Aneuploidy of Sex Chromosomes

- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions
- **Klinefelter syndrome** is the result of an extra chromosome in a male, producing XXY individuals
- Monosomy X, called ***Turner syndrome***, produces X0 females, who are sterile; it is the **only** known viable monosomy in humans

Incidence of Chromosomal Abnormalities in Newborns

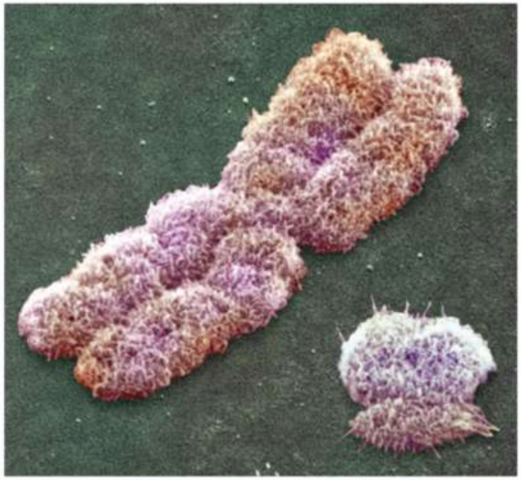
Type of Abnormality			Prevalence at Birth
Sex Chromosome Aneuploidy			
Males (43,612 newborns)			
	47,XXY		1/1000
	47,XYY		1/1000
Females (24,547 newborns)			
	45,X		1/5000
	47,XXX		1/1000
Autosomal Aneuploidy (68,159 newborns)			
	Trisomy 21		1/800
	Trisomy 18		1/6000
	Trisomy 13		1/10,000
Structural Abnormalities (68,159 newborns)			
(Sex chromosomes and autosomes)			
	Balanced rearrangements		
		Robertsonian	1/1000
		Other (reciprocal and others)	1/885
	Unbalanced rearrangements		1/17,000
All Chromosome Abnormalities			
	Autosomal disorders and unbalanced rearrangements		1/230
	Balanced rearrangements		1/500
Total			1/154

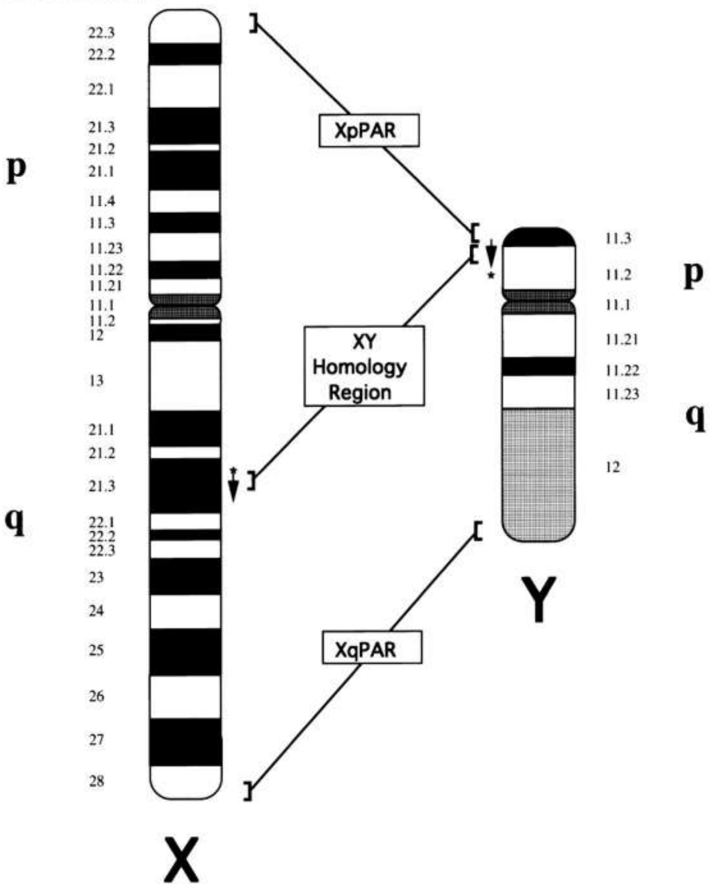
Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

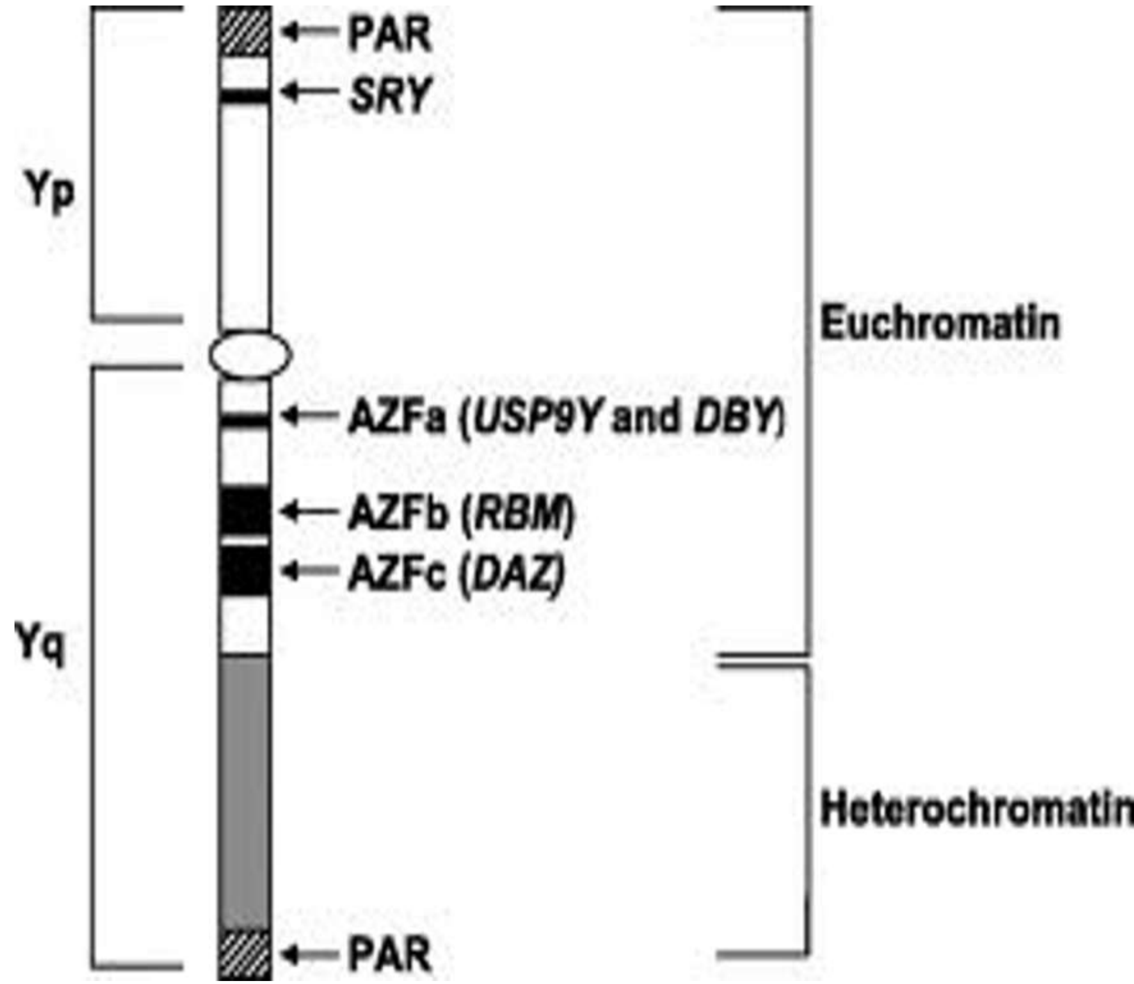
The Chromosomal Basis of Sex

- In humans and other mammals, there are two varieties of sex chromosomes: a larger X chromosome and a smaller Y chromosome
- Only the **ends of the Y** chromosome have regions that are **homologous** with corresponding regions of the X chromosome
- The ***SRY*** gene on the Y chromosome codes for a protein that **directs the development of male anatomical features**

Figure 15.5



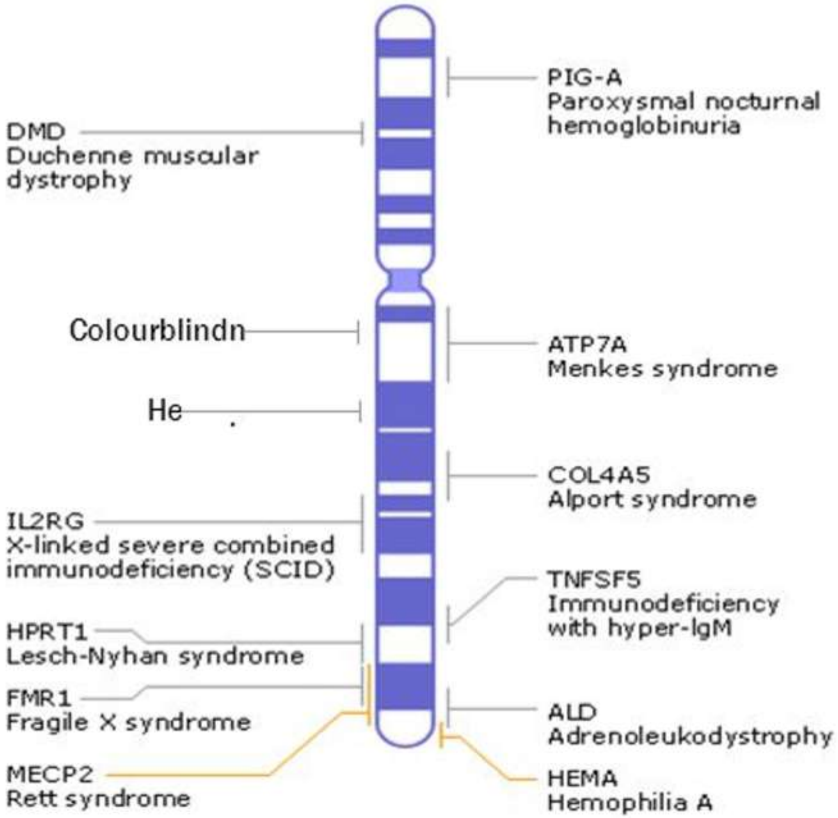




SRY (<u>S</u>ex-determining <u>r</u>egion <u>Y</u>)

