YU - Medicine Passion Academic Team

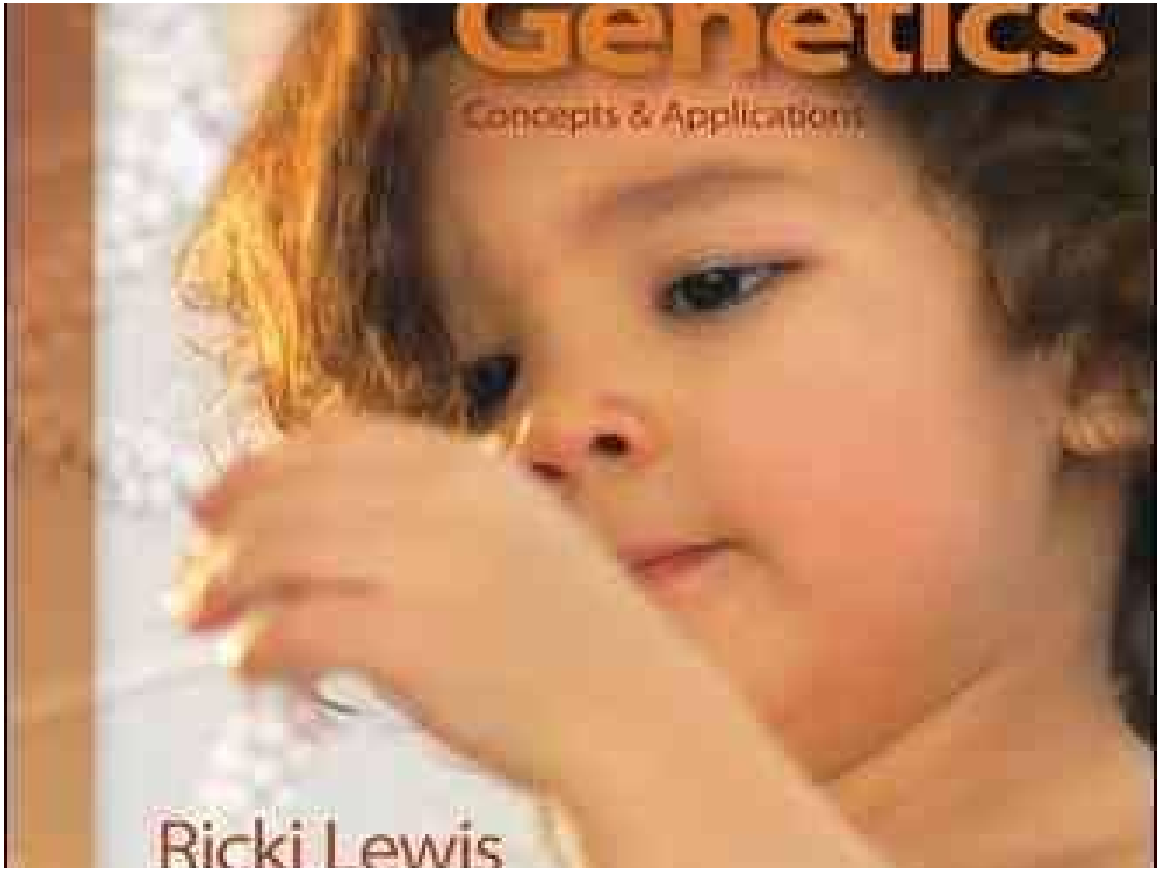
The Urogenital System

Sheet# 2 - Biochemistry

Lec. Title : Chromosomes

Written By : Rand Bumadian

If you come by any mistake , please kindly report it to shaghafbatch@gmail.com



Reference:Human Genetics Concepts and Applications 9th Edition

Chapter 13: Chromosomes

Cytogenetics

Cytogenetics is a subdiscipline within genetics deals with chromosome variations.

cytogenetist: a person who study the shapes of chromosomes, to know if it normal or not, (structural or numeric).

In general, excess genetic material has milder effects on health than a deficit.

When we have increase numbers there will be a survival person

while if we have decrease numbers usually it will be fetal, when we have deficiency in certain chromosomes.

Still, most large-scale chromosomal abnormalities present in all cells disrupt or halt prenatal development

Portrait of a Chromosome

A chromosome consists primarily of DNA and protein.

the function of this proteins may be :

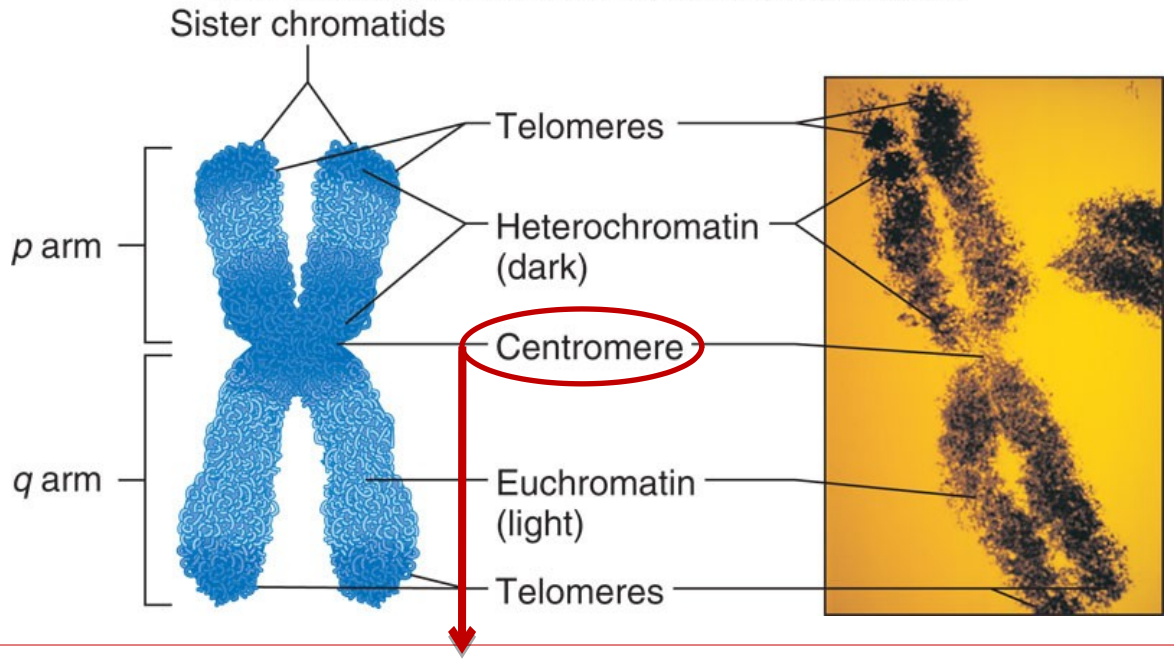
structural (maintenance of the shape) OR regulation of gene expression.

-According of that we have different types.

Distinguished by size and shape

Essential parts are:

- Telomeres
- Origins of replication sites
- Centromere



The anatomical structure of chromosomes and usually doesn't have genes.

Portrait of a Chromosome

Figure 13.1

هدول المناطق الي انا بركز عليهم لما بدي ادرس الكروموسومات

-this is a photo of chromosome during the metaphase (duplicated chromosomes which is a sister chromatids).

-and we know that the chromosomes is a DNA and proteins after folding.

Portrait of a Chromosome

Heterochromatin is darkly staining

- Consists mostly of repetitive DNA

Euchromatin is lighter-staining (contain active chains)

- Contains most protein-encoding genes

Telomeres are chromosome tips composed of many repeats of TTAGGG

- Shorten with each cell division

- Very important in replication.

Centromeres

The largest constriction of the chromosome and where spindle fibers attach

The bases that form the centromere are repeats of a 171-base DNA sequence (compared to 6 base in telomere).

Replicated at the end of S-phase

- Facilitated by **centromere protein A**

CENP-A is passed to next generation

- An example of an epigenetic change

Genetic: transferring the genetic material.

Epigenetic: transferring protein or sth that affect on gene control.

Subtelomeres

- The chromosome region between the centromere and telomeres
- Consists of 8,000 to 300,000 bases
  - الفرق الهائل بين اعداد القواعد بسبب انه عندي اطوال مختلفة من الكروموسومات.
- 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.

-gene family: group of genes make different proteins which will form a structures similar to each other.

-pseudogenes: some of the family's gene in the future will be inactive.

