

Chapter 7

Sex Determination & Sex Chromosomes

Mammals & *Drosophila*

Females are XX

Males are heterogametic (XY)

Males are not always the heterogametic sex.

We know for humans:

Males are 22, XY

Females are 22, XX

But, what is the evidence that the Y-chromosome determines maleness in humans?

About 1940, scientists identified two human abnormalities characterized by aberrant sexual development, Klinefelter and Turner syndromes.

Klinefelter Syndrome:

- genitalia and internal ducts usually male
- testes underdeveloped and fail to produce sperm
- although some masculine development occurs, feminine sexual development is not entirely suppressed resulting in slight breast enlargement
- frequency is about 2/1000 male births.
- 47, XXY

Turner Syndrome:

- female external genitalia and internal ducts
- rudimentary ovaries
- short stature (< 5 feet tall)
- webbed neck
- broad, shield-like chest
- frequency about 1/3000 female births
- 45,X

These data on Klinefelter and Turner syndromes indicate the Y-chromosome determines maleness in humans.

Both conditions result from nondisjunction of the X-chromosome during meiosis.

47, XXX Syndrome:

--frequency about 1/1200 female births

--highly variable in expression -- normal to underdeveloped secondary sexual characters, sterility, mental retardation.

48, XXXX and 49 XXXXX have been reported and all have been females.

In many cases, presence of additional X chromosome disrupts the delicate balance of genetic information necessary to normal female development.

47, XYY Jacob Syndrome:

--Patricia Jacobs, 1965

--9/315 males in a Scottish Maximum Security prison had 47,XYY

--Significantly taller than average

--Criminal acts of serious social consequences

--7/9 subnormal intelligence

--All 9 suffered personality disorders

Been studied in other criminal populations and found above average height (> 6 feet tall) and subnormal intelligence.

Frequency of males with this karyotype appears to be high in males in penal and mental institutions.

But, what about XYY males that are NOT incarcerated?

1974, Stanley Walzer and Park Gerald identified 20 XYY newborns in 15,000 at the Boston Hospital for Women to address this question.

Pressured to abandon the study.

Current research shows that many XYY individuals DO NOT exhibit any form of antisocial behavior and lead normal lives!

Sexual Differentiation in Humans

- During early embryonic development, every human embryo undergoes a period when it is potentially hermaphroditic.**
- By the 5th week of gestation, gonadal primordial tissue arise as a pair of ridges associated with each embryonic kidney.**

- Primordial germ cells migrate to these ridges where an outer cortex (capable of developing into an ovary) and an inner medulla (capable of developing into a testis) form.**
- Additionally, two sets of undifferentiated male (*Wolffian*) and female (*Mullerian*) ducts exist within each embryo.**
- If the cells of the genital ridge have the XY constitution, development of the medullary region into testis is initiated around the 7th week.**
- Once testis differentiation is initiated, embryonic testicular tissue secretes two hormones essential for continued male sexual development.**
- In the absence of a Y-chromosome, the cortex of the genital ridge forms ovarian tissue.**

- In the absence of male development, about the 12th week of fetal development, the oogonia within the ovaries begin meiosis and primary oocytes can be detected.**
- By the 25th week of gestation, all oocytes become arrested in meiosis and remain dormant until puberty is reach 10 to 15 years later.**
- In males, primary spermatocytes are not produced until puberty is reached.**

Development of Intersexuals (Hermaphrodites)

--*Time*; March 1, 2004

--True hermaphrodites are rare.

--Less extreme cases occur more frequently, estimated frequency is 0.2 -- 2.0% of live births.

--One explanation for some hermaphrodites, two eggs are fertilized in the womb -- one XX and one XY but rather than developing into twins, they merge to become one zygote.

--About 30 genetic and hormonal conditions can give rise to intersexuality with considerable variation in expression of the two sexes.

The Y-Chromosome & Male Development

While much of the Y-chromosome is genetically blank, it does share homology with the X-chromosome and carries genes for male development that are absent from the X-chromosome.

PAR -- *Pseudoautosomal Regions* -- this area shares homology with the X-chromosome and synapses and recombines.

NRV -- *Nonrecombining Region of the Y*

-- 20 genes in this region.

--12 of the genes can be grouped into 2 different groups

-- 5 of these 12 have homologs on the X-chromosome and are expressed in a wide range of tissues in addition to the testis. These seem to encode general cellular functions.

-- Remaining 7 lack X-homologs and are expressed only in testis.

SRY -- *Sex determining region of the Y* -- this area encodes TDF -- *Testis Determining Factor*.

TDF -- Genes responsible for somehow triggering the undifferentiated gonadal tissue of the embryo to form testis.

Because of heteromorphic sex chromosomes in humans, we would expect a 1:1 sex ratio.

Sex Ratio -- the actual proportion of male to female offspring.

Primary Sex Ratio -- reflects the proportion of males to females conceived in the population.

Secondary Sex Ratio -- reflects the proportion of males to females born in a population.

Secondary Sex Ratio for human populations determined in 1969

Caucasians in US -- 1.06

African Americans in US -- 1.025

Korea -- 1.15

Despite these ratios, it is still possible that the primary sex ratio is 1.0

Gender of 6,000 embryos and fetuses from miscarriages and abortions was determined in 1948.

