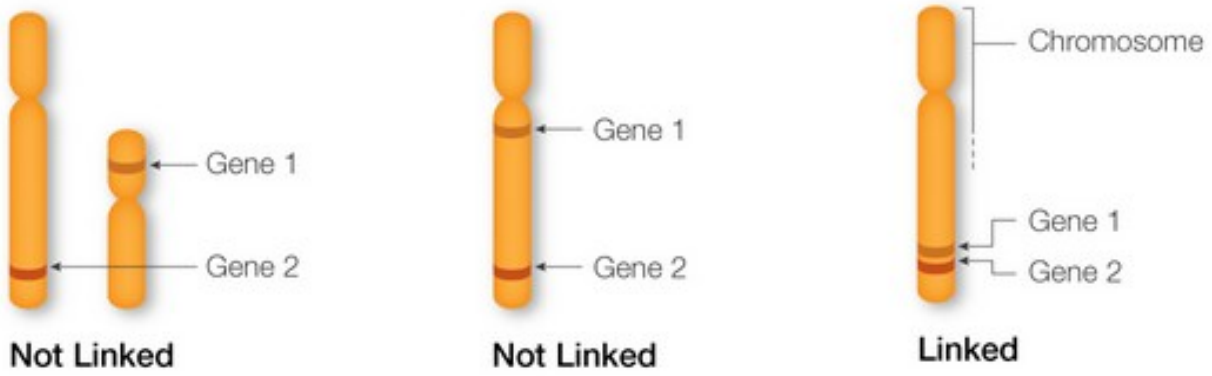
Week 6 Highlights

Genetic Linkage: It is the tendency of alleles at different loci to be inherited together, more often than predicted by chance alone. This usually happens because the two loci are very close together on the same chromosome. Such loci are called Linked Loci.

Linkage distorts the typical Mendelian dihybrid F2 phenotypic ratio. This is because linkage affects independent assortment of alleles at different loci.

For two loci on different chromosomes, independent assortment of chromosomes results in independent assortment of alleles.
For loci on the same chromosome, recombination between the loci can lead to independent assortment of alleles.
Recombination can occur freely for loci that are located far away on the same chromosome.
If loci are close together on the same chromosome, recombination between them is less likely. Therefore, independent assortment is affected. This leads to an over-representation of parental allele combinations and an under representation of recombinant allele combinations in the gamete pool.



