PATTERNS OF INHERITANCE: X-LINKED DISEASE

Date: September 30, 2005 *
Time: 9:35 am- 10:35 am *
Room: G-202 Biomolecular Building
Lecturer: Jim Evans
        4200A Biomolecular Building
        jpevans@med.unc.edu
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
Features of X-linked inheritance will be discussed, including dosage compensation, Lyonization, skewed X-inactivation and their clinical implications for families. Simple risk calculation in X-linked recessive disease will be explored.
A. X-Linked Inheritance

Unlike our autosomes, the two sex chromosomes in humans are wildly different in their physical characteristics. The X-chromosome is large and has many genes while the Y-chromosome is small and has very very few functional genes residing on it. Human males are “heterogametic”, possessing both an X and a Y chromosome, while females are “homogametic”, possessing two X chromosomes.

These differences in sex chromosome structure and distribution have important clinical ramifications for diseases that result from mutations in genes residing on the X-chromosome.

In order to correct for potential problems related to altered gene dosage, the phenomenon of “X inactivation” occurs in the female. During development of the female one of the X chromosomes is “inactivated” rendering most of the genes residing on it transcriptionally silent. In this way, gene dosage between males and females is adjusted for genes on the X-chromosome.
Principles of X-linked Inheritance

- Disease incidence in males >> in females
  - Carrier females (heterozygotes) are rarely affected
- Male to male transmission is never seen
- All daughters of an affected male are carriers

Figure 7
The clinical characteristics of X-linked recessive inheritance include:

1. Disease incidence is usually considerably greater and is more severe in males than females. Carrier females who are heterozygotes for an X-linked mutation are rarely affected.
2. Male to male transmission is never observed in X-linked diseases.
3. All daughters of an affected male are obligate carriers.

Transmission Risks for X-Linked Disease:

The calculation of transmission risks in X-linked disease depends critically on ascertaining whether the mother of an affected boy (who by virtue of being female is usually unaffected) is a carrier, or whether the boy with the disorder represents a new mutation.

- Is VR’s mom a carrier?
- Or was it a new mutation which resulted in hemophilia in VR’s brother?
- The answer to this question is critical in calculating her children’s risks
  - If it was a new mutation in her brother, her children’s risks would be negligible

Figure 8
The family history of VR is critical

- Her family history reveals that VR has an affected maternal uncle
- Since hemophilia is a relatively rare disease, this **strongly** suggests that the uncle and the nephew both have Hemophilia b/o a shared mutation
- Thus, VR’s mom is a carrier
In the above example since there is a clinical history of the X-linked disorder not only in both the probands brother and in her maternal uncle, one can be confident that the mother of our proband is an obligate carrier.

Thus the proband (denoted by the arrow) is at 50% risk for carrying the deleterious mutation. Each of her children thus has 25% chance of inheriting the mutant gene. Males who inherit the mutant gene would be affected while females would be carriers. Likewise, the proband’s brother carries the mutant X chromosome. All of his daughters will be carriers since he only has one X-chromosome that he can give to them. None of his sons will receive the mutation since by definition they inherit his Y-chromosome and not his X-chromosome.

**Mechanism of X Inactivation**

Mary Lyon conceived of what is now known as the “Lyon hypothesis” in order to explain how females compensate for the fact that they have a double dosage of each gene on the X-chromosome. The somatic cells of a female contain only one active X chromosome, the other X-chromosome is condensed and essentially inactive. Most of the genes on this inactive X-chromosome are “transcriptionally silent” and produce no product. This inactivated X-chromosome is the “Barr body” which can be seen under the microscope in cells from a female.

Inactivation of one of the two X-chromosomes in each cell is a random process that occurs early in embryonic life. The decision of whether the maternally or paternally derived X in the embryo is inactivated is random. Once inactivation of an X has occurred, all the cellular progeny of that particular cell will have the same X-chromosome (either maternal or paternal) inactivated.

This results in females being “mosaics”, a condition in which the cells of the female are not identical because each contains a randomly inactivated (either maternal or paternally derived) X-chromosome.

The phenomenon of X inactivation has significant clinical and biological implications. It provides one explanation of why occasional female carriers for an X-linked recessive disease manifests phenotypic characteristics of that disease:
At the time of random X inactivation chance sometimes results in skewed inactivation of the maternally or paternally derived X-chromosome. Thus, occasionally one will observe a female who manifests disease because it was the normal or non-mutated X that happened to be inactivated to a greater extent than the other X-chromosome.

X-Linked Dominant Inheritance

The vast majority of clinically significant X-linked diseases result from X-linked recessive mutations. Thus it is that only males are usually affected in X-linked recessive disorders because females have a “back-up copy” of a normal X-chromosome that compensates for the mutation on the other X-chromosome. Of course males have no “back-up copy” of their X-chromosome and thus manifest disease at a much higher incidents than females.

There are a few diseases however, in which X-linked dominant inheritance is observed. The characteristics of X-linked dominant inheritance can be seen in Figure 10.

![Figure 10]

Affected males transmit disease to all daughters and none of their sons

Affected females transmit disease to 50% of sons and 50% of daughters
The clinical characteristics of X-linked dominant inheritance include the following:

1. Daughters of affected males will always inherit the disorder.
2. Sons of affected males will never inherit the disorder.
3. Affected females will transmit the mutation to 50% of their offspring.
4. X-Linked dominant inheritance is very rare. (One example is Vitamin D resistant Rickets)

Y-Linked Inheritance

There is no evidence for Y-Linked pattern of inheritance of any human disease, due to the paucity of functional genes on the Y chromosome. There have been occasional reports of Y-linked traits. What would the inheritance pattern be of such disease or trait?