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Office hours: Tuesdays 1-2, Thursdays 11-12
(except this week, Thursday only 11-1)

The Plan for this week:

Today:
Sex chromosomes:
dosage compensation, meiosis, and aneuploidy

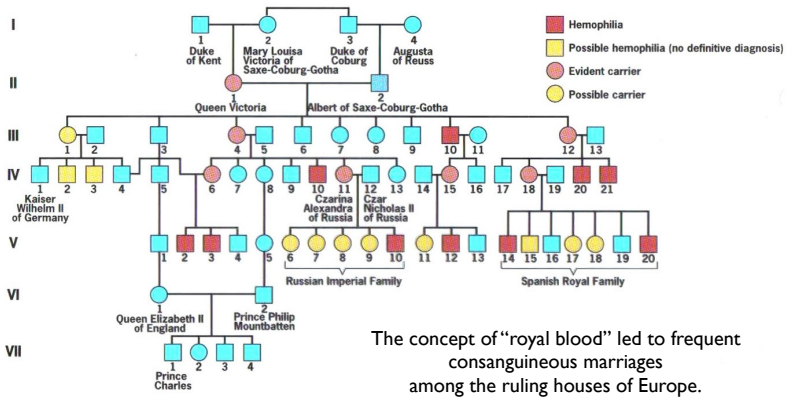
Wednesday/Friday:
Dissecting gene function through mutation (Chapter 7)

Professor Amacher already assigned the following reading and problems related to today's lecture:

Reading: Ch 4, p 85-88; Ch 6, p 195, 200; Ch 11, p 415; Ch. 18, skim p 669-677, Ch 13, 481-482
Problems: Ch 4, #23, 25; Ch 13, #24, 27 - 31

Let's talk about sex... chromosomes

We've learned that sex-linked traits show distinctive inheritance patterns



The concept of "royal blood" led to frequent consanguineous marriages among the ruling houses of Europe.

Examples of well known human sex-linked traits

Hemophilia A (Factor VIII deficiency)

Red/Green color blindness

Duchenne Muscular Dystrophy (DMD)

Male-pattern baldness*

*Note: male-pattern baldness is both sex-linked and sex-restricted - *i.e.*, even a homozygous female doesn't usually display the phenotype, since it depends on sex-specific hormonal cues.

Sex determination occurs by a variety of different mechanisms

Mating-type loci (in fungi) that "switch" their information

Environmental cues (crocodiles, some turtles, sea snails)

"Haplodiploid" mechanisms (bees, wasps, ants)
males are haploid, females are diploid

Sex chromosomes

We know the most about these mechanisms because
a) it's what we do, and b) it's also what fruit flies and worms do.

Plants, like animals, have both chromosomal and non-chromosomal mechanisms of sex determination.

The mechanism of sex determination is rapidly-evolving!

Even chromosome-based sex determination is incredibly variable

Mammals (both placental and marsupial), fruit flies, many other insects: *XX* ♀ / *XY* ♂

Many invertebrates: *XX* ♀ *or* ♂ / *XO* ♂ (*"O"* means "nothing")

Birds, some fish: ZW ♀ / ZZ ♂ (to differentiate it from the X and Y system)

Duckbilled platypus (monotreme, or egg-laying mammal):
$X_1X_1\ X_2X_2\ X_3X_3\ X_4X_4\ X_5X_5$ ♀ / $X_1Y_1\ X_2Y_2\ X_3Y_3\ X_4X_4\ X_5Y_5$ ♂ (!!?)

Note: these are given as *examples*. It's important that you know about mammals, but you don't have to memorize the others!

Definition: the "heterogametic" sex is the one with mismatched sex chromosomes (and thus two different classes of gametes, which determine the sex of the offspring). In mammals, males are heterogametic, but males are "homogametic" in bird species.

Even chromosome-based sex determination is highly variable

	XXX	*XX*	*XXY*	*XO*	*XY*	*XYY*	*OY*
Drosophila	dead	Normal female	Normal female	Sterile male	Normal male	Normal male	dead
Human	Normal female[1]	Normal female	Male with Klinefelter's syndrome (tall, usually sterile)	Female with Turner syndrome (short, sterile)	Normal male	Normal male[1]	dead

What does this tell us?

