Chromosomal abnormality

The human genome.

The human genome has approximately 25,000 genes, which are the individual units of hereditary of all traits.

Haploid: (N) one copy of genetic complement (23 chromosomes)

Diploid: (2N) two copies of genetic complement (46 chromosomes)

The DNA molecule has building blocks:

a- a pentose sugar (deoxyribose)

b- phosphate group

c- 4 types of bases

.purines (adenine and guanine)

.pyrimidines (thymine and cytosine)

Definitions

Gene: is a functional unit of DNA, length range from several hundred to >2. million bp.

Nucleotide: basic subunit of DNA, composed of one deoxyribose, one phosphate group and one base.

Exon: DNA segment that is retained in mature mRNA.

Interon: sequences of DNA that is excised in mature mRNA.

Mutation: variations between individuals that have an impact on the functioning of a gene.

Polymorphism: variations that do not have effect on the health or functioning of an organism.

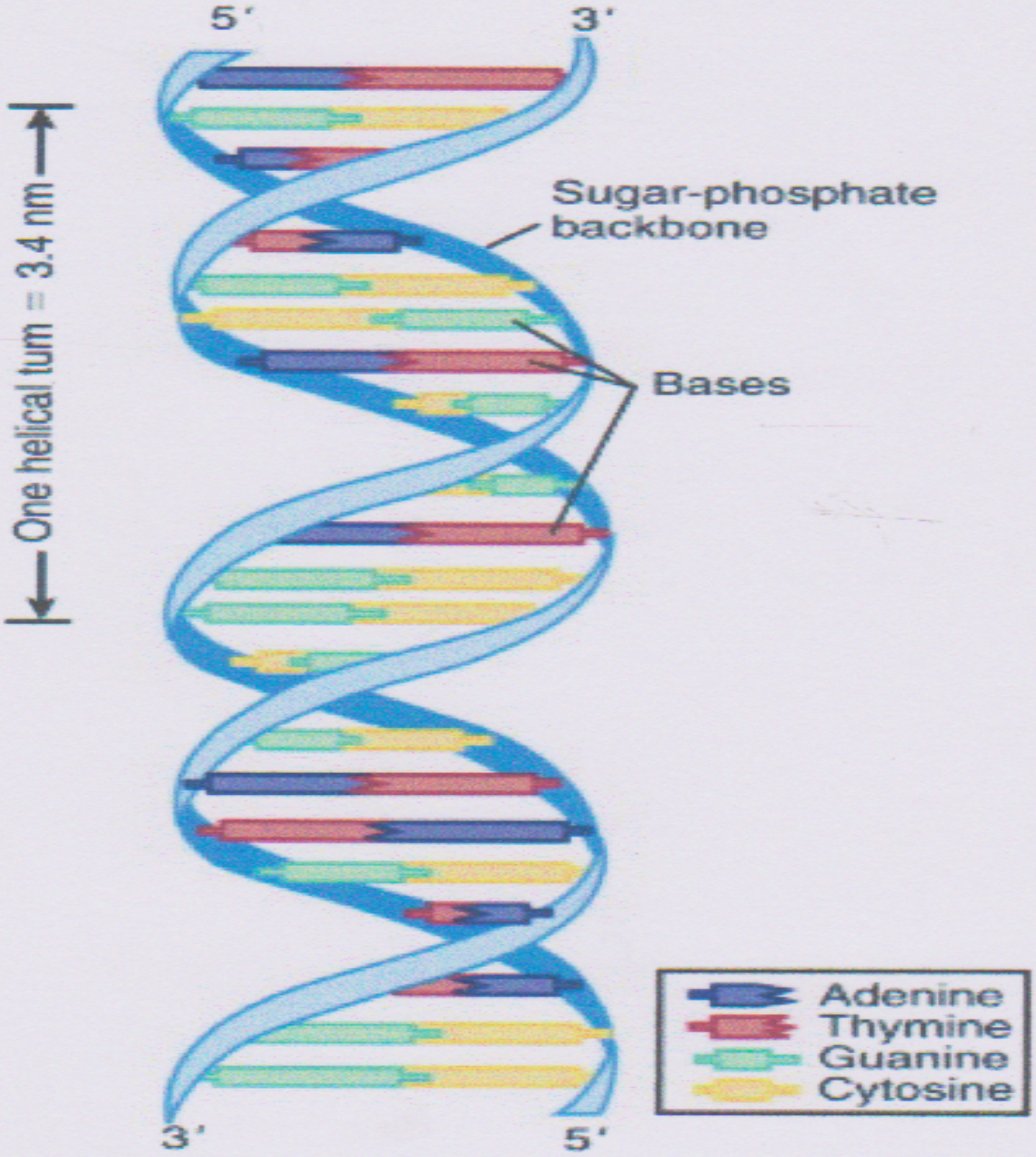
Allele: the gene at the homologous loci (identical pair of loci).

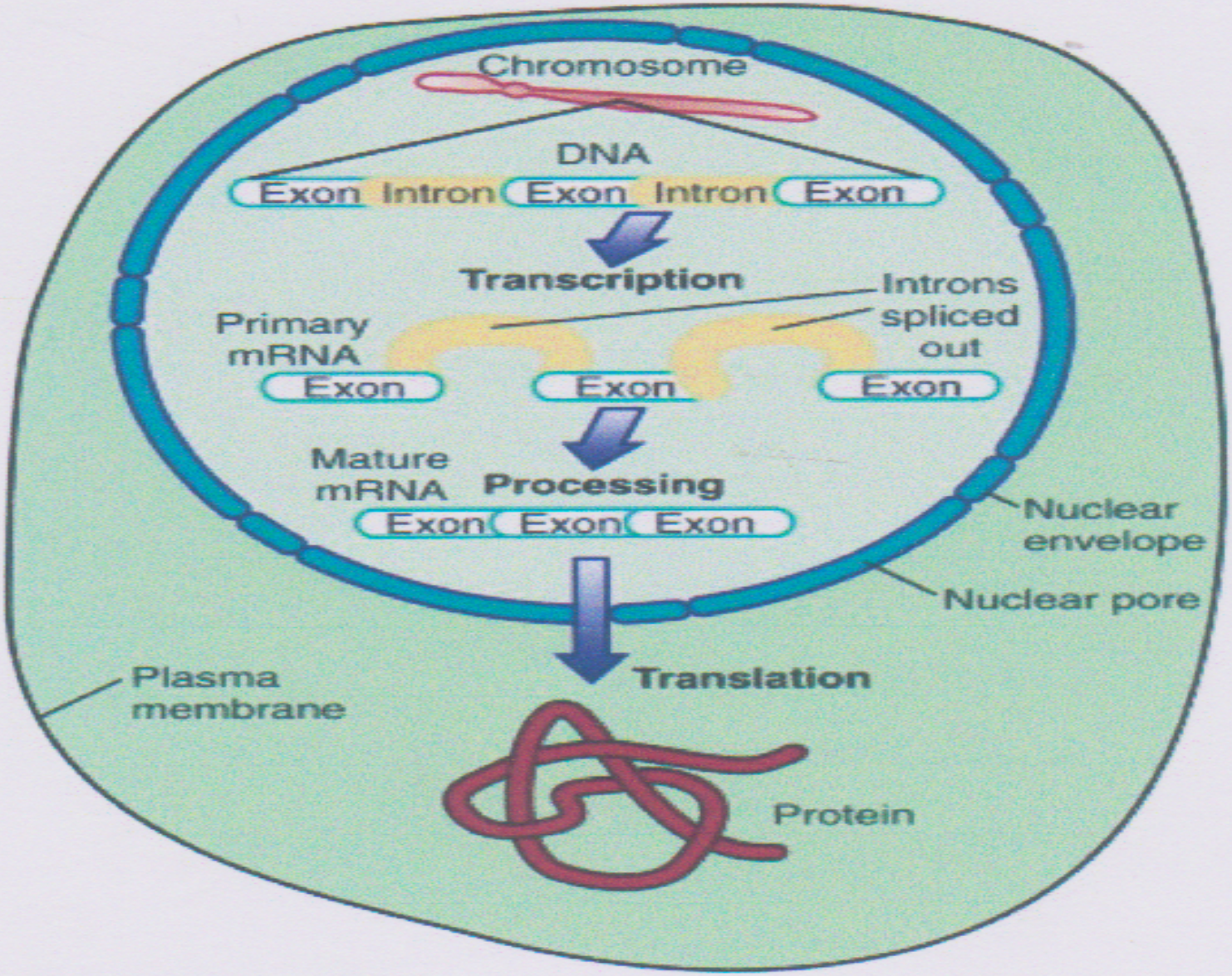
Heterozygous: when a person has a mutant gene at the locus in one chromosome but not at the homologous locus of the other.

Homozygous: a person having the same mutant gene at both homologous loci.

The structure and function of genes

The basic purpose of genes is the production of structural proteins and enzymes. This occur through a series of events termed transcription, processing and translation.


