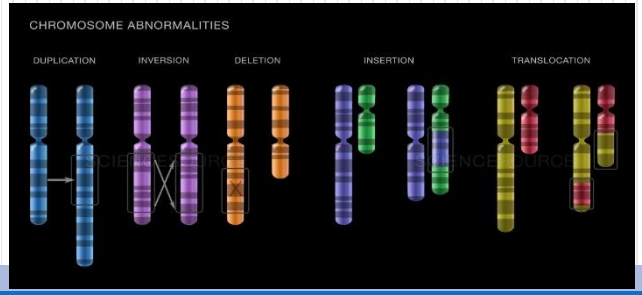


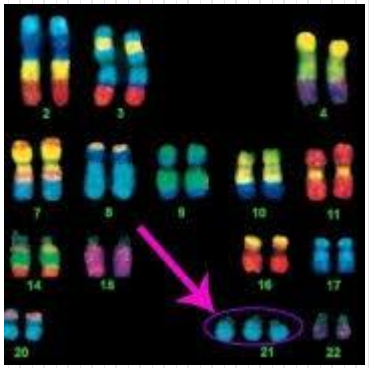
Chromosomes
Chromosomal abnormalities

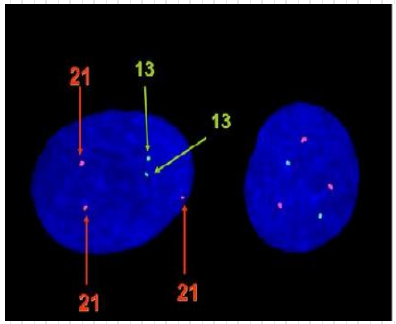
Lecture 8

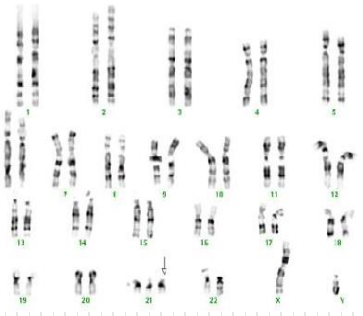
SLE254 Genetics and Genomics

Concepts of Genetics (12th ed)

Chapter 6: pages 151-174

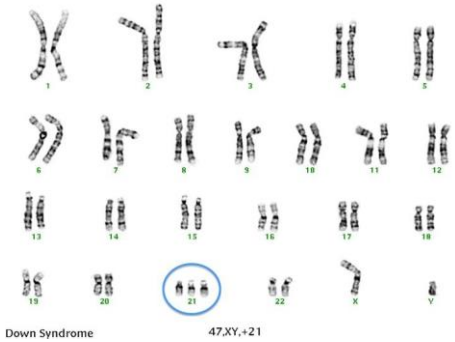




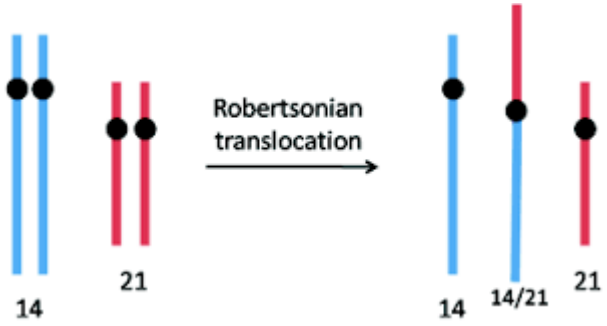


Chromosomal abnormalities- errors in cell division

- Two major types of chromosomal changes
  - A change in chromosomal number

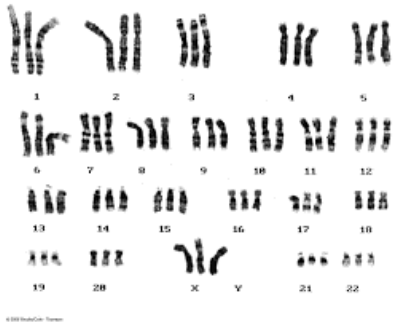


  - A change in chromosomal arrangement

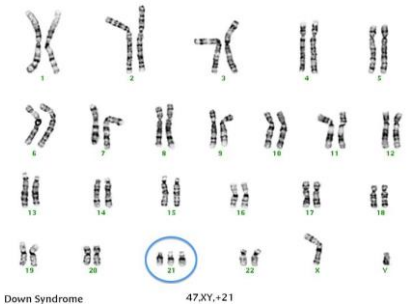


Changes in chromosome number

- Polyploidy
  - A chromosomal number that is a multiple of the normal haploid chromosomal set



- Aneuploidy
  - A chromosomal number that is not an exact multiple of the haploid set

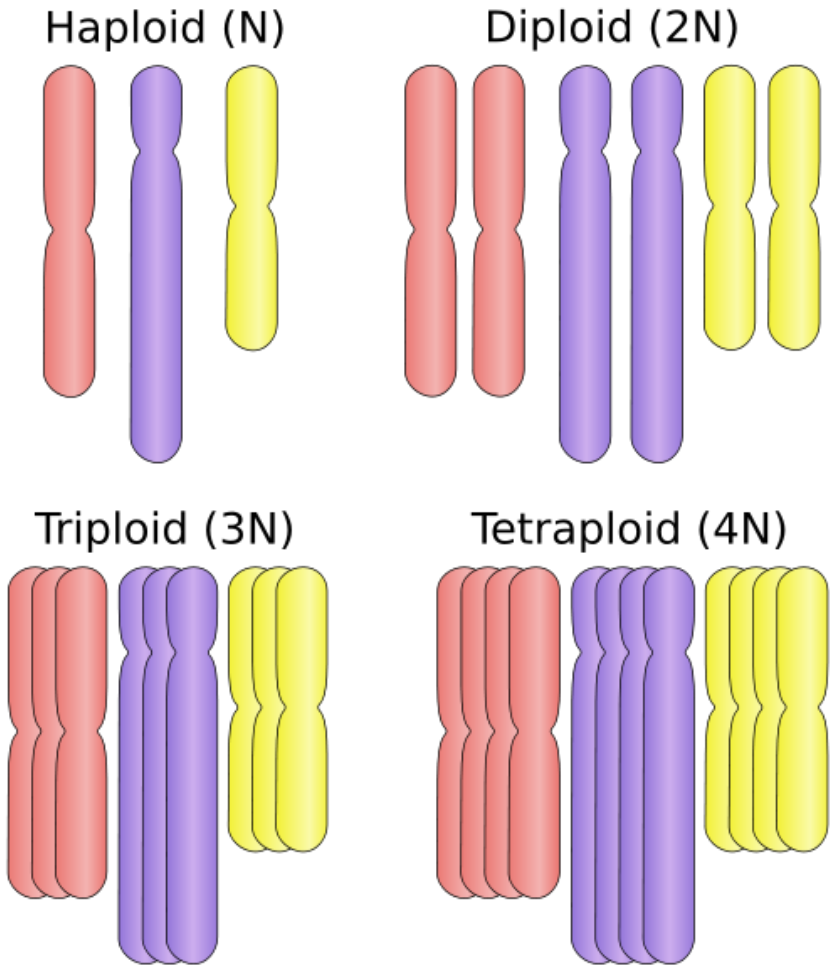


Effects of polyploidy and aneuploidy

- Polyploidy and aneuploidy are major causes of reproductive failure in humans
  - **Polyploidy** is seen only rarely in live births
  - The rate of **aneuploidy** in humans is much higher than in other primates and mammals; reasons for the difference are unknown

Polyploidy

- **Changes the number of FULL chromosome sets**
- Triploidy
  - A chromosomal number that is **three times** the haploid number, having three copies of all autosomes and three sex chromosomes
- Tetraploidy
  - A chromosomal number that is **four times** the haploid number, having four copies of all autosomes and four sex chromosomes



Origin of Polyploidy

- **Origin of polyploidy**
  - Addition of one or more sets of chromosomes identical to haploid complement of **same species (autopolyploidy)**
  - Combination of chromosome sets from **different species** as consequence of hybridization (**allopolyploidy**)
- **Figure 6-6**

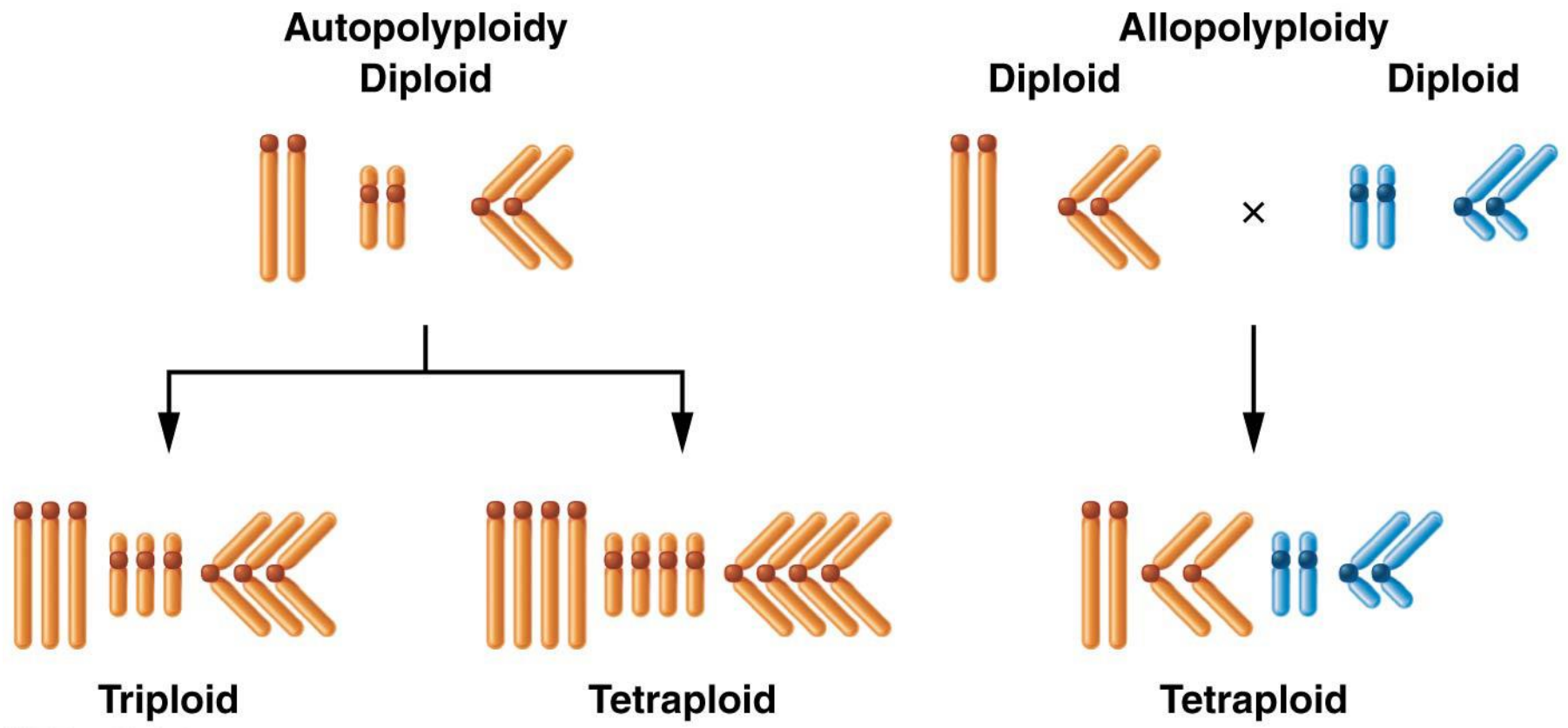
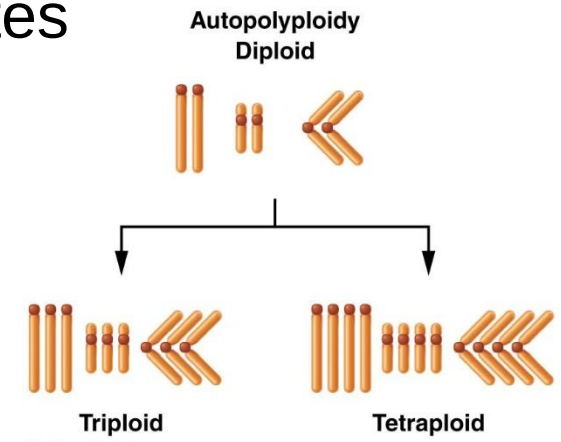

