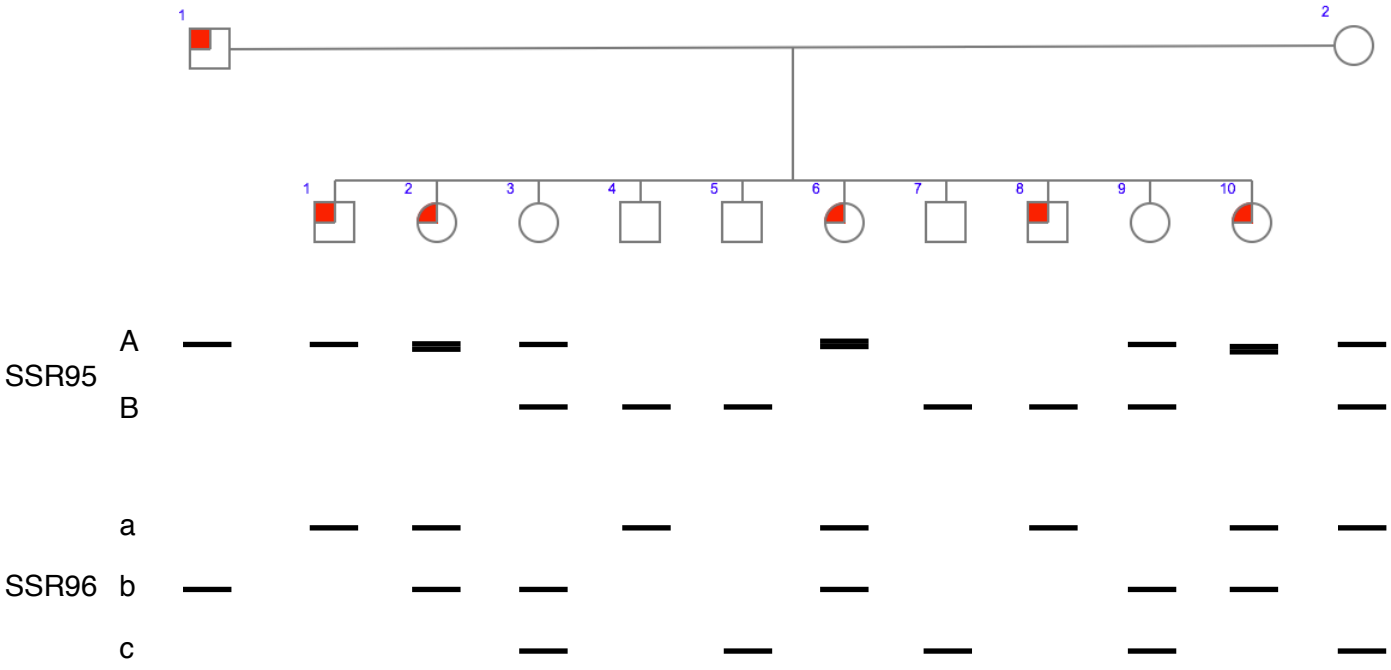
Bio393: Biomedical Genetics **Name:**_____
Problem Set #6
Due on Friday, May 17, 5 PM

Question 1:
You set out to genetically map color blindness with respect to short-sequence repeat (SSR) markers. Color blindness shows X-linked recessive inheritance and therefore is usually found in males. However, the mutant allele frequency is sufficiently high that colorblind females do occur.

Alleles: + (normal) cb (associated with color blindness)

Here is a family in which some individuals are affected:



(a) Diagram the two possible phase relationships between the SSR95 and SSR96 alleles in the mother.

$$\frac{A\ a}{B\ c} \qquad \frac{A\ c}{B\ a}$$

(b) Calculate the LOD score for linkage at θ = 0.1 between SSR95 and SSR96 in this family.

$$LOD_{0.1} = \log_{10} \frac{1/2 * (0.9)^8 * (0.1)^2 + 1/2 * (0.9)^2 * (0.1)^8}{(1/2)^{10}} = 0.343$$

(c) Identify a value of θ at which this family will yield a higher LOD score for linkage between SSR95 and SSR96. Calculate the LOD score for linkage between SSR95 and SSR96 at that new θ value.

Two out of 10 recombinant suggests that a theta of 0.2 would be better

$$LOD_{0.2} = \log_{10} \frac{1/2 * (0.8)^8 * (0.2)^2 + 1/2 * (0.8)^2 * (0.2)^8}{(1/2)^{10}} = 0.536$$

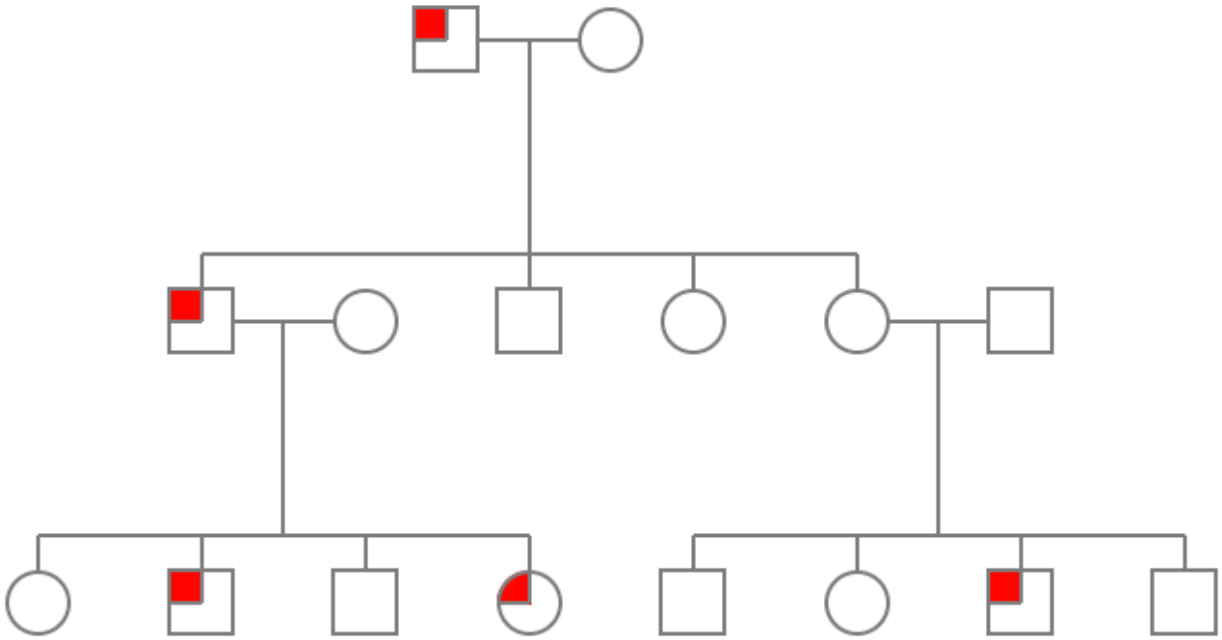
(d) Diagram the two possible phase relationships between the SSR95 and color blindness alleles in the mother.

$$\frac{A\ cb}{B\ +} \qquad \frac{A\ +}{B\ cb}$$

(e) Calculate a LOD score for linkage at θ = 0.1 between SSR95 and color blindness in this family.

$$LOD_{0.1} = \log_{10} \frac{1/2 * (0.9)^9 * (0.1)^1 + 1/2 * (0.9)^1 * (0.1)^9}{(1/2)^{10}} = 1.297$$

Question 3:
Syndactyly is a rare genetic condition inherited as an autosomal dominant trait. Unusually however, a person who has the defective allele responsible for syndactyly (N) does not always express the trait. The diagram below shows a pedigree of a family with syndactyly.



You find no history of syndactyly in the ancestors of individual I-2, II-2, and II-6. Assuming no new mutations exist, explain why or why not it is reasonable to conclude the following:

(a) Individual II-5 has the genotype nn at the syndactyly locus

It is not reasonable to conclude that individual II-5 is nn because she has offspring that have the genotype Nn, and (1) II-6 has no ancestors with syndactyly and (2) no new mutations are arising.

(b) Individuals II-4 and II-5 may have the same genotype at the syndactyly locus

It is reasonable that individual II-4 and II-5 both have the same genotype. Because II-4 has no offspring and both individuals do express the syndactyly trait, it is possible that they have different genotypes. However, we believe that II-5 has the genoypte Nn, and there is a 50% chance that II-4 has the same genotype.

(c) Individual II-2 has the genotype Nn at the syndactyly locus

It is not reasonable to conclude that II-2 is a carrier for syndactyly and not expressing because we see no family history of syndactyly for her and the affected offspring likely come from the father for this rare disorder.

(d) Individuals III-2 and III-7 have different genotypes at the syndactyly locus

Given that (1) syndactyly is a rare disorder, (2) II-2 and II-6 have no family history of the disorder, and (3) no new mutations are arising to cause syndactyly, it is likely that III-2 and III-7 both have the same genotype (Nn).

Question 4:
You are studying a dominant Mendelian disease via linkage analysis and are focusing on a single marker. Two large families have been genotyped at the same marker and scored for the disease.

In Family I, ten offspring are genotyped: eight children inherited a marker allele and a disease-causing allele without recombination; two children appear to be recombinants. You test many values of the recombination fraction (theta) and discover that theta = 0.2 gives the maximum odds ratio, which is 6.87 (LOD = 0.837).

In Family II, 20 offspring are genotyped: 17 children inherited a marker allele and a disease-causing allele without recombination; three children appear to be recombinants. You test many values of theta and discover that theta = 0.15 gives the maximum odds ratio, which is 223.4 (LOD = 2.34).

To combine data across Family I and Family II, you multiply odds ratios (add LOD scores). The final estimate of the odds of linkage relative to the null as 1534.8 (LOD = 3.18). Explain what is wrong with this calculation.

You can not combine LOD scores when they are calculated using different values of theta.