5′
3′
Sugar-phosphate backbone
Bases
One helical turn = 3.4 nm
Adenine
Thymine
Guanine
Cytosine
3′
5′

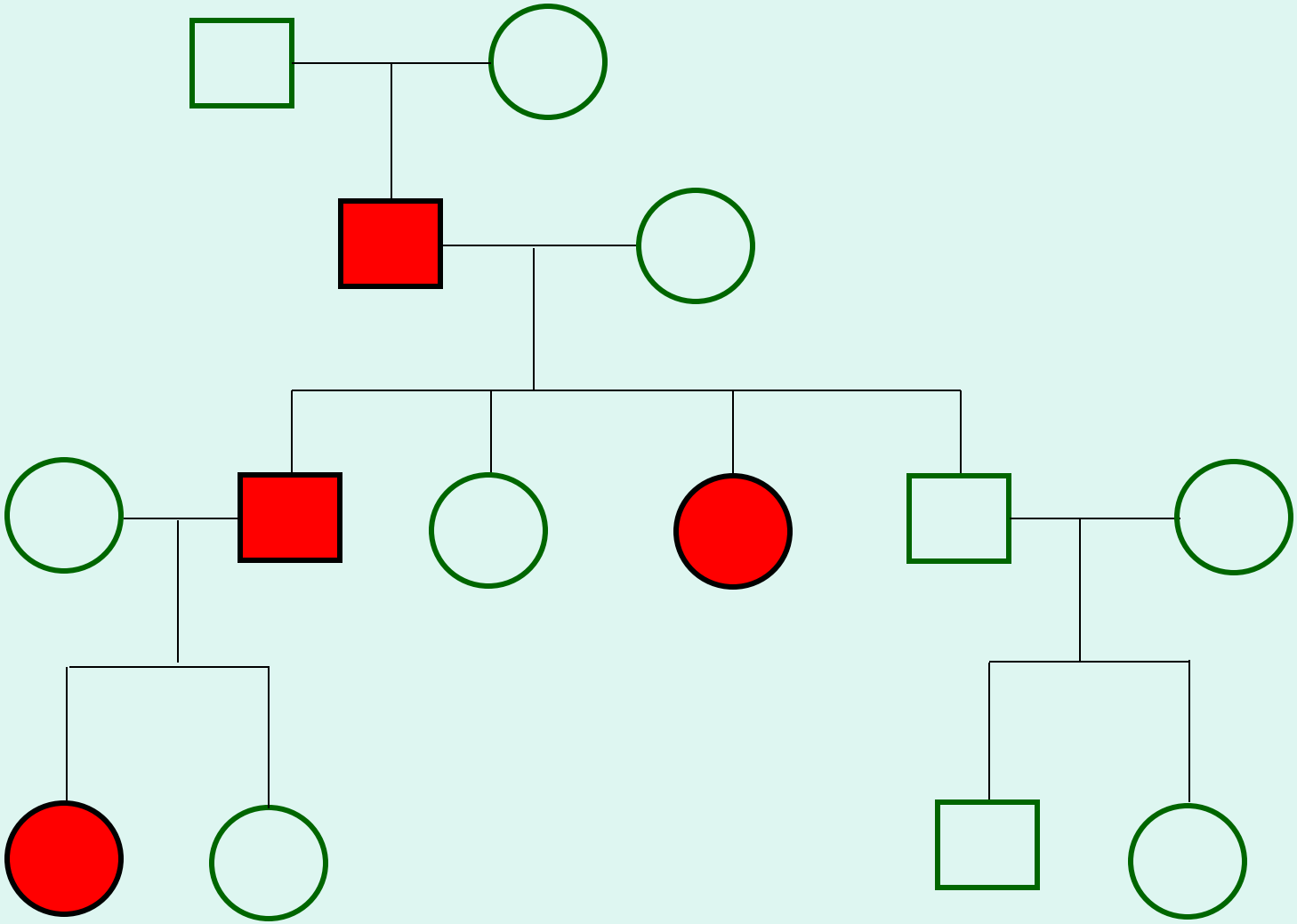

Chromosome
DNA
Exon
Intron
Exon
Intron
Exon
Transcription
Introns spliced out
Primary mRNA
Exon
Exon
Exon
Mature mRNA
Processing
Exon
Exon
Exon
Nuclear envelope
Nuclear pore
Translation
Plasma membrane
Protein

Patterns of inheritance

In managing the child with inherited disorder, 3 phases are critical:-

1. recognizing that the condition is inherited.
2. identifying the pattern of inheritance.
3. Clarifying the clinical nature of the disorder.

Autosomal dominant inheritance (A.D)



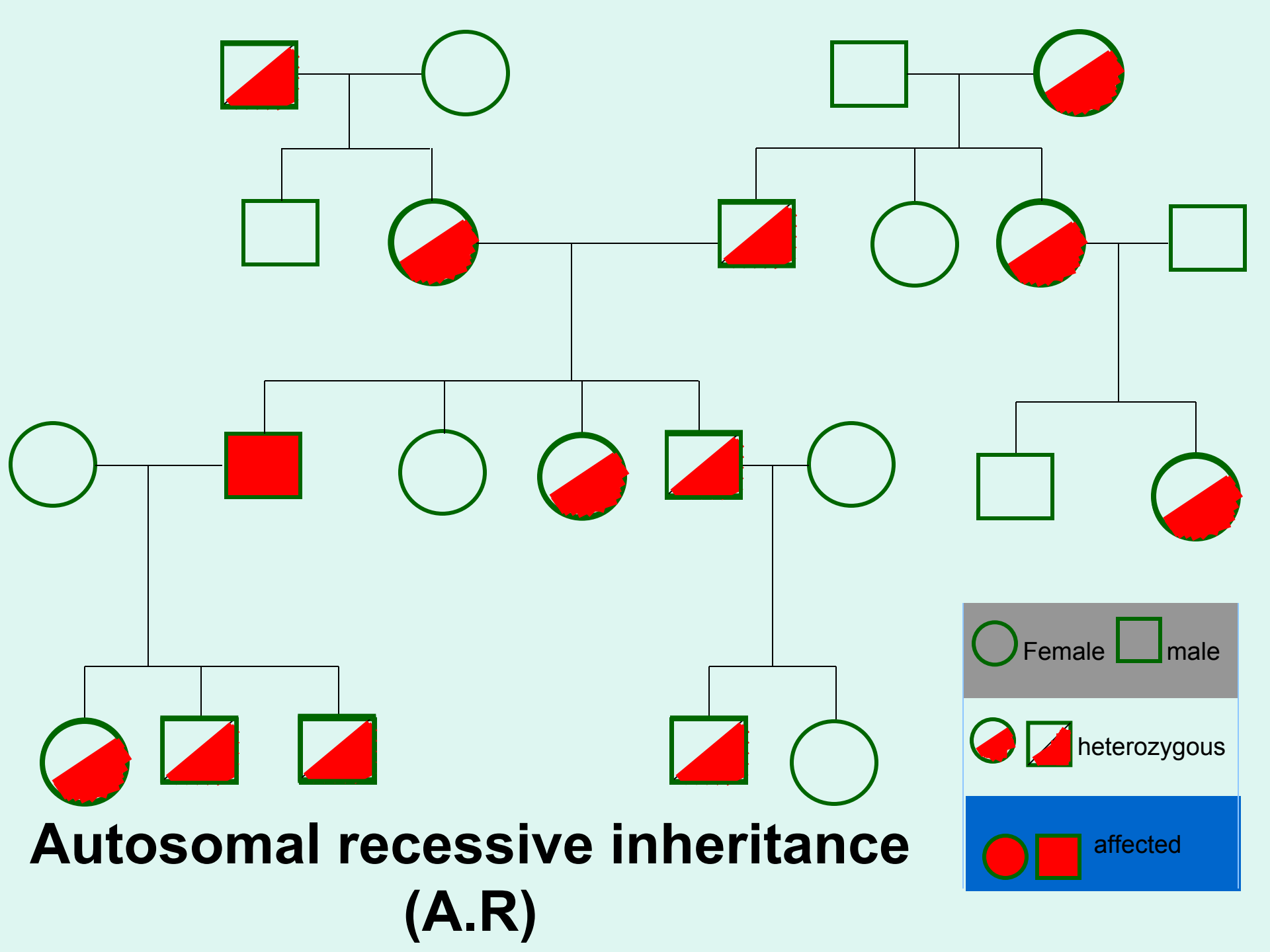
A.D

Characterized by:

1. Males and females affected equally.
2. The affected gene can arise by spontaneous mutation.
3. The disorder appears in a vertical pattern in pedigree.
4. Any child of an affected parent has a 50% risk of inheriting the disorder.

Examples:

O.i, craniosynostosis, Apert syndrome, neurofibromatosis I and II and Achondroplasia



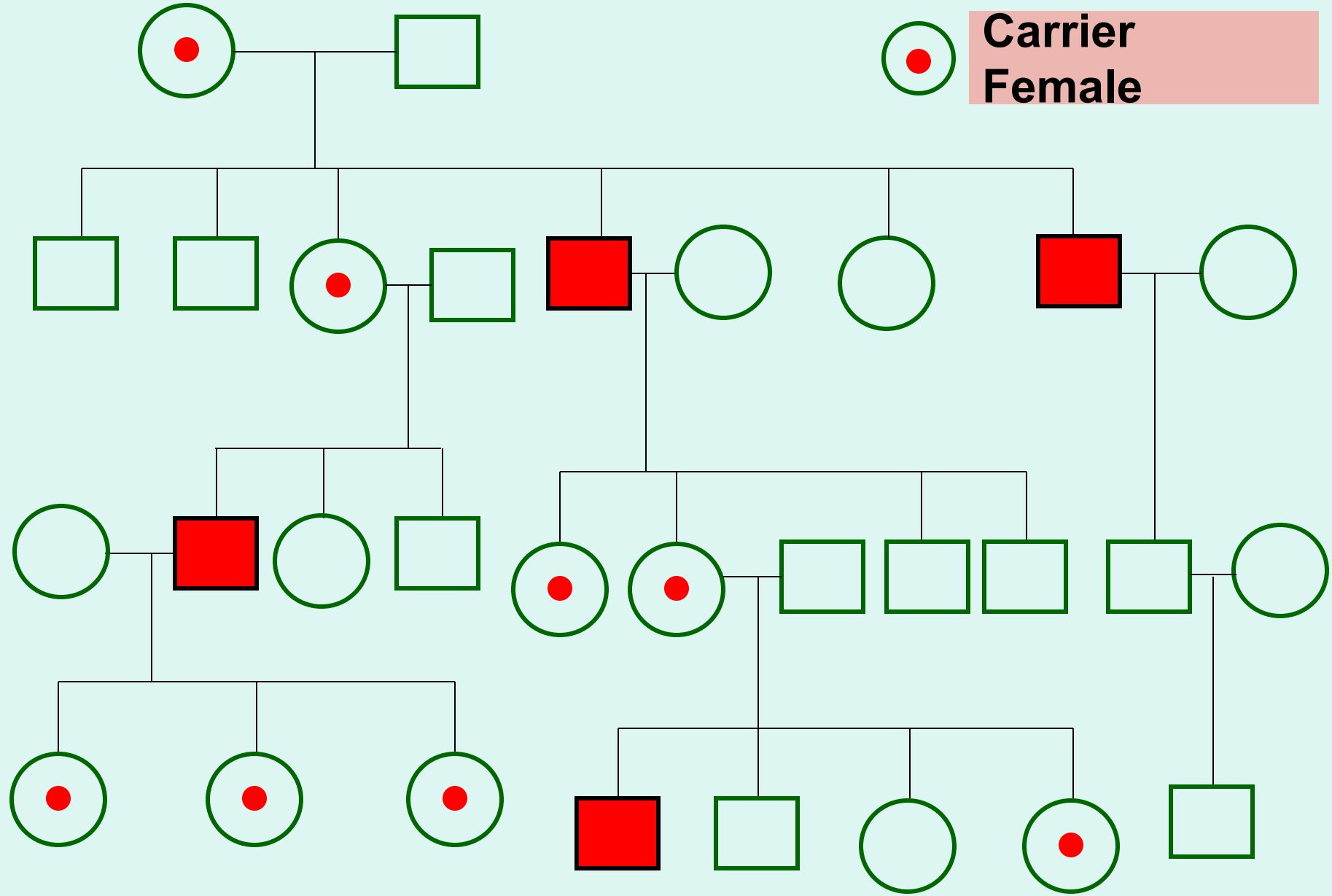
Autosomal recessive inheritance (A.R)

A.R

Characterized by:

1. Males and females affected equally.
2. Display a horizontal pattern in pedigrees.
3. If both parents are heterozygous, the chance of having affected child is 25%.
4. All children of affected person will be heterozygous.


