Genetic Diseases

By Dr. Ikram Abdul Latif

Hereditary disorders: Are derived from one parent, transmitted in the gametes through the generation &therefore are familial.

Congenital diseases: simply present at birth.

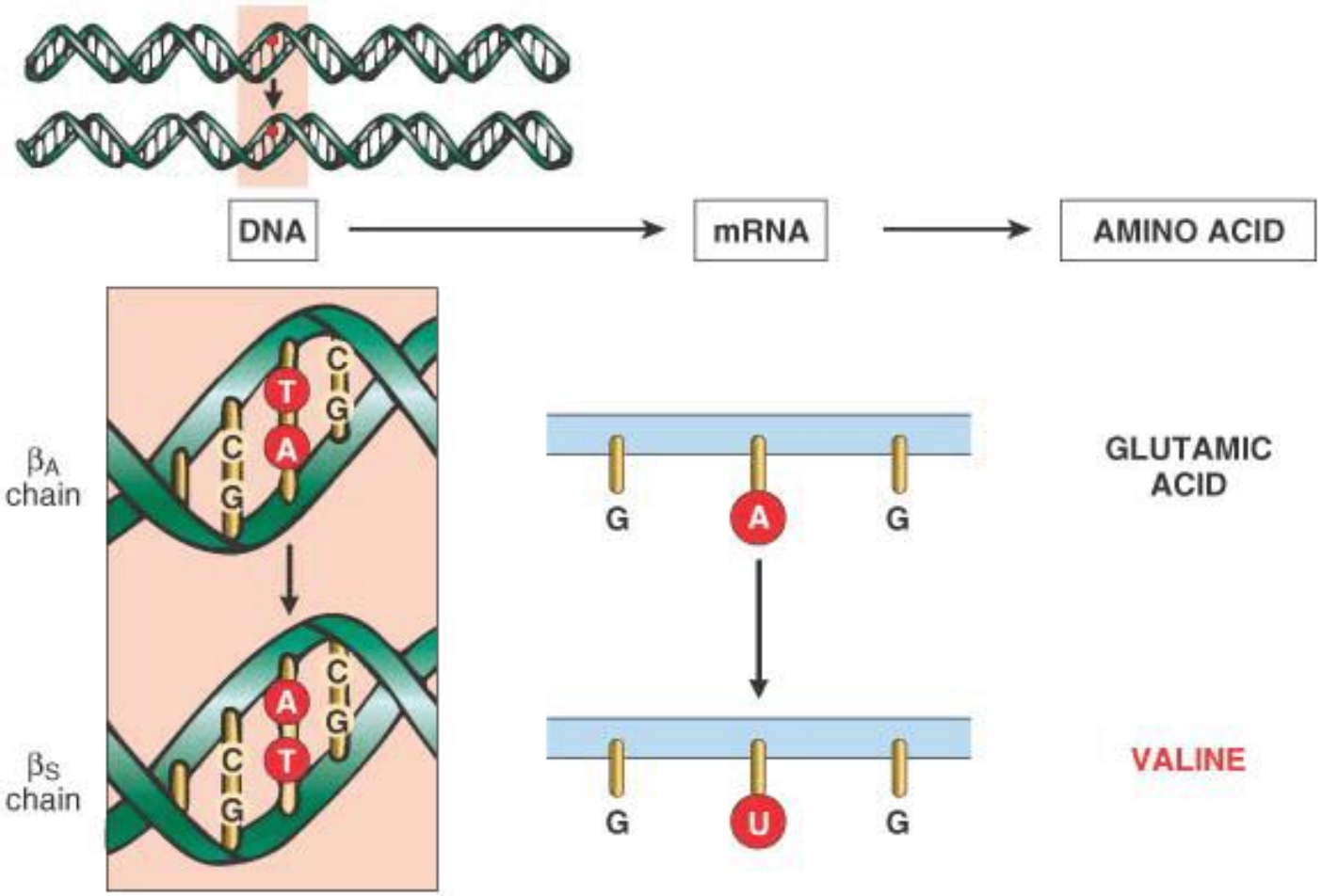
Note: not all genetic diseases are congenital &not all congenital diseases are genetic e.g congenital syphilis.

- **Mutations**: permanent changes in the DNA, those that affect *germ cells* are transmitted to the progeny &give rise to *inherited disease*, while if in the *somatic cells* are not transmitted to the progeny but important in causation of *cancers &some congenital malformations*.

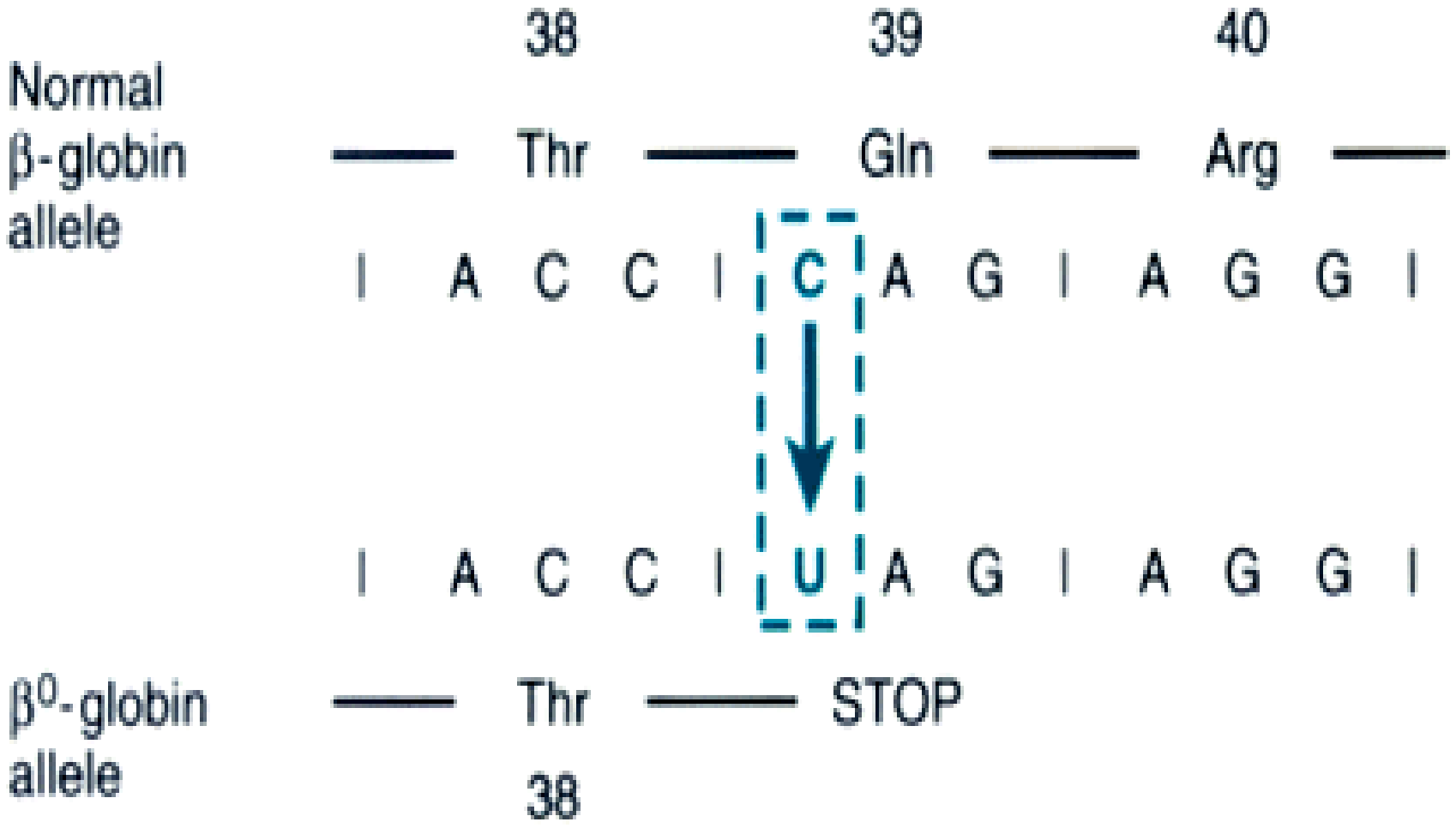
Types of mutations:

1- Point mutation: result from the substitution of a single nucleotide base by a different base----replacement of one amino acid in the protein product e.g sickle cell anemia, affecting the β-globin chain of hemoglobin, the nucleotide triplet CTC (or GAG in mRNA), which encodes glutamic acid, is changed to CAC (or GUG in mRNA), which encodes valine

, this type is called **missense** mutation.

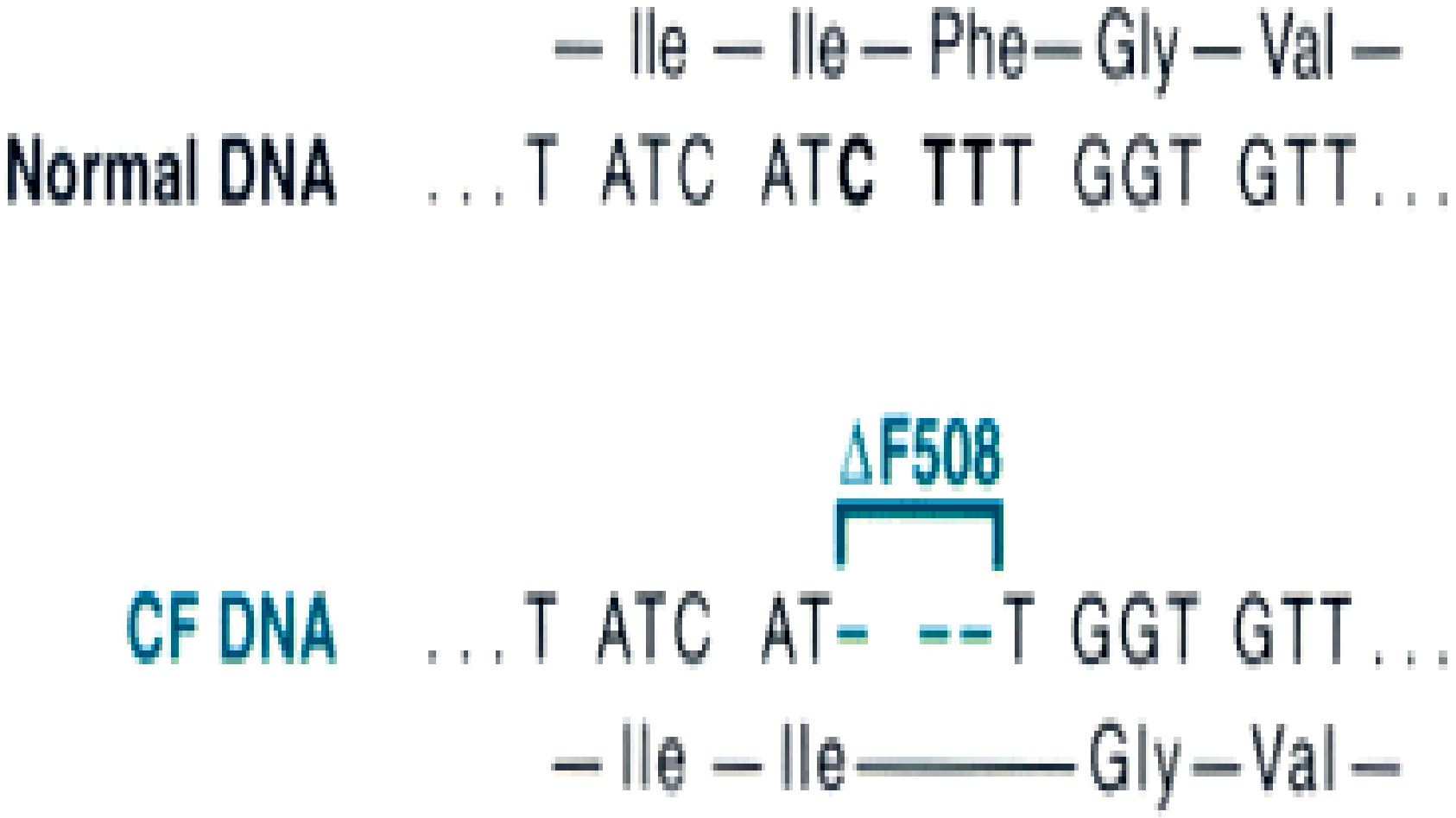

DNA
mRNA
AMINO ACID
βA chain
βS chain
T
A
C
G
C
G
A
T
C
G
C
G
G
A
G
G
U
G
GLUTAMIC ACID
VALINE

While if the point mutation change an amino acid codon to a chain termination codon, or *stop codon* ---interrupt translation &the resultant protein are rapidly degraded (**nonsense** mutation). a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) if U is substituted for C, resulting in premature termination of β-globin gene translation, and the short peptide that is produced is rapidly degraded causing deficiency of β-globin chains and severe form of anemia called β0 -thalassemia

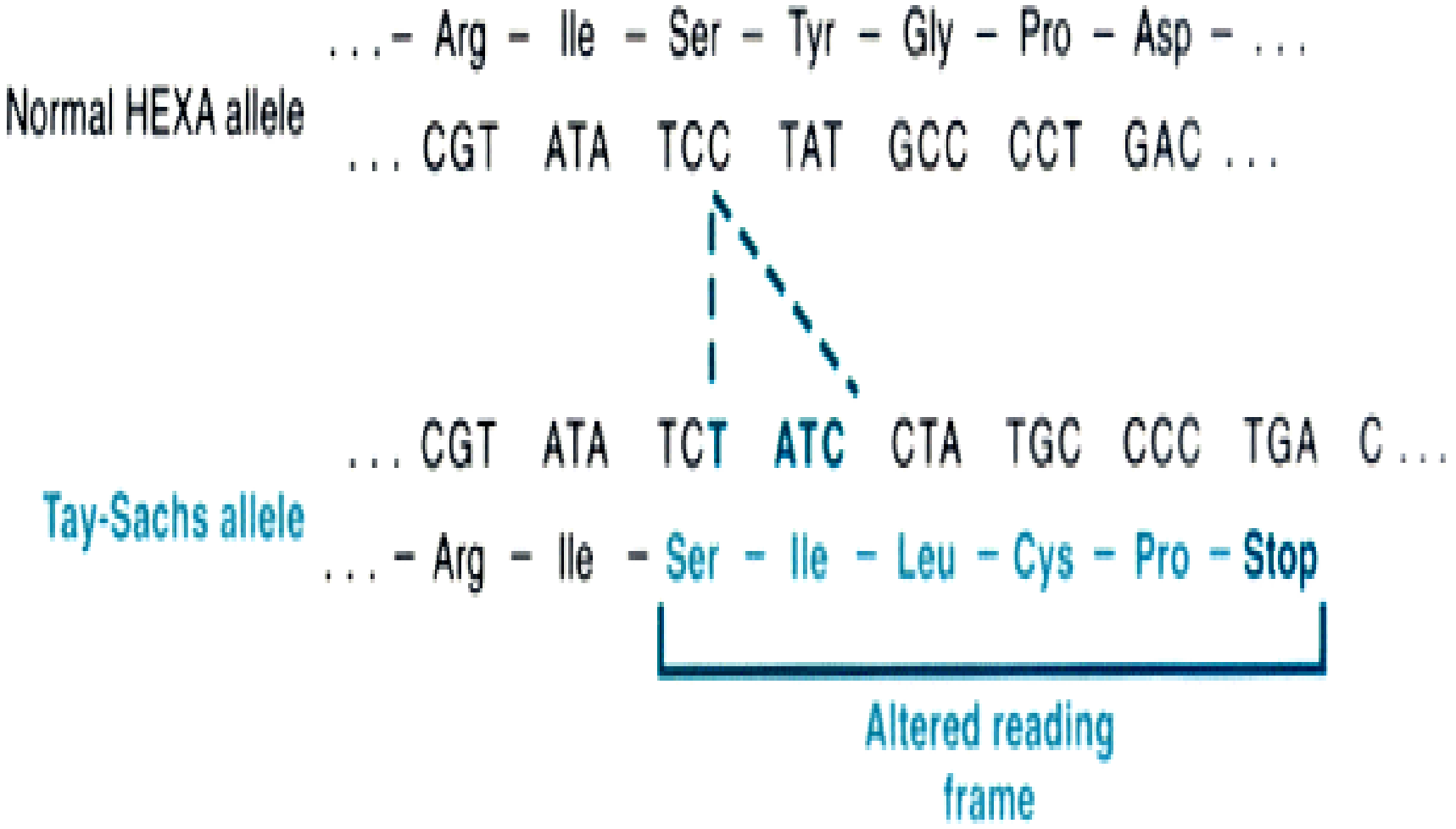

38
39
40
Normal
β-globin
allele
Thr
Gln
Arg
| A C C | C A G | A G G |
| A C C | U A G | A G G |
β0-globin
allele
Thr
STOP
38

2- Frameshift mutation: occur when the insertion or deletion of one or two base pair alter the reading frame of the DNA strand (if three or more this is not frame shift).