Subtelomeres

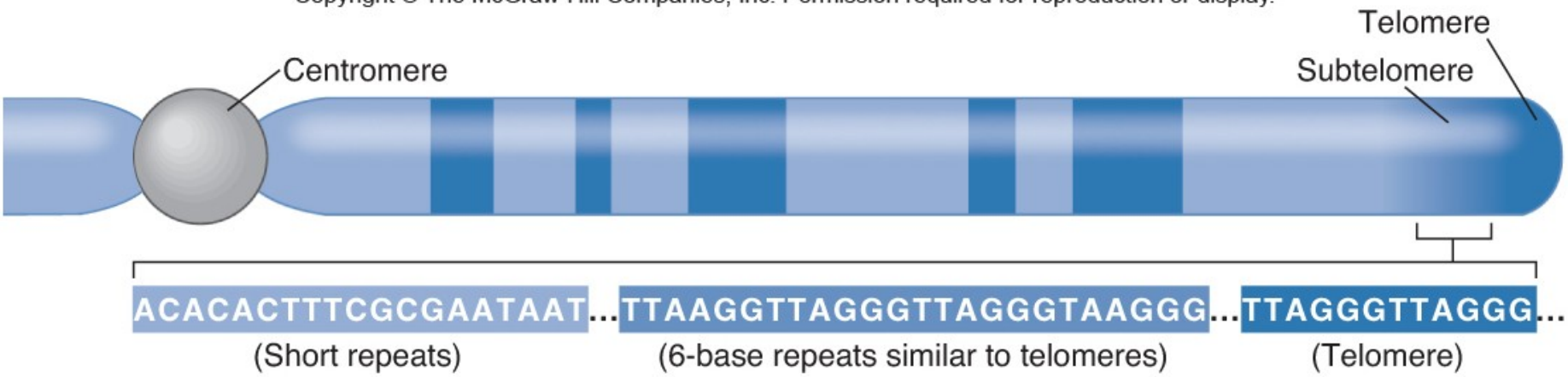


Figure 13.2

Karyotype

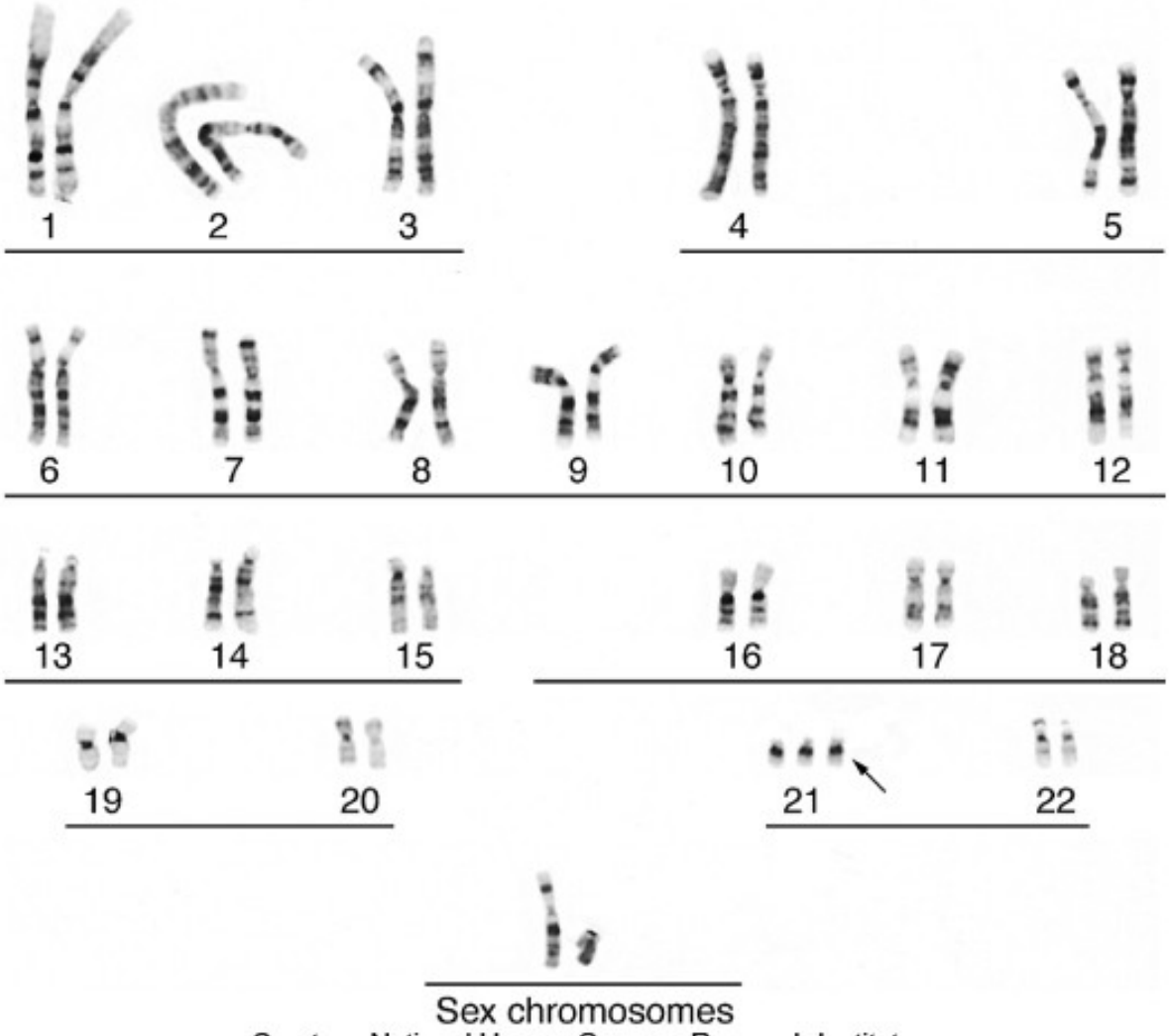
A chromosome chart

Displays chromosomes arranged by size and structure

Humans have 24 chromosome types (each pair is one type, X is a type and Y is a type)

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

Karyotype



Courtesy National Human Genome Research Institute

Figure 13.3

-7 groups.
-abnormal person: 3 chromosomes In site 21 .
-this is a male has 23 chromosomes pairs+.

Centromere Positions

حسب مكان السنترومير صنفهم

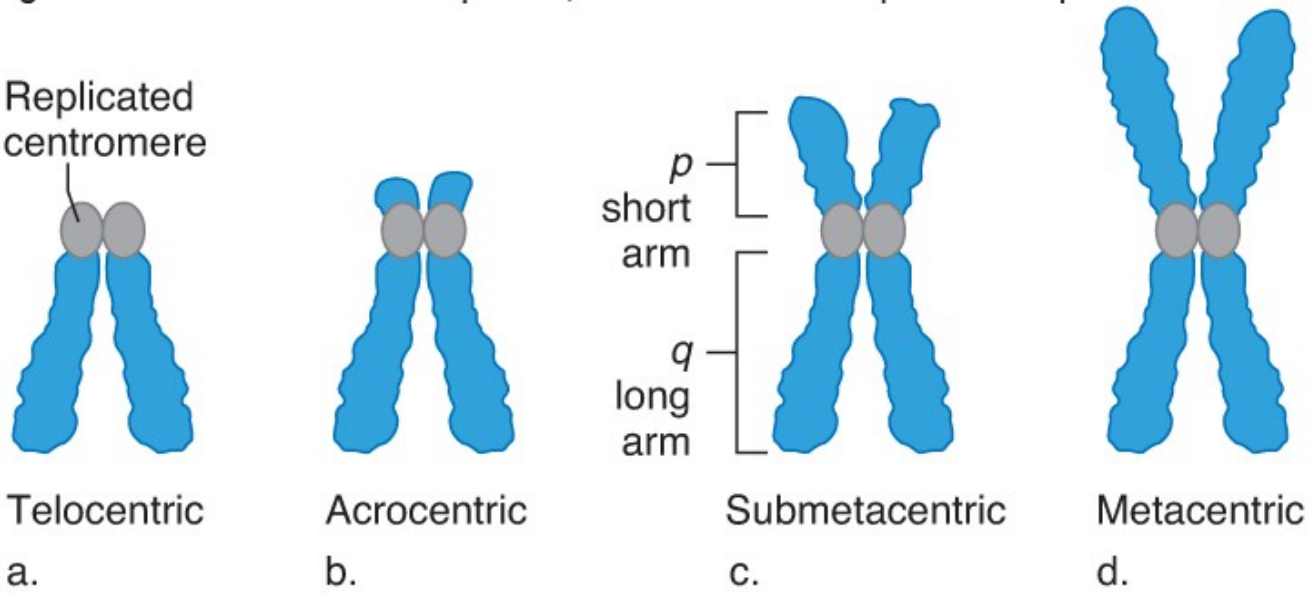
At tip – **Telocentric**

Close to end – **Acrocentric**

Off-center – **Submetacentric**

At midpoint – **Metacentric**

Figure 13.4



Karyotype

Karyotypes are useful at several levels

1) Can confirm a clinical diagnosis

2) Can reveal effects of environmental toxins

اعمل دراسة على بعض المواد الكيميائية واشوف تأثيرها على الكروموسومات

3) Can clarify evolutionary relationships

انه اشوف هل كروموسوماتنا بتتشابه مع كروموسومات كائن اخر , وهكذا

Visualizing Chromosomes

-Tissue I take to make a karyotype.

Tissue is obtained from person

- **Fetal tissue:** Amniocentesis
  Chorionic villi sampling
  Fetal cell sorting
  Chromosome microarray analysis
- **Adult tissue**: White blood cells
  Skinlike cells from cheek swab

Chromosomes are extracted

Then stained with a combination of dyes and **DNA probes**

Probing: using DNA which is connected with fluorescent material→ will give us a specific colors.

Amniocentesis

Detects about 1,000 of the more than 5,000 known chromosomal and biochemical problems

Ultrasound is used to follow needle's movement

Figure 13.5a

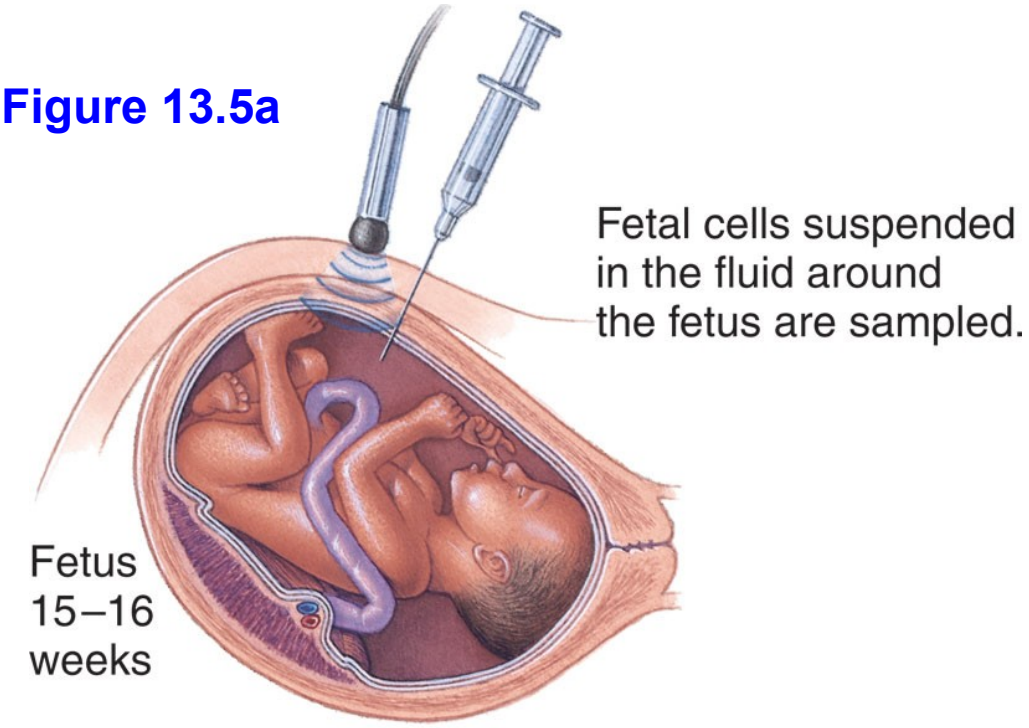
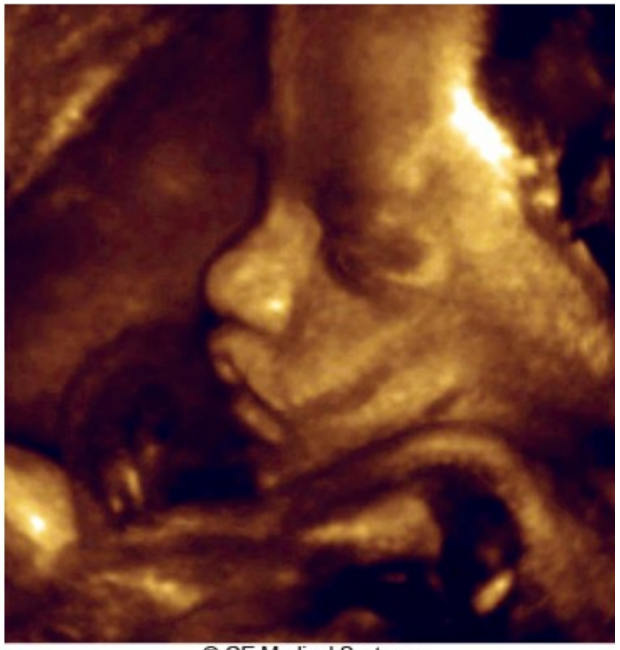


Figure 13.6



Chorionic Villi Sampling (CVS)

طريقة تانية بتنعمل ابكر لكن نحنا محتاجين ناس متخصصين اكتر لانه .معرضة جدا للاجهاض التلقائي نتيجة هالاشي

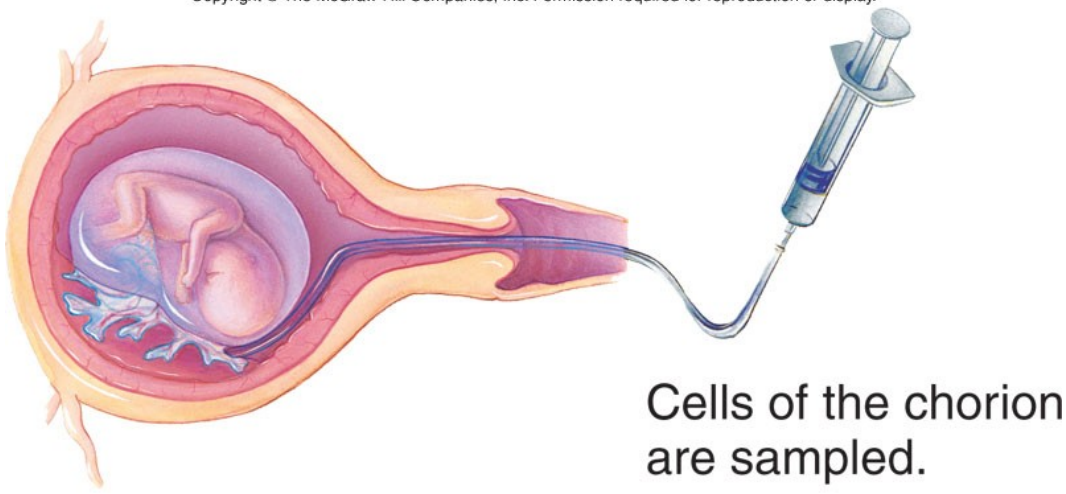
Performed during 10-12th week of pregnancy

Provides earlier results than amniocentesis

However, it does not detect metabolic problems

- And has greater risk of spontaneous abortion

Figure 13.5b



b. Chorionic villi sampling

Fetal Cell Sorting

Fetal cells are distinguished from maternal cells by a fluorescence-activated cell sorter
- Identifies cell-surface markers

A new technique detects fetal mRNA in the bloodstream of the mother

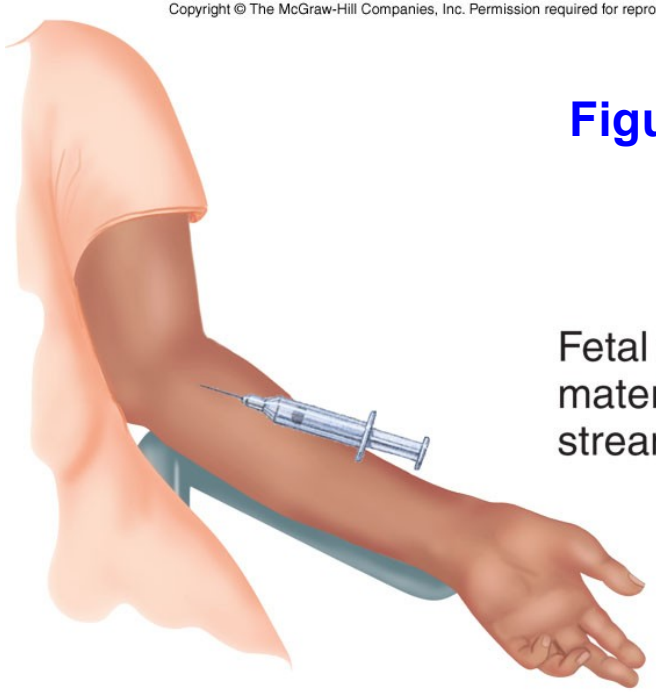
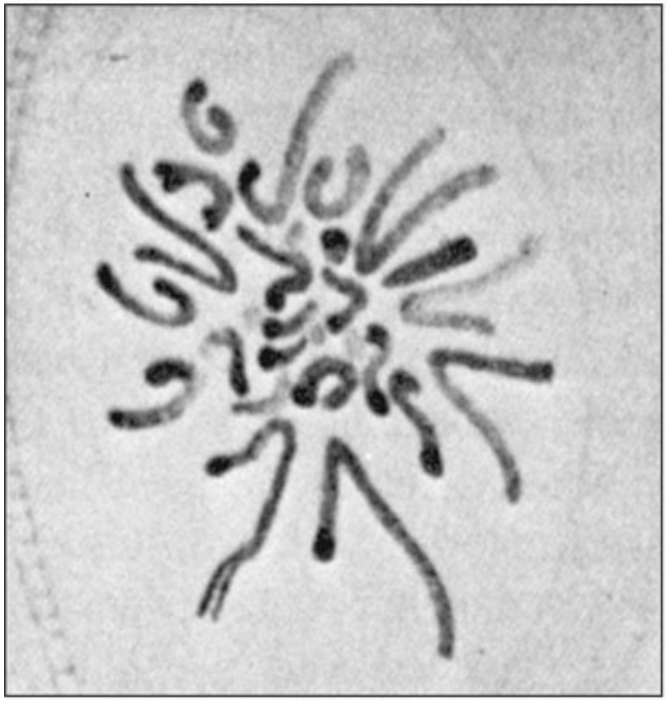


Figure 13.5c

c. Fetal cell sorting

Viewing Chromosomes

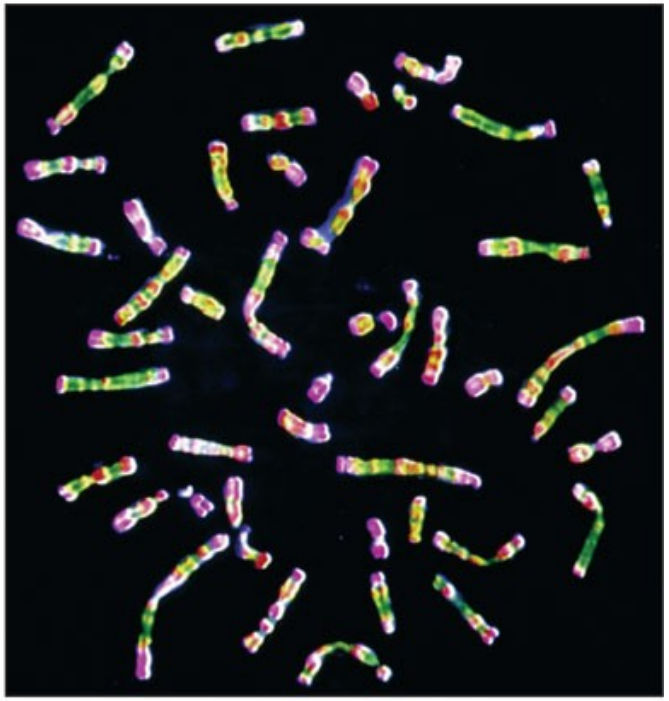
1882 **Figure 13.8** **Now**



a.

Drawing by German biologist Walther Flemming

Under the microscope you will see this image , you should arrange it.



b.

Micrograph of actual stained human chromosomes

Now , it is easier , the computer itself will arrange the chromosomes according to its sizes.

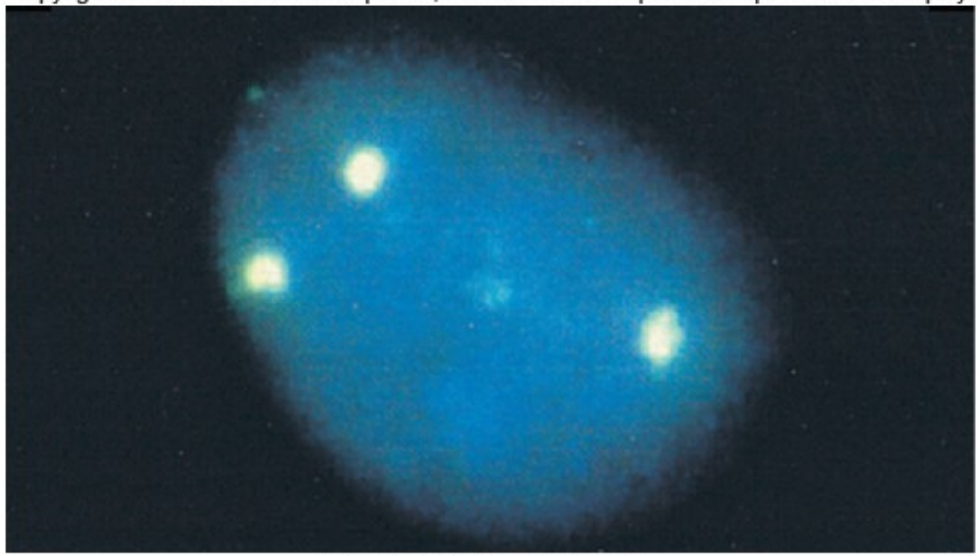
Staining Chromosomes

- In the earliest karyotypes, dyes were used to stain chromosomes a uniform color
- Chromosomes were grouped into decreasing size classes, designated A through G
- In the 1970s, improved staining techniques gave banding patterns unique to each chromosome
- Then researchers found that synchronizing the cell cycle of cultured cells revealed even more bands per chromosome

FISH

Fluorescence *in situ* hybridization

DNA probes labeled with fluorescing dye bind complementary DNA



© Courtesy Genzyme Corporation

Fluorescent dots correspond to three copies of chromosome 21

Figure 13.9

الفكرة كلها اني بحط بروب يمسكلي بالمادة الوراثية المكملة ل كروموسوم معين (21 مثلا) و بس اقدر اشوف نسخ الكروموسوم ح الاقي انه عندي 3 نسخ منه وهيك يكون عرفت انه في خلل

Human Genetics

Concepts and Applications

Ninth Edition

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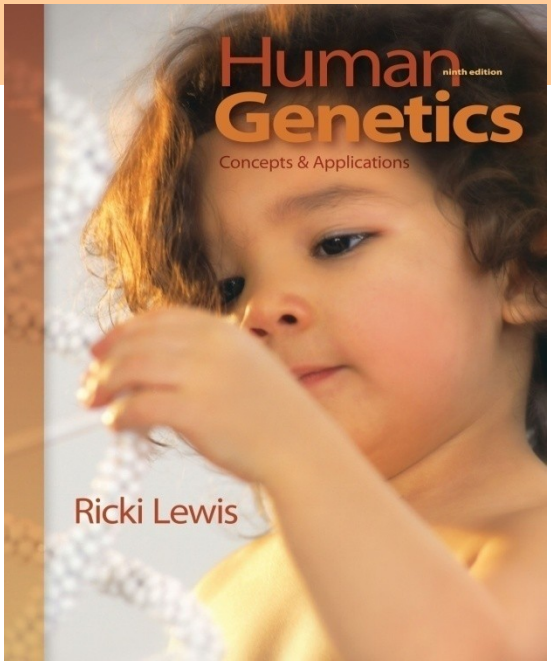

13 Chromosomes

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Chromosomal Shorthand

Table 13.1 Chromosomal Shorthand

Abbreviation	What It Means
46,XY	Normal male
46,XX	Normal female
45,X	Turner syndrome (female)
47,XXY	Klinefelter syndrome (male)
47,XYY	Jacobs syndrome (male)
46,XY, del (7*q*)	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)(*p*21.1; *q*34.1)	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

يعني العدد طبيعي لكن عندي فقدان لاحد اذرع الكرموسوم 7

Ideogram

A schematic chromosome map

Indicates chromosome arms (*p* or *q*) and delineates major regions and subregions by numbers.

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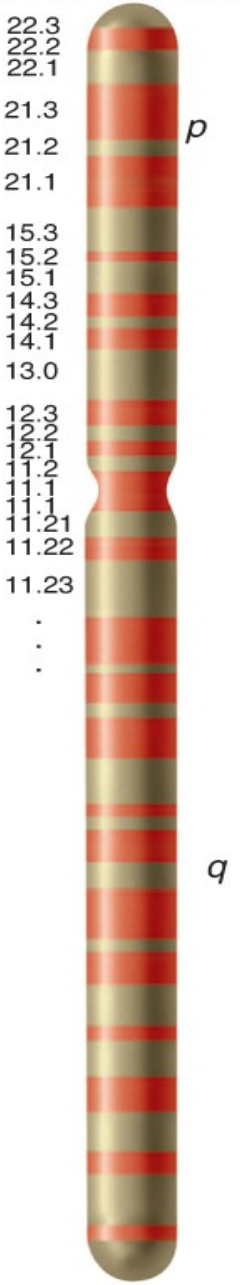


Figure 13.10

Chromosome Abnormalities

- A karyotype may be abnormal in two ways:
    1) In chromosome **number**
    2) In chromosome **structure**
- Abnormal chromosomes account for at least 50% of spontaneous abortions
- Due to improved technology, more people are being diagnosed with chromosomal abnormalities

Table 13.2 Chromosome Abnormalities

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

Polyploidy

-lethal kind of chromosomes abnormalities.

