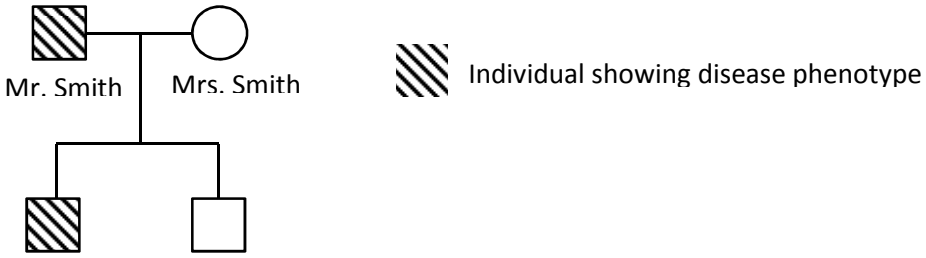
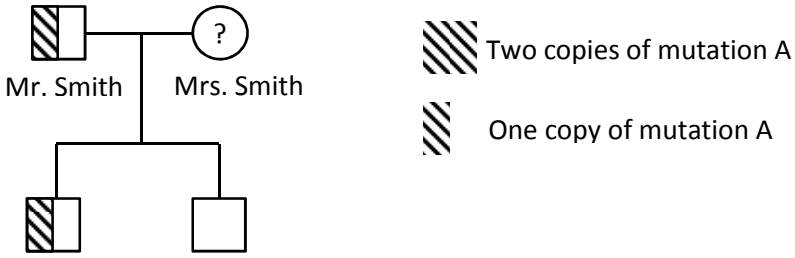
Bi188 2013 Homework 2
Due date: May 10th at 2:45 pm

Q1: Heredity and Disease

You are trying to characterize the hereditary mechanisms of a rare disease. You start your investigation with the family shown below.

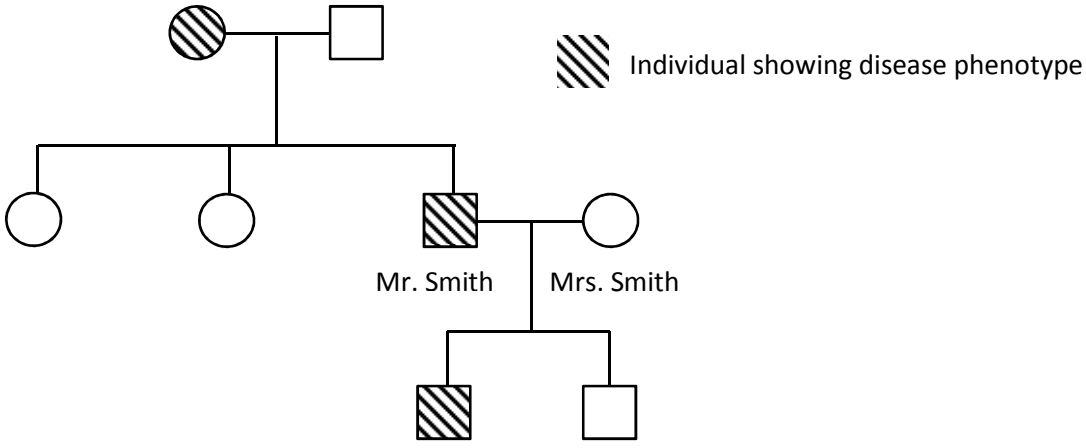


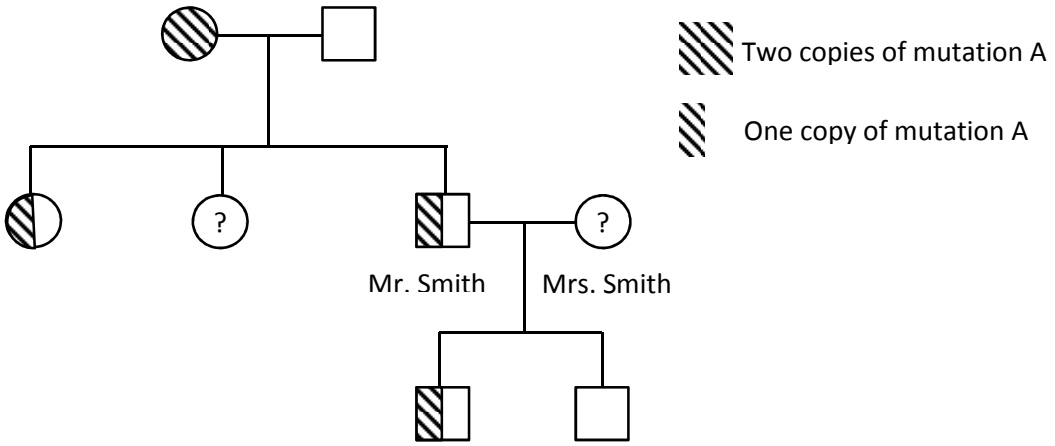
You suspect the disease is linked to a certain mutation A, so you attempt to genotype the family for A. Mrs. Smith, however, refused the test, so you now have the following genotypes:



1a) Propose a hereditary mechanism of the disease through mutation A linkage that fits the available information. Under your proposed mechanism, what will be the genotype of Mrs. Smith?

