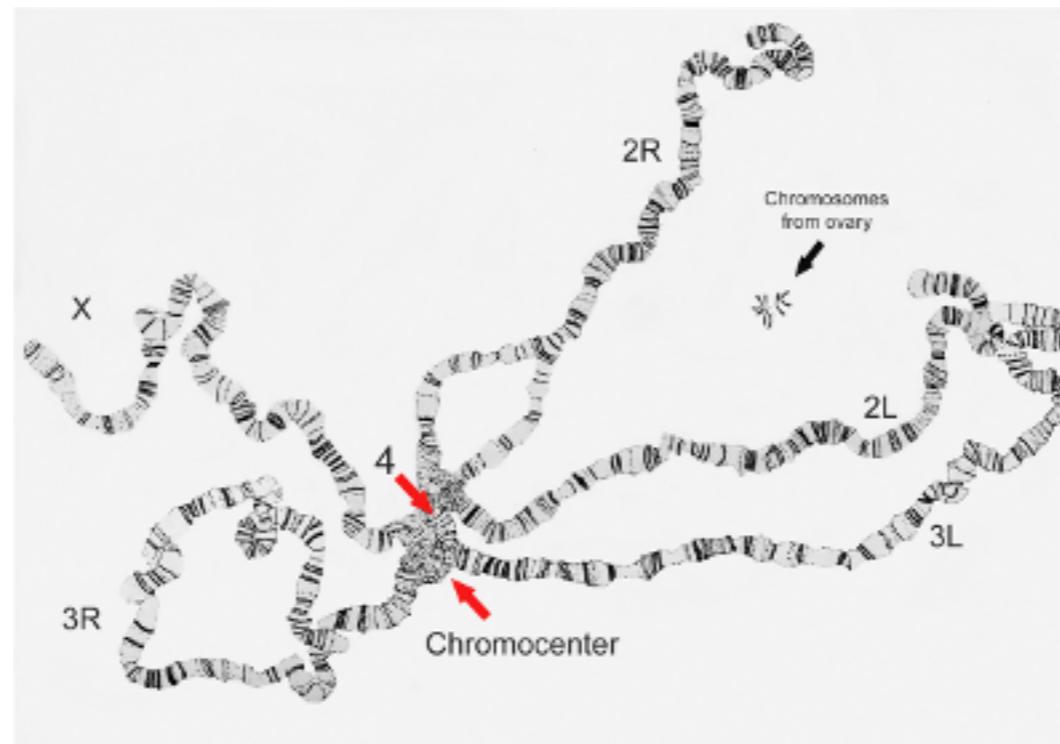


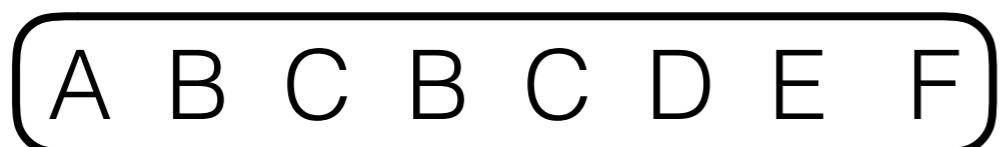
Chromosomal abnormalities



WT



Deletion BC



Duplication BC

Chromosomal abnormalities



WT



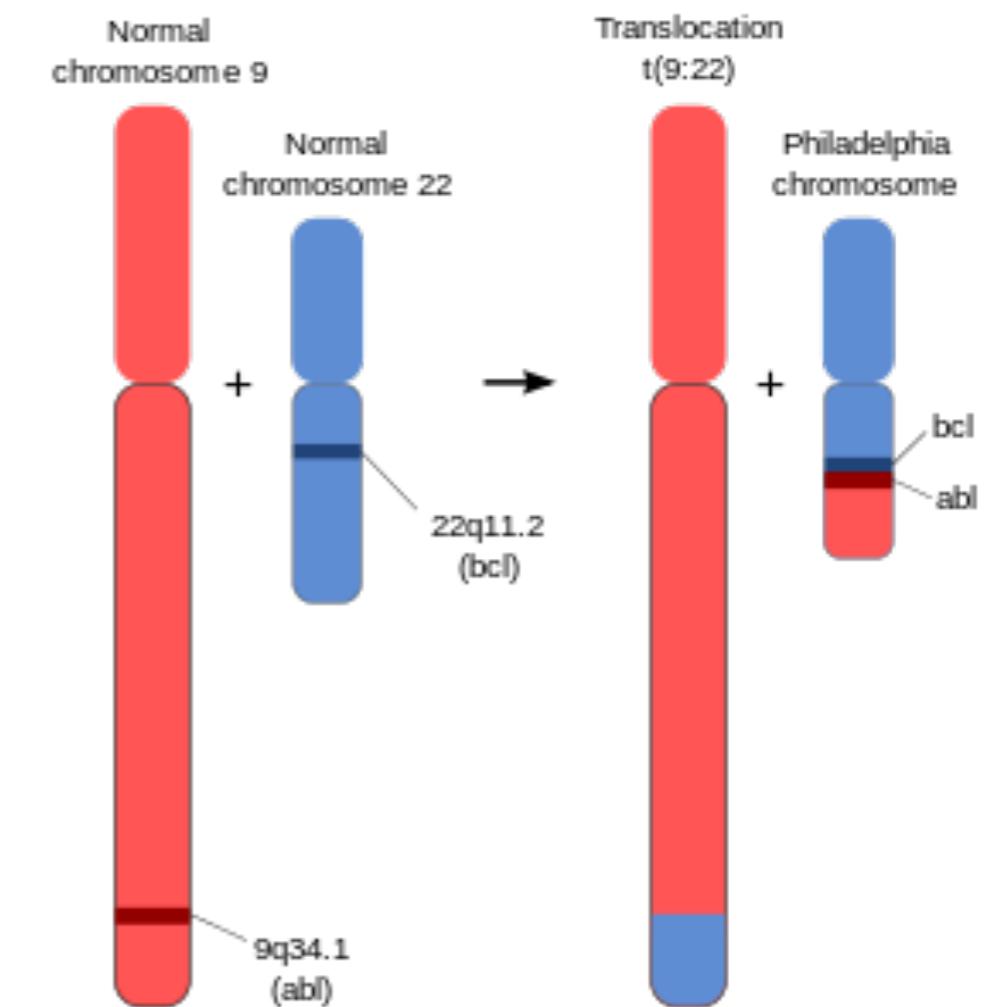
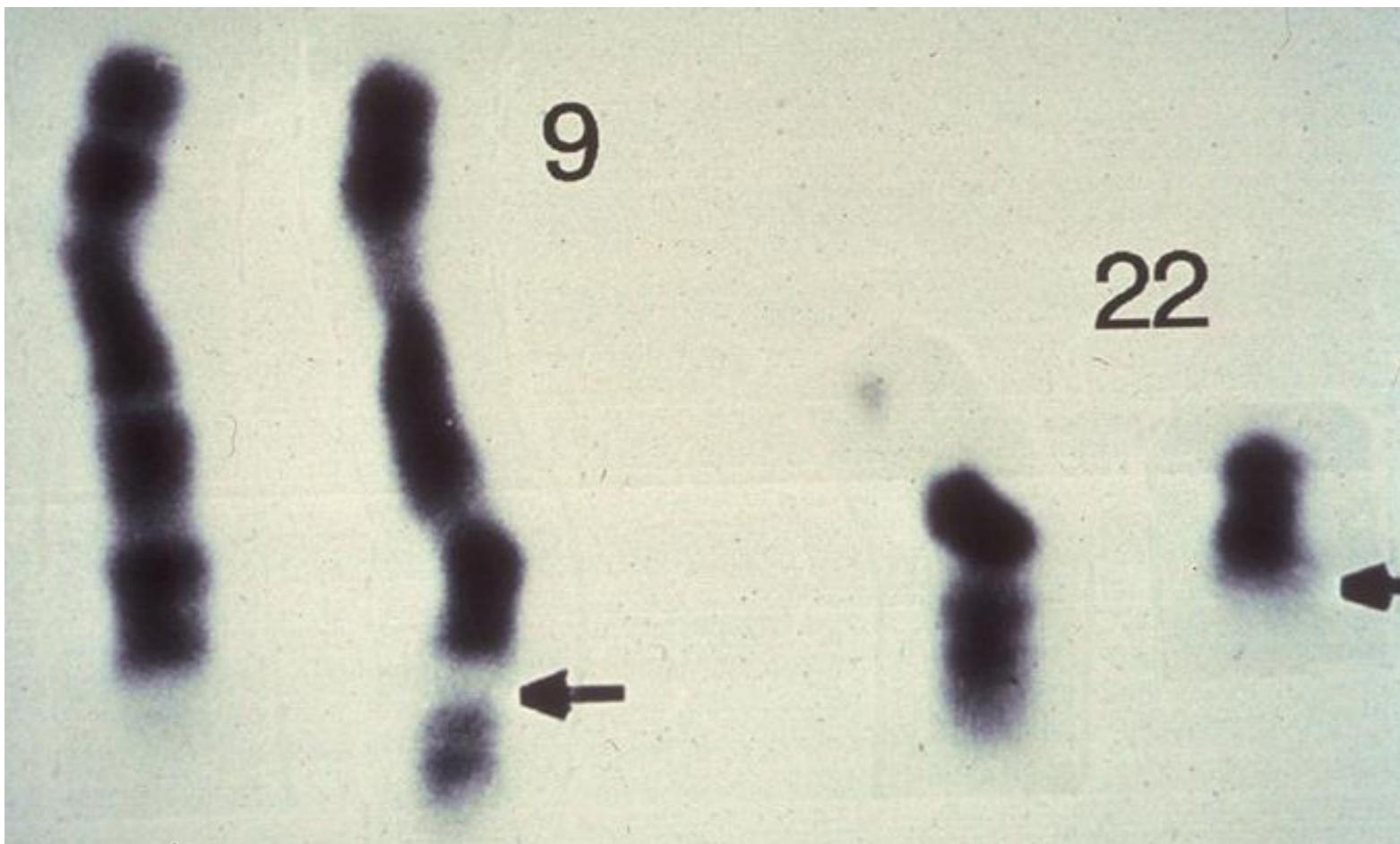
Inversion BCD