1. The human *Y* chromosome carries a "dominant" maleness gene (SRY or TDF).

2. In *Drosophila*, sex is not determined by the presence of the *Y*, but by the number of *X* chromosomes (actually the *X*-to-autosome ratio). The *Y* is only important for male fertility.

Sex-chromosome-based sex determination mechanisms pose two major challenges:

1. "Dosage compensation" - how to equalize the amount of gene expression from 1 vs. 2 chromosomes

2. Meiosis in the heterogametic sex - how do two unlike chromosomes separate from each other?

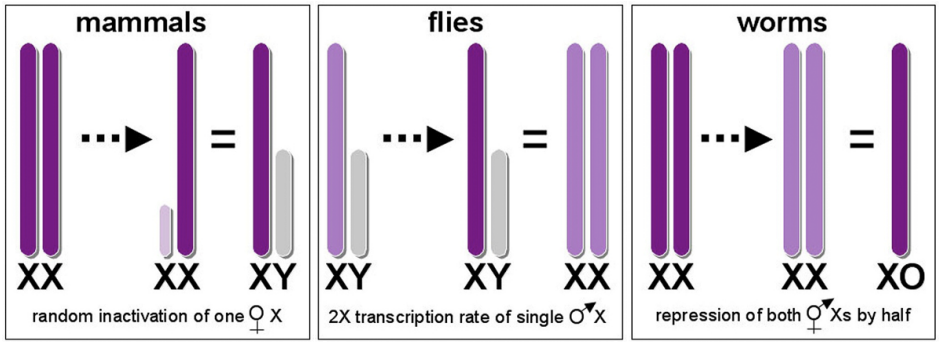
Mechanisms of dosage compensation, just like sex determination, show amazing variation

Mice, humans
XX ♀ / XY ♂

Fruit fly (*Drosophila*)
XX ♀ / XY ♂

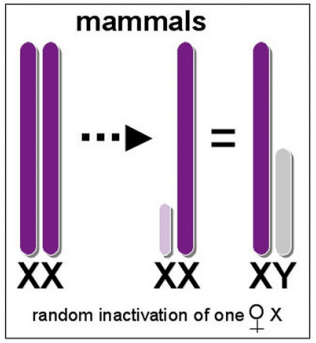
Nematode (*C. elegans*)
XX ♂ / XO ♂

How do these species equalize the expression of X-linked genes between the two sexes?



Sex determination and dosage compensation can be triggered independently

Mice, humans
XX ♀ / XY ♂



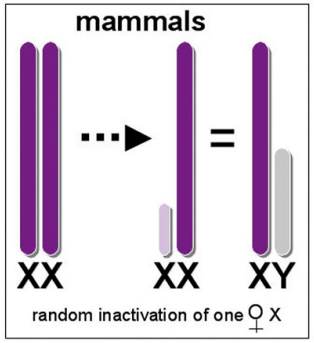
Note that in mammals, sex determination (*i.e.*, the development of sexually dimorphic anatomical features) and dosage compensation are determined independently, by separate mechanisms. The presence of a *Y* chromosome (or the TDF gene) specifies male sexual development, but *X*-inactivation is triggered in any cells having more than one *X* chromosome. Thus, *XXY* males (Klinefelter's Syndrome) undergo *X* inactivation.

Similarly, *XO* fruit flies are sterile (because the *Y* carries genes needed for sperm development), but develop as normal-looking males because they undergo dosage compensation.

X-inactivation in mammals occurs in early embryonic development.

The maternal and paternal X are inactivated randomly (or "stochastically") in cells of the early embryo.

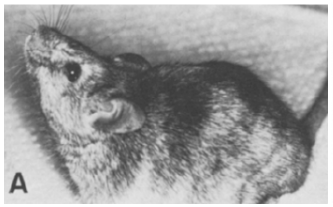
Mice, humans
XX ♀ / XY ♂



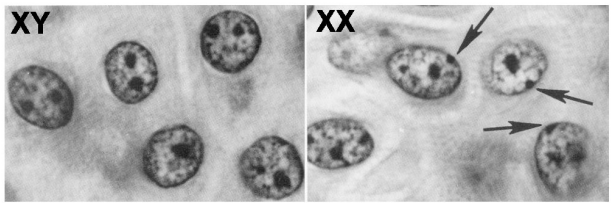
Random *X*-inactivation was proposed by Mary Lyon in 1961

Her argument was based on the "bridled," or "mosaic" appearance of coat colors in many female mice, but only extremely rare (and infertile) male mice

"Barr Bodies" (named for Murray Barr)



"brindled" mouse



Could these extra "heteropyknotic" or "heterochromatic" bodies in *XX* nuclei correspond to the inactive *X*?

