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CELS191 LECTURE MATERIAL

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CELS191 2025

Molecular Biology & Genetics

Lecture 17

X-inactivation

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Lecture 17 Objectives

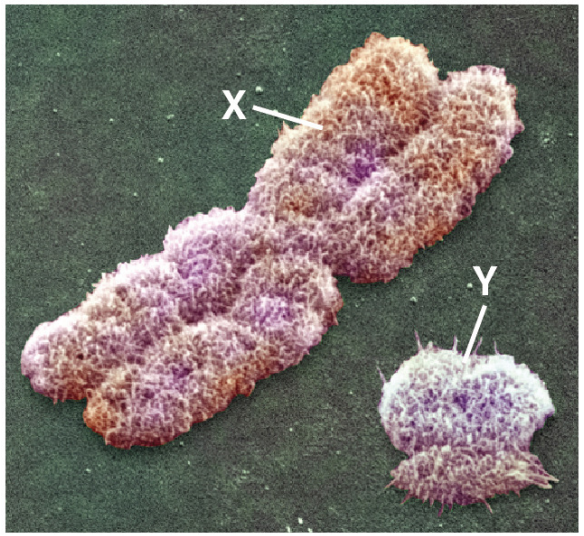
After you have revised this lecture you should be able to:

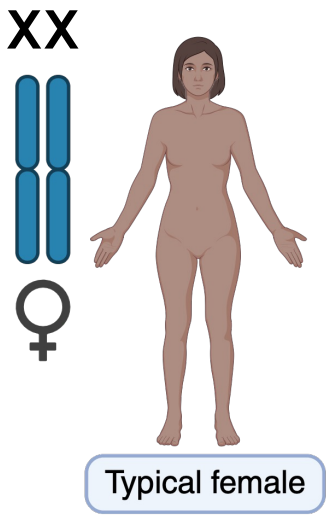
- Outline the Lyon Hypothesis and its connection to Barr bodies.
- Outline the concept & consequences of X-inactivation.

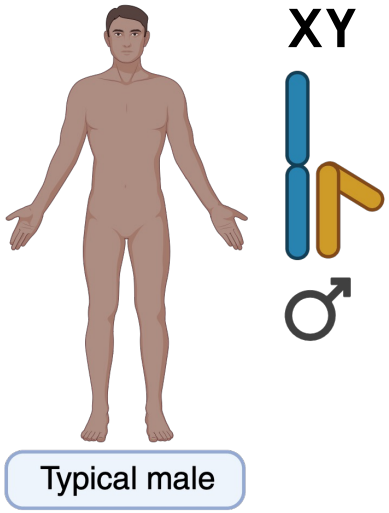
Links to Lecture 20
Textbook Figure 15.5
Image on Right: CELS191 Supplied via Biorender

Human Sex Determination

- Genes on the sex chromosomes (X & Y) determine the sex of the individual.
- The Y chromosome is smaller and has fewer genes than the X.







Sex Chromosomes

- Autosomes (chromosomes 1-22) are present in equal numbers in both male and female cells.
- In contrast, the sex chromosomes (and genes on these chromosomes) are present in unequal numbers in males and females.
- Why do we not see differences in genetic dosage between males and females for all X-linked genes?

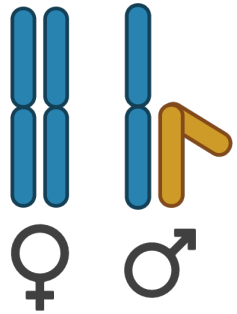


Image: Weaver & Hedrick 1992. Genetics (p100), Wm C Brown Publishers

X Inactivation: Lyon Hypothesis

Mary Lyon 1925–2014

- Dosage compensation through X-inactivation ("lyonization").
- One X chromosome in female (XX) cells is (largely) inactivated.
- Early in development, a random X is inactivated.
- Daughter cells maintain this inactivation.
- Females are a mosaic of cells with inactive paternal and maternal X chromosomes.
- Balances the doses of X chromosome gene expression in females and males.

