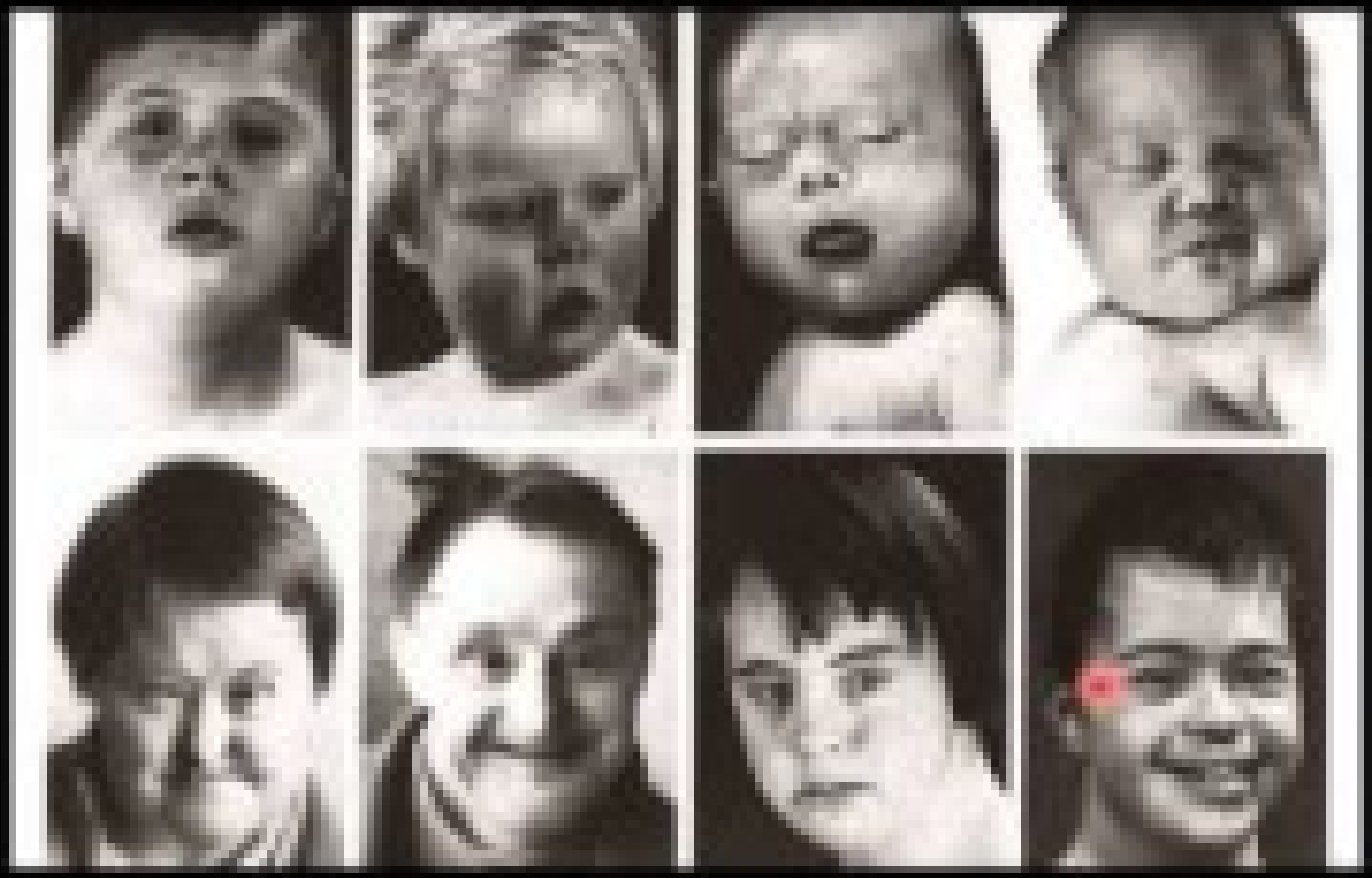


Medical Genetics Course

Dr. Bilal Azab

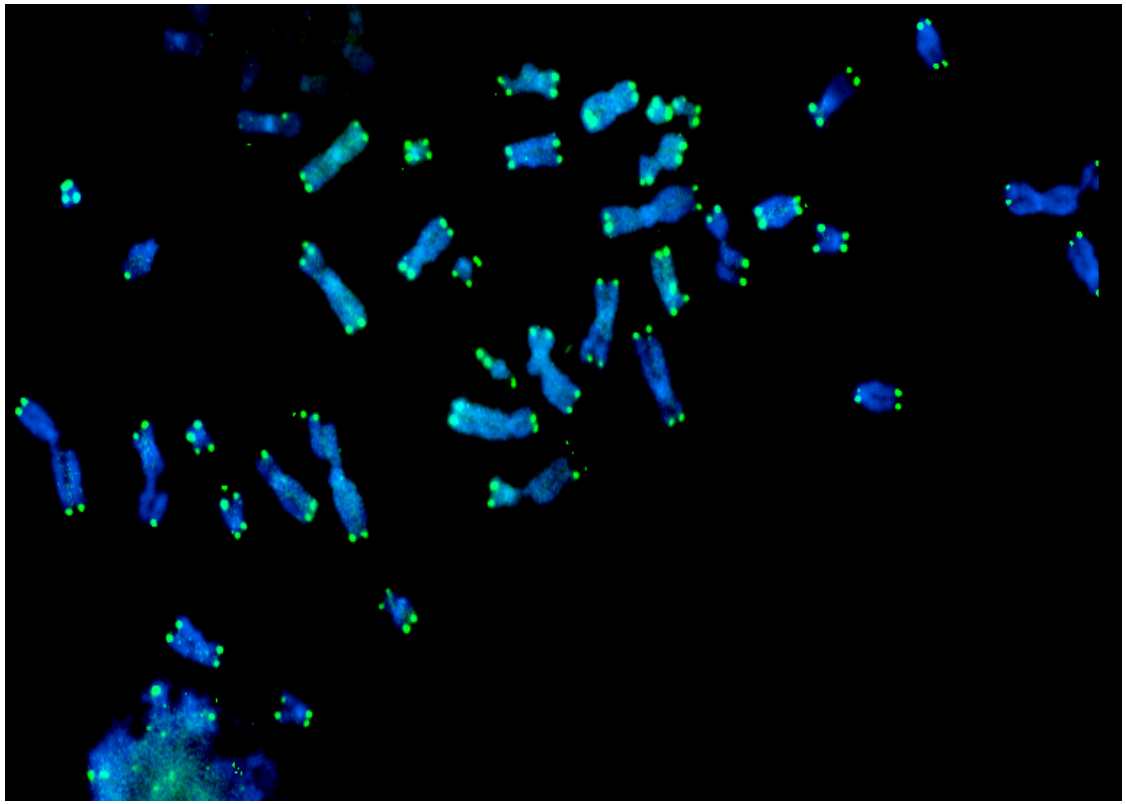
The University of Jordan
School of Medicine
Department of Pathology, Microbiology and Forensic Medicine

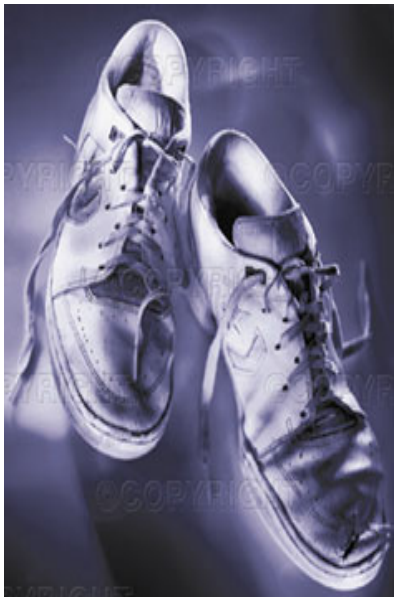
Email: b.azab@ju.edu.jo

Lecture link: https://youtu.be/NTUUryj3-qQ

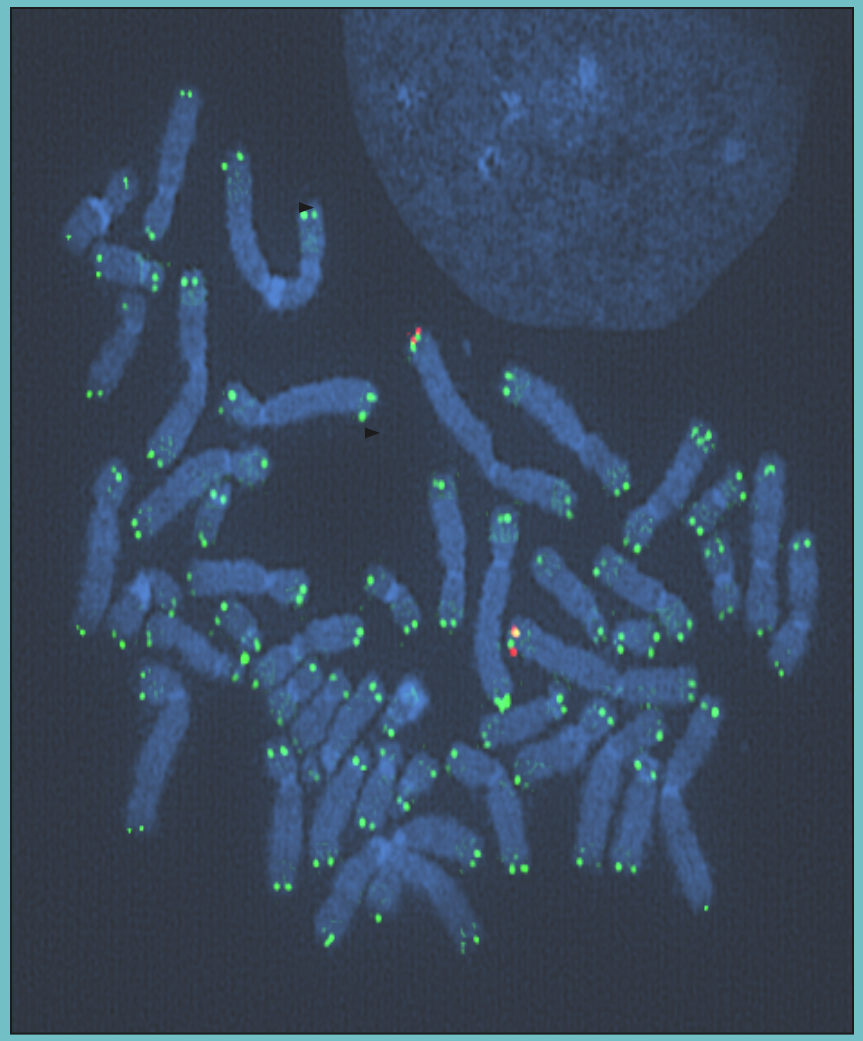
Telomere $(TTAGGG)_n$

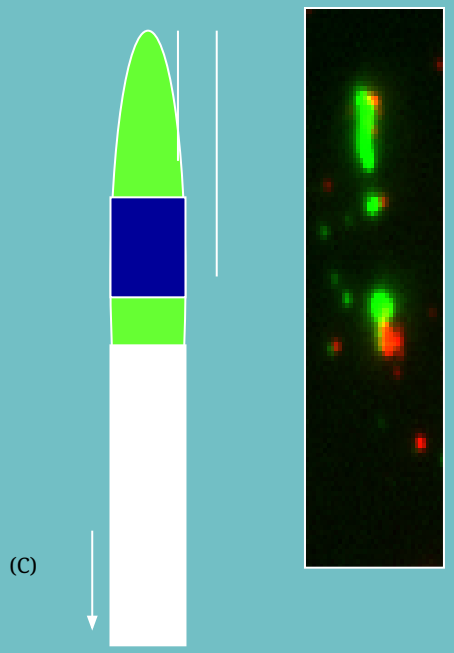
A specialized structure at the ends of eukaryotyic chromosomes. Maintain chromosomal integrity by preventing end-to-end fusion of chromosomes.

