

Sex Chromosome Disorders

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Sex chromosomes have a pivotal role in sex determination. Aberrations of sex chromosomes in diverse ways at different stages of development of an individual result in disorders of sex development (DSD); the understanding of which is often garbled. With a brief introduction to sex determination and sex chromosomes, this article aims to simplify the concept of DSDs.



核型 : 47, XXY

Cell No. : 003

Sex Determination

Sex determination has been an area of great interest. Sexual differentiation essentially epitomizes the maturation of phenotypic traits secondary to hormonal action which define the sex of an individual as per the society norms and behavior. Scientifically speaking, **sex determination may be looked at as having the following 4 components, inclusive of the phenotypic sex.** They are tabulated as follows:

Sex of an individual	Explanation
Chromosomal sex determination	Presence of Y chromosome dictates "male" sex and determines the genotypic sex.
Gonadal sex determination	Presence of testes is generally accepted to be a "male", while the presence of ovaries signifies "female" sex.

Differentiation of genitalia	The internal and external genitalia further define the phenotypic sex of an individual.
Development of secondary sex characteristics	Development of body hair, breasts, and other secondary sexual features are relevant in estimating the phenotypic sex of an individual.

Thus, in medicine, **one has to look at all these components before assigning “sex” to an individual**. Normally, all these 4 sub-components exist in a balanced equation concordant with each other; thus, a female is XX, has ovaries, has a vulva, vagina and has breast development and long scalp hair and typical distribution of pubic hair.

The male traits are similarly well defined and distinctly marked by testes, penis, scrotum and other portions of the male anatomy with underdeveloped breasts; however, these components occasionally go haywire and result in pathologies of sexual differentiation. The significance of these components becomes clear then.

Different types of sex determination



44
+
XX



44
+
XY



76
+
ZW



76
+
ZZ



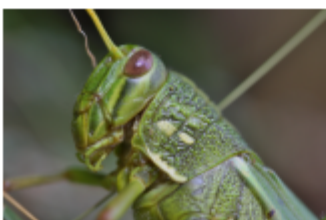
30
+
XX



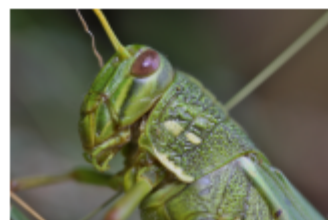
30
+
XY

OR

15
+
X



22
+
XX



22
+
X

Y Chromosome

Introduction



Image: "Nettie Stevens's microscope, Bryn Mawr College." By Bryn Mawr College. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

There are 2 sex chromosomes in humans — X and Y.

The **Y chromosome is quintessentially the "sex-determining" chromosome** as its presence or absence is the key determining factor in the sex of an individual. [Nettie Stevens](#) in 1905 discovered the Y chromosome at Bryn Mawr College while he was engrossed in the study of the mealworm *Tenebrio Molitor*. Holandric traits are those that are mediated through the genes present on the Y chromosome.