Image: CELS191 Supplied via Biorender

X Inactivation: Random Patterns

This image shows the random nature of X-inactivation in placental mammals

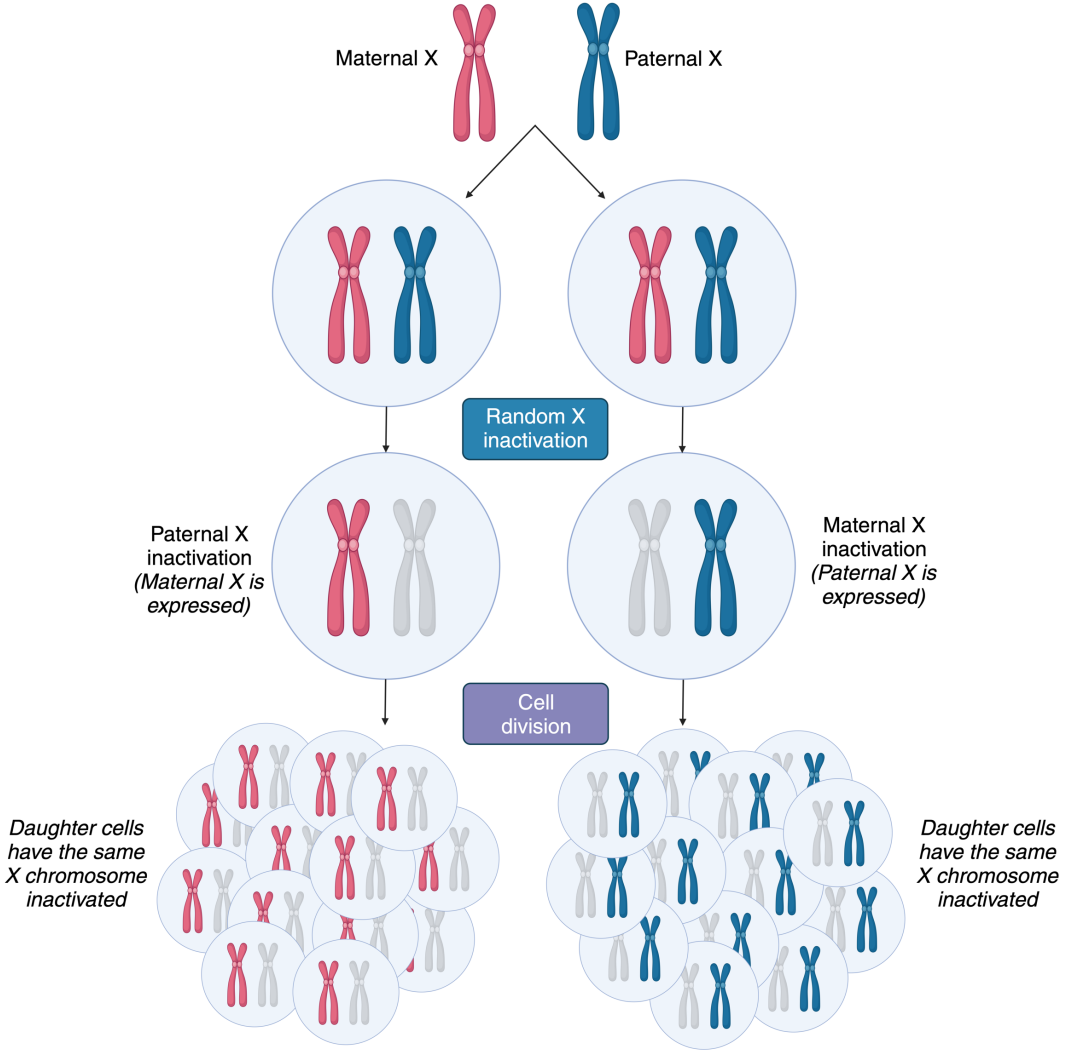
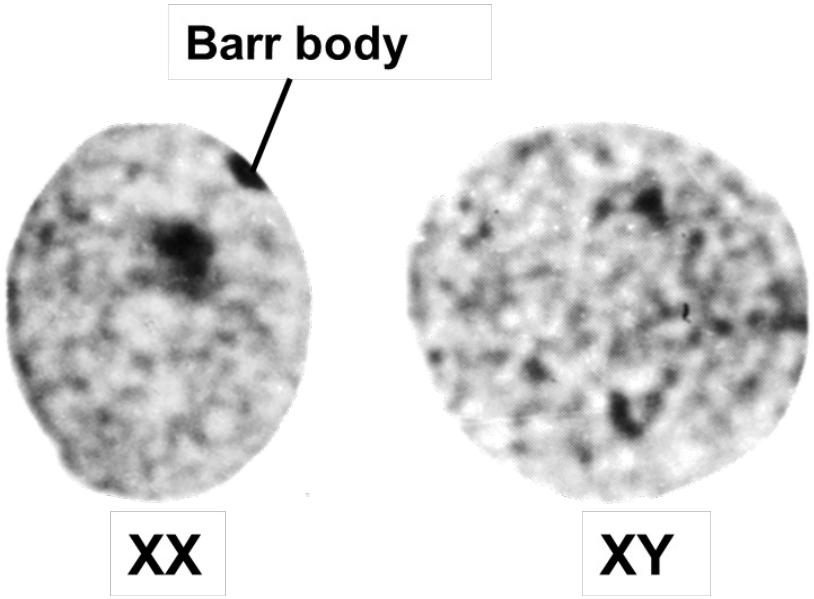


