

Nondisjunction

Failure of:

(1) chromosome pair to disjoin during MI or

(2) chromatids to separate in MII or mitosis.

- During anaphase I (**meiosis I**), homologous chromosomes separate and migrate to opposite poles.
- During anaphase II (**meiosis II**) and **mitosis**, sister chromatids separate and move to opposite poles.
- Normally, this separation ensures proper and equal distribution of chromosomes.
- ✓ However, if this separation fails to occur, it is called **nondisjunction**, leading to abnormal chromosome numbers.

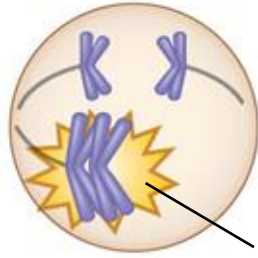
Abnormal Chromosome Number

- 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

- If nondisjunction occurs in *meiosis I*, homologous chromosomes fail to separate and migrate to opposite poles, resulting in daughter cells with abnormal chromosome numbers. All daughter cells will be abnormal: **half will be (n+1) and the other half will be (n-1)**.
- If nondisjunction occurs in *meiosis II*, sister chromatids fail to separate in one of the daughter cells. As a result, **50% of the daughter cells will have a normal chromosome number (n), while 25% will be (n+1) and 25% will be (n-1)**.

Figure 15.13-1

Meiosis I



Nondisjunction

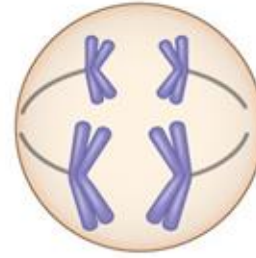
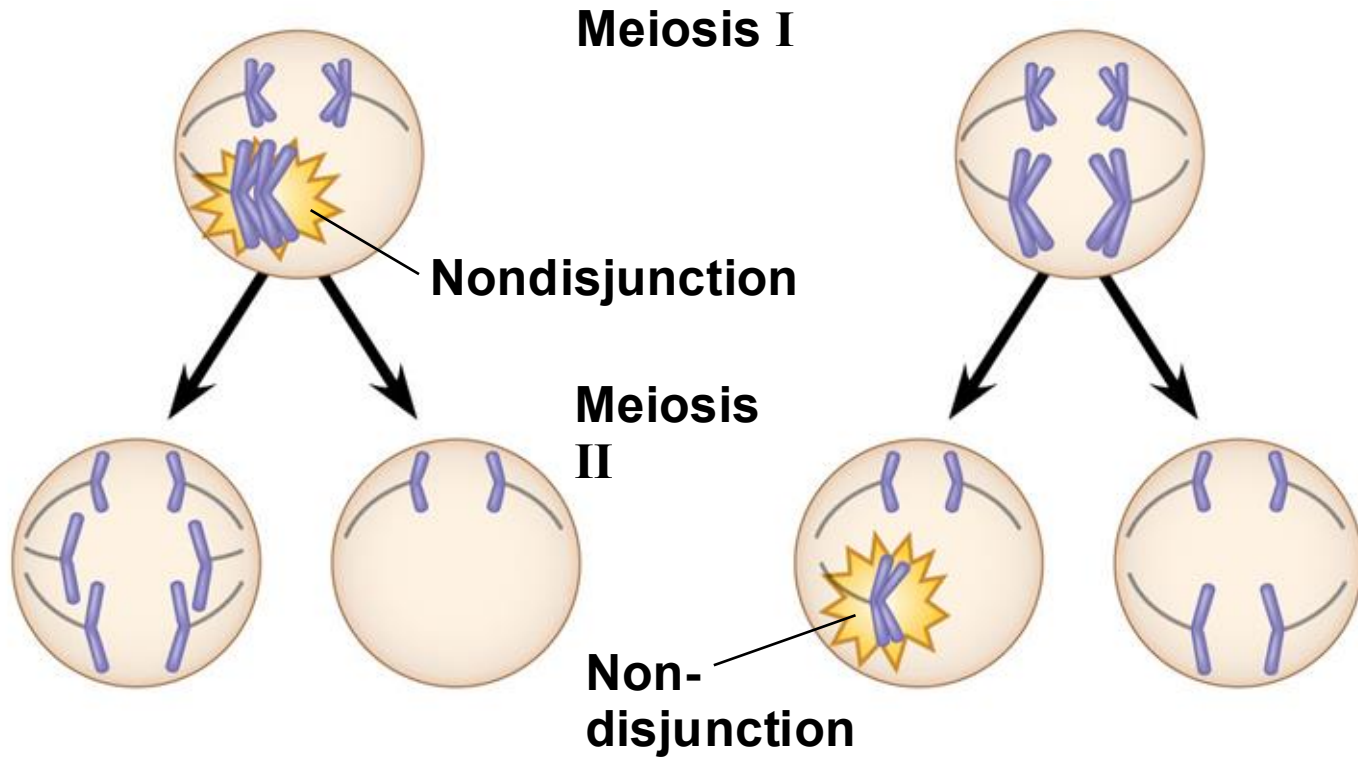
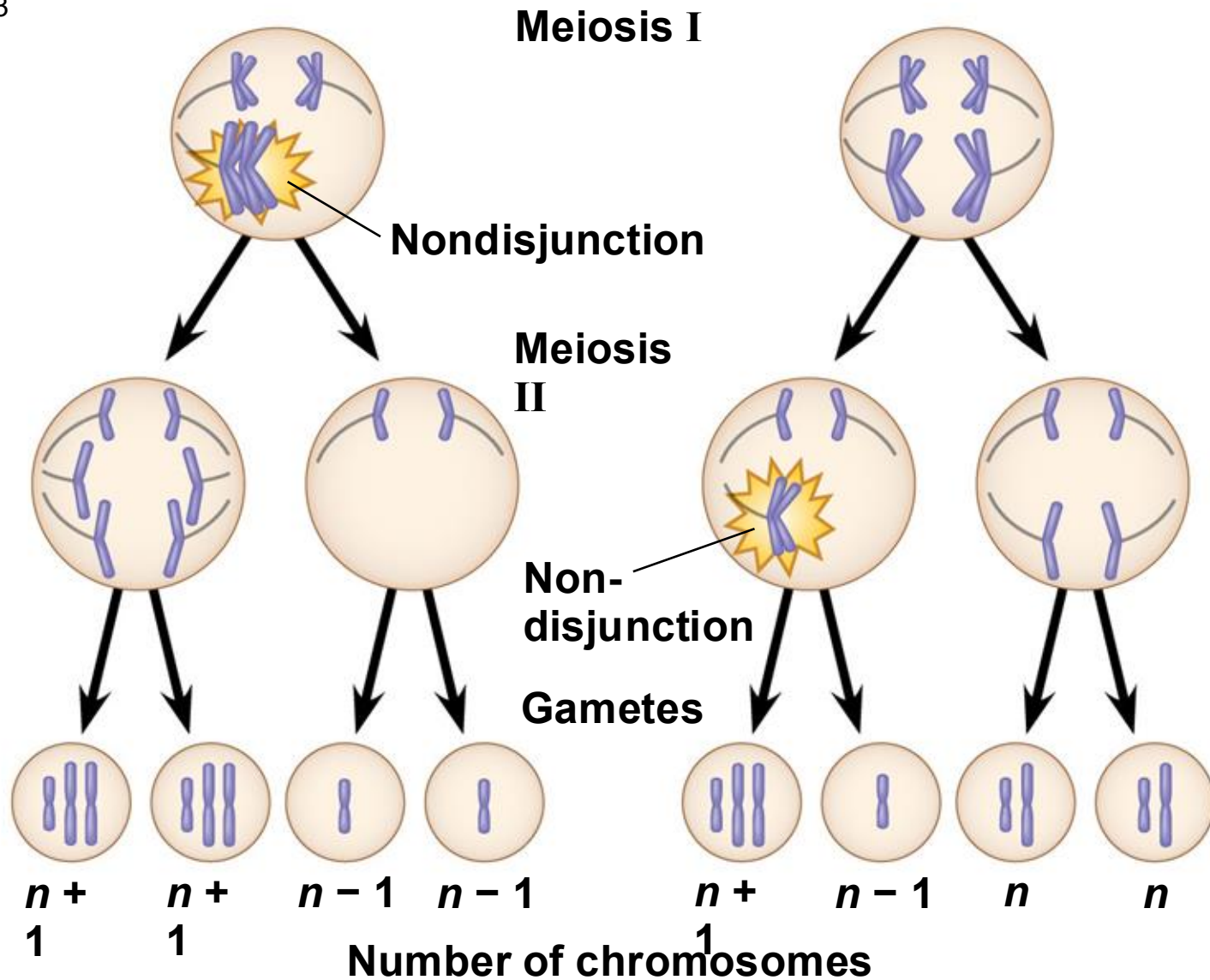


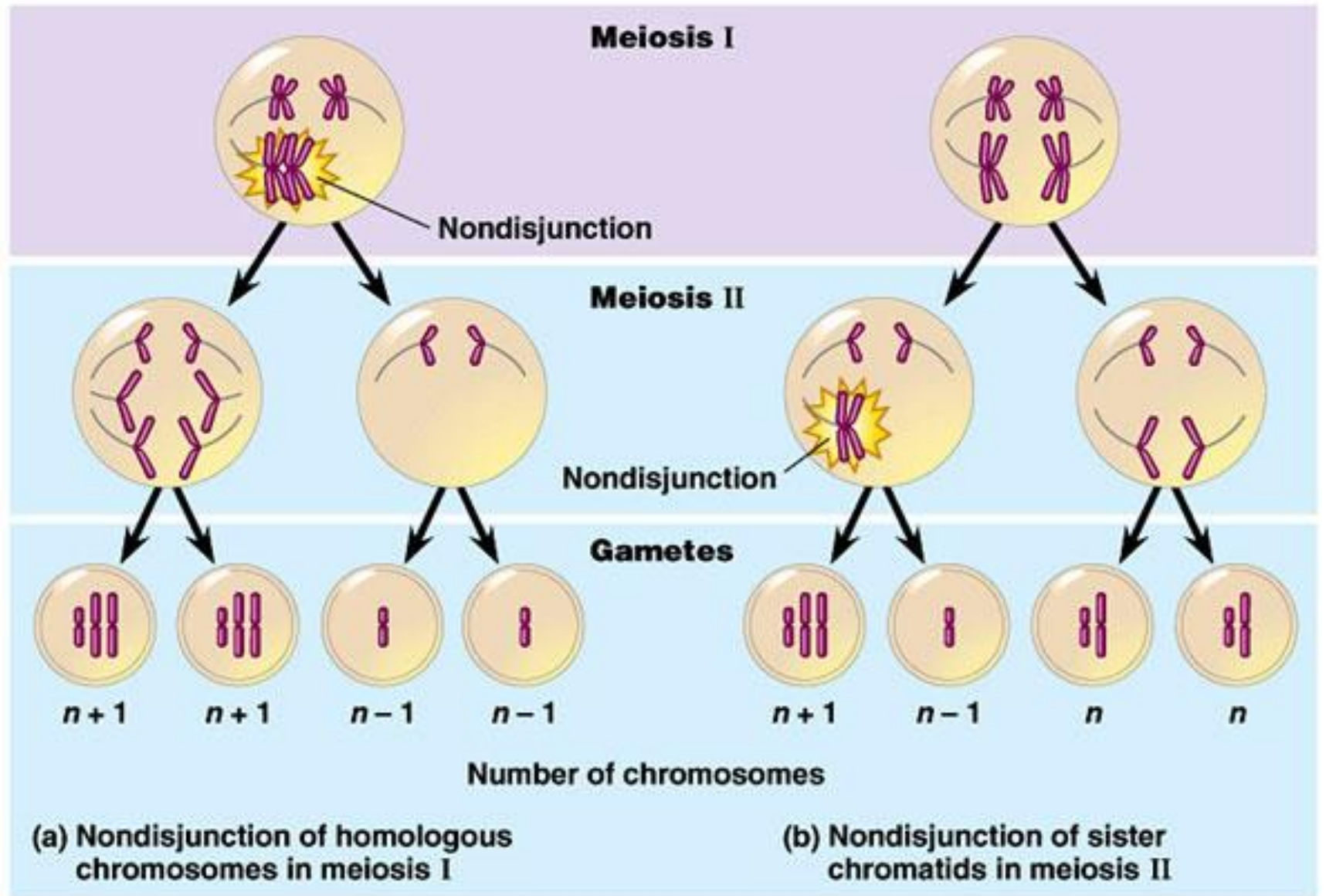
Figure 15.13-2





(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

- *Aneuploidy* is defined as the presence of an **extra or missing** chromosome, resulting in a chromosome number that is not an exact multiple of n .
- Aneuploidy could happen in **sex chromosomes or in autosomal chromosomes**.

- 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.

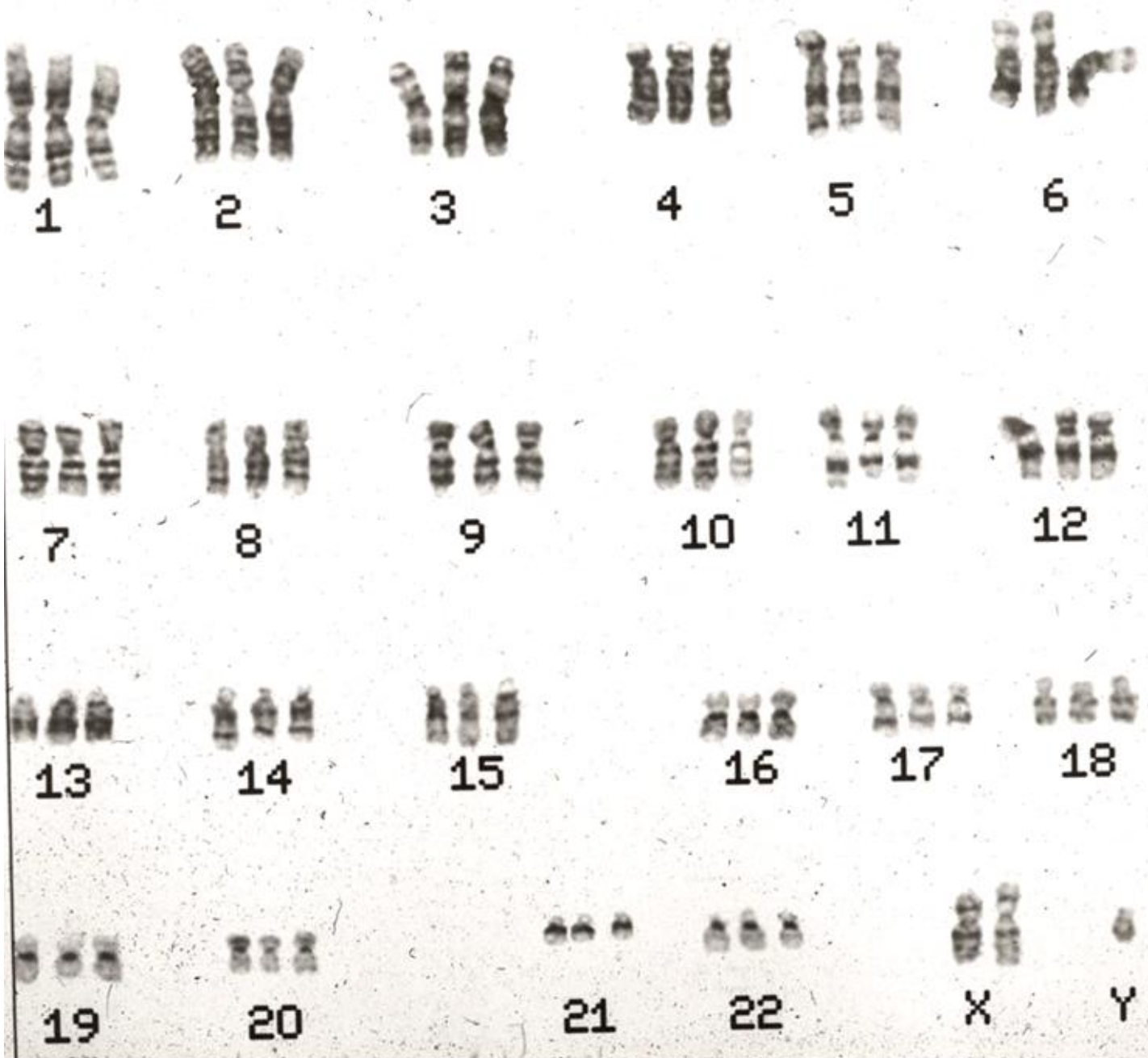
Monosomy

One chromosome of a pair missing.

- **Polyploidy** is a condition in which an organism has more than two complete sets of chromosomes
 - Triploidy ($3n$) is three sets of chromosomes
 - Tetraploidy ($4n$) 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

Number of chromosomes Sex chromosomes

Alterations of Chromosome Structure

There is no extra or missing chromosomes

- 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

➤ **Balanced chromosomal rearrangement:**

A rearrangement in which no genetic material is lost or gained, but the arrangement of the genetic material is abnormal, such as in a **translocation or inversion**.

➤ **Unbalanced chromosomal rearrangement:**

A rearrangement in which there is extra or missing genetic material, such as a **deletion or duplication**.

(a) Deletion



A deletion removes a chromosomal segment.



(b) Duplication

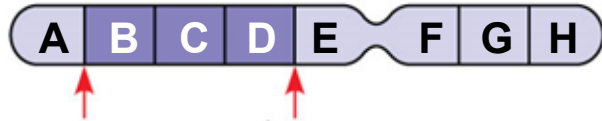


A duplication repeats a segment.



- ✓ A chromosomal inversion occurs when a segment of a chromosome breaks off, flips 180°, and reinserts into the same chromosome again. This changes the gene order without any loss of genetic material.

(c) Inversion



An inversion reverses a segment within a chromosome.



(d) Translocation



A translocation moves a segment from one chromosome to a nonhomologous chromosome.



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- ✓ A translocation is an exchange of genetic material between two chromosomes. A segment from one chromosome is cut and exchanged with a segment from another chromosome.

❖ What is the difference between recombination and translocation?

- ✓ *Recombination* is a **normal** physiological process that occurs between non-sister chromatids of homologous chromosomes, usually during prophase I of meiosis. It does **NOT** cause disease.
- ✓ *Translocation* is an exchange of genetic material between non-homologous chromosomes. It could be **pathological** and may lead to disease, such as the classic **t(9;22) translocation** causing **chronic myeloid leukemia**.

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 *Klinefelter Syndrome*

47,XYY

✓ If an individual has a **Y chromosome**, regardless of the number of X chromosomes, they will develop as **MALE** because the Y chromosome contains a region that directs male sexual development.

1/1000

1/1000

Females (24,547 newborns)

45,X *Turner Syndrome*

47,XXX

1/5000

1/1000

Autosomal Aneuploidy (68,159 newborns)

Trisomy 21 *Down Syndrome*

Trisomy 18

Trisomy 13

1/800

1/6000

1/10,000

Structural Abnormalities (68,159 newborns)

(Sex chromosomes and autosomes)

✓ **Balanced rearrangements**

Robertsonian

Other (reciprocal and others)

1/1000

1/885

✓ **Unbalanced rearrangements**

1/17,000

All Chromosome Abnormalities

Autosomal disorders and unbalanced rearrangements

Balanced rearrangements

1/230

1/500

Total

1/154

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

Risk of Down syndrome in live births (%)

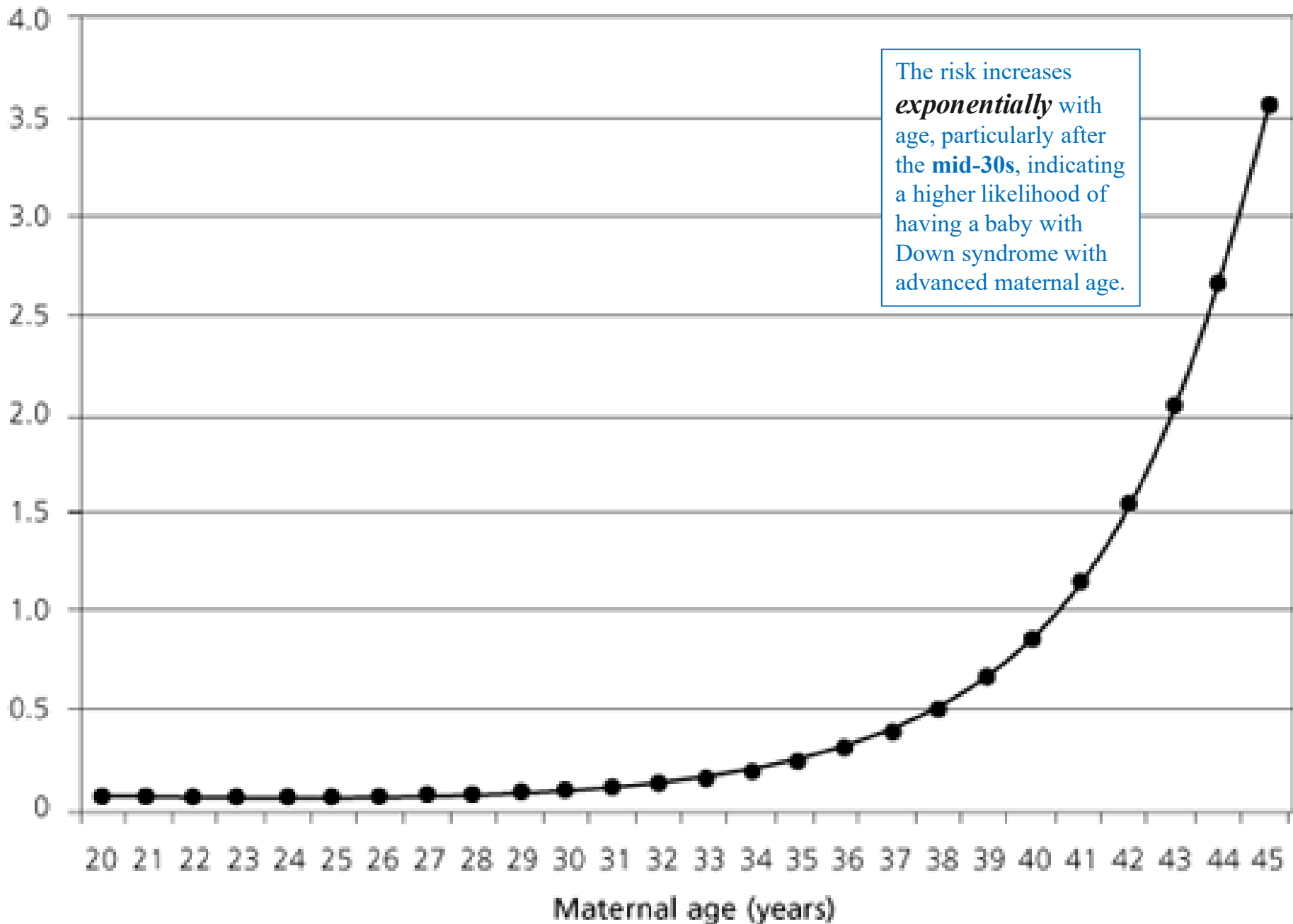
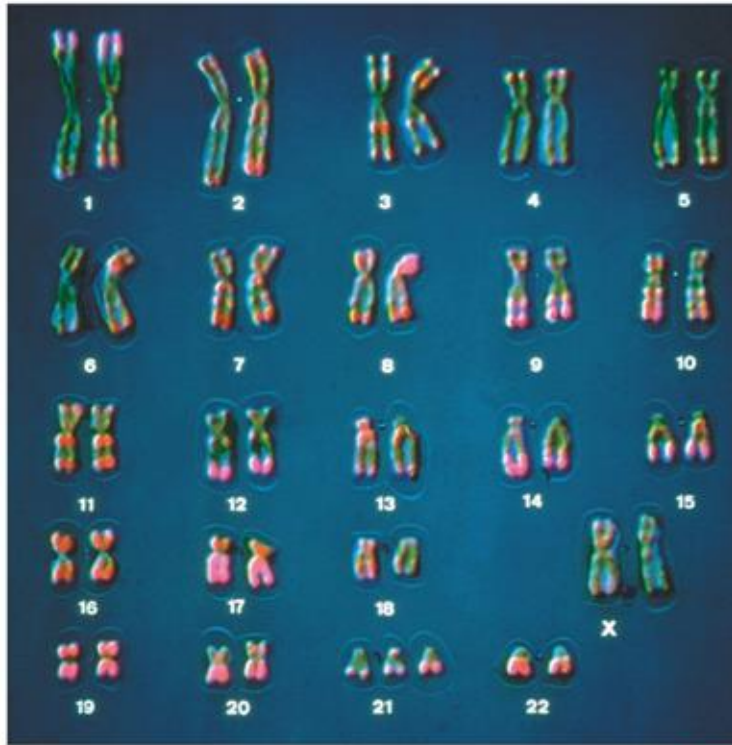


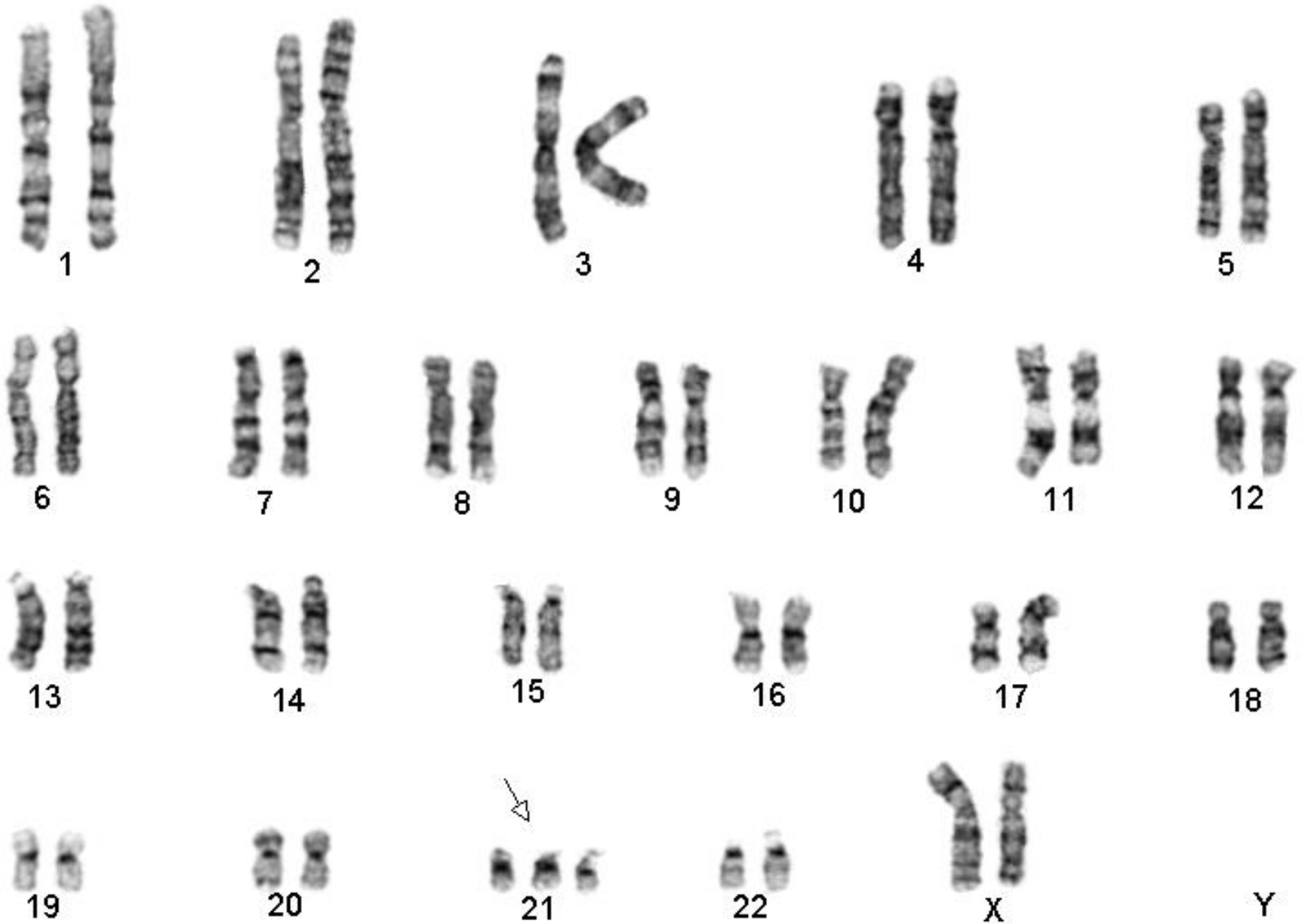
Figure 15.15

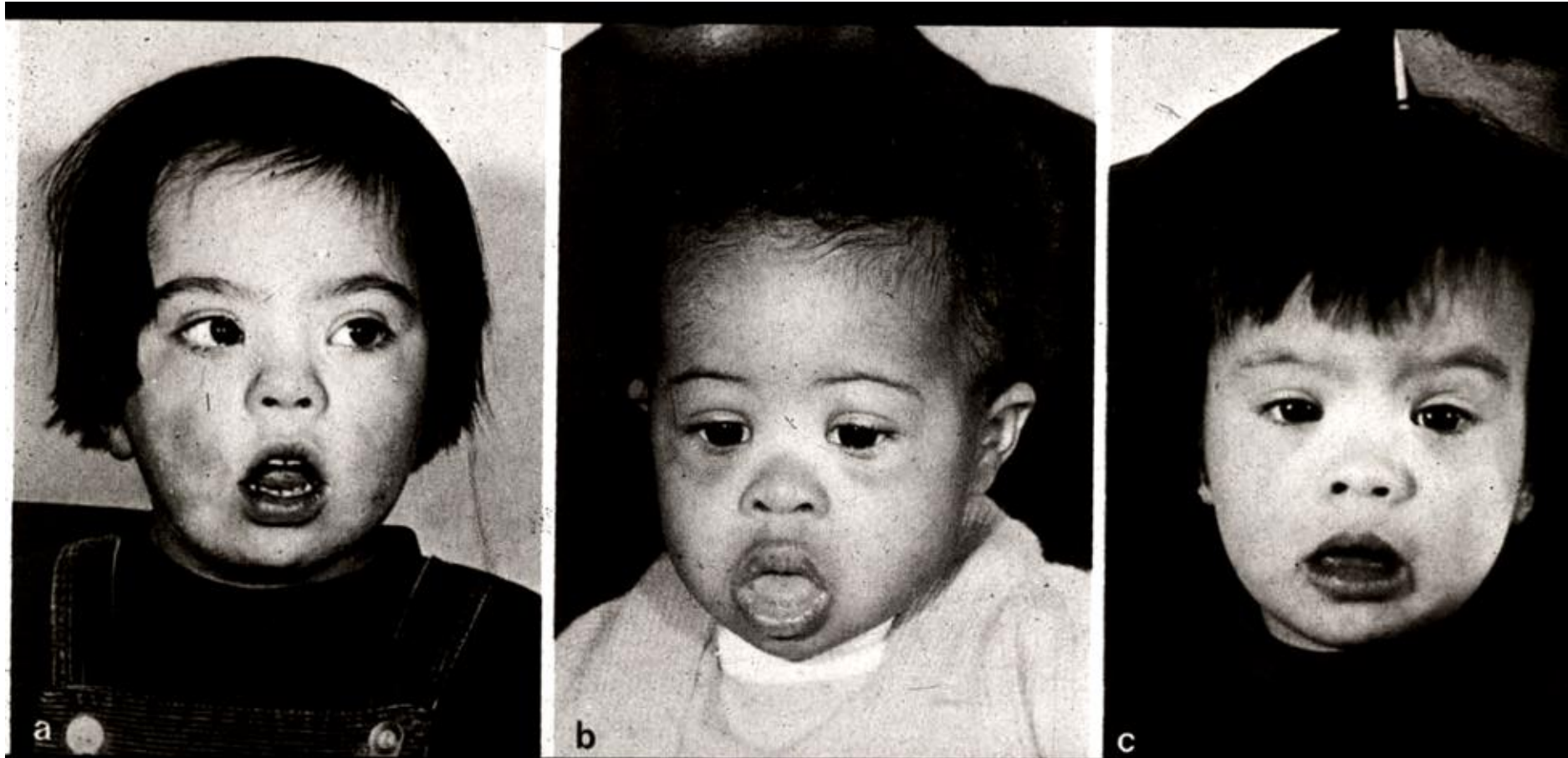


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Trisomy 21 occurs due to nondisjunction during **oogenesis**, meaning there is an increased rate of nondisjunction, especially with advanced maternal age. For unknown reasons, the male to female ratio in Down syndrome is **skewed**, with **more affected MALES** than **FEMALES**.

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





Male:Female Ratio - 3:2

Down Syndrome



Intellectual disability

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%)**

*Epicanthic folds

Protruding tongue

Intestinal problems

Gap between first and second toes

15-fold increase in risk for leukemia

*Simian line (transverse crease) (45%)

**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.

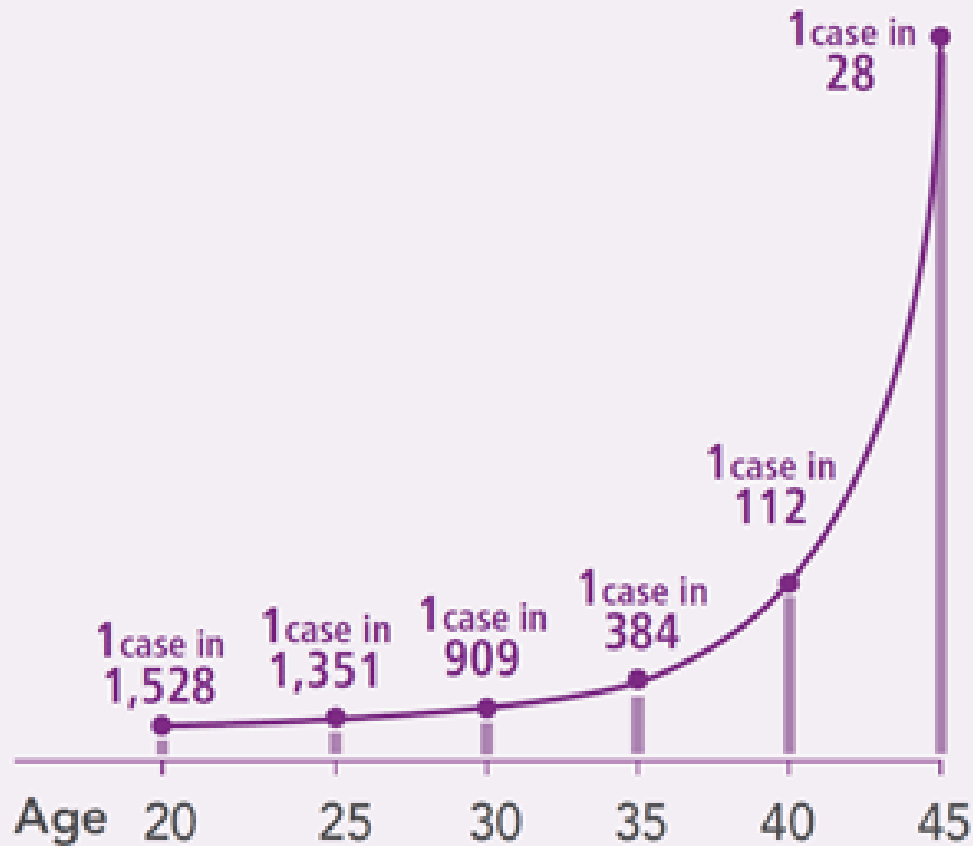
- ✓ **Hypotonia** is a state of low [muscle tone](#) (the amount of tension or resistance to stretch in a muscle), often involving reduced muscle strength
- ✓ CDH: Coronary heart disease narrowing of the small blood vessels that supply blood and oxygen to the heart. CHD is also called coronary artery disease.
- ✓ simian crease is a single line that runs across the palm of the hand.



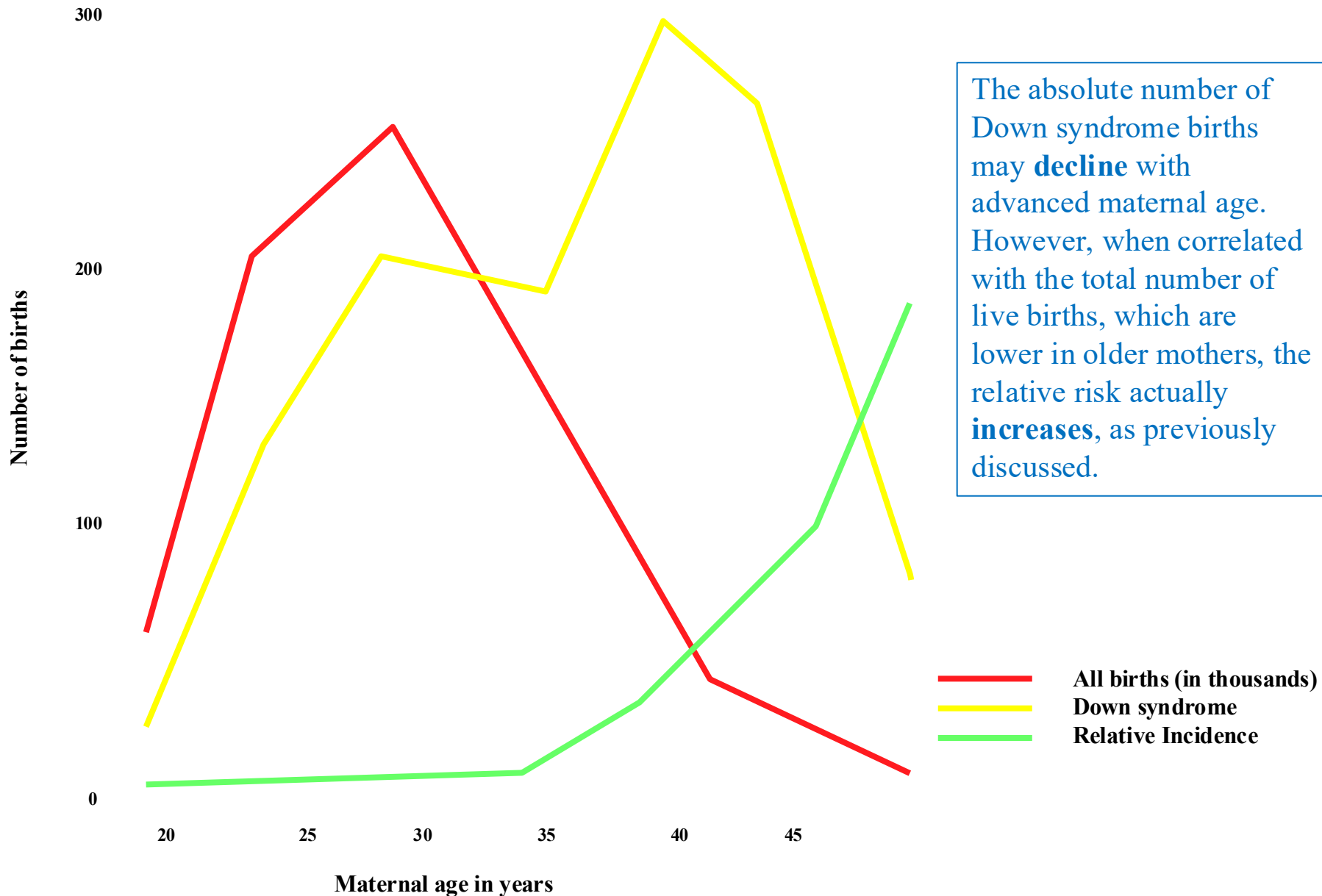
Distinct facial feature

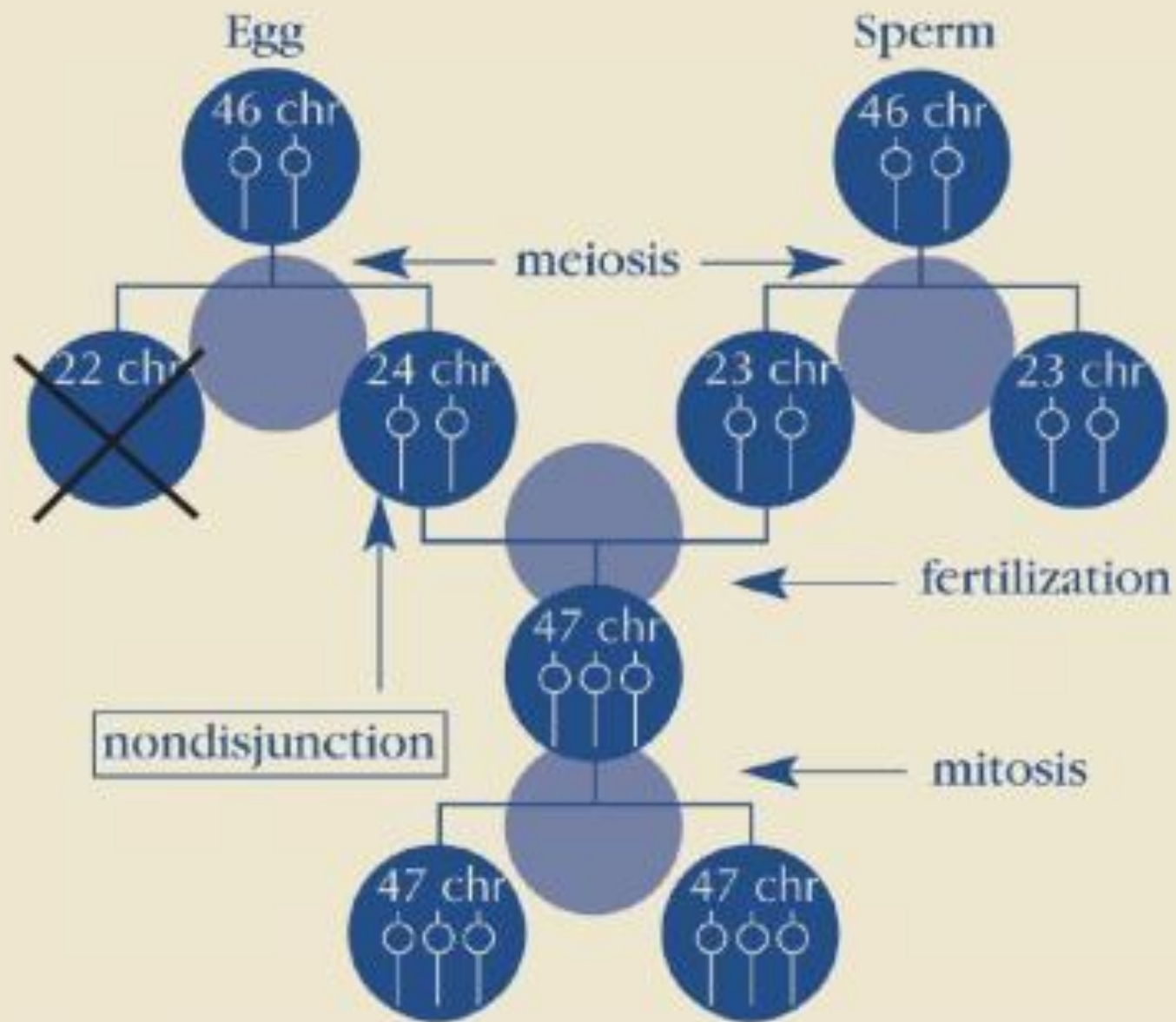
1 in 770 babies

PROBABILITY OF GIVING BIRTH TO A BABY WITH TRISOMY 21 BY WOMAN'S AGE

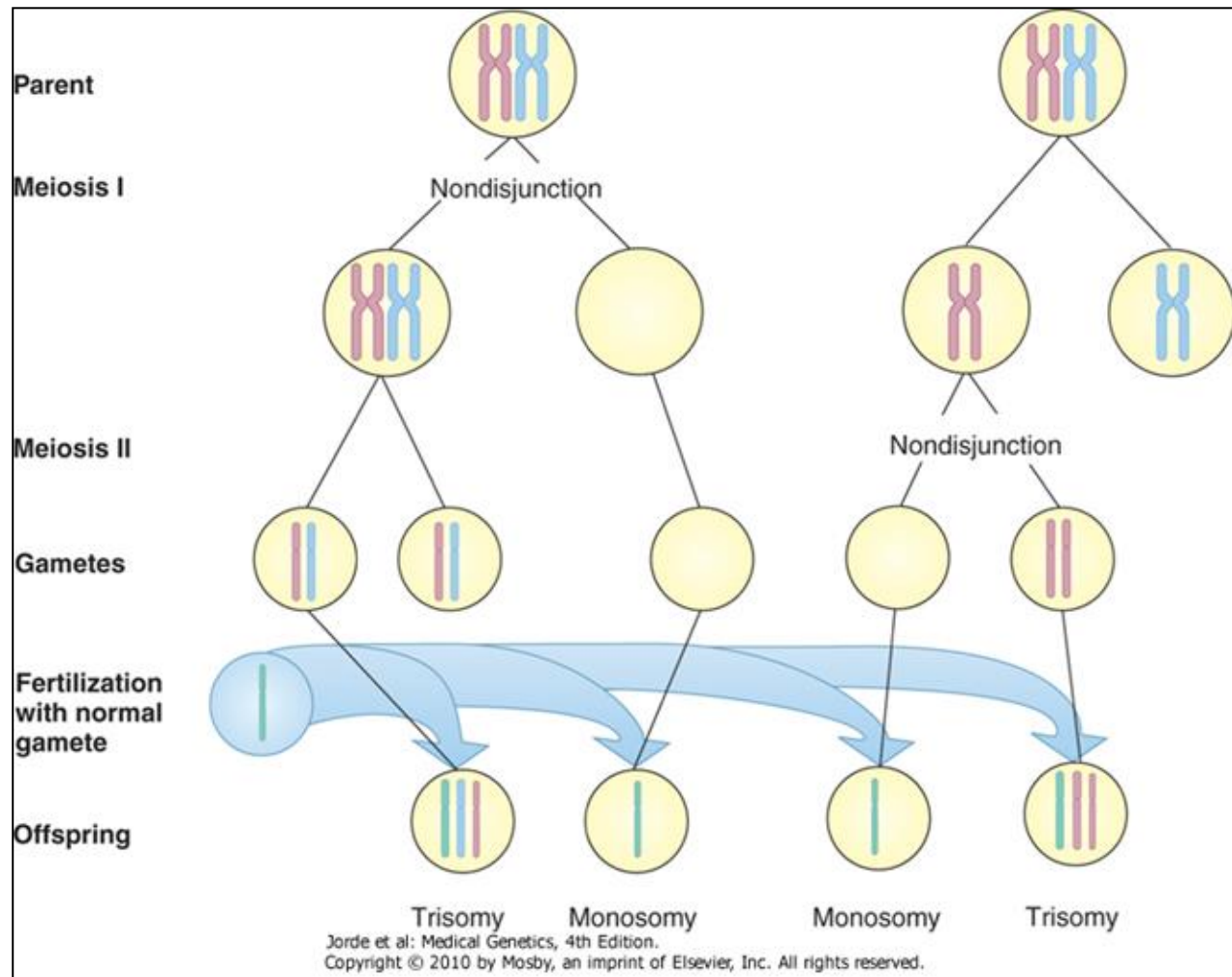


Maternal Age and Nondisjunction





Trisomy 21



➤ Maternal Errors: 94% of cases

- MI 64%
- MII 19%
- Indeterminate 11%

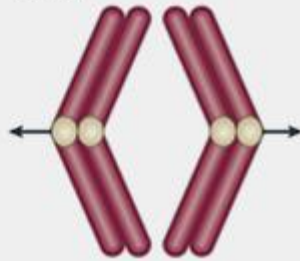
➤ Paternal Errors: 4.5% of cases

- MI 1%
- MII 3.5%

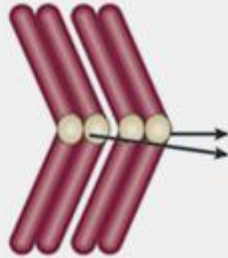
➤ Unknown: 1.5%

Meiosis I

Normal

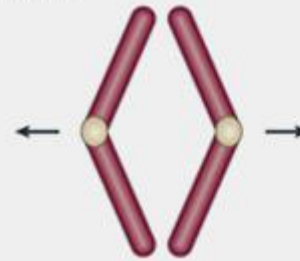


'True' non-disjunction

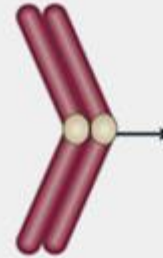


Meiosis II

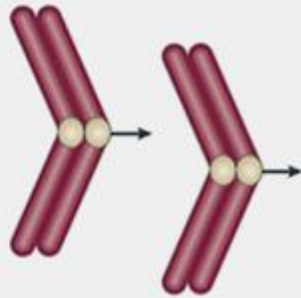
Normal



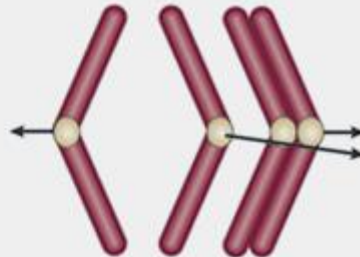
Non-disjunction



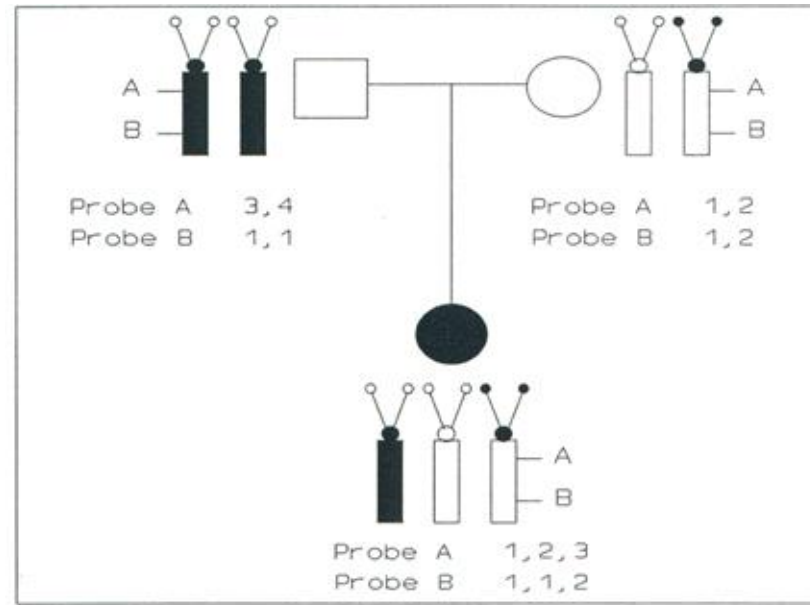
'Achiasmate' non-disjunction



Premature separation of sister chromatids



Causal Factors in Nondisjunction



See the next slide

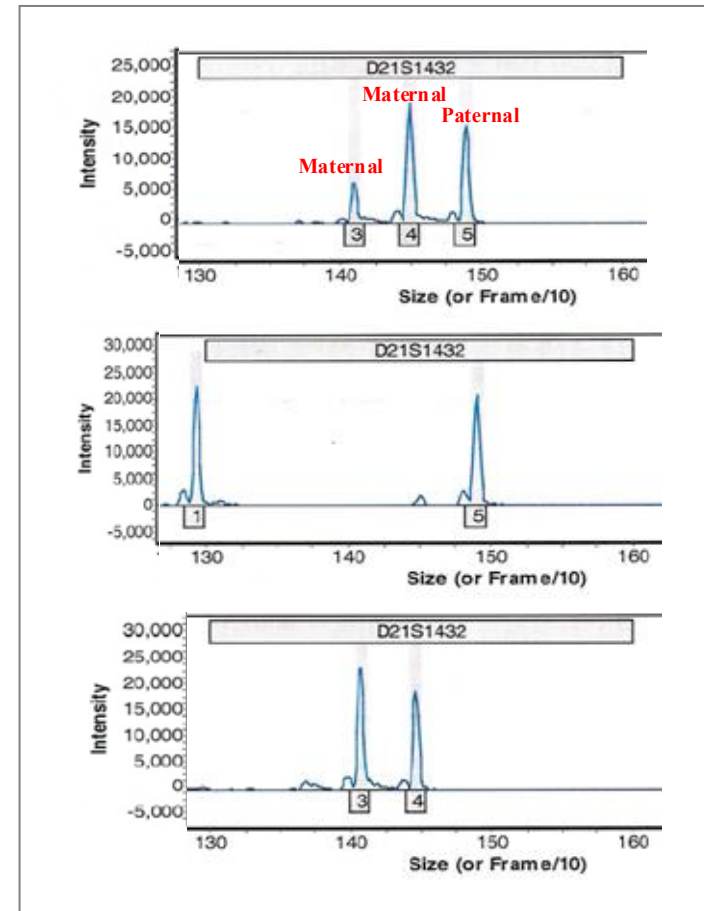
- It is possible to determine whether trisomy 21 is due to paternal or maternal nondisjunction by studying the three chromosomes present in a Down syndrome patient and comparing them to those of the parents.
- Chromosome 21 contains regions known as **polymorphic regions**. This polymorphism may be in the form of variation in repeat numbers. At certain regions on chromosome 21, there are DNA sequences that are repeated multiple times. These regions are typically non-coding, meaning they do not contain genes, but instead consist of repeated DNA sequences.
- For example, a sequence of three nucleotides, such as CCG, may be repeated a variable number of times. **The number of repeats can differ between the paternal and maternal chromosomes at the same region.**

- At a specific region (**region A**), the father may have repeat numbers 3 and 4, while the mother has repeat numbers 1 and 2. At another region (**region B**), the father may have repeats 1 and 1, and the mother has repeats 1 and 2. Each parent has two homologous chromosomes 21, and therefore two repeat values at each region.
- In a Down syndrome patient, three copies of chromosome 21 are present. Accordingly, when examining these regions, three repeat values will be detected.
- ✓ For example, at region A, the repeats may be 1, 2, and 3, while at region B, the repeats may be 1, 1, and 2.
- To determine the origin of the extra chromosome, these repeat patterns are analyzed. At region B, the repeat “2” is present only in the mother, indicating that one of the three chromosomes is of maternal origin. However, based on this region alone, it is not possible to determine whether the extra chromosome originated from the mother or the father, as the remaining repeats (1 and 1) could be derived from either parent.
- Therefore, a **more informative region must be examined**, such as region A. In region A, repeats 1 and 2 correspond to the mother, while repeat 3 corresponds to the father. This indicates that two chromosomes were inherited from the mother and one from the father, confirming that the extra chromosome is of **maternal origin**.

Evaluate the Origin of the Extra Chromosome Using Polymorphic Markers

- These regions represent **short tandem repeats (STRs)**, including tetranucleotide repeats in some cases. Such STRs are widely distributed along chromosomes and exhibit variability among individuals. Each chromosome produces a detectable signal for these STR markers, allowing comparison between parental and patient alleles.
- Markers on chromosome 21 (e.g., **D21S1432**) enable counting of repeat numbers and tracing the origin of the extra chromosome.
- In genetics, the **proband** refers to the individual who brings the family to clinical attention, typically (but not always) the patient. In this case, the Down syndrome patient has three chromosomes 21, each with a repeat value at a given marker. By tracing these repeats, it can be determined whether each chromosome is of maternal or paternal origin; in this example, the extra chromosome is of **maternal origin**.

Proband



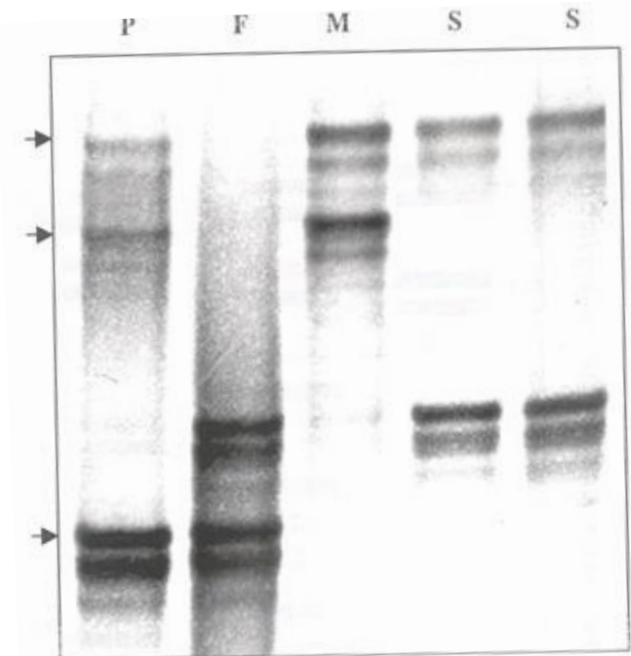
Father

Mother

D21S1432
Tetranucleotide STRP

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

- This figure demonstrates **gel electrophoresis analysis** based on the same principle used to determine the parental origin of chromosome 21 using STR markers.
- PCR amplification is performed using specifically designed primers that flank the short tandem repeat (STR) region. Because the number of repeats varies between individuals, the amplified DNA fragments **differ in size**. During gel electrophoresis, DNA fragments separate according to size; larger fragments migrate more slowly, while smaller fragments migrate faster, producing bands at **different positions** on the gel.
- In the parents, two bands are observed, representing the two homologous chromosome 21 copies inherited from each parent. The STR repeat in the mother is larger, therefore its band migrates more slowly compared to the paternal fragment.
- In the normal siblings, two bands are present: one inherited from the father and one from the mother, reflecting the normal diploid state.
- In contrast, **the proband (Down syndrome patient)** shows three bands corresponding to three copies of chromosome 21. Two of these bands match the maternal pattern, while one band matches the paternal pattern, indicating that the extra chromosome 21 is of **maternal origin**.



- ✓ The lanes represent the proband (P), father (F), mother (M), and siblings (S). Each band corresponds to one copy of chromosome 21 carrying a specific STR repeat length.

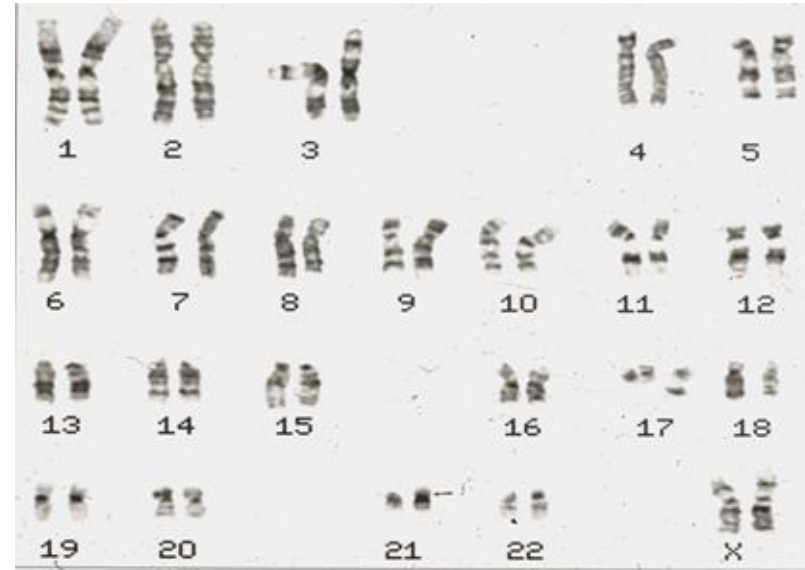
Trisomy	n	Maternal		Paternal		PZM (%)
		MI (%)	MII (%)	MI (%)	MII (%)	
<i>Acrocentrics</i>						
13	74	56.6	33.9	2.7	5.4	1.4
14	26	36.5	36.5	0.0	19.2	7.7
15	34	76.3	9.0	0.0	14.7	0.0
21	782	69.6	23.6	1.7	2.3	2.7
22	130	86.4	10.0	1.8	0.0	1.8
<i>Non-acrocentrics</i>						
2	18	53.4	13.3	27.8	0.0	5.6
7	14	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

^aAdapted from Hall *et al.* (6). MI, meiosis I; MII, meiosis II; PZM, post-zygotic mitotic.