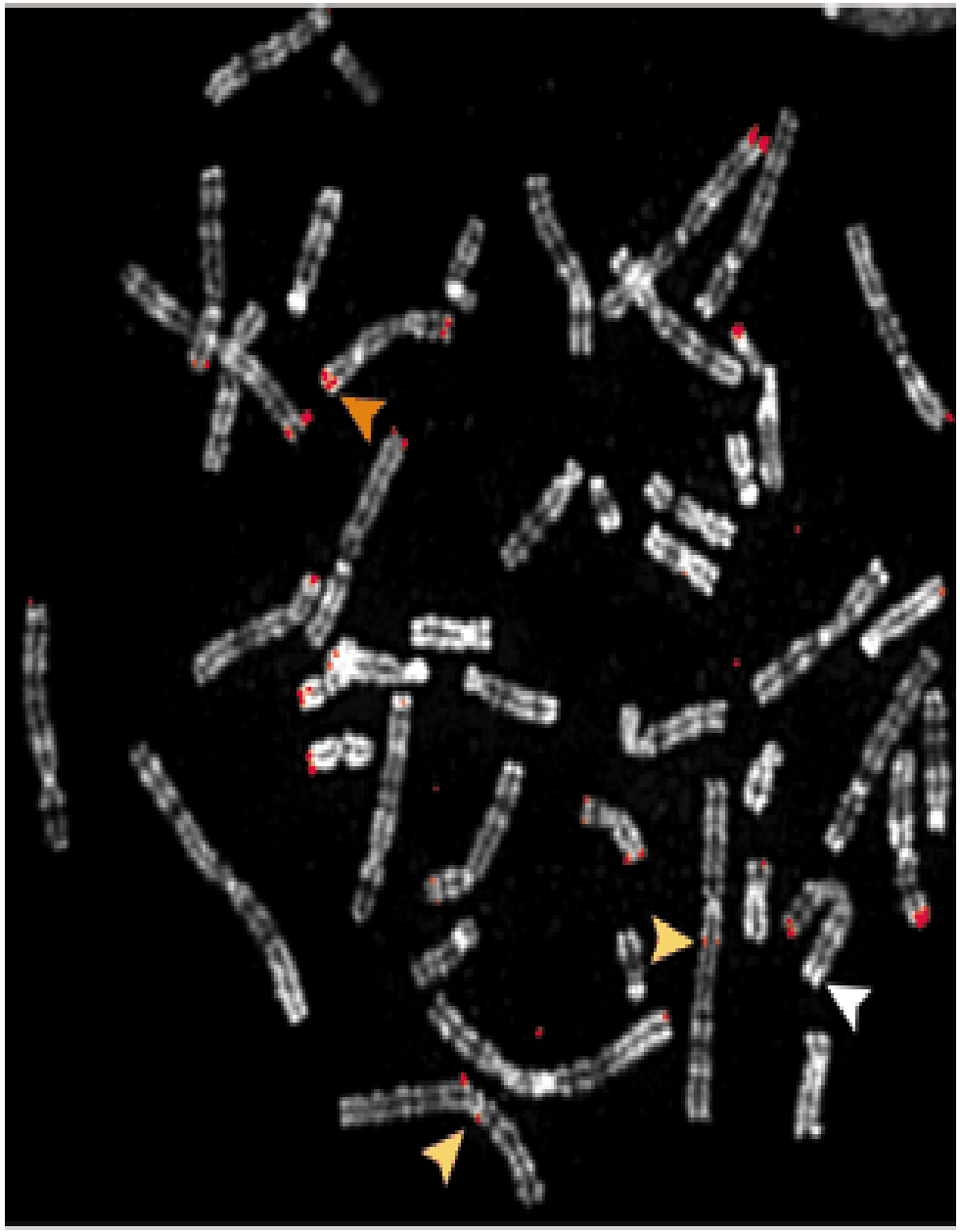




Human Sub-telomeric Regions







There is some sequence homology between subtelomeres

Nondisjunction

Failure of:

(1) chromosome pair to disjoin during MI or

(2) chromatids to separate in MII or mitosis.

Abnormal Chromosome Number

- In **nondisjunction**, pairs of homologous chromosomes do not separate normally during meiosis
- As a result, one gamete receives two of the same type of chromosome, and another gamete receives no copy

Figure 15.13-1

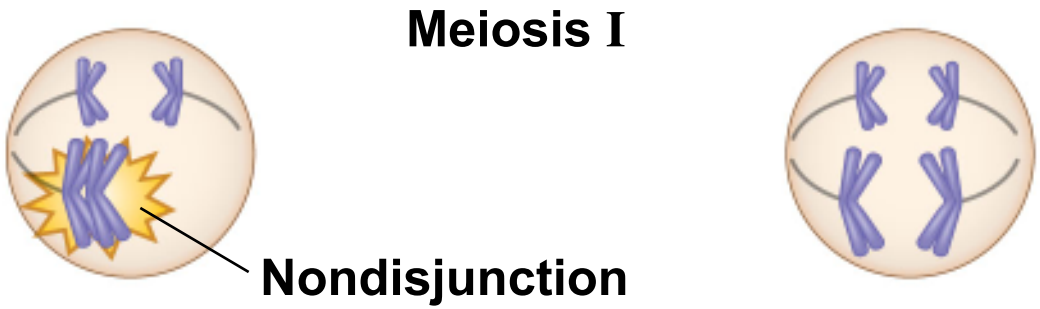


Figure 15.13-2

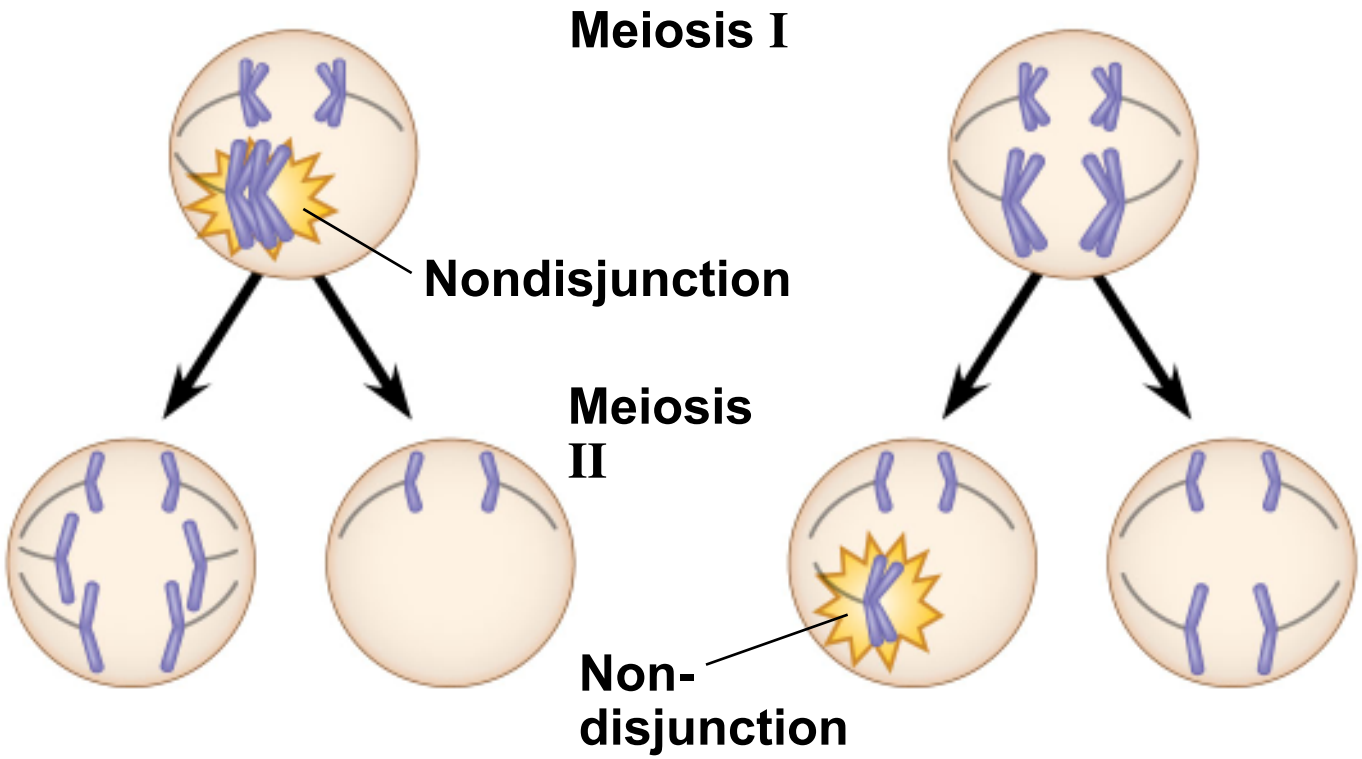
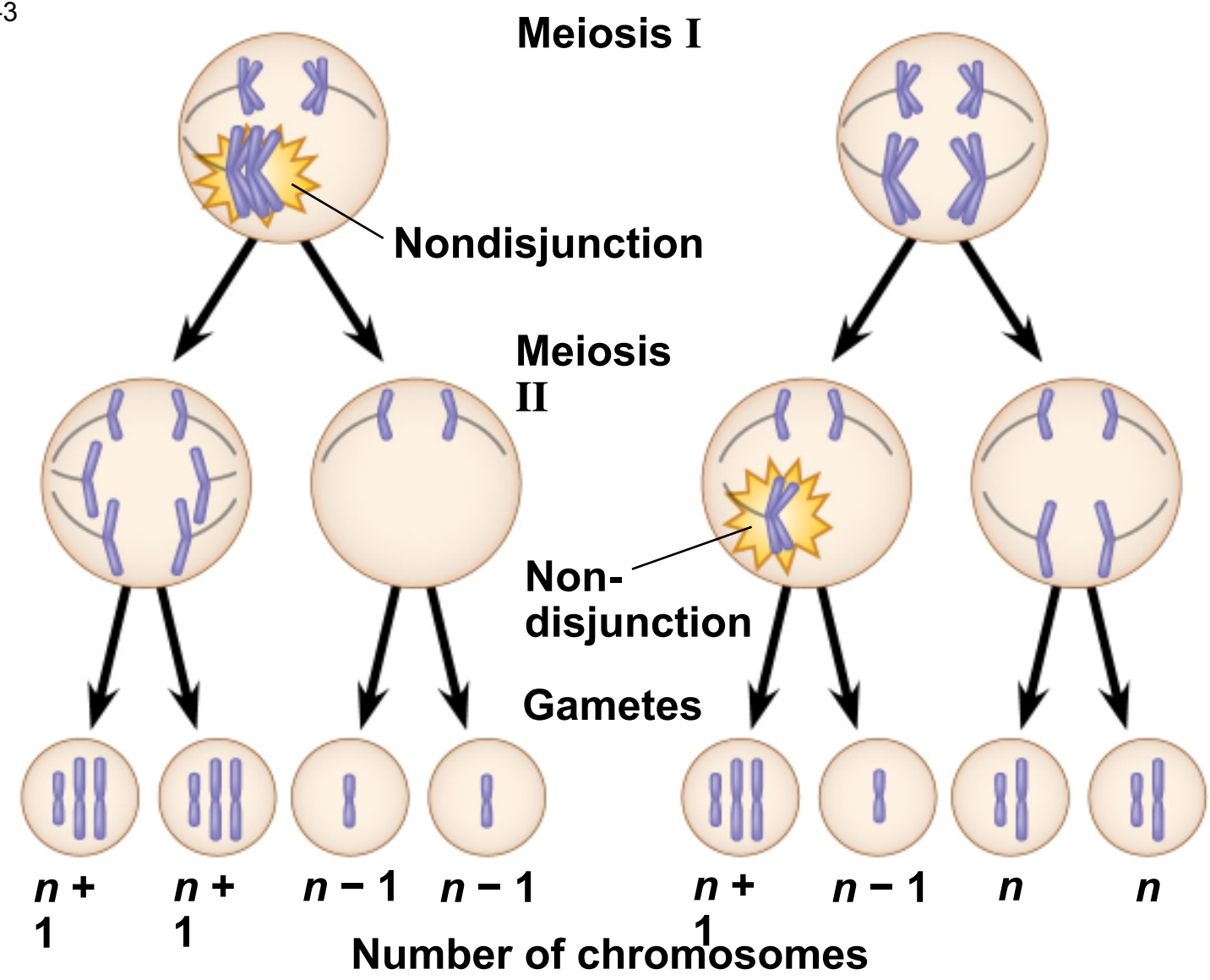
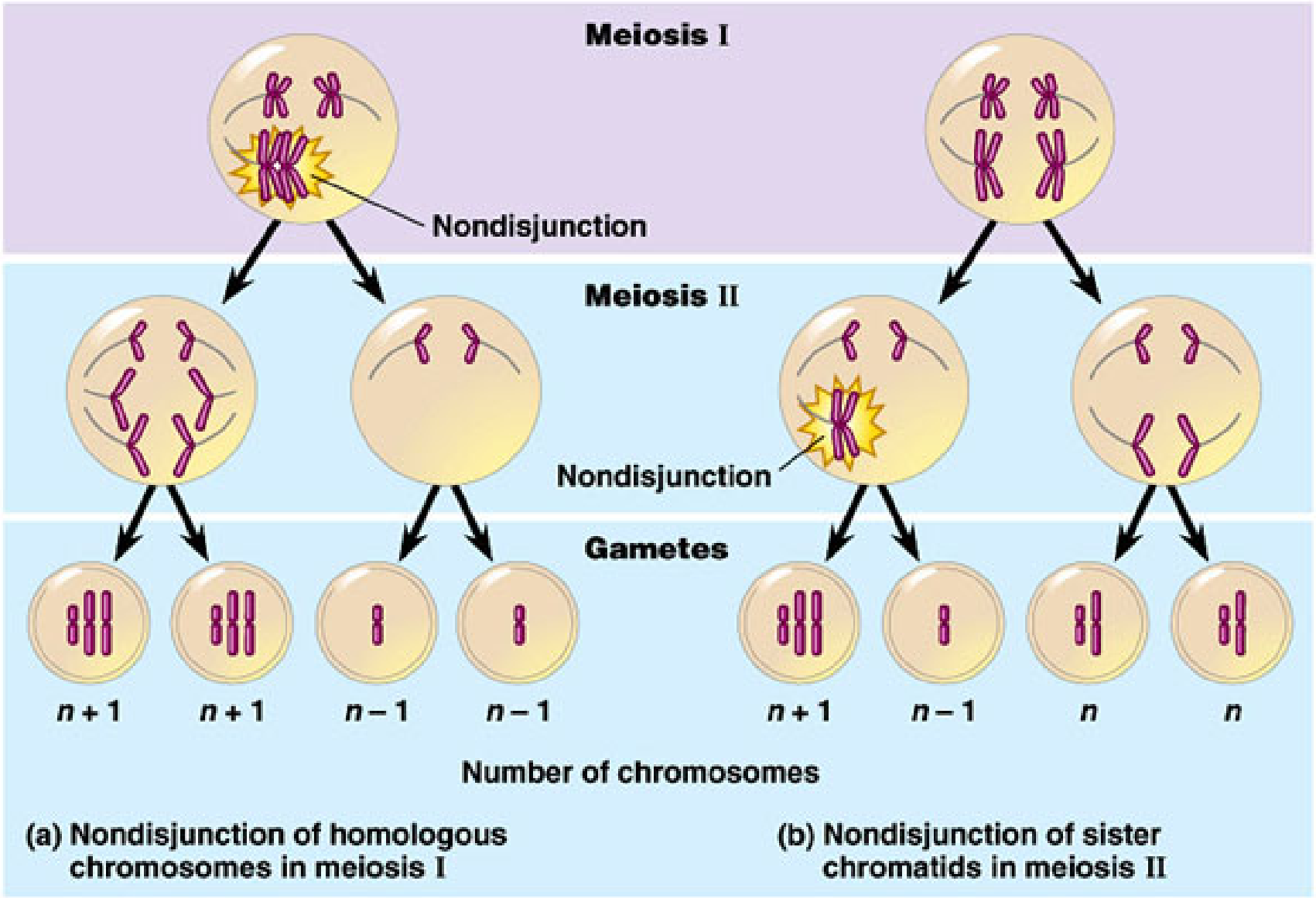


