C2005/F2401 '08 Lecture 20 -- Meiosis, Life Cycles, & Introduction to Genetics

Last update 11/25/2008 09:45 AM. A few minor typos were corrected; they are blocked in blue.

New Handouts: 20A -- **Super cycle and Nondisjunction** & 20B Crosses; not on web.
You'll also need Handouts 19A & B.

1. Wrap up of Karyotypes -- Chromosome Banding & Rearrangements

A. What do you see in a normal squash or karyotype? See notes of last time. To summarize, you can see

- Number of chromosomes
- Size, position of centromere, & banding pattern of each chromosome
- N & ploidy
- Sex chromosomes & autosomes

To review mitosis and karyotypes, try problem 8-8 parts A-D, & G.

B. What can you see in an abnormal karyotype?

1. 'Chromosomal' Mutations -- changes affecting whole chromosomes and/or large blocks of genes.

2. Types of chromosomal mutations

a. Rearrangements. You can pick up extra, missing and rearranged pieces. (If large enough, loss, additions, inversions, or translocations are visible.) Smaller changes must be detected using other methods. Remember -- bands contain multiple genes and so called 'gene mutations' involving single genes or bases are not visible in a karyotype.

b. Aneuploidy. You can see cases of missing or extra chromosomes. Most aneuploid fetuses abort spontaneously but a few survive to birth.

(1). Trisomy 21. The only autosomal aneuploidy that is not regularly lethal early in life is trisomy 21 or Down's syndrome. (Chromosome 22 may look smaller, but 21 is the autosome with the smallest amount of genetic information.) Individuals who are trisomic for chromosome 21 have multiple developmental problems which usually result in significant mental retardation, distinctive facial features and a tendency to develop Alzheimer's at a relatively early age. (The gene coding for the protein that clogs the brain in cases of Alzheimer's is on chromosome 21.) All these abnormalities are thought to be due to a "gene dosage" effect. All the gene copies are normal, but trisomics have 3 copies of the genes on chromosome 21 instead of 2. The extra copies of the genes produce extra protein (for a total of 3 doses instead of 2). The extra amount of protein is what messes up development.

(2). Aneuploidy of the sex chromosomes. This is usually not lethal as long as there is at least one X.

a. Examples. Individuals are known who are XXY, XO (O stands for no 2nd sex chromosome), XYY, XXX etc. Humans who are XO are female, but have certain abnormalities called Turner's syndrome. Humans who are XXY are male, and have Klinefelter's syndrome.

b. What determines maleness? The presence of Y or the absence of a second X? The sex of the aneuploid individuals described above indicates that it is the presence of the Y that is the male-determining factor in humans, not the absence of

the second X. The human Y chromosome has very few genes, but it has one critical gene (Sry) that triggers a sequence of events leading to male development; the default is female. (The case in fruit flies is different: XO flies are male, and XXY flies are female. In flies it is the ratio of X's to autosomes that determines sex.)

c. Why do XO and XXY survive? Why is an extra and/or missing X compatible with a more or less normal existence while a missing or extra autosome is almost always deadly? Because variation in the number of X's is "normal" -- females have twice as many as males, yet both males and females are "normal." So there must be a mechanism to cope with "extra" X's (or missing X's, depending on your point of view). See below.

d. FYI: Secondary Sex Characteristics. Most genes on X and Y have nothing to do with secondary sex characteristics (beard growth, breast development); most genes for secondary sex characteristics are autosomal (although some are on the X). Presence of Y determines which hormones are made and therefore which autosomal (and X linked) genes are turned on. If you add hormones externally, either sex can develop secondary sex characteristics of the other. Also note there is ***no*** correlation between unusual combinations of sex chromosomes and sexual preferences.

e. The birds & the bees. The mechanism of sex determination is similar in many other organisms, in that one sex has a matching pair of chromosomes (the homogametic sex) and the other has a non-matching pair (the heterogametic sex). Which is which, and the fine points of how the balance determines sex, varies. The sex ratio (males/females) is about 1:1 in all these cases because the heterogametic sex produces male-determining and female-determining gametes in equal proportions.

In birds, the female, not the male, is the heterogametic sex. In bees, one sex is diploid and one is haploid -- an extension of the sex-is-determined-by-chromosome-balance principle to the whole set of chromosomes. So when they say they are going to 'tell you about the birds and the bees', it's not a good way to explain human sex!

How do aneuploidies occur? Through mistakes in meiosis. Need to look at normal meiosis first.

