PATTERNS OF INHERITANCE: AUTOSOMAL RECESSIVE DISEASE

Date: August 16, 2005 *
Time: 8:00 am- 8:50 am *
Room: G-202 Biomolecular Building
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Office Hours: by appointment

*Please consult the online schedule for this course for the definitive date and time for this lecture.

The syllabus is meant to accompany the lectures and the material covered (other than that in italics) is considered important to your understanding of the subject.

Lecture Objective
This lecture will describe why the recognition of patterns of inheritance can be important in clinical medicine. You will learn about the general features of an autosomal recessive pattern of inheritance and discuss the mechanisms which typically underlie such inheritance. In addition you will be introduced to simple risk calculation, the concept of founder effect, Hardy Weinberg Equilibrium and how it can be useful in the clinical setting.
Why understand patterns of inheritance?

The recognition that human diseases can at times show familial patterns in their occurrence has been important in our understanding of fundamental mechanisms related to disease causation.

When you approach a patient in the clinical arena, your first task is to arrive at an accurate diagnosis, since it is only by doing this that you can embark on the proper course of therapy. The correct diagnosis is not always obvious; you will need to use all of the clues at your disposal. The recognition that a disease is genetic may be a significant clue to achieving this end and thereby successfully intervening in your patient's disease.

By taking a family history you may, for example discover that your patient’s condition is not unique to them but is shared by other family members. The recognition of such familial clustering can make the diagnosis tremendously more obvious and quickly lead you to the appropriate treatment. Not incidentally comes the accompanying ability in these instances to make the diagnosis in other family members and thus intervene in a beneficial way with their disease process as well.

Thus, it is useful for you to be able to quickly recognize specific patterns of human inheritance and disease.
Autosomal Recessive Disease

Autosomal Recessive diseases or traits are caused by alterations in genes that are located on the autosomes, and like dominant diseases, typically affect both males and females in equal proportions.

The important difference between recessive and dominant disease is that the disease allele in the recessive setting is recessive to the wild type allele and thus heterozygotes do not manifest abnormalities. Rather, one requires a mutation in both copies of a particular gene to manifest a recessive disease.

In the pedigree depicted in Figure 5 one sees the typical characteristics of an autosomal recessive disorder.
The clinical characteristics of autosomal recessive inheritance include the following:

1. The trait or diseases is typically confined to a single sibship. Thus autosomal recessive pedigrees appear to be "horizontal" rather than "vertical".
2. Both males and females are typically equally affected.
3. One sees an increased rate of consanguinity in parents of children with recessive disorders, due to the phenomenon of "identity by descent". Although seen in AR disorders at an elevated rate, it is not obligatory in AR pedigrees.

An important feature particularly in Autosomal Recessive Diseases is that of ethnic background.

**Founder Mutations:**
In any population that has been through a “population bottleneck”, or has been reproductively isolated (because of either social or geographical mechanisms) certain diseases are found at much higher rate than in other populations. A few examples include Ashkenazi Jews, those of Finish ancestry and French Canadians. This phenomenon is due to the “founder effect”.

**Mechanisms of AR inheritance:**
The mechanism of disease in autosomal recessive conditions is typically much simpler than that in dominant inheritance. Most mutations simply result in an inactive protein and when both alleles are mutated, little or no active protein is produced and a phenotype is manifest.

**Risk Calculation in Autosomal Diseases**
In autosomal dominant diseases the risk that a child will inherit the mutant gene from an affected parent is simply 50%. This is because the affected parent has two alleles and there is a 50/50 chance that he or she will transmit the mutation to any offspring.

