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MCB140: Second Midterm **Spring 2010**

Before you start, print your name and student identification number (S.I.D) at the top of <u>each</u> page. There are 11 pages including this page.

You will have 150 minutes for the 150-point exam. The value of each question is given at the beginning of the question.

Place your answer on the front of the page. Only answers in that space will be graded.
You may write in pencil; however, to preserve your rights to a regrade, you must write your answers in pen.

You are welcome to use the textbook, notes and a calculator. Wireless devices of any sort are not permitted.

Good luck!

This section is for grading. Do not write here.

1(20 [6, 7, 7])_____ 2(25)_____ 3(25)_____ 4(15)_____

5(20)_____ 6(20)_____ 7(25)_____

EXAM SCORE: _____

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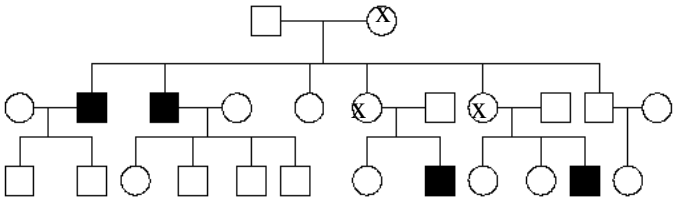
Question 1

(A) 6 points. Look at this pedigree

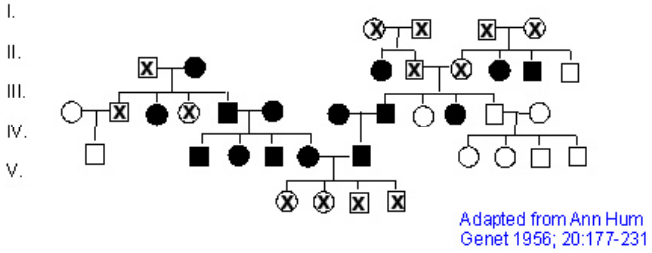


What is the likely inheritance pattern?

X-linked recessive

Indicate in the pedigree the people who are **for sure** are carriers (heterozygotes but healthy) of the disease allele.

(B) 7 points. Look at this pedigree of two extended families. The affected members are deaf.



What is the inheritance pattern?

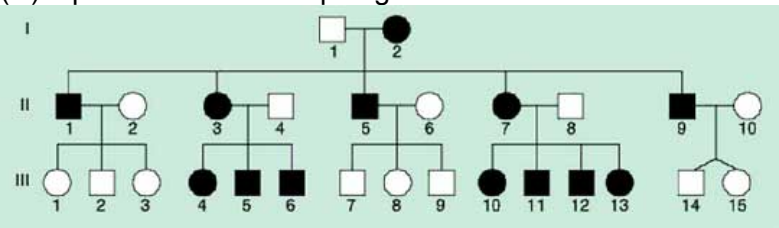
Recessive autosomal

Are there members who carry a disease allele? If so, who are they?

Explain why two deaf people can have offspring who have normal hearing

The mutations do complement (different genes)

(C) 8 points. Look at this pedigree



Explain this inheritance pattern.

Maternal Dominant

What is the most likely cause of this disease?

A mutation in mitochondrial DNA

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Question 2

You decide to study the adenine biosynthetic pathway in budding yeast.

You mutagenize haploid yeast cells and then select for cells that grow well on complete medium but fail to grow on medium lacking adenine, using replica-plating techniques. Several mutants are found. When grown on plates with a small amount of adenine, you notice that some mutants grow in colonies that are red, while others form white colonies.

Crossing the mutants show that they fall into one of two complementation groups, A and B. (A) forms red colonies and (B) forms normal whites colonies on limiting adenine. Both complementation groups are recessive to wild type. That is, all heterozygous diploids (one mutant allele and one wild type allele) can grow and form white colonies in the absence of adenine.

Next, you determine if the genes are linked. The mutant genes are designated ***a*** and ***b*****,** and the wild type genes are designated ***A*** and ***B***. You perform the following cross:

a B *x* ***A b***

Remember, both ***a B*** as well as ***A b*** cannot grow without adenine. ***a B*** colonies are red ***A b*** colonies are white when a little adenine is around. You expect that ***a b*** cells will not be able to grow on adenine, but you don't yet know whether they'll turn red. The phenotypes of the 60 haploid spore colonies resulting from 15 tetrads (***a B*** cells crossed with ***A b*** cells) are shown in the table below. In this table,

"+" means able to grow in the absence of adenine,
"-" means **un**able to grow in the absence of adenine,
"w" means white colonies,
"r" means red colonies when grown in low adenine.

