Meiosis & Sex Determination

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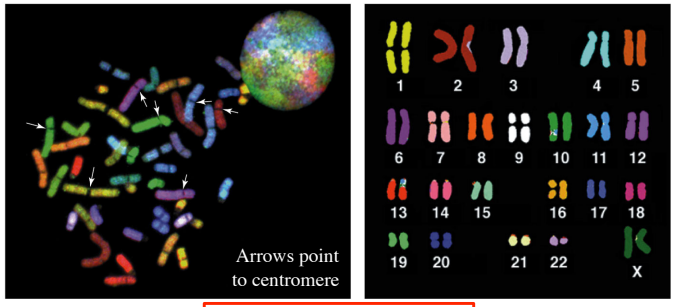
Learning Goals for This Lecture

- To appreciate that meiosis diversifies the genetic makeup of the next generation.
- To appreciate sex determination is genetically controlled in mammals (but not in all animals).
- To appreciate the science behind the discovery of the key sex determining gene.
- To understand the importance of dosage compensation and the differences among species as to how it occurs.
- To understand how traits can be sex-linked and appreciate the genetics used to assess sex-linkage.

Autosomes & Sex Chromosomes

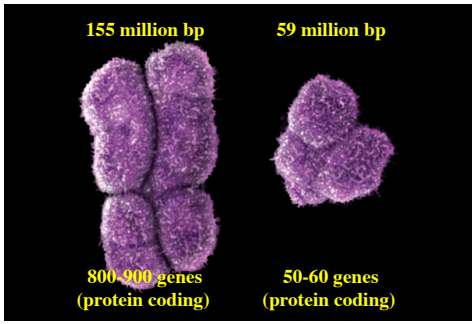
(humans have 22 autosome pairs and 1 pair of sex chromosomes)



Normally,
XX=Female & XY=Male

Different species have different chromosome numbers

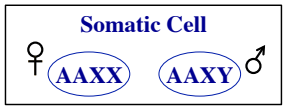
Human Sex Chromosomes



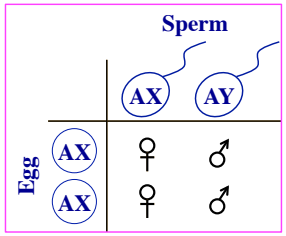
The evolution of the mammalian X and Y sex-determining chromosomes from ancestral chromosomes is thought to have occurred through a rapid gene loss from Y chromosome

Clark. (2014) *Nature* 508:463-465

Meiosis Generates Haploid Gametes
(fertilization results in diploid zygote)



- Human males are heterogametic (producing dissimilar gametes)
- Humans females are homogametic (producing only one type of gametes)



A: Autosomes

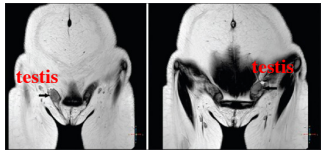
- Human (somatic) cells are diploid (two sets of chromosomes)
- Human sperms and eggs are haploid (one set of chromosomes)

Gender Test and Olympics
(testosterone level or DNA?)

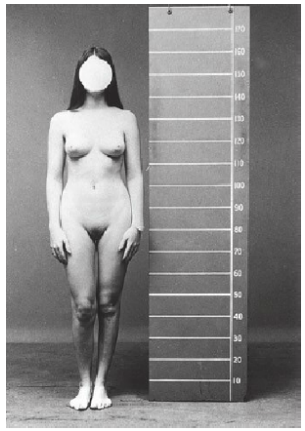
Caster Semenya was allowed to competent in 2012 as a woman only after gender test

Complete Androgen Insensitivity Syndrome
(patients carry a defective androgen receptor gene on X chromosome)

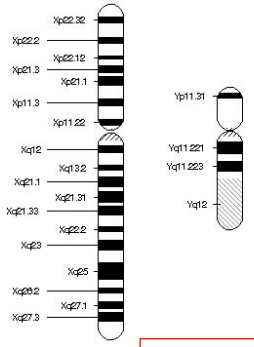
- Genotype: male (XY)
- Phenotype: female
- Develop female external characters, but are sterile



The primary and most well-known androgen is testosterone



Chromosomal Sex Determination
(the Y chromosome determines sex in mammals)



