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You have a yeast strain in the lab and you are characterizing it. You find that it is haploid, of the alpha mating type, and is phenotypically  $leu^- met^-$  (i.e. it requires added leucine and methionine for growth). You mate your strain with a wild-type strain of the opposite, **a**, mating type, allow sporulation, and characterize 100 tetrads. You find

47 tetrads with two  $leu^- met^-$  spores and two  $leu^+ met^+$  spores.

52 tetrads with two  $leu^- met^+$  spores and two  $leu^+ met^-$  spores.

1 tetrad with 1  $leu^- met^-$  spore, 1  $leu^+ met^+$  spore, 1  $leu^+ met^-$  spore and 1  $leu^- met^+$  spore.

What can you conclude about the *leu* gene in your strain and the *met* gene in your strain?  
In particular,

1) (4 points) Are these two genes linked?

2) (4 points) Can you say that one, neither or both of these genes is centromere-linked (i.e. that they map within a few centimorgans of the centromere?)

3) (4 points) You want to carry out complementation tests with a series of test strains of the alpha mating type. The original strain was also of the alpha mating type, so you decide to use the progeny from your tetrad analysis. You have no trouble finding a  $met^-$  spore of the **a** mating type, but observe that about 82% of the  $leu^-$  spores are of the alpha mating type.

Explain these results. What mapping information do they provide?

4. (4 points) Here is the sequence of the template strand of a DNA fragment:

5' GTACGACGAGTTCGACCTTCTCGCGAGCGCAGAA 3'

Which of the following would be the complementary, nontemplate, strand:

a) 5' TTCTGCGCTCGCGAGAAGGTCGAACTCGTCGTAC 3'

b) 5' AAGACGCGAGCGCTCTTCCAGCTTGAGCAGCATG 3'

c) 5' GTACGACGAGTTCGACCTTCTCGCGAGCGCAGAA 3'

d) 5' CATGCTGCTCAAGCTGGAAGAGCGCTCGCGTCTT 3'

5. (5 points) You have a piece of DNA that includes the sequence:

5' - GATGAGGATGAGGAGAAGTACCGGCCGCCGCTGCGCATCACAATATGTTTCAGT - 3'

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To amplify this DNA by PCR you would use a pair of primers containing which **two** of the following eight primers (you must get both primers right to get any credit -- circle **two** letters):

- a) 5' - GATGAGGATGAGGAGAAG- 3'
- b) 5' - CTACTCCTACTCCTCTTC - 3'
- c) 5' - CATCACAATATGTTTCAGT- 3'
- d) 5' - GTAGTGTTATACAAGTCA- 3'
- e) 5' - GAAGAGGAGTAGGAGTAG - 3'
- f) 5' - CTTCTCCTCATCCTCATC - 3'
- g) 5' - TGAAGGAGTATAACTACTAC- 3'
- h) 5' - ACTGAACATATTGTGATG- 3'

6. (4 points) Four wild-type alleles of the marker locus *STR7*; 1, 2, 3 and 4; are present in a human population in Hardy-Weinberg equilibrium. The frequency of allele 1 is 0.5, the frequency of allele 2 is 0.4, the frequency of allele 3 is 0.08 and the frequency of allele 4 is 0.02. What fraction of the population is homozygous for allele 4?

7. (4 points) A very poorly preserved DNA specimen is found at a crime scene. It is typed for the *STR7* marker locus and found to have a signal for allele 4. Because the sample is so poorly preserved, it is possible that another allele was present but not detected. What fraction of people from this population would be expected to have allele 4.

8. (4 points) Ann's father had Mount's dementia, a fully penetrant autosomal recessive learning disorder. Ann does not have the disease. The overall frequency of this disease in the population is 1/40,000. Assuming that Ann's husband has not been genetically tested, what is the risk to her children (i.e. what is the probability of their being affected)?

9. (4 points) Mount's dementia has one known disease allele (G56X) that accounts for 50% of identified mutations and a test for this allele is available. Neither Ann nor her husband has this allele. Now what is the risk to her children?