Translocation ABC-XYZ

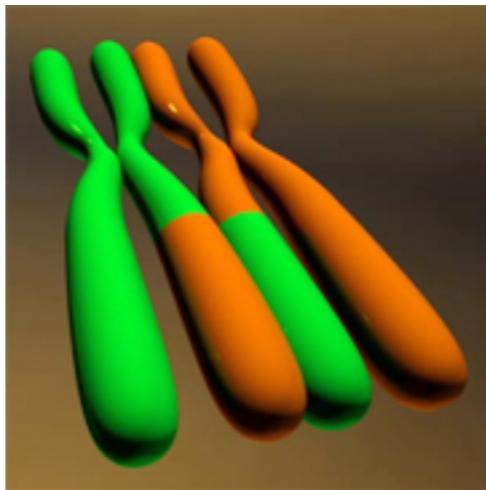
Fusion of two chromosomes

The Philadelphia chromosome: translocation



Janet Rowley

Recombination and mapping

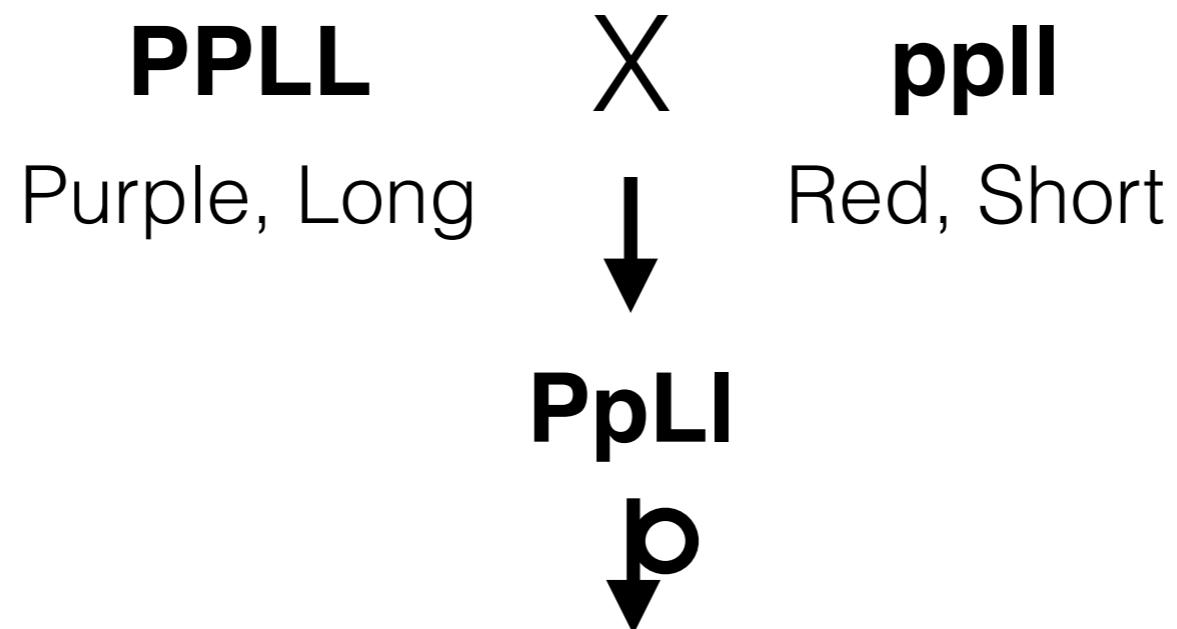




Reginald Punnett William Bateson

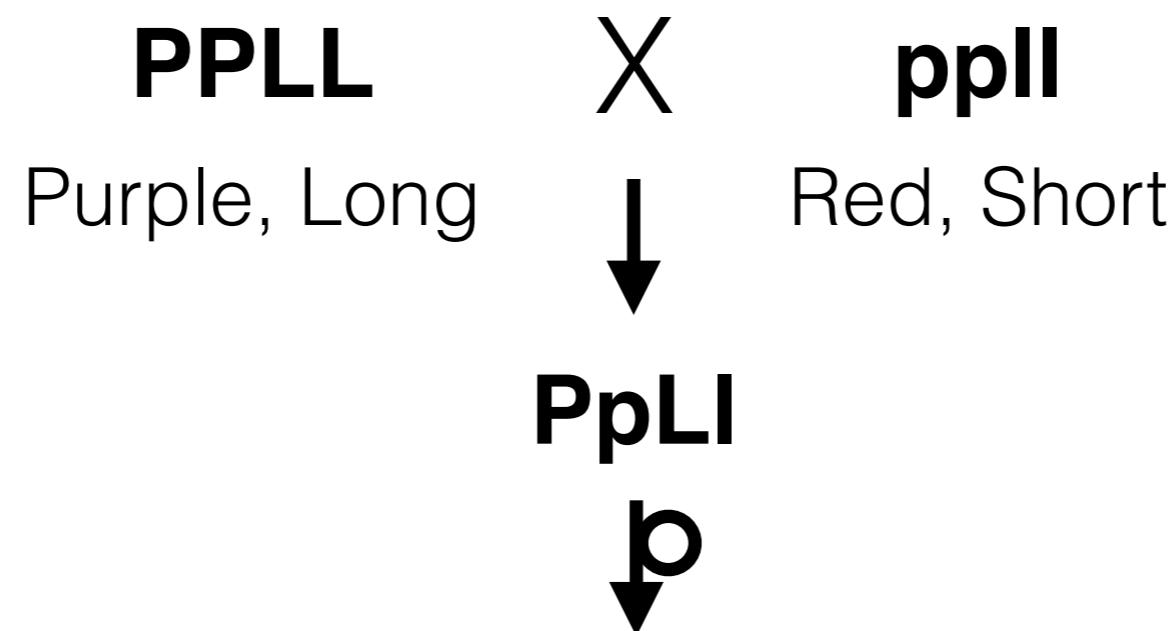


Bateson and Punnett's pea crosses



P= purple flower
p= red flower
L= long pollen
l= short pollen

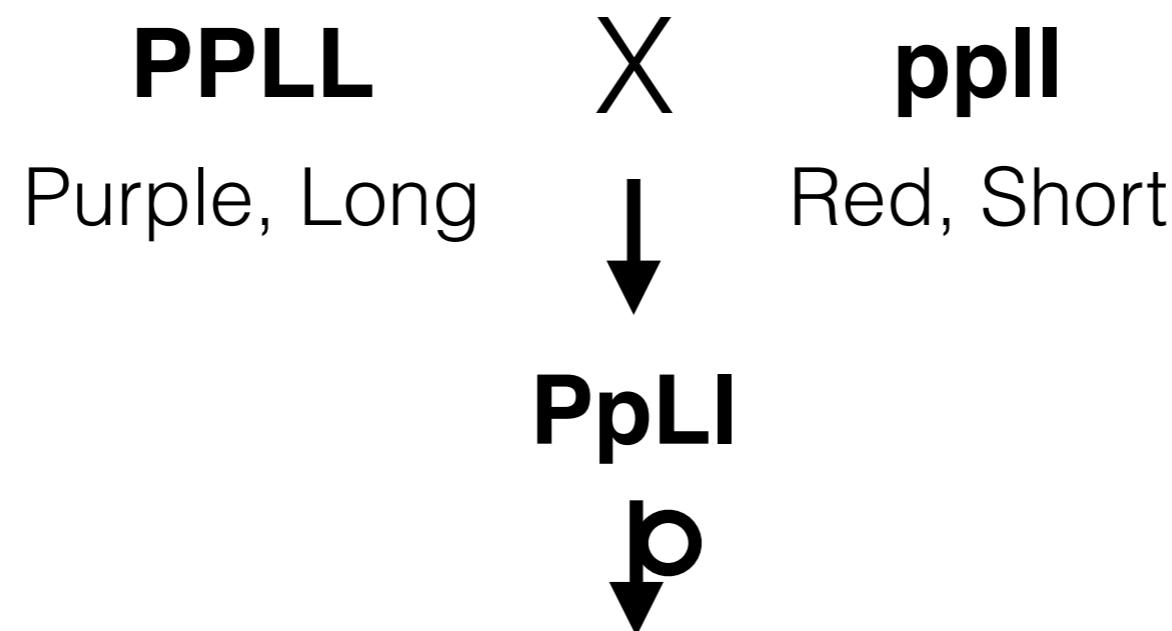
Bateson and Punnett's pea crosses



Phenotype	Expected number	Expected ratio
Purple Long	215	9
Purple short	71	3
red Long	71	3
red short	24	1

P= purple flower
p= red flower
L= long pollen
l= short pollen

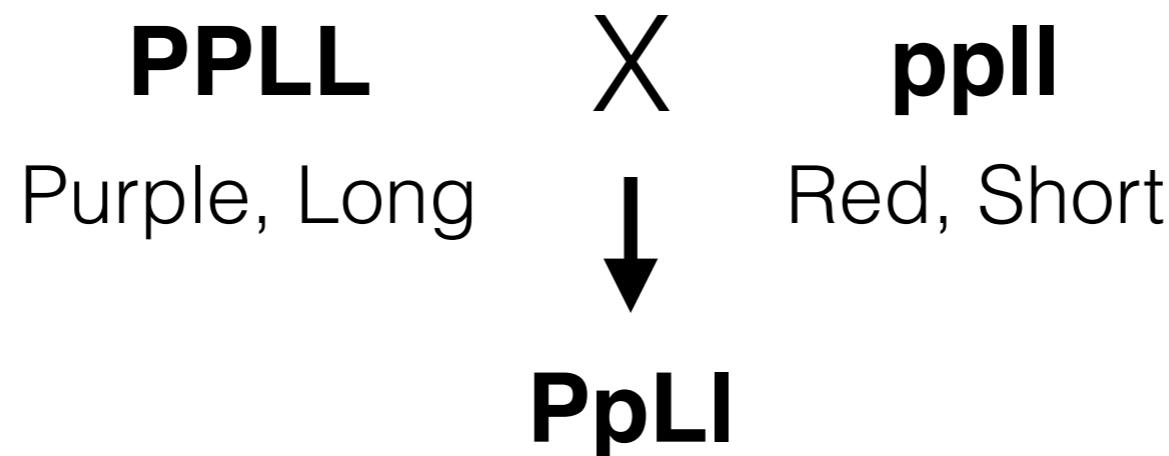
Bateson and Punnett's pea crosses



Phenotype	Expected number	Expected ratio	Observed number
Purple Long	215	9	284
Purple short	71	3	21
red Long	71	3	21
red short	24	1	55

P= purple flower
p= red flower
L= long pollen
l= short pollen

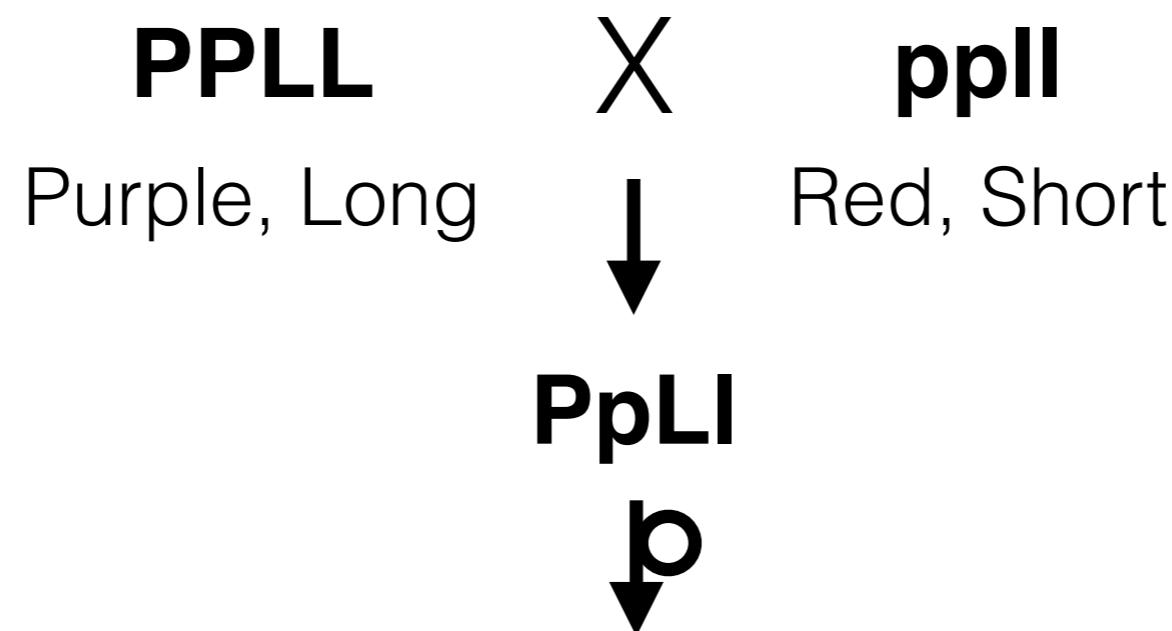
Bateson and Punnett's pea crosses



Parental = allelic combination found in parents
(most abundant classes, always paired)

Recombinant = allelic combination NOT found in parents
(least abundant classes, always paired)

