Changes in chromosome number

Reading: Hartwell pp516-525
Problem set at end

Changes in whole sets of chromosomes-changes in ploidy

Changes in # of individual chromosomes-aneuploidy

Some definitions

Ploidy is the # of sets of chromosomes

x is the number of chromosomes in a set.

Haploid # (n) is the number of chromosomes in a gamete.

For diploids, x = n

But in polyploids,
where the ploidy is > 2x, n > x

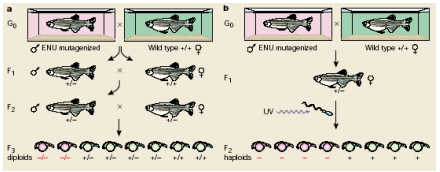
e.g., wheat is a hexaploid or 6x, where x = 7 and n = 21

Monoploids

Male bees and wasps are naturally occuring monoploids, which develop by parthenogenesis.

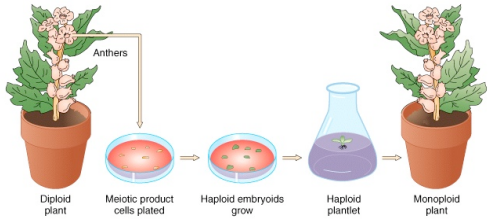
Can also generate experimentally.
e.g., zebrafish, many plants.

Zebrafish geneticists take advantage of monoploids in genetic screens.

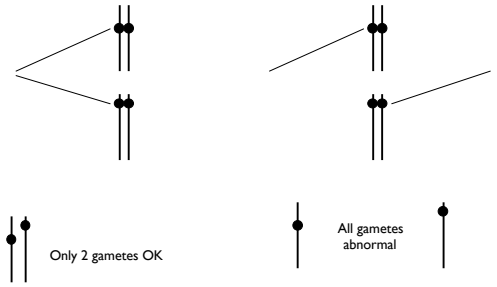


Need to be studying a phenotype that you can see during embryogenesis before monoploids die.

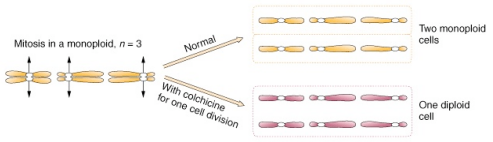
In plants, can generate monoploids by culturing meiotic products.



BUT sterile. In meiosis no pairing homologs.

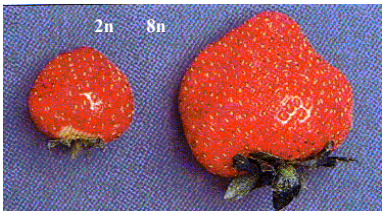


With increasing x, # of functional gametes decreases

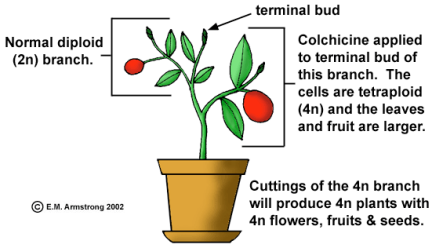


Tetraploids (4x), hexaploids (6x), octaploids (8x), ….

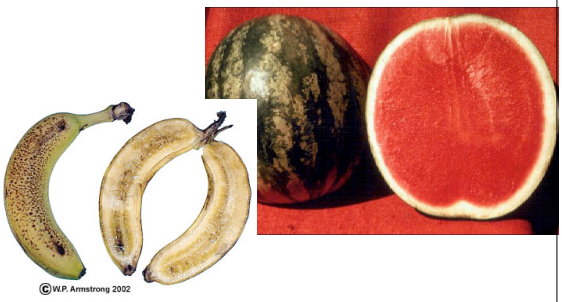
Increasing ploidy increasing size



Can artificially use colchicine to increase ploidy.



Triploids are sterile.