Cell with extra chromosome sets is **polyploid**

Triploid (3N) cells have three sets of chromosomes

- Produced in one of two main ways:
  - Fertilization of one egg by two sperm
  - Fusion of haploid and diploid gametes

Triploids account for 17% of all spontaneous abortions and 3% of stillbirths and newborn deaths

Triploidy

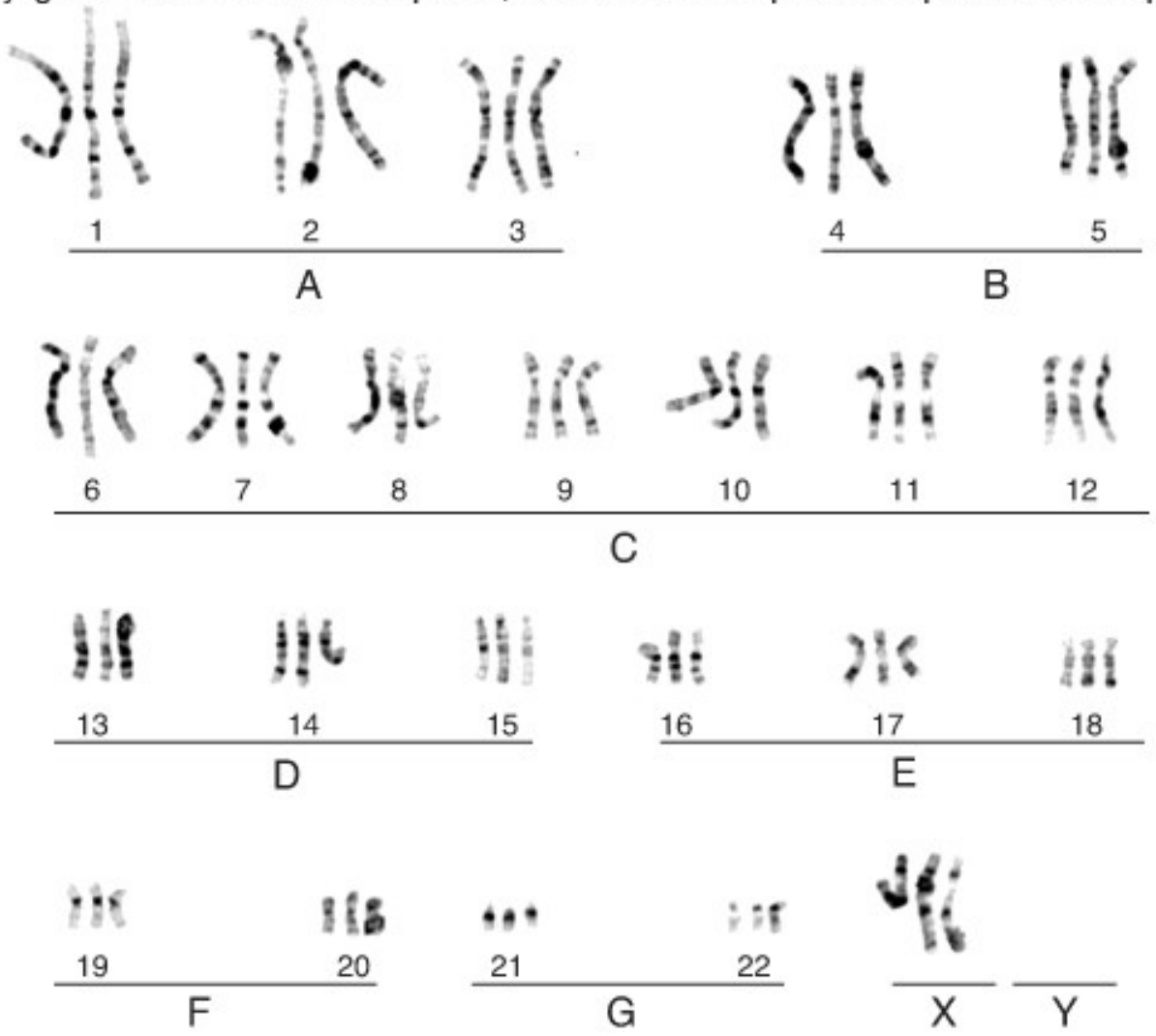


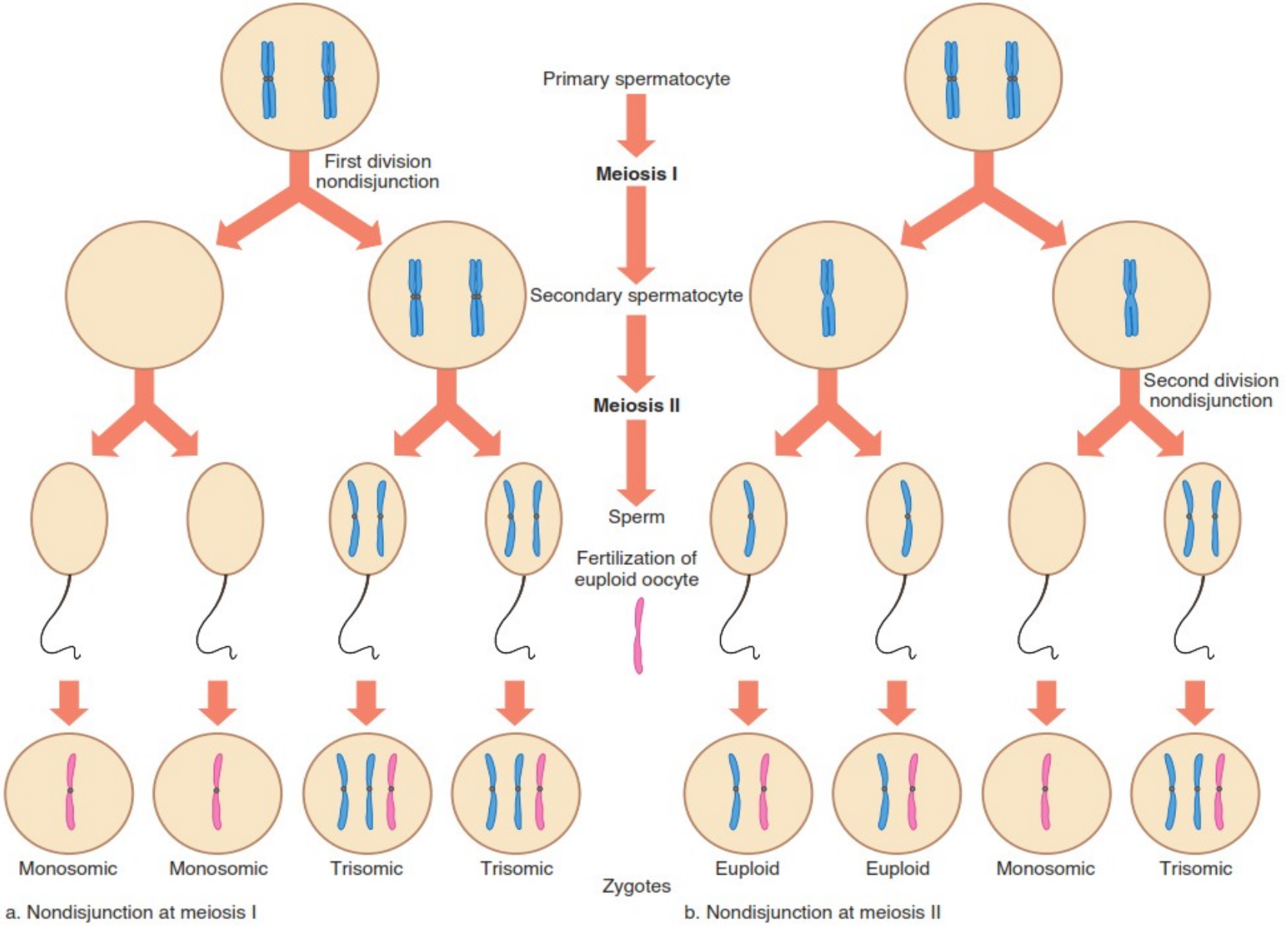
Figure 13.11

Aneuploidy

- A normal chromosomal number is **euploid**
- Cells with extra or missing chromosomes are **aneuploid**
- Most autosomal aneuploids are spontaneously aborted
- Those that are born are more likely to have an extra chromosome (**trisomy**) rather than a missing one (**monosomy**)

Nondisjunction

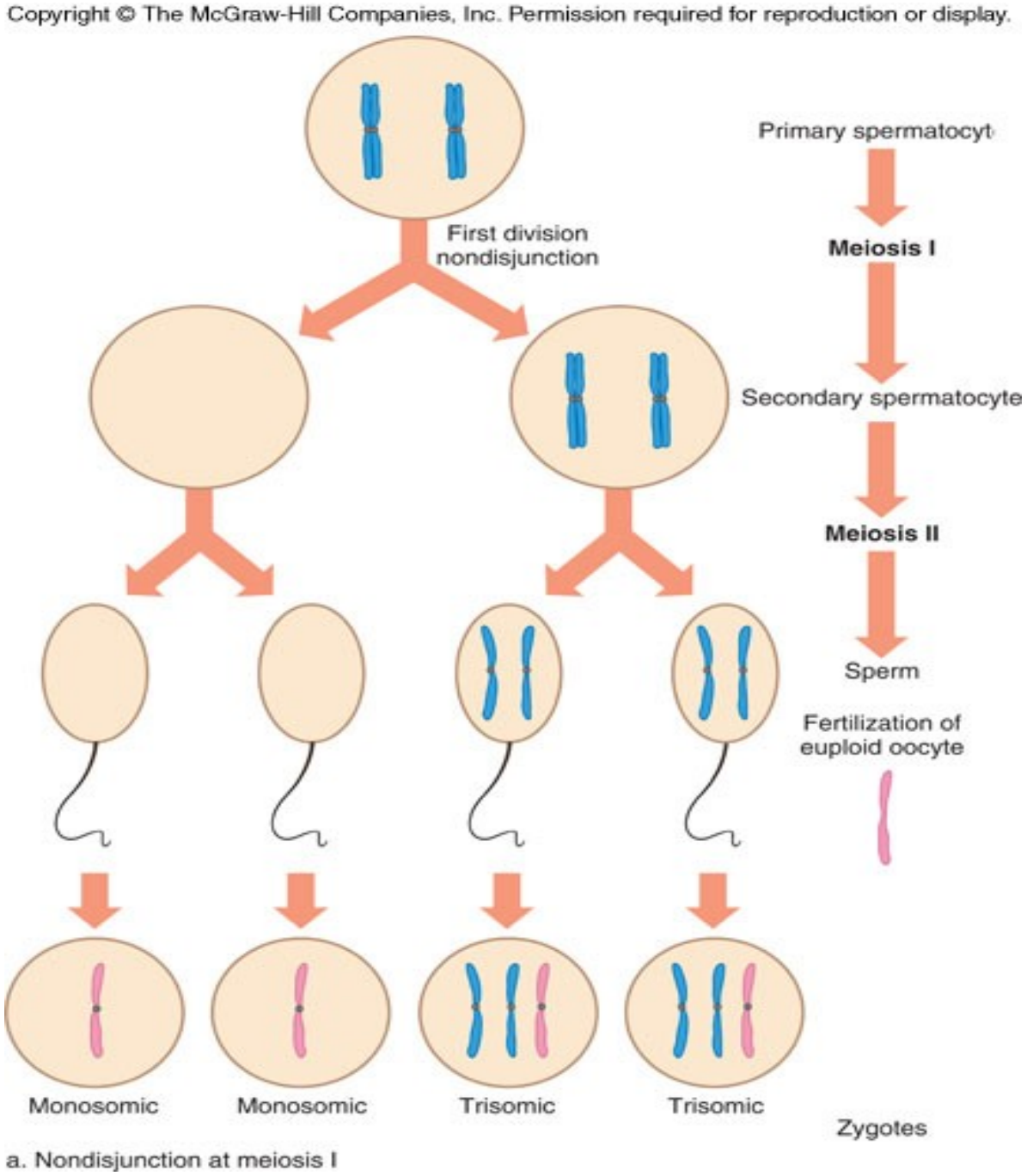
- The failure of chromosomes to separate normally during meiosis
- Produces gamete with an extra chromosome and another with one missing chromosome
- Nondisjunction during Meiosis I results in copies of both homologs in one gamete
- Nondisjunction during Meiosis II results in both sister chromatids in one gamete



كل ما كان الخطأ متأخر اكتر كل ما كان الموضوع اقل خطرا

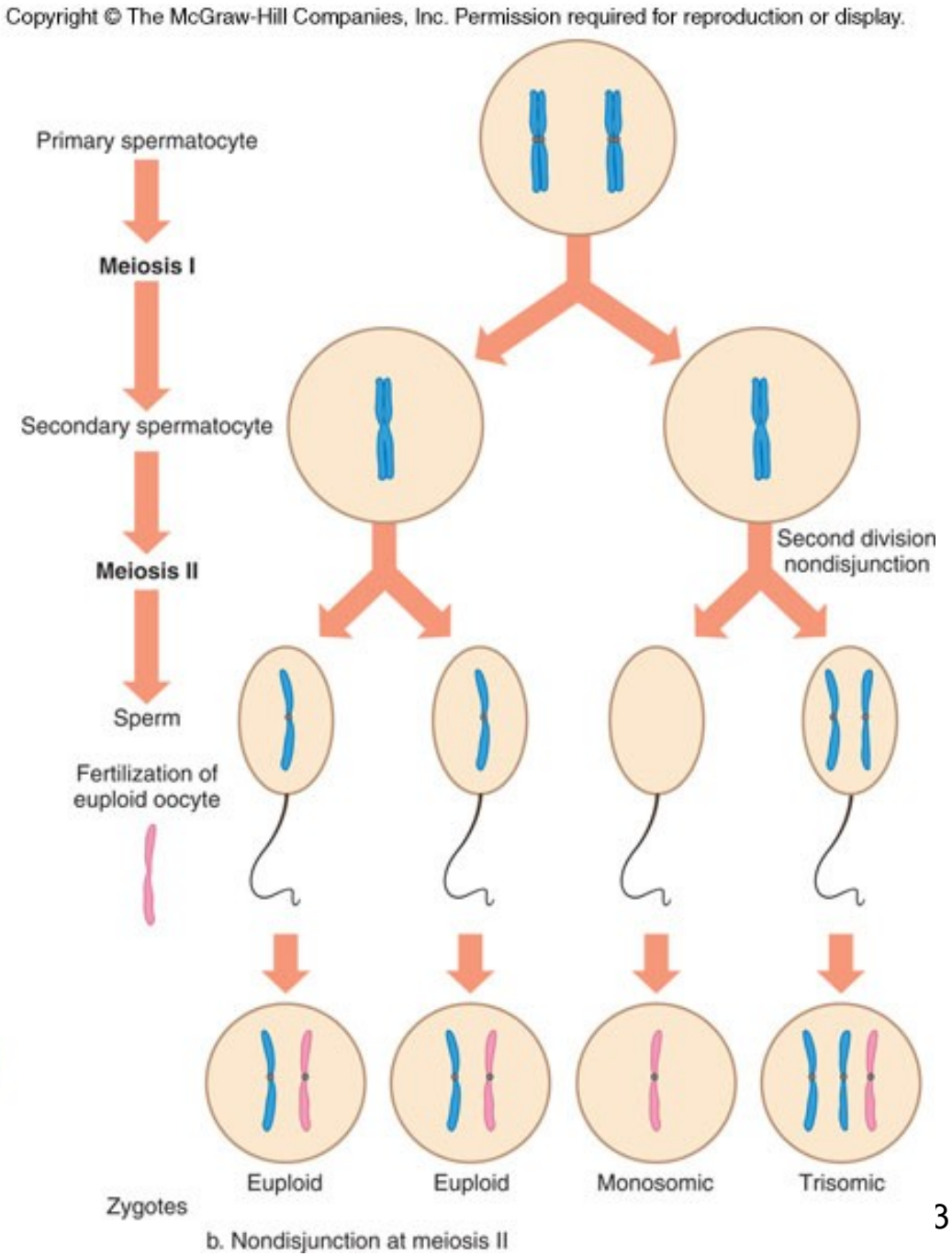
Nondisjunction at Meiosis I

Figure 13.12



Nondisjunction at Meiosis II

Figure 13.12



Aneuploidy

A mitotic nondisjunction

- Aneuploidy <u>can also arise during mitosis</u>, producing groups of somatic cells with the extra or missing chromosomes
  - الفكرة هون انه الخلل بصير بعد م يتكون الزيجوت (بانقسامات الجنين مو الاب او الام).
- An individual with two chromosomally-distinct cell populations is called a **mosaic**
- A mitotic nondisjunction event that occurs early in development can have serious effects on the health of the individual

Trisomies

- Most autosomal aneuploids cease developing as embryos or fetuses
- Most frequently seen trisomies in newborns are those of chromosomes 21, 18, and 13
- - Carry fewer genes than other autosomes

Table 13.4 Comparing and Contrasting Trisomies 13, 18, and 21

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

In late age pregnancy

Trisomy 21

- **Down syndrome**
- Most common trisomy among newborns
- Distinctive facial and physical problems

Figure 13.13

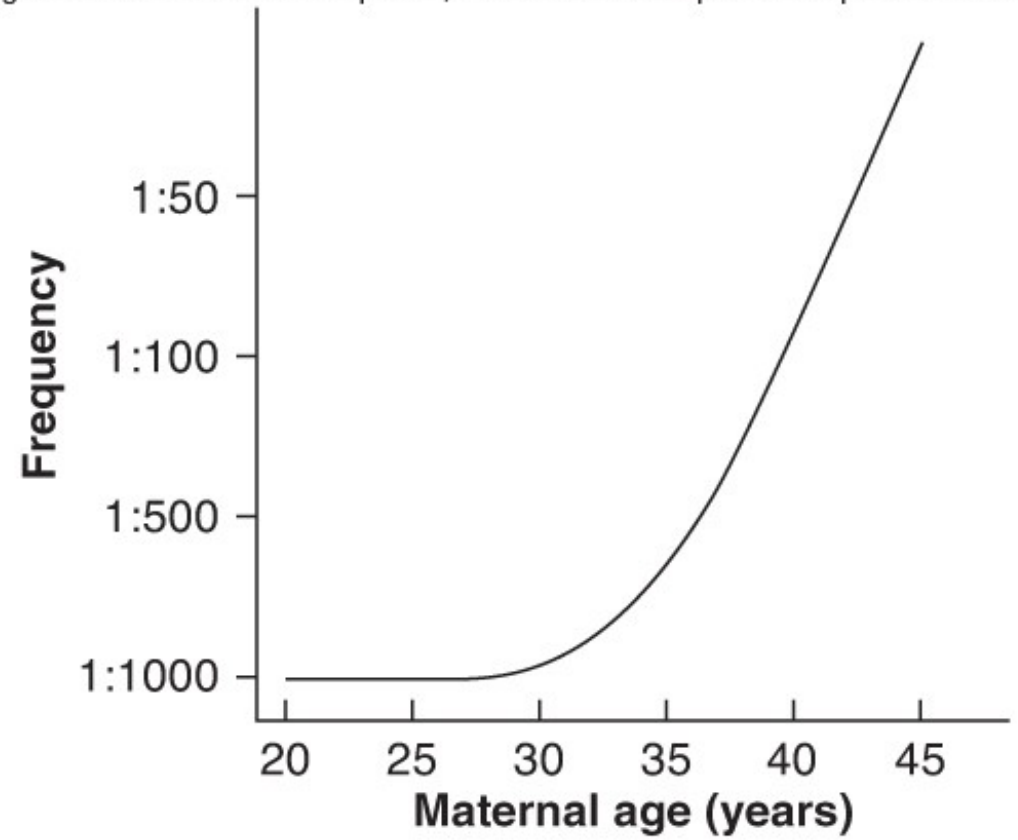
- Varying degrees of developmental disabilities
- Individuals more likely to develop leukemia
- Link with one form of Alzheimer disease

Table 13.5 Genes Associated with Trisomy 21 Down Syndrome

Gene Product	MIM	Signs and Symptoms (Phenotype)
Amyloid precursor protein (APP)	104760	Protein deposits in brain
Chromatin assembly factor I (CAF1A)	601245	Impaired DNA synthesis
Collagen type VI (COL6A1)	120220	Heart defects
Crystallin (CRYA1)	123580	Cataracts
Cystathione beta synthase (CBS)	236200	Impaired metabolism and DNA repair
Interferon receptor 1 (IFNAR)	107450	Impaired immunity
Kinase 1 (DYRK1A)	600855	Mental retardation
Oncoprotein ETS2 (ETS2)	164740	Skeletal abnormalities, cancer
Phosphoribosylglycinamide formyltransferase (GART)	138440	Impaired DNA synthesis and repair
Superoxide dismutase (SOD1)	147450	Premature aging

قصة الجدول انه هدول الجينات هنن الي بكون فيهم خلل عند مرضى داون وربطنا كل خلل جيني بالتأثير الي بأثره ع الانسان

The risk of conceiving an offspring with Down syndrome rises dramatically with maternal age



Trisomy 21 in liveborn infants

Figure 13.7

Trisomy 18

- **Edwards syndrome**

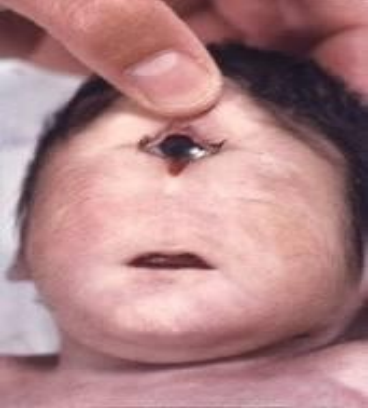
- Most due to nondisjunction in meiosis II in oocyte and do not survive

Figure 13.14a

a.