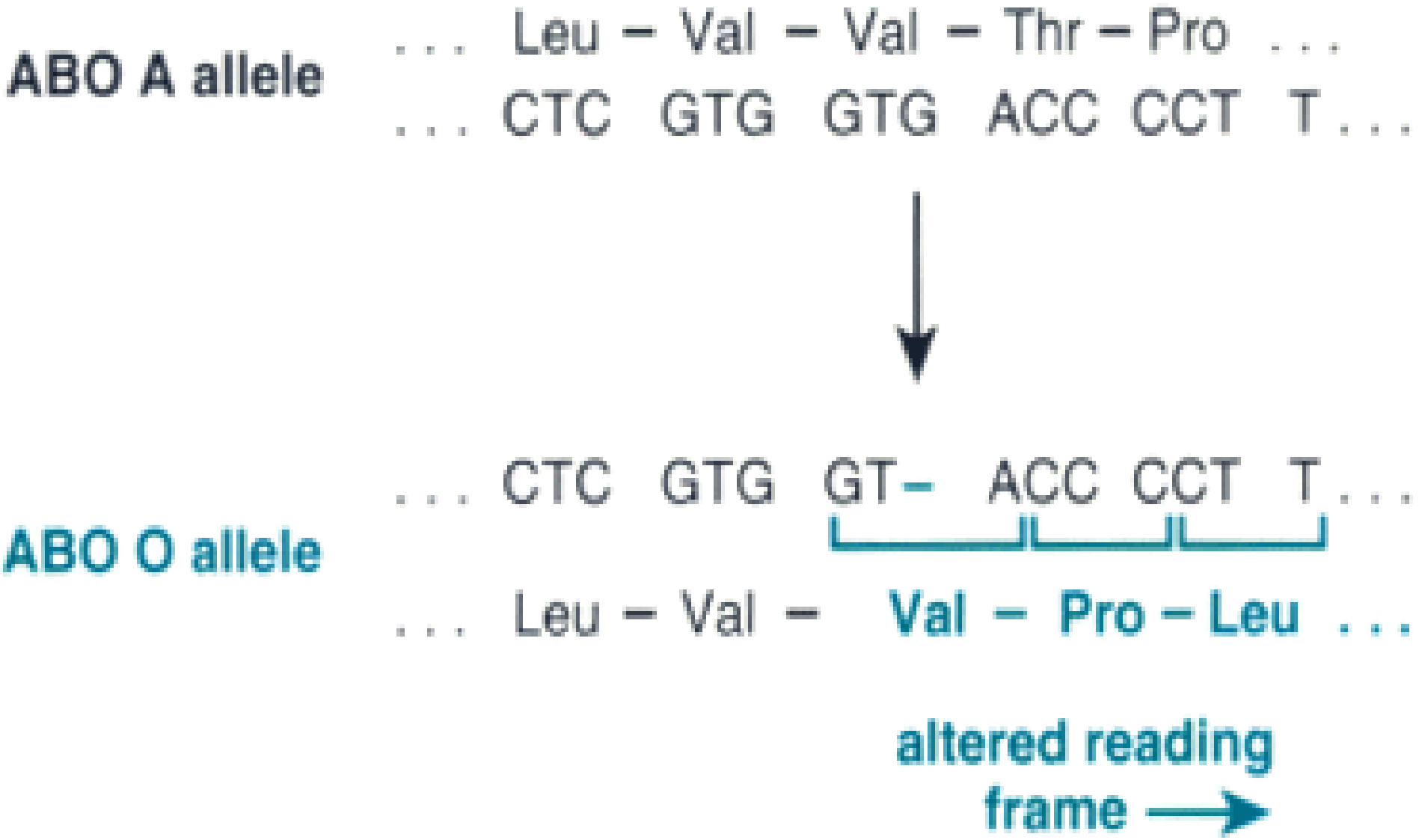
Three-base deletion in the common cystic fibrosis (CF) allele results in synthesis of a protein that lacks amino acid 508 (phenylalanine). Because the deletion is a multiple of three, this is not a frameshift mutation.



4 Four-base insertion in the hexosaminidase A gene, leading to a frameshift mutation. This mutation is the major cause of Tay-Sachs disease in Ashkenazi Jews.



Single-base deletion at the ABO (glycosyltransferase) locus, leading to a frameshift mutation responsible for the O allele



3- Trinucleotide repeat mutations

characterized by the amplification of a sequence of three nucleotide e.g in ***fragile X syndrome***, there are 250-4000 repeats of the sequence CGG within the gene called **FMR-1**.

In the normal population, the number of repeats is small 29, so amplification of FMR-1 giving rise to *mental retardation*.

We will discuss 4 types of genetic diseases:

1- Those resulting from mutation in single gene (**Mendelian disorders**).

2- Complex disorders involving multiple genes as well as environmental influences (**multifactorial inheritance**) e.g diabetes milletus.

3- Chromosomal disorders: These arise from structural or numerical alteration in the autosomes and sex chromosomes. Like monogenic disease, they are uncommon but associated with high penetrance

4- **Heterogenous group** that involve single gene but do not follow Mendelian rules of inheritance.

1- Diseases caused by single gene defects.

Approximately 1% of all adult admission to the hospital &6-8% of all pediatric hospital.

Mutation involving single gene follow one of three patterns of inheritance:

* autosomal **dominant**
* autosomal **recessive**
* **X-linked** diseases

A single gene mutation may lead to many phenotypic effects (pliotropy) e.g Marfan''s syndrome, the defect in the base of connective tissue---defect in skeleton, eyes, cardiovascular, all of them from mutation in fibrillin.

Conversely several different mutations may produce the same trait (genetic heterogeneity) e.g retinitis pigmentosa can be caused by several different types of mutation.

Autosomal dominant disorders:

1- At least one parent of an index case is affected (if manifested in heterozygous state)

2- Both males &females are affected.

3- When an affected person marries an unaffected one, every child has 50% chance of having the disease.

N*N------NN

N*N N*N NN NN

25% affected 25% affected normal normal

50% 50%

4- With every autosomal dominant disease, some patients do not have affected parents, so there is new mutation involving either the egg or the sperm from which they derived. Their siblings are neither affected nor at high risk of the disease.

5- Clinical features can be modified by *reduced penterance &variable expressivity.*

reduced penterance: Some patients inherit the mutant gene but are phenotypically normal.

variable expressivity: If the trait is seen in all individuals carrying the mutant gene but is expressed differently among individuals---

6- In many conditions, signs &symptoms do not appear until adulthood.

7- 50% reduction in normal gene products is associated with clinical symptoms.

8- Because a 50% loss of enzyme activity can be compensated for, involved genes not encode enzyme proteins.

2 main types of ***nonenzyme*** proteins are affected:

a- Those involved in regulation of complex metabolic pathways e.g familial hypercholesterolemia.

b- Key structural proteins e.g collagen &cytoskeletal components of red cell membrane e.g spectrin in hereditary spherocytosis.

Examples of autosomal dominant disorders:

- Marfan syndrome
- Hypercholesterolemia
- Polycystic kidney disease
- Hereditary spherocytosis
- Familial polyposis coli

Autosomal recessive disorders:

Manifested in homozygous state (occur when both of the alleles at a given locus are mutants, so characterized by the following features:

1- The trait does not usually affect the parents who are carriers, but siblings may show the disease.

2- Siblings have 25% risk for each birth (one chance in four).

3- If the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the proband is the product of a consanguineous marriage.

4- The expression of the defect tends to be more uniform than autosomal dominant.

5- *Complete penterance* is common.

6- Onset of signs &symptoms early in life.

7- New mutation occur but rarely detected clinically because the affected person is asymptomatic heterozygote, unless this heterozygous marry other heterozygous &produce affected offspring.

8- In heterozygote, equal amount of normal &defective enzymes are synthesized, cells with half of their complement of enzyme function normally &50% reduction not associated with clinical symptoms.

9- In many cases, enzyme proteins are affected by the mutation e.g phenylketonuria, thalassemia, sickle cell anemia.

N*N N*N

N*N*	N*N	N*N	NN
affected	carrier	carrier	normal
25%	25%	25%	25%

Examples of autosomal recessive disorders:

- Sickle cell anemia
- Thalassemia
- Glycogen storage disease
- Cystic fibrosis
- Phenylketonuria
- Wilson disease

X-linked disorders:

because most of the genes are carried on the X chromosome and very few are present on the Y chromosome, thus for the most part, sex linked disorders are X linked.

Most sex linked diseases are X-linked recessive

The usual pattern in clinical practice is that only males who carry the mutated gene on their X chromosome are clinically affected while female are usually silent carriers as males have only one X chromosome while female have two

These diseases are characterized by:

1- They are transmitted by heterozygous female only to sons who are hemizygous for the X chromosome.

2- Heterozygous female rarely express the full phenotypic change, but if there is inactivation of one of the X chromosome which is the normal X---full expression of the disease in heterozygous female.

3- An affected male does not transmit the disease to sons, but all daughters are carriers.

4- Sons of heterozygous mothers have 50% chance of affection.

5- There are few X-linked dominant &their inherited pattern characterized by transmition of the disease to 50% of sons &daughters of an affected heterozygous female.

XX* XY

XX XY XX* X*Y

sons are 50% affected

XX X*Y

X*X *XX XY XY

All daughters are carrier, sons not affected

Examples of X-linked disorders: •

Hemophilias A and B

Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)

Agammaglobulinemia

Duchenne muscular dystrophy

Diseases caused by mutation in structural proteins:

Marfan"s syndrome:

autosomal dominant disease of connective tissue fibrillin(a glycoprotein that is secreted by fibroblast), both quantitative &qualitative defects have been noted.

3 systems are mainly affected:

* *Skeletal abnormalities*:
* Slender patient with long legs, arms &fingers,
* high arched palate,
* hyperextensibility of the joints kyphosis &the chest shows pectus excavatum or pigeon chest deformity.

- *Eyes:*

bilateral dislocation or subluxation of the lens due to weakness of suspensory ligament (ectopia lentis).

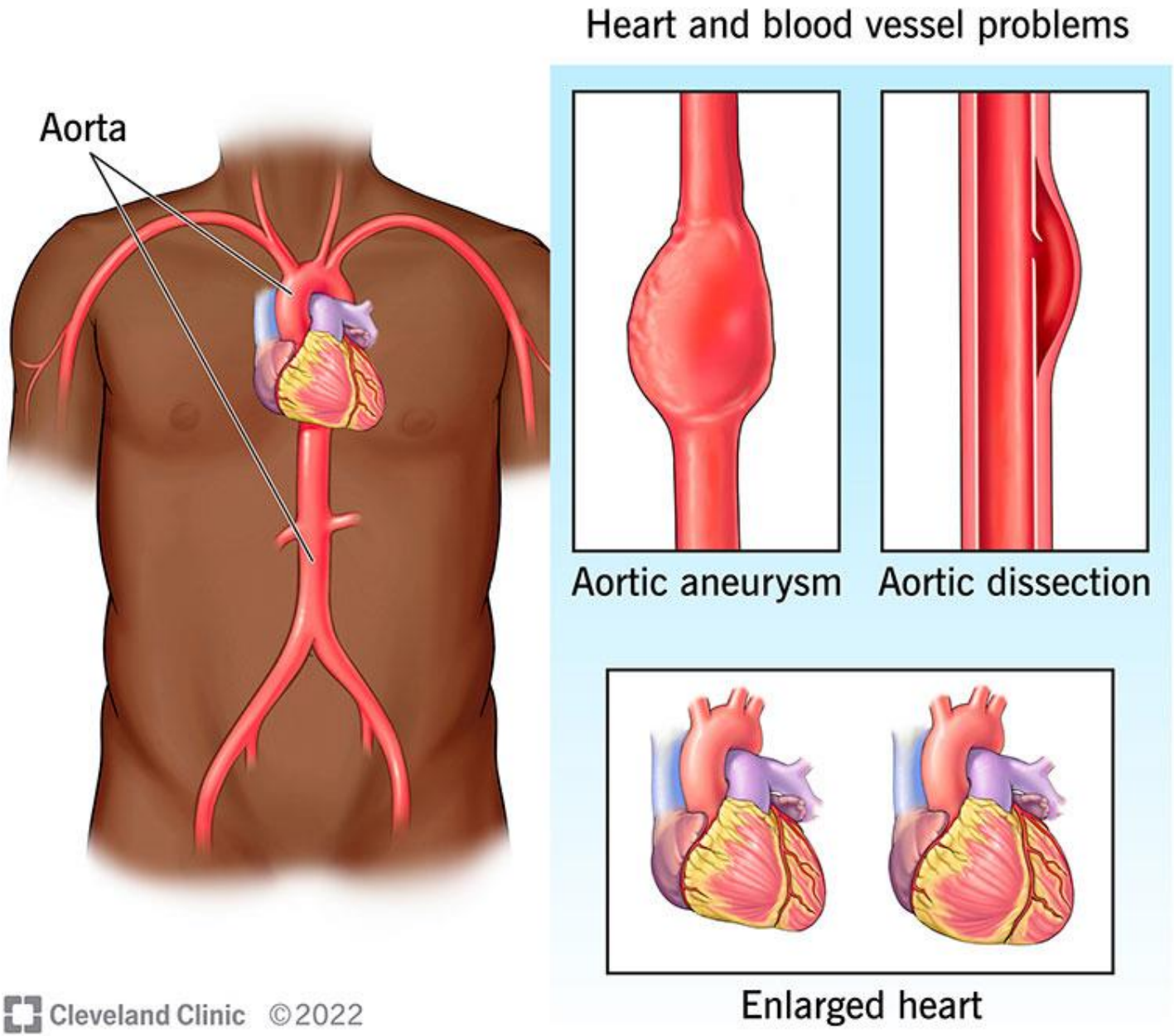
* *Cardiovascular system*:

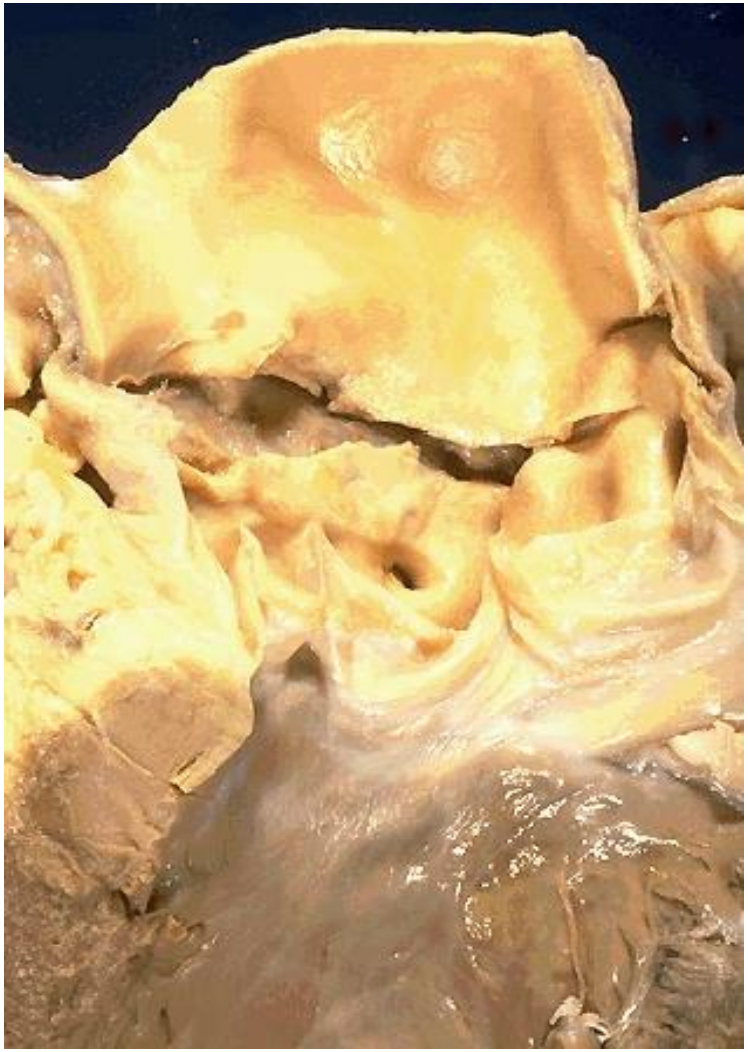
- Fragmentation of the elastic fibers in the tunica media of the aorta---aneurysmal dilatation &aortic dissection.
- dilatation of aortic valve ring---aortic incompetence.
- mitral &tricuspid valves regurgitation----congestive heart failure.

