7.03 Problem Set 1 Answer Key

1. You have isolated 6 mutant yeast strains that are uracil auxotrophs (ura$^-$). You wish to begin characterizing these mutants and decide to begin by crossing each mutant strain to the wild type strain and achieve the following results:

Cross	**Resulting diploid**
Mut 1 x WT	WT
Mut 2 x WT	WT
Mut 3 x WT	WT
Mut 4 x WT	WT
Mut 5 x WT	ura$^-$
Mut 6 x WT	WT
Mut 7 x WT	WT

a) What do these results tell you about each of the mutations in these strains?

Mutations 1-4,6,7 are recessive mutations (0.5 points)
Mutation 5 is a dominant mutation (0.5 points)
[1 point total]

b) You decide to do a complementation test. What further information will this provide you?

A complementation test will allow you to distinguish between mutations in the same gene versus mutations in different genes (0.5 points)

c) You obtain the following results from your complementation test:

	Mut 1	Mut 2	Mut 3	Mut 4	Mut 5	Mut 6	Mut 7
Mut 1	ura$^-$	ura$^-$	WT	WT	ura$^-$	ura$^-$	WT
Mut 2		ura$^-$	WT	WT	ura$^-$	ura$^-$	WT
Mut 3			ura$^-$	WT	ura$^-$	WT	ura$^-$
Mut 4				ura$^-$	ura$^-$	WT	WT
Mut 5					ura$^-$	ura$^-$	ura$^-$
Mut 6						ura$^-$	WT
Mut 7							ura$^-$

Sort these strains into complementation groups. Explain any ambiguities.

1,2,6
3,7

4
Mut 5 cannot be placed into a complementation group because the complementation test does not work on dominant mutations.

(0.25 points for each correct group assignment, 0.5 points for mutant 5 explanation) [1.25 points total]

d) When doing some background reading, you discover that mutations in previously characterized genes (Ura1, Ura2, and Ura3) also give a ura$^-$ phenotype. You decide to see if your strains are mutant in any of these genes. After testing Mut 1, you find it fails to compliment Ura2, but does compliment Ura1 and Ura3. Fill in the following table in a way that is consistent with this observation.

	ura1$^-$	**ura2$^-$**	**Mut1**	**Mut1 x ura1$^-$**	**Mut1 x ura2$^-$**
Ploidy	Haploid	Haploid	Haploid	Diploid	Diploid
Genotype	ura1$^-$	ura2$^-$	ura2$^-$	Ura1$^+$/ura1$^-$, ura2$^-$/Ura2$^+$	ura2$^-$/ ura2$^-$
Phenotype	ura$^-$	ura$^-$	ura$^-$	Ura+	ura$^-$

(0.25 points for each correct space) [2.25 points total]

2. A myotonic goat, also known as a fainting goat, is a goat whose muscles will freeze when it is startled, causing it to tip over. (An internet search for "fainting goat" will turn up many videos of this phenomenon.) This phenotype is caused by a recessive allele in a single gene.

You own a fainting goat with white hair. This hair color is the result of a single gene, and the allele for white hair is recessive. However, you want to breed gray fainting goats. You acquire a goat that is true-breeding for the dominant gray hair color allele (and homozygous for the dominant, non-fainting allele) and mate it with your white fainting goat.

a) What genotypes are present in the F1 generation? What phenotypes are present?

W = grey allele w = white allele F = non-fainting allele f = fainting allele

Genotype: All F1s are WwFf

Phenotype: All F1s are gray and non-fainting

½ point for genotype, ½ point for phenotype

b) You decide to cross the resulting F1 goats. What phenotypes are present in the F2 generation, and in what proportions?

The standard Mendelian ratio of two traits in F2 is 9:3:3:1, so in this case:

9 gray and non-fainting, 3 gray and fainting, 3 white and non-fainting, and 1 white and fainting.

½ point for 9:3:3:1 ratio, ½ point for correct phenotype in each category

c) In your F2, you have generated some of your desired goats: gray and fainting. However, what you really want is a line of true-breeding (homozygous at all alleles) gray and fainting goats. What fraction of the F2 goats **that are gray and fainting** will be true-breeding for both of those phenotypes?