الحيآة ".. قدْ تتعَثرر ,. ولكنَهآ لآ تتوقفْ .
والأمَلْ ".. قدْ يختفِي ,. ولكنه لآ يمووتْ .
والفُرَص ".. قدْ تضيَّع ,. ولكِنَهآ لآ تنتهيْ .
غادة سكيك



X- linked Recessive inheritance

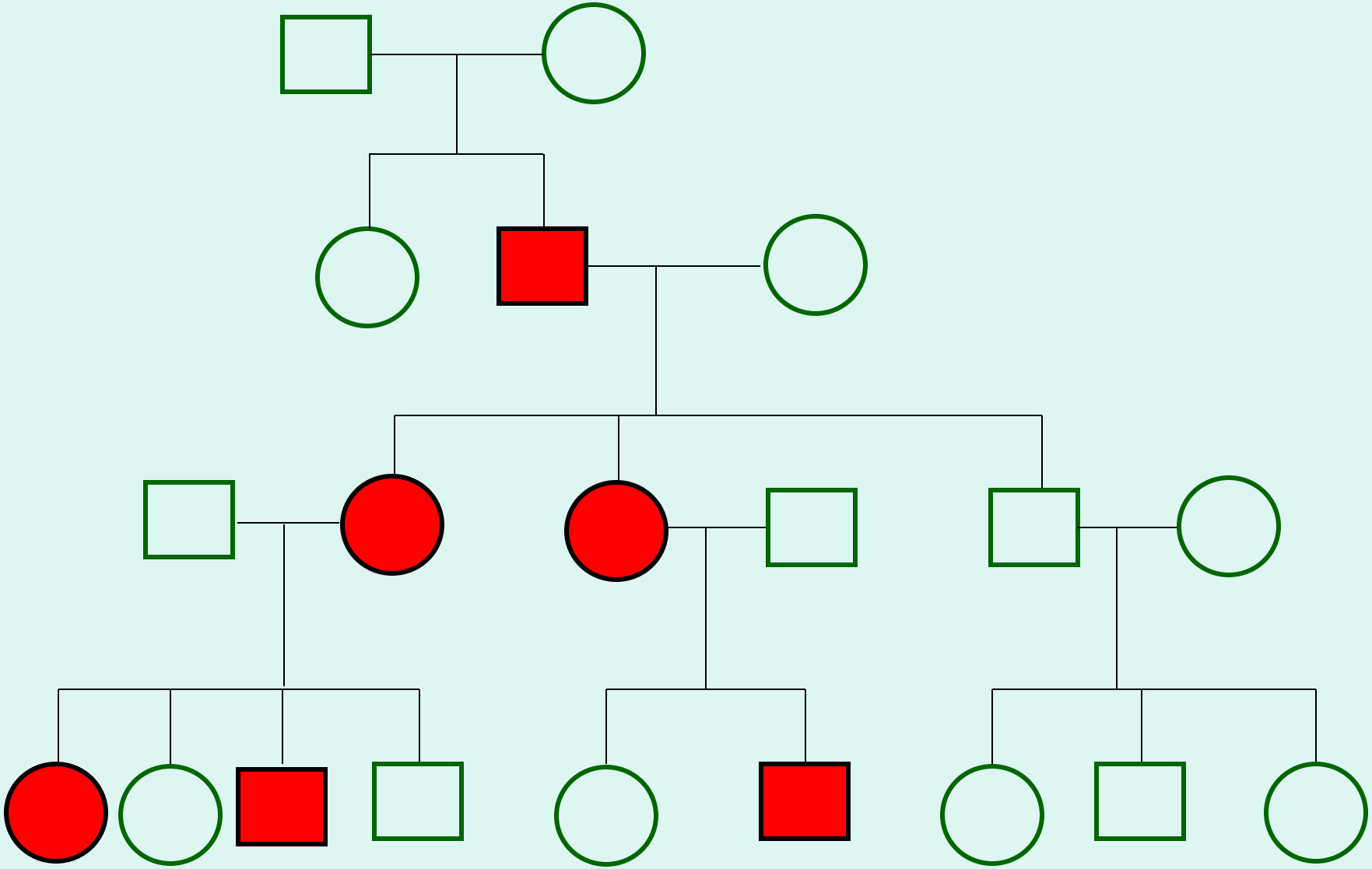
The disease carried on X-chromosome.

It is characterized by:

1. Only the males are clinically affected via carrier females.
2. If carrier female married from normal male 25% sons affected, 25% of daughters are carrier, and 50% of sibling dose not inherit mutated X-linked gene.
3. If affected male married from normal female all daughters will be carrier, all sons will be normal.
4. No father to son transmission.

Examples:

Hemophilia A and B, G6PD, D.M.D



X- linked dominant disease

Characterized by:

1. Both male and female affected but the disease more severe in male.
2. All of the daughters and none of the sons of affected man will be affected.
3. Both male and female offspring of affected females have 50% risk of a disease.

Examples:

Mel nick – needles syndrome ,vit. D – resistant Rickets and Incontinanta pigmenta.

Multifactorial inheritance

- There is a similar rate of recurrence(3-5%).1
- The risk of recurrence is related to the .2 .incidence of the disease
- Some disorder have a sex predilection.3
- The likelihood that both identical twins will.4 be affected with the same malformation is .less than 100%
- The risk of recurrence is increased when.5 .multiple family members are affected
- The risk of recurrence may be greater.6 .when the disorder is more severe

Chromosomal clinical abnormalities

The chromosomes are made up of DNA and other protein complexes, contain most of genetic information that is passed from one generation to the next.

Karyotype

1- number of chromosomes

i.e. 45, 46, 47 or 48

2- the sex chromosomes constitution

i.e. XX, XY, XXY, XXXY or X

3- any abnormalities found

t(13q14q), t21, 5p-

Normal karyotype

46, XX - 46, XY

Abnormal karyotype

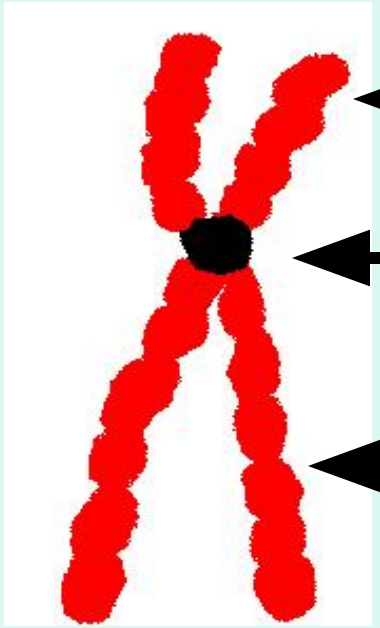
47, XY, +21

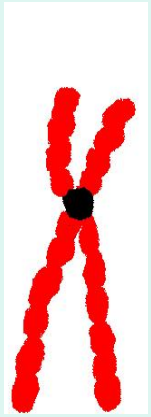
46, XX, t(13q14q)

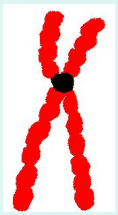
45, X

46,XX, 5p-

45,x /46,xY

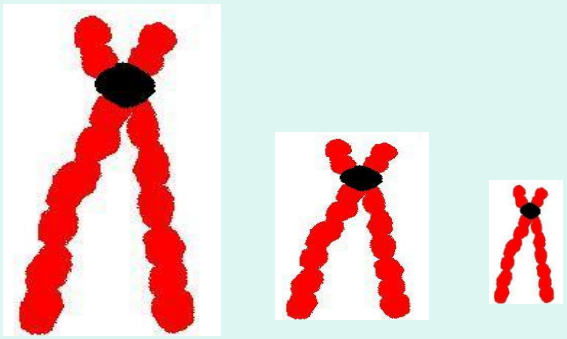






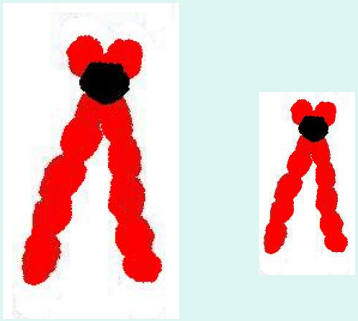
METACENTRIC

e.g. Group A



SUBMETACENTRIC

e.g: Group B+C



ACROCENTRIC

e.g: Group D+G

Centromere position

Chromosomal abnormality either in the .number or structure

Abnormalities in No.

The most common is trisomy which usually result from miotic non-disjunction and the most frequent examples are trisomy 21, 18, 13

Down syndrome

½ of trisomy 21 is aborted early in pregnancy. The incidence increase with maternal age from 1/733 of birth in those less than 30 years old 1/100 of the mother age more than 40 years and 1/50 if the mother age 45 years, and more than 95% of cases are due to non-disjunction
1% due to mosaicism 4%
due to translocation

C/F:

Hypotonia, microcephaly, flat occipit and face. Upward slanting palpebral fissure, epicanthic fold & Brush field spots of iris.

Ears: are small, low set and over folded upper helix.

Face: flat, protruded tongue, large cheeks and low flat nasal bridge.

