ANNOUNCEMENTS

- TODAY'S DISCUSSION MUST BE RESCHEDULED DUE TO AN UNAVOIDABLE FAMILY MATTER
- NEW TIME?

LECTURE 3: SEX DETERMINATION AND OTHER EXTENSIONS OF MENDELIAN GENETICS
JULY 7, 2011

1. Sex Determination (Chapter 4)
   - Different Mechanisms: Drosophila vs. Humans
   - Inheritance of sex-linked characteristics
   - Nondisjunction and the Chromosome Theory of Heredity
   - Dosage compensation
2. Extensions of Mendelian Genetics (Chapter 5)
   - Dominance, Incomplete Dominance, and Codominance
   - Penetrance and Expressivity
   - Lethal Alleles
   - Pleiotropic Alleles

SEX DETERMINATION

Sex determination: The mechanism by which sex is established

- In many organisms, sex is determined by a pair of sex chromosomes that differs between males and females.
  - Individual genes located on sex chromosomes are usually responsible for the sexual phenotypes.
- Autosomes are non-sex chromosomes which are the same for males and females (i.e. they have the same genes)

THERE ARE DIFFERENT WAYS TO DETERMINE SEX

XX-XY sex determination

- Females are XX
- Males are XY (the "heterogametic" sex)
  - Males have one X and one smaller Y chromosome
- X and Y are not generally homologous, but pair and segregate into different cells during meiosis
- e.g. some plants, insects, and reptiles, and all mammals

THERE ARE DIFFERENT WAYS TO DETERMINE SEX

XX-XO sex determination

- Females are XX
- Males are XO
  - Males have only one X (O indicates absence of a chromosome)
- e.g. grasshoppers and C. elegans

THERE ARE DIFFERENT WAYS TO DETERMINE SEX

ZZ-ZW sex determination

- Females are ZW (the "heterogametic" sex)
- Males are ZZ
- e.g. birds, snakes, butterflies, some amphibians, and some fishes

THERE ARE DIFFERENT WAYS TO DETERMINE SEX

<u>Diploid vs. Haploid sex determination</u>

- No sex chromosomes; instead, unfertilized (haploid) eggs result in males, while fertilized (diploid) eggs result in females
- e.g. bees, wasps, and ants

THERE ARE DIFFERENT WAYS TO DETERMINE SEX

- In addition, other mechanisms are possible, including genic sex determination in plants, fungi, and protozoans (no sex chromosomes), and environmental sex determination in many reptile species

SEX DETERMINATION IN *DROSOPHILA*

Table 4.1 Chromosome complements and sexual phenotypes in *Drosophila*

Sex-Chromosome Complement	Haploid Sets of Autosomes	X : A Ratio	Sexual Phenotype
XX	AA	1.0	Female
XY	AA	0.5	Male
XO	AA	0.5	Male STERILE
XXY	AA	1.0	Female
XX	AAA	0.67	Intersex

X:A ratio determines sex in Drosophila

X/A = 1.0 → female
X/A = 0.5 → male
1.0 > X/A > 0.5 → intersex

HOW DOES THIS WORK?

- There is an X-linked gene that determines "femaleness"

–This gene is inhibited (more on this later) by autosomal genes

–When there are more copies of the autosomal genes than the X-linked genes, "femaleness" is inhibited

–So, why have a Y?
 –The Y is necessary for male fertility

SEX DETERMINATION IN HUMANS

- Humans also use an XX-XY system, but it is the Y chromosome that is the "deciding factor" (well, sort of)
- How do we know that the Y determines "maleness"?
- Variations in sex chromosome complement (sex chromosome aneuploidy)

VARIATIONS IN SEX CHROMOSOME NUMBER

- XXY: Klinefelter Syndrome
  - 1/500 live births
  - These individuals are male
  - Small testes, gynocomastia, hip rounding , reduced facial and body hair (feminization), often sterility (no sperm production)
- XO: Turner Syndrome
  - 1/2000 live births
  - These individuals are female
  - Rudimentary ovaries, short stature, underdeveloped breasts, sterility, no real masculinization

VARIATIONS IN SEX CHROMOSOME NUMBER

- XYY condition: 1/1000 live births
  - These individuals are male
  - No obvious abnormal phenotype; possible slightly lower intelligence; tall
  - Elevated frequencies in prisons and mental institutions (nonviolent antisocial behavior)
- XXX condition: 1/1200 live births (estimated)
  - These individuals are female
  - These individuals are completely normal; in fact, only detected when karyotyped for another reason

CONCLUSION?

