedings manuscripts.

2. Methods

This study included 96 patients with sex chromosome DSD referred to the Center for Biomedical Research (CEBIOR), Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia, presenting over a period of 18 years (2004–2022). The patients comprised different age groups from 1 year old to 39 years old at first visit. Medical record are searched and tabulated for results of patients phenotype from clinical examination including assessment of external masculinization score (comprise of labioscrotal fusion, phallus length, gonad location, and location of urethral meatus). Cytogenetic studies were performed in the same center which followed the International System for Human Cytogenetic Nomenclature recommendations (ISCN, 2016), patients data were analyzed for the presence and percentage of Y chromosome. Gender on admission and final gender identity after genetic counselling by the multidisciplinary team of doctors and psychologist were tabulated and reported.

3. Result

Sex Chromosome DSD Karyotype Classifications

In this study 96 patients were diagnosed with sex chromosome DSD by their cytogenetic examination result. Pure numerical abnormalities were detected in 69.8 % (67/96), structural abnormalities were detected in 10,4 % (10/96), combined numerical and structural abnormalities were detected in 9.4 % (9/96), and pure chimeric abnormalities of 46,XX/46,XY were detected in 10.4 % (10/96) of sex chromosome DSD patients. Patients were divided into 5 (five) karyotype-based classifications: 45,X and variant without Y chromosome; 45,X/46,XY or Turner variant mosaicism with Y chromosome ; 47,XXY and variant; 46,XX/46,XY; and others (which include supermale or other structural abnormality of sex chromosome). Case frequency of each classification of sex chromosome DSD are provided in figure 1.

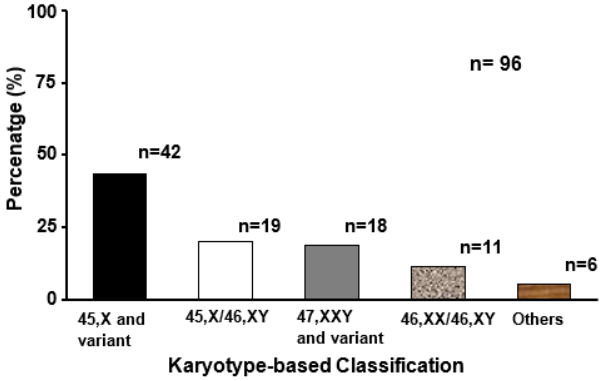

Figure 1. Classification based on karyotype of Sex Chromosome DSD cases in 2004-2022.

Among 42 cases of 45,X and variant without Y chromosome, the most cases found with percentage 61.9 % (26/42) have mosaic karyotype and 16 cases (37.2%) were of classic 45,X karyotype. In classification of 45,X/46,XY or 45,X with mosaicism with Y chromosome cases that are included were 45,X/46,XY (16/19 cases); 46,XY,r(Y)(90%)/45,X(10%) in 1 case; 47,XXY(1%)/46,XY(90%)/45,X(9%) in 1/19 case; and 45, X (7%)/ 47, XYY (91%)/ 48 XYYY (2%) in 1/19 case. Among cases of Klinefelter syndrome 11 cases (61.1%) have classic 47,XXY Karyotype, 2 cases (11.1%) has 48,XXXY Karyotype, and 5 cases (33.3%) have mosaic Karyotype with either 46,XX or 46,XY. Among cases of 46,XX/46,XY (chimeric) the number of Y chromosome presentation are varied. In 46,XX/46,XY (chimeric) cases were also included cases with karyotype 46,XX(69%) / 46,XY (22%) / 45,X (9%) in one of the cases. The karyotype that is included in others classification were found 6 cases with 6 different karyotype which are 46,XX/47,XXX(1%); XY(1)/46,XX(49); 46,XY/46, XY, + mar (3 %); 47,XYY(1%)/46,XY(90%)/45,X (9%); 47,XYY(91%)/45,X(7%)/48,XYYY(2%); and 46,XX del q23 -> q ter.

Gender identity and gender reassignment

In karyotype 45,X (TS) and variant without the presence of Y chromosome 100% (42/42) patients have female gender identity There are no gender change recorded for this karyotype classification. Although there is one case in which gender change were being observed on follow up home visit in a mosaic 46,XX/45,X patient, the cause suspected are masculinization that occurred because of PCOS (Polycystic Ovarii Syndrome). Because this patient refuse to come for follow up visit to discussed about the gender change and consult with psychologist, so it is not recorded in the medical record as a gender change.

In sex chromosome DSD patients classified as 45,X/ 46,XY (Turner syndrome with Y Chromosome) gender identity of majority of patients are male 73.7% (14/19) and female constitute 36.7% (5/19) cases. There are 2 cases of gender change in this classification, The first case of gender change is from male to female in a case with karyotype 45,X(84%)/46,XY(16%). The second case is a gender change from female to male in a case with karyotype 45,X

(65%) / 46,XY (35%). EMS in both cases are 3.5 and 3 respectively.

In 47 XXY (KS) and variant majority of patients have male gender identity in 88.9 % (16/18) cases, female gender identity was found in 5.5 % (1/18) case in which the karyotype result is 46,XX/47,XXY(4%), in 1 case gender identity is not available. In this classification there is one case of gender change recorded, in a case with Karyotype 47,XXY, from female to male. In this case the EMS recorded is 3. In 1 case with 47,XXY karyotype, with a previous gender at admission was female, but recent gender was not available, because the age of first visit is still 1 month old, and there are no follow up or control visit after that, so the team of doctors in CEBIOR could not determine the gender after she reach a more observable age. Her/his EMS was 4.

In the 46,XX/46,XY (chimeric) classification majority have male gender identity in 81.8 %(9/11) cases. In this classification female gender identity only recorded in 18.2 % (2/11) patients who have karyotype 46,XX(90%)/46,XY(10%) and karyotype 46,XX(98%)/46,XY(2%). No gender changes occurred in all cases of this classification. In others karyotype classification there are no gender changes recorded in 100% (6/6) cases.

Y Chromosome percentage in Turner syndrome and variant are all 0% for in this classification there is no mosaicism that included a karyotype with Y chromosome. It is found that 100% of cases of this classification were having a female gender identity.

In 45,X/ 46,XY (Turner syndrome mosaicsm with Y Chromosome) classification, Y chromosome percentage varied widely from 2% to 98%. The cases in which result in female gender identity is cases with Y chromosome percentage of 2%, 16%, 42%, 73%, and 87%. While all cases with male gender identity are cases with Y chromosome percentage of 35% or more.

Almost all cases of Klinefelter syndrome and variant are having a male gender identity for the exception of 1 case in which the karyotype is 46,XX /47,XXY(4%). The Y chromosome percentage are low at 4% and a mosaicism with 46,XX with much higher percentage. In one other case of Klinefelter syndrome in which the karyotype is 47,XXY patient's sex of rearing and gender of admission is female at the age of 4 years old, but after genetic counselling there was a gender reassignment to become male, counselling were done on the parent.

In cases of 46,XX/46,XY (chimeric), majority 81.8% (9/11) cases are having a male gender identity, while 18.2% (2/11) cases are having female gender identity. The Y chromosome percentage of the cases that have female gender are 2% and 10%. While the cases with male gender identity are having varied percentage from 4% to 99% of Y chromosome.

Cases that classified as others are the one that have structural abnormality of sex chromosome or cases with mosaic karyotype of supermale or having more than one Y chromosome; and mosaiscm with 47,XXX. In this classification 66.67% (4/6) cases are having male gender identity with Y chromosome percentage of 91%,93% and two cases with 100% percentage. Y chromosome percentage of the (2/6) cases in others classification which have a female gender identity is 0%.

Table 1. Gender changes in sex chromosome DSD cases

No	Karyotype	Gender on Admission	Recent Gender	MS Scor	Percentage of Chromosome
1	45,X(84%) /46,XY(16%)	M	F	3.5	16
2	45,X (65%) / 46,XY (35%)	F	M	3	35
3	47,XXY	F	M	3	100

Phenotype (External Masculinization Score/EMS)

In cases karyotype classification 45,X (TS) and variant 85.7% (36/42) EMS were found to be "0" ;in 2.4% (1/42) cases EMS were"0.5" ; in 4.7% (2/42) EMS "1" ; in 2.4% (1/42) cases EMS were "1.5".