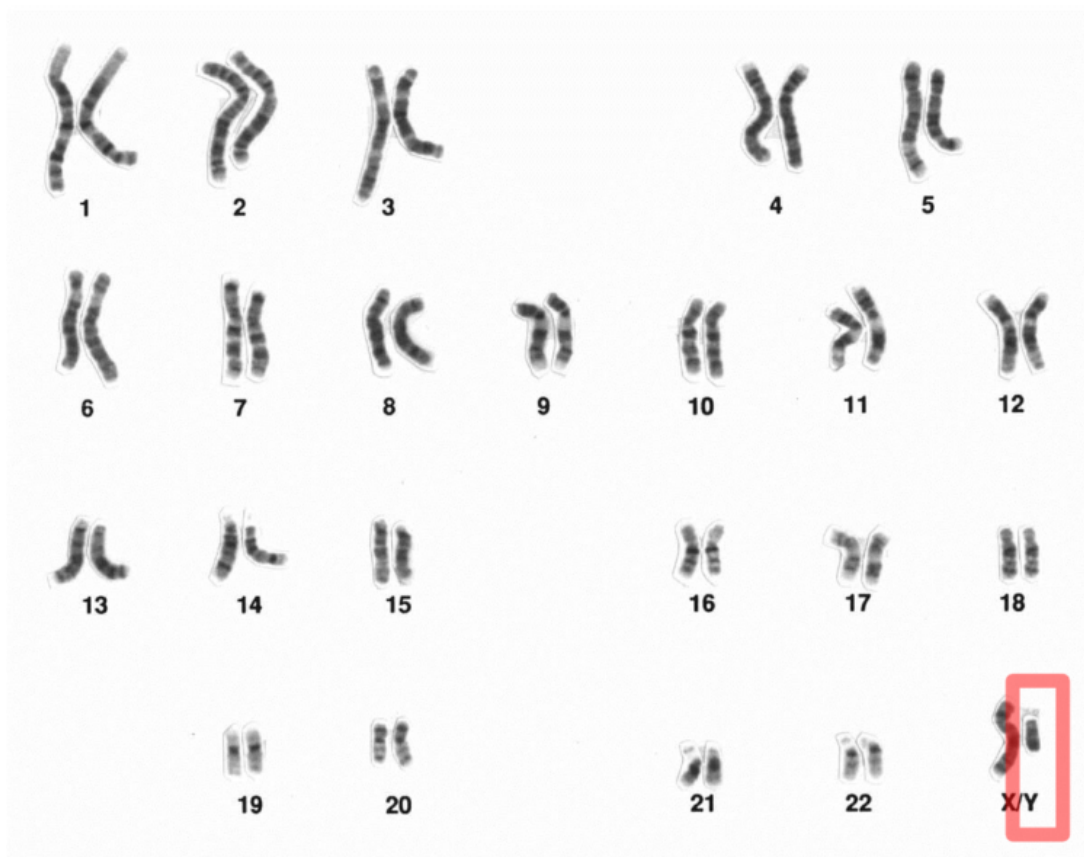
Structure

Consisting of about 59 million base pairs, the Y chromosome has **about 200 genes that have hemizygous representation**. This acrocentric chromosome is also one of the most rapidly evolving chromosomes in the human species.

The different important structural entities of the Y chromosome, along with their functional disposition, can be summarized as follows:

Structural entity	Function
Pseudoautosomal regions at the telomeres	Constituting about 5% of the Y chromosome, these regions in the short arm p are homologous to the corresponding parts of the X chromosome.
The non-recombining region of Y (NRY)	The majority of Y chromosome is not homologous to the X-chromosome and is termed as "NRY". Ancestry is determined by the study of single-nucleotide polymorphisms (SNPS) in these substrates.
SRY (sex determining region)	SRY gene locus on Y chromosome ensures TDF synthesis: Testis-determining factor protein . TDF, in turn, is crucial for the development of seminiferous tubules and male internal genitalia. SRY gene is instrumental in not only developing male characteristics, but is also responsible for the inhibition of the development of female characteristics. This process is mediated through the Anti-Mullerian Hormone .
DAZ 1	Gene deletion mutations of this locus often culminate in azoospermia.

Role of Y Chromosome in Sex Determination



Human male Karyotype after G-banding. Y chromosome highlighted. By National Human Genome Research Institute.

Time	Explanation
At 6 weeks	The human internal genitalia is ambipotent for a short time and then destined to become the female ovaries; however, the functional competent TDF from SRY functions as a switch, with subsequent formation of seminiferous tubules, testes, Leydig cells and Sertoli cells . Androgenic hormones like testosterone are secreted and lead to a development of male genitalia and characteristic traits.
At 8 weeks	Sertoli cells secrete Anti-Mullerian Hormone (AMH) which inhibits the development of female internal and external genitalia. Ovaries and paramesonephric duct (Mullerian) involute and disappear. Simultaneous development and growth of the mesonephric (Wolffian duct) occurs.