- The presence or absence of the Y chromosome determines sex in humans (usually - more on this later)

BASIC REPRODUCTIVE EMBRYOLOGY:

NATURE'S FIRST CHOICE IS "BOTH"

We all start out the same:

Indifferent gonads

+

Mullerian ducts (female) AND Wolffian ducts (male)

GONADAL SEX IS CHROMOSOMALLY DETERMINED

- SRY (Sex-determining region on the Y) encodes "testis determining factor" (TDF)
- TDF is the "maleness" signal for the indifferent gonads
  - In an XY individual, TDF signals the indifferent gonad to develop as testes.
  - In an XX individual, the absence of TDF leads the indifferent gonads to develop as ovaries

IN AN XY INDIVIDUAL:

Y chromosome (SRY/TDF)

↓

Indifferent gonads

\+

Mullerian ducts (female) AND Wolffian ducts (male)

IN AN XY INDIVIDUAL:

Y chromosome (SRY/TDF)

↓

Testes

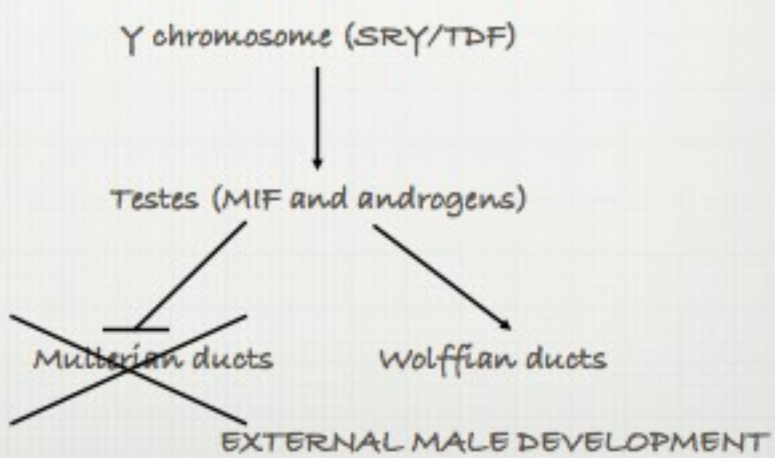
\+

Mullerian ducts (female) AND Wolffian ducts (male)

EVERYTHING ELSE IS HORMONAL

- Testicles secrete two important types of hormones:
  - Androgens, including testosterone
  - Mullerian Inhibiting Factor (MIF)

IN AN XY INDIVIDUAL:



IN AN XX INDIVIDUAL:

No SRY/TDF

Indifferent gonads

+

Mullerian ducts Wolffian ducts

(female) AND (male)

IN AN XX INDIVIDUAL:

No SRY/TDF

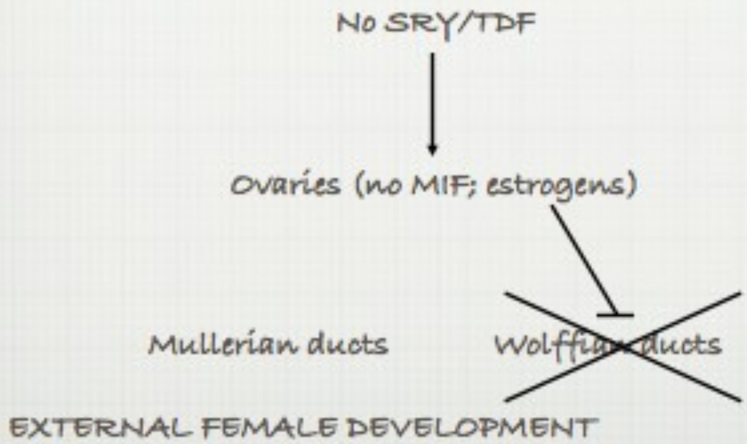
Ovaries (no MIF; estrogens)

