Paediatric

Genetics and Dysmorphology

Contents:-

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Basic of Genetics:-

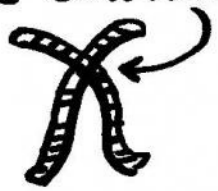
* Somatic cells → contains 46 chromosomes.
(diploid Nub) → 23 paired chromosome.
(44 Autosome ⅋ 2 sex chromosome.)

XX ♀ XY ♂

* germ cells → contain 23 chromosome.
(haploid) Nub) → single chromosome
22 Autosome ⅋ 1 sex chromosome

X ♀(ovum) Y ♂(Sperm)

* Each chromosome is composed of 2 chromatids attached to each other ē centromere



* gene is basic unite of inhiritance

* The human karyotype :- Modern banding techniques allow precise identification of each chromosome
(♀ 46 XX) (♂ 46 XY) (Nub - size - shape)

"Mechanisms of disease"

① _ Chromosomal disorders :-

- Numerical
  - Polypliody
  - Aneupliody
    - Monosomy
    - Trisomy.
- Structural
  - _ Deletion
  - _ Duplication

② Single gene disorders :- "Mendelian"

I. Automal dominant AD. diseases.
II. Autosomal Recessive AR. " .
III. X Linked dominant XLD. " .
IV. X Linked Recessive XLR. " .

③. MultiFactorial inhieritance. MCQ

Enviromental + Genetic Factors.

① CHD. ② pyloric stenosis ③ NTD.
④ Cleft lip & palate. ⑤ DDH
Other as atopy - DM I - Autism

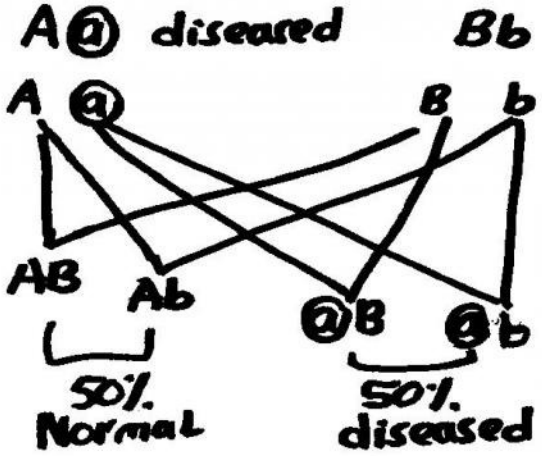
* Mendelian inheritance :-

① Autosomal dominant (AD) بالصفة السائدة

Characteristics :-

MCQ

① . The trait manifist in homomozygous & heterozygous state.
② . Both sex are equally affected. ♂ = ♀
③ . appeare in all generation .
④ . New mutation is comenon
⑤ . Risk → 50% affected - 50% Normal .



⊙ Example :- MCQ

* NeuroFibromatosis
* Tuberous sclerosis
* Achondroplasia
* Myotonic dystrophy
* H. Spherocytosis .
* Noonan's syndrome.
* MarFan " .
* Allagille " .
* Von willbrand disease.
* Hantigton disease.

② Autosomal Recessive (AR)

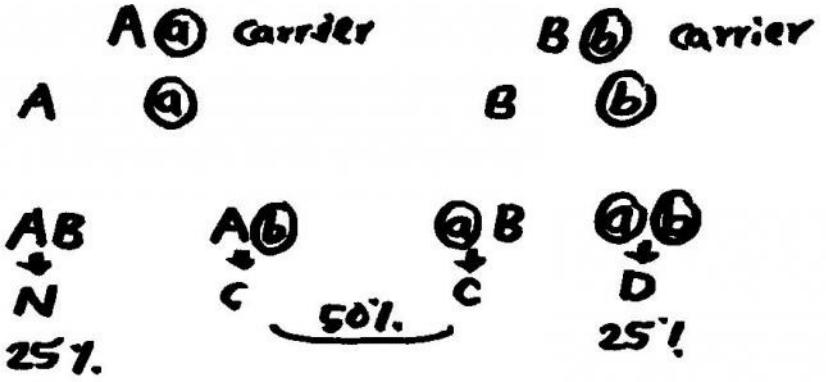
* characteristics :-

① The trait manifests only in homozygous state.

② Both sex are equally affected ♂ = ♀.

mcq ③ Consanguinity increases the risk of having an offspring ℰ AR disorder.

④ Risk → .25% Normal.
.25% Diseased.
.50% Carrier.



Example :- mcq

* Cystic Fibrosis
* Thalassemia - SCA - Fanconi anemia
* Congenital adrenal hyperplasia .CAH.
* Werdnig Hoffman disease.
* Ataxia Telangectasia
* wilson disease.
* Homocysteinuria
* IEM as → Glactosemia, → PKU, → GSD

③ X Linked Recessive (XLR)

→ ♂ affected & severe
→ ♀ carrier or mild disease

Characteristic Features.

