Exam Questions from Final Exam – Human Genetics, Nondisjunction, and Cancer, and Cumulative Questions

1. You are working on two different organisms -- the fruit fly *Drosophila* and the yeast *S. cerevisiae*. In each organism, you have isolated two unmapped mutations, C^- and D^-. C^- is a recessive mutation that causes the organism to be four times as large as its normal size. D^- is a recessive mutation that causes the organism to be two times as large as its normal size. Both mutations cause the misregulation of Gene E, to which the C^- and D^- mutations are linked. E^- is also a recessive mutation that causes the organism to be four times as large as its normal size.

Listed below are the genotypes of strains you have made to do different genetic tests. For each strain, briefly describe if and how the strain could be constructed if you were working with yeast or with *Drosophila*.

Your starting materials are: C^- haploid yeast, D^- haploid yeast, E^- haploid yeast, true-breeding C^- *Drosophila*, true-breeding D^- *Drosophila,* and true-breeding E^- *Drosophila*.

The manipulations you can use in your answer are: P1 transductions, matings, conjugations, tetrad analyses, inducing sporulation, transformations, isolating F' strains, and three factor crosses. **For each manipulation**, please state the **genotypes** of the strains you are manipulating.

Also, for each strain, list **all** of the possible genetic tests for which each strain could be used WITHOUT further modifications or matings. (Your choices are: complementation, dominant/recessive, cis, constitutive/uninducible, trans, epistasis.)

(a) genotype of this diploid strain is $C^- D^+ E^+ / C^+ D^+ E^-$
how to make this strain in yeast:

how to make this strain in *Drosophila*:

list **all** of the possible genetic tests for which this strain could be used:

(b) genotype of this haploid strain is C^- D^- E^+
how to make this strain in yeast:

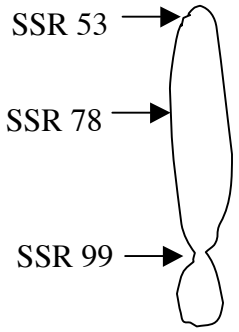
how to make this strain in *Drosophila*:

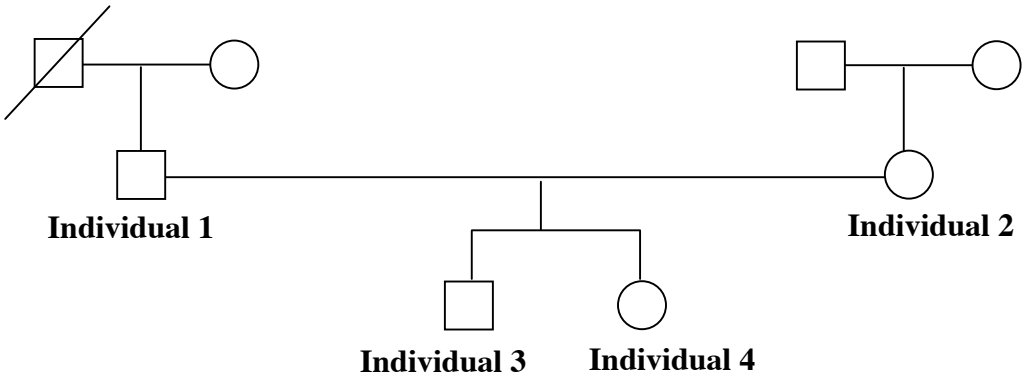
list **all** of the possible genetic tests for which this strain could be used:

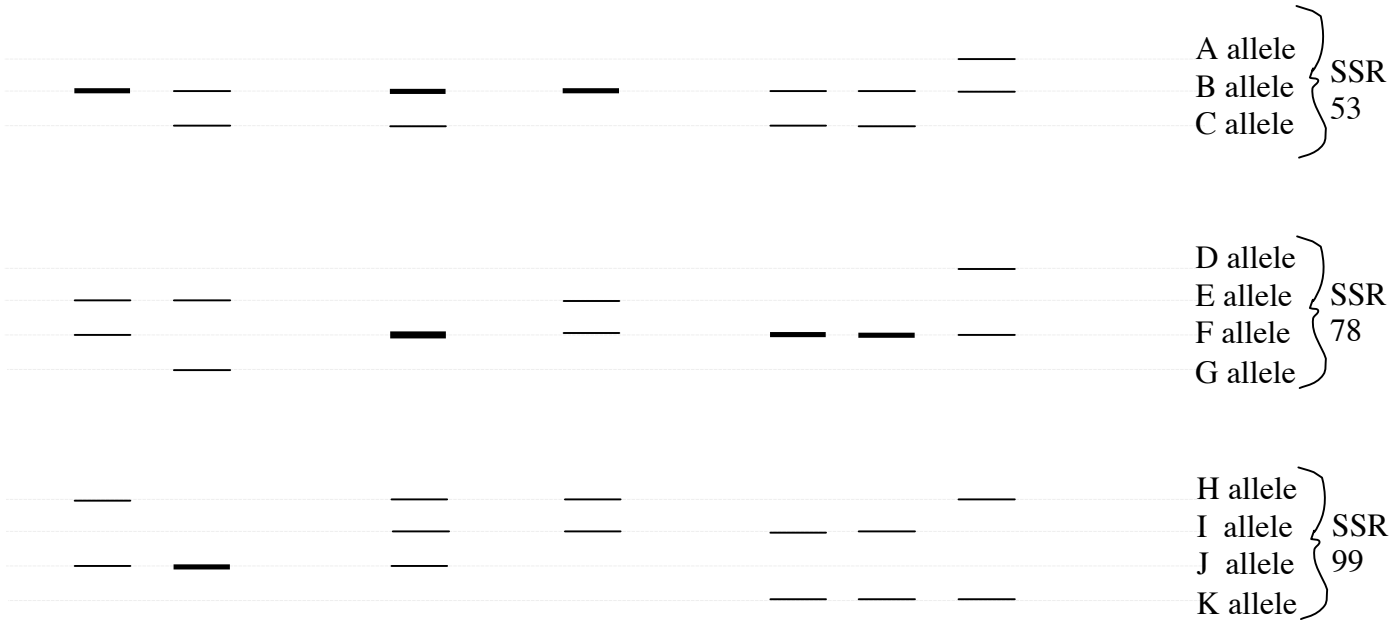
(c) Say you are studying C^- and D^- in a new species of bacterium which can be manipulated using transposons and P1 phage as *E. coli* can, but cannot maintain F and R factors. Given this, list **all** of the tests you could <u>not</u> perform in this bacterial species.

2. On the next page is a pedigree showing a couple that has a child with trisomy of chromosome 21. The schematic of a gel is also shown on the next page, and this gel reveals the genotypes of each member of the family at three different SSRs found on chromosome 21. A schematic of chromosome 21 is shown below, with the locations of the three SSRs marked. The constriction on the chromosome indicates the centromere.

<u>Schematic of Chromosome 21</u>







	Individual 3	Individual 4
maternally inherited allele(s) at SSR 53		
paternally inherited allele(s) at SSR 53		
maternally inherited allele(s) at SSR 78		
paternally inherited allele(s) at SSR 78		
maternally inherited allele(s) at SSR 99		
paternally inherited allele(s) at SSR 99		

(a) Fill in each row of the chart on the previous page to indicate which alleles each child inherited from each parent.

(b) Draw all phases of each parent (with respect to the three SSRs on chromosome 21) that are possible given everything you know about those parents. Make sure to draw the phases using the proper notation.

Father (individual 1):

Mother (individual 2):

(c) Which child has trisomy 21 (Individual 3 or Individual 4)? **(**Note: Make sure that your chart on page 3 is consistent with that child having trisomy 21.)

(d) During the development of which parent's gametes did the non-disjunction event occur (Individual 1 or Individual 2)?

(e) When in meiosis did non-disjunction occur (meiosis I or meiosis II)?

(f) Draw the following steps in the meiosis that created the gamete that led to the production of the child with trisomy 21 shown in the pedigree. Please label each SSR allele and the centromere on each homolog of chromosome 21. In each drawing, include chromsome 21 and one other chromosome of a different length that undergoes meiotic chromosome segregation normally. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the child with trisomy 21 with a star.)

3. After extensive genetic linkage studies, you map the locus for the ability to taste or not taste the compound PTC to a 2-centiMorgan (cM) region on human chromosome 7.

You then discover that some PTC non-tasters are homozygous for a 10-kb deletion within the implicated region. The deletion encompasses a gene you call gene Z. Your findings suggest but do not prove that the absence of gene Z results in the inability to taste PTC. You decide to test this hypothesis using a genetically modified mouse. The DNA sequences of the human and mouse Z genes are very similar but not identical. Like people who are PTC tasters, wild-type mice dislike the taste of PTC and won't eat food to which PTC has been added. You have available: 1) genomic DNA pieces with either the human or mouse Z genes and 2) mouse food with and without PTC.

(a) Would you choose to utilize transgenic or gene-targeting technologies to make your genetically modified mouse?

(b) What exact type of modification to the mouse genome would you make to test the hypothesis that the absence of gene Z results in inability to taste PTC? Explain your choice.

(c) Draw the DNA construct that you would use to modify the mouse genome, and explain how your construct would integrate into the mouse genome.

(d) What cell type would you put your DNA construct into? Include your choice of fertilized egg or ES cell, and what the genotype of the cells you would use should be.

(e) Explain what (if any) steps you will need to do to proceed from part **(d)** above to obtaining the final modified mouse you actually want.

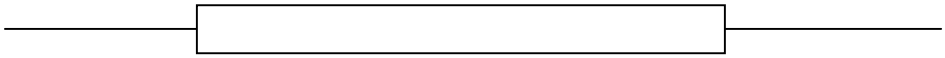
(f) Name the <u>two possible</u> phenotypic results you could get from the newly made mice, <u>and</u> the corresponding conclusions you would make based on each result.

(g) What additional modification would you make to the mouse you just made in order to test the hypothesis that the mouse and human Z genes are functionally interchangeable?

4. You have isolated three mutations in phage λ. One phage mutant is called **sm1⁻** and gives a small plaque phenotype (wild-type phage are **sm1⁺** and give large plaques). Another phage mutant is called **sm2⁻** and gives a small plaque phenotype (wild-type phage are **sm2⁺** and give large plaques). Note that the **sm1⁻** and **sm2⁻** mutations do not suppress each other. The third phage mutant is called **cI⁻** and gives a clear plaque phenotype (wild-type phage are **cI⁺** and give turbid plaques). You cross **sm1⁻** phage to **sm2⁻** phage by coinfecting *E. coli*. When the resulting lysate is plated, you count 2000 of the resulting plaques and find that 15 plaques are large and 1985 plaques are small.

(a) What is the genetic distance between the **sm1⁻** and **sm2⁻** mutations? (Be sure to label your answer with the correct units.)