Serious mental and physical disabilities

A distinctive feature: Oddly-clenched fists



Trisomy 13

Figure 13.14b

Patau syndrome

Very rare and generally do not survive 6 months

Serious mental and physical disabilities

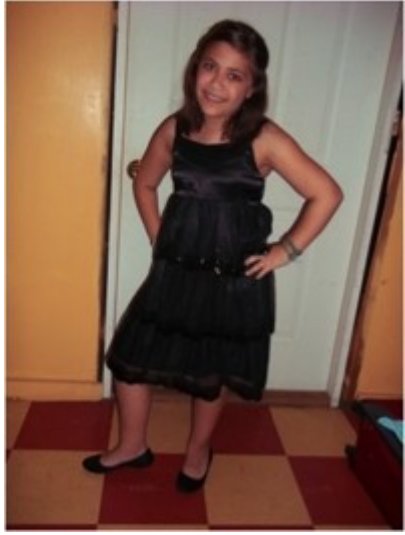
A distinctive feature: **Eye fusion**

Sex Chromosome Aneuploids

Table 13.6 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 Klinefelter syndrome
	XX	X	47,XXX triplo-X
		Y	45,Y nonviable
		X	45,X Turner syndrome
Male nondisjunction	X		45,X Turner syndrome
(meiosis I)	X	XY	47,XXY Klinefelter syndrome
Male nondisjunction	X	XX	47,XXX triplo-X
(meiosis II)	X	YY	47,XYY Jacobs syndrome
	X		45,X Turner syndrome
Male and female non-disjunction	XX	YY	48, XXYY syndrome

Turner Syndrome

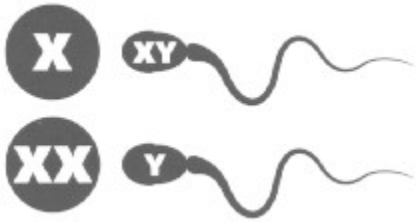


- Called the **XO syndrome**
- 1 in 2,500 female births
- 99% of affected fetuses die *in utero*
- Features include short stature, webbing at back of neck, incomplete sexual development (infertile), impaired hearing
- Individuals who are mosaics may have children

Triplo-X

- Called the **XXX syndrome**
- 1 in 1,000 female births
- Few modest effects on phenotype include tallness, menstrual irregularities, and slight impact on intelligence
- X-inactivation of two X chromosomes occurs and cells have two Barr bodies
- May compensate for presence of extra X

Klinefelter Syndrome



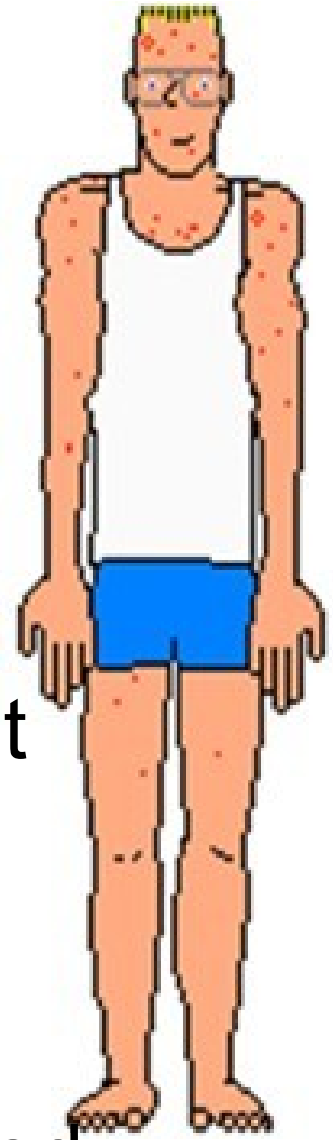
- Called the **XXY syndrome**
- 1 in 500 male births
- Phenotypes include:
  - Incomplete sexual development
  - Rudimentary testes and prostate
  - Long limbs, large hands and feet
  - Some breast tissue development
- Most common cause of male infertility

XXYY Syndrome

- Likely arises due to unusual oocyte and sperm
- Associated with more severe behavioral problems than Klinefelter syndrome
  - Obsessive compulsive disorder, learning disabilities
- Individuals are infertile
- Treated with testosterone

XYY Syndrome

- Also known as **Jacobs syndrome**
- 1 in 1,000 male births
- 96% are phenotypically normal
- Modest phenotypes may include great height, acne, speech and reading disabilities
- Studies suggesting increase in aggressive behaviors are not supported



Chromosome Structural Abnormalities

a. Normal sequence of genes

b. Deleted sequence of genes

Figure 13.15

c. Duplicated sequence of genes

d. Inverted sequence of genes

Human Genetics

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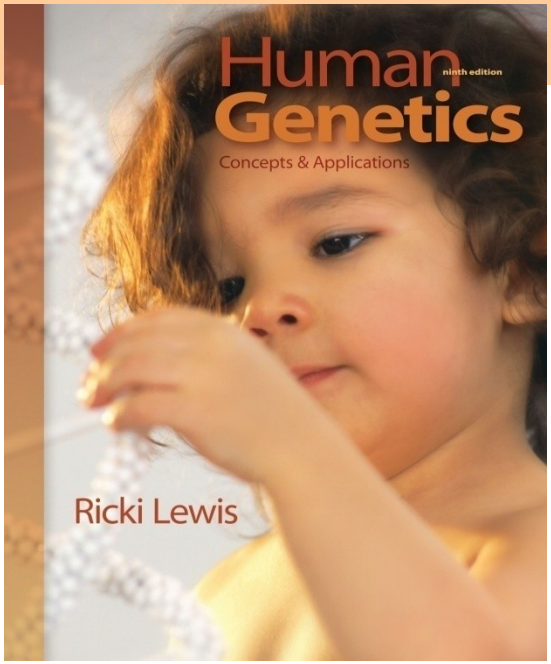

13 Chromosomes

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Deletions

A **deletion** refers to a missing genetic segment from a chromosome

Deletions are 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 $5p^-$

Duplications

A **duplication** refers to the presence of an extra genetic segment on a chromosome

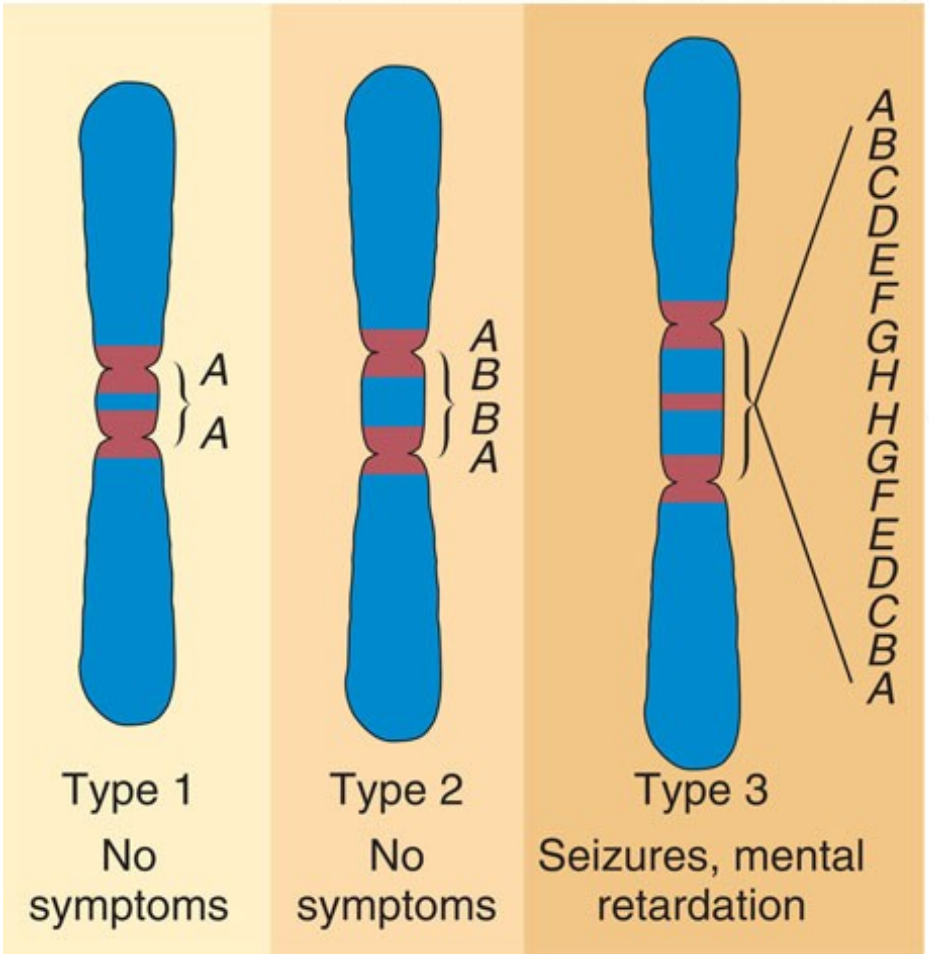
Duplications are often not inherited

- Rather they arise *de novo*

The effect of duplications on the phenotype is generally dependent on their size

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

Duplications in Chromosome 15



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

Figure 13.17

You don't have to know these features

You could have duplication without symptoms(the size of duplication is directly proportional with the severity of symptoms).

Translocations

In a **translocation**, two nonhomologous chromosomes exchange segments

There are two major types:

1) **Robertsonian translocation**

2) **Reciprocal translocation**

Robertsonian Translocations

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

- The short arms are often lost

Affect 1 in 1,000 people

Translocation carriers have 45 chromosomes

- Produce unbalanced gametes

Translocation Down Syndrome

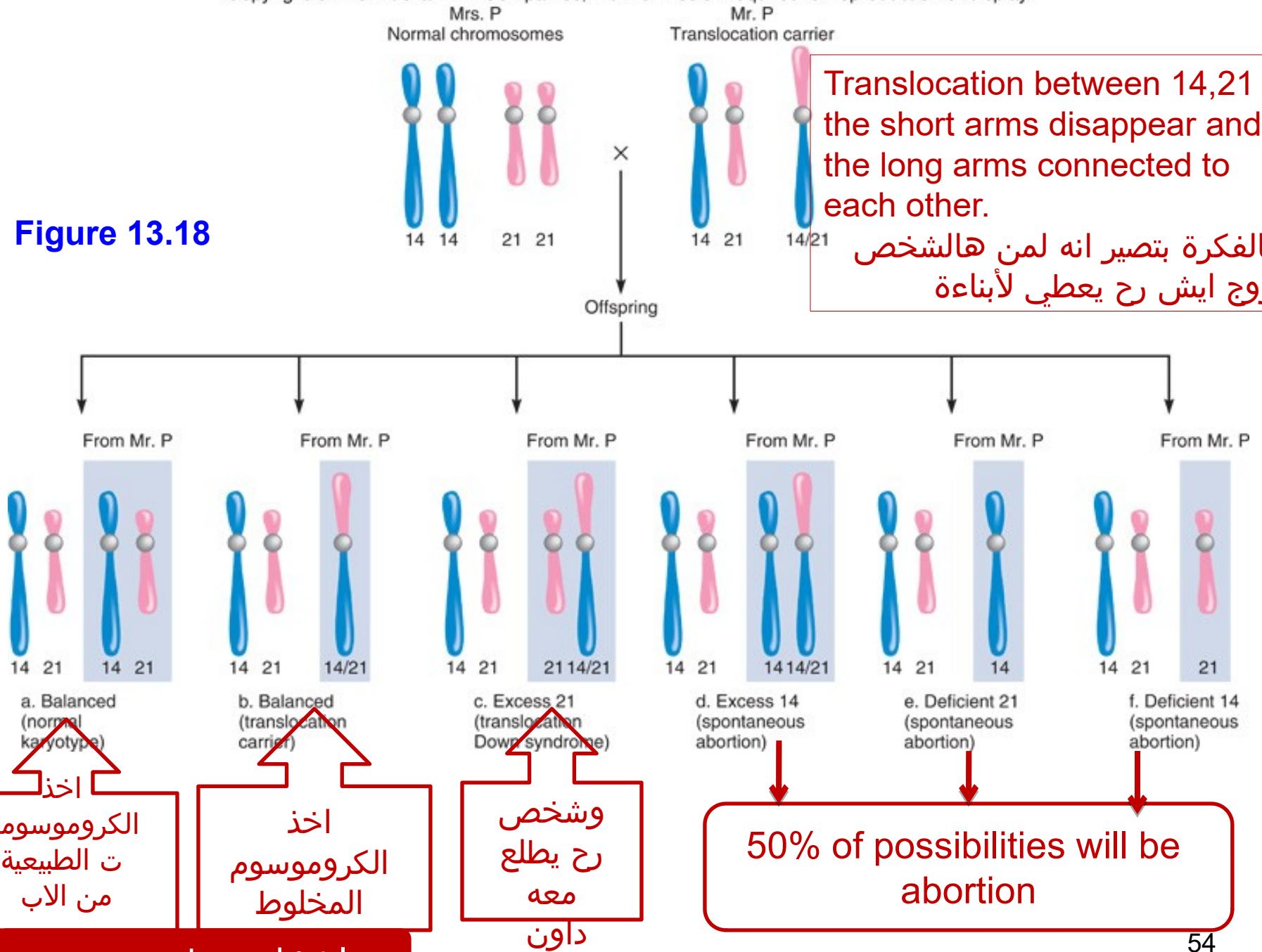
About 5% of Down syndrome results from a Robertsonian translocation between chromosomes 21 and 14

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

One of the parents is a translocation carrier

- They may have no symptoms
- However, the distribution of the unusual chromosome leads to various imbalances

Figure 13.18



Translocation between 14,21 , the short arms disappear and the long arms connected to each other.