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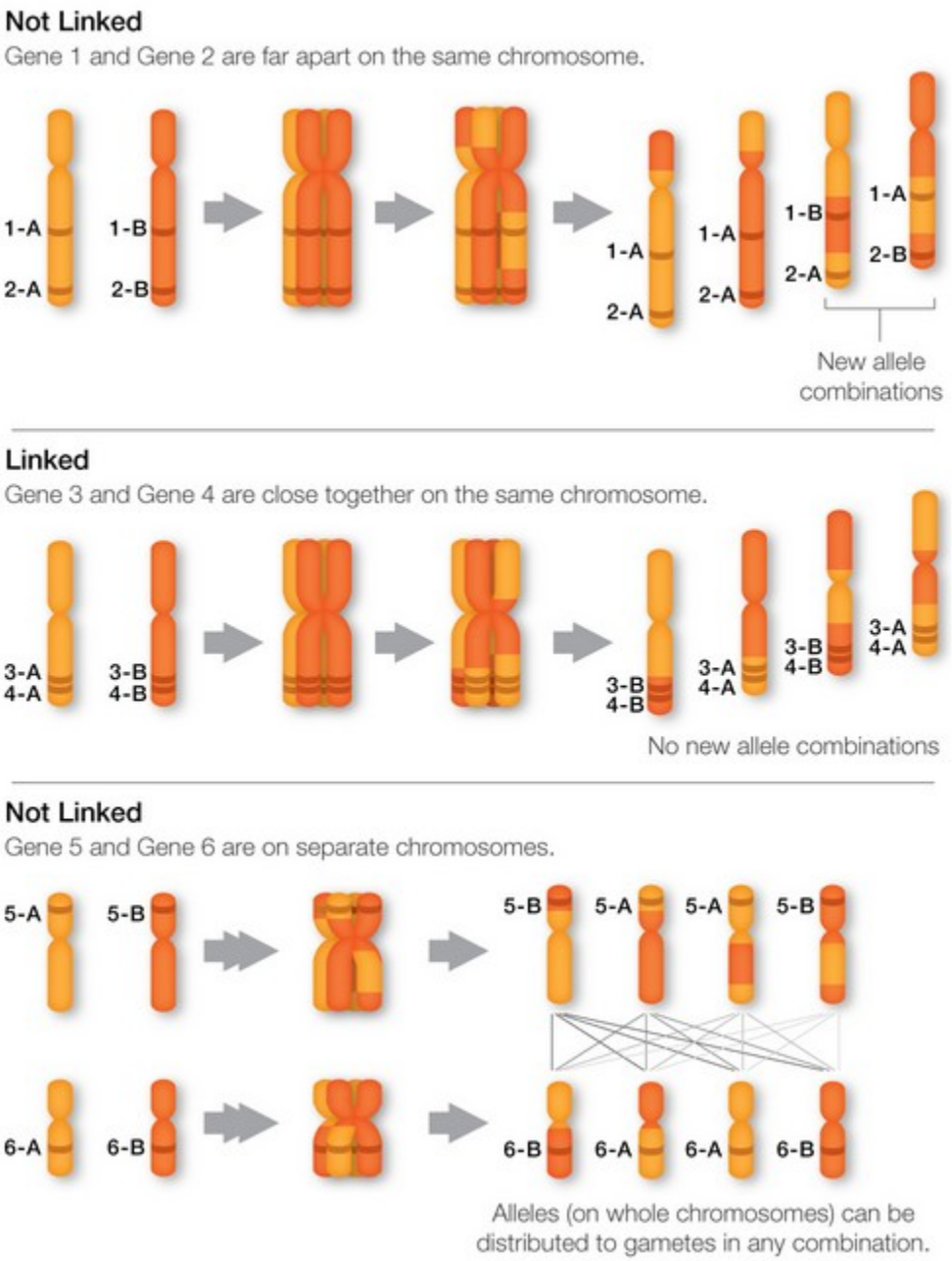


Two of the genes (1 and 2) are relatively far apart (top illustration). Each gene comes in two different versions, or alleles: A and B.

Since Gene 1 and Gene 2 are far apart, it is likely that a recombination event will happen between them. When this happens, the gametes end up with new allele combinations that were not present in the parent. That is, 1-B with 2-A, and 1-A with 2-B.

Gene 3 and Gene 4 (middle illustration) also come in two alleles each (A and B). But because these genes sit much closer together, it is less likely that a recombination event will happen between them. (Remember, the location of chromosome break points during recombination is random). Most of the time, 3-A and 4-A will stay together, and 3-B and 4-B will stay together. Genes 3 and 4 are linked.

Genes on separate chromosomes, such as Gene 5 and Gene 6, are never linked (bottom illustration). Each gamete gets a single copy, determined at random, of each chromosome. Because there is nothing holding them together, the alleles can pass to gametes in any combination.

(https://learn.genetics.utah.edu/content/pigeons/geneticlinkage/)

William Bateson, Edith Saunders and reginald Punnett discover Linkage in Sweet Peas:

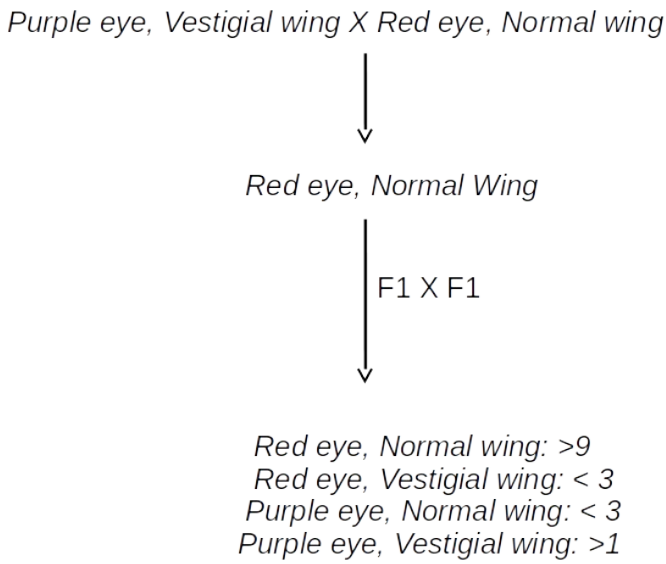
In 1905, William Bateson, Edith Rebecca Saunders, and Reginald Punnett were examining flower color and pollen shape in sweet pea plants (Bateson *et al.*, 1905) by performing dihybrid crosses similar to those carried out by Gregor Mendel. In particular, these researchers crossed homozygous pea plants that had purple flowers and long pollen grains with homozygous plants that had red flowers and round pollen grains (Pierce, 2005). Prior to the cross, the trio noted that purple flowers (P) were dominant over red flowers (p), and that long pollen grains (L) were dominant over round pollen grains (l). The F_1 generation of plants resulting from the PPLL x ppll cross was therefore doubly heterozygous (PpLl), and all of the F_1 plants had purple flowers and long pollen grains.

Next, Bateson, Saunders, and Punnett decided to cross the F_1 plants with each other. After this cross, the researchers expected the F_2 generation to have a 9:3:3:1 ratio (nine plants with purple flowers and long pollen grains, to three plants with purple flowers and round pollen grains, to three plants with red flowers and long pollen grains, to one plant with red flowers and round pollen grains). Instead, they observed the results shown in the table below (Bateson *et al.*, 1905), and these results were found to be statistically significant with a chi-square (c^2) value of 969.

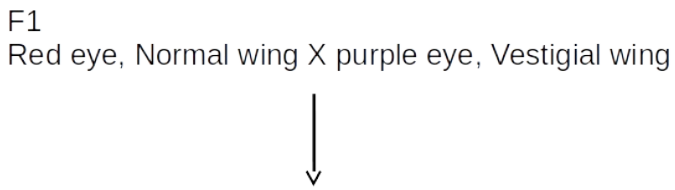
Phenotype	**Expected**	**Observed**	**(Observed-Expected)^2/Expected**
Purple, long	1199	1528	90.3
Purple, round	400	106	216.1
Red, long	400	117	200.2
Red, round	133	381	462.4
Total	2132	2132	$c^2 = 969.0$

Because the parental phenotypes reappeared more frequently than expected, the three researchers hypothesized that there was a “Coupling” or Linkage, between the parental alleles for flower color and pollen grain shape (Bateson *et al.*, 1905), and that this linkage resulted in the observed deviation from independent assortment.
(https://www.nature.com/scitable/topicpage/thomas-hunt-morgan-genetic-recombination-and-gene-496/)
(https://www.nature.com/scitable/topicpage/discovery-and-types-of-genetic-linkage-500/)

Thomas Hunt Morgan observed linkage in *Drosophila*



Morgan hypothesised that his results might be because independent assortment was affected. To find out if independent assortment was indeed affected, he performed a test cross of the F1. He found the following progeny phenotype distribution-



F_1 Gamete	Testcross Distribution	Gamete Type
pr⁺ vg⁺	1339	Parental
pr⁺ vg	151	Recombinant
pr vg⁺	154	Recombinant
pr vg	1195	Parental

He proposed that the parental type alleles were linked. He went on to propose that-

a) This was possibly because the two loci were close together on the same chromosome.
b) A “crossing over” between two homologus chromosomes could lead to the exchange of genetic material. This could occasionally break the linkage between two loci.
c) The probability of “crossing over” (or recombination) between two loci was directly proportional to the distance between them. Loci that were further apart were more likely to recombine than loci that were close together. Morgan imagined that genes on chromosomes were similar to pearls on a string (Weiner, 1999); in other words, they were physical objects. The closer two genes were to one another on a chromosome, the greater their chance of being inherited together. In contrast, genes located farther away from one another on the same chromosome were more likely to be separated during recombination. Therefore, Morgan correctly proposed that the strength of linkage between two genes depends upon the distance between the genes on the chromosome.