(b) By using DNA sequencing, you find that **sm1⁻** and **sm2⁻** are mutations in the same open reading frame. The size of the wild-type protein produced from this open reading frame is 55 kDa. The size of the protein product of an **sm1⁻** mutant gene is 44 kDa, and the size of the protein product of an **sm2⁻** mutant gene is 11 kDa. Using the rectangle below to indicate the DNA sequence of this open reading frame, draw in the **relative positions of:** the **sm1⁻** mutation, the promoter, the stop codon, the **sm2⁻** mutation, and the start codon.
(Keep in mind that, on average, one amino acid = 0.11 kDa.)



(c) Express phage λ's recombination rate by stating the number of kilobases of DNA that correspond to 1% recombination for this phage. Show all calculations.

(d) You next cross **cI⁻ sm1⁻** phage to **sm2⁻** phage. When the resulting lysate is plated out and 2000 plaques are examined, you find that you have isolated 15 large plaques (all 15 of which are turbid). Given this new information, draw a map of this phage showing the relative order of the **cI**, **sm1** and **sm2** loci in this box:
(Note: Keep in mind that **sm1⁻** and **sm2⁻** are mutations in the same open reading frame.)

5. A ship carrying 7,000 passengers is about to land on an island that has 33,000 occupants. Each of these two populations is at Hardy-Weinberg equilibrium before the ship's landing, and each population contains an equal number of males and females. Of the 7,000 ship passengers, only 21 are displaying the X-linked recessive trait "huge toes" (and all 21 are male). Of the 33,000 island occupants, only 6 have huge toes (and all 6 are male). When answering the following parts, show all of your calculations.

(a) On the ship before landing, what is your best estimate of the allele frequency for the allele that causes huge toes?

(b) If you select a female child at random from the island (before the ship lands), what would the probability be that she is a carrier of the allele for huge toes?

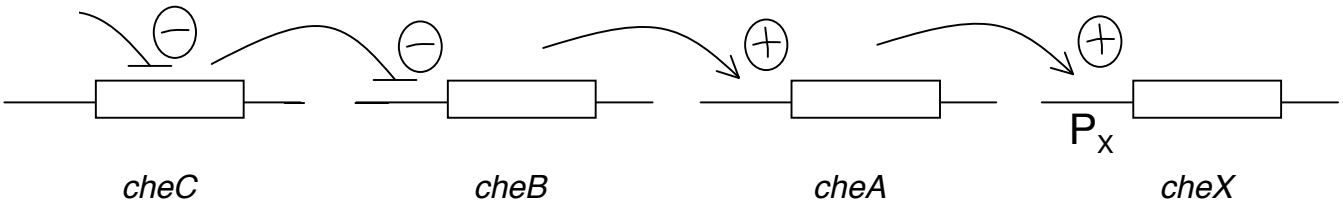
(c) Now the ship lands on the island, and the passengers and island occupants mate together randomly to produce the next generation "G2". What is your best estimate of the allele frequency for the allele that causes huge toes in generation "G2"?

(d) If you select one child from generation "G2" at random, what would the <u>total</u> probability be that it has huge toes? (Take both males and females into account.)

6. You are studying regulation of the *E. coli cheX* gene, a gene that is expressed in response to chemoattractants. *E. coli* expresses the *cheX* gene when chemoattractants are present in the medium, and this allows the bacteria to move towards the chemoattractants. You monitor the expression of the *cheX* gene in order to perform a genetic screen looking for mutants that do not properly regulate expression of *cheX*. In your screen, you isolate a series of mutant strains that either show constitutive or uninducible expression of *cheX*.

From the results of your screen, you deduce the following correct model for regulation of *cheX* expression. Keep in mind that this model is a genetic pathway that should not be interpreted as a molecular model.

chemoattractants

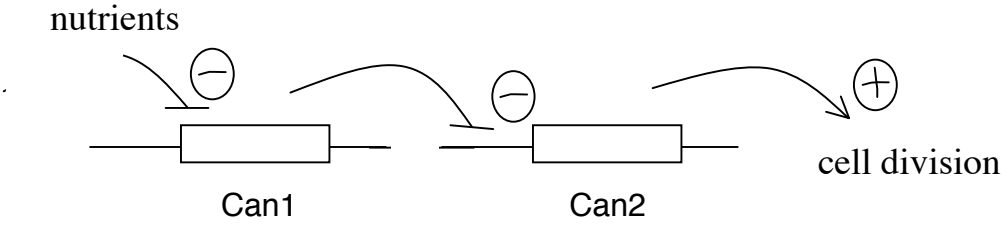


In your screen, you isolate four strains, each of which contains one of the following single mutations:
cheC1, which is in the **coding region** of *cheC*. This mutation gives a recessive phenotype.
cheB2, which is in the **coding region** of *cheB*. This mutation gives a constitutive phenotype.
cheA3, which is in the **coding region** of *cheA*. This mutation gives a recessive phenotype.
P_X^-, which is a deletion of the **promoter sequence** in front of *cheX*

Using this information, fill in the chart below. Fill in each box of the chart below with the word "**yes**" or the word "**no**." Please keep in mind that all sequences not included in the chromosomal genotypes are wild-type. Also please keep in mind that **all sequences not included in the F' plasmid genotypes are ABSENT from that plasmid.**
Genotypes are written in the format: (on the chromosome) / F' (on the F' plasmid).

Genotype of strain	Will *cheX* be expressed when chemoattractants are absent?	Will *cheX* be expressed when chemoattractants are present?
wild-type		
cheC1		
cheB2* / F' P_X^- *cheX+		
cheA3* / F' *cheC1		
cheX+ cheB2 cheA3		
P_X^- cheX+* / F' *cheC1* P_X+ *cheX+		

7. You are studying cancer progression in mice. Your results indicate that the following is one pathway for how mouse cell division is regulated.



You isolate a mutant strain of mice that contains a mutation (Can1^{-}) in the coding region of Can1. (Note that Can1 is a gene that encodes a monomeric protein). These mutant mice frequently develop cancer as young adults.

(a) Classify the Can1^{-} mutation as causing constitutive OR uninducible cell division.

(b) Classify the Can1^{-} mutation as dominant OR recessive.

(c) Classify the Can1^{+} gene as a proto-oncogene or a tumor suppressor gene.

(d) In a sentence, describe in general what the wild-type function of Can1 is in the cell.

You isolate a mutant strain of mice that contains a mutation (Can2^{-}) in the coding region of Can2. (Note that Can2 is a gene that encodes a monomeric protein). These mutant mice frequently develop cancer as young adults.

(e) Classify the Can2^{-} mutation as causing constitutive OR uninducible cell division.

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(f) Classify the Can2^{-} mutation as dominant OR recessive.

(g) Classify the Can2^{+} gene as a proto-oncogene or a tumor suppressor gene.

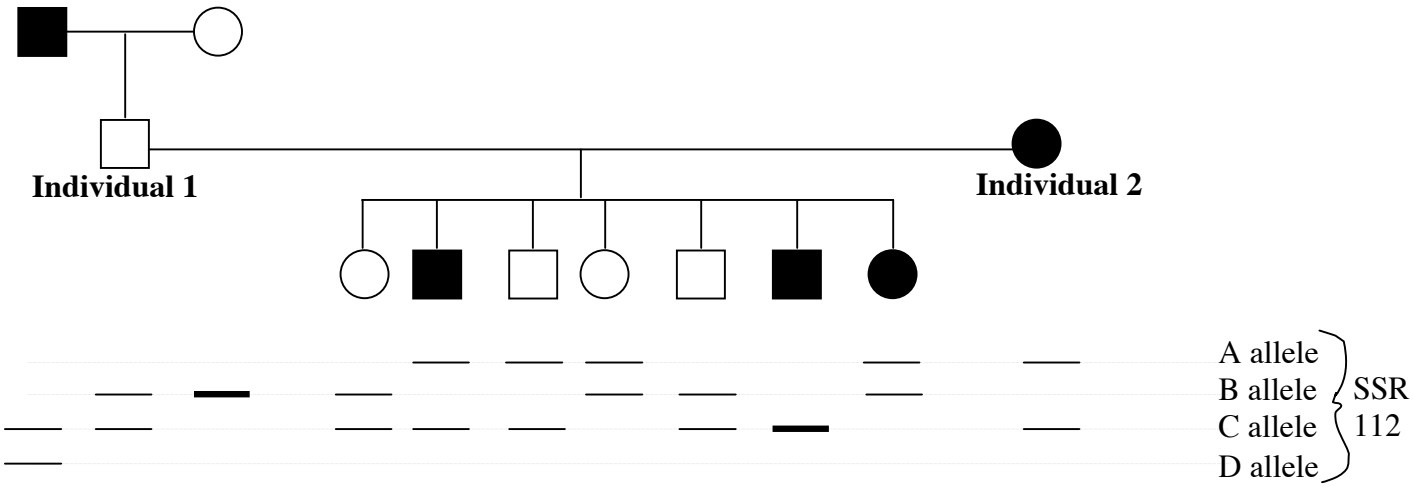
(h) In a sentence, describe in general what the wild-type function of Can2 is in the cell.

(i) You cross a $Can1^{+}/Can1^{-}$ heterozyous mouse to a wild-type mouse. Predict whether or not any of the progeny from this cross would develop cancer in early adulthood. Explain your answer in one or two sentences.

(j) If you analyzed a non-cancerous cell from the $Can1^{+}/Can1^{-}$ parent from part **(i)**, how many wild-type alleles of Can1 would be present?

(k) If you analyzed a cancerous cell from the $Can1^{+}/Can1^{-}$ parent from part **(i)**, how many mutant alleles of Can1 would be present?

8. You are mapping a certain rare disorder that is caused by an allele at the N locus. You suspect that the N locus is linked to SSR112 on human chromosome #17. You analyze the following family for these two loci. Assume complete penetrance and no new mutations. You will fill in the charts below in subsequent parts of the problem.



maternally inherited allele at SSR112							
paternally inherited allele at SSR112							

maternally inherited allele at the N locus							
paternally inherited allele at the N locus							

IF the condition is autosomal recessive [parts **(a)** and **(b)**] (Individual 2 is "nn")

maternally inherited allele at the N locus							
paternally inherited allele at the N locus							

IF the condition is autosomal dominant [parts **(c)** - **(e)**] (Individual 2 is "Nn")

Answer parts **(a)** and **(b)** as if the disorder is autosomal recessive and caused by the "n" allele, so that Individual 2 is "nn."

(a) Fill in the upper four rows of the chart using autosomal recessive inheritance for the disorder. Then answer below: **which parent's** alleles will you follow to correctly calculate a LOD score between the N locus and SSR 112 -- Individual 1 or 2?

(b) Draw all phases of the parent you chose in part **(a)** with respect to SSR 112 and the N locus that are possible given everything you know about that parent. Make sure to draw the phases using the proper notation.

Answer parts **(c)** through **(e)** as if the disorder is autosomal dominant and caused by the "N" allele, so that Individual 2 is "Nn."

