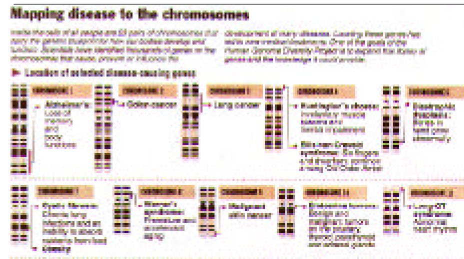
Mapping Disease to the Chromosomes

Human Genome Diversity Project



Human Genome Project

- **Phase One:** 85% of human genome sequence assembled & available to the public (14 mo.)
- **Phase Two:** Finish sequence to fill gaps & increase accuracy to 99.9%.

Chapter 15:
Chomosomal Basis of Inheritance

- Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles.
- Morgan Traced a Gene to a Specific Chromosome

Chromosomal Basis of Inheritance

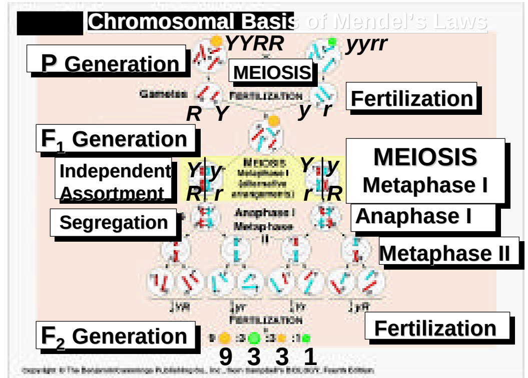
- Linked genes tend to be inherited together because they are located on the same chromosome.

Chomosomal Basis of Inheritance

- Human disorders due to chromosome alterations
- Extranuclear genes exhibit a non-Mendelian pattern of inheritance

Mendelian Inheritance: Behavior of Chromosomes During Sexual Life Cycles

- **Mendelian factors or genes are located on chromosomes.**
- **The chromosomes segregate and independently assort.**



Morgan Traced a Gene to a Specific Chromosome

- **Thomas Hunt Morgan (early 1900's) provided convincing evidence that Mendel's factors were located on chromsomes.**

Morgan's Fruit Flies: *Drosophila melanogaster*

- **Easily cultured**
- **Prolific breeders**
- **Short generation time**
- **Only four pairs of chromosomes that are easy to see in the microscope (3 autosomal pairs, 1 sex chromosome pair)**

Notes on Genetic Symbols

- **A gene's symbol is based upon the first mutant, non-wild type discovered.**
  - if the mutant is recessive, the first letter is lowercase (e.g. *w* = white eye allele in *Drosophila*)
  - if dominant, the first letter is capitalized (e.g. *Cy* = "curly")

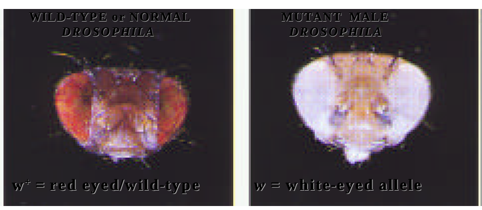
- **Wild-type trait is designated by a superscript $^+$. (e.g. Cy^+ = allele for normal, straight wings).**
- ***Wild type* is normal or most frequently observed phenotype.**

- Mutant phenotypes = phenotypes that are alternatives to the wild type and that are due to mutations in the wild-type gene.

Discovery of a Sex-Linked Gene

- After a year of culturing Morgan observed a single male with white rather than red eyes. Mated mutant white-eyed male with a red-eyed female.

MORGAN'S FIRST FLY EYES

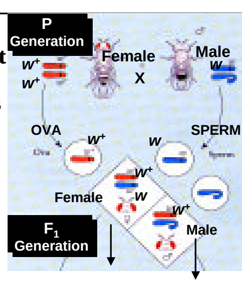


- **P generation:** w^+ w^+ (red-eyed female) x w (white-eyed male)
- **F_1 generation:** w^+ w (red-eyed female) x w^+ (white-eyed male)

Sex-Linked Inheritance

(Fig. 15.3)

Dominant Allele for Red Eyes is w^+

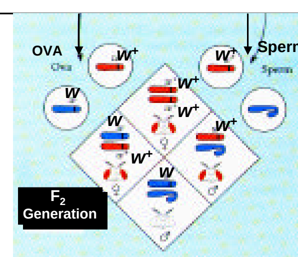


Recessive Allele for White Eyes is w

Y Chromosome (hooked) has no locus for eye color

Sex-Linked Inheritance

(Fig. 15.3)