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10. (5 points) Consider the following alignment:

	<b>L</b>	<b>V</b>	<b>I</b>	<b>S</b>	<b>E</b>	<b>D</b>
	<b>L</b>	<b>V</b>	<b>L</b>	<b>T</b>	<b>W</b>	<b>D</b>
position:	1	2	3	4	5	6

In which position (1-6) do you think that the BLOSUM alignment score is lowest?  
(explain why)

(4 points each). In each of the following there are two or more statements. One is true (generally, it is taken directly from your textbook) and the others have been modified so that to be untrue or misleading. Circle, check or otherwise designate the correct statement. Ambiguous marks (checking both, placing a mark between the two statements, etc.) will be considered wrong.

11. a) In forward genetics, one starts with the mutant phenotype.  
b) In reverse genetics, one starts with the mutant phenotype.
12. a) Two sequences are homologous if they are similar.  
b) Two sequences are homologous if they are descended from a common ancestral sequence.
13. a) The activity of single-stranded binding proteins allows replication to proceed by preventing supercoils from accumulating in front of the replication fork.  
b) The activity of topoisomerases allows replication to proceed by preventing supercoils from accumulating in front of the replication fork.
14. a) Recombinant progeny can result from either the recombination of genes or markers on the same chromosome or by independent assortment of genes on nonhomologous chromosomes.  
b) Progeny are described as recombinant only if they result from the recombination of genes or markers on the same chromosome.
15. a) A few species of bacteria (not including *E. coli*) can spontaneously take up DNA fragments from their environment in an a process known as natural transformation.  
b) *E. coli* can spontaneously take up DNA fragments from its environment in an a process known as natural transformation.
16. An equivalent mass of oligonucleotide primers and human chromosomal DNA are combined in a PCR reaction. During the annealing phase of the first cycle of the PCR reaction, a region of a human chromosome that is perfectly complementary to the primer is:
  - a) Equally likely to hybridize to the PCR primer and to the complementary strand of human DNA
  - b) Much more likely to hybridize to the complementary strand of human DNA than to hybridize to the PCR primer
  - c) Much more likely to hybridize to the PCR primer than to the complementary strand of human DNA

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17. The compound 3' deoxy adenosine triphosphate :
- a) is a natural precursor for DNA, but not RNA
  - b) is an inhibitor of RNA synthesis.
18. a) *FMR-1* alleles with an intermediate number of CGG triplet repeats (between 50 and 200) have no greater risk of mutation to alleles with a greater number of repeats (which are more likely to show symptoms), but do increase penetrance in the next generation (thereby increasing the chance that their progeny will show symptoms).
- b) *FMR-1* alleles with an intermediate number of CGG triplet repeats (between 50 and 200) do not generate fragile X symptom in most carriers, but have an increased risk of mutation to alleles with a greater number of repeats that do show symptoms.
19. a) Methyl-directed mismatch repair recognizes base pairs mismatched during replication.
- b) Methyl-directed mismatch repair recognizes base pairs mismatched due to methylation.
20. a) It is only when Myc and Max come together in a heterodimer that a transcriptional activator is formed.
- b) Max homodimers are transcriptional activators, but the Myc-Max heterodimer activates a distinct set of genes involved in cell proliferation.
21. a) DNA methylation in mammals is specific for GATC tetranucleotides.
- b) DNA methylation in mammals is specific for CG dinucleotides.
22. a) miRNAs are produced through processing from precursors that are encoded in non-protein-coding regions of plant and animal genomes.
- b) miRNAs are produced through processing from double-stranded RNA molecules such as viral genomes or experimentally produced RNAi molecules.
23. a) The relation between physical and genetic distances is remarkably constant across the human genome; the approximation  $1 \text{ cM} = 1 \text{ Mb}$ . is a useful rule of thumb in the case of humans, and variation is typically less than experimental error.
- b) The relation between physical and genetic distances is not constant across the genome; the approximation  $1 \text{ cM} = 1 \text{ Mb}$ . is a useful rule of thumb in the case of humans, but the actual value varies widely for different chromosomal regions.
24. a) Autozygosity is a term used to mean homozygosity for markers identical by descent and inherited from a recent common ancestor.
- b) Autozygosity is a term used to refer to homozygosity that results from mitotic recombination.
25. a) Alleles at separate loci that are associated with each other at a frequency significantly higher than expected by chance are said to be in linkage disequilibrium.
- b) Alleles at separate loci that are physically linked and common in a given population are said to be in linkage disequilibrium in that population.
26. a) A hypomorphic mutation produces either much less of a protein or a protein with reduced function.

