7.03 Final Exam

Name: _____

TA: Alex Bagley, Alice Chi, Dave Harris, Max Juchheim, Doug Mills, Rishi Puram, Bethany Redding, Nate Young

Section time: _____

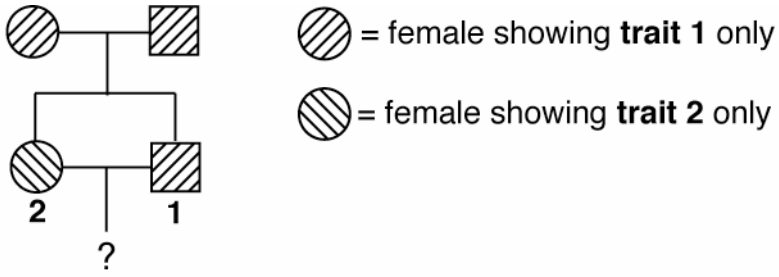
There are 13 pages including this cover page

Please write your name on each page.

Question 1	**24 points**
Question 2	**26 points**
Question 3	**18 points**
Question 4	**18 points**
Question 5	**12 points**
Question 6	**24 points**
Question 7	**36 points**
Question 8	**28 points**
Question 9	**14 points**

Name: _____

1. Consider the following mouse pedigree in which two different traits are segregating. Assume complete penetrance of all traits and that no new mutations arose in any of the individuals in this pedigree.



(a 6 pts.**)** Is **trait 1** autosomal recessive, autosomal dominant, or X-linked recessive? Explain your reasoning.

(b 6 pts.**)** Is **trait 2** autosomal recessive, autosomal dominant, or X-linked recessive? Explain your reasoning.

(c 6 pts.**)** Among 20 progeny from the cross between female **2** and male **1** the following phenotypes are observed: 10 have neither trait, 8 have **trait 1** and **trait 2**, 1 has **trait 1** only, and 1 has **trait 2** only. Given these results, is male 1 homozygous or heterozygous for **trait 1**, is male 1 homozygous or heterozygous for **trait 2**? Explain your reasoning.

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(d 6 pts.**)** From the frequencies given in part **c** calculate the genetic distance between **trait 1** and **trait 2** in cM. Show your work.

2. You have discovered a new strain of *E. coli* that is motile only when amino acids are present in the growth medium. In order to study how motility is regulated you introduce the transposon **Tn5** into a wild type strain on a phage vector. Because the phage carries mutations that prevent replication or integration of the phage into the chromosome, when you select for kanamycin resistance, each **Kan^r** clone will have a **Tn5** insertion at a different site in the chromosome. Among 1000 **Kan^r** clones you identify one mutant that is constitively motile even in the absence of amino acids (**mot^c**).

(a 4 pts.**)** You grow **P1** phage on the **mot^c** mutant strain and use the resulting lysate to infect a wild type strain selecting for **Kan^r** transductants. Out of 500 **Kan^r** transductants, all are constitutively motile (i.e. they have the same phenotype as the **mot^c** mutant). What does this result tell you about the relationship between the Tn5 insertion and the **mot^c** mutation? (It might be helpful to think about how you would interpret the opposite outcome that all of the **Kan^r** transductants showed normal motility (i.e. did not have the **mot^c** phenotype).

Name:

(b 8 pts.**)** Given the properties of the **mot^{c}** mutation described in part (**a**), what kind of gene has been mutated to produce the **mot^{c}** mutation. For your answer, diagram a simple regulatory pathway, with amino acids as the input and motility as the output, showing the normal function of the **mot^{c}** gene.

Next, you perform another transposon mutagenesis of wild type, but this time you use transposon **Tn10**, which confers resistance to the antibiotic tetracycline (**Tet^{r}**). You identify a **Tet^{r}** strain that is not motile even in the presence of amino acids, which you designate **mot1^{-}**. In a transduction experiment in which you grow **P1** phage on the **mot1^{-}**mutant, and then infect wild type, all of the **Tet^{r}** transductants are **mot^{-}**. To understand the relationship between **mot1^{-}** and **mot^{c}**, you use the P1 phage grown on **mot1^{-}** (**Tet^{r}**) to infect the **mot^{c}** (**Kan^{r}**) strain. Among 100 **Tet^{r}** transductants, 75 are also **Kan^{r}**.

