PEDIGREES AND PROBABILITY

The guidelines given below are designed to help you learn how to interpret pedigrees. Do not memorize these guidelines -- you should be able to generate each rule from the basic genetic principles of Mendelian and sex-linked inheritance. Look at each “rule” carefully. For a pedigree to be consistent with a specific mode of inheritance, which rules must be met? Which rules might apply, but are not absolutely required? Under which circumstances would the latter apply or not apply?

Guidelines for Interpreting Human Pedigrees

- Affected means that the person has the trait or phenotype being analyzed.
- Some rules apply only to rare traits, that is traits that occur infrequently in the population under examination. If a recessive allele is rare, assume that most unaffected individuals will not be carrying (that is, will not be heterozygous for) the allele.
- If a person is affected with a rare dominant trait, assume the person is heterozygous for the allele.
- Interpretation of pedigrees can be complicated by incomplete penetrance, variable expressivity, genetic heterogeneity, among other factors. For the our purposes, we will assume that there are no complicating factors and unless evidence to the contrary is presented.

Autosomal Recessive
1. trait appears in progeny of unaffected parents
2. about 1/4 of a sib group is affected
3. the trait breeds true
4. both sexes are equally affected
5. some degree of inbreeding is present (rare trait)

Autosomal Dominant
1. affected offspring have at least one affected parent
2. trait passed directly from affected individual to affected individual
3. trait is present in each generation
4. about 1/2 of the progeny of an affected individual exhibit the trait (rare trait)
5. two affected individuals may have an unaffected child (that is, the trait may not breed true)
6. both sexes are equally affected

X-linked Recessive
1. all daughters of affected males are carriers; all sons of affected females are affected
2. the phenotype is not transmitted from father to son but rather from father to grandson
3. phenotypic expression is higher in males than in females
4. affected female will have an affected father

X-linked Dominant
1. affected males produce all affected daughters and no affected sons
2. a heterozygous female will transmit the trait to about 1/2 of her sons and 1/2 of her daughters
Problem 1

a. A couple has two children of the same sex (the condition). What is the probability that both are boys (the event)?
b. You have a large jar containing thousands of marbles. Half are green and half are red. You draw two marbles at random from the jar. At least one of the marbles is red. What is the probability that the other marble is red? In other words, given that at least one marble is red (the condition) what is the probability that both are red (the event).

What is the relevance of this question to genetics?

Problem 2

Here is an interesting probability question relating to Mendel's work. During this century, close examination of Mendel's paper has led to the suggestion that Mendel failed to report crosses involving traits not showing independent assortment. This arises from the observations that all seven traits that Mendel studied do show independent assortment and that the pea plant has seven pairs of chromosomes.

Calculate the probability that by chance Mendel chose seven traits, each one located on a different chromosome, given that there are 7 pairs of chromosomes in the pea plant? Make the simplifying assumption that the seven chromosomes in the pea plant are of equal size and have about the same number of genes. Before trying to answer this question, work the following problem:

You have six dice. If all six dice are rolled, what is the probability that there will be a different number on each die (or, in other words, each of the six dice has a different number showing)?
Problem 3
a. Does a study of pedigrees always permit a person to determine whether an allele is dominant or recessive?
b. Why is it much easier to analyse human pedigrees for autosomal dominant traits than for autosomal recessive ones?
c. Why are parents of individuals homozygous for rare recessive alleles likely to be related?
d. Briefly discuss the conditions under which a recessive trait may appear to be inherited as a dominant one and vice versa and the precautions necessary in drawing conclusions from pedigree analysis.
e. As mentioned above, interpretation of pedigrees can be complicated by incomplete penetrance, variable expressivity, genetic heterogeneity, as well as other factors. Define each of these terms and give a specific example of how it would complicate the interpretation of pedigree data.

Problem 4
Individuals with Gorlin syndrome develop tumors at a very high frequency and show other developmental malformations. The trait shows 100% penetrance. Two individuals affected with Gorlin syndrome (but who are otherwise normal) marry and their first child is normal. This unfortunate couple then has a second child who does not have Gorlin syndrome but does have phenylketonuria (PKU), a disease state that results from a defect in phenylalanine metabolism. The genes for these two traits are on two different autosomal chromosomes. They decide to have a third child. What is the probability that this child will be normal?