(c) Fill in the lower two rows of the chart using autosomal dominant inhertance for the disorder. Then answer below: **which parent's** alleles will you follow to correctly calculate a LOD score between the N locus and SSR 112 -- Individual 1 or 2?

(d) Draw all phases of the parent you chose in part **(c)** with respect to SSR 112 and the N locus that are possible given everything you know about that parent. Make sure to draw the phases using the proper notation.

(e) How many times more likely is it that the data from this family arose because of linkage between the SSR 112 and N loci at $\theta = 0.2$ than because the two loci were unlinked? Show all calculations.

9. You have isolated an *E. coli* mutant that carries both an amber mutation in the HisC gene (HisC-am) and an amber suppressor mutation in a gene encoding a tRNA gene (Su^+). Therefore this strain is phenotypically His^+, meaning that it can grow without the amino acid histidine added to the medium. You obtain a strain which carries the HisC-am mutation and has a Tn5 insertion known to be linked to the HisC gene; this strain is phenotypically His^- and is kanamycin resisistant (Kan^r). The transposon is <u>not</u> in between HisC and the gene encoding the tRNA you are working with.

(a) You grow P1 phage on the HisC-am Tn5 strain and use the resulting phage lysate to infect the HisC-am Su^+ strain, selecting for Kan^r. Among 100 Kan^r transductants, you find that 20 are His^- and 80 are His^+. What distance are you measuring in this experiment, **and** what is that distance numerically?

(b) Next, you set up two reciprocal crosses. In the first cross you grow P1 phage on a bacterial strain that carries the Tn5 insertion described in part (**a**) and as well as the HisC-am and Su^+ mutations. You then use this phage lysate to infect a wild-type strain ($HisC^+$ and Su^-) and select for Kan^r. From 100 Kan^r transductants examined, 99 are His^+ and 1 is His^-.

In the second cross, you grow P1 phage on a bacterial strain that carries the Tn5 insertion and is $HisC^+$ and Su^-. You use this phage lysate to infect a bacterial strain with HisC-am and Su^+ mutations, selecting for Kan^r. From 100 Kan^r transductants examined, 90 are His^+ and 10 are His^-.

Draw a genetic map showing the relative positions of the Tn5 insertion, the HisC locus, and the tRNA gene in which the Su+ mutation is located.

10. Mendel's concept of the gene was first applied to a human trait in Archibald Garrod's landmark 1902 paper entitled "The Incidence of Alkaptonuria: A Study in Chemical Individuality." Alkaptonuria is a disease characterized by degenerative arthritis and by urine which turns black upon exposure to air. Because of an enzyme defect, the urine accumulates homogentisic acid, which oxidizes to form a black pigment.

As Garrod reported, and subsequent studies confirmed, 50% of individuals with alkaptonuria in the United Kingdom are offspring of first-cousin marriages. The total incidence of alkaptonuria in the United Kingdom is 1/250,000. Assume that, apart from first-cousin marriages, mating is random, and that that family size is the same in first-cousin matings as it is in random matings. Also assume that all cases of alkaptonuria are caused by the same mutation in one gene, and that mutation rates and selection are negligible.

(a) Is alkaptonuria an autosomal dominant or autosomal recessive disorder? Briefly justify your answer using information from the introduction to this question.

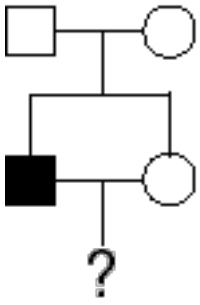
(b) In the United Kingdom, what is the frequency of the allele (call it allele AK) associated with alkaptonuria?

(c) In the United Kingdom, what is the frequency of heterozygotes (AK/+ individuals)?

(d) What is the expected proportion of all autosomal genes at which offspring of first cousins are homozygous by descent?

(e) Based on the data given here, estimate the frequency of first-cousin marriages in the United Kingdom.

11. Consider the following mouse pedigree in which the indicated male exhibits a distinctive rare trait. (Assume complete penetrance and that no new mutations arose in any of the individuals in this problem.)

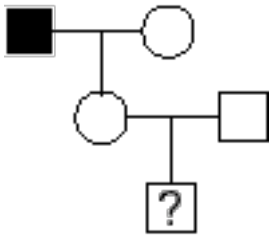


(a) Assuming that the trait is autosomal recessive, calculate the probability that an offspring from the indicated brother-sister mating will exhibit the trait.

(b) Assuming that the trait is X-linked recessive, calculate the probability that a male offspring from the brother-sister mating will exhibit the trait.

(c) Assuming that the trait is X-linked recessive, calculate the probability that a female offspring from the brother-sister mating will exhibit the trait.

(d) Consider the following mouse pedigree in which a male mouse that exhibits two different rare recessive X-linked traits (indicated by the filled symbol) is crossed to a true breeding wild-type female, and a female offspring from this cross is mated to a true-breeding wild-type male.



Given that the genes for the two traits are 10 cM apart on the X chromosome, calculate the probability that a male offspring from the mating will exhibit both traits.

12. The **cI** gene of phage lambda encodes a repressor protein that has a molecular weight of 24 kDa. You have isolated a phage mutant with a defective **cI** gene; this mutant therefore makes clear plaques rather than the normal turbid plaques. But you find that the mutant phage will produce turbid plaques when plated on an *E. coli* strain that contains an amber suppressing mutation in one of its tRNA genes. (The amber codon is UAG.) You find that the repressor protein is 16 kDa when the mutant phage are grown on wild-type *E. coli*, but is 24 kDa when the mutant phage are grown on an amber-suppressing strain of *E. coli*.

(a) What can you deduce about the nature of the **cI** mutation? Be as specific as possible about the kind of base change that caused the mutation and where exactly the mutation lies within the **cI** gene.

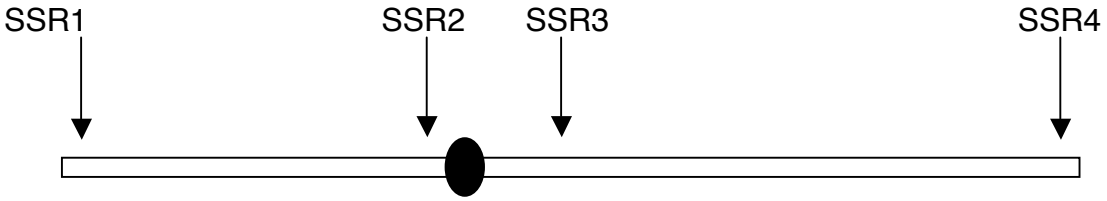
(b) Next you mutagenize the mutant phage described in part (**a)** to isolate a double mutant phage. These double mutant phage still form clear plaques when plated on wild type *E. coli.* However, when you examine the repressor protein produced by the double mutant phage grown on wild-type *E. coli*, you find that the protein is larger than the protein produced by the original single mutant phage. (The protein produced by the original single mutant phage is 16 kDa, whereas the protein produced by the double mutant phage is 17 kDa). Describe what kind of second mutation could give these results, assuming that the second mutation was caused by a single mutational event. Be as specific as possible about the nature of this second mutation.

(c) The codon for tryptophan is 5'-UGG-3'. Write out the DNA base sequence of the segment of the wild-type gene enocding $tRNA^{trp}$ that codes for the anticodon sequence of this tRNA. For your answer, only show the DNA strand that is used as the template for transcription of the $tRNA^{trp}$ molecule from the gene, indicating the 5' and 3' ends of this DNA strand.

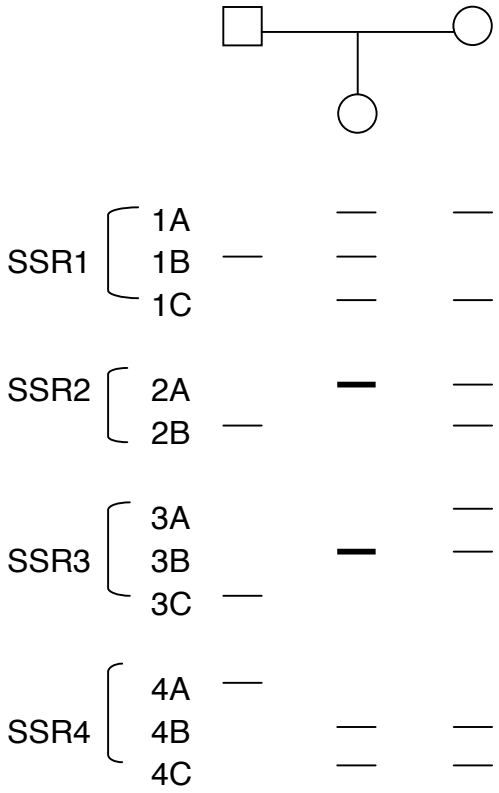
(d) Using the same format as in part **(c)**, write out the DNA base sequence of the same segment of the form of the tRNA gene that produces an amber-suppressing mutant version of $tRNA^{trp}$.

13. Your colleague, who is a medical geneticist, seeks your help in interpreting a patient: an XXY girl.

You prepare genomic DNA samples from the girl and from her parents. You confirm that the stated father is in fact the biological father by testing the family for a large number of autosomal SSRs. You also test the family for a series of SSRs distributed along the X chromosome, as shown below. The oval indicates the centromere.



The schematic of a gel is shown below, and this gel reveals the genotypes of each member of the family at four different SSRs found on the X chromosome:



(a) During the development of which parent's gametes did the non-disjunction event occur?

(b) In which division of meiosis did nondisjunction occur? Briefly explain your answer.

(c) Draw the following steps in the meiosis that created the gamete that led to the production of the XXY child shown in the pedigree. Please label each SSR allele and the centromere on each homolog of the X chromosome. Assume that SSR alleles 1A, 2A, 3B, and 4B are on a single chromosome in the mother's somatic cells. Draw these steps only:

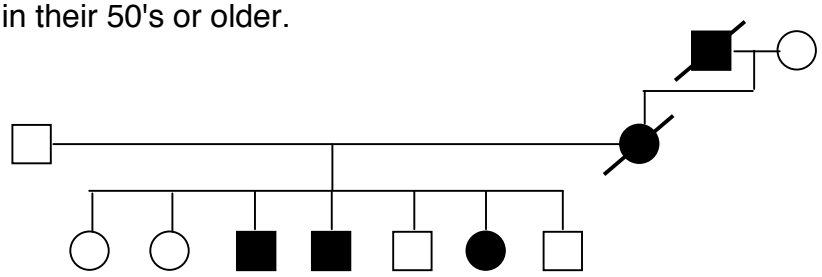
i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the XXY child with a star.)

(d) What might account for this girl having developed as a female despite the presence of a Y chromosome?

14. Your colleague seeks your advice regarding a family in which several individuals (filled circles or squares below) developed colon cancer in their 30's or 40's. All living, unaffected individuals are in their 50's or older.



