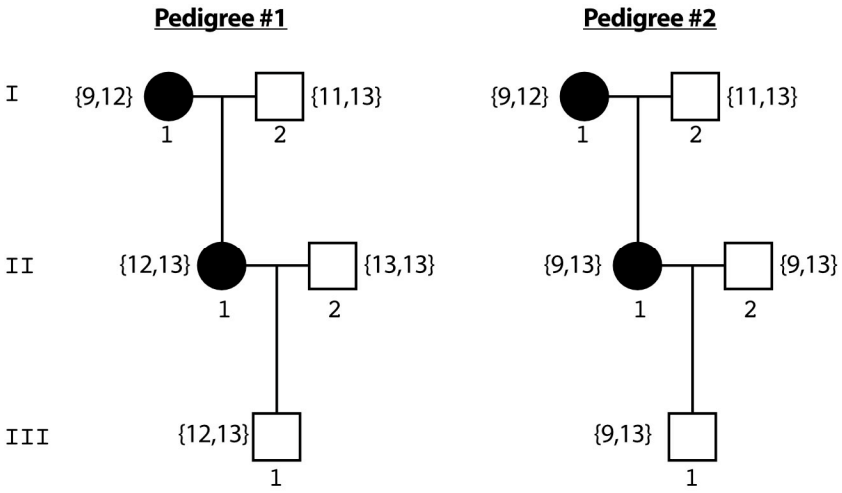
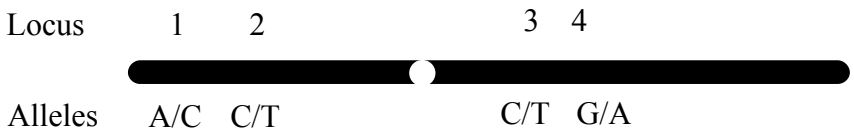
Problem Set 7
Genetics 371
Winter 2010

1. The two pedigrees below show inheritance of an autosomal dominant trait (D = disease, dominant; d = normal, recessive). Numbers in {curly brackets} indicate alleles of a microsatellite repeat polymorphic locus. For each pedigree, state whether the meiosis in II-1 is informative or uninformative, giving the parental types for II-1 in each case.



2. Consider the diagram below indicating the locations and alleles at four loci along human chromosome 3:



(a) Is locus 1 more likely to show linkage with locus 2 or locus 3? Why?

(b) Are the alleles of locus 1 more likely to be associated with the alleles of locus 2 or 3? Why?

(c) Assume the recombination distance between locus 3 and 4 is 20 cM. What does this imply about patterns of association between the alleles of locus 3 and 4?

(d) Assume the recombination distance between locus 3 and 4 is 1 cM, but no association exists among their alleles. Explain in either words, or using a diagram, how this could be possible.

3. Josh and Stan independently decide to perform an association study for Celiac's Disease. Each collects 1,000 cases and controls and genotype the same marker (which has alleles A and T). The contingency table from each study is shown below:

Josh's Study

	A	T	
Case	275	225	500
Control	225	275	500
	500	500	1000

Stan's Study

	A	T	
Case	290	210	500
Control	260	240	500
	550	450	1000

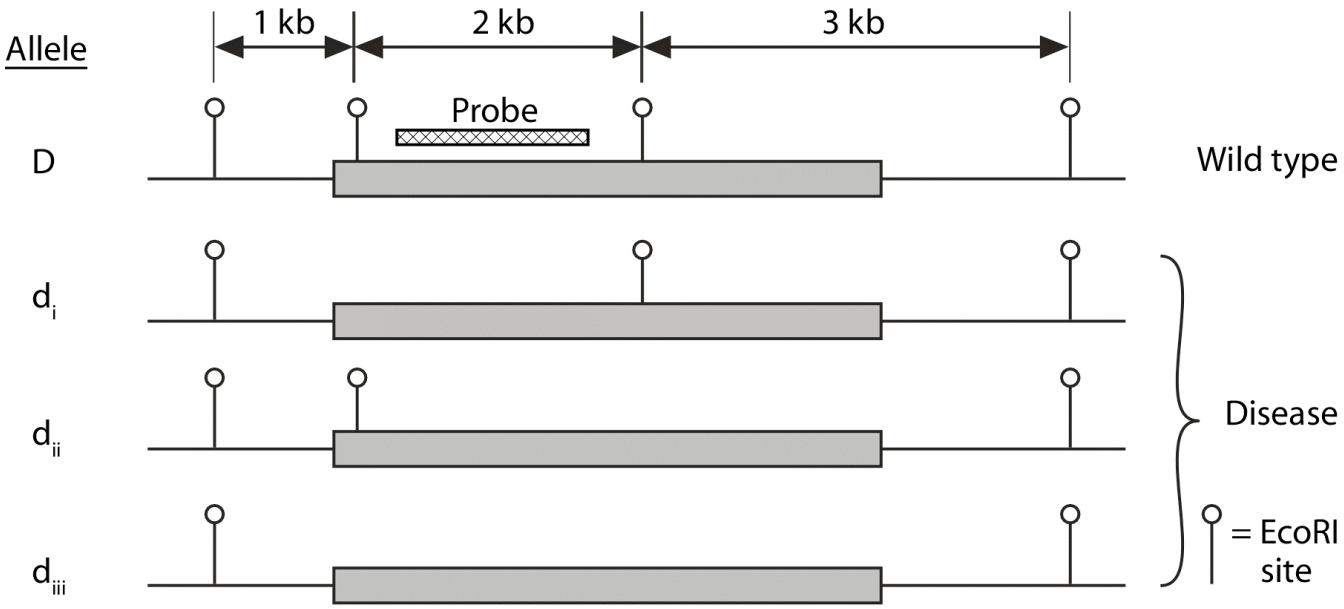
(a) Without doing a formal chi-square test, which study do you think will result in a more significant association and why?