Proportionally, you have 3 out of 16 gray and fainting goats. If you draw the Punnett square (or calculate each of the genotypes in some other way), you will see that 2 of those 3 gray fainting goats have the Wwff genotype, and one has the WWff genotype. Therefore, 1/3 of the gray fainting goats will be true breeding.

1point; ½ point given if correct logic is used but arrives at wrong number.

d) Design a cross that can determine whether a gray, fainting goat is true-breeding.

Cross the gray fainting goat with a white goat. If any white offspring are produced, the gray fainting goat is not-true breeding, since it must have one w allele in order for any of its offspring to be white. (Since it is a fainting goat, it must be true-breeding for the fainting trait, since the fainting allele is recessive.)

1 point for any cross that would work.

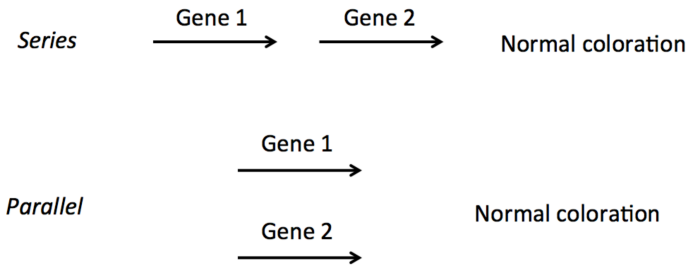
e) You decide to also breed your goats to have spots, which are caused by a single dominant allele. After some hard work, you have two goats that you know are heterozygous at all three alleles. If you cross them, what fraction of the resulting offspring will have all three **dominant** phenotypes?

There are many ways to do the math to solve this problem. One simple way to do it is to observe that, since the chance of getting a single dominant phenotype is ¾, and each phenotype is independent of the others, the probability of getting all 3 is ¾ * ¾ * ¾ = 27/64.

1 point; ½ point given if correct logic is used but arrives at wrong number.

3. You are studying the genetics of body color in the fruit fly, *Drosophila melanogaster*. You have discovered a strange new phenotype in which the flies have polka dots on their bodies. Based on your previous research on fly color, you hypothesize that two genes have an effect on this phenotype.

However, there are two ways that a pair of genes in a biochemical pathway can act: in series or in parallel. If the genes work in series, both genes are necessary for the fly to have wild-type coloration; therefore, **only one** gene would need to have its function disrupted in order for the fly to have the mutant phenotype. If the genes work in parallel, either one of the genes is necessary for the fly to have wild-type coloration; therefore, **both** genes need to have their function disrupted in order for the fly to have the mutant phenotype.



Another factor is the nature of each gene's mutant allele. The mutant allele in each gene can be either dominant or recessive. (Although mutations that disrupt gene function, known as loss-of-function mutations, are usually recessive, it is still possible for them to be dominant, so we need to consider that possibility.) This leads to six possible models for the pathway to work:

1. The genes work in series and both mutant alleles are dominant.
2. The genes work in series, and one mutant allele is dominant and one mutant allele is recessive.
3. The genes work in series and both mutant alleles are recessive.
4. The genes work in parallel and both mutant alleles are dominant.
5. The genes work in parallel, and one mutant allele is dominant and one mutant allele is recessive.
6. The genes work in parallel and both mutant alleles are recessive.

a) You have a true-breeding, polka-dotted fly and cross it with a wild-type fly. The resulting F1 generation all have normal body color, without any polka dots. Which of the six models listed above are still possible, given this experimental result? Explain your reasoning.

Models 3, 5, and 6 are still possible.

If model 1 or model 4 were true, both mutant alleles would be dominant, so both genes would have the mutant function, and the flies would have the polka dotted phenotype whether the genes worked in series or in parallel.

If model 2 were true, one of the genes (the one with the dominant mutant allele) would have the mutant function. Since the genes in this model work in series, a single gene with mutant function will have the mutant phenotype, and the flies would be polka dotted.

In models 3 and 6, both mutant alleles are recessive, so neither gene will have the mutant function, and the flies would have the wild-type phenotype whether the genes worked in series or in parallel.

In model 5, the gene with the dominant allele will have mutant function. However, since the genes work in parallel, both genes need to have mutant function in order to have the mutant phenotype.

