CHAPTER 15
THE CHROMOSOMAL BASIS OF INHERITANCE

OUTLINE

I. Relating Mendelism to Chromosomes
   A. Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles
   B. Morgan traced a gene to a specific chromosome: *science as a process*
   C. Linked genes tend to be inherited together because they are located on the same chromosome
   D. Independent assortment of chromosomes and crossing over produce genetic recombinants
   E. Geneticists can use recombination data to map a chromosome's genetic loci

II. Sex Chromosomes
   A. The chromosomal basis of sex varies with the organism
   B. Sex-linked genes have unique patterns of inheritance

III. Errors and Exceptions to Chromosomal Inheritance
   A. Alterations of chromosome number or structure cause some genetic disorders
   B. The phenotypic effects of some genes depend on whether they were inherited from the mother or father
   C. Extranuclear genes exhibit a non-Mendelian pattern of inheritance

OBJECTIVES

After reading this chapter and attending lecture, the student should be able to:

1. Explain how the observations of cytologists and geneticists provided the basis for the chromosome theory of inheritance.
2. Describe the contributions that Thomas Hunt Morgan, Walter Sutton, and A.H. Sturtevant made to current understanding of chromosomal inheritance.
3. Explain why *Drosophila melanogaster* is a good experimental organism.
4. Define linkage and explain why linkage interferes with independent assortment.
5. Distinguish between parental and recombinant phenotypes.
6. Explain how crossing over can unlink genes.
7. Map a linear sequence of genes on a chromosome using given recombination frequencies from experimental crosses.
8. Explain what additional information cytological maps provide over crossover maps.
9. Distinguish between a heterogametic sex and a homogametic sex.
10. Describe sex determination in humans.
11. Describe the inheritance of a sex-linked gene such as color-blindness.
12. Explain why a recessive sex-linked gene is always expressed in human males.

13. Explain how an organism compensates for the fact that some individuals have a double dosage of sex-linked genes while others have only one.
14. Distinguish among nondisjunction, aneuploidy, and polyploidy; explain how these major chromosomal changes occur and describe the consequences.
15. Distinguish between trisomy and triploidy.
16. Distinguish among deletions, duplications, translocations, and inversions.
17. Describe the effects of alterations in chromosome structure, and explain the role of position effects in altering the phenotype.
18. Describe the type of chromosomal alterations implicated in the following human disorders: Down syndrome, Klinefelter syndrome, extra Y, triple-X syndrome, Turner syndrome, *cri du chat* syndrome, and chronic myelogenous leukemia.
19. Define genomic imprinting and provide evidence to support this model.
20. Explain how the complex expression of a human genetic disorder, such as fragile-X syndrome, can be influenced by triplet repeats and genomic imprinting.
21. Give some exceptions to the chromosome theory of inheritance, and explain why cytoplasmic genes are not inherited in a Mendelian fashion.

KEY TERMS

chromosome theory of inheritance
wild type
mutant phenotype
sex-linked genes
linked genes
genetic recombination
parental type
recombinants
linkage map
cytological map
Duchenne muscular dystrophy
hemophilia
Barr body
nondisjunction
aneuploidy
trisomic
monosomic
polyploidy
deletion
duplication
inversion
translocation
Down syndrome
fragile *X* syndrome

LECTURE NOTES

I. Relating Mendelism to Chromosomes

A. Mendelian inheritance has its physical basis in the behavior of chromosomes during sexual life cycles

Genetics	Cytology
1860s: Mendel proposed that discrete inherited factors segregate and assort independently during gamete formation	1875: Cytologists worked out process of mitosis 1890: Cytologists worked out process of meiosis
1900: Three botanists (Correns, de Vries, and von Seysenegg) independently rediscovered Mendel's principles of segregation and independent assortment	
1902: Cytology and genetics converged as Walter Sutton, Theodor Boveri, and others noticed parallels between the behavior of Mendel's factors and the behavior of chromosomes. For example: • Chromosomes and genes are both paired in diploid cells. • Homologous chromosomes separate and allele pairs segregate during meiosis. • Fertilization restores the paired condition for both chromosomes and genes.	

Based upon these observations, biologists developed the *chromosome theory of inheritance* (see Campbell, Figure 15.1). According to this theory:

- Mendelian factors or genes are located on chromosomes.
- It is the chromosomes that segregate and independently assort.

B. Morgan traced a gene to a specific chromosome: *science as a process*

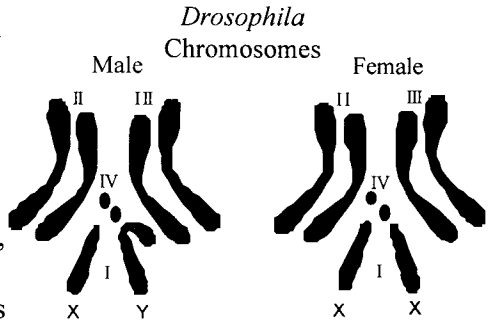
Thomas Hunt Morgan from Columbia University performed experiments in the early 1900s which provided convincing evidence that Mendel's inheritable factors are located on chromosomes.

I. Morgan's choice of an experimental organism

Morgan selected the fruit fly, *Drosophila melanogaster*, as the experimental organism because these flies:

- Are easily cultured in the laboratory
- Are prolific breeders
- Have a short generation time
- Have only four pairs of chromosomes which are easily seen with a microscope

There are three pairs of autosomes (II, III, and IV) and one pair of sex chromosomes. Females have two *X* chromosomes, and males have one *X* and one *Y* chromosome.



Morgan and his colleagues used genetic symbols that are now convention. For a particular character:

- A gene's symbol is based on 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 the mutant is dominant, the first letter is capitalized. (e.g., *Cy* = "curly" allele in *Drosophila* that causes abnormal, curled wings.)
- Wild-type trait is designated by a superscript +. (e.g., Cy^+ = allele for normal, straight wings.)

Wild type = Normal or most frequently observed phenotype (see Campbell, Figure 15.2)

Mutant phenotypes = Phenotypes which are alternatives to the wild type due to mutations in the wild-type gene

2. Discovery of a sex linkage

After a year of breeding *Drosophila* to find variant phenotypes, Morgan discovered a single male fly with white eyes instead of the wild-type red. Morgan mated this mutant white-eyed male with a red-eyed female. The cross is outlined below (see also Campbell, Figure 15.3).

w = white-eye allele
w^+ = red-eye or wild-type allele

Drosophila geneticists symbolize a recessive mutant allele with one or more lower case letters. The corresponding wild-type allele has a superscript plus sign.

P generation:

w^+w^+ red-eyed ♀ × w white-eyed ♂

F_1 generation:

w^+w red-eyed ♀ × w^+ red-eyed ♂

The fact that all the F_1 progeny had red eyes, suggested that the wild-type allele was dominant over the mutant allele.

F_2 generation:

w^+w^+ red-eyed ♀ ww^+ red-eyed ♀

w^+ red-eyed ♂ w white-eyed ♂

White-eyed trait was expressed only in the male, and all the F_2 females had red eyes.

Morgan deduced that eye color is linked to sex and that the gene for eye color is located only on the X chromosome. Premises for his conclusions were:

- 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 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 = Genes located on sex chromosomes. The term is commonly applied only to genes on the X chromosome.

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

Genes located on the same chromosome tend to be linked in inheritance and do not assort independently.

Linked genes = Genes that are located on the same chromosome and that tend to be inherited together.

- Linked genes do not assort independently, because they are on the same chromosome and move together through meiosis and fertilization.
- Since independent assortment does not occur, a dihybrid cross following two linked genes will not produce an F_2 phenotypic ratio of 9:3:3:1.

T.H. Morgan and his students performed a dihybrid testcross between flies with autosomal recessive mutant alleles for black bodies and vestigial wings and wild-type flies heterozygous for both traits (see Campbell, Figure 15.4).

b	= black body	vg	= vestigial wings
b^+	= gray body	vg^+	= wild-type wings

b^+bvg^+vg	×	$bbvgvg$
gray, normal wings		black, vestigial wings

- Resulting phenotypes of the progeny did not occur in the expected 1:1:1:1 ratio for a dihybrid testcross.
- A disproportionately large number of flies had the phenotypes of the parents: gray with normal wings and black with vestigial wings.
- Morgan proposed that these unusual ratios were due to linkage. The genes for body color and wing size are on the same chromosome and are usually thus inherited together.