(b) If Josh and Stan were studying the same disease and genotyped the same marker, explain how they could arrive at two different sets of numbers in the tables above.

(c) Assume the chi-square value for Josh's study is 9.6 leading to a p-value of 0.0019. What are the null and alternative hypotheses and how do you interpret the p-value? Do these data allow you to claim that the A allele causes Celiac's disease? Why or why not?

4. [*Before you panic: This question is too long to be an exam question, but we do expect you to understand and to be able to work any part of this kind of question.]*

In humans, EcoRI restriction fragment length polymorphisms (RFLPs) distinguish unaffected (**D**) from disease (**d_i, d_{ii}, d_{iii}**) alleles of a gene associated with an **autosomal recessive** disease:



A microsatellite repeat polymorphism at a **separate** locus can have any of four different alleles (**Alleles 1, 2, 3, or 4**).

Pedigrees from **two separate families** in which some family members show the disease are depicted at the end of this question. The gel images below each pedigree show the results of testing for the disease gene (RFLP)* and the microsatellite site. Each person's DNA sample is shown directly below that person.

*"RFLP"=Southern blot of EcoRI-cut DNA probed with the fragment indicated in the picture above

(a) The phenotype of the pedigree members (disease vs. healthy) is not shown. Based on the RFLP results on the Southern blot, **fill in the phenotypes** to show affected individuals as appropriate.

(b) Use the space below each child's gel sample to indicate whether the gametes that made that child are **parental (P)** or **non-parental types (NP)**.

(c) Based just on the number of recombinant and non-recombinant types you see, estimate the map distance between the disease gene and the microsatellite site (show your calculations). Remember to count gametes from both parents in your calculations.

(d) Now do a LOD score analysis of the same data to arrive at a more statistically sound estimate of the genetic map distance between the two loci. Show your calculations for the **first pedigree** for a **q value of your choice**, then fill in the table to show the complete LOD score values for **both pedigrees**.

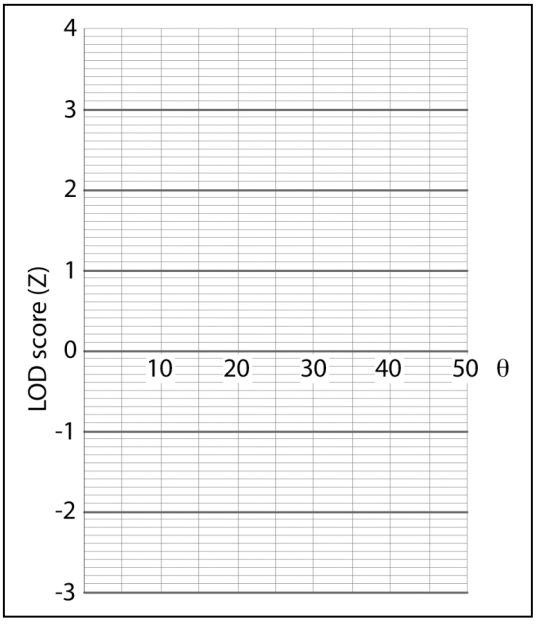
θ value for which you are showing your LOD score calculation: _____

LOD score calculation for that value of θ:

First pedigree	
θ	LOD score
5	
10	
15	
20	
25	
30	
35	
40	
45	
50	

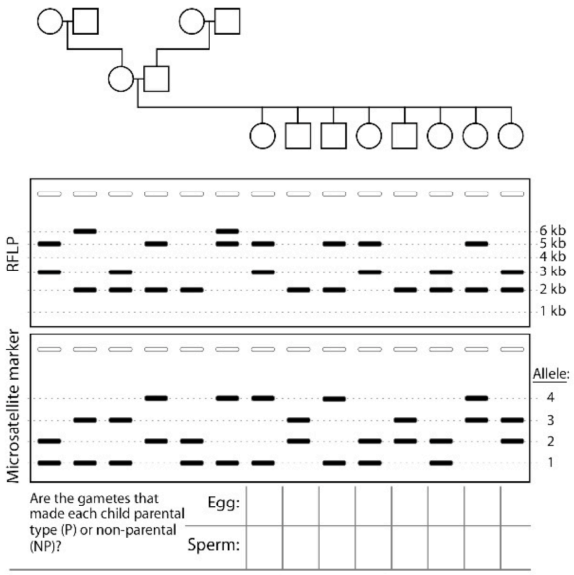
Second pedigree	
θ	LOD score
5	
10	
15	
20	
25	
30	
35	
40	
45	
50	

(e)Do the data show statistically significant evidence for or against linkage between the two loci? If so, at what distance(s) are the two loci linked? Support your answer by plotting the relevant data on the LOD score graph.



Pedigrees for Problem 4:

First pedigree:



Second pedigree: