03-621 Week 4

Advanced Quantative Genetics

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Analysis of Single Gene Traits

Every human chromosome contains **at least** one gene that is defective in a monogenic disorder.

- Although single-gene disorders *individually* are relatively rare, *collectively* they are important contributors to human disease.

Single gene traits are also known as "Monogenic Traits / Disorders". Traits for which different alleles at a single gene are sufficient to specify different phenotypes.

- There may be more than two phenotypes
- There may be more than two alleles
- Dominance may be complete or incomplete, or there may be co-dominance.

Note: there may be *more than one gene* that affects the trait and whose alleles can produce similar or related phenotypes.

Some of the most common single gene disorders in humans include:

- Thalassemia (Chromosome 16/11), reduced amounts of hemoglobin; anemia, bone and spleen enlargement. Affects 10% of Italy.
- Sickle-cell anemia (Chromosome 11), abnormal hemoglobin; sickle-shaped red cells, anemia, blocked circulation, increased resistance to malaria. Affects 1/625 African-Americans
- Hypercholesterolemia (Chromosome 19), missing protein that removes cholesterol from the blood, heart attack by age 50. Affects 1/122 of French Canadians.

To calculate progeny risk, we need to know (or estimate) the genotypes of the parents

- Even if relevant gene(s) are known, not all the possible disease-causing alleles (which individually may be rare or new mutations) are identified, so molecular diagnostics are not always helpful.
- We can't do intentional test crosses to figure out the genotypes of individuals with dominant phenotypes... but sometimes they appear in pedirees.

Mendelian Traits

- Discrete binary phenotypes
- Two alleles at a single gene
- Complete dominance
- No effect of environment

- Full penetrance and expressivity
- No sex-linkage
- Not sex-limited
- No parent-of-origin effect.

These traits are described completely by Mendel's Law of Equal Segregation, and can be drawn into Punnett squares with expected ratios.

If mating is random and there are **two alleles** at a given locus with frequencies p and q, the distribution of genotype frequencies *in the population* is given by the binomial expression:

$$1 = (p + q)^2 = p^2 + 2pq + q^2$$

This is known as the **Hardy Weinberg Principle**.

A Problem in Human Genetics

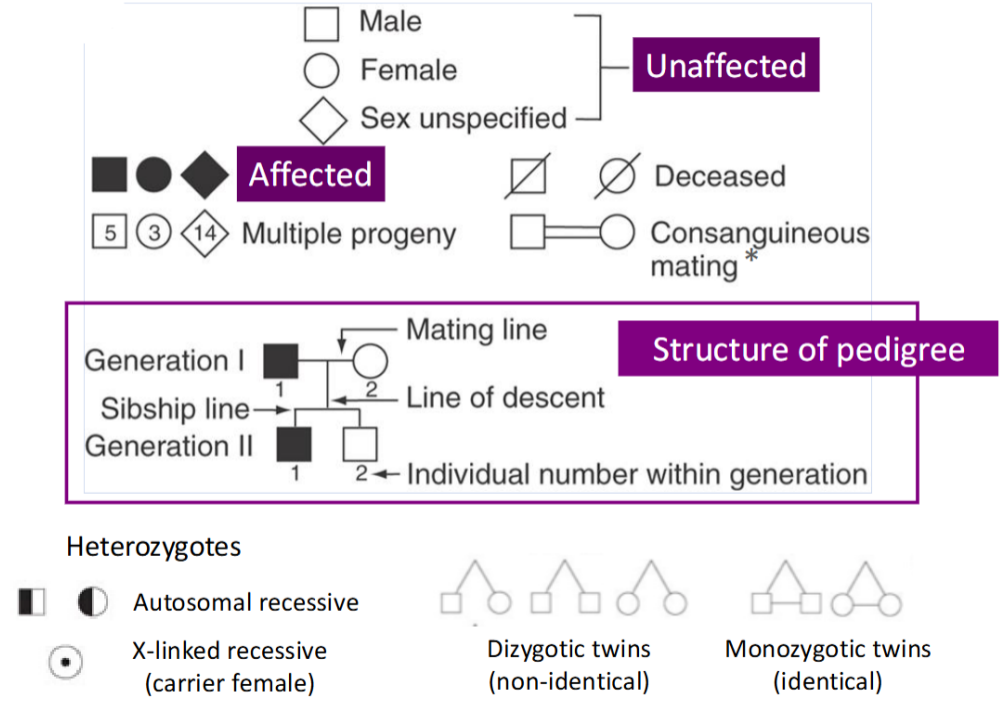
Human genetics have the issue of small progeny numbers.

- In Mendel's Pea Experiment, he crossed round x wrinkled peas, and counted the F1 and F2 progeny. There were 5474 round peas and 1850 wrinkled peas in F2. (nearly perfectly 3:1 ratio)
- Suppose we have two humans heterozygous for Cystic fibrosis (for reference, Cystic fibrosis occurs with two recessive alleles.) We only get 4 children. There's a $0.75^4 \approx 0.32$ chance that none of them will exhibit the disease at all.

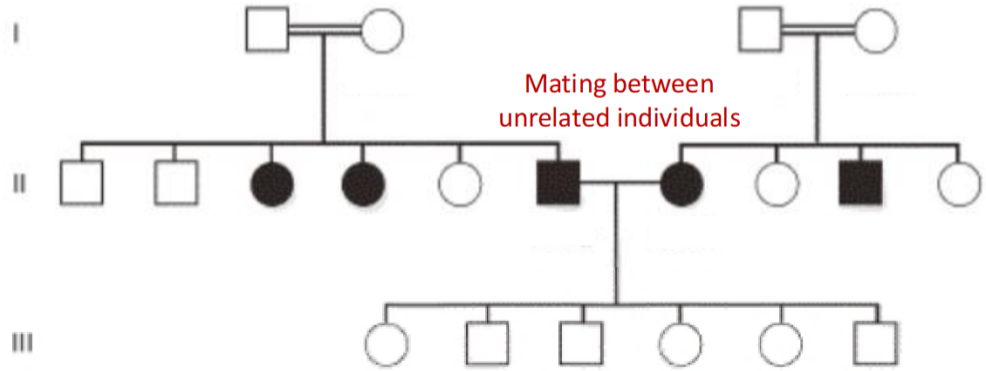
Analysis of Single Gene Traits using Human Pedigrees

1. Infer the mode of inheritance from pedigree patterns
    - Dominant/Recessive
    - Autosomal/Sex chromosome-linked
        - Map chromosomal location, identify gene, and run diagnostic tests/treatments
2. Genetic counseling: How to estimate risk
    - Probability of carrier status in parent
    - Risk of disease in progeny

Reading Human Pedigrees



Consider these human pedigrees for congenital deafness (an autosomal recessive trait):



How do we know the trait is recessive?

- If the trait were dominant, then the parents in generation I must have the trait!

How come the children on generation III do not have the trait, if both parents do?

- The parents must be in different complementation groups!
- The offspring of generation III are all double heterozygotes.

How to Analyze Pedigrees

- Identify the mode of inheritance from patterns in the pedigree:
  - Recessive autosomal traits
  - Dominant autosomal traits

  - Recessive X-linked traits
  - Dominant X-linked traits (few known)
  - Y-linked traits (very few known)
- It is easier to **rule out** a mode than to prove one conclusively
- When two or more modes cannot be ruled out, we must assess their **relative probabilities**

Frequent Features

Autosomal Recessive Disorders

1. Affected progeny can have two unaffected parents (frequent for rare traits)
2. Males and females are affected in equal proportion
3. Male-to-male transmission can occur
4. Recessive traits are more commonly expressed in **inbred** familes or populations

Recessive traits are more commonly expressed in **inbred** familes or populations.

- If one common ancestor carries a recessive allele, then at least some of the children in II would be heterozygotes.
- If inbreeding occurs in any future generation with two heterozygotes, their children would have a chance of expressing the recessive trait.