D. Independent assortment of chromosomes and crossing over produce genetic recombinants

Genetic recombination = The production of offspring with new combinations of traits different from those combinations found in the parents; results from the events of meiosis and random fertilization.

1. The recombination of unlinked genes: independent assortment of chromosomes

Mendel discovered that some offspring from dihybrid crosses have phenotypes unlike either parent. An example is the following test cross between pea plants:

YY, Yy	= yellow seeds	RR, Rr	= round seeds
yy	= green seeds	rr	= wrinkled seeds

P generation:

YyRr yellow round	×	yyrr green wrinkled

Testcross progeny:

_ YyRr yellow, round	_ yyrr green, wrinkled	Parental types (50%)
_ yyRr green, round	_ Yyrr yellow, wrinkled	Recombinant types (50%)

Parental types = Progeny that have the same phenotype as one or the other of the parents.

Recombinants = Progeny whose phenotypes differ from either parent.

In this cross, seed shape and seed color are unlinked.

- One-fourth of the progeny have round yellow seeds, and one-fourth have wrinkled green seeds. Therefore, one-half of the progeny are *parental types*.
- The remaining half of the progeny are *recombinants*. One-fourth are round green and one-fourth are wrinkled yellow – phenotypes not found in either parent.
- When half the progeny are recombinants, there is a 50% frequency of recombination.
- A 50% frequency of recombination usually indicates that the two genes are on different chromosomes, because it is the expected result if the two genes assort randomly.
- The genes for seed shape and seed color assort independently of one another because they are located on different chromosomes which randomly align during metaphase of meiosis I.

2. The recombination of linked genes: crossing over

If genes are totally linked, some possible phenotypic combinations should not appear. Sometimes, however, the unexpected recombinant phenotypes do appear.

As described earlier, T.H. Morgan and his students performed the following dihybrid testcross between flies with autosomal recessive mutant alleles for black bodies and vestigial wings and wild-type flies heterozygous for both traits.

b = black body vg = vestigial wings
b^+ = gray body vg^+ = wild-type wings

b^+bvg^+vg gray, normal wings	×	$bbvgvg$ black, vestigial wings

Phenotypes	Genotypes	Expected Results If Genes Are Unlinked	Expected Results If Genes Are Totally Linked	Actual Results
Black body, normal wings	$\frac{b\ vg^+}{b\ vg}$	575		206
Gray body, normal wings	$\frac{b^+vg^+}{b\ vg}$	575	1150	965
Black body, vestigial wings	$\frac{b\ vg}{b\ vg}$	575	1150	944
Gray body, vestigial wings	$\frac{b^+vg}{b\ vg}$	575		185

$$\text{Recombination Frequency} = \frac{391 \text{ recombinants}}{2300 \text{ total offspring}} \times 100 = 17\%$$

Morgan's results from this dihybrid testcross showed that the two genes were neither unlinked or totally linked.

- If wing type and body color genes were unlinked, they would assort independently, and the progeny would show a 1:1:1:1 ratio of all possible phenotypic combinations.
- If the genes were completely linked, expected results from the testcross would be a 1:1 phenotypic ratio of *parental types only*.
- Morgan's testcross did not produce results consistent with unlinkage or total linkage. The high proportion of parental phenotypes suggested linkage between the two genes.
- Since 17% of the progeny were recombinants, the linkage must be incomplete. Morgan proposed that there must be some mechanism that occasionally breaks the linkage between the two genes (see Campbell, Figure 15.5).
- It is now known that *crossing over* during meiosis accounts for the recombination of linked genes. The exchange of parts between homologous chromosomes breaks linkages in parental chromosomes and forms recombinants with new allelic combinations.

E. Geneticists can use recombination data to map a chromosome's genetic loci

Scientists used recombination frequencies between genes to *map* the sequence of linked genes on particular chromosomes.

Morgan's *Drosophila* studies showed that some genes are linked more tightly than others.

- For example, the recombination frequency between the *b* and *vg* loci is about 17%.
- The recombination frequency is only 9% between *b* and *cn*, a third locus on the same chromosome. (The cinnabar gene, *cn*, for eye color has a recessive allele causing "cinnabar eyes.")

A.H. Sturtevant, one of Morgan's students, assumed that if crossing over occurs randomly, the probability of crossing over between two genes is directly proportional to the distance between them.

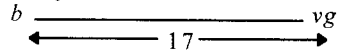
- Sturtevant used recombination frequencies between genes to assign them a linear position on a chromosome *map* (see Campbell, Figure 15.6).

- He defined one *map unit* as 1% recombination frequency. (Map units are now called *centimorgans*, in honor of Morgan.)

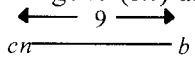
Using crossover data, a map may be constructed as follows:

Loci	Recombination Frequency	Approximate Map Units
b vg	17.0%	18.5*
cn b	9.0%	9.0
cn vg	9.5%	9.5

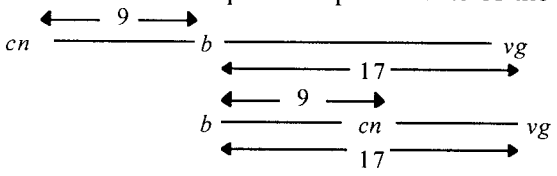
1. Establish the relative distance between those genes farthest apart or with the highest recombination frequency.



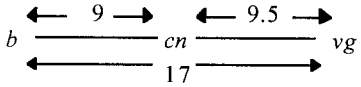
2. Determine the recombination frequency between the third gene (*cn*) and the first (*b*).



3. Consider the two possible placements of the third gene:



4. Determine the recombination frequency between the third gene (*cn*) and the second (*vg*) to eliminate the incorrect sequence.



So, the correct sequence is *b–cn–vg*.

> Note that there are actually 18.5 map units between *b* and *vg*. This is higher than that predicted from the recombination frequency of 17.0%. Because *b* and *vg* are relatively far apart, double crossovers occur between these loci and cancel each other out, leading us to underestimate the actual map distance.

If linked genes are so far apart on a chromosome that the recombination frequency is 50%, they are indistinguishable from unlinked genes that assort independently.

- Linked genes that are far apart can be mapped, if additional recombination frequencies can be determined between intermediate genes and each of the distant genes.

Sturtevant and his coworkers extended this method to map other *Drosophila* genes in linear arrays (see Campbell, Figure 15.7)

- The crossover data allowed them to cluster the known mutations into four major linkage groups.
- Since *Drosophila* has four sets of chromosomes, this clustering of genes into four linkage groups was further evidence that genes are on chromosomes.

Maps based on crossover data only give information about the relative position of linked genes on a chromosome. Another technique, *cytological mapping,* locates genes with respect to chromosomal features, such as stained bands that can be viewed with a microscope.

- The ultimate genetic maps are constructed by sequences, or DNA; in this case, distances between gene loci can be measured in nucleotides.

II. Sex Chromosomes

A. The chromosomal basis of sex varies with the organism

In most species, sex is determined by the presence or absence of special chromosomes. As a result of meiotic segregation, each gamete has one sex chromosome to contribute at fertilization.

Heterogametic sex = The sex that produces two kinds of gametes and determines the sex of the offspring.

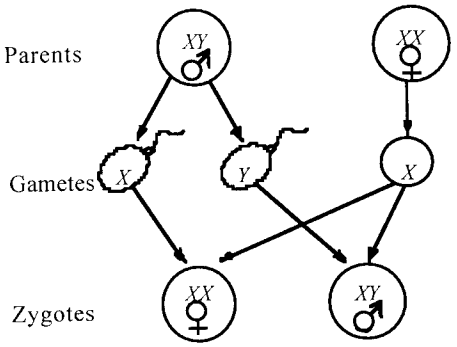
Homogametic sex = The sex that produces one kind of gamete.