Image: Weaver & Hedrick 1992. Genetics (p100), Wm C Brown Publishers

X Inactivation: Barr Bodies

- Inactivated X condenses into a Barr body.
- A Barr body is a highly condensed structure that lies against the nuclear envelope in cells of females, but not in males.
- Most genes on this inactivated chromosome are not expressed.

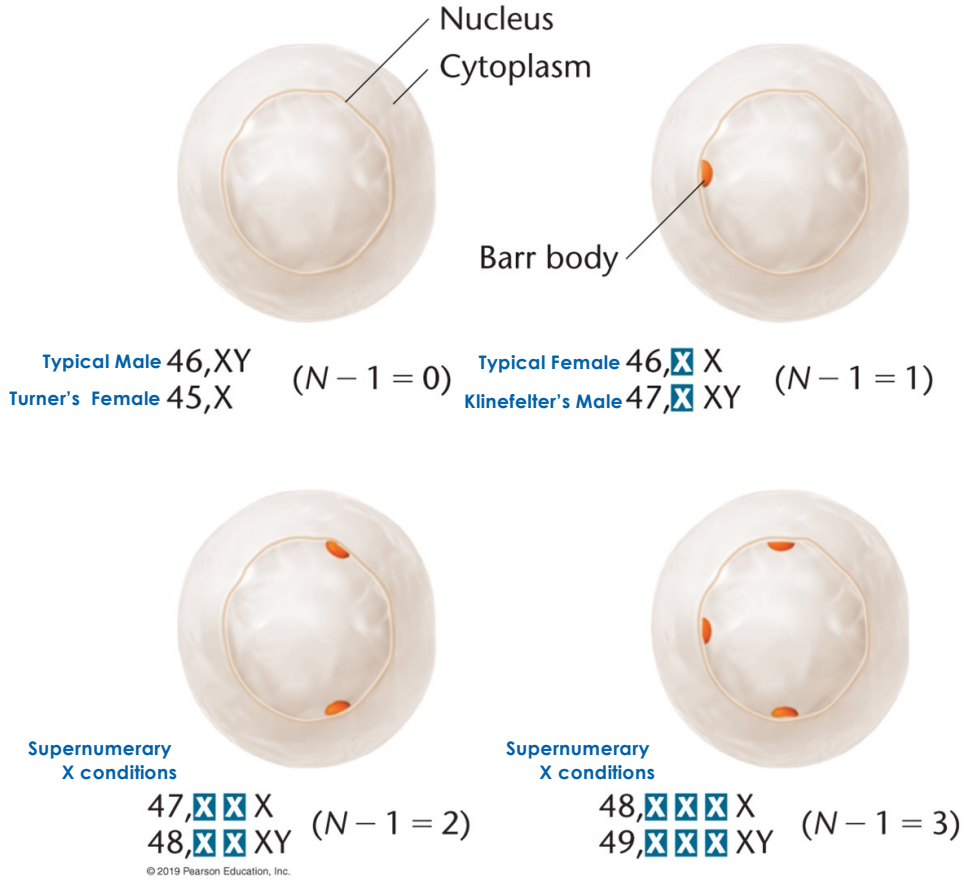


Modified Figure 5.5: Concepts of Genetics 12ed, Klug et al.