* Death from aortic rupture may occur at any age.
* Variable expression of the features above between different patients.


CM
1 2 3 4 5 6 7

Marfan syndrome







Disease caused by mutation in receptor proteins:

Familial hypercholesterolemia:

1- Autosomal dominant dis., heterozygotes have 2-3 folds elevation of plasma cholesterol level, remain asymptomatic until adulthood when develop xanthoma along tendon sheaths &premature coronary artery dis.

2- While homozygotes are much more severely affected, cutaneous xanthoma in childhood &dying from myocardial infarction MI in the age of 15 years.

3- It is caused by mutation in the gene that specifies the receptor for low density lipoproteins LDL.

4- Cholesetrol may be derived from diet or from endogenous synthesis,

endogenous synthesis of cholesterol &LDL begins in the liver.

Normally, there is LDL receptors in the hepatocytes, so LDL binds to the receptors &formation of very low density lipoproteins VLDL which undergo lipolysis &converted into intermediate density lipopt. IDL, then to the liver (LDL receptor) again.

Mutation in LDL receptor gene---accumulation of LDL cholesterol in the plasma, in addition the absence of LDL receptor on the liver impair the transport of IDL to the liver---accumulation of IDL that converted to LDL.

The discovery of the critical role of LDL receptors in cholesterol homeostasis has led to the rational design of drugs that lower plasma cholesterol by increasing the number of LDL receptors.

based on the ability of certain drugs (**statins**) to suppress intracellular cholesterol synthesis by inhibiting the enzyme HMG CoA reductase. The reduction in intracellular cholesterol allows greater synthesis of LDL receptors by removing the braking action of cholesterol on LDL receptor synthesis


DermNet™
All about the skin


Te Whatu Ora
Health New Zealand



Diseases caused by mutation in enzymes proteins:

Phenylketonuria (PKU)

1- Inborn error of metabolism, it is autosomal recessive dis.

2- homozygotes have severe lack of phenylalanine hydroxylase--- hyperphenylalaninemia &PKU leading to decrease formation of myelin, epinephrine, norepinephrine, myelin, dopamine, thyroxin and melanin

3- The biochemical abnormality in PKU is an inability to convert phenylalanine into tyrosine. In normal children, less than 50% of the dietary intake of phenylalanine is necessary for protein synthesis. The remainder is converted to tyrosine by the phenylalanine hydroxylase system.

When phenylalanine metabolism is blocked because of a lack of PAH enzyme, shunt pathways come into play, yielding several intermediates that are excreted in large amounts in the urine and in the sweat. These impart a strong musty or mousy odor to affected infants. It is believed that excess phenylalanine or its metabolites contribute to the brain damage in PKU. Concomitant lack of tyrosine, a precursor of melanin, is responsible for the light color of hair and skin.

4- The affected infants are normal at birth but within few weeks to 6 months---increase phenylalanine in plasma with severe mental retardation, inability to walk, inability to talk, seizures, decrease pigments of the skin &hair, eczema, musty odor of sweat.

Treatment: restriction of phenylalan. intake early in life.

5- Many clinically normal PKU patients treated with diet early in life &reach child bearing age, most of them have high serum phenylalan. because dietary treatment is discontinued after reaching adulthood, children born to them are mentally retarded &have many congenital abnormalities---maternal PKU.

Glycogen storage disorders (Glycogenosis):

An inherited deficiency of any of the enzyme involved in glycogen synthesis or degradation, result in excessive accumulation of glycogen or abnormal form of glycogen in various tissue.

Glycogen is most often stored within the cytoplasm or sometimes within the nuclei, one variant called **Pompe** dis.---lysosomal storage dis. because the deficient enzyme localized to the lysosomes.

Most glycogenosis are inherited as autosomal **recessive** dis.

On the basis of pathophysiology they grouped into **3 categories**:

1- Hepatic form: liver cotains several enzyme that synthesize or break down glycogen, so deficiency of an enzyme result in enlargement of the liver due to storage of glycogen &hypoglycemia due to failure of glucose production e.g Glucose 6 phosphatase enzyme deficiency called Von Gierke

2- Myopathic form: In striated muscles glycogen derived by glycolysis, when enzyme are deficient so glycogen storage dis. of the muscle (muscle weakness), typically characterized by muscle cramps after exercise &failure of the exercise to induce an evolution in blood lactate level due to block in glycolysis (McArdle disease) result from deficiency of muscle phosphorylase enzyme

3- Two other forms of glycolysis do not fit into either of the above two

Pompe disease due to deficiency of lysosomal acid maltase so deposition of glycogen in every organ but cardiomegaly is prominent .

Brancher glycogenosis is due to deposition of abnormal glycogen with effect on the liver, heart, muscles…

Diseases caused by mutation in protein that regulate cell growth:

2 classes of genes that regulate cell growth:

prooncogenes &cancer suppressor genes.

mutation affecting these genes----tumor.

5% of all CA, there is mutation affecting certain tumor suppressor genes are present in all cells of the body including germ cells--- transmitted to the offspring.

Neurofibromatoses type 1 &2:

Neurofibromatoses type 1: accounts for 90% of the cases &characterized by:

1- Multiple neurofibroma in the form of pedunculated nodules protruding from the skin , they are discrete, unencapsulated, soft, sometimes the tumor form large multilobar masses (plexiform NF).They are derived from schwan cells, similar tumors may occur along nerve trunk, cauda equine, cranial nerves, orbit, tongue &GIT.

2- Pigmented skin lesions (café-au-lait spots), sometimes overlie a NF.

3- Pigmented iris hamartomas (Lisch nodules), no clinical symptoms but helpful in the diagnosis.

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* NF type1 gene on chromosome **17**, it encodes a protein that act as negative regulator of ras oncoprotein.
* NF type 2 on chromosome **22**, rarer than type 1, in addition to NF, Café-au-lait spots +bilateral acaustic neuroma

Significance of NF:

1- Disfiguring condition.

2- Serious by its location e.g within the spinal cord.

3- In 3% of patient, NF leads to neurosarcoma.

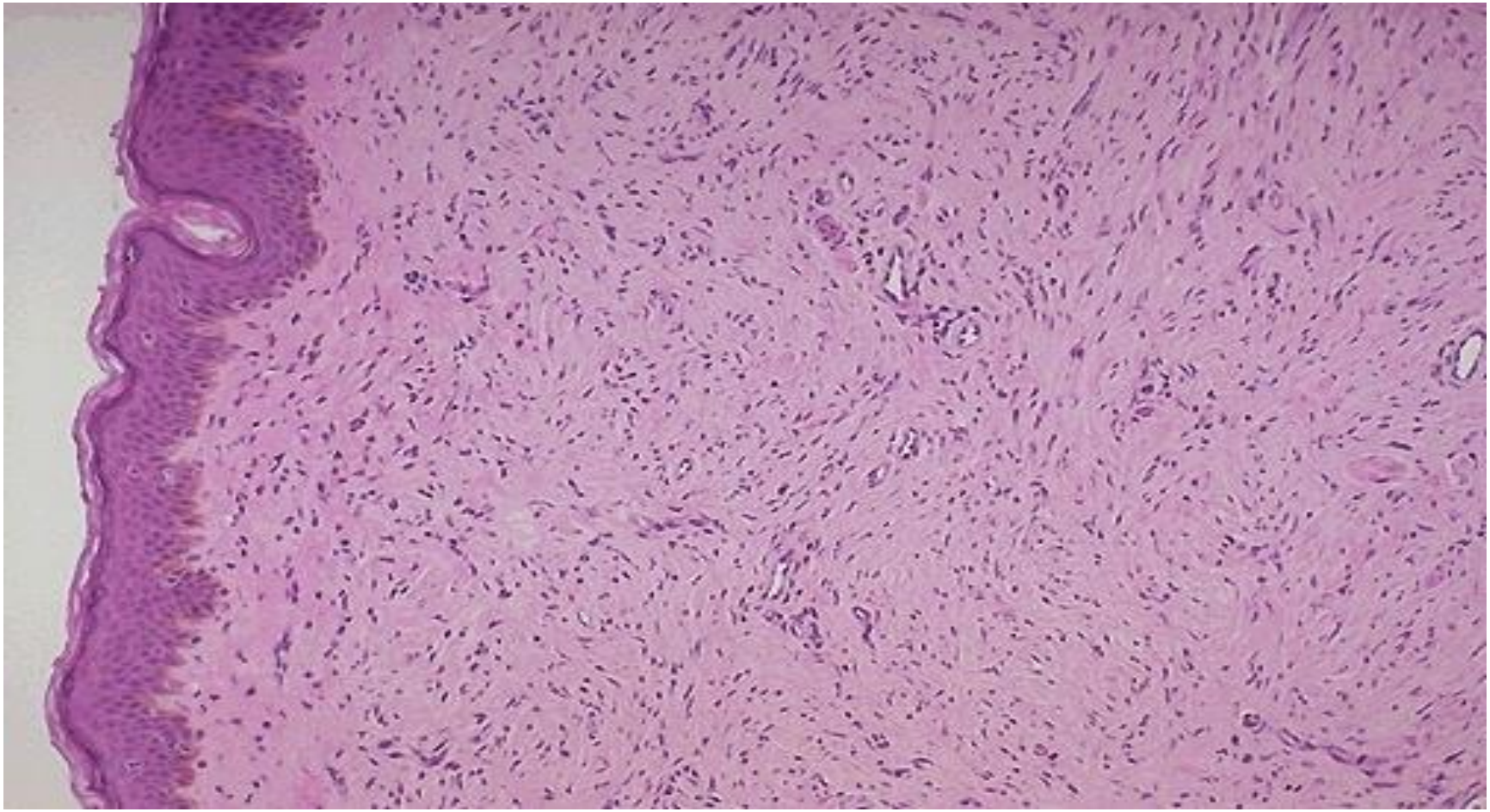
Usually malignant in the plexiform tumor attached to large nerve trunk of the neck or extremities.

4- These patients are at greater risk of developing other tumors like optic glioma, menigioma & pheochromocytoma.

5- 30-50% of patients have associated skeletal abnormalities like scoliosis, bone cysts.







Disorders with multifactorial inheritance:

Multifactorial trait may be defined as one governed by the additive effect of 2 or more genes of small effects but conditioned by environmental influences.

There is some threshold effect so that the disorder becomes manifested

The following features characterized multifactorial inheritance:

1- The risk of expressing a multifactorial disorder is conditioned by the number of mutant genes inherited, so the risk is greater in siblings of patient having severe expression of the dis. Also the greater the number of affected relatives, the higher the risk for other relatives.

2- The rate of recurrence of the disorder is 2-7% is the same for all first degree relatives, so if parents have one affected child, the risk that the next child will be affected is 2-7%.

3- Identical twins will be affected less than 100%(about 20-40%) but is much higher greater than the chance that both nonidentical twins will be affected.

4- The risk of recurrence of the phenotypic abnormality in subsequent pregnancies depends on the outcome in previous pregnancies.

When one child affected---7% chance of the next child, while after 2 affected siblings---9% .

Multifactorial inheritance underlies DM, hypertension, gout, schizophrenia, manic depression, congenital heart dis., some skeletal abnormalities.

Cytogenetic disorders:

chromosomal aberrations:

Karyotype is a paragraphic representation of a stained metaphase spread in which the chromosomes are arranged in order of decreasing length.

Giemsa stain used, each chromosome have alternating light &dark bands of variable width.

1:200 newborn infants has some form of chromosomal abnormalities,

50% of first trimester abortion is due to chromosomal abnormalities.

Chromosomal abnormalities either in:

*number or structure,

& may affect

*autosomes or sex chromosomes.

What is Mitosis?

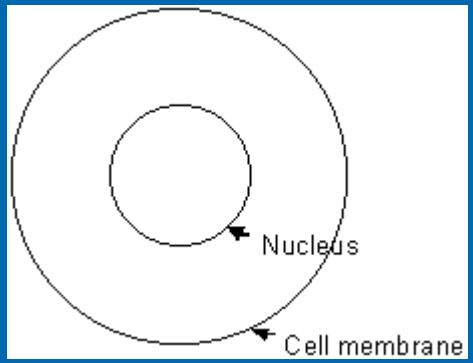
- Mitosis produces two daughter cells that are identical to the parent cell.
- If the parent cell is haploid (N), then the daughter cells will be haploid.
- If the parent cell is diploid, the daughter cells will also be diploid.
- This type of cell division allows multicellular organisms to grow and repair damaged tissue.

Phases of Mitosis

- humans have a diploid number of 46.

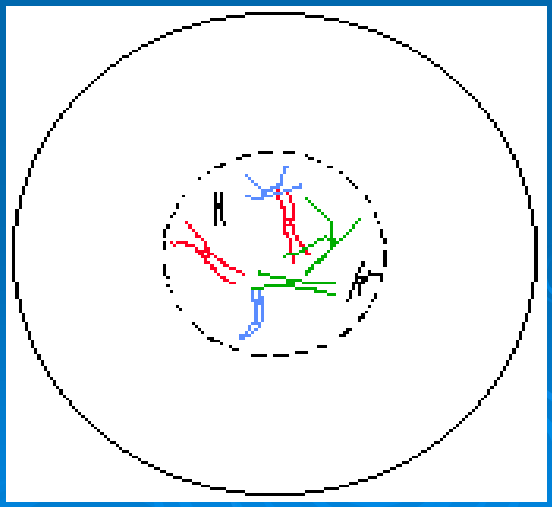
Interphase

- Chromosomes are not visible because they are uncoiled



Prophase

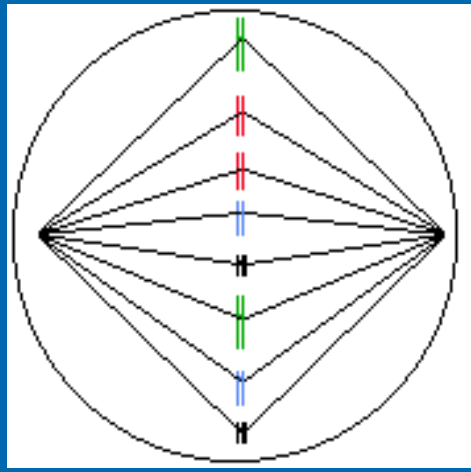
- The chromosomes coil.
- Ex. cell with 8 chromosomes. Each chromosome has 2 chromatids for a total of 16 chromatids.



Phases of Mitosis

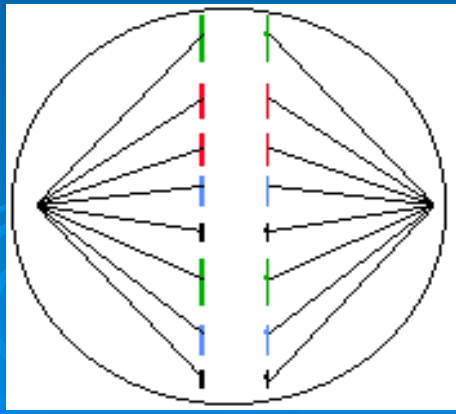
Metaphase

- The chromosomes become aligned.
- cell with 8 chromosomes. Each chromosome has 2 chromatids for a total of 16 chromatids.



