C2005/F2401 '07 Lecture 20 -- Meiosis, Life Cycles, & Introduction to Genetics

Last update . Handouts: 20A (**Super cycle** **and** **Nondisjunction.**) Also need 19A & B.

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

A. What do you see in a normal squash or karyotype?

1. Can see number of chromosomes, size and shape (determined by position of centromere) for each chromosome and can identify each individual chromosome by banding techniques. (Banding = procedure to stain chromosomes with standard dyes; different dyes give different patterns of dark and light regions. Each band = block of 100's of genes, not a single gene.)

2. Each species has a standard karyotype with a fixed number of chromosomes. You can use similarities and differences to evaluate relationships between species and to detect certain abnormalities which we will discuss later. Same number in all body (somatic) cells and in each generation.

3. Important general features of a (normal) karyotype -- 'N' and 'ploidy' were explained last time.

4. Homologs

a. Definition: Homologs = all the chromosomes of each type. Except for sex chromosomes, homologs have same size, banding pattern, & position of centromere (shape).

b. Number: There are 2 homologs = 2 of each type of chromosome in diploid cells. One from mom, one from dad.

c. Relationship of genes on homologs; alleles. Homologs (except for sex chromosomes) carry homologous DNA. They carry the same genes, in the same order, in corresponding places (loci), but they do not necessarily carry the same version (allele) of each gene.

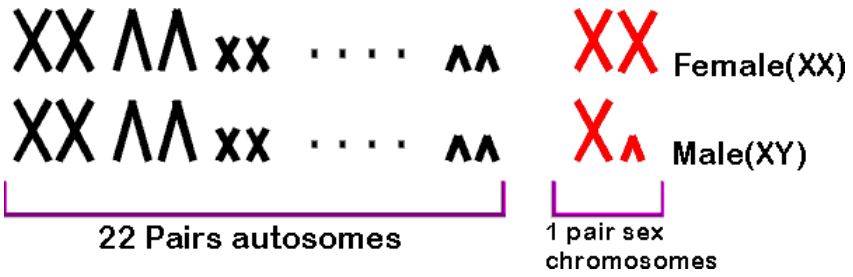
For example, the gene for eye color is in the same place on both homologs, but the "eye color gene" on a particular chromosome could be the blue-determining version or the brown-determining version. Each alternative version of a gene is called an allele. Each homolog carries one allele of the eye color gene. Homologs carry the same genes, but not necessarily the same alleles.

Another example: Consider the gene for the beta chain of Hemoglobin -- the beta chain gene is always in the same position, but the chromosome could carry the Hb A or Hb S allele (version) in the Hb position (locus).

d. Sister chromatids vs homologs: Sister chromatids = 2 halves of a doubled chromosome. Why are they identical? Because they contain the two products of a semi-conservative DNA replication. Homologs **need not be** identical -- each came from a different source (a different parent). Important: be sure you know the difference between homologs (homologous chromosomes) and sister chromatids. **See problem 8-8, part A.**

5. Human karyotypes -- sex chromosomes & autosomes. See Sadava 9.15 (9.13) 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.

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



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 that do not look alike but act as a pair during meiosis. The 22 pairs of chromosomes that are the same in both sexes are called autosomes. The remaining pair are called sex chromosomes, and the big one is called the X chromosome and the little one the Y chromosome. So females are XX and males are XY.

B. What can you see in an abnormal karyotype?

1. 'Chromosomal' Mutations as vs 'gene' mutations.

a. 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) from looking at karyotypes. Many of these abnormalities are associated with known genetic conditions -- diseases and/or tendencies thereto.

b. Large changes that are visible in a karyotype are known as "chromosomal" mutations. Only changes in large sections containing many genes (kilobases not bases) are visible in karyotypes.

c. Changes that are too small to be visible in a karyotype are usually called "gene mutations." Changes of a few bases or even a few genes **cannot** be detected in a karyotype. Remember that each band on a chromosome is a large block containing hundreds of genes.

2. What can you see?

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.

b. Aneuploidy. You can see cases of missing or extra chromosomes, as explained last time. 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 Alzheimers at a relatively early age. (The gene coding for the protein that clogs the brain in cases of Alzheimers 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? See below. To review mitosis and karyotypes, try problem **8-8 parts A-D, & G.**

II. Overview of Meiosis

A. What is meiosis for?

1. Need for meiosis/reduction division -- to keep karyotype & ploidy constant from generation to generation.

Most of the cells of most higher organisms are diploid. Humans, for example, have 46 chromosomes, or 23 pairs, in virtually all of their cells. If eggs and sperm also have 46 chromosomes, the next generation, formed from the fusion of an egg and a sperm, would have 92 chromosomes. But clearly the chromosome # does not double each generation. So the eggs and sperm, unlike all other cells, must have only 23 chromosomes and be haploid. So there must be a

way to make haploid cells from diploid cells. There is, and the process is called meiosis. During meiosis, one chromosome from each *pair* is picked at random so that the resulting haploid has 23 chromosomes instead of 23 pairs. Then 2 such haploids fuse, during fertilization, to give you back a diploid with 23 pairs.

2. Why bother with all this? Why sex?

After all, you could start the next generation with one complete diploid cell from either parent and save yourself a lot of trouble! Some organisms do reproduce this way, at least some of the time, but most organisms engage in sexual reproduction. They probably do so because each cycle of meiosis, followed by fusion, allows for a new combination of chromosomes. (Crossing over, which occurs at meiosis, also allows for new combinations of genes within chromosomes as well.) So it looks like sexual reproduction is useful because it allows reshuffling of the genetic material (same argument as for bacteria). Reshuffling is needed to give new variety (for selection to act on) and/or for repair (& replacement) of damaged copies.

