Note: If the handout links don't work, look in the handout list.

UN2005/UN2401 '18 Lecture #22

Last Updated: 12/4/17

Handouts: 22A – Monohybrid Crosses
22B – Pedigrees and Co-dominance

You will also need handout **21A** if we get to topic IX (Details of Meiosis).

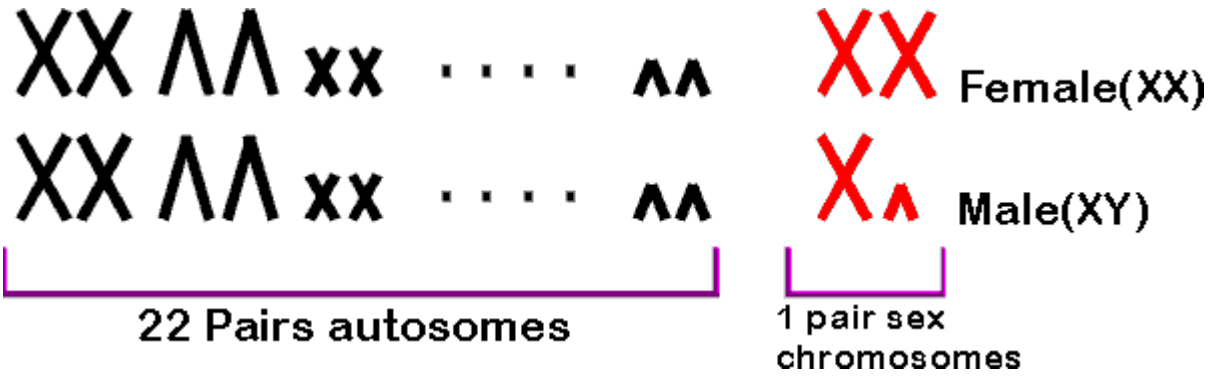
There are many examples and details included here to provide interesting background. Not all these examples will be discussed in class. However, all the basic issues should be clear after reading the notes and doing the problems.

I. Karyotypes, cont.

A. Normal Human Karyotypes

1. Sex chromosomes & autosomes

If you do karyotypes on human cells, you will discover that the pattern is different from males and female, as follows:



a. Males vs Females: Both sexes have 22 pairs of chromosomes that look the same regardless of sex, but the 23rd pair is not the same in both sexes.

- In females, the 23rd pair consists of 2 large chromosomes that look alike.
- In males the 23rd pair consists of a large and a small chromosome

b. Autosomes vs sex chromosomes: The 22 pairs of chromosomes that are the same in both sexes are called autosomes. The remaining pair are called sex chromosomes.

c. X vs Y. The big sex chromosome is called the X chromosome and the little one the Y chromosome. So females are XX and males are XY.

d. X & Y are homologs. The X and Y do not look alike, but they do have regions of homology, and act as homologs, that is, act as a pair during meiosis and separate at the first div. of meiosis.

- So gametes get a Y or an X, not both.
- If parent is XY, ½ the gametes get an X and ½ get a Y.
- X is much larger than Y; most genes on the X have no homolog on the Y.

e. Other factors to keep in mind:

- Not everyone is XX or XY (more details on this below).
- Sexual preference is not determined by the number of X's and/or Y's.
- Gender self identification may not match a person's XX or XY makeup.
- Most genes for secondary sex characteristics are on autosomes, not on the X or Y.
- Y is small, and carries few genes, but it includes SRY, the gene that triggers male development. (How this works will be covered next term.)

2. Human Karyotypes -- pictures and activities. See Sadava fig. 11.20 (11.21) for a real human karyotype. Many more examples can be found on the web. (Try the images on Google for a large assortment.) If you want to try making a karyotype for yourself, go to http://bluehawk.monmouth.edu/~bio/karyotypes.htm For another simulation try http://www.biology.arizona.edu/human_bio/activities/karyotyping/karyotyping.html

B. Human Aneuploidy

1. Terminology -- Cells with extra or missing chromosomes (2N + 1, or N -1, etc.) are called aneuploid.

2. How do aneuploidies occur? Through mistakes in meiosis. Mistakes can affect autosomes or sex chromosomes. (See Nondisjunction Handout, 21C.)

3. What types of aneuploidy survive?

a. Aneuploidy involving most autosomes is lethal. Aneuploids for most autosomes abort spontaneously and only a few trisomies involving the smallest chromosomes regularly survive to birth.

b. Aneuploidy of the sex chromosomes is usually not lethal as long as there is at least one X.

- Individuals can be X0 or XXY. (O stands for no 2nd sex chromosome.)
- X0 = Turner's Syndrome; relatively normal female
- XXY = Klinefelter's Syndrome ; relatively normal male
- X is a big chromosome with lots of genes. Why are extra or missing X's tolerated? See below.

II. Patterns of Inheritance -- An example and the general principles -- See Top half of Handout 22A

A. What are the Big Issues to consider?

1. *How are genes/genotypes inherited,* and

2. *How does a particular* ***genotype*** (state of the genetic information) *determine* ***phenotype*** (appearance, function, etc)?

B. How do you figure out the pattern of Inheritance?

1. General procedure – This is the same whether gene in question is on the X or on an autosome.

2. First Example – an X-linked Gene. We'll start by looking at a trait controlled by a gene on the X.

3. General Case – see bottom of handout 22-A for inheritance of a trait controlled by a gene on an autosome.

Note: The term "trait" is used in several different ways. It usually means whatever property you are following. Depending on the circumstances, it can mean the overall property you are considering such as coat color, OR it can mean the form (phenotype) of that property that you are following, such as orange coat color. So people speak of "the fur color trait" or "the orange color trait" depending on the context. ("Trait" is also sometimes used to refer to the carrier or heterozygous condition, as in "she has the sickle cell trait" meaning she has no symptoms, but carries one allele for sickle cell.)

C. An example for a gene on the X

Gene: Consider a gene on the X such as the one that determines orange vs black coat color. The gene has 2 alleles – orange and black.
Cross: Suppose you mate a heterozygous female cat X orange male (see top left of handout 22A).

For a different classic example of inheritance of a sex-linked trait, see Sadava fig. 12.18 (12.20).

Offspring: How do you figure out what will happen? Follow the steps below. (Each step is drawn on handout for each parent.)

1. Draw parental chromosomes with proper alleles.

a. Number of gene copies.

(1). For genes on the X: Male has only one copy (allele) of the gene, female has two copies (alleles).

(2). For a genes on an autosome (discussed below): both male and female have two alleles of each gene.

b. Reminder of Terminology (for an individual with two alleles).

(1). Homozygosity: If both alleles are the same, individual is said to be homozygous or a homozygote. In this case, a female cat can be either homozygous black or homozygous orange.

(2). Heterozygosity: If the two alleles are different, the individual is said to be heterozygous or to be a heterozygote.