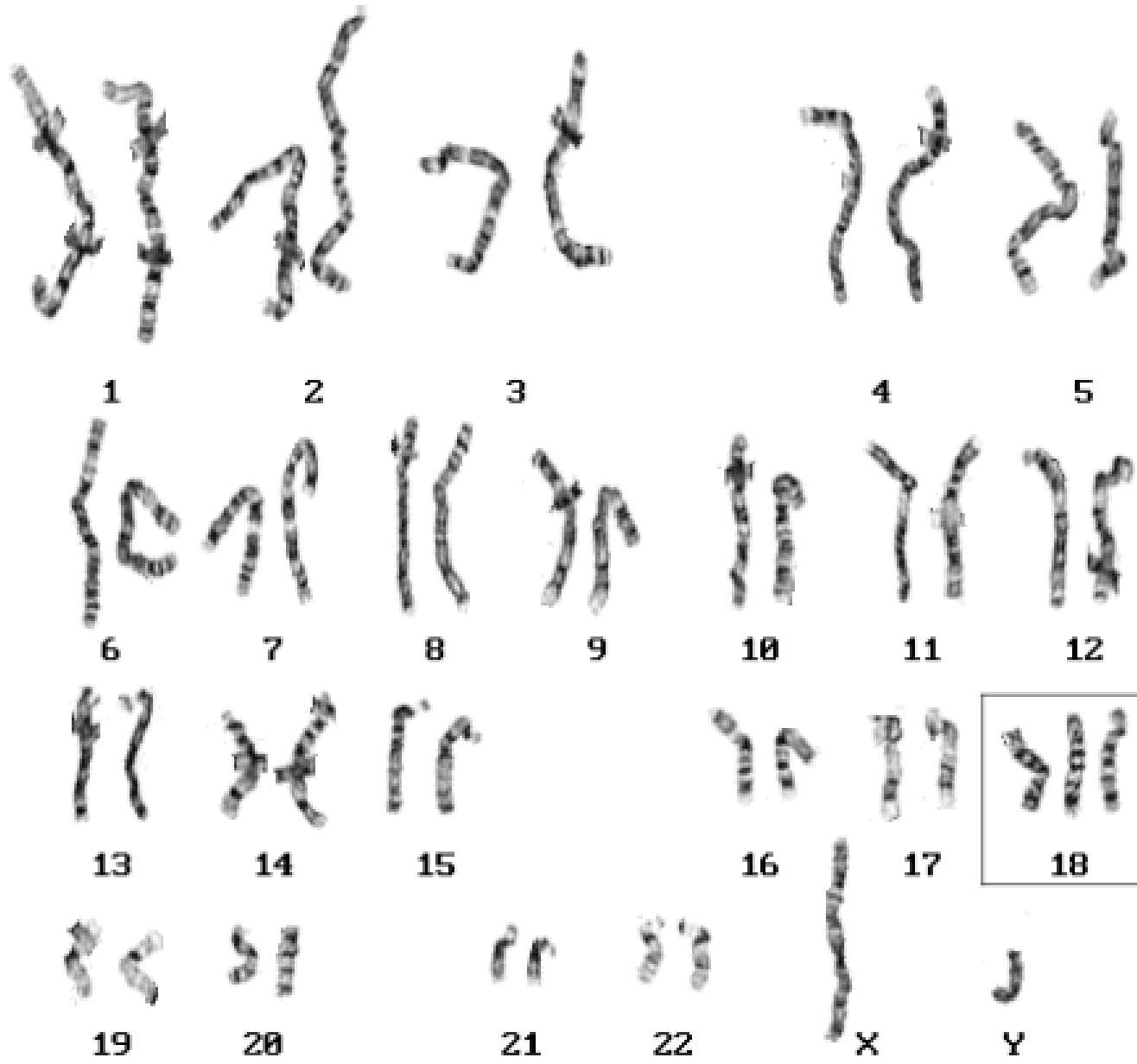
- Non-disjunction can occur during zygotic mitosis. It may involve **acrocentric or non-acrocentric** chromosomes, and in fact, non-disjunction can affect any chromosome. The paternal and maternal chromosomal contributions can therefore be observed across different chromosomes.
- **Trisomy 21** resulting from non-disjunction associated with **advanced maternal age** is not applicable to other chromosomal non-disjunction events.

Partial Trisomy 21 (21q)

- If you examine the karyotype including chromosome 21, you will observe two entities. There is no extra chromosome 21 present as a separate chromosome. Instead, chromosome 21 — which is an **acrocentric chromosome** — contains a q arm and a p arm.
- The p arm is NOT clinically relevant in this context because loss or gain of the p arm of an acrocentric chromosome usually has no clinical significance.
- In this karyotype, one chromosome 21 shows a **centromere attached to two q arms**. These two q arms result from an abnormal chromosomal arrangement, most likely inherited from one of the parents.
- Therefore, there are effectively **three q arms** of chromosome 21 present:
 - ✓ **one q arm from a normal chromosome 21**
 - ✓ **another q arm from the second chromosome 21**
 - ✓ **an additional q arm attached abnormally**
- Since the clinically important genetic material in acrocentric chromosomes is located in the **q arm**, *this arrangement is equivalent to having three copies of chromosome 21 genetic material.*
- Thus, even though this individual **has 46 chromosomes**, one chromosome 21 carries two q arms, functionally **equivalent to a complete third chromosome 21**, resulting in **partial trisomy 21**.

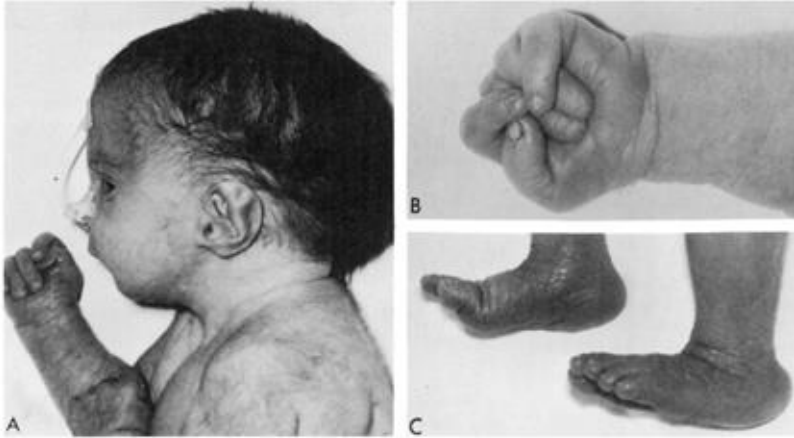


- ❖ **If this abnormal chromosome originated from one parent — for example from the sperm — while the other chromosome 21 came from the egg, the question becomes: how many chromosomes did the father have?**
- If the father was clinically normal, he most likely had **45 chromosomes**, not 46 or 47.
- This suggests that the father carried **only one chromosome 21**, but that chromosome contained two q arms (a rearranged chromosome 21). Despite this abnormal arrangement, he could remain **clinically normal** because there is no loss or gain of essential genetic material (balanced rearrangement).
- During spermatogenesis:
 - ✓ 50% of the sperms will carry the chromosome with **two q arms**.
 - ✓ 50% of the sperms will be **missing chromosome 21**.



Karyotype: 47,XY,+18

Trisomy 18 (Edward syndrome)



➤ Findings:

- ✓ CHD (95%) **congenital heart disease**
- ✓ Failure to thrive (FTT)*
- ✓ Mental retardation
- ✓ Growth retardation
- ✓ **Hypertonia**
- ✓ Prominent Occiput
- ✓ Low-set, malformed ears
- ✓ Short sternum
- ✓ Intestinal Abnormalities
- ✓ Unusual hand position (**clenched fist**) where the fingers are flexed in a specific, abnormal manner
- ✓ Rocker bottom feet

***Failure to thrive** (FTT), more recently known as faltering weight or weight faltering, is a term used in pediatric and adult medicine, as well as veterinary medicine (where it is also referred to as ill thrift), to indicate insufficient weight gain or inappropriate weight loss.



Trisomy 13 (Patau syndrome)

➤ Findings:

- CHD (85%)
- Mental retardation (intellectual disability, which is a key feature in most of chromosomal abnormalities)
- Hyper- or hypotonia
- Scalp defects
- Microcephaly (head circumference is smaller)
- Small eyes
- Low-set, malformed ears
- Cleft lip/palate
- Polydactyly and syndactyly*
- Polycystic kidneys
- Rocker-bottom feet



*Syndactyly (from Greek συν- = "together" plus δακτυλος = "finger") is a condition wherein two or more digits are fused together

- The only **viable** autosomal numerical abnormalities are **trisomy 13, 18, and 21**.
- ❖ Does that mean nondisjunction only happens in trisomy?
- ✓ No. Trisomy can happen to any chromosome. However, only these three trisomies can **survive to birth**. Most other trisomies are **lethal during pregnancy**, but a small percentage of trisomy 13, 18, and 21 reach life.
- ❖ What about *monosomies* ?
- ✓ Monosomy can also occur for chromosomes 13, 18, and 21, but they are **lethal and do NOT survive to birth**.
- Even though trisomy adds extra genetic material and causes severe clinical manifestations, **monosomy is even more deleterious**, to the point that **affected embryos do not survive**.
- Extra genetic material (trisomy) is *less harmful* than missing genetic material (monosomy).