3. How reshuffling works

a. Reshuffling Chromosomes.

Suppose one person has 2 identical copies of chromosome #1 and 2 identical copies of chromosome #2. (Draw these chromosomes in one color, say pink.) Another person has 2 copies of chromosome #1 that are the same as each other but different from the copies in the first person, and similarly for chromosome #2. (Draw these chromosomes in another color, say white.) The offspring of these two people will have a mixture of "pink" and "white chromosomes. After several generations, it will be possible to get all conceivable combinations of "pink" and "white" chromosomes. **(See problem 8-4 parts A & B.)**

b. Reshuffling genes:

In addition to reshuffling whole chromosomes, equivalent parts of chromosomes can be reshuffled or exchanged. Homologous chromosomes pair and can exchange equivalent sections during meiosis by crossing over. (This is equivalent to what happens to bacteria during transformation, transduction, etc., but in eukaryotes the process is restricted to prophase I of meiosis.) See Sadava 9.17 & 9.18 (9.15 & 9.16) or Becker fig 20-17 (18-17). Note: the term "genetic recombination" usually refers to reshuffling of genes by crossing over. It is sometimes used in a more inclusive sense to mean all kinds of reshuffling (of genes and/or chromosomes) whether crossing over is involved or not.

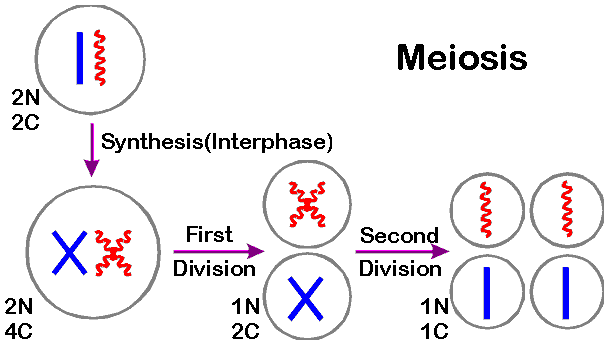
B. What happens to chromosomes during meiosis? -- **see Handout 19B, and picture below.**

1. DNA synthesis occurs first -- before division. Meiosis is preceded by DNA duplication just as mitosis is. During the S before meiosis (or mitosis) the cell doubles the DNA content and # of chromatids per chromosome. So cell starts with pairs of doubled chromosomes = 4 copies of each chromosome.

2. Products: There are 4 products, each haploid (from meiosis), instead of 2 products, each diploid (from mitosis). To cut the number of copies of each chromosome from 4 to one requires 2 division, not one.

3. Two divisions of meiosis: 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? The first division cuts the chromosome number per cell in half from 2N to N and cuts the DNA content per cell in half from 4c to 2c ("c" is defined below). The second division halves the DNA content per cell (from 2c to c), halves the number of chromatids/chromosome (from 2 to 1) and halves the total chromatid # per cell (from 2N to N). What happens in a cell with one pair of chromosomes is as follows:



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 (18-3) for a similar diagram of meiosis in a cell with 2 pairs of chromosomes.

Handout 19B 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.

C. Definition of c

"c" is a measure of DNA content per cell, not the number of chromosomes or chromatids.

c = minimum DNA content per haploid cell of an organism = DNA content of haploid cell before S (with unreplicated chromosomes) = DNA content of one set of chromatids. C is NOT equal to N; c is the DNA content of N chromosomes (with one chromatid/chromosome).

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. 20-9 (18-9). For nicer pictures see Sadava 9.16 (9.14) or Becker 20-5 & 20-6 (18-5 & 18-6).

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 20-7 (18-7) 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. 20-10 [18-10])

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 20B.

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 [18-4] 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) [18-4 (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) [18-4 (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 20B 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 20B, 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 20B: 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. usually all other separations of chromosomes and chromatids usually 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.

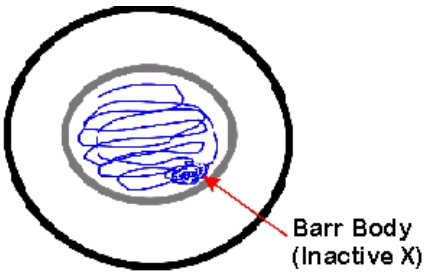
VI. Inactive X's and Barr bodies -- Why extra or missing X's are usually tolerated and extra or missing autosomes are not

A. Lyon Hypothesis = inactive X Hypothesis

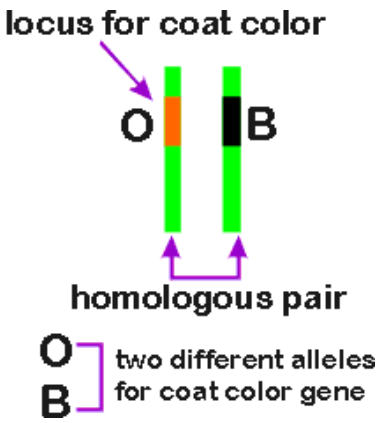
The idea that extra X's are genetically inert is called the Lyon hypothesis (or the inactive X hypothesis). According to the Lyon hypothesis, every female is a mosaic, since some of her cells use her maternal X to make proteins and some use her paternal X.

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? Intro. to 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 [18-2].)

Next time: How is orange vs black color inherited? And how does genotype determine phenotype?