Figure 15.13-3



(a) Nondisjunction of homologous chromosomes in meiosis I

(b) Nondisjunction of sister chromatids in meiosis II



- **Aneuploidy** results from the fertilization of gametes in which nondisjunction occurred
- Offspring with this condition have an abnormal number of a particular chromosome

- A **monosomic** zygote has only one copy of a particular chromosome
- A **trisomic** zygote has three copies of a particular chromosome

Trisomy

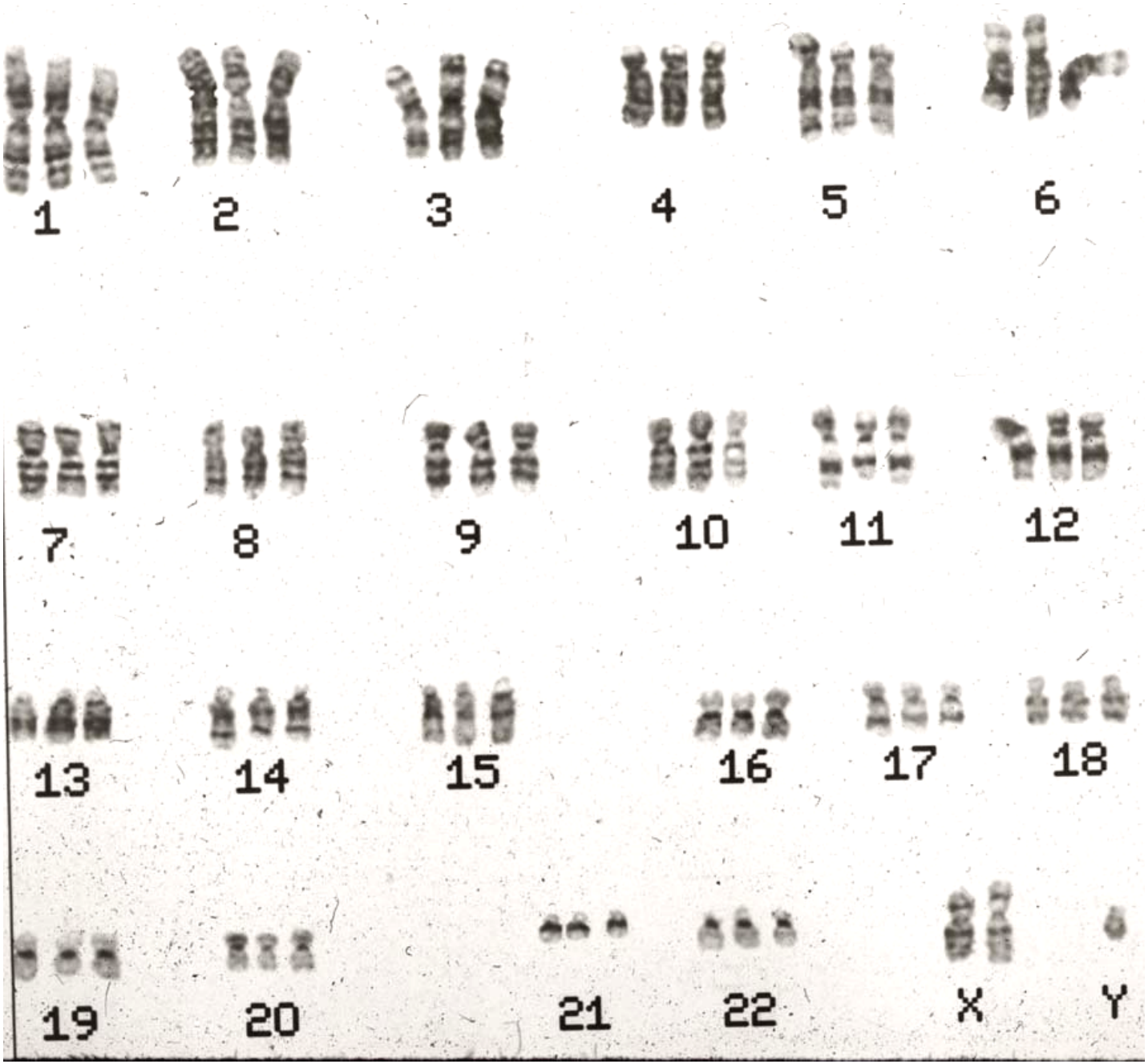
Additional (3 rather than 2) chromosome.

Monosomy

One chromosome of a pair missing.

- **Polyploidy** is a condition in which an organism has more than two complete sets of chromosomes
  - Triploidy (3*n*) is three sets of chromosomes
  - Tetraploidy (4*n*) is four sets of chromosomes
- Polyploidy is common in plants, but not animals
- Polyploids are more normal in appearance than aneuploids

Euploid - any chromosome number that is an exact multiple of the number of chromosomes in a normal haploid gamete (n). Most somatic cells are diploid (2N).
haploid (1 set), diploid (2 sets), triploid (3 sets), tetraploid (4 sets)



Triploidy 69,XXY

Alterations of Chromosome Structure

- Breakage of a chromosome can lead to four types of changes in chromosome structure
  - **Deletion** removes a chromosomal segment
  - **Duplication** repeats a segment
  - **Inversion** reverses orientation of a segment within a chromosome
  - **Translocation** moves a segment from one chromosome to another

Figure 15.14a

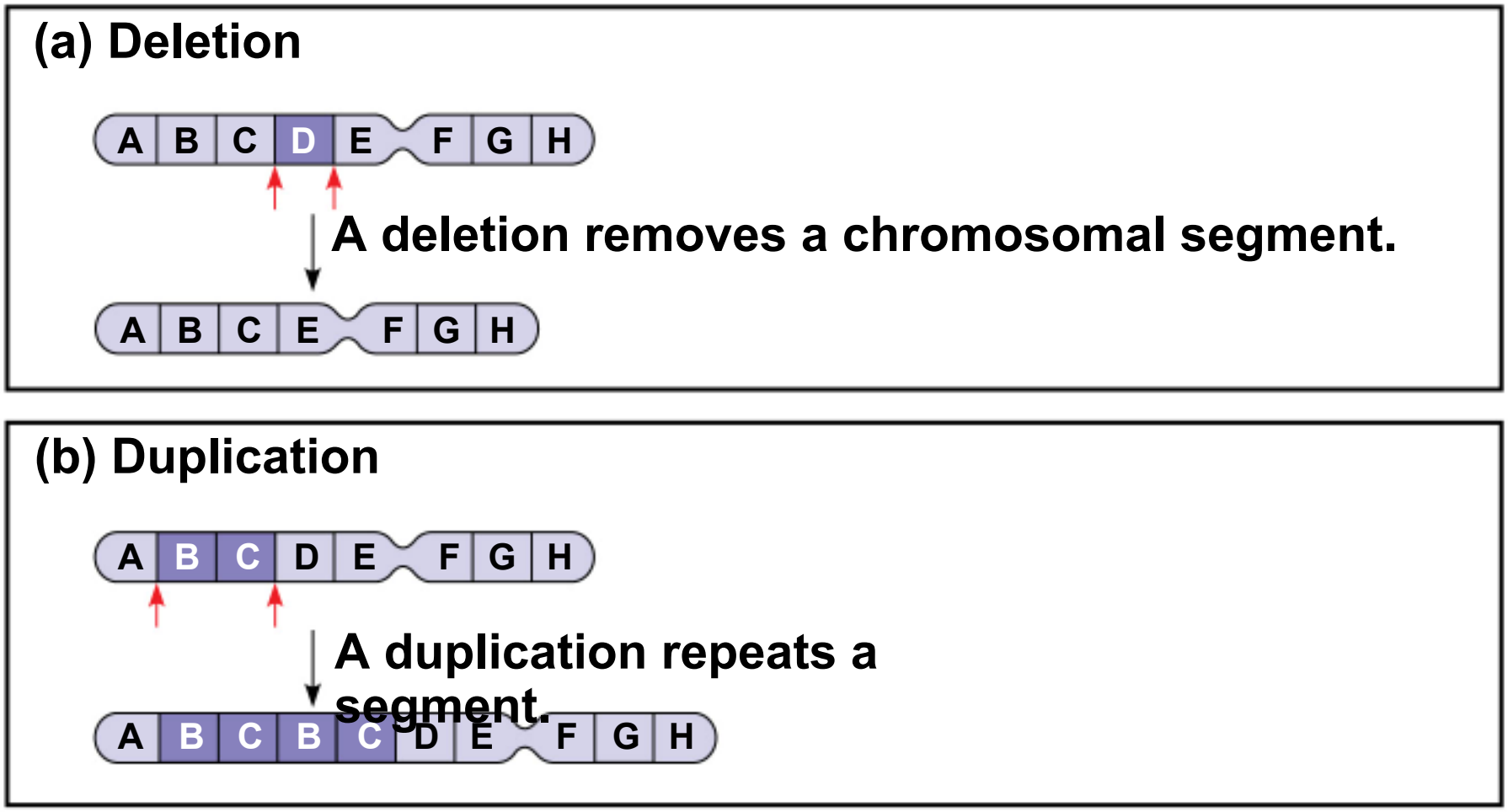
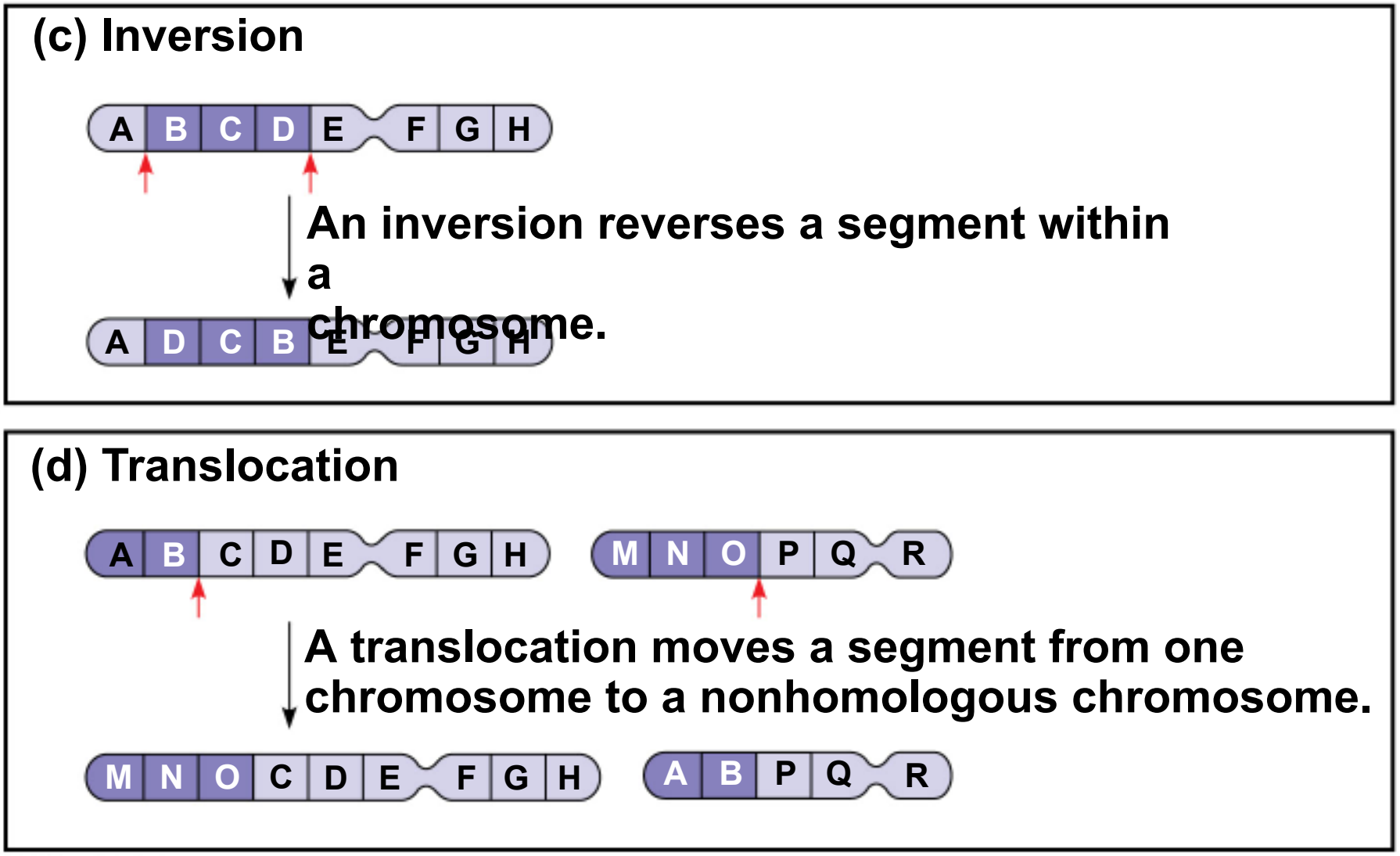