(c 6 pts.**)** What is the distance between **mot1^{-}** and **mot^{c}** mutations, expressed as a cotransduction frequency? Could these mutations be in the same gene? Explain.

(d 8 pts.**)** You pick one of the **Tet^{r}** and **Kan^{r}** transductants described above and find that is displays constitutive motility in the absence of amino acids. Using this new information, diagram a regulatory pathway for regulation of motility as the output, showing the normal function of the **mot1^{-}** and **mot^{c}** genes and amino acids.

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3. You have isolated a new mutation in the Lac I (Lac repressor) gene, which you call **LacI-1**. A **LacI-1** mutant constitutively expresses ß-galactosidase. When the **LacI-1** mutation is combined with an amber suppressing allele of $tRNA^{trp}$, the resulting double mutant gives uninducible expression of ß-galactosidase.

(a 6 pts.**)** What kind of mutation is **LacI-1**? Be as specific as you can.

(b 6 pts.**)** Is it possible that the codon that has been mutated in **LacI-1** is a Trp codon? Explain why or why not.

(c 6 pts.**)** Where in the Lac repressor protein is the amino acid whose codon has been mutated in **LacI-1** likely to be? Describe the location as precisely as you can in terms of the known functional parts of the repressor.

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4. You have isolated two mutants in haploid yeast that are sensitive to UV radiation. When exposed to a standard dose of UV, wild type yeast cells survive to 10^{-1} (i.e. 10% survive), whereas a **rad 1** mutant survives to 10^{-3} and a **rad 2** mutant survives to 10^{-4}.

(a 4 pts.**)** You mate **rad 1** and **rad 2** mutant strains to form a diploid, which shows the same UV sensitivity as a wild type diploid. What does this result tell you about the **rad 1** and **rad 2** mutations? Explain.

(b 8 pts.**)** When the diploid isolated in part (**a**) is sporulated, three tetrad types are found that can be distinguished on the basis of the UV sensitivity of each spore clone.

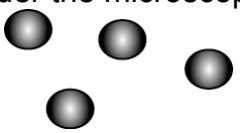
Type 1	Type 2	Type 3
10^{-3}	10^{-3}	10^{-1}
10^{-3}	10^{-4}	10^{-1}
10^{-4}	10^{-7}	10^{-7}
10^{-4}	10^{-1}	10^{-7}

Out of a total of 50 tetrads, 40 are Type 1, 8 are Type 2, and 2 are Type 3.
Are the **rad 1** and **rad 2** mutations linked? If so, how far apart are they in cM?

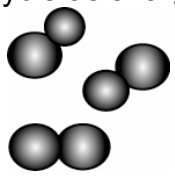
(c 6 pts.**)** What is the degree of radiation sensitivity of a **rad 1 rad 2** double mutant? Is this result consistent with one of these mutants being defective in a DNA repair process and the other defective in a DNA damage checkpoint? Explain your reasoning.

Name:

5. The position of a yeast cell in the cell cycle can be determined by the size of the bud. Unbudded cells are in G1 phase, small budded cells are in S phase, and large budded cells are in M phase. You have two ways to block the cell cycle and you want to determine the relative order in which they function. The first is with the extracellular pheromone α-factor, which blocks the cycle in the G1 phase. Cells that have been treated with α-factor for several hours arrest in G1 and appear under the microscope like this:



When α-factor is removed, these cells will resume the cell cycle. The second reagent you have is a temperature sensitive **cdc7** mutant. At 23˚C this mutant grows normally, but at 37˚C the **cdc7** mutant arrests the cell cycle as a large budded cell:



When these cdc7 cells are returned to 23˚C these cells will resume the cell cycle.

(a 6 pts.**)** In the first experiment, you incubate the **cdc7** mutant in the presence of α-factor at 23˚C for several hours. You then transfer 1000 cells to 37˚C in medium without α-factor. After several hours at 37˚C in the absence of α-factor how many cells should be present (a cell that has not divided will count as a single cell regardless of the size of the bud). Draw a picture of how you would expect the cells to appear under the microscope.

(b 6 pts.**)** In the second experiment, you incubate the **cdc7** mutant at 37˚C for several hours. You transfer 1000 cells to 23˚C, in the presence of α-factor. After several hours at 23˚C, in the presence of α-factor how many cells would be present (again, a cell that has not divided will count as a single cell regardless of the size of the bud). Draw a picture of how you would expect the cells to appear under the microscope.

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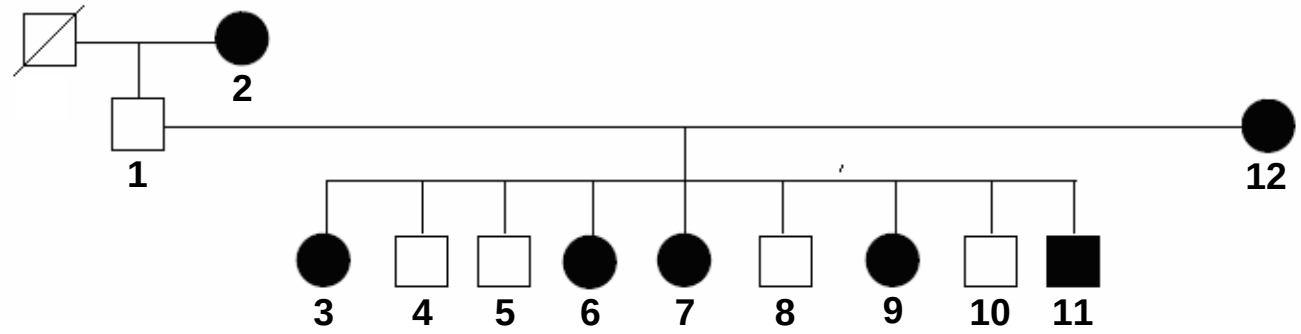
6.. **(a** 8 pts.**)**. In a human population $^{1}/_{10,000}$ individuals exhibit a recessive trait. Given that mating in the population is random, what fraction of the recessive alleles will be present in homozygotes? (An answer accurate to 10% is acceptable).

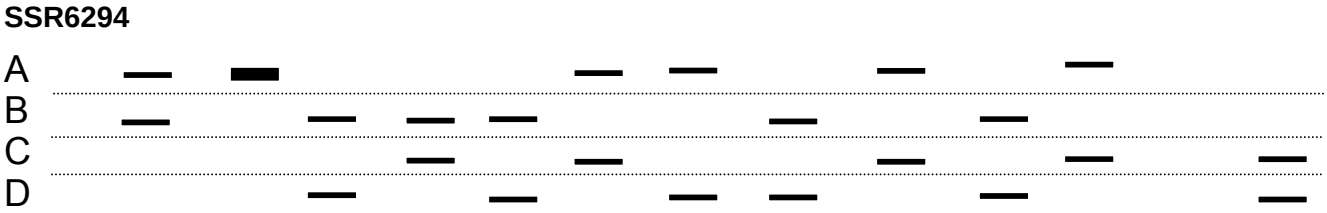
(b 8 pts.**)**. If the fitness of the homozygotes is 0.2, what selective advantage of the heterozygote would have been necessary during human evolution to maintain the current allele frequency for the trait?

(c 8 pts.**)**. If the frequency of first cousin in the population is 0.01, what fraction of homozygous individuals will come from first cousin marriages? (An answer accurate to 10% is acceptable).

Name:

7. Cystic fibrosis (CF) is one of the most common autosomal recessive disorders in European populations. You are a human geneticist conducting genetic linkage studies on the locus responsible for CF. Below is a pedigree from a family showing a high incidence of CF. As indicated, one of the males in the pedigree is deceased and no DNA is available from this individual. The segregation pattern for two different Simple Sequence Repeat markers (SSRs) is shown. You suspect that SSR6294 may be closely linked to the disease-causing allele ('q').





(a 8 pts.**)** Fill in the charts above for both the maternally and paternally inherited alleles at **SSR6294** and the **CF** locus.

Individual

	3	4	5	6	7	8	9	10	11
paternally inherited allele at SSR6294									
paternally inherited allele at the CF locus									

Individual

	3	4	5	6	7	8	9	10	11
maternally inherited allele at SSR6294									
maternally inherited allele at the CF locus									

Name:

(b 6 pts.**)** Diagram the possible phase(s) between the CF alleles and SSR6294 alleles in the father.

(c 6 pts.**)** Based on the pedigree data, what θ value would give the maximum LOD score?

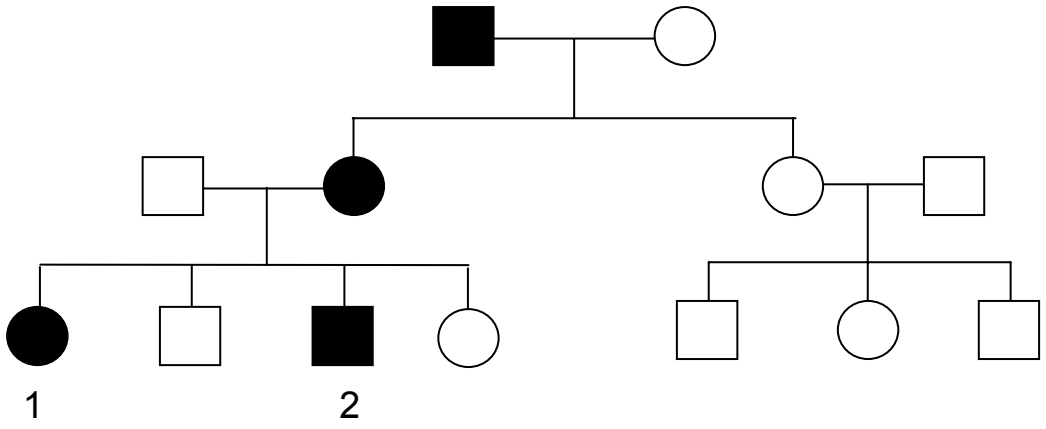
(d 8 pts.**)** Using the value of θ determined in part **c**, calculate the LOD score for linkage between SSR6294 and the CF locus in this family.

(d 8 pts.**)** Suggest two ways you might be able to obtain a higher LOD

(i) Using SSR6294

(ii) Not using SSR6294

8. The following pedigree shows a family that is affected by a rare form of familial cancer. Affected individuals typically form multiple tumors in a variety of tissues throughout their life.



(a 6 pts.**)** What is the mode of inheritance for this trait?

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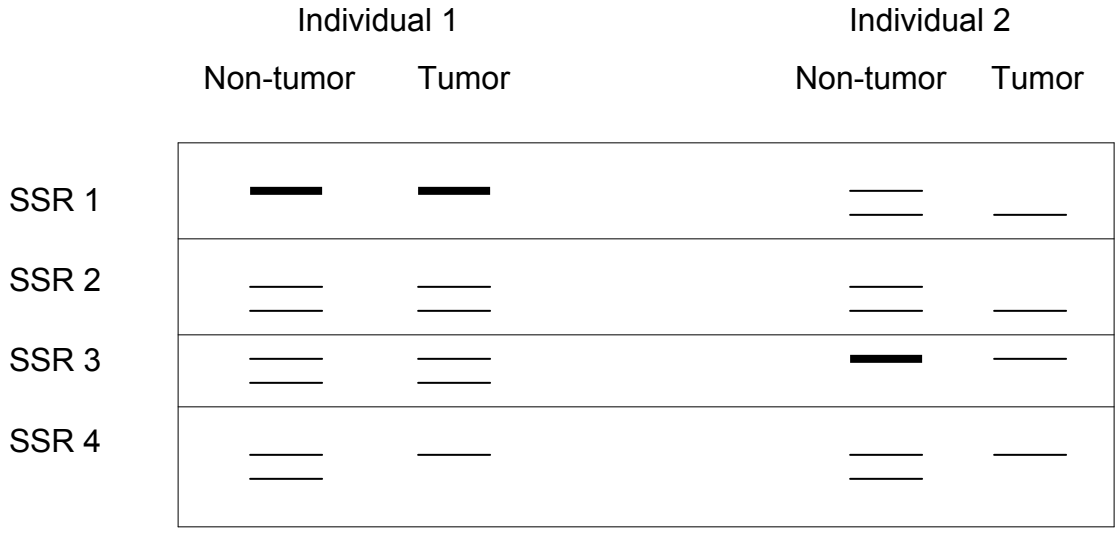
Based on linkage studies you are confident that the causative mutation is on Chromosome 4. To gather more mapping data you analyze four Simple Sequence Repeat markers (SSRs) on Chromosome 4 in tumor and non-tumor tissue of the two individuals labeled above. You find the following:



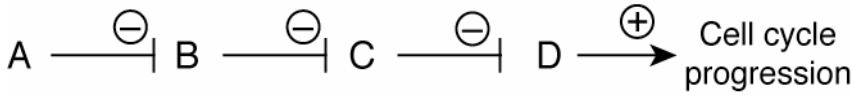
(b 8 pts.**)** Propose a mechanism that would account for the transformation of normal tissue to tumor in Individual 2. Your answer should specify whether the mutation affects a tumor suppressor gene or an oncogene.

(c 8 pts.**)** In tumor tissue from Individual 2, there is only one SSR2 allele. From which parent did Individual 2 inherit this specific allele (mother, father or inconclusive)? Briefly explain your reasoning.

(d 6 pts.**)** Based on the above analysis of SSR markers, to which SSR(s) is the causative mutation most closely linked?

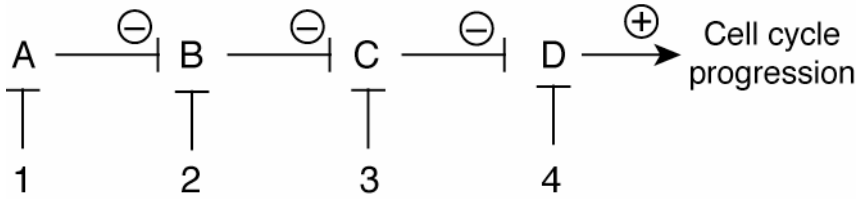
Name: _____

9. Consider the following hypothetical pathway for regulation of cell cycle progression in the mouse:



(a 7 pts.**)** Which gene(s) in this pathway would you attempt to knock out in order to promote uncontrolled cell division?

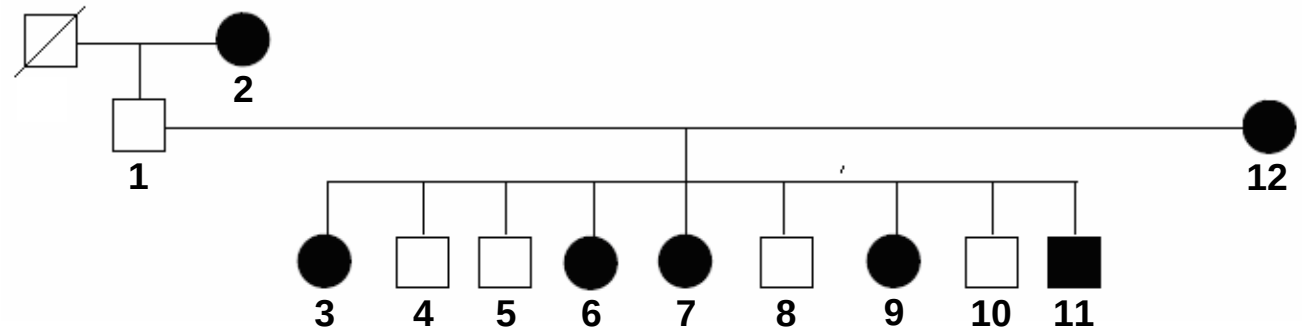
A company has recently generated four drugs (numbered 1-4) that can specifically inhibit each of the four gene products in this pathway



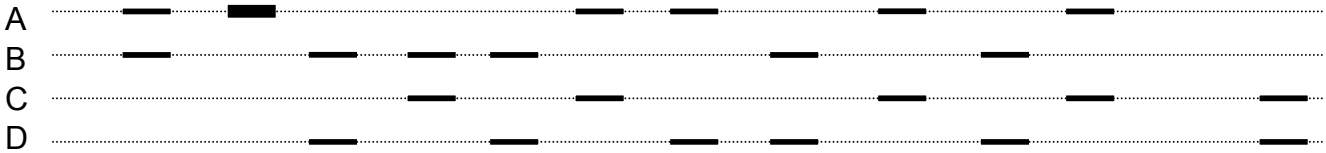
(b 7 pts.**)** Which drug(s) acting alone would you predict to be effective in fighting cancer in each of the knockouts generated in part (**a**).

7.03 Fall 2006 Final Answer Key

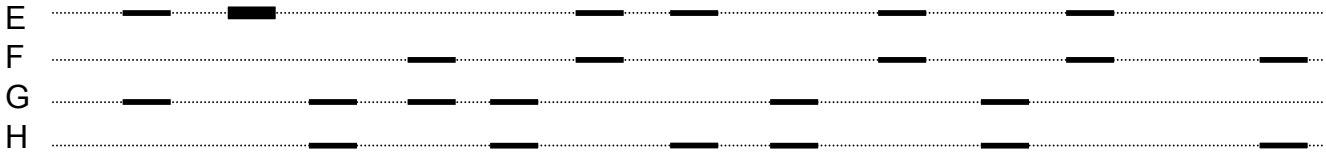
Cystic fibrosis (CF) is one of the most common autosomal recessive disorders among European populations. You are a human geneticist conducting genetic linkage studies on the locus responsible for CF. Shown below is a pedigree from a family showing a high incidence of CF. There are no DNA samples available from the deceased individual. You suspect that the simple sequence repeat SSR6294 is closely linked to the disease-causing allele ('q').



SSR6294



SSR37



Individual

	3	4	5	6	7	8	9	10	11
paternally inherited allele at SSR6294									
paternally inherited allele at the CF locus									

	3	4	5	6	7	8	9	10	11
maternally inherited allele at SSR6294									

maternally inherited allele at the CF locus									

(a) Fill in the charts above for both the maternally and paternally inherited alleles at **SSR6294** and the **CF locus**.

(b) Diagram the possible phase(s) between the disease and SSR6294 alleles in the father.

(c) Calculate the LOD score for linkage at θ = 0.1, 0.2, 0.3, and 0.4 between SSR6294 and the CF locus in this family.

(d) Based on the pedigree data, what θ value would give the maximum LOD score?

(e) Predict the map distance (cM) between SSR6294 and the CF locus.

(f) You want to obtain a higher LOD score in order to publish your results. Suggest a method to obtain a LOD Score ≥ 3…

(i) Using SSR6294

(ii) Not using SSR6294

(g) Another SSR (SSR37) has been proposed to be linked to the CF locus and SSR6294. Calculate the overall LOD score for linkage between SSR6294 and SSR37.

(i) Calculate the LOD score for linkage at $\theta = 0.1$ between SSR37 and SSR6294 treating Individual 1 as the **only** relevant parent.

(ii) Calculate the LOD score for linkage at $\theta = 0.1$ between SSR37 and SSR6294 treating Individual 12 as the **only** relevant parent.

(iii) Calculate the **overall** LOD score for linkage at $\theta = 0.1$ between SSR37 and SSR6294.