Linkage & Gene Mapping in Eukaryotes

(CHAPTER 5- Brooker Text)

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BIO 184
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Linkage and Crossing Over

- In eukaryotic species, each linear chromosome contains a long piece of DNA
  - A typical chromosome contains many hundred or even a few thousand different genes
- The term linkage has two related meanings
  - 1. Two or more genes can be located on the same chromosome (location)
  - 2. Genes that are close together tend to be transmitted as a unit (transmission)
• Chromosomes are called **linkage groups**
  – They contain a group of genes that are linked together

• The number of linkage groups is the number of types of chromosomes of the species
  – For example, in humans
    • 22 autosomal linkage groups
    • An X chromosome linkage group
    • A Y chromosome linkage group

• Genes that are far apart on the same chromosome may independently assort from each other
  – This is due to **crossing-over**

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**Crossing Over May Produce Recombinant Phenotypes**

• In diploid eukaryotic species, linkage can be altered during meiosis as a result of crossing over

• **Crossing over**
  – Occurs during prophase I of meiosis at the **bivalent** stage
  – Non-sister chromatids of homologous chromosomes exchange DNA segments
• Genetic maps allow us to estimate the relative distances between linked genes, based on the likelihood that a crossover will occur between them.
• Experimentally, the percentage of recombinant offspring is correlated with the distance between the two genes:
  – If the genes are far apart → many recombinant offspring
  – If the genes are close → very few recombinant offspring
• Map distance = \( \frac{\text{Number of recombinant offspring}}{\text{Total number of offspring}} \times 100 \)
• The units of distance are called map units (mu)
  – They are also referred to as centiMorgans (cM)
• One map unit is equivalent to 1% recombination frequency

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**Trihybrid or 3-Point Crosses**

• Data from trihybrid crosses yields information about map distance and gene order:
  – Example, we will consider fruit flies that differ in body color, eye color and wing shape:
    – \( b = \) black body color
    – \( b^* = \) gray body color
    – \( pr = \) purple eye color
    – \( pr^* = \) red eye color
    – \( vg = \) vestigial wings
    – \( vg^* = \) normal wings
• Analysis of the F₂ generation flies will allow us to map the three genes
  – The three genes exist as two alleles each
  – Therefore, there are $2^3 = 8$ possible combinations of offspring
  – If the genes assorted independently, all eight combinations would occur in equal proportions

• In the offspring of crosses involving linked genes,
  – Parental phenotypes occur most frequently
  – Double crossover phenotypes occur least frequently
  – Single crossover phenotypes occur with “intermediate” frequency

• The combination of traits in the double crossover tells us which gene is in the middle
  – A double crossover separates the gene in the middle from the other two genes at either end

• In the double crossover categories, the recessive purple eye color is separated from the other two recessive alleles
  – Thus, the gene for eye color lies between the genes for body color and wing shape
Which ones are the double crossover recombinants?

- **Calculate the map distance between pairs of genes**
  - To do this, one strategy is to regroup the data according to pairs of genes
    - From the parental generation, we know that the dominant alleles are linked, as are the recessive alleles
    - This allows us to group pairs of genes into parental and nonparental combinations
      - Parentals have a pair of dominant or a pair of recessive alleles
      - Nonparentals have one dominant and one recessive allele
    - The regrouped data will allow us to calculate the map distance between the two genes
3-Point Mapping

• vg-b recombinants are:
  – vg-b^+
  – vg^-b

3-Point Mapping

• Now lets look at b-pr, recombinants?
  – b-pr^+
  – b^-pr
3-Point Mapping

• Now let's look at vg-pr, recombinants?
  – vg-pr+
  – vg⁺-pr

A 3-point cross

\[
\begin{align*}
\text{P} & \quad \varphi \text{vg b pr/ vg b pr} \times \varphi \text{vg⁺ b⁺ pr⁺/ vg⁺ b⁺ pr⁺} \\
\text{F₁ (all identical)} & \quad \text{vg b pr/ vg⁺ b⁺ pr⁺} \\
\text{Test cross} & \quad \varphi \text{vg b pr/ vg⁺ b⁺ pr⁺} \times \varphi \text{vg b pr/ vg b pr} \\
\text{Test cross progeny} & \quad \\
1779 & \quad \text{vg b pr} \\
1654 & \quad \text{vg⁺ b⁺ pr⁺} \\
252 & \quad \text{vg⁺ b pr} \\
241 & \quad \text{vg b⁺ pr⁺} \\
131 & \quad \text{vg⁺ b⁺ pr} \\
118 & \quad \text{vg b⁺ pr} \\
13 & \quad \text{vg b pr⁺} \\
9 & \quad \text{vg⁺ b⁺ pr} \\
\end{align*}
\]

\[
\begin{align*}
\text{(b)} & \quad \text{vg} \quad \text{pr} \quad \text{b} \quad \text{12.3 m.u.} \quad \text{6.4 m.u.} \quad \text{17.7 m.u.}
\end{align*}
\]
3-Point Mapping

• Now double check ourselves?
  12.3 + 6.4 = ?
  18.7

But 18.7 does not equal 17.7 why?

3-Point Mapping

• Didn’t include the double crossover events in your determination of vg and b:
  – A more accurate distance would be calculated using all numbers of recombinants
    • Need to count double crossover two times WHY?
      – Because in order to get all exchanges between vg and b then would occur twice
• When the distance between two genes is large
  – The likelihood of multiple crossovers increases
  – This causes the observed number of recombinant offspring to underestimate the distance between the two genes

Interference

• The product rule allows us to predict the likelihood of a double crossover from the individual probabilities of each single crossover

\[
\text{P (double crossover)} = \text{P (single crossover between } b \text{ and } pr) \times \text{P (single crossover between } pr \text{ and } vg) \\
= 0.064 \times 0.123 = 0.0079
\]

• Based on a total of 4,197 offspring
  – The expected number of double crossover offspring is

\[
= 4,197 \times 0.0079 = 33
\]
Interference

• Therefore, we would expect 33 offspring to be produced as a result of a double crossover

• However, the observed number was only (13+9)=22!
  – 9 with gray bodies, purple eyes, and normal wings
  – 13 with black body, red eyes, and vestigial wings

• This lower-than-expected value is due to a common genetic phenomenon, termed \textbf{positive interference}
  – The first crossover decreases the probability that a second crossover will occur nearby

• Interference (I) is expressed as
  \[ I = 1 - C \]
  - where C is the coefficient of coincidence

  \[ C = \frac{\text{Observed number of double crossovers}}{\text{Expected number of double crossovers}} \]

  \[
  C = \frac{22}{33} = 0.67
  \]

  \[ I = 1 - C = 1 - 0.67 \\
  = 0.33 \text{ or } 33\%
  \]
  – This means that 33% or 1/3 of the expected number of crossovers did not occur
• Since I is positive, this interference is positive interference

• Rarely, the outcome of a testcross yields a negative value for interference
  – Negative value would suggest that a first crossover enhances the rate of a second crossover

• The molecular mechanisms that cause interference are not completely understood
  – However, most organisms regulate the number of crossovers so that very few occur per chromosome