X Inactivation: Lyon Hypothesis & Barr Bodies

- Evidence for this hypothesis comes from the study of sex aneuploid conditions.
- Regardless of how many X chromosomes are possessed, all but one of them appear to be inactivated as Barr bodies.

Image shows the occurrence of Barr bodies in various human karyotypes where all X chromosomes except one (N-1) are inactivated

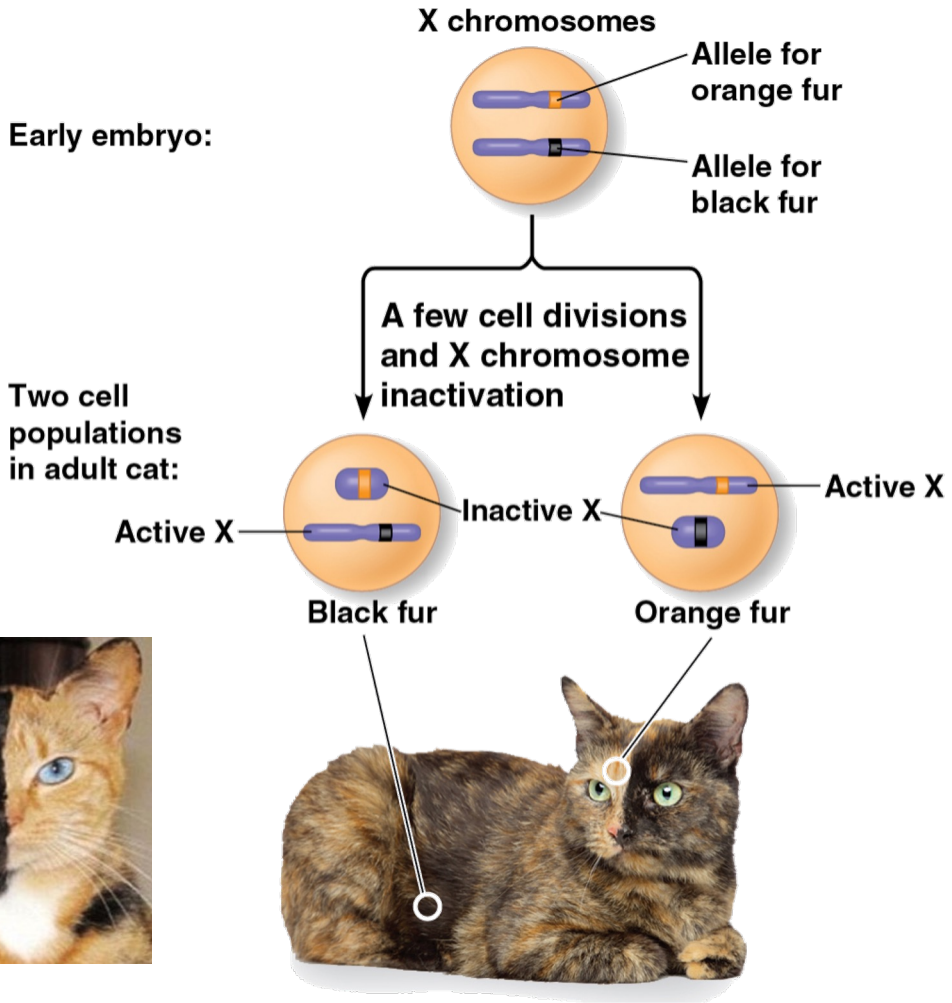


Some Common Human Aneuploids

Syndrome	Chromosomes	Sex	Incidence
Klinefelter	XXY	M	1/1000
Turner	XO	F	1/5000
supernumerary Y	XYY	M	1/1000
supernumerary X	XXX	F	1/1000
other	XXXX	F	rare
other	XXXY	M	rare
other	XXYY	M	rare

X Inactivation: Calico cat

- X-inactivation occurs in all cells early in embryonic development.
- Random inactivation of X chromosomes leads to mosaic patterning.
- Once inactivation occurs, all descendant cells will have the same X inactivated.

