NAME: _____

STUDENT ID #: _____

MCB 140 FINAL EXAM

Spring 2007

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REMINDERS

You have 180 minutes for the 225 point exam.

Print your name and ID# on each page of the exam. You will lose points if you forget to do this.

There are 17 pages total, including this cover page. The last two pages are work space (no problems). All pages must be turned in.

Only the front of each page will be graded. If you use the back of a page, transcribe your answer to the front of the page.

Use a non-programmable calculator.

----------(Do not write below this line)----------

1 (25) _____	10 (15) _____
2 (11) _____	11 (10) _____
3 (2) _____	12 (10) _____
4 (2) _____	13 (15) _____
5 (7) _____	14 (20) _____
6 (3) _____	15 (10) _____
7 (35) _____	16 (5) _____
8 (10) _____	17 (10) _____
9 (15) _____	18 (20) _____

TOTAL _____ / 225

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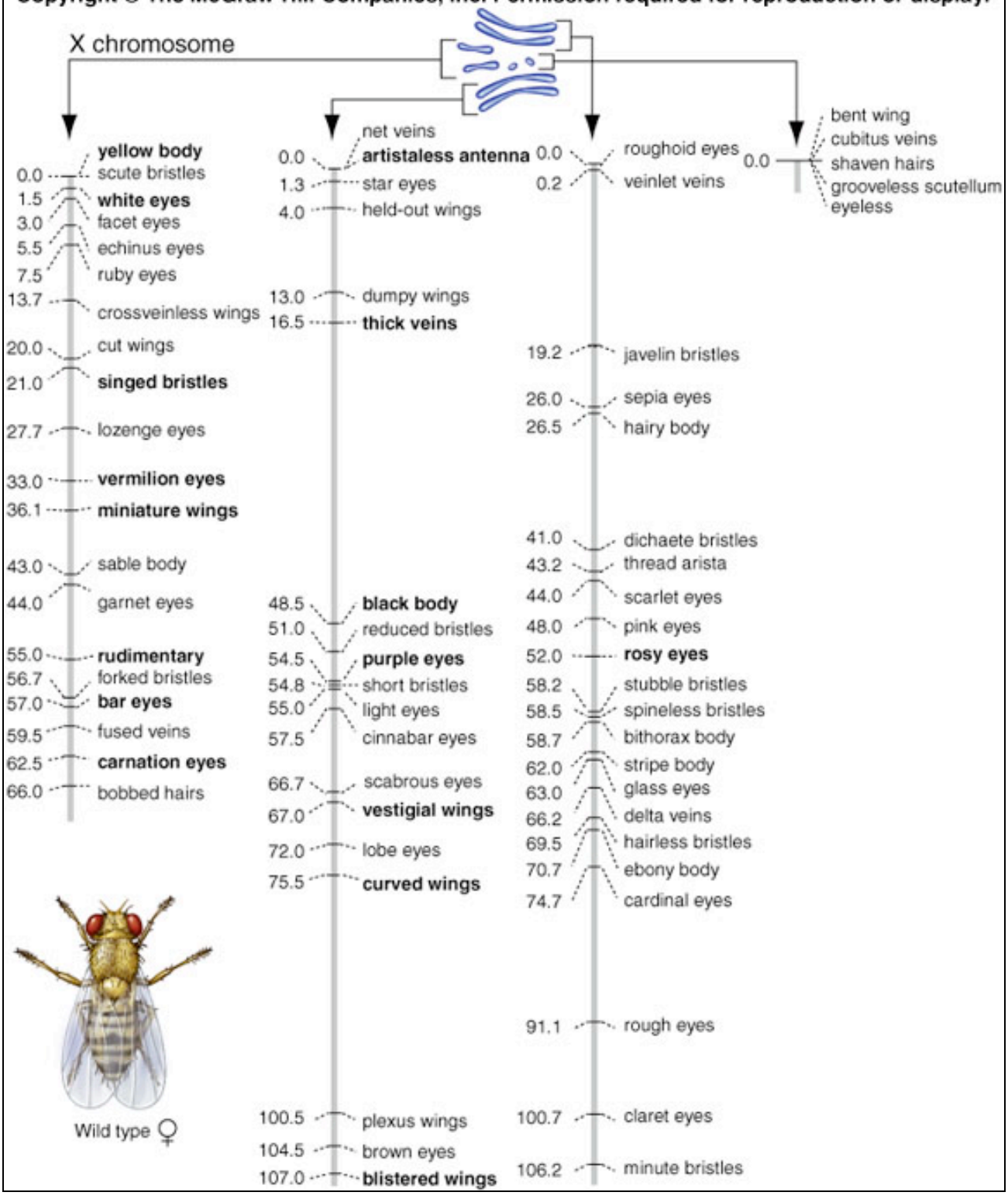
Questions on Prof. Urnov's section

