5 GENETICS

BASIC CELL GENETICS

Chromosomes

- Are parts of chromatin material of the nucleus which carry genetic information.
- They are composed of DNA chain (deoxyribo nucleic acid) frame work of protein.
- They are made up of genes.

Morphology of chromosomes

Each chromosome is composed of two long thin parallel strands called chromatids held to gather at one spot called centromere. Each chromosomes has two short arms (P) and two long arms (q)

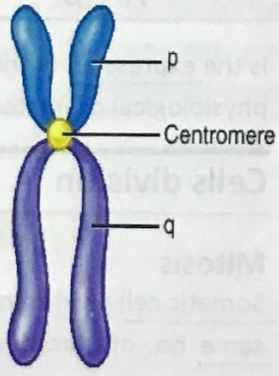


Fig (1): morphology of chromosome

Number of Chromosomes

- Number of chromosomes in somatic cell is 46 chromosomes which are arranged in 23 pairs.
- 22 pairs are similar in both female and male and are called 'Autosomes'.
- One pair is variable according to sex:
  - XX in female
  - XY in male.

Gene

1. It is a segment of DNA.
2. It is the basic hereditary unit.
3. Each gene has a precise locus on the chromosome
4. The two genes which occupy the same locus on two homologous chromosomes are called alleles.
5. Homozygous state = 2 identical alleles at a given locus.
6. Heterozygous state = non identical alleles at a given locus.
7. Hemizygous state = only one member of gene pair. Since males have only one X chromosomes, they said to be hemizygeous to X–linked genes.

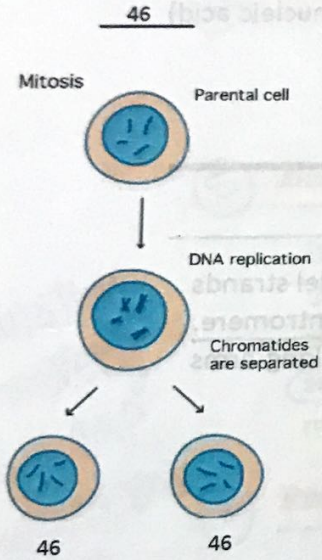


FIG (2): Mitosis

Karyotyping

Is the study of chromosomal arrangement in a single prepared cell.

Genotyping

Is the study of genes system in an individual.

Phenotyping:

Is the expression of the gene as physical, biochemical or physiological character

Cells division

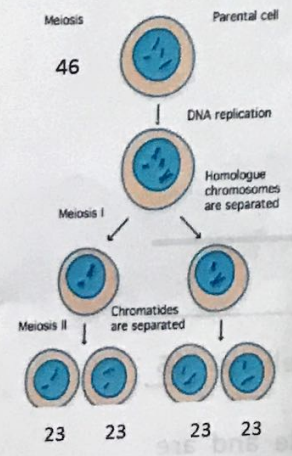


Fig (3): meiosis

Mitosis

Somatic cell divides into 2 daughter cells, each of which contains the same no. of chromosomes like mother cell i.e., (46). It occurs in somatic cells.

Meiosis

It occurs in germ cell in 2 steps:

- 1st meiotic division leading to 2 daughter cells, each contains the ½ no. of chromosomes of mother cell i.e., (23).
- 2nd mitotic division gives 4 cells, each contain 23 chromosomes Meiosis occurs in germ cells

KARYOTYPING

Definition

Is the study of chromosomes analysis in a single prepared cell giving information about the number and structure of present chromosomes.