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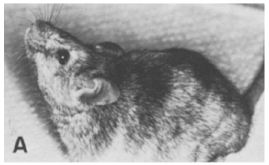


"brindled" mouse

Tortoiseshell

Calico

Tortoiseshell and Calico coat patterns in cats also reflect X-inactivation. Both patterns indicate heterozygosity at the *X*-linked *Orange* locus (*Oo*), and are thus almost always female (rare males are thought to be *XXY*). The Calico pattern results from a combination of the *Oo* mosaicism and a separate gene called *white spotted*

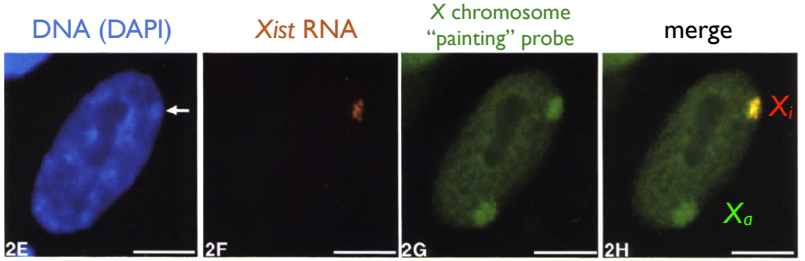
The mechanism of *X*-inactivation is still only partially understood.

It involves the production of noncoding RNAs from a region on the *X* chromosome called the *Xic* (*X* inactivation center)

Both *X* chromosomes initially produce both *Xist* and *Tsix*, but eventually a "choice" is made (it's not clear what breaks the symmetry between the two *X*s). After this tipping point, only the inactive *X* (X_i) continues to produce *Xist*.

This RNA spreads out to coat the whole chromosome!

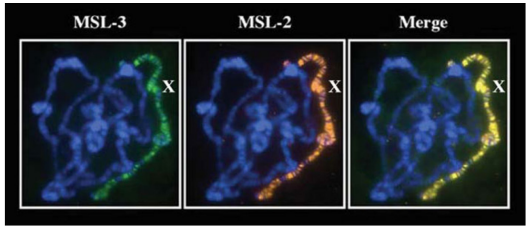
Somehow this leads to recruitment of other factors that shut off most genes on X_i.



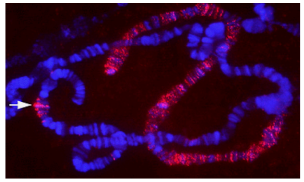
Clemson *et al.*, JCB 1996

Dosage compensation mechanisms in flies and worms involve recruitment of protein complexes to the male and hermaprhodite X chromosomes, respectively

Drosophila polytene chromosomes



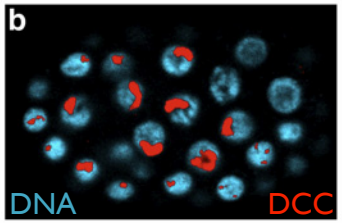
MSL= "male-specific lethal"



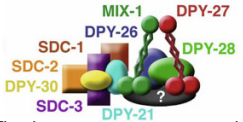
Like mammalian X-inactivation, this process requires expression of noncoding RNAs (*rox* genes) from the X chromosome.

However, it results in upregulation (rather than silencing) of the male *X*.

C. elegans embryo

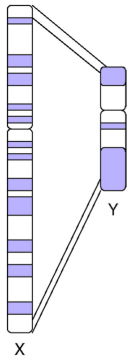


SDC= "sex determination and dosage compensation"



The dosage compensation complex (DCC) in *C. elegans* includes some proteins that are only expressed in hermaphrodites.

So how does the heterogametic sex accomplish meiosis?



Mammalian sex chromosomes have "pseudoatosomal regions" (PARs)

Why do human sex chromosome aneuploidies cause developmental problems?

45, XO - Turner Syndrome

only 1 in 50 (or fewer) *XO* fetuses survives to birth*
(yet 1 in 2,500 women is affected)

Women with Turner Syndrome show pleiotropic developmental disorders, and are infertile.

If one *X* chromosome is usually inactivated, then why do *XO* females show differences from *XX* females?

1. Not all genes on the *X* are subject to *X*-inactivation:

Genes in the pseudoautosomal region (PAR) are not dosage-compensated.
One of them, the *SHOX* gene, is likely responsible for the short stature of women with Turner Syndrome (and possibly the taller-than-average stature of *XYY*, *XXY*, and other extra-sex-chromosome karyotypes)

About 10% of genes on the *X* outside the PAR also "escape" *X* inactivation
Low expression of noncompensated genes may account for the *somatic* phenotypes associated with the *45, XO* karyotype

2. *X*-inactivation is a *somatic* process

Both *X* chromosomes are normally active in the female *germline*
(reproductive tissue, including premeiotic and meiotic cells).
A single *X* chromosome is lethal to developing oocytes.

*XO females that survive to birth and adulthood may be *mosaic* for the *XO* karyotype.
Alternatively, they may carry genes that modify the severity of the consequences of having a single *X*.

Why do human sex chromosome aneuploidies cause developmental problems?

47, XXY - Klinefelter's (or Klinefelter) Syndrome

Affects ~1 in 500 males (only *XYY* is more common)

Has mild somatic consequences - normal intelligence, tall stature.

Klinefelter's is often not discovered until puberty, or even later.

However, 95-99% of males with Klinefelter's Syndrome are infertile, or nearly so.
Testes are underdeveloped and few if any mature sperm are made.

Why?

An extra copy of *SHOX* in the PAR may cause tall stature.

The extra *X* chromosome is not inactivated in the germline, leading to defects in gonadogenesis and hormonal regulation.

An unpaired *X* chromosome leads to death of spermatocytes
(which, in turn, leads to atrophy of the testes).

Mosaicism & Chimerism

In rare cases, an organism will be made up of cells of 2 distinct genotypes.
This can happen in at least 2 different ways.

The more common way is for an embryo to undergo a mitotic error early in development, which usually results in chromosome loss. If the resulting cells can survive without the chromosome, both populations of cells may continue to expand, resulting in a ***mosaic*** embryo.

Some cases of Down syndrome are thought to be relatively mild because the extra copy of Chromosome 21 was lost at an early division, resulting in a mosaic embryo.

In animals with sex determination mechanisms based on *X*/autosome ratio, loss of an *X* chromosome can result in a "gynandromorph (half male, half female)

In future lectures, we will discuss how mosaicism can be a useful experimental tool in fruit flies and worms, and how also how it can be an indicator of elevated rates of chromosome loss in yeast.

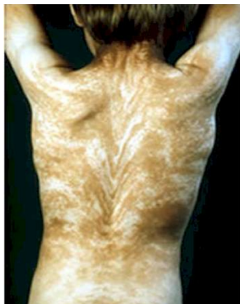
The Chimera
of Greek mythology

Tiger Swallowtail (Papilio glaucus) gynandromorph
(left half male, right half female)

A much rarer kind of mosaicism, ***chimerism*** results from the fusion of two fertilized eggs very early in development (the "vanishing twin"). This leads to the body being made up of two genetically distinct sets of cells.

This may go undetected (especially if both zygotes have the same sex chromosome makeup), but will sometimes be evident due to phenotypic differences between the two genotypes - for example, differences in pigmentation (see image on the right) or sex determination, resulting in intersex phenotypes.

Chimerism has been the basis for numerous court cases of disputed parentage (and was also incorporated into the plot of a CSI episode).



Lines of Blaschko are an indicator
of chimerism

Ethical issues arising from our understanding of the consequences of aneuploidy

Prenatal "karyotyping" by chorionic villi sampling (CVS) or amniocentesis is often used to analyze fetal chromosomes,
and is routinely suggested to women over 35.
(These procedures can be performed on mothers of any age, but there are small risks involved in CVS and amniocentesis,
and younger women are at a lower risk for aneuploid fetuses.)

This knowledge creates potential dilemmas when a fetus will have inevitable health issues (*e.g.*, Trisomy *13*, *18*, or *21*).

Things may get even more complicated for many people when there is an issue of mild or moderate severity (*e.g.*, *XXY*)

As genome haplotype mapping and sequencing become cheaper,
we will likely have access to vastly more detailed information about the genetic makeup of unborn humans.

The legal system hasn't begun to wrestle with this.