Figure 15.14b



Human Disorders Due to Chromosomal Alterations

- Alterations of chromosome number and structure are associated with some serious disorders
- Some types of aneuploidy appear to upset the genetic balance less than others, resulting in individuals surviving to birth and beyond
- These surviving individuals have a set of symptoms, or syndrome, characteristic of the type of aneuploidy

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*

Down Syndrome (Trisomy 21)

- **Down syndrome** is an aneuploid condition that results from three copies of chromosome 21
- It affects about one out of every 700 children born in the United States
- The frequency of Down syndrome increases with the age of the mother, a correlation that has not been explained

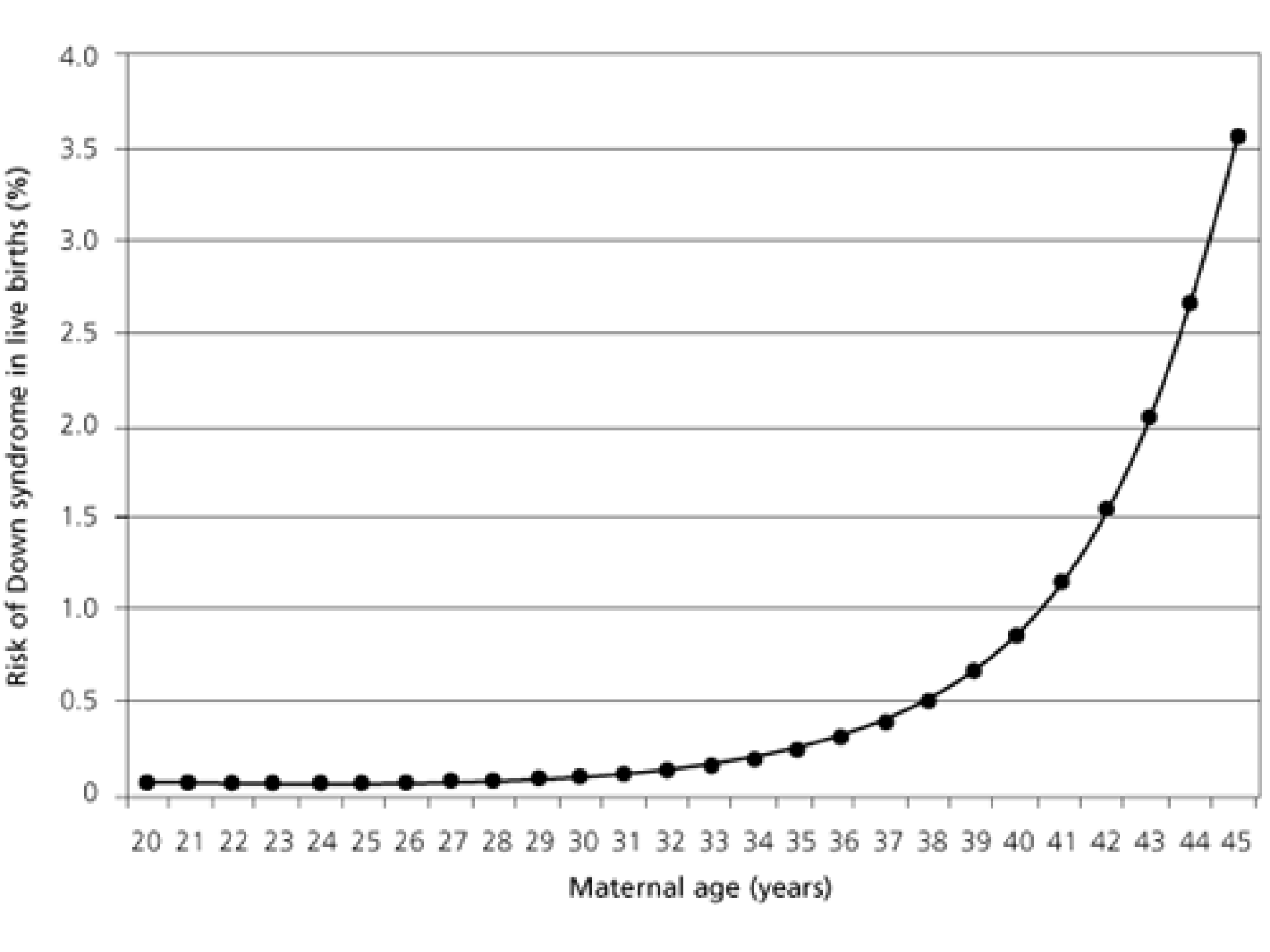
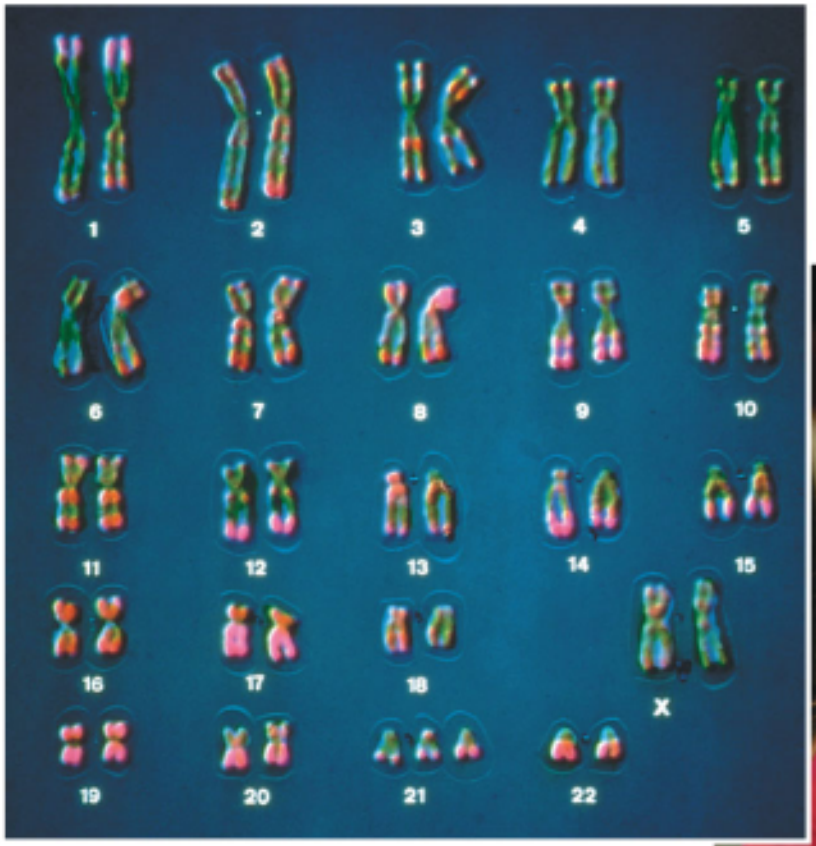
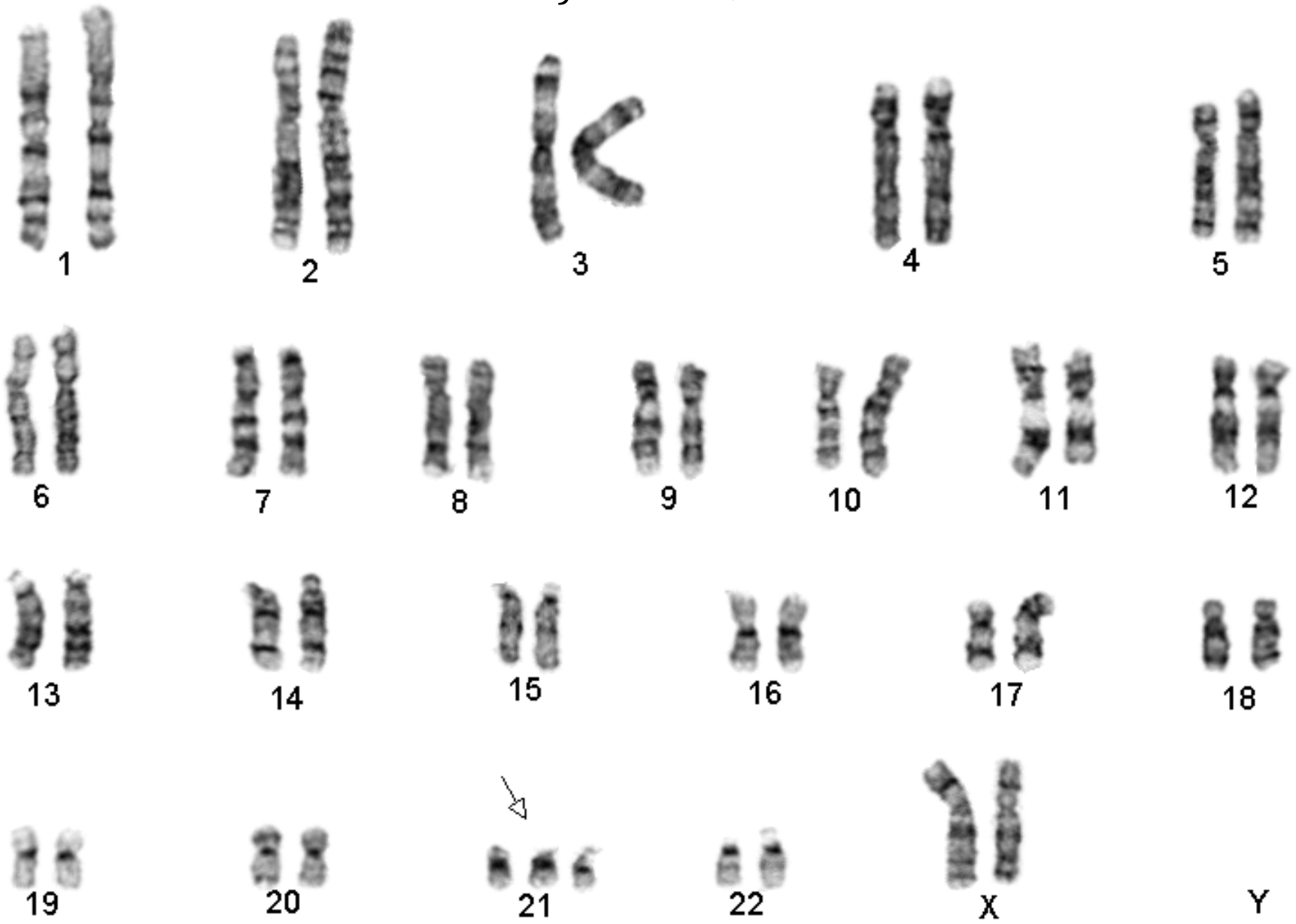
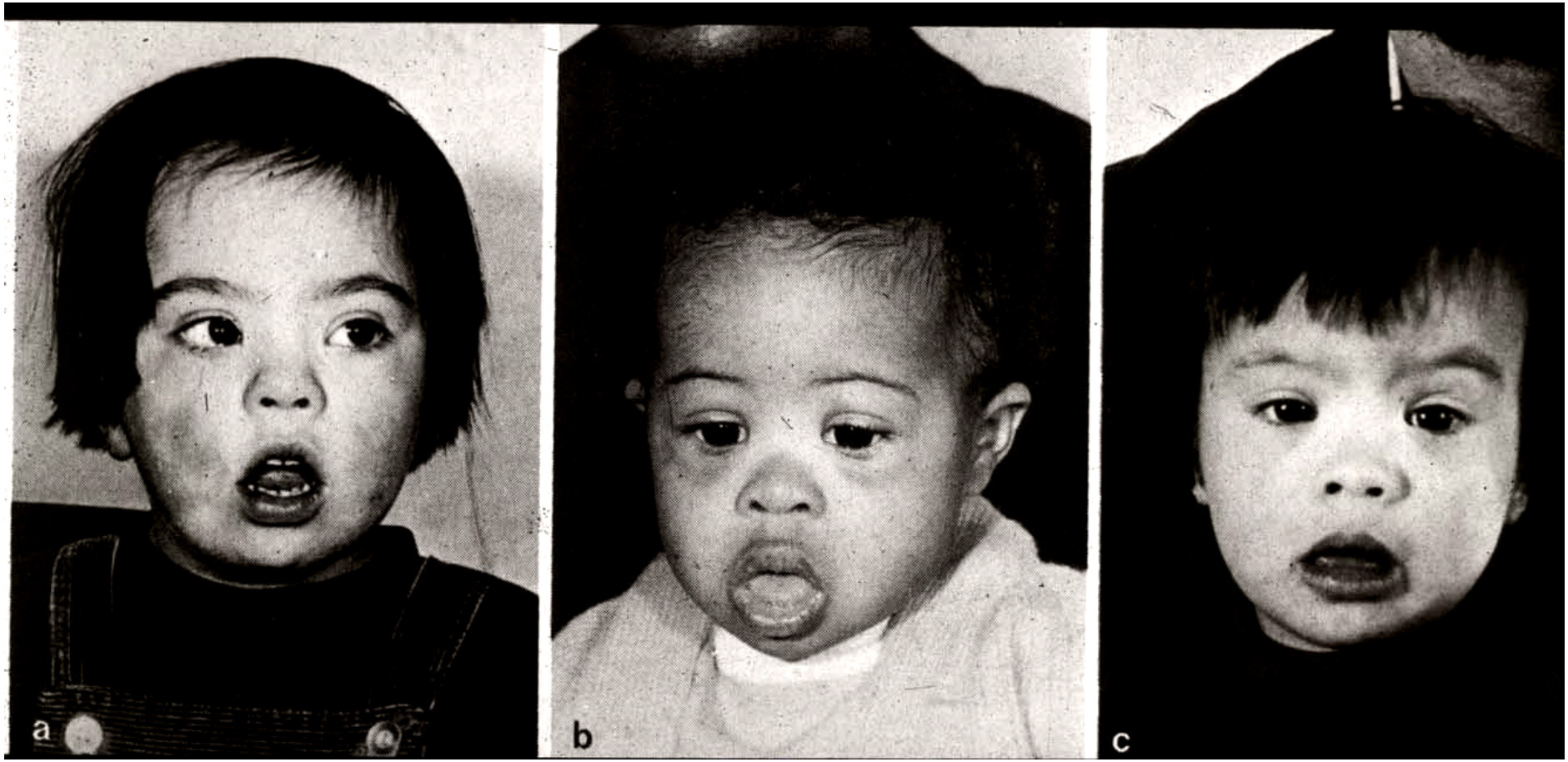