Bananas, seedless watermelons are seedless because they are triploid

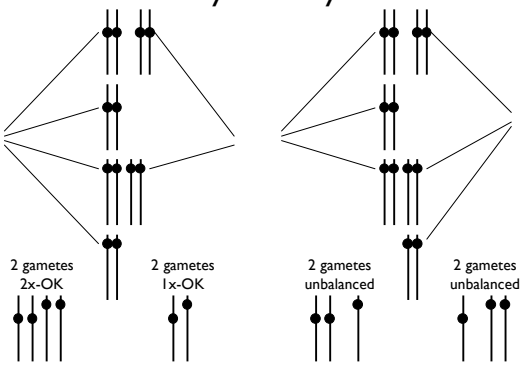
Generated by crossing diploid and tetraploid

2x x 4x

↓

3x

But why are they sterile?

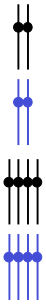


Up until now we have been dealing with autopolyploids, which contain multiple sets of chromosomes from the same species. Allopolyploids are produced from sets of chromosomes of closely related species.

Closely related chromosomes from different species are not homolgous, but are referred to as homeologous.

Homeologous chromosomes do not pair during meiosis and this can lead to problems.

If cross two related species, ok until meiosis.



Homeologous chromosomes don't pair, which leads to sterility.

But by doubling the chromosomes, generate an allopolyploid (amphidiploid) that is fertile

One successful allopolyploid is Triticale

Triticum (wheat)

6n =42

Gametes: 3n = 21

Secale (Rye)

2n =14

gametes: n = 7

Sterile hybrid

4n = 28

Chromosome doubling with colchicine.

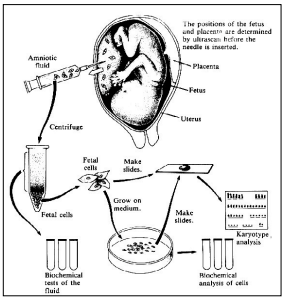
Fertile 'Triticale'

8n =56

Triticale combines the high protein content of wheat with the high lysine levels and ability to adapt to marginal environments of rye.

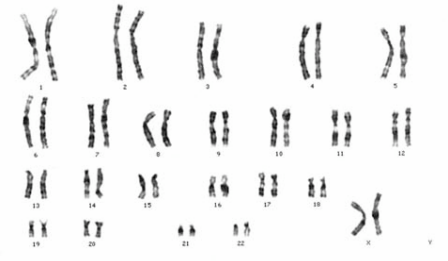
Aneuploidy

Amniocentesis

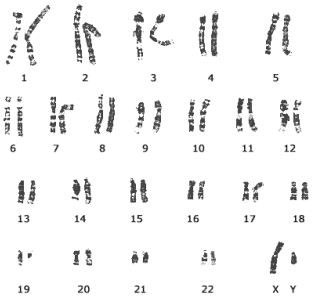


Chromosomes can be identified by their size and banding pattern...

Normal female, XX



Normal male, XY

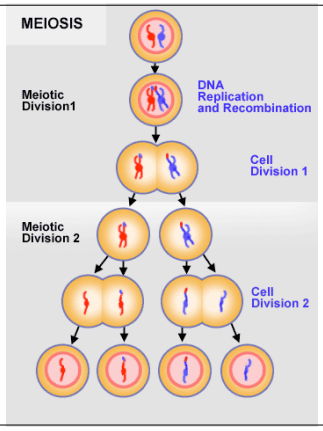


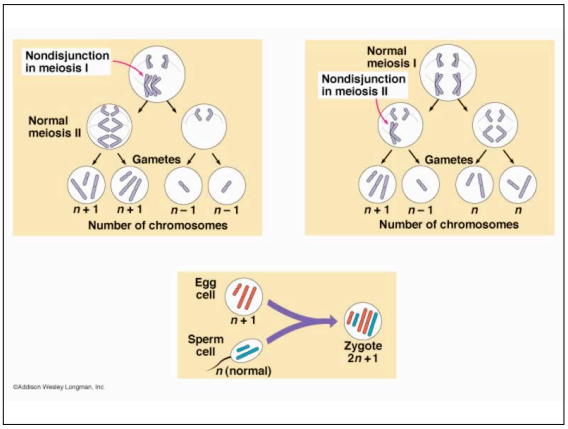
Meiosis results in gametes with a single set of chromosomes!