- **F_2 generation:**
  $w^+ w^+$ red-eyed female
  $w^+ w$ red-eyed female
  w^+ red-eyed male
  w white-eyed male

- **Morgan deduced that eye color is linked to sex and that the gene for eye color is located only on the X chromosome.**

- **If eye color is located only on the X chromosome, then females (XX) carry two copies of the gene, while males (XY) have only one.**

- **Since the mutant allele is recessive, a white-eyed female must have that allele on both the X chromosomes, which was impossible for F_2 females in Morgan's experiment.**

- **A white-eyed male has no wild-type allele to mask the recessive mutant allele, so a single copy of the mutant allele confers white eyes.**
- ***Sex-linked* = genes located on sex chromosomes.**

Linked Genes Tend to be Inherited Together

- **Genes located on the same chromosome tend to be linked in inheritance and do not assort independently ….moving together through meiosis and fertilization.**

- Since independent assortment did not occur, a dihybrid cross following two linked genes will not produce an F_2 phenotypic ratio of (9:3:3:1)

Dihybrid Testcross:

- Experiment: Autosomal recessive mutant alleles for black bodies & vestigial wings and wild type flies heterozygous for both traits.

- Result: expected 1:1:1:1, got (parental phenotypes) 965:944: (recomb. phenotypes) 206:185
- Concluded that body color and wing size were on the same chromosome and are inherited together.

Independent Assortment & Crossing Over Cause Genetic Recombination

- Genetic recombination = production of offspring with new combinations of traits different from those found in the parents.

- ....results from the events of meiosis and random fertilization.

Recombination of Unlinked Genes: Independent Assortment of Chromosomes

- Mendel discovered that some offspring from dihybrid crosses have phenotypes unlike either parent..

- Parental types are progeny with same phenotype as one or the other parent.

- Recombinants are progeny whose phenotypes differ from either parent.

Recombination of Linked Genes: Crossing Over

- If genes are totaly linked, some possible phenotypic combinations should not appear....sometimes, unexpected recombinant phenotypes do appear.

- How do we explain this… … … … how about an experiment?

Crossing Over: Recall Earlier Experiment

- Morgan's fly room…dihybrid testcross resulted in the 965:944:206:185 rather than 575 : 575 : 575 : 575 for a recombinant frequency of 17%

  391 recomb./2300 total x 100 = 17%

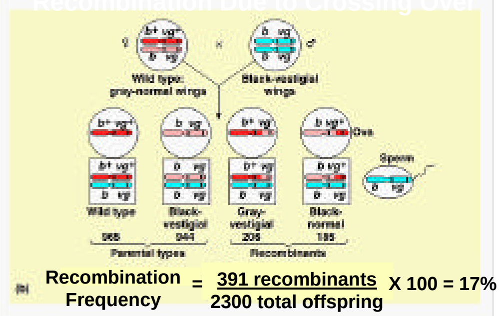
- Morgan's testcross:
  - if genes unlinked, they would assort independently (1:1:1:1).
  -if genes linked, they would produce 1:1 parental types only.
- Neither result was seen… although more parental types suggested linkage between the two genes.

- The 17% recombinants suggested incomplete linkage, so Morgan proposed some mechanism that will break the linkage between the two genes.
- What was the mechanism....?

- Answer: Crossing over during prophase of meiosis I - where exchange between parts of homologous chromosomes breaks linkages in parental chromosomes and forms recombinants with new allelic combinations.

Recombination Due to Crossing Over

Recombination Due to Crossing Over



Recombination Data:
Maping a Genetic Locus on a Chromosome

- A genetic map represents the linear sequence of genes along a chromosome.
- Assumption: probability of a crossover between 2 genetic loci is proportional to the distance separating those loci.

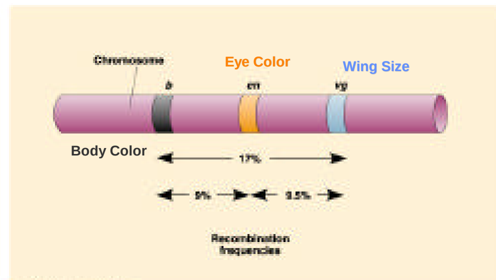
Linkage Map

- This map is not a measure of distance or length, but of the sequence of genes along a chromosome....no precise location of the gene.
- 1 map unit = 1% recombinant frequency.