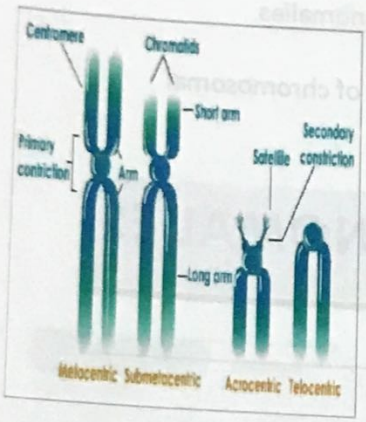


Fig (4) position classification

Identification of the chromosomes

Position classification

Classify the chromosomes according to the position of centromere into

- **Metacentric:** centromere in medium position.
- **Submetacenteric** : centromere is mid way between the middle and end of the chromosome.
- **Acrocentric:** centromere is near the end of the chromosomes.
- **Telocentric:** centromere is present at terminal position.

Denver classification

Classification of the chromosomes according to the length into groups, from A to G . The longest chromosomes (group A) include chromosomes form 1-3.The shortest chromosomes (group G) include chromosomes 21-22.



Fig (5) : banding classification

Banding classifications

The chromosomes are stained into bands white and black , each chromosome has charchrestic band distribution (stripped pattern) , ,Banding technique helps in :

- Idenfication of each chromosome from other.
- Idenfication of different segments of each chromosome



Fig (6): normal karyotyping

Normal karyotyping

- 46 XX (female)
- 46XY (Male)

Indications of Karyotyping:-

1. Unsown mental retardation
2. Dysmorphic child
3. Ambiguous genitalia
4. Infertility of unknown causes
5. Repeated abortion or still birth
6. Parents with a child of chromosomal anomalies
7. Carrier detection
8. Amniocentesis for antenatal diagnosis of chromosomal anomalies

NB

FISH

(Fluorescent in Situ Hybridization)

It is powerful technique using labeled DNA probes that are attached specifically with the chromosomes being studied

It helps to visualization the specific regions of each chromosomes even the small ones . It helps to detect the chromosomal micro deletion

CHROMOSOMAL ANOMALIES

Numerical Anomalies

1 Trisomy

- One chromosome excess.
- number of chromosomes are 47
- it is classified into:
  - **Autosomes trisomy**
    - Down syndrome: trisomy 21.
    - Edward syndrome: trisomy 18.
    - Patau syndrome: trisomy 13.
  - **Sex chromosomes trisomy**
    - Klienfilter syndrome: xxy.
    - Super female: xxx.

2 Monosomy

- One chromosome less.
- The number of the chromosomes is 45. e.g.: Turner syndrome (45 xo)
- Monosomy in autosomes is lethal.

3 Mosiascism

- Two lines of cells in the same individual.
- One cell line contains 46 chromosomes.
- Other cell lines contain 47 chromosomes e.g.: mosaic Mongol.

Structural anomalies

1 Deletion

Is loss of a portion of chromosome due to breakage of chromosome by radiation, chemicals or viral infection e.g, deletion of chromosome 5 (= Cri – du chat syndrome).

2 Micro deletion

Very small deletion can be detected microscopically using FISH technique.

- William's syndrome: micro deletion of chromosome 7.
- Digorge syndrome: micro deletion of chromosome 22.

3 Duplication:

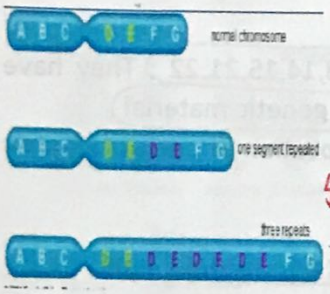


Fig (7): duplication

It is the presence of an extra piece of chromosome. It is usually resulting from unequal cross over between two chromosomes. Two copies of a segment are present on the chromosome.

4 Inversion

It occur due to double break in the same chromosome with inversion of the broken segment and reversal of the order of the bands in the chromosomes

5 Isochromsome:

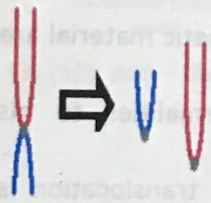


Fig (8): isochromsome

Centromere of submetacenteric chromosome divides transversely Instead of longitudinal division →chromosomes, one with 2 short arms and another with 2 long arms

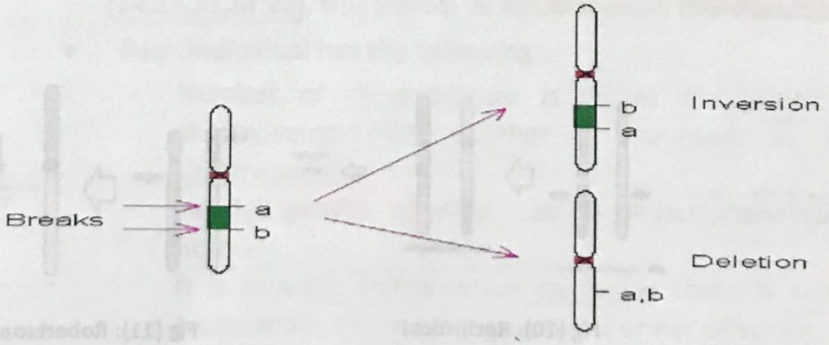


Fig (9): inversion & deletion

6 Translocation

Definition

Inter exchange of genetic material between non homologous chromosomes.
There are two types

Reciprocal translocation

- Break on two different chromosomes followed by genetic material exchange between the two chromosomes.
- Reciprocal translocation does not cause genetic change of the individuals as they have the normal chromosomal material i.e. normal phenotype (balanced translocation)
- Their off spring may have unbalanced translocation due to loss or gain of chromosomal material e.g. : partial trisomy 6 or partial monosomy 4.

Robertsonian translocation

- It occurs in acrocentric chromosomes eg : 13,14,15,21,22 . They have very small short arms that contain no essential genetic material
- Robertsonian translocation is a result of translocation of one acrocentric chromosome into another one as follow
  - Short arms of 2 chromosomes are lost
  - Long arms fuse together to make a long one chromosome
  - Robertsonian translocation in a person →
    - Number of chromosomes is 45 as the two translocated chromosomes are counted as one
    - Normal phenotype as all the essential genetic material are present
    - Risk of transmission of genetic abnormalities to his offspring e.g. Down syndrome
    - The person who develops Robertsonian translocation is known as translocation carrier.

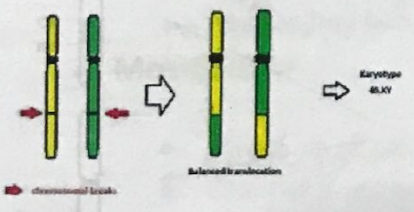


Fig (10): Reciprocal translocation

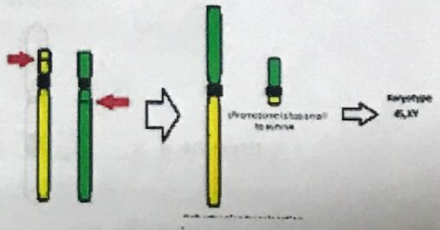


Fig (11): Robertsonian translocation

TRISOMY 21

(Down syndrome)

It is the most common trisomy due to an extra chromosome 21 leading to 47 chromosomes in the cells.

Genetic types

The extra chromosome may be a result from:

Non disjunction: 95% of cases.

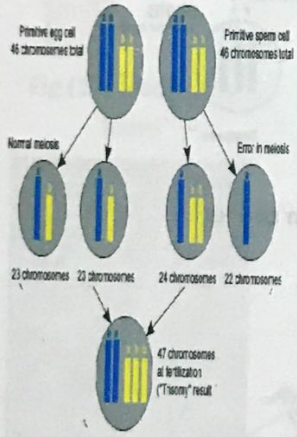


Fig (12): non – disjunction

- It is a result of an error at meiosis
- The pair of chromosomes 21 fail to separate ,so that one gamete has two chromosome21 , and one has non
- Fertilization of the gamete with two chromosomes 21 give arise to a zygote with trisomy 21
- The extra chromosome is usually maternal.
- The incidence of non-disjunction Mongol is increased with increase in mother's age (age dependent). At age :
  - 30 years → 1/1000.
  - 35 year → 1/350
  - 40 year → 1/100
  - 45 year → 1/50.
- The extra chromosome can be paternal due to meiotic non disjunction during spermatogenesis
- Parent chromosomal analysis is not indicated