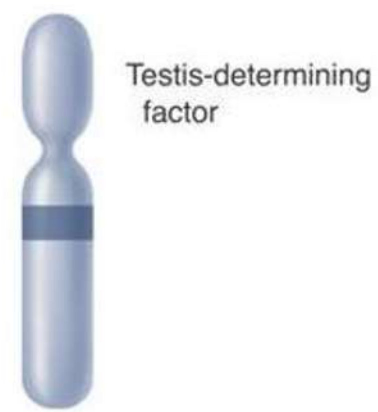
Sex Chromosomes

X chromosome



900-1600 genes

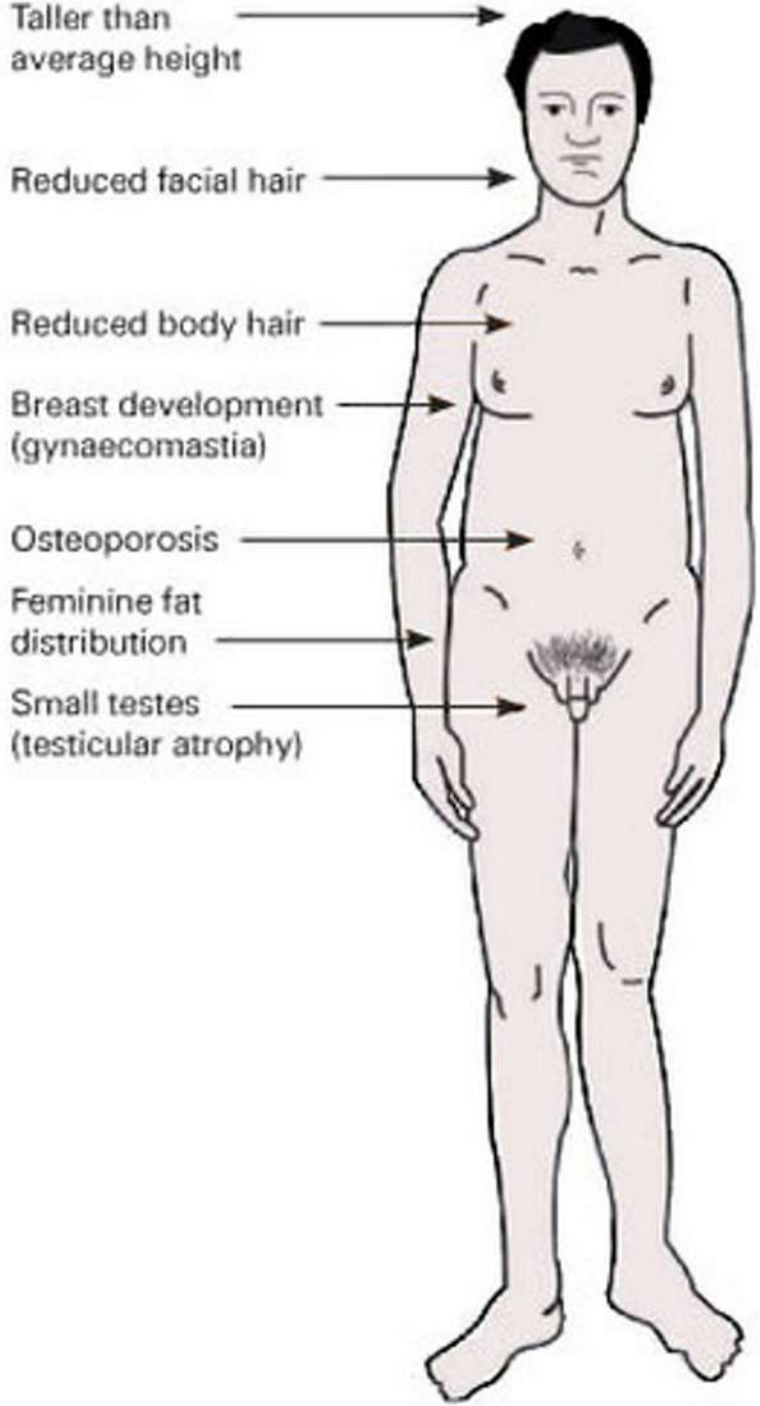
Y chromosome

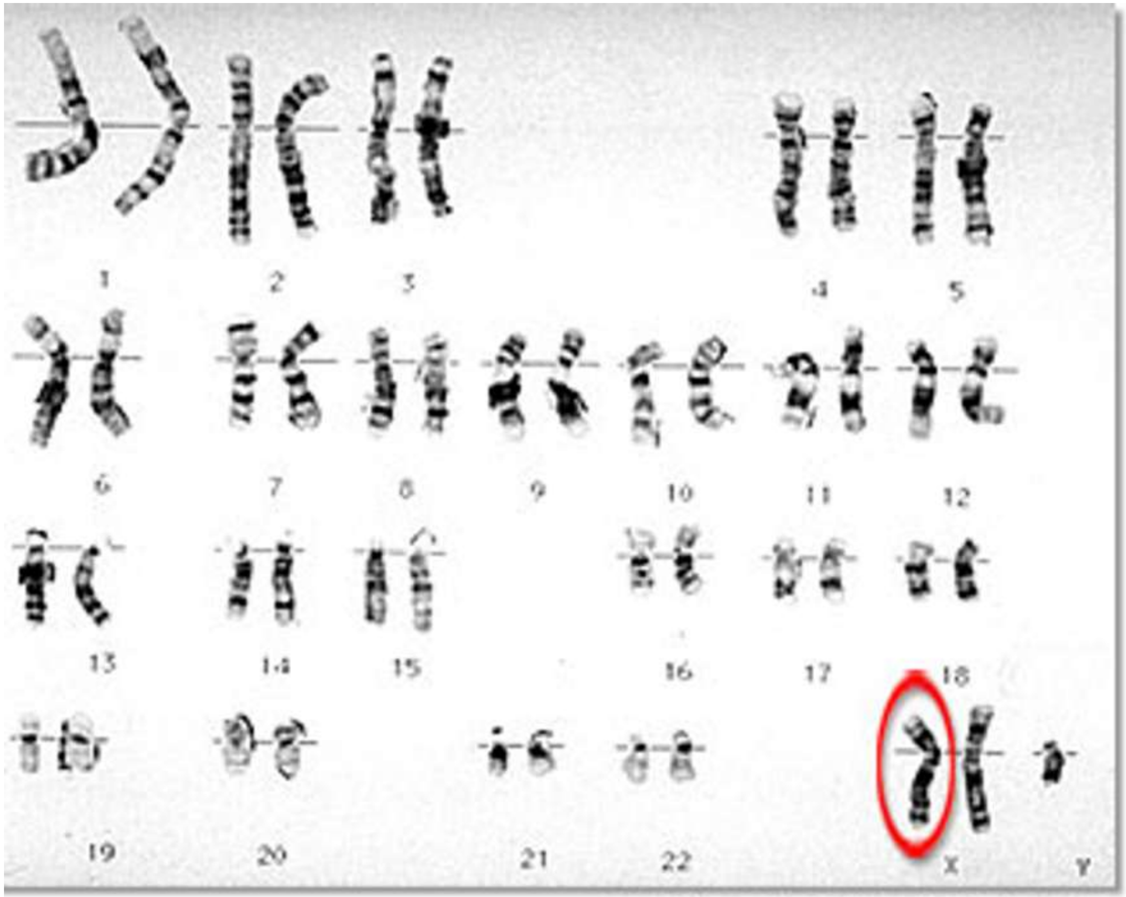


70-200 genes

Kleinfelter's syndrome (or Klinefleter's)

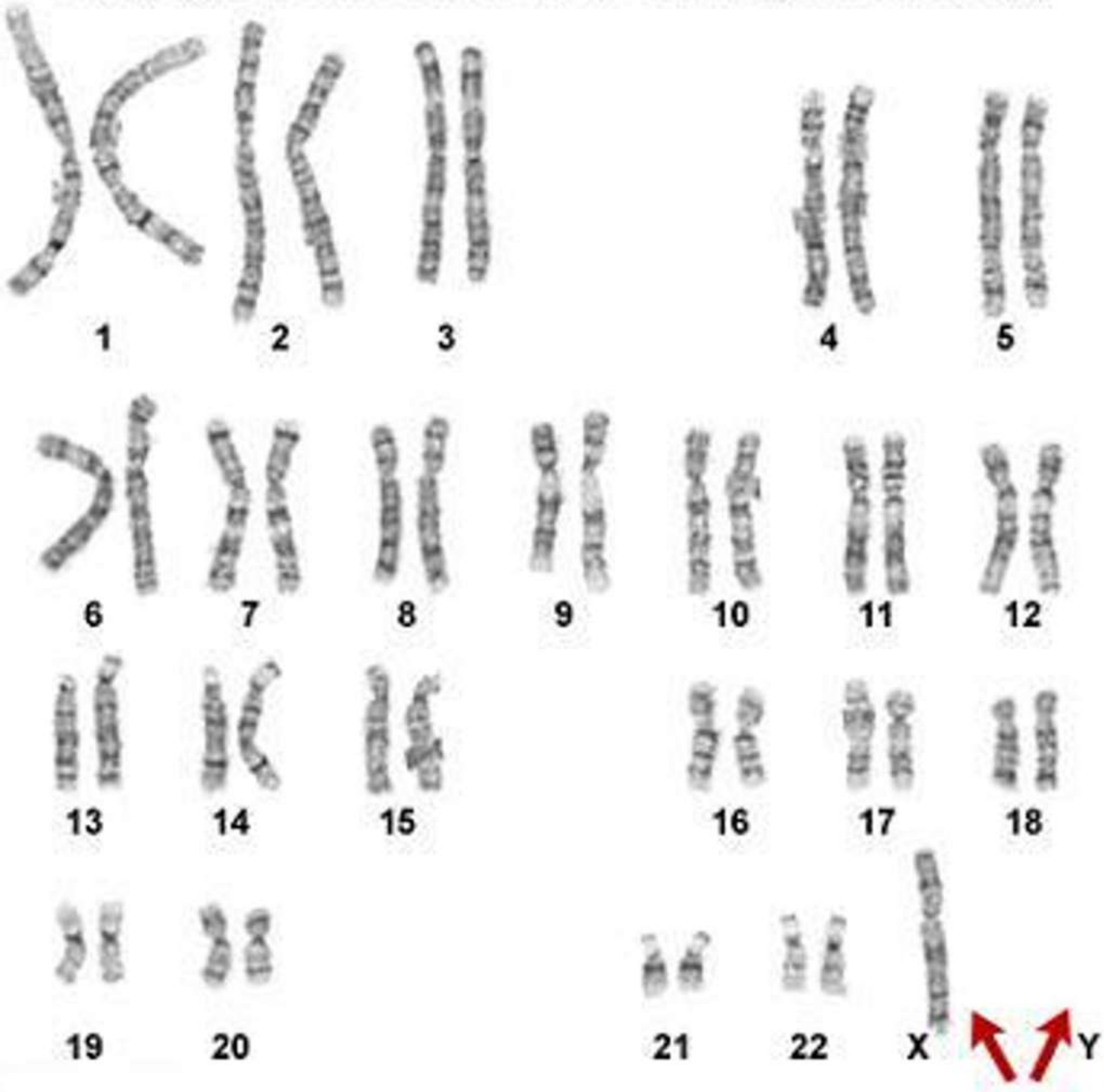
- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present.

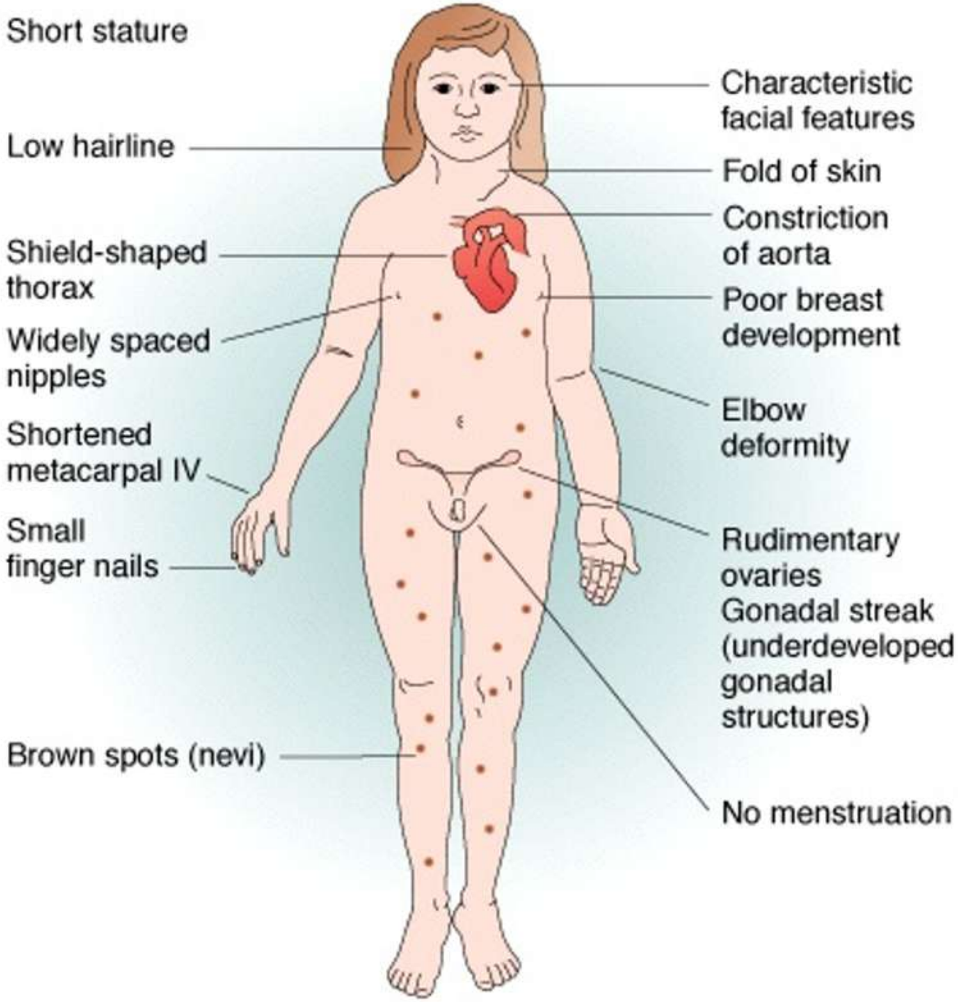




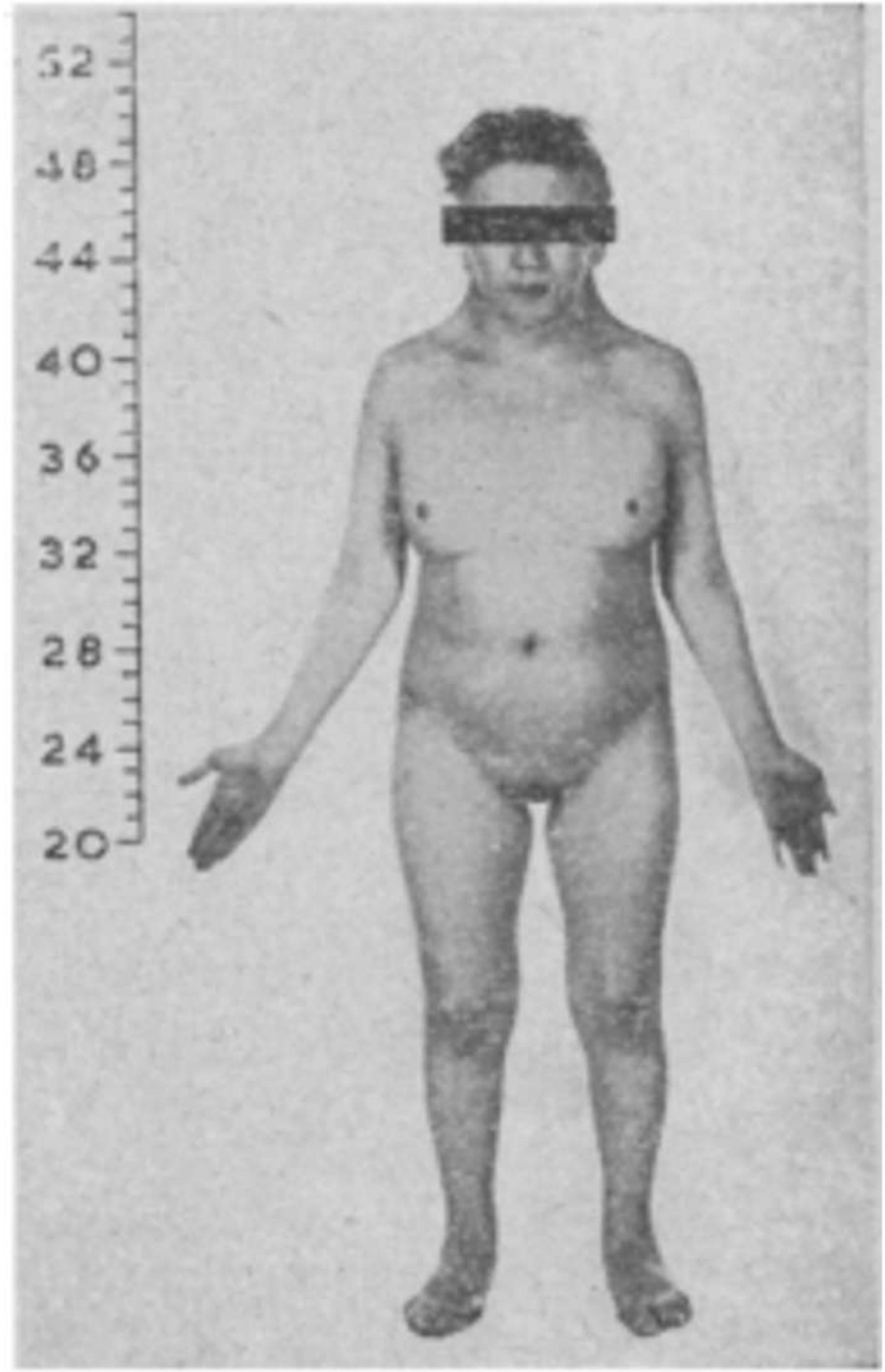
medgen.genetics.utah.edu

Karyotype From a Female With Turner syndrome (45,X)