- Fetal mortality was higher in males**
- Primary sex ratio in US Caucasians = 1.079**
- More recent data suggest 1.20 -- 1.60**

Why?

Dosage Compensation

Females = XX

Males = XY

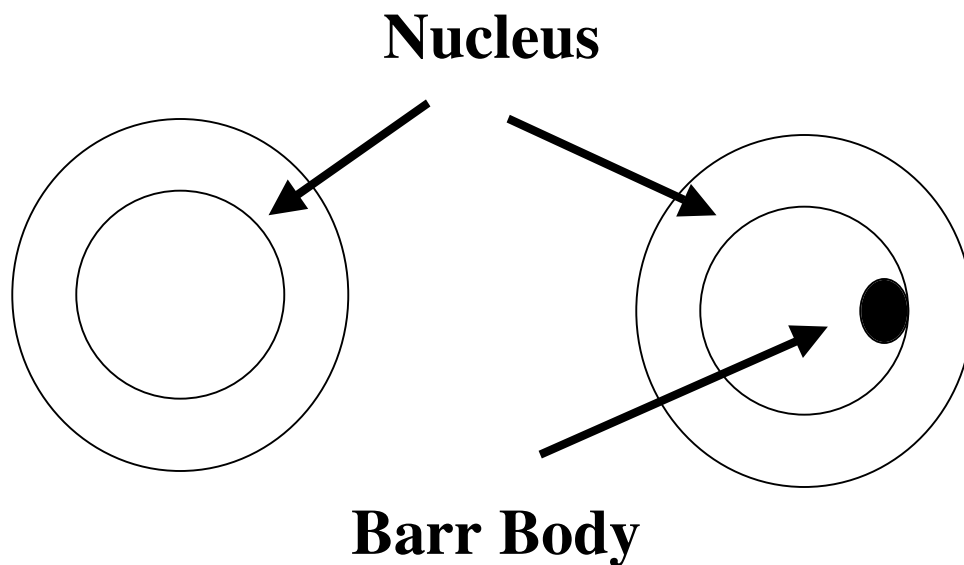
Dosage problem between female and male for X-linked traits. This should also be seen in X and Y syndromes.

Murray L. Barr and Ewart G. Bertram worked with interphase nerve cells of cats.

Darkly staining body against nuclear envelope in females but not males.

--Inactivated X-chromosome -- Barr body

-- Provides a mechanism for Dosage Compensation of X-linked genes.



45, X

47, XXX

48, XXXX

47, XXY

Why are these not normal?

Inactivation does not occur early enough in development of those cells destined to form gonadal tissue or,

Not all of each x-chromosome forming the Barr Body is inactivated.

Other Questions:

- 1. Which X-chromosome is inactivated?**
- 2. Is inactivation random?**
- 3. Is the same X-chromosome inactivated in all somatic cells?**

1961 Mary Lyon & Liane Russell (independent)

- 1. Inactivation is random**
- 2. Occurs early in embryonic development**
- 3. All progeny cells have the same X chromosome inactivated.**

LYON HYPOTHESIS

Mammalian females are mosaics for all heterozygous x-linked traits.

Red-green color blindness --

Hemizygous males are fully color-blind

Heterozygous females display mosaic retinas with patches of defective color perception and surrounding areas of normal color vision.

Anhidrotic ectodermal dysplasia

Hemizygous males show absences of teeth, sparse hair growth, and lack of sweat glands.

Heterozygous females reveal patches of tissues without sweat glands.

Calico Cats.

Mechanism of X-Inactivation

XIST (X-Inactive Specific Transcript) gene in X-Inactivation Center (XIC)

Expressed only on x-chromosome that will be inactivated.

- 1. Transcription of XIST prior to inactivation**
 - 2. RNA stays in nucleus**
 - 3. DNA and RNA sequence of XIST -- No ORF therefore, no translation.**
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Sex-determination in *Drosophila*

Females = XX

Males = XY

Y-chromosome lacks male determining factors but contains information critical to male fertility.

Ratio of X-chromosomes to autosomes is important for sex determination.

Male determination factors in *Drosophila* are located autosomally.

Some female determining factors are located on the X-chromosome.

Genic Balance Theory -- A threshold for maleness is reached when X:A is 1:2, presence of additional X alters this balance and results in femaleness.

Mechanism of sex determination is unclear but:

***Sxl* -- Sex-lethal -- Master switch for activation of at least 4 separate regulatory genes.**

***Sxl* is activated when $X:A = 1.0$, and results in female development. If $X:A = 0.5$, male development.**

Mutations in *Sxl* kill female embryos but have no effect on male embryos.

Dosage Compensation in *Drosophila*

- No X-chromosome inactivation.**
- Male X-linked genes are transcribed at 2X the level compared to X-linked genes in females.**
- Dosage compensation is regulated by at least 4 autosomal male specific lethal genes.**
- These genes are under the control of Sxl.**
- Mutations in any of these genes severely reduces the increased expression of X-linked genes in males, causing lethality.**