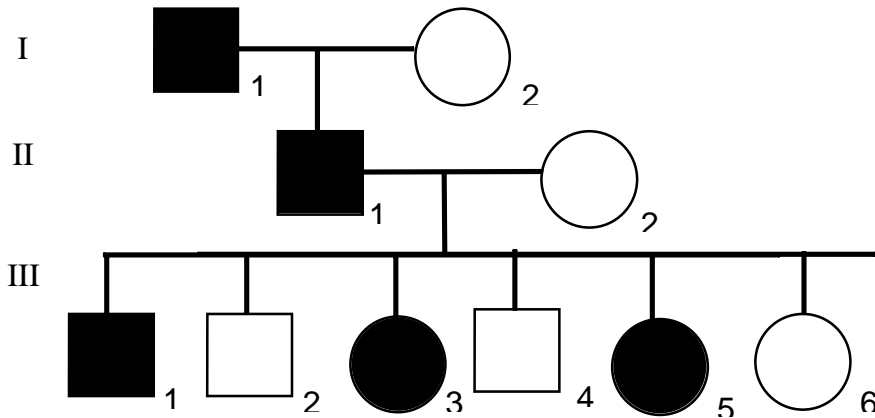


This pedigree shows a family affected by an autosomal dominant genetic disease. Genotypes for five markers, A through E, are shown



The genotypes are:

- | | | | |
|------|--|-------|--|
| I-1 | A _{1,2} B _{1,2} C _{1,2} D _{1,2} E _{1,2} | III-1 | A _{1,4} B _{1,4} C _{1,4} D _{3,4} E _{1,4} |
| I-2 | A _{3,3} B _{3,3} C _{3,3} D _{3,3} E _{3,3} | III-2 | A _{3,4} B _{3,4} C _{3,4} D _{3,4} E _{3,4} |
| II-1 | A _{1,3} B _{1,3} C _{1,3} D _{1,3} E _{1,3} | III-3 | A _{1,4} B _{3,4} C _{3,4} D _{1,4} E _{1,4} |
| II-2 | A _{4,4} B _{4,4} C _{4,4} D _{4,4} E _{4,4} | III-4 | A _{3,4} B _{3,4} C _{3,4} D _{3,4} E _{3,4} |
| | | III-5 | A _{1,4} B _{1,4} C _{3,4} D _{1,4} E _{1,4} |
| | | III-6 | A _{3,4} B _{3,4} C _{3,4} D _{1,4} E _{1,4} |

1. (12 points; two points per pair of markers) For each individual in the third generation (III-1, III-2, III-3, III-4, III-5 and III-6) of this pedigree indicate whether they are **recombinant**, **nonrecombinant** or **indeterminate** for each pair of **markers listed** (Fill in each of the 36 squares with **yes**, **no** or **maybe**). (Yes, there are another four pairs -- BE, CD, CE and DE -- not listed on the table.)

individual	A B recombinant ?	A C rec.	A D rec.	A E rec.	B C rec.	B D rec.
III-1	No	No	Yes	No	No	Yes
III-2	No	No	No	No	No	No
III-3	Yes	Yes	No	No	No	Yes
III-4	No	No	No	No	No	No
III-5	No	Yes	No	No	Yes	No
III-6	No	No	Yes	Yes	No	Yes

2. (3 pt.) Considering only the data for marker locus **A** (i.e. ignoring the other markers), what is the approximate lod score for linkage **between A and the disease gene** with $\theta = 0$?
 With no recombinants, you can use the special case $.3(n)$ where n = number of nonrecombinants,
 $.3(6) = 1.8$

3. (3 pt.) Considering only the data for marker locus **B**, what is the approximate lod score for linkage **between B and the disease gene** with $\theta = 0$?
 Since there is 1 recombinant, $\theta = 0$ (or the condition that they are linked, i.e. no recombinants) is impossible and the **lod score is $-\infty$** .

4. (3 points) These five marker loci are linked. What is the most likely order on the genome? You know that A is to the left of B. Possibilities are ABCDE, CDEAB, ACDEB, AEDCB etc..

DEABC. CBAED received only 2 points due to the statement in the question that “A is to the left of B.”

5. (3 points) What is the minimum number of recombination events observed, and which progeny are recombinant (from III-1, III-2, III-3, III-4, III-5 or III-6; **list all that apply**)?

4 events observed; III-1, III-3, III-5, III-6 are recombinant

6. (3 points) Which one of the following statements best describes the location of the disease gene?

- | | | |
|---------|--------------------|---------------------------|
| a) At A | f) Between A and B | k) Between B and D |
| b) At B | g) Between A and C | l) Between B and E |
| c) At C | h) Between A and D | m) Between C and D |
| d) At D | i) Between A and E | n) Between C and E |
| e) At E | j) Between B and C | o) Between D and E |

You cannot say that the disease is at A, it could be anywhere between E-B based on the recombination events observed. At A, A-E, or A-B got 1 point (choices a, f, and i).

(4 points each). In each of the following there are two or more statements. One is true. Usually, it is taken directly from your textbook or from my lecture. In other cases, it might come from the scientific literature. Others have been modified so as to be untrue or misleading. Circle the letter next to the one correct statement. In some cases, you might not know enough to be sure that statement is correct but you should be able to identify the others as bogus in some way.

