LECTURE 4: PEDIGREE ANALYSIS

Reading: Ch. 2, p. 29-33; Ch. 4 p. 103-104

Problems: Ch. 2, solved prob III; also 2-6, 2-8, 2-9, 2-11, 2-23 – 2-28, 2-29a; Ch. 4, solved prob III; also 4-22, 4-23, 4-25 – 4-29, 4-34; Ch. 11, 11-19, 11-21

Calvin Bridges was able to figure out the inheritance pattern and mechanism of nondisjunction because he was able to observe many progeny – enough to see the exceptions! How do geneticists study inheritance in humans where large numbers of progeny are rarely available?

Human Genetics

-no controlled crosses
-depends on family records
-rarely get large numbers of progeny to analyze statistically (hard to distinguish Mendelian ratios); usually requires large pedigrees
-mistaken paternity can confuse the issue
-even with these potential drawbacks, thousands of human traits/disease have been identified; check the OMIM (Online Mendelian Inheritance in Man) database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

Pedigrees are diagrams that indicate the relationships among family members. They are used to identify dominant and recessive (and autosomal versus sex-linked) traits in humans. The affected individual through whom the pedigree is discovered is called the **propositus**.

Some pedigree conventions (see Fig. 10.16, p. 272 for more symbols):

□ Unaffected male ■ Affected male
O Unaffected female ● Affected female
O—■ Mating
O═■ Consanguineous mating (mating between relatives)

Autosomal dominant trait:

Traits caused by dominant alleles are the easiest to identify. Dominant mutant alleles may have phenotypes due to haploinsufficiency (half the normal "dose" of gene product) or may produce proteins that gain novel functions (*gain of function*), instead of impair protein function. Gain of function mutations may create hypermorphic or neomorphic alleles or alleles that result in proteins that act in a "dominant negative" fashion to negate the function of the wildtype copy.

Examples:

Achrondroplasia (dwarfism, OMIM 100800) can result from FGFR3 mutations. A single amino acid substitution in the kinase domain can cause constitutive (non-regulated) activation of the receptor. Other dominant mutations are those that cause increased receptor affinity for the FGF ligand. (Activated FGFR3 expression in chondrocytes induces their differentiation into cartilage and bone.)

Piebald spotting (OMIM 172800; OMIM 164920) can be caused by mutations in the c-kit protooncogene (required for neural crest development). A mild form of the trait can result from a deletion of the c-kit gene (haploinsufficiency), and more severe forms can be caused by mutations in the tyrosine kinase domain that likely cause the mutated receptor to act as a "dominant negative" receptor.

Brachydactyly (malformed hands, short fingers; OMIM 112500; OMIM 600726) was the first syndrome reported with Mendelian autosomal dominant inheritance (Farabee, 1903). Dominant mutations in Indian Hedgehog (a secreted molecule) can cause the syndrome, perhaps due to haploinsufficiency or by dominantly interfering with another Hedgehog signal.

We will go over a pedigree for Huntington's disease (p. 30, Fig. 2.20 from your book). Huntington's disease (OMIM 143100) is a late onset disease caused by an autosomal dominant allele. Symptoms of the disease include intellectual deterioration, slurred speech, severe depression, and jerky irregular movements, all caused by neural degeneration.

Characteristics of autosomal dominant traits:
-Every affected person has at least one affected parent.
-When the trait (or disease) is rare in the population, shows vertical pattern of inheritance in the pedigree (affected males and females in each generation).
-An affected parent will pass the trait to half his/her progeny, with sons and daughters equally affected.
-Deleterious dominant traits (mutations) are unlikely to be passed to the next generation, with the exception of late-onset traits like Huntington disease.

Autosomal recessive trait:
There are many human homozygous recessive traits -- mutant phenotypes in these cases are caused because there is a *loss of function* (or modified function) of the protein due to the mutation. There are pedigrees for the recessive condition, cystic fibrosis, in your textbook (p. 31, Fig. 2.21).

Examples of autosomal recessive traits are albinism (lack of pigment, OMIM 203100), Phenylketonuria (amino acid metabolism defect, OMIM 261600), Sickle-cell anemia (OMIM 603903), and Tay-Sachs disease (OMIM 272800). We will go over a pedigree for Cystic Fibrosis (OMIM 219700), which is the most commonly inherited recessive disease among Caucasians in the US (about 1 in 2000).

