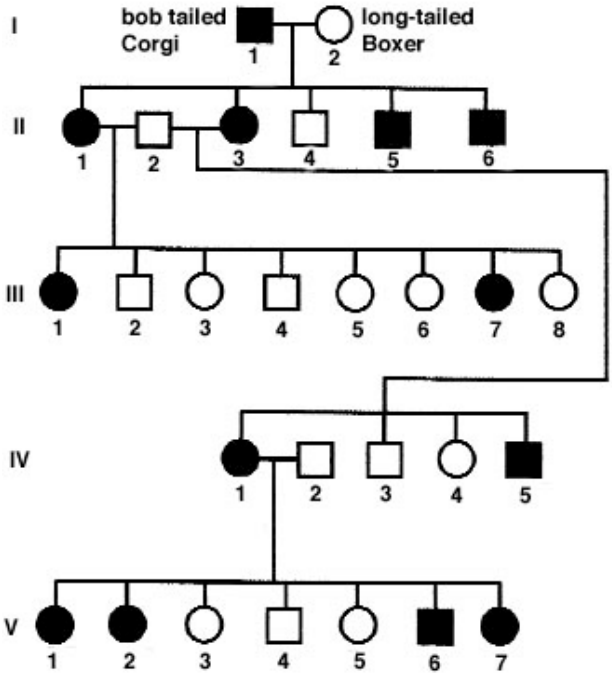
BICD100 Midterm (10/27/10) KEY

1. Variation in tail length is characteristic of some dog breeds, such as Pembroke Welsh Corgis, which sometimes show a "bob tail" (short tail) phenotype (see illustration below, left). A bob tailed male Corgi was mated with a female from a true-breeding line of long tailed Boxers. Female progeny of this cross were "backcrossed" repeatedly to males from the true-breeding long tailed Boxer line to generate the pedigree shown below.



a. Assuming that the bob tailed trait is fully penetrant, which of the following are <u>possible</u> modes of inheritance for this trait? Circle all that are possible (8 pts).

i. autosomal recessive	ii. X-linked recessive
<u>iii. autosomal dominant</u>	iv. X-linked dominant

b. Among the progeny of matings between bob tailed males and females of generation V, 1/2 had the bob tailed phenotype, 1/4 had the long tailed phenotype, and 1/4 had a tailless phenotype. Based on this and information provided earlier (do not take into account any information given later!), which of the following types of mutations could be causing the bob tailed phenotype seen in the Corgis? Circle each one that is possible (8 pts).

The information in this paragraph tells you the trait is semi-dominant, not fully dominant.

i. A gain of function mutation that is fully dominant to wild type

ii. <u>A gain of function mutation that is semi-dominant to wild type</u>

iii. A loss of function mutation that is recessive to wild type

iv. <u>A loss of function mutation that is semi-dominant to wild type</u>

Further analysis led to the finding reported in the journal *Mammalian Genome* in 2001 that the bob tailed phenotype in Pembroke Welsh Corgis is due to allelic variation in the T gene, which encodes a transcription factor (a protein that binds to DNA upstream of other, so called "target" genes and regulates their transcription). Sequencing of T alleles determining the bob tailed phenotype revealed several differences relative to non bob tail (wild type) alleles, as summarized in the table below. Note that genes are composed of exons (which contain the protein coding information) and introns (which are spliced out of mRNA before it is translated).

Change #	**Location of change**	**Change in DNA sequence relative to wild type allele**	**Effect on protein levels, gene expression pattern, and protein sequence**
1	Upstream of ATG start codon	A to C	None
2	Intron 1	G to A	None
3	Exon 1	C to G	Normal gene expression pattern and protein levels, but changes isoleucine codon to methionine codon
4	Intron 2	G to A	None
5	Exon 2	C to T	None
6	Intron 3	T to A	None
7	Intron 6	C to T	None
8	Exon 8	T to C	None

c. Based on the information provided in this table, which of these changes could be correctly described by the term given? Put your answer on the line provided by indicating the appropriate change # shown in the table. If there is more than one possibility, then just name one. If none of the changes could be described by the term given, so state (12 pts).

