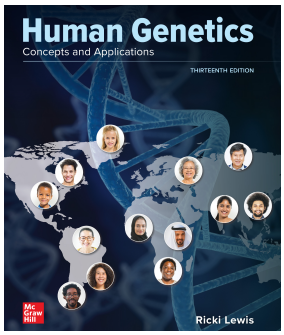
Because learning changes everything.®

Chapter 13

Chromosomes

Thirteenth Edition

Ricki Lewis



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Learning Outcomes 1

1. List the major parts of a chromosome.
2. List the types of chromosomes based on centromere position.
3. Describe the ways that chromosomes are obtained, prepared, detected, and depicted in detail.
4. Explain how atypical chromosome numbers arise.
5. Distinguish polyploidy from aneuploidy.
6. Describe specific aneuploid conditions.
7. Distinguish between the consequences of having balanced versus unbalanced chromosomes.

2

Learning Outcomes 2

8. Describe deletions, duplications, and the two major types of translocation.
9. Distinguish the two types of inversions.
10. Describe the consequence of having an isochromosome.
11. Describe the consequence of having a ring chromosome.
12. Explain how a person could inherit both copies of a DNA sequence from one parent.
13. Describe how inheriting both copies of DNA from one parent can affect a person's health.

3

Cytogenetics

Cytogenetics is the classical area of genetics that links chromosome variations to specific traits, including illnesses.

Excess genetic material has milder effects on health than a deficit

Large-scale chromosomal abnormalities present in all cells disrupt or halt prenatal development

- As a result, only 0.65% of all newborns have chromosomal anomalies that produce symptoms.

4

Portrait of a Chromosome 1

A chromosome consists primarily of DNA and proteins with a small amount of RNA.

Chromosomes are distinguished by size and shape

The essential parts of a chromosome are:

- Telomeres
- Origins of replication sites
- Centromere

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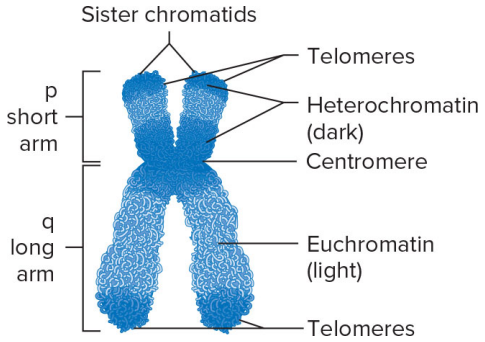
Portrait of a Chromosome 2



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Portrait of a Chromosome 3

Heterochromatin is darkly staining.

- Consists mostly of repetitive DNA

Euchromatin is lighter-staining.

- Contains most protein-encoding genes

Telomeres are chromosome tips composed of many repeats of TTAGGG.

- Shorten with each cell division

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Centromeres

Largest constriction of the chromosome and where spindle fibers attach

- Lie within vast stretches of heterochromatin.

Bases that form the centromere are repeats of a 171-base DNA sequence

Replicated at the end of S phase

- Facilitated by **centromere protein A**

CENP-A is passed to next generation

- Example of an epigenetic change

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Subtelomeres 1

Chromosome regions between the centromere and telomeres

Consists of 8,000 to 300,000 bases

Near telomere the repeats are similar to the telomere sequence

Contains at least 500 protein-encoding genes

- About 50% are multigene families that include pseudogenes

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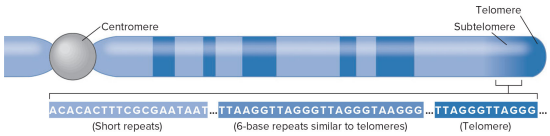
Subtelomeres 2



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Karyotype 1

A chromosome chart

Major clinical tool

Displays chromosomes arranged by size and structure

Humans have 24 chromosome types

- Autosomes are numbered 1–22 by size
- Sex chromosomes are X and Y

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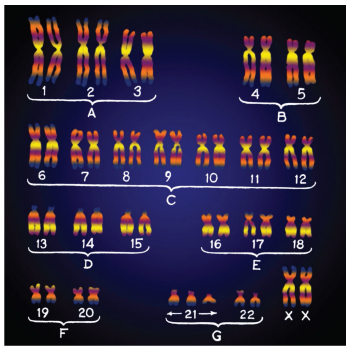
Karyotype 2



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Karyotype 3

Karyotypes are typically performed on cells during mitotic metaphase, when DNA coils tightly, enabling it to be visualized

