

## Lecture 2 Meiosis and Genetic Recombination

You Should Be Able To

Explain how new combinations of alleles arise for genes on different chromosomes

Explain how new combinations of alleles arise for genes on the same chromosomes

Explain why the maximum frequency of recombination between two genes is 50%

-recombination is at the heart of genetics, the transmission of information

-different version of a gene = alleles, we receive two copies of one gene, each from one parent and hence we are diploids

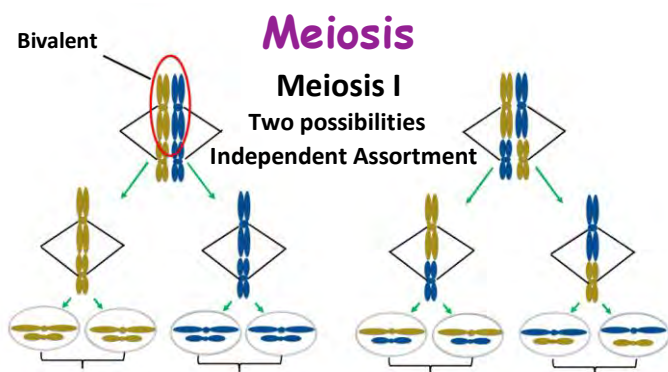
-recombination = the process that generates the new combination of alleles that are transmitted from parents to children, it produces diversity – we don't have the same combinations of genes

-genetic and hence phenotypic variation of organisms in population is crucial for its survival, some of those variants are advantageous in the environment which allows the species to continue

-genetic information that is transmitted is packaged in gametes which carry one copy of genes, meiosis is a process by which gametes are generated and recombination accomplished

-meiosis: two division process comprised of meiosis one and meiosis two

meiosis one → chromosome number halved as a bivalent is formed in metaphase, when mitotic spindle is formed and microtubules attach to centromere pulling two members of the bivalent apart which leads to products having only one copy of chromosomes and not two



meiosis two → chromosome number preserved as sister chromatids are pulled apart by the meiotic spindle opposed to chromosomes in meiosis one

-this (without any recombination) gives us two different combinations of genes, but that is not what we get because the way that the bivalents orientate is random, both can be on either side with same probability – **independent assortment** = the way bivalents orientate and segregate is independent, each pair of chromosomes behaves independently of the other – end up with four combination in this case ( $2^n$ ,  $n$  = number of bivalents)

-if organism is completely homozygous the recombination can

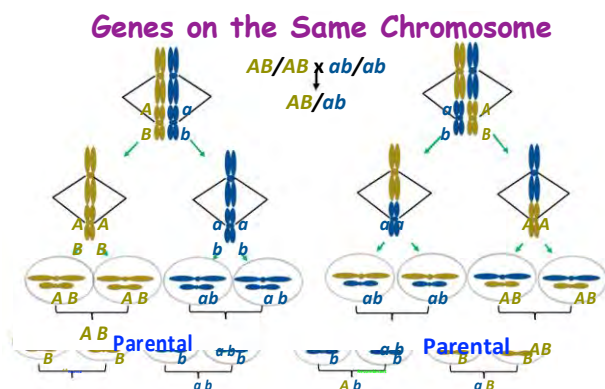
occur but there wouldn't be any genetic consequence since there is only one copy of gene it can transmit, therefore we need at least two heterozygous genes in order for recombination to have a genetic effect – parents (the parental generation) must have sent different versions of alleles (prodigy is F1 generation)

→ if we look at two genes A/a and B/b these can either be on the same or on different chromosomes which will affect the result of their recombination

a) on different chromosomes – process that gives new different combination is independent assortment in meiosis one, giving us two parental combinations and two recombinant ones

-the frequency of recombination between genes on different chromosomes is 50%

\*\* AA;BB means genes A and B are on different chromosomes whereas AA/BB means there are on the same chromosomes\*\*



b) genes on the same chromosomes – independent assortment has not given us recombination, we end up with parental combinations again, what gives us recombination of genes on the same chromosomes then?

