Lecture 6

Until now our analysis of genes has focused on gene function as determined by phenotype differences brought about by different alleles or by a direct test of function – the complementation test.

For the next five lectures our analysis will be concerned with the tests of gene position starting with the position of genes on chromosomes and finally mapping point mutations at the resolution of single nucleotide pairs.

We've taken it for granted that genes reside on chromosomes, but how do we know this? Let's review the properties of gene segregation.

Consider a cross between individuals that differ in two different traits:

A/A, B/B × a/a, b/b

The gametes from one parent will be **A**, **B** and from the other parent **a, b**

These gametes will then give an F_1 generation of all **A/a, B/b**

Crosses between F_1 individuals will give an F_2 generation with a 9 : 3 : 3 : 1 phenotypic ratio.

The best way to look at segregation is by a **test cross** of the F_1 heterozygote to a homozygous recessive individual. This way the allele inherited from the heterozygous partent can be ascertained directly from the phenotype of the offspring.

A/a, B/b × a/a, b/b

The possible gamete genotypes from the F_1 will be:

A, B	**a, b**	**A, b**	**a, B**
(parental)	(parental)	(recombianant)	(recombinant)

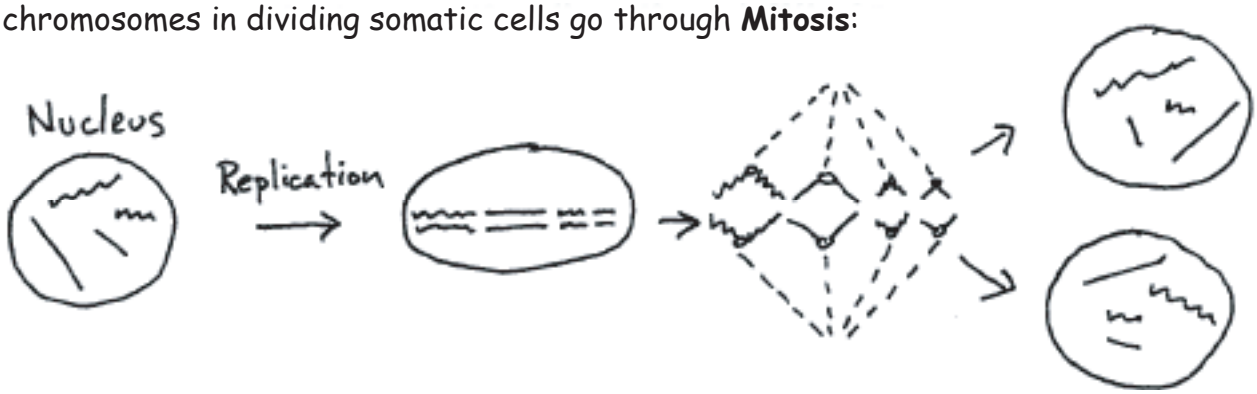
The corresponding genotypes of the offspring in the testcross will be:

A/a, B/b **a/a, b/b** **A/a, b/b** **a/a, B/b**

Note that each genotype will have a unique and identifiable phenotype

Each offspring receives either one or the other parental allele: **gene segregation**.
For most gene pairs each of the four classes of gametes appears at the same frequency – indicating that the two genes segregate independently: **independent assortment**.
At the turn of the century microscopes allowed people to watch chromosomes in the nuclei of dividing cells. (Human cells, for example, contain 46 chromosomes.)

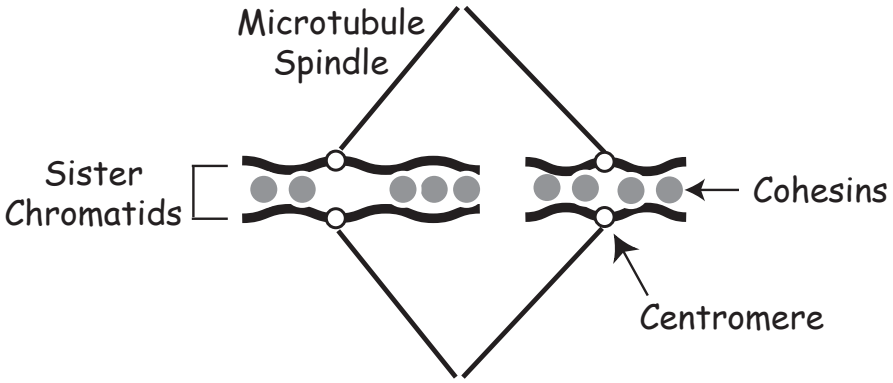
The chromosomes in dividing somatic cells go through **Mitosis**:



The net result of mitosis is to distribute a replica of each chromosome into the two daughter cells.