Bateson and Punnett's pea crosses

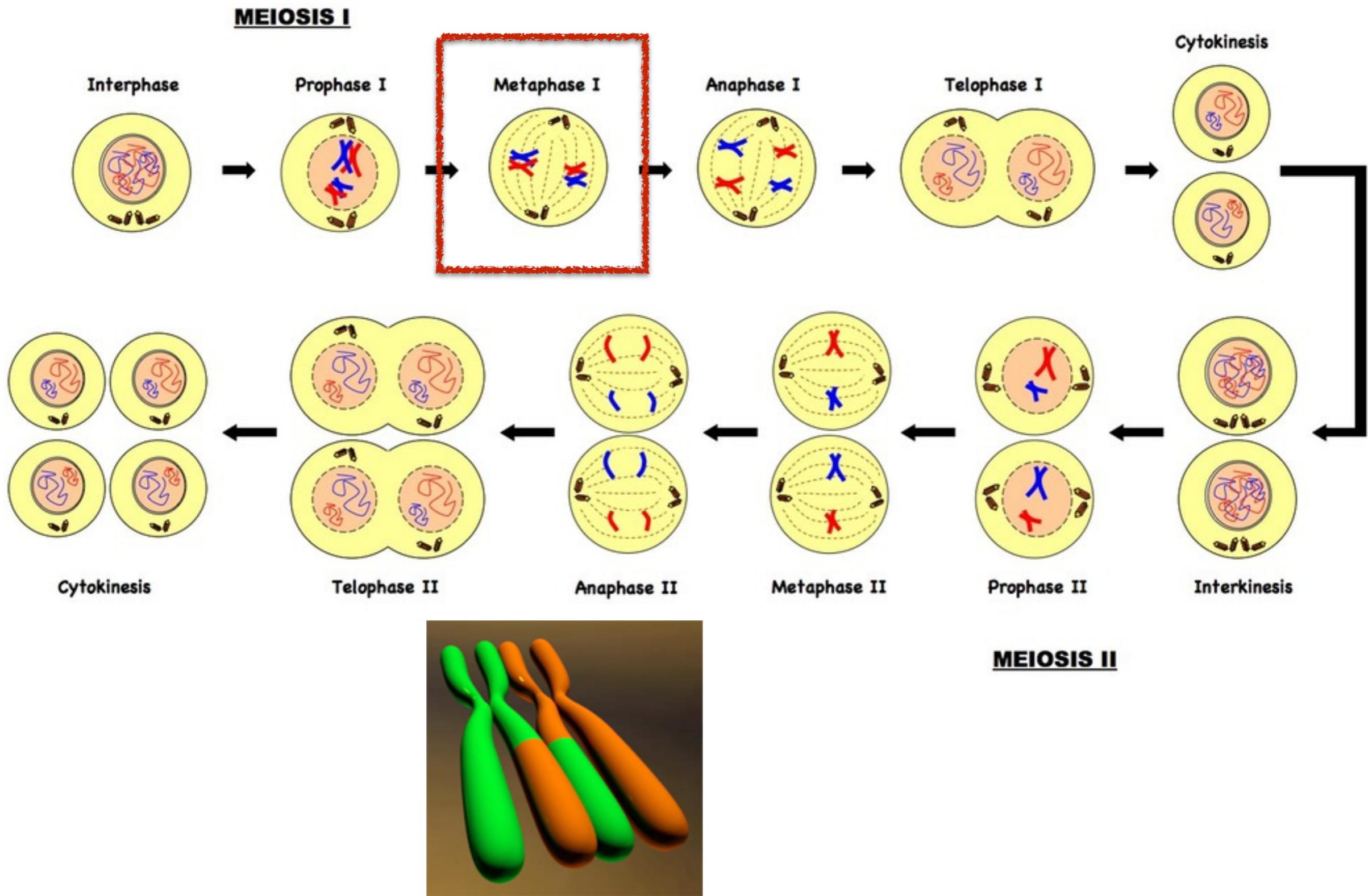


Phenotype	Expected number	Expected ratio	Observed number
Purple Long	215	9	284
Purple short	71	3	21
red Long	71	3	21
red short	24	1	55

P= purple flower
p= red flower
L= long pollen
l= short pollen

Which are recombinant
and parental offspring?

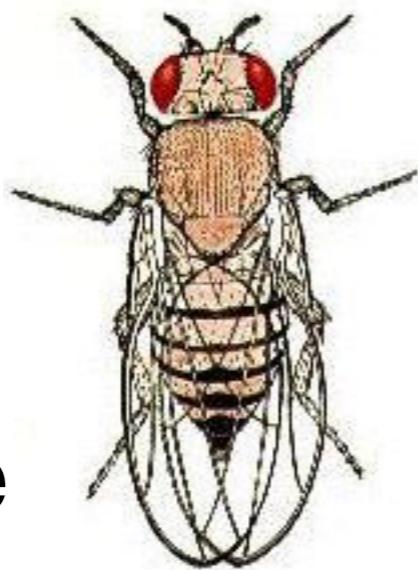
Meiosis: A reductional division in two acts



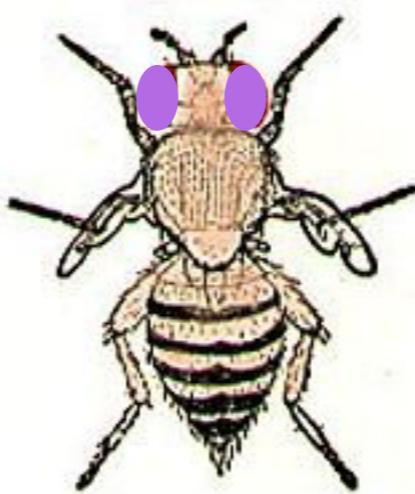
The fly room at Columbia



Wild-type

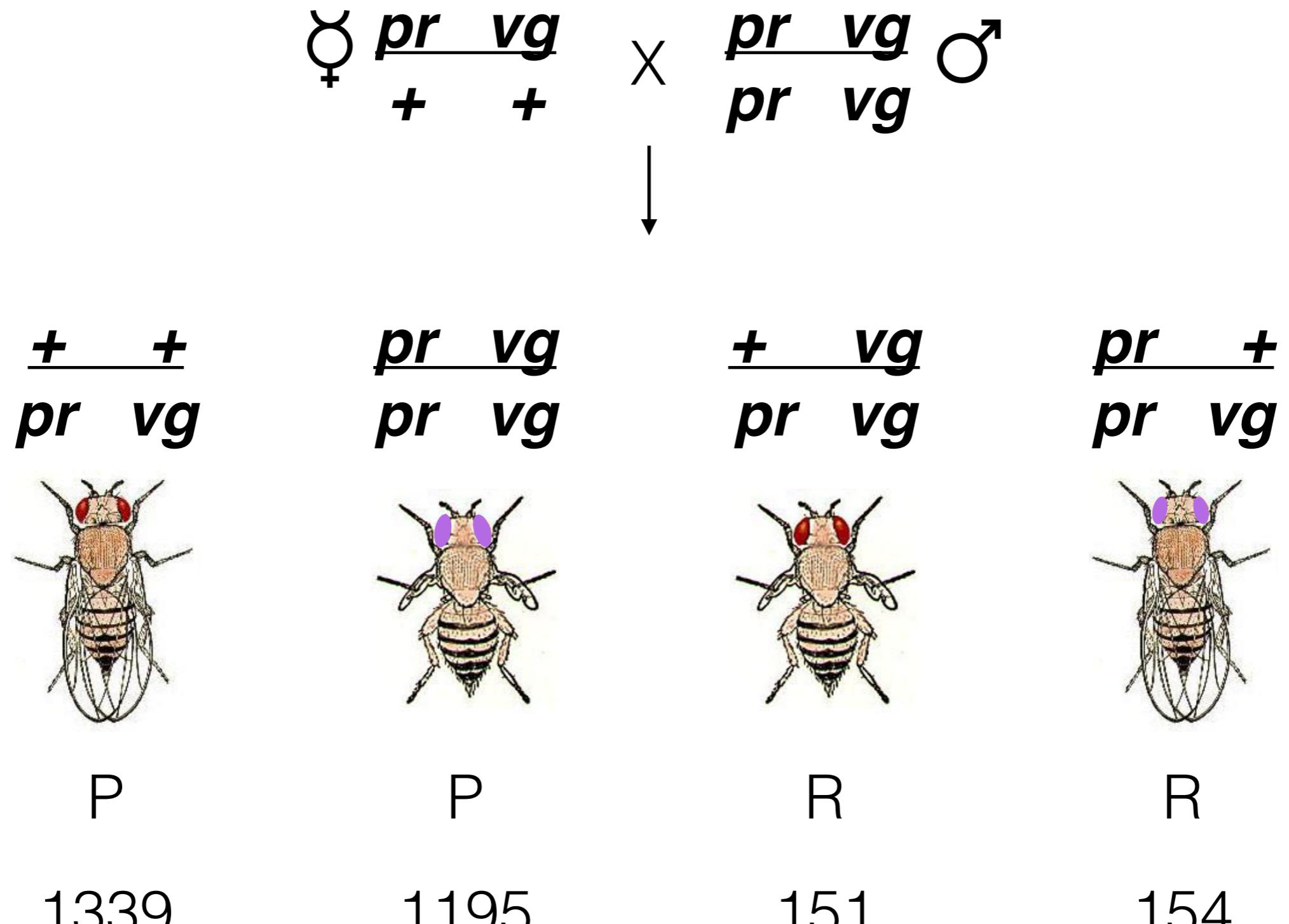


$+$ +



Purple eyes,
vestigial wings

pr vg



Expectation is equal proportion of each class

Total = 2839

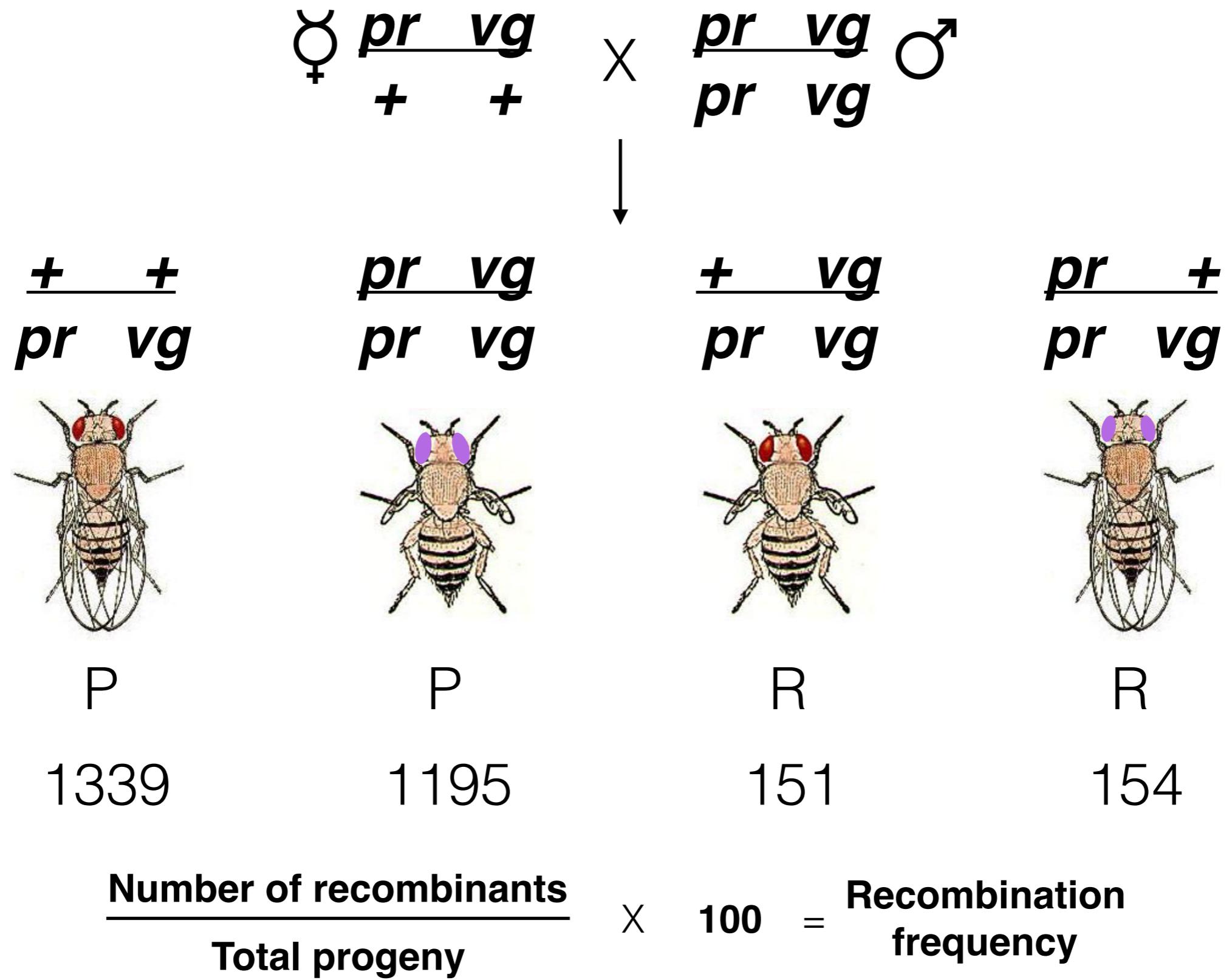


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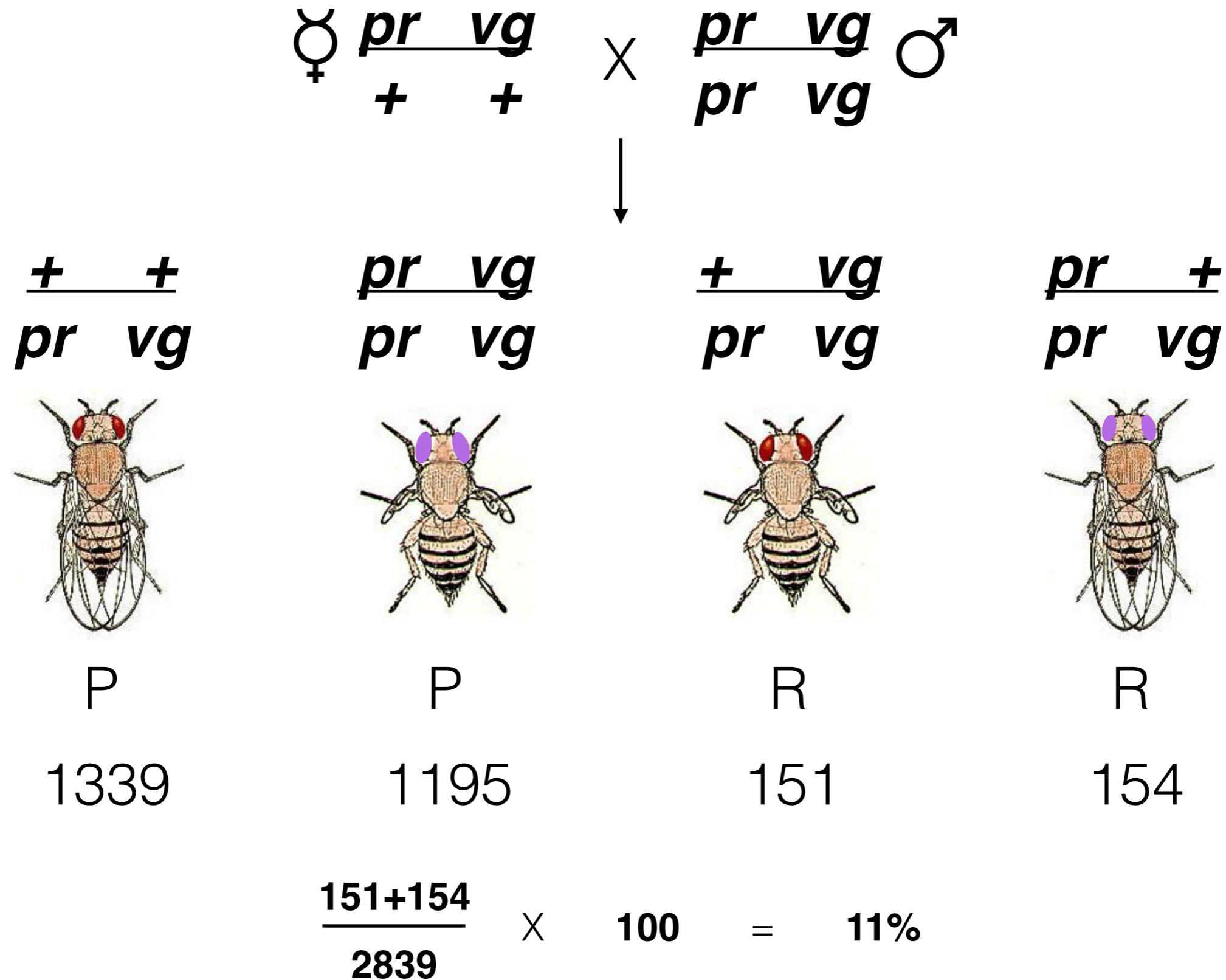
Alfred Sturtevant

$$\frac{\text{Number of recombinants}}{\text{Total progeny}} \times 100 = \text{Recombination frequency}$$

1% RF = 1 map unit = 1 centiMorgan



Total = 2839



Total = 2839

Recombination is the exchange of genetic material between homologous chromosomes

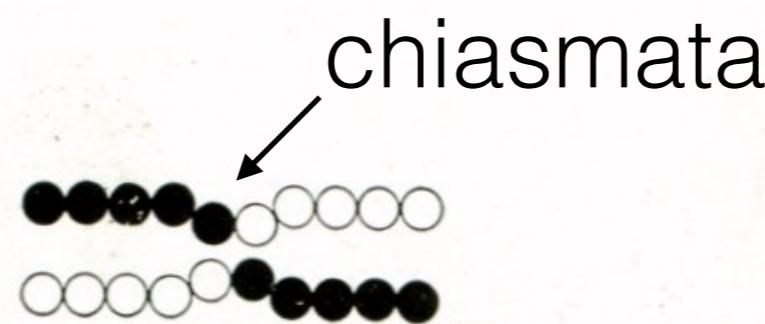
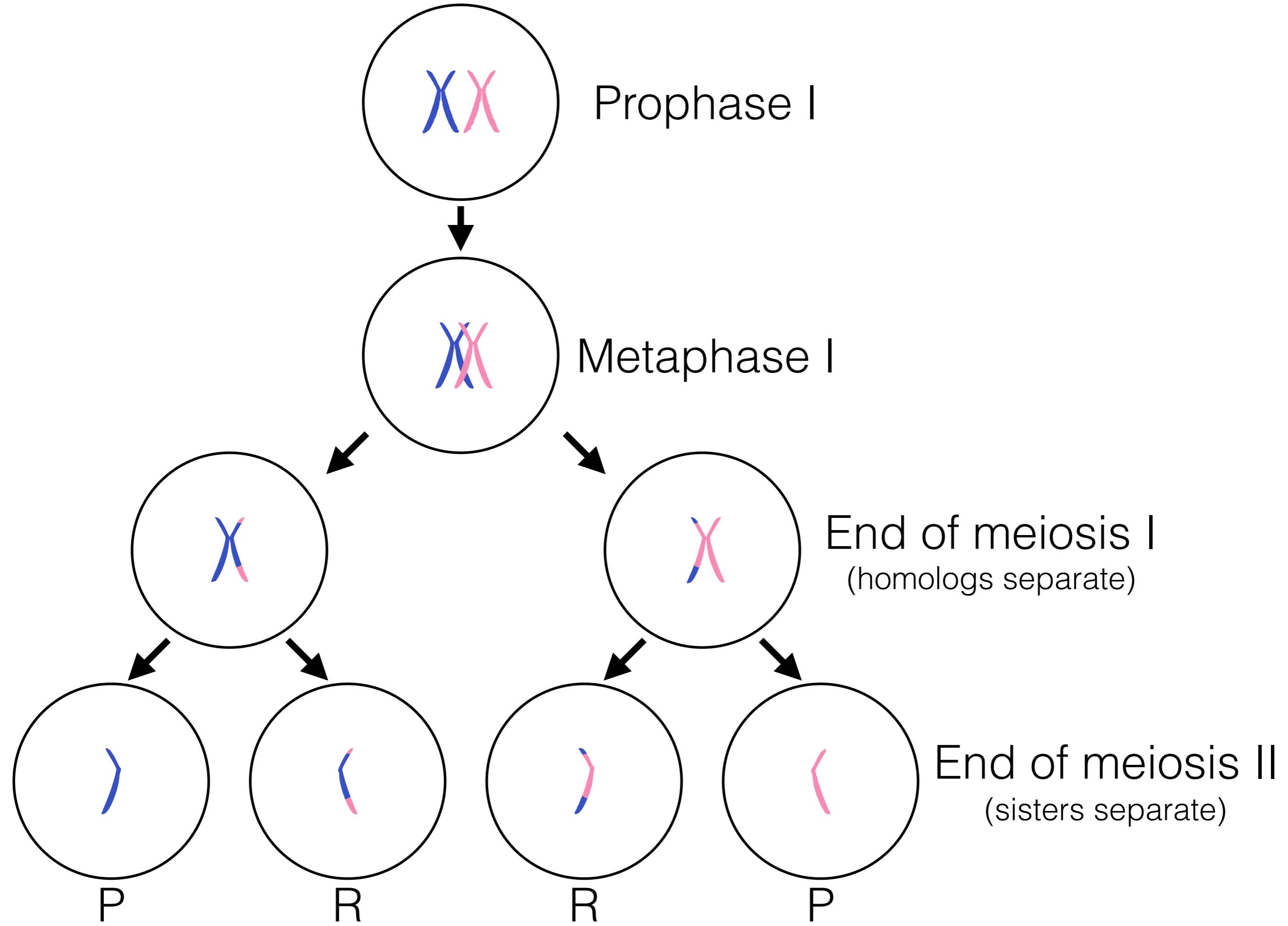
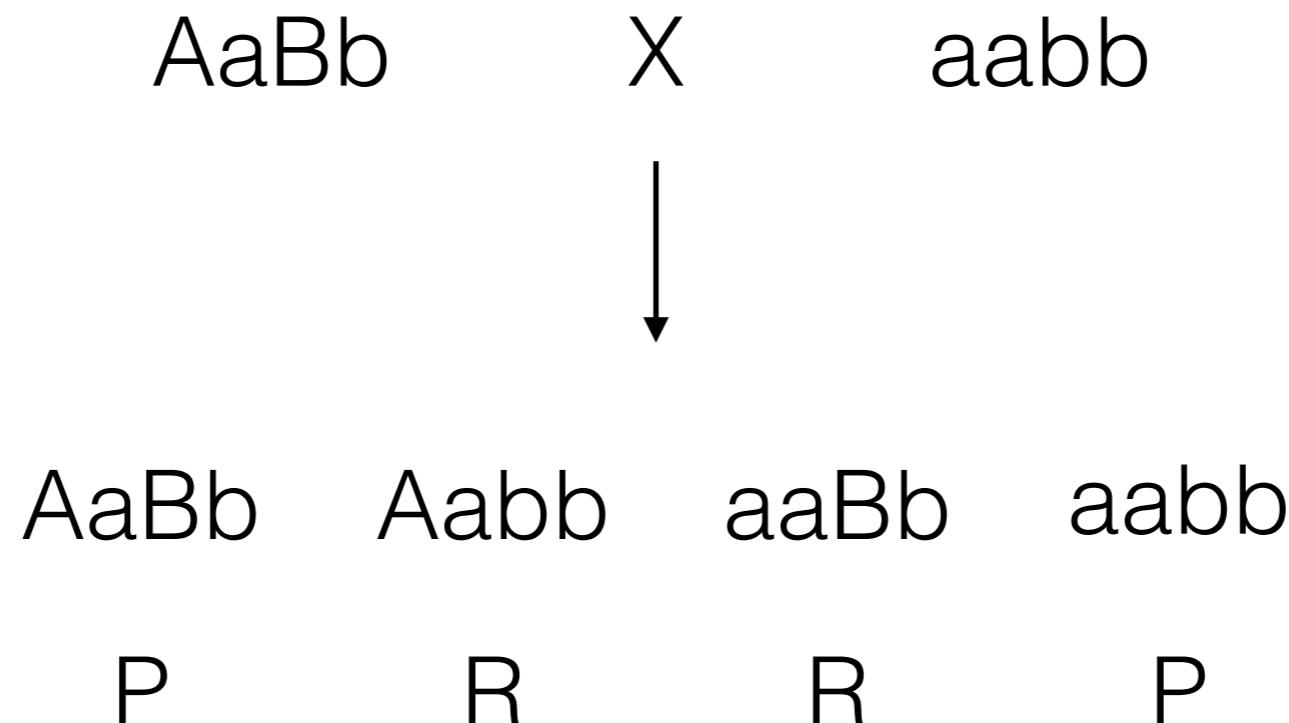


FIG. 64. Scheme to illustrate a method of crossing over of the chromosomes.



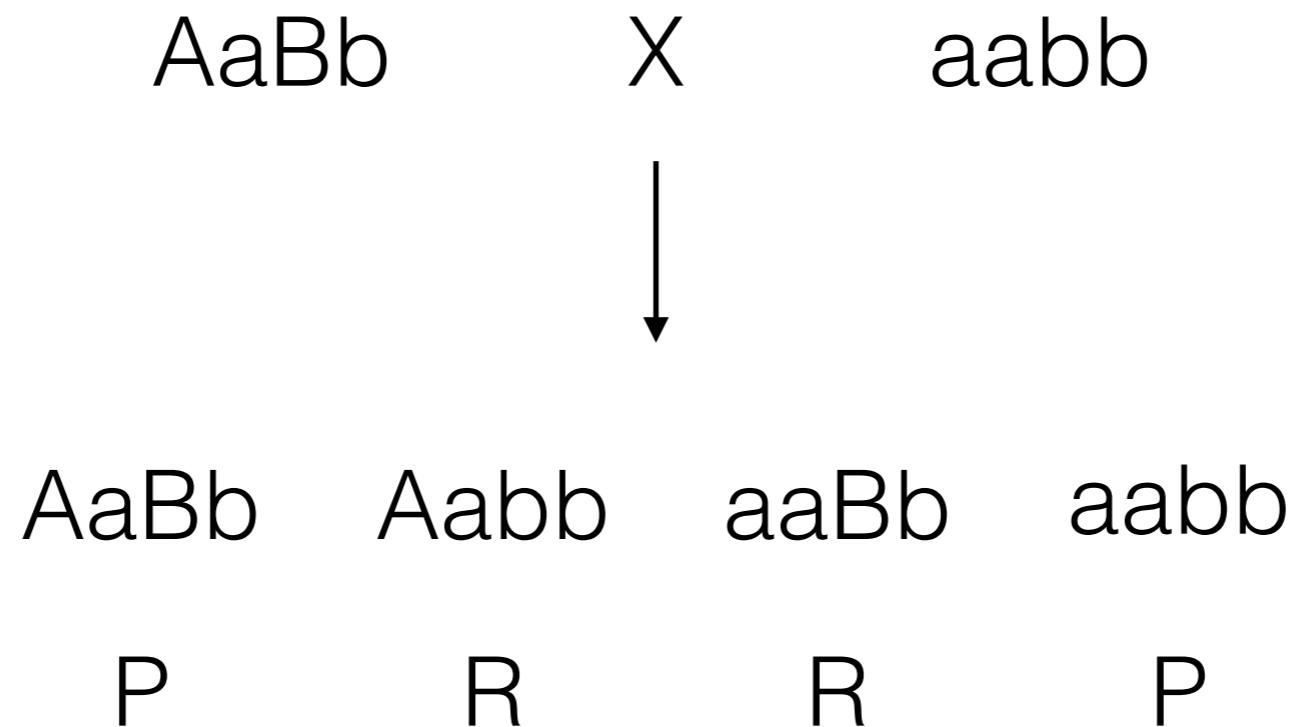
Independent assortment defines the limit of linkage at 50 cM



All four classes occur in equal ratios

$$\frac{\text{Number of recombinants}}{\text{Total progeny}} \times 100 = \text{Recombination frequency}$$

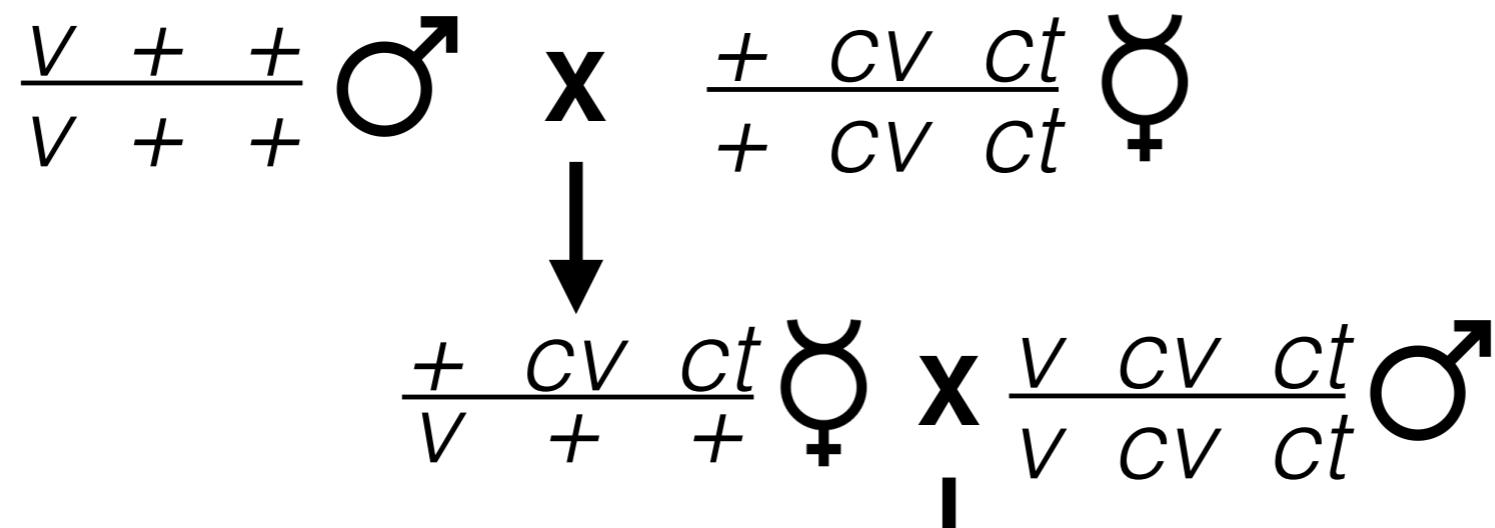
Independent assortment defines the limit of linkage at 50 cM



All four classes occur in equal ratios

$$\frac{2^*x}{2^*x + 2^*x} \times 100 = 50\%$$

A three-factor cross



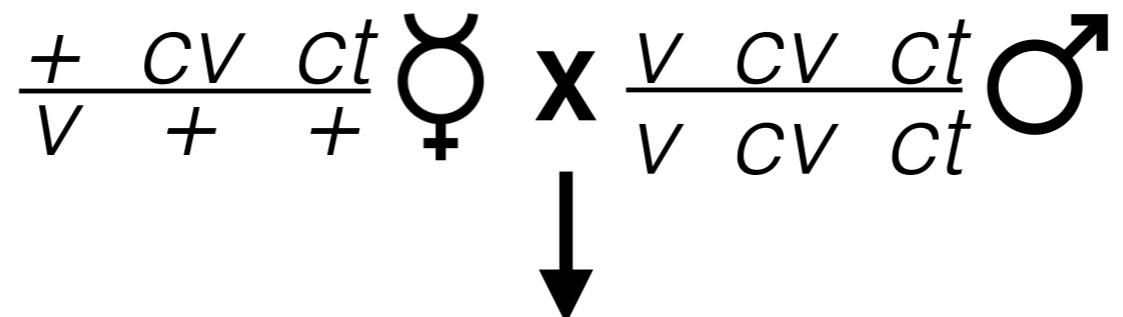
Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

v = vermillion eyes

ct = cut wings

cv= crossveinless wings

+ = red eyes and normal wings



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

$$\begin{array}{c}
 + \quad CV \quad ct \quad \text{P} \\
 V \quad + \quad + \quad \text{P}
 \end{array}$$

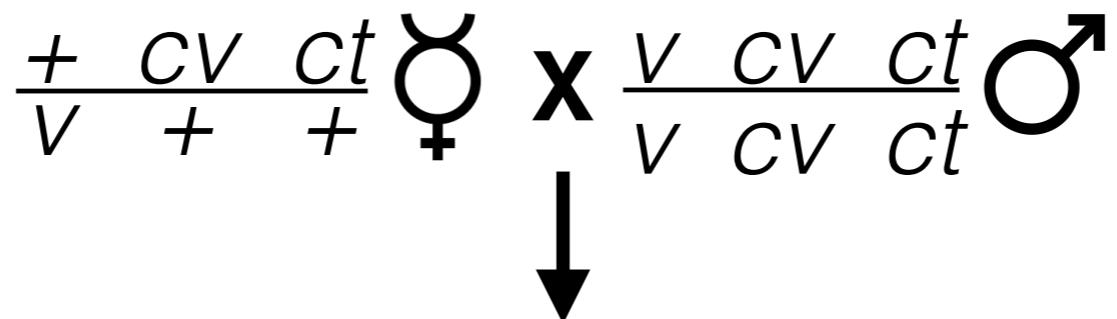
1. Determine parental class, label

v = vermillion eyes

ct = cut wings

cv= crossveinless wings

+ = red eyes and normal wings



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
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Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

$+ \quad CV \quad ct$ **P**
 $v \quad + \quad +$ **P**
R **R**
R **R**
R **R**
R **R**

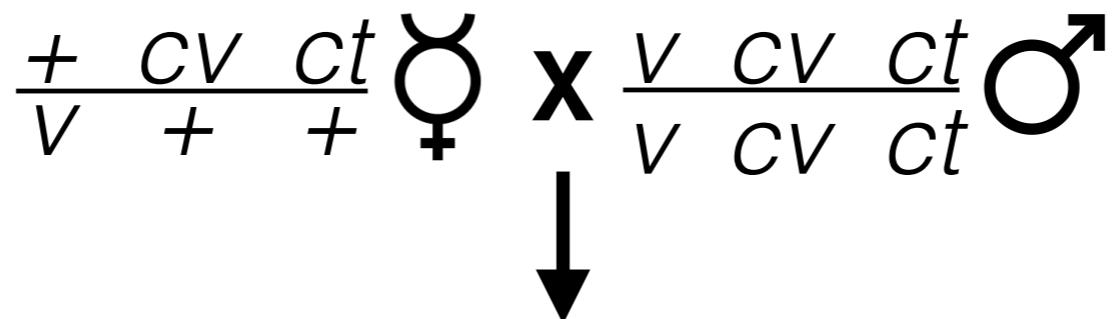
1. Determine parental class, label
2. Are all classes present?

v = vermillion eyes

ct = cut wings

cv = crossveinless wings

$+$ = red eyes and normal wings



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

$+ \quad CV \quad ct$ **P**
 $v \quad + \quad +$ **P**
R
R
R
R
R
 $+ \quad CV \quad +$ **R**
 $v \quad + \quad ct$ **R**

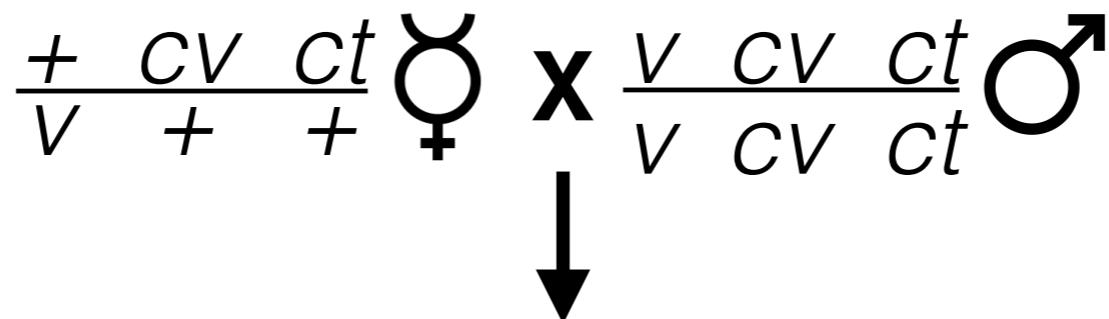
1. Determine parental class, label
2. Are all classes present?
3. Least abundant class is double recombinant, tells gene in middle

v = vermillion eyes

ct = cut wings

cv = crossveinless wings

$+$ = red eyes and normal wings



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

+ CV ct	P
V + +	P
+ + ct	R
V CV +	R
+ + +	R
V CV ct	R
+ CV +	R
V + ct	R

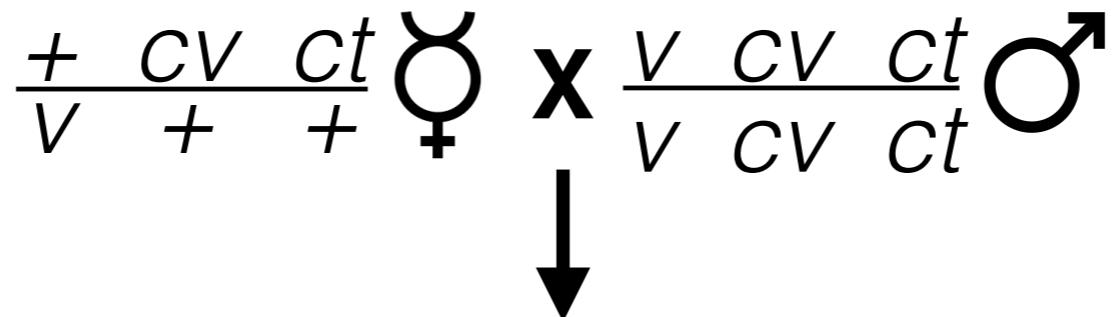
1. Determine parental class, label
2. Are all classes present?
3. Least abundant class is double recombinant, tells gene in middle
4. Write out the genotypes of the offspring

v = vermillion eyes

ct = cut wings

cv= crossveinless wings

+ = red eyes and normal wings



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
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Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

$+ \quad CV \quad ct$ P
 $v \quad + \quad +$ P
 $+ \quad + \quad ct$ R
 $v \quad CV \quad +$ R
 $+ \quad + \quad +$ R
 $v \quad CV \quad ct$ R
 $+ \quad CV \quad +$ R
 $v \quad + \quad ct$ R



1448 total progeny

1. Determine parental class, label
2. Are all classes present?
3. Least abundant class is double recombinant, tells gene in middle
4. Write out the genotypes of the offspring
5. Calculate distance from one gene to middle gene **v to ct**

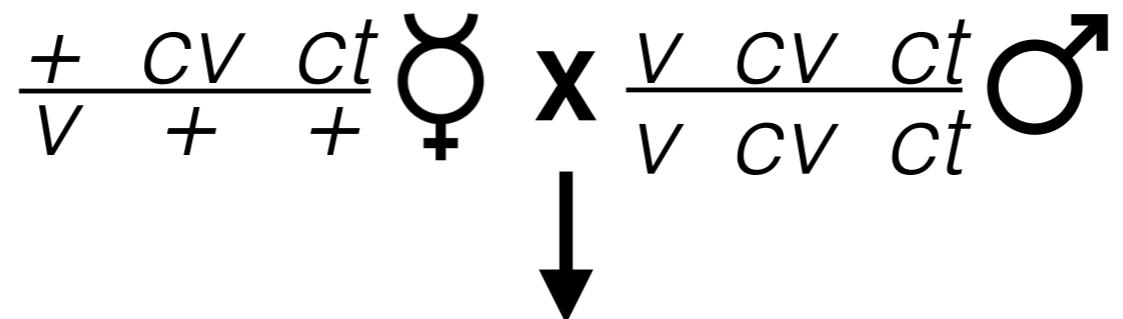
v = vermillion eyes

ct = cut wings

cv = crossveinless wings

$+$ = red eyes and normal wings

$$\frac{94+89+5+3}{1448} \times 100 = 13.2\%$$



Eye Phenotype	Crossvein Phenotype	Cut Phenotype	Number of offspring
Red	No crossvein	Cut wing	580
Vermillion	Crossvein	Normal wing	592
Red	Crossvein	Cut wing	40
Vermillion	No crossvein	Normal wing	45
Red	Crossvein	Normal wing	94
Vermillion	No crossvein	Cut wing	89
Red	No crossvein	Normal wing	5
Vermillion	Crossvein	Cut wing	3

$+ \quad CV \quad ct$ P
 $v \quad + \quad +$ P
 $+ \quad + \quad ct$ R ←
 $v \quad CV \quad +$ R ←
 $+ \quad + \quad +$ R
 $v \quad CV \quad ct$ R ←
 $+ \quad CV \quad +$ R ←
 $v \quad + \quad ct$ R ←

1448 total progeny

- Determine parental class, label
- Are all classes present?
- Least abundant class is double recombinant, tells gene in middle
- Write out the genotypes of the offspring
- Calculate distance from one gene to middle gene
- Calculate distance from the other gene to middle gene **cv to ct**

v = vermillion eyes

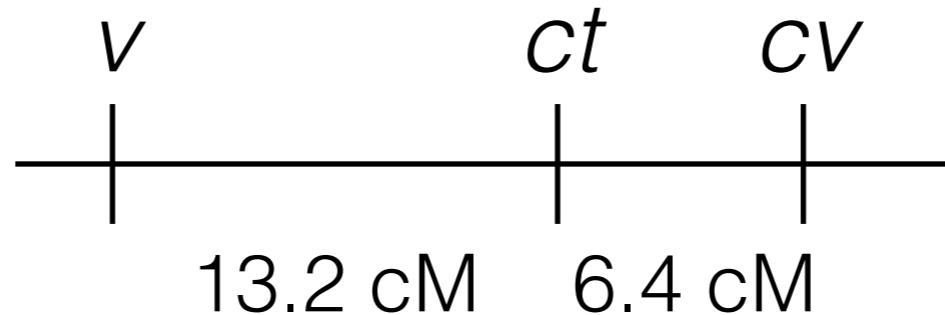
ct = cut wings

cv = crossveinless wings

+ = red eyes and normal wings

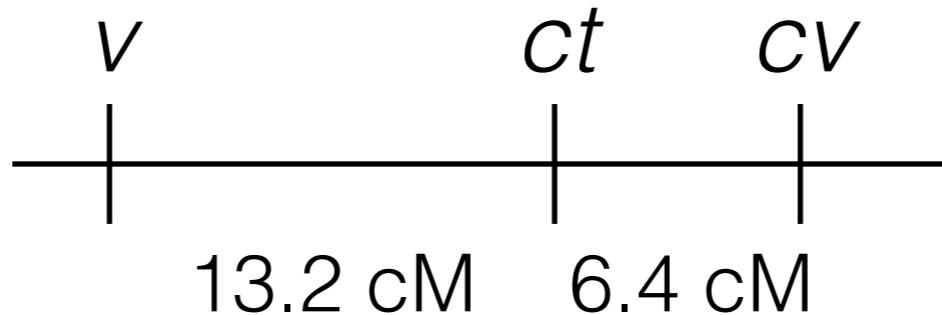
$$\frac{40+45+5+3}{1448} \times 100 = 6.4\%$$

Our first genetic map



1. Order by least abundant class
2. Arbitrary which genes on ends
3. Class v to cv undercounts because double recombinants look like parentals

Our first genetic map

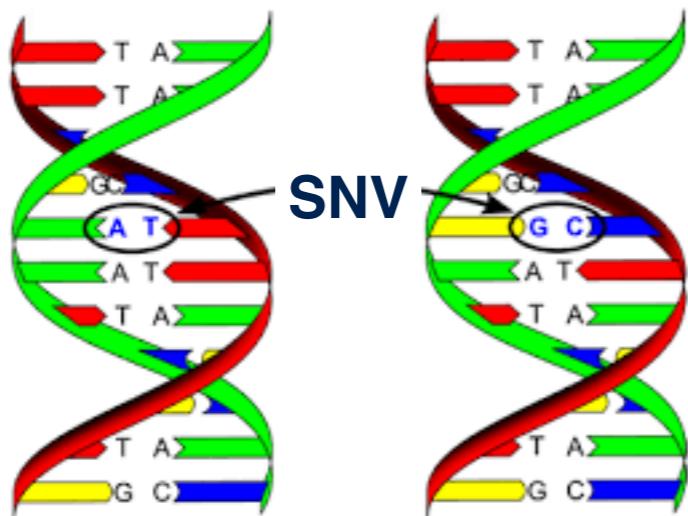


1. Order by least abundant class
2. Arbitrary which genes on ends
3. Class *v* to *cv* undercounts because double recombinants look like parentals

We have a better way!

Molecular markers are often used for genetic mapping

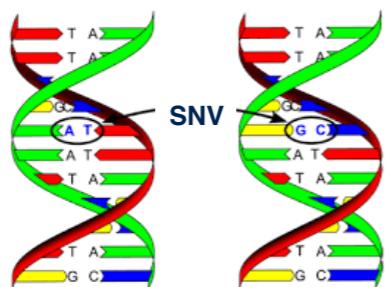
- Single nucleotide variants



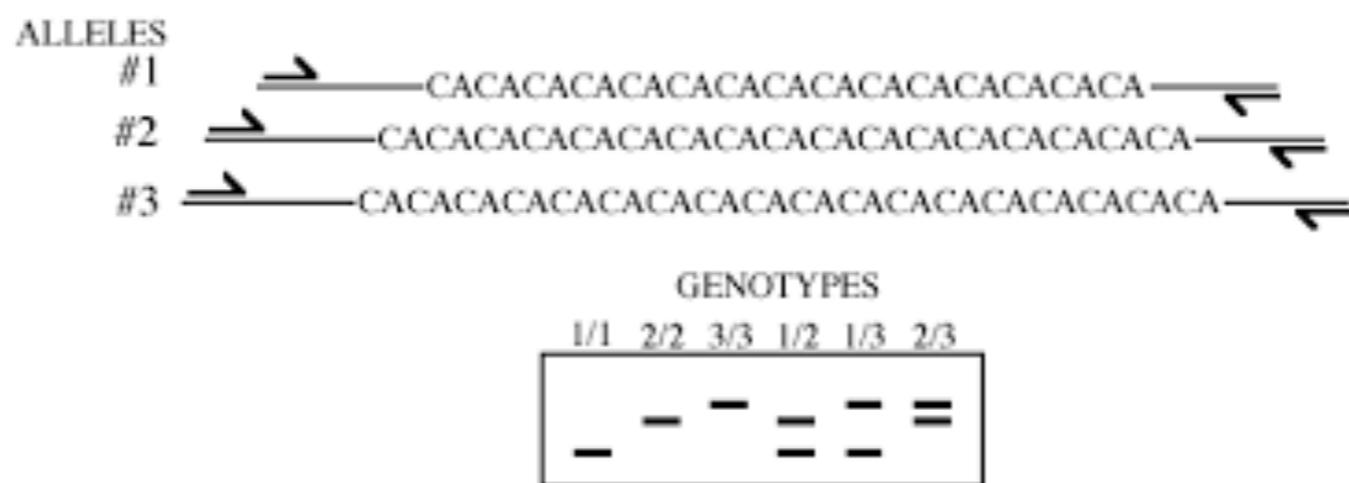
Detected by sequencing,
hybridization (array), or PCR.

Molecular markers are often used for genetic mapping

- Single nucleotide variants

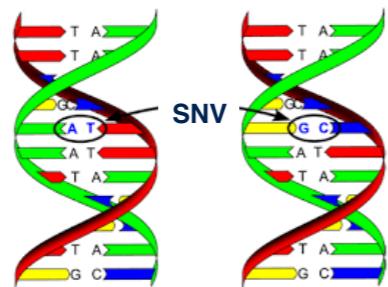


- Microsatellite or short-tandem repeats (STRs)



Molecular markers are often used for genetic mapping

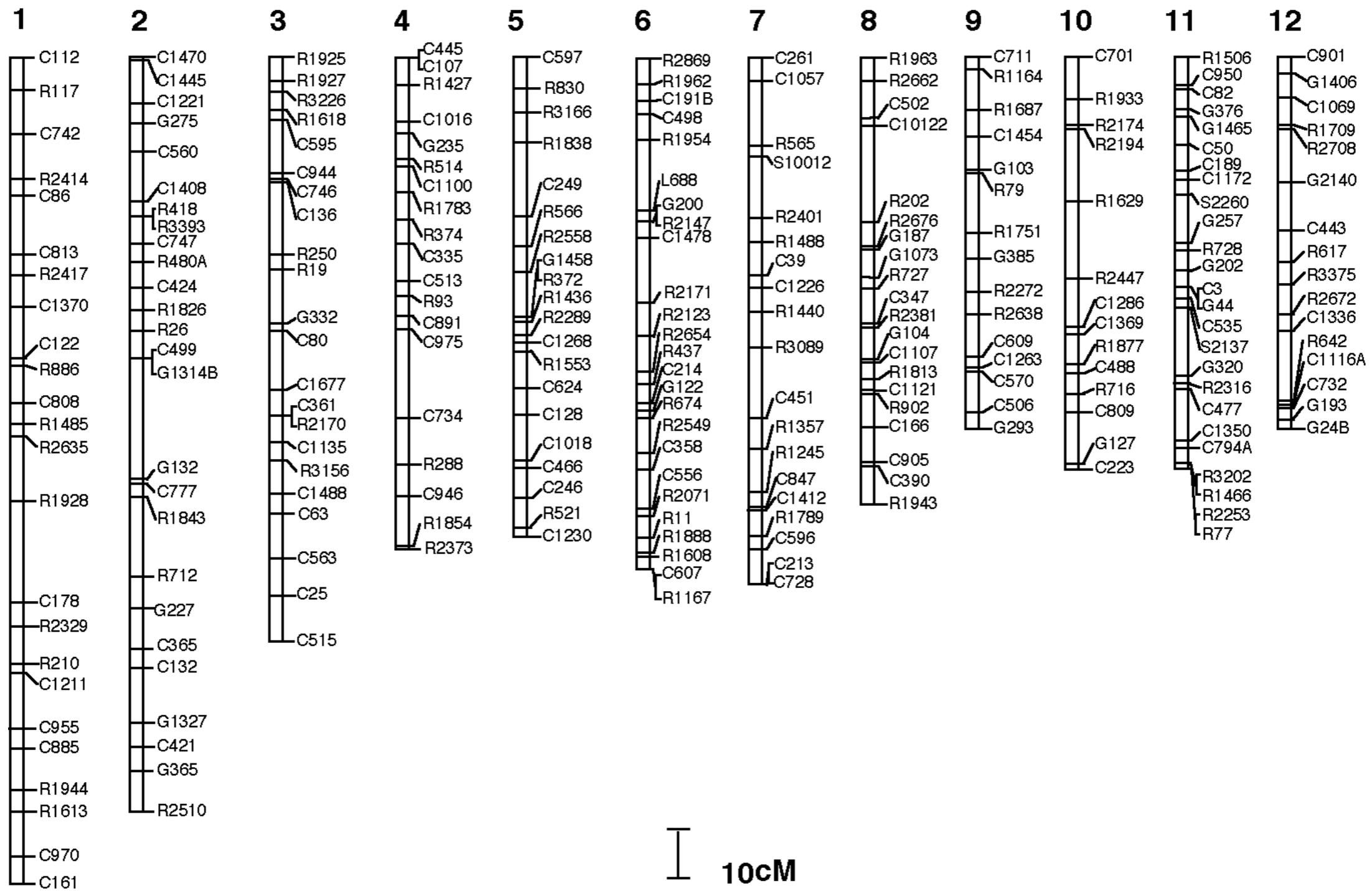
- Single nucleotide variants



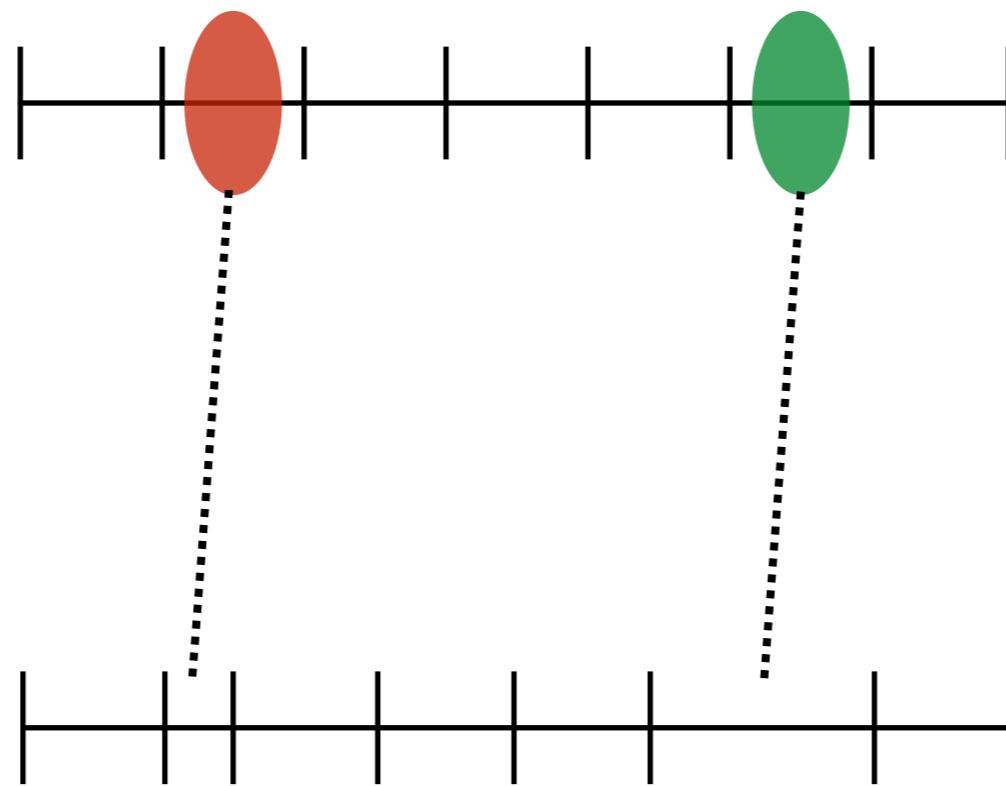
- Microsatellite or short-tandem repeats (STRs)

- Insertion/deletion variants

Molecular markers are used most of the time



What do regions of more or less recombination do to the linkage map?



Imagine markers
every 10 kb

Genetic map stretches
and contracts based
on recombination rates

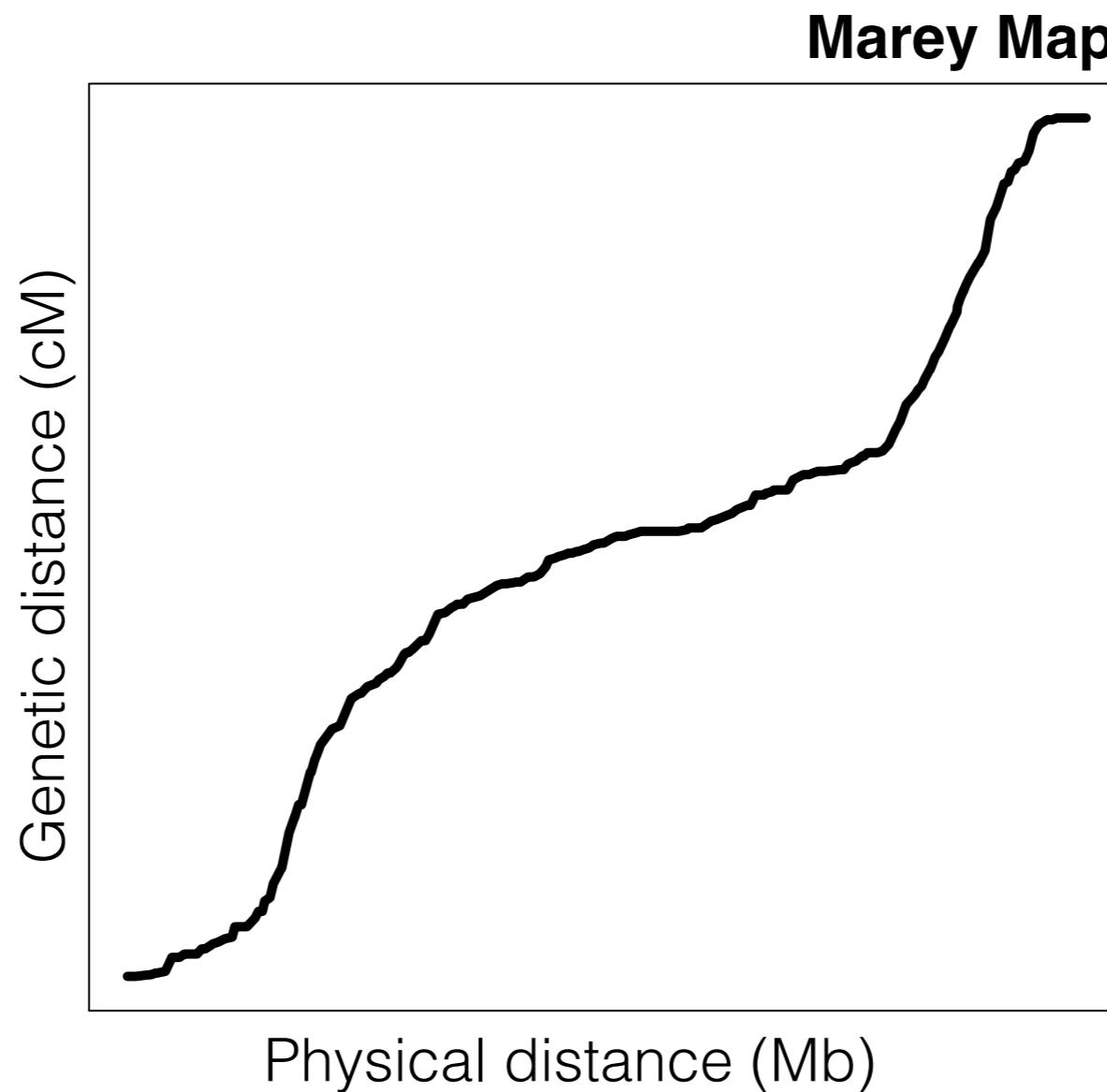


Less recombination (cold spot)



More recombination (hot spot)

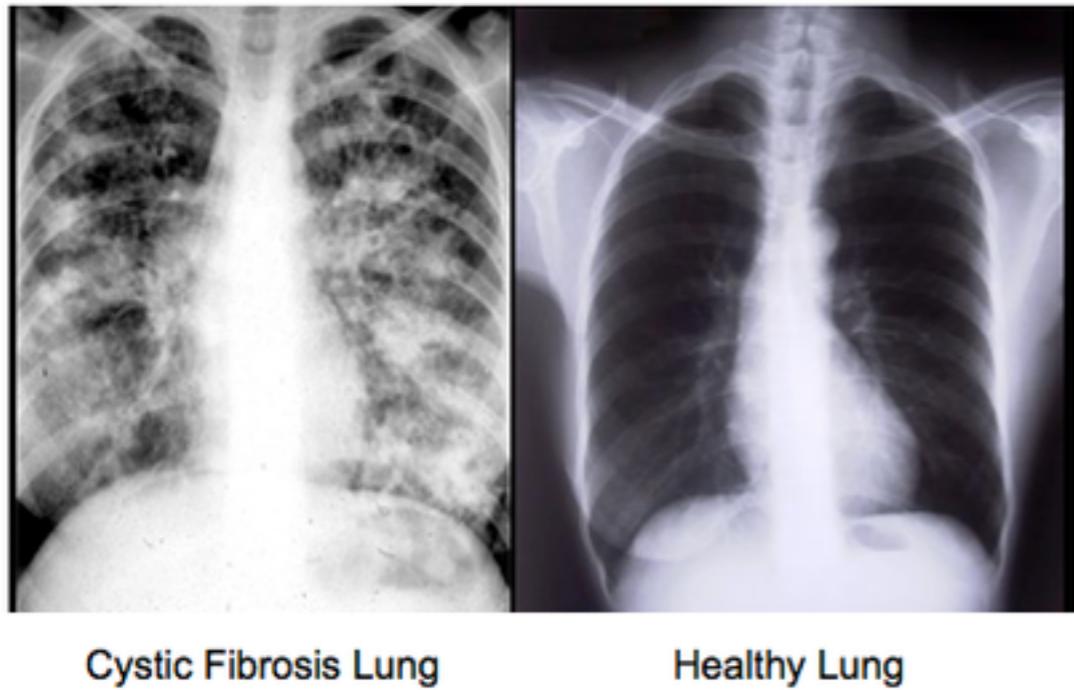
What do regions of more or less recombination do to the linkage map?