(3). If an individual (such as an XY male) has only one allele of a gene, these terms do not apply. FYI for those who like terminology: The male is said to be 'hemizygous' for genes on the X.

2. Go through DNA replication to double DNA, chromatids/chromosome and # alleles/cell. Note sister chromatids are identical (if no crossing over**) but homologs need not be.

a. Alleles on Sister chromatids must be identical. Sister chromatids must be identical (if there is no crossing over) since the two sister chromatids are the 2 products of a single, semi-conservative, DNA replication. (See ** below for why crossing over can be ignored here.)

b. Alleles on Homologs need not be identical -- one homolog came from the mother and one homolog came from the father. Homologs DO need to have the same genes (loci) lined up in the same order -- they just don't have to have the same alleles of these genes. (But see c.) In this case, for the heterozygous female cat, one homolog has the orange allele of the coat color gene (at the coat color locus), and the other homolog has the black allele of the coat color gene. (For a diagram and a summary of the terminology, see III-E below.)

c. Are X & Y homologs? The Y chromosome and the X are considered homologs, in the sense that they pair during meiosis, but they have almost no genes in common. (In crosses, we are ignoring the very small region of homology between X and Y chromosomes which allows them to pair.) We are assuming that genes on the X do not have corresponding alleles on the Y, and vice versa.

3. Go through meiosis to get gametes: Homologs separate at first division and sister chromatids separate at second division. This produces 4 gametes -- two different kinds, but in equal proportions **.

Note: Crossing over does not make any significant difference here because you are following only one gene at a time. When you start considering two or more genes at a time, then you have to take crossing over into account, and we'll explain how to do that later. We're ignoring it now, because the gametes come out the same (for the **one gene under consideration) whether there is crossing over or not. See Becker fig 25-14 (20-13 or 20-14) or Sadava fig. 12.16 (12.18). Crossing over occurs in some of these figures, but you still get two gametes with one allele of the gene (Y in Becker or B in Sadava) and two gametes with the other allele (y or b) from one meiosis.

4. Offspring Genotypes: Do fusion of gametes from both parents (fertilization) to get zygote genotypes. You can use a Punnett square (or simple probability) to keep track of all combinations and expected proportions (for a large sample of offspring). This gives you the **genotypes** of the offspring that develop from the zygotes (= kittens).

5. Offspring Phenotypes: Look at genotypes and infer phenotypes of offspring Consider what phenotype results from each genotype. Figure out all possible phenotypes and what proportions they are expected to occur in.

a. The procedure so far (steps 1-5) applies to all crosses, no matter how many genes are involved, and whether the genes are on the X or on autosomes. However, how to predict phenotype from genotype depends on factors such as dominance and X inactivation, which are discussed below.

b. How phenotype relates to genotype in this case: If cat has only black (or only orange) alleles, you get a black (or orange) cat. If cat has both alleles, you get a tortoiseshell cat -- a cat with patches of black fur and patches of orange fur. Why is this? Because of X inactivation, which is explained below. Cat is black in areas where X with B allele is the active X; cat is orange in areas where X with O allele is the active X.

c. Relating genotype to phenotype in general

- For genes on the X, only one allele is active (transcribed) in any one cell.
- For genes on an autosome, both alleles are usually active (transcribed) in each cell.
- If both copies of the gene can be active, you have to consider the net effect.

  (1). In many cases, one allele → working peptide and other allele does not.

  (2). In some cases, one allele → working peptide and other allele gives an altered, but working, peptide -- as in HbA vs HbS or bloodtypes A and B. Many examples to follow.

6. Terminology (for genes on the X): In this course, and in many other contexts, the terms 'sex-linked' and 'X-linked' are used interchangeably, so sex linked = 'on the X chromosome.' If a gene is on the Y chromosome, a different term is used (holandric). Some biologists use the term 'sex-linked' to refer to genes on *either* the X or the Y. However, since there are very few genes on the Y, genes referred to as 'sex-linked' are almost always on the X (no matter how the term 'sex-linked' is used).

III. Inactive X's and Barr bodies -- Why are extra or missing X's usually tolerated, while extra or missing autosomes are not?

A. Lyon Hypothesis = inactive X Hypothesis = dosage compensation in mammals

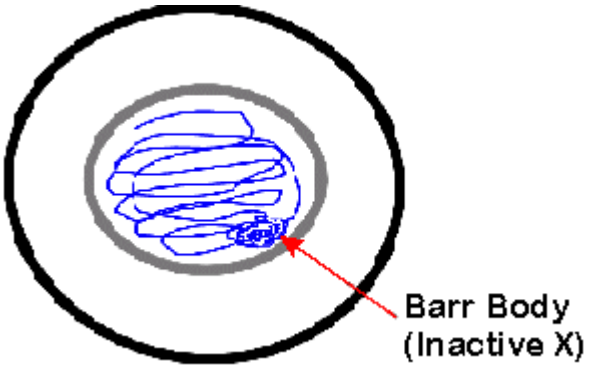
1. The Concept: The idea that extra X's are genetically inert is called the Lyon hypothesis (or the inactive X hypothesis). According to the Lyon hypothesis, every female is a mosaic, since some of her cells use her maternal X to make proteins and some use her paternal X. Each cell uses only one X, and any additional copies are inactivated.

2. The Point: This is the method of dosage compensation in mammals. Why are extra or missing X's usually tolerated, while extra or missing autosomes are not? Because all 'extra' X's (but not autosomes) over 1 are inactivated in each cell of the adult. There is usually no inactivation of genes on autosomes -- with few exceptions, both copies of the respective gene are active (transcribed, etc.)

3. Discovery: How was X inactivation discovered? From looking at the inheritance of coat color in cats!!

B. Barr bodies

You can actually see the inactive X during interphase because it forms a Barr body. There are 2 X chromosomes in every female cell, but (according to the inactive X hypothesis) only 1 of them works (is transcribed) most of the time. In general, if there are extra X chromosomes, all the extras are inactive, whether the cell is male or female. The inactive X's remain tightly coiled during interphase and are called Barr bodies. (So you can tell the sex of the cell without doing a karyotype.) Note that inactive X chromosomes are replicated, but not transcribed.



C. When do Barr bodies form? How do you get the mosaic?

Fertilized egg (zygote) → ball of cells → each XX cell inactivates one X at random → each cell divides by mitosis → descendants with same X on/off. Once an X is inactivated, it generally remains inactivated through succeeding mitoses, so all mitotic descendants of a single cell (a clone) have the same X on and the same X off → all cells in one area (or with same lineage) have same X on/off.

Germ line cells (which will go through meiosis) turn both X's back on before gametes are made, before meiosis occurs. So either one of the two X chromosomes can be used or inactivated in the next generation.