Autosomal Dominant Disorders

1. Affected individuals always have an affected parent (mother or father, except when a mutation first arises)
2. Phenotype frequently appears in every generation (recessives can skip)
3. On average 50% of progeny are affected
4. Trait can be transmitted from both males and females to both sons and daughters

Some **dominant lethal** traits can be transmitted because the phenotype does not manifest before reproductive age.

X-linked Recessive Disorders

1. Phenotype appears much more frequently in males than females
2. All daughters of an affected male are "carriers" (unaffected heterozygotes)
3. In the next generation, half the sons of these carriers show the phenotype
4. An affected female always has an affected father
5. Reciprocal crosses (switched sexes) give different results

For example, red-green colorblindness.

X-linked Dominant Disorders

1. Affected individuals always have an affected parent
2. Affected males pass the condition to ALL their daughters, but not their sons
3. Affected heterozygous females pass the condition to HALF their daughters AND sons
4. On average, more affected females than males (consequence of (2) and (3))

(2, 3, 4 are unique, but can only be assessed via probabilities of pedigrees). There are few known examples, one of which is brown tooth enamel.

Y-linked Disorders

Y-linked disorders are transmitted exclusively from fathers to sons. For example, hairy ear rims.

Calculating Risks in Pedigree Analysis

What is the probability that a child has X disease?

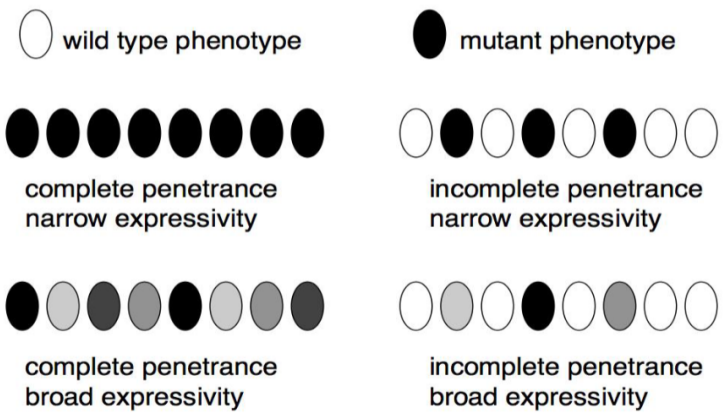
- Usually, the type of disease (e.g., autosomal recessive) will be given.
- If the disease is "rare", then it can be assumed that people sampled from the population would be homozygous for the allele without the disease.
- We may have to write probabilities of genotypes for multiple generations before the child we care about, since we might not know their genotypes either.

Bayesian Analysis to Account for Conditional Information

1. Identify all the different scenarios that can explain the observations
2. For each scenario, calculate the **prior probability** and **conditional probability**
3. Multiply the prior probability by the conditional probably to obtain a **joint probability** for each scenario
4. Determine what fraction of the total joint probability is represented by each individual scenario, to get a **posterior probability** for each scenario.

Variable Expression of Nucleus-Encoded Phenotypes

- **Penetrance:** % of individuals with a particular mutant genotype who display the corresponding phenotype
  - 100% = complete penetrance
  - <100% = incomplete penetrance
- **Expressivity:** degree of severity with which a given phenotype is expressed in an individual with the corresponding genotype



X-Inactivation

Inactivation of one X chromosome in females equalizes X-linked gene expression in XX and XY genotypes. ("dosage compensation")

- The inactive X is recognized cytologically as a condensed "Barr body".
- Heterozygous females may display a recessive trait or have a milder version of a dominant trait than affected males because half of the time the gene would be unactivated.
  - As a consequence, some traits may be exclusively heterozygous (e.g., Dwarfism), since the homozygous genotype is lethal.

A heterozygous female is a **genetic mosaic** containing cell clones that express one or the other allele of X-linked genes.

- An example of this is calico cats. The different colors of fur are caused by different alleles being expressed.
- 99% of calico cats are female. The remaining 1% male calico cats are caused by the rare XXY genotype.