You speculate that colon cancer in this family might be caused by either:

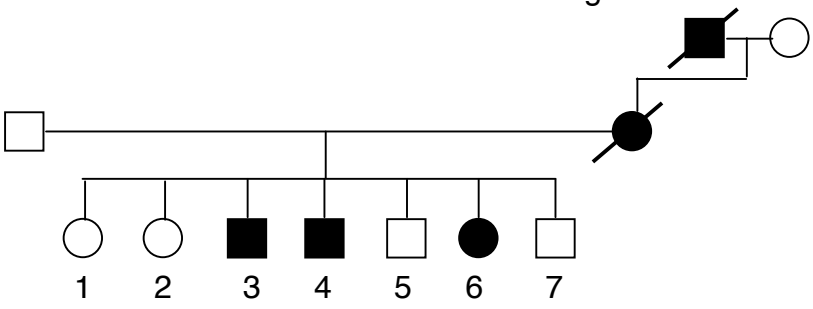
1) germline transmission of a mutation in the APC gene (causing the autosomal dominant disease known as FAP, familial adenomatous polyposis)

or

2) germline transmission of a mutation in the MSH2 gene involved in DNA mismatch repair (causing the autosomal dominant disease known as HNPCC, hereditary nonpolyposis colon cancer)

(a) You obtain blood DNA samples from all living family members, as well as colon tumor DNA samples from the three living, affected individuals. Your colleague is surprised when you test both the blood and colon tumor DNAs for several SSRs known to show no genetic linkage to either APC or MSH2. How would you use these test results in considering the likelihood of FAP versus HNPCC?

You identify an SSR that is located within an intron of the APC gene, and a second SSR that is located within an intron of the MSH2 gene (which is involved in mismatch repair). You type blood DNA samples for these SSRs and obtain the following results:



		1	2	3	4	5	6	7	
an SSR w/in APC	A	—	—			—			— A
	B		—	—		—		—	— B
	C	—		—	—	—	—	—	C
	D				—	—	—		D
an SSR w/in MSH2	A	—		—			—	—	A
	B			—	—	—	—		B
	C		—			—		—	— C
	D	—	—		—	—	—		— D

You find out that individuals 3 and 4 are twins, but it has not been determined whether they are monozygotic (MZ) or dizygotic (DZ).

(b) Calculate a LOD score for linkage at $\theta = 0$ between the colon cancer locus and the APC locus in this family, assuming that individuals 3 and 4 are DZ twins. Show your calculations.

(c) Does your calculation in part **(b)** change if you assume that individuals 3 and 4 are MZ twins? If so, show how it changes.

(d) Are these data consistent with the specific hypothesis that colon cancer in this family is caused by germline transmission of a mutation in APC? Briefly justify your answer.

(e) Are these data consistent with the specific hypothesis that colon cancer in this family is caused by germline transmission of a mutation in MSH2? Briefly justify your answer.

(f) Would your answer to part **(e)** change if you learned that individual 2 had been diagnosed with cancer of the ovary at the age of 35? Briefly explain your answer.

15. Wild-type *E. coli* bacteria are motile (that is, they can swim around). You have isolated a non-motile strain that you designate **mot1⁻**. In order to find a transposon linked to **mot1⁻ ,** you start with a large collection of many *E. coli* strains, each one harboring one different random **Tn5** insertion in an otherwise wild-type genome. (These insertion strains are kanamycin resistant (**Kan^r**) and motile (**mot$^+$**).) You grow **P1** phage on a mixture of the entire collection of **Tn5** insertion strains, and then use the resulting phage lysate to infect the **mot1⁻** mutant and select for **Kan^r** transductants. Out of 500 **Kan^r** transductants, 1 is motile (and 499 are non-motile). You designate this motile **Kan^r** transductant "**strain 1**." Next, you grow **P1** phage on **strain 1** and use the resulting phage to infect your original **mot1⁻** strain, selecting for **Kan^r** transductants. Out of 100 **Kan^r** transductants, 70 are motile and 30 are non-motile.

(a) What is the distance between the **Tn5** insertion and **mot1**, expressed as a cotransduction frequency?

(b) Next, you isolate a second non-motile mutant, designated **mot2⁻**. You grow **P1** phage on **strain 1** and use the resulting phage to infect your **mot2⁻** strain. After selection, you isolate 100 **Kan^r** transductants. All of these transductants are non-motile. Based on this result, what conclusion can you draw about the distance between the **mot2** locus and the **Tn5** insertion harbored by **strain 1**?

(c) Finally, you isolate a third non-motile mutation designated **mot3⁻**. You discover that the **mot3** mutation is an allele of the **mot1** gene. To determine the relative order of the **mot3** and **mot1** loci, you set up two different transduction experiments. First, you grow **P1** phage on a derivative of **strain 1** that also carries **mot1⁻** , and then you use the resulting phage to infect your **mot3⁻** strain, selecting for **Kan^r** transductants. Out of 500 **Kan^r** transductants 12 are motile and 488 are non-motile. Second, you grow **P1** phage on a derivative of **strain 1** that also carries **mot3⁻** , and use the resulting phage to infect your **mot1⁻** strain, selecting for **Kan^r** transductants. Out of 500 **Kan^r** transductants, all are non-motile.

Draw a genetic map showing the relative order of the **Tn5**, **mot1** and **mot3** loci.

16. In order for yeast cells use the amino acid arginine as a nitrogen source, arginine is broken down by the enzyme arginase. You find that the arginase gene is highly transcribed when arginine is present in the medium, but that the arginase gene is not transcribed at all when there is no arginine present. You have identified the gene for the arginase enzyme, which you designate **Arg1**. An allele in this gene (**Arg1⁻**) has the following properties:

Arginase activity

	+ arginine	–arginine
Wild type	–	+
Arg1⁻	–	–
Arg1⁻ / Arg1⁺	–	+

(a) You isolate a mutation, designated **Arg2⁻**, which causes the recessive phenotype of uninducible arginase expression. When you mate an **Arg2⁻** haploid mutant to an **Arg1⁻** haploid mutant, the resulting **Arg2⁻ / Arg1⁻** diploid shows normal arginase expression and regulation. What does this result tell you about the nature of the **Arg2⁻** mutation?

(b) What can you deduce about the normal role of wild-type **Arg2** in arginase regulation?

(c) Next, you isolate a mutation, designated **Arg3⁻**, which causes constitutive arginase expression. You cross an **Arg3⁻** haploid mutant to an **Arg1⁻** haploid mutant, and induce sporulation of the resulting diploid (which shows normal regulation of arginase). This gives the following tetrad types. Out of a total of 50 tetrads, 8 are Type One, 7 are Type Two, and 35 are Type Three.

Type One	Type Two	Type Three
constitutive	uninducible	constitutive
uninducible	uninducible	constitutive
uninducible	regulated	uninducible
regulated	regulated	uninducible

Are the **Arg3** and **Arg1** loci linked? If so, how far apart are they in cM?

(d) You cross an **Arg3⁻** haploid mutant to an **Arg2⁻** haploid mutant, and induce sporulation of the resulting diploid. This gives the following tetrad types. Out of a total of 50 tetrads, 35 are Type Four, 8 are Type Five, and 7 are Type Six.

Type Four	Type Five	Type Six
constitutive	constitutive	constitutive
constitutive	constitutive	constitutive
regulated	regulated	uninducible
uninducible	regulated	uninducible

Does an **Arg3⁻ Arg2⁻** double mutant haploid yeast strain have the phenotype of regulated, constitutive, or uninducible?

(e) Which tetrad type (Four, Five, or Six) contains the most double mutant spores?

(f) On the basis of all of the information given in this problem, diagram a linear genetic pathway to explain the regulation of arginase. For your model, include the wild-type **Arg1**, **Arg2** and **Arg3** genes. Also show how the amino acid arginine itself might act.

17. One in 20,000 human males is an (infertile) XX male (due to a translocation that moves the sex-determination gene Sry onto an X chromosome). If an XX male has a twin, what is the likelihood that the twin is an XX male, assuming that:

(a) The twins are dizygotic.

(b) The twins are monozygotic.

One in 200 individuals in the industrialized world suffers from HNPCC (Hereditary Non-Polyposis Colon Cancer), an autosomal dominant trait. If an individual with HNPCC has a twin, what is the likelihood that the twin has HNPCC, assuming that:

(c) The twins are dizygotic.

(d) The twins are monozygotic.

For mothers 30 years of age, the incidence of trisomy 21 is one per 885 births. Consider an individual (born to healthy 30-year-old parents) who has trisomy 21 due to meiotic non-disjunction in the mother. If the trisomic individual has a twin, what is the likelihood that the twin has trisomy 21, assuming that:

(e) The twins are dizygotic.

(f) The twins are monozygotic.

18. Consider a codominant blood antigen where individuals homozygous for one allele express only antigen M, individuals homozygous for the other antigen express only antigen N, and heterozygous individuals express both N and M antigens. In a study of three populations, you determine the genotype frequencies of individuals that express only M or only N.

(a) Based on this information, fill in the table below, giving the N and M allele frequencies for each population, and state whether each population is in Hardy-Weinberg equilibrium.

	Frequency expressing		Allele frequencies		
Population	**M only**	**N only**	**M**	**N**	**H-W equilib (yes or no)?**
1	0.25	0.25			
2	0.36	0.16			
3	0.01	0.64			

(b) Consider a deleterious allele in a human population which has a selective disadvantage S = 1 in the homozygote and a selective disadvantage S = 0.1 in the heterozygote. The mutation rate is $\mu = 10^{-5}$ for this allele. In a balance between new mutation and selection, what will the steady state allele frequency be? (Your answer can be an estimate accurate to ± 10%. Assume random mating.)

(c) If a different recessive disorder occurs at a frequency of 10^{-3} in the offspring of first cousins in a population, what is the probability that a brother-sister mating from the same population would produce a child with the disorder? (Assume that selection and mutation rates are negligible.)

