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

Harvard-MIT Division of Health Sciences and Technology
HST.161: Molecular Biology and Genetics in Modern Medicine, Fall 2007
Course Directors: Prof. Anne Giersch, Prof. David Housman

## Problem #1

 The incidence of cystic fibrosis is 1 in 1600 live births in Denmark, 1 in 3600 live births in Bulgaria and 1 in 10,000 live births in Hong Kong.
a. Calculate the allele frequency for normal and cf alleles in each population.

b. What is the risk of having a child with cf of a couple in which the wife is from Denmark and the husband is from Hong Kong assuming no previous family history of cf for either parent.

c. A woman from Bulgaria marries a man from Denmark who has a sister with cystic fibrosis. What is this couple's risk of having a child with cf?

d. A cystic fibrosis test has been developed which identifies the 32 most frequent mutant cf alleles in the Danish population. The allele frequency of these alleles sum to 92% of the mutant cf alleles present in the Danish population. When the same test is applied to the Bulgarian population the alleles it identifies sum to 78% of  the mutant alleles in the Bulgarian population. Three couples, a Danish couple, a Bulgarian couple and a couple in which the wife is from Bulgaria and the husband is from Denmark are considering taking this test. How much will the risk for each couple change of having a cystic fibrosis child if each member of the couple has a negative test outcome.

# Problem #2

The DNA sequences present in several copies on the X chromosome responsible for the most frequent genetic cause of hemophilia A are located between 250 and 300 kbp upstream from the start of transcription of the factor VIII gene and in intron 22. A diagram of the location these sequences (labeled Int 22h-1, Int 22h-2 and Int 22h-3) and their orientation relative to each other is shown below.



Factor VIII gene

26    22  1    ~0.3 Mb    >‹~0.1 Mb›  Xqter

To centromere    Int22h-1      Int22h-2      Int22h-3
                 (intragenic)  (proximal)    (distal)

Recombination between either of these sequences and a copy of the repeat sequence located in intron 22 of the factor VIII gene results in an inversion which inactivates the factor VIII gene.

Draw the possible outcome of crossover events between one of the repeat sequences located between 250 and 300 kbp upstream from the start of transcription of the factor VIII gene and the intron 22 copy of the repeat sequence. What transcription product would be produced by the gene produced as a product of this recombination event? Why would this outcome be expected to cause severe hemophilia A?

What would be the outcome of PCR for each of the exons of the factor VIII gene from patients with severe hemophilia A as a consequence of a crossover event involving the repeat sequences?

Explain how Southern blotting with a cDNA probe for factor VIII could reveal the presence of a crossing over event which causes the loss of function of the factor VIII gene.

Explain how a PCR assay to detect the inactivation of the factor VIII gene as a consequence of such an event.

What would be the possible genetic consequences if the sequence Int 22h-2 and Int 22h-3 were present in the same position upstream of the factor VIII gene but in the opposite orientation, while the copy in intron 22 of the repeat sequence was not changed in orientation.

(Use diagrams to explain your answers to these questions when appropriate.)

# Problem # 3

The population of the Lake Woebegone area of Minnesota is concentrated in five cities surrounding the Lake each of 10,000 people. The five cities have different origins and behavior patterns of their inhabitants. Svenska, at the east end of the Lake, was originally populated by a group of 100 people who migrated from Sweden in 1855, Ariga, at the west end of the Lake was originally populated by 100 people who migrated from Japan in 1857. Polyangeles, at the North end of the Lake was founded in 1892 by a group of 50 people from Svenska and 50 people from Ariga. The population of Polyangeles have intermarried completely, with individuals originally from Ariga and Svenska marrying people from the other city with the same likelihood as individuals from their own city. Marriage in subsequent generations occurred completely independently of the city of origins of a person's parents, grandparents or greatgrandparents. Monoangeles, located at the South end of the Lake was founded in 1905 by a group of 75 people from Svenska and 25 people from Ariga. However, in Monoangeles, people originally from Ariga married only people from Ariga and people from Svenska married only people from Svenska and this pattern of choice of marriage partner continued in all subsequent generations. The fifth city, Cousinia, on the Northwest arm of the lake, was originally founded by two couples from Svenska. The population of this city, chooses its marriage partners as randomly as possible from the population of Cousinia. There is no intermarriage since the founding of each city between the people of that city and any individuals from outside the city. The blood bank in each city has kept records of every individual in the city for ABO blood groups.

The data for each of the five cities is as follows—match each city number with the correct city name explaining your reasoning.

To solve this problem you will need to understand the genetic determination of ABO blood group phenotype. One good source of information on this topic is
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=rbcantigen.chapter.ch05ABO
The article by James Crow entitled "Felix Bernstein and the First Human Marker Locus" (which I have placed on the class website as a pdf file) gives a good explanation of how ABO blood group genetics was first worked out and could help you to understand the genetics of the ABO blood group system you will need to know to solve this problem.

Data from the bloodbanks of the five cities surrounding Lake Woebegone stated as the frequencies of individuals tested at that blood bank with each of the four blood types in the ABO system.

City 1

| | |
|---|---|
| O | 0.42 |
| A | 0.30 |
| B | 0.22 |
| AB | 0.06 |

City 2

| | |
|---|---|
| O | 0.385 |
| A | 0.37 |
| B | 0.17 |
| AB | 0.055 |

City 3

| | |
|---|---|
| O | 0.49 |
| A | 0.15 |
| B | 0.32 |
| AB | 0.04 |

City 4

| | |
|---|---|
| O | 0.39 |
| A | 0.61 |
| B | 0 |
| AB | 0 |

City 5

| | |
|---|---|
| O | 0.36 |
| A | 0.45 |
| B | 0.13 |
| AB | 0.06 |

**Problem # 4**

Single nucleotide polymorphisms have been identified in the second intron of a number of genes including the beta globin gene, the cftr gene, the fgfr2 gene and the factor VIII gene. Each SNP has been genotyped by clinics in New York, San Francisco, Toronto, London, Paris and Rome. The allele frequencies for each SNP were 0.5 for each allele in all of these populations. Four patients are seen in the clinic in New York. A patient with sickle cell anemia is shown to be homozygous for the A allele at the SNP site in the beta globin gene. A second patient, who has cystic fibrosis, is shown to have the deltaF508 allele at the cftr locus and is homozygous for the C allele at the SNP site in intron 2 of the cftr gene. The third patient is the son of a mother with achondroplasia and carries the C allele at the SNP site in intron 2 on the chromosome 4p he has received from his mother. The fourth patient has hemophilia A and is shown to have the inversion involving intron 22 jn  the factor VIII gene referred to in problem 2 above and carries the G allele at the SNP site in intron 2 of the factor VIII gene. A similar series of patents is seen in each of the other five clinics i.e. a patient with sickle cell anemia, a cystic fibrosis patient homozygous deltaF508 mutation, patient who is the son of a mother with achondroplasia and a patient has who hemophilia A and is shown to have the inversion involving intron 22 jn  the factor VIII gene. What are your predictions for the genotype at the relevant SNP site for the patients with each disease in each clinic? Explain your reasoning.

# Problem # 5

a. A father has three daughters who each give birth to a son with Duchenne Muscular Dystrophy. The father does not have DMD himself. Propose an explanation for the occurrence of DMD in this family.

b. Identical twin girls are born. One is diagnosed with DMD, the other is normal. The father is normal, while the mother is shown to be a heterozygous carrier of a deletion of exon 44 of the dystrophin gene. Propose an explanation for these findings.