Recitation Section 16 Answer Key
April 6-7, 2005

Recombination and Pedigrees

A. Chromosomes and Recombination

1. What is the physical basis of the genetic phenomenon of gene recombination?

Recombination of genes occurs because of the physical swapping of pieces of chromosomes during meiosis.

2. Why is the recombination frequency between two genes correlated with the physical distance between the two genes?

Recombination frequency (genetic distance) is determined by the frequency of the recombination events between the two genes in meiosis. The greater the physical distance between the two genes, the more likely are they to recombine during any given meiosis event.

3. Recombination can occur anywhere along the length of the chromosome. However, we have been relying on the fact that genes are inherited as discreet units. How do we reconcile these two things? (Hint: think about what usually is the difference between two alleles of the same gene.)

Recombination of genes occurs because of the physical swapping of pieces of chromosomes during meiosis. The swapping can occur anywhere along the chromosome, including in any part of a gene. However, the differences between alleles are generally as small as a difference of a single base pair (or as large as a deletion of a region of a gene). As a result, the only thing that matters for the purposes of determining the genotype (and phenotype) of the offspring is whether as the result of the recombination event, the site of the difference between alleles moved to the other chromosome or not.

4. Why is the highest possible recombination frequency 50%?

The recombination frequency between two genes is equal to the proportion of offspring in which a recombination event occurred between the two genes during meiosis. The recombination frequency between two genes cannot be greater than 50% because random assortment of genes generates 50% recombination (non-linked genes produce 1:1 parental to non-parental. Thus, the recombination frequency would be non-parental/total → 1/(1+1) = 50%).

B. Pedigrees

In 1901 a physician in London named Archibald Garrod had some new patients with an unusual condition: when their urine came into contact with air it turned black.

1. What is the wild-type phenotype?

Because this is the phenotype everyone has had a lot of experience with, we can unambiguously determine that the wild-type phenotype is urine staying yellow when contacting air.

2. What is the assay?

Expose urine to air and see if it turns black

3. Who are the mutants?

The patients whose urine turns black when contacting air.

Fascinated, Garrod decided to study the disease more.

4. How could he go about determining whether the disease shows dominant, recessive, or codominant inheritance?
   In an ideal experimental world, he would set-up a series of test crosses between affected and unaffected individuals, but because this disease is in humans, he could not. Instead, he analyzed the pedigrees and mode of inheritance of the disease in several large families.

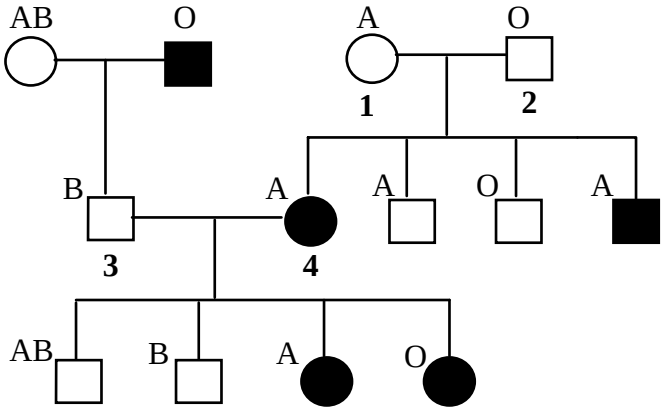
5. What is your prediction for mode of inheritance of this disease? Why?
Because the phenotype is so rare, the disease is likely to be recessive. It is in fact recessive and very rare.

6. The fact that Garrod saw a number of cases was in fact due to high degree of first cousin marriages in the community where he worked. Such consanguineous matings are often very useful in identifying the modes of inheritance of rare traits. Why is that?
People who are related to each other are more likely to have alleles in common. For rare recessive traits, sometimes the best hope of seeing a number of patients who all exhibit the trait is to observe a population or a large family where consanguineous marriages are common. These populations are likely to have the rare allele at a higher frequency, and, therefore, the frequency of affected individuals should also be higher than in a reference population.

7. What, if anything, could he do to study the inheritance pattern experimentally in the lab?
He could look for an animal model for the disease. Given the similarities between mouse and human urination, chances are high that some mice might exhibit this phenotype. Once he found the mice, he could start crossing them and designing gene cloning procedures. This last part is only possible now, not in 1901.

As it turned out, the gene for Alkaptonuria (ALK) is on human chromosome 9 and is linked to the gene encoding the ABO blood group, with a recombination frequency of 11% between the loci.

A pedigree of a family with the disease is shown below, with affected individuals indicated in black. In addition, the blood type of family members is given.



The two alleles at the ALK locus will be denoted ALK^+ and ALK^-.

8. The three alleles at the ABO blood group locus will be denoted I^A, I^B (which are co-dominant) and I^O (which is recessive to I^A and I^B).
   i) What is the genotype of individual 1 at the ALK and ABO loci?
   $\frac{I^O\ ALK+}{I^A\ ALK-}$ *or* $\frac{I^O\ ALK-}{I^A\ ALK+}$

ii) What is the genotype of individual 2 at the ALK and ABO loci?