Autopolyploidy
Diploid
Triploid
Tetraploid
Allopolyploidy
Diploid
Diploid
×
Tetraploid
Duplication of entire set of chromosomes single species
Combination of entire set of chromosomes between 2 species

Figure 6-6

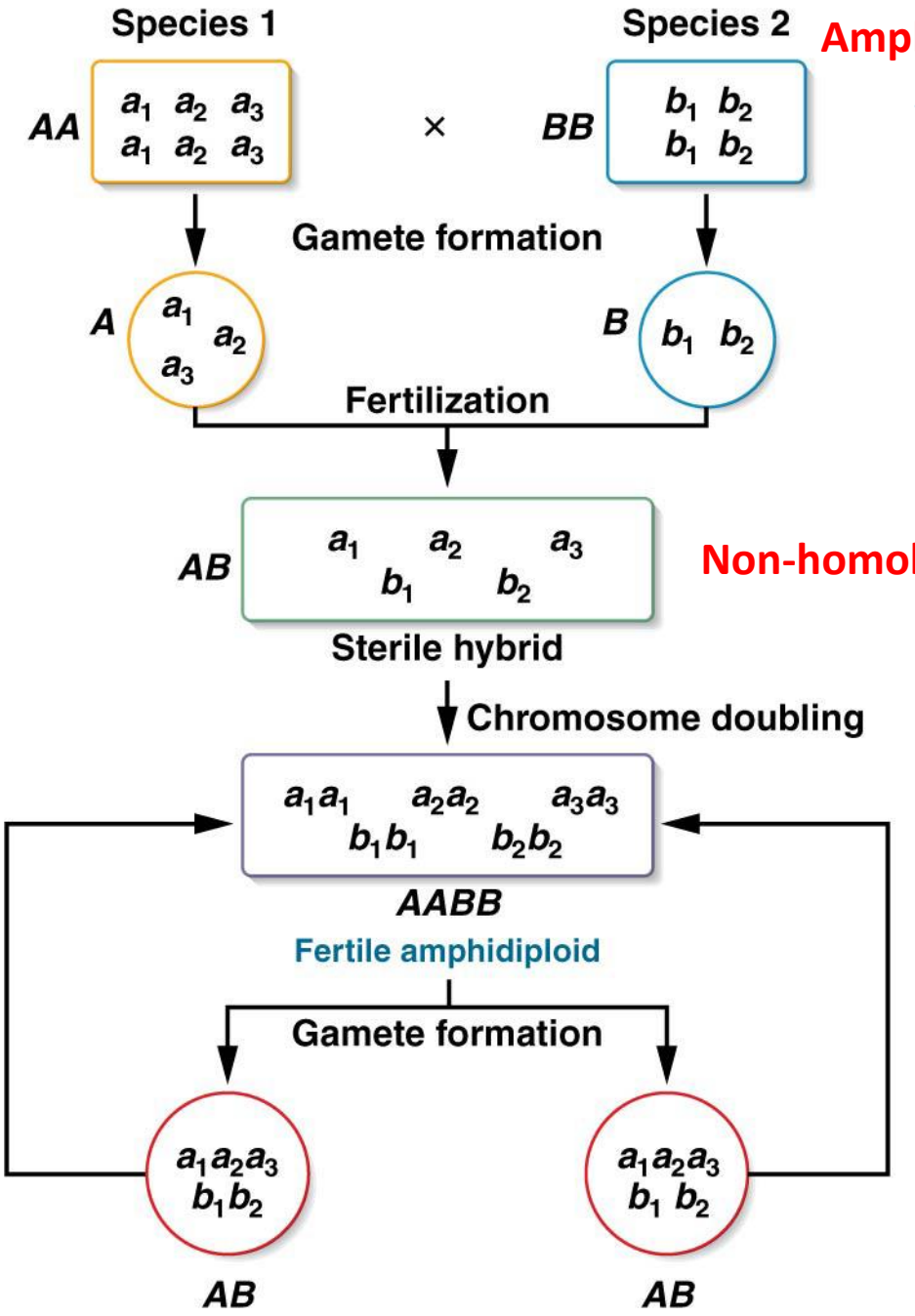
Autopolyploidy

- **Autopolyploidy**
  - Each identical set of chromosomes is identical to parent species
  - Arises in several ways
    - Diploid gamete is produced
    - Two sperm fertilize one ovum (rare)
  - More prevalent in natural population; produce balanced gametes



Allotetraploid and Amphidiploid

- **Allotetraploid**
  - Polyploid contains equivalent of four haploid genomes derived from **separate species**
- **Amphidiploid**
  - Allotetraploid where both original species are known (**Figure 6-8**)
  - Amphidiploid plants often found in nature
  - Amphidiploid form of *Gossypium* (cotton plant) (**Figure 6-9**)



Amphidiploid

Allotetraploid where both original species are known

Non-homologous- unbalanced, sterile

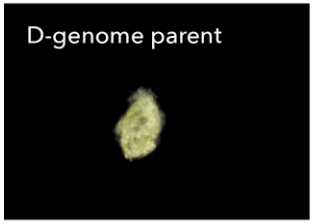
Natural or induced doubling*

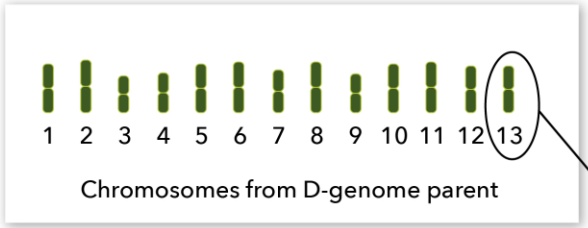
Homologous pairing- tetraploid

Figure 6-8

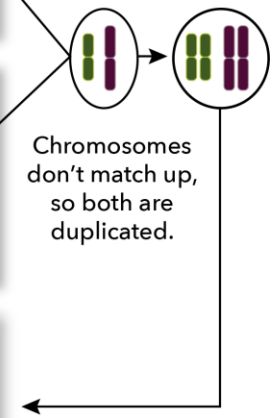
Advantages of evolving tetraploidy: Better suited to different environments, stress tolerance, salt resistant seeds, big cotton balls!

Americas

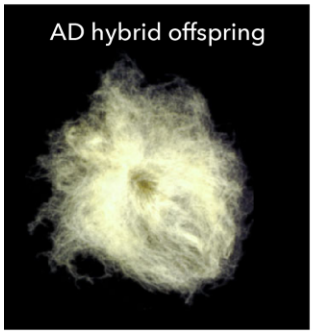


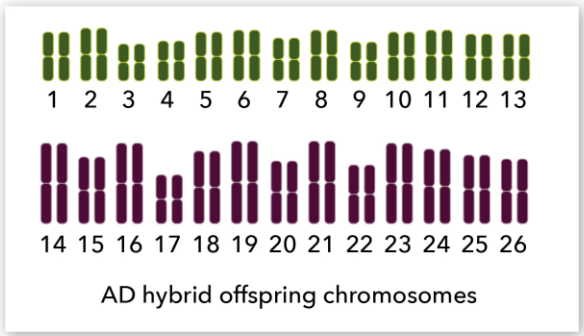


Africa- ancestor



Hybrid gave rise to at least 6 species Including modern cultivars





Caribbean
Hawaii
Galapagos Islands

1-2 Mya 1 hybridization event

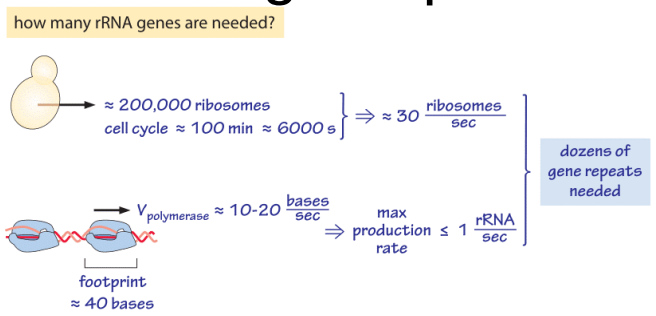
http://learn.genetics.utah.edu/content/cotton/evolution/

Endopolyploidy

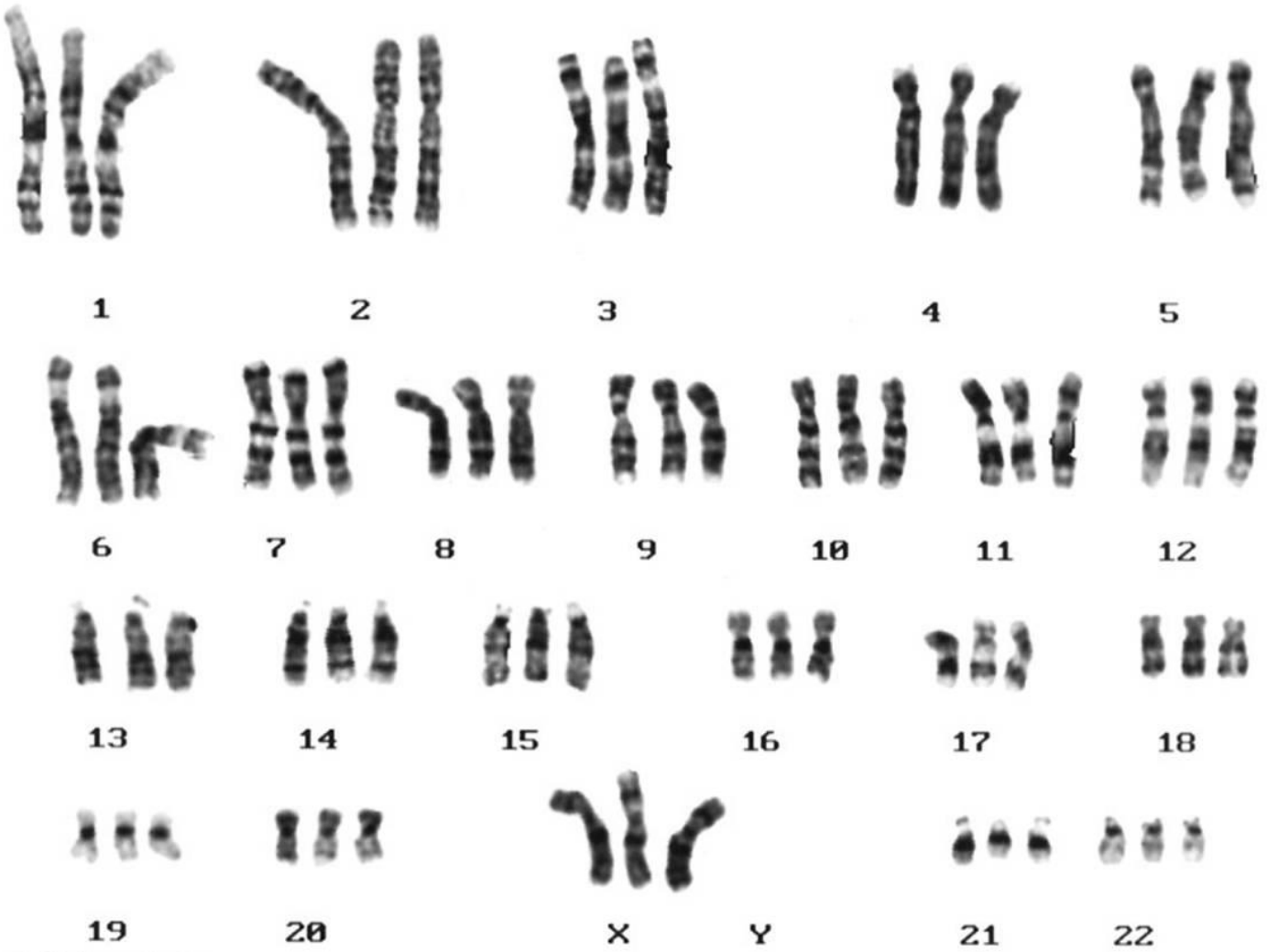
- **Endopolyploidy**
  - Condition where only **certain cells** in diploid organism are polyploid

  - Liver cells often contain 4n, 8n, or 16n
  - Set of chromosomes replicates repeatedly ***without nuclear division*** (**S phase**)

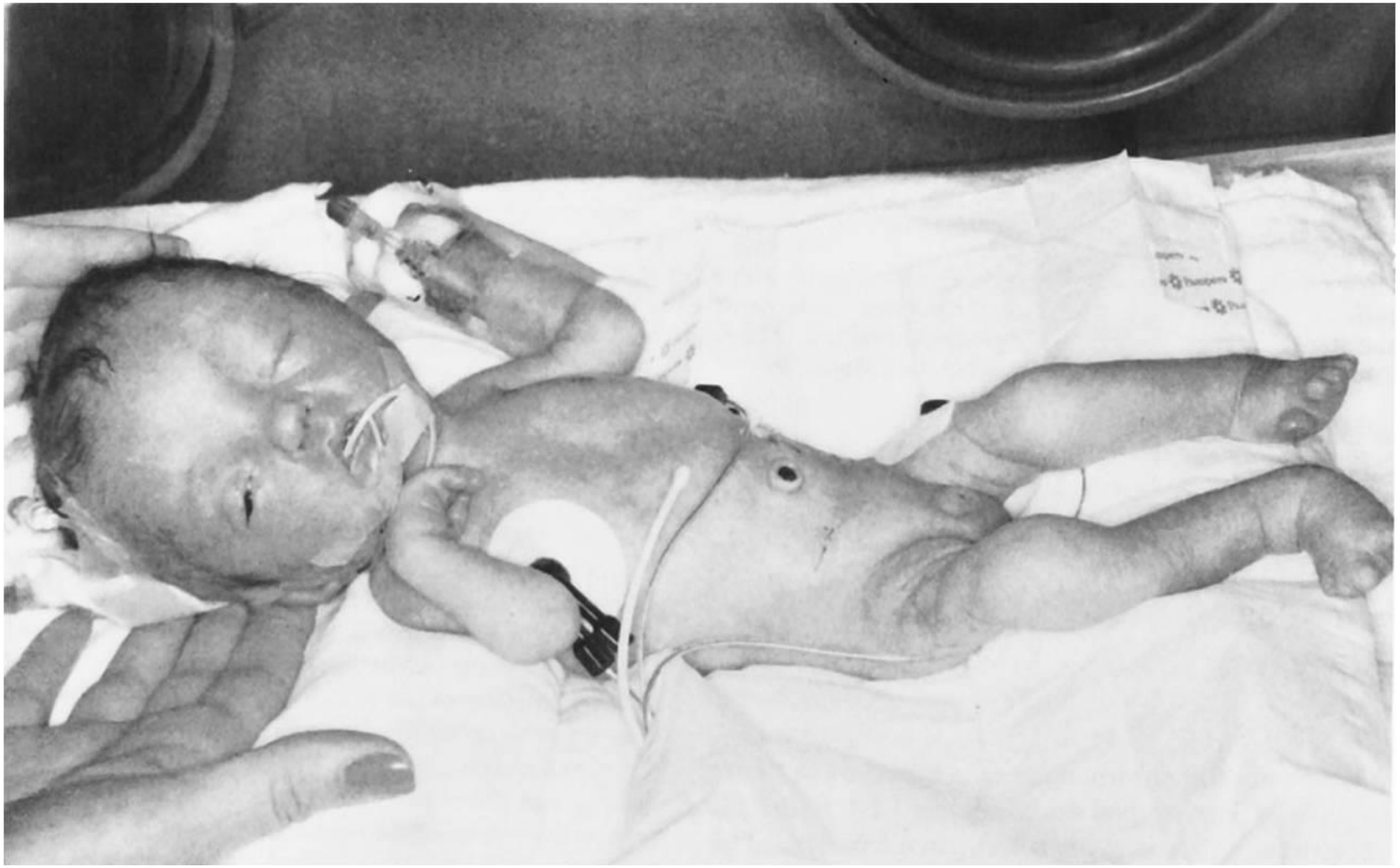
  - WHY? Unclear but could be due to requirements of high levels of gene products



Polyploidy – a triploid karyotype



Polyploidy – a triploid infant



Aneuploidy

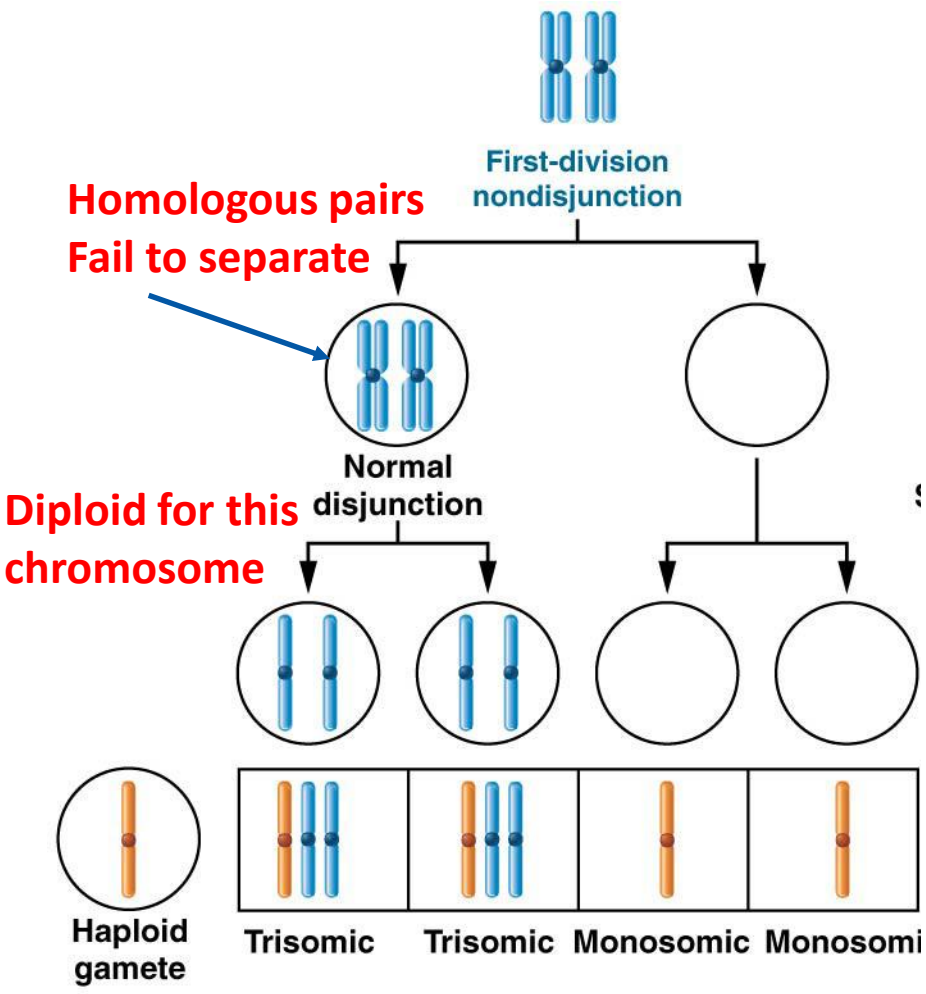
- Changes the number of **individual chromosomes**
- Monosomy
  - A condition in which **one member of a chromosomal pair is missing**; one less than the diploid number (2n – 1)
- Trisomy
  - A condition in which **one chromosome is present in three copies**, and all others are diploid; one more than the diploid number (2n + 1)

Causes of aneuploidy

- **Nondisjunction**
  - The failure of homologous chromosomes to separate properly during meiosis
  - Gives rise to chromosomal variation
  - Paired homologs fail to disjoin during segregation
  - Nondisjunction during meiosis I or II
- **Figure 8-1**
- **Varied mechanisms**

topoisomerase II, condensin, or separase

Non-disjunction at Meiosis



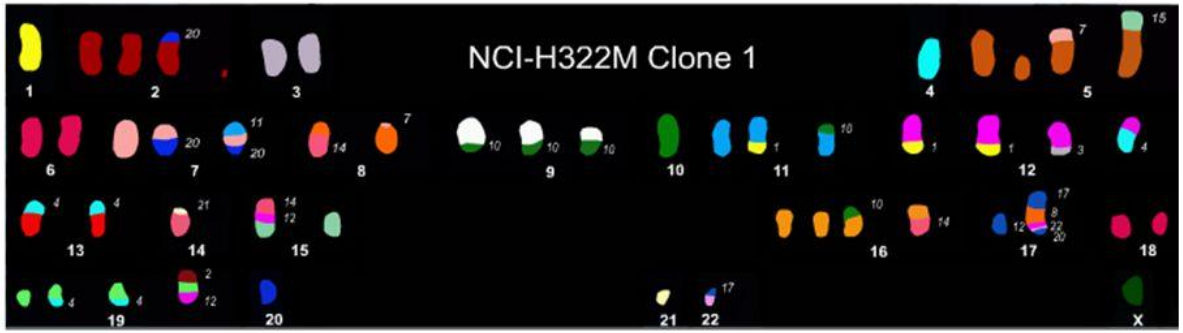
Fertilization with a haploid gamete- resulting zygotes

Figure 6.1

Consequences of aneuploidy

- Aneuploidy also is associated with most cancers

Tumour karyotype



Spectral karyotyping showing *chromosomal aberrations* in cancer cell lines

Consequences of aneuploidy

- Aneuploidy is the leading cause of reproductive failure in humans
  - Results in spontaneous abortions and birth defects
- Aneuploidy also is associated with most cancers

Table 6.5 Chromosomal Abnormalities in Newborns

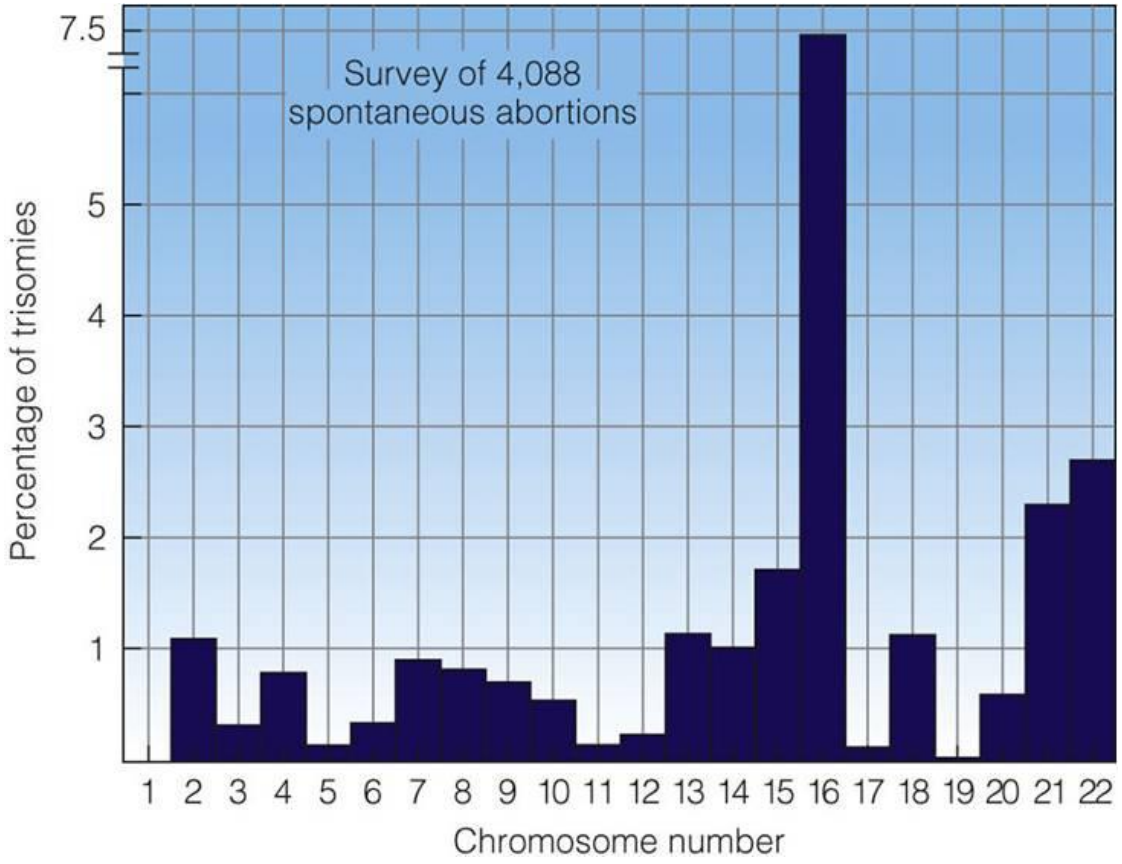
Abnormality	Approximate Frequency
45,X	1/7,500
XXX	1/1,200
XXY	1/1,000
XYY	1/1,100
Trisomy 13	1/15,000
Trisomy 18	1/11,000
Trisomy 21	1/800
Structural abnormalities	1/400

Effects of monosomy and trisomy

- Autosomal monosomy is a lethal condition
  - Eliminated early in development (spontaneous abortion)

- Autosomal trisomy is relatively common
  - Most result in spontaneous abortion
  - Four types can result in live births (8, 13, 18, 21)

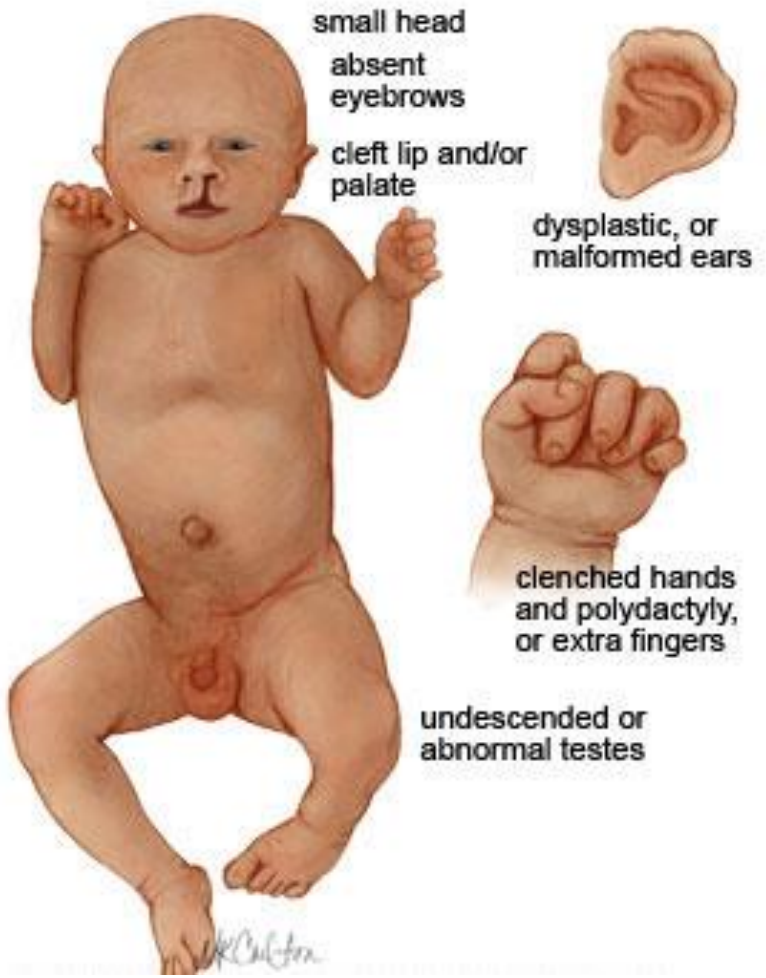
Aneuploidy - trisomies



- Most autosomal trisomies are lethal.
- Up to 50% of chromosomal abnormalities in miscarriages
- Trisomies for chromosomes 1,3, 12 and 19 are rare
- Trisomy 16 – about 30% of all cases.
  - Not clear why
- Only trisomy 8, 13, 18 and 21 allow live births
  - Only trisomy 21 survive until adulthood

Trisomy 13: Patau syndrome (47,+13)

- A lethal condition
- 1/15,000 live births
- 97% fetal loss, those born die usually within months, some have lived 10 years
- Over 20 symptoms, including facial malformations, eye defects, extra digits, malformation of brain and nervous system, congenital heart defects

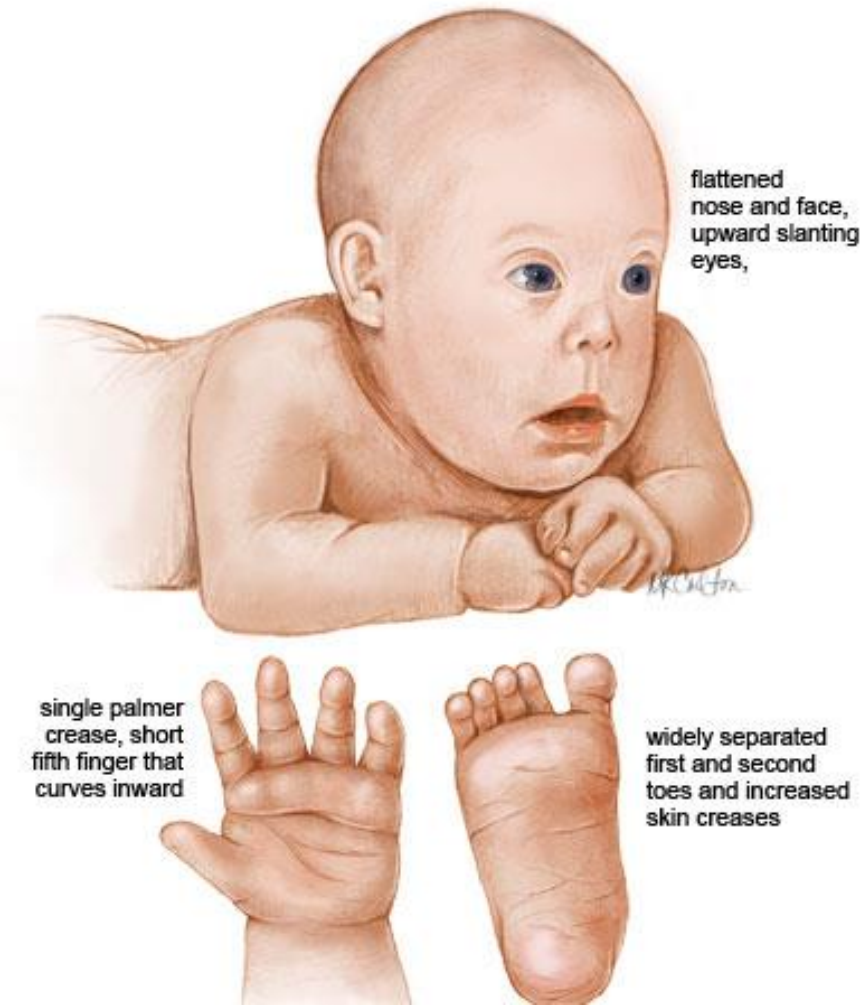


Trisomy 18: Edwards syndrome (47,+18)

- A lethal condition
- 1/11,000 live births
- 80% female
- survival 2-4 months
- Small size, slow growth, mental retardation, clenched fists with malformed feet, heart abnormalities

Trisomy 21: Down syndrome (47,+21)

- 0.5% of all conceptions, and 1/800 live births
- Aneuploidy involving the presence of an extra copy of chromosome 21, resulting in Down syndrome
- First chromosomal abnormality discovered in humans
- The only autosomal trisomy that allows survival into adulthood



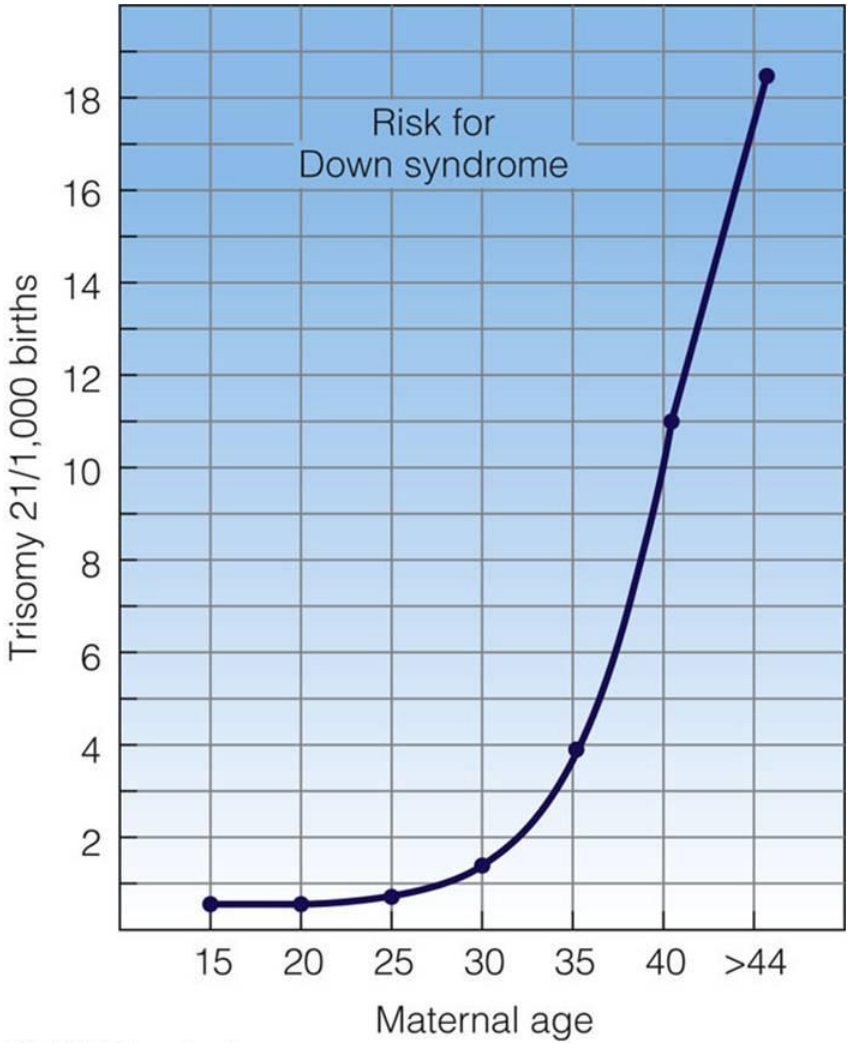
Down syndrome Symptoms

Mental impairment	99%
Stunted growth	90%
Increased skin back neck	80%
Low muscle tone	80%
Facial dysmorphia	80%
Slanted eyes	60%

The average IQ of a young adult with Down syndrome is 50, equivalent to the mental age of an 8- or 9-year-old child.

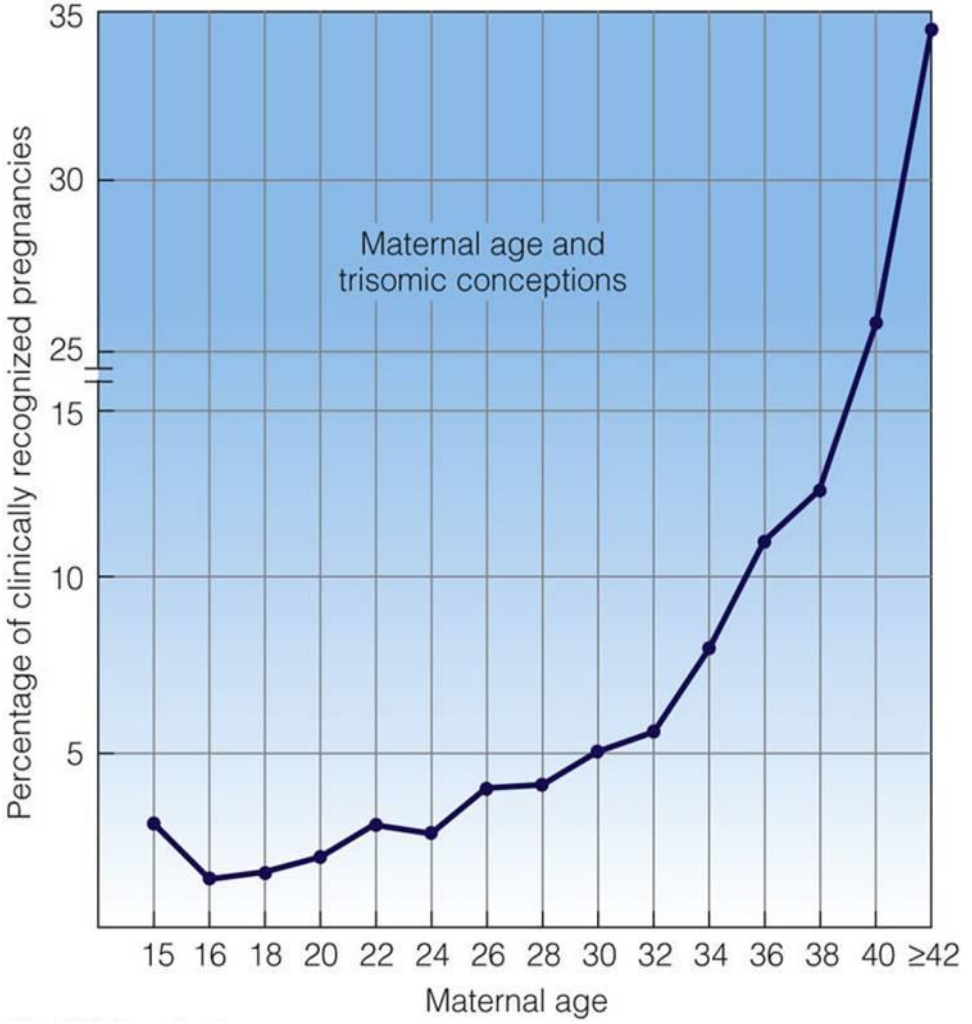
Maternal age and trisomies

- Maternal age is the leading risk factor for trisomy
- For trisomy 21, 94% of nondisjunctions occur in the mother, 6% in the father
- The majority of nondisjunction events occur in meiosis I in oocytes



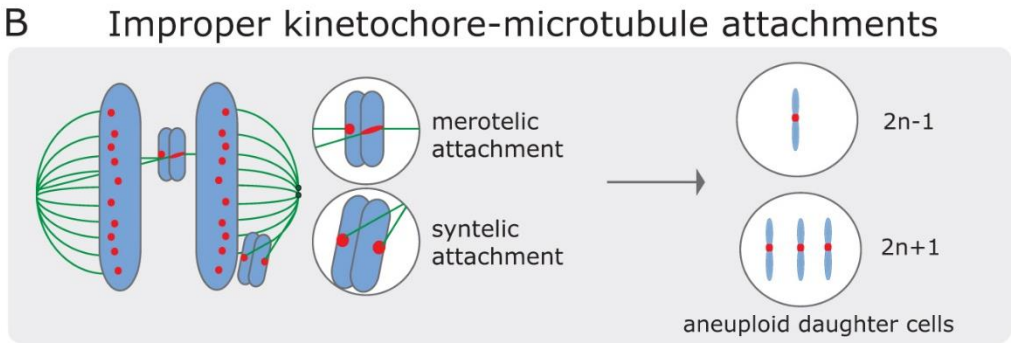
Maternal age and trisomies

- By age 42 about 1/3 identified pregnancies are trisomic
- Meiosis I is not completed until ovulation, so eggs produced at age 40 have been in meiosis I for more than 40 years.
- Intracellular events or environmental agents may have damaged the cell, so aneuploidy can result when meiosis resumes at ovulation



Why is maternal age a risk factor?

- Meiosis is not completed until ovulation
  - Intracellular events may increase risk of nondisjunction, resulting in aneuploidy
- Maternal selection
  - Embryo-uterine interactions that normally abort abnormal embryos become less effective
- Loss of cohesion may contribute to incorrect microtubule-kinetochore attachment



Aneuploidy of the sex chromosomes

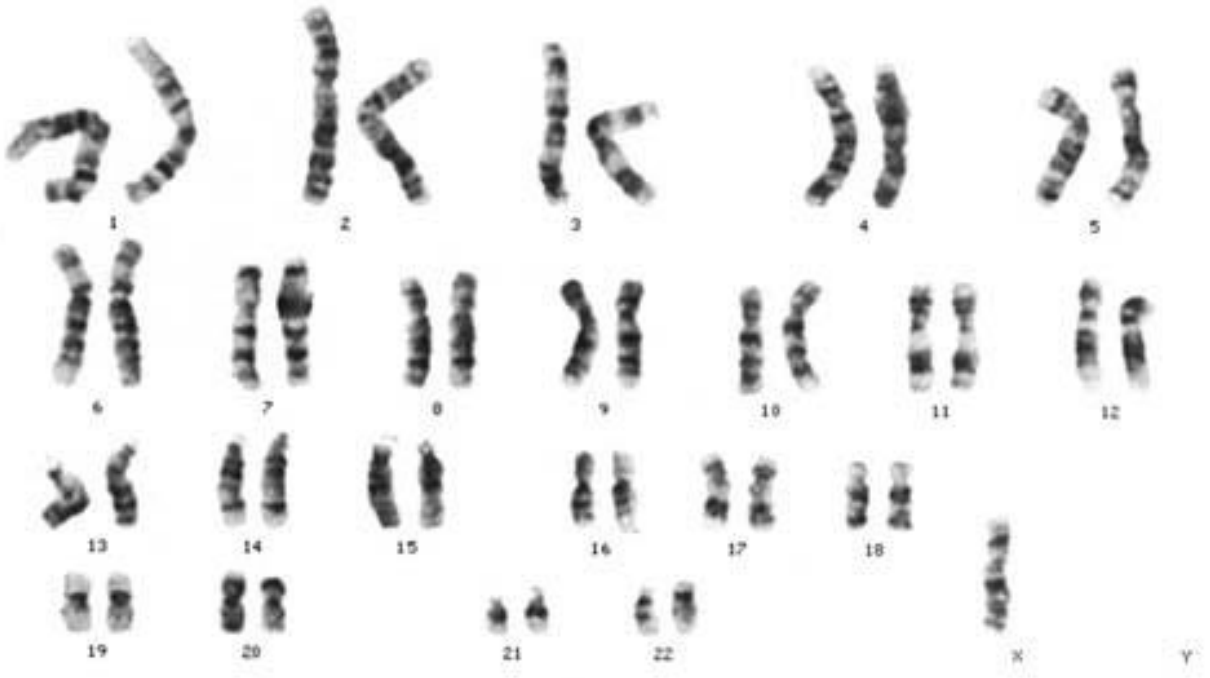
- Aneuploidy of sex chromosomes involves both X and Y chromosomes

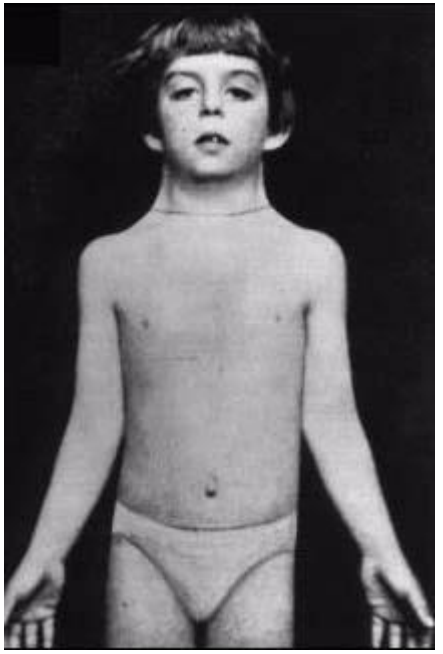
- A balance is needed for normal development
- At least one copy of the X chromosome is required for development
- Increasing numbers of X or Y chromosomes causes progressively greater disturbances in phenotype and behaviour

Turner syndrome (45, X)

- Monosomy of the X chromosome (45,X) that results in female sterility
  - One MZ twin with Turner syndrome demonstrates the striking effect of the absence of one X chromosome
  - Females with Turner syndrome are short and wide-chested, webbed neck, with rudimentary ovaries, heart defects, kidney problems

Turner syndrome (45, X)

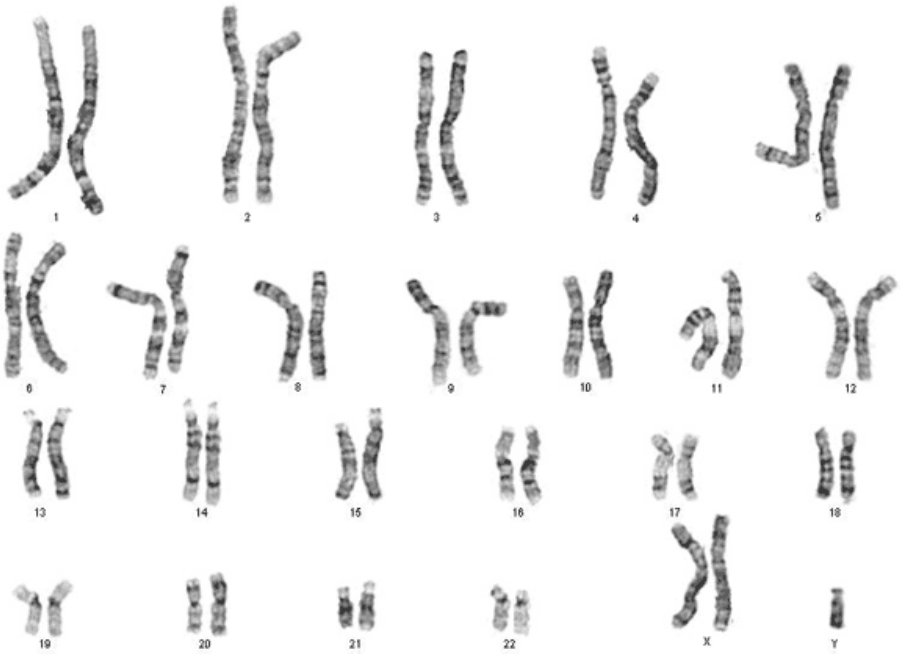


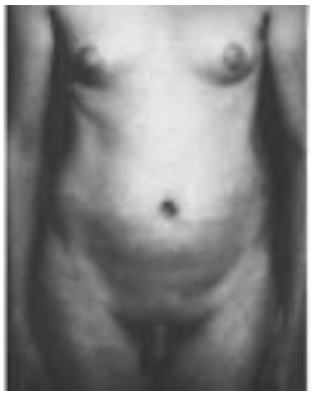


- Two chromosomes are needed for normal development of the ovary, growth and nervous system development in females

Klinefelter syndrome (47, XXY)

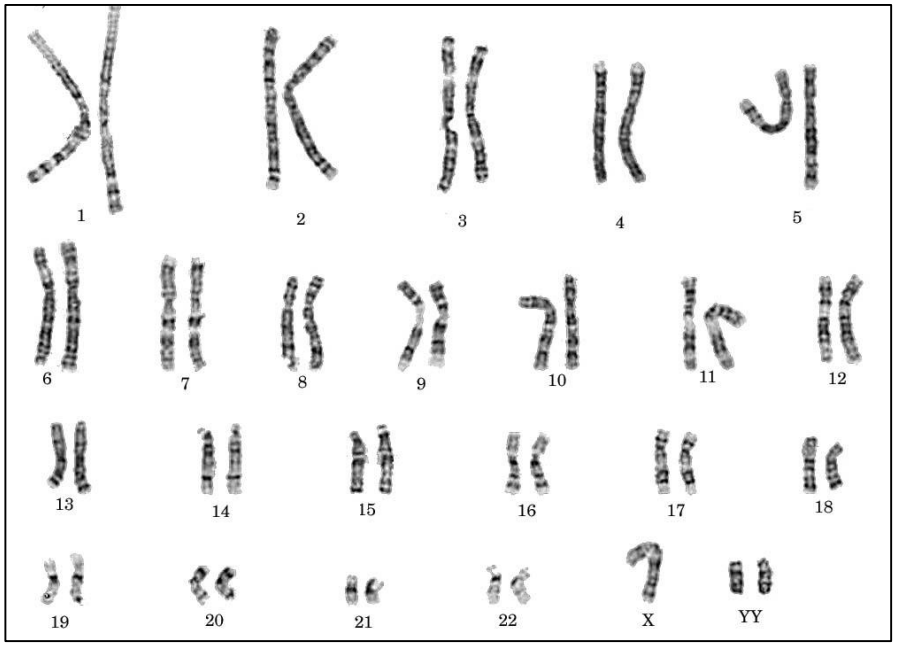
- Aneuploidy of the sex chromosomes involving an XXY chromosomal constitution
- 1/1000 live births
- Males with some female features that become apparent after puberty, sterile
- Some have learning difficulties
- Other more severe forms are XXXY and XXXXY





XYY Syndrome (47,XYY)

- XYY males are relatively normal
- They tend to be taller than average, and some have personality disorders and subnormal intelligence
- Early studies suggested they may be prone to violent behaviour, but this has not been substantiated
- Most XYY males lead normal lives, however, there is a much higher proportion of these males in prison (???)



Remember

Changes in the number of sex chromosomes have less impact than changes in the number of autosomes

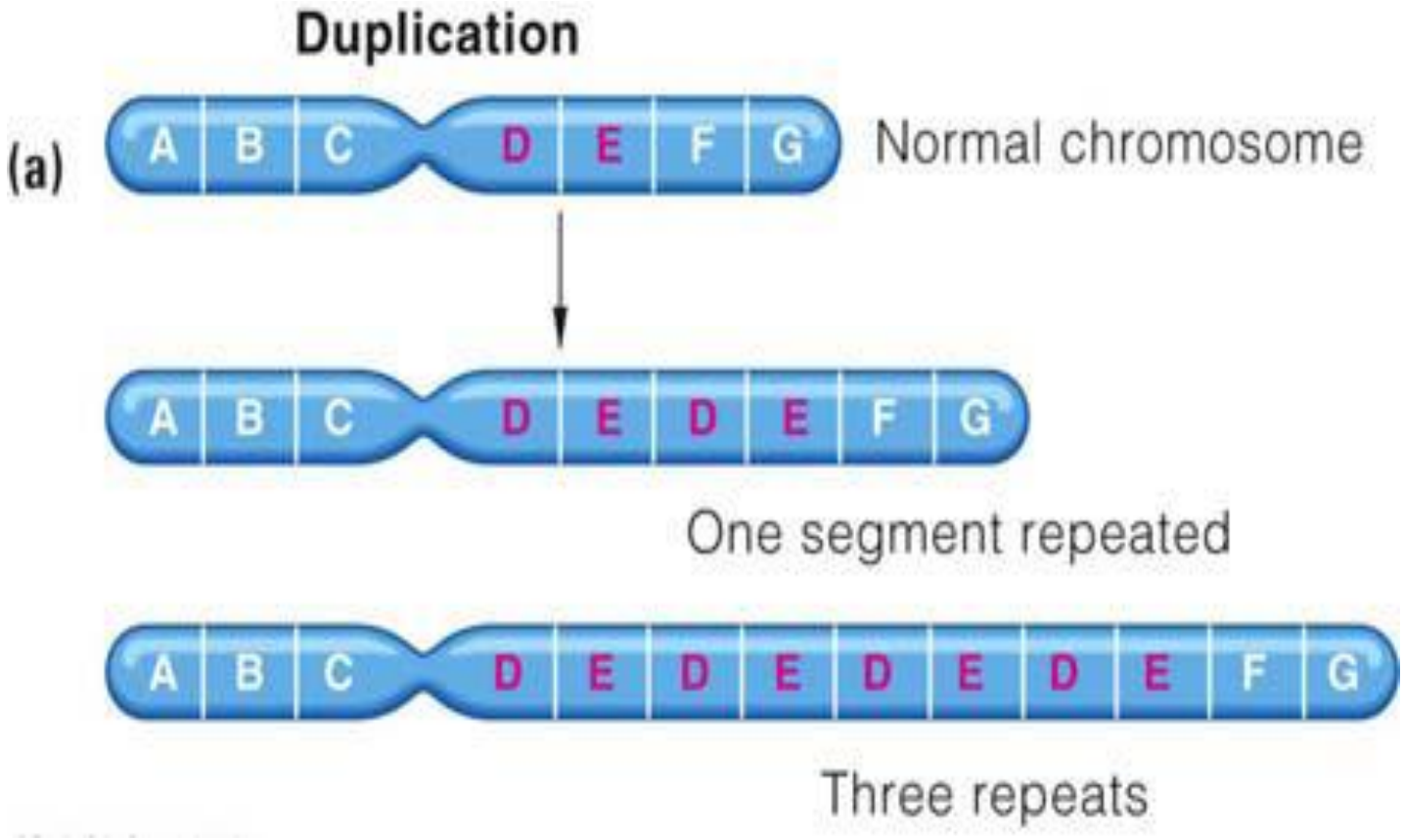
Thoughts on why?

Structural alterations within chromosomes

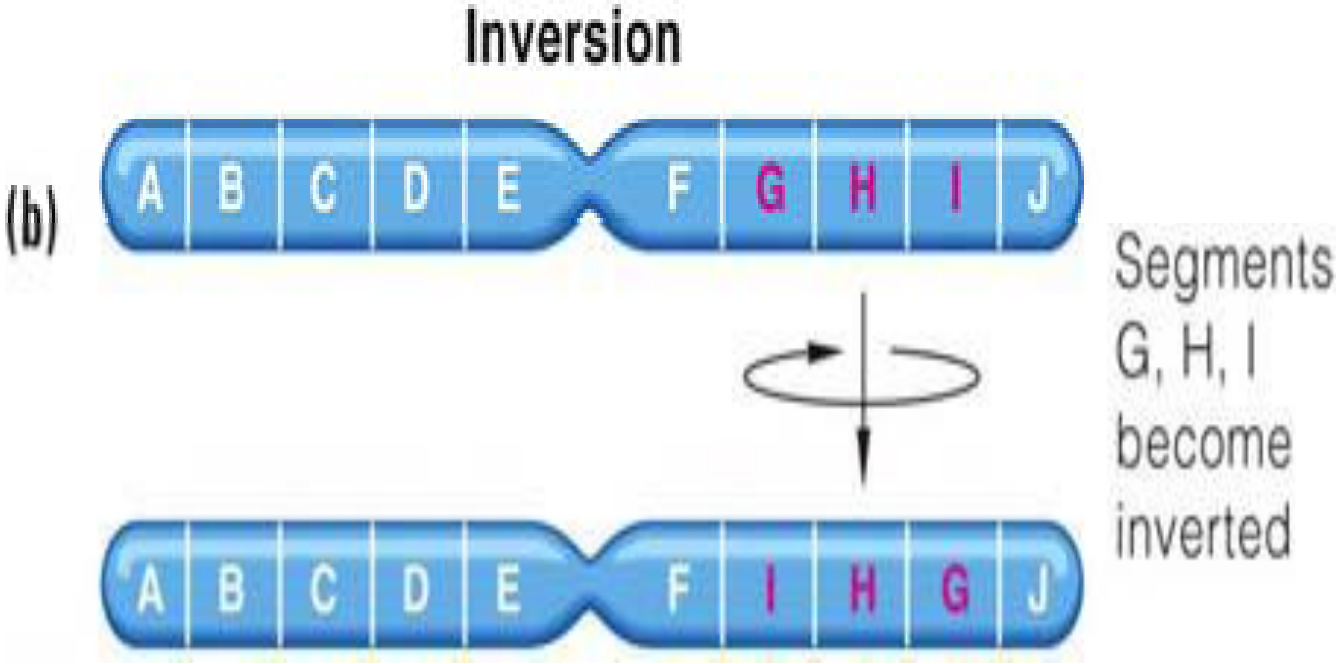
- Changes in the **arrangement of chromosomes**

- Duplication
- Deletions
- Translocations
- Inversions

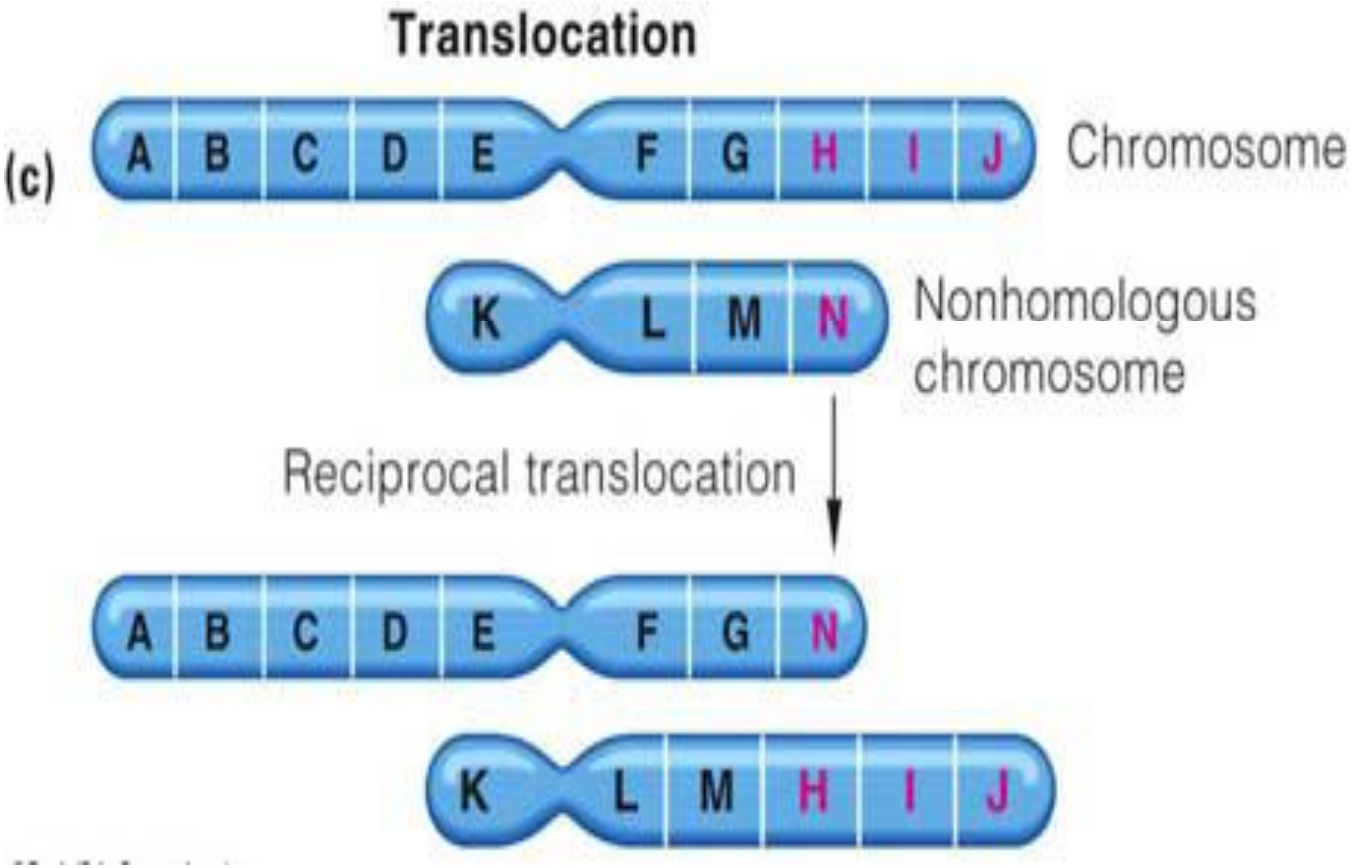
Structural alterations within chromosomes



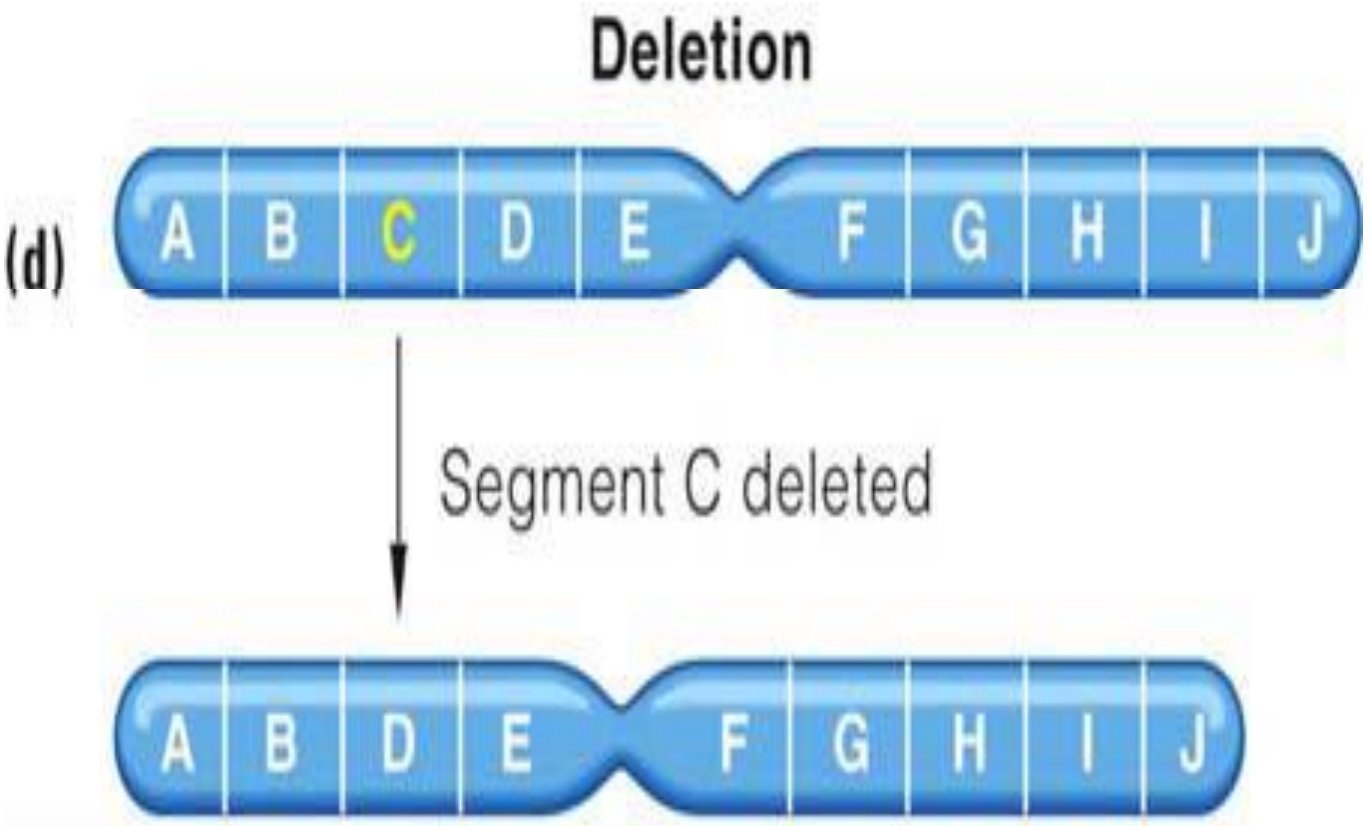
Structural alterations within chromosomes



Structural alterations within chromosomes



Structural alterations within chromosomes



Deletions

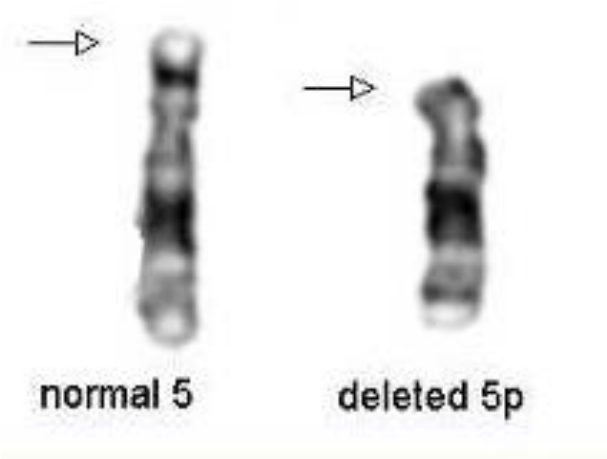
- Deletions involve loss of chromosomal material
- Deletions of chromosomal segments are associated with several genetic disorders
  - Cri du chat syndrome
  - Prader-Willi syndrome

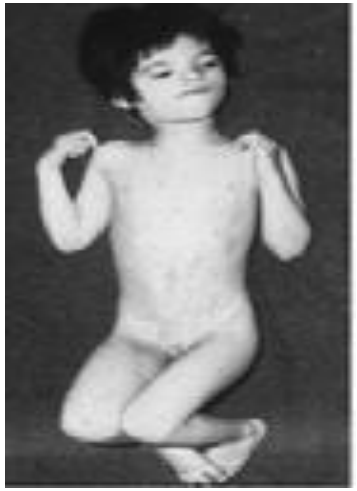
Table 6.3 Chromosomal Deletions

Deletion	Syndrome	Phenotype
5p−	Cri du chat syndrome	Infants have catlike cry, some facial anomalies, severe mental retardation
11q−	Wilms tumor	Kidney tumors, genital and urinary tract abnormalities
13q−	Retinoblastoma	Cancer of eye, increased risk of other cancers
15q−	Prader-Willi syndrome	Infants: weak, slow growth; children and adults: obesity, compulsive eating

Deletions – Cri du chat

- Cri du chat syndrome
- A deletion of the short arm of chromosome 5
- Associated with an array of congenital malformations, the most characteristic of which is an infant cry that resembles a meowing cat. Also, metal retardation, microcephaly, hypotonia.





Loss of genes causes the phenotype

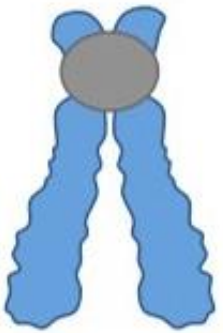
Translocations

- Translocation involves exchange of chromosome parts
  - Often produces no overt phenotypic effects
  - Can result in genetically imbalanced and aneuploid gametes

Robertsonian translocation

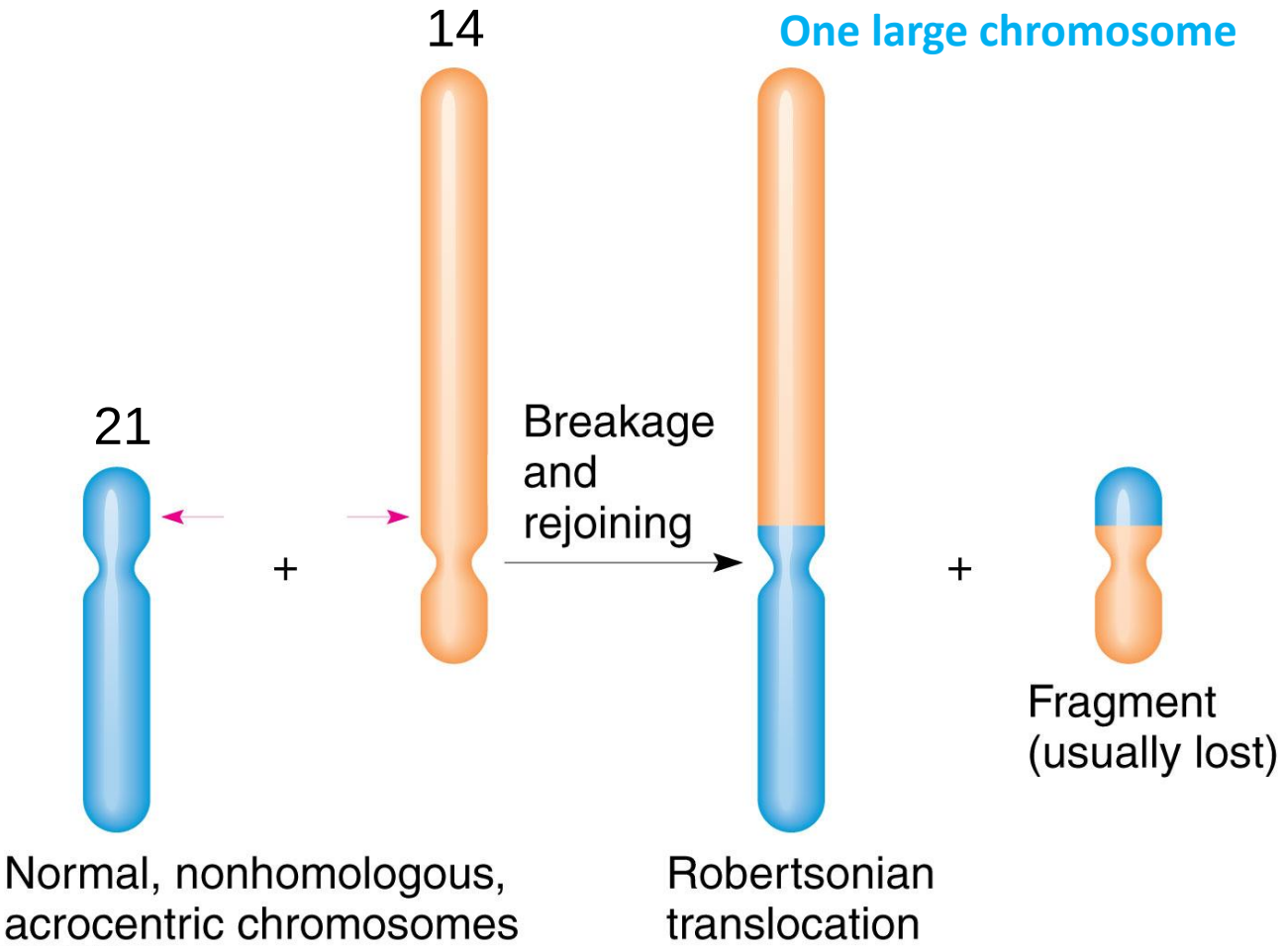
- A Robertsonian translocation is where **two acrocentric chromosomes are joined at their centromere**
  - E.g. chromosome 14 and 21
  - A translocation resulting in Down syndrome
  - In effect, Robertsonian translocation makes Down syndrome a heritable genetic disease
- Potentially present in one in three offspring

p arm so short but still visible



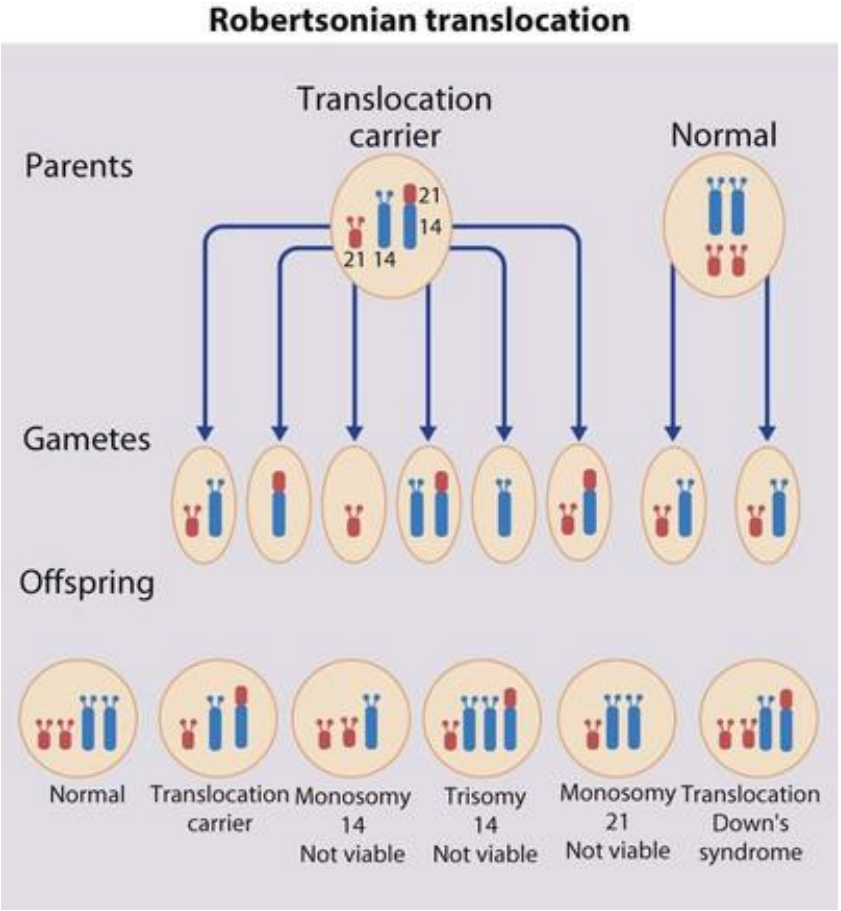
Acrocentric

Robertsonian translocation



Robertsonian translocation

- About 5% of Down syndrome involve a Robertsonian translocation
- Someone carrying the translocation is phenotypically normal but produce six types of gametes
  - Three of these result in lethal conditions
  - One produces a Down syndrome child
  - One is a translocation carrier
  - One is chromosomally normal



Translocations