1. The following is Fig. 5.13 from your textbook. It shows one of the most majestic achievements of the scientific method: a map of the Drosophila genome obtained without any knowledge of the chemical basis of heredity – i.e., solely via genetic analysis.



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(a) (5 pts) We talked about the fact that unlinked genes recombine at a frequency of 50%. That said, for some reason, the genetic distance on Chr. 1 between two linked genes, **aristaless antenna** and **blistered wings,** is a whopping 107 map units. How could this impossible value have been experimentally measured? Did they observe recombination 107% of the time?!

(b) (20 pts) A white-eyed, male with normal veins on its wings and a body of wild-type color is mated to a red-eyed female with thick-veined wings and a black body. All the progeny of this cross are wild-type. Female progeny of this cross are mated to white-eyed males with thick veins on their wings and a black body. One thousand progeny from this cross are phenotyped. Write out the phenotypic classes observed in this progeny and the number of flies in each class, assuming perfect compliance with the genetic distances shown above, and perfect compliance with Mendel's laws.

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Questions on Prof. Cline's section

For each question below (2-6), **BRIEFLY EXPLAIN** your answer, **even** if your answer is, "there is **no logical basis** from Genetic principles and/or vocabulary for an answer other than "can't say", based on the information provided." Remember not to overthink the questions.

2. Consider two different dominant gain-of-function alleles of the same gene in the German Shepherd dog. Q^A is an antimorph, while Q^H is a hypermorph. The phenotype of the null *Q* allele is no tail, and the mutant allele is fully recessive.

(a) (2 pts): What can you say about the likely phenotype of a $Q^A/+$ German Shepherd?

(b) (2 pts): Would you expect the mutant phenotype of $Q^A/+$ dogs to be qualitatively similar to that of $Q^H/+$ dogs, or instead be qualitatively different?

(c) (2 pts): Q^A/Q^H dogs are wildtype. Would it be correct therefore to say that the two gain-of-function alleles complement?

(d) (3 pts): If we "reverted" the dominance of Q^A and Q^H, generating Q^{A*} and Q^{H*} respectively, what would the likely phenotype be of a Q^{A*}/Q^{H*} dog?

(e) (2 pts.): In light of the information given you in part c above, what, if anything, could you predict about the phenotype of a $Q^{A,H}/Q^+$ dog, if you were told that Q^A and Q^H satisfy expectations for a cis-trans test for allelism? Assume that $Q^{A,H}$ is a doubly mutant allele created by recombination between Q^A and Q^H (not very likely, of course).

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3. (2 pts.) The mutagen ethylmethane sulfonate will generate null alleles, but it is particularly effective at generating a wide spectrum of hypomorphic point mutants as well. Brenner and crowd used proflavin as the mutagen for the *rII* gene of phage T4 in their famous experiments exploring the nature of the genetic code. They demonstrated that the genetic code was commaless in part by showing that certain of their point mutant alleles could be suppressed by certain other of their point mutant alleles. Do you think that some of the mutations they induced in *rII* by proflavin would likely be suppressed by some of the mutations that one might typically induce in *rII* by ethylmethane sulfonate?