II. Overview of Meiosis

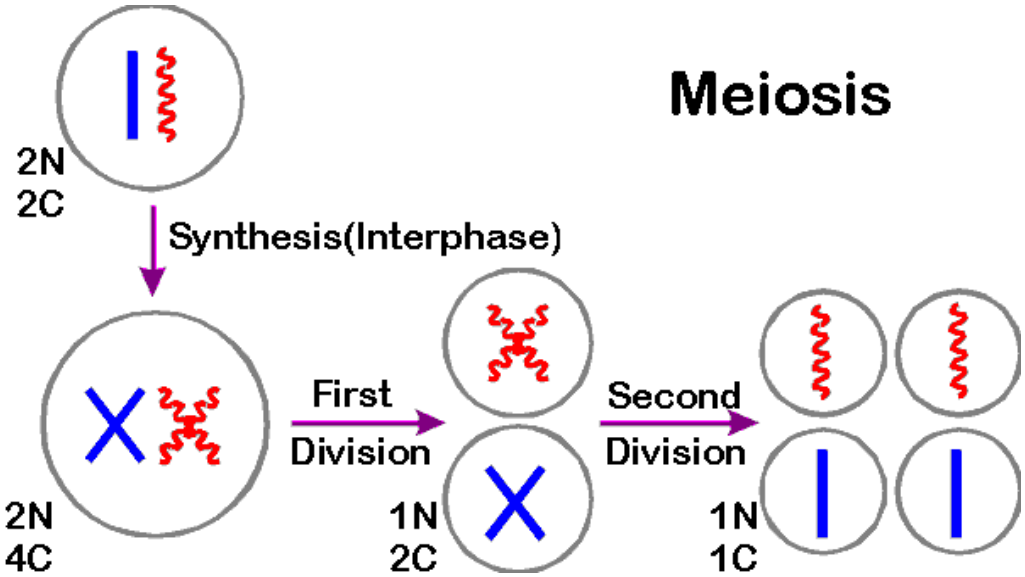
What happens to chromosomes during meiosis? -- **see Handout 19C, and picture below.** To summarize (more details in last lecture):

1. DNA synthesis occurs first -- before division. Just as in mitosis.

2. Products: There are 4 products, each haploid (from meiosis), instead of 2 products, each diploid (from mitosis).

3. Number of Divisions Meiosis consists of two divisions. (Mitosis has only one.) The first division of meiosis separates homologs; the second division of meiosis separates sister chromatids.

4. What happens to N, c and # of chromatids/chromosome in meiosis? The first division cuts the chromosome number & DNA content per cell in half. The second division cuts in half the DNA content per cell, the number of chromatids per chromosome, and the total number of chromatids per cell. What happens in a cell with one pair of chromosomes is shown on the bottom of handout 19C and below:



Picture above shows **all cells** at each stage -- before DNA synthesis, after S, after 1st div, and after 2nd div. See Becker fig. 20-3 for a similar diagram of meiosis in a cell with 2 pairs of chromosomes.

Handout 19B (top) shows a different view of the stages shown above. It emphasizes the 'chromosome cycle' -- the number of chromosomes, the number of chromatids, and the DNA content **per cell** at each stage. It summarizes the chromosome cycle for cells with one chromosome pair (N = 1), for 3 pairs (N = 3), and for any general value of N.

To review Meiosis (so far), and compare to Mitosis, do (or finish) problems 8-1, 8-2 (parts A to E), 8-3, & 8-8 (parts A-D & G).

III. The Mechanism of Meiosis -- see handout 19A.

A. Steps: These are diagrammed in detail on handout 19A, and comparisons to mitosis are summarized there. For similar diagrams of mitosis vs. meiosis see Sadava 9.19 (9.17) or Becker fig. 20-8 (20-9). For nicer pictures see Sadava 9.16 (9.14) or Becker 20-5 & 20-6.

B. What if N >1? Handout 19A shows what will happen to a cell with 1 pair of chromosomes. (2N cell, N =1.) If there are additional chromosome pairs (N > 1), each pair will line up independently at metaphase I. This has important genetic implications, as will be discussed later.

C. Prophase I -- Some Differences from Mitosis

1. Crossing over. This is the time when recombination occurs by a "cut & rejoin" mechanism, which switches equivalent sections of chromosomes between 2 members of a pair. Recombination requires pairing, so homologous chromosomes are paired in pro. I of meiosis but not mitosis. More details to follow. (Pictures of pairing are shown in the texts.)