D. How is mosaic detected? From looking at the phenotype of heterozygous females. See E for an example.

E. Summary of Basic Genetic Terminology & Historical Background

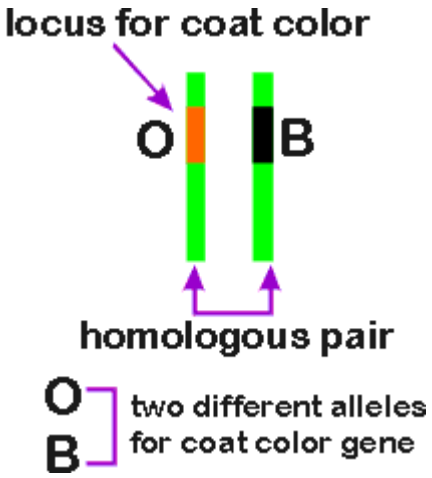
Lyon actually figured out the inactive X existed from studying coat color in cats. In cats, a gene controlling coat color is on the X. The position of the gene is known as the ***locus*** of the gene. This gene has two ***alleles*** (alternate forms); one → black coat color and the other → orange. One of the alleles is present at the coat color locus on every X. The Y chromosome does not carry an allele of the coat color gene. What genotype and phenotype are cats?

1. Genotype:

a. Males. Males have only one X, which carries either the black or the orange allele,

b. Females. Females have two X's, so they carry two alleles of the coat color gene -- one on each X. The ***genotype*** of a female can be

(1). homozygous black (have 2 black alleles)
(2). homozygous orange (have 2 orange alleles) or
(3). heterozygous (have one allele of each color), as shown in figure.



2. Phenotype:

a. Males. Males have only one allele of the coat color gene, so normal male cats are all black or all orange. (They may have regular stripes, superimposed on the black or orange, but the background color is either all black or all orange -- they don't have areas of orange and areas of black).

b. Females. The ***phenotype*** of a female can be orange, black or patchy (with areas of each color). Only heterozygous females are patchy.
All this makes sense if only one copy of the X works in each patch so only one copy of the coat color gene works per cell (and per patch). Rare patchy males are XXY (Klinefelter's Kats).

Note "Patchy" is called tortoise shell, not tabby; calico = patchy plus white. (Tabby = regular pattern of stripes that occurs in both males and females.)

To review Genetic Terminology so far, try 8R-1. (Also see Becker fig. 25-12 [20-2].)

F. How does genotype determine phenotype in this case? (Biochemical Details FYI)

How does a gene specify orange or black? In all cases, to figure out how genotype and phenotype correspond, you need to consider the enzymes and pathways involved. Current understanding of this case is as follows:

1. Black Part -- how is black pigment made?

Gene A is probably on an autosome. All colored cats probably make black pigment.

2. Orange part -- how is orange pigment made?

A gene on the X (call it gene C) codes for an enzyme that converts the black stuff into orange stuff. (The difference in color is probably caused by a different arrangement of pigment granules.) This gene has two alleles, which we have called "O" and "B".

3. What determines orange vs black?

What differs between orange and black cats is the activity of the second enzyme (enzyme C). If the second enzyme is active, the black pigment is converted to orange. If the second enzyme is inactive, the black pigment remains black.

How the alleles of gene C determine color:

- The O allele → working peptide → catalyzes conversion of black stuff into orange.
- The B allele → no working peptide → no conversion of black stuff into orange so black color shows up (black not masked).

For a sample problem on sex linked inheritance, try problem 9-9 A & C. (Part B depends on a discussion of dominance, which will be considered later.)

IV. How does Inheritance Work for Autosomal Genes? See Handout 22 A.

A. Why does it matter if the gene of interest is on an autosome, not on the X? What's different?

1. Two copies of the gene in every cell -- doesn't matter if individual is male or female.

2. No inactivation of one allele -- both alleles can be transcribed, translated, etc. and have effects.

B. Examples:

1. Blue (bl) vs Brown (br) eye color. For a different classic example of inheritance of an **autosomal trait** see Sadava fig. 12.1 (12.2 & 12.3) or Becker figs. 25-11 & 25-13 (20-10 & 20-11). For bkg info see previous figs. & table 12.1 in Sadava. New Terms are in bold.
Note: This example is worked out in great detail below, but we may skip to the general case.)

2. General Case -- AA X A*A* (This is worked out in detail in notes below.)

C. General Procedure

1. Crosses to consider: You start with homozygous bl X homozygous br or AA X A* A* (= **parental generation**), to get heterozygous offspring bl br or AA* (first filial generation or $\mathbf{F_1}$); then you cross two F_1's to get the next ($\mathbf{F_2}$) generation. (See handout.)

2. How to analyze the cross -- steps 1-5 are the same as above, but outcome is different.

3. Genotypes of gametes and zygotes -- genotypes are determined as shown on handout.

a. The steps are the same as in the case for sex linked genes, (steps 1-4), but outcome is different..

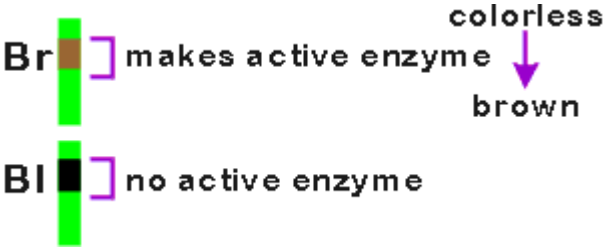
b. Gametes are different -- for autosomal genes, the gametes produced by a heterozygous male or female are identical.

c. Genotypes of zygotes, and their proportions, are different for autosomal genes (like eye color) and sex-linked genes (like coat color).

4. Phenotypes of offspring (step 5) -- phenotypes depend on the roles of the products of the bl and br or A and A* alleles. There is no inactivation of autosomes, so you need to figure out what phenotype of heterozygote will be. What will it look like? The usual answer for eye color, is, "it will be brown, because brown is dominant." But why is br dominant to bl? Will A be dominant to A* or vice versa? What is the underlying mechanism?

a. You need to consider what the two alleles do.

- br allele → enzyme; catalyzes conversion of colorless stuff → brown
- bl allele → no active enzyme; no brown stuff made. Eye appears blue (due to light scattering) in absence of brown pigment.



b. So what happens in heterozygote (when both alleles are present)? What will it look like?

- br allele → enzyme → synthesis of brown pigment.
- Presence of bl allele has no effect on action of br allele or its products. Therefore eyes of heterozygote are brown.

c. This situation (dominance of allele coding for active enzyme) is common -- Usual Features

- Enzyme is produced constitutively; number of copies of gene (with active alleles) determine amount of mRNA and protein made.
- One allele → active enzyme → job done; other allele → no (active) enzyme; without active enzyme job doesn't get done.
- In heterozygote, one allele → active enzyme; other allele → no enzyme. Total amount of enzyme is 1/2 the amount in a normal (homozygote), but it is enough to get the job done. Therefore, effects of allele that produces enzyme override effects of allele that → no enzyme.
- Note it is the ***products*** of the alleles (the enzymes, proteins, etc.) that determine what will happen in a heterozygote, not the alleles themselves. In this case, the effect of the normal allele is dominant to the effect of the allele that makes no product. This is the usual case, but there are exceptions. Other possibilities are discussed below.