4. (2 pts) To move DNA around, fly workers generally use an engineered immobile genetic source of P-element transposase called "delta-2,3", derived from DNA that was originally introduced into an M-strain animal. After many generations, will female flies from the delta-2,3 strain eventually come to behave like P-strain females and generate eggs with a P cytotype?

5. The mechanism of sex determination can be remarkably messy in some species, with different races of the same species having different GSD systems operating. Consider such a species in which race Q has a ZZ-ZW system of the active W type, while race R of the same species (but geographically isolated from the other) has an XX-XY system of the active Y type. The Z and X chromosomes of the two races are essentially identical genetically, and this sex chromosome carries 10% of all the genes. In contrast, the W and Y chromosomes carry very few genes.

(a) (2 pts) Which, if either, of the two races is/are likely to need a sex-chromosome dosage compensation system?

(b) (2 pts) Which, if either, of these species is likely to use a sex-chromosome:autosome balance system of sex determination?

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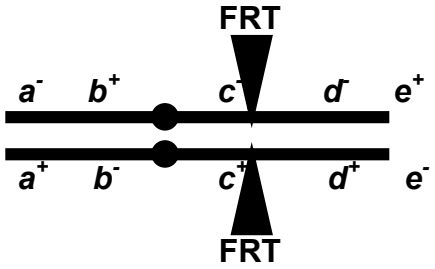
(c) (3 pts) If you crossed a Q strain male with an R strain female, what would you expect the sexual phenotype(s) of the offspring to be?

6. (3 pts) Given the following genotype of fruit fly:



…where a^- through e^- are recessive, cell-autonomous mutant alleles that can generate distinguishable clone phenotypes on the thorax (back) of the adult.

If a brief pulse of "Flippase" were introduced during the development of this fly to induce a single clone of phenotypically e^- mutant tissue on the adult thorax (without respect to what other mutant phenotypes that e^- clone might exhibit), what would you expect the phenotype to be of the **twin-spot partner** of that e^- clone with respect to these **five** genes? (**no explanation needed**)

Questions on Prof. Brem's section

7. (35 pts) Imagine that you are studying genetic differences between the Junglefowl and Leghorn varieties of chicken, whose pictures we saw in class. You mate the parents to generate F1's and then cross the F1's among themselves to get 100 F2 birds.

You first get interested in the quantitative trait of egg weight. By linkage analysis, you map a very strong locus that appears to explain essentially all the genetic variation in egg weight in the cross. The LOD score is highly significant and you are convinced that the trait is Mendelian, controlled by the single locus you have mapped. The Junglefowl parent is homozygous for one allele, called J; the Leghorn parent is homozygous for another allele, called L. The phenotypes among the F2's look like this:

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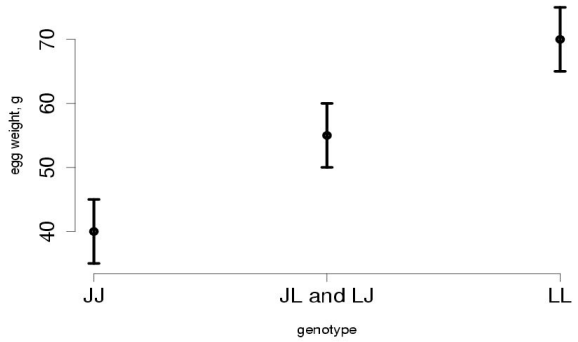
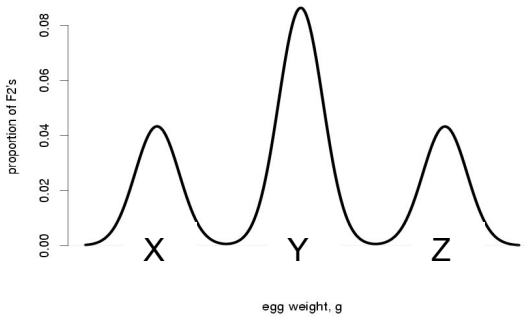


(a) (5 pts) What is the effect of gaining an L allele at this locus?

(b) (5 pts) The distribution of egg weights among the 100 F2 birds looks something like this:



Give the phenotype values (egg weight in grams) corresponding to positions X, Y, and Z.