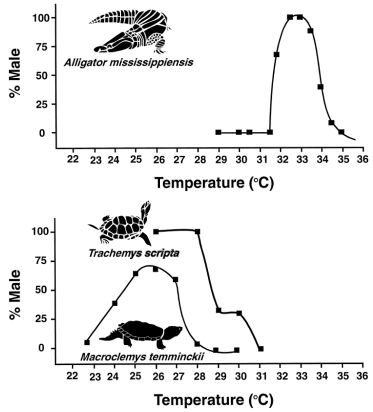
Primary sex determination
Determination of the gonads

Secondary sex determination
Affects the bodily phenotype outside the gonads.

Female is the default program

All Roads Lead to Rome

(animals use different mechanisms to determine sex)



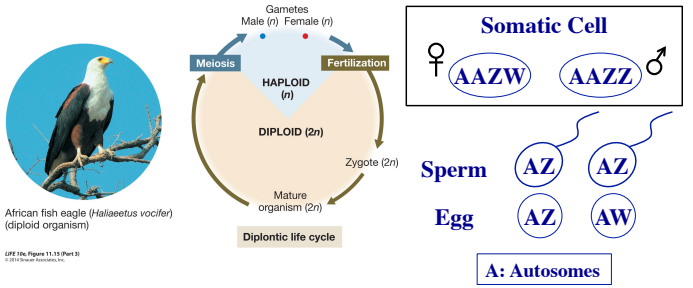
Environmental Sex Determination

- temperature
- location
- population size
- sex of others

Crain & Guillette. (1998) *Anim. Reprod. Sci.* 53:77-86

Chromosomal Sex Determination

(female birds are heterogametic while male birds are homogametic)

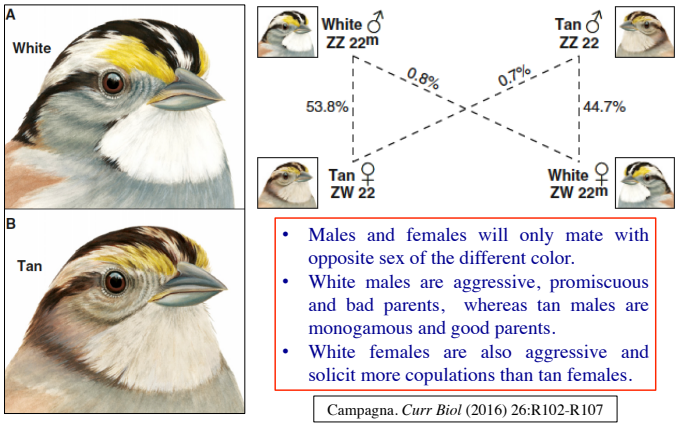


African fish eagle (*Haliaeetus vocifer*) (diploid organism)

Drosophila **females are XX and males are XY like in mammals, but the Y chromosome is not necessary for sex determination. Instead, sex is determined by the number of X chromosomes (two Xs to be female and one X to be male)**

A Bird Species with Four Sexes

(the white-throated Sparrow has two color morphs for both sexes)



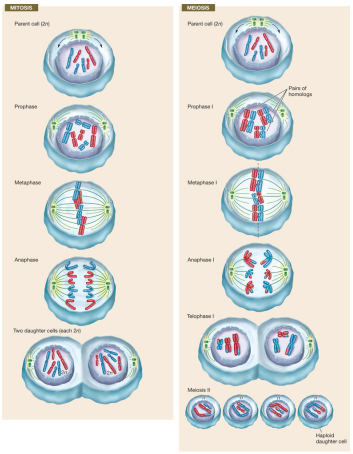
- Males and females will only mate with opposite sex of the different color.
- White males are aggressive, promiscuous and bad parents, whereas tan males are monogamous and good parents.
- White females are also aggressive and solicit more copulations than tan females.