Anaphase

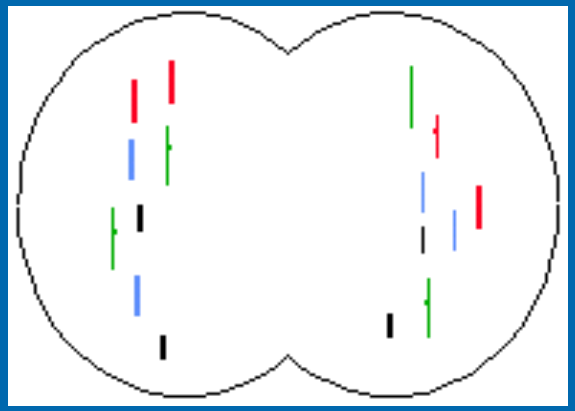
- The chromatids separate; the number of chromosomes doubles.
- The drawing shows a cell with 16 chromosomes. Each chromosome has 1 chromatid for a total of 16 chromatids.



Phases of Mitosis

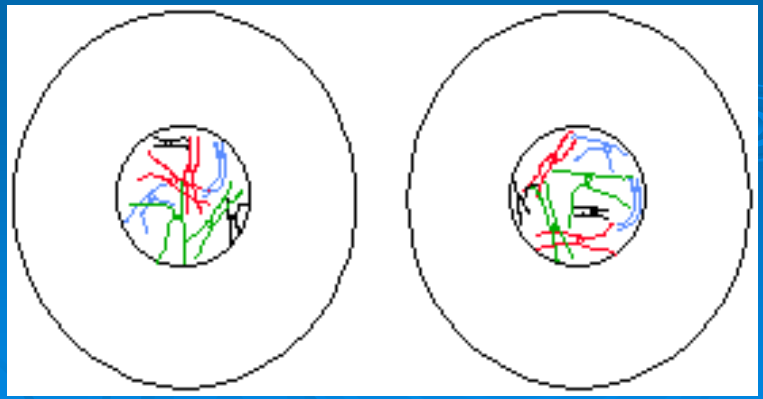
Telophase

- The cell divides into two.
- cell with 16 chromosomes. Each chromosome has 1 chromatid for a total of 16 chromatids.



Interphase

- The chromosomes have two chromatids each.



What is meiosis?

- Meiosis produces daughter cells that have one half the number of chromosomes as the parent cell.
- $2N \rightarrow N$
- Meiosis enables organisms to reproduce sexually.
- Gametes (sperm and eggs) are haploid.
- Meiosis involves two divisions producing a total of four daughter cells.

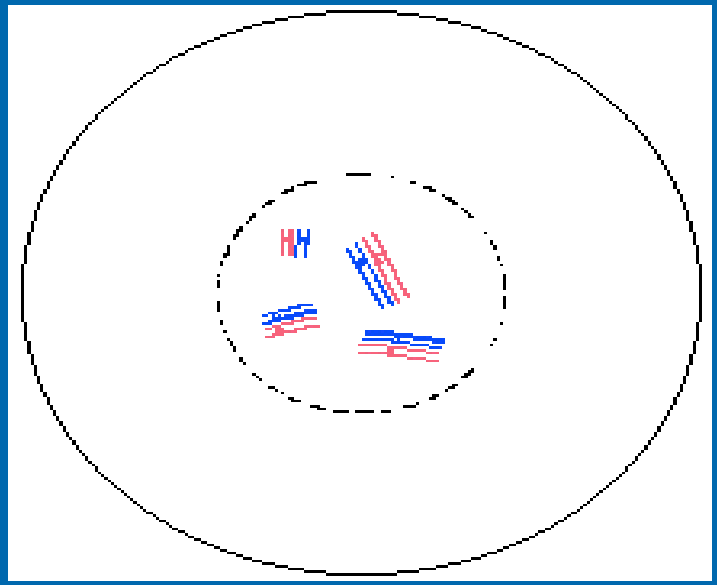
Phases of Meiosis

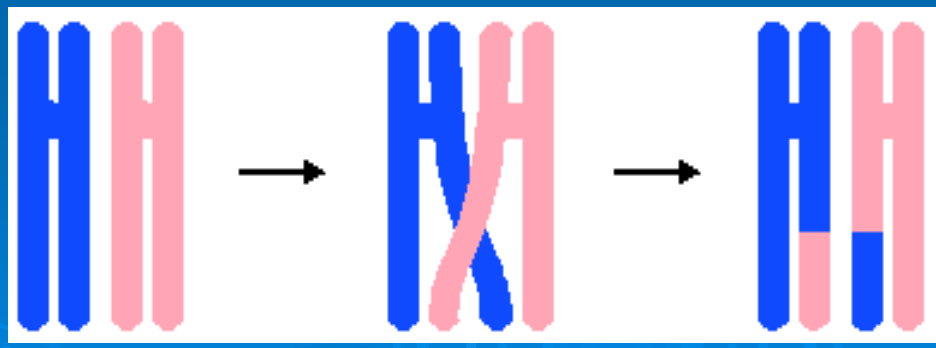
- A cell undergoing meiosis will divide two times; the first division is meiosis 1 and the second is meiosis 2.
- In the first meiotic division, the number of cells is doubled but the number of chromosomes is not. This results in 1/2 as many chromosomes per cell.
- The second meiotic division is like mitosis; the number of chromosomes does not get reduced.

Phases of Meiosis

Prophase I

- Homologous chromosomes become paired.
- Crossing-over occurs between homologous chromosomes.

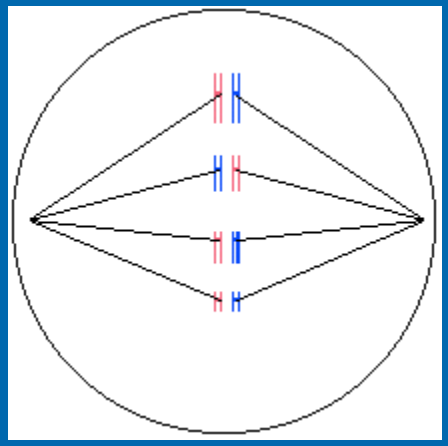




Phases of Meiosis

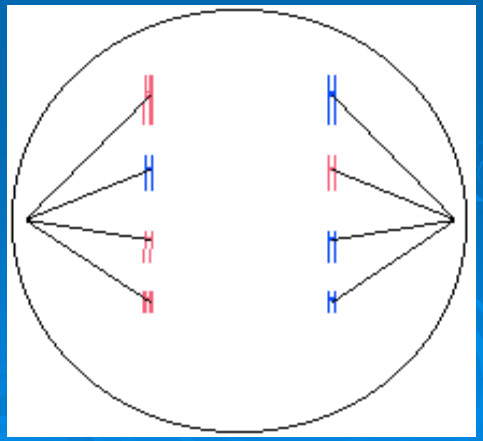
Metaphase I

- Homologous pairs become aligned in the center.
- The random alignment pattern is called independent assortment.

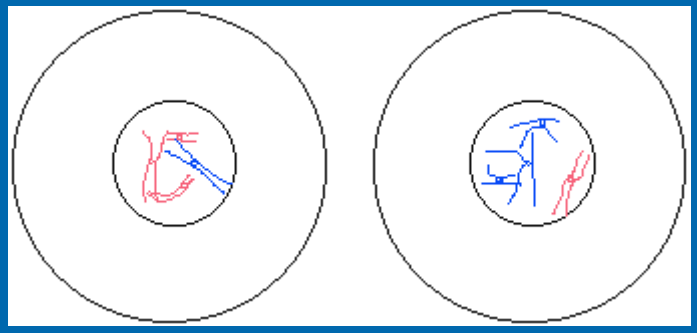


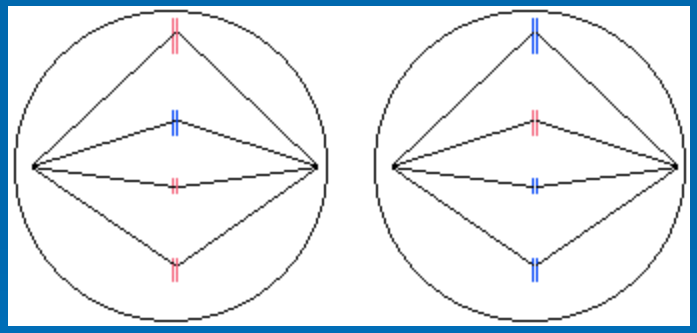
Anaphase I

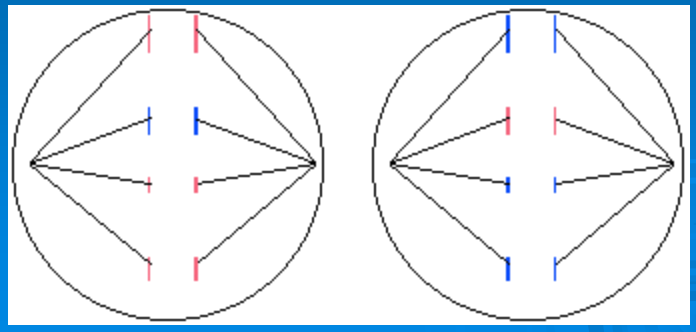
- Homologous chromosomes separate

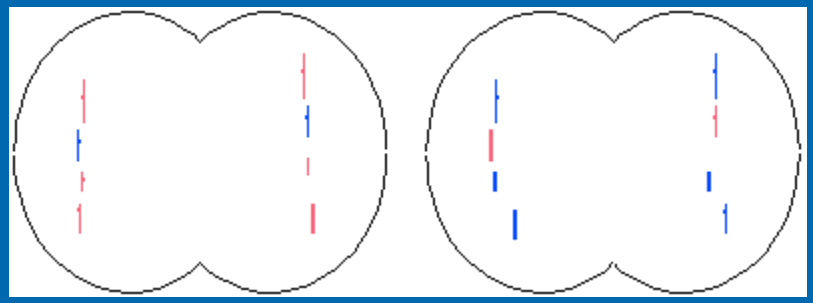


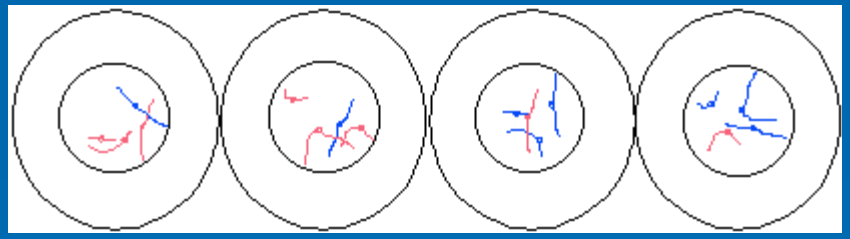
Phases of Meiosis II



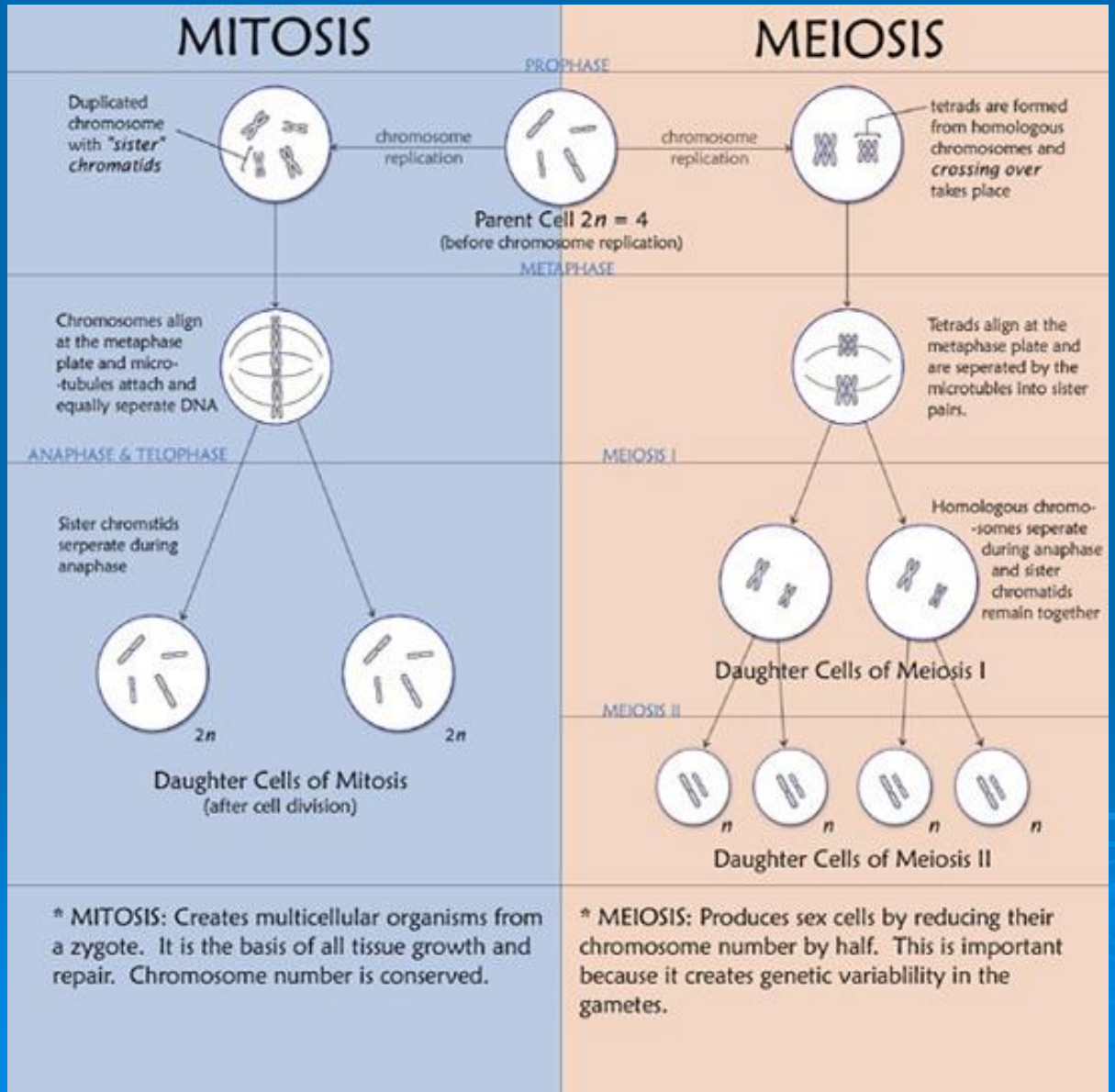








Mitosis and Meiosis



Numerical abnormalities:

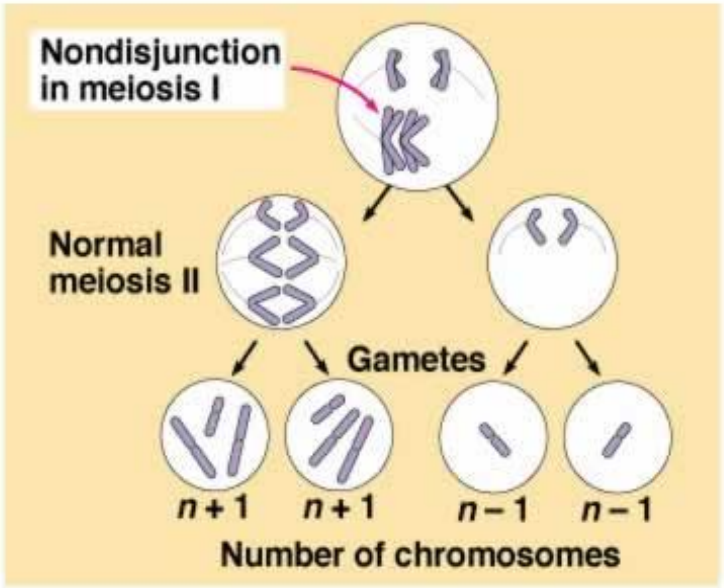
Normal chromosome count is 46 i.e 2n =46, any exact multiple of the haploid number is called euploid, chromosomal number such as 3n & 4n called polypoid usually result in spontaneous abortion.