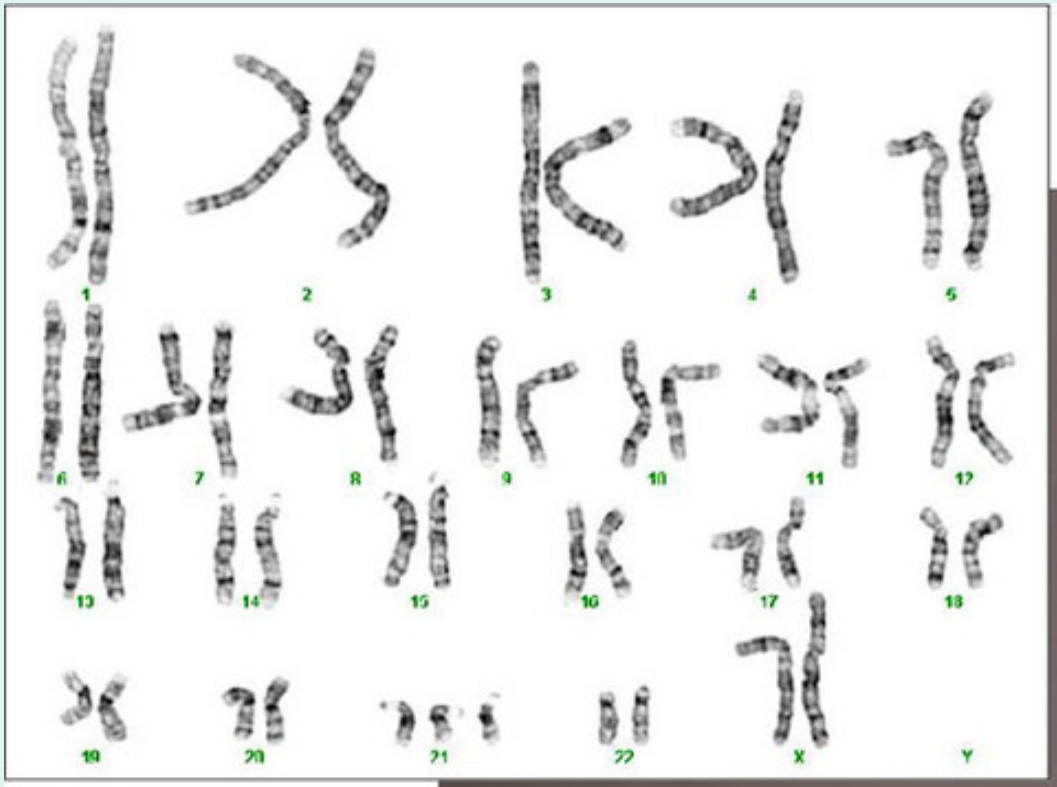
Skeleton: short broad hands, single simian crease, hypoplasia of middle phalanx of 5^{th} finger and gap between big toe and 2^{nd} finger and short stature.

Heart: 50% incidence of CHD most characteristic is A-V septal defect and the most common is VSD.

I-Q: 36-65 median 45

Other: high arched palate, intestinal atresia, hirschsprung disease and imperforated anus.

They are liable for leukemia and Alzheimer disease. *All women should be offered screening for Down syndrome* in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin (β-hCG), unconjugated estriol, inhibin, and α-fetoprotein)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20
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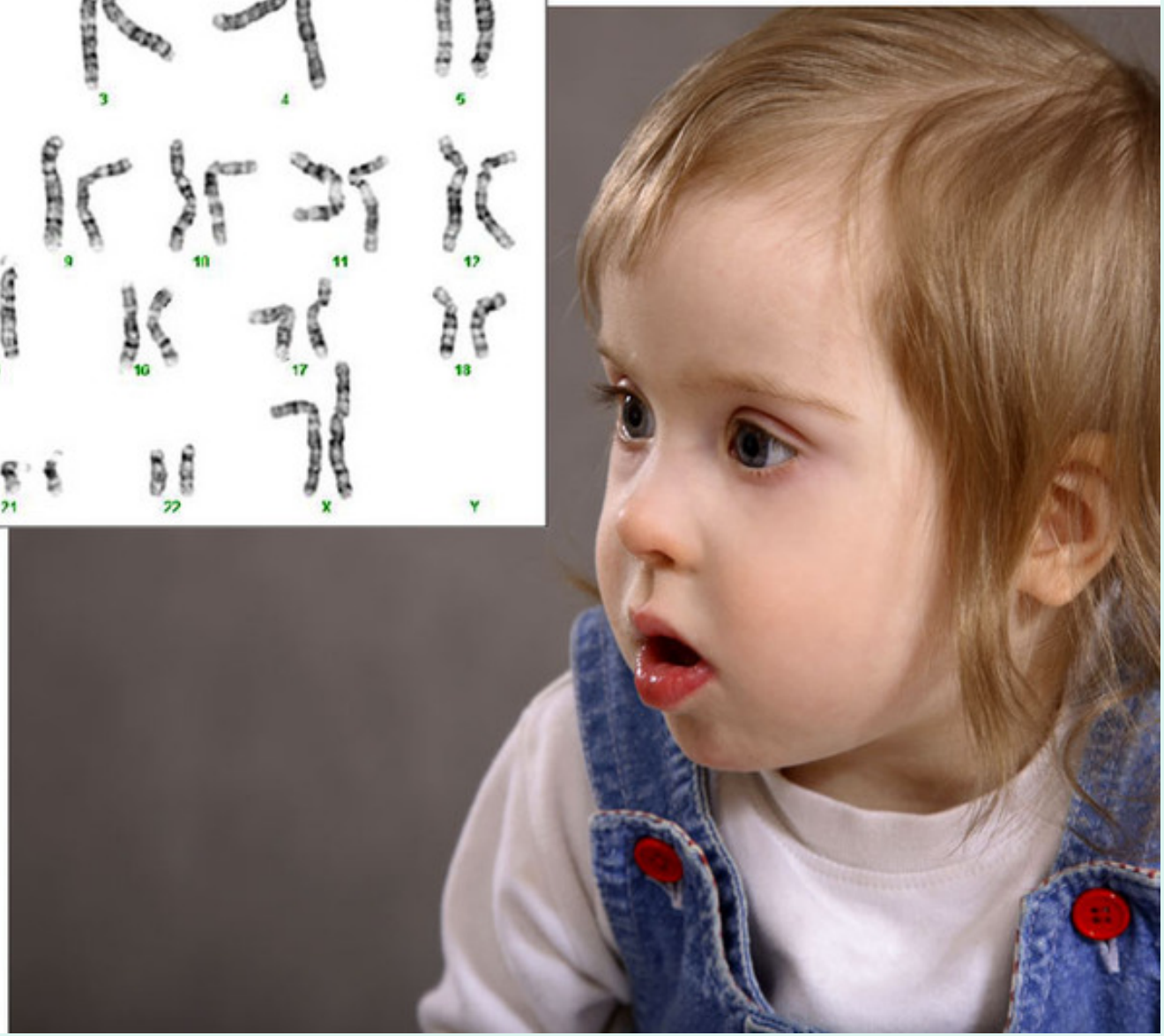
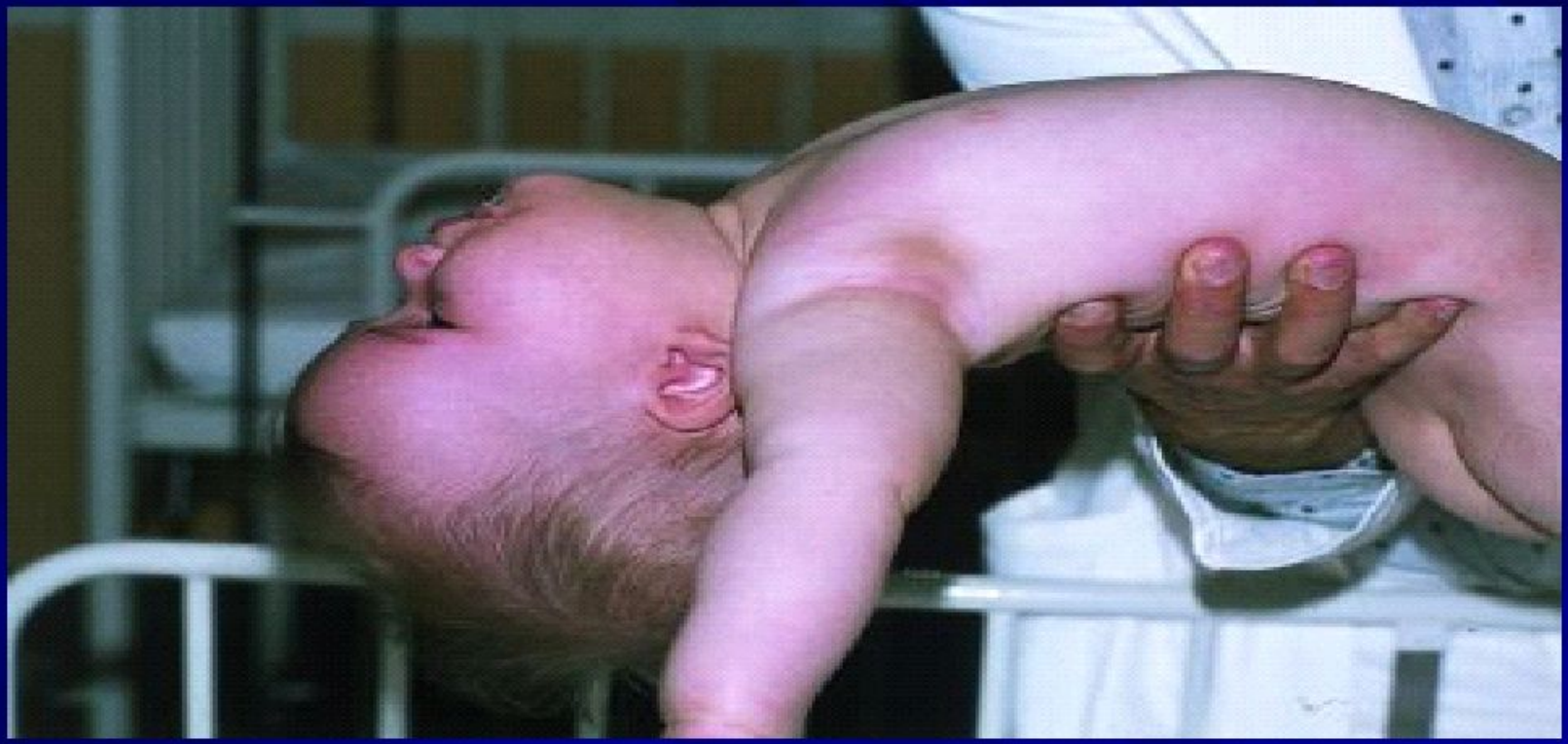
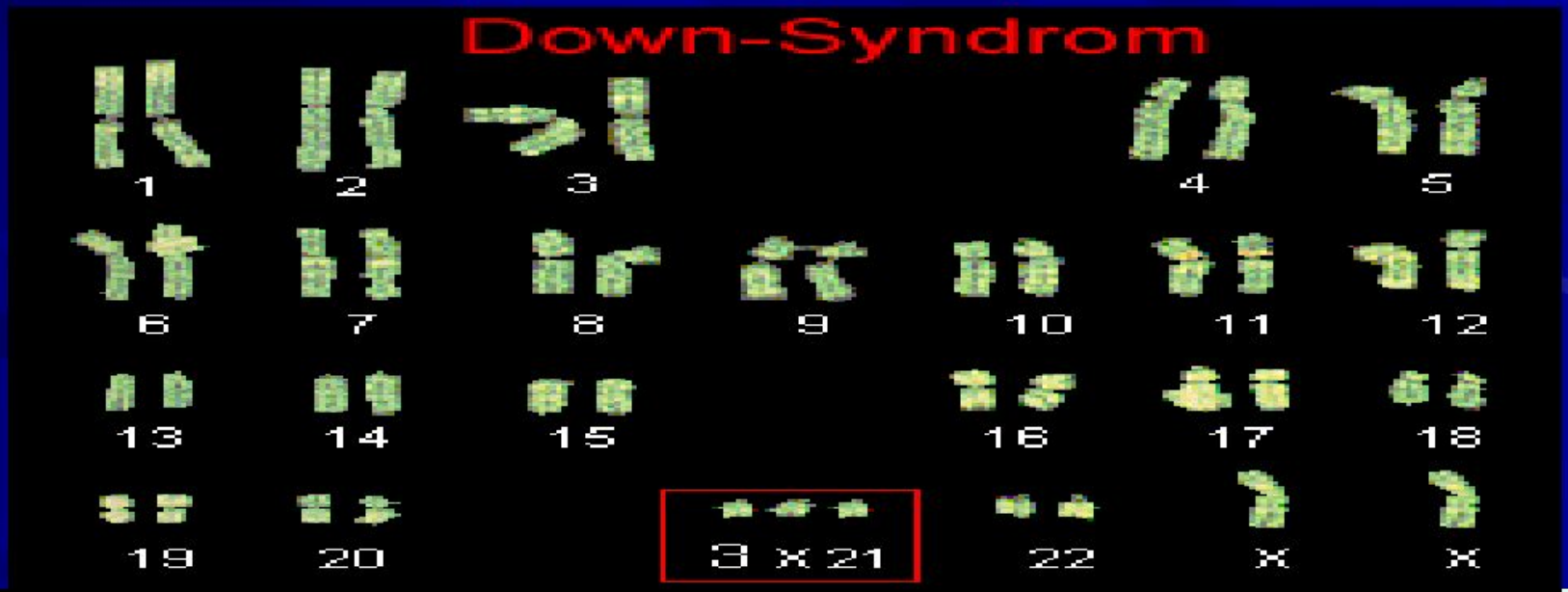
22
X
Y