Problem 5
Tay Sachs disease (TSD) is an inborn error of metabolism that results in death by the age of 2. You are a genetic counselor and one day you interview a phenotypically normal couple who consult you because the man had a female first cousin (on his fathers side) who died from TSD and the woman had a maternal uncle with TSD. There are no other known cases in either of the the families and none of the mating were/are between related individuals. Assume that this trait is rare in this population.
a. Using standard pedigree symbols, draw pedigree of this couple’s families showing the relevant individuals.
b. This couple wants to know what the probability is that they both are heterozygous for the PKU allele.
c. They also want to know what the probability is that neither is heterozygous.
d. Finally they ask the probability that one of them is heterozygous but the other is not. (Hint: the answers to b, c and d should add up to 1)
Problem 6

Consider the pedigree shown above which illustrates the inheritance of a very rare disease state:

(i) What is the mode of inheritance of this disease state? (Assume that the trait shows complete penetrance.)
   a. autosomal dominant
   b. autosomal recessive
   c. probably autosomal recessive, but could be sex-linked recessive
   d. sex-linked recessive
   e. probably sex-linked recessive, but could be autosomal recessive

(ii) Individuals IV6 and IV7 plan to marry. What is the probability that IV7 is heterozygous for the disease allele?
   a. 1    b. 1/2    c. 1/8    d. 1/3    e. 1/6

(iii) What is the probability that both IV6 and IV7 are heterozygous and that their first child will have the disease?
   a. 1/9    b. 1/36    c. 1/64    d. 3/4    e. 1/48

(iv) What is the probability that both IV6 and IV7 are homozygous for the normal allele of this gene?
   a. 1/9    b. 7/16    c. 5/18    d. 7/24    e. none of these answers
**Problem 7**

Individual V-3 from the pedigree below plans to marry his first cousin, individual V-4. The sister of the prospective groom suffers from a very rare genetic disease. The prospective groom's father is unhappy with the match. He argues that his son should pick a mate who is not in any way related to the family. The father and son go to a genetic counselor and ask the following questions:

a. What is the mode of inheritance of this disease state?

b. Given this pedigree, what is the probability that the prospective bride (V-4) is a carrier of the progeria allele?

c. Read about the Hardy Weinberg Law in Chapter 21. If the frequency of this disease is 1/10,000 (one affected individual in every 10,000), what is the probability that the son will marry a carrier if he picks a mate at random from the population?

Generation

I

II

III

IV

V

prospective groom

prospective bride

**Problem 8**

If a man of blood group AB marries a woman of blood group A whose father was of blood group O, what different blood groups can this man and woman expect their children to belong to?
Problem 9

The following pedigree was taken from a recent publication on the genetics of familial male precocious puberty. Individuals with this syndrome generally show signs of puberty by age 4.

Choose the best conclusion from the choices below:

a. The gene for this trait must be located on the Y chromosome.
b. This trait probably is sex-linked recessive, with the mothers of affected males being carriers.
c. This trait is likely to be autosomal dominant with the sex ratio skewing due to chance.
d. This is an autosomal dominant trait showing sex-limited inheritance.

Problem 10

In a maternity ward, four babies become accidentally mixed up. The ABO types of the four babies are known to be O, A, B, and AB. The ABO types of the four sets of parents are determined. Indicate which baby belongs to each set of parents:

a. AB X O  
b. A X O  
c. A X AB  
d. O X O
Problem 11
One day a man comes into the office of a genetic counselor. He is suffering from a very rare genetic disease. The genetic counselor puts together the following pedigree of the man's family. The genetic counselor then tells the man that he cannot pass the trait onto his sons, but that, even if he marries a normal woman, all of his daughters are out of luck: they will all have the genetic disease.

i) What mode of inheritance did the genetic counselor imply with his advice to the man?
   a. X-linked recessive    b. autosomal recessive    c. X-linked dominant
   d. autosomal dominant    e. Y-linked

ii) Do you agree with the conclusions of the counselor and the advice that he gave?
   a. Yes, since the trait is very rare, recessive inheritance is eliminated and the counselor's advice is sound.
   b. No. Recessive inheritance is still a likely possibility and the man should have been informed of that.
   c. No. Autosomal dominant inheritance is clearly indicated. In that case, if the man marries a phenotypically normal woman, there is a 50:50 chance that any child would be affected.
   d. Yes and no. The counselor has good reason to suspect X-linked dominant inheritance, but he should have also considered another mode of inheritance as a possibility.
   e. Yes and no. The counselor was correct in his conclusion about the mode of inheritance, but incorrect in his predictions about the possible progeny of the man.