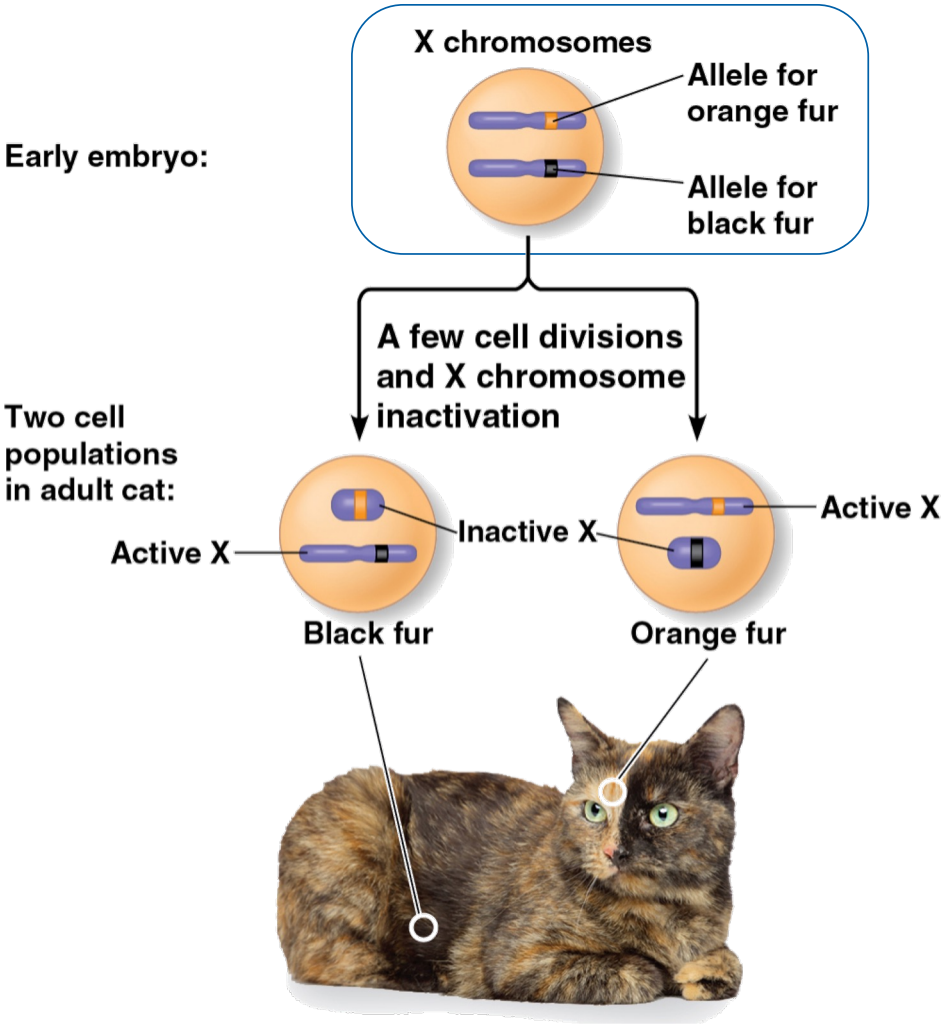


X Inactivation: Calico cat

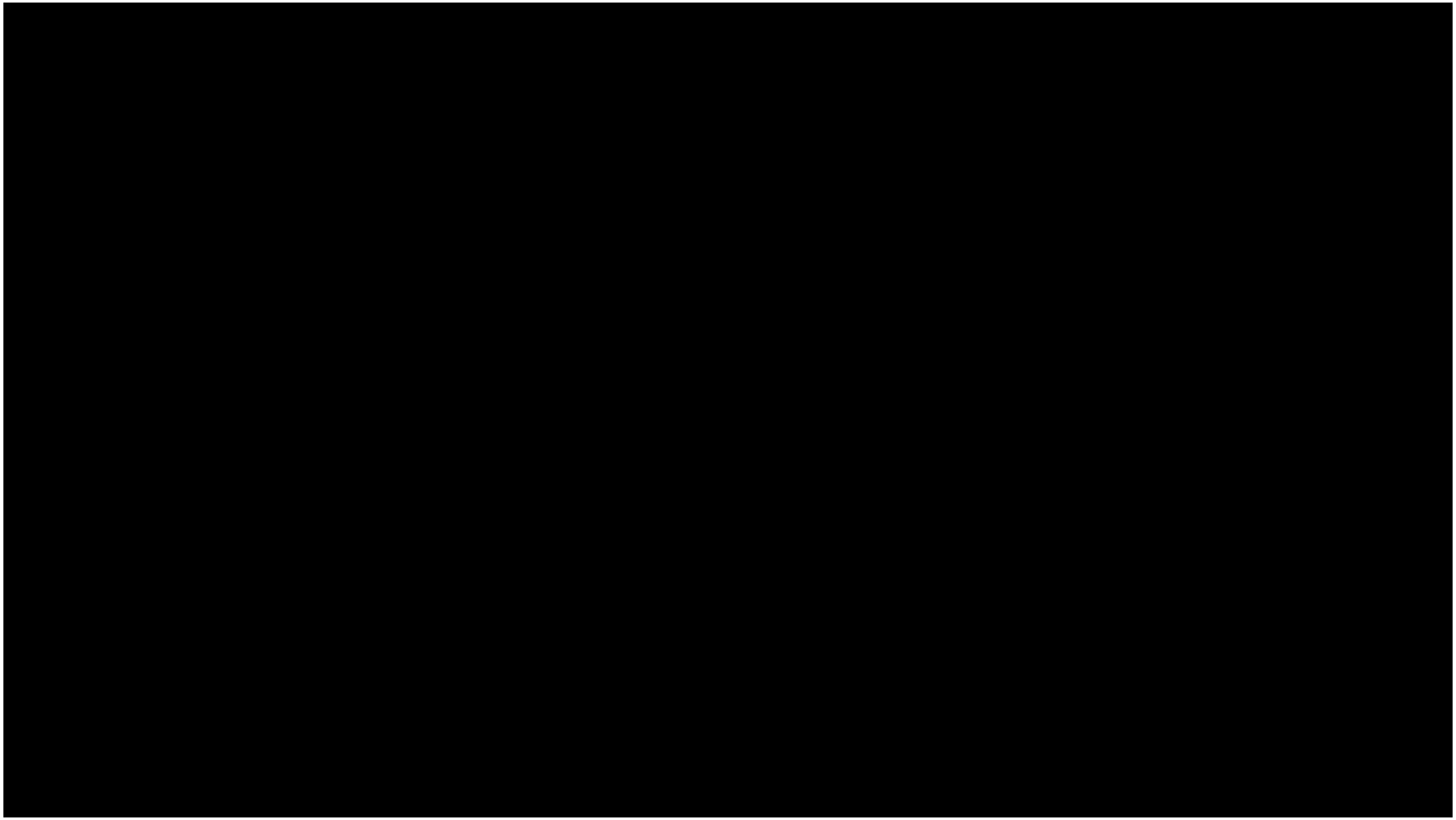
- X-inactivation is visible in calico cats as they carry two different alleles (versions) of the fur colour gene and are therefore heterozygous for that particular allele.

More on alleles in Lecture 18

- Calico cats are therefore all female. Male cats either have black or orange fur.



Core Slide



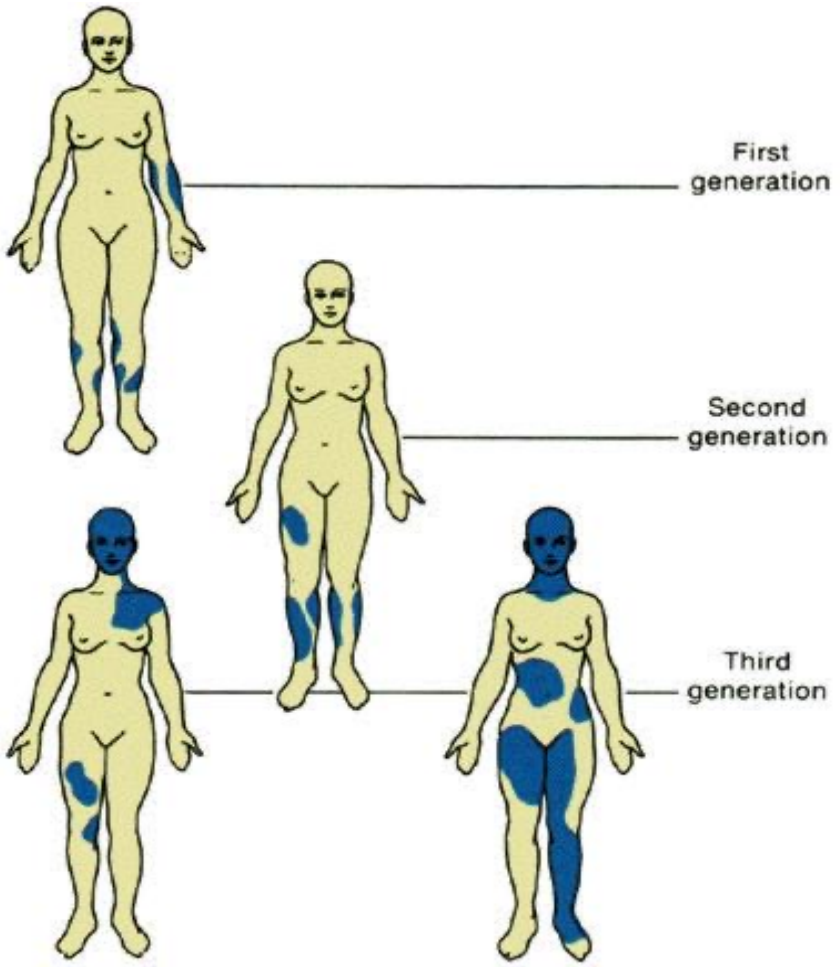
YouTube Video: Why women are stripey.

Image: Griffiths et al 1993. An Introduction to Genetic Analysis (p221), Freeman

X Inactivation:
Human example

- Anhidrotic ectodermal dysplasia (absence of sweat glands) is a human example where we can see the effects of X-inactivation in heterozygous females.

- Females exhibit mosaic patterning. The blue patches here represent affected cells with no sweat glands.



Core Slide

- Many genetic diseases map to the X chromosome.
- Often these diseases are more common in males.
- Most do not show a mosaic effect in heterozygous females because the gene products can move around the body.
- For example, clotting factor protein involved in Haemophilia is present in blood and able to move around body. *(Revisit in Lecture 20)*