Campbell, Figure 15.8 shows four chromosomal systems of sex determination.

1. The chromosomal basis of sex in humans

Mammals, including humans, have an *X-Y* mechanism that determines sex at fertilization.

- There are two chromosomes, *X* and *Y*. Each gamete has one sex chromosome, so when sperm cell and ovum unite at fertilization, the zygote receives one of two possible combinations: *XX* or *XY*.
- Males are the heterogametic sex (*XY*). Half the sperm cells contain an *X* chromosome, while the other half contain a *Y* chromosome.



- Females are the homogametic sex (*XX*); all ova carry an *X* chromosome.

Whether an embryo develops into a male or female depends upon the presence of a *Y* chromosome.

- A British research team has identified a gene, *SRY* (sex-determining region of Y), on the *Y* chromosome that is responsible for triggering the complex series of events that lead to normal testicular development. In the absence of SRY, the gonads develop into ovaries.
- *SRY* probably codes for a protein that regulates other genes.

B. Sex-linked genes have unique patterns of inheritance

Some genes on sex chromosomes play a role in sex determination, but these chromosomes also contain genes for other traits.

1. Sex-linked disorders in humans

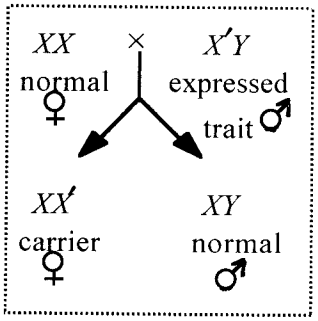
In humans, the term *sex-linked traits* usually refers to *X*-linked traits.

- The human *X*-chromosome is much larger than the *Y*. Thus, there are more *X*-linked 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).
- Examples of sex-linked traits in humans are color blindness, *Duchenne muscular dystrophy* and hemophilia.

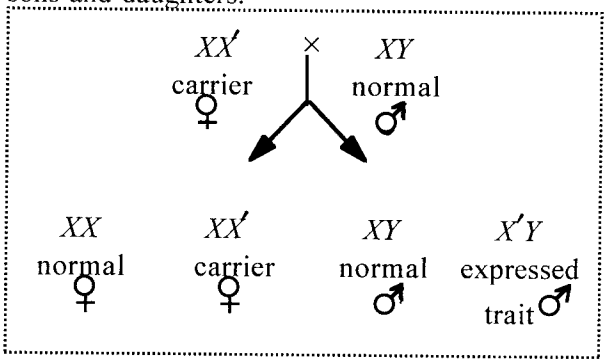
Fathers pass *X*-linked alleles to all their daughters only.

- Males receive their *X* chromosome only from their mothers.
- Fathers cannot pass sex-linked traits to their sons.



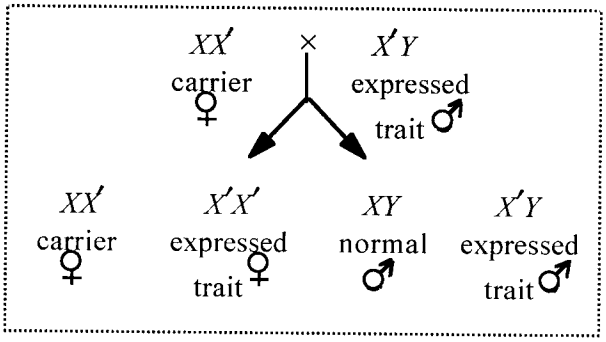
Mothers can pass sex-linked alleles to *both* sons and daughters.

- 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.

- Females have two *X* chromosomes, therefore they can be either homozygous or heterozygous for sex-linked alleles.
- There are fewer females with sex-linked disorders than males, because even if they have one recessive allele, the other dominant allele is the one that is expressed. A female that is heterozygous for the trait can be a *carrier*, but not show the recessive trait herself.
- A carrier that mates with a normal male will pass the mutation to half her sons and half her daughters.
- If a carrier mates with a male who has the trait, there is a 50% chance that each child born to them will have the trait, regardless of sex.