i. nonsense mutation ___**none**_____ ii. frameshift mutation __**none**_____

iii. silent mutation __**1,2, and 4-8**____ iv. missense mutation _____**3**_____

v. functionally neutral polymorphism _**1,2, and 4-8**__ vi. point mutation ____**any (all)**_____

d. Functional studies on T protein encoded by the allele causing the bob tailed phenotype showed that this version of the protein cannot bind to DNA upstream of appropriate target genes under conditions where wild type T protein can bind. When wild type protein and bob tail allele-encoded protein are mixed together in equal proportions, approximately 50% of normal binding is observed. Together with all the information provided earlier, which of the following is the most likely explanation for the genetic basis of the bob tailed phenotype in Pembroke Welsh Corgis? Circle only one (6 pts).

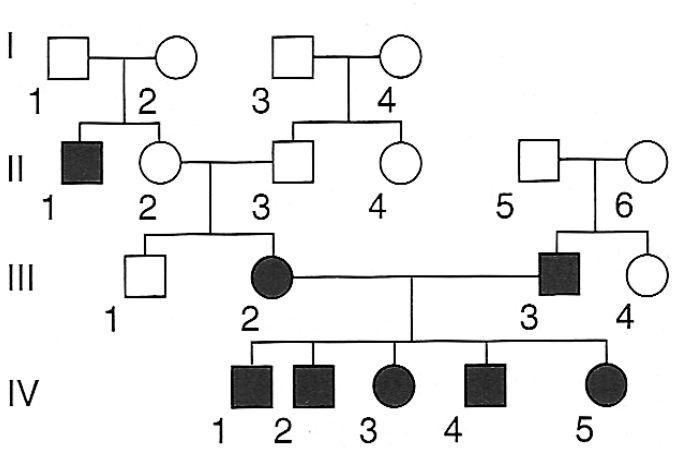
i. The bob tail phenotype is caused by a hypermorphic mutation in the T gene

ii. The bob tail phenotype is caused by a neomorphic mutation in the T gene

iii. The bob tail phenotype is caused by a loss of function mutation in T gene, which is haploinsufficient

iv. The bob tail phenotype is caused dominant negative mutation in the T gene **(not this one because information provided indicates that mutant gene product does not antagonize function of wild type product in heterozygotes).**

2. Deafness in humans can be caused by mutations in a variety of different genes encoding proteins involved in development and function of the inner ear. The pattern of inheritance of deafness in two human families (related by the marriage of III-2 and III-3) is shown here.



a. Assuming this trait is fully penetrant, circle each of the following modes of inheritance that can be excluded by the data shown. For each mode you name, give a reason why it can be excluded, referring to specific individuals in the pedigree (15 pts):

i. X-linked recessive: can be excluded because in order for III-2 to be affected, she would have had to inherit a copy of the mutation from both parents. Her mother could be a carrier but her father II-3 could not (he does not show the trait so does not have the mutation if it is fully penetrant)

ii. autosomal recessive: **This is the most likely mode of inheritance (not excluded)**

iii. X-linked dominant: can be excluded because of every affected individual whose parents are both unaffected (II-1, III-2 and III-3)

iv. autosomal dominant: ditto above

v. maternal inheritance: can be excluded because of the appearance of the trait in II-1, III-2, and III-3, whose mothers were all unaffected

b. III-1 and III-4 met at the wedding of III-2 and III-3 and eventually also got married. Still assuming the trait is fully penetrant, what is the probability that their first child will be deaf? If the probability is different for a boy vs. girl, clearly state the difference. Show the fractions you are multiplying together to get your final answer. (6 pts)

Since this trait appears to be autosomal recessive, the probability is not different for a boy vs. girl.