Disorders of Sex Development (DSD)

DSDs have always fascinated different sociopolitical and medical groups for diverse reasons. The basic understanding of DSDs is equally tantalizing.

The [European Society for Paediatric Endocrinology \(ESPE\)](#) in collaboration with the [Lawson Wilkins Pediatric Endocrine Society \(LWPES\)](#) in 2006 set out on the herculean task of standardizing nomenclature and description of DSDs for taxonomical benefits. DSDs as a term implied a **congregation of disorders with abnormal chromosomal, gonadal or phenotypic sex**. In other words, a congenital condition marked by atypical

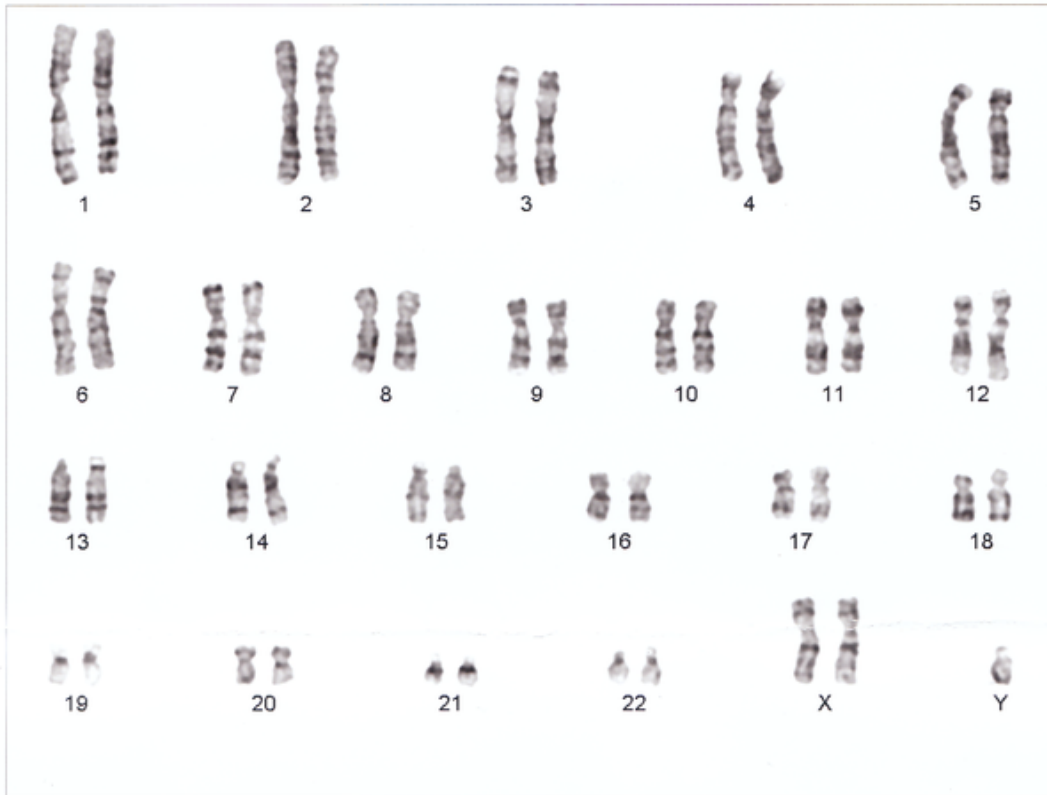
development of chromosomal, gonadal or anatomical sex is known as DSDs. Genetic studies are a testament to the increasing significance of chromosomal aberrations in these disorders.