Problem 12
What pattern(s) of inheritance can be ruled out for the following pedigrees? What is the most likely mode of inheritance in each case assuming that the trait is very rare?
Problem 13
Two phenotypically normal Californians marry and produce a son affected with a rare genetic disease. Influence by the litigious society in which they live, the mother of the children sues the father claiming that he has passed "bad genes" on to their son. As a geneticist you are asked to testify in court as an expert witness about the validity of her claim.

a. From the pedigree below (which is of an unrelated family), what is the mode of inheritance of this disease state?
b. How do you testify in court?
**Problem 14**
Suppose that a husband and wife are both heterozygous for an autosomal recessive allele for albinism. If they have two children, what is the probability that both of the children will have the same phenotype with respect to pigmentation?

**Problem 15**
Huntington's chorea is a rare, fatal disease that usually develops in middle age. It is caused by an autosomal dominant allele. A phenotypically normal man in his early twenties learns that his father has developed Huntington's chorea.

a. What is the probability that he himself will develop the symptoms later on?
b. What is the probability that his son will develop the symptoms in later life?

**Problem 16**
Two first cousins (whose fathers were brothers) are planning to marry and raise a family. A common uncle (brother to their fathers) died in childhood of amaurotic idiocy. This is the only occurrence of the disease in this family. The cousins wish to have an estimate of the chance that the first child they produce will be affected with the disease, so that they can decide whether to have their own child or to adopt.

a. Draw a pedigree of this family.
b. Assuming that this is a very rare autosomal recessive disease state (showing 100% penetrance), determine the probability that their first child will have the disease.
c. Answer the question in b assuming that the mode of inheritance is X-linked recessive.
d. They marry and the four children that they produce are affected females. What is the probability that their fifth child will be affected?
Problem 17
You are a genetic counselor and one afternoon, you interview a couple who are planning to marry and have a family. Both individuals have a family history of a syndrome resulting from growth hormone deficiency. Such a deficiency results in midgets who have normal body proportions but are small due to the hormone deficiency. You question them about their family history and they tell you the following:

The prospective groom has a maternal aunt with this condition. His paternal and maternal grandparents, his parents, and all other aunts and uncle are normal. His prospective bride has a male cousin (son of her father's sister) with this condition, but all other members of her family (grandparents, parents, aunts and uncles) are normal. Neither individual has any siblings.

a. Draw a pedigree of the two families. Include the three generations mentioned and the relevant aunts, uncles and cousin.
b. What is the mode of inheritance of this disease?
c. They ask the following question: If our first two children are normal, does that mean that there is a good chance that we are not both heterozygous? How would you answer this question? Try to frame your answer in terms of an illustrative probability calculation. Think about a simple, useful calculation that would help them to understand the answer to their question.

Problem 18
A man is brachydactylous (very short fingers, rare Mendelian dominant), and his wife is not. Both can taste the chemical phenylthiocarbamide (Mendelian dominant, polymorphic), but both their mothers could not.

a. Give the genotypes of the couple.

If they have eight children, what is the probability of:
b. All being brachydactylous
c. None being brachydactylous
d. All being tasters
e. All being nontasters
f. All being brachydactylous tasters
g. None being brachydactylous tasters
h. At least one being a brachydactylous taster
i. The first child being a brachydactylous nontaster
j. The first two children being brachydactylous
Problem 19
In the following pedigree, a black dot represents the occurrence of an extra finger and a black square represents the occurrence of an eye disease.

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a. What can you tell about the inheritance of an extra finger?
b. What can you tell about the inheritance of the eye disease?
c. What were the genotypes of the original parents?
d. What is the probability that a child of individual 4 will have an extra finger? Will have the eye disease?
e. What is the probability that a child of individual 12 will have an extra finger? Will have the eye disease?

Problem 20
As a genetic counselor, you routinely advise individuals or couples about the inheritance of genetic disorders and, given their family histories, about the possible risks of genetic disease in their offspring. On a typical day you meet with an engaged couple (both phenotypically normal) with the following family histories. The man has a brother who died of Duchenne-type muscular dystrophy (an X-linked recessive fatal condition that results in death before the age of 20). His prospective bride, whose family has no history of this disease, is concerned that their sons will be afflicted with the condition. How do you advise them?

The sister of this man (from above) is planning to marry the brother of the woman (from above). How would advise this couple. What are their chances of having an affected offspring?
Problem 21
Alkaptonuria is a simply inherited autosomal recessive trait. A *normal* couple have an *affected* child. Find the probability that:

a. The next two children will have alkaptonuria.
b. Of the next 4 children, 1 will have alkaptonuria
c. The father of the affected child is heterozygous for the recessive allele.
d. The paternal grandmother is heterozygous for the recessive allele.
e. The next child will be a heterozygote.
f. A child of a normal sister of the affected child will be heterozygous.
g. Any sibling of the affected child will be affected.
h. There will be no affected individuals among the next 3 siblings of the affected child.