Chromosomal Inheritance, Sex Linkage \& Sex Determination:

## Early 1900s

$\checkmark$ Number of chromosomes generally is constant within species.
$\checkmark$ Varies widely among species (sometimes between sexes).

Order
Anguilliformes
Aulopiformes Beloniformes
Characiformes
Cyprinodontiformes Goldfish Mugiliformes
Perciformes

2n
44
42
48
54
44-58
94
48
40-48

## Eukaryotic cell cycle: cell growth, mitosis, and interphase

Eukaryotic Cell Cycle


G1: Cell prepares for chromosome replication.
S: DNA replicates and new chromosomes (sister chromatids) are formed.
G2: Cell prepares for mitosis and cell division.
M: Mitosis

Presynthesis gap

## Mitosis:

Replication of DNA (chromosome duplication) followed by one round of cell division. Results in two "identical" cells, with exception of the mutations that might occur during DNA replication.

## Meiosis:

Replication of DNA (chromosome duplication) followed by two rounds of cell division. Results in 4 haploid daughter cells (gametes) that possess $1 / 2$ the amount of DNA of the parent cell.

Mutations also arise during meiosis.
Crossing-over and random assortment occur during meiosis.

## 2 N


gametes

## Mitosis (somatic cells):

1. Occurs in haploid ( 1 N ) and diploid ( 2 N ) somatic cells.
2. Continuous process - 4 cytologically distinct stages.

Prophase Chromosomes shorten, thicken, and become visible by light microscopy.

Centrioles move apart and mitotic spindle begins to form.
Centrioles migrate to opposite sides of nucleus and nuclear envelope begins to disappear.

Metaphase Nuclear envelope disappears completely. Replicated chromosomes held together at the centromere are aligned on equator of the spindle (metaphase plate).

Anaphase Centromeres split and daughter chromosomes migrate to opposite poles. Cell division (cytokinesis) begins.

Telophase Nuclear envelopes reform, chromosomes become extended and less visible, and cell division continues.

## Meiosis (germ cells):

1. Occurs at a particular point in the life cycle.
2. Two successive divisions (meiosis I and meiosis II) of a diploid (2N) nucleus after one DNA replication (chromosome duplication) cycle.
3. Cell division (cytokinesis) results in 4 haploid (1N) cells from a single parent cell.

- Animals: gametogenesis -> gametes
- Plants: sporogenesis -> meiospores


## Meiosis I:

1. Chromosomes are reduced from diploid (2N) to haploid (1N).
2. Four stages

Prophase I: Similar to prophase of mitosis, except that homologous chromosomes pair and cross-over. Spindle apparatus begins to form, and nuclear envelope disappears.

Metaphase I: Chromosome pairs (bivalents) align across equatorial plane. Random assortment of maternal/paternal homologs occurs (different from metaphase of mitosis).

Anaphase I: Homologous chromosome pairs separate and migrate toward opposite poles.

Telophase I: Chromosomes complete migration, and new nuclear envelopes form, followed by cell division.

## Meiosis II:

1. Similar to mitotic division.
2. Also four stages:

Prophase II Chromosomes condense.
Metaphase II Spindle forms and centromeres align on the equatorial plane.

Anaphase II Centromeres split and chromatids are pulled to opposite poles of the spindle (one sister chromatid from each pair goes to each pole).

Telophase II Chromatids complete migration, nuclear envelope forms, and cells divide, resulting in 4 haploid cells. Each progeny cell has has one chromosome from each homologous pair, but these are not exact copies due to crossing-over.

## Mitosis

## Fig. 12.5



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## Meiosis

Fig. 12.9


## Fig. 12.11 Comparison of mitosis and meiosis in a diploid cell



## Fig. 12.11 Comparison of mitosis and meiosis in a diploid cell

| Single- <br> chromatid <br> chromosomes | Cell <br> division |
| :--- | :--- |

Anaphase


## Significant results of meiosis:

1. Haploid cells are produced because two rounds of division follow one round of chromosome replication.
2. Alignment of paternally and maternally inherited chromosomes is random in metaphase I, resulting in random combinations of chromosomes in each gamete. Number of possible chromosome arrangements $=2^{n-1}$.

For 22 autosomes there are 2,097,152 possible arrangements!
3. Crossing-over between maternal and paternal chromatids during meiosis I provides still more variation. Moreover, the crossing-over sites vary from one meiosis to another.


## Why all the sex---why is recombination beneficial?

1. Recombination is not always beneficial. It can be costly (recombination load) because it reshuffles beneficial combinations of alleles that are well suited to the environment.
2. But environments are variable and changing, so allelic combinations that are well suited to one environment may not be well suited to future environments.
3. Recombination can increase the efficiency of selection by eroding the linkage between different genes (Hill-Robertson effect).
4. Depends on the interaction among genes (epistasis)
5. If interactions between two genes are favorable (+ epistasis), then recombination may be selected against.
6. If the interactions are deleterious (- epistasis), then recombination may increase.
7. Recombination rates (like everything else)are subject to selection and evolve.

1902: Walter Sutton and Theodor Boveri

## Chromosome theory of inheritance:



Fiforen

1. Independently recognized that the transmission of chromosomes from one generation to the next parallels inheritance of Mendelian factors.
2. Mendelian factors (genes) are located on chromosomes.
3. Support for theory subsequently derived from study of sex chromosomes.

Sex chromosomes:
Chromosomes or group of chromosomes in eukaryotes in which the sexes are represented differently.

Designated $X$ and $Y$ in species in which the male is heterogametic (XY). W and $Z$ in species in which the female is heterogametic (WZ). Autosomes:

All of the other chromosomes.

Sex chromosomes in humans and Drosophila:

## Females XX

Homogametic (one type of gamete, X )

## Males XY

Heterogametic
(two types of gametes, X or Y )

Fig. 12.17:
Pattern is same for:
$P \times P \& F_{1} \times F_{1}$
a)

$F_{1}$ genotypes: $\quad \underbrace{1 / 2 X X} \quad \underbrace{1 / 2 X Y}_{1 / 2}$
$F_{1}$ phenotypes: $1 / 2$ female $1 / 2$ male

Pattern is reversed in other species:
Birds (Aves), butterflies (Insecta: Lepidoptera), and some fish (Pisces):

| Female | WZ |
| :--- | :--- |
| Male | ZZ |

Plants - lots of different systems for sex determination.
Drosophila uses $X$ chromosome autobalance to determine sex.
Other eukaryotes (e.g., yeast) use genic system

- allele determines sex.


## Discovery of Sex linkage:

1910: Thomas Hunt Morgan (Nobel Prize 1933)


Experiments with Drosophila demonstrated chromosome theory of heredity.

1. Discovered a mutant white-eyed male fly (wild type color is red).
2. Next, crossed wild type female with white-eyed male. All $F_{1}$ offspring had red eyes (therefore white is recessive).
3. Crossed $F_{1} \times F_{1} \Rightarrow F_{2}(3,470$ red/782 white) .
4. All white-eyed flies also were male.
5. Morgan hypothesized that eye color gene is located on the $X$ chromosome.
6. Ratio of white and red-eyed flies is $1 / 4.4$ (observed) $\ll 1 / 3$ (expected); white-eyed flies have lower viability.

Fig. 12.18

## Parental Cross

a)

| P generation | Parent 1 $\%$ | Parent 2 $\delta^{\circ}$ |
| :--- | :--- | :--- |
| Parental <br> phenotype | Red eyes <br> (wild type) | White <br> eyes |
| Diploid <br> parental <br> genotype | $w^{+}$ | $w^{+}$ |


$\mathrm{F}_{1}$ genotypes: $1 / 2 w^{+} / w($ or $+/ w), \quad 1 / 2 w^{+} / Y($ or $+/ /)$
$F_{1}$ phenotypes: $1 / 2$ female, $1 / 2$ male
All red-eyed (wild type)

## $F_{1} \times F_{1}$

b)

$\mathrm{F}_{2}$ genotypes: $1 w^{+} / w, 1 w^{+} / w^{+}, 1 w^{+} / \mathrm{Y}, \quad 1 w / \mathrm{Y}$
$F_{2}$ phenotypes: $3 / 4$ red eyes $\left(2 \rho, 1 \delta^{\circ}\right) \frac{1 / 4}{}$ white eyes ( $1 \delta^{\circ}$ )

Assuming eye color gene is located on the $X$ chromosome:

1. Males are hemizygous ( $w / Y$ ) because there is no homologous gene on the $Y$ chromosome.
2. Females are either homozygous (w+/w+) or heterozygous (w+/w).
3. $F_{1}$ flies were $w+/ w$ (females) and $w+/ Y$ (males).

