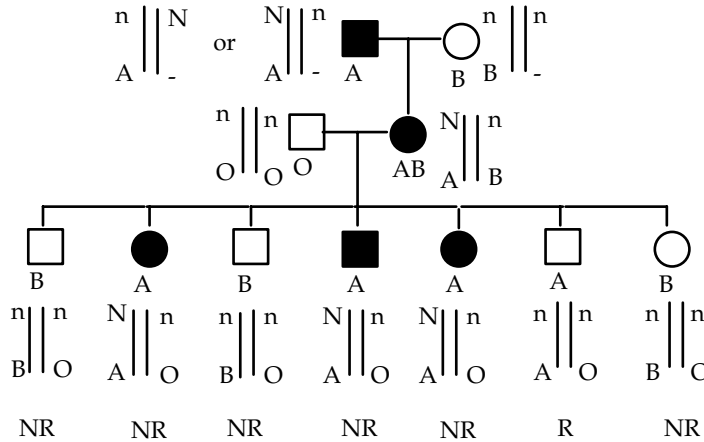


Lecture XI Answers

(By Bridget Quinn, Tutorial Program)

1. The following is a pedigree showing the linkage of the ABO blood group/nail-patella syndrome. Nail-patella syndrome is an autosomal dominant disorder with nail dysplasia, hypoplastic patella and other bony abnormalities.



- Can you determine the phase in the mother II-2? **See above.**
- Which children are recombinants? **See above.**
- Set up the expression for the lod score, z , for this pedigree.

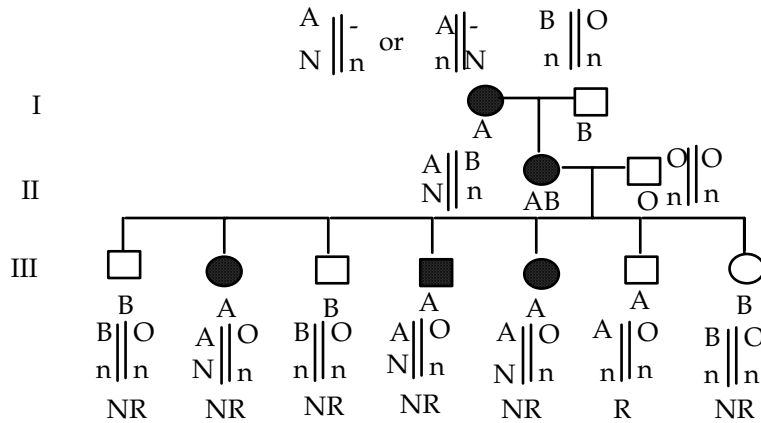
$$z = \log_{10} \frac{(1-\theta)^6(\theta)^1}{(0.5)^7} \quad \text{Where } \theta = \text{recombination frequency.}$$

This is the easy reduced formula for calculating the lod score. See the note at the end of this problem set for a brief review of LOD scores.

2. Data collected on 20 families yielded the following LOD scores for nail patella syndrome and ABO.

| θ | 0 | 0.1 | 0.2 | 0.3 | 0.4 |
|----------|------|------|------|-----|-----|
| | 1.01 | 2.88 | 1.98 | .79 | .31 |

What does the family shown in the pedigree contribute to the lod score? Combining the data from this family with the data in the table below, what would you say about the possibility of linkage between ABO and nail patella syndrome?



Analysis of the data shows that 6 of the seven children are nonrecombinants and 1 of the seven children is a recombinant.

| θ | 0 | .1 | .2 | .3 | .4 |
|------------|------|--------------|-------|--------|-------|
| | 1.01 | 2.88 | 1.98 | 0.79 | 0.31 |
| Family III | - | 0.831 | 0.826 | 0.654 | 0.377 |
| | - | 3.711 | 2.806 | 0.8554 | 0.687 |

With the addition of Family III, linkage is established at $\theta=0.1$. The highest value, a lod score of 3.7, indicates that the genes are 5011 times more likely to be linked than unlinked. (Use the 10^3 or the antilog button on your calculator to get this number.) By convention, linkage is considered established at a lod of 3 when the genes are 1000 times more likely to be linked than unlinked.

Lod Scores: A Brief Review

- Human do not produce enough progeny to use the simple calculation for recombination frequency.
- **Lod Score** (z) is a statistical test used to determine if two loci are linked or unlinked in the human genome.
- It can be used because lod score data from different families is **additive**, eliminating the problem of insufficient sample size.
- Lod score (log of the odds) can be defined as the \log_{10} of the odds that the loci are linked at a certain θ divided by the odds that they are unlinked.

$$\text{LOD} = \log_{10} \frac{P(\text{linked at a certain } \theta)}{P(\text{independent assortment})}$$

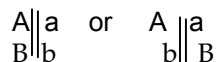
By convention if the **lod is ≥ 3** , that is the odds of linkage is 1000:1, the genes are considered linked. If the **lod is < -2** , that is the odds of linkage are 1:100, the genes are considered unlinked.

Calculating the Lod Score For a Given Family

A. Review of Terminology

Linkage phase- arrangement of the alleles at two loci relative to each other

Example- an individual heterozygous at two loci can have the alleles arranged in two different ways:



Cis or coupling- the allele arrangement in an individual heterozygous at two loci in which the dominant alleles are on one chromosome and the recessive alleles are on the other.

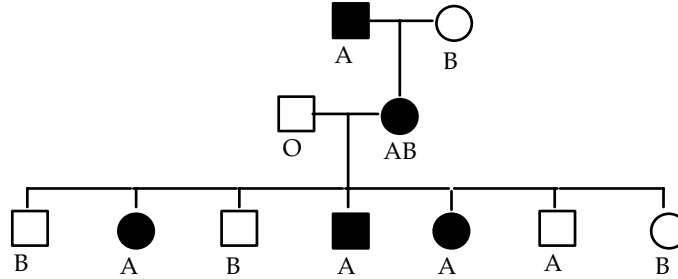


Trans or repulsion- the allele arrangement in an individual heterozygous at two loci in which the dominant alleles are on different chromosomes.

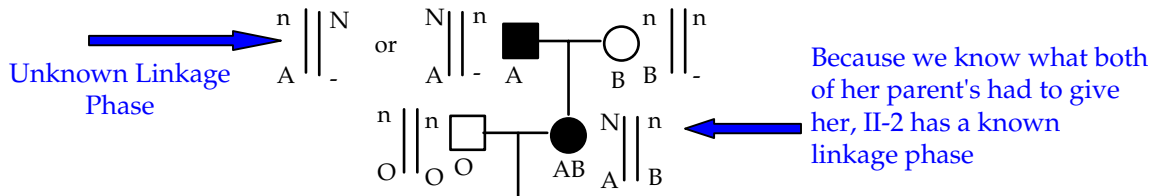


B. Algorithm for Calculating Lod Scores

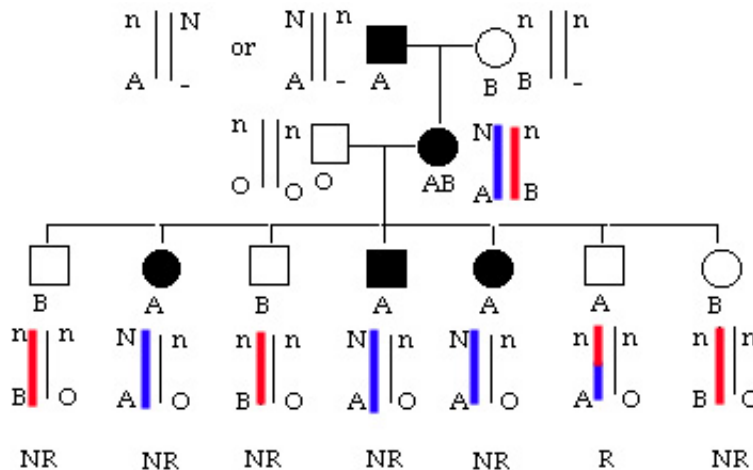
Example Pedigree from Problem 1:



- Determine if the linkage phase of the parents can be definitively determined. (You will need data from h/her parents to definitively determine a person's linkage phase.)
 If yes, you will use the formula for known phase
 If no, you will use the formula for unknown phase- **You will not need to use this formula in this class, but be prepared to recognize if a person has unknown phase.**



- Set the **linkage phase** of all progeny using the parent's linkage phase. Determine if chromosome of each progeny is a recombinant or a nonrecombinant chromosome relative to the parent.



- Plug the data into the appropriate formula (see below) for **all values of θ**
- Add **all values of θ** for the new family to the existing data
- Common mistakes include:

Incorrectly counting R and NR
 Forgetting to take the log
 Adding a single lod to the table

| | |
|---|--|
| <p>LOD Equation for Known Phase</p> $\text{Lod} = z = \log_{10} \frac{(1-\theta)^{\text{NR}} (\theta)^{\text{R}}}{(.5)^{\text{Total}}}$ <p>Where: 1-θ = frequency of no recombination θ = recombination frequency NR = number of nonrecombinants R = number of recombinants Total = total number of progeny</p> | <p>LOD Equation for Unknown Phase- Remember, you will not need to use this formula in this class.</p> $\text{Lod} = \log_{10} \frac{R_1 + R_2}{2}$ <p>R₁ = ratio if the parent's alleles are in cis R₂ = ratio if the parent's alleles are in trans</p> $\text{Ratio} = \frac{(1-\theta)^{\text{NR}} (\theta)^{\text{R}}}{(.5)^{\text{Total}}}$ |
|---|--|

- In reality, Lod scores are calculated by a computer and read off a graph.