Translocation 4 %

14
15
21
22

- **A chromosome 21 is translocated into another chromosome (14,15,21,or 22), this known as Robertsonian translocation**
- **Such individual has the following**
  - Number of chromosomes is 45 as the joined 21 chromosome into another is counted as one chromosome
  - Has full genetic material , so his or her phenotype is normal
  - It is called a translocation carrier as there is risk to transmit the Down syndrome to his or her offspring.

- During gametogenesis of translocation carrier, 6 possible gametes can be produced as shown in the figure (13)

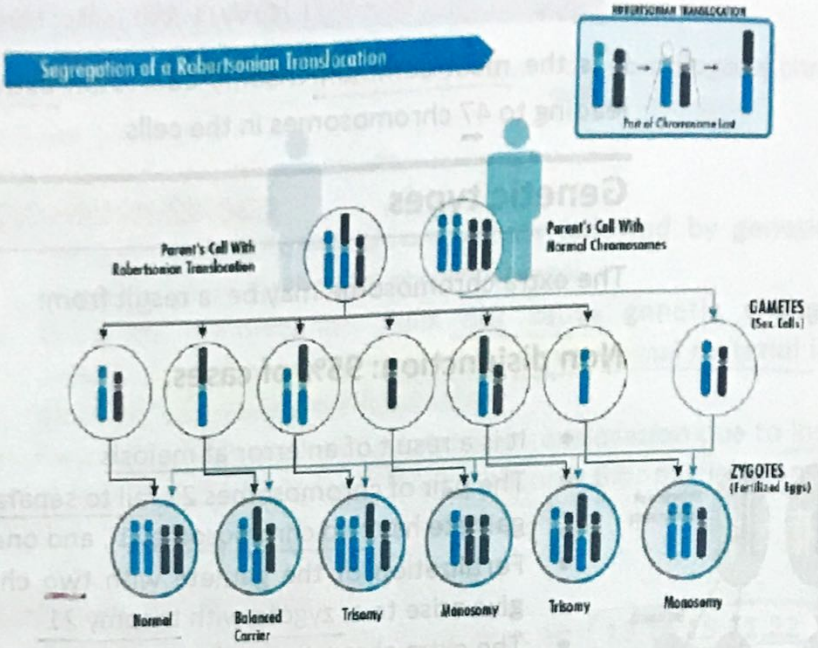


Fig (13): gametogenesis of translocation carrier

- **Parent chromosomal analysis is indicated**
- **Risk of recurrence is.**
  - If translocation 21/15 or 21/14 is one of three.
  - If translocation 21/21 is 100%

Mosaic mongolism 1%:

- Some of cells are normal and others are trisomy 21.
- Has two lines of cells, one of which contains 47 chromosomes & the other contains 46 chromosome.
- It is usually resulting from post zygote non disjunction.

Clinical picture

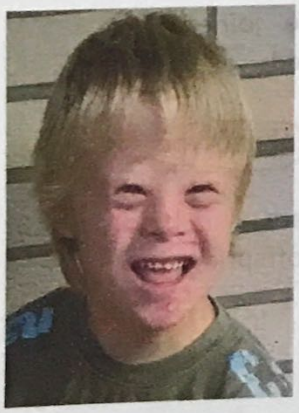


Fig (14): Mongol

- Mental retardation (IQ 25-50 %).
- Growth retardation with delayed motor functions.
- Generalized hypotonia (floppy baby). ↓↓ muscle tone
- Physical features which include:

Head

- Microcephaly.
- Brachycephaly = flat occiput.
- Fine silky hair



Fig (15): brachycephaly

Eyes



Fig (16); brush field

UBEHAN

- Upward slanting.
- Hypertolorism (wide distance between eyes).
- Epicanthic fold with narrow palpebral fissure.
- Brushfield iris (round grayish spots in iris).,disappears after age of 1 year
- Apparent squint.

Ears: low seated ears.

Nose: flat nasal bridge.

Mouth: protruded tongue due to small mouth cavity (micrognathia).

Neck: broad short neck.

Hand

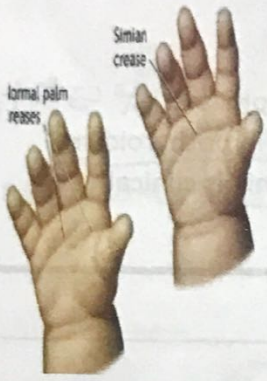


Fig (17): mongol's hand

- Short broad hand with short fingers (brachydactly)
- Hypoplasia of middle phalanx of 5th finger. → Incurved finger (clinodactyly).
- Single transverse palmar crease (Simian crease).

Foot: gap between 1st and 2nd toes.

Genitalia: small pens and testicle. Infertility is Common



Fig (18): foot of Down syndrome

= sandal gap

Associated congenital anomalies:

ASD, VSD, MR, TR = A-V canal defect

- Cardiac: endocardial cushion defect, VSD, ASD.
- GIT : duodenal atresia, Imperforate anus, & Hirschspring disease,
- Renal anomalies.
- Congenital hypothyrodism = cretenism

Complications

HAL RACMA

1. Recurrent infections due to immunodeficiency
2. Leukemia: Mongol is 20 times more risky for leukemia than normal.
3. Autoimmune dis: auto immune thyroiditis → hypothyroidism.
4. Heart failure
5. Risk of atlanto-axial subluxation which can lead to paralysis.
6. Risk for coeliac disease.
7. Increased risk of myopia and acquired cataract.

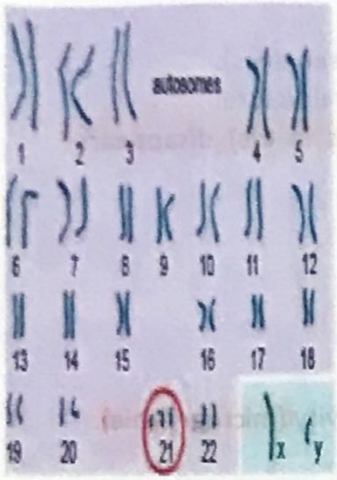


Fig (19): trisomy 21

Investigations

1. Karyotyping : for the Down syndrome to detect genetic types;
   - Non disjunction type : 47 chromosomes with excess 21 chr.
   - Translocation: 46 chromosomes with excess 21 chromosomes translocated.
   - Mosiac type: cells with 47 chromosome & cells with 46 chromosome.
2. X –ray chest to detect cong. heart disease
3. X – ray hand to detect hypoplasia of middle phalanx. of 5th Finger
4. Hormonal assay: T3, T4 TSH for detection of hypothyroidism.
5. CBC and bone marrow examination if leukemia is clinically suspected.

Treatment

1. No specific treatment
2. Treatment of associated infections or cong. Anomalies.
3. Educational programs according to IQ:
   - Mild MR (as in mosaic) : educable
   - Moderate MR : trainable.
   - Severe: Non educable non trainable.

Causes of death

- Recurrent infection.
- Leukemia
- Cong. anomalies
- Accidents.

ACLi

Antenatal Diagnosis of mongolism

1. Invasive: amniocentesis and karyotyping of amniotic cells .
2. Triple test (non-invasive) by analysis of maternal blood for 3 biochemical markers.
   - Increased maternal α fetoprotein.
   - Decreased Unconjugated esteriol .
   - Increased Serum human chorionic gonadotropin. HCG
   - Triplet test detects 60% of all Down syndrome.
3. Ultrasound

NSC

   - Nuchal thickness (thickening of the soft tissue at the back of the neck)
   - Short femur
   - Congenital heart disease (AV canal defect).

