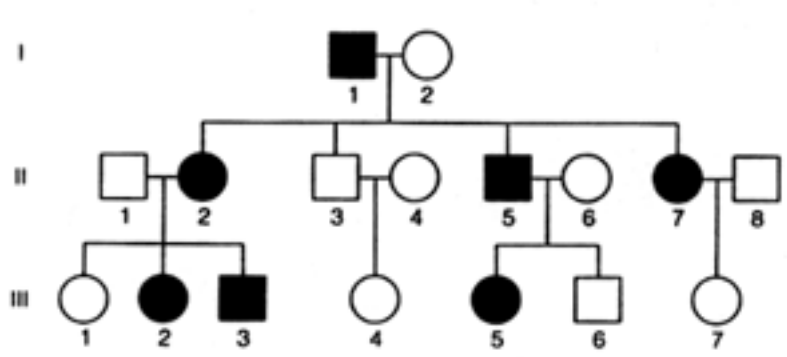
Pedigree Analysis

Basic principles
If more than one individual in a family is afflicted with a disease, it is a clue that the disease may be inherited. A doctor needs to look at the family history to determine whether the disease is indeed inherited and, if it is, to establish the mode of inheritance. This information can then be used to predict recurrence risk in future generations.

A basic method for determining the pattern of inheritance of any trait (which may be a physical attribute like eye color or a serious disease like Marfan syndrome) is to look at its occurrence in several individuals within a family, spanning as many generations as possible. For a disease trait, a doctor has to examine existing family members to determine who is affected and who is not. The same information may be difficult to obtain about more distant relatives, and is often incomplete.

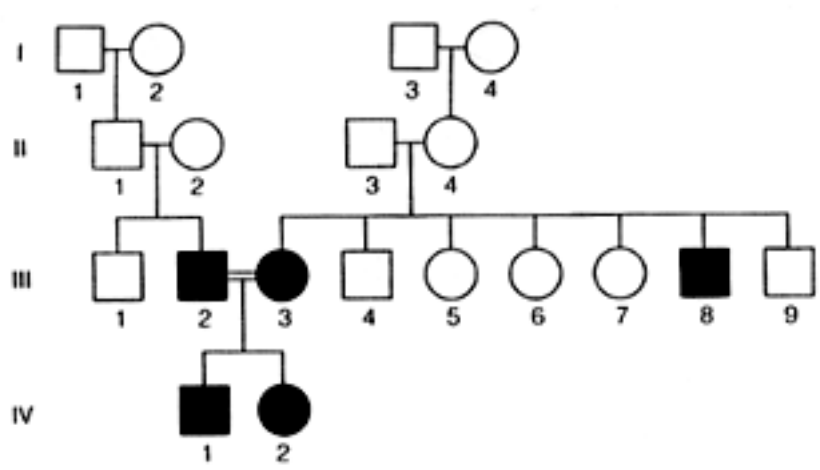
Once family history is determined, the doctor will draw up the information in the form of a special chart or family tree that uses a particular set of standardized symbols. This is referred to as a pedigree. In a pedigree, males are represented by squares □ and females by circles ○. An individual who exhibits the trait in question, for example, someone who suffers from Marfan syndrome, is represented by a filled symbol ■ or ●. A horizontal line between two symbols represents a mating □—○. The offspring are connected to each other by a horizontal line above the symbols and to the parents by vertical lines. Roman numerals (I, II, III, etc.) symbolize generations. Arabic numerals (1,2,3, etc.) symbolize birth order within each generation. In this way, any individual within the pedigree can be identified by the combination of two numbers (i.e., individual II3).

Dominant and recessive traits
Using genetic principles, the information presented in a pedigree can be analyzed to determine whether a given physical trait is inherited or not and what the pattern of inheritance is. In simple terms, traits can be either dominant or recessive. A dominant trait is passed on to a son or daughter from only one parent. Characteristics of a dominant pedigree are: 1) Every affected individual has at least one affected parent; 2) Affected individuals who mate with unaffected individuals have a 50% chance of transmitting the trait to each child; and 3) Two affected individuals may have unaffected children.



Recessive traits are passed on to children from both parents, although the parents may seem perfectly "normal." Characteristics of recessive pedigrees are: 1) An individual who is affected may have parents who are not affected; 2) All the children of two affected individuals are affected; and 3)

In pedigrees involving rare traits, the unaffected parents of an affected individual may be related to each other.



The reason for the two distinct patterns of inheritance has to do with the genes that predispose an individual to a given disease. Genes exist in different forms known as alleles, usually distinguished one from the other by the traits they specify. Individuals carrying identical alleles of a given gene are said to be homozygous for the gene in question. Similarly, when two different alleles are present in a gene pair, the individual is said to be heterozygous. Dominant traits are expressed in the heterozygous condition (in other words, you only need to inherit one disease-causing allele from one parent to have the disease). Recessive traits are only expressed in the homozygous condition (in other words, you need to inherit the same disease-causing allele from both parents to have the disease).