X:

Y:

Z:

(c) (5 pts) What proportion of the F2 chickens do you expect with phenotypes falling under each peak?

X:

Y:

Z:

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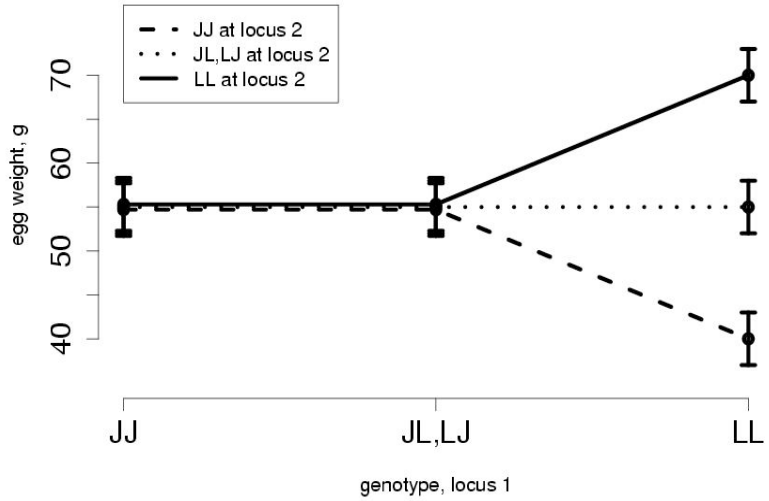
Now imagine a totally different scenario where you map two loci that control egg weight, which you refer to as locus 1 and locus 2. These loci are on different chromosomes. The phenotypes among the F2's now look like this:



Note that the *x* values represent genotype at locus 1, whereas the different line styles represent genotype at locus 2.

(d) (5 pts) Imagine a graph of the distribution of phenotypes among the F2's given this new two-locus model. It would look similar to the one you saw in (b), with phenotype on the *x* axis and the proportion of F2's on the *y* axis. How many peaks would the plot have and what would be the values on the *x* axis for the midpoint of each peak, as in (b)?

(e) (5 pts) What is the genotype of an F1 chicken? Remember that locus 1 and 2 are on different chromosomes.

(f) (5 pts) What is the total number of cells in a Punnett square representing the cross between two F1's to form an F2?

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(g) (5 pts) As you just described in (d), the distribution of phenotypes among the F2's has several peaks. For each peak, give the proportion of F2's you expect to fall under it. Your answer should consist of several fractions, one for each peak.

8. (10 pts) Imagine that peanuts with high oil content make better peanut butter. Explain why a plant breeder selling to farmers would prefer for oil content in peanuts to have a high heritability.

9. (15 pts) Consider a biased coin with a probability of coming up heads of 0.1 on any given flip.

(a) (5 pts) If you do four coin flips, what is the probability of all four being heads?

(b) (5 pts) If you do four coin flips, what is the probability of seeing anything BESIDE the result of all heads?

(c) (5 pts) If you have a roll of these coins and you give one to each of 100 students, who each do four coin flips, how many students are likely to come up with all heads?