5. Dominance -- terminology and symbols.

a. Dominance vs recessiveness: Whenever effects of one allele (really the products of the allele) override effects of another allele, the first allele is said to be **dominant** and the second allele is said to be **recessive. Note that dominance is not always complete. See table below and details in section IV.**

b. Allele Symbols: In this example, br is dominant and bl is recessive. In situations like this, the symbols B and b (upper and lower case of same letter) are often used for the pair of alleles. Using two forms of the same letter emphasizes we are dealing with two forms (alleles) of the same gene, **not** different genes.

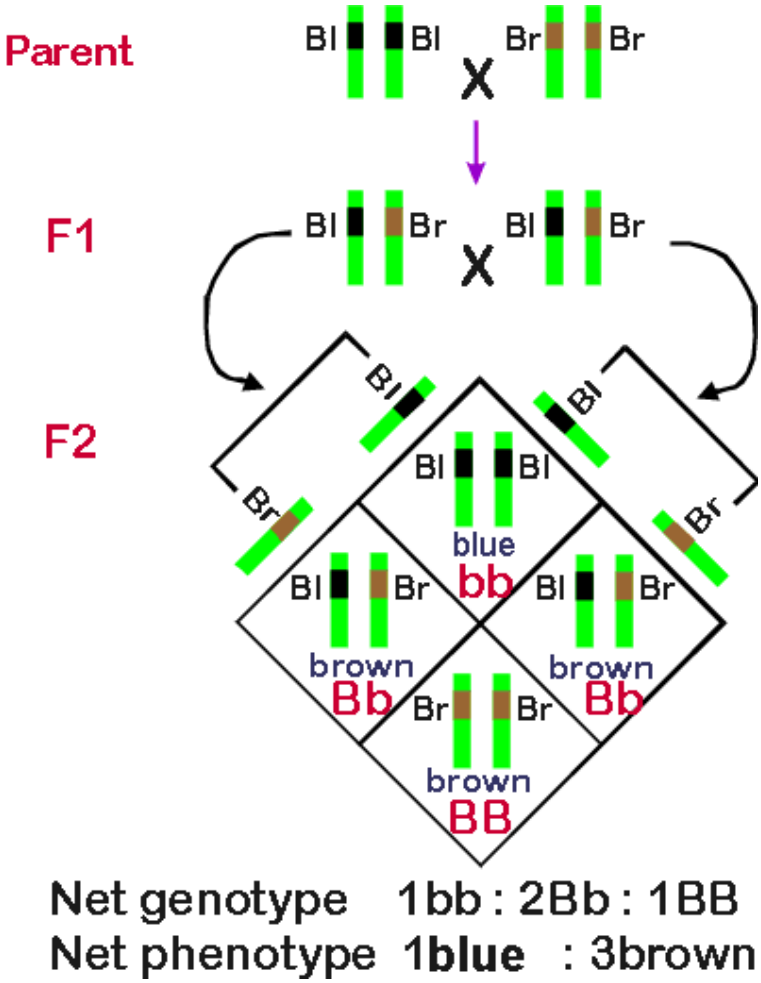
c. Phenotypes vs genotypes: Whether you use B & b or bl & br, it is usually wise to use **one** set of symbols for the phenotypes (blue and brown) and a DIFFERENT set of symbols for the alleles (bl and br or B and b.) Using the same terms (blue & brown) for alleles/genotypes and traits/phenotypes can cause lots of unnecessary confusion.

See Next Page for a Diagram of the blue/brown example

For a review of the terminology and a sample cross with an autosomal gene, try problem 9-1. For more practice, try 9-3 & 9-4.

Note that Becker and Sadava (9th ed) both have genetics problems at the end of the respective chapters. Sadava 10th ed. has 'in chapter' problems at the end of each section called 'Recap.' (Answers to most problems in Sadava are in the back of the book.) Answers to problems in Becker are in the Solutions Manual, which should be on reserve in the NW corner Science Library. Tell Dr. M if you have any trouble finding it. In Becker, questions are at the end of ch. 20 in the 8th ed. and Ch. 25 in the 9th. The problems are the same in both editions except for the insertion of a problem on Down Syndrome (5-27) in the 9th ed.

6. Summary of results for parents → F1 → F2 (Blue/Brown Example)



D. General Case -- see bottom of 22A for genotypes; see table below for phenotypes. Very similar to Bl/Br example.

1. Alleles:

- Assume A = normal allele (such as the version of the PAH gene or HD gene that encodes normal protein).
- A* = mutant or altered allele (such as the version of the PAH gene that causes PKU or the version of the HD gene that cause Huntington's disease)
- See table below for other examples of A and A* alleles

2. Crosses -- Genotypes

a. P X P → F1

Parents = AA X A*A*.
Figure out gametes from each parent.
Mix gametes to get zygotes;
Get all heterozygotes -- AA* -- in first generation of offspring (F_1)

b. When cross two F1's → F2

Parents = AA* X AA*
Figure out types of gametes from each parent
Mix gametes to get zygotes.
Not all zygotes are the same. You get:
1:2:1 genotype = AA: AA*: A*A* in second generation of offspring (F_2)
or you expect 1/4 AA, 1/2 AA* and 1/4 A*A*

3. Phenotypes in F2. Remember there is no inactivation for autosomal genes. So # of phenotypes and their proportions depend on the answer to the question: what will AA* look like? Proportions of genotypes are 1:2:1. How many phenotypes, and in what proportions?

- Assume A → normal enzyme or peptide
- A* → No peptide or altered peptide

Phenotype of AA* depends on how altered the product of A* is, whether it interferes with action of normal enzyme, etc. AA* can look like AA, A*A* or in between. A* can be dominant to A, or A and A* can be co-dominant, or either allele can be only partially dominant over the other. (See table.) It all depends on what the job of gene A is and how different the product of allele A* is from the product of allele A. Here is a summary table for autosomal cases (1-4) and for sex linkage (5). See next section for more details.

Ratios given in the table are for the F2 from AA X A*A*. Cases (1) - (4) are autosomal; (5) is for sex linkage (for comparison).

	Case	AA* Phenotype	Pheno. Ratios	Phenotypes	Examples
(1)	A dominant to A*	normal	3:1	Normal: Mutant**	PKU, CF, eye color
(2)	A* dominant to A	mutant	1:3	Normal: Mutant	HD (Huntington's disease) HC (hypercholesterolemia)
(3)	Partial dominance = incomplete dominance	in between	1:2:1	Normal: In between: Mutant[#]	flower color (red, white or pink)
(4)	A, A* co-dominant	in between or mix	1:2:1	Normal: Both Alleles Expressed: Mutant	AB blood type
(5)	A, A* on X chromosome; A dominant	organism normal; cells are normal or mutant	----	----	Hemophilia, Red-Green Color Blindness

Notes:
** In all cases considered in the table, the A allele (and corresponding phenotype) is classified as 'normal', and the A* allele (and corresponding phenotype) is classified as 'mutant. However, in some cases of inherited variation, both alleles and phenotypes are considered 'normal,' as in blue vs brown or orange vs. black. In other cases, it is not clear cut what is 'normal' and what is not.