Down-Syndrom
1
2
3
4
5
6
7
8
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10
11
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15
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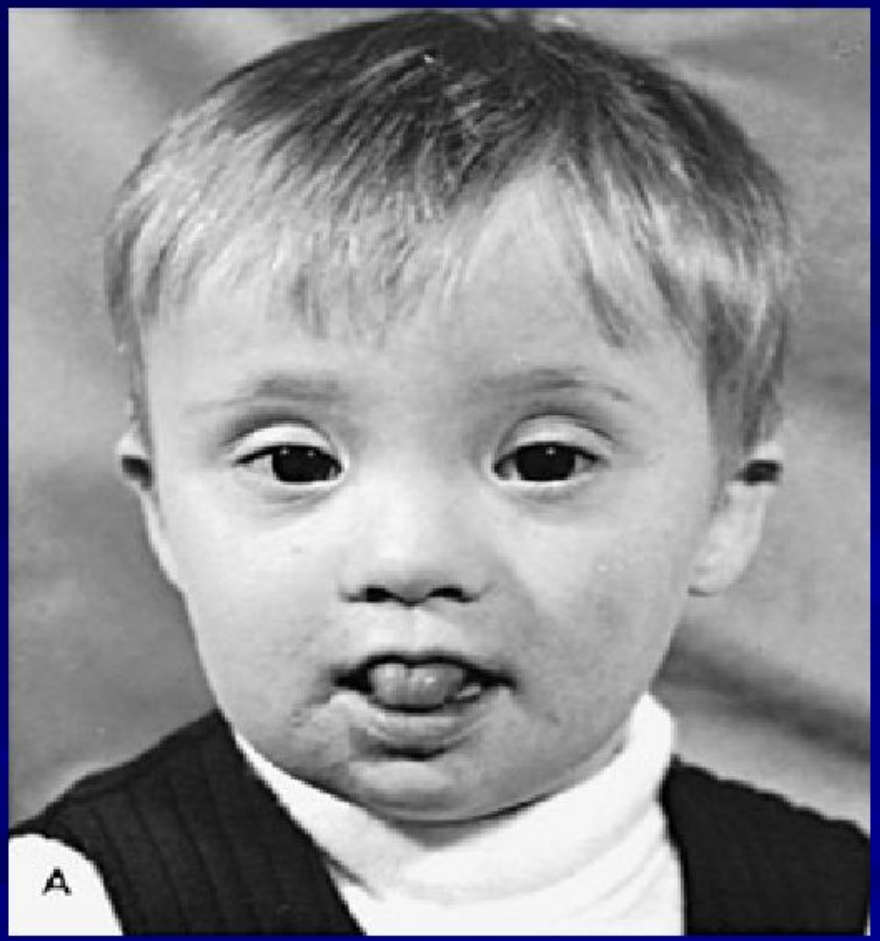
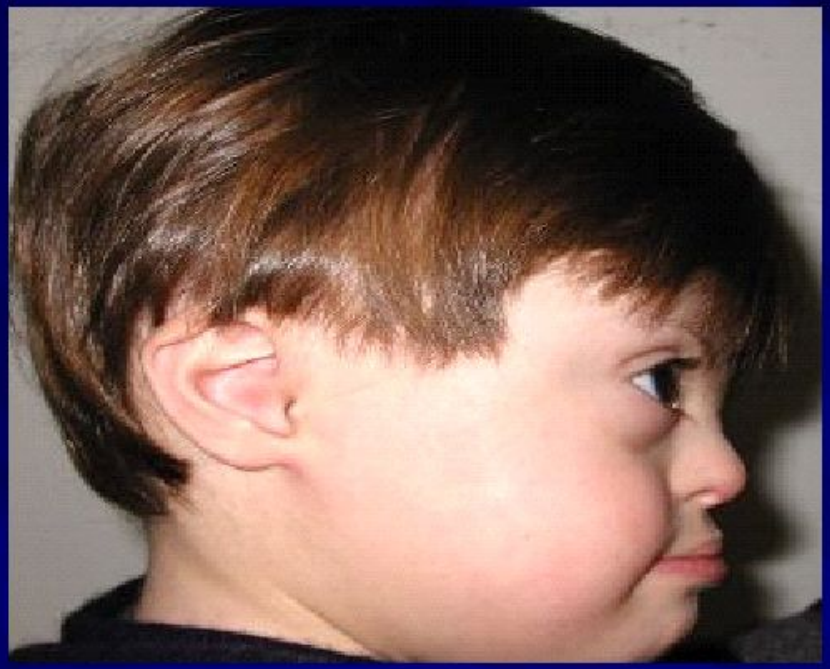
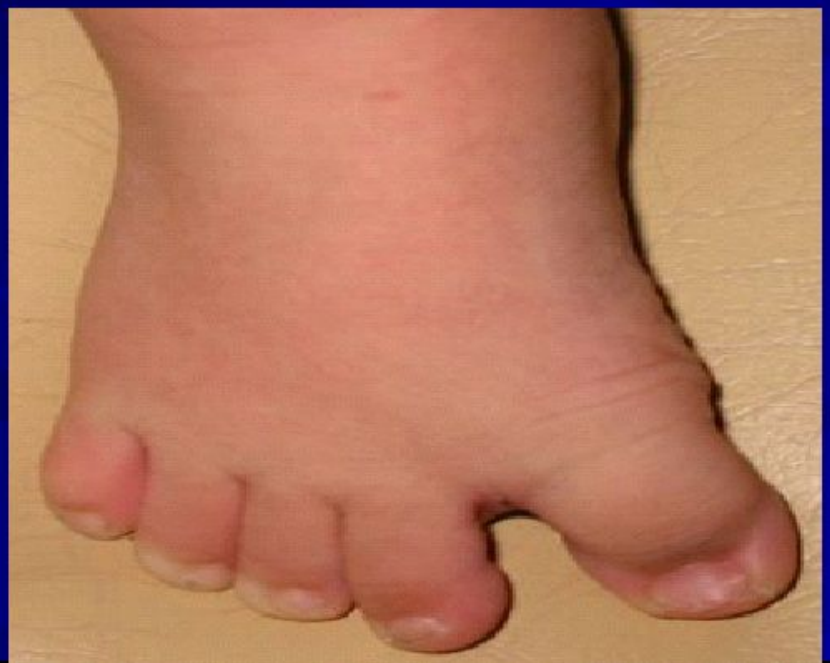
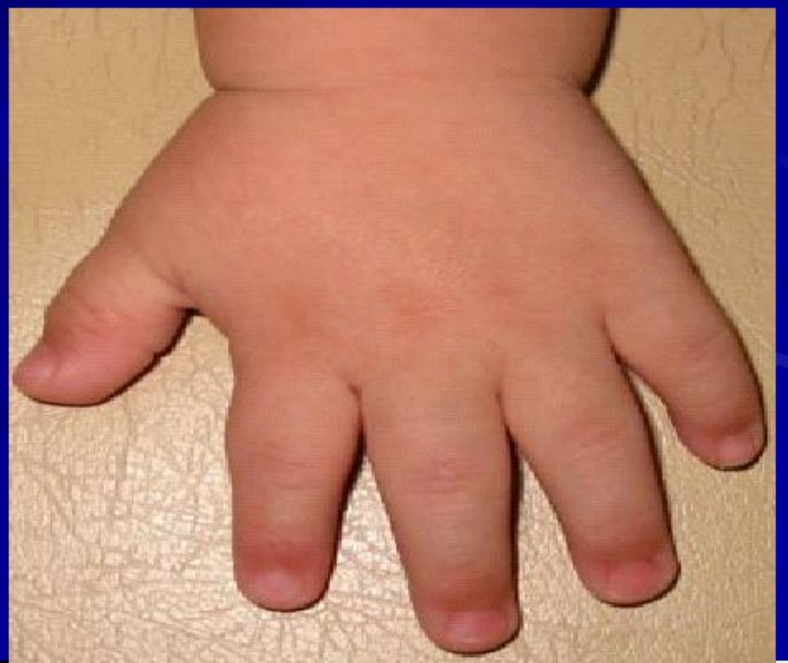
19
20
3 x 21
22
X
X