Probability that III-1 is affected is 2/3, same for III-4. If both are carriers, probability that child is affected is ¼. So overall probability that child is affected is 2/3 x 2/3 x ¼ = 4/36 (1/9)

c. Years later, IV-5 marries a deaf man from an unrelated family, and they have six children, all of whom have normal hearing. Which of the following phenomenon the most likely explanation of this outcome? Circle only one (6 pts).

i. epistasis

ii. incomplete penetrance (assuming, unlike you did in parts a and b, that this is possible)

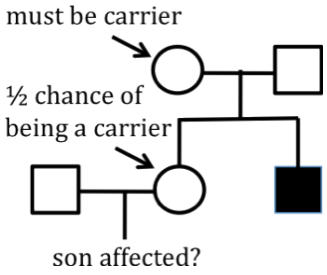
iii. complementation

iv. pleiotropy

v. variable expressivity

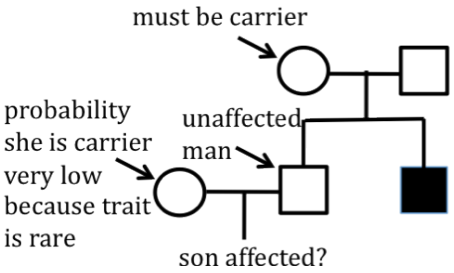
3. Duchenne muscular dystrophy (DMD) is caused by a rare X-linked recessive allele. It results in progressive muscular wasting and usually leads to death before age 20. Assume that members of these families who are not mentioned are unaffected. In answering the questions below, show the fractions you are multiplying together to obtain your final answer.

a. What is the probability that the first son of an unaffected woman with an affected brother will be affected (6 pts)?
½ chance that woman is carrier x ½ chance she will pass trait on to her the trait on to her son (in which case he would be affected) = <u>1/4</u>



b. If the first son of the woman described in part a turns out to be affected, what is the probability that her second son will be affected (6 pts)?
Based on this information, we now know that the woman is a carrier so this changes the answer to <u>1/2</u>

c. What is the probability that a son of an unaffected man with an affected brother will be affected (6 pts)?
The unaffected man's son can only inherit this trait from his mother, who is extremely unlikely to be a carrier since the trait is rare. Therefore the probability is (approximately) <u>zero</u>.



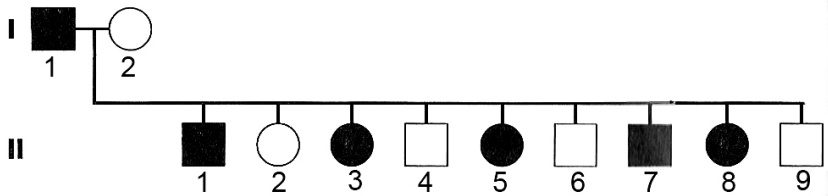
4. In corn (maize), true-breeding lines have been developed that are either resistant or sensitive to a certain pathogenic fungus. When resistant plants are crossed as females to sensitive males, all the progeny are resistant. When resistant plants are crossed as males to sensitive females, all the progeny are sensitive. Like most plants, maize does not have sex chromosomes. Briefly, how can this result be explained (8 pts)?

This could be explained by maternal inheritance (the trait is determined by a gene in the chloroplast or mitochondrial genome).

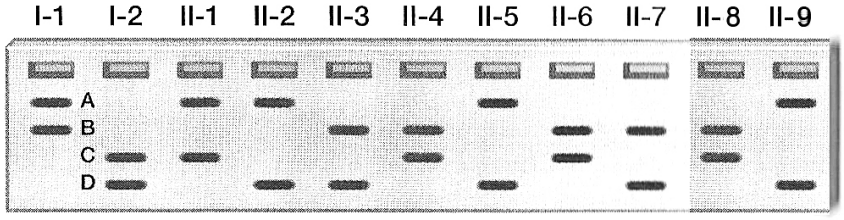
5. In the Chinese primrose, slate flower color is recessive to blue, and red stigmas are recessive to green. Each trait is determined a single gene, and these genes are linked at 25 cM. A plant with slate flowers and red stigmas was crossed to one from a line that is true-breeding for both dominant traits. If the F1 progeny are crossed together, what phenotypic classes would you expect to find among the F2 progeny in what proportions (12 pts)? NOTE: tables showing expected proportions of F2 progeny for two linked genes with complete dominance are attached at end of exam (pg 8).