Cri-du- chat syndrome

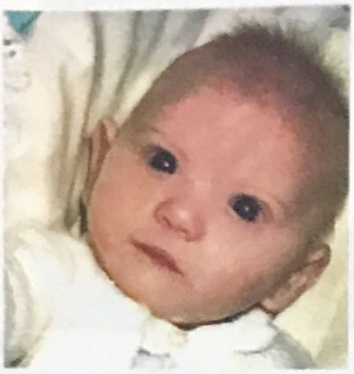


Fig (20) Cri –Du –Chat

It is due to deletion of chromosome no. 5 characterized by:

1. Mental retardation.
2. Growth retardation.
3. Hypotonia.
4. Microcephaly with round face.
5. Hypertelorism.
6. Congenital heart diseases. VSD
7. Characteristic cat likes crying due to abnormal laryngeal development.

Turner syndrome

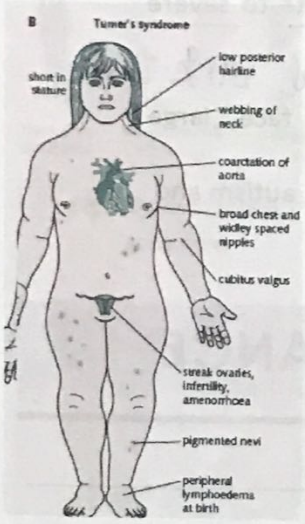


Fig (21): turner

1. Karyotyping is 45 XO.
2. Female phenotyping
3. Short stature.
4. Low set ears.
5. Webbing of the neck.
6. Widely spaced nipples.
7. Congenital heart disease (aortic coarctation).
8. Pigmented mole (naevi)
9. Renal : horseshoe kidney &double renal pelvis
10. Edema of LLs due to lymph edema in neonates and may persist.
11. Cubitus vulgus.
12. Juvenile external genitalia
    - absent axillary & pubic hairs
    - breast is not developed.
    - 1ry amenorrhea (infertility).
13. Mentality is normal in most cases.

Klienfilter syndrome

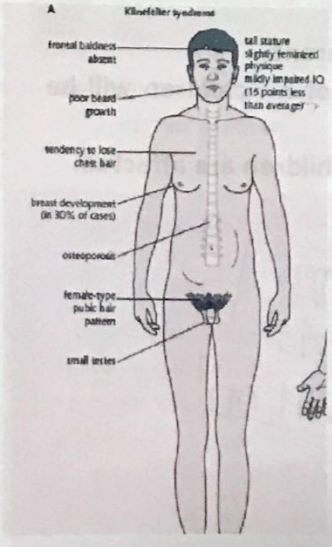


Fig (22): Klienfilter syndrome

1. Karyotype is 47 xxy
2. Male phenotype characterized by:
3. Tall stature.
4. Poor growth of facial hair.
5. Gynecomastia.
6. Feminine distribution of fat.
7. High pitched sound.
8. Sparse or minimal pubic hair.
9. Testicular atrophy with small penis (infertility).
10. Mentality is usually normal but some have educational and psychological problems.

Super female

- Karyotype is 47 (XXX) characterized by:
- Poor secondary sex character
- Infertile with mental retardation.