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- b) A hypomorphic mutation produces much less of a protein while an antimorphic mutation produces a protein with reduced function.
27. a) Yeast (*S. cerevisiae*) can grow vegetatively as either haploid or diploid cells.  
b) Yeast (*S. cerevisiae*) grow vegetatively as diploid cells; haploid cells mate soon after sporulation.
28. a) Small regulatory RNAs like *lin-4* RNA may play a much larger role in development than originally suspected, and not only in nematodes.  
b) Small regulatory RNAs like *lin-4* RNA are a novel feature of gene regulation in nematodes.
29. a) Recombinant inbred strains are obtained by transformation of an inbred strain with recombinant DNA.  
b) Recombinant inbred strains are obtained by systematically inbreeding the progeny of a cross.
30. a) Congenic mouse strains are identical except for a single locus and are generated by repeated backcrossing.  
b) Congenic mouse strains are obtained by transformation of a standard (non-inbred) strain with recombinant DNA.

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For each of the following statements, indicate for which of the five model organisms (*Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Caenorhabditis elegans*, *Arabidopsis thaliana*, *Mus musculus*) it is true. These are 45 true-false questions, worth 1 point each.

Statement.	<i>S. c.</i>	<i>D. m.</i>	<i>C. e.</i>	<i>A. t.</i>	<i>M. m.</i>
Undergoes mitotic divisions both as a diploid and as a haploid.					
Gene disruption using homologous recombination is routinely used for reverse genetics.					
This organism does not have sex.					
XX individuals are females and XY individuals are males.					
Self-fertilization allows a heterozygous allele in a single individual to be homozygous in the next generation.					
There are fewer than 10,000 genes.					
The genome size is under 300 Mb..					
Many genes undergo trans-splicing.					
The majority of genes have no introns.					

(5 points) Define bulk segregant analysis.

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In diagramming developmental signaling pathways, the symbol ---| is used to indicate repression; the activity of one gene negatively regulates the activity of the next.

For the pathway **A ---| B ---> C** if A is on, then B will be off. If B is on, then C will also be on. You are studying mutations that affect vulval development in *C. elegans* and you have defined two genes, *vuv-1* and *vuv-2*. Loss-of-function mutations in *vuv-1* result in hermaphrodites with the multivulva phenotype while loss-of-function mutations in *vuv-2* result in a vulvaless phenotype.

(5 points) Which of the following regulatory pathways would be consistent with these results?

- vuv-1* ---> *vuv-2* ---> vulva formation.
- vuv-1* ----| *vuv-2* ---> vulva formation.
- vuv-1* ---> *vuv-2* ----| vulva formation.
- vuv-1* ----| *vuv-2* ----| vulva formation.
- vuv-2* ---> *vuv-1* ---> vulva formation.
- vuv-2* ----| *vuv-1* ---> vulva formation.
- vuv-2* ---> *vuv-1* ---| vulva formation.
- vuv-2* ----| *vuv-1* ---| vulva formation.

(5 points) In further studies you find that a *vuv-1; vuv-2* double mutant looks identical to a *vuv-2* single mutant (i.e. vulvaless). Which of the pathways is most consistent with this result?

- vuv-1* ---> *vuv-2* ---> vulva formation.
- vuv-1* ----| *vuv-2* ---> vulva formation.
- vuv-1* ---> *vuv-2* ----| vulva formation.
- vuv-1* ----| *vuv-2* ----| vulva formation.
- vuv-2* ---> *vuv-1* ---> vulva formation.
- vuv-2* ----| *vuv-1* ---> vulva formation.
- vuv-2* ---> *vuv-1* ---| vulva formation.
- vuv-2* ----| *vuv-1* ---| vulva formation.

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(5 points) Define hybrid dysgenesis

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18. (7 points) You want to test the effect of expressing Sxl protein in the wing imaginal disc of male fruit fly (*Drosophila*) larvae. Describe the method(s) that you would use to do this experiment. Include information on how you would produce the necessary strains.

19. (4 points) What do you think the effect of expressing Sxl in the wing imaginal disc of a male fruit fly would be? Explain.