+

Mullerian ducts Wolffian ducts

(female) AND (male)

IN AN XX INDIVIDUAL:



SEX DETERMINATION IN HUMANS

- The Y chromosome does only ONE thing: sends the TDF signal to the indifferent gonad
- All other sex determination is hormonal and directed by genes on other chromosomes

SEX LINKAGE

- Sex-linked Characteristics: Characteristics determined by genes located on the sex chromosomes
- X-linked characteristics (most): Characteristics controlled by genes on the X chromosome
- Y-linked characteristics: Characteristics controlled by genes on the Y chromosome

SEX LINKAGE

- First person to explain sex-linked inheritance was Thomas Hunt Morgan working on Drosophila
  - Carried out a series of genetic crosses to try to understand the inheritance of a white-eyed characteristic.

FIRST CROSSES

RED ♀ × WHITE ♂

↓

ALL RED

- Conclusion:
  - Red is dominant to white
- Question: What should happen when we cross the F1 red progeny together?

SECOND CROSS

EXPECTED:

3 RED: 1 WHITE

	R	r
R	RR	Rr
r	Rr	rr

ACTUAL RESULTS

Rr ♀ X Rr ♂

↓

All females red (1/2 of total)

1/2 males red

1/2 males white

- 3:1 ratio is preserved, but in an unusual way
- Hypothesis: inheritance is influenced by sex of individual

RECIPROCAL CROSSES (REVERSE GENDERS OF PARENTS)

White ♀ X Red ♂

↓

All females red

All males white

F1 CROSS

RED ♀ x WHITE ♂

↓

1/2 of both sexes are red

1/2 of both sexes are white

- This is not a 3:1 ratio (1:1)
- Hypothesis: what if the white gene is on the X chromosome?

FIRST CROSSES

X^RX^R ♀ x X^rY ♂

	X^R	X^R
X^r	X^RX^r	X^RX^r
Y	X^RY	X^RY

ALL OF BOTH SEXES WILL BE RED-EYED

F1 CROSS

- ALL FEMALES, 1/2 OF MALES RED
- 1/2 OF MALES WHITE

	X^R	X^r
X^R	X^RX^R	X^RX^r
Y	X^RY	X^rY

RECIPROCAL CROSS

- CROSS WHITE FEMALES TO RED MALES
- ALL SONS ARE WHITE; ALL DAUGHTERS ARE RED

	X^r	X^r
X^R	X^RX^r	X^RX^r
Y	X^rY	X^rY

F1 CROSS

1/2 OF ALL F2 PROGENY ARE RED, AND 1/2 ARE WHITE

	X^R	X^r
X^r	X^RX^r	X^rX^r
Y	X^RY	X^rY

NONDISJUNCTION AS PROOF OF THE CHROMOSOME THEORY OF HEREDITY

- Morgan and Bridges had correlated an unusual pattern of inheritance with an unusual pattern of chromosome segregation
  - The white gene appeared to segregate with the X chromosome
- But nothing was **proved**, yet
- Bridges also noticed some exceptional (unexpected) progeny classes
  - flies that weren't predicted by his hypothesis, occurring at a frequency of about 1/1000

EXCEPTIONAL PROGENY

White ♀ X Red ♂

↓

Expect: All females red

All males white

Exceptions: white females

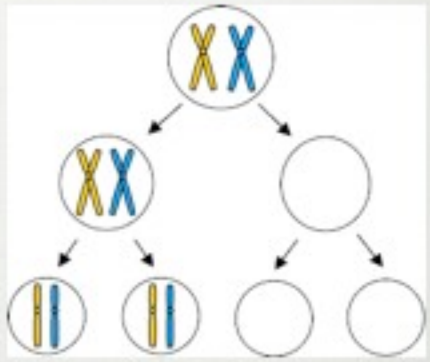
red males

EXPLANATION: X-CHROMOSOME NONDISJUNCTION

- At meiosis I, homologous chromosomes normally separate, or "disjoin" from one another
- At meiosis II, sister chromatids disjoin
- "Nondisjunction" = the failure of two chromosomes to properly separate at either meiotic division, resulting in one cell with two copies of the chromosome, and one with no copies