Campagna. *Curr Biol* (2016) 26:R102-R107

Meiosis

- **Reduces the chromosome number from diploid to haploid**
  Each chromosome of the homologous pairs assorts randomly and independently
- **Generates genetic diversity among the products**
  Crossing over (recombination) of homologous pairs shuffles the parental DNA

Consists of two nuclear divisions but DNA is replicated only once



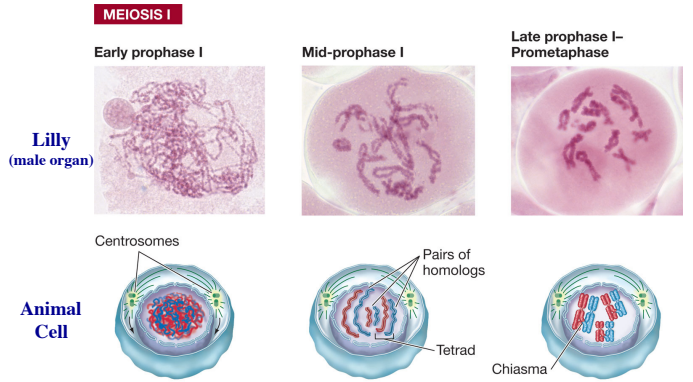
LIFE 10e, Figure 11.19

Mitosis & Meiosis

Meiosis differs from mitosis chiefly by the pairing of homologs, which allows recombination to occur, and by the failure to separate the centromeres at the end of metaphase I.

Meiosis Generates Haploid Gametes

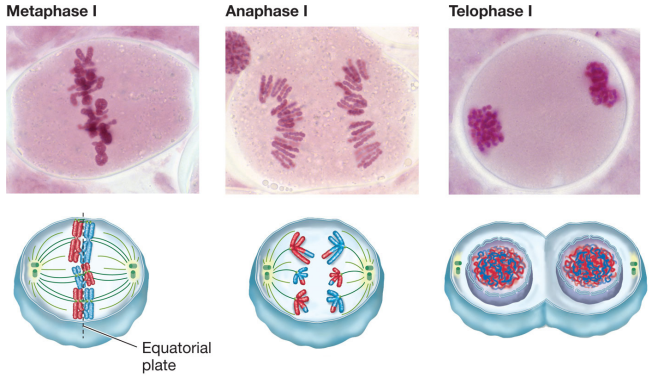
(consists of two nuclear divisions but DNA is replicated only once)



LIFE 10e, Figure 11.16 (Part 1)

Meiosis Generates Haploid Gametes

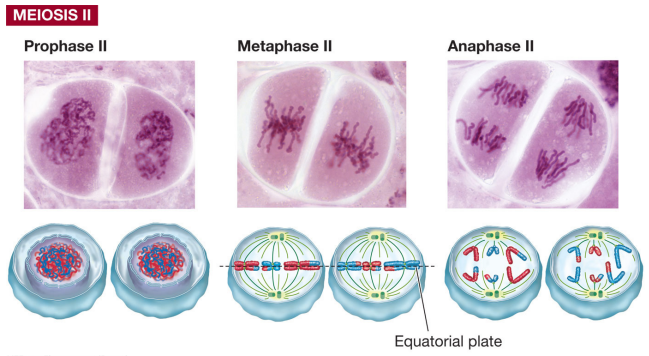
(consists of two nuclear divisions but DNA is replicated only once)



LIFE 10e, Figure 11.16 (Part 2)

Meiosis Generates Haploid Gametes

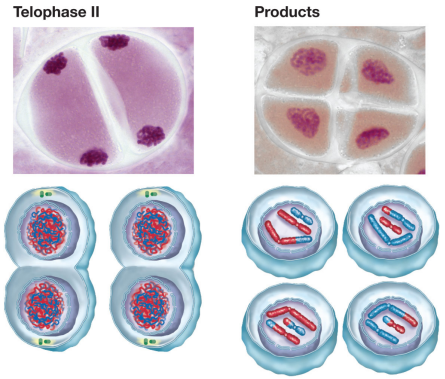
(consists of two nuclear divisions but DNA is replicated only once)



LIFE 10e, Figure 11.16 (Part 3)