Genetic Map Construction

- **Sturtevant (1917) reasoned that different frequencies reflect different distances between genes...if two genes are far apart, there is a greater probability that a crossover event will separate them, than if they are close.**

Using Recombination Frequencies to Construct a Linkage Map (Fig. 15.6)

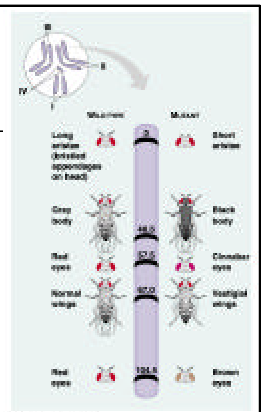


Partial Genetic Map: *Drosophila* Chromosome II

This fly has four pairs of chromosomes & the entire genome is now known.

See *Science* 24 March 2000

(Fig. 15.7)



SEX CHROMOSOMES

- **Chromosomal basis of sex varies with the organism**
- **Humans:**
  - All ova have X chromosomes
  - Half sperm have X and half have a Y chromosome

Sex-Linked Genes have Unique Patterns of Inheritance

- **In most species, sex is determined by presence or absence of special chromosomes.**

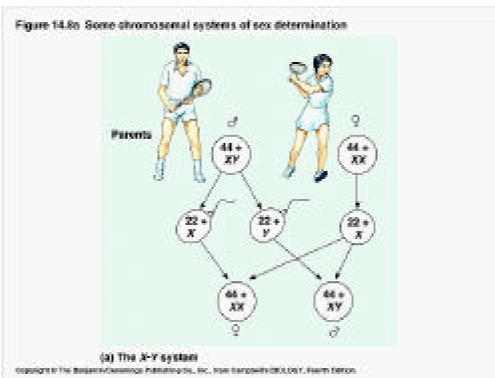
  As a result of meiotic segregation, each gamete has one sex chromosome to contribute at fertilization.

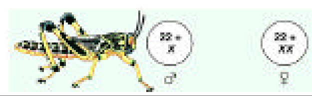
Chromosomal Basis of Sex in Humans

- **Mammals (us) have an *X-Y* mechanism that determines sex at fertilization.**
- **Each gamete has one sex chromosome, so when sperm and ovum unite at fertilization, the zygote receives one of two possible combinations: *XX* or *XY***

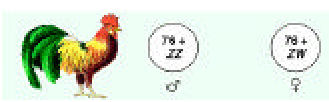
- Males: Heterogametic
- *XY (*half sperm X, half Y)
- Females: Homogametic *XX*

- The ***Big*** Question…. who determines the sex of the child….the mother or the father?

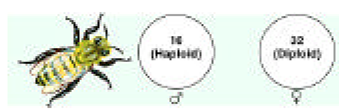




- X-O System: grasshopper, crickets, roaches…only one sex chromosome (X), so females are XX and males are XO, so sperm cell either carries an X or no chromosome.



- Z-W System: birds, some fishes and some insects the sex chromosome is in the <u>ovum</u>, not the sperm.
- Males are ZZ, Females ZW.
- The Z-W are used to avoid confusion with the X-Y system.



- Haplo-Diploid System: no sex chromosomes in most ants, bees, wasps, some mites.
- Females develop from fertilized eggs (diploid), unfertilized eggs (haploid) become males.

Sex-Linked Disorders in Humans

- The term Sex-Linked usually refers to X-linked traits.

  - Human X-chromosome is much larger than Y so there are more X-linked traits than Y-linked traits.

- Most X-linked genes have no homologous loci on the Y chromosome.

- Most genes on the Y chromosome not only have no X counterparts, but they encode traits found only in males (e.g. testis-determining factor).

Sex-Linked Traits in Humans

- Color-blindness
- Duchenne muscular dystrophy (1 : 3500 males)
- Hemophilia (bleeding disorder)-sex-linked recessive trait

Sex-Linked Factoids:

- Fathers pass X-linked alleles to all of their daughters.
- Males receive their X chromosome only from their?
- Fathers cannot, therefore, pass sex-linked traits to their?

- Males receive X chromosome only from their mother so far more males have sex-linked disorders than females.
- Fathers cannot pass sex-linked traits to their sons.

- Mothers can pass sex-linked alleles to both daughters & sons (only X chromosomes & could be either passed).
- Females receive two X chromosomes, one from each parent.

