Genetics

Modified no. 11

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بسم الله الرحمن الرحيم

Clinical cytogenetics

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Autosomal Aneuploidy

- Aneuploid

Euploidy means the cell has a normal or exact multiple of the full set of 23 chromosomes (like 46, 69, or 92 chromosomes).

Aneuploidy means the cell has an **abnormal number** of individual chromosomes (like 45 or 47), not a full set difference., increase or decrease in the number of a single set of chromosomes

- Monosomy

One copy of chromosome , eg; monosomy X, Monosomy 13

Not compatible with life Because a deletion of chromosome means a deletion of thousands of genes , must of them dies in the first trimester

- Trisomy

Extra chromosomes ,

Seen in live Births with small chromosomes Trisomy eg Trisomy 13, Trisomy 18, Trisomy 21

→ ***the body can tolerate excess genetic material more readily than it can tolerate a deficit of genetic material***

- ***nondisjunction***

The reason behind Aneuploidy

Means that chromosomes failed to disjoin /separate, leading to increase or decrease in chromosomes

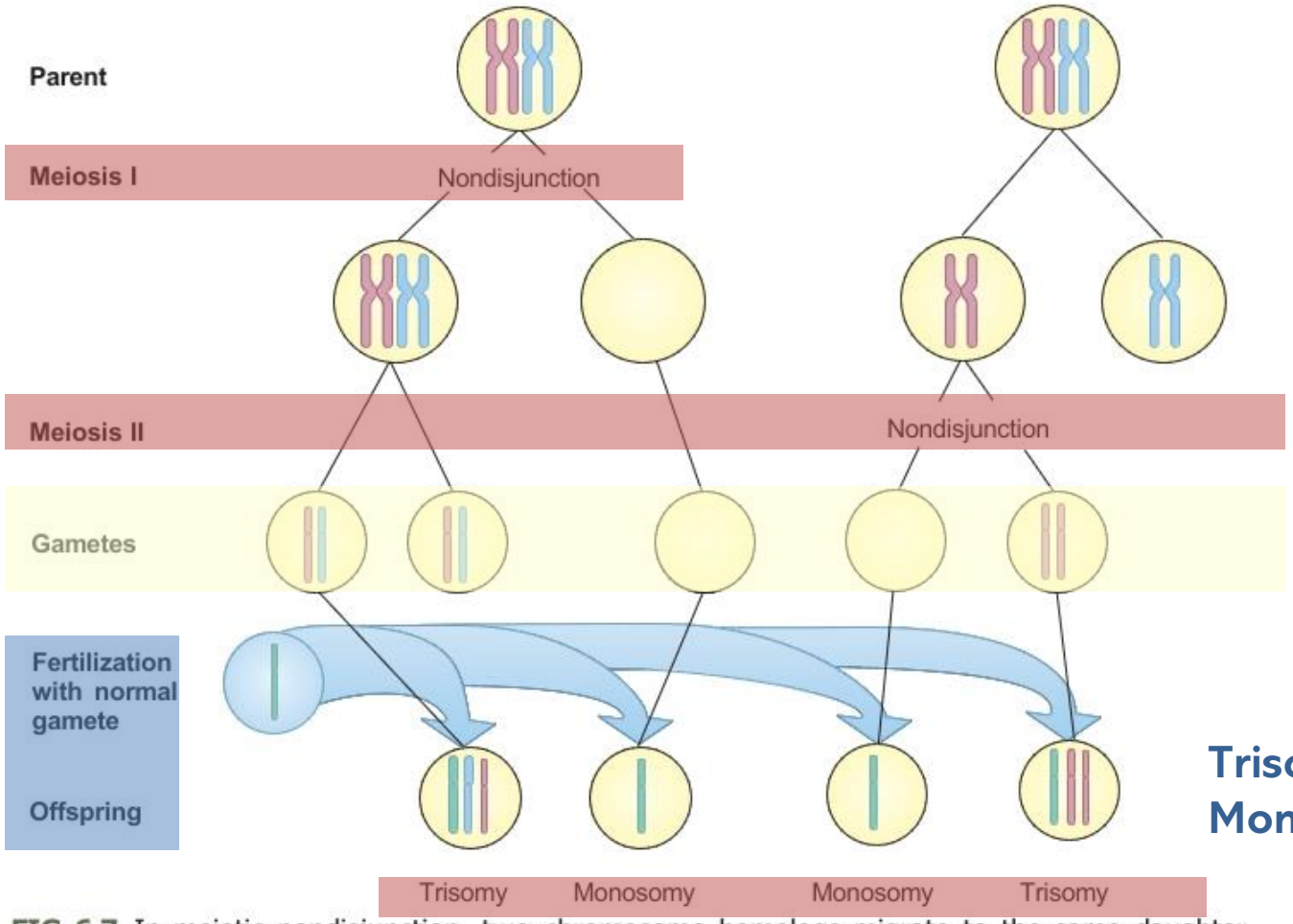
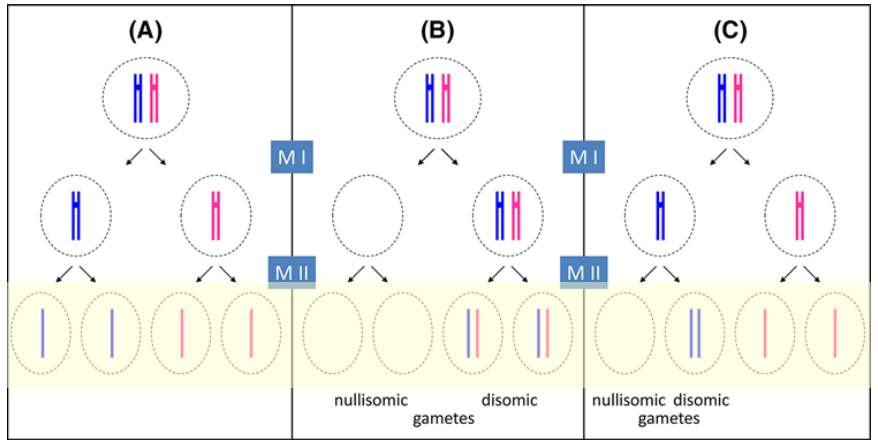