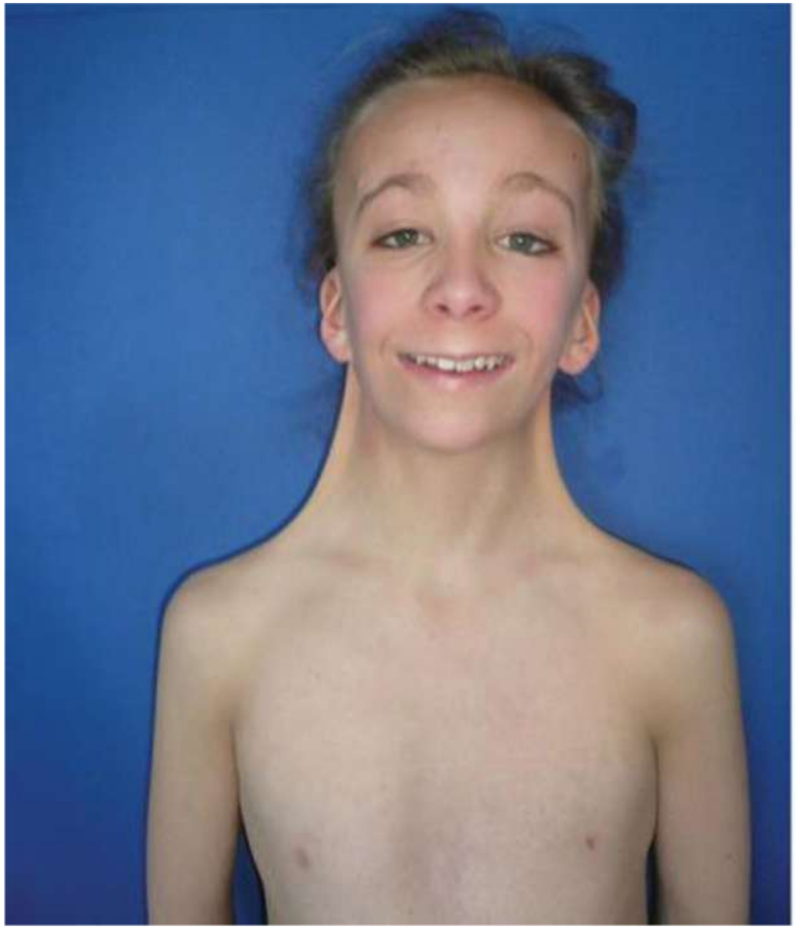




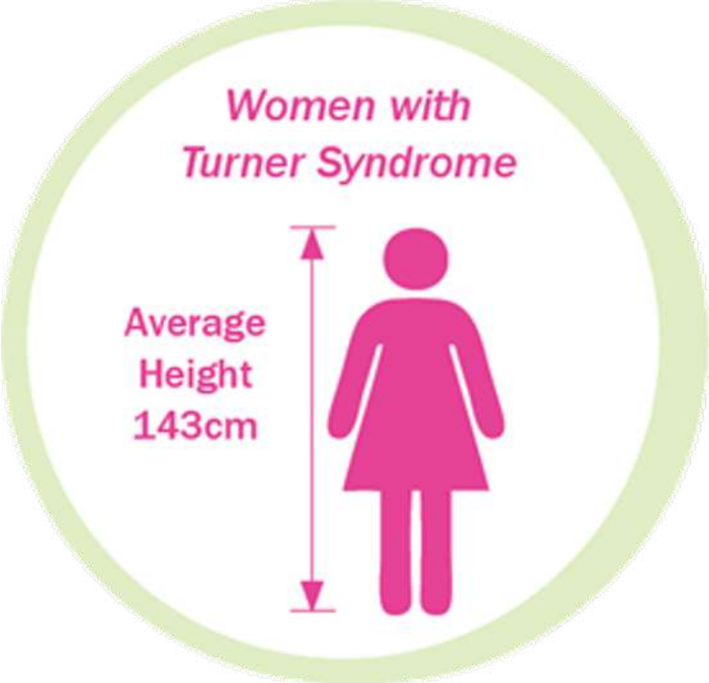
Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation



52
48
44
40
36
32
28
24
20

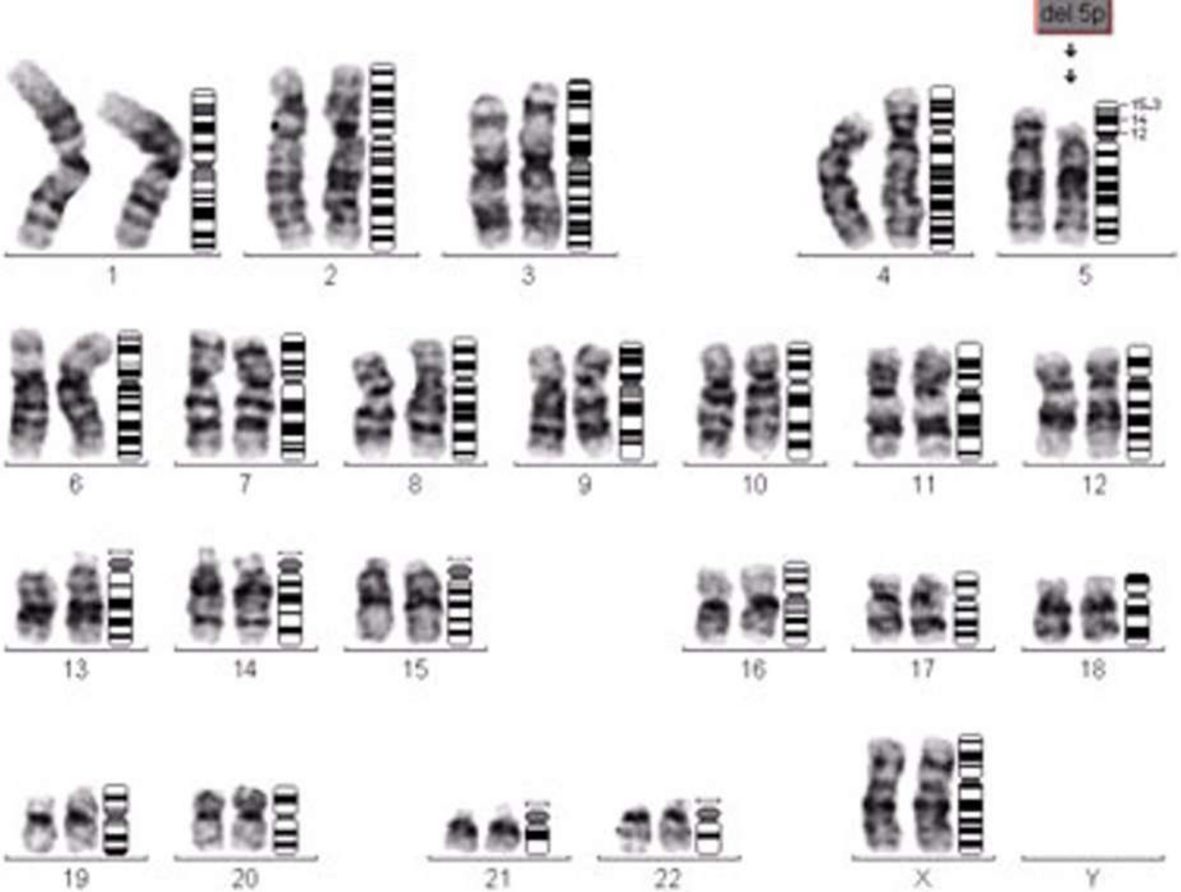



Medscape
Source: Expert Rev Dermatol © 2009 Expert Reviews Ltd


Women with
Turner Syndrome
Average
Height
143cm

Disorders Caused by Structurally Altered Chromosomes

- The syndrome *cri du chat* ("cry of the cat"), results from a specific deletion in chromosome 5
- A child born with this syndrome is mentally retarded and has a catlike cry; individuals usually die in infancy or early childhood
- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes


del 5p
15.3
14
12
1
2
3
4
5
6
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8
9
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12
13
14
15
16
17
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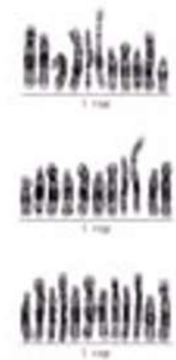
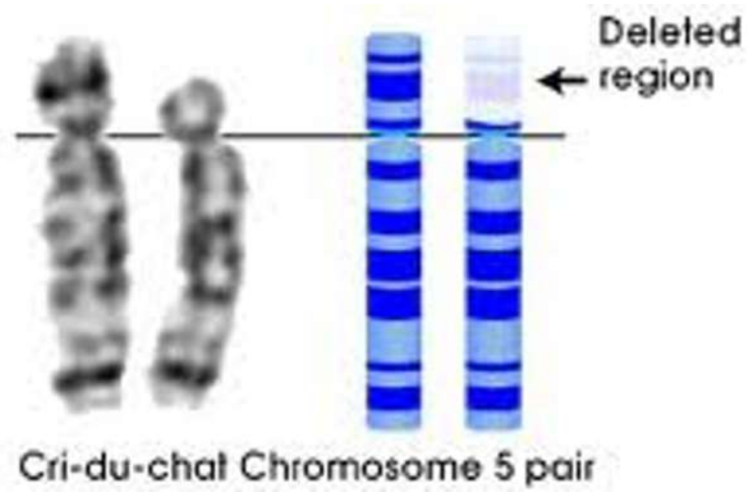
20
21
22
X
Y