Nondisjunction in meiosis I or II results in gametes with an extra or missing chromosome.

When these gametes fuse, the fusion results in zygotes with an extra or missing chromosome, a situation termed aneuploidy!

What are the consequences of aneuploidy in humans?



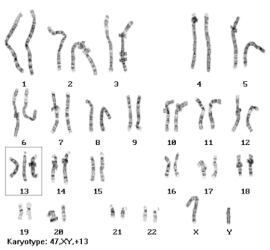


Autosomes first!

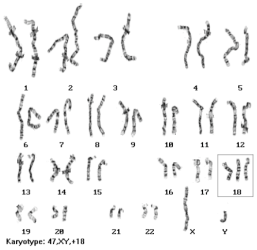
All monosomic (43 autosomes; missing an autosome) spontaneously abort (miscarriage).

Almost all trisomic (45 autosomes; an extra autosome) fetuses spontaneously abort!
There are exceptions.

Trisomy 13; Patau Syndrome

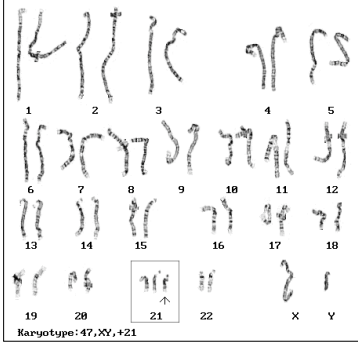


Trisomy 18; Edwards Syndrome

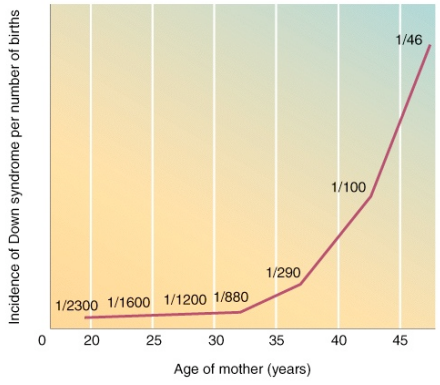


Many fetuses spontaneously abort
Those that make it die in first year

Trisomy 21; Down Syndrome



Can survive to age 50
Mental retardation



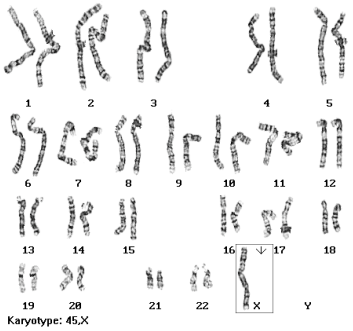
But, why do aneuploid fetuses die?

1000s of genes are over or under expressed!
Resulting in genetic imbalance.

(the consequences of genetic imbalance are different in plants and animals.)

But the rules are different for the sex chromosomes!

Turner syndrome, XO

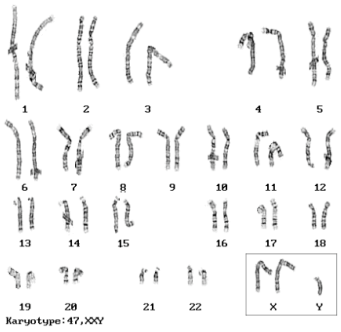


Female
Short, wide-chested
Underdeveloped breasts
Rudimentary ovaries
Sterile
Normal intelligence

ALL autosomal monosomics die, BUT XO individuals often survive and can be relatively normal!!!

There is something different about the autosomes and sex chromosomes.

Klinefelter syndrome, XXY

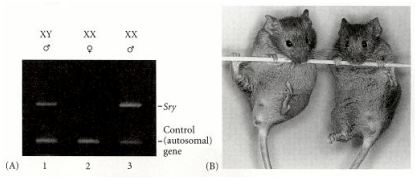


Male
Phenotype of syndrome not apparent until puberty
Breast development
Low fertility
Subnormal intelligence

The Y chromosome is necessary and sufficient for male development!