In autosomal recessive disease, for an individual to be affected both parents must carry one mutant allele and each must transmit that mutant allele to the offspring. Thus the risk for two heterozygote parents having an affected offspring is 1/4. A corollary of this is that the risk for a phenotypically normal offspring of two heterozygote parents for being a carrier of a highly penetrant recessive disease is 2/3. In order to envision this, a Punnet square is useful to analyze as depicted:
Risk Calculation in AR Disease

The risk of two heterozygote parents having an affected offspring is 1/4

The chance that a phenotypically normal offspring is a carrier is 2/3

Figure 6
The Hardy Weinberg Equation

The Hardy Weinberg equation simply describes, in mathematical terms, the distribution of alleles of a gene within a population. There are several assumptions that must be met for the HW equation to apply (you will hear more about this from Dr. Threadgill), but typically the equation does describe the situation very well for disease genes in human populations.

The equation is:

\[ p^2 + q^2 + 2pq = 1 \]

Where \( p \) = the frequency of an allele in the population and \( q \) = the frequency of the alternate allele in that population.

Think about it. We are diploid, receiving one allele from mom and one from dad in every case for autosomal genes.

Thus, the chance that we will receive two “\( p \)” alleles is simply \( p \times p \), or \( p^2 \).

Likewise, the chance that we will receive a \( q \) allele from both mom and dad is \( q \times q \), or \( q^2 \).

The chance that we will receive a \( p \) from mom and a \( q \) from dad is \( p \times q \) and the chance we’ll receive a \( p \) from dad and a \( q \) from mom is \( p \times q \), so the overall chance of having a \( p \) and a \( q \) is \( 2 \times p \times q \), or \( 2pq \).

Since these are the only three possibilities for a gene with only two alleles, they must add up to one.

Use of the HWE in a clinical situation to calculate risk

Say a Caucasian woman who is a patient of yours has an autosomal recessive disease like cystic fibrosis (CF; a severe disease of the lungs and digestive tract) for which the Caucasian population incidence is 1/400.

She has married a man from the same population and they are concerned about the possibility of having a child with cystic fibrosis. They ask you what the likelihood is that the child she is pregnant with has this disease. Since she has CF and thus has two mutant alleles, you know that she must have transmitted a mutant allele to her fetus. What you need now to figure out is the chance that her husband also transmitted a mutant allele to the fetus. Thus, you need to know what the chance is that he is a carrier for CF.

Here is how you use the HWE to calculate their risk:
The population incidence among newborns for this disease is 1/400. You know that anyone who has the disease must have inherited two mutant alleles and we can designate them as \( q^2 \) (the chance of having received the mutant allele, \( q \), from both mom and dad).

Thus it is easy to calculate \( q \) (just take the square root of \( q^2 \))

So now we know that in this population, the frequency of the mutant allele, \( q \), is 1/20 (the square root of 1/400)

Since there are only two alleles for this gene in the population, \( p + q \) must add up to 1, so \( p = 1 – q \). This is 0.95 which is pretty close to 1.

*If you are a real stickler you can do the calculation using \( p = 0.95 \), but typically for ease of calculation in such a situation we consider \( p \) to be equal to 1.*

So, now we know our values for \( p \) and for \( q \) (that is, the frequency of these two alleles in the population) and can calculate \( 2pq \), or the carrier frequency in the population.

\[
2pq = 2 \times 1 \times \frac{1}{20} = 1/10.
\]

Thus, the chance that your patient’s husband is a carrier for this autosomal recessive disease is 1/10.

To calculate the fetus’ risk of having inherited two mutant alleles and thus having cystic fibrosis, simply multiply the chance that the mom carries a mutant allele (1) times the chance that she will transmit a mutant allele (1), times the father’s risk of being a carrier (1/10) times the chance of him passing on the mutant allele (1/2)

**Chance of a child of this couple being affected by CF:**

\[
1 \times 1 \times \frac{1}{10} \times \frac{1}{2} = 1/20
\]

Think about why it is critical to know what population someone comes from and what population your frequency of disease data was derived in. For example, how would the calculation change if she had married a Japanese man, if you were told that CF is much rarer in the Japanese population and that the newborn frequency of CF in Japan is 1/4,000?