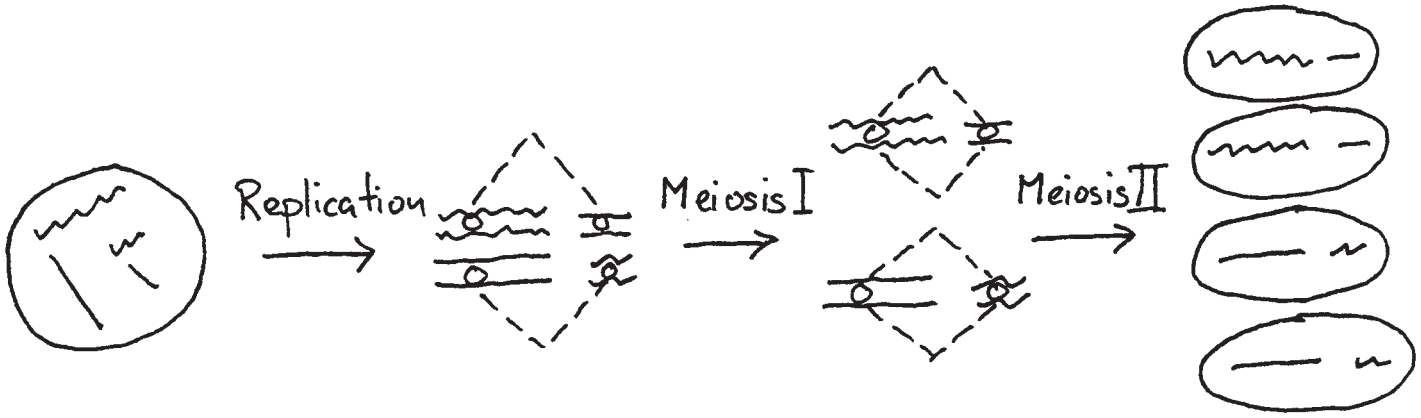
The stages of mitosis are as follows:

i) **Interphase**; DNA replication
ii) **Prophase**; Chromosomes condense and centromeres attach to microtubule spindle
iii) **Metaphase**; Chromosomes align
iv) **Anaphase**; Sister chromatids move apart
v) **Telophase**; Nuclei reform



The cell has evolved a simple mechanical mechanism to insure that after mitosis each daughter cell has received exactly one copy of each chromosome. (Failure of proper chromosome segregation is known as nondisjunction). The steps in the mechanism are as follows: 1) After DNA replication two daughter chromosomes known as sister chromatids are held together by ring-like proteins known as cohesins. 2) As chromosomes align in metaphase, microtubule spindles attach to centromeres on each chromatid. 3) Once all of the chromatids are attached to spindles a protease known as separase becomes active (Actually unattached chromatids produce a signal to keep separase inactive and only when every chromatid pair is under tension generated by spindles pulling in opposite directions is the inhibitory signal turned off.) 4) Finally, active separase cleaves the cohesin proteins detaching sister chromatids and allowing them be pulled apart by the spindle to be distributed to different daughter cells.

Cells in production of germ cells such as pollen undergo a very different kind of division, **Meiosis**.



Meiosis differs from mitosis in two fundamental respects: 1) in meiosis there are two rounds of chromosome segregation for one round of synthesis so each germ cell receives only one of the two homologous chromosomes and 2) in meiosis the homologs pair with one another then move to opposite poles.

Chromosomes behave in meiosis the same way that Mendel showed genes to behave. Each germ cell receives only one of the two homologs, a behavior that is analogous to gene segregation.

The relative alignment of chromosomes is arbitrary which is analogous to independent assortment of genes.

Errors in chromosome segregation during meiosis are known as **nondisjunction** events. In humans the most common result of a nondisjunction gives rise to three copies of chromosome 21 (known as trisomy 21) the result of which is a condition known as Down syndrome. Down syndrome occurs in ~1/800 live births. It is the most common trisomy because extra copies of any of the other autosomes is usually lethal.