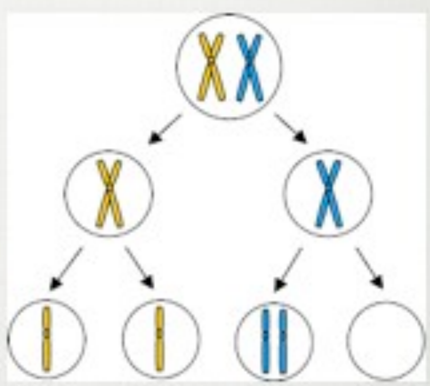
NONDISJUNCTION

- At meiosis I: both homologs segregate to the same cell
- One gamete now has two copies of this chromosome, the other has none
- The gamete with two copies possesses one copy of EACH homolog
- What happens when these gametes fuse with a normal gamete from the other parent?



NONDISJUNCTION

- At meiosis II: both sister chromatids segregate to the same cell
- One gamete now has two copies of this chromosome, the other has none
- The gamete with two copies possesses two identical copies of the SAME homolog
- What happens when these gametes fuse with a normal gamete from the other parent?



BACK TO THE FLIES

- The cross: X^rX^r x X^RY
- If nondisjunction of the X (in the female) occurs, we get one gamete with two white-bearing X chromosomes, and one with no X chromosomes at all

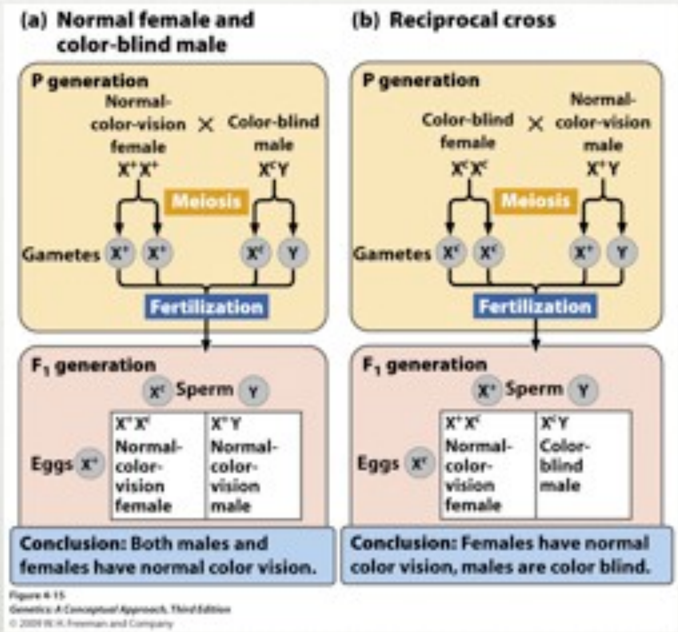
	X^rX^r	("O")
X^R	$X^rX^rX^R$ (DEAD)	X^RO (male)
Y	X^rX^rY (female)	OY (dead)

This is where our rare exceptions come from

SO:

- The exceptional females were XXY, and the exceptional males were XO (no Y)
- Proof: when chromosomes nondisjoin, so do alleles of genes - genes reside on chromosomes

X-LINKED COLOR BLINDNESS IN HUMANS



DOSAGE COMPENSATION

- Females have two copies of every X-lined gene
- Males possess only one copy
- Females should produce twice the amount of gene product/protein
- This is usually lethal (more on this later)
- Dosage compensation equalizes the amount of protein produced by X-linked genes in the two sexes.

DOSAGE COMPENSATION

- There are several mechanisms for dosage compensation:
  - Flies: double the activity of genes on the X chromosome of the male
  - C. elegans: halve the activity of both X chromosomes in the female.
  - Placental mammals: X Inactivation - inactivate genes on one X chromosome.