The mechanisms behind inconsistencies in chromosomal and gonadal sex leading to humans to be, in scientific terms, **hermaphrodites** (intersex, the problem with genital development in the infants) have been unearthed. This condition is renamed as disorders of sex differentiation as new terminology. Strictly sex-linked regions of X and Y chromosomes are with closely regulated genes and control mechanisms. Normal meiosis I exchange occurs in the pseudoautosomal region with rare crossing over.

Recombination outside the pseudoautosomal region leads to multiple permutations and combinations of mutations with consequential disorders of sex development (DSD's) spanning across complete gonadal dysgenesis to mixed gonadal dysgenesis or ambiguous genitalia.

Accordingly, a simplified classification of DSD based on the karyotype of an individual may be tabulated as follows:

Individual karyotype	Possible DSDs
Sex chromosome DSD	<ul style="list-style-type: none"> • 45, X/46, XY (mixed gonadal dysgenesis, ovotesticular DSD) • 47, XXY (Klinefelter syndrome) and variants • 46, XX/46, XY (chimeric, ovotesticular DSD) • 45, X (Turner syndrome) and variants
46, XX DSD	<ul style="list-style-type: none"> • Testicular DSD results from conditions like cryptorchidism and hypospadias. • Ovotesticular DSD with ovotestis or one of each where a smaller percentage of patients have both testicular and ovarian tissue. • Ovarian maturation abnormalities and gonadal dysgenesis culminate into ovotesticular DSD and testicular DSD. <ul style="list-style-type: none"> • Androgen excess in conditions resulting from: <ul style="list-style-type: none"> ◦ maternal etiology ◦ fetal disorders like congenital adrenal hyperplasia (CAH) ◦ fetoplacental reasons • Other disorders like Atresia of external genitalia, cloacal exstrophy.
46, XY DSD	<ul style="list-style-type: none"> • Androgen formation dysregulation in pathologies like androgen biosynthesis defect, partial and complete central or peripheral androgen insensitivity, and disorders of antimüllerian hormone or receptor function. • Testicular developmental anomalies such as complete and partial gonadal dysgenesis. <ul style="list-style-type: none"> • Other causes like cloacal exstrophy, hypospadias.



核型 : 47, XXY

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Klinefelter Syndrome. Human Chromosome-type XXY. By Nami-ja .

The various genetic mutations associated with these disorders can be memorized as follows:

Disorder	Mutation
XY gonadal dysgenesis	SRY, DAX1, SOX9, NR5A1 mutations. XY complete gonadal dysgenesis (CGD) is claimed by a mere 15% by mutation or deletion of SRY, and most have normal SRY.
XX testicular DSD	SRY translocation to X, SOX9 duplication, SOX3 duplication. Most of these patients have a translocated copy of SRY and develop as males.
XX ovotesticular DSD	SRY translocation to X, SOX9 duplication, SOX3 duplication, other genes involved in male sex determination. 15–20% have no SRY and have ambiguous genitalia providing evidence of male sexual development. The issue is rather too much gene product.
Testis: Incomplete masculinization: CAIS, PAIS: Azoospermia, Oligospermia	AZF deletions, DAZ deletions, USP9Y mutation, DDX3Y deletion
Ambiguous genitalia	
Ovary: CAH	XX virilisation

The incidence of sex chromosome abnormalities is about 1 in every 300 males, and 1 in every 650 females.