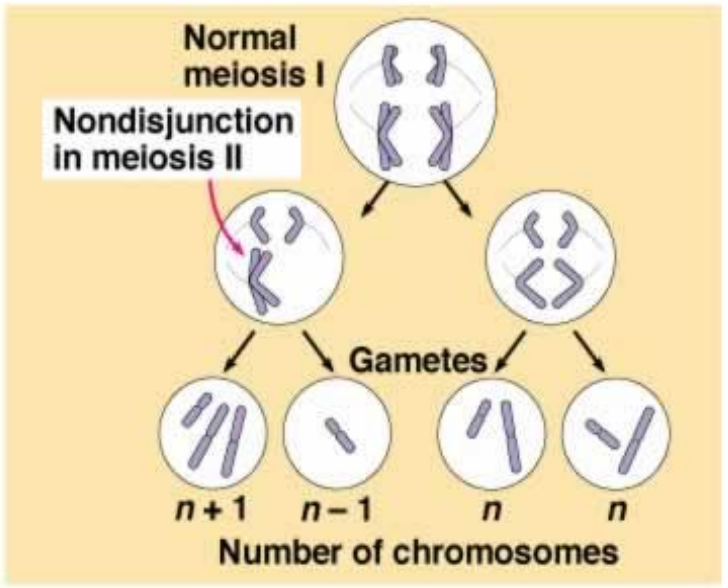
Any number which is not an exact multiple of n called aneuploid.

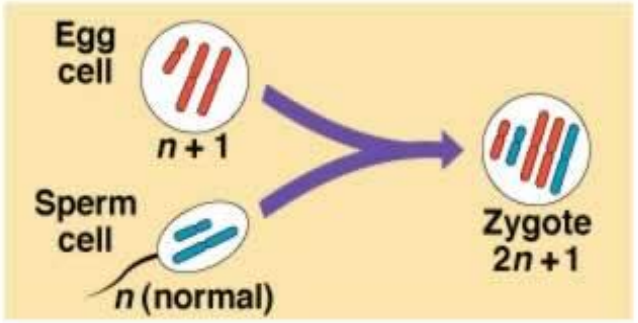
The chief cause of aneuploidy is **non disjunction** of a homologous pair of chromosome at first meiotic division or failure of sister chromatides to separate during the second meiosis.

When non disjunction occurs at time of meiosis, the gametes formed have either extrachromosome (n+1) or1 less chromosome (n-1), then fertilization lead to either trisomy (2n+1) or monosomy (2n-1).

Nondisjunction







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Autosomy (monosomy of autosomes) involving an autosome is incompatible with life, while monosomy involving sex chromosomes is compatible with life.

* Mosaicism: term used to describe the presence of 2 or more populations of cells in the same individual, mosaicism affecting sex chromosomes is common while autosomal is not.

Structural abnormalities:

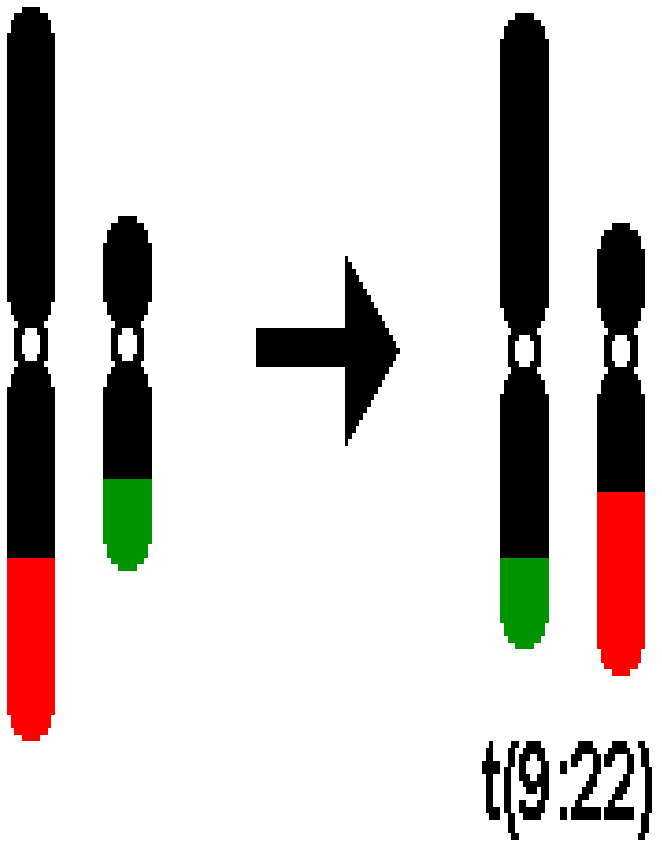
involve breakage of the chromosome &then rearrangement, patterns of rearrangement as follows:

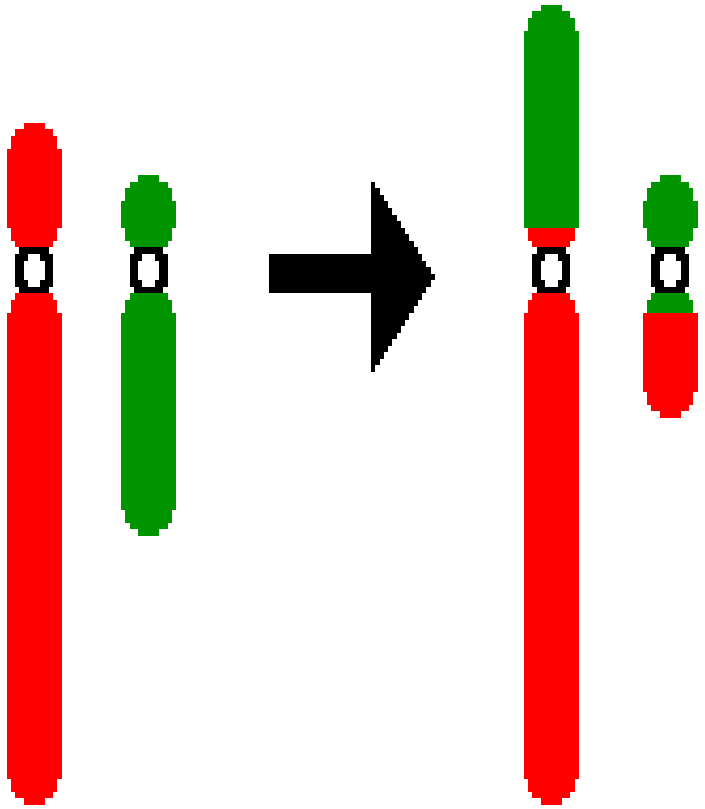
1- Translocation: transfer of a part of one chromosome to another chromosome, the process usually reciprocal (i.e fragment exchanged between chromosome)

A special pattern is called centric fusion type or *Robertsonian* translocation involving 2 acrocentric chromosomes, typically the breaks occur close to the centromere,

typically the breaks occur close to the centromere, transfer of the segment lead to one very large chromosome &one small, the short segments are lost &the carrier has 45 chromosome, such loss is compatible with life, but difficulties arise during gametogenesis--- formation of unbalanced gametes--- abnormal offspring.

Philadelphia chromosome(reciprocal translocation) which is important in the etiology of chronic myeloid leukemia



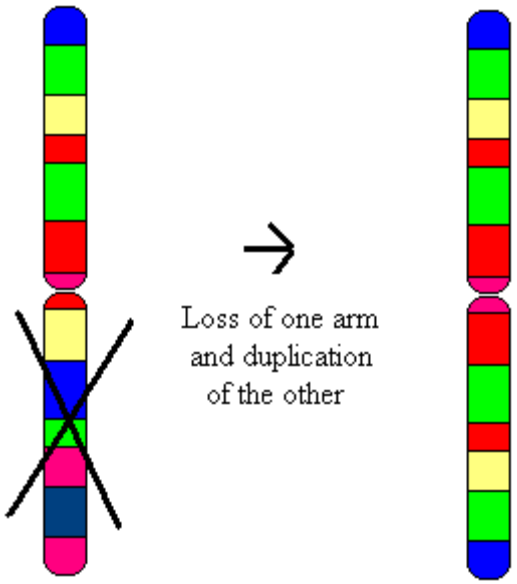


t(14;21)(p11;q11)

2- Isochromosomes:

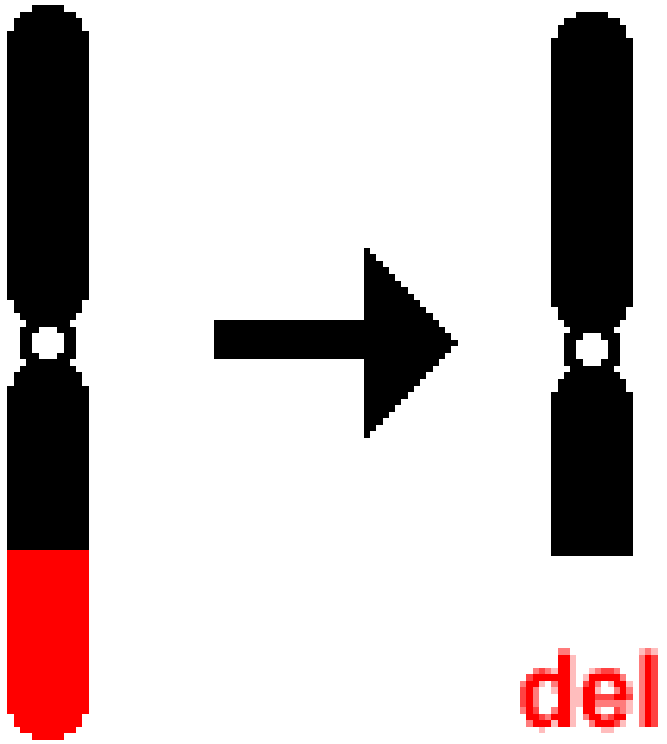
result when the centromere divides horizontally rather than vertically, one of the 2 chromosomes is then lost.

2- Isochromosome



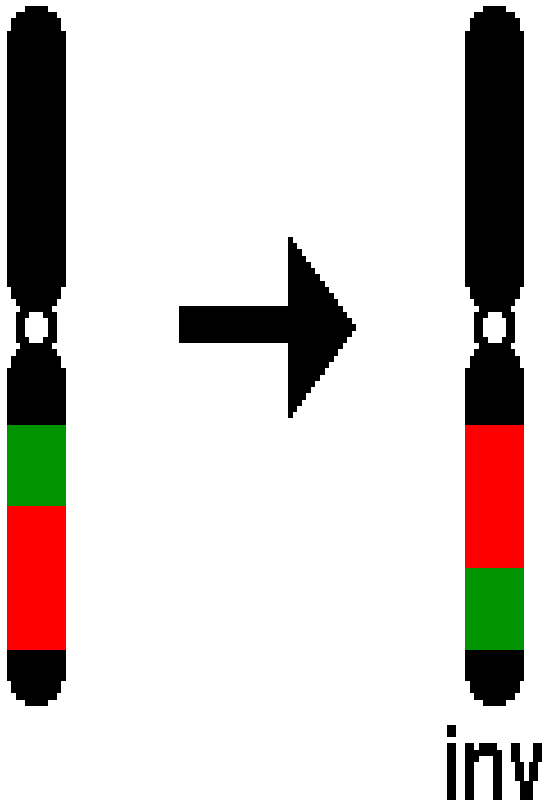
3- Deletion: involve loss of a portion of a chromosome, single break may delete a terminal segment.

2 interstitial breaks with reunion of the proximal &distal segment may result in loss of intermediate segment, the isolated fragment almost never survive.

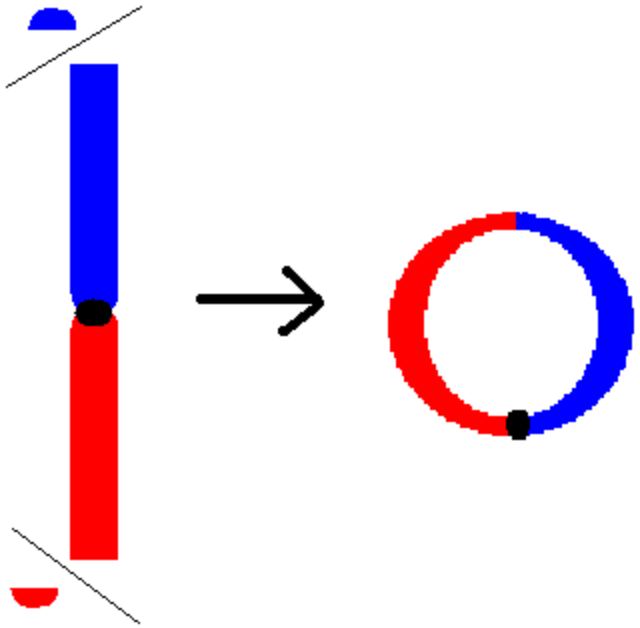

del

4- Inversion: occur when there are 2 interstitial breaks in a chromosome &the segment reunites after a complete turnaround.

5- Ring chromosome: is a variant of deletion, after loss of segments from each end of the chromosome, the arms uniting to form ring.


inv

5- Ring chromosome



Notes:

* Chromosomal disorders may be associated with absence (deletion or monosomy), excess (trisomy), or abnormal rearrangement (translocation).
* In general loss of chromosomal material produces more severe defects than does gain of chromosomal material.

*Imbalances of sex chromosome (excess or loss) are tolerated much better than are similar imbalance of autosomes & often produce subtle manifestation, sometimes not detected at birth, usually it is infertility that detected at adolescence.

Most cases are due to de novo changes (i.e parents are normal and recurrence in siblings is low).

** de novo change: Alteration in a gene for thew first time in one family member as a result of mutation in a germ cell (egg or sperm) or in fertilized egg

- Cytogenic disorders involving autosomes:

Trisomy mainly (21, 18, 13).

Trisomy 21 (Down syndrome):

Is the most common, chromosomal count is 47, the most common cause is meiotic non disjunction in the ovum, the parents are normal but maternal age is important, in women more than 45---1:25 birth.

- In 4%, the extrachromosomal material is translocation of long arm of chromosome 21 to 22 or 14.
- 1% is mosaicism with mixture of 46 &47 chromosome

- Clinical features:

1- Mental retardation.

2- Epicanthic folds &flat facial profile.

3- Abundant neck skin.

4- Simian creases.

5- Congenital heart defects &is the principle cause of death in addition to serious infection.

Patients with Down syndrome have abnormal immune responses that predispose them to serious infections, particularly of the lungs, and to thyroid autoimmunity.