→ a chiasma at meiosis I

-bivalents at diplotene = chromosomes are very condensed and we can see the bivalents, we can see regions that have contact between the two ends of the bivalent – two non-sister chromatids interact

-this is a region where there has been an exchange from one chromosome to another → this crossover is called a **chiasma** (happens on a bivalent which only exist in meiosis I)

-what is the product? A recombinant combination, we'll get one chromatid with parental combination and one with a new combination on each chromosome in the bivalent

-how do we know this is true, that there is an actual exchange?

Barbara McClintock and Harrier Creighton did genetic experiments on maize – need individuals heterozygous for alleles of two genes, they chose two genes, one affects colour of kernels and other one controls the composition of the starch in the endosperm which also alters the appearance

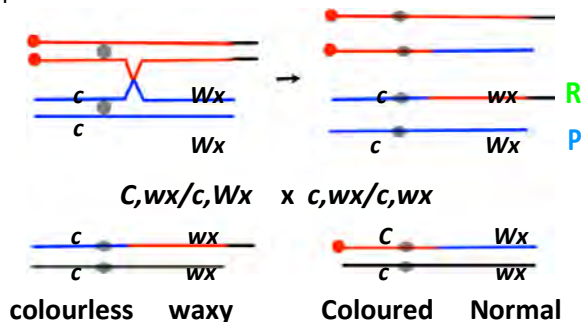
→ one parent was  $cc/WxWx$  which gives colourless normal kernels and other was  $CC/wxwx$  which gives coloured waxy kernels (this chromosome also had a blob of chromatin on one end and a translocation of chromatin on the other end, so we could distinguish the two ends and also the two parental chromosomes when we do the experiment)

-the question asked was is genetic recombination due to crossing over of chromatids? Result of meiosis was: two parental and two recombinant chromatids – one recombinant has a knob and the other the translocation, while on the parent knob and translocation are on the same chromatid

-we can't look at haploid gamete so we have to do a cross – we do a **test cross** = test the heterozygote with the homozygote for the recessive phenotype and look at the phenotype to confirm the genotype

-the results confirmed chiasm leads to genetic recombination – look at the chromosomal differences

-two processes can result in recombination:



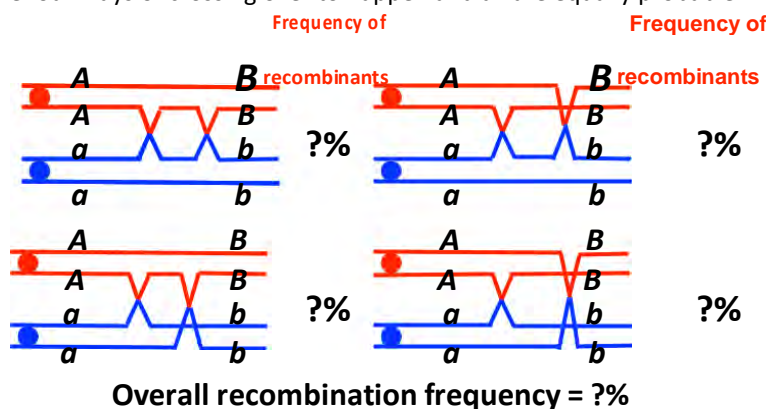
→ Independent Assortment for Genes on Different Chromosomes

→ Chiasma Formation/Crossing-over for Genes on the Same Chromosome

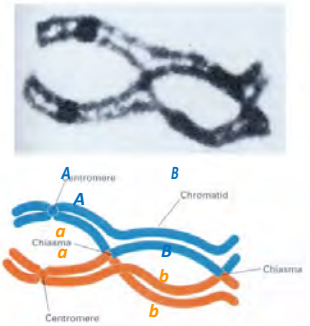
-the frequency of recombination between genes on different chromosome is always 50%, what about the same chromosome? We need to think about the relationship between crossing over and the frequency of recombination  
-the number of chiasma affects this, 0 chiasm = 0% frequency, 1 chiasm (1 crossover) = 50% frequency, 2

chiasma (2 crossovers) = ? - more than one way of crossover

-we have four ways of crossing over to happen and all are equally probable



-think about the frequency of all of these possibilities and then work out the average to get the overall frequency, something to think about



## Lecture 3 Recombination Frequency and Genetic Linkage

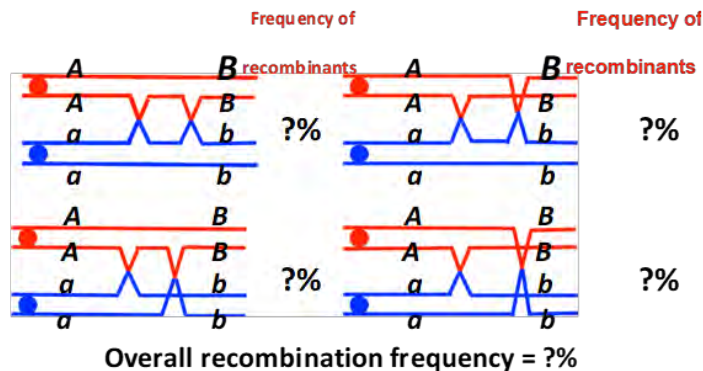
You Should Be Able To

Calculate the recombination frequency from the results of a two-point test cross

Construct a genetic map using the results of a three-point test cross

-crossing over and the frequency of recombination: the frequency of recombination between genes on different chromosomes is always 50%, what about the same chromosome? We need to think about the relationship between crossing over and the frequency of recombination

-the number of chiasma affects this, 0 chiasm = 0% frequency, 1 chiasm (1 crossover) = 50% frequency, 2 chiasma (2 crossovers) = ? - more than one way of crossover

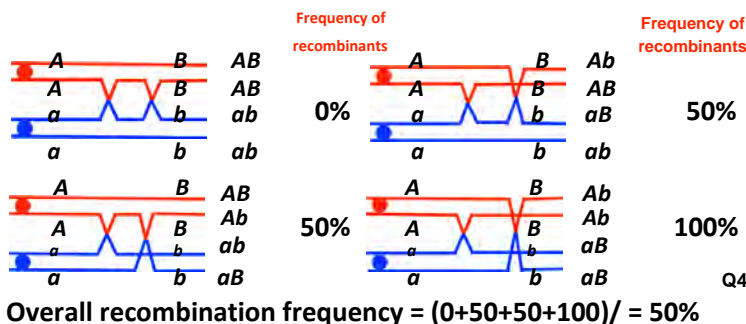


-we have four ways of crossing over which can happen and all are equally probable

-think about the frequency of all of these possibilities and then work out the average to get the overall frequency, something to think about

-work out what we get in each scenario and look if combinations are parental or new to calculate the frequency of recombination

-then we average it end up with 50%



-the maximum frequency of recombination between genes on the same chromosome is 50% - we wouldn't get more even if we have more chiasma

- the frequency of recombination between genes on different chromosome is always 50% as well due to independent assortment

→ therefore, the **maximum frequency of recombination between any two genes is 50%**

-**genetic linkage**: genes that show <50% recombination are said to be linked – are on the same chromosome, if they were on different chromosomes the frequency would be 50%, they are physically and genetically linked

-however, genes that are on the same chromosome may show 50% recombination and be genetically unlinked even though they are physically linked and on the same chromosome due to one or more crossovers that are occurring on average since they are so far apart from each other but still on the same chromosome

-crossing over gives reciprocal products → two recombinants are reciprocal, where one has one allele the other has the opposite (A – b and a – B); these combinations are equal in frequency to parental combinations (A – B and a-b)

-measuring the frequency of recombination: looking at outcomes of two different test-crosses

→ the phenotype of the progeny is dependent on the allele that is inherited from the heterozygous parent (since the other parent is homozygous recessive)

### Cross A

Phenotype	Number
AB	225
Ab	230
aB	235
ab	210
	1000

### Cross B

Phenotype	Number
AC	412
Ac	93
aC	107
ac	388
	1000

-cross A: the number of each progeny class is roughly the same, the frequency of the recombination is about 50% → gene A is not linked to gene B

-cross B: the number of each progeny class is not the same → gene A is linked to gene C

-frequency of recombination = no. recombinants / total progeny \* 100

-what is the frequency of recombination between genes A and C? if the genes are linked, the parental combinations will be more frequent than the recombinants, so in this case parentals are AC and ac since the frequency is 412 and 388 compared to 93 and 107 of the recombinants (Ac and aC)

-hence, we can write the genotypes of the parental generation as AC/ac x ac/ac

→ frequency of recombination =  $(93 + 107) / 1000 * 100 = 20\%$

-if the two genes are closer together it is less likely crossover will occur, the closer the genes are the less likely the crossover is – so we can use the frequency of recombination of genes as a guide for their distance on the chromosome → this was realised by a group lead by Thomas Hunt Morgan – said we can use the frequency of recombination to make a gene map of the chromosome, with 1% recombination being one map unit named 1 centimorgan in honour of Thomas Hunt Morgan

-making a genetic map: three-point test cross – more informative as we get three distances from one experiment, we get eight possible phenotypes of the progeny which come in reciprocal pairs too

**Aa Bb Cc x a,b,c/a,b,c**

Phenotype	Number
ABC	242
abc	238
Abc	145
aBC	155
AbC	77
aBc	73
ABc	33
abC	37
	<b>1000</b>

- which is the parental recombination, and what are the recombinants? ABC and abc are the parental combinations as they are the most frequent class (242 and 238), we can't have recombination more than 50% → so genotypes were A,B,C/a,b,c x a,b,c/a,b,c

-map distance = % recombination

for A – B we look at phenotypes which are not AB or ab hence

recombination frequency =  $(145+155+77+73) / 1000 * 100 = 45$

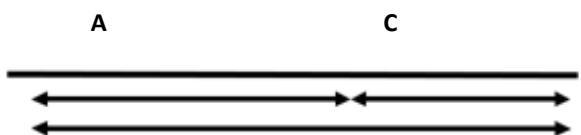
→ 45 map units distance between A and B

-repeat the same for A - C

recombination frequency =  $(145+155+33+37) / 1000 * 100 = 37\%$  → 37 map units distance

-and then lastly for B-C

recombination frequency =  $(33+37+77+73) / 1000 * 100 = 22\%$  → 22 map units distance



-making the map: first position the genes that are the furthest apart  
-we got 45 from A to B and not 37 + 22, why is that? → next lecture

## Lecture 4

*You Should Be Able To*

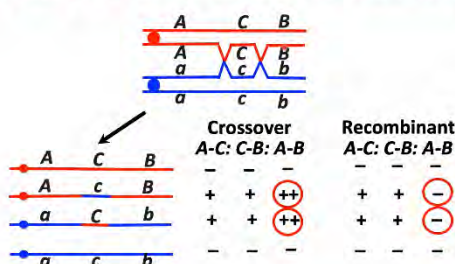
*explain why double crossovers lead to an underestimate of the genetic distance between genes*

*explain the factors affecting the frequency of recombination between genes on the same chromosome*

-from the last lecture: making the gene map - we got 45 from A to B and not 37 (A-C) + 22 (C-B), why is that? Effect of a double crossover

-so, we have a chromosome with genes A,B and C on it with crossover happening between A and C, C and B and A and B, as a

## Effect of a Double Crossover



result we get two parental combinations and two recombinants (chromatids) – one crossover between A-C and C-B, but two between A-B (the two previous ones since they were in between of A and B)

-but when we look at the genes, after the crossover happens the chromatids are no longer recombinant for A and B, which is why the crossover between A and B was not counted when we measured the distance, we did not see the recombinants as they cancelled each other out

-the double crossovers are therefore not counted when calculating the distance

-correcting for double crossovers: simply adding 37 and 22, is it the right answer? When we look at the progeny phenotype, the double crossovers are ABc and abC which are the least frequent, since they are the results of two crosses and are hence less frequent (less probable two crossovers in a row will happen than just one, and other combinations require just one)

-if we add these when calculating the % recombination frequency and hence the map units, when adding them we multiply by two since they do represent two crossovers

-this way we would get 59, which does indeed equal the previous 37 + 22



-are crossing-overs independent? Does having one crossover between two chromatids affect the probability of having another one between those chromatids in the same meiosis?