A








مشكلتك
ليست سنواتك التي ضاعت،
ولكن
سنواتك القادمة التي ستضيع حتما
إذا ما واجهت الدنيا بنفس العقلية.
د.مصطفى محمود

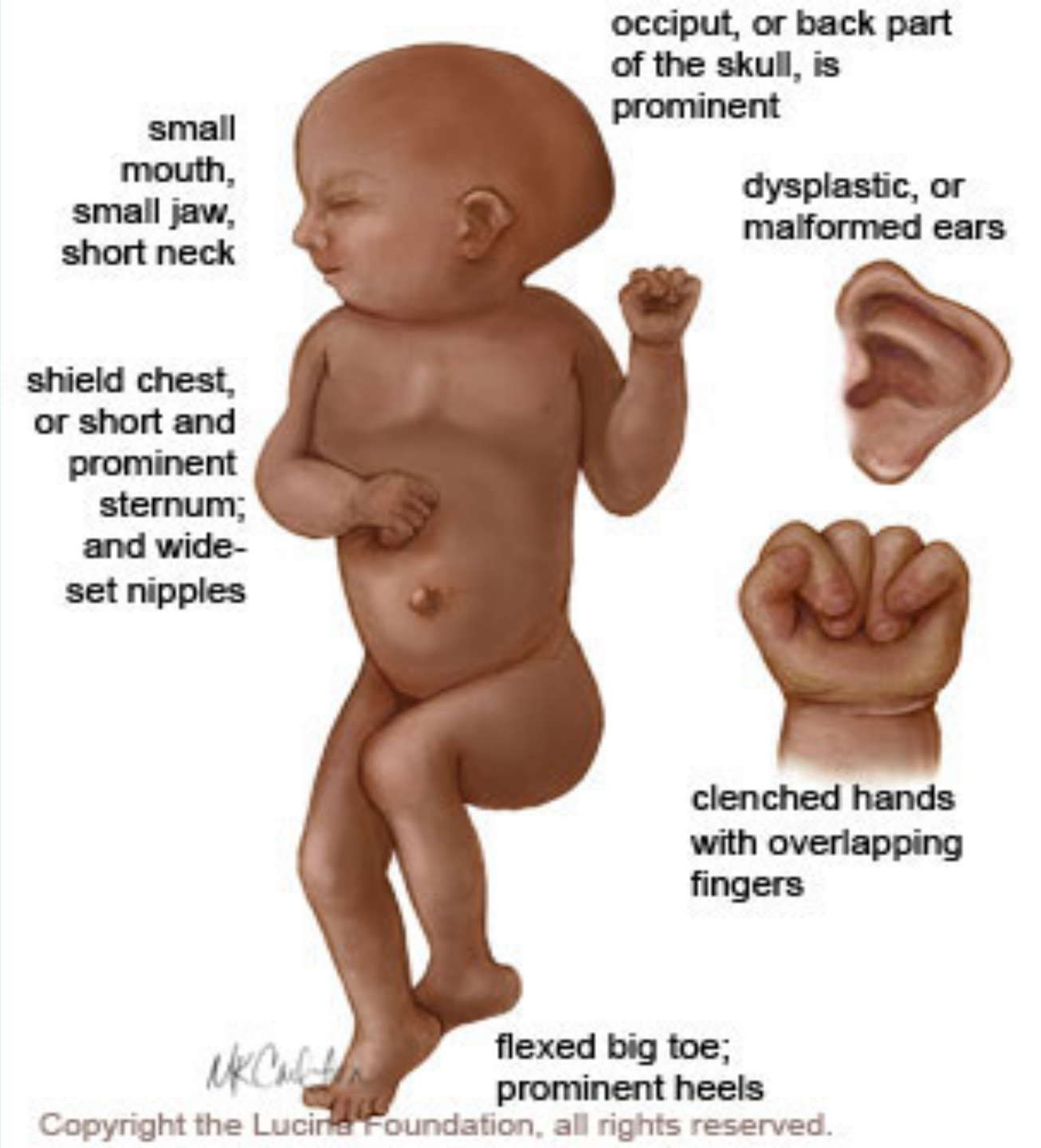
Trisomy18 47,XY,+18

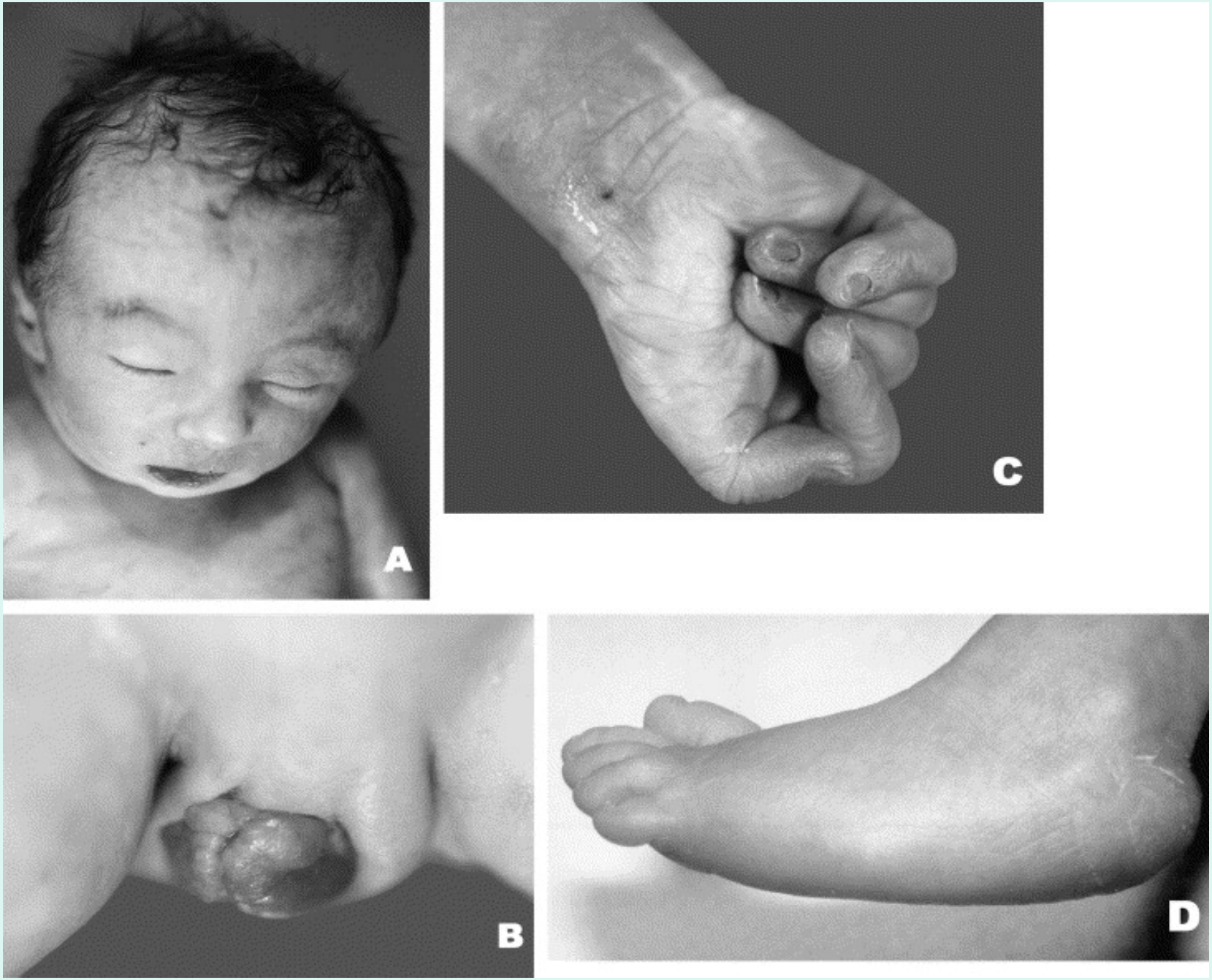
Edward's syndrome

Incidence 1/6000 births

C/F:

microcephaly with very prominent occipital region, hypertonia, lowbirth weight corneal opacity, micrognathia, closed fist with index finger overlapping the 3rd digit and the 5th digit overlapping the 4th.rocker bottom feet, hypoplastic nails, cardiac defect in 90% of cases, renal anomalies. 95% lethal in 1st yr.




A
C
B
D

Klinfelter syndrome

47, XXY

These individual have male karyotype with an extra X chromosome and the phenotype is male. Incidence is 1/575 – 1000 newborn male. The extra X chromosome is maternal in origin in 54% of cases and paternal in 46%.

C/F:

Male with tall stature and have gynecomastia in 80% of cases and secondary sex development may be delayed usually have a zoospermia, small testis and infertile, spare facial hair and increase incidence of pulmonary disease, varicose veins and cancer of breast. 25% have mild degree of mental retardation.

Treatment:

Replacement therapy with long acting testosterone, should begin at 11- 12 years of age.