| $F_{1} \times F_{1}$ | $\mathbf{w + ( X )}$ | $\mathbf{Y}$ |
| :--- | :---: | :---: |
| $\mathbf{w + ( X )}$ | $\mathbf{w + / w +}$ | $\mathbf{w + / Y}$ |
|  | $\mathbf{X X}$ | $\mathbf{X Y}$ |
| $\mathbf{w}(\mathbf{X})$ | $\mathbf{w + / w}$ | $\mathbf{w / Y}$ |
|  | $\mathbf{X X}$ | $\mathbf{X Y}$ |

Morgan's hypothesis confirmed by reciprocal crosses:

| P Cross | $\mathbf{w}(X)$ | $\mathbf{Y}$ |
| :--- | :---: | :---: |
| $\mathbf{w + ( X )}$ | $\mathbf{w + / w}$ | $\mathbf{w + / Y}$ |
|  | $\mathbf{X X}$ | $\mathbf{X Y}$ |
| $\mathbf{w + ( X )}$ | $\mathbf{w + / w}$ |  |
|  | $\mathbf{X X}$ | $\mathbf{w + / Y}$ |
|  | $\mathbf{X Y}$ |  |


| P Cross | $w+(X)$ | $Y$ |
| :--- | :---: | :---: |
| $w(X)$ | $w / w+$ | $w / Y$ |
|  | $X X$ | $X Y$ |
| $w(X)$ | $w / w+$ | $w / Y$ |
|  | $X X$ | $\mathbf{X Y}$ |

If you reverse the sexes and results differ $\rightarrow$ the trait is sex-linked.

| P Cross | $\mathbf{w + ( X )}$ | $\mathbf{Y}$ |
| :--- | :---: | :---: |
| $\mathbf{w ~ ( X )}$ | $\mathbf{w / w +}$ | $\mathbf{w / Y}$ |
|  | $\mathbf{X X}$ | $\mathbf{X Y}$ |
| $\mathbf{w}(\mathbf{X})$ | $\mathbf{w} / \mathbf{w +}$ | $\mathbf{w} / \mathbf{Y}$ |
|  | $\mathbf{X X}$ | $\mathbf{X Y}$ |

$\Rightarrow F_{1}$ of red-eyed females and white-eyed males

## Morgan' s student Calvin Bridges discovered "non-disjunction":

1. Discovered 1 / 2000 are either white-eyed female or red-eyed male.
2. Hypothesized that $X$ chromatids failed to separate in meiosis. Calvin Bridges discovered non-disjunction.
3. Possible outcomes (aneuploidy $=$ chromosomes absent or present in unusual number).
4. $\mathrm{YO} \quad \Rightarrow \quad$ die (no $X$ chromosome)
5. $X X X \quad \Rightarrow \quad$ die (extra $X$ )
6. $X^{w+} 0 \Rightarrow$ red-eyed sterile males (no $X$ from mother)
7. $X^{w} X^{w} Y \quad \Rightarrow \quad$ white-eyed females (two $X$ from mother)

## Fig 12.20 Nondisjunction in meiosis involving the X chromosome

## a) Normal X chromosome segregation

b) Nondisjunction in meiosis I
c) Nondisjunction in meiosis II


## Fig. 12.21 Rare primary nondisjunction during meiosis in a whiteeved female



Fig. 12.23, Parallel behavior between Mendelian genes and chromosomes:

## Illustrates: <br> Mendel's Principle of Independent Assortment



Sex determination, 2 main mechanisms:

1. Genotypic sex determination

Y chromosome
X chromosome
2. Environmental sex determination
e.g., Turtles use temperature
$>32^{\circ} \mathrm{C}$ produces females
$<28^{\circ}$ C produces males


## 1. Genotypic sex determination

1. Sex chromosomes play a decisive role in the inheritance and determination of sex.
2. Two methods:
3. Y chromosome mechanism (e.g., humans and other mammals)
4. X chromosome-autosome balance system (e.g., Drosophila, Caenorhabditis elegans nematode)

## Evidence for the Y chromosome mechanism:

1. Y chromosome confers maleness and determines sex.
2. Verified by studies of non-disjunction aneuploidy:

XO "Turner Syndrome"
$\checkmark$ Female
$\checkmark$ Sterile
$\checkmark$ 1/10,000 (most XO fetuses die before birth).
$\checkmark$ Survivors show below average height, poorly developed breasts, and immature sexual organs

XXY "Klinefelter Syndrome"
Male
$\checkmark$ 1/1000
$\checkmark$ Above average height, under-developed testes, and breast development in ~50\%

XYY-Male with above average height, fertility problems.
XXX-Female, normal though sometimes less fertile.