فالفكرة بتصير انه لمن هالشخص يتزوج ايش رح يعطي لأبناءة

اخذ الكروموسوما ت الطبيعية من الاب

اخذ الكروموسوم المخلوط

وشخص رح يطلع معه داون

50% of possibilities will be abortion

اشخاص طبيعيين

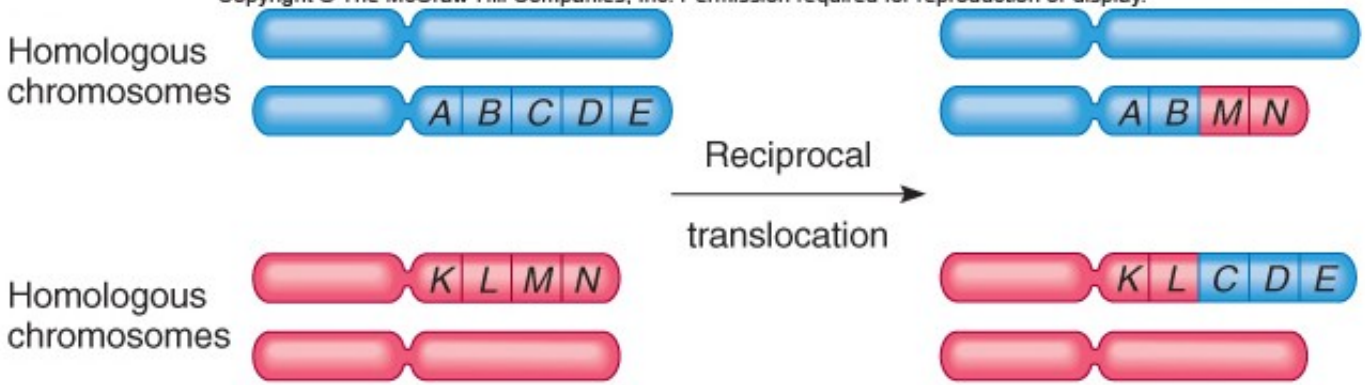
Reciprocal Translocations

Two nonhomologous chromosomes exchange parts

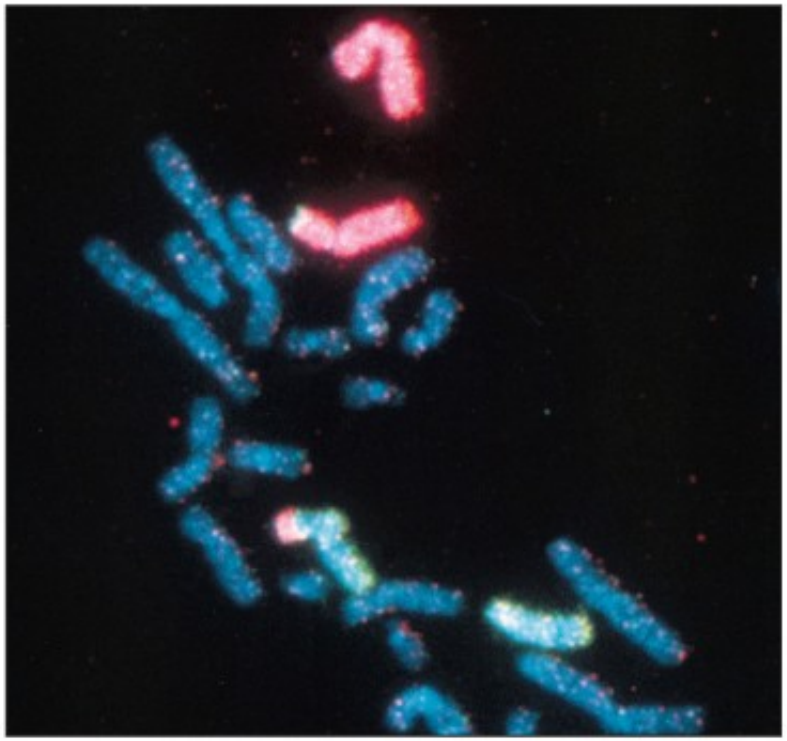
About 1 in 500 people are carriers

- Are usually healthy because they have the normal amount of genetic material (but it is rearranged)

However, if the translocation breakpoint interrupts a gene, there may be an associated phenotype



a.



b.

Courtesy Lawrence Livermore National Laboratory

Figure 13.19

Inversions

An **inversion** is a chromosome segment that is flipped in orientation

5-10% cause health problems (eg. Cancers) probably due to disruption of genes at the breakpoints

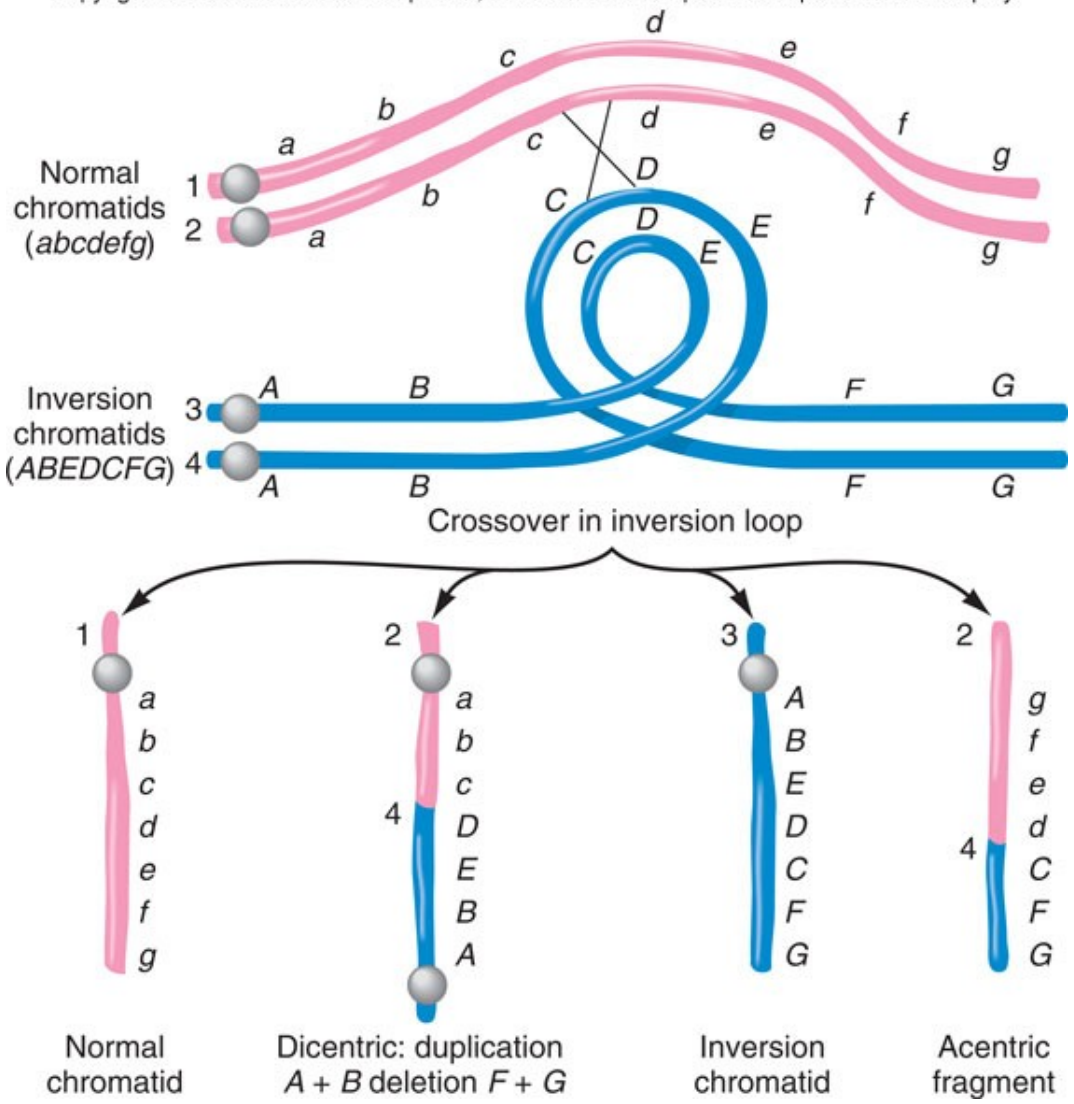
Paracentric inversion = Inverted region does NOT include centromere