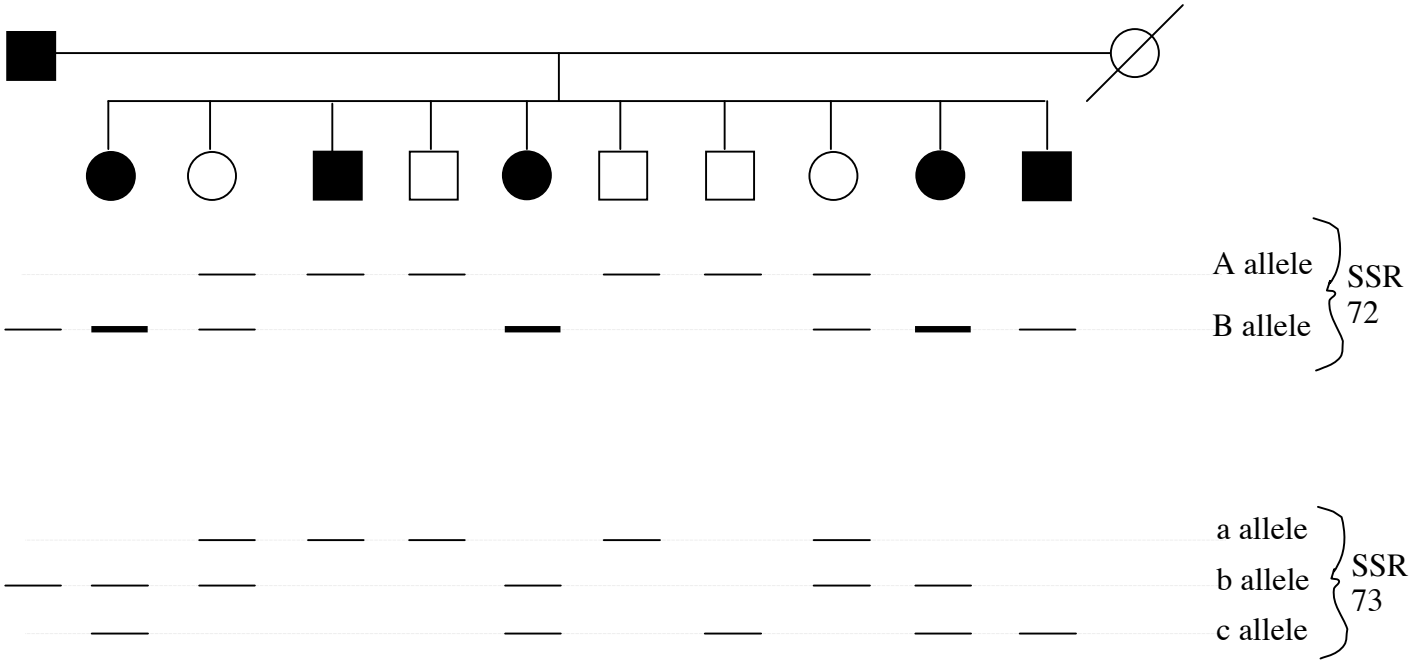
19. HNPCC (Hereditary Non-Polyposis Colon Cancer) shows autosomal dominant inheritance in humans. As discussed in 7.03, some individuals with HNPCC are heterozygous for a loss-of-function mutation in the mismatch repair gene MSH2. These individuals frequently develop cancer of the colon, ovary, uterus, or other organs before age 50.

(a) Which of the following two approaches would yield a better mouse model of HNPCC:
-- random integration of a transgene consisting of a mutant human MSH2 gene (from a human HNPCC patient)
OR
-- knockout of the mouse MSH2 gene?
Briefly justify your answer.

(b) Would you expect mice that are homozygous for the modification you chose in part **(a)** to develop cancer more quickly, more slowly, or at the same rate as mice that are heterozygous for that modification? Briefly justify your answer.

20. Your project is to genetically map the locus for color blindness, an X-linked recessive trait, with respect to SSR markers. Like many X-linked recessive traits, color-blindness is usually found in males. However, the mutant allele frequency is sufficiently high that colorblind females do occur. In this problem, **+** stands for the allele that leads to normal vision, and **clr** stands for the allele associated with color-blindness. Assume complete penetrance and no new mutations.

Here is a family in which some individuals are colorblind:



(a) What is the (deceased) mother's genotype at SSR72?

(b) What is the (deceased) mother's genotype at SSR73?

(c) Diagram all possible phase relationships between the SSR72 and SSR73 alleles in the mother.

(d) Calculate the LOD score for linkage at $\theta = 0.2$ between SSR72 and SSR73 in this family.

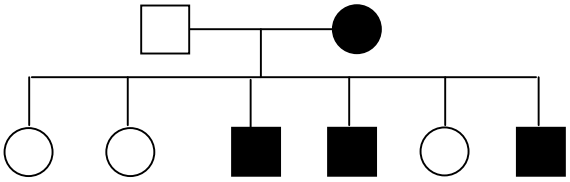
(e) Diagram all possible phase relationships between the alleles at SSR72 and the color blindness locus in the mother.

(f) Calculate a LOD score for linkage at $\theta = 0.1$ between SSR72 and the color blindness locus in this family.

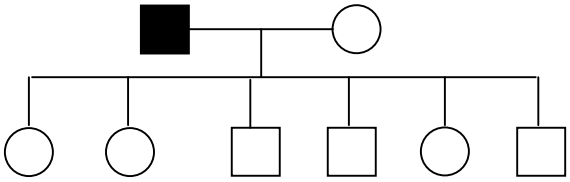
(g) If SSR72, SSR73, and the color blindness locus are all located close together in the same region of the X chromosome, what is their most likely order on the chromosome?

21. The following three crosses involve mice from either true-breeding mutant strains or true-breeding wild-type strains. For this problem, you can assume that a mouse is true-breeding if its parents are not shown in the pedigree. In each case, mice exhibiting the rare mutant traits are indicated by solid symbols. Square symbols designate males and circles designate females. In each case, describe the mode(s) of inheritance that are consistent with the data (your choices are: autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant). Assume that traits are completely penetrant, and that no new mutations have arisen.

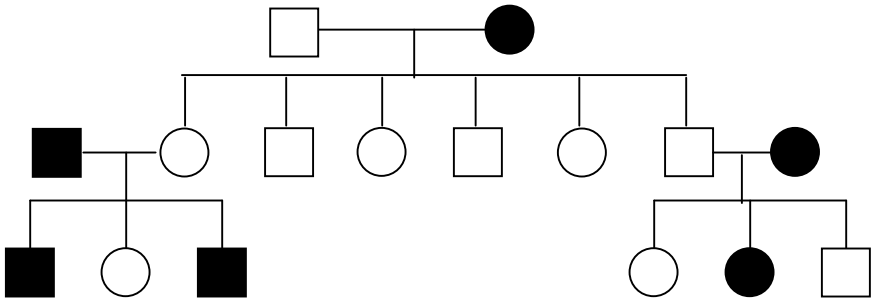
(a)



(b)



(c)



22. *E. coli* can utilize the sugar melibiose after induction of the enzyme melibiase. Melibiase is expressed when bacteria grow in a growth medium that contains melibiose, but not on medium that lacks melibiose. You have isolated a mutation called **mut1** that expresses melibiase constitutively, even on growth medium that lacks melibiose. In order to study melibiase regulation, you isolate an insertion of **Tn5::LacZ** into the melibiase structural gene. (Note that **Tn5** confers kanamycin resistance.) A strain with this insertion shows expression of ß-galactosidase on growth medium that contains melibiose, but not on medium that lacks melibiose.

(a) You grow P1 phage on a bacterial host that carries the **Tn5::LacZ** insertion into the gene encoding melibiase. You then use the resulting phage lysate to infect a **mut1 lacZ⁻** bacterial strain, selecting for kanamycin resistance. Among the Kan^r transductants, 5% give constitutive expression of ß-galactosidase, whereas 95% only express ß-galactosidase when melibiose is present. Is **mut1** linked to the melibiase structural gene and, if so, what is the distance from the **Tn5-LacZ** insertion to **mut1** (in terms of cotransduction frequency)?

(b) You obtain an **F'** plasmid that carries the melibiase structural gene. (This **F'** includes chromosomal sequences that span >100 kbp on either side of the melibiase gene.) You choose a Kan^r transductant from part (**a**) that gives constitutive ß-galactosidase expression, and mate the **F'** plasmid into this strain. The resulting merodiploid still gives constitutive expression of ß-galactosidase. What does this observation tell you about the nature of **mut1**?

(c) You further examine the **F'** strain constructed in part (**b**), and find that melibiase expression is regulated normally despite the fact that ß-galactosidase expression is constitutive. State what this observation tells you about the nature of **mut1**.

(d) Draw a linear genetic pathway for the regulation of melibiase, showing the wild-type functions of mut1, the melibiase gene, and the sugar melibiose. Do not invoke more than one unknown trans-acting regulator in your pathway.

(e) How does the molecular defect caused by the **mut1** mutation specifically act to misregulate LacZ gene expression?

23. The sequence of the amber stop codon is 5'UAG3'. One can isolate bacterial strains that carry mutations in genes encoding tRNAs such that they will encode mutant tRNAs that recognize the amber stop codon (as opposed to wild-type tRNAs, which recognize one of the 61 non-stop codons). You are trying to isolate single mutations in tRNA genes that will suppress an amber (TAG) mutation. To increase the frequency of such mutations, you use a mutagen that produces transition mutations (i.e. C•G to T•A and T•A to C•G base changes).

(a) Which tRNA genes could in principle be altered by the mutagen to give the desired suppressor mutation?

(b) For each answer you gave in part **(a)**, write out the DNA sequence of the part of the wild-type gene encoding the wild-type tRNA that encodes for the anti-codon portion of that tRNA. (Label the 5' and 3' ends of both DNA strands, and indicate which strand is used as the *template* during transcription of the tRNA).

(c) For each answer you gave in part **(a)**, write out the DNA sequence of the part of the mutant gene encoding the amber-suppressing mutant tRNA that encodes for the anti-codon portion of that tRNA. (Label the 5' and 3' ends of both DNA strands, and indicate which strand is used as the *template* during transcription of the tRNA).

24. You are studying the yeast genes needed to metabolize organic phosphates. The key regulated enzyme is phosphatase, which is needed to release inorganic phosphate from organic phosphate compounds in the medium. Phosphatase is not expressed when yeast are grown in growth medium that contains inorganic phosphate, but is induced to high levels when yeast are grown in growth medium with no inorganic phosphate. You have isolated a mutation (which you call **pho4$^-$**) that causes the recessive phenotype of <u>uninducible</u> phosphatase regulation.

	Phosphatase activity	
	+ phosphate	–phosphate
Wild type	–	+
pho4$^-$	–	–
pho4$^-$ / pho4$^+$	–	+

Starting with an uninducible **pho4⁻** strain, you isolate three different double mutant strains (called Suppressor Strains #1, #2, and #3) that restore phosphatase expression (when the yeast are grown on growth medium without phosphate) to these suppressor strains of yeast, even though they each harbor the **pho4⁻** mutation.

(a) Suppressor Strain #1 shows regulated expression of phosphatase. You cross Suppressor Strain #1 haploid yeast to wild-type haploid yeast. Induction of sporulation in the resulting diploid gives the following tetrad types. (Type One is the most abundant class.)

Type One	Type Two	Type Three
regulated	regulated	regulated
regulated	regulated	regulated
regulated	regulated	uninducible
uninducible	regulated	uninducible

What kind of mutation could produce the behavior of Suppressor Strain #1? Be as explicit as possible and explain your reasoning.

(b) Suppressor Strain #2 also shows regulated expression of phosphatase. You cross Suppressor Strain #2 haploid mutant yeast to wild-type haploid yeast. Induction of sporulation in the resulting diploid gives only one tetrad type that is observed, even though you analyze 1000 tetrads.

Type Four
regulated
regulated
regulated
regulated

What kind of mutation could produce the behavior of Suppressor Strain #2? Be as explicit as possible and explain your reasoning.