FIG 6-7 In meiotic nondisjunction, two chromosome homologs migrate to the same daughter cell instead of disjoining normally and migrating to different daughter cells. This produces monosomic and trisomic offspring.

Extra image



Normal

Meiosis I Nondisjunction

Meiosis II Nondisjunction

Trisomy →47 chromosome

Monosomy→45 chromosome

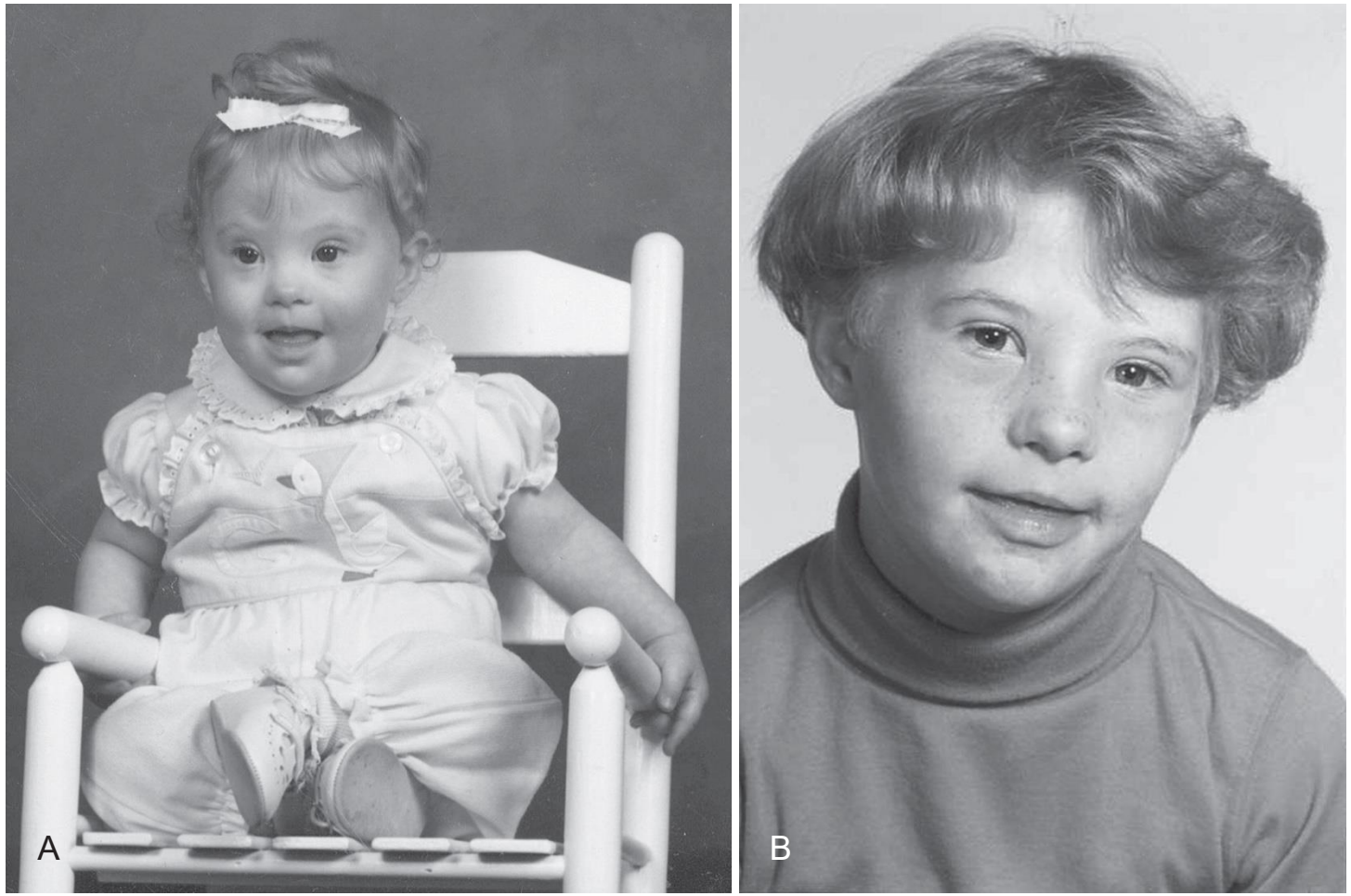
Trisomy 21

- Trisomy 21 (karyotype 47,XY,+21 or 47,XX,+21)

  47 = total number of chromosomes (normally 46, so here there's one extra).
  XY = biological male. **XX**= biological female
  +21 = there is an extra copy of chromosome 21 (3 instead of 2).