Campbell, Figure 15.9 depicts the transmission of sex-linked recessive traits.

Because males have only one *X*-linked locus, any male receiving a mutant allele from his mother will express the trait.

- Far more males than females have sex-linked disorders.
- Males are said to be hemizygous.

Hemizygous = A condition where only one copy of a gene is present in a diploid organism.

2. *X*-inactivation in female mammals

How does an organism compensate for the fact that some individuals have a double dosage of sex-linked genes while others have only one?

In female mammals, most diploid cells have only one fully functional *X* chromosome.

- The explanation for this process is known as the *Lyon hypothesis*, proposed by the British geneticist Mary F. Lyon.
- In females, each of the embryonic cells inactivates one of the two *X* chromosomes.
- The inactive *X* chromosome contracts into a dense object called a *Barr body*.

Barr body = Located inside the nuclear envelope, it is a densely staining object that is an inactivated *X* chromosome in female mammalian cells.

- Most Barr body genes are not expressed.
- They are reactivated in gonadal cells that undergo meiosis to form gametes.

Female mammals are a *mosaic* of two types of cellsÑthose with an active maternal *X* and those with an active paternal *X*.

- Which of the two *X*s will be inactivated is determined randomly in embryonic cells.
- After an *X* is inactivated, all mitotic descendants will have the same inactive *X*.
- As a consequence, if a female is heterozygous for a sex-linked trait, about half of her cells will express one allele and the other cells well express the alternate allele.

> Examples of this type of mosaicism are coloration in calico cats and normal sweat gland development in humans (see Campbell, Figure 15.10).

X chromosome inactivation is associated with DNA methylation.

- Methyl groups ($-CH_3$) attach to cytosine, one of DNA's nitrogenous bases.
- Barr bodies are highly methylated compared to actively transcribed DNA.

What determines which of the two *X* chromosomes will be methylated?

- A recently discovered gene, *XIST* is active *only* on the Barr body.
- The product of the *XIST* gene, *X-inactive specific transcript*, is an RNA; multiple copies of *XIST* attach to the *X* chromosome inactivating it.

Many questions have yet to be answered.

- How does *XIST* initiate *X*-inactivation?
- What determines which *X* chromosome in each of a female's cells will have an active *XIST* gene and become a Barr body?

III. Errors and Exceptions in Chromosomal Inheritance

A. Alterations of chromosome number or structure cause some genetic disorders

Meiotic errors and mutagens can cause major chromosomal changes such as altered chromosome numbers or altered chromosomal structure.

1. Alterations of chromosome number: aneuploidy and polyploidy

Nondisjunction = Meiotic or mitotic error during which certain homologous chromosomes or sister chromatids fail to separate.

- Meiotic nondisjunction:
  - May occur during meiosis I so that a homologous pair does not separate (see Campbell, Figure 15.11a)
  - May occur during meiosis II when sister chromatids do not separate (see Campbell, Figure 15.11b)

- Results in one gamete receiving two of the same type of chromosome and another gamete receiving no copy. The remaining chromosomes may be distributed normally.

- Mitotic nondisjunction:
  - Also results in abnormal number of certain chromosomes
  - If it occurs in embryonic cells, mitotic division passes this abnormal chromosome number to a large number of cells, and thus, can have a large effect.

Aneuploidy = Condition of having an abnormal number of certain chromosomes

- Aneuploid offspring may result if a normal gamete unites with an aberrant one produced as a result of *nondisjunction*.
- An aneuploid cell that has a chromosome in triplicate is said to be *trisomic* for that chromosome.
- An aneuploid with a missing chromosome is said to be *monosomic* for that chromosome.
- When an aneuploid zygote divides by mitosis, it transmits the chromosomal anomaly to all subsequent embryonic cells.
- Abnormal gene dosage in aneuploids causes characteristic symptoms in survivors. An example is Down's syndrome which results from trisomy of chromosome 21.

Polyploidy = A chromosome number that is more than two complete chromosome sets.