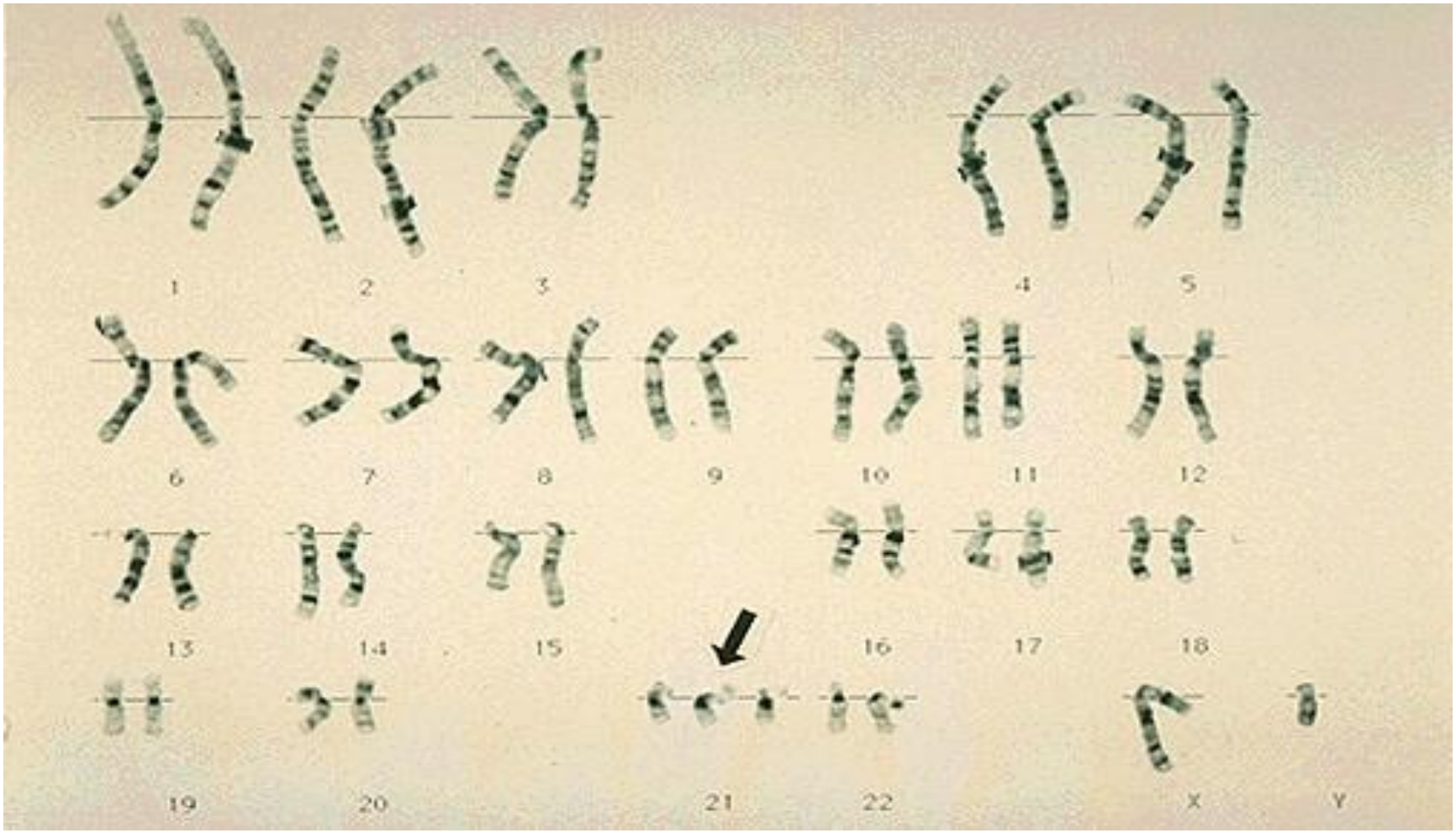
6- Umbilical hernia.

7- Intestinal stenosis.

8- Hypotonia.

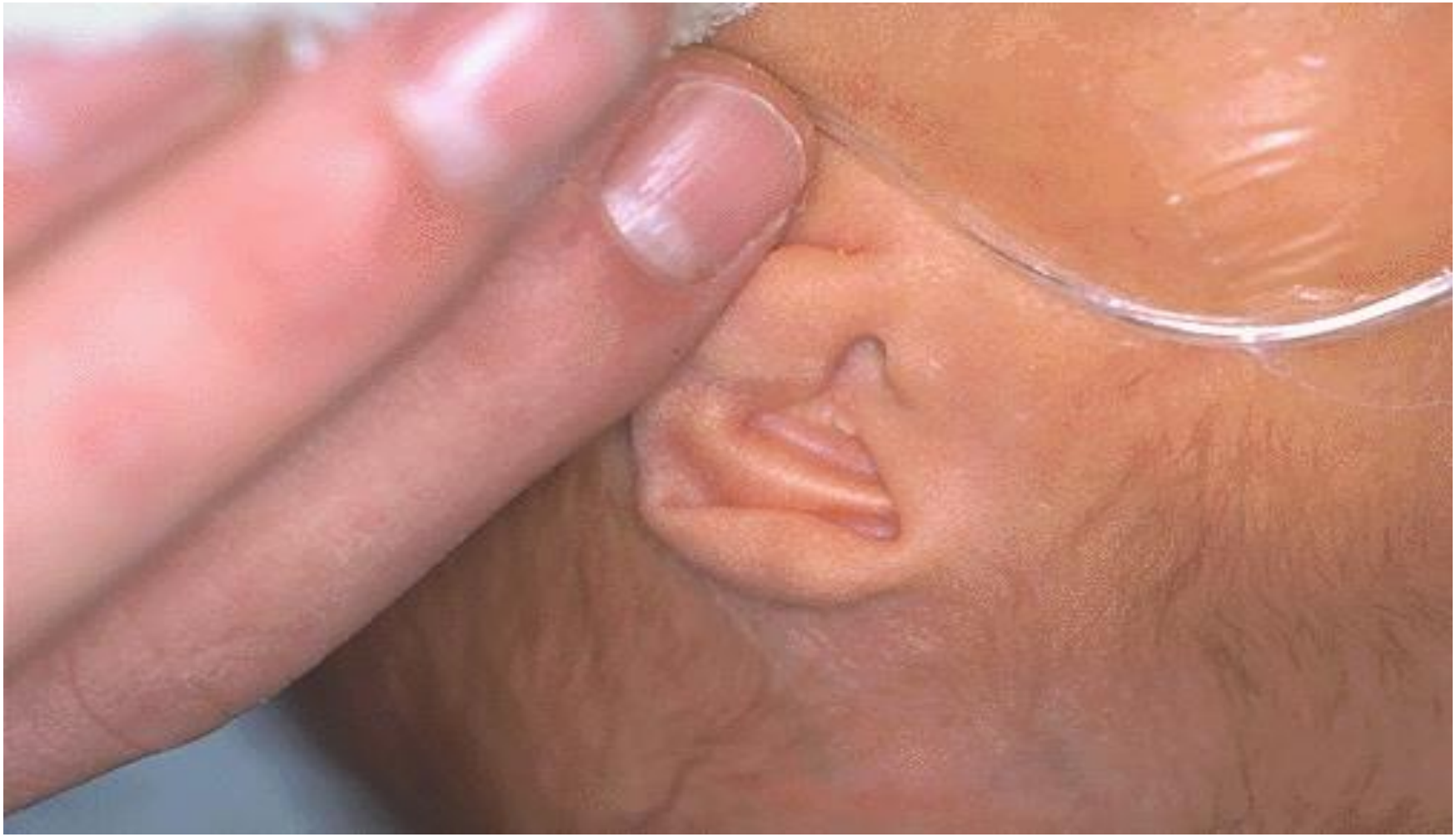
9- Gab between first &second toe.

10- Predisposition to leukemia.


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- **Trisomy 13 (Patau syndrome):**

1- Microcephaly &mental retardation.

2- Microphthalmia.

3- Cleft lips &palate.

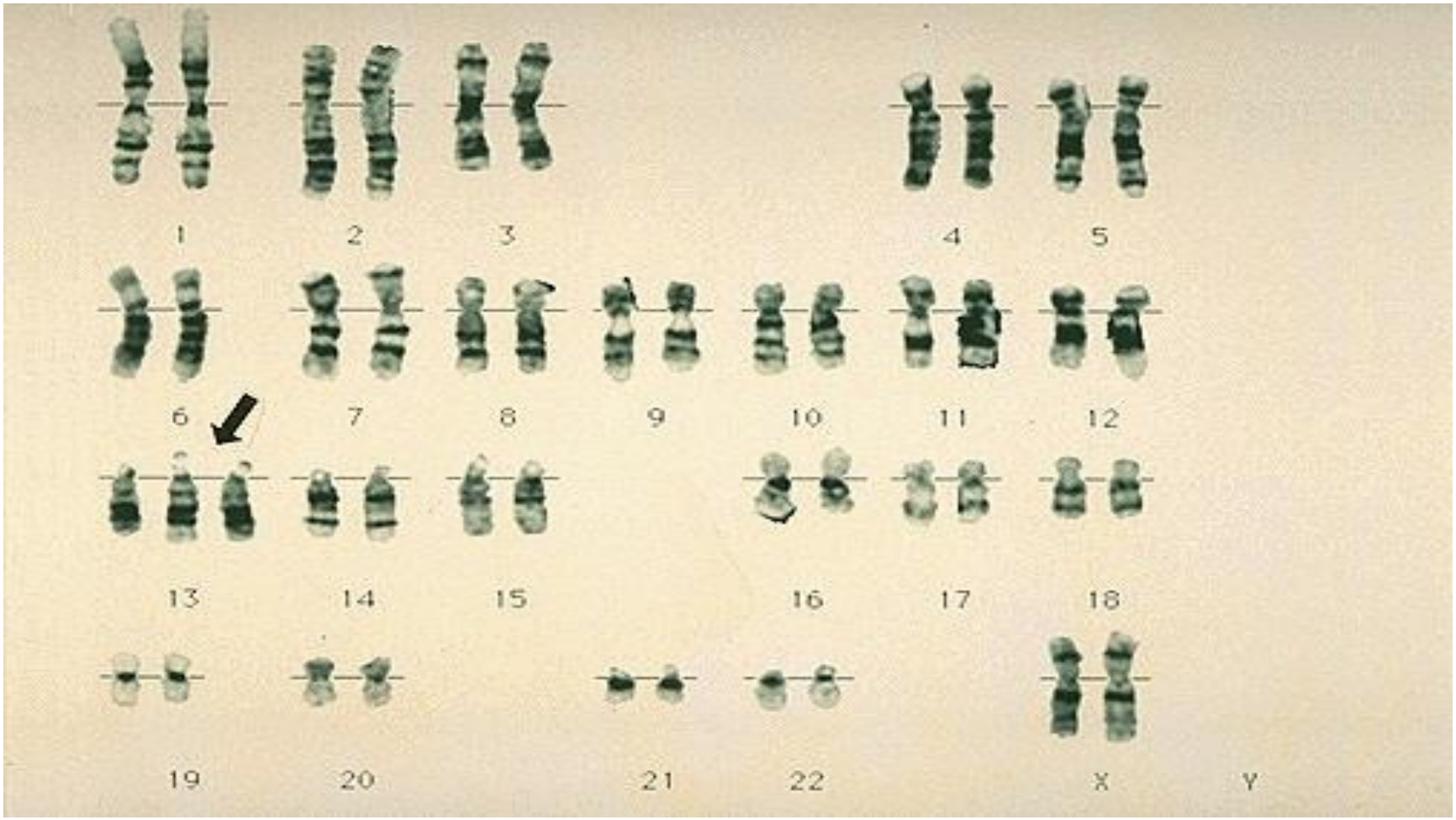
4- Cardiac defects.

5- Umbilical hernia.

6- Renal defects.

7- Polydactyly.

8- Rocker-bottom feet.


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- ***Cytogenetic disorders involving sex chromosomes:***

Are compatible with life due to:

1- Lyonization of X chromosome.

2- Scant amount of genetic information carried by Y chromosome

One of the X chromosome is inactivated early in fetal life &called Bar body.

Extra Y chromosome readily tolerated because the only information carried by it is related to male differentiation.

- ***3 disorders*:**

1- Klinefilter syndrome:

Male hypogonadism develop when there are at least 2 X chromosome &one or more Y chromosome.

Karyotype: most patients are 47,XXY in 80% and mosaic in 20%.

- **Causes:**

* Advanced maternal age.

* History of irradiation of either parent.

- **Clinical features:**

*Hypogonadism

* marked testicular atrophy (infertility)

* gynecomastia

* reduced facial &body hair (failure of male secondary sexual characteristics development)

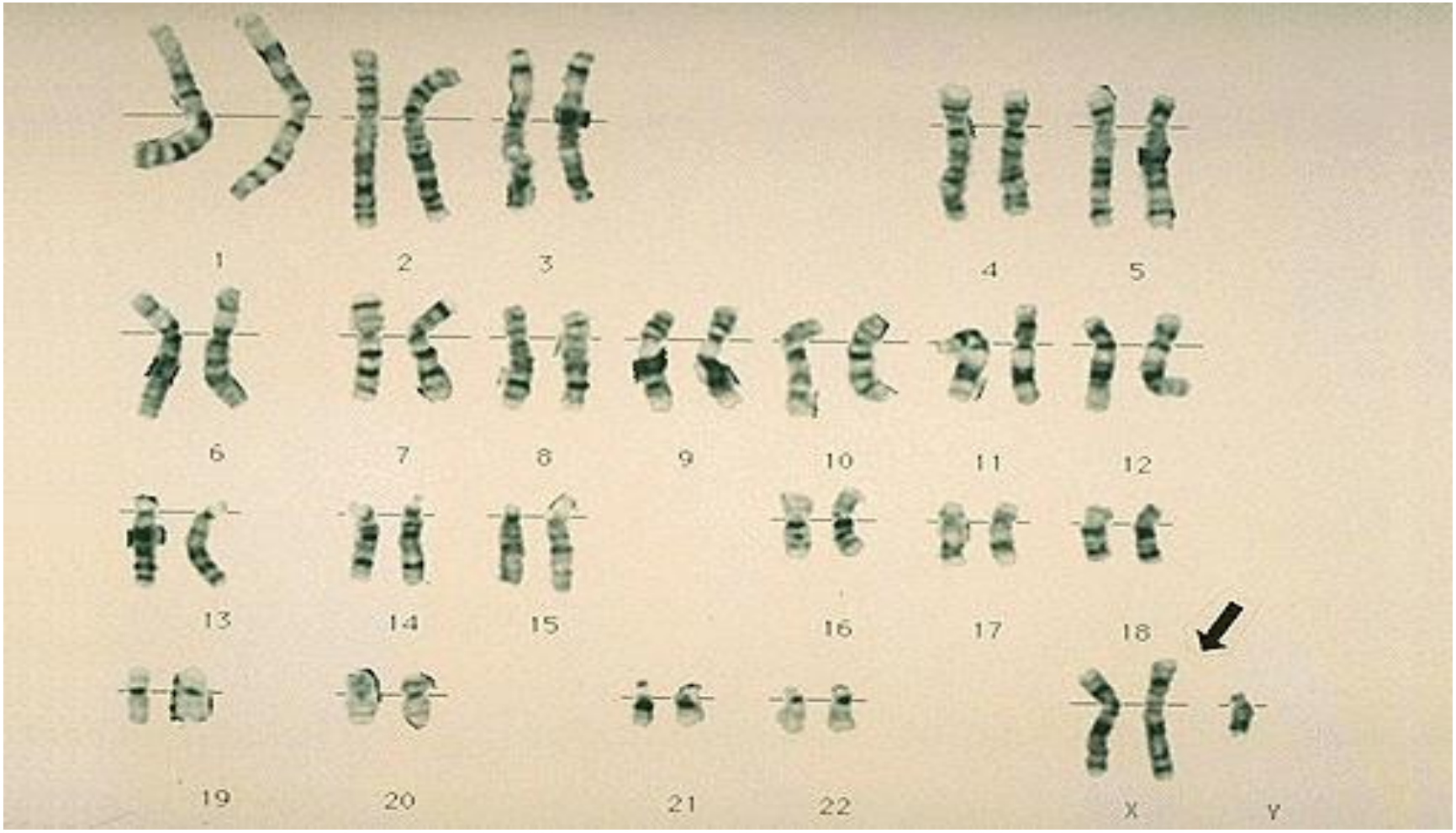
* increase length between the soles &pubic bones, **which creates the appearance of an elongated body.**

* serum testosterone decrease

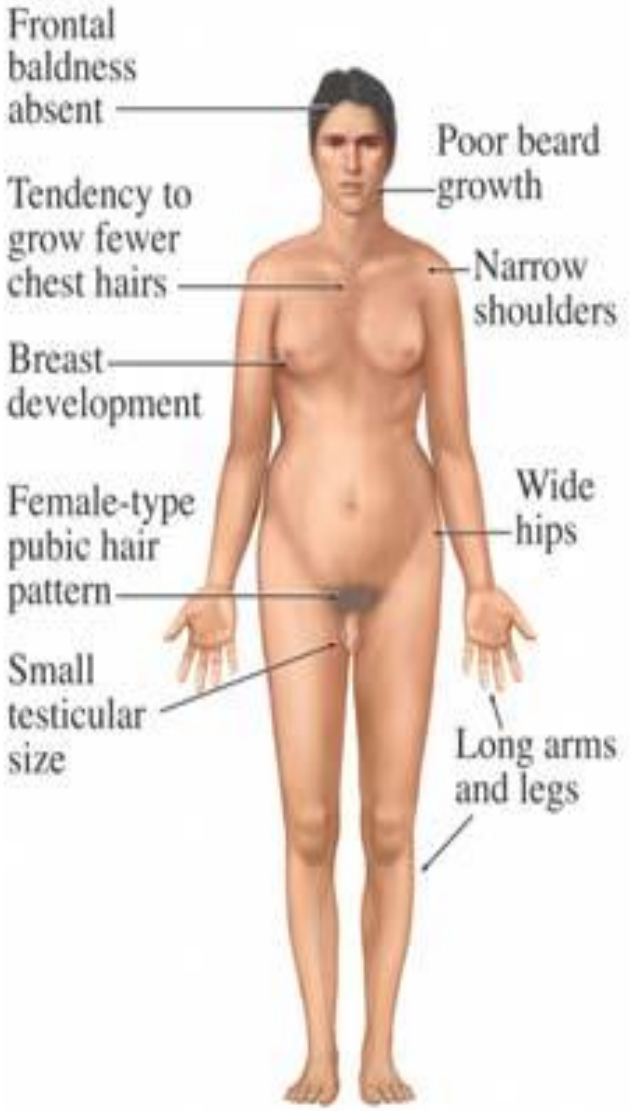
* some with mental retardation.