[#] For human diseases, if an AA* individual has symptoms, the disease is usually classified as dominant, not partially dominant, even if A*A* is sicker than A*A.

V. Examples of Phenotypes.

A. A* is recessive -- Bl vs Br or PKU

1. Mechanism. In these cases, lack of an enzyme usually causes a block in metabolism. The resulting symptoms (for a disease) can be due to the buildup of intermediates and/or to the lack of end product. The individual is normal as long as there is at least one A (normal) allele that → some working enzyme. So AA and AA* or A_ genotypes have normal phenotypes (they look and act the same). But A*A* individuals have no enzyme; they have a block in metabolism and have the disease.

2. Examples:

- Phenylketonuria (PKU) -- can't break down the amino acid phenylalanine → tyrosine. See Sadava fig. 15.6 (15.7) & table 15.1.
- Galactosemia -- can't break down and get energy from galactose
- Tay-Sachs disease (TS) -- can't break down a complex lipid in nerve cells
- Cystic fibrosis (CF) -- can't transport ions properly in and out of cells. See Sadava table 15.2.

3. Treatment by alteration of diet. In some cases, manipulating the diet gets around the block and prevents symptoms. (For a comparison of strategies to treat genetic diseases, see Sadava Fig. 15.17 (15.19)). Examples:

a. PKU -- Block is in conversion of the amino acid phenylalanine (phe) to tyrosine due to lack of enzyme. (Enzyme = PAH = phenylalanine hydroxylase.) You need to provide just enough phe so person can make proteins and grow, but you need to keep phe levels low so none is left over, since excess can not be broken down and disposed of. Excess phe (or compounds derived from it) interfere with brain development and cause severe mental retardation. The altered diet is extremely successful -- average IQ of untreated person (on normal diet) is 53; average IQ of treated person is 93. All newborns in the US are screened for this condition. See Sadava fig. 15.15 (15.17).

b. Galactosemia -- block is in conversion of galactose to glucose. Need to eat a diet without galactose (that means without milk, since the sugar in milk is lactose, a disaccharide of glu and gal). Provide glucose instead as an energy source.

4. Protein or Gene replacement

a. Why can't you just add the missing protein? The protein usually gets broken down before it reaches its target cells. This is what usually happens; only a few proteins (mostly those that function in blood such as insulin and clotting factors) can be supplied from outside.

b. Why Gene therapy. It should be easier to target intact genes to the right cells than it is to target intact proteins. Also, once the genes reach the correct cells, they should continue to make proteins for a long time, perhaps for the life of the person. Everyone assumes this will work eventually, but so far, gene therapy has not been very helpful, and there have been some serious setbacks. However the field is looking up! See Sadava fig. 15.18 (15.20) for outline of the procedure & 'working with data' at the end of chapter 15 (in 10th ed) for an example.

5. In some cases you can't do anything much to avoid the block in metabolism (except prevention). Protein (or gene) replacement isn't feasible, and changing diet doesn't help. Examples:

a. TS (Tay Sachs Disease). Lipid is made irrespective of diet -- it is continually made and broken down ("turned over") in nerve cells of normal people; in people with TS the lipid is made but can't be removed so it just piles up until it destroys the nerve cells and causes death, usually by age 5. (See note 1 below at **.)

b. CF (cystic fibrosis) -- Defect is in protein needed for ion transport in and out of cells. Protein is not made or is not transported to the right place in the cell. You can't usually get around the actual defect (but see note 2 at ##) but can relieve symptoms (accumulation of mucus in lungs, etc.) and extend length and quality of life; gene therapy is in the works. Eventually added genes should produce protein that is targeted correctly to the right part of the cell, and allow normal ion transport.

**Note 1: In some cases it is possible to treat diseases caused by the toxic buildup of intermediates or byproducts by using inhibitors that slow down buildup of the toxic product. (In these cases you can't block toxic product production completely without lethal consequences.) More treatments of this kind ('substrate reduction') are under development.

Note 2: Not all people with CF have the same mutation There are drugs that modulate the effects of several of the rare mutations. More drugs are under development to help treat the more common mutations. (The drugs seem to help the protein reach the right place in the cell, but are very expensive.) If you are curious, see the web site of the CF foundation.

For a problem involving a typical recessive autosomal disease see 9-8. For a problem on genetic testing see 9-13.

B. A* is dominant

1. Mechanisms are various. Either

a. Not enough (normal) protein. 1/2 usual amount of protein isn't enough; protein can be catalytic and not shovel fast enough or structural and not hold up the roof. Examples: HC (hypercholesterolemia) & actute intermittent porphyria (See 'The Madness of King George')

b. Presence of abnormal protein. Abnormal protein can cause problems directly; functioning of abnormal protein can interfere with normal. Example: HD (Huntington's disease)

2. Examples of dominant diseases:

a. Hypercholesterolemia (HC). HC is due to a defect in the carrier (receptor) for uptake of cholesterol from the blood. Heterozygotes have half the usual carrier level, and half the rate of uptake. Blood cholesterol gets too high, causing premature heart attacks. See Sadava 17.3A (8th ed.) Homozygotes (who are quite rare) have no receptor and have even higher levels of blood cholesterol; they have heart attacks at extremely early ages. This disease (or the mutant allele that causes the disease) is considered dominant, although it is really partially dominant -- homozygotes have less function and more severe symptoms than heterozygotes. (Human diseases are usually considered dominant if a heterozygote has symptoms. See below for details of how human diseases are classified as dominant or recessive.)

b. Huntington's Disease (HD). A defective protein gums up the brain causing degeneration of nerve function. Symptoms do not occur until later in life, usually well after reproductive age. (Age of onset depends on extent of defect in gene/protein. If defect is worse, age of onset is earlier.) In this case, the altered protein encoded by the mutant allele appears to interfere with the functioning protein made by the normal allele. This disease is completely dominant -- homozygotes and heterozygotes have similar symptoms.

3. Treatment:

a. HC. *Try to up regulate (increase) protein production, or reduce the need for it.*

(1). Treatment. Diet and cholesterol-lowering drugs (statins) are the standard treatment. The drugs inhibit enzymes of cholesterol synthesis.

(2). Possible gene therapy. If gene therapy is tried, it will probably not involve adding a normal copy of the defective gene, as one normal copy is already present in most affected people (who are heterozygotes). Instead, the genetic engineering methods will attempt to change regulation -- to ***increase*** gene expression ('up-regulate') the normal allele which is already there.