Hint: to solve this problem, you will need to determine the phenotype (-r, -w, +r or +w) expected for each of the anticipated gene combinations (***a b, a B, A b*****,** and ***A B***), and you will have to consider the possibility that ***a*** or ***b*** might be epistatic to ***b*** or ***a*** with regard to color phenotype.

Tetrad	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
	-r	-r	+w	-r	-r	-w	+w	-r	-r	-w	+w	-w	-r	-w	-r
	-r	-w	+w	-r	-w	-r	-r	-w	+w	-w	-w	-r	-w	-r	-w
	-w	+w	-r	-w	-r	+w	-r	-w	-w	-r	-r	-w	+w	-r	-w
	-w	-r	-r	+w	-w	-r	-w	-r	-r	-r	-r	-r	-r	-w	-r
Answer B.	PD	TT	NPD	TT	PD	TT	TT	PD	TT	PD	TT	PD	TT	PD	PD

(A) 5 points. Do ***a b*** cells grow as red colonies or do they remain white when grown in low adenine? Explain your answer.

ab will be red. The TT and NPD hold the answer. E.g. the NPD ascus has 2 abs, and thus ab is red

(B) 10 points.For each tetrad in the table on the previous page, indicate in the table above whether the tetrad is parental ditype (**PD**), nonparental ditype (**NPD**) or tetratype (**TT**).

PD: aB (r), aB (r), Ab (w), Ab (w)
NPD : aB (r), ab (r), AB (w), AB (w)
TT: aB (r), ab (r), AB (w), aB (w)

(C) 10 points. Are complementation groups A and B
1/ represented by genes that are close together on the same chromosome
2/ on separate chromosomes
3/ far apart on the same chromosome?

Explain your answer:

3/: NPD is rare, they are the same chromosome. TT is common, this not tightly linked

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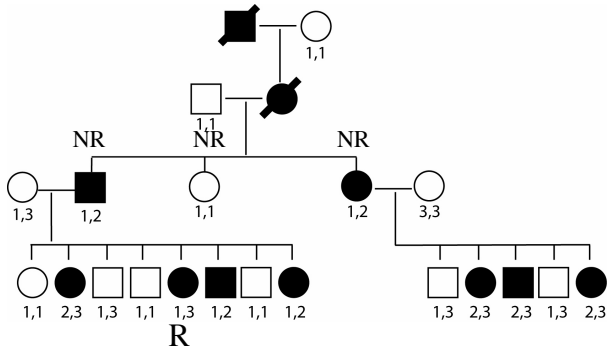
Question 3

Below is a pedigree of a family showing the inheritance pattern of an allele that causes a phenotype that is characterized by an additional thumb/big toe on each hand and foot. The affected individuals are otherwise unremarkable. The disease allele appears to be linked to an SSR with at least three variants, 1, 2, and 3. The genotypes are indicated below each individual



(A) 15 points. Can you use this family to find a LOD score that is greater than 3? Show the calculation

You can score the parent given the phasing of the disease. 3 parents and 12 children are NR, one child is a recombinant:

1/16 recombinant, known phasing:

LOD score is 3.19

(B) 10 points. It appears the marker maps closely to the gene Sonic Hedgehog (Shh), the expression of which in the developing hand affects the number of digits. You also know that mice homozygous null for Shh die early in embryogenesis from malformation in many parts of the body including the nervous system, gut and heart, and in addition, they also have only one digit per extremity. What sort of mutation could cause the observed phenotype observed in the family above?

A mutation in a regulatory region (enhancer) of the Shh gene that cause extra (ectopic) expression in the developing limbs, causing an extra digit.