- The principle clinical effect is sterility, only rare patient are fertile.
- **Histologically:**

Hyalinization of tubules which appear as ghost like in contrast lydig cells are prominent.

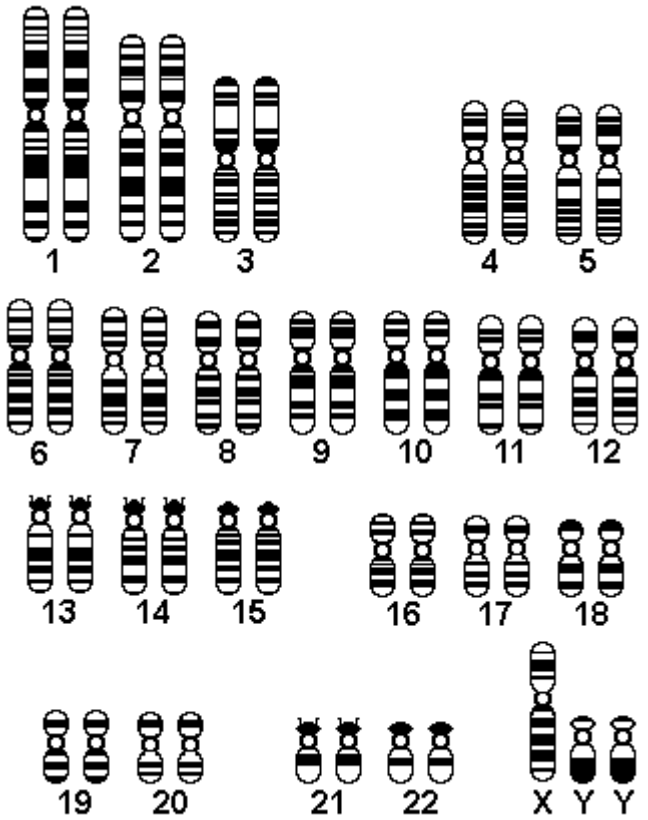

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Klinfilter syndrome



2- XYY males:

Due to non disjunction at the second meiotic division, most are phenotypically normal, but taller than usual also with antisocial behavior.


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3- Turnner syndrome:

Characterized by hypogonadism in phenotypic female result from partial or complete monosomy of X chromosome

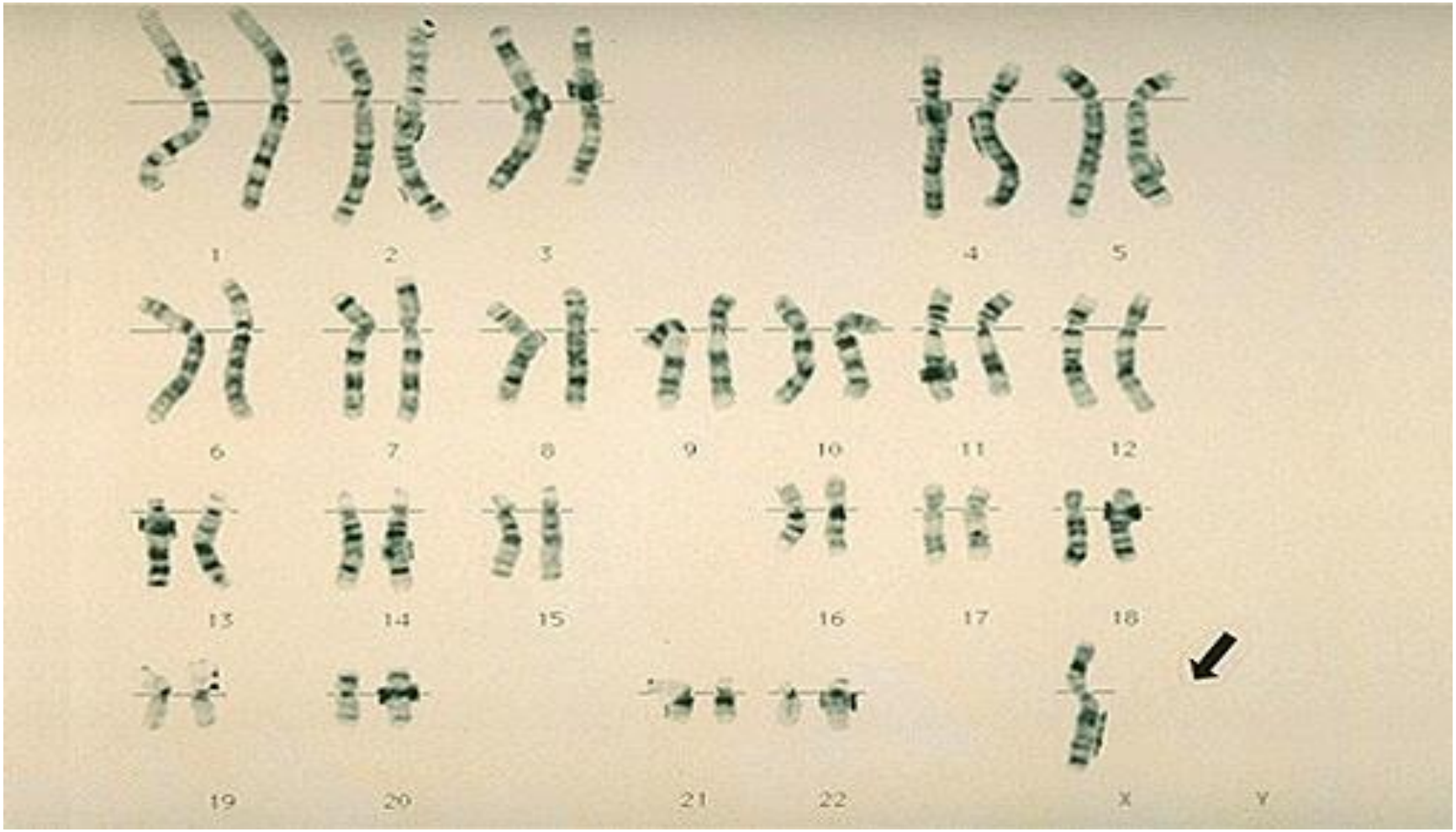
Karyotype: 45 XO .

- **Clinical features:**

* Short stature.
* Low posterior hair line.
* Cubitus vulgus (increase in carrying angle of the arms).
* Shield like chest with widely spaced nipples
* High arched palate.

* Lymphoedema of the hands &feet.
* Variety of congenital malformation e.g horseshoe kidney, coarctation of aorta.
* Failure of development of secondary sexual characteristics.

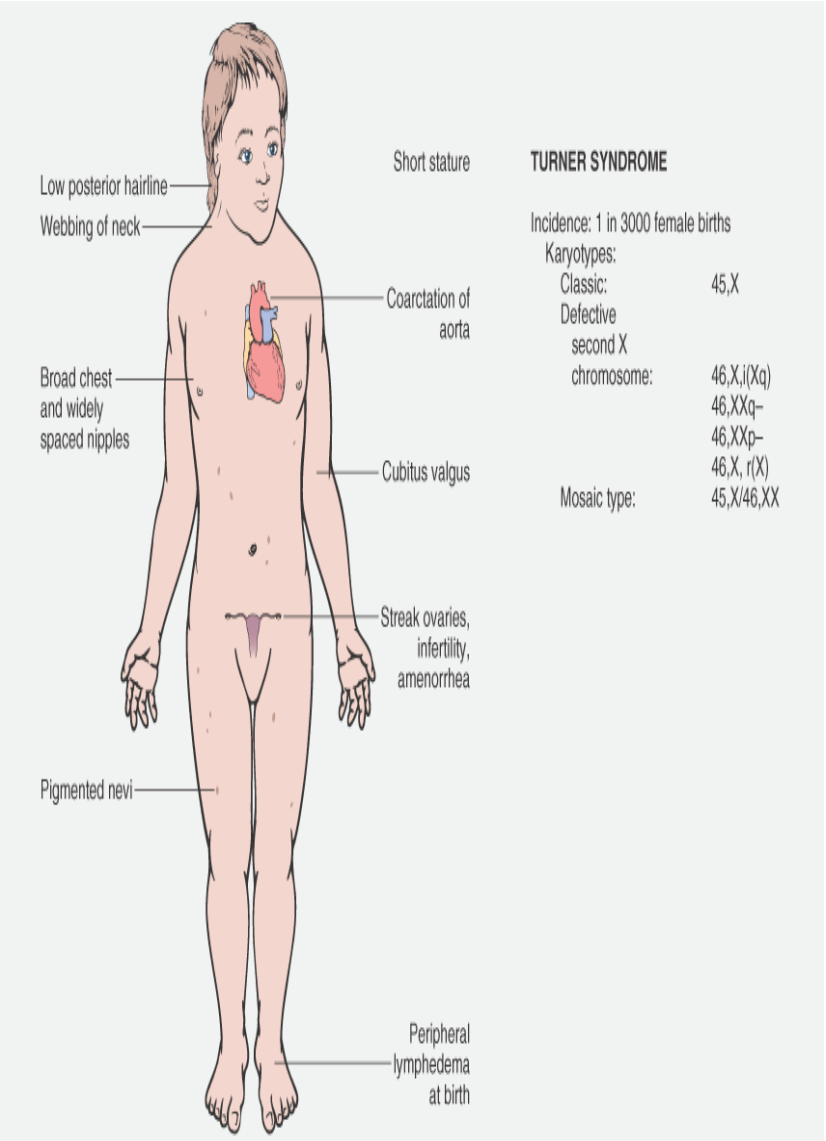
* Genitalia remain infantile (little pubic hair, primary amenorrhea.
* Ovaries fibrosed which is devoid of follicles.
* Ovarian estrogen decrease with no feed back inhibition so increase pituitary gonadotrophins.


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Turner's syndrome







- ***Single gene disorders with atypical patterns of inheritance:***
- Three groups of diseases resulting from mutation affecting single genes do not follow the mendelian rules of inheritance:

1- Diseases caused by triplet repeat mutation: (Fragile X syndrome):

- The mutation is characterized by long repeating sequence of three nucleotide, so disrupt the function of that gene (FMR-1).
- It is characterized by mental retardation &an abnormality of X chromosome.

- It is one of the most common causes of familial mental retardation in males, the only distinctive physical abnormality in 80% of postpubertal males is macroorchidism.

- This disease is X-linked but unlike other X-linked diseases, 20% of males with the diseases are clinically &cytogenically normal (carrier males).
- Presence of mental retardation in 50% of the carrier females .

- These unusual features have been related to the number of triplet repeat, in normal population, the number of repeat is small about 29 (**range 6-55**) whereas affected individuals have 250-4000 repeat so called **full mutation** &the carrier male &females (55-200) are **premutation**.

- This disease is X-linked but unlike other X-linked disorders;

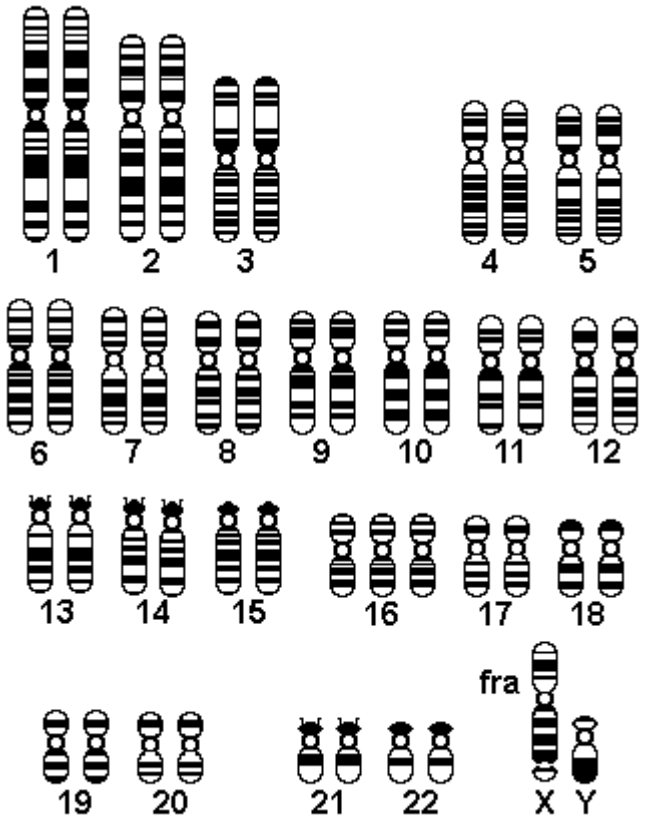
1. Carrier males: (20%) of males carry a fragile X mutation do not manifest the typical neurological or physical characteristics of fragile X. these carrier males (also known as “transmitting males”

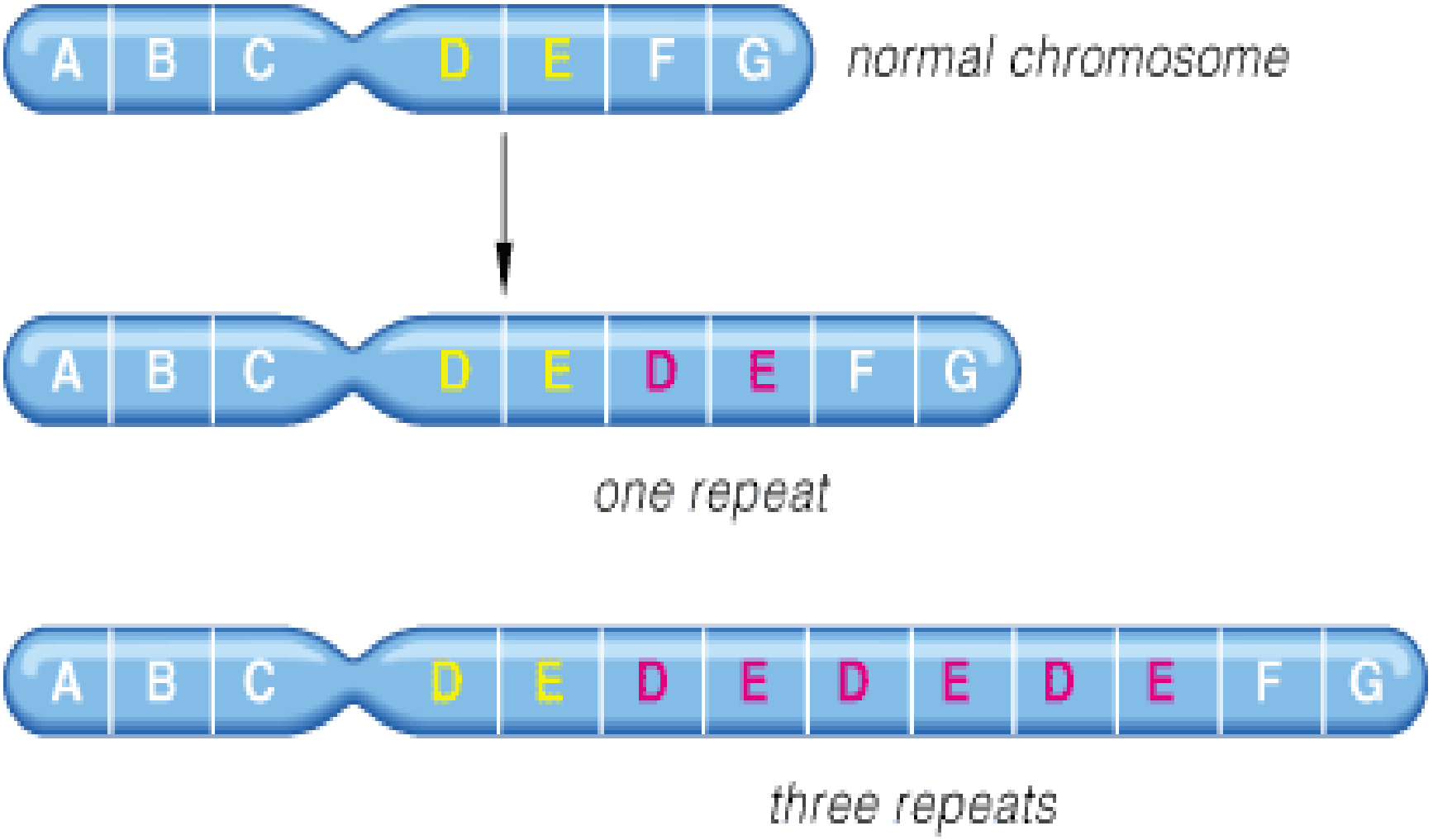
2. Carrier females are also affected: (30% to 50%) of carrier women with the fragile X mutation on one chromosome show features of mild cognitive impairment or other behavioral disturbances and some develop premature ovarian failure.