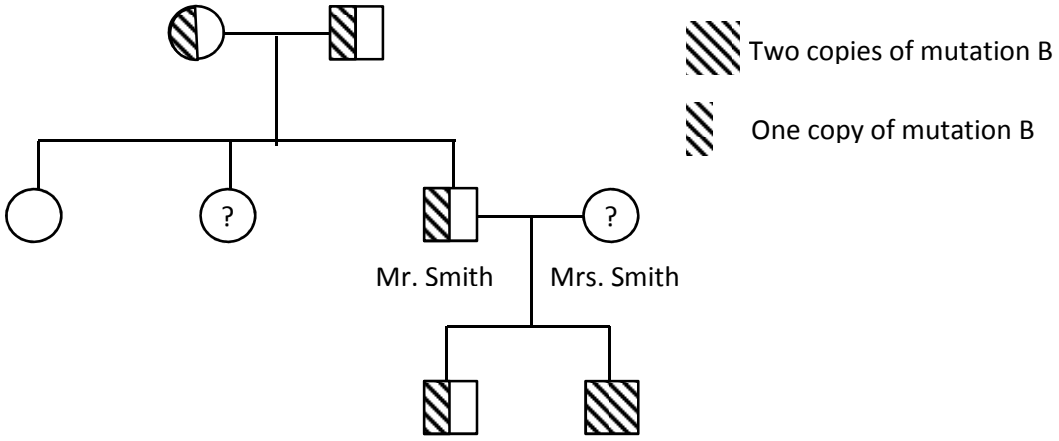
Eager to verify your hypothesis, you expanded the genotyping of mutation A to the parents and siblings of Mr. Smith. The phenotype and genotype results are as follows:





1b) Does your proposed mechanism still fit the new information? Why?

You suspect that another mutation B might also play a role in the disease. You genotyped the Smiths again for mutation B.



1c) Given the new information on genotypes of mutation B, propose a new hereditary mechanism consistent with everything you know so far. What are the possible genotypes (both A and B) for the untested individuals under your model?

Question 2: Mutations and Cancer

A) You are an investigator with a collection of 100 primary ovarian tumors, normal ovarian tissue taken at the time of surgery, plus blood samples from each patient. One ovarian tumor sample shows a rate of somatic mutation that is two orders of magnitude higher than any of the rest. What is a plausible explanation?

B) Genes acting as oncogenes can be activated by multiple mechanisms including point mutations, as is the case for the RAS oncogenes. What kind of additional events can also lead to oncogene activation (give two)?

C) BRCA1 and 2 were originally discovered by studying families with a high incidence of breast cancer that appeared to be inherited. A major confounding problem was that the rate of non-inherited sporadic breast cancer is very high. This confounds classical genetic mapping strategies. What additional criteria can be imposed to help focus on inherited alleles as was done in this case, and as might be done in others with a similar confound from sporadic cases? In contemporary times, on a budget that does not permit you to do entire genome sequencing, how could you identify these breast cancer tumor suppressor genes, if they were still unknown? Answer each question in two to three sentences.

Question 3: Genomics Approaches to Identify Mutations

The case: a child with lymphoma comes into your or your collaborator's clinic. This child has two full-blooded siblings from their biological parents. The child's mother says that several of her close family members (maternal relatives of the lymphoma patient) have died from different types of cancer, but that no one particular type of cancer runs in the family. Assume that you are able to obtain any tissue sample from the child or her immediate family members and that you have the money and resources to do sequencing (including RNA-Seq, ChIP-Seq, etc.) on many samples.

(1) The most immediate problem to solve is finding the cause of the child's lymphoma so her doctors can give her the best treatment. How would you do this? Include in your answer how you would collect the cell samples, what cells you would compare them to, what type of sequencing you would do, how you would detect mutations, and how you would know if a found mutation was causing changes in the cell (versus being silent).

(2) Whenever there is a family history of cancer or a case of very early-onset cancer, it is a possibility that the family in question has a causative heritable mutation. If this is the case for this child, the rest of her family might also be more susceptible to cancer. How would you determine if your lymphoma patient has an inherited mutation that made her more susceptible to her lymphoma? How will you determine who else in her family has the mutation? You may give a brief answer to this part. Three to four sentences should suffice.