BIOL 300 – Foundations of Biology
Summer 2017 – Telleen
Lecture Outline

Extensions of Mendelian Inheritance

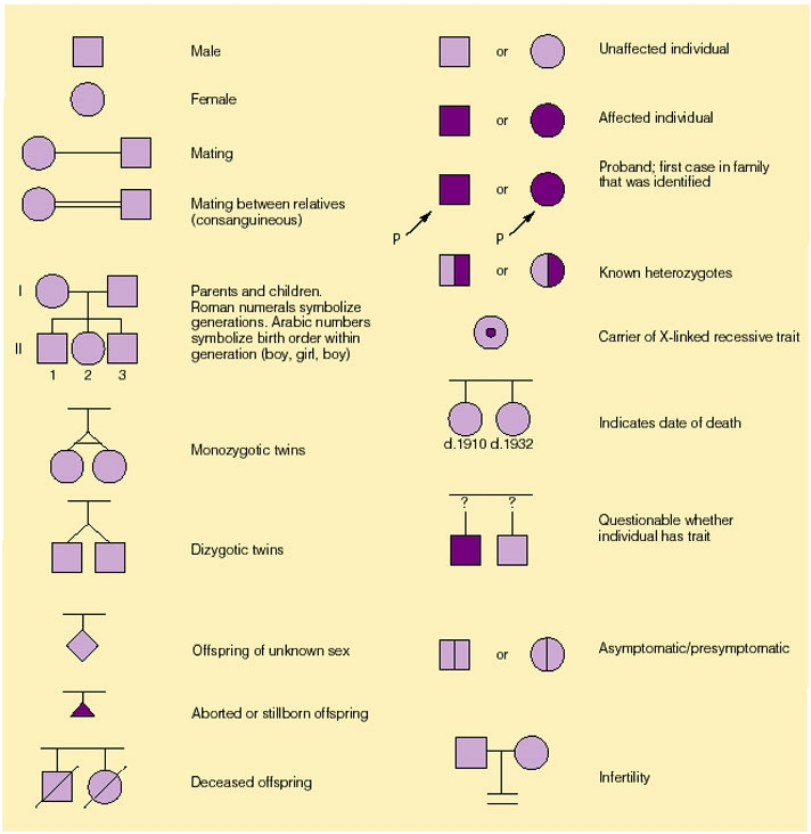
I. Sex determination in humans

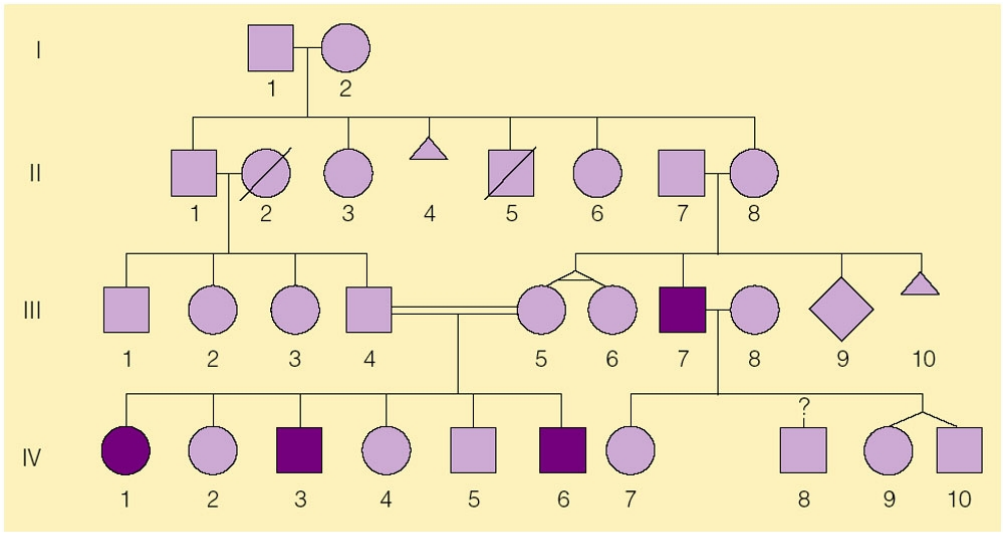
A. Sex in humans is determined by a pair of chromosomes called the **sex chromosomes**.
B. The sex chromosomes come is two varieties: **X** and **Y**.
C. The sex chromosomes are paired together in Meiosis even if they are different, but X and Y only pair together in a small region on the tip of the short arm
D. **Females have two X chromosomes, while males have one X and one Y**. It is not possible to have only two Y chromosomes.
E. As a result, **the sex of the offspring is determined by the father's genetic contribution** (he can contribute an X or a Y) because the mother will always contribute an X chromosome to her gametes/eggs.
F. We need to cover this here so that we can talk about the inheritance of certain kinds of traits with genes located on the X and Y chromosomes
G. Genes located on the X or Y chromosome are referred to as X- or Y-linked.