Anticipation: This refers to that the clinical features of FXS worsen with each successive generation, as carrier male may have **40%** risk of transmitting the disease to their grandsons who inherit a premutation from their grandfather that is amplified to a full mutation in their mothers’ ova)

Affected male: have moderate to severe mental retardation, epilepsy in 30% of cases, aggressive behavior in 90% of cases, (autism and anxiety disorder/hyperactivity disorder affecting 50% to 75% of males. 2-5% of patients diagnosed first with non syndromic autism have a mutation in the FMR1 gene. The typical physical phenotype includes; a long face with a large mandible, large everted ears, and large testicles (macroorchidism).

Diagnosis: by cytogenetic demonstration of the fragile site or by DNA probe analysis.


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A B C D E F G
normal chromosome
A B C D E D E F G
one repeat
A B C D E D E D E D E F G
three repeats


A
B
C

2- Diseases caused by mutation in mitochondrial genes:

Mitochondria contain several genes encodes for enzymes of oxidative phosphorylation, usually the ovum contain the large part of mitochondria, so the inheritance of mitochondrial gene is maternal.

- Disease caused by mitochondrial genes are rare:
- ***Leber"s optic neuropathy***---progressive bilateral loss of central vision.

3- Diseases associated with genomic imprinting:

Prader Willi &Angleman syndromes:

All humans inherit two copies of each gene, carried on homologous maternal &paternal chromosomes &there is no difference between normal homologous genes.

But now functional difference exists between maternal &paternal genes is called genomic imprinting.

- Genomic imprinting; is an epigenetic process resulting in differential inactivation of either maternal or paternal alleles of certain genes.
- Maternal imprinting implies that the maternal allele is inactivated, whereas the paternal imprinting refers to inactivation of the paternal allele.

Prader Willi syndrome and Angelman syndrome: both arise from deletion of band of long arm of chromosome 15, but have different clinical features

Prader Willi: mental retardation, short stature, hypotonia, hypogonadism, obesity, small hands &feet.

Causes: Occurs when the paternal 15q12 which is the only functional allele is deleted, leaving behind the “silenced” maternal gene product.

- ***Angleman syndrome:***

* Mental retardation.
* ataxic gait.
* seizures.
* inappropriate laughter called happy puppet syndrome.

Causes: occurs when the maternal 15q12 which is the only functional allele is deleted, leaving behind only the “silenced” paternal gene product.

Because DNA methylation affect gene expression, it is strongly suspected that imprinting is associated with differential DNA methylation of paternal &maternal genes.

DIAGNOSIS OF GENETIC DISEASES

Genetics & Human Diseases

- **About 4,000 human diseases are thought to be inherited**

- **Scientists are making good progress figuring out where genes are located on chromosomes and in understanding how the mutations in genes cause disease**

Genetic Analysis

- In general, genetic testing can be divided into prenatal and postnatal analysis.
- It may involve

- ❑ Karyotype analysis
- ❑ FISH,
- ❑ molecular diagnostics (PCR), or
- ❑ a combination of these techniques.

Karyotype Analysis of Human Chromosomes

Karyotype preparation and analysis

- Cells (from blood, amniotic fluid, etc) are grown *in vitro* (in a cell culture dish) to increase their number
- Cell division is then arrested in metaphase with **colchicine** (prevents mitotic spindle from forming)
- Cells are centrifuged and lysed to release chromosomes
- Chromosomes are stained with Geimsa stain, photographed, and grouped by size and banding patterns

photograph of the 46 human chromosomes in a somatic cell, arrested in metphase.



Limitations of karyotype analysis

- resolution of this technique is fairly low
- it is applicable only to cells that are dividing or can be induced to divide in vitro.

FISH
“Fluorescence in Situ Hybridization ”

“Fluorescence in Situ Hybridization ”-FISH

- FISH utilizes DNA probes that recognize sequences specific to chromosomal regions.
- The probe binds to its complementary sequence on the chromosome and thus labels the specific chromosomal region that can be visualized under a fluorescent microscope.

polymerase chain reaction (PCR)

polymerase chain reaction (PCR)

- Many genetic diseases are caused by alterations at the nucleotide level (i.e., mutations) that cannot be detected by FISH

advantages over other techniques:

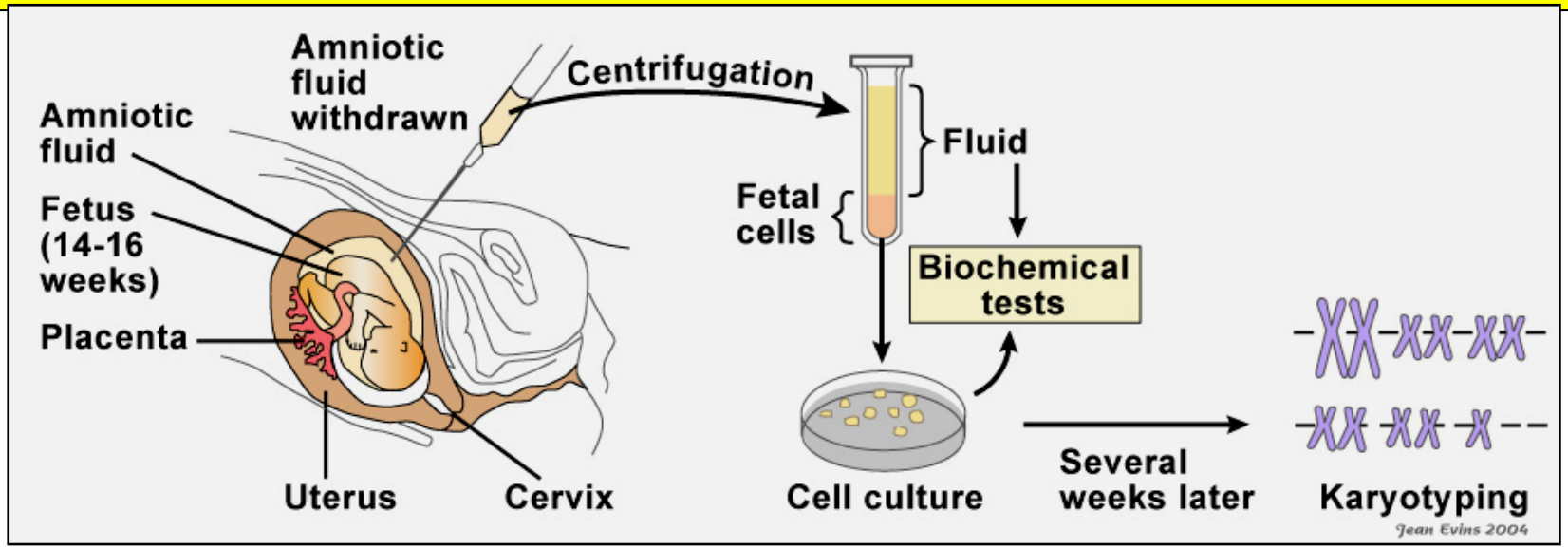
- It is remarkably sensitive.
- The use of polymerase chain reaction (PCR) allows several million-fold amplification of DNA or RNA, making it possible to utilize as few as 1 or 100 cells for analysis. A few drops of blood or a piece of biopsy tissue can supply sufficient DNA for PCR amplification.

Prenatal testing

- ***is testing for diseases or conditions in a fetus or embryo before it is born.***
- ***The aim is to detect birth defects such as neural tube defects, Down syndrome, chromosome abnormalities, genetic diseases and other conditions.***

- Diagnostic prenatal testing can be by invasive methods or non-invasive methods.

Amniocentesis



- ***Used on pregnant women over 35 years of age***
- ***Performed during weeks 15-17 of pregnancy***
- ***A needle is inserted into the amniotic sac***
- ***Amniotic fluid with fetal cells is removed***
- ***A karyotype of the fetal chromosomes is prepared***

Scientific Breakthroughs

Greater insights into disease will be achieved

Cures may be found

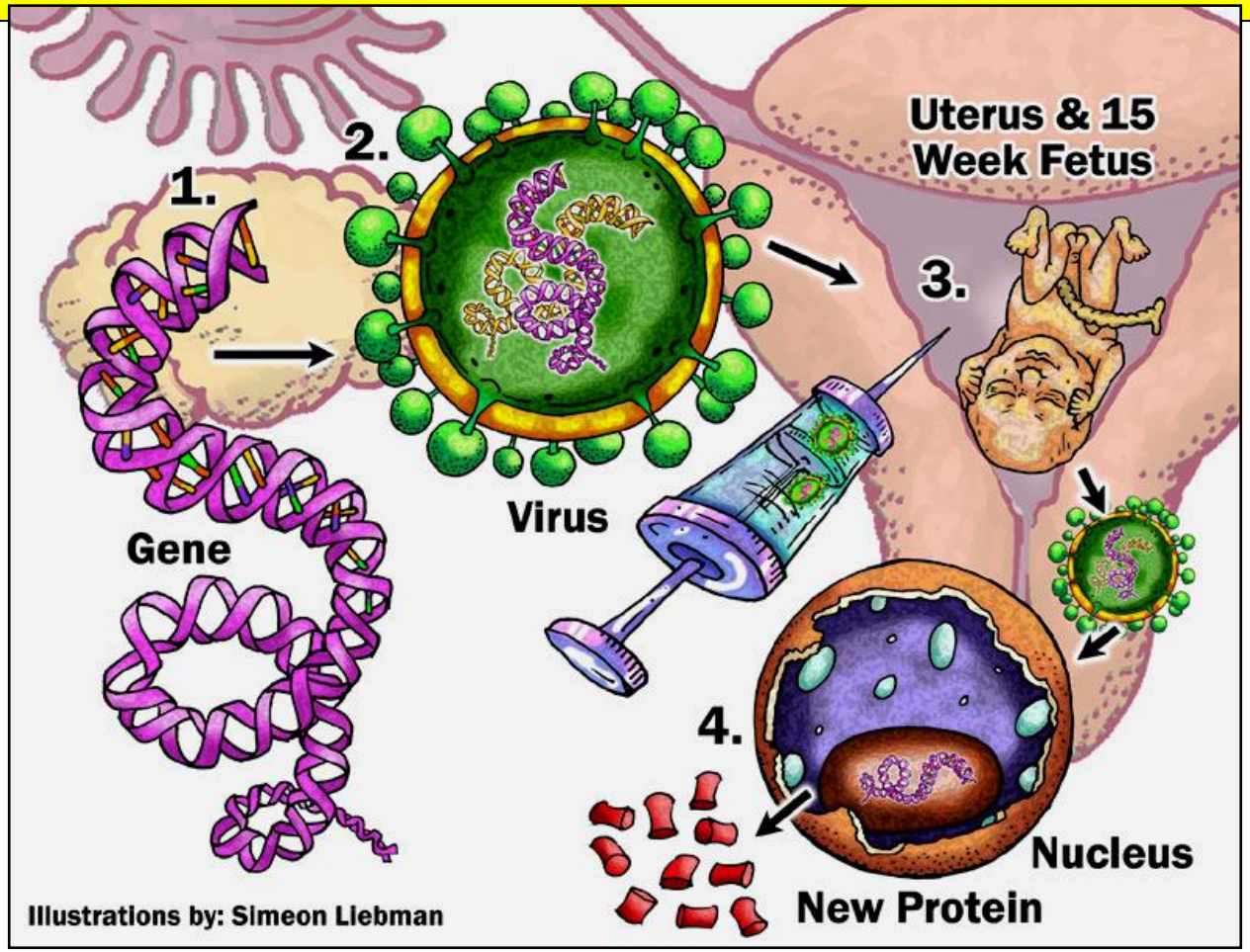
Incurable diseases may be prevented

There will be new insights into the evolutionary origins of humans

Gene Therapy

- Genetic alteration of somatic cells to treat disease.
- Researchers inject genes that are targeted to treat a particular disease in to a patient's blood stream.
- When the genes arrive at the site of the defective genes, they produce chemicals that can treat the problem.

Steps in Gene Therapy In Utero



Genetic Counseling

- Can help couples obtain valuable information about the parents' genetic makeup .
- It can help potential parents to evaluate genetic risk factors in childbearing and enable them to make intelligent decisions.
- It includes analysis of parental medical records and family histories to construct a family pedigree.

Indications for Genetic Analysis

- *Prenatal genetic analysis*
- should be offered to all patients who are at risk of having cytogenetically abnormal progeny. It can be performed on cells obtained by amniocentesis, on chorionic villus biopsy material, or on umbilical cord blood.

Detecting Birth Defects

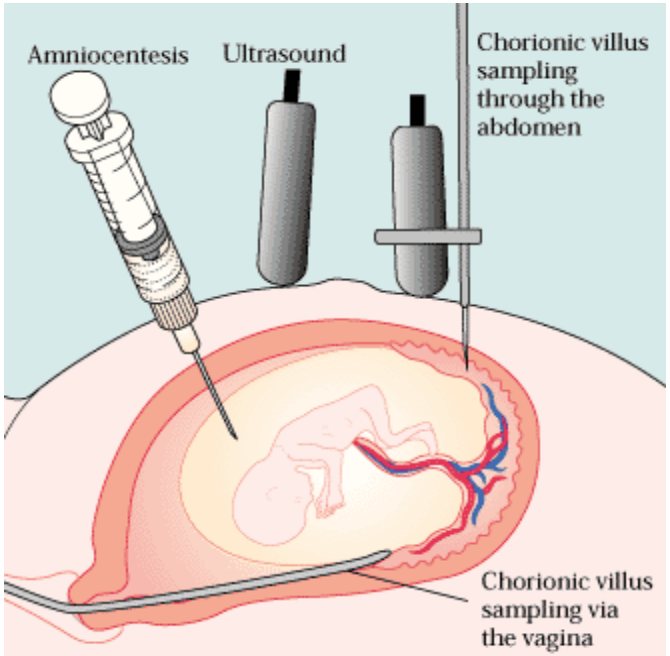
Amniocentesis

Chronic Villus Sampling

Ultrasound Sonography

Maternal Blood Test

- Some important indications:
- A mother of advanced age (>34 years), because of greater risk of trisomies
- A parent with a previous child with a chromosomal abnormality
- A parent who is a carrier of an X-linked genetic disorder (to determine fetal sex).
- Fetal abnormality observed on ultrasound
- A parent who is carrier of structurally abnormal chromosome (in such cases, the gametes may be unbalanced, so the progeny would be at risk for chromosomal disorders).



Methods of screening in pregancy

- *Postnatal genetic analysis*
- is usually performed on peripheral blood lymphocytes.
- Multiple congenital anomalies
- Unexplained mental retardation and/or developmental delay
- Suspected aneuploidy (e.g., features of Down syndrome)
- Suspected sex chromosomal abnormality (e.g., Turner syndrome
-)Suspected fragile X syndrome
- Infertility (to rule out sex chromosomal abnormality)
- Multiple spontaneous abortions (to rule out the parents as carriers of balanced translocation; both partners should be evaluated).