Meiosis Generates Haploid Gametes

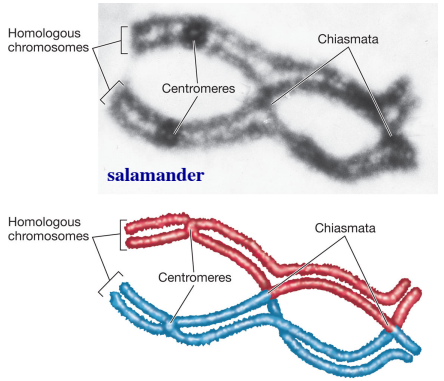
(consists of two nuclear divisions but DNA is replicated only once)



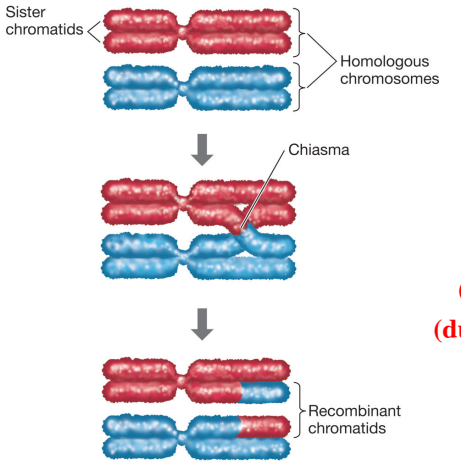
LIFE 10e, Figure 11.16 (Part 4)

Genetic Exchange between Chromatids

(crossing over diversifies genetic background in offspring)



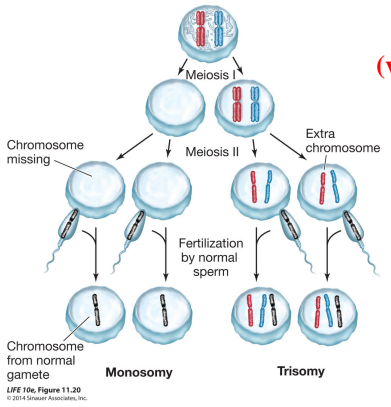
LIFE 10e, Figure 11.17



LIFE 10e, Figure 11.18

Genetic Exchange between Chromatids

(during prophase I)



LIFE 10e, Figure 11.20

Nondisjunction

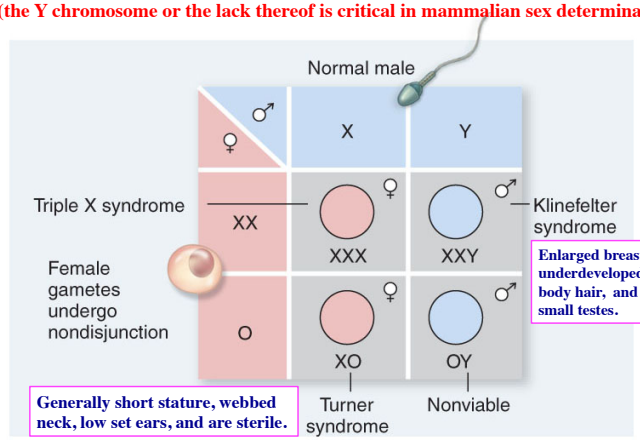
(when meiosis goes wrong)

- **Homologous chromosomes fail to separate during cell division**
- **Can occur during both divisions (meiosis I and II)**

Down's Syndrome
(Trisomy 21)

Nondisjunction of Sex Chromosomes

(the Y chromosome or the lack thereof is critical in mammalian sex determination)

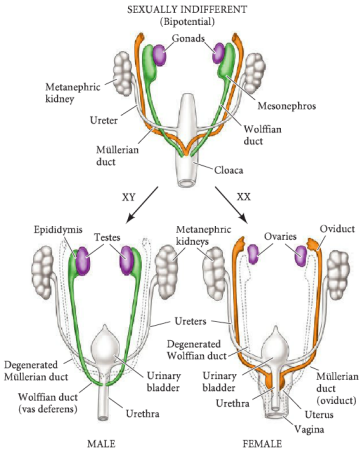


Enlarged breasts, underdeveloped body hair, and small testes.

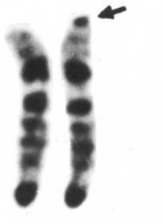
Generally short stature, webbed neck, low set ears, and are sterile.

Searching for the Sex Determining Factor on Y

(clues from infertility clinics)

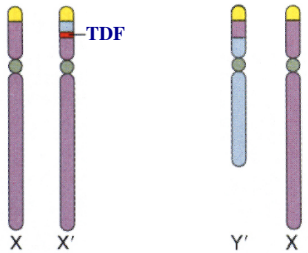


The gonads of early embryos are undifferentiated (bipotential)



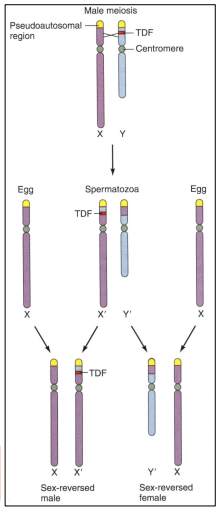
People with infertility problems had a little piece of Y chromosome stuck on the end of the X chromosome (sex-reversed males).

Illegitimate Recombination between X and Y Causes Sex Reversal



Sex-Reversed Male
(male but genetically XX)

Sex-Reversed Female
(female but genetically XY)



Result from rare crossover events between the X and Y chromosomes during meiosis in the male gametes

Mapping the Testis Determining Factor

(using DNA from both sex reversed males and females)

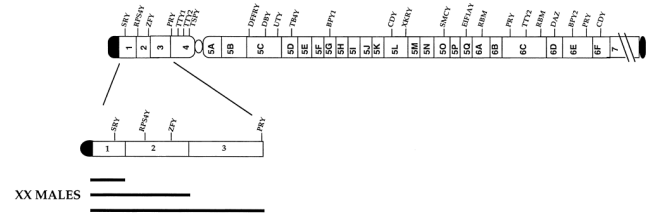
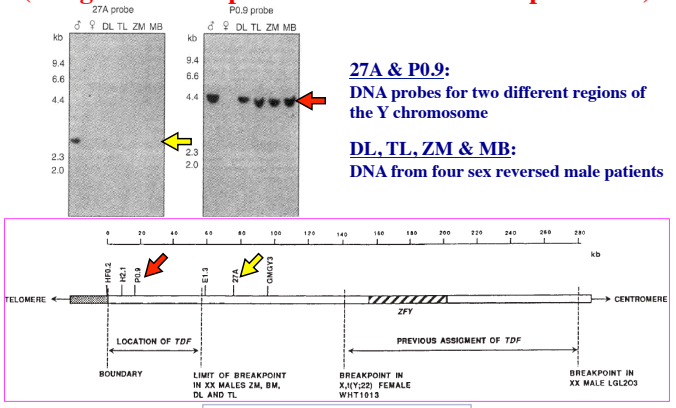


Figure 1 Schematic representation of the human Y chromosome indicating genes and gene families distributed throughout the long and short arms. Numbers indicate deletion intervals. Deletion intervals 1 to 3 on Yp define the three cases of (Y+) XX males.

McElreavey & Cortes. (2001) *Semin. Reprod. Med.* 19:133-139

Mapping the Testis Determining Factor
(using DNA from patients with the smallest piece of Y)

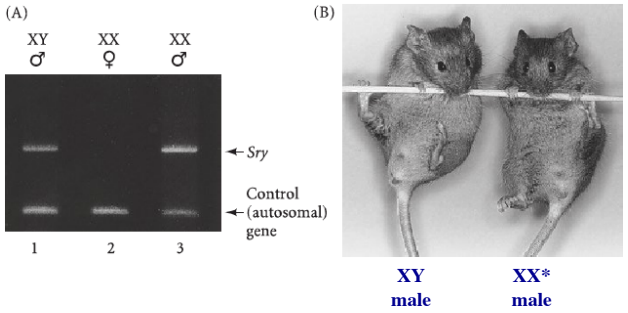


27A & P0.9:
DNA probes for two different regions of the Y chromosome

DL, TL, ZM & MB:
DNA from four sex reversed male patients

Palmer *et al*. (1989) *Nature* 342:937-939

The Transcription Factor SRY Is Sufficient to Induce Sex Reversal



Koopman *et al*. (1991) *Nature* 351:117-121

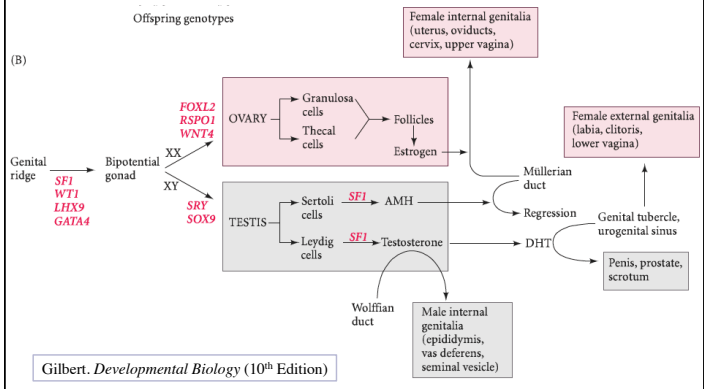
What would be the expected result of an *Sry* knockout in an XY genotype?

a. No effect
b. Trick question (no Sry gene to knock out)
c. Sex reversal to female

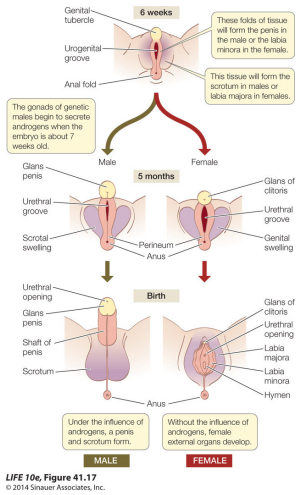
What would be the expected result of an *Sry* knockout in an XX genotype?

a. No effect
b. Trick question (no *Sry* gene to knockout)
c. Sex reversal to male

Sry Sets in Motion A Gene Cascade that Determines Male Sex



Gilbert. *Developmental Biology* (10th Edition)



LIFE 10e, Figure 41.17
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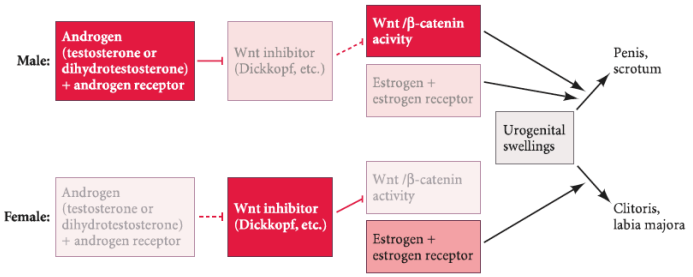
Sex Hormones Control Secondary Sexual Determination

Once the gonads form, they produce sex hormones to influence the development of the sexual phenotype outside the gonads, including male and female duct systems and the external genitalia.

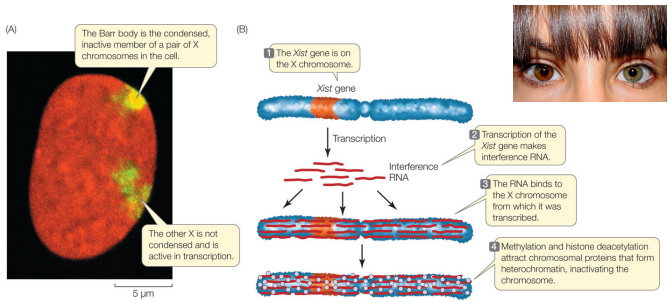
Sex Hormones Control Secondary Sexual Determination



The female program is default
(i.e. starts if androgen or the receptor absent)

Gilbert. *Developmental Biology* (10th Edition)

Dosage Compensation
(half of humans are likely genetic mosaics)



LIFE 10e, Figure 16.21
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Females heterozygous for genes on the X chromosome are genetic mosaics because one of the two Xs is randomly inactivated.
(Murray Barr & Ewart Bertram, 1949; Susumu Ohno, 1959; Mary Lyon, 1961, 1962)

Dosage Compensation
(a need to equalize the expression of X-lined genes)

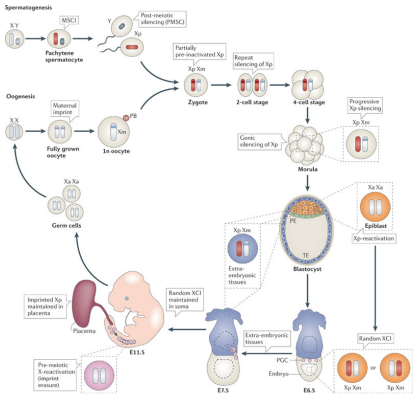
Dosage compensation ensures an equal expression of genes from the sex chromosomes even though females have two X chromosomes and males have only one.

Organisms use different mechanisms to equalize expression of X-linked genes:

- **Humans (mammals) inactivate one of two female X chromosomes.**
- **Flies double transcription from the single male X chromosome.**
- **Worms reduce transcription by half from each female X chromosome.**

There are parts of human (mammalian) Y chromosome, which are called "pseudoautosomal regions", contain nucleotide sequences (genes) that are homologous to those on the X, and such genes can escape inactivation.

The Cycle of X Chromosome Inactivation (XCI)



Two-cell to blastocyst stage:
- Selective inactivation of the paternal X chromosome (Xp) but not the maternal X (Xm)
- Inactivation maintained in extraembryonic tissues

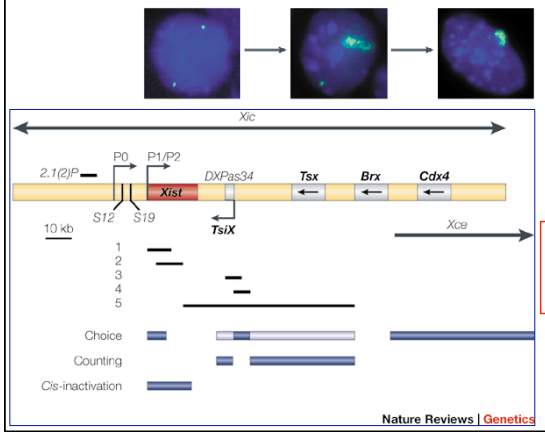
Inner cell mass (epiblast):
- Reactivation of Xp
- Random inactivation of either Xm or Xp
- Inactivation maintained in somatic cells

Primordial germ cells (PGCs)
- Reactivation of inactivated X
- Maintained in germ cells

Lee. (2011) *Annu. Rev. Mol. Cell Biol.* 12:815-826

How Does Random X Inactivation Occur?

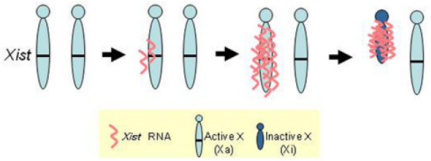
(regulated by a region on X called "X inactivation center" or Xic)



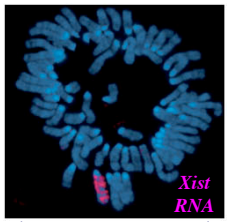
- Counting
- Choice
- Inactivation

How Does Random X Inactivation Occur?

(*X-inactive specific transcript* or *Xist* is an essential regulator)



http://www.nig.ac.jp/english/highlight/685/689.html



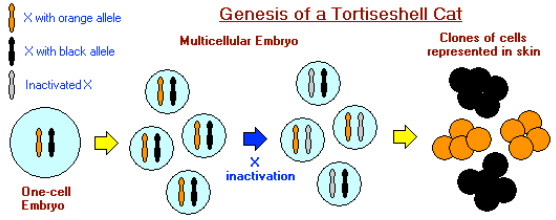
Ng *et al.* (2007) *EMBO Rep.* 8:34-39

- *Xist* is a long non-coding RNA (lncRNA) transcribed from an X-linked gene that is both necessary and sufficient to inactivate one X chromosome.
- *Xist* is initially transcribed from both X chromosomes but binds to only one X chromosome, making it inactive for transcription of other genes.
- Once the decision is made to inactivate one of the X chromosomes, it continues to produce *Xist* while the active X chromosome does not.

http://www.nature.com/scitable/topicpage/sex-chromosomes-in-mammals-x-inactivation-522

Example of Genetic Mosaics

(as a result of XCI)



Female

Male

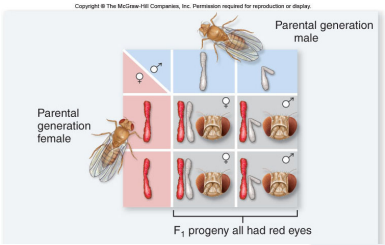
X

?