1 point: 1/6 point for each correctly reasoned model

b) You cross the F1 flies to generate the F2 generation. What proportion of wild-type to polka-dotted flies would be expected for each of the models that were **not** rejected in part a?

The genotype of the F1 generation is $A^+A^-B^+B^-$, where A and B are the two genes and + is the wild-type allele and – is the mutant allele.

For model 3, we have our standard 9:3:3:1 ratio of genotypes: 9 $A^+\_B^+\_$, 3 $A^+\_B^-B^-$, 3 $A^-A^-B^+\_$, and 1 $A^-A^-B^-B^-$, since both genes are recessive. Since the genes are in series, a single gene with the mutant function will cause the mutant phenotype, so all of the 3 $A^+\_B^-B^-$, $A^-A^-B^+\_$, and $A^-A^-B^-B^-$ individuals will have the mutant phenotype. Therefore, the expected ratio of wild-type to mutant phenotypes is 9:7.

For model 6, we have a similar case to model 3, but since the genes are in parallel, only the case where both genes have the mutant function—$A^-A^-B^-B^-$— will have the mutant phenotype. Therefore, the expected ratio of wild-type to mutant phenotypes is 15:1.

For model 5, the ratio can be calculated the following way:
Since the genes work in parallel, both genes need to have the mutant function in order to have the mutant phenotype. Therefore, we need to multiply the probabilities of each gene having the mutant function. The probability of the gene with the dominant mutant allele having the mutant function is ¾, since the allele is dominant and you are crossing two heterozygotes for the allele. The probability of

the gene with the recessive mutant allele having the mutant function is ¼, since the allele is recessive and you are crossing two heterozygotes for the allele. Therefore, the fraction of offspring with mutant function at both alleles is ¾ * ¼ = 3/16, and the ratio of wild-type to mutant phenotypes is 13:3.

1.5 points, ½ point for each model's ratio. If wrong models were used based on answer to the last question, full credit is given if the ratios are correct for the models that were answered for, as long as 3 or more models were calculated. If 1 or 2 models were calculated based on a wrong answer to part a, max of 1 point.

c) You take 30 flies from F2 and see that 6 of them have polka dots. Using the χ^2 test, which of the remaining models can be rejected? Use the table of χ^2 values below for your calculations.

p value:	.995	.975	0.9	0.5	0.1	0.05	0.025	0.01	0.005
df = 1	.000	.000	.016	.46	2.7	3.8	5.0	6.6	7.9
df = 2	.01	.05	.21	1.4	4.6	6.0	7.4	9.2	10.6
df = 3	.07	.22	.58	2.4	6.3	7.8	9.3	11.3	12.8

The expected number of wild-type and polka-dotted flies out of 30 for each model are:

Model 3—9:7 ratio, so 9/16 * 30 = 16.875 wild-type flies and 7/16 * 30 = 13.125 polka-dotted flies

Model 5—13:3 ratio, so 13/16 * 30 = 24.375 wild-type flies and 3/16 * 30 = 5.625 polka-dotted flies

Model 6—15:1 ratio, so 15/16 * 30 = 28.125 wild-type flies and 1/16 * 30 = 1.875 polka-dotted flies

For all calculations here, we use 1 degree of freedom, since there are 2 categories.

Model 3: $\chi^2 = (24 - 16.875)^2 / 16.875 + (6 - 13.125)^2 / 13.125 = 6.876 > 3.8$, so we reject model 3.

Model 5: $\chi^2 = (24 - 24.375)^2 / 24.375 + (6 - 5.625)^2 / 5.625 = 0.031 < 3.8$, so we can not reject model 5.

Model 6: $\chi^2 = (24 - 28.125)^2 / 28.125 + (6 - 1.875)^2 / 1.875 = 9.68 > 3.8$, so we reject model 6.

1.5 points, ½ point for each model. Credit for calculating models that should have already been rejected same as in part b.

d) When you bring your results to your adviser, she points out that you haven't considered the possibility that you original, true-breeding polka-dotted fly simply had a recessive allele at a single gene that caused the polka dots. Can you use the χ^2 test with your observation that 6 out of 30 of the F2 flies had polka dots to reject this possibility? If not, how many flies would you need in order to reject this one-gene hypothesis, assuming that you will observe polka dotted flies in the exact ratio predicted by the two-gene model that you didn't reject in part c? (Don't worry about an exact number; anything within 20 of the exact number is fine.)

If the phenotype were caused by a single recessive allele, the expected F2 ratio of wild-type to mutant flies would be 3:1. Therefore, we would expect 30 * ¾ = 22.5 wild-type flies and 30 * ¼ = 7.5 polka-dotted flies. Doing a χ^2 test, we find that

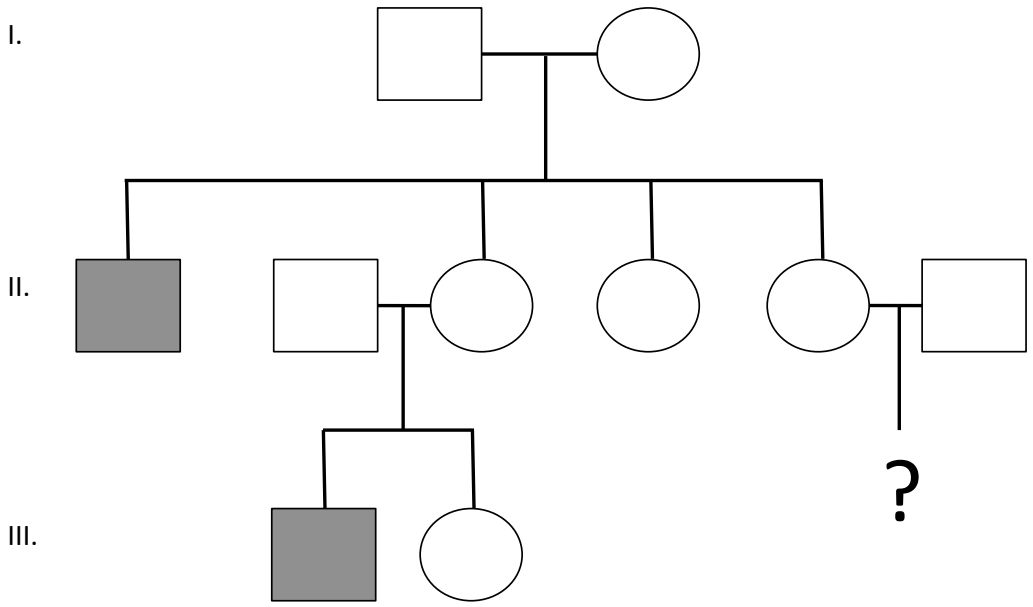
$$\chi^2 = (24 - 22.5)^2 / 22.5 + (6 - 7.5)^2 / 7.5 = 0.4 < 3.8$$

so we can not reject this hypothesis based on our data.

To find how many flies you'd need to differentiate between the models using a χ^2 test assuming you observe an exact ratio of 13:3 in your flies, just do the test with an increasing number of flies until your χ^2 value is above 3.8, which happens at 183 flies. (This isn't how you'd do the actual statistical analysis in real life, since you'd also have to account for the fact that your observed ratio won't always exactly equal your expected ratio.)

½ point for chi-squared test
½ point for correct number of flies needed (¼ point given for correct logic but wrong number)

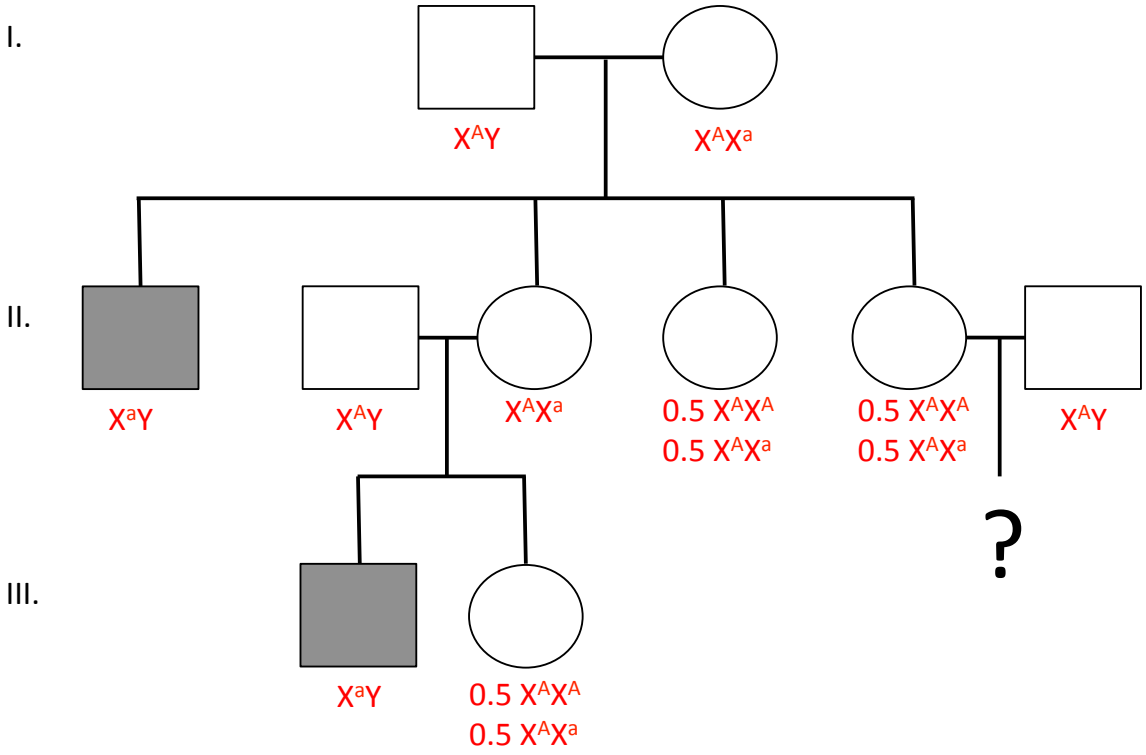
4. You are a genetic counselor who has just been hired by a family with the following pedigree, where filled symbols indicate diseased individuals.



a) What is the most likely mode of inheritance for this disease?

X linked recessive (1 point)

b) On the pedigree, assign genotypes to all individuals in the pedigree. If there are any ambiguities, list all possible genotypes and the probability of each.



0.1 points for each correct genotype assignment, 1 point total

c) The family wants to know what the probability is that the child indicated by ? will be affected by this disease. In your answer, state all possible genotypes for each parent. State probability of each genotype and disease phenotype for both male and female offspring. Assume no new mutations arise and that the disease allele is rare.

Parent 1: 0.5 X^AX^A 0.5 X^AX^a
Parent 2: 1.0 X^AY

If child is male:
0.75*1= **0.75 X^AY** (½* ½)+(½*1) = ¾ X^A from mom, 1.0 Y from dad
0.25*1= **0.25 X^aY** (½* ½)+(0) = ¼ X^a from mom, 1.0 Y from dad
p(disease) = 0.25

If child is female:
0.75*1= **0.75 X^AX^A** (½* ½)+(½*1) = ¾ X^A from mom, 1.0 X^A from dad
0.25*1= **0.25 X^AX^a** (½* ½)+(0) = ¼ X^a from mom, 1.0 X^A from dad
p(disease) = 0.0

0.25 points for each correct genotype (1 point total)
0.25 points for each correct disease probability (0.5 points total)
[1.5 total] Full points given if did not separate final answer by sex

d) The first child is a male with the disease. Does this change the probability that a second child will also be disease free? If so, state the new probability for both male and female children.

Yes. Now that we have an established genotype of Parent 1, X^AX^a, we can recalculate the probably genotypes and disease phenotypes of any future offspring.

If child is male:
0.5 X^AY 0.5 X^A from mom, 1.0 Y from dad
0.5 X^aY 0.5 X^a from mom, 1.0 Y from dad
p(disease) = 0.5

If child is female:
0.5 X^AX^A 0.5 X^A from mom, 1.0 X^A from dad
0.5X^aX^A 0.5 X^a from mom, 1.0 X^A from dad
p(disease) = 0.0

1 point for noting the probability will change
0.25 points for each correct probability (0.5 points total)
[1.5 total] Full points given if did not separate final answer by sex