Note: Crossing over (recombination) involves cutting and rejoining of double stranded DNA molecules; production of mRNA (splicing) involves cutting and rejoining of single stranded RNA molecules.

2. Duration. Prophase I in meiosis is generally much longer and more complex than prophase in mitosis. (Both texts divide prophase into early, mid and late substages; Becker 20-6 (20-6 & 20-7) has even more details if you are curious.) Pro. I can be very prolonged -- in human females, it lasts from before birth to the time the egg is shed. Consequences of this very long pro. I are discussed below.

D. Products of human meiosis (see Sadava 42.3 (43.3) or Becker fig. 20-9 [20-10])

1. In Females: When female germ cells go through meiosis, the equivalent of 4 haploid nuclei are formed, but only one ends up in an egg. The genetic material that would end up in the "other 3" nuclei is shunted aside --it forms small structures called polar bodies. The egg contains (at least) the amount of cytoplasm that would be sufficient for 4 meiotic products and the genetic information of only one.

2. In males: When male germ cells go through meiosis, 4 sperm are formed.

IV. Life Cycles -- How do meiosis and mitosis fit together? Or how does 1 multicellular organism give 2? Or better, for organisms engaging in sexual reproduction, how do 2 (parents) give 1(offspring)?

A. Supercycle -- Handout 20A (top).

1. General idea -- Overview

Many different life cycles are possible, depending on the number of mitotic divisions that follow meiosis and/or fusion. The diagram on the top of handout 20 labeled "Supercycle" shows a generalized life cycle and explains the terminology. (Sadava 9.14 (9.12) or 28.4 (29.2) is equivalent; Becker fig. 20-4 is similar.) If an organism goes through all the stages shown, then it has both haploid and diploid phases.

2. Haploid vs Diploid Life Cycles

a. Diploid Life Cycle. What you get if meiosis → gametes. An organism can skip most of the stages on the left half of the supercycle diagram and go directly from germ cells to gametes. Such an organism has a basically diploid life cycle, as humans do. See Becker, fig. 20-4 (d) [18-4 (d)].

b. Haploid Life Cycle. What you get if the zygote divides immediately by meiosis, not mitosis. An organism can skip most of the right half of the diagram if the zygote divides immediately by meiosis, not mitosis. Such an organism has a basically haploid life cycle. Some simple algae are like this. See Becker fig. 20-4 (b).

3. Alternation of Generations What you get if you don't skip any stages; common in plants.

- Most plants go through both haploid and diploid phases, with mitotic divisions of both haploids and diploids. However the haploid phase is so short (involves so few mitotic divisions) that the haploid form of the organism is usually not visible to the naked eye.
- Both phases may be visible. A few of the simpler plants, such as moss, produce both haploid and diploid forms that are visible to the naked eye. See Sadava 28.3 & 28.5 (29.5 & 29.9) and/or Becker fig. 20-4 (c). You can see both the sporophyte (spore bearing form of plant) and the gametophyte (gamete bearing form of plant).
- For moss, the green fuzzy stuff is haploid and produces gametes, so it is called the gametophyte = gamete-bearing plant. Two gametes fuse to form a zygote, which divides by mitosis to produce the brown stalks (diploid) on top of the green mat. Some cells of the stalk go through meiosis to produce spores (inside the capsule at the end of the stalk), so the stalk is called a sporophyte = spore-bearing plant.

4. Gametes and Spores -- Terminology

- Two ways to get gametes -- by meiosis of 2N or specialization of N cells. Moss produces gametes by specialization of haploid cells; humans produce gametes by meiosis of diploids.
- Products of meiosis can be spores or gametes. In moss, the products of meiosis are called spores, not gametes, because the meiotic products are going to divide by mitosis (before specializing to make gametes). In humans, the products of meiosis are

called gametes.

- Gametes vs spores: If meiotic products will never divide by mitosis, but simply fuse to form a zygote, then they are called gametes. If the meiotic products are going to divide by mitosis, then they are called spores. {Q&A}

5. Super cycle can reduce to haploid or diploid life cycle

a. Diploid Life Cycle. If meiosis → gametes. No mitotic division of haploids. No spores.

b. Haploid Life Cycle. If zygote → immediate meiosis. (Meiosis → spores, not gametes.) No mitotic division of diploids. No germ cells.

B. Some implications of this cycle:

1. The Problem of Development. If zygote→ us by mitosis; how does development work? If all cells have the same DNA, why do cells make different proteins? In other words, why are the genes 'expressed' differently in different cell types? What sets and maintains the switches? How differential gene expression is set up and maintained is not entirely understood, but will be discussed some more next term.

2. Forensics. Virtually all the cells of the adult have the same DNA. Therefore you can can compare DNA from a suspect to DNA found at the scene of the crime. It doesn't matter what types of cells the DNA comes from -- hair, saliva, blood, sperm, etc.

3. Amniocentesis. If all cells of fetus have same genes/DNA/chromosomes, you can test the DNA or chromosomes of any fetal cell to look for abnormalities, even if the gene involved only affects (makes proteins in) certain specialized tissues. If you identify a fetus that will have sufficiently serious disabilities, you have the option to consider a therapeutic abortion. There are several current ways to test fetal cells, and more ways are under development. The most common current method is amniocentesis (testing fetal cells from amniotic fluid). *Some examples: these will not be discussed in class but are included FYI.*

a. Gene Mutations. You can look at DNA sequence (by PCR, use of probes, etc) for smaller changes affecting one or a few genes and/or nucleotides (so called "gene" mutations). Sometimes you can look at the protein the gene makes as in case (1) below, but sometimes you have to look at the DNA instead as in case (2). Some examples:

(1). Tay-Sachs disease. The gene that causes Tay-Sachs disease (when mutant) codes for an enzyme. The enzyme is made in many cell types, including the cells in the amniotic fluid. Using amniotic fluid cells, you can look at the DNA or measure the enzymatic activity of the protein made from the gene.

(2). PKU. The gene that causes phenylketonuria or PKU (when mutant) codes for an enzyme (PAH) that is made only in liver cells. So using amniotic fluid cells, you can't measure the activity of the enzyme. But you can test the state of the gene itself (in amniotic fluid cells) to see if the gene is normal or mutant.

b. Chromosome Mutations. Since you can do banding, you can tell all the chromosomes and chromosome regions apart. Therefore you can detect large abnormalities affecting whole chromosomes and/or large blocks of genes (so called "chromosomal" mutations) from looking at karyotypes as discussed previously.

To review life cycles, cell cycle, etc. and how they all fit together, try 8-11 and/or 8-14.

V. Non disjunction -- see handout 20A bottom.

A. Where do individuals with missing and extra chromosomes come from?

Answer: Mistakes in Meiosis. Two types of mistakes:

- Homologs can fail to separate (fail to "disjoin") properly at first division (= 1st div. nondisjunction), or
- Sister chromatids can fail to separate properly at second division (= 2nd div. ND).

Either way, nondisjunction gives gametes with extra and/or missing chromosomes (aneuploidy). See handout 20A, bottom half of page. When an aneuploid gamete (= gamete with missing or extra chromosomes) from one parent meets a normal gamete from another parent, then a monosomic or trisomic zygote is formed. The zygote can divide by mitosis to produce an aneuploid individual. Aneuploid zygotes containing missing or extra autosomes usually do not develop into viable individuals, but aneuploid zygotes containing missing or extra sex chromosomes (XO, XXY, XXX etc.) are usually viable as long as there is at least one X. (Why is this? See below.)

On handout 20A: Note that second division ND can involve either the "straight" or the "wiggly" chromatids, but only one case is shown. Also note that the "empty" cell is not really empty -- it is only missing a chromosome from the pair involved in ND. It has all the other chromosomes, but they are not shown to keep the picture as simple as possible. ND is an error than generally affects only one event at a time -- one pair of chromatids or one pair of homologs fails to separate at one stage of meiosis. Only one mistake per meiosis is likely -- usually all other separations of chromosomes and chromatids proceed normally. See Sadava 9.20 (9.18).

B. What types of aneuploidy are common? See above for details.

1. Trisomy 21.

2. Aneuploidy of the sex chromosomes.

To review Nondisjunction, try 8-8E & 8-9.

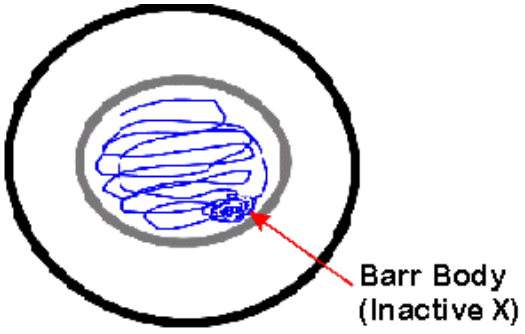
VI. Inactive X's and Barr bodies -- Why are extra or missing X's usually tolerated, while extra or missing autosomes are not?

A. Lyon Hypothesis = inactive X Hypothesis

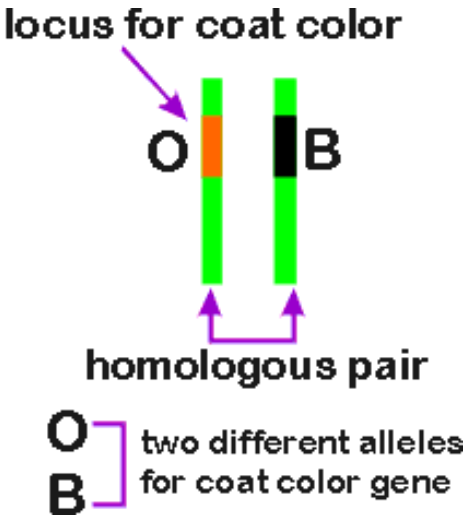
The idea that extra X's are genetically inert is called the Lyon hypothesis (or the inactive X hypothesis). According to the Lyon hypothesis, every female is a mosaic, since some of her cells use her maternal X to make proteins and some use her paternal X.

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. How is mosaic detected? Summary of Basic Genetic Terminology



Consider coat color in cats. This is how Lyon actually figured out the inactive X existed. 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.

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

Females have two X's, so they carry two alleles of the coat color gene -- one on each X. A female can be ***homozygous*** black (have 2 black alleles), be ***homozygous*** orange (have 2 orange alleles), or be ***heterozygous*** (have one allele of each color), as shown in figure. Females 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.)

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

Fertilized egg (zygote) → ball of cells → each 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 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.

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

VII. Patterns of Inheritance -- An example and the general principles -- See Top half of Handout 20B

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)?

We'll start by looking more closely at the example of orange/black coat color in cats and then go on to other examples and the general case.

B. How do you figure out the pattern of Inheritance? -- an example for a gene on the X -- the orange fur color trait**. For a different classic example of inheritance of a sex-linked trait, see Sadava 10.23. (For this, and many of the other figures in this lecture, the fig. or table # is the same in the 7th & 8th editions of Purves/Sadava.)

***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.)*

Consider a gene on the X such as the one that determines orange vs black coat color. Suppose you mate a tortoiseshell female cat X orange male (see handout 20B). 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. For genes on the X: Male has only one copy (allele) of the gene, female has two copies (alleles). For a genes on an autosome), both male and female have two alleles of each gene. Autosomal case will be discussed next time; is shown on bottom of 20B.

b. Review of terminology (for an individual with two alleles). If both alleles are the same, individual is said to be homozygous or a homozygote. In this case, a homozygous cat can be either homozygous black or homozygous orange. If the two alleles are different, the individual is said to be heterozygous or to be a heterozygote. A tortoiseshell cat must be heterozygous.

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. Sister chromatids must be identical since they are the 2 products of a single, semi-conservative, DNA replication. (See ** below.)

b. Homologs need not be identical -- one came from the mother and one 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. 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.

3. Go through meiosis: Homologs separate at first division and sister chromatids separate at second division. This produces 4 gametes -- two different kinds, but in equal proportions (again assuming no crossing over**).

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 20-13 (20-14) or Sadava 10.19. Crossing over occurs in both 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).

4. Do fusion of gametes from both parents to get zygotes (cats). You can use a Punnett square (or simple probability) to keep track of all combinations and proportions. This gives you the genotypes of the offspring (zygotes).

5. Look at genotypes and infer phenotypes of offspring = what develops from zygotes. Consider all possible combos and what proportions they occur in. Note that in this case there is no dominance, so phenotype follows directly from genotype. 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. Cat is black in areas where X with B allele is on active X; cat is orange in areas where X with O allele is on active X. (See below for mechanism of determination of black vs. orange.)

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. 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).

C. How does genotype determine phenotype?

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.

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, called "O" and "B" above.

3. What determines orange vs black?

What differs between orange and black cats is the activity of the second enzyme. 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).

4. General Case.

- We will see many cases like this where one allele → working peptide and other allele does not.
- This is not always the case -- sometimes one allele → working peptide and other allele gives an altered, but working, peptide, as in HbA vs HbS or bloodtypes A and B.
- What happens to phenotype (in a heterozygote) usually depends on job of peptide, and whether gene is on X or autosome. More examples next time.

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.)

Next time: How does inheritance work for autosomal genes? See bottom of handout 20B.