Karyotypes are useful at several levels

They can:

- Confirm a clinical diagnosis
- Reveal effects of environmental toxins
- Clarify evolutionary relationships

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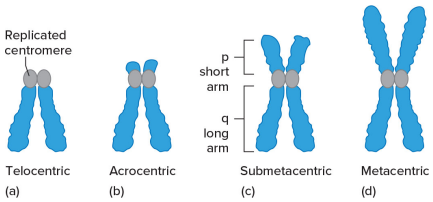
Centromere Positions

- **Telocentric**—At the tip
- **Acrocentric**—Close to center
- **Submetacentric**—Off-center
- **Metacentric**—At center



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Detecting Chromosomes

Chromosomes can be imaged from any type of human cell that has a nucleus (RBCs do not).

The most common application of human chromosome testing is in prenatal diagnosis.

- Chromosomes are also checked in relatives of people known to have atypical chromosomes, to explain infertility, or to diagnose or track cancers.

Techniques

- Older approaches: amniocentesis and chorionic villus sampling (CVS)
- Newer approaches: Cell-Free Fetal DNA Testing

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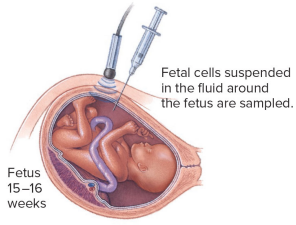
Amniocentesis 1

- A needle is used to remove a small sample of amniotic fluid from the uterus of a pregnant woman
- Ultrasound is used to follow needle's movement



(a) Amniocentesis

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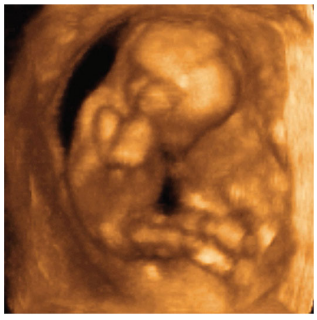
Amniocentesis 2



(c) Ultrasound image

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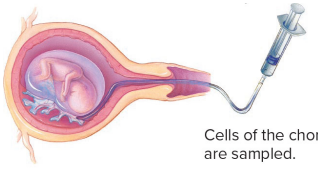
Chorionic Villus Sampling

Performed during 10 to 12th week of pregnancy

Provides earlier results than amniocentesis

Does not detect metabolic problems

- Has greater risk of spontaneous abortion



(b) Chorionic villus sampling

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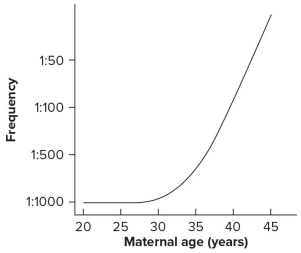
The Maternal Age Effect

- For many years amniocentesis was limited to women over age 35, when the risk of the procedure equals the risk of miscarriage, which rises with maternal age



Trisomy 21 in liveborn infants

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Staining Chromosomes

Early karyotypes used generalized stains

- These could not distinguish chromosomes of similar size, which were considered in groups.

Improved staining techniques gave banding patterns unique to each chromosome

Fluorescence *in situ* hybridization (FISH)

- DNA probes labeled with fluorescent dye bind complementary DNA sequences on chromosomes
- Use of an algorithm applies a unique false color to each chromosome, "painting" a karyotype from several fluorescent dyes.

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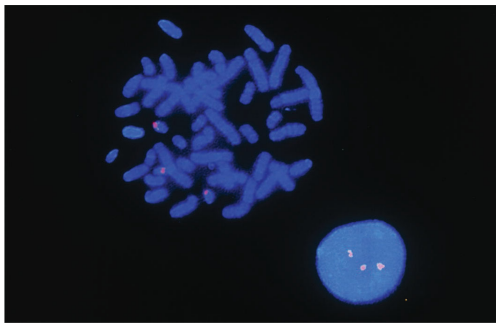
FISHing for Chromosomes



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Cell-Free Fetal DNA Testing 1

In a pregnant woman, about 20% of small DNA pieces found in the blood come from the placenta, and therefore represent the fetus

Tests of cell-free fetal DNA are done at 10 weeks or later, and are rapidly replacing older techniques

- Called noninvasive prenatal diagnosis or testing.

Analysis of cell-free fetal DNA is based on proportions.

- Entire genomes can be reconstructed from the DNA pieces.

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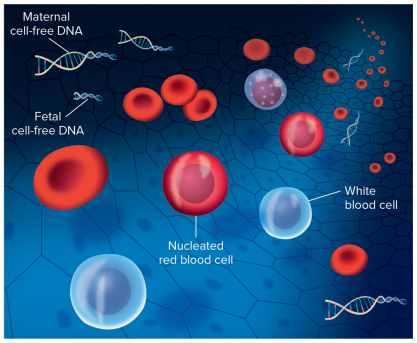
Cell-Free Fetal DNA Testing 2



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Chromosomal Shorthand 1

The information in a karyotype is abbreviated by listing the chromosome number, sex chromosome makeup, and atypical

Symbols and shorthand describe the type of aberration

- After the shorthand, numbers correspond to bands and subbands

A chromosomally normal male is designated 46,XY and a female 46,XX.

- Bands and subbands identify specific genes.

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Chromosomal Shorthand 2

Abbreviation	Meaning
46,XY	Normal male
46,XX	Normal female
45,X	A female with one X
47,XXY	A male with an extra X
47,XYY	A male with an extra Y
46,XY,del (7q)	A male missing part of the long arm of chromosome 7
47,XX,+21	A female with trisomy 21 Down syndrome
46,XY,t(7;9)(p21.1; q34.1)	A male with a translocation between the short arm of chromosome 7 at band 21.1 and the long arm of chromosome 9 at band 34.1
48,XXYY	A male with an extra X and an extra Y chromosome

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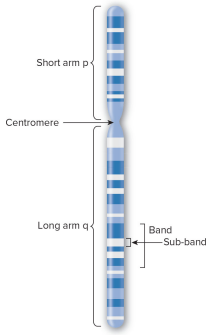
Ideogram

Graphical representations called **ideograms** depict the arms (p or q), bands, and subbands of chromosomes aberration

- Major regions are delineated by banding patterns



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Chromosome Abnormalities 1

Karyotype may be abnormal in:

- Chromosome number
- Chromosome structure

Abnormal chromosomes account for at least 50% of spontaneous abortions, yet only 0.65% of newborns have them.

- Therefore, most embryos and fetuses with atypical chromosomes stop developing before birth.

More people are being diagnosed with chromosome abnormalities due to improved technology

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Chromosome Abnormalities 2

Type of Abnormality	Definition
Polyploidy	Extra chromosome sets
Aneuploidy	An extra or missing chromosome
Monosomy	One chromosome absent
Trisomy	One chromosome extra
Deletion	Part of a chromosome missing
Duplication	Part of a chromosome present twice
Translocation	Two chromosomes join long arms or exchange parts
Inversion	Segment of chromosome reversed
Isochromosome	A chromosome with identical arms
Ring chromosome	A chromosome that forms a ring due to deletions in telomeres, which cause ends to adhere
Chromothripsis	One or more chromosomes shatters

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Polyploidy

Cell with extra chromosome sets

Triploid (3N) cells have three sets of chromosomes

- Produced by:
  - Fertilization of one egg by two sperm
  - Fusion of haploid and diploid gametes
- Account for 17% of all spontaneous abortions and 3% of stillbirths and newborn deaths

Polyploids are common among flowering plants

- Fish farmers raise triploid salmon

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Triploidy

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Aneuploidy 1

Normal chromosomal number is **euploid.**

Cells with extra or missing chromosomes are **aneuploid.**

Autosomal aneuploids are spontaneously aborted.

- Those born are more likely to have an extra chromosome (**trisomy**) rather than a missing one (**monosomy**).

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Aneuploidy 2

- Arises during mitosis, producing groups of somatic cells with the extra or missing chromosomes
- Individual with two chromosomally-distinct cell populations is called a **mosaic**
- Mitotic nondisjunction event that occurs early in development can have serious effects on the health of the individual

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Nondisjunction

- Meiotic error that causes aneuploidy
- Produces gamete with an extra chromosome and another with one missing chromosome
- Nondisjunction during meiosis I results in copies of both homologs in one gamete
- Nondisjunction during meiosis II results in both sister chromatids in one gamete

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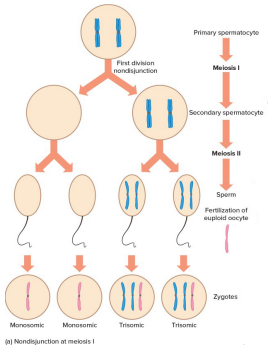
Nondisjunction at Meiosis I



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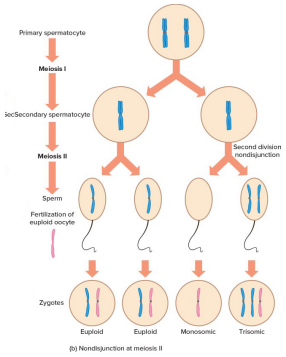
Nondisjunction at Meiosis II



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Autosomal Aneuploids

Most autosomal aneuploids cease developing long before birth

Frequently seen trisomies in newborns are those of chromosomes 21, 18, and 13.

- Carry fewer genes than other autosomes

Table 13.3 Comparing and Contrasting Trisomies 13, 18, and 21

Type of Trisomy	Incidence at Birth	Percentage of Conceptions That Survive 1 Year After Birth
13 (Patau)	1/12,500–1/21,700	<5%
18 (Edwards)	1/6,000–1/10,000	<5%
21 (Down)	1/800–1/826	85%

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Trisomy 21

Down syndrome

- Most common trisomy among newborns
- Distinctive facial and physical problems

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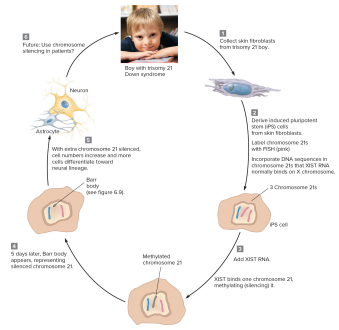
Turning off the extra chromosome 21

- One application of genome editing uses the mechanism of X inactivation to "turn off" the extra chromosome of trisomy 21, silencing the extra genetic information



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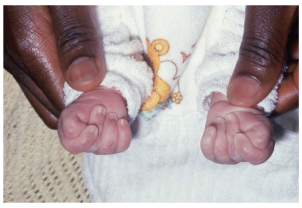
Trisomy 18

Edwards syndrome

- Due to nondisjunction in meiosis II in oocyte and generally do not survive
- Serious mental and physical disabilities
- Distinctive feature— Oddly-clenched fists



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Trisomy 13

Patau syndrome

- Very rare and generally do not survive 6 months
- Serious intellectual disability
- Great physical disability
- Most striking feature is fusion of the developing eyes into one large eyelike structure in the center of the face, or a small or absent eye
- There may be extra fingers and toes

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Sex Chromosome Aneuploids 1

- People with sex chromosome aneuploidy have extra or missing sex chromosomes.
- Some conditions can result from nondisjunction in meiosis in the male *or* female.
- Sex chromosome aneuploids are generally associated with much less severe symptoms and characteristics than autosomal aneuploids.

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Sex Chromosome Aneuploids 2

Table 13.4 How Nondisjunction Leads to Sex Chromosome Aneuploids

Situation	Oocyte	Sperm	Consequence
Normal	X	Y	46,XY normal male
	X	X	46,XX normal female
Female nondisjunction	XX	Y	47,XXY syndrome
	XX	X	47,XXX triplo-X
		Y	45,Y nonviable
		X	45,X syndrome
Male nondisjunction (meiosis I)	X		45,X syndrome
	X	XY	47,XXY syndrome
Male nondisjunction (meiosis II)	X	XX	47,XXX triplo-X
	X	YY	47,XYY syndrome
	X		45,X syndrome
Male and female nondisjunction	XX	YY	48,XXYY syndrome

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Turner (XO) Syndrome

About 1 in 2,500 female births

99% of affected fetuses die in utero

Features:

- Short stature
- Webbing at back of neck
- Incomplete sexual development (infertile)
- Impaired hearing

Individuals who are mosaics may have children

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Triplo-X Syndrome

- About 1 in every 1,000 female births
- Few modest effects on phenotype include tallness, menstrual irregularities, and slight impact on intelligence
- The lack of symptoms reflects the protective effect of X inactivation—all but one of the X chromosomes is inactivated.

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Klinefelter (XXY) Syndrome

About 1 in 500 male births

Features include:

- Incomplete sexual development
- Rudimentary testes and prostate
- Long limbs, large hands and feet
- Some breast tissue development

The most common genetic or chromosomal cause of male infertility.

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47,XXYY Syndrome

About 1 in 17,000 newborn boys

Arises due to unusual oocyte and sperm

Associated with more severe behavioral problems than Klinefelter syndrome

- AAD, obsessive compulsive disorder, learning disabilities

Individuals are infertile

Treated with testosterone

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Jacobs (XYY) Syndrome

One in 1,000 male births

Arises from nondisjunction in the male, producing a sperm with two Y chromosomes that fertilizes a normal oocyte

96% are phenotypically normal

Modest features

- Great height
- Acne
- Speech and reading disabilities

Studies suggest increase in aggressive behaviors are not supported

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Atypical Chromosome Structure

A chromosome can be structurally atypical in several ways:

- It may have too much or too little genetic material
- It may have a stretch of DNA that is inverted or moved and inserted into a different type of chromosome

Atypical chromosomes are:

- *Balanced* if they have the normal amount of genetic material
- *Unbalanced* if they have extra or missing DNA sequences.

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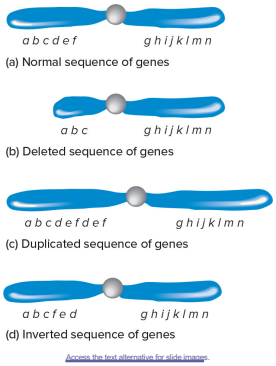
Chromosome Abnormalities



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Deletions

Missing genetic segment from a chromosome

Often not inherited

- Rather they arise *de novo*

Larger deletions increase the likelihood that there will be an associated phenotype

Cri-du-chat (cat cry) syndrome

- Deletion 5p⁻

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Duplications

Presence of an extra genetic segment on a chromosome

Often not inherited

- Rather they arise *de novo*

Effect on the phenotype is generally dependent on their size

- Larger duplications tend to have an effect, while smaller ones do not

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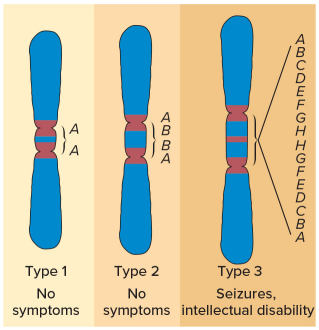
Duplications in Chromosome 15



Poor muscle tone
Epicanthal folds
Small size
Intellectual disability
Seizures
Developmental delay
Curved spine (scoliosis)
Learning disabilities
Autistic features
- poor speech
- hand flapping
- lack of eye contact
- need for routine

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Translocations

Two nonhomologous chromosomes exchange segments

Translocations can be inherited because they can be present in carriers, who have the normal amount of genetic material, but it is rearranged

Types:

- **Robertsonian translocation**
- **Reciprocal translocation**

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Robertsonian Translocations

Two nonhomologous acrocentric chromosomes break at the centromere and their long arms fuse

- Short arms are often lost

About 1 in 1,000 individuals are carriers

Translocation carriers have 45 chromosomes

- May not have symptoms
- By produce unbalanced gametes
  - This can lead to spontaneous abortion or birth defects.

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Translocation Down Syndrome

5% of Down syndrome results from a Robertsonian translocation between chromosomes 21 and 14

Tends to recur in families, who also have more risk of spontaneous abortions

One of the parents is a translocation carrier

- May have no symptoms
- Distribution of the unusual chromosome leads to various imbalances

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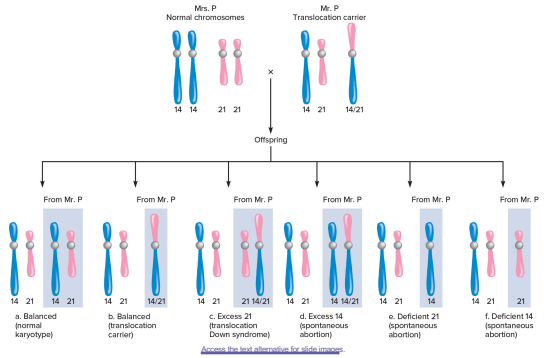
A Robertsonian Translocation



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Reciprocal Translocations 1

Two nonhomologous chromosomes exchange parts.

About 1 in 600 people is a carrier for a reciprocal translocation.

- Usually healthy because they have the normal amount of genetic material.

If translocation breakpoint interrupts a gene, there may be an associated phenotype.

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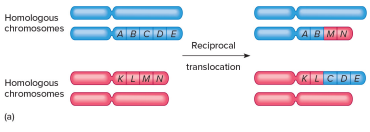
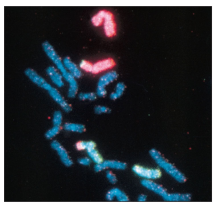
Reciprocal Translocations 2





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Inversions

- Chromosome segment that is flipped in orientation
- 5 to 10% cause health problems probably due to disruption of genes at the breakpoints
- **Paracentric inversion**—Inverted region does not include centromere
- **Pericentric inversion—**Inverted region includes centromere
- Inversions with devastating effects can be traced to meiosis, when a crossover occurs between the inverted chromosome segment and the noninverted homolog.

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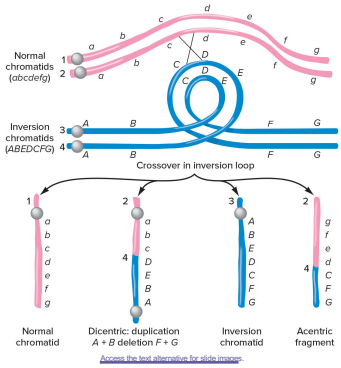
Paracentric Inversion



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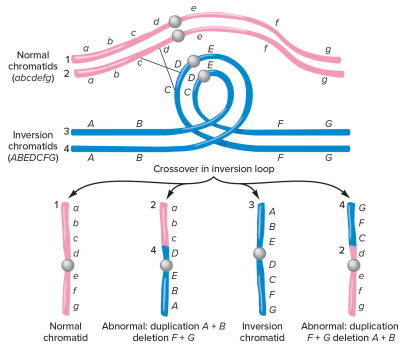
Pericentric Inversion



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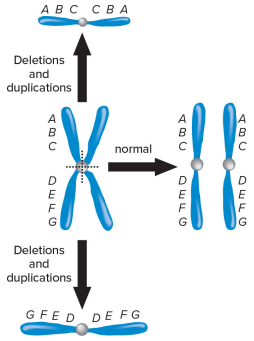
Isochromosomes

- Chromosomes with identical arms
- Formed when centromeres divide along the incorrect plane during meiosis
- Isochromosomes are known for chromosomes 12 and 21 and for the long arms of the X and the Y.



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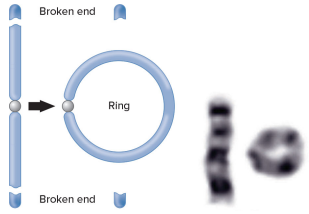
Ring Chromosomes

- Occur in 1 of 25,000 conceptions
- Arise when telomeres are lost and sticky chromosome ends fuse
- Genes can be lost or disrupted causing symptoms



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Causes of Chromosome Aberrations

Abnormalities	Causes
Numerical Abnormalities	
Polyploidy	Multiple fertilization or diploid gamete leads to extra sets of chromosomes
Aneuploidy	Nondisjunction (in meiosis or mitosis) leads to lost or extra chromosomes when not all chromatid pairs separate in anaphase
Structural Abnormalities	
Deletions and duplications	Translocation
	Crossover between a chromosome that has a pericentric inversion and its noninverted homolog
Translocation	Exchange between nonhomologous chromosomes at parts that are unstable due to symmetrical DNA sequences
Inversion	Breakage and reunion of fragment in same chromosome, but with wrong orientation
Dicentric and acentric chromatids	Crossover between a chromosome with a paracentric inversion and its noninverted homolog
Ring chromosome	A chromosome loses telomeres and the ends fuse, forming a circle
Chromothripsis	Up to three chromosomes spontaneously shatter

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Uniparental Disomy (UPD) 1

Inheritance of two chromosomes or chromosome parts from the same parent is called **uniparental disomy (UPD)**

Requires the simultaneous occurrence of two rare events

- Nondisjunction of the same chromosome in *both* sperm and egg
- Trisomy followed by chromosome loss

Many cases of UPD are probably never seen

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Uniparental Disomy (UPD) 2

Uniparental disomy causes symptoms if it creates a homozygous recessive state associated with an illness, or if it affects an imprinted gene.

Examples:

- A woman with cystic fibrosis inherited two copies of her mother's chromosome 7 (bearing the mutant *CFTR* allele) and neither of her father's.
- Some children with Prader-Willi syndrome have inherited two chromosome 15 from their mothers.
- Some children with Angelman syndrome have inherited two chromosome 15 from their fathers.

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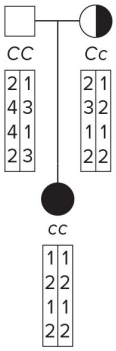
Uniparental Disomy (UPD) 3



Haplotype bars indicate specific chromosomes.

Woman with cystic fibrosis (CF)

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