Linkage Map:
This is a map of the loci on chromosomes. The distances between loci indicate the frequency of recombination between them. Hence, this is also called “linkage map”. Please note that this is not a physical map of the chromosome.

The Map Unit is centi Morgans. According to A H Sturtevant, 1% recombination is equal to one centi Morgan (cM).

Sturtevant develops the first Linkage Map:
Soon after Morgan presented his hypothesis, Alfred Henry Sturtevant, a 19-year-old Columbia University undergraduate who was working with Morgan, realized that if the frequency of crossing over was related to distance, one could use this information to map out the genes on a chromosome. After all, the farther apart two genes were on a chromosome, the more likely it was that these genes would separate during recombination. Therefore, as Sturtevant explained it, the "proportion of crossovers could be used as an index of the distance between any two factors" (Sturtevant, 1913). Collecting a stack of laboratory data, Sturtevant went home and spent most of the night drawing the first chromosomal linkage map for the genes located on the X chromosome of fruit flies (Weiner, 1999).

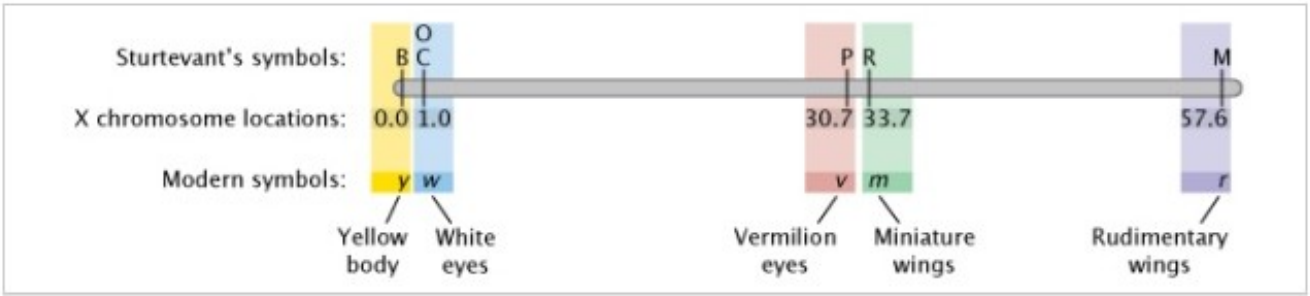


Figure 3: Sturtevant's *Drosophila* gene map.
In Sturtevant's gene map, six traits are arranged along a linear chromosome according to the relative distance of each from trait B. Traits include yellow body (B), white eyes (C, O), Vermillion eyes (P), miniature wings (R), and rudimentary wings (M).

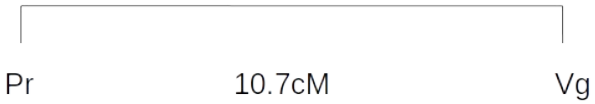
Constructing a linkage map from a two point test cross:

Two-Point Test Cross

F1
Red eye, Normal wing X purple eye, Vestigial wing

F_1 Gamete	Testcross Distribution	Gamete Type
pr⁺ vg⁺	1339	Parental
pr⁺ vg	151	Recombinant
pr vg⁺	154	Recombinant
pr vg	1195	Parental
Total	2839	

Frequency of Recombinants = (151 + 154)/ 2839 = 0.107



Limitation of two point test cross: Recombination frequency is 0.5.

Three Point Test Cross:

Step 1: determine the Parental and Recombinant types.
Parentals: These are the most numerous
Single Recombinants (Single Cross Overs)
Double Recombinants (Double Cross Overs): Least numerous.

Step 2: Determine the Gene Order.
When compared to the parental type, only the middle allele is moved in the double recombinant.

Step 3: Determine the linkage distances.

Step 4: Draw the map.

Step 5: Calculate Interference.

Interference (I) = 1- Coefficient of Coincidence

C.o.C = Observed number of double recombinants
Expected number of double recombinants