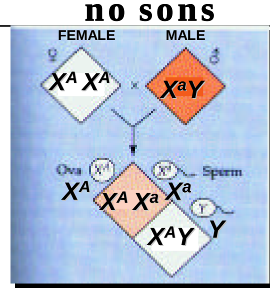
- Mothers pass on one X chromosome (either maternal or paternal homologue) to every daughter and son.

- If a sex-linked trait is due to a recessive allele, a female will express the trait only if she is homozygous.

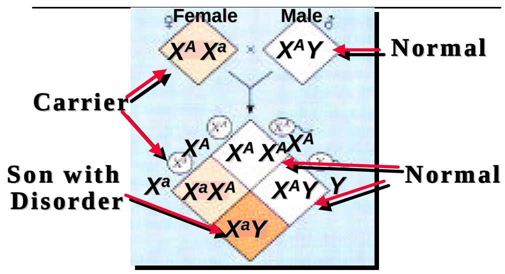
- There are therefore fewer females with sex-linked disorders.....why?

- Even if females have one recessive allele, the other dominant allele is the one that is expressed.....if heterozygous, then she can be a carrier and not show the recessive trait.

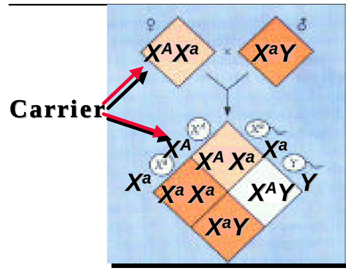
Father transmits mutant allele to all daughters but to no sons



Female carrier passes mutation to half her sons & daughters



Female carrier mates with mutant male, then each child has 50%of being affected, regardless of sex



X-Inactivation in Females: See Calico Cat Example

- Read about X-Inactivation in Females....where the embryonic cells inactivate one of the the X chromsomes...the inactive X is reactivated in gonadal cells that undergo meiosis to form gametes.

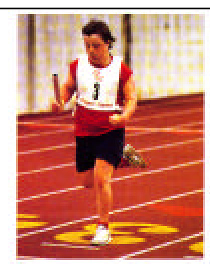
Alterations of Chromosome *Number or Structure* Has Consequences

- Chromosomal Number Alterations: Nondisjunction = meiotic or mitotic error during which certain homologous chromosomes or sister chromatids fail to separate.
- Figure 15.11

Aneuploidy

- Condition of having an abnormal number of certain chromosomes.
  - triplicate chromosome = trisomy
  - missing chromosome= monosomic
- Turner Syndrome is XO
- Down syndrome is trisomy of chromosome 21 affecting 1 of 700.

Karyotype: Trisomy 21 Down Syndrome



Down Syndrome:
Nondisjunction During Gamete Formation

- Characteristic facial features
- Short stature
- Heart defects
- Susceptibility to respiratory infection, leukemia, Alzheimer's
- Mental retardation

Down Syndrome

- Correlates with maternal age… why?
  Possibly because:
  Related to long lag time between first meiotic division during mother's fetal life and completion of meiosis at ovulation.

- Maybe older women have less chance of miscarrying a trisomic embryo.

Polyploidy

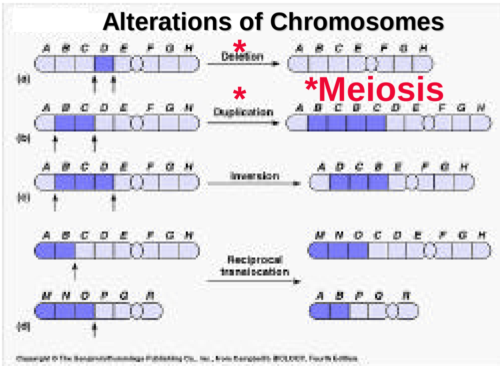
- A chromosome number is more than two complete chromosome sets.
  - Triploidy = three haploid sets (3N)
  - Tetraploidy = four haploid set (4N)

Other Sex Chromosome Aneuploidy: Abnormal Chromsome Number

- Review Klinefelter Syndrome, Extra Y, Triple-X Syndrome, Turner Syndrome.

Chromosomal Alterations: Structure

- Deletions
- Duplication
- Inversion
- Translocation
  see Fig. 15.12 and review sources of these errors.



Extranuclear Genes:

- Found in cytoplasmic organelles such as plastids (plants) and mitochondria.
  - in mammals mitochrondrial DNA is exclusively maternal (ovum contributes most of cytoplasm)

- Cytoplasmic genes are not distributed by segregating chromosomes during meiosis.

Chapter 16

- Gene inheritance depends on precise replication of DNA… how does that happen?