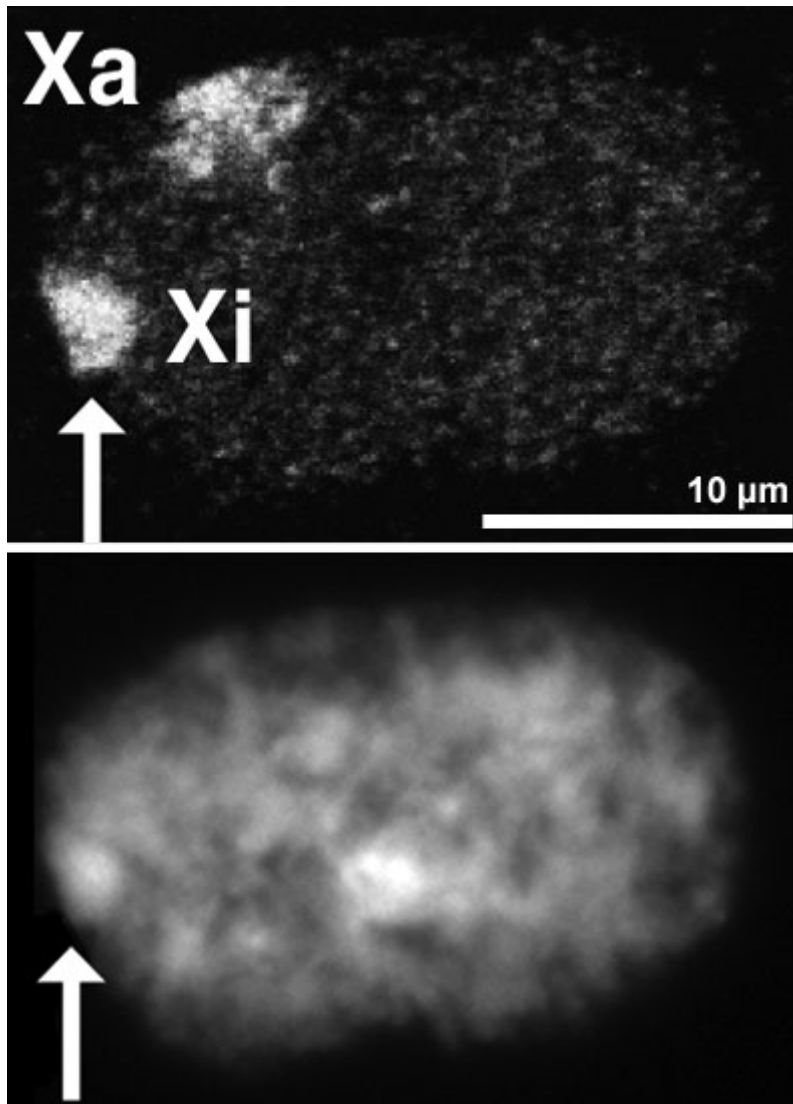
Sex Chromosome Aneuploidies

Aneuploidy for the X chromosome is among the **most common of cytogenetic abnormalities**. This phenomenon is rather well endured by the body due to an analogous naturally existing experience known as Dosage compensation. In order to ensure equal expression of X-linked genes in both sexes, females through epigenetic silencing mechanisms undergo deliberate functional inactivation of X-linked genes on 1 chromosome. This **X-inactivation equalizes the expression of X-linked genes between the sexes**.

Two X chromosomes are necessary for ovarian maintenance, but one must be inactivated for the normal development. In a female nucleus, a number of inactive X's is $nX-1$. FISH for histone variants indicates Xi.

The XIC is critical to X inactivation. **X inactivation is brought on by XIST ncRNA from Xi** which spreads along Xi resulting in epigenetic silencing of most genes on Xi. The consequence is [monoallelic gene expression](#). The inactivated X chromosome is identified as the "Barr body" in buccal mucosa samples tested for sex determination.

No X inactivation emanates in biallelic gene expression.



[Image](#): "Nucleus of a female amniotic fluid cell. Top: Both X-chromosome territories are detected by FISH. Shown is a single optical section made with a confocal microscope. Bottom: Same nucleus stained with DAPI and recorded with a CCD camera. The Barr body is indicated by the arrow, it identifies the inactive X (Xi)." by Steffen Dietzel - Steffen Dietzel, Dissertation an der Universität Heidelberg, 1996. License: [CC BY-SA 3.0](#)

The most relevant and frequent sex chromosome aneuploidies have been summarized as follows:

Feature	47,XXY Klinefelter syndrome	47, XYY (Supermales)	47, XXX Trisomy X (Superfemales)	45, X Turner syndrome
Prevalence	1 in 600 male births	1 in 1000 male births	1 in 1000 female births	1 in 2500 to 4000 females
Clinical phenotype	Tall male	Tall, but otherwise typical appearance	Hypotonia delayed milestones, language, and learning difficulties, tend to be taller than average	Short stature, webbed neck, lymphedema, risk for cardiac abnormalities
Cognition/intelligence	Verbal IQ reduced to the low-normal range, educational difficulties	Verbal IQ reduced to low-normal range, language delay, reading difficulties	Normal to low-normal range (both verbal and performance IQ decreased)	Typically normal, but performance IQ lower than verbal IQ
Behavioral phenotype	No major disorders, tendency to poor social adjustments, but normal adult relationships.	Subject with specific behavioral problems likely associated with lower IQ	Typically no behavioral problems, some anxiety and low self-esteem, reduced social skills	Typically normal, but impaired social adjustment
Sex development/fertility	Hypogonadism, azoospermia, infertility	Normal	Reduced fertility in some, premature ovarian failure	Gonadal dysgenesis, delayed maturation, infertility.
Variant karyotypes			48,XXXX, 49,XXXXX increased severity with additional X's	46, Xi(Xq), 45, X/46, XX mosaics, other mosaics.

Prognosis

The most common cause of ambiguous genitalia in infants is **congenital adrenal hyperplasia**. Not only is this a socially awkward situation, but it is also a medical emergency, as well as a majority of these individuals, have salt-wasting nephropathy which could have life-threatening implications like vascular dysregulation and kidney failure. Hence, proper diagnosis of these patients at a very early age cannot be over-emphasized.

Diagnosis

The diagnostic tests in infants with ambiguous genitalia are:

1. Chromosomal analysis
2. Endocrine screening
3. Serum test
4. Androgen receptor levels test
5. Renal bladder ultrasonography to exclude congenital adrenal hyperplasia
6. Genitography to determine ductal anatomy

CT scans and MRI to identify internal anatomy.

Treatment

A targeted multi-centric team approach is the standard of care.

The various specialties which form an essential part of this team can be summarized as follows:

- Neonatologists
- Surgeons-pediatric, urology, plastic surgery
- Endocrinologists
- Ethicists
- Geneticists
- Social workers and counselors
- Pediatricians

Parents should be cognizant of the patient's condition and should be encouraged to take an active part in the management of the same. The ultimate desired outcome is the **provision of appropriate medical care and optimum social counseling** to help these individuals lead a near normal life.

Surgery

Surgical reconstruction is advocated in DSDs which can undergo lots of controversies. It is recommended between the age of 6 and 18 months.

Summary

In the current scheme of events, the **sex of an individual is determined by a congregation of different factors** like chromosomal sex, gonadal sex, and phenotypic sex.

Y chromosome is right called the sex-determining chromosome. Every human is destined to be a female unless intervened by the Y chromosome substrates which switch off the development towards female internal and external genitalia and regulate the development of testes and the male characteristic sex traits.

There are different regions of Y chromosome which are intricately and strictly regulated to bring about the sexual differentiation. SRY gene and its product TDF are instrumental for the initiation of the chemical cascade which results in the formation of the male sex.

There are multiple points where [genetic mutations](#) and [chromosomal aberrations](#) can disrupt the normal physiological pathway of sexual development resulting in Disorders of

Sex Development (DSDs).

The DSDs can be **classified according to the genetic makeup and the predisposing etiopathogenesis** which results in inconsistencies in the gonadal and chromosomal sex of an individual.

Sex chromosome aneuploidies are generally well tolerated due to the natural phenomenon of X inactivation and dosage compensation existent in females. **The inactivated X chromosome is identified as the “Barr body.”**

Early diagnosis of DSDs is a must. There are diverse social and medical implications involved. Parental education and proper counseling is a must for optimum care of these individuals.

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