(3) Why not 'protein therapy' -- adding the missing protein? In most cases where a protein is missing, adding the protein doesn't help. Why not? Because the added protein is degraded before it can reach its target, that is, the specific cell type or compartment where it is needed. Adding insulin or other hormones does help, because hormones normally travel through the blood and function extracellularly, not intracellularly.

b. HD. **T***ry to down regulate (decrease) the production of (bad) protein, get rid of it, or mitigate its effects.*

(1). Treatment. No treatment currently exists. Prevention is the only option. Therapeutic abortion is problematic here, as affected individuals can be asymptomatic for 40-50 years before they develop the disease. (Attempts are underway to find drugs that interfere with the effects of the mutant protein in this and other neurodegenerative diseases.)

(2). Gene therapy. If gene therapy is tried here, it will involve attempts to silence (down-regulate) the abnormal allele, possibly by anti-sense technology (adding RNA complementary to mRNA or the equivalent RNAi technique). The issue here is to ***decrease*** gene expression.

(3). Diagnosis. Pre-symptomatic diagnosis is possible -- you can determine from DNA tests if a person (who is still healthy) carries the defective allele and will develop HD eventually. For a discussion of the issues involved here, both biological and otherwise, see *Mapping Fate* by Alice Wexler. (She is from a family with the condition.)

For a problem on inheritance of a dominant condition, see 9-12. For a review of the relationship between dominance and enzyme function, see 9-18.

C. Incomplete or partial dominance. Example -- red vs white vs pink flower color.

1. Idea: In cases above, AA* looked like one parent or other (or for a human disease, the person either had symptoms or not). What if the heterozygote looks or acts in between? This is usually called incomplete or partial dominance. Incomplete dominance occurs because the amount of protein produced in a heterozygote is a limiting factor. In this case, having 1/2 the usual amount of protein gets the job 1/2 done.

2. Example: In some plants, crosses between red-flowered plants and white-flowered homozygous plants → F_1 offspring with pink flowers. In this case, the flower color gene controls pigment production. An AA* plant makes 1/2 of the pigment in an AA. The red pigment is spread more thinly giving a pink appearance. See Sadava fig. fig. 12.9 (12.11). Incomplete dominance could occur because the amount of enzyme encoded by gene A is limiting in pigment production, or because the gene A encodes a protein that is a pigment itself (so only 1/2 as much is made), or because gene A regulates production of the pigment.

3. Terminology: Incomplete and partial dominance are synonymous; they are similar to, but not exactly the same as, co-dominance, the next case.

4. Reminder on Disease Terminology: If a disease or abnormal condition is partially dominant, it is usually considered to be dominant. (As for HC, discussed above. You only need one A* to show an effect; you don't need two.) More details on this below in section III.

Look at problem 9-7. One of the cases here (you figure out whether it's A or B) is an example of incomplete dominance.

D. Co-dominance.

1. Idea: In all cases so far, one allele → inactive or defective product. What if each allele produces a working product, but the products are different? Then each product will "do its thing" unaffected by the other.

2. Example #1 -- MN blood type: This is controlled by one gene with two co-dominant alleles. Each allele codes for a slightly different version of the same cell surface protein. (The protein is not an enzyme; its normal function is unknown.)

3. Example #2 -- ABO blood type. This is controlled by one gene with 3 alleles; 2 of the alleles are co-dominant. See Sadava fig. 12.10 (12.12). or handout 22B (same as diagram below).

a. Role of gene product: The gene codes for an enzyme that adds sugars to proteins on the surfaces of red blood cells (RBC's).

b. Role of Different Alleles The 3 alleles of the gene code for variant forms of the same enzyme.

c. Dominance Relationships: Two of the alleles (I^A and I^B) are co-dominant to each other and both are dominant over the third allele (i).

d. Mechanism

(1) The two co-dominant alleles -- code for variant (working) forms of the same enzyme. The substrate binding sites of the two forms are slightly different. Therefore the two different forms of the enzyme bind slightly different sugars, and add different sugars to the surfaces of red blood cells (RBC's).

(a). I^B -- One working form of the enzyme, coded for by the I^B allele, adds the sugar galactose to the surface of RBC's. RBC with galactose → B blood type. (On handout and in picture below, G on cell surface = galactose.)

(b). I^A -- The other working type of enzyme, coded for by the I^A allele, adds the modified sugar N-acetyl galactosamine (NAGA). RBC with NAGA → A blood type. (On handout and in picture below, A on cell surface = N-**a**cetyl galactosamine.)

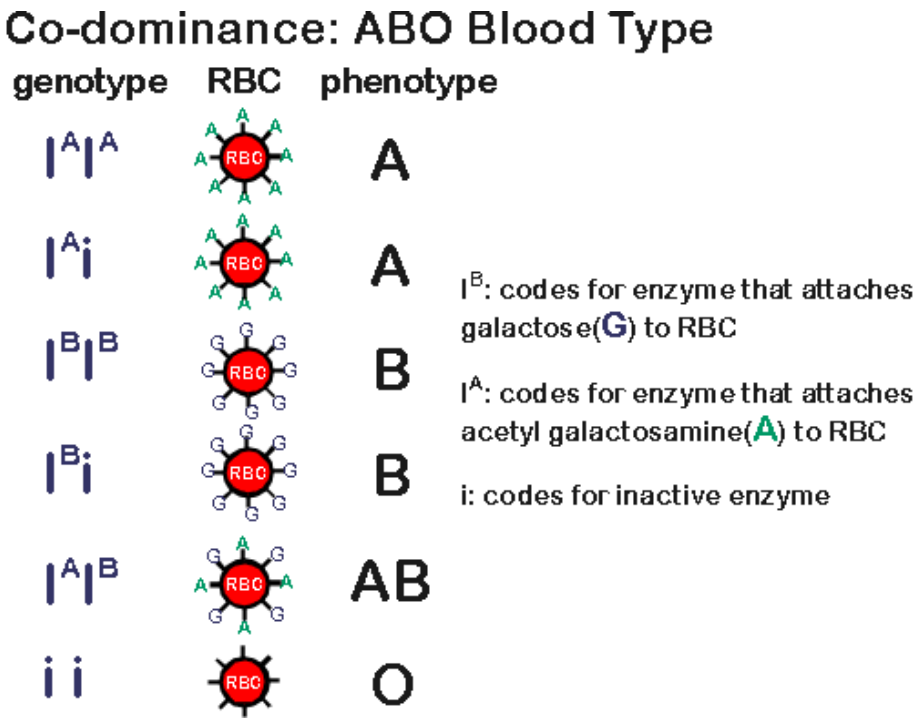
(2) The i allele -- codes for an inactive (non working) enzyme; cells with ii genotype → no enzyme → no sugars added. If no sugars → O blood type.

e. Heterozygotes: How genotype & phenotype match up.