- **Down Syndrome**
- The name "Down syndrome" comes from the English physician John Langdon Down, who first described the clinical picture in 1866.The exact genetic cause of Down syndrome — an extra copy of chromosome 21 (trisomy 21) — was discovered covered in 1959.

- **Clincal presentation**
- **Facial features**: Low nasal root, Upward slanting palpebral fissures (eye openings), Small over folded ears , Flat forehead, Brachycephaly (shortened skull)
- **Simian crease:** in 50% (also called a single transverse palmar crease) is a single line that runs across the palm
- **Hypotonia:** decrease in Muscle tone



Epidemiology
1:800-1000 life births the most common aneuploidy that is compatable with life the Frequency increases when the maternal age is older than 36 Or younger then 20 years

"Mongolism" is an outdated, offensive, and no longer acceptable term that was historically used to refer to what is now correctly called Down syndrome.

FIG 6-8 **A,** An infant with Down syndrome, illustrating typical features of this disorder: upslanting palpebral fissures, redundant skin of the inner eyelid (epicanthic fold), protruding tongue, and low nasal bridge. **B,** Same girl as in **A,** 7 years later. Note that the typical features are present but less obviously expressed. **C,** A karyogram of a male with trisomy 21.

Trisomy 21

- **Medical complications**

1. obstruction of the duodenum or **atresia** (closure or absence) of the esophagus
2. the risk of developing **leukemia** is 15 to 20 times higher
3. 40% of these individuals are born with structural **heart defects**

→ The most common of these is an atrioventricular **(AV)** canal, a defect in which the interatrial and interventricular septa fail to fuse normally during fetal development.

Moderate to **severe** **mental retardation** (IQ ranging from 25 to 60) accounts for 10% of all cases of mental retardation

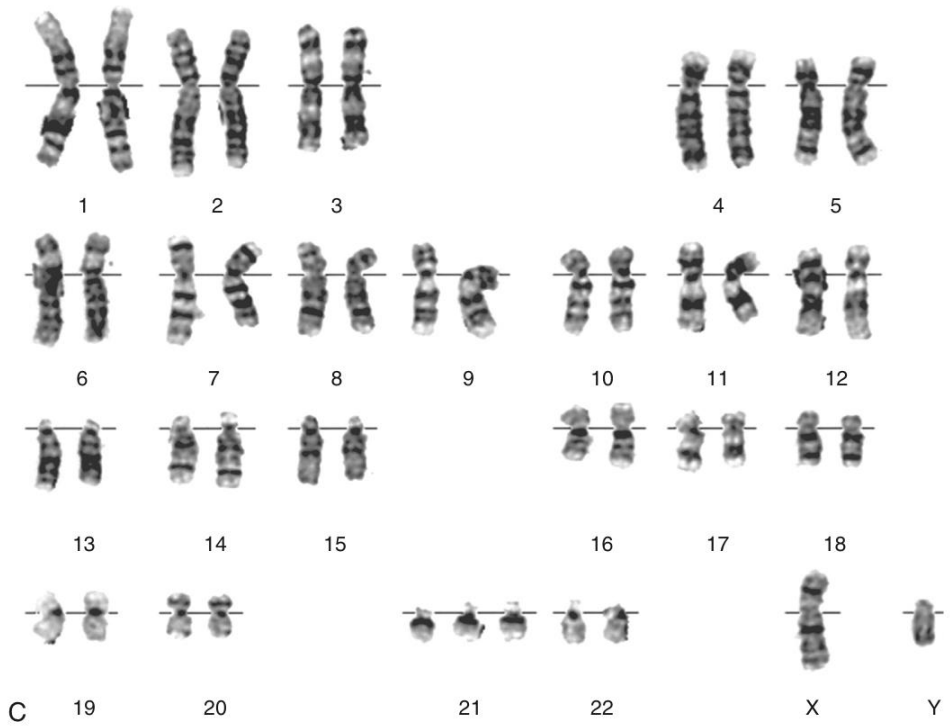


FIG 6-8 **A,** An infant with Down syndrome, illustrating typical features of this disorder: upslanting palpebral fissures, redundant skin of the inner eyelid (epicanthic fold), protruding tongue, and low nasal bridge. **B,** Same girl as in **A,** 7 years later. Note that the typical features are present but less obviously expressed. **C,** A karyogram of a male with trisomy 21.

We have a total of 47 chromosomes.

During chromosomal analysis, we need to count 20 metaphase cells to assess chromosomal abnormalities, and we look for trisomy 21. This can also be demonstrated using FISH (Fluorescence In Situ Hybridization)

Read to understand how to follow up and manage a baby with Down syndrome

CLINICAL COMMENTARY 6-1

Anticipatory Guidance and Health Supervision in Children with Down Syndrome

An approach termed *health supervision* and *anticipatory guidance* has evolved for the care and treatment of persons with genetic syndromes and chronic diseases. After a thorough study of the disease in question (including an extensive literature review), basic guidelines are established for the screening, evaluation, and management of patients. If followed by the primary care practitioner or the specialist, these guidelines should help to prevent further disability or illness. We illustrate the health supervision and anticipatory guidance approach with the current guidelines for care of children with Down syndrome.

- As mentioned in the text, AV canals are the most common congenital heart defect seen in newborns with Down syndrome. Surgical correction of this condition is appropriate if it is detected before 1 year of age; after this time, pulmonary hypertension has been present too long for surgery to be successful. Accordingly, it is now recommended that an echocardiogram be performed during the newborn period and no later than 6 months.
- Because Down syndrome patients often have strabismus (deviation of the eye from its normal visual axis) and other eye problems, they should be examined regularly by their physician. If any symptoms or signs are observed, the patient is referred to an ophthalmologist familiar with Down syndrome. In asymptomatic children, an ophthalmological examination before the age of 4 years is recommended to evaluate visual acuity.
- Hypothyroidism is common, especially during adolescence. Therefore, thyroid hormone levels should be measured annually.
- Sensorineural and conductive hearing loss are both seen in children with Down syndrome. The routine follow-up should include a hearing test at birth and every 6 months until 2 years of age, with subsequent testing as needed.
- Instability of the first and second vertebrae has led to spinal cord injuries in some older Down syndrome patients. It is thus suggested that imaging studies be carried out in children with neurological symptoms and in those planning to participate in athletic activities.
- Referral of infants and children with Down syndrome to preschool programs to provide intervention for developmental disabilities is an important component of routine care.

Similar series of guidelines have been developed for children with trisomy 18, Williams syndrome, and Turner syndrome. In principle, the anticipatory guidance and health supervision approach can be applied to any genetic disease for which there is sufficient knowledge.

The degree of intellectual disability in Down syndrome varies. Some children with Down syndrome can attend special education schools, where their intellectual abilities are further developed, and they may continue through the educational system. However, others may have more severe intellectual disability, making them unable to benefit from such educational programs.

Trisomy 21

- their survival rates are significantly decreased
  - Due to heart defects. However, advances in medicine and surgical techniques have made it possible to correct these defects. Still, most affected children only survive until the age of five, and few live much longer.
- Males with Down syndrome are nearly always sterile
- females with this condition can reproduce, although approximately 40% fail to ovulate
- A female with Down syndrome has a 50% risk of producing a gamete with two copies of chromosome 21

When a female with Down syndrome produces egg cells during meiosis, 50% of the eggs may carry one copy of chromosome 21 (normal), while the other 50% may carry two copies of chromosome 21 due to nondisjunction. If a normal sperm fertilizes an egg with one copy of chromosome 21, the resulting embryo will have a normal number of chromosomes. However, if the egg has two copies of chromosome 21 and is fertilized by a normal sperm (which adds one more copy), the embryo will have three copies of chromosome 21, leading to trisomy 21, or Down syndrome.

Trisomy 21

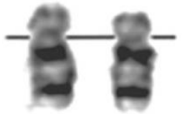
- 95 % Nondisjunction during meiosis 1 or 2 . 5% of cases result from translocation.
- the extra chromosome is contributed by the mother in 90% to 95% of trisomy 21 cases(75% of cases happens during miosis 1).

We use the mother's age to determine the incidence of Down syndrome. It's important to remember that oocytes are formed during fetal development in females, so if a woman becomes pregnant in her 40s or later, the oocyte used will be aged, increasing the likelihood of non-disjunction.

- Mosaicism is seen in approximately 2% to 4% of trisomy 21 live births. This means that some cells are normal, while others contain an extra chromosome 21.
- 47,XY,+21[10]/ 46,XY[10] This means that half cells are normal, while other half contain an extra chromosome 21.

- The most common cause of mosaicism in trisomy is a trisomic conception followed by loss of the extra chromosome in some cells during mitosis in the embryo

TRISOMY 18



18

Chromosome 18 has a small p arm and is prone to non-disjunction, which can lead to Edwards syndrome.

- Trisomy 18 (47,XY,+18).
- Edwards syndrome
- is the **second most common autosomal trisomy**, with a prevalence of about **1 per 6,000** live births
- **is the most common chromosome abnormality among still-borns** with congenital malformations

FIG 6-9 A girl with full trisomy 18 at 3 years **(A)** and 13 years **(B)** of age. She shows the typical facial features of an older child with short palpebral fissures and ear variations. **A** also depicts the overriding of the index finger onto the third finger, a characteristic finding of the hands in the syndrome.

Weight is reduced compared to gestational age. Characteristic features include distinctive facial appearance, small ears, short sternum, short big toes, and congenital heart defects

TRISOMY 18

- About 50% of infants with trisomy 18 die within the first several weeks of life
- Marked developmental disabilities, most of them can not walk

- More than 95% of infants with Edwards syndrome have complete trisomy 18
- 90% of trisomy 18 cases are the result of a maternally contributed extra chromosome. Nondisjunction usually maternal in origin

TRISOMY 13

- Trisomy 13 (47,XY,+13)
- Patau syndrome

Happen 1 in 10000

Multiple malformations are present, primarily facial clefts such as cleft lip and cleft palate. Other features include a broad nose, small eyes, and polydactyly. The survival rate is similar to that of Edwards syndrome, with approximately 95% of affected infants dying within the first year of life. In trisomy 13 (Patau syndrome), developmental progress is significantly delayed. However, some affected individuals are able to communicate with their families, although varying degrees of intellectual disability are present.

FIG 6-10 An 8-year-old girl with full trisomy 13 showing her small eyes and prominent, wide nose.

TRISOMY 13

- 80% of patients with Patau syndrome have full trisomy 13
- Most: Translocation

- the risk of bearing a child with this condition increases with advanced maternal age
- **estimated that 95% or more of trisomy 13 conceptions are spontaneously lost** during pregnancy.

TRISOMIES, NONDISJUNCTION, AND MATERNAL AGE

- Downs Syndrome: Among mothers younger than 30 years of age, the risk is less than 1/1,000. It increases to approximately 1/400 at age 35 years, 1/100 at age 40, and approximately 1/25 after age 45.
- Most other trisomies, including those in which the fetus does not survive to term, also increase in prevalence as maternal age increases.

- **older women are less likely to spontaneously abort a trisomic pregnancy**
- an **ovum produced by a 45-year-old woman is itself about 45 years old.** And this increase tendency of non disjunction

TRISOMIES, NONDISJUNCTION, AND MATERNAL AGE

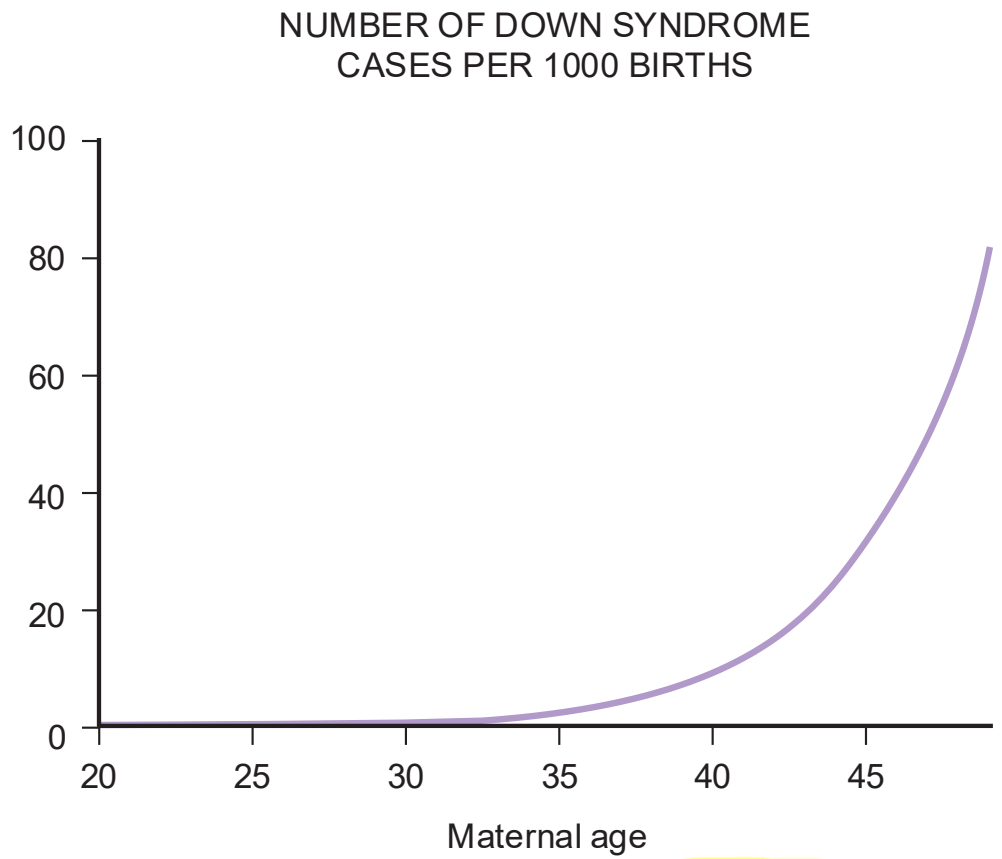


FIG 6-11 The prevalence of Down syndrome among live births in relation to age of the mother. The prevalence increases with maternal age and becomes especially notable after the age of 35 years. (Data from Hook EB, Chambers GM. *Birth defects*. 1977;23[3A]:123-141.)

Pregnancy after the age of 35 is generally considered higher risk, as the incidence of chromosomal non-disjunction increases with maternal age.

TRISOMIES, NONDISJUNCTION, AND MATERNAL AGE

- Factors that may affect the frequency of nondisjunction in women.....

→ Only maternal age (The main factor)

- approximately three fourths of Down syndrome children are born to mothers younger than 35 years of age.

•Although the risk of Down syndrome increases significantly after maternal age 35, about 95% of children with Down syndrome are born to mothers younger than 35, since the majority of births occur in this age group.

- Paternal age: Minor effect . Because sperm are generated continuously, they do not age.

Sex Chromosome Aneuploidy

- about 1 in 400 males and 1 in 650 females

- because of X inactivation - are less severe
  - Due to X-inactivation, when there is an increase in the number of X chromosomes, more of them will be inactivated. This helps to reduce the severity of the effects. In the case of monosomy (when one X chromosome is missing), if the inactive X chromosome is removed and the active X chromosome remains, problems can still occur, but they are generally less severe.

- With the exception of a complete absence of X chromosome material, all of the sex chromosome aneuploidies are compatible with survival

MONOSOMY OF THE X CHROMOSOME (TURNER SYNDROME)

- (45,X) or (45, XO) was described by Henry Turner in 1938

(1) proportionate short stature

(2) sexual infantilism and ovarian dysgenesis

(3) a pattern of major and minor malformations.

- a triangle-shaped face
- a broad, "webbed" neck
- the chest is broad and shield-like in shape
- Many: congenital heart defects
- 50%: structural kidney defects
- Normal intelligence

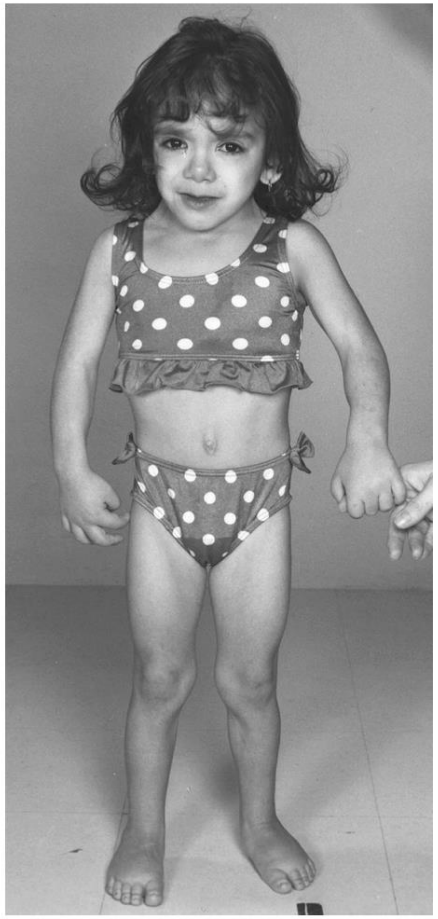


FIG 6-12 A girl with Turner syndrome (45,X). Note the characteristically broad, webbed neck. Stature is reduced, and swelling (lymphedema) is seen in the ankles and wrists.

MONOSOMY OF **THE** X CHROMOSOME (TURNER SYNDROME)

- exhibit proportionate short stature and do not undergo an adolescent growth spurt

- Mature height is reduced by approximately 20 cm comparing to mature hight

- Instead of ovaries, most females with Turner syndrome have streaks of connective tissue.
- they **do not usually develop secondary sexual** characteristics, and **most women with this condition are infertile**
- Teenagers with Turner syndrome are typically treated with estrogen

Estrogen promotes the development of secondary sexual characteristics in females. In patients with Turner syndrome, estrogen is given to help improve the appearance of secondary sexual features and to prevent the development of osteoporosis in the future.

MONOSOMY OF **THE** X CHROMOSOME (TURNER SYNDROME)

- 50% of these patients have a 45,X karyotype
- 30% to 40% are mosaics, most commonly 45,X/46,XX and less commonly 45,X/46,XY rare
- 10% to 20% of patients with Turner syndrome have structural X chromosome abnormalities involving a deletion of some or all of the short arm

- 60% to 80% of monosomy X cases are caused by the absence of a paternally derived sex chromosome while the remaining cases result from the absence of the maternally-derived X chromosome. This typically occurs during early mitosis in the embryo or during meiosis in leading to the lacks an X chromosome.

- the great majority (more than 99%) of 45,X conceptions are lost prenatally

CLINICAL COMMENTARY 6-2

XX Males, XY Females, and the Genetic Basis of Sex Determination

During normal meiosis in the male, crossover occurs between the tip of the short arm of the Y chromosome and the tip of the short arm of the X chromosome (Fig. 6-13). These regions of the X and Y chromosomes contain highly similar DNA sequences. Because this resembles the behavior of autosomes during meiosis, the distal portion of the Y chromosome is known as the **pseudoautosomal region.** It spans approximately 2.5 Mb.

Just centromeric of the pseudoautosomal region lies a gene known as *SRY* (sex-determining region on the Y). This gene, which is expressed in embryonic development, encodes a transcription factor that interacts with other genes to initiate the development of the undifferentiated embryo into a male (including Sertoli cell differentiation and secretion of müllerian-inhibiting substance). In particular, the protein product of *SRY* binds to an enhancer element that regulates expression of the *SOX9* gene, which in turn regulates a series of genes that promote male development while repressing ovarian development. *SRY* thus acts as a key regulatory switch in sex determination. When the mouse *Sry* gene is inserted experimentally into a female mouse embryo, a male mouse is produced. Loss-of-function mutations of *SRY* can produce individuals with an XY karyotype but a female phenotype. *SOX9* acts as the next switch in this pathway, and *SOX9* mutations can produce sex reversal (XY females) and campomelic dysplasia (malformations of bone and cartilage).

Approximately 1 of every 20,000 males presents with a phenotype similar to Klinefelter syndrome (without increased height), but chromosome evaluation shows that they have a normal *female* karyotype (46,XX). It has been demonstrated that these XX males have an X chromosome that includes the *SRY* gene. This is a result of a faulty crossover between the X and Y chromosomes during male meiosis, such that the *SRY* gene, instead of remaining on the Y chromosome, is transferred to the X chromosome. The offspring who inherits this X chromosome from his father consequently has a male phenotype. Conversely, an offspring who inherits a Y chromosome that lacks the *SRY* gene is an XY female. These females have gonadal streaks rather than ovaries and have poorly developed secondary sexual characteristics.

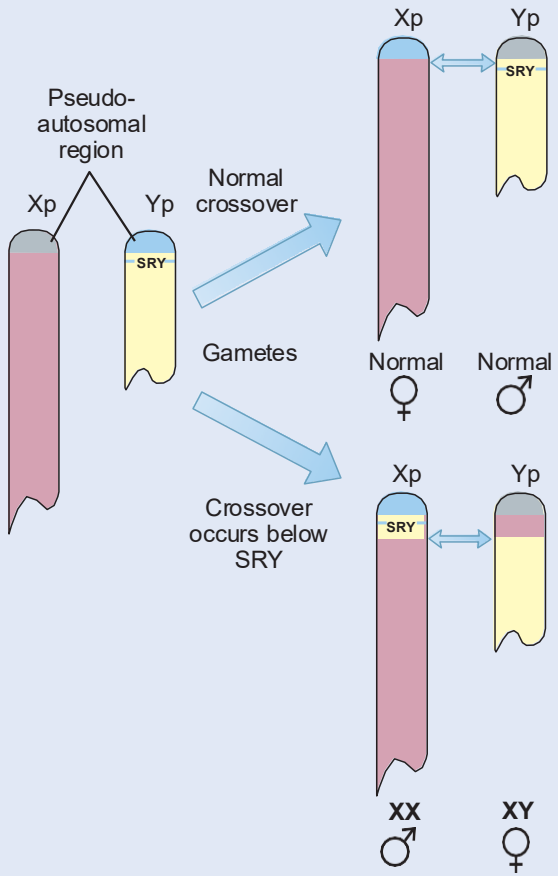


FIG 6-13 The distal short arms of the X and Y chromosomes exchange material during meiosis in the male. The region of the Y chromosome in which this crossover occurs is called the pseudoautosomal region. The *SRY* gene, which triggers the process leading to male gonadal differentiation, is located just outside the pseudoautosomal region. Occasionally, the crossover occurs on the centromeric side of the *SRY* gene, causing it to lie on an X chromosome instead of on the Y chromosome. An offspring receiving this X chromosome will be an XX male, and an offspring receiving the Y chromosome will be an XY female.

The doctor said that we need to read the paragraph and explained what is in boxes here

There is a region between the X and Y chromosomes, located at their terminal ends, that is homologous; this region is called the pseudo-autosomal region (PAR). These regions on the X and Y chromosomes align with each other during mitosis and meiosis. Although the X and Y chromosomes are different, they share similarities in certain genes, such as the amylase gene, which helps them align properly during cell division.

The sex-determining region Y (SRY) gene, located on the Y chromosome, plays a crucial role in male differentiation. This gene triggers the development of male characteristics during embryonic development. Typically, the SRY gene is found on the Y chromosome, which is why males, who carry an X and a Y chromosome (46, XY), develop male characteristics.
However, during crossover (recombination) in meiosis, the SRY gene can sometimes be translocated from the Y chromosome to the X chromosome. If this occurs, a person with two X chromosomes (46, XX) could develop male characteristics, because the SRY gene is present and active, even though the individual has two X chromosomes.
Conversely, if the Y chromosome lacks the SRY gene (due to a mutation or deletion), a person with the typical 46, XY karyotype might develop female characteristics. This is because the lack of the SRY gene prevents the initiation of male development, resulting in female characteristics despite having one X and one Y chromosome.
Thus, it is possible for a female to have a 46, XY karyotype but lack the SRY gene

KLINEFELTER SYNDROME

- A 47,XXY karyotype
- 1/500 to 1/1,000 male births
- Described **in 1942 by Harry Klinefelter**
- **Taller than avera**ge
- Disproportionately long arms and legs
- Most males with Klinefelter syndrome are sterile (primary hypogondism and small testicle size)
- Gynecomastia (breast development) is seen in approximately one third
- Reduced body hair
- Reduced muscle mass
- Usually are not mentally retarded, the IQ is on average 10 to 15 points lower than that of the affected individual's siblings

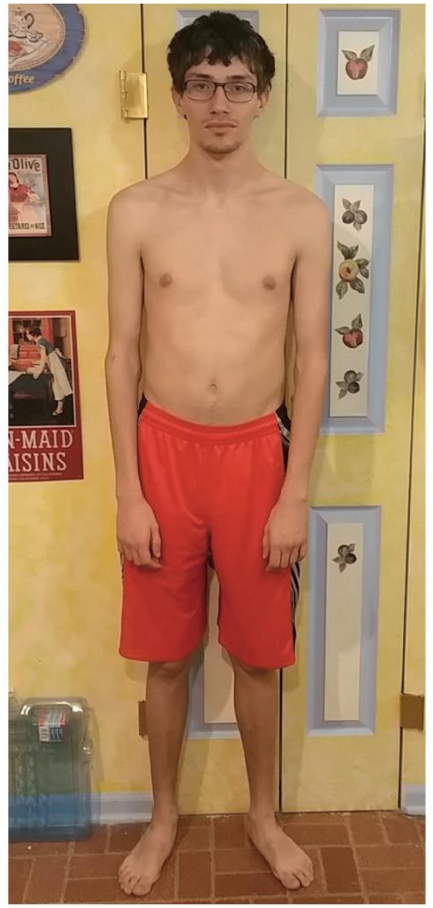


FIG 6-14 A male with Klinefelter syndrome (47,XXY). Stature is increased, gynecomastia may be present, and body shape may be somewhat feminine.