## Genotypic sex determination (cont.)

## Dosage Compensation for X-linked Genes in Mammals:

$\checkmark \quad$ Two copies of $X$ occur in females (XX), and one in males (XY).
$\checkmark \quad$ Gene expression must be equalized during development to avoid death.
$\checkmark$ Different organisms use different dosage compensation systems.

## Genotypic sex determination (cont.)

## Dosage Compensation for X-linked Genes in Mammals:

$\checkmark \quad$ Female somatic cell nuclei contain a Barr body-a condensed, inactivated $X$ chromosome.
$\checkmark \quad$ Most genes are inactivated but not all.
$\checkmark \quad$ Inactive $X$ is randomly chosen in each cell at 16 days post-fertilization in humans.
$\checkmark \quad$ Barr bodies - easily visible under the light microscope.

http://www.mun.ca/biology/scarr/Barr_Bodies.jpg

## Genotypic sex determination (cont.)

## Dosage Compensation for X-linked Genes in Mammals:

$\checkmark$ Descendants of each cell line have the same inactivated $X$, resulting in a mosaic. But different cell lines have different inactivated $X$.
$\checkmark \quad$ Results in mosaic color pattern seen in calico cats (X-linked genes for black and orange hair are inactivated randomly).


http://www.bio.miami.edu/dana/pix/calico_over view.jpg

## Genotypic sex determination (cont.)

## Dosage Compensation for X-linked Genes in Mammals:

$\checkmark$ Barr-body effect allows extra $X$ chromosomes to be tolerated well (e.g., XXY possess 1 inactivated X; XXX possess 2 inactivated X, etc.).

Autosomal duplications usually are lethal.
Regulated by specific loci, $X$ inactivation center (Xic). Another gene, Xist, produces RNA that coats and silences the extra $X$.

http://epigenie.com/epigenie-learning-center/epigenetics/epigenetic-regulation/

Genotypic sex determination (cont.)
Gene for "Maleness" on the Y chromosome:
$\checkmark$ Gene(s) on the $Y$ chromosome produce "testis-determining factor".
$\checkmark \quad$ Results in gonad differentiation during development.
$\checkmark \quad$ Other differences between sexes are secondary results of hormones and other factors produced by the gonads.
$\checkmark \quad$ Human $\operatorname{SRY}$ (sex-determining region $\underline{Y}$ ) is the sex-determining gene that produces "TDF" protein.
$\checkmark$ TDF is a transcription factor that upregulates expression of SOX9, which occurs in the same region of the $Y$ chromosome.

http://biol.|f1.cuni.cz/ucebnice/en/gender.htm

Genotypic sex determination (cont.)
X chromosome-autosome balance system - Drosophila:
$\checkmark \quad Y$ does not determine sex (XXY is female, XO is male).
$\checkmark \quad$ Sex is determined by the ratio of $X$ chromosomes to autosomes (A).

| Normal female | AA and $X X$ | $1: 1$ |
| :--- | :--- | :--- |
| Normal male | AA and $X Y$ | $1: 2$ |

$\checkmark \quad$ In contrast to mammals, $X$ chromosome on male is up-regulated so that transcription level equals that of XX female.

For aneuploid flies:

| Female | $\mathrm{X}: \mathrm{A} \geq 1.0$ |
| :--- | :--- |
| Male | $\mathrm{X}: \mathrm{A} \leq 0.5$ |
| Intersex | $0.5 \leq \mathrm{X}: \mathrm{A} \leq 1.0$ (sterile, mixed traits) |

Fig. 19.13

## Alternative exon splicing controls sex determination of Drosophila

-Sex is determined by X:A ratio.
-SxI (sex lethal) gene determines the pathways for males and females.
-If $\mathrm{X}: \mathrm{A}=1$, all introns and exon 3 (which contains the stop codon) are removed.
-If X:A = 0.5, no functional protein is produced.


Genotypic sex determination (cont.)
X chromosome-autosome balance system - Caenorhabditis:
$\checkmark \quad$ Caenorhabditis elegans (nematode) also uses autosome balance.
$\checkmark$ Two sexes, hermaphrodites (XX) and males (XO).
$\checkmark$ Hermaphodite $=$ possess both testes and ovaries.
$\checkmark \quad$ Dosage compensation limits transcription of each $X$ on a hermaprhodite to $\mathbf{1 / 2}$ that of single $X$ on male.

http://www.mun.ca/biology/desmid/brian/BIOL3530/DB_11/DBNGerm.html

http://genesdev.cshlp.org/content/17/8/977/F1.expansion.html