(1). Type AB: I^AI^B individuals have a mixture of both enzymes and a mixture of sugars on their RBC → AB blood type.

(2). Type A & B: Both homozygous I^A and heterozygous I^Ai have only one type of enzyme and N-acetyl galactosamine on their RBC's and are type A; similarly both I^BI^B and I^Bi have galactose and are type B.

f. Multiple alleles: This gene has 3 different alleles. Any gene can have many alleles because many different variants of the same DNA sequence are possible. Often the alleles divide into two classes, those → functional enzyme and those → nonfunctional enzyme. In this case, two of the alleles → two slightly different but functional enzymes. For another example of multiple alleles, see Sadava fig. 12.8 (12.10).



See problem 9-2 for a simple case of co-dominant inheritance. See 9-5 for a review of the genetics of the ABO blood type. For role of ABO in transfusions, see Sadava fig. 12.10 (12.12).

E. Sex Linked Genes -- How can alleles on the X chromosome be dominant or recessive?

1. No dominance at cell Level -- Effects of Inactive X. Since only one X chromosome works per cell, a heterozygous female should be a mosaic. Some cells should use the X with the mutant allele and have a mutant phenotype; some cells should use the normal X and have a normal phenotype. This is what occurs, so there is no dominance on the ***cell*** level in a female,

2. Dominance exists at level of the organism. If half the cells express allele A and half express allele A*, the organism as a whole may have a normal or mutant phenotype. Therefore, even with the inactive X, you can have dominance on an ***organismic*** level for genes on the X.

3. Examples where the normal phenotype is dominant (at the organismic level):

a. Hemophilia. Hemophilia is caused by a lack of a clotting factor encoded by a gene on the X chromosome. Gene has alleles H and h. (H = good allele = A; h = inactive allele = A*) In a heterozygous Hh female, only one X chromosome works per cell, so woman is mosaic -- the H allele is used in some cells and the h allele in the others. Therefore 1/2 her cells will make good clotting factor and half will make none. However the clotting factor is secreted into the blood, so her blood will contain clotting factor. Even though some cells make clotting protein and some don't, her blood overall will contain enough clotting protein so there'll be no problem. (Remember the usual case is that 1/2 of the usual amount of enzyme is enough; the clotting factor is an enzyme.)

b. Colorblindness. A female heterozygous for red/green color blindness is heterozygous for red/green light receptors. The genes for the receptors are on the X. However heterozygous women usually have normal red/green vision since aprox. every other cell has good light receptors. In this case, the mosaic is so finely grained it isn't noticeable. See Sadava fig. 12.19 (12.21).

To review issues of dominance of X-linked traits, look at 9-9B and 9-14.

VI. Dominance & Genetic Conditions -- some additional features to consider.

Sections VI & VII are included here for reference. They overlap much of the material above.

A. Disease vs variation: Some of the examples above involve "normal variation" -- blue vs brown eyes, orange vs. black cats. Neither blue nor brown is considered "abnormal" or "mutant." Some examples involve genetic diseases, where one phenotype is clearly "abnormal" and the other is not. In some cases, it is not clear cut what is "normal" and what is not.

B. Inherited Diseases -- how to define a disease as dominant or recessive. Terminology for genetic diseases

1. Dominant conditions: If one A* causes disease = effects of A* show up even in presence of A = A*_ is sick (whatever allele is in the blank), then you call A* and/or the disease it causes dominant. It doesn't matter if if two A* alleles are worse than one, and A*A* is sicker than A* A. As long as both homozygotes and heterozygotes have symptoms, the disease is considered dominant, although strictly speaking it should be considered partially dominant (if homozygous A*A* is sicker than a heterozygote).

2. Recessive conditions: If it takes two A* alleles to cause disease, so only homozygotes (A*A*) are affected, allele and/or disease it causes are called recessive.

3. How is this terminology different than usual? In many cases, A* is considered dominant if AA* and A*A* have the same phenotype. Conversely, A is considered dominant if AA* and AA have the same phenotype. If AA* has an "in between" phenotype, then neither allele is considered to be dominant or A* is said to be partially dominant. For genetic diseases, A* is usually considered dominant if AA* has symptoms, even if they are not as severe as for A*A* (as for hypercholesterolemia.)

VII. Summary of Options for Treatment, Diagnosis & Prevention of Genetic Diseases

A. Alteration of Diet -- in some cases altering the diet can avoid or alleviate the consequences of genetic blocks. Details above for PKU, galactosemia.

B. Drugs -- in some cases drugs can alter enzyme production or activity and circumvent (or alleviate) consequences of genetic blocks. (See details above for Hypercholesterolemia and CF). Drugs are often more effective when combined with an alteration of diet.

C. Protein or Gene replacement -- Protein replacement works in a few cases, and gene therapy is under development; see above.

D. Prevention -- what can you do if there is no treatment?

1. Why carrier testing? (For recessive conditions.)

A*A* or aa individuals come primarily from marriages of two heterozygotes (affected individuals don't usually marry and reproduce). If one parent is AA and one is Aa, child can not inherit the disease since child cannot inherit two a's. In other words, a couple (with normal pheno) is at risk of having an affected child only if both parents are Aa. If potential parents are tested, and are both Aa, they can avoid having an aa child by various procedures -- adoption, artificial insemination, egg donation, etc. Or they can do prenatal testing as follows.

2. How do you do Carrier Testing for recessive conditions?

How can you detect carriers if their phenotype is normal? Carriers or heterozygotes usually produce about 1/2 as much enzyme as homozygous normal. This occurs because transcription of structural genes is often not regulated, so all copies of the gene are expressed (transcribed) constitutively. AA individuals have two copies of the gene, so they make two units of mRNA and a corresponding amount of protein (100%). AA* (Aa) heterozygotes have only one copy of the (working) gene so they make one unit of (working) mRNA and 1/2 as much protein (50%). As long as some enzyme is present, there is no block in metabolism and the "job gets done." That is why Aa and AA have the same gross phenotype. But their enzyme levels are different, and this allow testing and detection of carriers. (DNA tests can also detect many carrier states.)

3. Amniocentesis, prenatal testing & therapeutic abortion

Cells of fetus can be harvested by amniocentesis (sampling of fluid surrounding the fetus). Fetal cells can be tested for DNA and/or enzyme levels and for chromosomal abnormalities. If mutation causing a disease is known, DNA can be tested directly. For recessive conditions, enzyme levels in fetal cells can be tested; in an aa fetus, enzyme level will be zero. (DNA must be tested if cells in

amniotic fluid do not express the enzyme/gene.) If parents wish to do so, an affected fetus can be aborted. Whether a therapeutic abortion is appropriate, or not, is an ethical question to which there is no simple answer; the question is more difficult when the outcome of the disease is uncertain, or symptoms normally develop only at an advanced age (as for Huntington's). An alternative for couples at serious risk of passing on an inherited disease is PGD; see below.

4. PGD = preimplantation genetic diagnosis.

This involves fertilization *in vitro* followed by screening of early embryos prior to implantation. Embryos are checked for specific genetic mutations and only embryos lacking these specific mutations are implanted. This works because it is possible to remove one of the cells of the early embryo and test it without compromising the ability of the remaining cells to develop into a complete human being. For details see http://www.emedicine.com/MED/topic3520.htm.

VIII. Pedigrees and Ratios -- How do you follow the pattern of inheritance?

See handout 22B.

A. Ratios: How do you tell if a condition is dominant or recessive ?

For experimental plants and animals, you start with parents of known genotype, say a homozygous normal X homozygous affected, and cross them to get descendants (first an F_1 and then an F_2 generation). Each case should produce characteristic ratios of phenotypes (normal: in between: mutant) in the F_2. (See table above.)

1. If gene is autosomal, in F_2 expect phenotypic ratios of 3:0:1 (known as 3:1), or 1:0:3 (known as 1:3) -- if one allele is dominant, or 1:2:1 if alleles are partial or co-dominant. Note that dominance relationships depend on structure and function of gene product, not gene itself.

Problem 9-7 is an example of the use of ratios.

2. If a gene is sex-linked (on the X), the ratios of normal to affected will be different than those given above, and (at least in some cases) ratios will be different depending on which parent (normal or affected) is the female and which is the male. See Sadava 12.18 (12.20).

3. Terminology -- be sure to master these terms -- they are used in the Learner's Manual and in Exam Problems.

a. Test Cross: A cross of an individual (usually of dominant phenotype) with a homozygous recessive. For example, A_ X aa or A_B_ C_ X aabbcc. The results will tell you what is in the blank -- a dominant or recessive allele.

b. Backcross: A cross of an offspring (usually F1) to one of the parents, usually the homozygous recessive parent. (This is equivalent to a test cross, but the homozygote is a parent instead of a sibling or another individual of the same generation.) This is possible in many plants and animals, but of course, not in humans.

c. Reciprocal Cross: A cross where the sex of the parents is reversed, but all other factors are the same. For example, if you did tall, white male X short, red female, the reciprocal cross would be tall, white female X short, red male. Both crosses are tall white X short red, but in the first case the tall, white parent is the male, and in the second, reciprocal cross, the tall, white parent is the female.

For inheritance of X-linked traits (using ratios), see Problem 9-10.

B. Pedigrees -- How do you tell if a new human condition is dominant or recessive?

The obvious thing is to do the crosses as above and look at the ratios of phenotypes. But you can't cross people! So you look at pedigrees = crosses already done for you.

1. Example of a pedigree = top example on handout 22B. See also Sadava figs.12.7 & 12.19 (12.9 & 12.21).

Standard Symbols for Pedigrees:	
Squares = males	Circles = females
Roman numerals refer to generations.	
Filled in symbols = ■ or ● = affected individuals = people who have the condition or disease you are tracking.	Empty symbols = unaffected (normal) individuals.

Note: *a*ffected means "has whatever condition we are talking about." It is not the same as ***in***fected, which means "has been invaded by an infectious organism," such as a bacterium or a virus.

2. General procedure for analyzing pedigrees:

a. Use trial and error! You make a guess -- say, let's assume condition is autosomal and dominant. Then you try to assign each individual in the pedigree a genotype consistent with this assumption. If it works, that means condition could be autosomal dominant. If it doesn't work, you've ruled out autosomal dominant. You try to narrow down the possibilities as much as possible.

b. Don't Use Proportions*:* In most pedigrees the proportions of affected **:** normal in each marriage are not significant because the sample sizes are too small. If a Aa marries an aa and has a few kids, you don't expect to get an exact 1:1 ratio of Aa: aa in the offspring. Proportions are only useful in very large pedigrees or families with many descendants.

c. Do Use Impossible vs Possible. What matters in most pedigrees is whether the pedigree is possible -- could these parents have these kids and vice versa? You test for what is possible or not, not whether proportions from each individual family fit the expected.

d. Likely vs Unlikely. If more than one type of inheritance is possible (say dominant or recessive) consider which is more likely or requires less assumptions.

3. How you analyze top case on handout 22B:

a. How you rule out dominance -- because affected person (filled symbol) has normal parents. (Normal kids are consistent with a dominant parent; normal parents are not consistent with a dominant kid.)

b. How you show this condition could be recessive -- assign a genotype to each individual. Start with the affected person (II-1), who must be aa, then parents (must be Aa), then kids (also Aa). Spouse of affected person is A_ -- could be Aa or AA; if condition is rare, you assume spouse is AA.

c. Sex Linkage -- is it possible here? Check it out and see! You should be able to see why condition in this pedigree can not be recessive and sex linked. (Could affected mom have normal son?)

4. Things to note about second case shown on handout 22B.

a. This pedigree is consistent with dominant inheritance. Note that parents of II-1 have the condition being traced but her children do not. This is perfectly consistent with dominant inheritance -- If II-1 is Dd, one of her parents must have had D, but her kids can be dd.

b. This pedigree is consistent with recessive inheritance if and only if I-1 is a heterozygote (= carrier). It is very unlikely that I-1 is a carrier of the same condition affecting his spouse **if** the condition is rare, and the two partners are unrelated. If condition is common, what then?

c. Possible vs Likely: So both dominant and recessive inheritance are possible. But which is more likely, dominant or recessive? Does it depend on the frequency of the condition?

d. Could this condition be sex-linked? Try it for yourself. You should be able to see why condition could be dominant & sex-linked but not recessive & sex-linked.

For typical problems involving pedigrees, see 9-11 & 9-15.

IX. The Details Of Meiosis.

See Handout 21A. Details in Topic VII of previous lecture (# 21).

A. Why discuss this now? To follow inheritance of more than one gene requires knowledge of details of meiosis, in particular recombination (at prophase I) and independent assortment (at metaphase I). The previous lecture has all the details of the following:

B. Steps: These are diagrammed in detail in parallel to the steps of mitosis on handout 21A.

C. Prophase I -- Some Differences from Mitosis -- especially recombination/crossing over.

D. Metaphase I -- Important difference from Meiosis Chromosomes line up in pairs, not individually.

E. Products of human meiosis (see Sadava fig. 42.4 (43.3) or Becker fig. 25-8 (20-9))

1. In females: You get one large (haploid) egg per meiosis.
2. In males: When male germ cells go through meiosis, 4 sperm are formed.

To review Meiosis, and compare to Mitosis, fill in the table in Lecture 21, and do or finish problems 8-1, 8-2 (parts A to E), 8-3, & 8-8 (parts A-D & G). .

Next Time: Following inheritance of more than one gene at a time – consequences of recombination and independent assortment. If time, how we approach genetics of a population as vs. individuals.