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Risk of Down syndrome in live births (%)
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Maternal age (years)

Figure 15.15



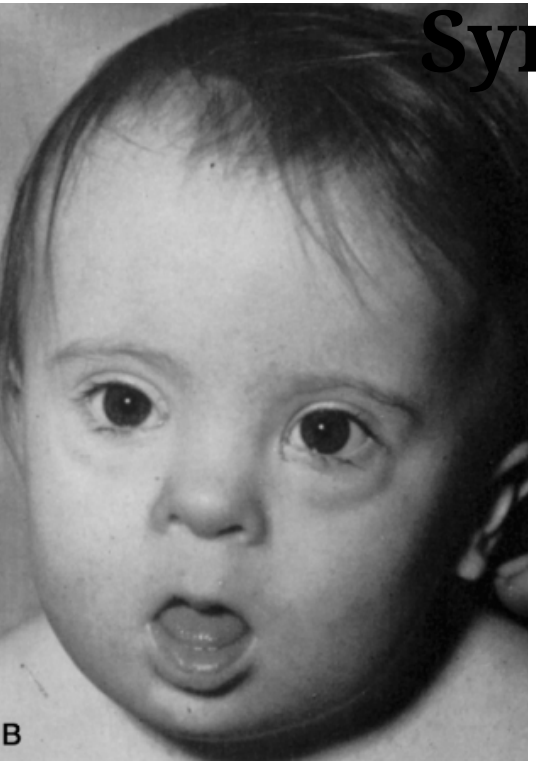
Most common numerical abnormality in liveborns is Trisomy 21 (Down syndrome)

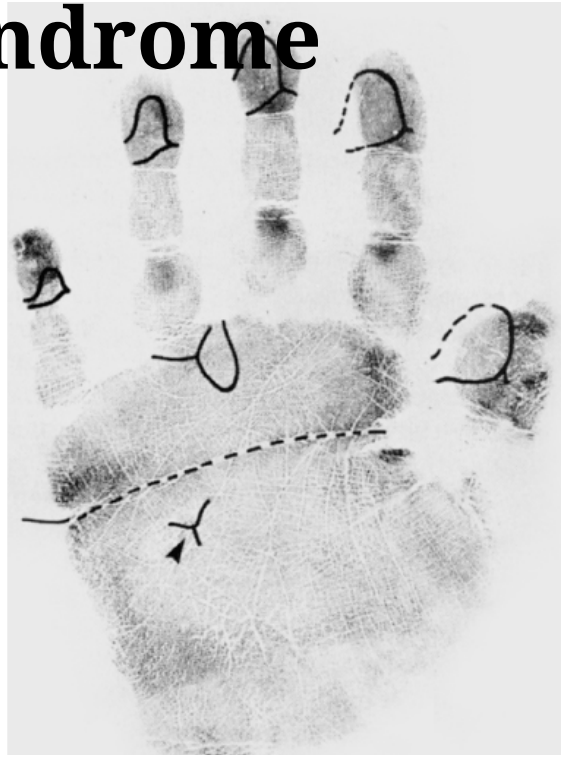




Male:Female Ratio -
3:2

Down Syndrome



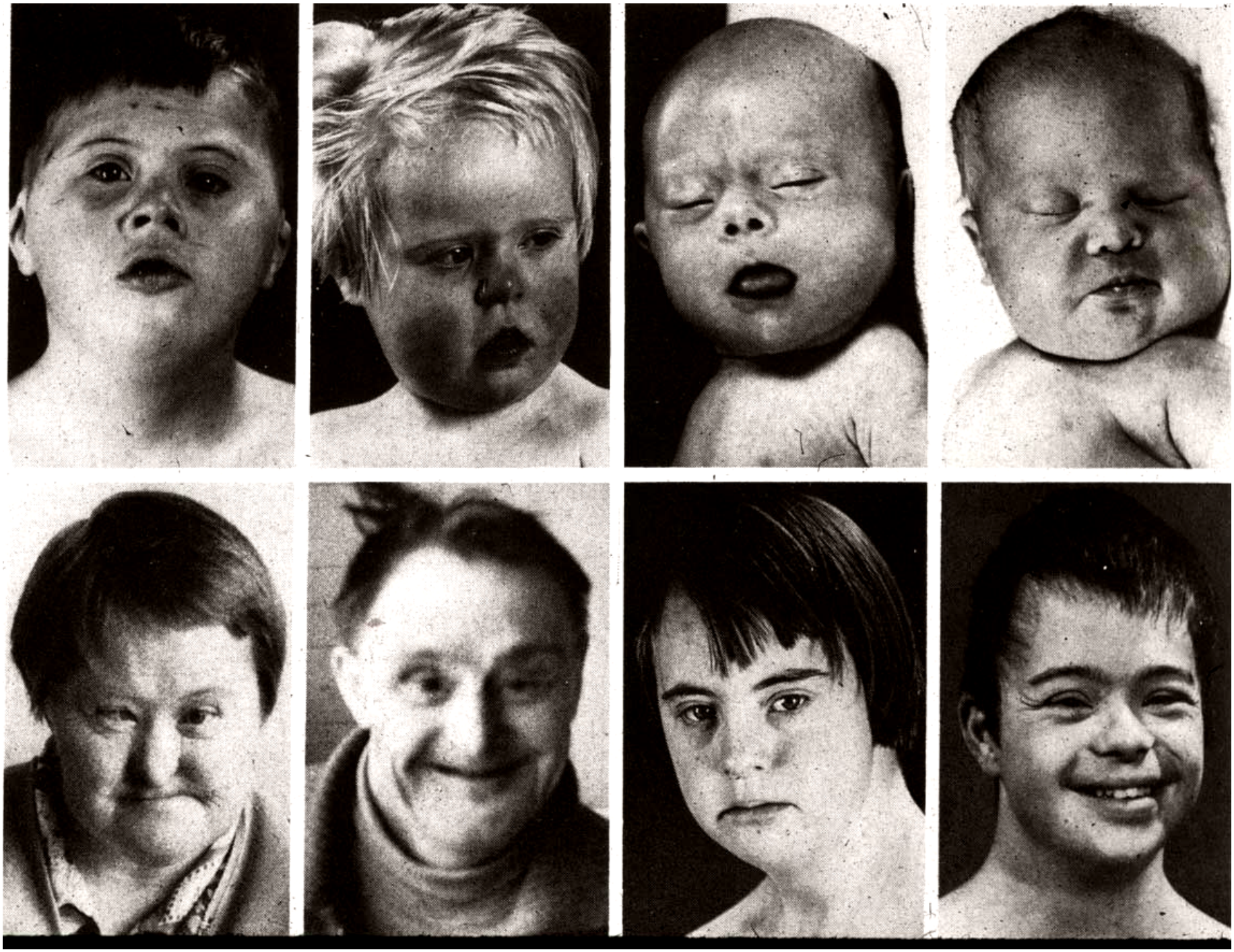


Mental retardation (IQ 25-50)
*Low nasal bridge (90%)
*Hypotonia (80%)
*Up slanting palpebral fissures (80%)
Small, low-set ears (60%)
*Congenital heart disease (30%-50%)**
*Simian line (transverse crease) (45%)

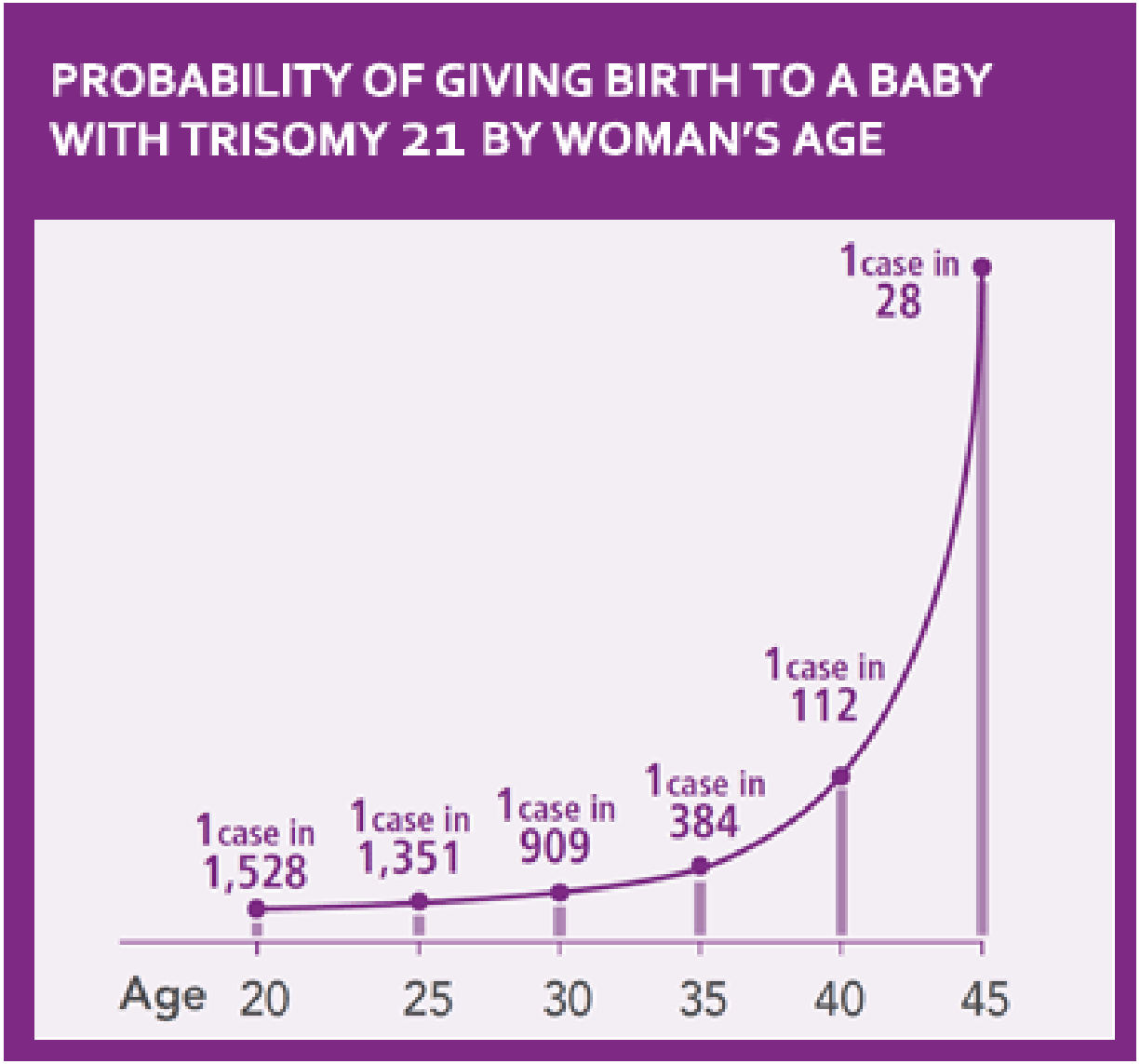
*Epicanthic folds
Protruding tongue
Intestinal problems
Gap between first and second toes
15-fold increase in risk for leukemia

These features are easily recognized at birth.

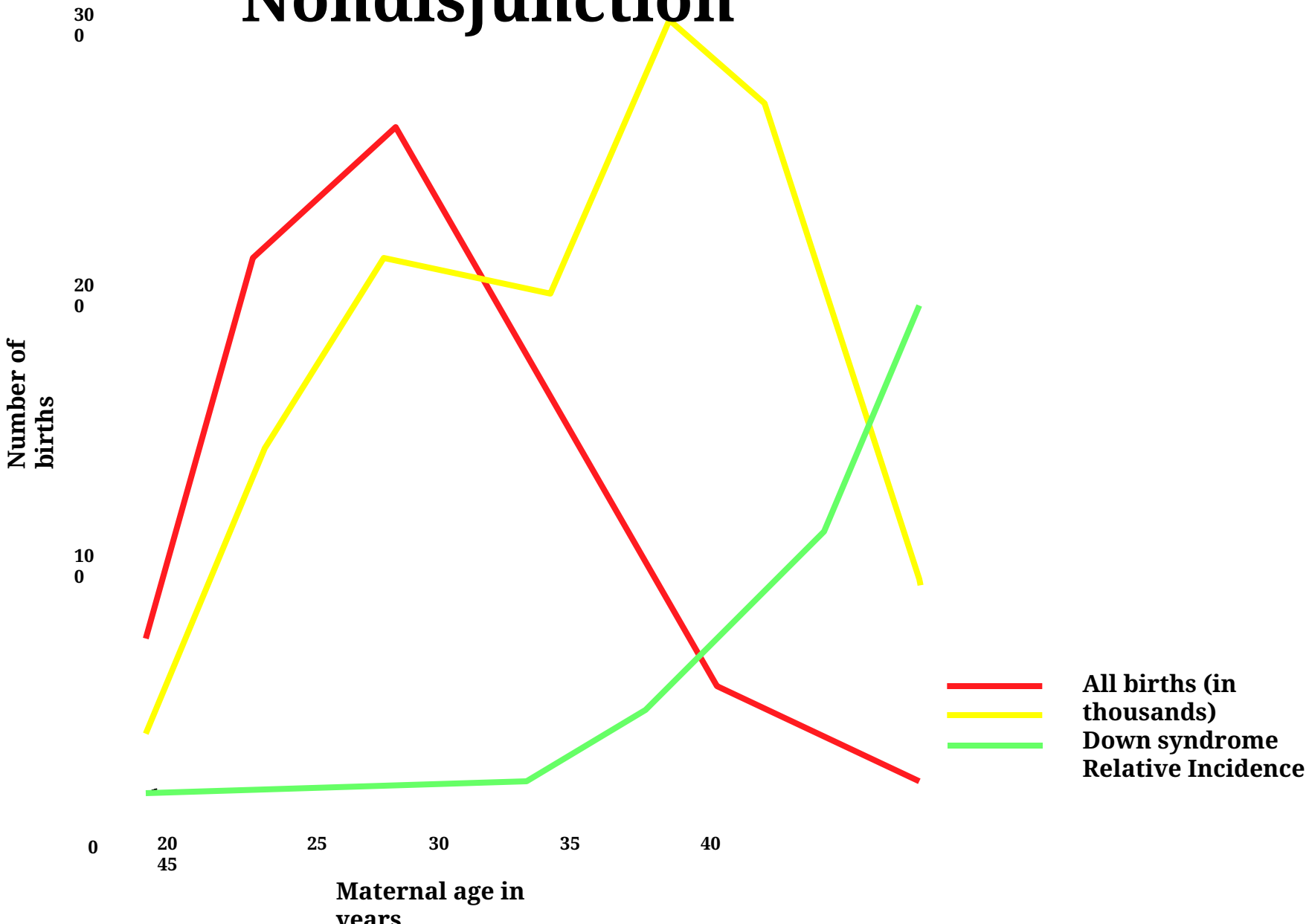
**The congenital heart problems noted in people having Down syndrome include ventricular septal defect (VSD) and arterioventricular defects (AV) canal. Approximately 40% with congenital heart disease die during the first year.

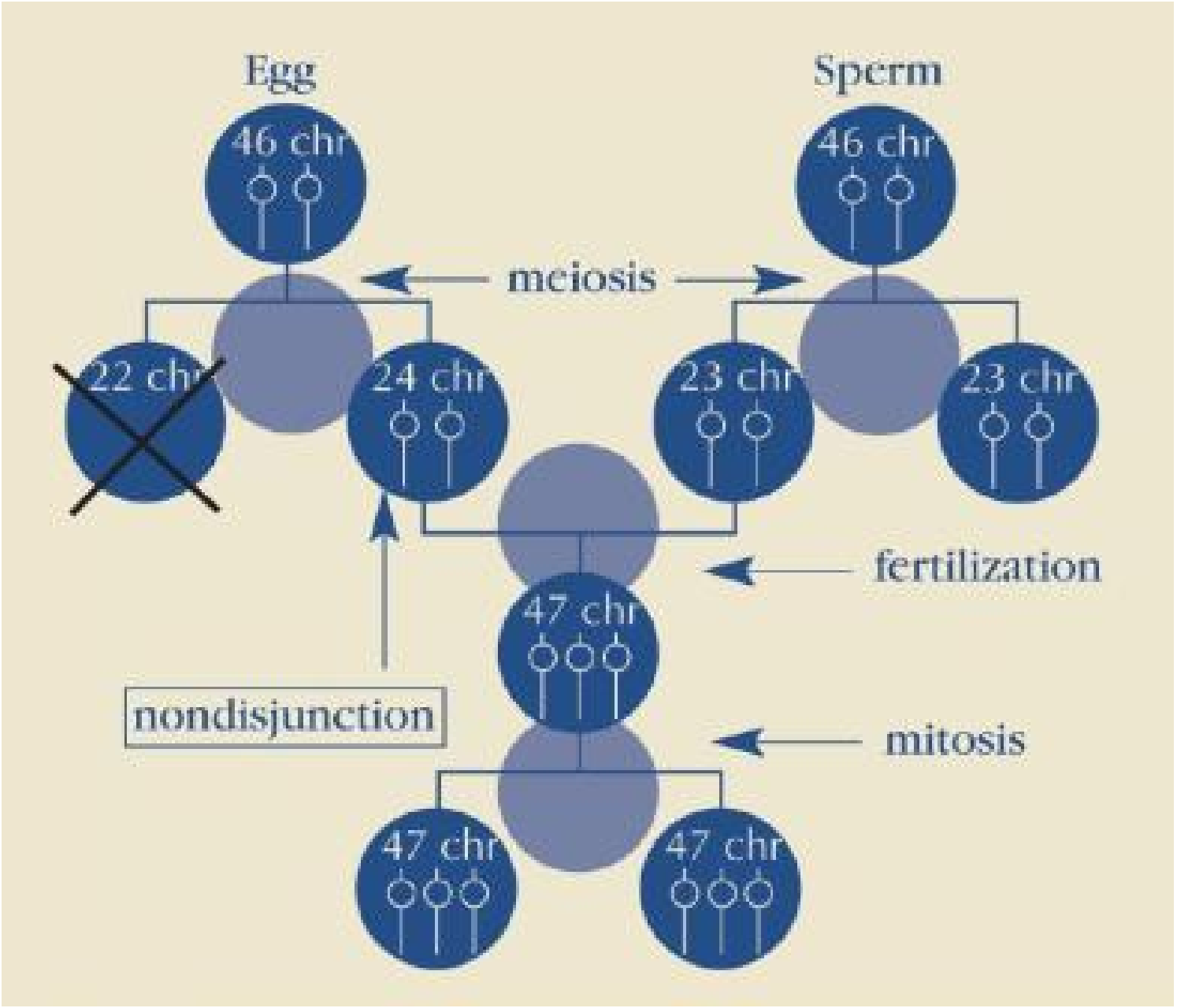


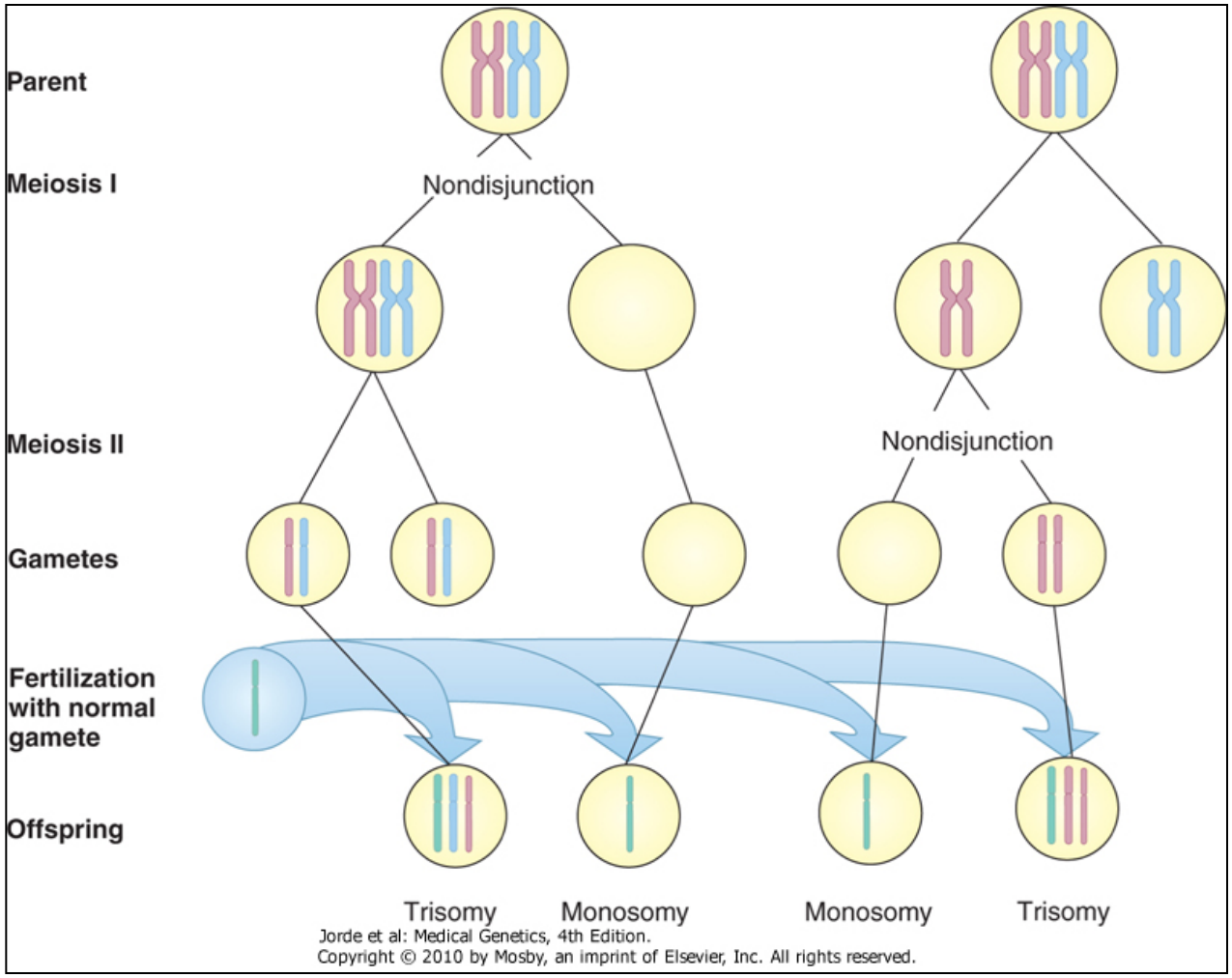
1 in 770 babies



Maternal Age and Nondisjunction




Egg
Sperm
46 chr
46 chr
meiosis
22 chr
24 chr
23 chr
23 chr
fertilization
47 chr
nondisjunction
mitosis
47 chr
47 chr

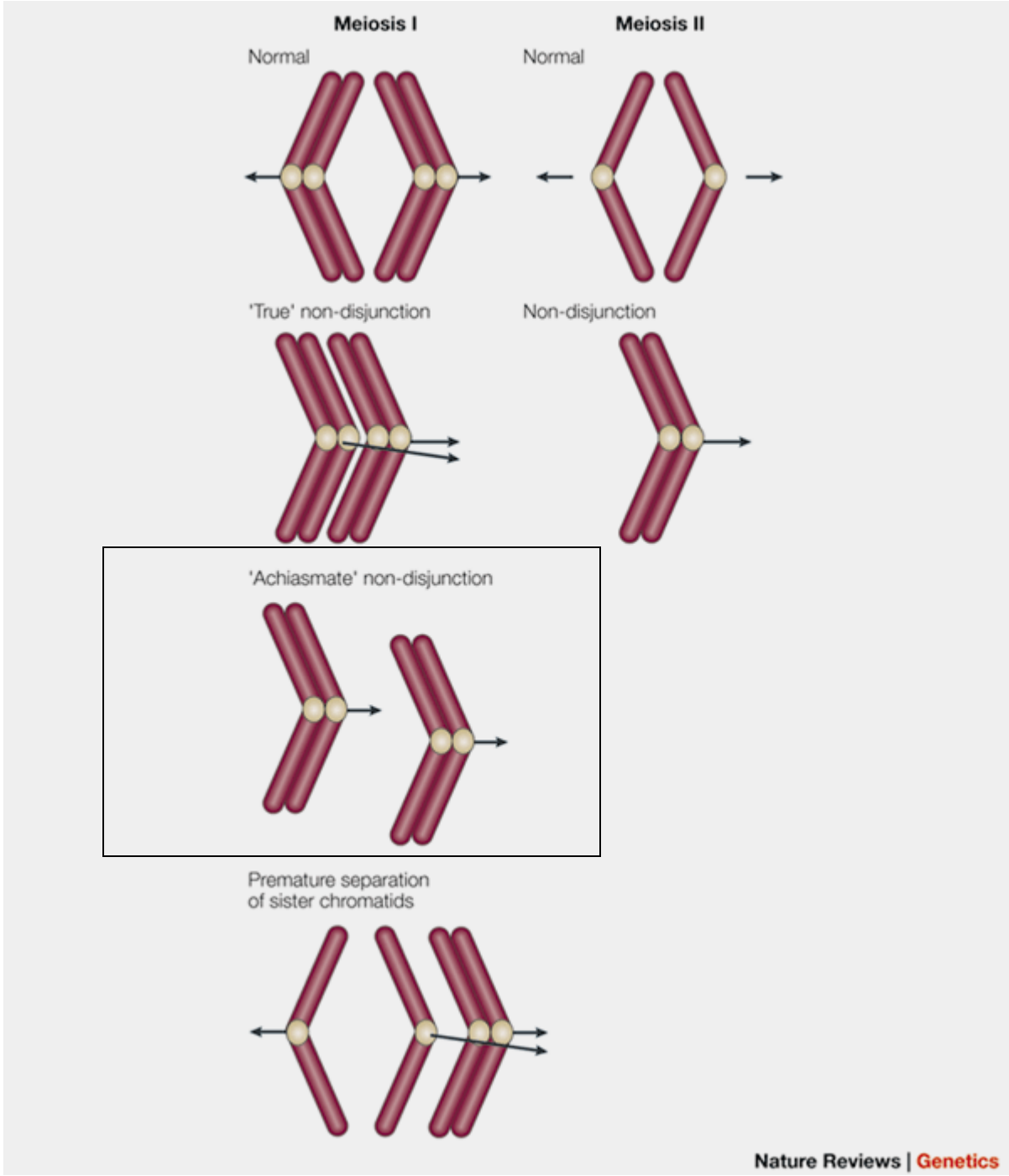


Trisomy 21

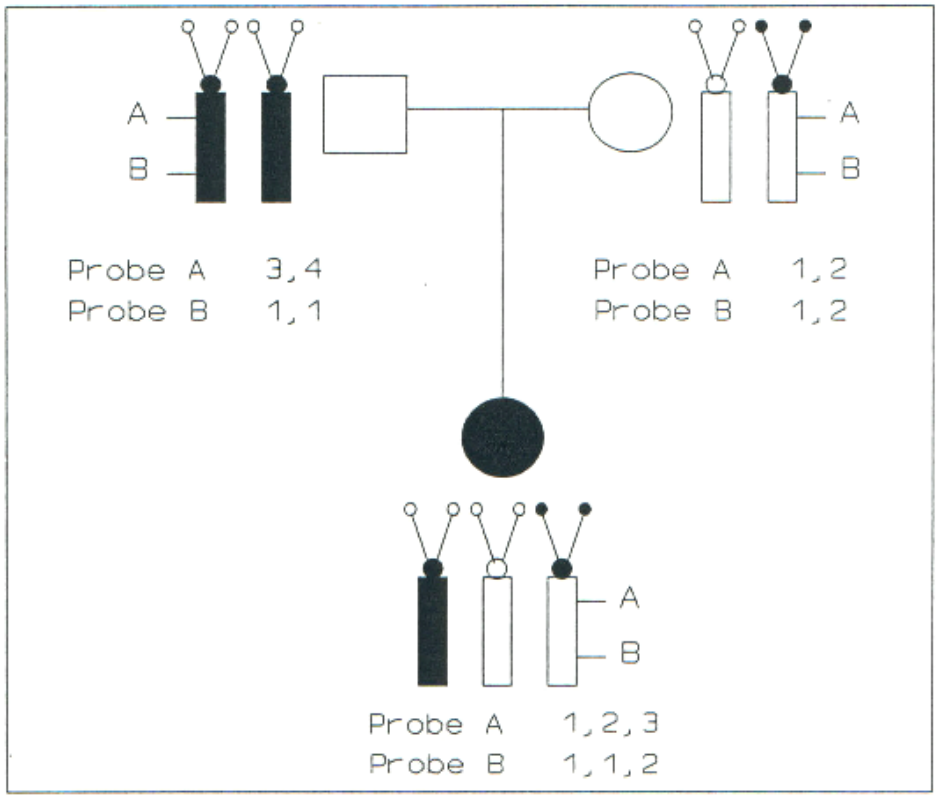
Maternal Errors: 94% of cases
MI 64%
MII 19%

Paternal Errors: 4.5% of cases

- **MI 1%**
- **MII 3.5%**


Meiosis I
Meiosis II
Normal
Normal
'True' non-disjunction
Non-disjunction
'Achiasmate' non-disjunction
Premature separation
of sister chromatids
Nature Reviews | Genetics

Causal Factors in Nondisjunction

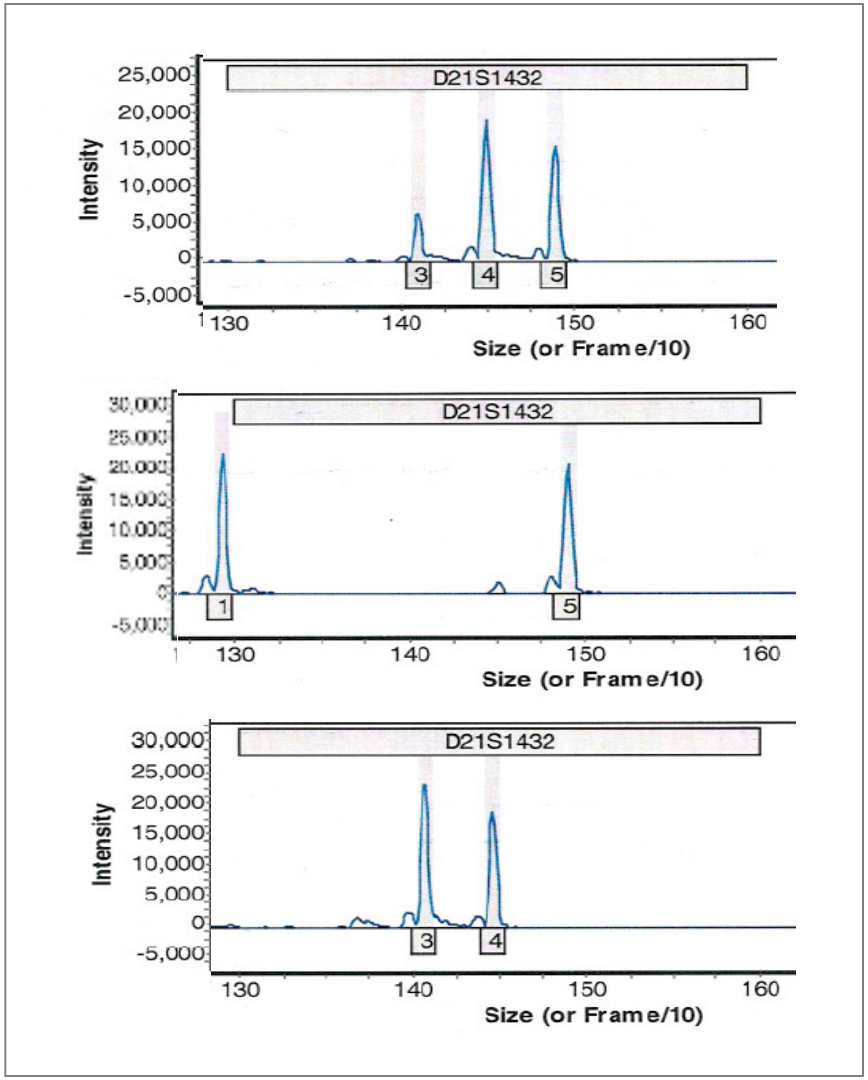


Evaluate the Origin of the Extra Chromosome Using Polymorphic Markers

Proband

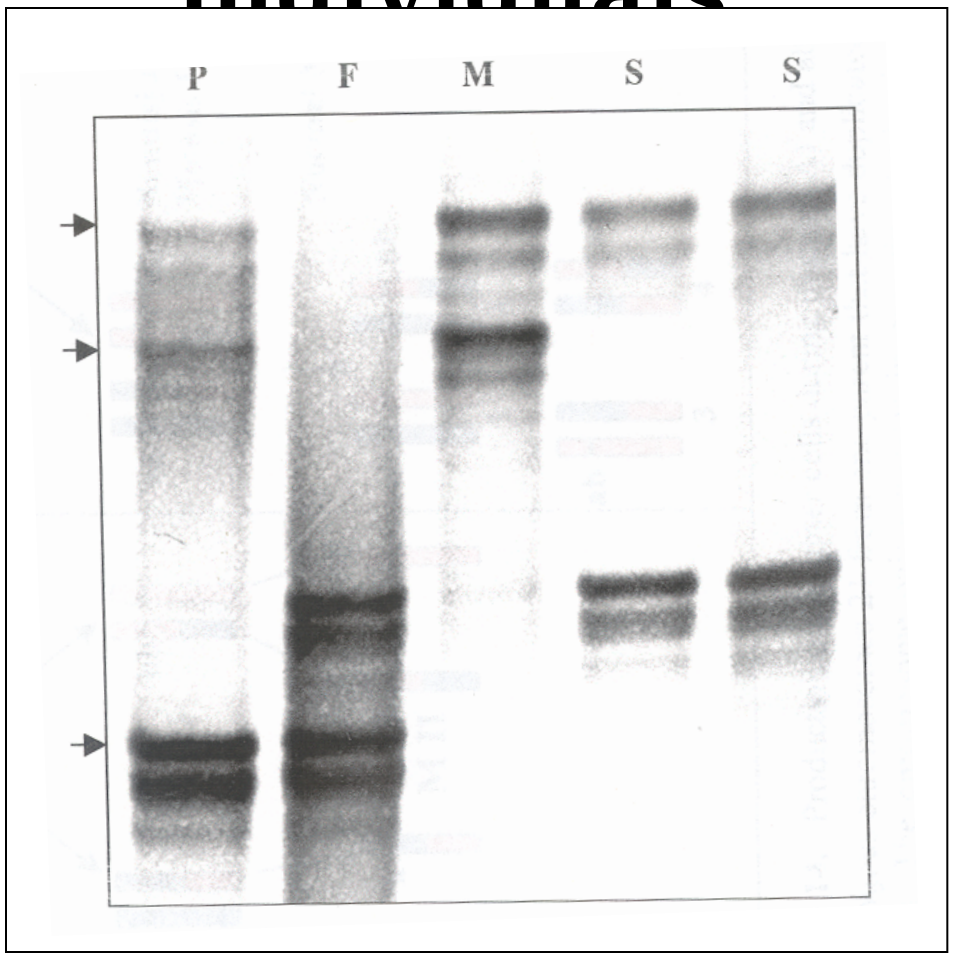
Father

Mother



D21S1432 Tetranucleotide STRP

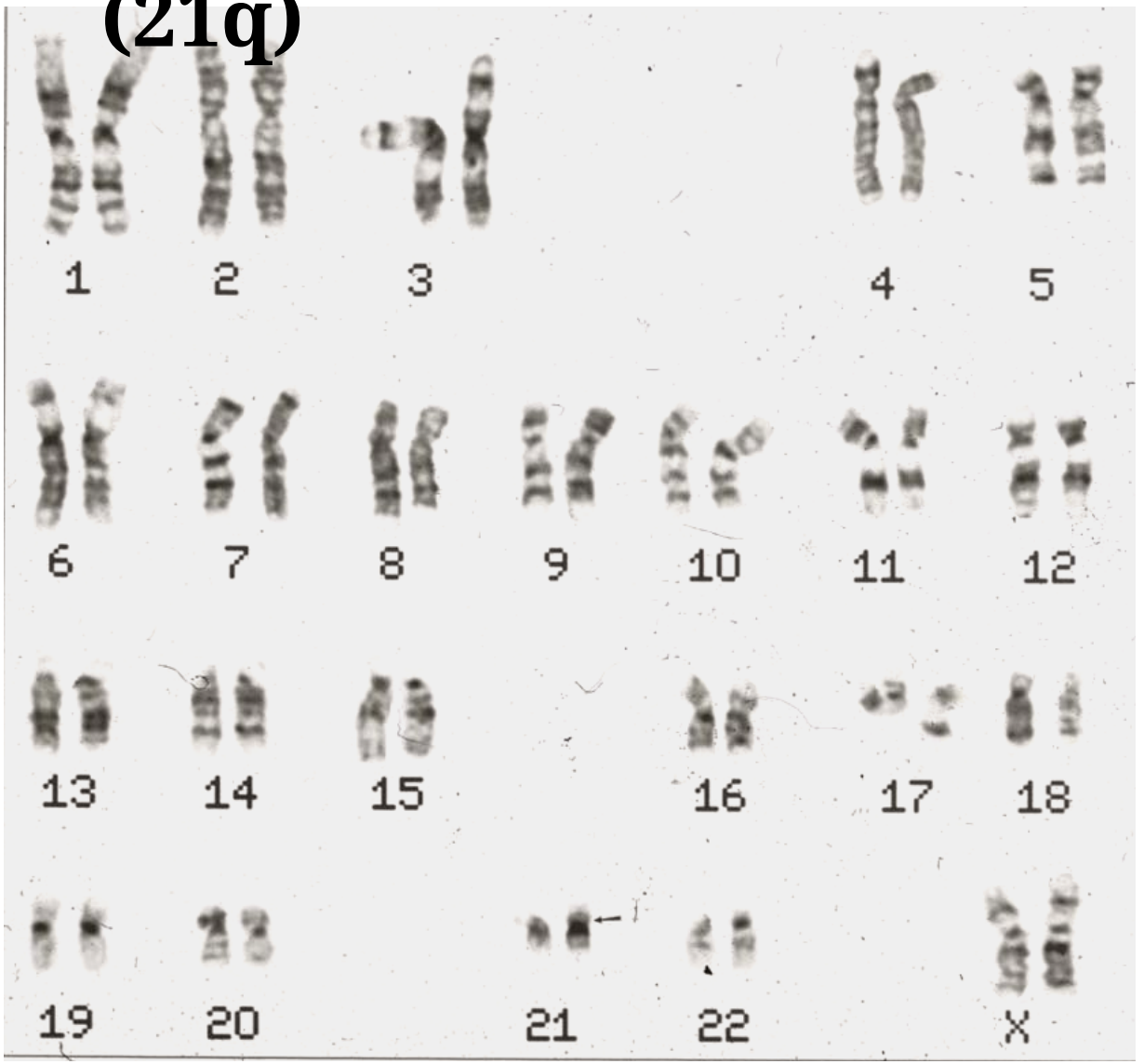
DNA markers can be used to determine the parental origin of the extra chromosome in trisomic individuals