- *Triploidy* is a polyploid chromosome number with three haploid chromosome sets (3N).
- *Tetraploidy* is polyploidy with four haploid chromosome sets (4N).
- Triploids may be produced by fertilization of an abnormal diploid egg produced by nondisjunction of all chromosomes.
- Tetraploidy may result if a diploid zygote undergoes mitosis without cytokinesis. Subsequent normal mitosis would produce a 4N embryo.
- Polyploidy is common in plants and important in plant evolution.
- Polyploids occur rarely among animals, and they are more normal in appearance than aneuploids. Mosaic polyploids, with only patches of polyploid cells, are more common than complete polyploid animals.

2. Alterations of chromosome structure

Chromosome breakage can alter chromosome structure in four ways (see Campbell, Figure 15.12):

- Chromosomes which lose a fragment lacking a centromere will have a deficiency or *deletion*.
- Fragments without centromeres are usually lost when the cell divides, or they may:
  - Join to a homologous chromosome producing a *duplication*.
  - Join to a nonhomologous chromosome (*translocation*).
  - Reattach to the original chromosome in reverse order (*inversion*).

Crossing-over error is another source of deletions and duplications.

- Crossovers are normally reciprocal, but sometimes one sister chromatid gives up more genes than it receives in an unequal crossover.
- A nonreciprocal crossover results in one chromosome with a deletion and one chromosome with a duplication.

Alterations of chromosome structure, can have various effects:

- Homozygous deletions, including a single X in a male, are usually lethal.
- Duplications and translocations tend to have deleterious effects.
- Even if all genes are present in normal dosages, reciprocal translocations between nonhomologous chromosomes and inversions can alter the phenotype because of subtle *position effects*.

Position effect = Influence on a gene's expression because of its location among neighboring genes.

3. Human disorders due to chromosomal alterations

Chromosomal alterations are associated with some serious human disorders.

Aneuploidy, resulting from meiotic nondisjunction during gamete formation, usually prevents normal embryonic development and often results in spontaneous abortion.

- Some types of aneuploidy cause less severe problems, and aneuploid individuals may survive to birth and beyond with a set of characteristic symptoms or *syndrome*.
- Aneuploid conditions can be diagnosed before birth by *fetal testing*.

Down syndrome, an aneuploid condition, affects 1 out of 700 U.S. children (see Campbell, Figure 15.13).

- Is usually the result of trisomy 21
- Includes characteristic facial features, short stature, heart defects, mental retardation, susceptibility to respiratory infections, and a proneness to developing leukemia and Alzheimer's disease
- Though most are sexually underdeveloped and sterile, a few women with Down syndrome have had children.
- The incidence of Down syndrome offspring correlates with maternal age.
  - May be related to the long time lag between the first meiotic division during the mother's fetal life and the completion of meiosis at ovulation.
  - May be that older women have less chance of miscarrying a trisomic embryo.

Other rarer disorders caused by autosomal aneuploidy are:

- *Patau syndrome* (trisomy 13)
- *Edwards syndrome* (trisomy 18)

Sex chromosome aneuploidies result in less severe conditions than those from autosomal aneuploidies. This may be because:

- The *Y* chromosome carries few genes.
- Copies of the *X* chromosome become inactivated as Barr bodies.

The basis of sex determination in humans is illustrated by sex chromosome aneuploidies.

- A single *Y* chromosome is sufficient to produce maleness.
- The absence of *Y* is required for femaleness.

Examples of sex chromosome aneuploidy in males are:

Klinefelter Syndrome

Genotype: Usually *XXY*, but may be associated with *XXYY*, *XXXY*, *XXXXY*, *XXXXXY*.

Phenotype: Male sex organs with abnormally small testes; sterile; feminine body contours and perhaps breast enlargement; usually of normal intelligence.

Extra Y

Genotype: *XYY.*

Phenotype: Normal male; usually taller than average; normal intelligence and fertility.

Abnormalities of sex chromosome number in females include:

Triple-X Syndrome

Genotype: *XXX.*

Phenotype: Usually fertile; can show a normal phenotype.