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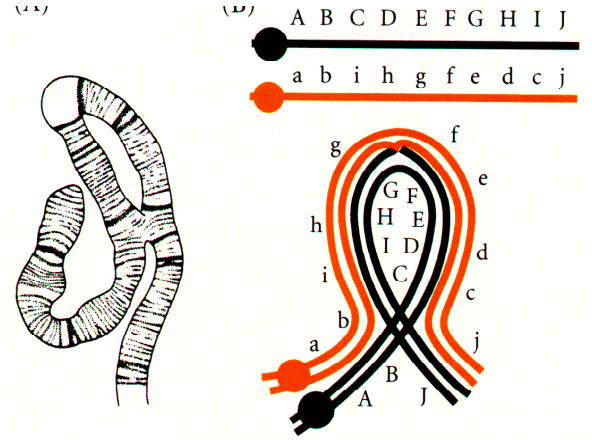
Question 4

The figure below is of a polytene chromosome on the left. The closed loop is caused by pairing of chromosomes, half of which have an inversion. The panel on the right shows the alignment of these chromosomes during meiosis.



(A) 15 points. Draw the consequences of a crossover between chromatids at a position between G and F (g and f) for the meiotic products. Indicate which products can contribute to functional gametes.

* A B C D E F G H I J	**yes**, this is a fine chromosome
* a b i h g F E D C B A *	**no**, torn apart, two centromeres
j c d e f G H I J	**no**, no centromeres, lost
* a b i h g f e d c j	**yes**, will be fine, all genes are present

(B) 5 points. Inversions are important for balancer chromosomes in flies. Balancer chromosomes have other characteristics as well. Want are these characteristics?

Inversions to prevent (productive) cross overs during meiosis

One or more haploinsufficient genes (lethal when homozygous, recognizable phenotype when heterozygous)

(C) 5 points. Why are these characteristics important, in combination with the inversions for the function of a balancer chromosome?

You can maintain heterozygous lethal or sterile stocks without genotyping (or knowing the genes)

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Question 5

Colon (endgut) cancer is one of the most common inherited cancer syndromes known. Among the genes found to be involved in familial colorectal cancer are: *MSH2* and *MSH6* both on chromosome 2 and *MLH1*, on chromosome 3.

(A) 5 points. Are *MSH2 MSH6* and *MLH1* proto-oncogenes or tumor suppressor genes?

Tumor suppressor genes

(B) 5 points. Do you expect that most cells in the body of affected individuals are heterozygote or homozygote for any of the genes?

Most cells will be heterozygous. (Tumor cells might be homozygous null)

MSH2 MSH6 and MLH1 proteins help to repair mistakes made in DNA replication.
(C) 5 points. How do these genes promote cancer?

Mistakes made in replication, if NOT repaired will result in random mutations that will in time contribute to cancer

(D) 5 points. Speculate why these genes preferentially cause colon cancer, but to a lesser extent cancer at other sites in the body (they have been demonstrated to play a role in Small Cell Lung Carcinoma). Keep in mind what sort of environment the cells in the colon are exposed to.

Cells in the colon are exposed to a very unfriendly environment and turn over quickly. Thus, much cell division is needed. If DNA duplication is more prone to errors, most mutations will accumulate in these dividing cells and help cause the cancer.

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Question 6

The cortex is a layered structure generated by the migrations of neurons from their birthplace deep in the cortex to more superficial positions near the surface. Cues from the neurons' environment guide their radial migrations. The human doublecortin phenotype is caused by an X-linked mutation that leads to a defect in the organization of the cortex. Neurons fail to migrate in mutant males leading to gross defects in cortical development. In heterozygous females, there are two populations of neurons: those that completely fail to migrate as they do in mutant males and those that migrate normally.

a) Explain the difference in phenotype between males and females. (10 points)

migration of cells in females in determined by which X-chromosome is inactivated.
If mutant X-chromosome is inactivated -> normal migration
If normal X-chromosome is inactivated -> no migration

b) In what cells do you think that the doublecortin gene is likely to function. (10 points)

The mutation must act in the cells that carry it (cell autonomous). There is enough guidance signal around in the heterozygotes, so it does not function in the cell that provide the guidance cues

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Question 7

You are working with a fresh isolate of *E. coli*, and find that it can grow on starch. The starch degrading enzyme amylase is made only at low levels under normal growth conditions, but when starch is added to the *E. coil* culture the levels of amylase enzyme increase 100-fold. You isolate three mutants that affect amylase synthesis. The mutant **A-** is in the structural gene for amylase and prevents the synthesis of amylase enzyme. Both the **B-** and **C-** mutations, which are linked to **A-**, have expression of amylase even in the absence of starch. The table below gives the amylase enzyme activities for a set of strains in either the presence or absence of the inducer starch. **There are hints in the later part of this question that you can use to confirm some of the answers to the earlier part of this question.**