Penetrance and expressivity

Penetrance is the probability that a disease will appear in an individual when a disease-allele is present. For example, if all the individuals who have the disease-causing allele for a dominant disorder have the disease, the allele is said to have 100% penetrance. If only a quarter of individuals carrying the disease-causing allele show symptoms of the disease, the penetrance is 25%. Expressivity, on the other hand, refers to the range of symptoms that are possible for a given disease. For example, an inherited disease like Marfan syndrome can have either severe or mild symptoms, making it difficult to diagnose.

Non-inherited traits

Not all diseases that occur in families are inherited. Other factors that can cause diseases to cluster within a family are viral infections or exposure to disease-causing agents (for example, asbestos). The first clue that a disease is not inherited is that it does not show a pattern of inheritance that is consistent with genetic principles (in other words, it does not look anything like a dominant or recessive pedigree).

Pretest

Fifteen molecular genetic questions from very easy to insanely difficult. If you know the answer to the final question, please go snorkeling Wednesday afternoon and skip this part of the meeting. The answers to the questions are given at the end.
Success!
BJK

Question 1.
The organized structure of DNA is found in the nucleus of the cell. Different organisms have different numbers of these structures. Humans have 23 pairs of these.
a. genome
b. codon
c. chromosome
d. gene

Question 2.
This is a group of three bases on a tRNA molecule that are complimentary to an mRNA codon.
a. peptide
b. anticodon
c. codon
d. amino acid

Question 3.
Which of the following DNA base sequences is complementary to this base sequence: ACGGATTAG
a. TGCCTAATC
b. GATTGCCGT
c. UGCCUAAUC
d. GAUUGCCGT

Question 4.
Which of the following does NOT occur in DNA replication? The original double helix
a. unwinds
b. bonds between base pairs are broken
c. the unpaired strands split into codons
d. all occur

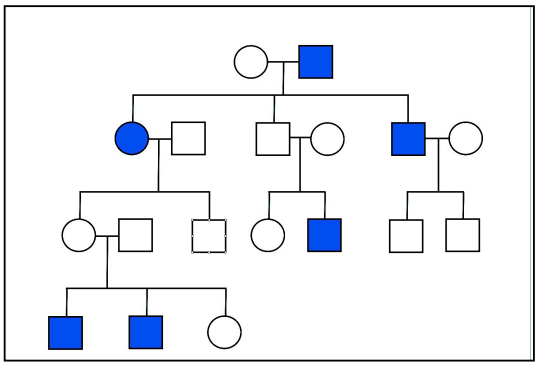
Question 5.
Thirty percent of the bases in DNA extracted from a prokaryotic cell is adenine. What percentage of cytosine is present in this DNA?
a. 10
b. 20
c. 30
d. 40

Question 6.
All cells of a species (except for the sex cells) contain the same amount of DNA. However, the cells of multicellular organisms vary in both structure and function from one tissue type to another. This specialization is evidence that most of the DNA in a cell is
a. inactive
b. removed as the cell matures
c. converted into protein
d. converted into glycoprotein

Question 7.
Refers to a close association of genes or other DNA sequences on the same chromosome. The closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together.
a. linkage
b. crossing over
c. meiosis
d. base pair

Question 8.
A blue-eyed man marries a brown-eyed woman. They have one child, who is blue eyed. What are the genotypes of all the individuals mentioned?
Child . . .
Father . . .
Mother . . .

Question 9.
In what fashion is the disorder in this pedigree inherited?
a. X-linked dominant
b. X-linked recessive
c. Autosomal dominant
d. Autosomal recessive



Question 10.
Approximately what percentage of all pregnancies result in the birth of a child with a significant genetic disease or birth defect that can cause crippling, mental retardation, or early death?
a. 0.01%
b. 0.1%
c. 3%
d. 8%

Question 11.

When a pseudodominant pattern is recognized in a pedigree, this might indicate:

a. incomplete penetrance
b. absence of consanguinity in the family
c. a high carrier frequency
d. a digenic disorder

Question 12.

The difference between a polymorphism and a mutation. Which of the statements is <u>true</u>?

a. a polymorphism in a gene never results in a change in the amino acid sequence of a protein
b. a mutation in a gene always results in a change in amino acid sequence of the protein
c. a mutation occurs in less than 1% of individuals in a population
d. a polymorphism occurs in less than 1% of individuals in a population

Question 13.

Red-green color blindness is X-linked in humans. If a male is red-green color blind, and both parents have normal color vision, which of the male's grandparents is most likely to be red-green color blind?

a maternal grandmother
b maternal grandfather
c. paternal grandmother
d paternal grandfather
e either grandfather is equally likely

Question 14.

If 1 out of every 250,000 people have Disease X, a nonlethal autosomal recessive disorder, what is the approximate carrier frequency of this disease? (Assume Hardy-Weinberg equilibrium).

a. 1/1000
b. 1/500
c. 1/250
d. 1/50
e. 1/25

Question 15.

The heterozygote carrier frequency (2pq) for an X-linked recessive disease with a disease frequency of 1/10,000 is greater than the heterozygote carrier frequency for an autosomal recessive disease with a disease frequency of 1/1,000,000.

a. True
b. False