ss slate; Ss and SS blue flowers
rr red; Rr and RR green stigmas
ss rr X SS RR -> <u>s r</u> (alleles in coupling or cis conformation)
S R
Table shows that expected frequencies of the following progeny classes are as follows:
64% with blue flowers and green stigmas; 11% with blue flowers and red stigmas; 11% with slate flowers and green stigmas; 14% with slate flowers and red stigmas

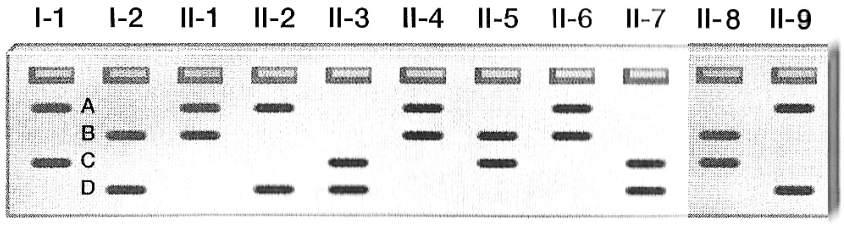
6. This pedigree shows the pattern of inheritance of a fully penetrant, autosomal dominant disorder in a human family. DNA samples were taken from each individual and analyzed via PCR for alleles at two different microsatellite loci, with the results shown in the gels below.



Microsatellite number 1



Microsatellite number 2



a. Which of these markers appears to be most closely linked to the dominant allele causing this trait (5 pts)?

#2 (1 looks unlinked)

b. For the marker you named in part a, identify the individual(s) (by number) that inherited recombinant chromosomes (8 pts).

II-1 only

c. For the marker you named in part a, calculate the recombination frequency and give the map distance indicated by the data. Your answer here will be graded based on consistency with your answer in part b (6 pts).

1 recombinant out of 9 possible recombinants: 11% recombination (11 cM)

d. Calculate the LOD score at the degree of linkage you specified in part c. Here too, your answer will be graded based on consistency with your answers in parts b and c (12 pts).
[LOD score at X cm = $\log_{10}$ (probability of linkage at X cM)/(probability of no linkage)]

LOD score = $\log_{10}$ $(0.056)(0.445)^8/(0.25)^9$
= $\log_{10}$ $(0.056)(0.001538)/(0.000004)$
= $\log_{10}$ (21.52)
= <u>1.33</u>

e. Which of the following can be concluded? Circle all that apply (6 pts).

i. Data for this family alone is sufficient to conclude that the marker and trait gene are linked.

<u>>ii. Data for this family provide some evidence of linkage, but more families would need to be analyzed and the LOD scores added together before we could conclude that the marker and trait gene are linked.</u>

iii. Data for this family provide some evidence of linkage, but the LOD score for this family would need to be calculated at other degrees of linkage before we could conclude that the market and trait gene are linked.

7. Wild type eye color in Drosophila is brick red due to a mixture of red and brown pigments, which are synthesized through the action of parallel, independent biosynthetic pathways. The X-linked recessive white eye color mutation isolated by T.H. Morgan knocks out both pathways (it affects one gene required for the function of both pathways). Many other eye color mutants have also been isolated, including brown, scarlet, and buff (all of which are recessive). In brown mutants, the red color is missing; in scarlet mutants, the brown color is missing. In the table below, the eye color phenotypes of parents and progeny are given for various crosses carried out with individuals from true-breeding lines (WT stands for wild type). Note differences in the outcome of reciprocal crosses for some pairwise combinations of mutations. Male and female progeny of each cross had the same eye color phenotypes unless stated otherwise.

Female parent **>** Male parent **V**:	**brown**	**scarlet**	**buff**	**white**
brown		WT	WT females, buff males	WT females, white males
scarlet	WT		WT females, buff males	WT females, white males
buff	WT	WT		buff females, white males
white	WT	WT	buff	

a. Which of the following can be concluded from the results above? Circle all that apply (12 pts).