	Amylase activity in units		
	No starch	With starch	
A+ B+ C+	1	100	
A- B+ C+	0	0	
A+ B- C+	100	100	
A+ B+ C-	100	100	
A- B+ C+ / F' **A+ B+ C+**	1	100	
A+ B- C+ / F' **A+ B+ C+**	100	200	
A+ B+ C- / F' **A+ B+ C+**	2	200	
A+ B- C+ / F' **A- B+ C+**	100	100	
A- B- C+ / F' **A+ B+ C+**	1	100	
A+ B+ C- / F' **A- B+ C+**	1	100	
A- B+ C- / F' **A+ B+ C+**	1	100	

(A) 5 points. Give as complete a description as you can of the properties of the **B-** mutation, and propose a molecular function for the regulatory component that is affected by the **B-** mutation.

B- Constitutative
Dominant
Cis-Acting

Operator site (repressor binding site)

(B) 4 points. Give as complete a description as you can of the properties of the **C-** mutation, and propose a molecular function of the regulatory component that is affected by the **C-** mutation.

C- Constitutative
Recessive
Trans-acting

C is the repressor

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You isolate a new mutation **D-** that alters amylase expression. You determine in an other experiments that **D-** is **not** linked to **A-**, **B-**, or **C-**. The properties of some strains with the **D-** mutation are shown below.

	Amylase activity in units	
	No starch	With starch
D+	1	100
D-	1	1
D- / F' **D+**	1	100
D- A-	0	0
D- B-	100	100
D- C-	100	100

(C) 2 points. Is **D-** Uninducible or constitutive?
Is **D**- dominant or recessive?

Uninducible
Recessive

(D) 2 points. Is the function affected by the **D-** mutation most likely to act in trans or only in cis to the amylase gene?

D acts in trans, thus cannot be the regulatory site

(E) 2 points. Is the **D-** mutation most likely to act earlier or later than **B-** in the pathway for amylase regulation?

Earleir. D- phenotype is hidden by B-. B- is epistatic to D-. B- acts later.

(F) 2 points. Is the **D-** mutation most likely to act earlier or later than **C-** in the pathway for amylase regulation?

Earlier. D- phenotype is hidden by C-. C- is epistatic to D-. C- Acts later.

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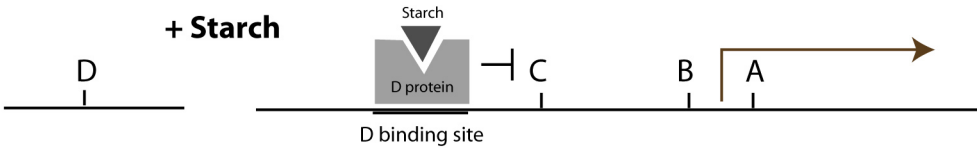
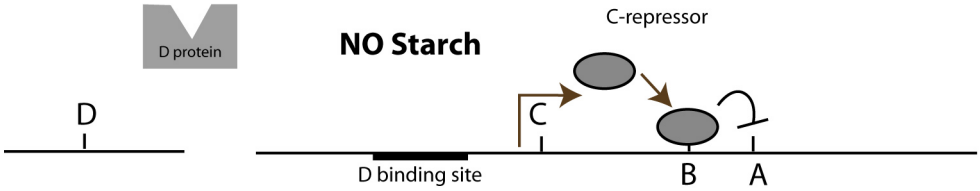
By performing biochemical experiments you find that the protein encoded by the **D-** mutation binds starch and binds DNA at a site near the **A-, B-** and **C-** mutations as shown on the diagram below.

-------(**D** binding site)----------(**C-**)----------(**B-**)----------(**A-**)----------

(G) 10 points. Propose a molecular model that accounts for the behavior of the **A-, B-, C-** and **D-** mutations and that explains how starch acts as an inducer of amylase expression. Be as specific as you can.



D + Starch blocks the expression of the C inhibitor; A is active



Without starch, D does NOT block C. C repressor is made and blocks A