7. DNase I hypersensitivity sites are typically:

b) cell type-specific and intergenic.

8. **a) The autoregulatory Sxl protein promotes its own synthesis through RNA splicing, resulting in a productive mRNA, thereby acting as a self-reinforcing on/off switch.**

9. **b) Nonsense mediated decay is a cellular mechanism of mRNA surveillance leading to degradation of mRNAs bearing premature stop codons.**

10. **c) Epigenetic imprints generally persist throughout the life of a mammal, but are erased during the passage of a gene through the germ line into the next generation.**

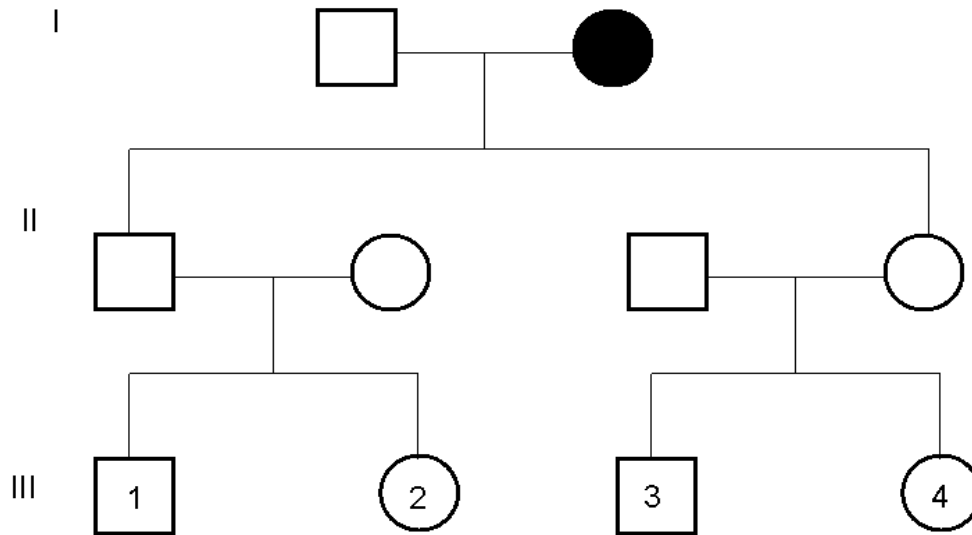
11. **a)** Autozygosity is a term used to refer to homozygosity **by descent from a common ancestor**.
12. **a)** There is **great** conservation of the primary sequence of histones among all eukaryotes and this correlates with conservation in the nature of regulatory histone modifications between species.
13. **a)** **Prokaryotic** mRNAs tend to be **polycistronic** while **eukaryotic** mRNAs tend to be monocistronic.
14. **a)** The variable θ in lod score analysis represents **expected recombination frequency**.

Which of the following is true (4 points):

15. **d)** **Autozygosity mapping but not lod score analysis** depends on common ancestry and you can combine results from different populations in pedigree analysis but not autozygosity mapping.
16. Explain your answer to number 15 (5 points):

Autozygosity mapping relies on using markers that are identical due to ancestry by descent.

Lod scores, however, are a tool to test a model of linkage. Different markers can be linked to the same gene in different families, so common ancestry is not required. In fact, different pedigrees are often combined together in order to obtain a statistically significant population size for analysis.



17. (3 points) In the case of an autosomal dominant trait with incomplete penetrance
b) All of the grandchildren are at equal risk.
18. (3 points) In the case of a maternally imprinted trait with incomplete penetrance
a) 1 and 2 are at risk but 3 and 4 are not.
19. (3 points) In the case of a paternally imprinted trait with incomplete penetrance
c) 3 and 4 are at risk but 1 and 2 are not.
20. (3 points) In the case of a (rare) sex-linked trait
b) Only 3 is at risk.

Reminder:

maternally imprinted – mother’s allele is silenced (inheritance of a mutant allele from the father causes disease)

paternally imprinted – father’s allele is silenced (inheritance of a mutant allele from the mother causes disease)

21. (12 points) Compare and contrast the mechanism of action of cellular microRNAs in animals with the action of siRNAs derived from double-stranded RNA precursors. Be sure to describe both similarities and to illustrate how the two differ.

Differences (2 points each):

- miRNA originates from cellular genes, siRNA is often foreign dsRNA or from repeats
- miRNA binds imperfectly, while siRNA binds perfectly
- miRNA generally represses translation of its target, the siRNA target is marked for degradation

Similarities (3 points each, need at least 2):

- both pathways involve the RISC complex
- both are processed to approximately 21-23 nt in size by DICER
- both are examples of complementary based repression

22. (8 points) Explain the difference between genetic heterogeneity and polygenic determination, using examples (You have to define the terms. You can make up the examples).

Genetic heterogeneity – The same disease or phenotype is caused by any one of multiple genes (BRCA1-BRCA2 is a good example)

Polygenic determination – multiple alleles at 2 or more loci (several genes) are required together for the phenotype (pigmentation and height are examples)