Turner syndrome

45, X

Due to loss of part or all of one X chromosome. The single X chromosome is maternal in origin in 80% of cases. The incidence is 1/2500-5000 live born females.

C/F:

phenotype is female with low birth weight, short stature. 50% of them have neonatal peripheral edema of dorsum of hands and feet. Low posterior hair line prominent ears and epicanthic fold, high arched palate, broad chest with widely spaced nipples (shield chest), cubitus valgus and hyperconvex nails.

During the 1st 3 year of life, rate of growth is normal, then it decelerate, so they are short stature with mean adult height of 143 cm. Recurrent otitis media occur in 75% of patients. Sensorineural hearing deficit is common.

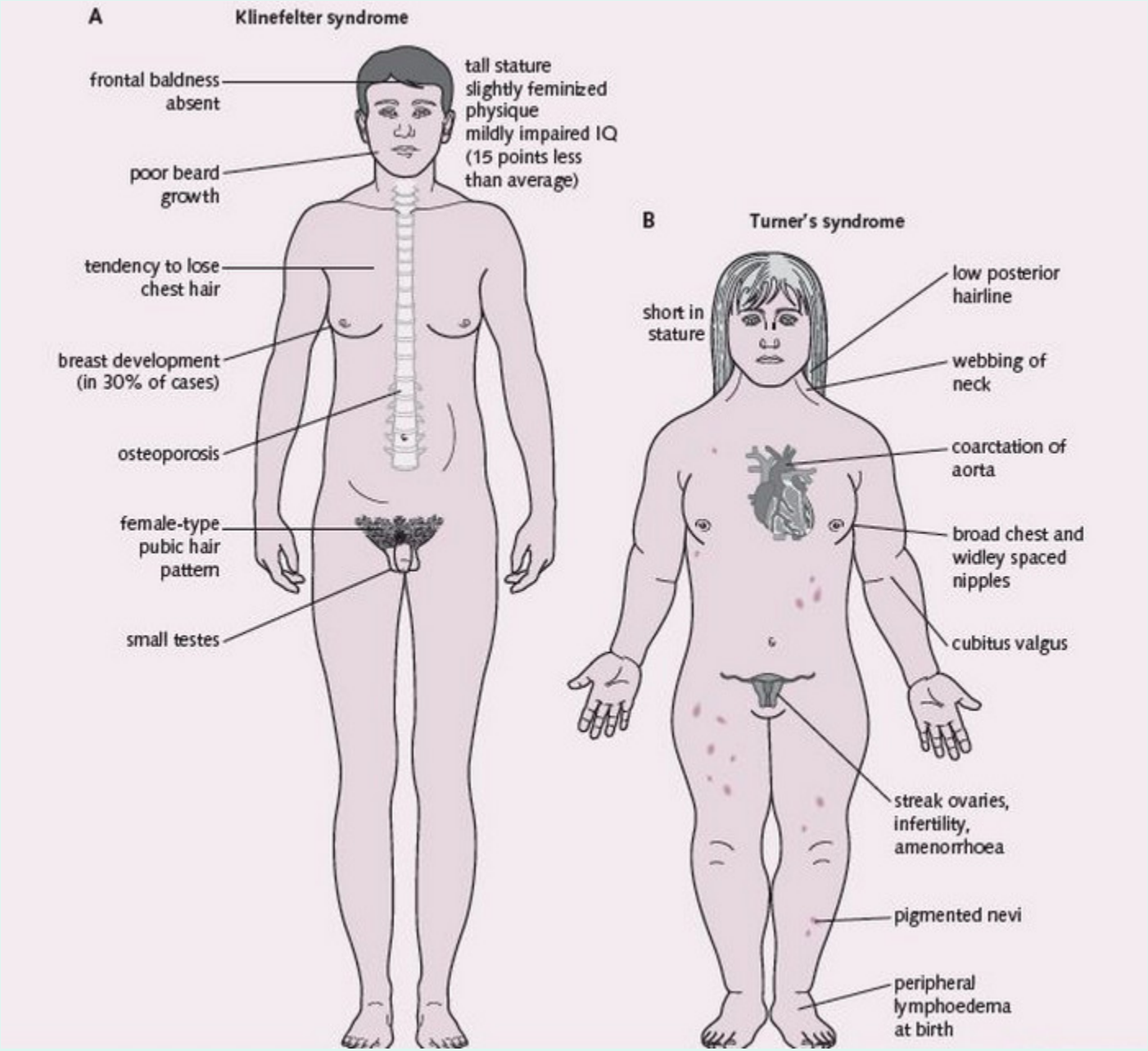
1/3rd of cases recognized at birth because of limb edema and extra skin or nabbing of neck. 2nd 1/3rd of cases recognized at childhood because of short stature. The last 1/3rd not recognized until they show failure of development of puberty because of under development of glands and 2ndary sex character do not occur in 90%, so most cases are infertile. Cardiovascular malformations are common, mostly bicuspid aortic valve, aortic stenosis and coarctation of aorta. Renal malformations are also common, which include pelvic kidney and horseshoe kidney. I.Q is normal but may be some hearing disabilities.

