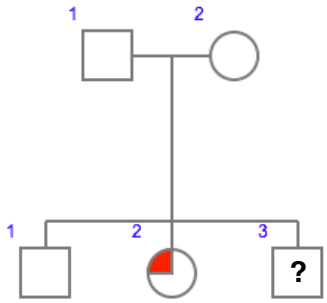
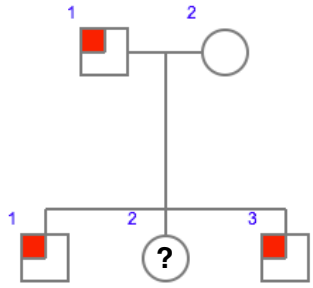
Bio393: Genetic Analysis **Name:**_____
Problem Set #6
Due on Friday, March 2, 3 PM

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.

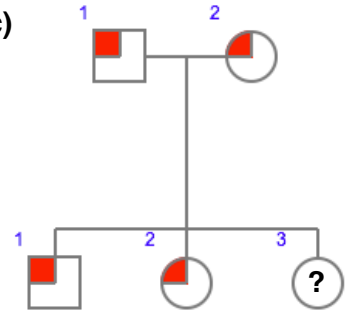
(a)



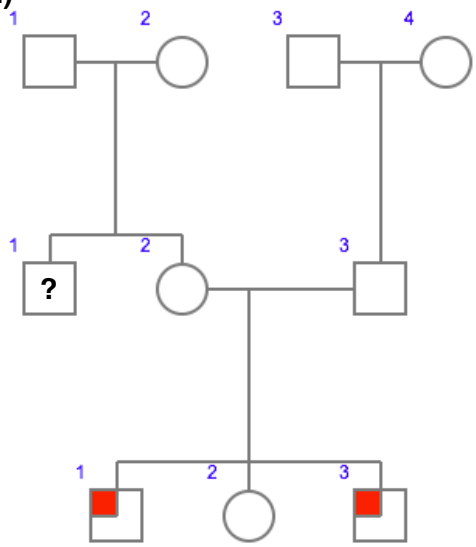
(b)



(c)



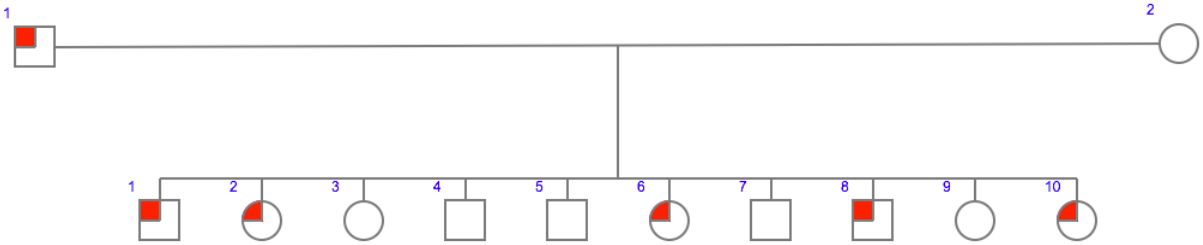
(d)

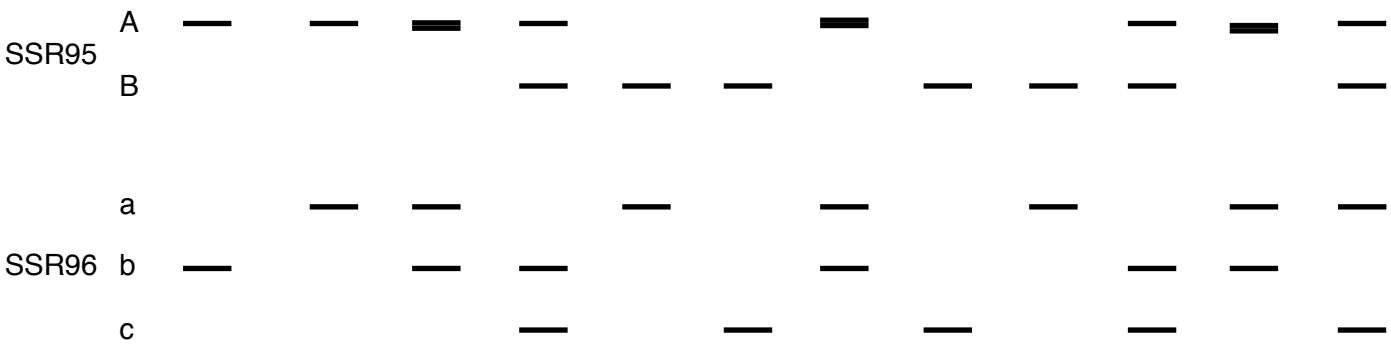


Question 2:
You set out to genetically map color blindness with respect to short-sequence repeat (SSR) markers. Color blindness shows X-linked recessive inheritance and therefore is usually found in males. However, the mutant allele frequency is sufficiently high that colorblind females do occur.

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.

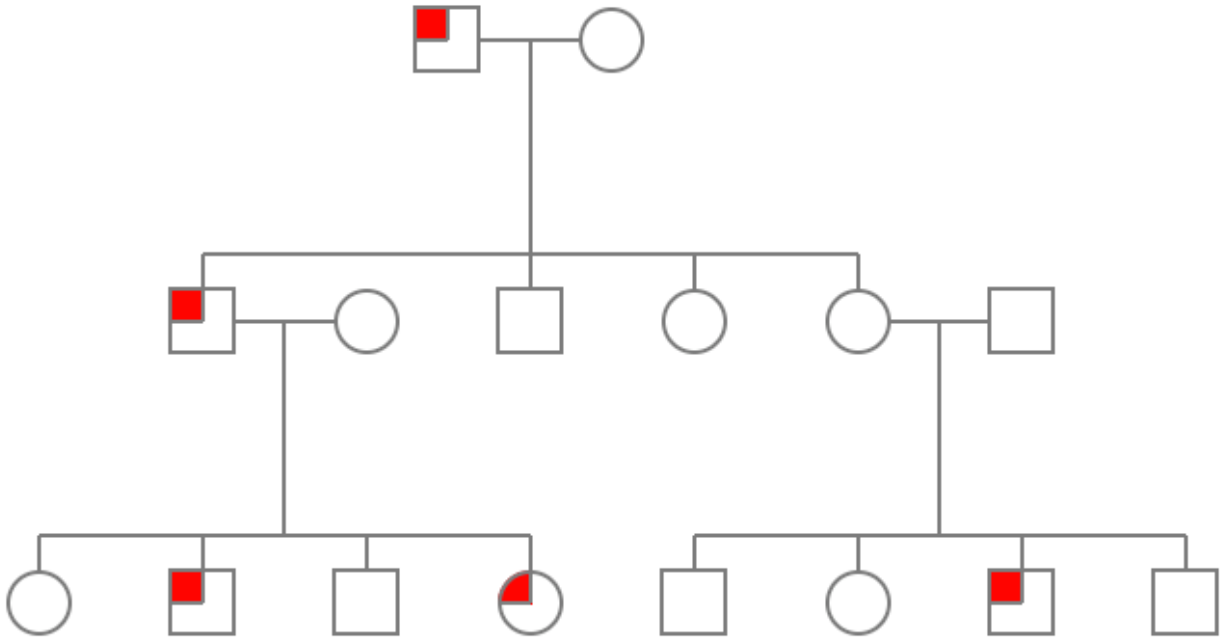
(b) Calculate the LOD score for linkage at $\theta = 0.1$ between SSR95 and SSR96 in this family.

(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.

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

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

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

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

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

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

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.

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