II. Mendelian inheritance in humans

A. It is more difficult to follow genetic inheritance in humans because we can't just make any cross we would like and produce large numbers of progeny to follow the traits we are interested in. Also, human generation time is too long to conduct meaningful experiments in a single lifetime.
B. These limitations make human genetics analysis more challenging than some other genetic systems (like Mendel's peas), but it is still possible.
C. Segregation and independent assortment occur with human traits
    1. Albinism is an example. It is a recessive trait (A- = normal, aa = albino)
    2. Albinism results from the lack of a gene involved in pigment production. One copy of the gene is sufficient to produce enough pigment for the normal phenotype, so lack of pigment only occurs in individuals homozygous for the mutant form of the gene.
    3. Inheritance of two traits in humans also follows Mendel's principle of independent assortment.

D. We can identify genetic traits because they have a predictable pattern of inheritance worked out by Mendel
E. Pedigree Charts
    1. **Pedigree charts** are the basic method for the analysis of genetic inheritance in humans
    2. They present genetic information on a family in an easily readable chart
    3. They allow the inheritance pattern of a trait to be followed through several generations
F. Pedigree charts use a standard set of symbols (an example is below)





1. Generations are labeled with Roman numerals (I, II, III, IV, V,…)
2. Children are written in birth order from left to right
3. Any person can be identified by his or her generation and number, e.g. III-4 (who in this example unwisely married her first cousin, III-5)

III. Modes of transmission of disease alleles in pedigrees

A. There are six basic patterns of inheritance of disease alleles in humans

1. Autosomal recessive
2. Autosomal dominant
3. X-linked recessive
4. X-linked dominant
5. Y-linked
6. Mitochrondrial

Extensions and violations of Mendel's First Law

Mendel got lucky with the traits that he chose for making his model, but there are plenty of complications to Mendel's relatively simple model of heredity even though in general terms it is correct. Try to think about the violations of Mendel's model as extensions or additions to it. Remember this is how science works: we make models and constantly refine them to better fit the data. We can still follow genes around by understanding what the chromosomes are doing in Meiosis, even if the traits/genes superficially violate Mendel's Law of Segregation.

I. Sex Linkage

A. We discussed **sex linkage** already in the context of humans, but other organisms also have sex chromosomes.

B. Other organisms do not necessarily have X and Y chromosomes, or even sex chromosomes at all! Sex determination is not always related to chromosome set, and when it is there are many different ways sex chromosomes can work.

C. Sex linkage, as it occurs in humans, violates the Law of Segregation because males only carry one copy of each X-linked gene and each Y-linked gene while females carry no Y-linked genes at all. Mendel's First Law states that each individual must carry two copies of each allele.

D. This still makes sense because we understand that in humans sex chromosomes still behave as a pair in Meiosis even though they can be different.

II. Incomplete Dominance and Codominance

A. Mendel's First Law states that one allele is always dominant over the other allele in a heterozygote. However, this is not always true.

B. In the flowering plant snapdragon (*Antirrhinum majus*), flower color is under the influence of a single gene. One of the alleles is **incompletely dominant** over the other. This actually makes it easier to follow the trait through the F_1 and F_2 generations of a monohybrid cross because we can tell phenotypically which are heterozygotes since they have a different phenotype that either homozygote.

Pure-breeders: ***RED*** **flowers (RR) x** ***WHITE*** **flowers (R′R′)**

F1s: **All *PINK* flowers (RR′)**

F2s: **¼ Red (RR)**
½ Pink (RR′)
¼ White (R′R′)

Incomplete dominance among alleles of the gene governing flower color in the snapdragon. Heterozygotes are pink, and differ phenotypically from either homozygote.

C. Since neither allele is dominant, it would be incorrect to use uppercase and lowercase letters as Mendel did. Rather than using R and r (which imply dominance), both alleles are usually written in uppercase with one of them follow by an apostrophe.
D. At the molecular level, one functional allele of a gene involved in pigment synthesis only produces half the amount of red pigment as two functional alleles (i.e. RR' vs RR, when only R alleles produce red pigment). The RR' genotype does not produce enough pigment to produce dark red flowers, so they appear pink instead.
E. In some cases both alleles are expressed in a heterozygous state, each in its pure form. This is called **codominance**.
F. A classic example is the MN blood group gene in humans
    1. The MN blood group gene codes for an enzyme that adds a sugar group to a protein found of the surface of red blood cells. The M allele differs slightly from the N allele so that the M form adds a different sugar group than the N form. Homozygotes express only one of the sugar groups ($L^M L^M$ or $L^N L^N$) and heterozygotes express both ($L^M L^N$).
    2. In a classic Mendelian cross, the F_2 would fall into the following genotypic and phenotypic classes:
        ¼ $L^M L^M$ Phenotype M
        ½ $L^M L^N$ Phenotype MN
        ¼ $L^N L^N$ Phenotype N
    3. The preferred nomenclature for codominance is to choose a capital letter to represent the gene and then assign superscripts of different letters to denote the alleles, as shown in the above example. This helps geneticists distinguish between codominant alleles and incompletely dominant alleles at a glance.

III. Multiple Alleles

A. Mendel's First Law also made the assumption that there are two, and only two, alternative alleles for each gene. This is not always true, as the human **ABO blood group gene** nicely illustrates.

