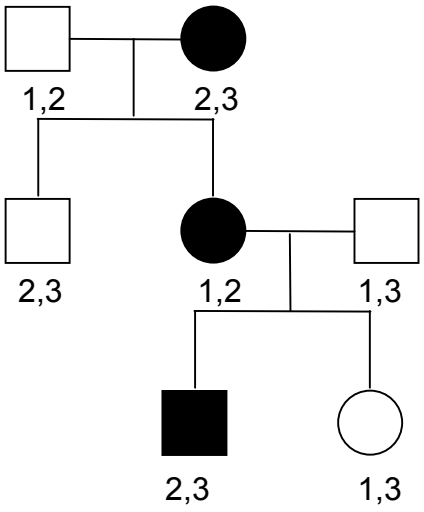
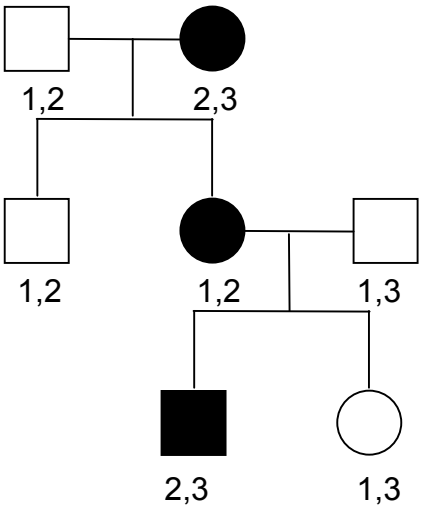
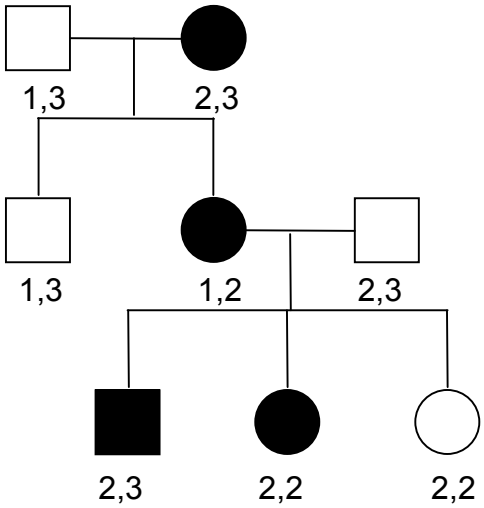
1. Consider these examples of a dominant autosomal disease segregating in families caused by a mutation in a single gene. The numbers below the individuals in the pedigrees represent genotypes at a particular DNA marker. Assume that in each family, individual I-2 is heterozygous at the disease locus and, in this individual, the disease allele is on the same homolog as the marker allele 2.



Family I



Family II



Family III

(a) A “founder” is any individual without a parent in the pedigree. For each family, identify the number of non-recombinants and recombinants among the non-founders only. Use only these non-founders to compute the odds (or LOD=log of the odds, whichever you prefer) that the disease-causing mutation is located 1 map unit from the marker, r = 0.01.

(b) Given the data from all three families taken together, calculate the overall odds ratio for the model in which the disease locus and the marker are linked at 1 map unit distance.

(c) What does it mean to have an odds ratio less than 1 (a LOD score less than 0)?

(d) Give an explanation for the difference in odds ratios between the families that you calculated in (a).

(e) Imagine that Family III had a totally different set of genotypes for the marker instead of what's given above, such that in analyzing the pedigree you found zero recombinants. For this new data set, calculate the odds or LOD of linkage between the disease mutation and the marker at r = 0.01 in Family III. These odds are different from the result you got in (a) for Family I, yet in both cases there are no recombinants. Why? Which kind of family would a geneticist prefer to work with?

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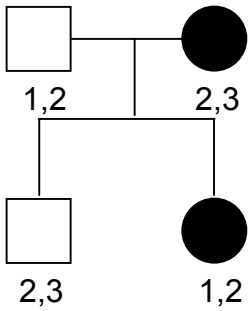
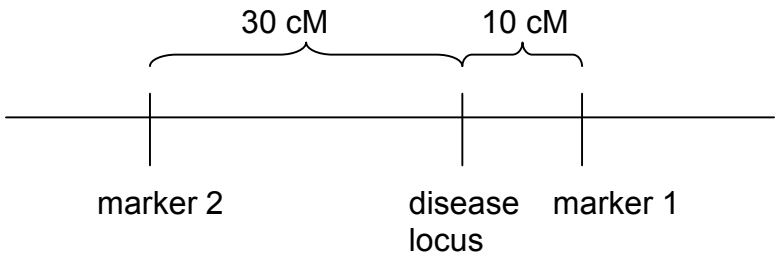
2. Consider the following pedigree representing a dominant disease caused by a mutation in a single autosomal gene, and genotypes at a single DNA sequence marker. Assume that individual I-2 is heterozygous at the disease locus:



(a) Given a guess for the recombination fraction r between the disease mutation and the marker, why can't you calculate an odds of this pedigree using the formula odds = $[(1-r)^n r^k]/[0.5^{r+k}]$?

(b) Establish how to resolve this, which is called "the phase problem," and calculate the true odds for r = 0.1.

3. Imagine that you are studying a simple Mendelian disease. The true position of the mutation locus responsible for the disease is flanked by two markers, one exactly 10 cM away and the other exactly 30 cM away:



As an experimental geneticist you don't start out knowing the underlying truth about where the locus is; you start out only with data. Imagine your data are as follows: you have a pedigree consisting of 10 non-founder individuals (10 meioses) scored for the disease phenotype and for genotypes at each of the two markers. When tracing the co-inheritance between marker 1 and the disease, you find exactly 1 recombinant individual out of 10. When tracing the co-inheritance between marker 2 and the disease, you find exactly 3 recombinant individuals out of 10. These data give a point estimate for the distance between the markers and the disease locus of 10 cM and 30 cM, respectively. As we discussed in class, these are only estimates inferred from the data. However, in this case each estimate happens to corresponds to the true distance—the absolute, underlying correct answer.

(a) Calculate the odds ratio for r=0.1 for marker 1, and calculate the odds ratio for r=0.3 for marker 2.

(b) Again, each model you considered in (a), *i.e.* the estimated genetic distance between the markers and the disease locus, represents the correct answer. Given that the model you considered for marker 1 is equally as correct as the model you considered for marker 2, why are the odds ratios different?