(c) Suppressor Strain #3 shows constitutive expression of phosphatase. You cross Suppressor Strain #3 haploid yeast to wild-type haploid yeast, and induce sporulation of the resulting diploid (which shows regulated expression of phosphatase). This gives the following three tetrad types. (Type Five is the most abundant class).

Type Five	Type Six	Type Three
constitutive	constitutive	constitutive
constitutive	constitutive	constitutive
regulated	regulated	uninducible
uninducible	regulated	uninducible

Give an explanation for the type of mutation that could produce the behavior of Suppressor Strain #3.

25. Shown below is a hypothetical scheme for the formation of eye pigment in *Drosophila*.

The enzyme encoded by the **Pr** gene converts a purple pigment into the normal red pigment in the eye. The **pr**$^{-}$ allele causes the recessive phenotype of purple eyes. The enzyme encoded by **Bl** gene converts a blue pigment into the purple pigment. The **bl**$^{-}$ allele causes the recessive phenotype of blue eyes. Both the **Pr** and **Bl** genes are on the X chromosome. A male from a true-breeding blue-eyed strain is crossed to a female from a true-breeding purple-eyed strain.

(a) All of the F_1 female progeny from this cross have normal eyes. What colored eyes should the F_1 male progeny have?

(b) An F_1 female fly (with normal eyes) is crossed to a wild-type male, and a large number of male progeny from this cross are examined. Among the male progeny, there are flies with normal red eyes, flies with purple eyes, and flies with blue eyes. You notice that significantly more male progeny have blue eyes than have purple eyes. Give an explanation why this should be the case.

(c) Given that the **Pr** and **Bl** genes are 16 cM apart on the X chromosome, determine the number out of 100 male progeny from the cross in part (**b)** that should have purple eyes, blue eyes, or normal red eyes.

Number

Purple-eyed males:

Blue-eyed males:

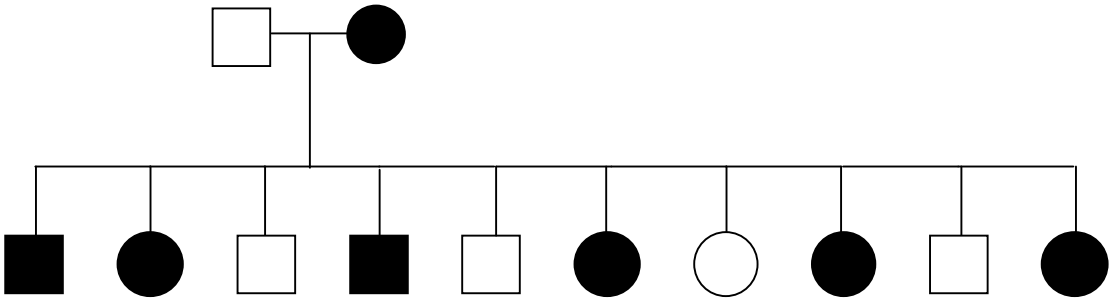
Red-eyed males:

_____

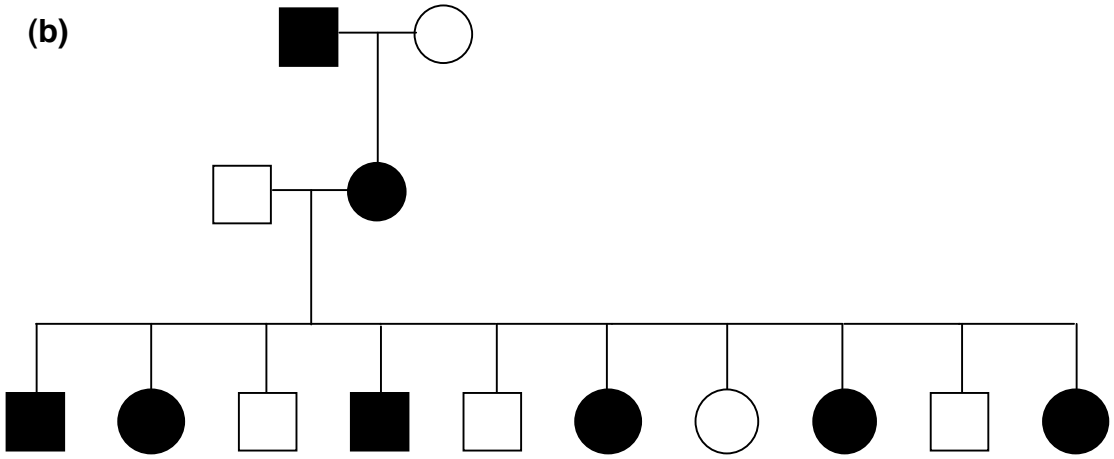
Total = 100

26. When setting out to determine the chromosomal location of a rare human disease gene by genetic linkage analysis (LOD scores), it is useful to calculate the theoretical maximum LOD score that a family of a given size and structure might contribute. For each of the families shown below, calculate, for $\theta = 0$, the theoretically maximum LOD score that could be obtained using an SSR that is genetically inseparable from (shows no recombination with) the disease locus (for a disease that is autosomal dominant). Assume that DNA samples are available for all **living** individuals. Also assume complete penetrance and no new mutations.

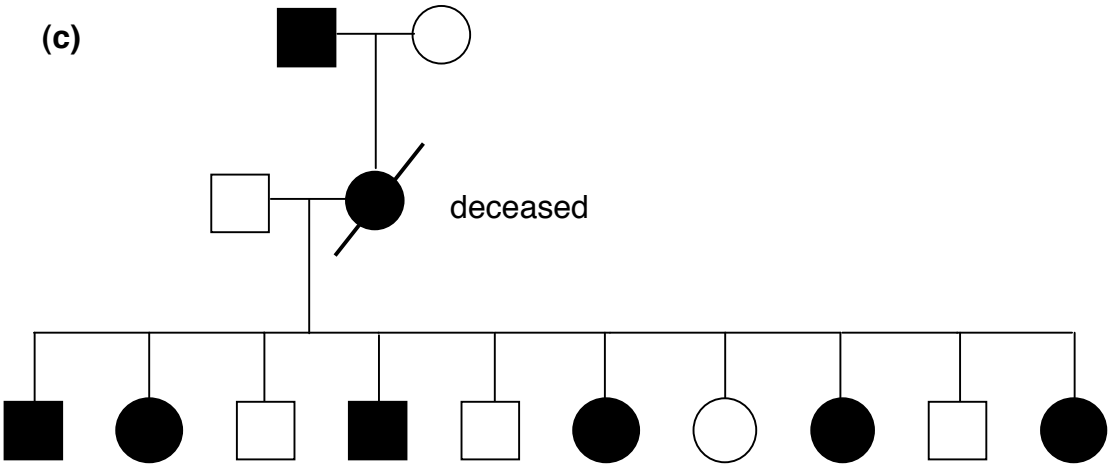
(a)



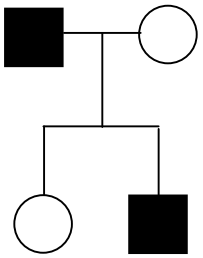
(b)



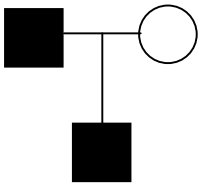
(c)



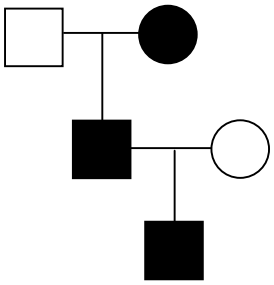
(d)



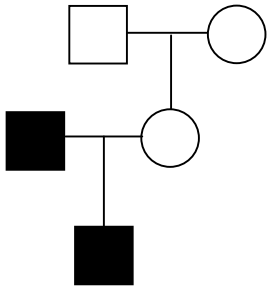
(e)



(f)



(g)



27. You discover a frame-shift mutation in an X-linked gene called SPG in a man who is infertile because of poor sperm production. You postulate that the SPG frameshift mutation is the cause of the man's poor sperm production.

(a) You obtain genomic DNA samples from other men with poor sperm production and sequence their SPG gene. You find that six such men, apparently unrelated, are mutant in SPG. Is it possible that these six men carry the same frameshift mutation found in the first man because of the mutation having been passed through many generations? Explain your answer.

Your classmate discovers an X-linked male-sterile mutant that arose in her mouse colony. She has on hand the mother of this mutant mouse, who gives birth to many sons, all of whom are sterile. Having heard about your studies of the human SPG gene, she discovers that her male-sterile mice are mutant in the mouse SPG gene. You want to know whether the human and mouse SPG genes are functionally interchangeable.

(b) Propose an experiment involving a mouse transgene (but no knockouts and no sequencing) that would test whether the mouse and human SPG genes are functionally interchangeable. When creating engineered mice, the following 8 steps need to be considered. **For the mouse you make**, please state:

i) whether you are using pronuclear injection or gene targeting techniques
ii) what DNA you would introduce into the mouse cells (also draw the DNA)
iii) whether you would put the DNA into a fertilized egg or ES cells
iv) what is the genotype of the fertilized egg or the ES cells you would start with
v) where in the mouse genome the DNA you introduced would integrate
vi) whether creating the mouse should involve the generation of a chimera or not
vii) which additional breeding steps you would do to make the mouse you wanted
viii) two possible phenotypic results you could get from the newly made mice, and the corresponding conclusions you would make based on each result

28. You have isolated two different X-linked mutations in *Drosophila* that affect eye color. Wild-type *Drosophila* have red eyes, whereas flies that carry the **w** mutation have white eyes, and flies that carry the **rng** mutation have orange colored eyes. Both the **w** and **rng** mutations cause recessive phenotypes. (That is, crosses to wild-type of flies from either true-breeding **w** or **rng** strains give F_1 progeny with normal red eyes.)

(a) A male from a true-breeding **w** strain is crossed to a female from a true-breeding **rng** strain. All of the female F_1 progeny from this cross have orange colored eyes. What colored eyes should the male F_1 progeny have?

(b) Are the **w** and **rng** mutations alleles of the same gene, or alleles of different genes? Explain your reasoning.

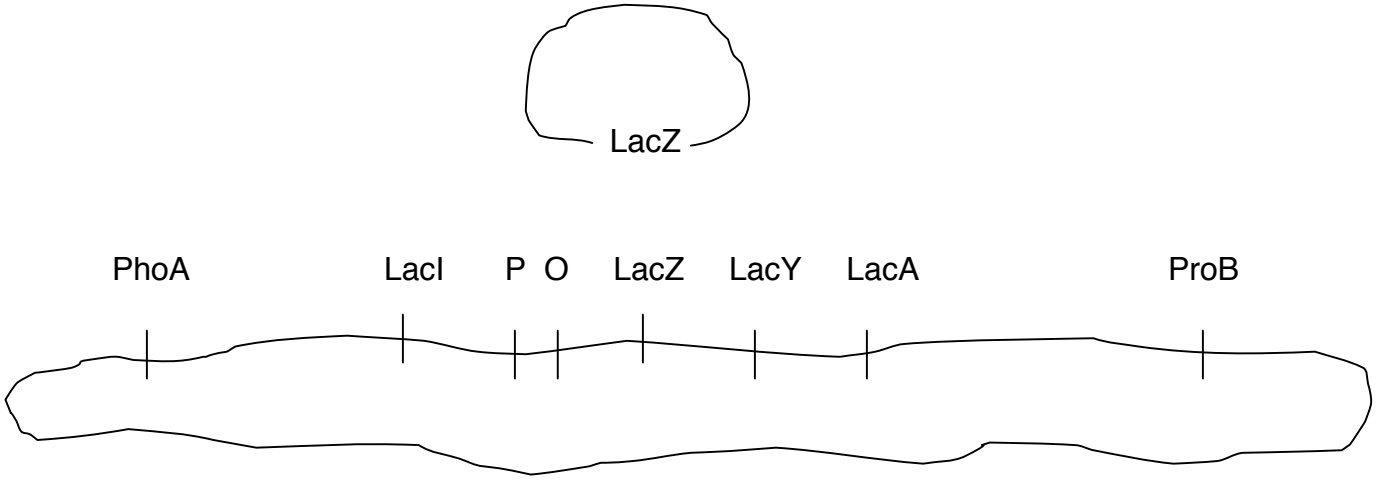
(c) A female F_1 fly (with orange eyes) is crossed to a wild-type male and 1000 male progeny from this cross are examined. Among the male progeny, there are 496 flies with white eyes, 499 flies with orange eyes, and 5 flies with normal red eyes. What is the distance between **w** and **rng** in cM? (Be sure to state any assumptions that you make.)

(d) A mutation that causes short bristles (known as **sh**) is linked to the **w** and **rng** loci. A fly from a true-breeding **sh w** strain (short bristles, white eyes) is crossed to a fly from a true-breeding **rng** strain (long bristles, orange eyes). The female F_1 progeny are then crossed to wild-type males and only males from this cross are examined. The following phenotypic classes and numbers are seen:

Bristle Length	Eye color	Number of MALE flies
Short	white	398
Long	orange	405
Short	orange	90
Long	white	102
Short	red	5

Draw a genetic map showing the relative order of the **sh**, **w**, and **rng** loci.

29. You have constructed an **F'** plasmid that carries the **LacZ** gene. Because the **F'** plasmid carries only the coding sequence of the **LacZ** gene, the **Lac** operon's cis regulatory sequences, and **LacY** and **LacA** genes, are not included on the **F'** plasmid. A diagram of the **F'** plasmid, as well as the host chromosome's **Lac** operon and flanking genes, is shown below.



(a) The **F'** plasmid carrying **LacZ** is transferred into an F- donor strain with a wild-type copy of the **Lac** operon on its chromosome. An **Hfr** is isolated from this strain that can transfer **ProB$^+$** within 10 minutes of mating to a **ProB$^-$** recipient. Draw the origin of transfer on the **F'** plasmid in the diagram above, using the following symbol: ◀ showing the correct orientation for the direction of transfer.

(b) In the space below, draw a diagram showing the organization of the chromosome in the Hfr isolated in part (**a)**. Be sure to show all copies of the **Lac** operon genes and the integrated **F** factor including the orientation of the origin of transfer, and all other markers included in the diagram provided to you above.

(c) Will the **Hfr** isolated in part (**a)** be able to use lactose as a carbon source? Explain why or why not**.**

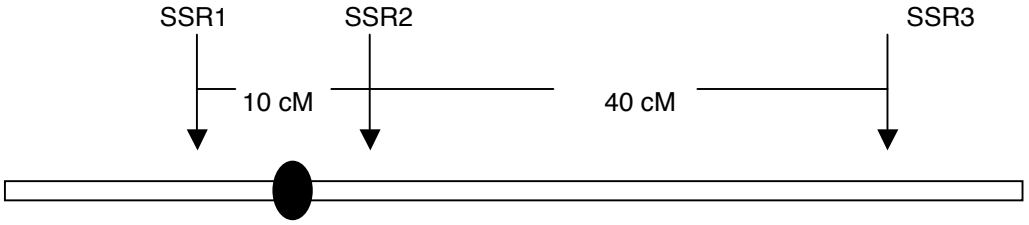
(d) The **Hfr** isolated in part (**a)** is mated to a strain that has a mutation causing the recessive phenotype of constitutive expression of the **Lac** operon. From this mating, you wish to isolate recombinants that show normal **Lac** regulation. Would you expect such recombinants to arise early or late after mating is initiated? Explain briefly.

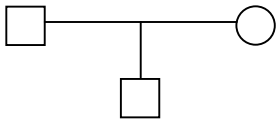
30. The **PyrG** gene is found to lie about 40 kb away from the group of **Lac** genes on the *E. coli* chromosome. You grow P1 phage on a **PyrG$^+$ LacZ$^-$** strain, and then use the resulting phage lysate to infect a **PyrG$^-$ LacI$^-$** strain, selecting for **PyrG$^+$** (the ability to grow without supplemental pyrimidine nucleotides being added to the medium). Among 100 **PyrG$^+$** transductants, 5 show normal regulation of ß-galactosidase, 25 show constitutive expression of ß-galactosidase, and 70 show uninducible expression of ß-galactosidase.

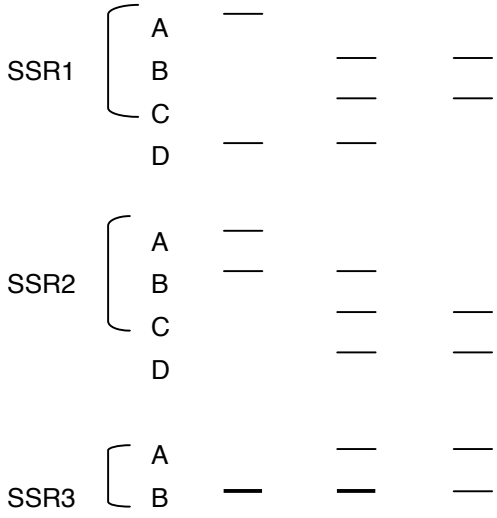
For the reciprocal cross, you grow phage P1 on a **PyrG$^+$ LacI$^-$** strain, and then infect a **PyrG$^-$ LacZ$^-$** strain, selecting for **PyrG$^+$**. Among 100 **PyrG$^+$** transductants, 20 show normal regulation of ß-galactosidase, 50 show constitutive expression of ß-galactosidase, and 30 show uninducible expression of ß-galactosidase.

Draw a diagram of this region of the chromosome that shows where the **PyrG** gene maps relative to **LacZ** and **LacI**.

31. Only a small fraction of human fetuses with trisomy 18 survive to birth, and most of those surviving to birth die in infancy. You prepare DNA samples from umbilical cord blood of a newborn baby with trisomy 18, and from his parents. The schematic of a gel is shown below, and this gel reveals the genotypes of each member of the family at three different SSRs found on chromosome 18. The oval on the diagram of chromosome 18 indicates the centromere.







(a) Did nondisjunction occur before fertilization (during the development of the gametes in the parents) or after fertilization (in the developing embryo)?

In answering the remaining questions, assume that nondisjunction occurred during meiosis.

(b) During the development of which parent's gametes did the non-disjunction event occur?

(c) In which division of meiosis did nondisjunction occur?

(d) Draw the following steps in the meiosis that created the gamete that led to the production of the child with trisomy 18 shown in the pedigree. Please label each SSR allele and the centromere on each homolog of chromosome 18. Assume that SSR alleles 1B, 2C, and 3A are on a single chromosome in the mother's somatic cells. Assume that SSR alleles 1D, 2A, and 3B are on a single chromosome in the father's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the child with trisomy 18 with a star.)

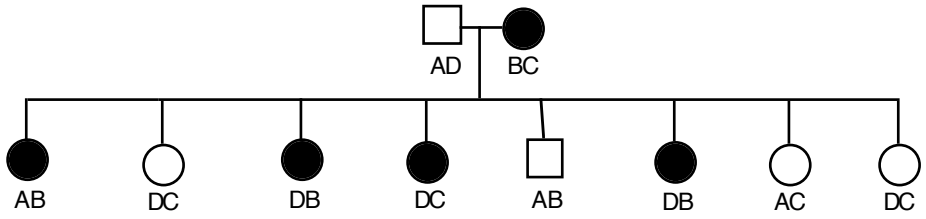
(e) In humans, how many chromatids are normally present in the first polar body?

(f) In humans, how many chromatids are normally present in the second polar body?

(g) In this case of trisomy 18, how many chromatids would have been present in the first polar body?

(h) In this case of trisomy 18, how many chromatids would have been present in the second polar body?

32. In some families, breast cancer displays autosomal dominant inheritance. Here is one such family, with the results of typing for SSR126 (the SSR126 alleles are designated A, B, C, and D):

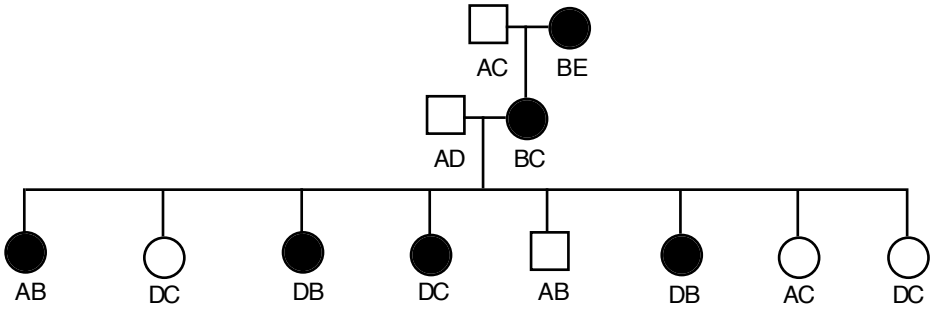


In analyzing this family, we will make three simplifying assumptions:

1) That penetrance is complete in females; all females with the mutation get breast cancer.
2) That males cannot get breast cancer, even if they carry the mutation.
3) That the father is homozygous, as the mutation is rare.

(a) Calculate the LOD score for linkage between breast cancer and SSR126 at $\theta = 0.1$.

One year after your original study, you recover DNA samples from a previous generation and type them for SSR126 (results shown below).



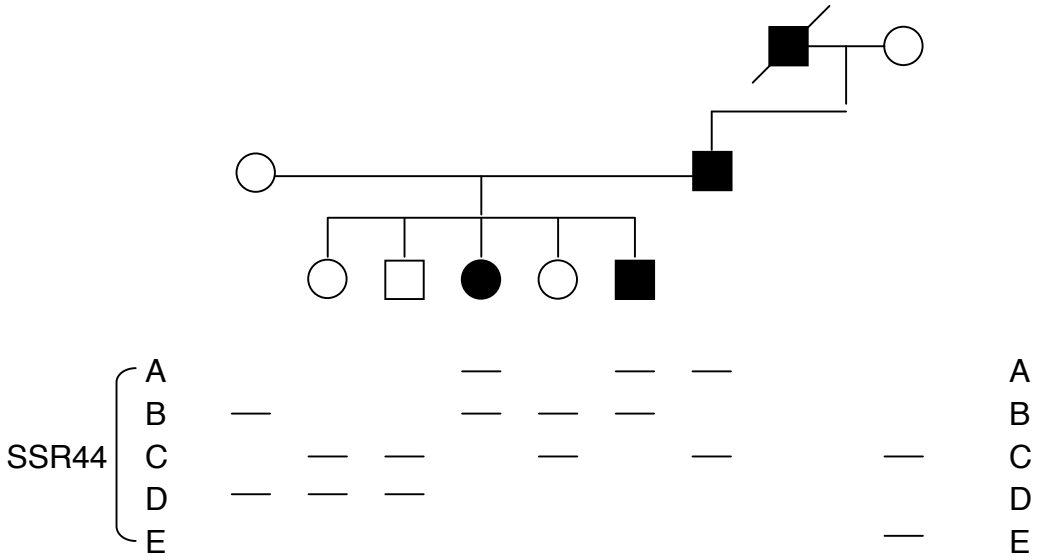
(b) Recalculate this family's LOD score for linkage between breast cancer and SSR126 at $\theta = 0.1$.

(c) No woman in this family developed breast cancer before the age of 37, despite the presence of a predisposing mutation. Why does it take so long for the predisposing mutation to manifest itself? (Focus on the cellular level in your answer. A ONE SENTENCE answer is sufficient.)

(d) You subsequently pinpoint, at the molecular level, the gene whose allele predisposes to breast cancer in this family. You name the gene BRCA, and demonstrate that affected women in this family are heterozygous for a loss-of-function mutation in BRCA. You identify a mouse homolog of the human BRCA gene and generate a mouse model of breast cancer. You create mice that are heterozygous for a loss-of-function mutation in BRCA. You cross these BRCA +/- mice with each other and obtain 185 progeny, 125 of which are BRCA +/-, and 60 of which are +/+. What might explain these breeding results?

33. You are genetically mapping the locus that determines a rare skin disease that shows autosomal dominant inheritance.
Alleles: + (normal) SD (associated with skin disease)

Here is a family in which some individuals are affected. Assume complete penetrance and no new mutations.



(a) Which parent(s) is/are informative with respect to linkage between the skin disease gene and SSR44?

(b) What allele at SSR44 did the affected father inherit from his (deceased) father?

(c) Diagram the phase relationship between the skin disease locus alleles and the SSR44 alleles in the affected father.

(d) Calculate the LOD score for linkage at $\theta = 0.1$ between the skin disease gene and SSR44 in this family.

(e) How many families of this exact type would be needed to achieve a publishable LOD score at $\theta = 0.1$?

34. Consider an autosomal gene at which a rare allele (call it allele **a**) results in homozygotes (**aa**) having only 20% of the number of offspring as average individuals in the population. Assume random mating.

(a) What is the value S for **aa** homozygotes?

Heterozygotes (**Aa**) have a 50.1% chance of surviving an infectious viral disease that afflicts all children in the population. On average, individuals in this population have a 50.0% chance of surviving this infectious disease.

(b) What is the value h associated with allele **a**?

(c) What is the frequency of allele **a** in the population? Show your calculations and state any simplifying assumptions that you make.

(d) What is the frequency of heterozygotes among newborn children?

(e) Suppose that the virus causing the infectious childhood disease is completely eradicated. Estimate the frequency of allele **a** 50 generations later.

35. You have isolated a Tn5 insertion in an otherwise wild-type *E. coli* strain that is linked to the gene encoding the MalT activator protein. Tn5 carries a marker for kanamycin resistance (Kan^R). You grow P1 phage on the strain with the Tn5 insertion and use the resulting phage to infect a $MalT^-$ strain. Among 100 resulting Kan^R transductants, 20 express no maltase activity and 80 express maltase normally. Note that the MalT gene is unlinked to the gene encoding the maltase enzyme MalQ.

(a) What is the distance between the Tn5 insertion and MalT, as expressed as a cotransduction frequency?

(b) You grow P1 phage on a $MalT^-$ Kan^R transductant isolated in part **(a)**, and use the resulting phage to infect a $MalT^C$ mutant that is an otherwise wild-type strain. The $MalT^C$ protein binds DNA regardless of whether the inducer maltose is present. The following results are obtained:

Phenotype	number of Kan^R transductants
uninducible	80
constitutive	19
regulated	1

Next you perform the reciprocal cross by growing P1 phage on a $MalT^C$ Kan^R strain carrying the same Tn5 insertion as above. You use the resulting phage to infect a $MalT^-$ mutant that is an otherwise wild-type strain. The following results are obtained:

Phenotype	number of Kan^R transductants
uninducible	20
constitutive	80

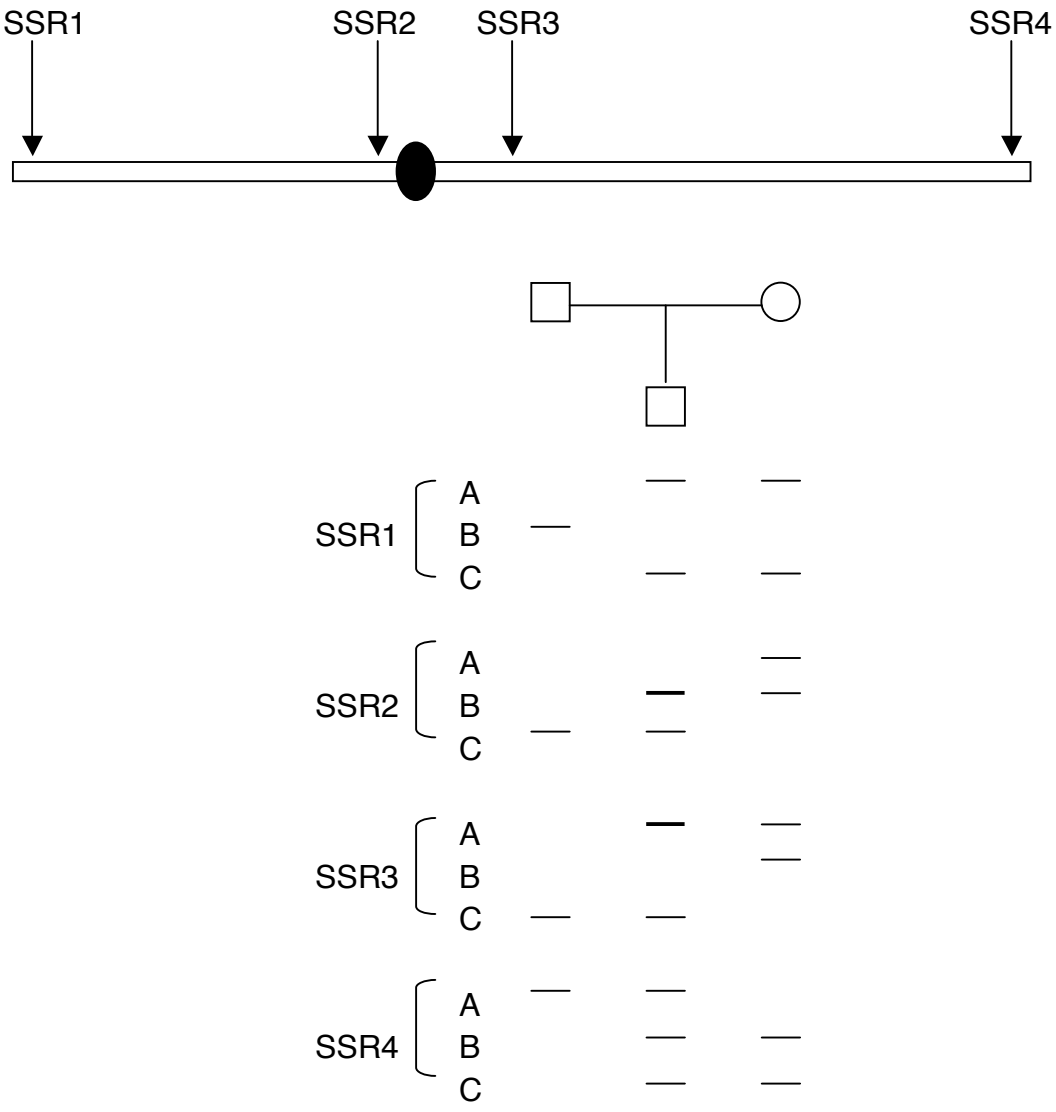
Draw a diagram of the recombination event(s) (that occurred between the transduced DNA and the chromosome) that gave rise to the single regulated transductant from the first cross. Your diagram should clearly show the relative order of Tn5, $MalT^-$, and $MalT^C$ (but cotransduction distances are not necessary).

(c) You have isolated a Tn10 insertion that is linked (50% cotransduction) to a mutant ochre tRNA suppressor allele (Su^+) in an otherwise wild-type *E. coli* strain. The Tn10 insertion carries a marker for tetracycline resistance (Tet^R) and is not linked to MalT. You grow P1 phage on this Tet^R Su^+ strain and use the resulting phage to infect a $MalT^-$ strain. Out of the 100 Tet^R transductants, 50 express maltase normally and 50 express no maltase activity. What type of mutation is $MalT^-$? (Be as specific as possible.)

(d) You grow P1 phage on the Tet^R Su^+ strain from part **(c)** and use the resulting phage to infect a $MalT^-$ $MalT^C$ double mutant. Out of the 100 Tet^R transductants, 50 express maltase constitutively and 50 express no maltase activity. Is the phenotype of a $MalT^-$ $MalT^C$ double mutant regulated, constitutive, or uninducible?

36. You are called by your family physician to provide an expert genetic opinion on an unusual patient: an XXX boy.

You prepare DNA samples from the boy and from his parents. You confirm that the stated father is in fact the biological father by testing the family for a large number of autosomal SSRs. The schematic of a gel is shown on the next page, and this gel reveals the genotypes of each member of the family at four different SSRs found on the X chromosome. The oval on the diagram of the X chromosome indicates the centromere.



(a) During the development of which parent's gametes did the non-disjunction event occur?

(b) In which division of meiosis did nondisjunction occur?

(c) Draw the following steps in the meiosis that created the gamete that led to the production of the XXX child shown in the pedigree. Please label each SSR allele and the centromere on each homolog of the X chromosome. Assume that SSR alleles 1C, 2B, 3A, and 4C are on a single chromosome in the mother's somatic cells. Draw these steps only:

i) the cell in metaphase I with its chromosomes lined up showing any crossover events occurring

ii) the two cells in metaphase II with their chromosomes lined up

iii) the four final products of the meiosis (Please indicate the gamete that led to the creation of the XXX child with a star.)

(d) What might account for this boy's having developed as a male despite the presence of three X chromosomes?

(e) How would you account for the absence in the XXX boy of a paternal allele for SSR1?