KLINEFELTER SYNDROME

- The extra X chromosome is derived maternally in about 50% of Klinefelter cases
- The syndrome increases in incidence with advanced maternal age
- It is estimated that at least half of 47,XXY conceptions are spontaneously aborted
- **Mosaicism** In 15% of patients, there is a possibility of viable sperm production.

- **48,XXXY and 49,XXXXY karyotypes**

→ have **a male phenotype**, but **the degree of mental deficiency and physical abnormality increases with each additional X chromosome.**

- **Testosterone therapy** Is recommended for middle-aged adults, it can enhance secondary sex characteristics and reduce the risk of osteoporosis.

In general, patients are infertile, except in cases of mosaicism.

TRISOMY X

- **47,XXX karyotype**
- 1/1,000 females
- Benign consequences Due to X inactivation, these patients have two inactivated X chromosomes.

- these females sometimes suffer from sterility, menstrual irregularity, or mild mental retardation But in most cases, patients are fertile and have good mental development.

- 90% of cases are the result of nondisjunction in the **mother**
- Females have also been seen with four, five, or even more X chromosomes

→ Each additional X chromosome is accompanied by increased mental retardation and physical abnormality.

The doctor said that we need to know for each disease that whether the nondisjunction comes maternally or paternally and which contributes more

47,XYY SYNDROME

- Males with this karyotype tend to be taller than and they have a 10- to 15-point reduction in average IQ
- Its incidence in the male prison population (This suggests that this karyotype may predispose individuals to criminal and violent behavior more than the general population) was discovered to be as high as 1/30, compared with 1/1,000 in the general male population

- evidence of minor behavioral disorders, such as hyperactivity, attention deficit disorder, and learning disabilities.

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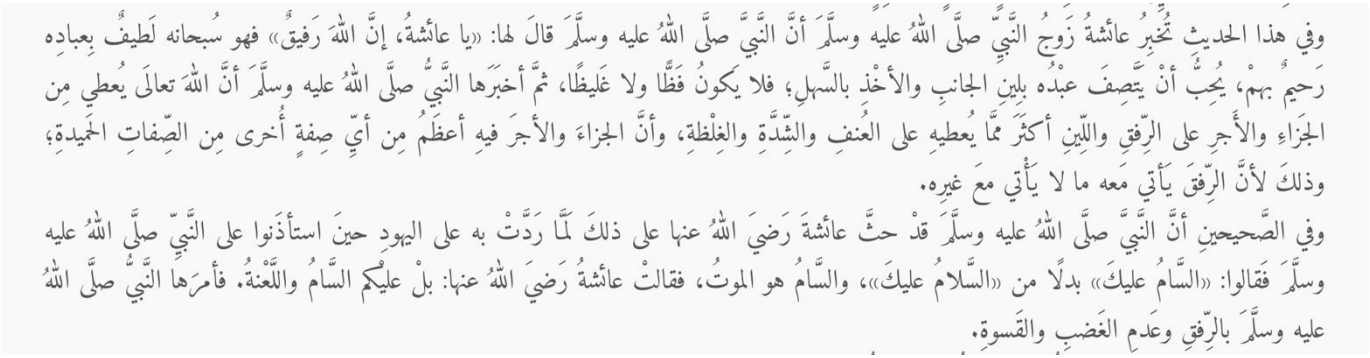

وفي هذا الحديث تُخبِرُ عائشةُ زَوجُ النَّبيِّ صلَّى اللهُ عليه وسلَّمَ أنَّ النَّبيَّ صلَّى اللهُ عليه وسلَّمَ قالَ لها: «يا عائشةُ، إنَّ اللهَ رَفيقٌ» فهو سُبحانه لَطيفٌ بِعبادِه رَحيمٌ بهم، يُحِبُّ أنْ يتَّصِفَ عبدُه بلِينِ الجانبِ والأخْذِ بالسَّهلِ، فلا يكونُ فَظًّا ولا غَليظًا، ثمَّ أخبَرَها النَّبيُّ صلَّى اللهُ عليه وسلَّمَ أنَّ اللهَ تعالَى يُعطي مِن الجَزاءِ والأَجرِ على الرِّفقِ واللِّينِ أكثرَ ممَّا يُعطيهِ على العُنفِ والشِّدَّةِ والغِلْظةِ، وأنَّ الجزاءَ والأجرَ فيهِ أعظَمُ مِن أيِّ صِفةٍ أُخرى مِن الصِّفاتِ الحَميدةِ؛ وذلكَ لأنَّ الرِّفقَ يَأتي معه ما لا يَأتي معَ غيرِه.

وفي الصَّحيحينِ أنَّ النَّبيَّ صلَّى اللهُ عليه وسلَّمَ قدْ حثَّ عائشةَ رَضيَ اللهُ عنها على ذلكَ لَمَّا رَدَّتْ به على اليهودِ حينَ استأذَنوا على النَّبيِّ صلَّى اللهُ عليه وسلَّمَ فَقالوا: «السَّامُ عليكَ» بدلًا من «السَّلامُ عليكَ»، والسَّامُ هو الموتُ، فقالتْ عائشةُ رَضيَ اللهُ عنها: بلْ عليكُم السَّامُ واللَّعْنةُ. فأمرَها النَّبيُّ صلَّى اللهُ عليه وسلَّمَ بالرِّفقِ وعَدمِ الغَضبِ والقَسوةِ.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!