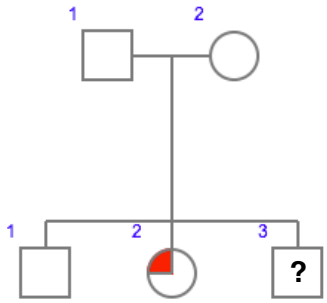
Bio393: Genetic Analysis **Name:**_____
Problem Set #6
Due on Friday, March 2, 3 PM

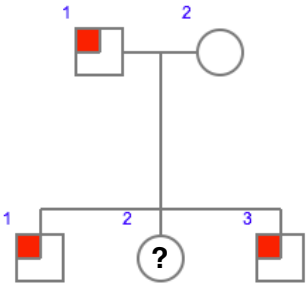
Question 1:
Each of the families below exhibits a different, extremely rare genetic disorder. Individuals expressing the trait (the disorder) are indicated by symbols with red sections. Assume that no new mutations have arisen in any of the individuals shown. Consider the following possible modes of inheritance: (i) X-linked recessive with complete penetrance, (ii) autosomal recessive with complete penetrance, (iii) autosomal recessive with 70% penetrance, (iv) autosomal dominant with complete penetrance, (v) autosomal dominant with 70% penetrance. For each pedigree state which, if any, of these five modes of inheritance are not possible. For the modes of inheritance that are possible, calculate the probability that the individual indicated by a "?" is affected.

(a)



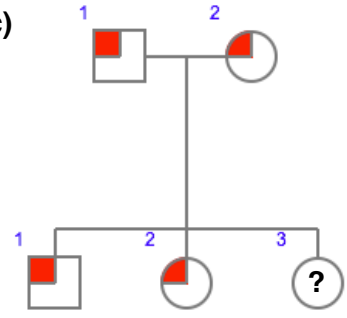
i. Not possible because individual I-1 is not affected.
ii. Possible, individual II-3 has a 1/4 chance of being affected or 1/2 of being a carrier
*iii. Possible, individual II-3 has a 1/4 * 7/10 chance of being affected or 7/40.*
iv. Not possible, neither parent is affected
*v. Possible, one parent must be a carrier but not fully penetrant. The probability that individual II-3 will be affected is 1/2 * 7/10 = 7/20*

(b)



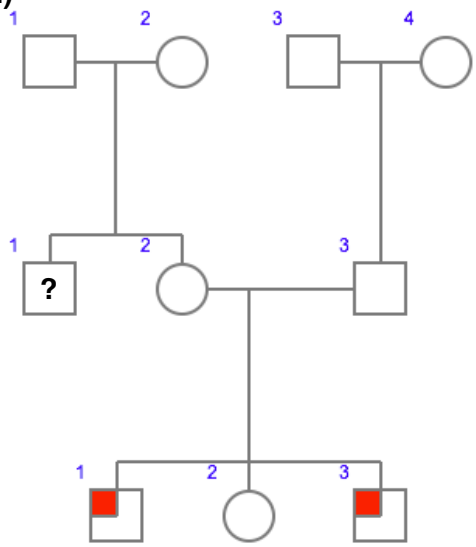
i. Possible if individual I-2 is a carrier. II-2 has a 1/2 chance of being affected
ii. Possible, same as i, 1/2 chance of being affected
*iii. Possible, because of penetrance the chance is 1/2 * 7/10 = 7/20*
iv. Possible, 1/2 chance of individual II-2 being affected
*v. Possible, same logic as iv except penetrance changes the chance to 1/2 * 7/10 = 7/20*

(c)



i. Possible, individual II-3 has 100% chance of being affected
ii. Possible, individual II-3 has 100% chance of being affected
iii. Possible, individual II-3 has 100% chance of inheriting the affected allele but a 7/10 chance of being fully penetrant so 7/10 chance overall
iv. Possible, because the disease is rare both parents are likely heterozygotes, individual II-3 has a 3/4 chance of being affected
*v. Possible, same logic as iv, because the disease is rare both parents are likely heterozygotes, individual II-3 has a 3/4 chance of being affected, but penetrance makes the chance 3/4 * 7/10 = 21/40*

(d)



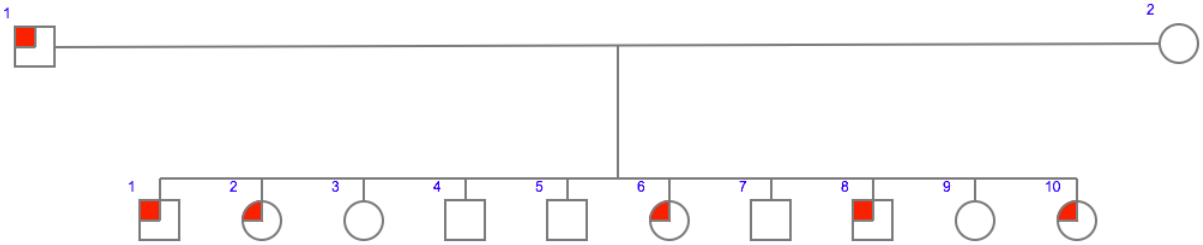
i. Possible, individual II-1 has 1/2 chance of being affected
ii. Possible, but pretty unlikely both parents would have to be carriers. For a rare disease, it is highly unlikely.
iii. Possible, but pretty unlikely both parents would have to be carriers. For a rare disease, it is highly unlikely.
iv. Not possible, no affected individuals in generations I or II
*v. Possible, individuals in generations I or II would have to be not fully penetrant. Individual I-1 or I-2 could be a carrier and not penetrant for the disease. Because it is a rare disease, we expect that both would not be carriers. If one is a carrier, then II-1 has a 1/2 * 7/10 or 7/20 chance of expressing the disease.*

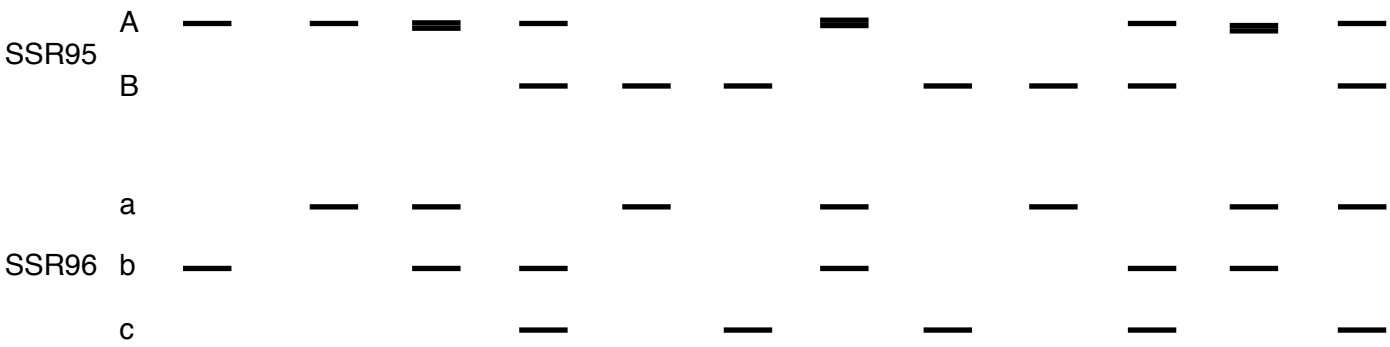
*However, we also do not know what side of the pedigree the allele conferring the dominant phenotype would come from, so we need to take into account that probability (1/2). 1/2 * 1/2 * 7/10 = 7/40*

Question 2:
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

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

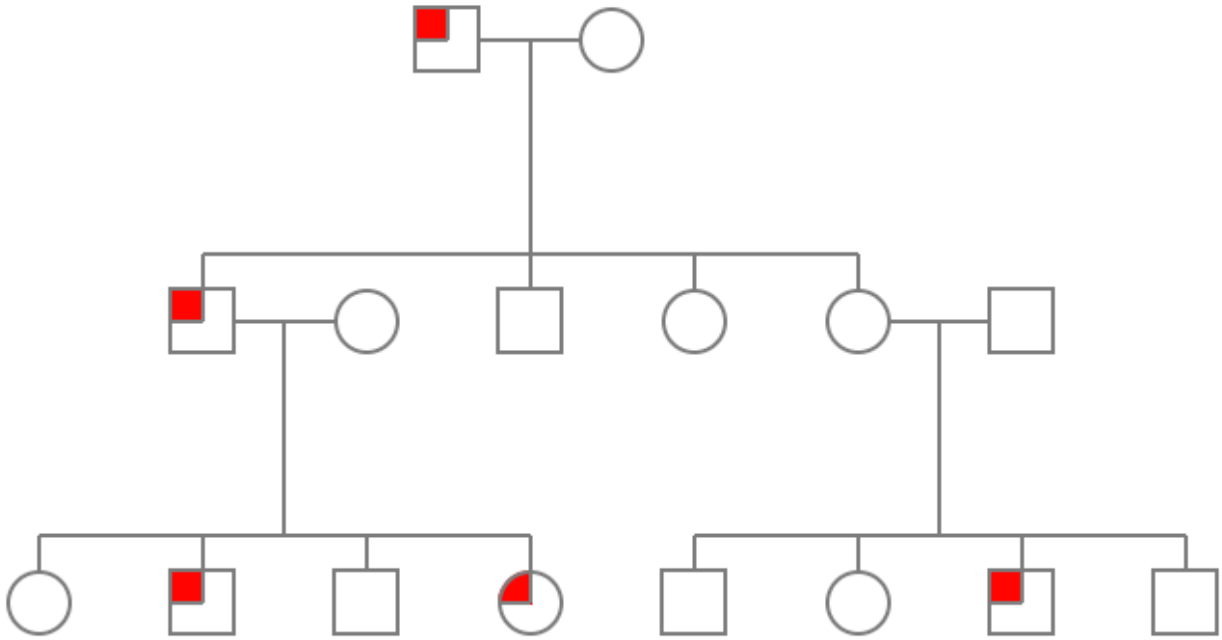
(d) Diagram the two possible phase relationships between the SSR95 and color blindness alleles in the mother.

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

(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.

Question 5:
Circle the correct answer.

(a) Which type of variant is <u>easiest</u> to map using family-based analyses?

1 - Rare variants with variable penetrance
2 - Common variants with variable penetrance
3 - Rare variants with high penetrance
4 - Common variants with high penetrance

(b) Which type of variant is <u>easiest</u> to map using population-wide analyses?

1 - Rare variants with variable penetrance
2 - Common variants with variable penetrance
3 - Rare variants with high penetrance
4 - Common variants with high penetrance