X-INACTIVATION

- The Lyon hypothesis:
  - In 1961, Mary Lyon proposed that darkly staining bodies in the nuclei of female cats (now known as Barr bodies) were inactive X chromosomes.
  - Within each female cell, one of two X chromosomes becomes inactive early in embryogenesis
  - The choice of "which X" inactivates is random

DOSAGE COMPENSATION

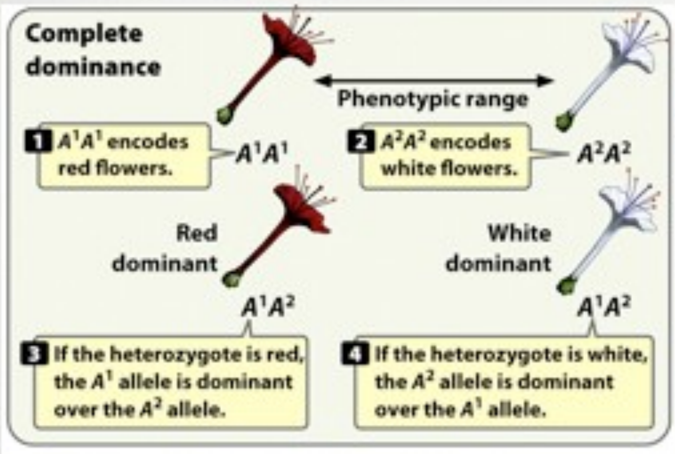
Figure 4-17
Genetics: A Conceptual Approach, Third Edition

- Females are mosaic for expression of X-linked genes
- All descendants of a cell inactivate the same X
- So, neighboring cells have the same X inactivated
- This produces a patchy mosaic pattern in heterozygous females.
- e.g. tortoiseshell cat

CHAPTER 5: EXTENSIONS OF MENDELIAN GENETICS

- Dominance, Incomplete Dominance, and Codominance
- Penetrance and Expressivity
- Lethal Alleles
- Pleiotropic Alleles

HETEROZYGOTE PHENOTYPE DETERMINES TYPE OF DOMINANCE



Complete dominance: Heterozygote has the same phenotype as the dominant homozygote

HETEROZYGOTE PHENOTYPE DETERMINES TYPE OF DOMINANCE

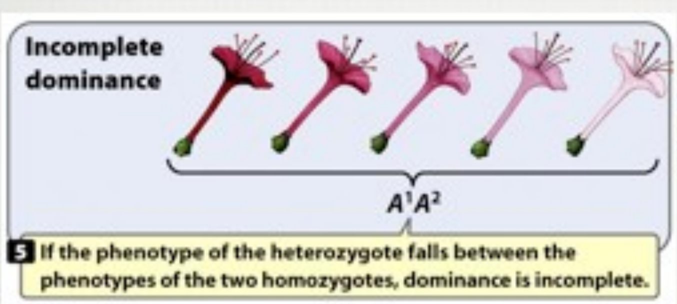


Figure 5-2
Genetics: A Conceptual Approach, Third Edition

Incomplete dominance: Heterozygote phenotype is intermediate between the homozygotes

ANOTHER POSSIBILITY: CODOMINANCE

Table 5.1 Differences between dominance, incomplete dominance, and codominance

Type of Dominance	Definition
Dominance	Phenotype of the heterozygote is the same as the phenotype of one of the homozygotes.
Incomplete dominance	Phenotype of the heterozygote is intermediate (falls within the range) between the phenotypes of the two homozygotes.
Codominance	Phenotype of the heterozygote includes the phenotypes of both homozygotes.

Table 5-1
Genetics: A Conceptual Approach, Third Edition

EXAMPLE OF CODOMINANCE: THE MN BLOOD TYPES

- MN locus encodes one of the types of antigens on the red blood cells
  - Foreign MN antigens do not elicit a strong immunological reaction (unlike ABO and Rh)
- Two alleles:
  - L^M encodes the M antigen
  - L^N encodes the N antigen

EXAMPLE OF CODOMINANCE: THE MN BLOOD TYPES

- L^ML^M express the M antigen ☒ M blood type
- L^NL^N express the N antigen ☒ N blood type
- L^ML^N express both M and N antigens ☒ MN blood type

<u>Exhibit codominance</u>: simultaneously express the phenotypes of both homozygotes

FOR NEXT TIME:

- ☐ ATTEND YOUR DISCUSSION SECTION TOMORROW - PROBLEM REVIEW FOR EXAM 1
- ☐ EXAM 1: FIRST HOUR ON MONDAY. CHAPTERS 1-4.
- ☐ BE SURE YOU'VE FINISHED CHAPTER 5 FOR THE SECOND HOUR'S LECTURE