Pericentric inversion = Inverted region includes centromere

Inversions may impact meiotic segregation

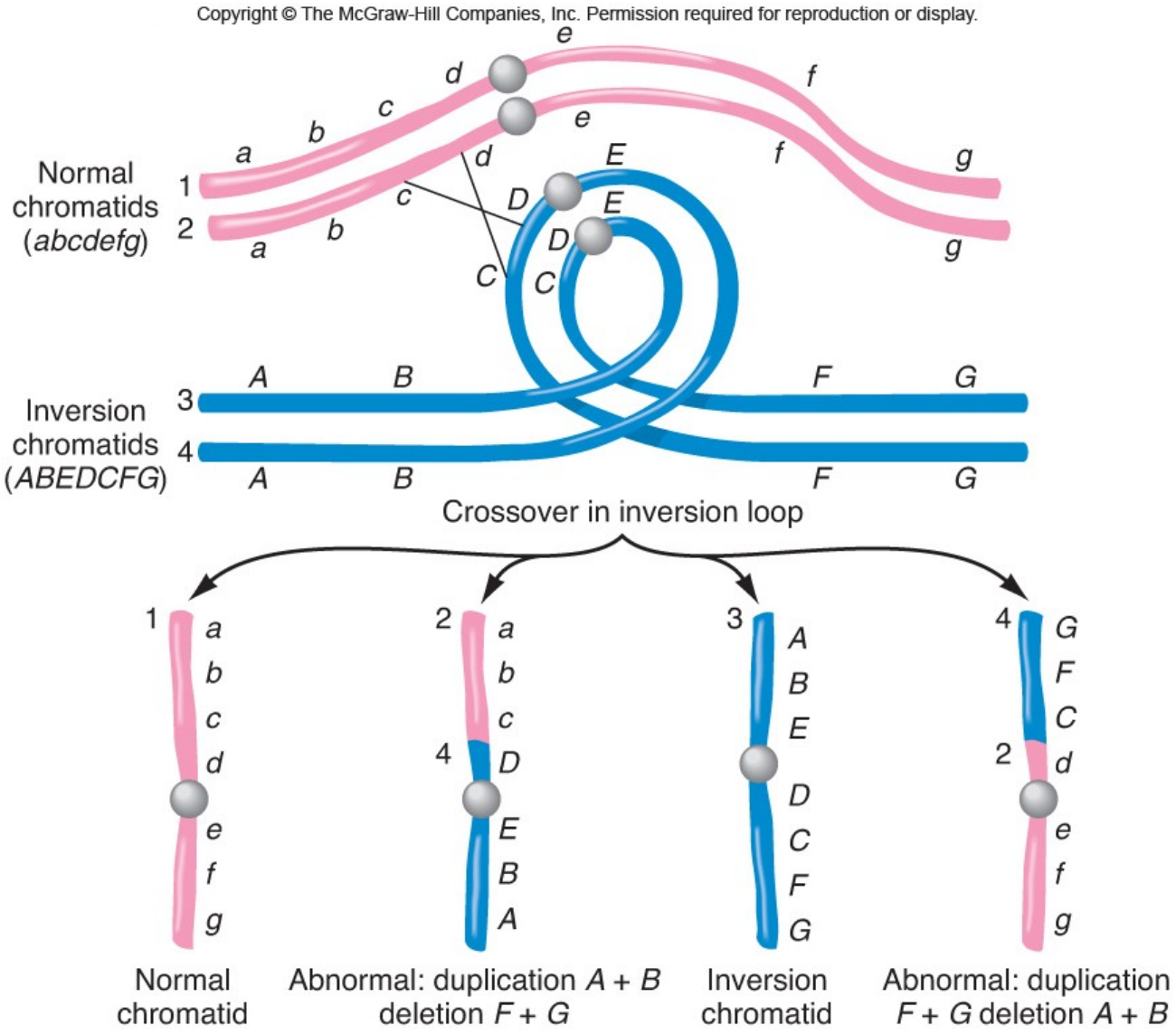
Segregation of a Paracentric Inversion

Figure 13.20



Segregation of a Pericentric Inversion

Figure 13.21

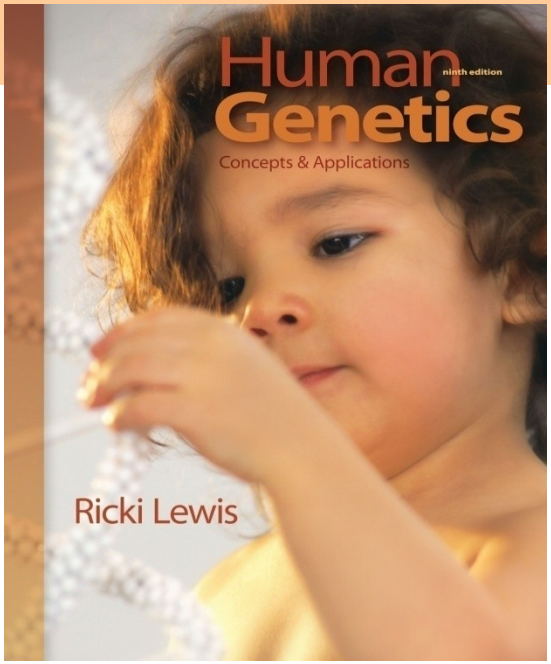


Human Genetics

Concepts and Applications

Ninth Edition

RICKI LEWIS



13 Chromosomes

PowerPoint® Lecture Outlines
Prepared by Johnny El-Rady, University of South Florida

Isochromosomes

Chromosomes with identical arms

Form when centromeres divide along the incorrect plane during meiosis

-it will divided into 2 short arms together and 2 long arms connected with each other

فبالتالي بطلع معي
كروموسومات ذراعينهم
متطابقات شكلا

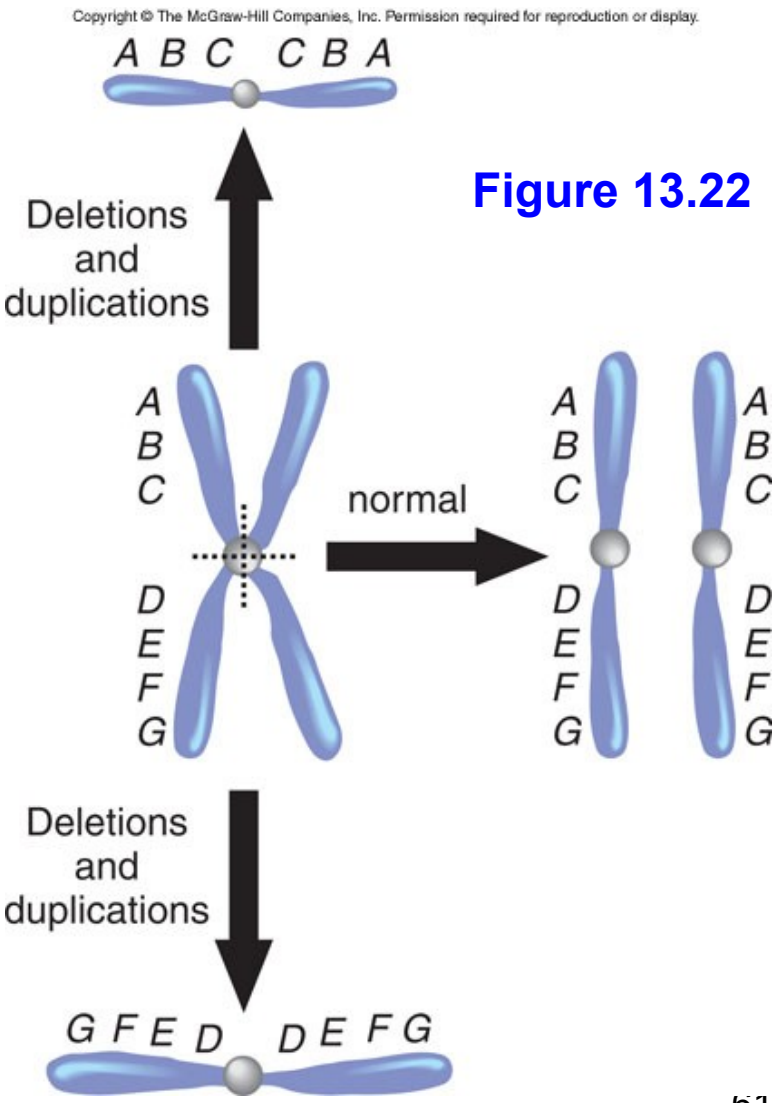
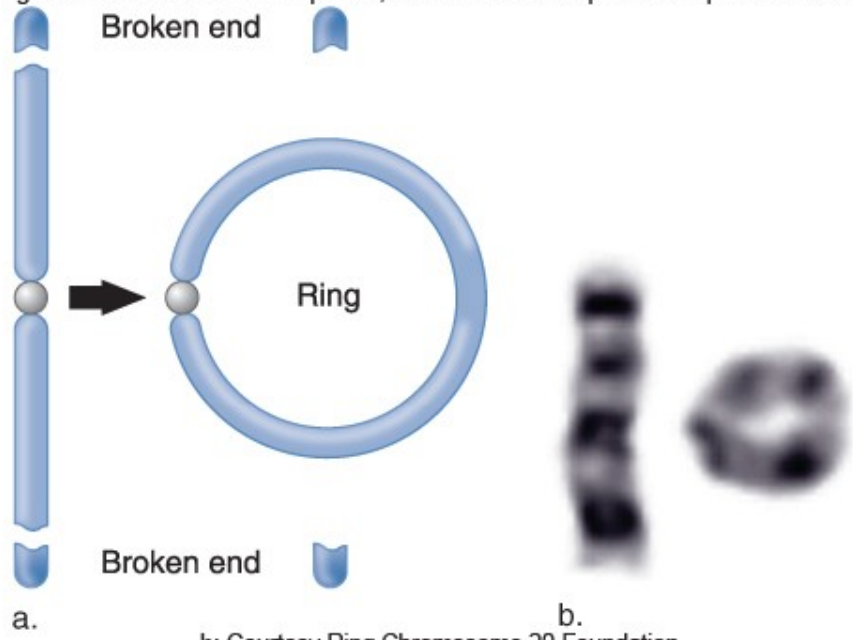


Figure 13.22

Ring Chromosomes

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

Figure 13.23



b: Courtesy Ring Chromosome 20 Foundation

Table 13.7 Causes of Chromosomal Aberrations

Abnormalities	Causes
Numerical Abnormalities	
Polyploidy	Error in cell division (meiosis or mitosis) in which not all chromatid pairs separate in anaphase
	Multiple fertilization
Aneuploidy	Nondisjunction (in meiosis or mitosis) leading to lost or extra chromosomes
Structural Abnormalities	
Deletions and duplications	Translocation
	Crossover between a chromosome that has a pericentric inversion and its noninverted homolog
Translocation	Exchange between nonhomologous chromosomes
Inversion	Breakage and reunion of fragment in same chromosome, but with wrong orientation
Dicentric and acentric	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

Uniparental Disomy

Inheritance of two chromosomes or chromosome parts from the same parent

UPD requires the simultaneous occurrence of two rare events

1) Nondisjunction of the same chromosome in both sperm and egg

2) Trisomy followed by chromosome loss

Uniparental Disomy

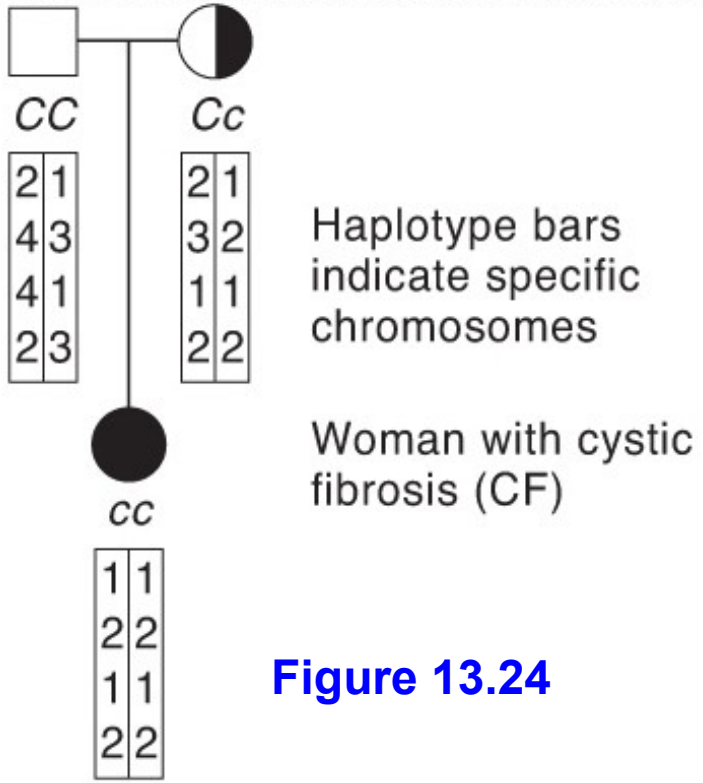


Figure 13.24

,, من ناحية المرض
الاب طبيعي والام حاملة للمرض.
الطفلة بتكون اخدت نسختين الكروموسوم من الام فبالتالي بتطلع مصابه

القصة هون انه بيجي الطفل عنده نسختين من الكروموسوم رقم 20 مثلا, ما في ولا نسخة من الاب!!!
هاد الشي بسبب انه كروموسومات الام بتكون ما انقسمت فبتكون اعطته النسختين من عندها, والاب ما بكون اعطى ولا نسخة من هاد الكروموسوم فبالتالي عند الاخصاب لقينا انه نسختين الكروموسوم 20 من الام مصدرهم