Characteristics of rare autosomal recessive traits:
-Most affected individuals have unaffected parents.
-Requires the chance union of unrelated carriers (heterozygotes). Rare recessive traits are more likely to show up in a pedigree when spouses are related to one another (because relative share alleles due to their common lineage). Many of the classical human genetic studies have been dependent upon mating of relatives, mainly first cousins.
-Matings between two carriers will produce normal progeny and affected progeny in a ratio of approximately 3:1. Affected progeny will include both males and females.
-The pattern of inheritance is often **horizontal** (several generations of unaffected individuals, but then several siblings in one generation are affected).
-Note: if a trait is extremely common in the population, it may be inherited in a vertical pattern.

X-linked recessive trait:
Examples of X-linked recessives are red-green colorblindness (recognized by E.B. Wilson in 1911; see OMIM 303800, 303900) and Duchenne Muscular Dystrophy (OMIM 310200). Perhaps the best known X-linked recessive disease is hemophilia A (OMIM 306700), a disease that was seen in the descendents of Queen Victoria of England. We will look at a simplified version of this pedigree.

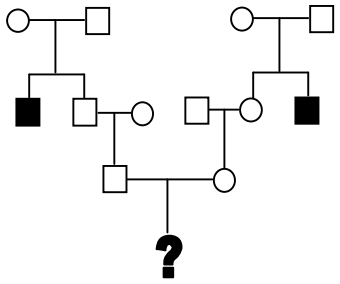
Characteristics of **rare** X-linked recessive traits:
-More males than females are affected (hemizygousity of the X in males reveals phenotype).
- All of the sons of an affected mother will be affected. (Sons receive their only X chromosome from their mother).
- Half the sons of a carrier mother will be affected. All daughters of carrier mothers will be normal, but half will be carriers.
-All the children of affected males will be normal. Affected fathers do not pass the mutant allele to their sons (as sons inherit Y, not X, from their fathers), but do pass the mutant allele to their daughters (all of whom are carriers).
-The trait often skips a generation: affected grandfather to carrier female to affected son.
-The trait appears in successive generations when a sister of an affected male is a carrier (half her sons will show the trait).

X-linked dominant trait: (we will finish this next time)
Very few of the X-linked rare mutations on the X chromosome are dominant to the wild-type allele. Hypophosphatemia (Vitamin D-resistant rickets, OMIM 307800), toe webbing, constitutional thrombopathy and hereditary enamel hypoplasia (OMIM 130900) are examples of X-linked dominant traits. We will look at a pedigree for hypophosphatemia (Fig. 4-23).

Characteristics of rare X-linked dominant traits:
-More females than males show the mutant phenotype.
-Affected males pass on the condition to all of their daughters but to none of their sons.
-One-half the sons and daughters of an affected female will show the trait.
-Generally, X-linked dominant traits tend to be milder in females than males.

Y-linked trait:
A Y-linked trait would pass from an affected father to all of his sons, and then from them to their grandsons, etc. Besides the determination of maleness itself, no clearcut Y-linked traits have showed up, although genes controlling fertility, long ear hair, gonad cancers, and physical stature have been implicated as Y-linked traits. The Y has few genes and human females do perfectly well without it.

Calculating risks in pedigree analysis:
A couple discovers that they both had an uncle who died of Tay-Sach's disease. What is their chance of producing a child with Tay-Sach's?



•The man's grandparents were carriers (T/t) since they produced an affected child.
•The man's father has a 2/3 chance of being a carrier (T/t). (Do the Punnett square to see why!)
•Assume the man's mother is T/T, because t is a rare allele. Thus, if the father is T/t, then the man himself has a 1/2 chance of being T/t.

•The overall probability of the man being a carrier is the chance that his father is Tt times his chance of being T/t if his father is T/t = 2/3 x 1/2 = 1/3.
•The pedigree for the woman is the same as for the man, so her overall chance of being a carrier is also 1/3.
•If both the man and woman are T/t, then the chance of their having an affected child (t/t) is 1/4. The overall probability of them having an affected child is 1/3 x 1/3 x 1/4 = 1/36.