>i. buff is X-linked

ii. buff is autosomal

>iii. buff is dominant to white

iv. buff is epistatic to white

v. white is dominant to buff

vi. white is epistatic to buff

vii. scarlet and brown are X-linked

>viii. scarlet and brown are autosomal

ix. scarlet and brown affect the same gene

>x. scarlet and brown affect different genes

b. If white is epistatic to scarlet, what phenotypic classes do you expect to find among the F2 progeny obtained by crossing together F1s from the scarlet female X white male cross, and in what proportions (12 pts)?

Call the recessive scarlet allele s and dominant allele S. Call the X chromosome with the recessive white mutation on it X^w and an X chromosome with a wild type allele on it X^+. Scarlet female ss X^+X^+ x white male SS X^wY → F_1 progeny: X^+X^w Ss wild type females, X^+Y Ss wild type males. Here is the Punnett Square predicting the progeny of a cross between these F1s:

	S X^w	**S X^+**	**s X^w**	**s X^+**
S X^+	SS X^+X^w WT F	SS X^+X^+ WT F	Pp X^wX^+ WT F	Ss X^+X^+ WT F
S Y	SS X^wY white M	SS X^+Y WT M	Ss X^wY white M	Ss X^+Y WT M
s X^+	Ss X^wX^+ WT F	Ss X^+X^+ WT F	ss X^wX^+ scarlet F	ss X^+X^+ scarlet F
s Y	Ss X^wY white M	Ss X^+Y WT M	ss X^wY white M*	ss X^+Y scarlet M

***because white is epistatic to scarlet**

(continued, next page)

Overall, <u>6/16 wild type females, 4/16 white males, 3/16 wild type males, 2/16 scarlet females, 1/16 scarlet males</u>. Note that to receive any credit on this problem, you had to show that you were thinking in terms of independent assortment of two genes, one autosomal and one on the X chromosome. Most students struggled with this question, even after answering part a correctly. However, this question is extremely similar to problem set 3 question #1 – it differs only in that the two genes affect the same trait (eye color) in this case and there is an epistasis relationship dictating that the phenotype of the ss X^wY double mutant is white.

c. In the F2 generation obtained by crossing together F1 progeny from the brown female X scarlet male cross, the following progeny were observed: 9/16 WT, 3/16 brown, 3/16 scarlet, 1/16 white (with no differences between males and females). Crosses between white F2s showed that they always bred true (all the progeny always had white eyes). Deduce the genotypes of flies from this F2 population that gave the following progeny when crossed together. Use B and b to represent dominant and recessive alleles of the brown gene, and S and s to represent dominant and recessive alleles of the scarlet gene. For full credit, alleles of <u>both</u> B and S genes must be given for <u>both</u> parents. In any case where there is more than one possible genotype, just name one (12 pts).

From this information, you should deduce that the 1/16 with white eyes are the bb ss double mutants (additive phenotype lacking red and lacking brown).

2 WT F2s → all progeny WT :
one parent BB SS, other one Bb/BB Ss/SS (or one parent BB Ss and other Bb SS)

2 scarlet F2s → ¾ scarlet, ¼ white: **both parents Bb ss (the ¼ white are the bb ss double mutants)**

white F2 X WT F2 → ¼ WT, ¼ brown, ¼ scarlet, ¼ white: **white parent bb ss and WT parent Bb Ss**

d. If a white eyed female from the F2 population described in part c is crossed to a male with white eyes due to the presence of Morgan's X-linked recessive white mutation (but having no other eye color mutations), what phenotypic classes do you expect to find in the next generation in what proportions (8 pts)?

This is a complementation question. As above, the F2 with white eyes is bb ss but has wild type alleles for the X-linked white gene (you know this because the brown and scarlet mutants crossed together originally were from true breeding lines). The male with white eyes is X^wY but has only wild type alleles for B and S.

So the cross is X^+X^+ bb ss x X^wY BB SS ->
all females X^+X^w Bb Ss (wild type) and all males X^+Y Bb Ss (wild type)