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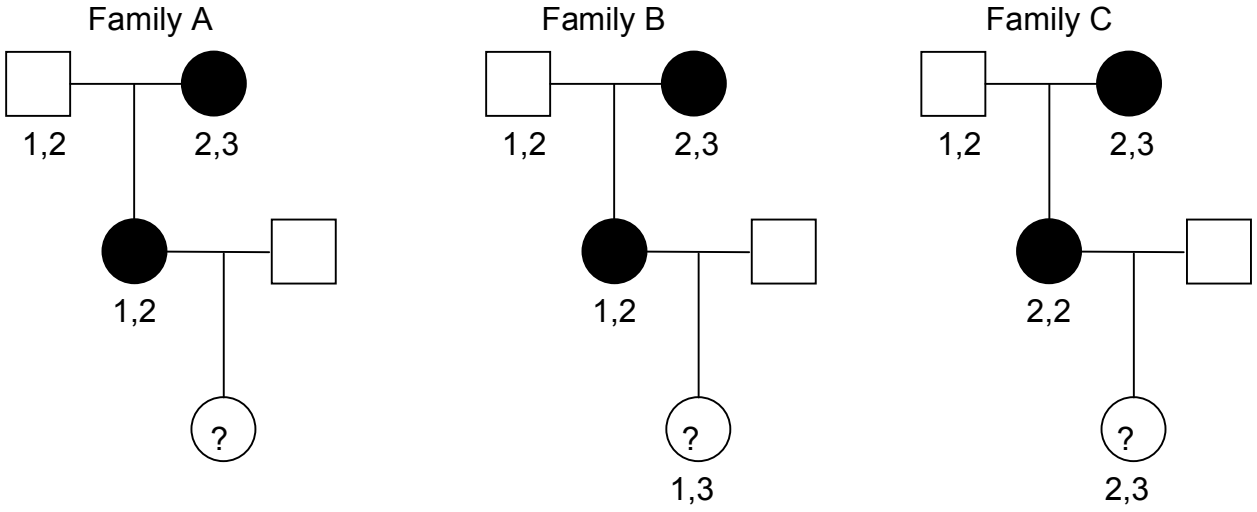
10. (15 pts) The segregation of a fully penetrant Mendelian disease in several small families is shown below, along with the genotypes at a DNA sequence marker 30 cM from the disease locus. For each family, infer from the data what the likelihood is that the individual of unknown phenotype is affected with the disease.



A:

B:

C:

11. (10 pts) In modern linkage analysis, we look for instances of recombination between a marker locus whose genetic position is known, and the unknown locus causing our phenotype of interest—say, a disease. We count the proportion of recombinants in a pedigree, but then use this number to test different "models" or guesses for the value of the recombination fraction (the probability of recombination) between the marker and the disease locus. Explain why we explore many potential values for this quantity when the number of recombinants in the pedigree is already known.

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12. (10 pts) Imagine that you are studying a Mendelian dominant disease via linkage analysis and are focusing on a single marker. You have two large families whose members have been genotyped at the marker and scored for the disease.

In Family I there are 10 meioses; in 8 of them, alleles at your marker and the disease locus appear to have been inherited without recombination, and in the other 2 there was a recombination. You test many values of the recombination fraction and discover that r = 0.2 gives the maximum odds ratio, which is 6.87 (LOD = 0.837).

In Family II there are 20 meioses; in 17, alleles at the marker and disease locus were inherited without recombination, while 3 meioses represent recombinations. You test many values of r and discover that r = 0.15 gives the maximum odds ratio, which is 223.4 (LOD = 2.34).

Finally, you know that the way to combine data across Familiy I and Family II is to multiply odds ratios (add LODs), so you do this for a final estimate of the odds of linkage relative to the null as 1534.5 (LOD = 3.19). In one or two sentences explain what's wrong with this calculation.

13. (15 pts, 5 each) Imagine you are doing a genome-wide linkage analysis study in Finnish families looking for the genetic determinants of blood pressure in humans. You have five multi-generational families; each individual is genotyped at 1000 markers and his/her blood pressure is measured. A recent, published study in Icelandic families identified a highly significant locus on chromosome 10 that was responsible for blood pressure variation. You look through your results and see no significant linkage between the phenotype and the disease in your data. Your nearest marker to this locus is 30 cM away.

Give three reasons why you might have failed to find linkage to the chromosome 10 locus. Please explain each reason with one or two sentences, or you will not receive credit for your answer.

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14. (20 pts) We learned in class about *golden*, a mutation in zebrafish that arose randomly in a colony of fish of a common strain growing in the lab. Imagine that a colleague is studying a common haploid lab strain of yeast. One day she comes into the lab and sees a hot pink colony on her petri dish, in the midst of hundreds of normal whitish-yellow ones. Thus, the hot pink strain arose from the progenitor via spontaneous mutation during mitosis under normal lab conditions. She isolates a single cell from the hot pink colony and allows it to grow again into a colony via mitosis; the colony once again is hot pink, confirming that it wasn't just an environmental fluke. Fascinated, she wants to identify the mutation(s) responsible for the hot pink phenotype.

(a) (10 pts) She proposes a genetic experiment as follows: (1) Cross the hot pink strain to the original wild-type progenitor to form a diploid, (2) sporulate it to form F1 haploids, (3) establish a set of markers and genotype all progeny, (4) score all progeny for the hot pink colony phenotype, and then (5) use linkage mapping to find the genetic loci responsible for hot pink colony formation. You know that linkage analysis works fine in haploids. And a simple single-generation cross is also a fine idea, since one can generate lots of progeny in yeast. Nonetheless you have to break it to her that even if the hot pink trait is Mendelian, her idea can't possibly work. Why not?

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(b) (10 pts) Propose an alternative way to map the hot pink locus.

15. (10 pts) A mutation in a tumor suppressor gene that causes cancer is usually:

(a) (5 pts) A gain or loss of function? Why?

(b) (5 pts) Dominant or recessive? Why?

16. (5 pts) We learned in class about two strains of rice differing in their tolerance for submergence under water. The submergence sensitive strain was homozygous for a deletion of the entire Sub1A gene. Assume that the submergence tolerant strain was

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homozygous for wild-type Sub1A. What would you expect the phenotype of a heterozygote to be and why?

17. (10 pts) On a petri dish, *C. elegans* worms can sense and move toward bacterial cells, which the worms eat. This is thought to be mediated by small molecules in high concentrations near bacteria, since worms will also move toward a drop of certain "attractant" chemicals like salt and cyclic nucleotides. This behavior is called chemotaxis; assume that rapid chemotaxis toward salt is always critical for the worms to find food. You mutagenize a colony of worm clones and identify a mutant that chemotaxes more slowly to salt than wild-type laboratory worms do. In parallel, a colleague who has been collecting wild *C. elegans* isolates from mushroom compost shows you that one of her wild strains chemotaxes to salt more slowly than wild-type laboratory worms do.

You do a genetic mapping experiment with each strain separately, the mutagenesis product and the wild isolate. In each case you identify the polymorphism that causes slow chemotaxis. In which strain would you expect a more dramatic mutation, like a large deletion or severe amino acid change, and why?

18. (20 pts) You are studying leaf length in two strains of Arabidopsis, Col and L*er*. In wild-type plants Col leaves are on average 1 cm in length, while those of L*er* are 3 cm long.

(a) (10 pts) Before bothering with genetic mapping, you get excited about a previously characterized gene, LEAF-1, which you think might be causative for the difference between your parent strains. However, there are no coding polymorphisms in LEAF-1 and its expression isn't different between the two strains. Undaunted, you decide to test the role of LEAF-1 by engineering each strain with the entire LEAF-1 gene deleted. The leaf lengths of the strains are below.

	Col	L*er*
Wild-type	1 cm	3 cm
LEAF-1 delete	0.2 cm	2.8 cm

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Assume that the data are all correct and that LEAF-1 does not vary between the strains. Briefly suggest a model to explain why comparing a LEAF-1 knockout in Col to wild-type Col shows a big effect, but comparing a LEAF-1 knockout in L*er* relative to wild-type L*er* does not show a big effect.

(b) (10 pts) Now you finally get down to business, doing a cross and a whole-genome linkage scan. You find linkage to a region containing another good candidate, LEAF-2. Expression of LEAF-2 appears the same between the two strains. However, there is a large deletion in the coding sequence of LEAF-2 in Col relative to L*er*. Now that you see this big fat polymorphism, you want to confirm the role of LEAF-2 in the cross. So again you do knockouts of this new gene in each strain. The leaf lengths of the strains are below.

	Col	L*er*
Wild-type	1 cm	3 cm
LEAF-2 delete	1 cm	1 cm

Briefly suggest a model to explain why comparing a LEAF-2 knockout in L*er* to wild-type L*er* shows a big effect, but comparing a LEAF-2 knockout in Col relative to wild-type Col does not show a big effect.

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