But what on Y is important for male development?

SRY is both necessary and sufficient for male development



The mouse on the left is XY and the mouse on the right is XX and has an SRY transgene-- both are phenotypic males

Yet another difference between sex chromosomes and autosomes. Autosomal trisomies die, but XXY, XYY and XXX trisomies survive.

BUT WHY?

One of the first clues came from Liane Russell

Mice heterozygous for a recessive coat color mutation (c) on an autosome had wild-type (dark) fur. (homozygotes have white fur)

X chromosomes autosome

But a strain carrying a reciprocal translocation (more on these later) between X and the autosome was variegated, having patches of wild-type and mutant fur.

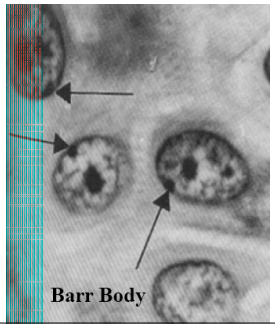
In other words, having the wild-type coat color gene fused to X resulted in a mutant phenotype in some tissues.

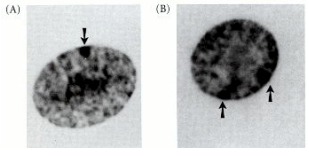
Additional results

X-linked mutations sometimes result in variegated phenotype in females.

Females that are heterozygous for a mutant version of the glucose-6-phosphate dehydrogenase gene that lacks activity and produces an electrophoretic variant were analyzed. When tissue from these individuals was analyzed, it possessed activity and contained both isoforms. If isolated cells were cultured and then examined, the clones either had G-6-PD activity or lacked it, expressing only a single isoform.

Murray Barr noted that the nuclei of female but not male cats contained a darkly stained element. This is now known as a Barr body.





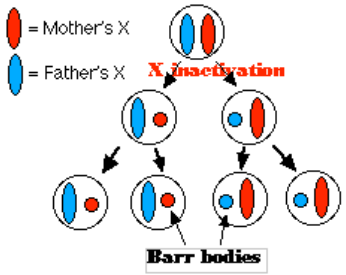
XX XXX

One Barr body Two Barr bodies

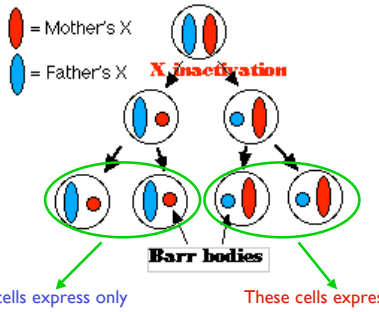
Karyotype	# Barr bodies
XY	0
XO	0
XX	1
XXX	2

In 1961 Mary Lyon proposed that in mammals, the dose of gene products was equalized between males and females by inactivating one of the X chromosomes in females. The inactive X is the Barr body. This mechanism of dosage compensation is often referred to as the Lyon hypothesis.

In mammalian females, early in embryonic development <u>each cell</u> inactivates one X chromosome



Whoa!!! All mammalian females are mosaic!!!

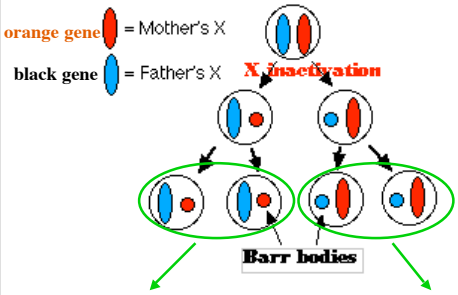


These cells express only paternal X chromosome genes.

These cells express only maternal X chromosome genes.

X inactivation results in black and orange patches on Calico cats.