B. The ABO blood group is under the control of three different alleles: I^A, I^B, and i, which creates six possible genotypes:

I^AI^A (phenotype A)	I^BI^B (phenotype B)
I^Ai (phenotype A)	I^Bi (phenotype B)
I^AI^B (phenotype AB)	ii (phenotype O)

C. In this system, I^A and I^B are co-dominant alleles that are both dominant to i. The i allele codes for a non-function version of the enzyme that adds a sugar group to the external surface of red blood cells. The I^A and I^B alleles each code for a slightly different version of the enzyme, adding either the A or B form of the sugar.

IV. Lethal Alleles

G. Mendel's First Law, which predicts a 3:1 ratio among the F2 generation in a monohybrid cross, makes the implicit assumption that all offspring of the cross are equally viable and this live long enough to be counted.

H. Many alleles, however, are absolutely necessary or at least extremely vital for survival or health of an embryo during early development. Usually, if a gene is that important, the body makes more than enough gene product to compensate for the loss of one copy of the gene. Therefore, mutations in such genes are usually **recessive** and are called **recessive lethal alleles** because they cause the death of the embryo only in the homozygous state. Often, the development of such embryos is arrested very early and the embryo is either shed by the mother as a spontaneous miscarriage or is "reabsorbed" by the mother's body.

I. Each one of us is a carrier for a few lethal alleles. Fortunately, it is unlikely that we will mate with someone who is a carrier for a lethal or sub-lethal allele at the same gene locus. If we do, an average of ¼ of our children will either be miscarried or severely malformed.

J. The inheritance of a lethal allele is difficult to follow in a family because only normal embryos will survive to term. Whether the miscarriage was caused by homozygosity for a lethal allele or for some other reason may never be known. However, the fertility of the couple is reduced by 25%.

V. Environmental Influence

A. Some traits that are under the control of a single gene are also **strongly influenced by the environment**. This can also affect the expected Mendelian ratios in a monohybrid cross

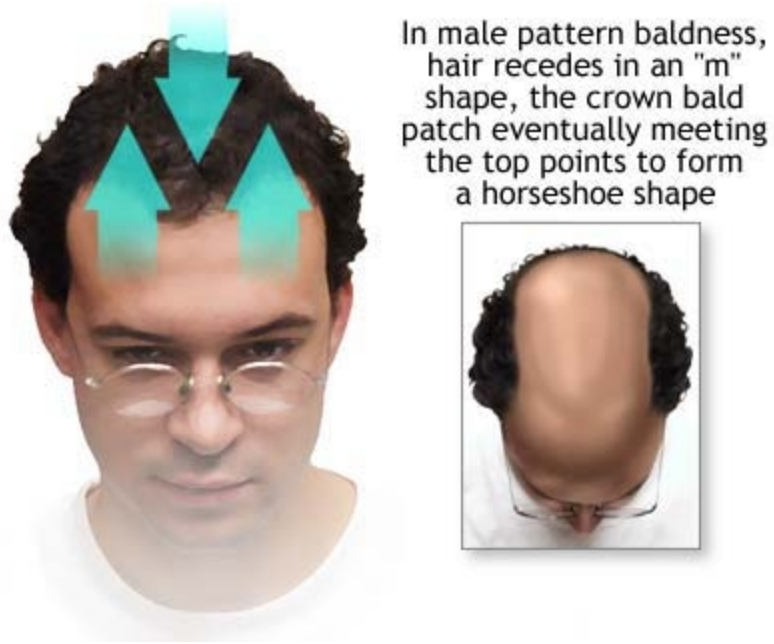
B. One example is **temperature-sensitive alleles**. The proteins coded by these alleles only operate at low temperatures, not at higher ones

C. Himalayan rabbits and Siamese cats have a temperature sensitive allele in a gene that codes for an enzyme that makes dark pigment. The enzyme is only active in parts of the body that are relatively cool (ears, nose, extremities), while the core body areas are too warm for the protein to fold properly

D. Most cats and rabbits that are homozygous for this allele therefore have pigmented fur on their extremities (nose, ears, paws)
E. However, if these cats or rabbits are raised in a tropical climate, they often do not express the pigment at all and are white all over

VI. Hormonal Influence

H. Some alleles are dominant in one sex and recessive in the other due to the presence or absence of sex hormones
I. The classic human example of a hormonally influenced allele is the allele that causes male-pattern baldness
    i. Early-onset baldness (usually before age 25)
    ii. Hair is progressively lost in the pattern show below
    iii. The allele (B) is autosomal and is dominant over the normal allele (b = no baldness) in men
    iv. However, the allele is recessive (b) in women, which is why women rarely suffer from pattern baldness. Moreover, women who are homozygous for the pattern baldness allele (bb) have a much later onset of phenotype than males and they tend to lose hair in a more random pattern
    v. Male production of DHT appears to be responsible for the dominance of the allele in men. Men who do not produce testosterone (due to abnormalities of the genitalia or accidental loss of the testicles) do not get pattern bald, even if they carry a copy of the baldness allele



	Homozygous normal	Heterozygous	Homozygous bald allele
Male	normal	bald	bald
Female	normal	normal	bald (mild)