-we can measure that by taking the observed frequency of double crossovers over the expected frequency of double crossovers, and see how they compare = coefficient of coincidence

coefficient of coincidence = observed freq. of doubles / expected freq. of doubles

-how do we measure?

Observed frequency = take the double crossover products over the total products (33+37/1000), which is equal to 70/1000 = 0.07 (7%)

Expected frequency = from our map we take the calculated frequencies for A-C and C-B which are crossovers that need to both occur to get our double A-B recombinants, so the map tells us the frequency of both of the crossovers independently (0.37 and 0.22), since they have to both occur in the same meiosis we multiply their probabilities, hence  $0.37 \times 0.22 = 0.0814$  (8.14%)

-put the numbers in our equation, end up with  $0.07/0.0814 = 0.86$

-it can also be measured directly by taking the observed number of doubles / expected number (which is 0.0814 or the probability x 1000 is the number of progeny)

A,B,C/a,b,c x a,b,c/a,b,c		
Phenotype	Number	
ABC	242	A. 0.033
abc	238	
aBC	155	B. 0.037
Abc	145	C. 0.073
AbC	77	D. 0.070
aBc	73	E. 0.077
ABc	33	(33 + 37)
abC	37	1000
	1000	

→ the observed double crossover frequency is less than expected, so the two events are not independent, indicating that having one crossover makes it less likely that the second will appear in the same meiosis, they interfere

-interference =  $(1 - \text{coefficient of coincidence}) = 1 - 0.86 = 0.14$

-we are not really sure why there should be interference and there is probably more reason behind it, could be due to the protein machinery that carries out cross over, we don't know

-genetic and physical (actual distance) chromosome maps – what relationship do they have?

-what is the length of the human genome in cM? and what is the relation between that and the physical length? There are more ways of measuring this.

-can use the fact that one chiasma (= one crossover) gives 50% recombination, from the image of human chromosomes in meiosis we can see the positions of chiasma, we can count them and multiply by 50, getting an estimate of cM in the genome, this gives about 2 500 cM

-what about females? As female meiosis starts before birth and is paused until ovulation it is a bit trickier but we can still count chiasma in prophase (in males it's in metaphase) – the estimate we get from females is 3 500 cM (close enough)

-we can also do the same thing we did in the 3 point test cross, measuring the number of recombinants for two different genetic markers over the whole progeny, not very easy to do for the whole genome, which is why we can look at different base pairs at the same position in the genome, one inherited from the father and one from the mother

-doing that we get a genetic map of 2 590 cM in males and 4 280 cM in females

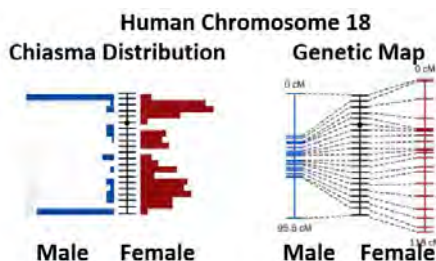
→ average of all these numbers is 3200 cM and the length of our genome is  $3.2 \times 10^9$  bp, so we can work out the number of bp per one cM which gives  $10^6$  bp per 1 cM

-variation between sexes, individuals and meiosis:

-recombination per molecules in each miosis in different males vary, males on the left have fewer than males on right

-situation in females is similar, but the average of crossing over in meiosis is overall higher

-crossing-over events are not distributed randomly → chiasma distribution



-the black ladder represents the chromosome and dot the centromere -number of chiasma at each position is plotted on both sides

-distribution is not uniform in both males and females, however the pattern is different – only similarity is there is few chiasma around the centromere

-the effect on the genetic map: regions which have lots of chiasma formed are further in the genetic part (sparse areas) whereas regions that don't are more dense (black ladder is mol. distance)

-why do frequencies differ so much across the chromosome? Recombination hot spots = regions where there's a very high probability of a crossing over occurring – particular sequences recognised by PRDM9 or zinc finger protein (has particular base pair motifs) which modifies the histones, allowing the crossing over machine to bind