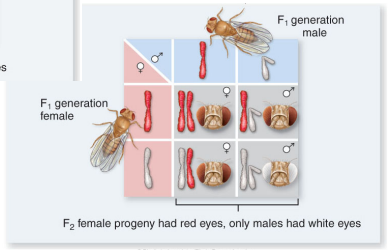
- Can this cross result in female tortoiseshell kittens?
- Can this cross result in male tortoiseshell kittens?

Can you clone your tortoiseshell kitten using iPS cells and expect:
(a) the same genetic makeup?
(b) the same color pattern?

Sex-Linked Segregation

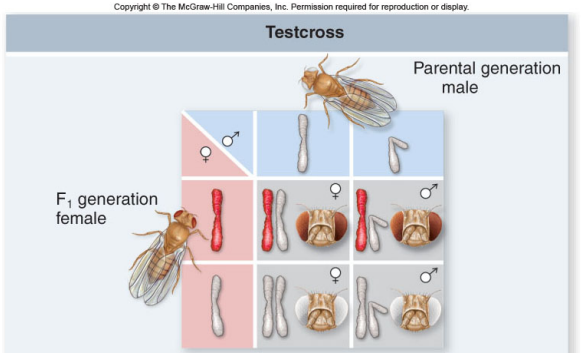


Why no F1 females with white eyes?

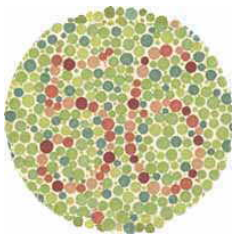


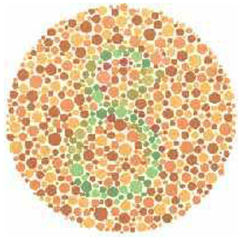
Why no F2 females with white eyes?

Sex-Linked Segregation



Sex-Linked Traits
(controlled by genes on the X chromosome)





Color Blindness
(can result from a defect in one of three genes found on X chromosome)

Sex-Linked Traits
(controlled by genes on the X chromosome)

Will the children be colorblind if the father is colorblind and the mother is not a carrier?

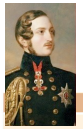
Father (normal vision) X^CY

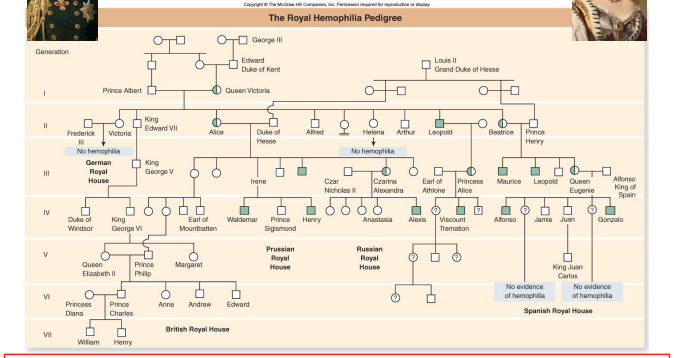
Mother (carrier) X^CX^c

	X^C	Y
X^C	X^CX^C Daughter (normal vision)	X^CY Son (normal vision)
X^c	X^CX^c Daughter (carrier)	X^cY Son (colorblind)

Inheritance of a colorblindness allele

The Lineage of Prince Albert & Queen Victoria





Hemophilia patients have deficiencies in expression of coagulation factors (genes found on X chromosome; cuts can be fatal due to unstoppable bleeding)

Key Concepts from This Lecture

1. **Meiosis results in haploid gametes containing randomly assorted and rearranged parental alleles that diversify the genetic makeup of the next generation.**
2. **Sex is genetically determined in mammals, and the female program is default.**
3. **The Y chromosome contains the gene for the transcription factor SRY which allows for formation of the testes.**
4. **Sex hormones control secondary sexual characteristics and reproductive functions.**
5. **Dosage compensation is the process by which the imbalance between two X chromosomes in females and one X chromosome in males is adjusted; this occurs by the inactivation of one X chromosome in females during embryogenesis in mammals.**