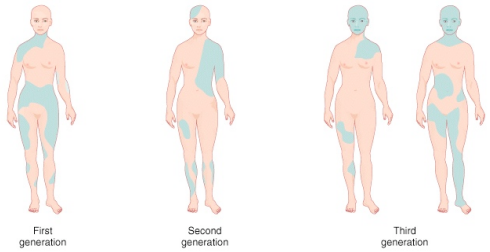
Female Calico cats have black and orange alleles of an X-linked gene.



These cells express only paternal black gene.

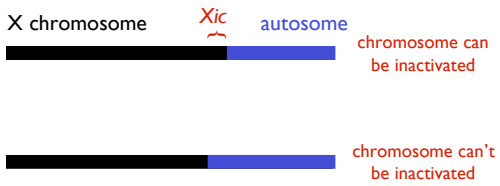
These cells express only maternal orange gene.

Certain X-linked inherited traits result in mosaicism in females.
e.g., anhidrotic ectodermal dysplasia



But how is only one X inactivated?

Studies of X:autosome translocations defined a specific site on X, known as the X-inactivation center (*Xic*), that was required for inactivation.



The *Xic* contains a gene that encodes and RNA with no protein-coding capacity (*Xist)*

- *Xist* RNA coats the inactive X
- A chromosome containing a deletion of part of *Xist* results in a chromosome that is always active.
- The expresssion of an antisense RNA of *Xist* known as *Tsix* is correlated with the lack of *Xist* expression.
- *Xist* is necessary for X inactivation and is regulated by *Tsix*.

But no one understands how chromosomes are counted.

One model proposes that a limiting factor or factors encoded by autosomes binds to the *Xic* region to regulate *Xist* expression. There is enough to inhibit *Xist* only a single X chromosome.

Garriga Problem Set 1

In Hartwell, do problems 14.29 and 14.30.

1. You cross a male mouse with light colored fur, which is caused by a recessive mutation in an X-linked gene, to a female mouse with dark fur that is homozygous for the wild-type fur gene and heterozygous for a mutation that removes the function of the Xist gene.

What are the phenotypes and genotypes of the female progeny?

2. You have a triploid watermelon, which is sterile.

a) How was the triploid watermelon generated?

b) You find a rare seed in your triploid watermelon. You plant the seed and find that it grows into a fertile watermelon (one with seeds). What might have happened?

c) What do you think is the ploidy of the fertile watermelon?

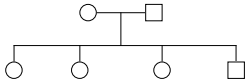
3. A woman has a daughter with Turners syndrome (X0). The father has hemophilia because of a defect in an X-linked clotting factor gene.

Explain how the Turners daughter could have been produced if she has hemophilia. Be specific.

Explain how the Turners daughter could have been produced if she does not have hemophilia. Be specific.

4. (a tough one) You want to study dosage compensation in kangaroos. Marsupial sex is determined in the same way as in mammals, XX leads to female development and XY leads to male development. Female marsupials have Barr bodies, but males do not. You begin by cloning several genes, and you search for genes that contain polymorphisms in the kangaroo population that can be detected in both both RNA and genomic DNA. You find RNA / DNA polymorphisms for two of the genes located on the X chromosome (X1 and X2), and one of the genes located on an autosome (A1). a indicates one allele and b indicates the other allele. You head to the local zoo and analyze the DNA and RNA extracted from blood samples of a known kangaroo pedigree.

DNA	X1a/X1b	X1b/Y
	X2a/X2b	X2b/Y
	A1a/A1a	A1b/A1b
RNA	X1a	X1b
	X2a	X2b
	A1a	A1b



DNA	X1a/X1b	X1a/X1b	X1b/X1b	X1b/Y
	X2a/X2b	X2b/X2b	X2a/X2b	X2b/Y
	A1a/A1b	A1a/A1b	A1a/A1b	A1a/A1b
RNA	X1a	X1a	X1b	X1b
	X2a	X2b	X2a	X2b
	A1a and A1b	A1a and A1b	A1a and A1b	A1a and A1b

From the results shown above what would you conclude about kangaroo dosage compensation?