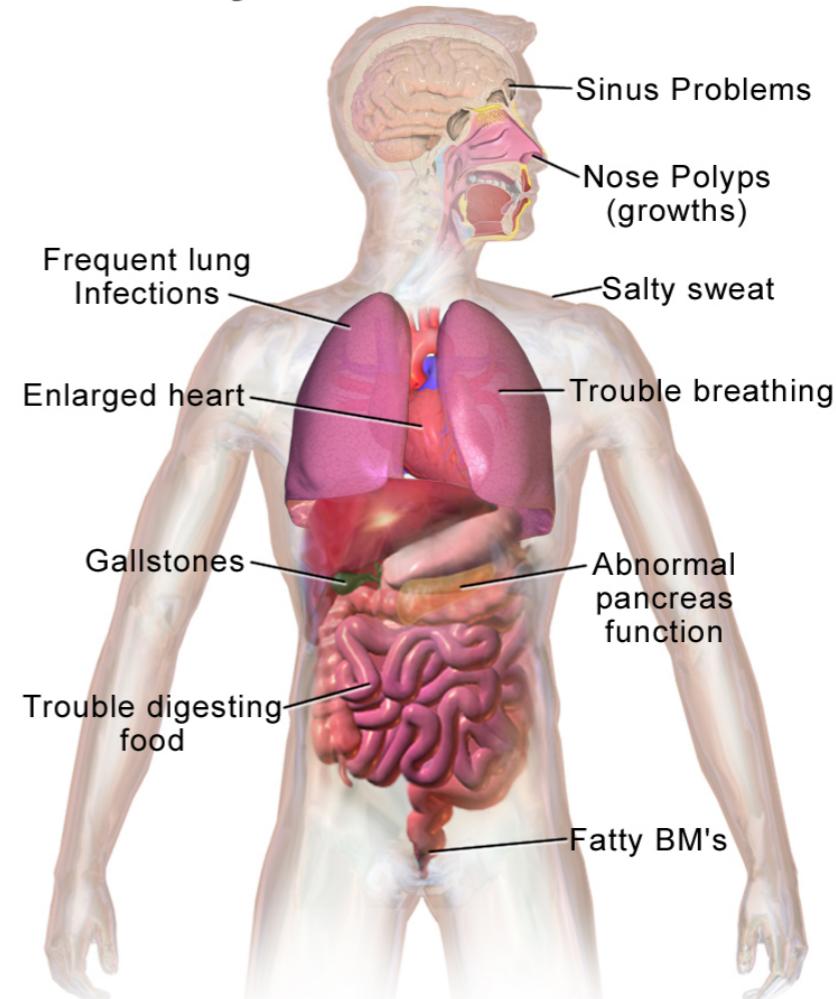
Why do we care?

Is this technique “old-fashioned”?

Cystic fibrosis is a debilitating disorder

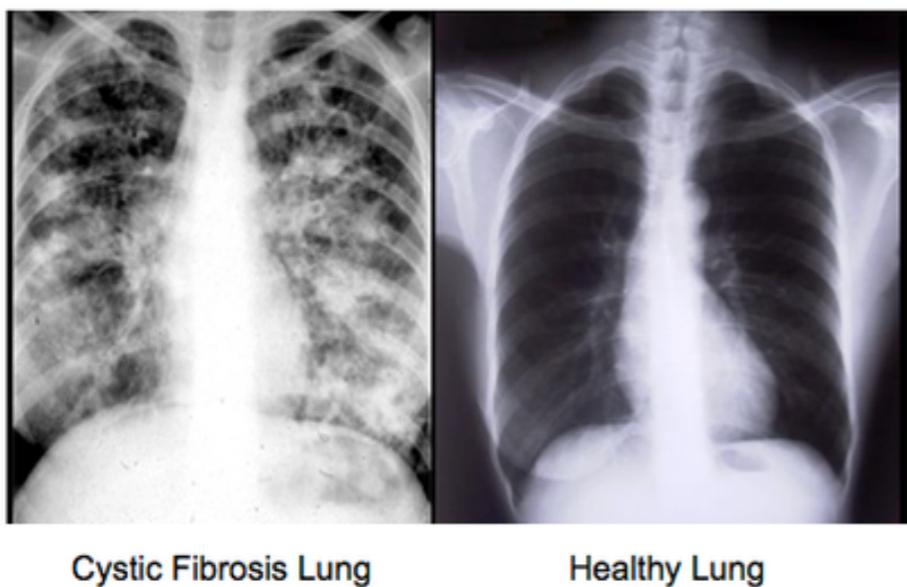


Health Problems with Cystic Fibrosis

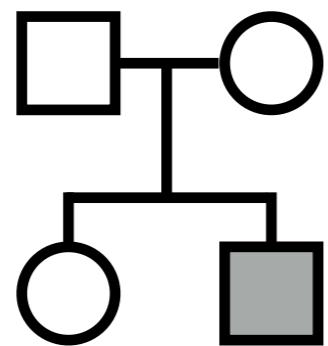


- Rare disease affects 1/10,000 live births
- Breathing difficulties caused by thick mucus
- Pancreas, liver, kidneys, and intestine are also deficient

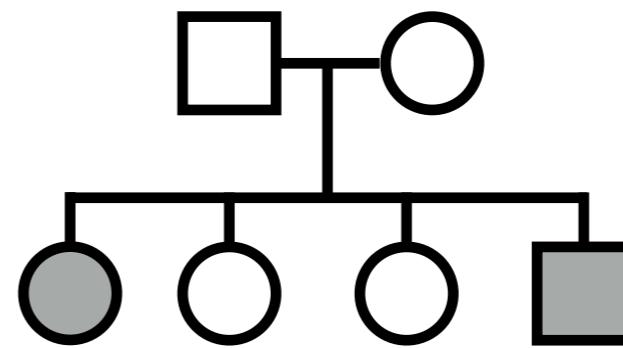
Cystic fibrosis is inherited in families



- Unaffected male
- Unaffected female
- CF male
- CF female



Family #1

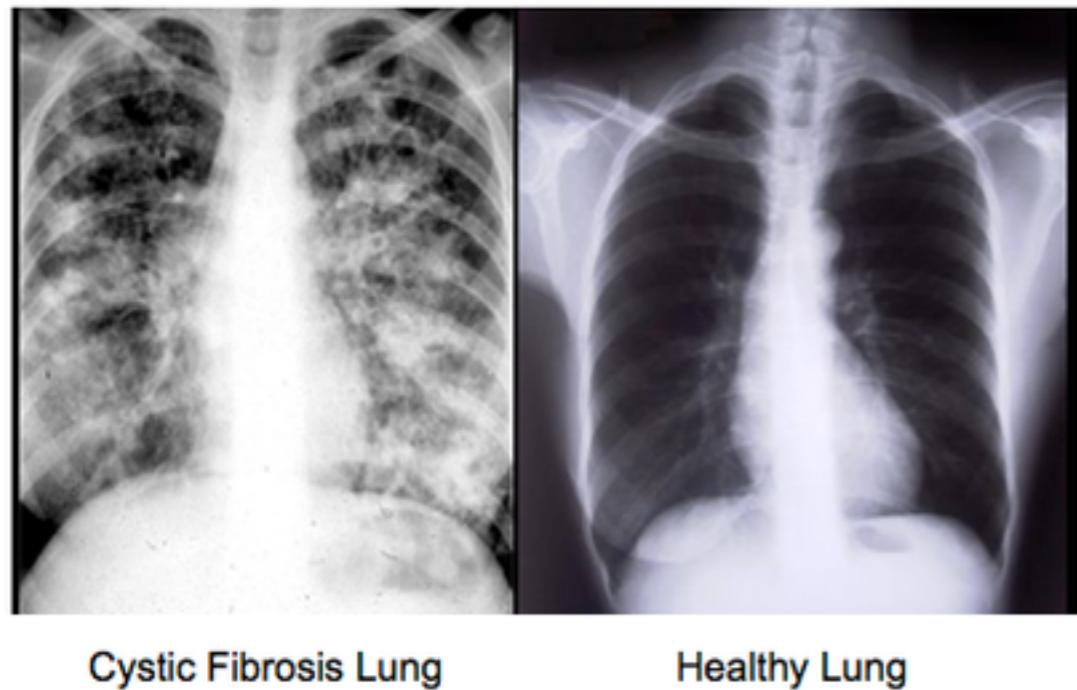


Family #2

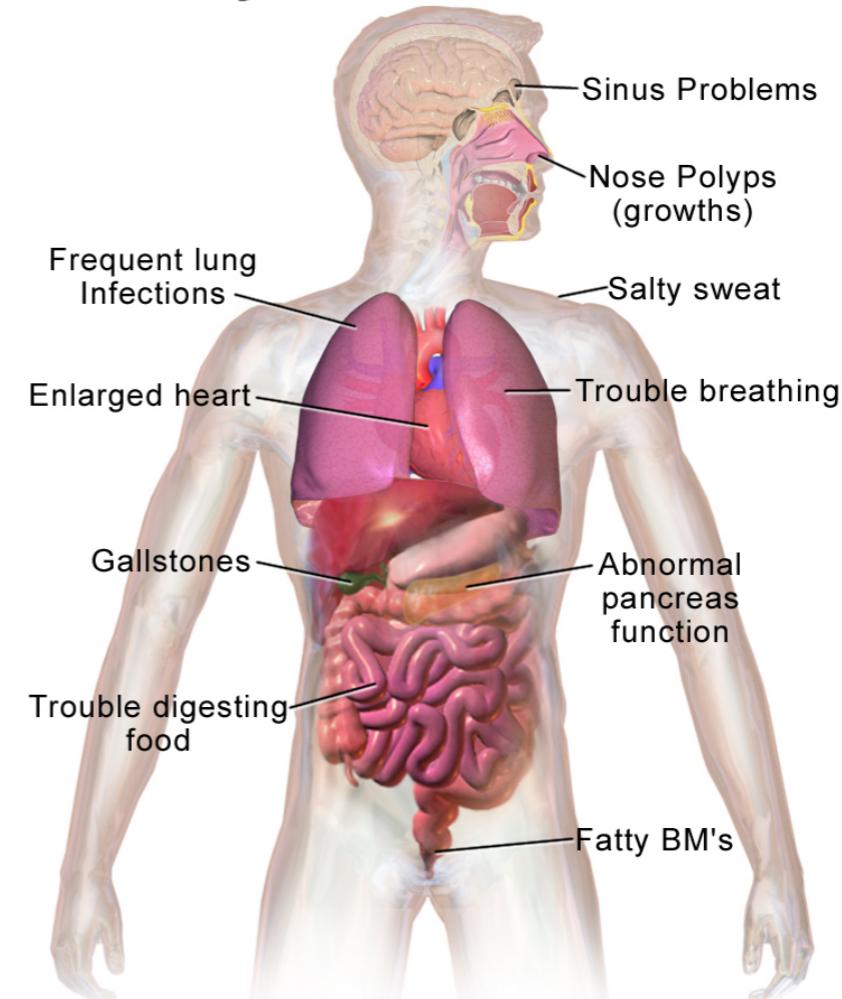
What is the trait?

Dominance?

What about cystic fibrosis and today's topic?



Health Problems with Cystic Fibrosis



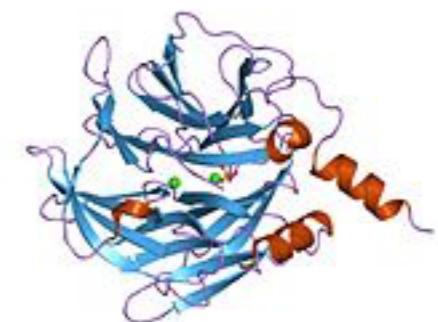
Where is the gene that when mutated causes cystic fibrosis?

How would you map it?

Linkage to allozymes

Allozymes are enzymes with activities that vary from person to person

PON1 is a hydrolase used for detoxifying cells.
Activity varies from person to person.



68 families with at least two children with and without CF were phenotyped for *PON1* activity and CF.

Found linkage to *PON1* and chromosome 7

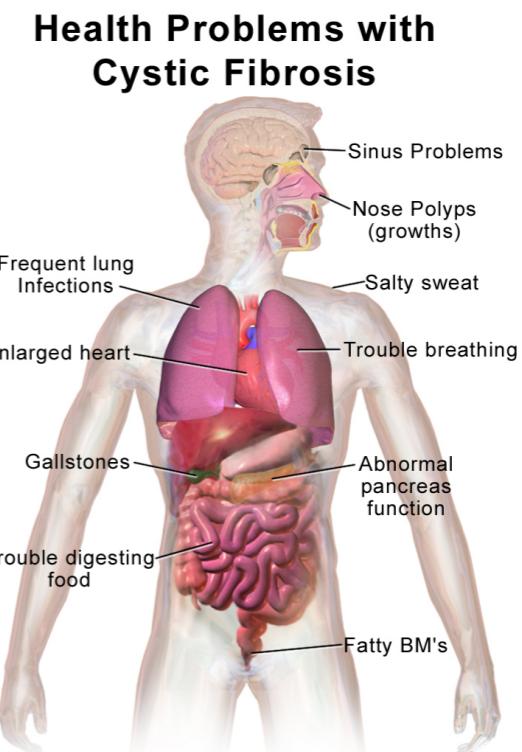
What have we learned so far?

CF is rare – 1/10,000 births

Autosomal recessive disorder

Not caused by chromosomal aberrations or NDJ

Linked to *PON1* on chromosome 7



Genetics is a powerful discovery and analytical tool