$\frac{I^O \text{ ALK+}}{I^O \text{ ALK-}}$

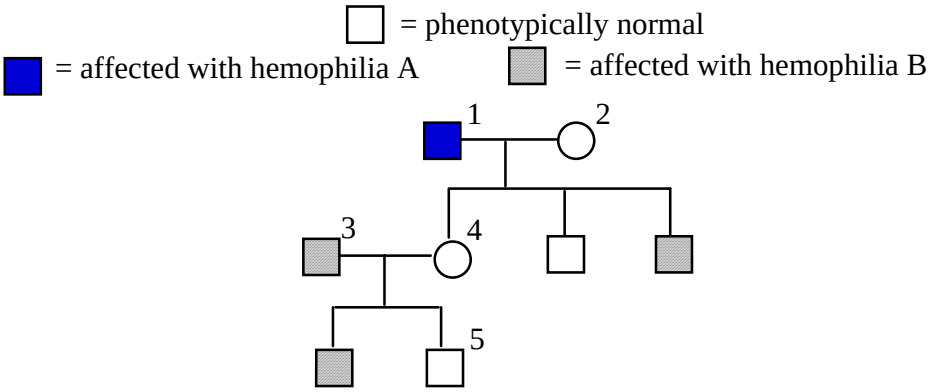
iii) What is the genotype of individual 3 at the ALK and ABO loci? Which alleles of each gene are carried on the chromosome he inherited from his father and which alleles are carried on the chromosome he inherited from his mother?

Individual 3 must have gotten an I^O ALK- chromosome from Dad, since that is the only kind of chromosome Dad has. To be type B, and not express Alkaptonuria, Individual 3 must have gotten an I^B ALK+ chromosome from Mom.

iv) Individuals 3 and 4 are expecting their fifth child. A physician draws a prenatal blood sample and determines that the child has blood type B. Is it likely that the child will have alkaptonuria? Explain your answer.

Individual 4 got an I^A ALK- chromosome from her Mom and an I^O ALK- chromosome from Dad. For the new child to have blood type B, it must have gotten I^O ALK- from its Mom (#4), and the chromosome carrying an I^B allele from its Dad (#3). If no recombination occurred, then the chance of getting I^B ALK+ chromosome from its Dad is 50%. The chance of getting the other chromosome, I^O ALK- is also 50%. However, since the blood type is B, the child couldn't have gotten the I^O allele from its Dad. Also, without recombination, there would be no chance of getting I^B ALK-. This means, that without recombination, the child would have the I^O ALK-/I^B ALK+ genotype, and thus, would not exhibit alkaptonuria. However, since recombination frequency is 11%, there is some chance that this child will have alkaptonuria (i.e. inherit the I^B ALK- from its Dad).

9. Consider the pedigree below showing the inheritance of two X-linked diseases, hemophilia A and hemophilia B . Hemophilia A is due to a lack of one clotting factor, and hemophilia B is due to a lack of a different clotting factor. These two clotting factors are encoded by two different genes, located at different positions on the X chromosome. Note that no individual shown in this pedigree is affected with both hemophilia A and hemophila B.



i) Write the genotypes for the following individuals at both the hemophilia A and hemophilia B disease loci. Clearly define your genotype symbols.

Individual	Genotype
1	$X^{aB}\,Y$
2	$X^{Ab}X^{AB}$
3	$X^{Ab}Y$
4	$X^{Ab}X^{aB}$
5	$X^{AB}Y$

X^{aB} *X chromosome with allele for hemophilia A, recessive phenotype*

X^{AB} *X chromosome with wild-type alleles, dominant phenotype*

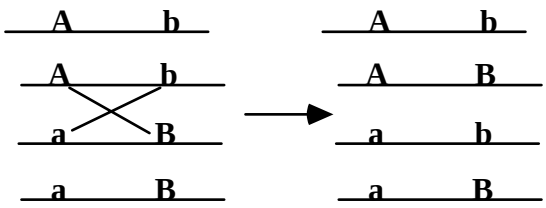
X^{Ab} *X chromosome with allele for hemophilia B, recessive phenotype*

X^{ab} *X chromosome with alleles for hemophilia A and hemophilia B, recessive phenotype*

ii) How do you account for individual 5 not being affected with either hemophilia A or hemophilia B?

During meiosis, there was recombination between the X chromosomes in individual #4. Each line in the drawing below represents a double stranded DNA molecule – 1 sister chromatid. The top two are the sister chromatids from the chromosome individual #4 got from her Mom (#2). Similarly, the two bottom lines represent the sister chromatids individual #4 got from her Dad (#1).

X chromosomes of Individual #4:



A cross-over between the A and B loci resulted in two new recombinant gametes:

A B (X^{AB}) *and* *a b* (X^{ab})

Individual #5 received the X^{AB} *chromosome from his mother (#4) and the Y chromosome from his father (#3), thus he is not affected with either hemophilia A or hemophilia B.*