In cases of 45,X/ 46,XY or TS mosaicism with Y karyotype 5.3% cases (1/19) were found to have "6.5" EMS ; 5.3% case (1/19) with "6" EMS; 5.3 % case (1/19) with "5.5" EMS ; 5.3 % case (1/19) with "5" EMS; ; 15.8 % case (3/19) with "4.5" EMS; 10.5% case (2/19) with "3" EMS; 10.5% case (2/19) with "1" EMS;15.8 % case (3/19) with "0" EMS. All EMS result in this classification is categorized as ambiguous genitalia (EMS less than 7).

In cases of 47,XXY and variant 5.5% cases (1/18) were found to have "11" EMS ; 11.1% case (2/18) with "9" EMS; 5.5 % case (1/18) with "8.5" EMS ; 11.1 % case (2/18) with "7" EMS; 5.5 % case (1/18) with "5" EMS; 11.1 % case (2/18) with "4" EMS ; 5.5 % case (1/18) with "3" EMS; 5.5 % case (1/18) with "2.5" EMS; and 5.5 % case (1/18) with "0" EMS

In cases of 46,XX/46,XY karyotype classification 9.1% cases (1/11) were found to have "8.5" EMS ; 9.1% case (1/11) with :"7.5" EMS; 9.1 % case (1/11) with "3.5" EMS ; 18.2 % case (2/11) with "3" EMS; 9.1 % case (1/11) with "1.5" EMS; 18.2 % case (2/11) with "1" EMS; 9.1 % case (1/11) with "0.5" EMS; 9.1 % case (1/11) with "0" EMS.

In cases of others karyotype classification 16.7% cases (1/6) were found to have "5" EMS ; 16.7% case (1/6) with :"1" EMS; and 33.3 % case (2/6) with "0" EMS

4. Discussion

45,X and variant without Y chromosome

Among sex chromosome DSD, cases found to be the most prevalent are 45,X (Turner syndrome) and variant. Sex chromosomes have direct effects on cells and tissues outside of the reproductive tract, which are not mediated through gonadal hormones.[12] Phenotypes may be impacted by PAR (pseudoautosomal region) genes that are dosage sensitive. But since the SRY gene that are present in Y chromosome are non existent in TS, the phenotype of external genitalia ambiguity (hence the EMS score) and gender ambiguity are scarce.

Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 46,XX individuals of reproductive age. Cardinal features of PCOS include hyperandrogenism, irregular periods, and insulin resistance. Observations of

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individuals with gene mutations affecting androgen metabolism suggest that androgens may influence the development of gender identity. Other studies show that although PCOS patients are less likely to identify with a traditional feminine gender scheme compared to age-matched peers, the prevalence of gender incongruence in PCOS patients is not higher than in the general population.[13] Duration and severity of PCOS can negatively affect the self-image of patients, lead to a disturbed identification with the female-gender scheme and, associated with it, social roles. [14] In cases where PCOS are diagnosed in a mosaic Turner syndrome patient from karyotyping analysis, further examination by a more sensitive methods like FISH (Fluorescent in situ hybridization) analysis are needed to detect the presence of Y chromosome or SRY gene detection by PCR.

45,X/46,XY or 45,X mosaicism with Y chromosome

In Turner syndrome with Y chromosome karyotype classification the variability of Y chromosome are widely varied in cases with female gender identity, with Y chromosome percentage 2% to 87 %. While cases with male gender identity have more percentage of Y chromosome (from 35% to 98%). Majority (14/19) of cases with this karyotype are with male gender identity, while only minority (5/19) cases is with female gender identity. This shown the tendency of having a male gender in this karyotype classification are higher than female gender.

In research on infertility cases in China, The mosaic 45,X/46,XY karyotype is a common sex chromosomal abnormality in infertile men. High frequency of Y chromosome microdeletions were detected in male patients with 45,X/46,XY mosaicism. [15] It possibly is recommended for patients with mosaic 45,X/46,XY to also have a follow up of molecular examination of AZF gene. The degree of mosaicism varies with a higher percentage of Y-bearing cells in other tissues/organs than in blood, as has already been shown . [16] Even if gonadal tissue is most crucial for these analyses, it is not practical to evaluate it. As a result, blood analysis in TS patients may not be able to access the actual levels of mosaicism.[17] But gonadal malignancy is a threat that should be one of the focus of management in 45,X/46,XY.[18]

Low EMS score affect the probability of gender dysphoria. From 19 cases of 45,X/46,XY, 2 cases are having a gender change from the initial gender on admission. One case from male to female and the other is from female to male. In both cases EMS score is less than 7, in which for a male gender is considered ambiguous. So it is probable that Low EMS score is also associated with gender change later on in life.

47,XXY (Klinefelter syndrome) and variant

Almost all cases of 47,XXY and variant are having a male gender for the exception of 1 case with female gender in which the karyotype is 46,XX /47,XXY(4%). The EMS for this case is 0. The low percentage of Y chromosome probably affect the hormonal and phenotype, so directly and indirectly take part in gender determination. There also have been a case report in the American Journal of Psychiatry, of an individual with karyotype 47,XXY who have gender dysphoria since childhood and as an adult requested gender reassignment from male to female. Her genetic disorder has likely predisposed her to gender dysphoria , although it is a rare condition, since typically patients with Klinefelter syndrome identify or choose to identify themselves as males. [19]

46,XX/46,XY (Chimeric)

In cases of 46,XX/46,XY (chimeric) no gender change is recorded. The Y chromosome percentage of the cases that have female gender are 2% and 10%. While the cases with male gender identity are having a more varied percentage from 4% to 99% of Y chromosome. It was discovered that while Y chromosome detection in an individual, regardless of percentage, can be a cause for a male gender identity, however female gender identity tends to emerge if Y chromosome percentage are lower, in this case both are 10% and lower. In the other hand the phenotype in this case EMS score does not seem to depend on the percentage of Y chromosome. For example in cases with karyotype 46,XY(98%)/46,XX(2%) and 46,XY(99%)/46,XX(1%) are both having EMS score 3, but there are also cases with karyotype 46,XY (85%)/ 46,XX (15 %) and 46,XY (70%)/46/XX(30%) are having EMS score 8.5 and 7.5 respectively.

Other sex chromosome DSD

In this classification 4/6 cases are having male gender identity with Y chromosome percentage of 91%,93% and two cases with 100% percentage. In one case (2/6) in which the individual have female gender identity, the Y chromosome percentage is 0 % and SRY gene is not present. SRY gene if present is expressed in several structures, including brain; early conceptus; and genitourinary system. It is the gene that involved in male sex determination, and on an animal model where the sample are devided into 4 groups (XX, and XY mice with ovaries (females) and XX and XY mice with testes (males)) it was found that sex chromosome genes contribute directly to the development of a sex difference in the brain, independent of their gonadal status.[20] Although in reality the expression of Sry in the genital ridges typically results in their development of testes, whereas the absence or dysfunction of Sry leads to the development of ovaries. In all cases of others classification, the EMS seems to be lower than 7, showing an ambiguous genitalia. Fluorescence in situ hybridization (FISH) analysis using X and Y centromere-specific probes can be used to assess for sex chromosome mosaicism. In cases where karyotyping examination failed to show a Y chromosome material in an individual with an ambigous phenotype, probes specific for the SRY gene can be used to ascertain for Yp rearrangements. Chromosomal microarray analyses such as array CGH or SNP microarrays can detect submicroscopic gene variations. But still there are limitation because CGH may fail to detect balanced chromosomal translocations and low level mosaicism.[11]

Phenotype

External genitalia and internal reproductive anatomy is one of (but not the only) important factors influencing proper gender assignment at birth, sex of rearing and also management of DSD influenced proper gender assignment after diagnosis. [21,22] Diagnostic uncertainty can delay or lead to inappropriate gender assignment, with a need for gender reassignment at a later stage. Preference for male sex assignment, delayed diagnosis and sociocultural circumstances can later complicate gender reassignment after diagnosis. [23] The external masculinization score (EMS) provides a standardized format to summarize clinical features in newborn infants with ambiguous genitalia. EMS for those cases reared as male usually higher than for cases reared as female. [21] To measure EMS will objectively describe how far is the degree of masculinization of external genitalia. The score result of EMS is between 0-12.[24,25] EMS score < 7 can be mentioned as ambiguous genitalia. While EMS 7-9 is mentioned as under masculinized.[26]

In this study karyotype classification 45,X (TS) and variant all EMS result are less than 2 (0-1,5). Gender on admission are all female. EMS of <7 is classified as ambiguous genitalia if genotype contained Y chromosome. So EMS are not actually relevant to be measured in TS and variant without Y chromosome cases . Tanner score are not routinely recorded in the medical record, except in the cases of 45,X (TS) and variant, because the diagnosis of TS should be a foremost consideration in any female with unexplained growth failure or pubertal delay. [27]

In Sex Chromosome DSD cases with a component of Y chromosome, phenotype of external genitalia are relatively more masculinized than cases without Y chromosome. In 47,XXY (KS) and variant EMS is between 0-11. While in cases of 45,X/ 46,XY or TS mosaicism with Y karyotype EMS are between 0-6,5. All EMS result in this classification is categorized as ambiguous genitalia (EMS less than 7).

In cases of 46,XX/46,XY karyotype classification EMS recorded between 0-8,5. The result are quite variable between ambiguous genitalia and under masculinized category. In cases of others karyotype classification EMS of karyotype with component of Y chromosome are found to be between 0-5, categorized as ambiguous genitalia if there are component of Y chromosome present.

Karyotyping is the most crucial approach to determine aneuploidy in sex chromosomal DSD, but arrays or sequence-based techniques can provide more details. When compared to the typical male range, the hormonal profiles of patients with sex chromosomal DSD and a Y-chromosome sequence-containing karyotype showed high levels of LH and FSH and low levels of AMH, inhibin B, and testosterone.[(28)] Hormones are more than mechanistic links in the translation of genotype to phenotype: by virtue of their pleiotropic effects on gene expression, hormones structure the underlying genetic variances and covariance. [29] So it is imperative to have hormonal level evaluation in each DSD cases for an optimal diagnosis and management. Limitation of this study is the lack of hormonal description in each DSD classification to have a better understanding of the hormonal influence to gender identity and phenotype.

Gender Changes

The great majority of people with DSD come to identify as male or female, matching the gender they were assigned at birth. Nonetheless, 8% of people with DSD experience non-binary gender identity, gender dissatisfaction, discomfort, or dysphoria; these symptoms are most commonly observed in patients with 46,XY DSD and genital hypovirilization at birth.

5. Conclusion

In karyotype 45,X and variant, without Y chromosome the gender identity is female in all cases. In karyotype 45,X/ 46,XY or TS with mosaicism with Y chromosome or part of Y chromosome that contain SRY gene, the gender identity are dominantly male, without regard of the percentage of Y chromosome in the mosaicism. In karyotype 47,XXY and variant, majority male gender identity is observed. In karyotype 46,XX/46,XY dominantly male gender identity are observed, except in cases the percentage of karyotype with Y chromosome are much lower than karyotype without Y chromosome. In other classification of sex chromosome DSD, with variation of structural abnormality, the presence of Y chromosome or SRY gene also support a male gender identity result.

The presence and percentage of Y chromosome in the karyotype support a male gender identity result. In sex chromosome DSD cases, a thorough physical and hormonal examination are needed for every cases of DSD to minimalized gender dysphoria in the future. Sex chromosome DSD constitute a high karyotype diversity and wide phenotypic abnormalities that necessitates careful clinical and cytogenetic evaluation for proper phenotype-genotype correlation.

Ethical Approval

There is no ethical approval for this research.

Conflicts of Interest

All authors have no conflict of interest in this article.

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