Deleted region
Cri-du-chat Chromosome 5 pair

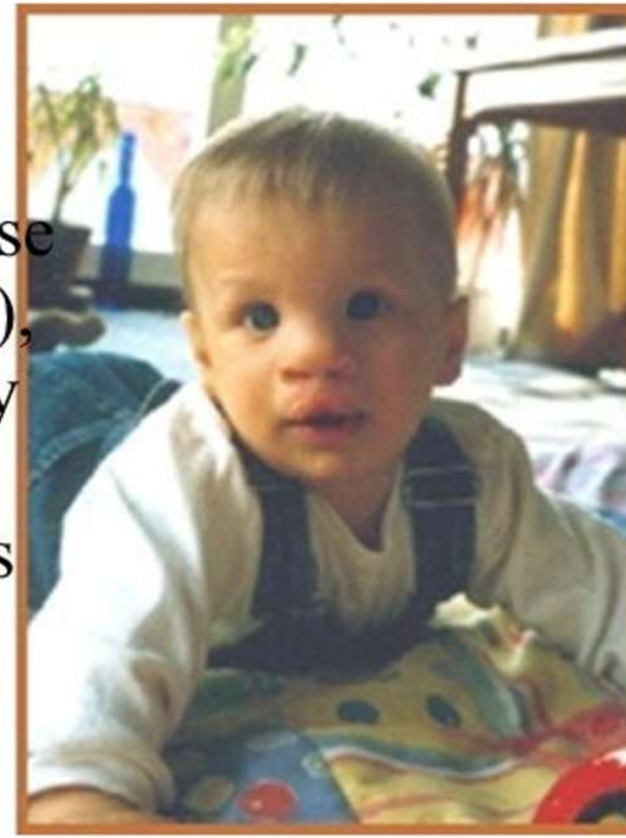
Symptoms of cri du chat syndrome are mostly those of looks. People who have this syndrome have very distinct looks. They have:

- Small heads (microcephaly)
- Unusually round face
- Small chin
- Eyes that are very far apart
- Folds of skin over their eyes
- Small nose bridge

Symptoms occur inside the body also. Heart defects, muscular/skeletal problems, hearing or sight problems, and poor muscle tone are all possible. When children diagnosed with Cri Du Chat grow, they usually have difficulty walking and talking correctly. They might have behavior problems like hyperactivity and aggression. Also, some may have severe mental retardation

Cri-du-chat Symptoms

- Approximately 75% of the patients with cri-du-chat syndrome die within the first few months of life and about 90% before they are aged 1 year. These figures are from an older study (1978), and decreased morbidity and mortality are most likely with contemporary interventions. Survival to adulthood is possible.
- Pneumonia, aspiration pneumonia, congenital heart defects, and respiratory distress syndrome are the most common causes of death.



Disorders Caused by Structurally Altered Chromosomes

- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes

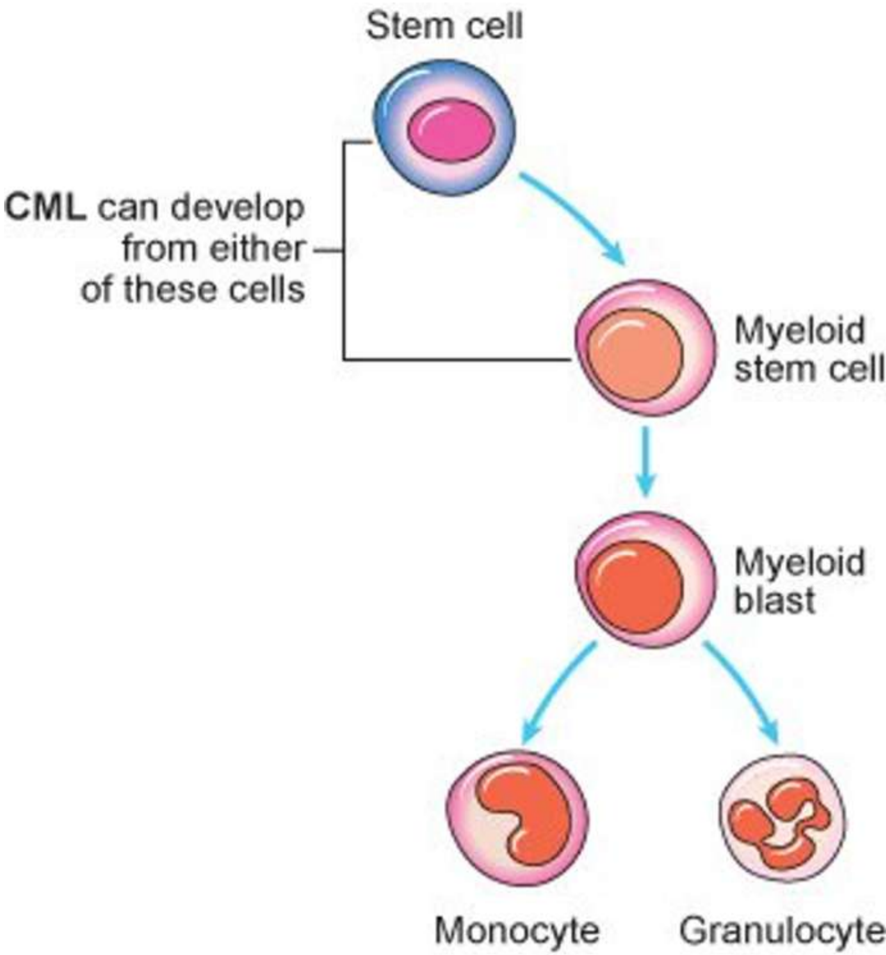
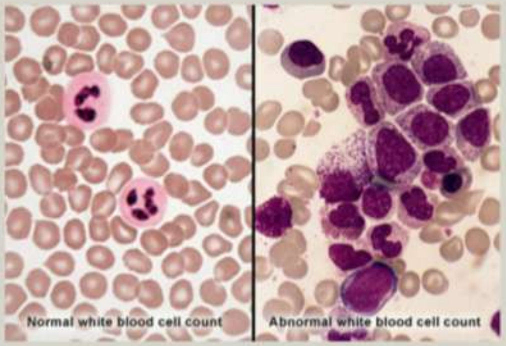


Diagram showing which cells CML can start in
© CancerHelp UK

What is leukemia?

A cancer found in the blood and bone marrow, caused by too many white blood cells in the body. The white blood cells don't let the body fight disease and prevent the body from making red blood cells and platelets.



4 types of leukemia

Acute lymphoblastic leukemia

Found in lymphoid cells
Grows quickly
Common in children
6,000 cases a year

Acute myelogenous leukemia

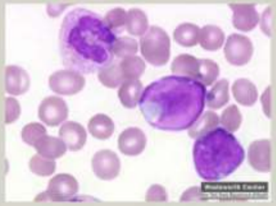
Found in myeloid cells
Grows quickly
Common in adults and children
18,000 cases a year

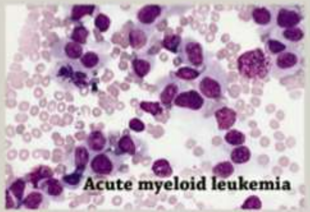
Chronic lymphoblastic leukemia

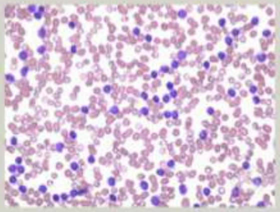
Found in lymphoid cells
Grows slowly
Common in adults 55+
15,000 cases a year

Chronic myelogenous leukemia

Found in myeloid cells
Grows slowly
Common in adults
6,000 cases a year







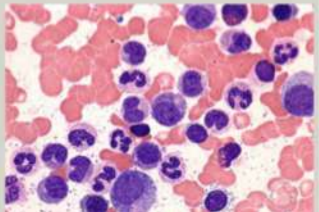
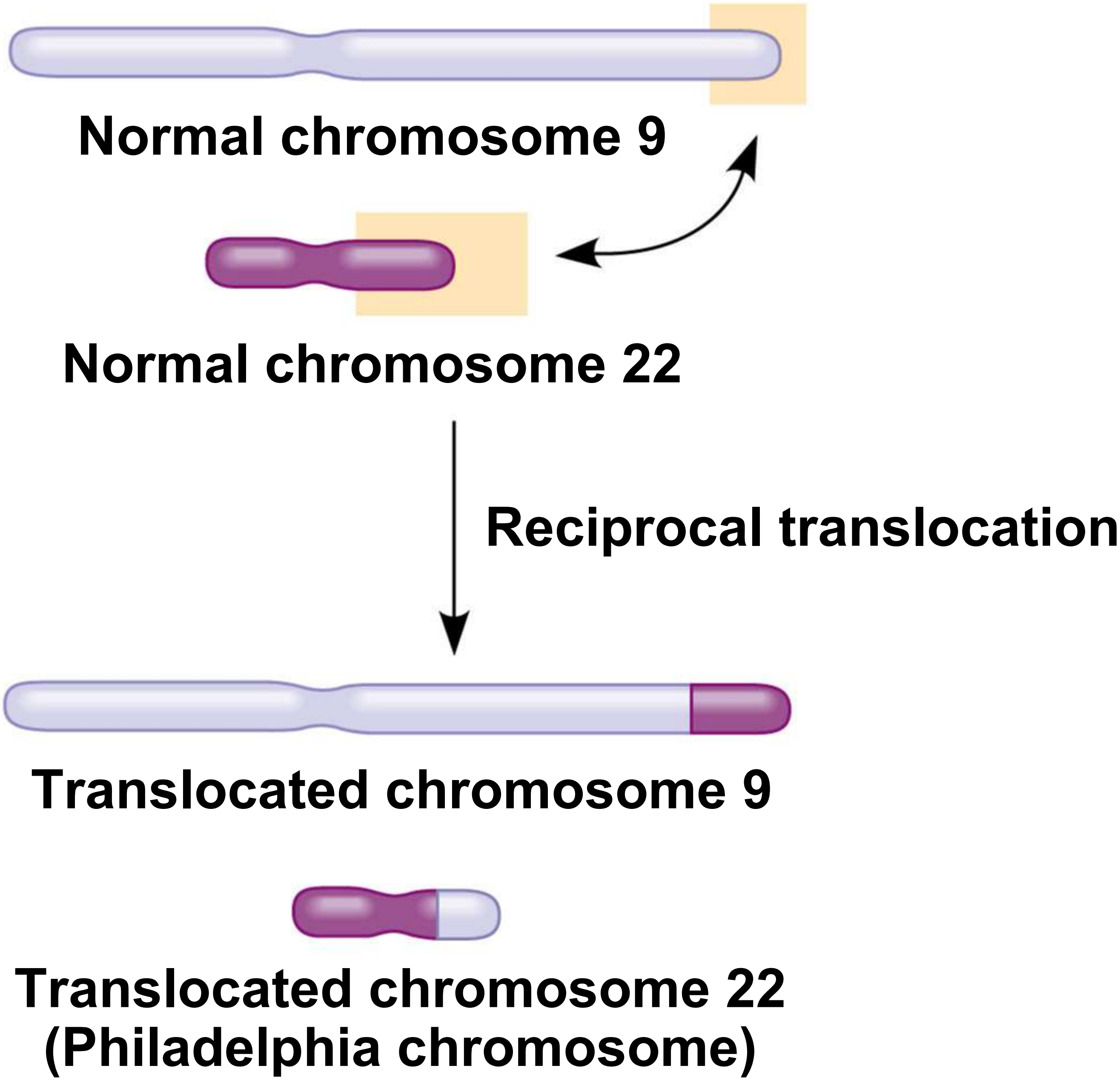
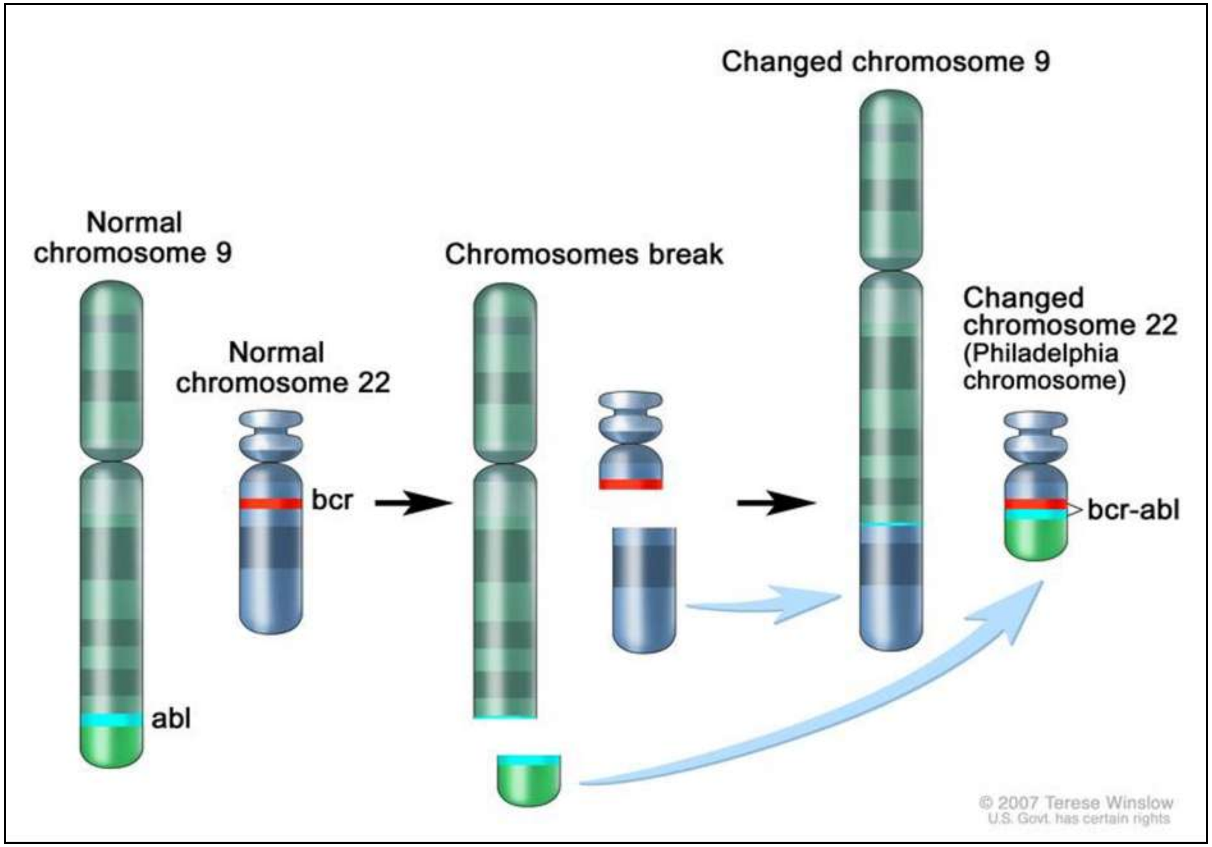


Figure 15.16

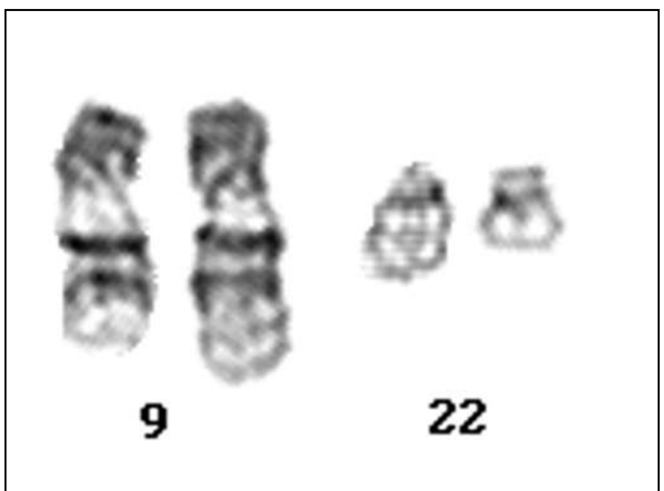

Normal chromosome 9
Normal chromosome 22
Reciprocal translocation
Translocated chromosome 9
Translocated chromosome 22
(Philadelphia chromosome)



result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein

The ABL tyrosine kinase activity of *BCR-Abl* is elevated relative to wild-type ABL

Abl gene expresses a membrane-associated protein, a tyrosine kinase, the BCR-Abl transcript is also translated into a tyrosine kinase. The activity of tyrosine kinases is typically controlled by other molecules, but the mutant tyrosine kinase encoded by the BCR-Abl transcript results in a protein that is "always on" or continuously activated, which results in unregulated cell division (i.e. cancer)



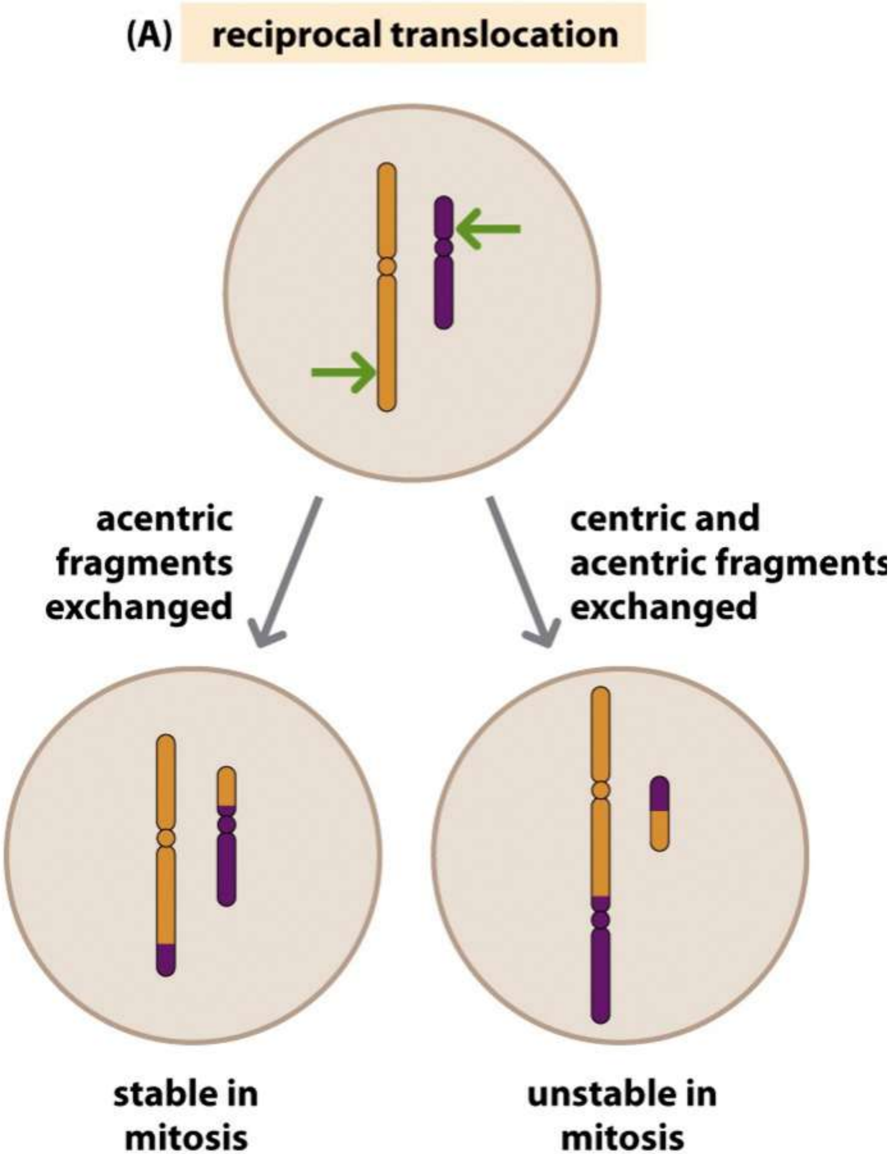
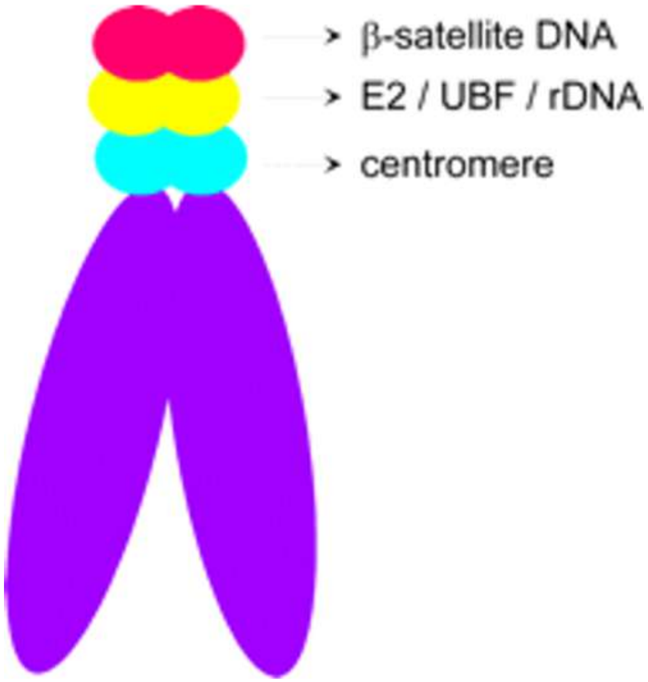


Figure 2.23 Human Molecular Genetics, 4ed. (© Garland Science)

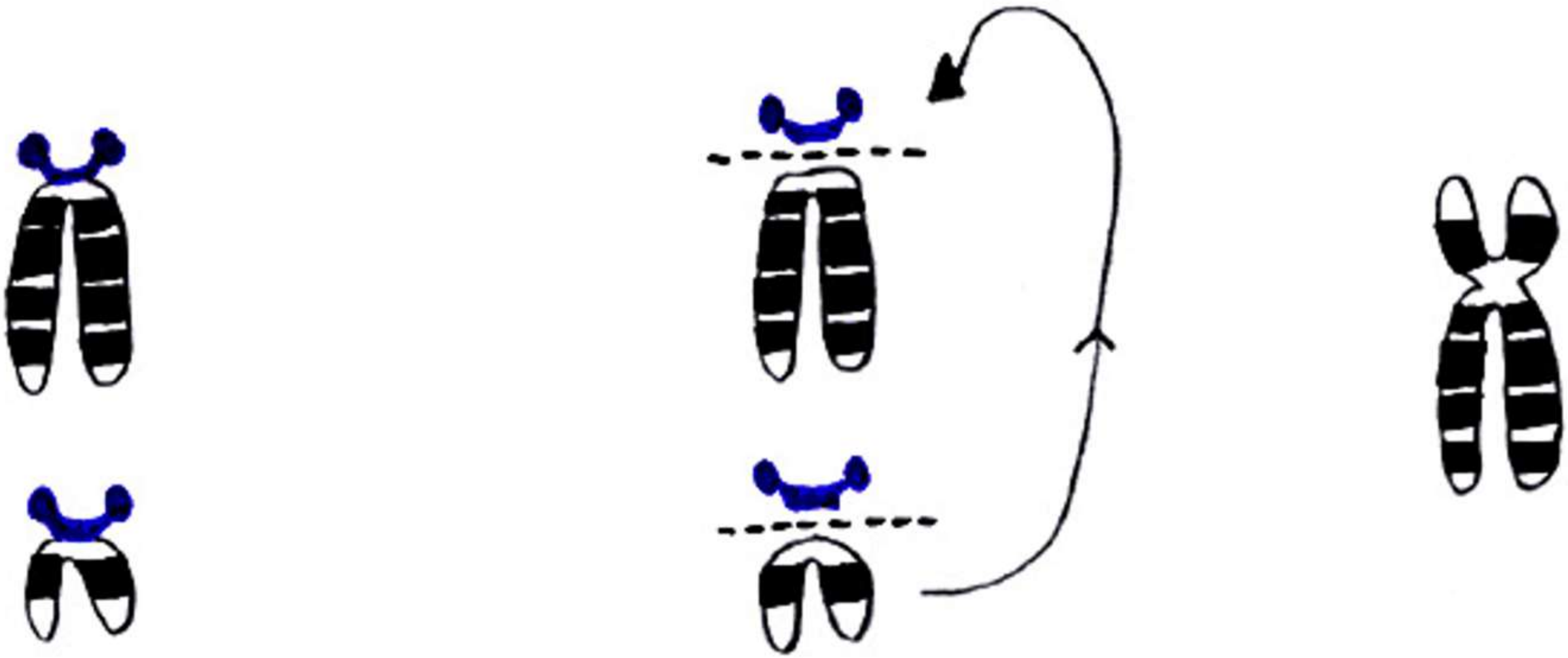
(A) Reciprocal translocation. The derivative chromosomes are stable in mitosis when one acentric fragment is exchanged for another; when a centric fragment is exchanged for an acentric fragment, unstable acentric and dicentric chromosomes are produced.

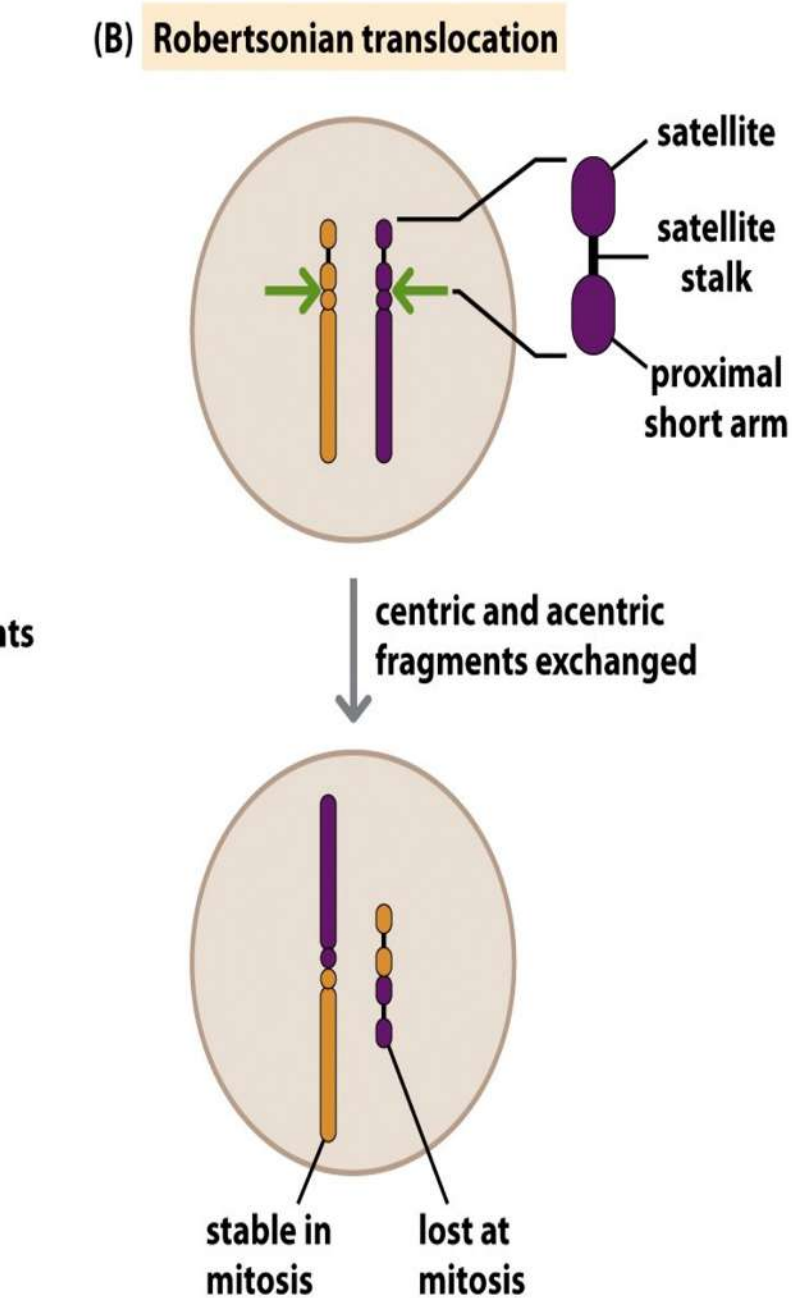
If an acentric fragment from one chromosome is exchanged for an acentric fragment from another, the products are stable in mitosis, however exchange of an acentric fragment for a centric fragment results in acentric and dicentric chromosomes that are unstable in mitosis.

- **A robertsonian translocation** is a specialized type of translocation between two of the five types of **acrocentric** chromosome in human (13,14,15,21,and 22) the short arm is very small and very similar in DNA content ,each contains **1-2Mb** of tandemly repeated rRNA genes sandwiched between two blocks of heterochromatic DNA



Robertsonian translocation
(with chromosome #14 and chromosome #21)





(B) Robertsonian translocation. This is a highly specialized reciprocal translocation in which exchange of centric and acentric fragments produces a **dicentric chromosome** that is nevertheless stable in mitosis, plus an acentric chromosome that is lost in mitosis without any effect on the phenotype. It occurs exclusively after breaks in the short arms of the human acrocentric chromosomes 13, 14, 15, 21, and 22.

The short arm of the acrocentric chromosomes consists of three regions: a proximal heterochromatic region (composed of highly repetitive noncoding DNA), a distal heterochromatic region (called a chromosome satellite), and a thin connecting region of euchromatin (the satellite stalk) composed of tandem rRNA genes. Breaks that occur close to the centromere can result in a dicentric chromosome in which the **two centromeres** are so **close** that they can function as a **single centromere**. The loss of the small acentric fragment has no phenotypic consequences because the only genes lost are rRNA genes that are also present in large copy number on the other acrocentric chromosomes

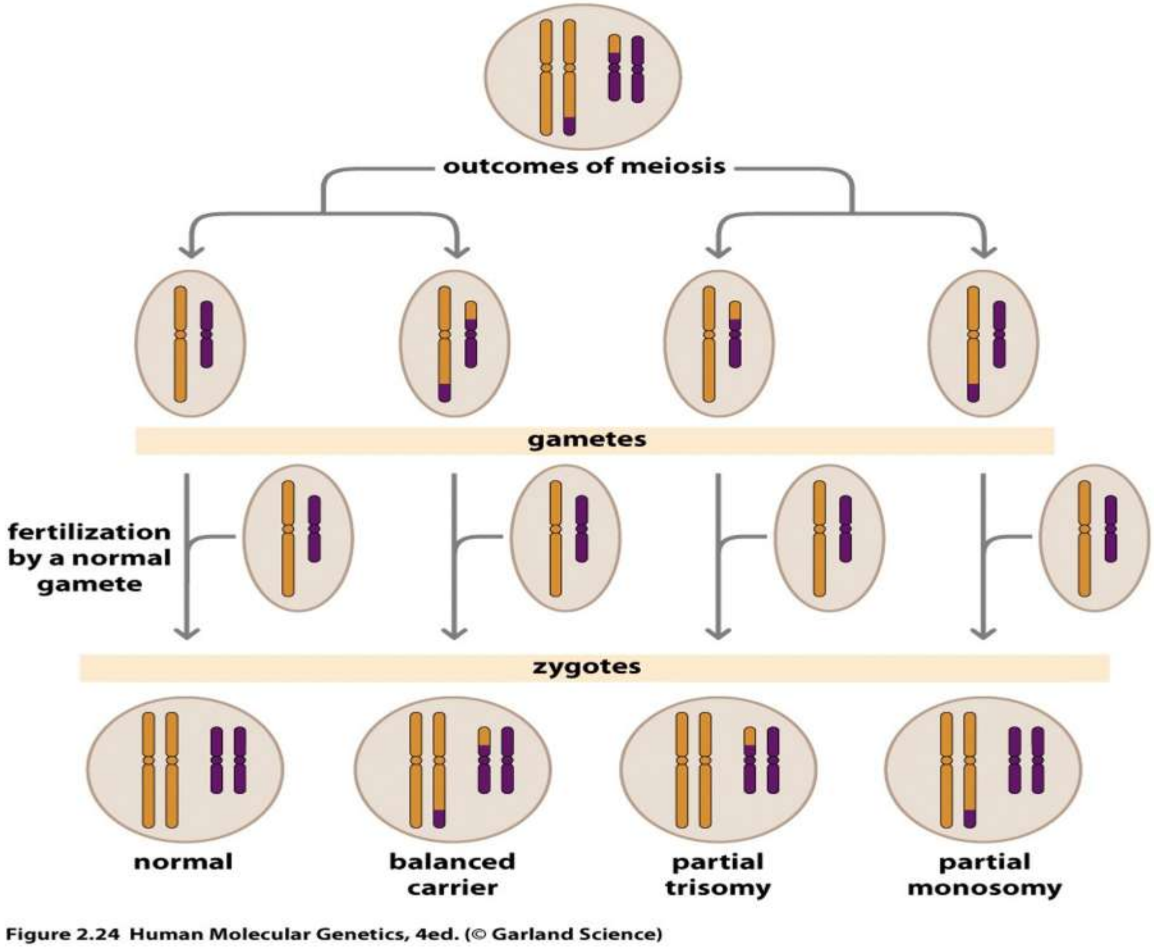


Figure 2.24 Possible outcomes of meiosis in a carrier of a balanced reciprocal translocation. Other modes of segregation are also possible, for example 3:1 segregation.

The relative frequency of each possible gamete is not readily predicted.

The risk of a carrier having a child with each of the possible outcomes depends on its frequency in the gametes and also on the likelihood of a conceptus with that abnormality developing to term.

- A carrier of a balanced Robertsonian translocation can produce gametes that after fertilization give rise to an entirely normal child ,a phenotypically normal balanced carrier , or a conceptus with full trisomy or full monosomy for one of the chromosomes involved

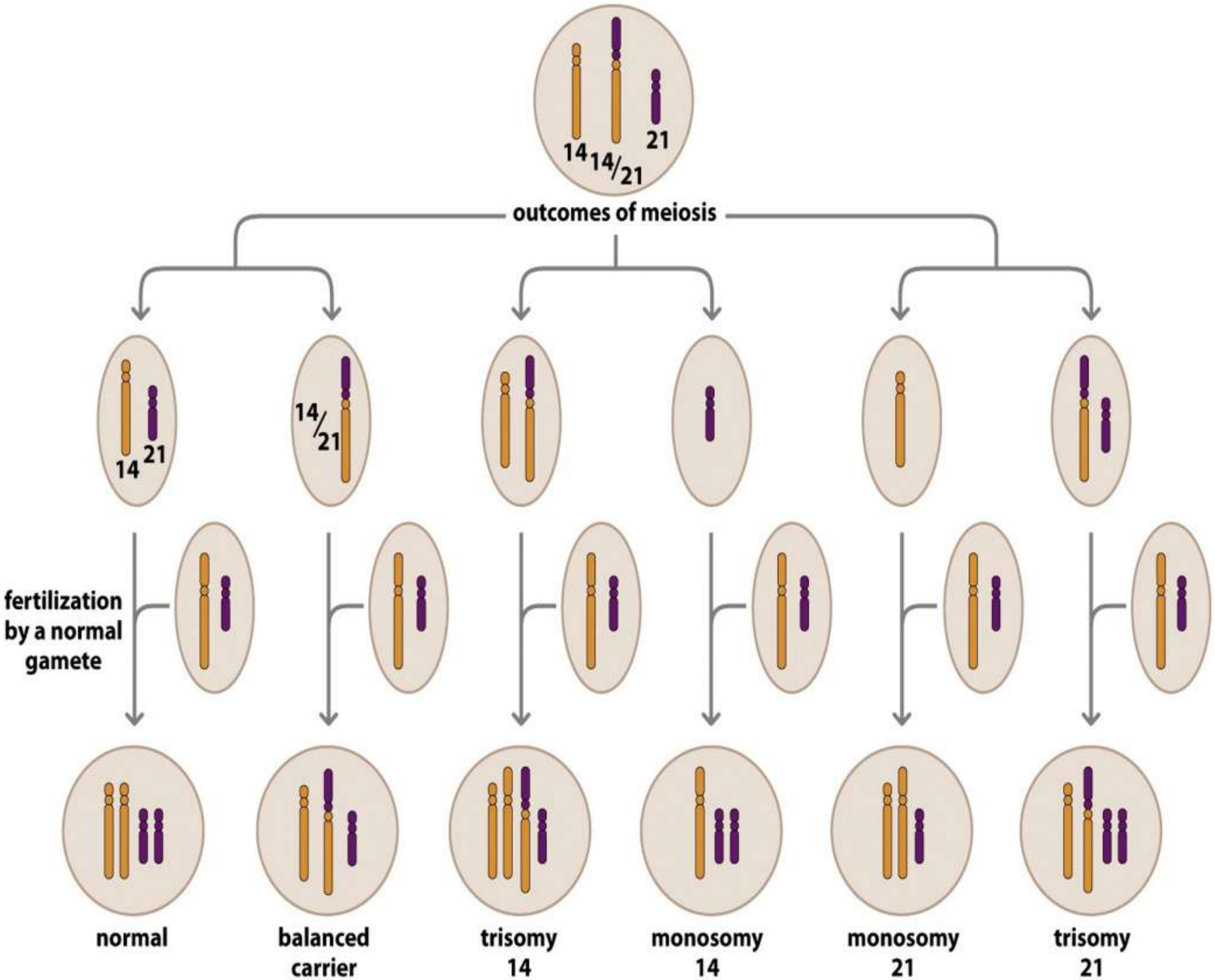


Figure 2.25 Human Molecular Genetics, 4ed. (© Garland Science)

Figure 2.25 Possible outcomes of meiosis in a carrier of a Robertsonian translocation.
Carriers are asymptomatic but often produce unbalanced gametes that can result in a monosomic or trisomic zygote. The two monosomic zygotes and the trisomy 14 zygote in this example would not be expected to develop to term.