Turner Syndrome

Genotype: *XO* (only known viable human monosomy).

Phenotype: Short stature; at puberty, secondary sexual characteristics fail to develop; internal sex organs do not mature; sterile.

Structural chromosomal alterations such as deletions and translocations can also cause human disorders.

- Deletions in human chromosomes cause severe defects even in the heterozygous state. For example,
  - *Cri du chat* syndrome is caused by a deletion on chromosome 5. Symptoms are mental retardation, a small head with unusual facial features and a cry that sounds like a mewing cat.
- Translocations associated with human disorders include:
  - Certain cancers such as *chronic myelogenous leukemia* (CML). A portion of chromosome 22 switches places with a small fragment from chromosome 9.
- Some cases of Down syndrome. A third chromosome 21 translocates to chromosome 15, resulting in two normal chromosomes 21 plus the translocation.

B. The phenotypic effects of some genes depend on whether they were inherited from the mother or the father

The expression of some traits may depend upon which parent contributes the alleles for those traits.

- Example: Two genetic disorders, *Prader-Willi syndrome* and *Angelman syndrome*, are caused by the same deletion on chromosome 15. The symptoms differ depending upon whether the gene was inherited from the mother or from the father.
- Prader-Willi syndrome is caused by a deletion from the *paternal* version of chromosome 15. The syndrome is characterized by mental retardation, obesity, short stature, and unusually small hands and feet.
- Angelman syndrome is caused by a deletion from the *maternal* version of chromosome 15. This syndrome is characterized by uncontrollable spontaneous laughter, jerky movements, and other motor and mental symptoms.
- The Prader-Willi/Angelman syndromes imply that the deleted genes normally behave differently in offspring, depending on whether they belong to the maternal or the paternal homologue.

- In other words, homologous chromosomes inherited from males and females are somehow differently *imprinted*, which causes them to be functionally different in the offspring.

Genomic imprinting = Process that induces intrinsic changes in chromosomes inherited from males and females; causes certain genes to be differently expressed in the offspring depending upon whether the alleles were inherited from the ovum or from the sperm cell (see Campbell, Figure 15.14).

- According to this hypothesis, certain genes are imprinted in some way each generation, and the imprint is different depending on whether the genes reside in females or in males.
- The same alleles may have different effects on offspring depending on whether they are inherited from the mother or the father.
- In the new generation, both maternal and paternal imprints can be reversed in gamete-producing cells, and all the chromosomes are re-coded according to the sex of the individual in which they now reside.
- *DNA methylation* may be one mechanism for genomic imprinting

Affecting about one in every 1500 males and one in every 2500 females, *fragile X syndrome* is the most common genetic cause of mental retardation.

- The "fragile *X*" is an abnormal *X* chromosome, the tip of which hangs on the rest of the chromosome by a thin DNA thread.

Fragile X syndrome's complex expression may be a consequence of maternal genomic imprinting.

- The syndrome is more likely to appear if the abnormal *X* chromosome is inherited from the mother rather than the father; this is consistent with the disorder being more common in males.
- Fragile x is unusual in that maternal imprinting (methylation) does not silence the abnormal allele but rather, somehow causes the syndrome.

C. Extranuclear genes exhibit a non-Mendelian pattern of inheritance

There are some exceptions to the chromosome theory of inheritance.

- Extranuclear genes are found in cytoplasmic organelles such as plastids and mitochondria.
- These cytoplasmic genes are not inherited in Mendelian fashion, because they are not distributed by segregating chromosomes during meiosis.

In plants, a zygote receives its plastids from the ovum, not from pollen. Consequently, offspring receive only maternal cytoplasmic genes.

- Cytoplasmic genes in plants were first descaribed by Karl Corens (1909) when he noticed that plant coloration of an ornamental species was determined by the seed bearing plants and not by the pollen producing plants (see Campbell, Figure 15.15).
- It is now known that maternal plastid genes control variegation of leaves.

In mammals, inheritance of mitochondrial DNA is also exclusively maternal.

- Since the ovum contributes most of the cytoplasm to the zygote, the mitochondria are all maternal in origin.

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