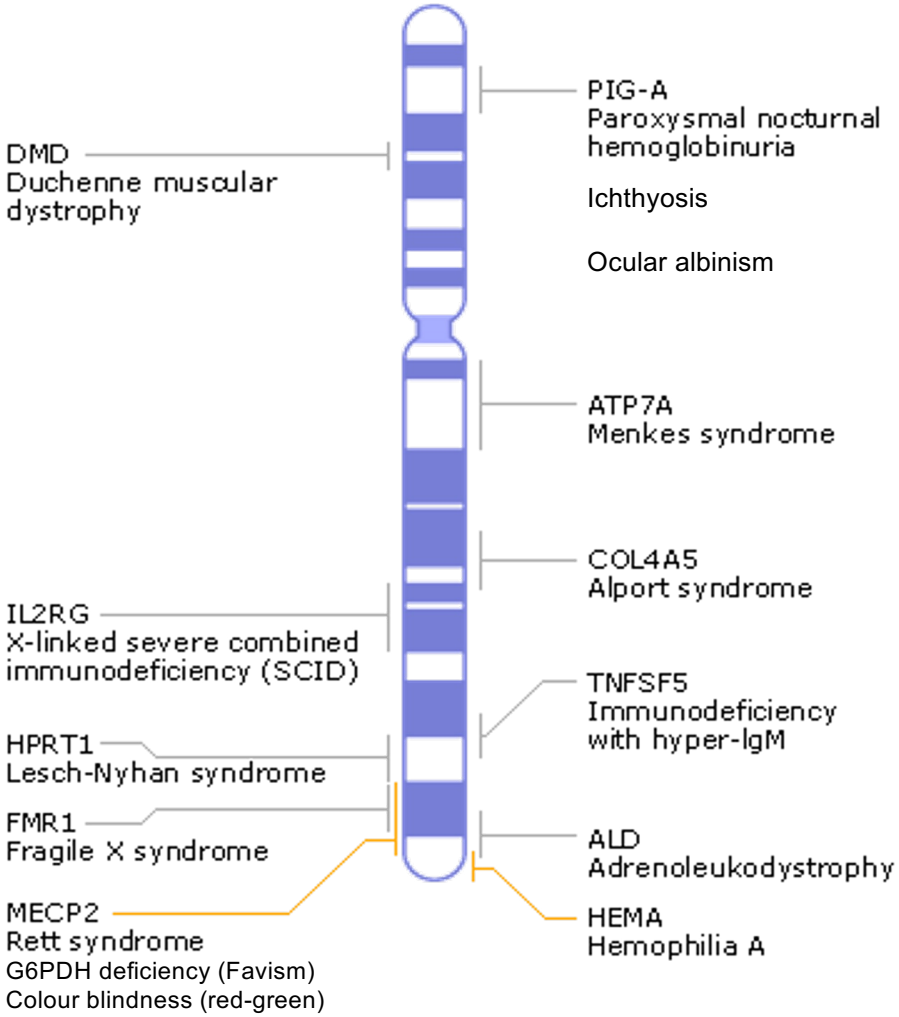


Image: National Library of Medicine, USA

Gene Dosage Compensation: Alternative Strategies

Wallaby

In marsupials, including the wallaby, the paternal X chromosome is selectively inactivated.

Drosophila

In *Drosophila* males the expression of genes on the X chromosome are up-regulated (increased).

Practice Question

An XXY human will:

(A) exhibit Turner syndrome.

(B) have a Barr body in each nucleus.

(C) be an abnormal female.

(D) be a monosomic.

Practice Question

A female is colour blind in one eye only. Her father is colour blind in both eyes. The cause of the female's condition could be:

(A) X-inactivation in a heterozygote.

(B) a somatic mutation.

(C) damage to one eye.

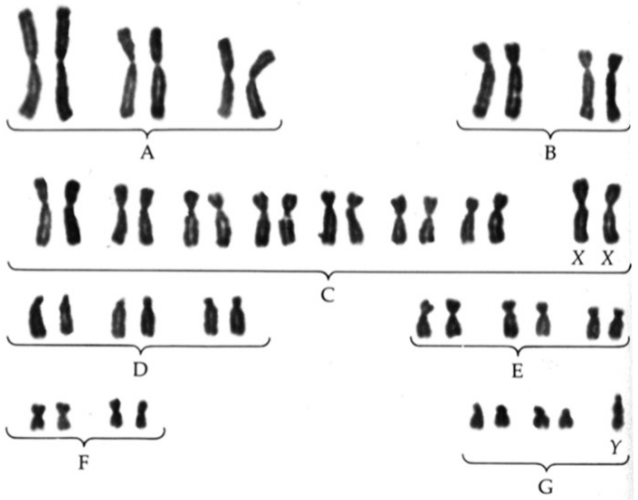
(D) any of the above.

Lecture 17 Summary

- Sex chromosomes are present in unequal numbers in humans. Females (XX) have twice as many X chromosomes than males (XY), and therefore twice as many copies of X-linked genes.
- X-inactivation is a mechanism that compensates for differences in genetic dosage of X-linked genes in females. Early in embryonic development one X chromosome is inactivated in each cell.
- Inactivated X chromosomes are called Barr bodies and most of the genes on this chromosome are not expressed.
- As a result of X-inactivation, the cells of females and males have the same effective dose (one active copy) of almost all X-linked genes.

Objective-Based Questions

- The karyotype on the right is from a person with _____.
  - How many Barr bodies would you find in the nuclei of cells from this individual?
  - Is this individual MALE or FEMALE?



- Why does X-inactivation occur in mammals?
- What is a Barr Body?
- Random inactivation of X chromosomes in placental mammals can led to mosaic patterning. Describe an example of mosaic patterning. Outline why most genetic diseases do NOT show a mosaic effect in carrier females?

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