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The Biological Basis of Binary Sex Differentiation

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Abstract

While gender is (by definition) influenced by social factors and hence subject to change as society changes, sex reflects biology, which is fixed in the time scale of a human lifepan. Gender, given its definition, may not fit into two categories. This has led to confusion in some parts of society and the media regarding the binary nature of sex.
This paper sets out a brief description of sex differentiation of the foetus, and the conditions that lead to disorders of sexual differentiation. It concludes that sex is binary and that disorders of sexual differentiation are predictable, given a combination of the binary nature of sex and the propensity of the human genome for nondisjunction and genetic mutations.

Keywords: gender, sex, differentiation

1. Sex is binary

In the realm of human biology, some facets are well-established, including the binary framework of sex differentiation. While we acknowledge the diverse experiences and conditions of individuals, it remains paramount to discern the biological drivers determining sex.

1.1 The Fundamentals of Sexual Reproduction

Central to evolutionary biology, sexual reproduction in mammals requires the union of two distinct gametes: sperm from males and ova from females. The offspring predominantly bear either XX or XY chromosomes, which determine their biological sex.

1.2 The Developmental Journey of Sex Differentiation

Initially, an embryo is bi-potential - it holds the potential for either male or female development. The Y chromosome's SRY gene leads to the production of testis determining factor (TDF) which differentiates the bi-potential gonad into a testis. In its absence, the gonad develops into an ovary. This chromosomal direction gives rise to development of Leydig cells in the testis, which secrete testosterone in the male foetus. The exposure to testosterone leads to the development of male internal and external sex organs, without it, the organs develop typical female characteristics.

1.2 Diving Deeper into Intersex Conditions

Intersex conditions, or Disorders of Sex Development (DSD), demand a meticulous and compassionate exploration:

1.2.1 Hypospadias.

Often inaccurately grouped with DSD, hypospadias involves a variation in the urethral opening's location in males – instead of being at the end (glans) of the penis, the urethra opens into the early glans, the shaft of the penis or the scrum. While it might require medical intervention for functionality, its prevalence shouldn't be misconstrued as challenging the binary delineation of sex. Boys born with hypospadias have

been found to display characteristics not distinguishable from other boys, other than being slightly more masculine[1].

1.2.2 Chromosomal Variations.
Conditions like Turner's Syndrome (45X0) and Klinefelter's Syndrome (47XXY) arise from nondisjunction events during cell division. Nondisjunction is an error in chromosomal separation at the time of cell division. This can result in extra chromosomes in some daughter cells and fewer in others. Most of these abnormalities are not compatible with life – the commonest exceptions being trisomy 21 – Down Syndrome. Nondisjunction of sex chromosomes can also be compatible with life, namely Karyotypes 45X0, 47XXY, 47XYY. Having no X chromosome (i.e., 45Y0) is not compatible with life. There is also triple X syndrome, 47XXX, leading to phenotypically normal females and 47XYY leading to phenotypically normal males.

Turner Syndrome occurs when cells have a 45X0 pattern. The full haplo-insufficiency occurs when one gamete fails to provide a sex chromosome and the resulting offspring is 45XO throughout every diploid cell in the body. In this circumstance, the child has external genitalia that are female and is infertile.

Around half of people with Turner Syndrome are mosaics. This occurs when sex chromosome non-disjunction is in the post-zygotic cell division. As a result, the diploid cells in the body are a mix of X0 cells with either XX or XY cells. The extent of the syndrome clearly differs with the mix of the mosaic. Almost always, infertility results.

Remove hypospadias and Karyotype abnormalities and the remaining rates of DSD are one per 1000 to one per 4500 live births.

DSDs have several causes but the pathways are predictable given the facts presented above. If an XX fetus is exposed to testosterone, the foetus can develop masculinized genitalia to varying degrees– but gonads remain female (ovaries) and they will not develop a male gamete. If an XY foetus has insensitivity to testosterone, this will lead to external genitalia being phenotypically female, but gonads will remain male (testes) and a uterus is absent.

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1.3 Disorders of sexual differentiation

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1.3.1 Congenital adrenal hyperplasia (CAH).

The first case is most often due to a mutation in the genes that control enzymes in the pathway to steroid synthesis, a condition called congenital adrenal hyperplasia. This autosomal recessive condition caused mainly by defects in the steroid 21-hydroxylase (CYP21) gene on chromosome 6p21[2]. This gene codes an enzyme responsible for making essential mineralocorticoids and glucocorticoids. In the absence of these enzymes the adrenals are overstimulated leading to an excess of other hormones in the pathway – including testosterone. It is often a life-threatening disorder owing to lack of mineralocorticoids and failure to maintain salt balance. Most XX newborns with this condition are predominantly phenotypically female, for example, they may have an enlarged clitoris and some posterior labial fusion. However, some have ambiguous or even fully masculinized genitalia. Such individuals are at high psychological risk of gender dysphoria when they are raised as males (12.1%) or as females (5%)[3]. For highly masculinized CAH children, being raised male is a viable option and

a portion of those raised females will develop a desire to be male and vice versa. In these circumstances it seems wise to proceed with caution and suggest that no external genital surgery should be performed until gender identity has been reasonably established.

1.3.2 Androgen insensitivity syndrome (AIS).
The second case, another extremely rare condition, occurs when a child with XY sex chromosomes lacks a testosterone receptor peripheral target cells (this can be complete or incomplete, and can affect some or all androgenic receptors). Such individuals develop testes because their Y chromosome functions normally making TDF. The testes secrete (often high levels of) testosterone, but the “end organs” of the testosterone are insensitive, hence the fetus develops female external genitals with undescended or partially descended testes and no uterus. They are infertile.

It's essential to underscore that genuine DSDs, when we exclude conditions like hypospadias, are extremely rare, occurring in less than one per 1000 live births. Furthermore, many of these DSDs arise from genetic mutations that, tragically, often result in infertility or present significant health challenges.

Conclusions

Sex is binary. Below are exclusively binary expressions of mammalian sexuality.

(1) Mammalian life is not possible without the combination of a female produced gamete (ovum) and a male produced gamete (sperm) there is no third way.
(2) No person with a Y chromosome can make a female gamete, and no person lacking a Y chromosome can make a male gamete.
(3) To produce fertile offspring, the sex chromosome in the haploid male gamete (sperm) must contain either an X or a Y chromosome.
(4) Sex differentiation is fundamentally anchored by the presence or absence of the Y chromosome, the presence of which leads to male characteristics, its absence leads to female.

While DSDs add layers of complexity to this narrative, they result from rare mutations within this foundational framework and almost always are associated with infertility.

The anomalies described in this paper, while important to acknowledge, don't nullify the binary foundation of sex. They are not part of a polygenic spectrum of sexual expression any more than having cystic fibrosis is part of a polygenic diversity of lung function or having haemophilia is part of a polygenic spectrum of clotting function.

A clear demarcation between biological sex and gender identity is pivotal. The former revolves around chromosomes and reproductive anatomy, while the latter embodies a spectrum of identities with input from biology, psychology and society. Informed, sensitive dialogues ensure that our societal understanding is both scientifically accurate and humanely considerate.

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