

7.03 PROBLEM SET 7

BASED ON LECTURES 30-36
THIS PROBLEM SET WILL NOT BE GRADED

1) Cancer is a term used to describe a number of diseases characterized by unregulated cell growth. Cancers typically are associated with genetic changes, which can range from point mutations to large-scale chromosome abnormalities. The net effect of such mutations generally is the release of cells from their normal growth constraints.

The results from a sarcoma study involving ten individuals recently were reported. Wild-type and tumor cells were analyzed to determine the genotype of a gene involved in cell cycle regulation. In all cases, wild-type cells were heterozygous, carrying a wild-type allele and a previously uncharacterized allele. In contrast, all tumor cells were homozygous with two copies of the uncharacterized allele.

a) Based on the above information, is it more likely that this gene is an oncogene or tumor suppressor gene? Explain.

The unknown allele identified in this study was sequenced. A mutation was detected in the promoter region of one study participant. In the other nine study participants, sequencing disclosed a mutation in the coding region of this allele.

b) Describe how these mutations could result in a cancer phenotype.

c) Offer an explanation for the different frequencies observed between the two types of mutations detected in this study.

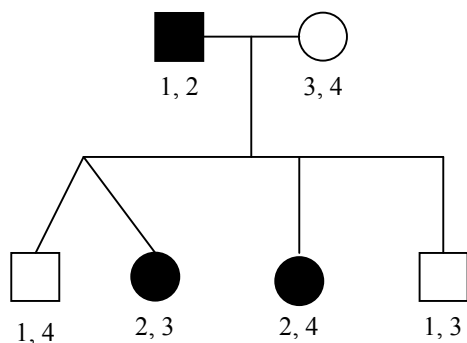
The results from a carcinoma study recently were reported. Of the ten individuals examined, nine were homozygous recessive for a gene involved in the detection of altered DNA.

d) Is this gene more likely to be an oncogene or tumor suppressor gene? Explain.

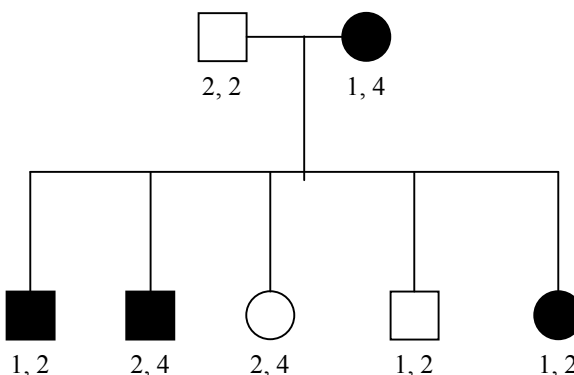
e) Propose a hypothesis to account for how the homozygous recessive condition could lead to carcinoma development.

2) You have been interested in a rare genetic disorder for some time. After conducting an exhaustive search, you identified three families with this disorder in the US. Preliminary findings suggest that the gene causing this disorder may be linked to a specific SSR. This SSR locus has four alleles, each with a different number of repeats. To begin your analysis, you constructed a pedigree for each of the three families. The pedigrees are listed below (affected individuals are darkened and the SSR genotype is listed below each individual).

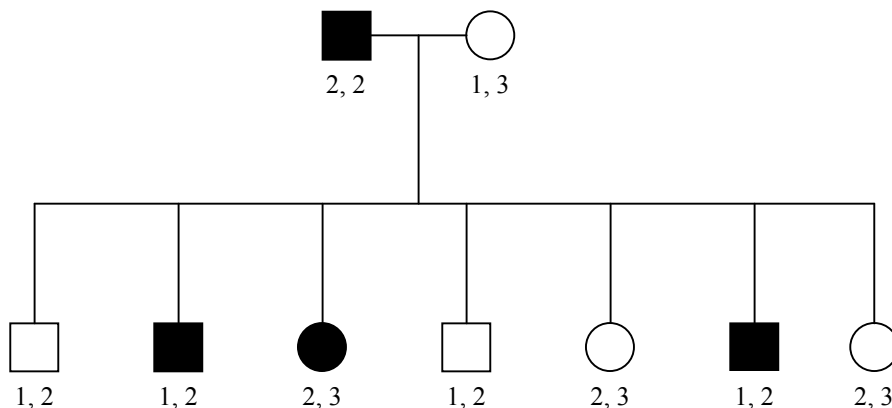
FAMILY #1



FAMILY #2



FAMILY #3



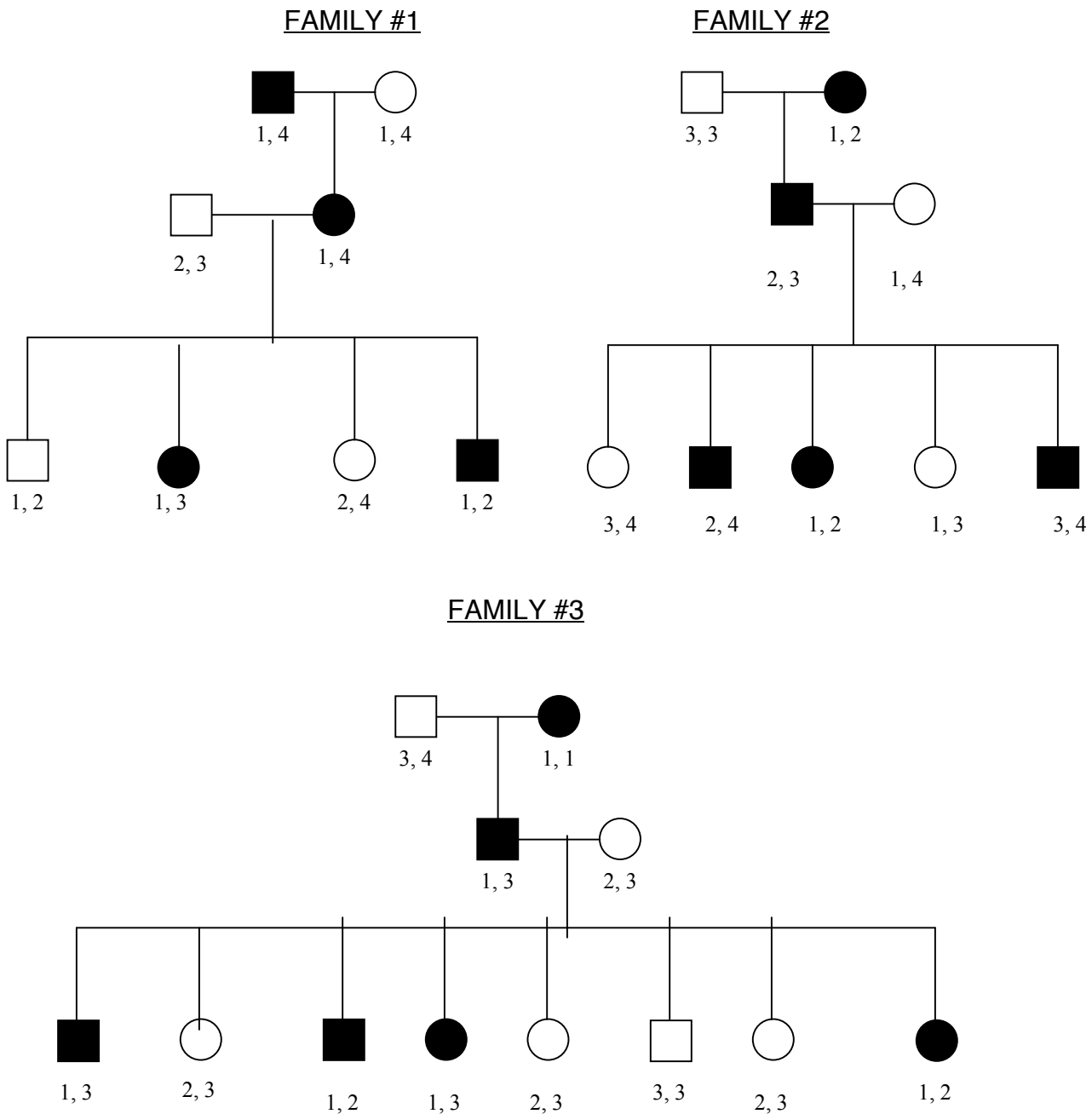
a) What is the most likely mode of inheritance for this disorder?

We will use information in the pedigree to calculate a LOD score for each family.

b) Which of these families can be used to calculate a LOD score to test for linkage between the SSR marker and the gene of interest? Explain.

c) Calculate the LOD score at theta (θ) values of (.05, .1, .2, .3, and .4). Which θ value shows the highest odds of linkage for each family?

Three families with this disorder also were identified in Argentina. In contrast to the US families, genetic information is available for three generations in these families. The pedigree for each family is listed below.



d) Which of these families can be used to calculate a LOD score? Which is the relevant parent in each pedigree?

e) Calculate the LOD score at theta (θ) values of (.05, .1, .2, .3, and .4). Which θ value shows the highest odds of linkage for each family?

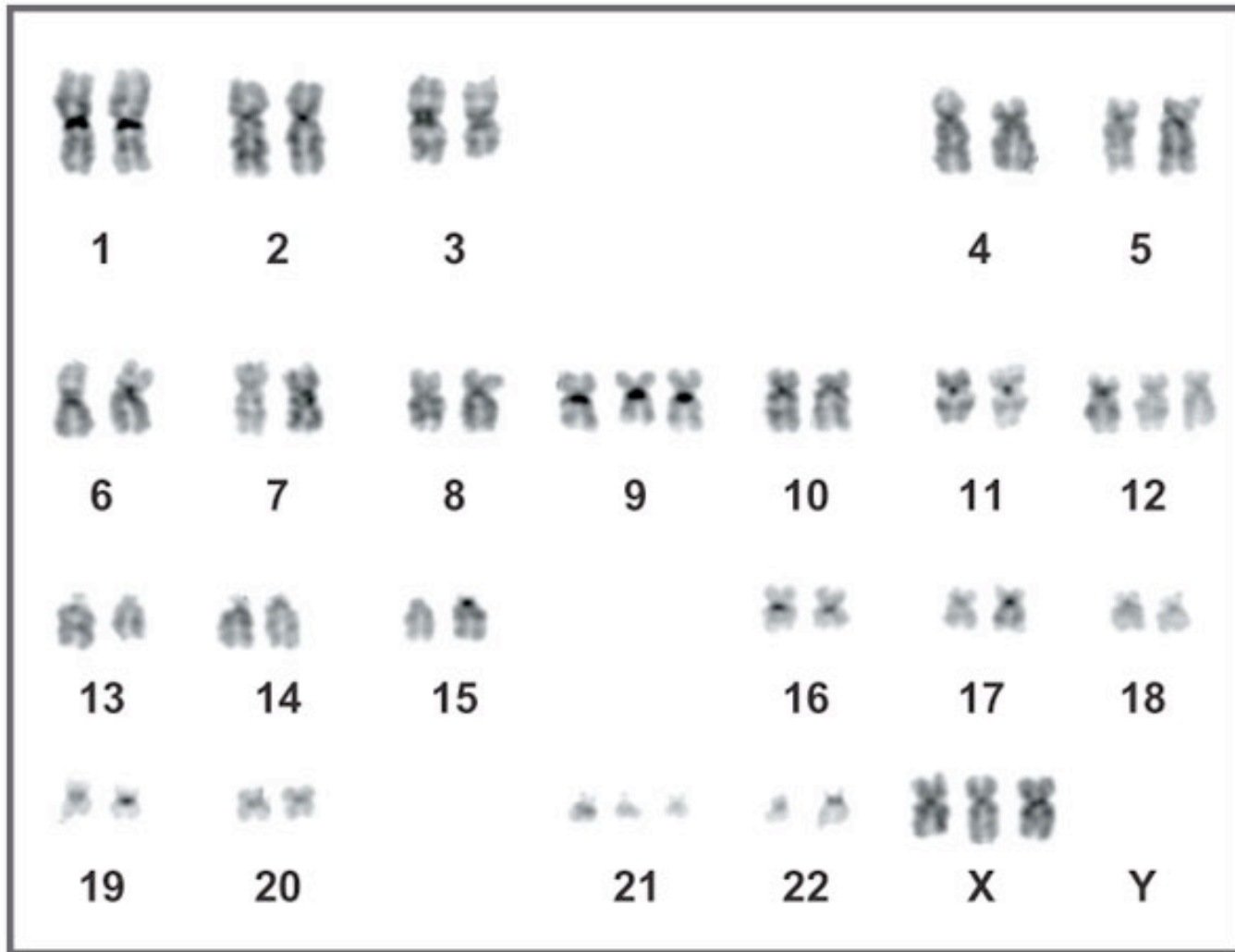
f) Plot the LOD score for each theta value for the US and Argentine families. Is the curve similar for the various families?

g) Do the LOD scores for the US families suggest linkage? Do the LOD scores for the Argentine families suggest linkage? Explain.

h) Can the results from the Argentine and US families be combined? If so, what is your final conclusion regarding linkage between the gene of interest and SSR marker?

3) Chromosome abnormalities are associated with a number of disorders including some cancers. Duplications, for example, have been detected in some carcinomas and inversions in some lymphomas. It is believed that the analysis of such abnormalities could provide important clues to key oncogenic events and perhaps suggest potential avenues for cancer treatment.

The karyotype for a specific type of carcinoma is displayed below.



a) Identify the chromosome abnormalities evident in this karyotype.

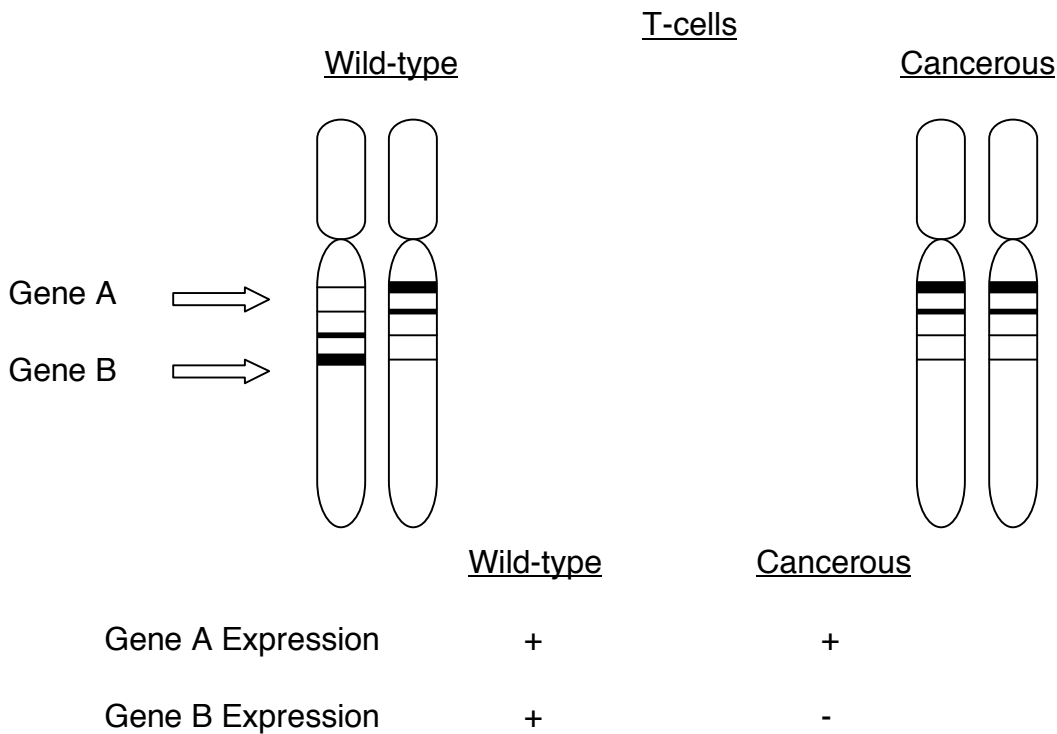
Sixteen individuals with a specific carcinoma were screened for chromosomal aberrations. In eleven of these individuals, the short arm of chromosome eight is longer in wild-type cells compared to cancer cells.

b) Which type of abnormality exists in the cancer cells? Explain.

c) Describe how the chromosome abnormality listed in **part “b”** could lead to carcinoma development.

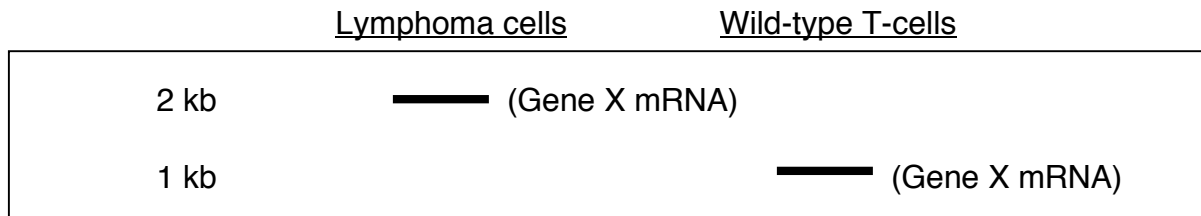
d) In each of the eleven individuals described above, a subset of cancer cells was aneuploid. Why wasn't aneuploidy observed in all cancer cells?

One goal of an on-going lymphoma study is to determine if a correlation exists between a chromosome #2 aberration and lymphoma development. Some early results from this study are listed below.



e) Is there a chromosome abnormality? Describe a mechanism to account for the development of the cancer phenotype.

Wild-type T-cells express Gene X at high levels. A type of T-cell lymphoma is heterozygous for a specific translocation that is absent in wild-type cells. Despite the translocation, lymphoma cells continue to show high levels of Gene X expression. The results from Northern blot analysis of mRNA isolated from lymphoma or wild-type T-cells are shown below).



f) Propose a hypothesis to account for the results shown above.

The Gene X transcripts from lymphoma or wild-type T-cells were translated using an *in vitro* system. The resulting polypeptides were assayed for tyrosine kinase activity (see results below).

	<u>Transcripts from lymphoma cells</u>	<u>Wild-type transcripts</u>
<u>Activity Level</u>	+++	-

g) Based on the above results, propose a mechanism to account for development of the cancer phenotype.