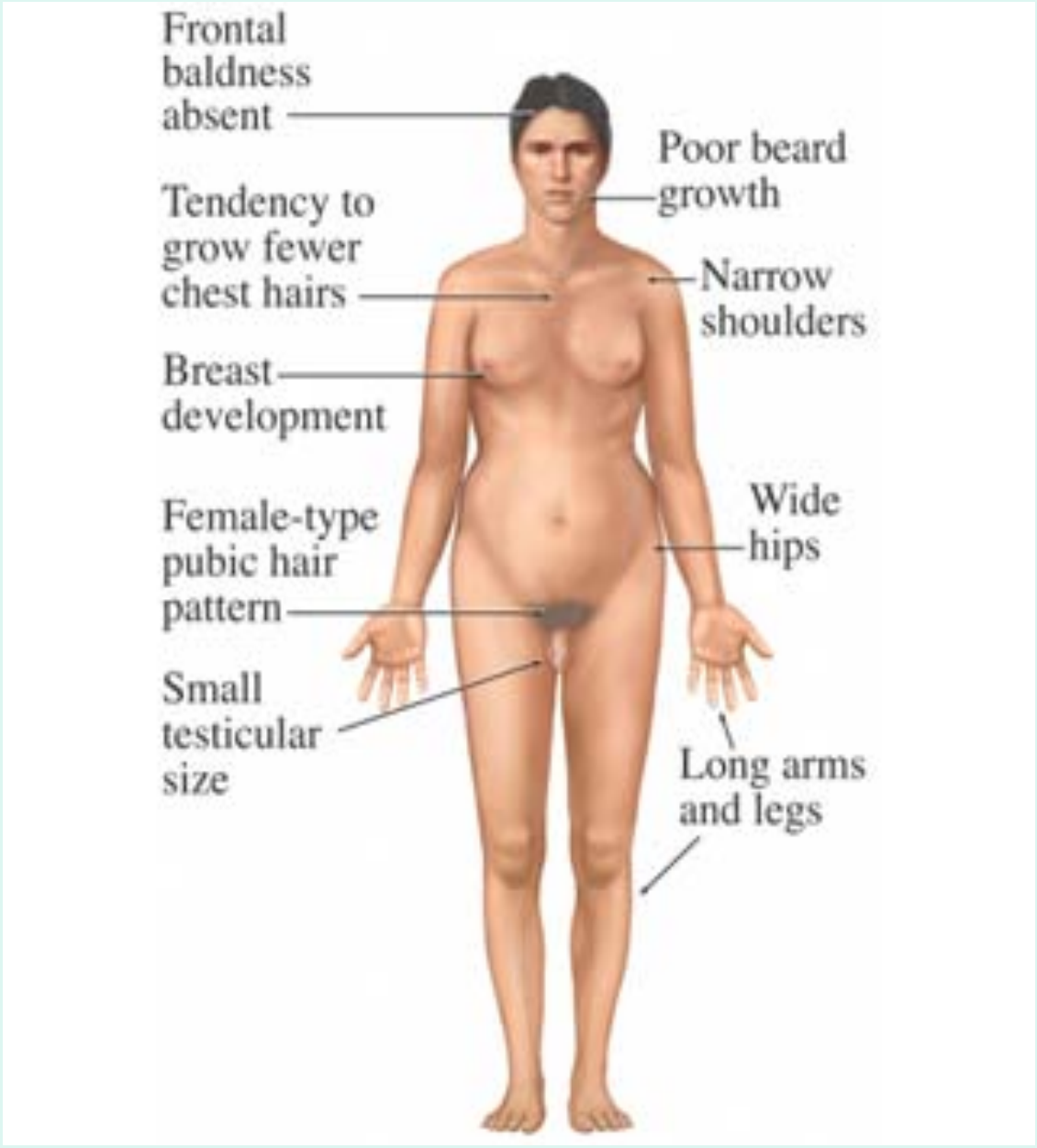
Diagnosis

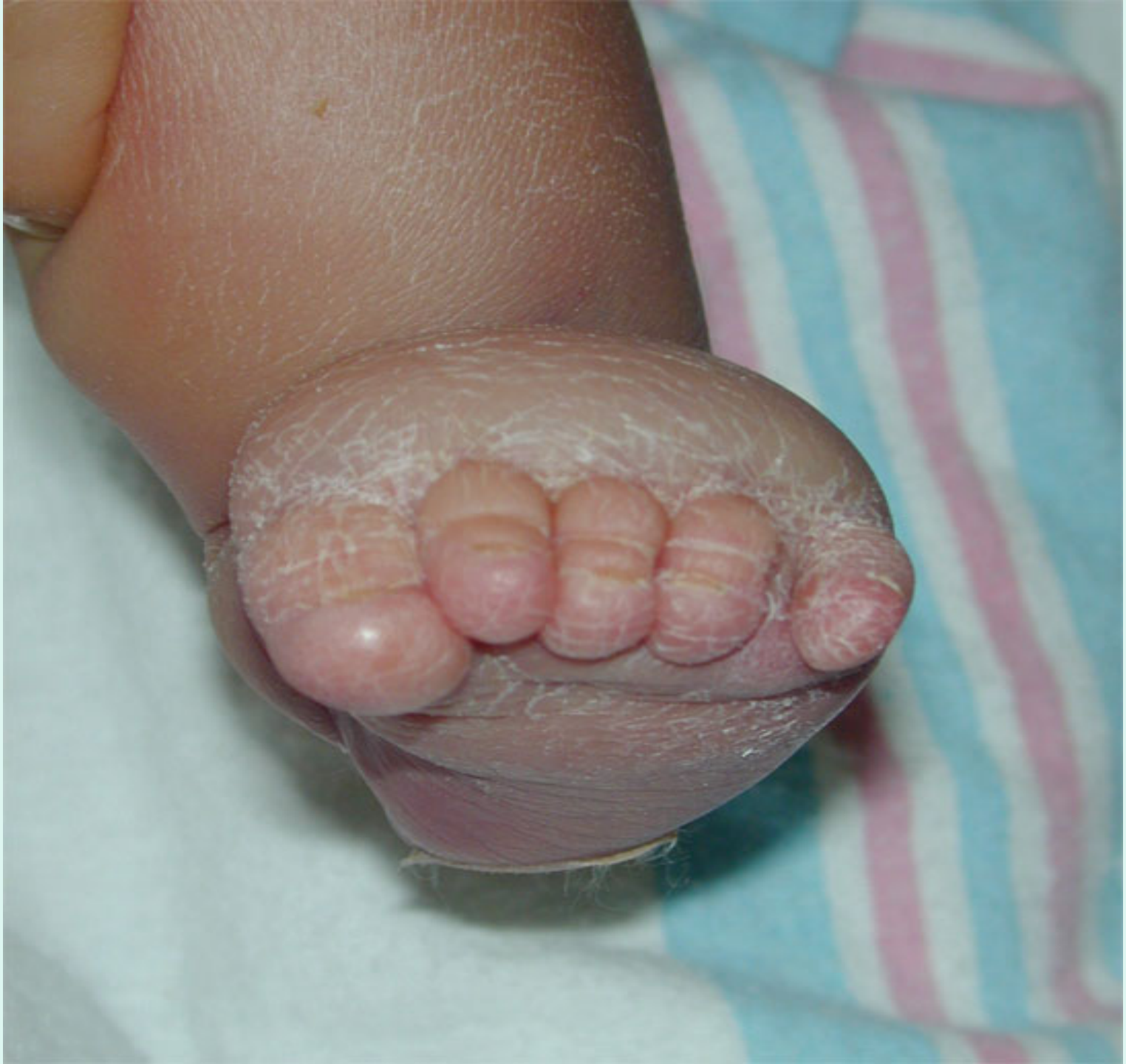
1. Chromosomal study must be done on blood sample.
2. U/S of heart, kidneys and ovaries.
3. FSH level study.
4. Thyroid antiperoxidase Abs. should be checked periodically if positive we have to do T3, T4 and TSH.

Treatment:

1. Recombinant growth hormone alone or in combination with anabolic steroid.
2. Replacement with estrogen at 12-14 year.
3. Surgical removal of gonads in those with Y chromosome material.
4. Psychological support.
5. Ovum donation or invitro fertilization.


A
Klinefelter syndrome
frontal baldness absent
poor beard growth
tendency to lose chest hair
breast development (in 30% of cases)
osteoporosis
female-type pubic hair pattern
small testes
tall stature
slightly feminized physique
mildly impaired IQ (15 points less than average)
B
Turner's syndrome
short in stature
low posterior hairline
webbing of neck
coarctation of aorta
broad chest and widley spaced nipples
cubitus valgus
streak ovaries, infertility, amenorrhoea
pigmented nevi
peripheral lymphoedema at birth


Frontal baldness absent
Poor beard growth
Tendency to grow fewer chest hairs
Narrow shoulders
Breast development
Wide hips
Female-type pubic hair pattern
Small testicular size
Long arms and legs

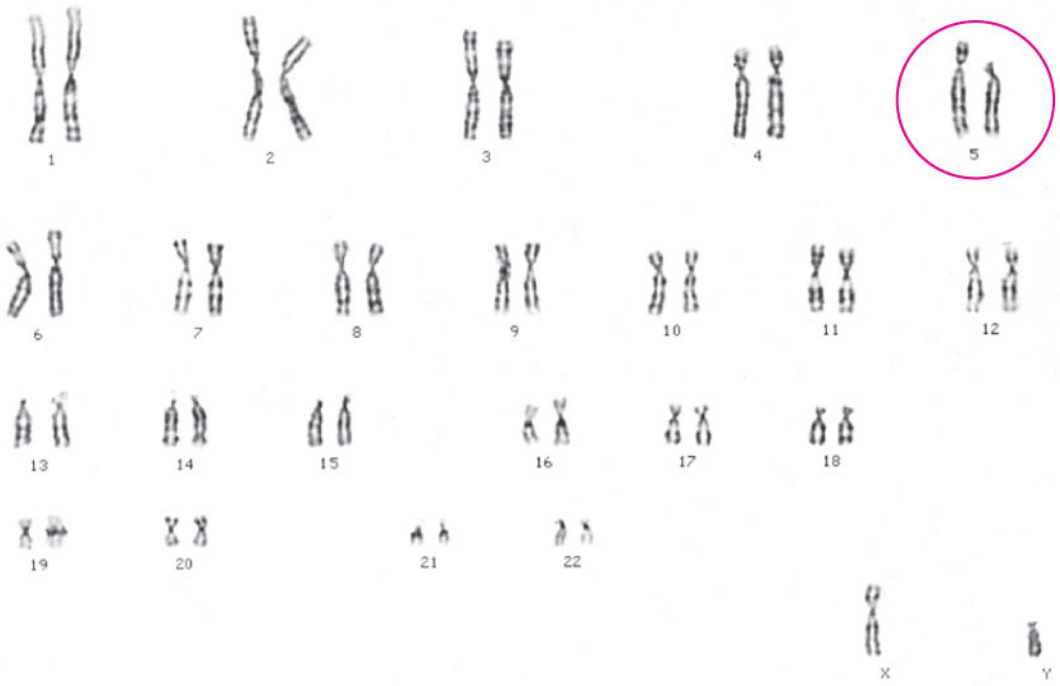


Cri- du – chat syndrome.

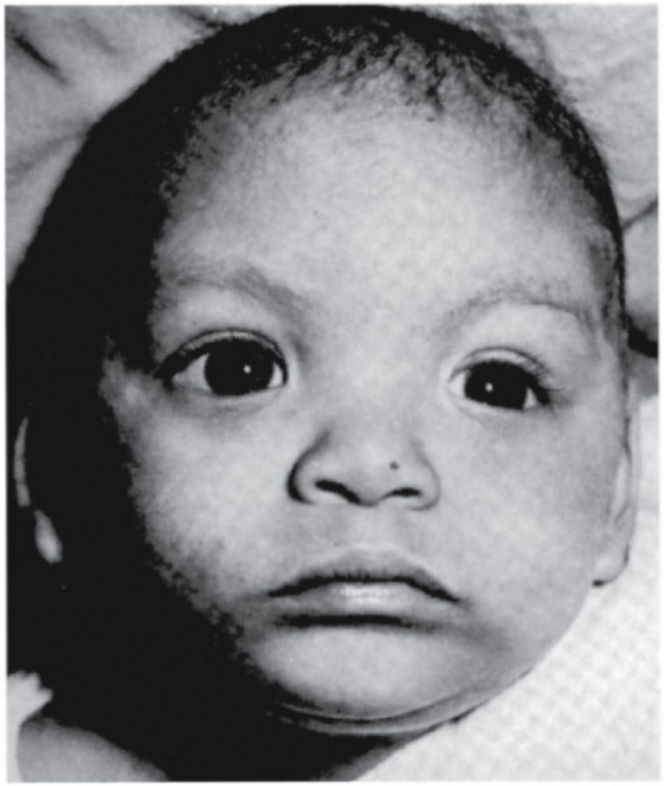
46, XX, 5p-, 1/50000

Hypotonic, short stature, characteristic cry (like cat voice) microcephaly, moonlike face, hypertelorism, bilateral epicanthic folds, high arched palate, wide & flat nasal bridge, mental retardation & long survival.

a) Karyotype (G banding)



b) Individual with Cri-du-chat syndrome



فراشه مسلمه

العتاب واللوم

شرف لا يستحقه البعض

لذلك لا تمنح هذا الشرف إلا لمن يستحق

Genetic Counseling

w hen a child is born with multiple congenital anomalies or a family is diagnosed with a genetic disorder, talking with the family is not easy. Giving bad news is always difficult, and the information is often somewhat technical. However, it is important to provide the family with as much information as possible so that they can make informed decisions. Genetic counseling has been defined as “an educational process that seeks to assist affected and/or at risk individuals to understand the nature of a genetic disorder, its transmission and the options available to them in management and family planning

TALKING TO FAMILIES

The first is the prenatal diagnosis of a congenital anomaly or genetic disease. This is a very difficult situation, and the need for information is urgent because a family must often decide whether to continue or to terminate a pregnancy. The second type of situation occurs when a child is born with a congenital anomaly or genetic disease. This also requires urgent information, and decisions must be made immediately with regard to how much support should be provided for the child and whether certain types of therapy should be attempted. The third situation arises later in life when (1) a diagnosis with a genetic implication is made, (2) a couple is planning a family and there is a family history of the problem (e.g., a couple in which one person carries a translocation or is a carrier of cystic fibrosis), or (3) an adolescent or young adult has a family history of an adult-onset genetic disorder (e.g., Huntington's disease or breast cancer).

Indication of genetic counseling

- **Advanced parental age.1**
  - **Maternal age >35 yr**
  - **Paternal age >50 yr**
- **Previous child with or family history of.2**
  - **Congenital abnormality**
  - **Dysmorphology**
  - **.M.R**
  - **Chromosome abnormality**
  - **Metabolic disorder**
  - **Single gene disorder**
  - **Isolated birth defect**

- Adult onset genetic disease .3
- Cancer
- Huntington disease
- consanguinity .4
- Teratogen exposure .5
- Repeated pregnancy loss or infertility.6
- Pregnancy screening abnormality.7
- Heterozygote screening based on ethnic risk.8
- Follow up to abnormal neonatal genetic.9 testing

PRENATAL DIAGNOSIS AND PREVENTION

Many different methods of prenatal diagnosis are available, depending on the specific genetic disorder. The use of ultrasonography allows prenatal diagnosis of anatomic abnormalities such as neural tube defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening