HST.161 Molecular Biology and Genetics in Modern Medicine
Fall 2007

Question 1

Based on what you learned in our clinic on Rett syndrome, address the following questions.
a. What enzymatic function is missing in patient J. Explain clearly what the substrate and product of the enzymatic reaction catalyzed by this enzyme are.

b. What data supports the view that if a method for correcting the enzyme deficiency were to be developed, it is likely that patient J will undergo considerable clinical improvement.

Question 2.

Based on what you learned in our clinic on phneylketonuria, address the following questions.

a. Explain how patient M's status affected status for PKU was originally identified. Be explicit in your answer describing an initial screening test and a confirmation test that was carried out and describe the rationale for each test used in identifying her as affected with PKU.

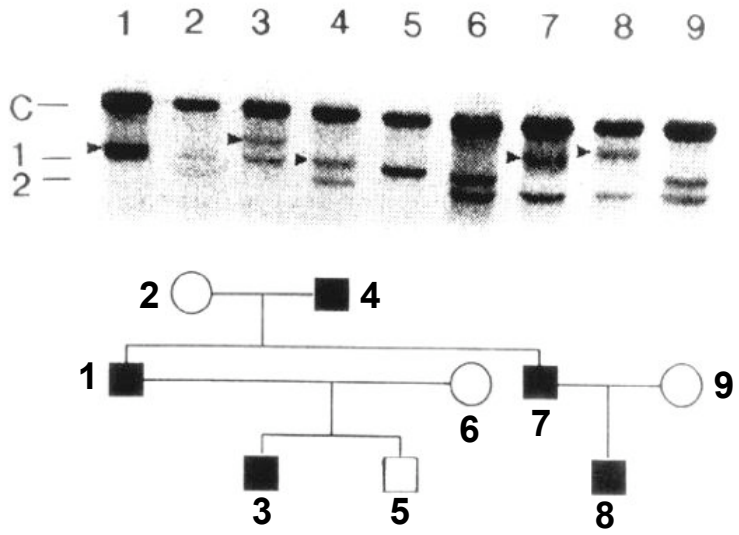
b. Explain how patient M is currently being treated to address the difficulties associated with her PKU status and why this treatment is effective.

c. When patient M reaches adulthood and chooses to have children of her own, what major concerns will she have related to her PKU status. How should these concerns be addressed?

Question 3. The myotonic dystrophy gene was mapped to chromosome 19 through linkage to the secretor locus. A series of RFLP markers were then tested to determine the position of the gene on chromosome 19 with greater precision.

a. (2 points) Approximately how many informative meiosis could allow localization of the gene to within a 1 centimorgan interval? Explain your answer.

b. (2 points) Explain how linkage disequilibrium could be helpful in localizing the gene more precisely. Include in your explanation a clear statement of the assumptions which must be correct in order for linkage disequilibrium to be useful in more precisely localizing the gene.



c. (2 points) A series of RFLPs were tested for their association with the myotonic dystrophy gene. The Southern blot shown above was carried out on a family with myotonic dystrophy. The numbers 1 and 2 indicate the positions of the two alternative alleles of an RFLP on chromosome 19 which were under examination for linkage to the myotonic dystrophy gene. What property of this RFLP is unusual in this Southern blot?

d. (2 points) What is the explanation at the level of DNA sequence for the unusual behavior of this RFLP?

e. (2 points) Explain how the data shown in this figure provides a physical explanation for the phenomenon of genetic anticipation. (Include in your answer a brief explanation of the term “genetic anticipation”.)

Question 4. (3 points) Anne Smith and Richard Jones were both born deaf, attended the same school for the deaf, married and had five children three boys and two girls. All of their children were born deaf. Neither Anne’s parents nor Richard’s parents were deaf. Based on these facts alone what modes of Mendelian inheritance would be compatible with Anne and Richard’s family? For each mode of inheritance comment on whether a new mutation could be relevant to explaining the pattern of inheritance in the family.

b. (3 points) Anne's sister Rachel, who was not deaf, met Richard's brother, Mark who also was not deaf while visiting at the school. Rachel and Mark married and had four children. Two of the children were born deaf, one boy and one girl. What is the ***most likely*** mode of inheritance for deafness in the family based on these new facts? Explain your answer.

Question 5. (30 points) A screening test for colon cancer involves testing by PCR for the presence of cells which carry certain mutations in the Kras gene in stool. Explain the rationale for this test.

a. What types of mutations in the Kras gene is the test designed to detect? (3 points)

b. How could these mutations contribute to the etiology of a colon tumor? (3 points)

Three patients have positive results in this test and undergo colonoscopy.

Patient 1, 47 years of age, has hundreds of colonic polyps and a malignant tumor which is surgically removed.

c. What gene would you screen for mutation in the tumor and in the DNA of the patient? (3 points)

d. Explain to the patient how mutations in this gene can contribute to her polyps and to the development of her cancer. (4 points)

e. Explain to the patient the possible increased risk for colon cancer to other members of her family who carry the same mutation as she does. (3 points)

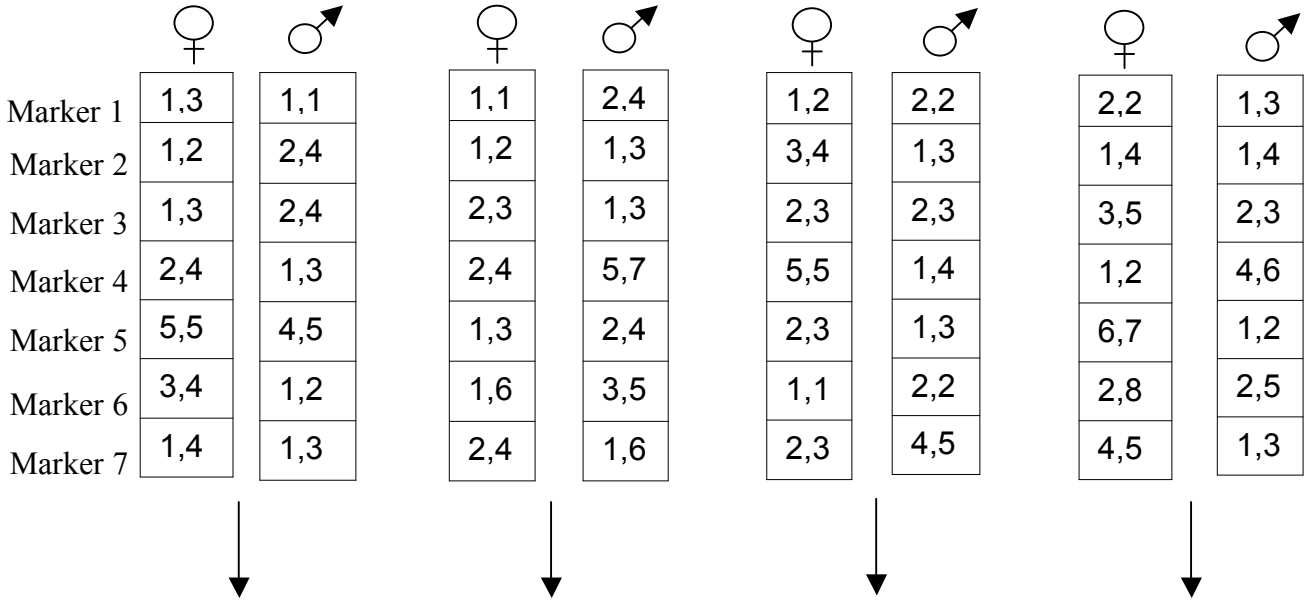
Patient 2, 52 years of age, has no polyps but does have a malignant tumor, When the tumor is removed it is shown to have microsatellite instability. The patient an only child also has three first cousins ages 47,51 and 53 who have recently been diagnosed with colon cancer with microsatellite instability.

f. Which class of genes would you test for mutation in the germline DNA of the patient in this case? (3 points)

g. Explain to the patient how mutation in one of these genes could contribute to the development of his cancer. (3 points)

h. If DNA samples can be obtained from the three first cousins before the mutation screening is carried out, explain how these samples can be used to narrow the search for the mutation in the gene likely to be contributing to the high frequency of occurrence of colon cancer in this family. (4 points)

Question 6. (6 points) Prader-Willi syndrome, which includes mental retardation and an inability to be satiated, is caused by the absence of expression of genes in a critical region of chromosome 15 which is subject to genomic imprinting. The maternal copies of these genes are not expressed. In a normal individual expression of the copies of these genes from the paternal chromosome 15 is necessary and sufficient to support normal development. Two men and two women each have Prader-Willi syndrome. The genotypes of the affected individuals, as well as their parents, have been determined at 7 different polymorphic sites on chromosome 15.



	Man 1	Man 2	Woman 1	Woman 2
Marker 1	1,3	1,4	2,2	2,2
Marker 2	1,2	1,3	1,3	4,4
Marker 3	1,3	1,3	3,3	3,3
Marker 4	2,4	2,5	4,5	1,1
Marker 5	5,5	1	2	7,7
Marker 6	3,4	5,6	1	2,2
Marker 7	1,4	1,2	3,4	4,4

For each of these four individuals, (Man 1, Man2, Woman 1 and Woman 2) give an explanation of the chromosomal event which gave rise to their Prader-Willi syndrome. Please indicate, when possible, whether the relevant events occurred in meiosis I or meiosis II.

a. Man1 (2 points)

b. Man 2 and Woman 1 (2 points)

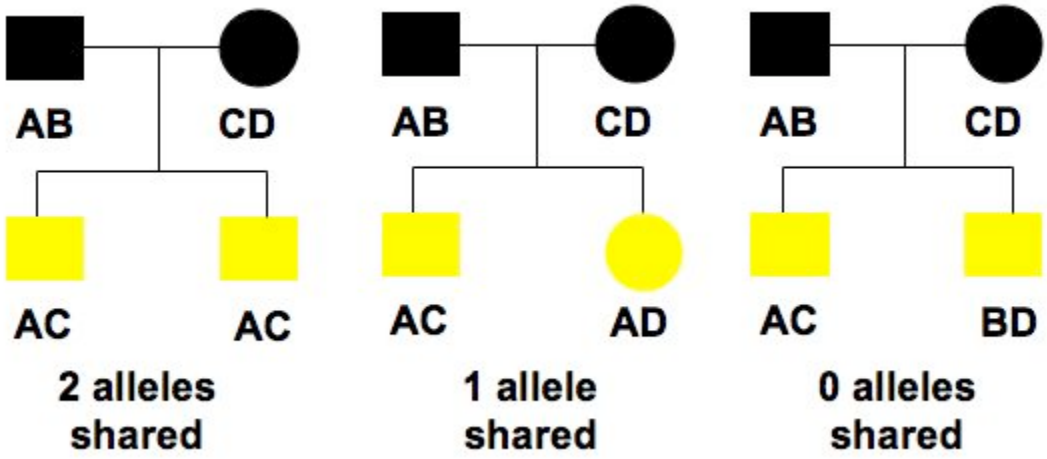
c. Woman 2 (2 points)

Question 7

The population frequency of Crohn's disease is approximately 0.3%.The likelihood of an inidividual having Crohn's disease is 20 fold higher for siblings than for the general population. Two strategies for a genome wide search to identify the chromosomal sites of genes contributing to Crohn's disease are under consideration. A and B described below. Two possible models for the genetic basis of susceptibility to Crohn's disease C and D are given below. Match a genome wide search strategy to a model for Crohn's disease susceptibility based on the likelihood that the genome wide search strategy is most likely to be effective given the model of the genetics of the disorder. Explain why the strategy you match to each model is most likely to yield meaningful results for that model.

Strategy A

Five hundred pairs of siblings affected both affected with Crohn's disease and their parents are collected. Highly polymorphic DNA markers spaced 10 cM apart spanning the gneome are genotyped for each family grouping. Sibpairs are scored as to whether they match for two, one or zero alleles inherited from their parents as shown below. Deviations from a 25:50:25 ratio for the three classes expected by chance will be considered to be evidence of linkage between a susceptibility allele and the DNA marker.



Strategy B

2,500 individuals with Crohn's disease are identified and 2,500 individuals age and sex matched without Crohn's disease are collected as well. SNP polymorphisms approximately 100 kbp apart throughout the genome selected to be haplotype tagging SNPs are genotyped in both groups. A deviation in allele frequency between the cases and controls is taken as evidence that a gene predisposing to to Crohn's disease is located in the vicinity of the marker.

Model A

Crohn's disease susceptibility is contributed to by alleles at five loci in the population. For each of these loci, a single major allele with an allele frequency of 20% in the population is responsible for susceptibility to crohn's disease.

Model B

Crohn's disease susceptibility is contributed to by alleles at five loci in the population. For each of these loci, there are one hundred alleles each with an allele frequency of 0.2% in the population which are responsible for susceptibility to Crohn's disease.