Fragile x chromosome



Fig (23): fragile X syndrome

- It is a fragile site on X chromosome.
- It affects male while females are carriers.
- Characterized by :
  - Mental retardation : moderate to severe IQ 20-80
  - Macroorchidism
  - Characteristic feature (long face ,large ears and broad forehead)
  - Other : mitral valve prolapse , autism and hyperactivity

MODES OF INHERITANCE

Autosomal dominant

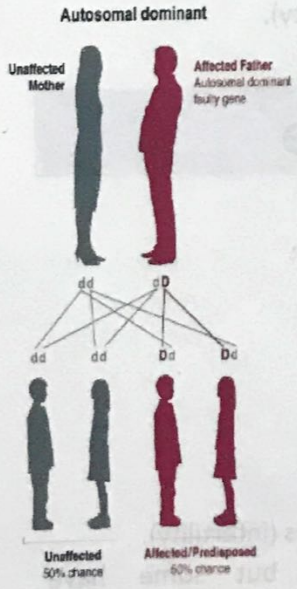


Fig (24): autosomal dominant

- The gene is carried on autosome.
- Defect in one gene is enough to express the trait.
- Affects males as well an females.
- Each affected person has as affected parent.
- Homozygous affected person (DD) all of his children will be affected.
- Heterozygous person (Dd), 50% of his children are affected.

Examples

1. Congenital spherocytosis.
2. Poly cystic kidney.
3. Von will brand disease
4. Familial hypercholesterolemia.
5. Achondroplasia.
6. Oesteogenesis imperfecta.
7. Neurofibromatosis.
8. Huntington chorea.
9. Marfan syndrome
10. Tuberous sclerosis

CVP
FAO
NHtm

Autosomal recessive:

- The gene is carried on autosome.
- 2 genes should be affected to express the trait (rr) (Homozygous state).
- One gene affection (heterozygous state) is called carrier (Rr).
- Affect males as well as females.
- Both parents of the affected child are carriers (normal phenotypes).

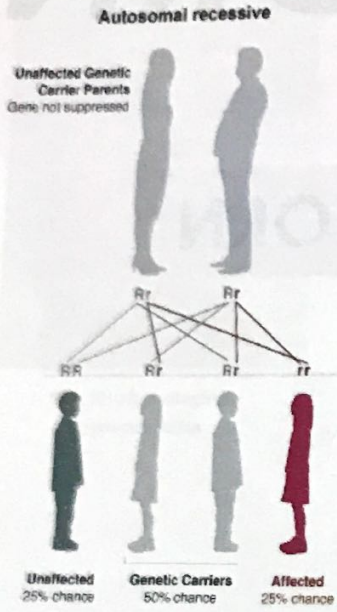


Fig (25): autosomal recessive

Examples

1. Galactosaemia.
2. Wilson Dis.
3. Gaucher dis.
4. Phenylketonuria.
5. Cystic fibrosis.
6. Mucopolysaccharoidosis.
7. Glycogen storage disease
8. Sickle cell anemia
9. Thalassemia
10. Werding – Hoffman disease

GW
GP
GMC
SWt

X- Linked recessive:

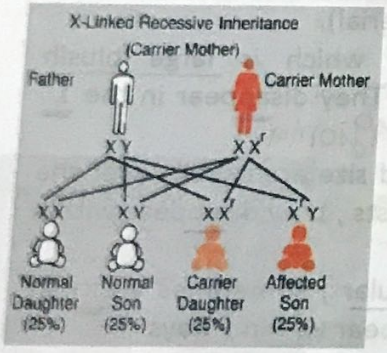


Fig (26): X linked recessive carrier mother

- The gene is carried on X chromosome.
- In male (hemizygous) the affection of one single gene express the trait.
- In Heterozygous females, one gene affection means carrier
- In Homozygous females, two gene affection means disease
- The disease is usually transmitted from female carrier to her sons.
- The females are rarely affected, only if father is a case and the mother is carrier.

Examples

- G6PD deficiency
- Hemophilia.
- Duchene myopathy.
- Color blindness.
- Nephrogenic diabetes insipidus.
- Siderobalstic anaemia.
- Fragile x syndrome
- Hunter syndrome

GHD
CNS
FH

X- Linked dominant

It differs from x – linked recessive in that only one mutant gene in female can express the trait i.e., the heterozygote female is not a carrier, she is a case. E.g. Familial hypophasophatemic rickets.