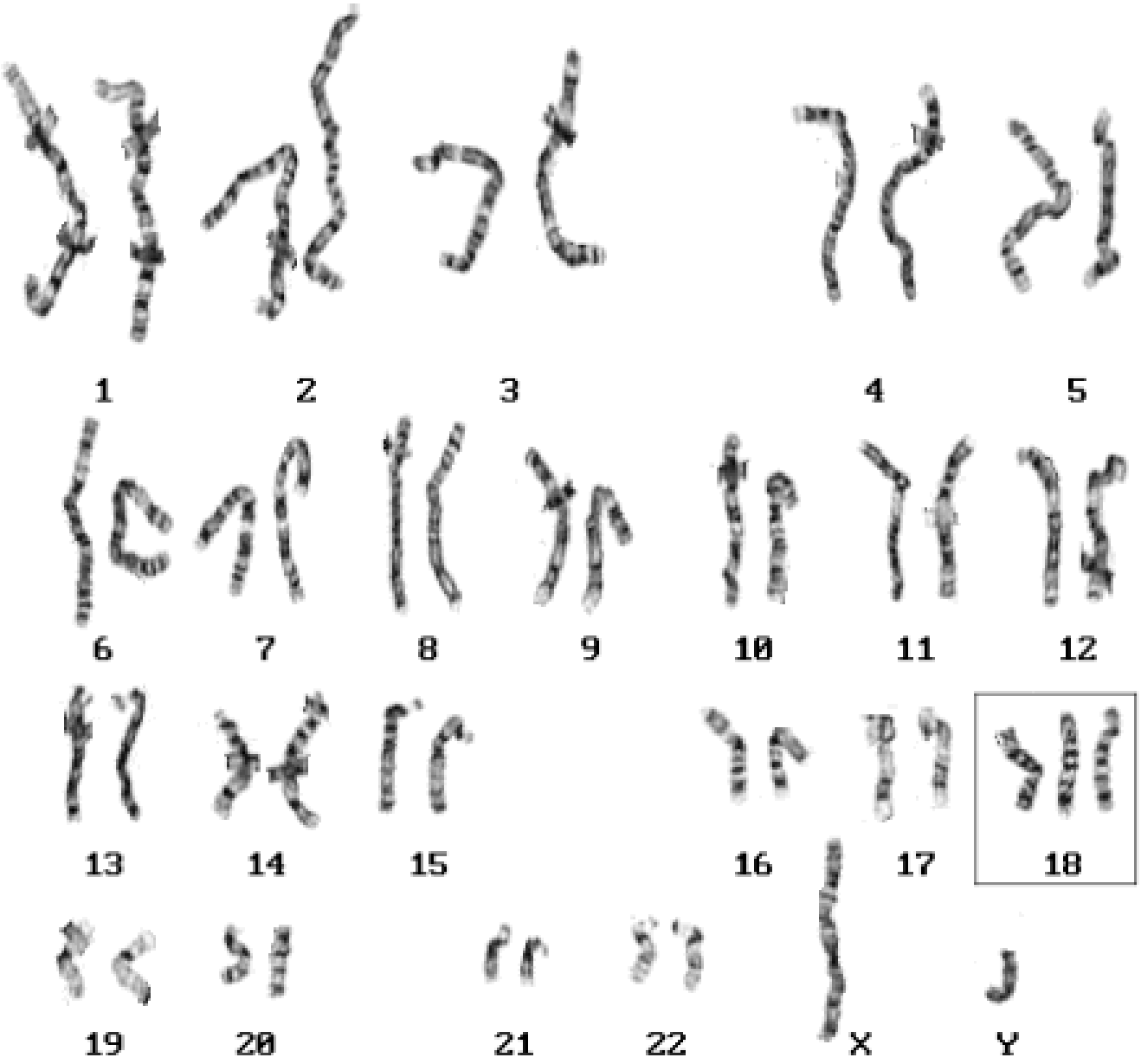


Trisomy	n	Maternal		Paternal		PZM (%)
		MI (%)	MII (%)	MI (%)	MII (%)	
Acrocentrics						
13	74	56.6	33.9	2.7	5.4	1.4
14	26	36.5	36.5	0.0	19.2	7.7
15	34	76.3	9.0	0.0	14.7	0.0
21	782	69.6	23.6	1.7	2.3	2.7
22	130	86.4	10.0	1.8	0.0	1.8
Non-acrocentrics						
2	18	53.4	13.3	27.8	0.0	5.6
7	14	17.2	25.7	0.0	0.0	57.1
8	12	50.0	50.0	0.0	0.0	50.0
16	104	100	0.0	0.0	0.0	0.0
18	150	33.3	58.7	0.0	0.0	8.0

[a]Adapted from Hall *et al.* (6). MI, meiosis I; MII, meiosis II; PZM, post-zygotic mitotic.

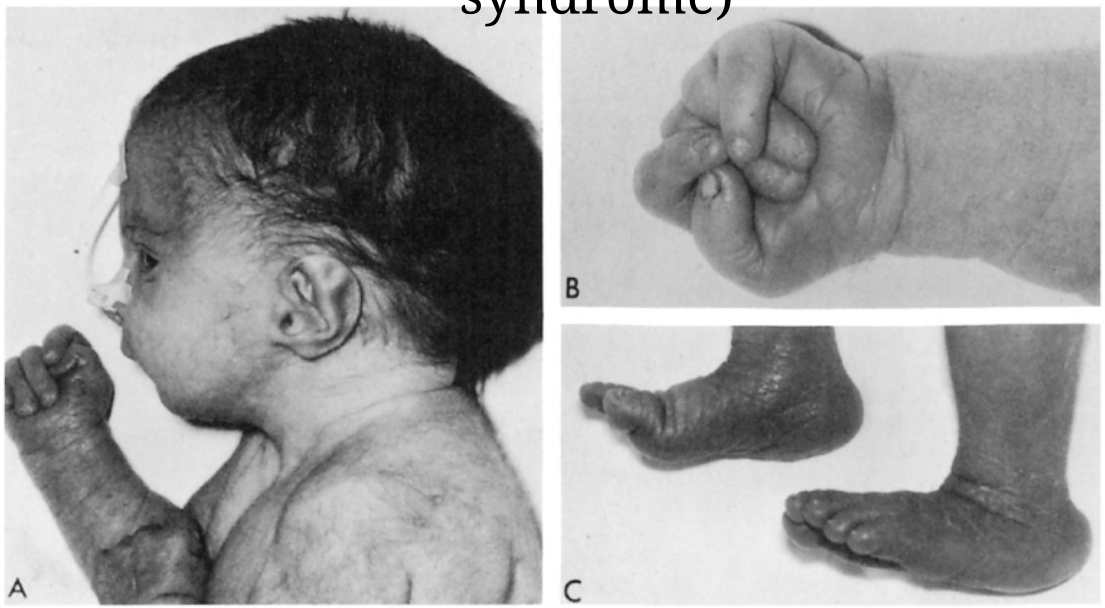
Partial Trisomy 21 (21q)





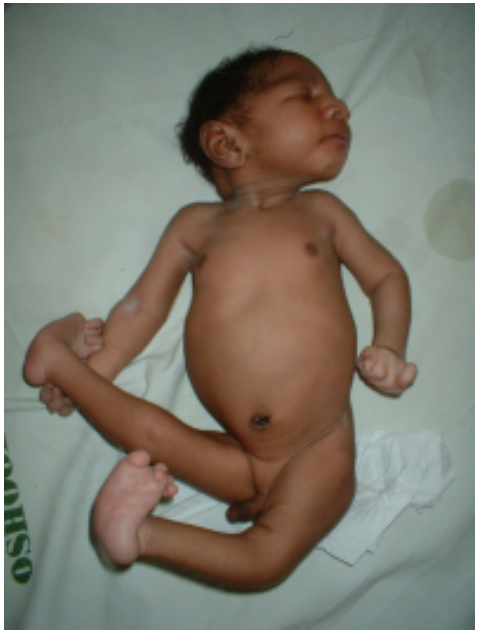
Karyotype: 47,XY,+18

Trisomy 18 (Edward syndrome)

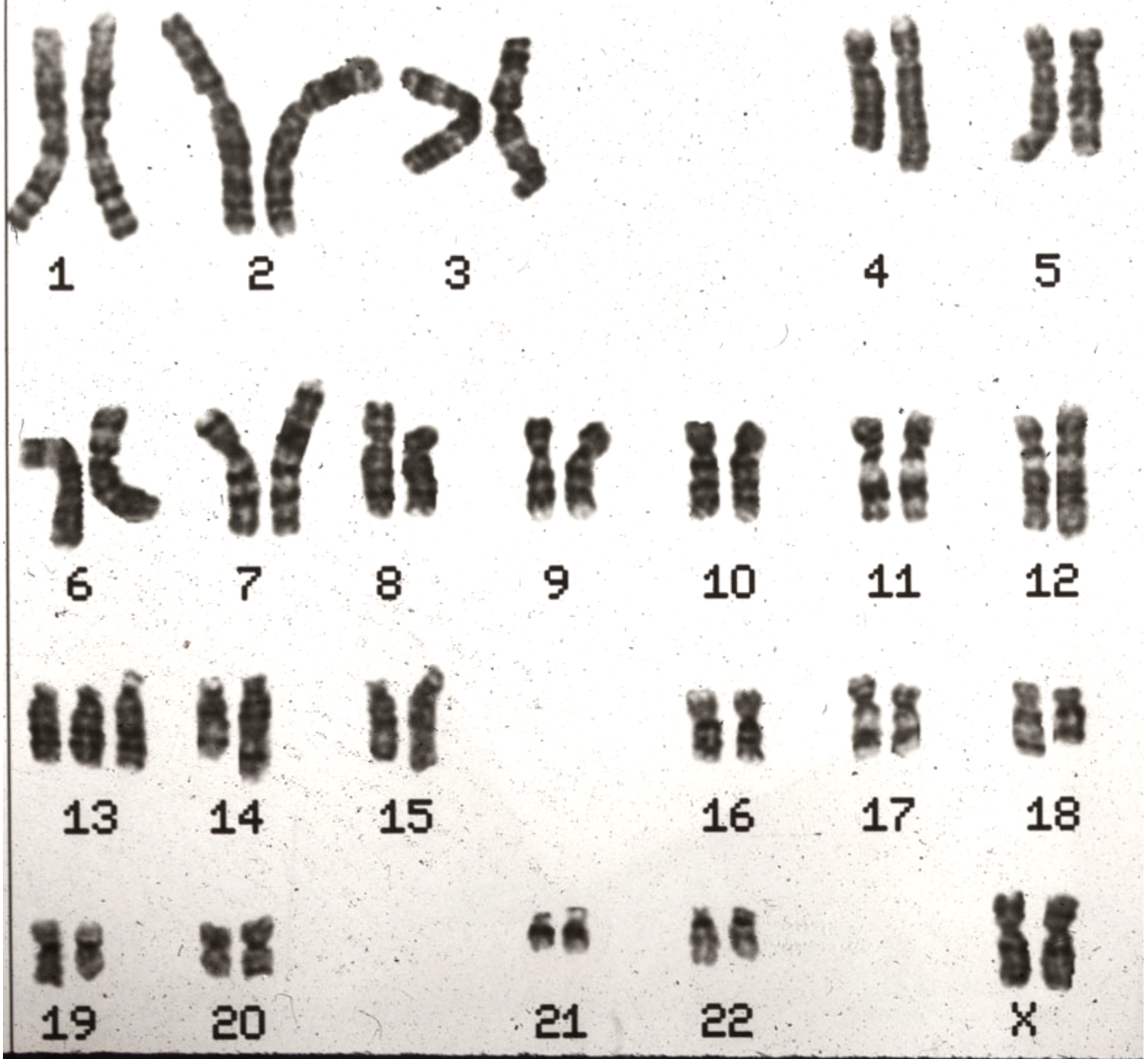


Finding

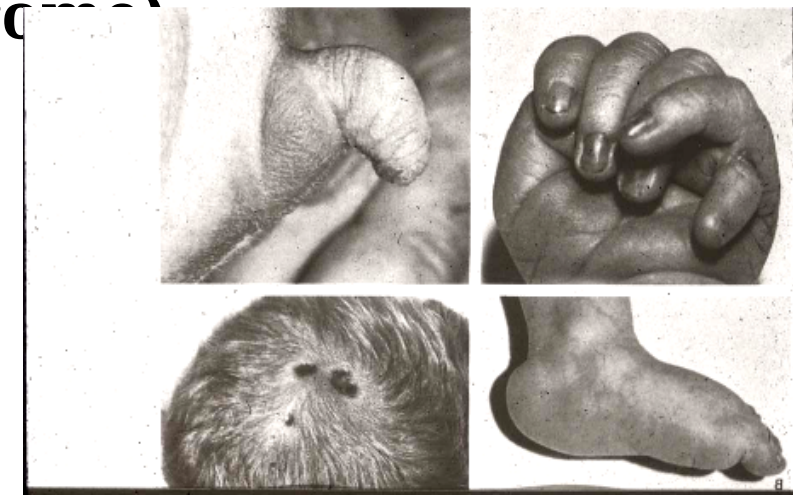
CHD (95%)
Failure to thrive (FTT)
Mental retardation
Growth retardation
Hypertonia
Prominent Occiput



Low-set, malformed ears
Short sternum
Intestinal Abnormalities
Unusual hand position
Rocker bottom feet


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X

Trisomy 13 (Patau syndrome)



Findings:

CHD (85%)
Mental retardation
Hyper- or hypotonia
Scalp defects
Microcephaly
Small eyes
Low-set, malformed ears
Cleft lip/palate
Polydactyly and syndactyly
Polycystic kidneys