① Only Females can transmit the disease to their son.

MCQ ②. NO male to male transmission.

③. Affected males will have only carrier daughters.

* Female carriers Risk → her son → 50% affected
                          → her daughter → 50% carrier

Carrier ♀ × Normal ♂

	X	Y
X	XX Nor	XY Nor
⊗	⊗X car	⊗Y Dis

* Male affected Risk → his son ⇝ 100% Normal.
                      → his daughter ⇝ 100% carrier.

	X	Y
X	XX	XY
⊗	⊗X	⊗Y

XX Nor; XY Nor; ⊗X Car; ⊗Y Nor

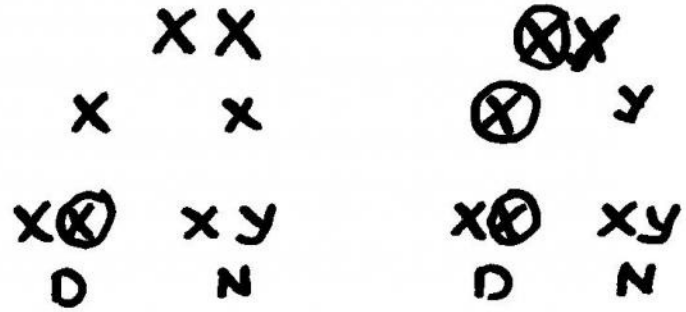
Example :-

MCQ * Hemophilia A & B * G6PD anemia.
* Duchenne MS dystrophy
* Fragile X Syndrome.
* Hunter's Syndrome (Mps II)
* Color Blindness.
* wiskot_aldrich Syndrome.

④ X Linked dominant (XLD)

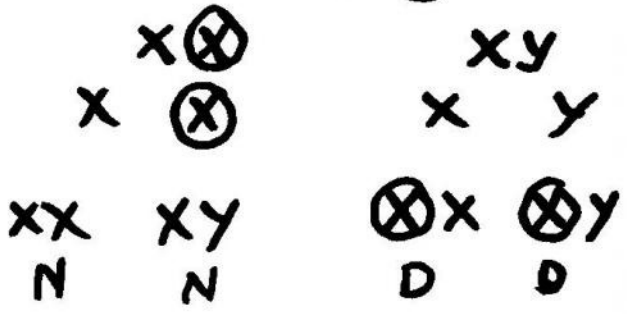
Criteria :-

* affected Father transmit the disease to all daughter but never to his sons.



- ♀ 100% diseased
- ♂ 100% Normal.

* affected Mother transmit the disease to 50% of her offspring whether males or females.



Example :-

M(Q)
1. X Linked hypophosphatemia.
2. Rett Syndrome.
3. Most cases of Alport Syndrome
4. incontinentia pigmenti

-MCQ
-case
-clinic

Down Syndrome

* Trisomy 21 it's most common trisomy Compatible ē life
* Incidence 1:650 or 1:700 live bone infants.
* Karyotyping 47XX+21 or 47XY+21

Types

① Non disjunction 94%***

* result in error of Meosis
→ Failure of separation of Chromosome 21 during Meosis of maternal oocyte
* it's Related to Maternal age
* Risk of recurrence is 1%. ↑ē↑ maternal age

Maternal Age	Risk of Down Syndrome
30y	1:900
35y	1:385
40y	1:100
45y	1:37

② Robertsonian Translocation 5%

* occure when extra Chromosome 21 is joined onto another Chromosome usually D group (13-14-15) or G (21-22) → unbalanced translocation

↓↓

Needs parental Chromosomal Analysis

→ if mother carrier balanced translocation → Risk of recurrence 10-15%

→ if the Father → Risk of recurrence 2.5-5%

→ if the mother carrier of unbalanced translocation 21q:21q

↓↓

⑧ Risk of recurrence 100%

③ Mosiacism. 1%

* Some cells have normal chromosomes & some cell have trisomy 21.
* phenotype may be Milder.

- MCQ
- case
- clinic

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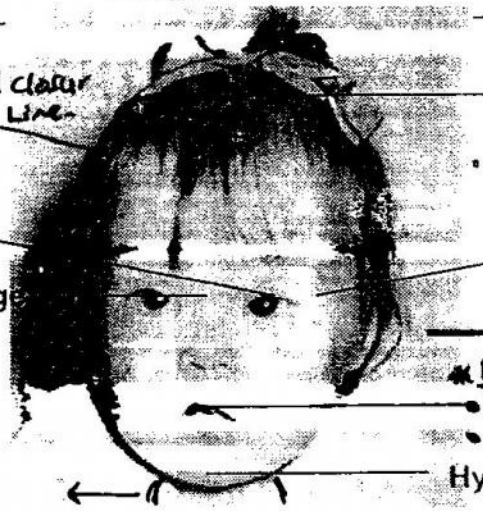
* Clinical Features :- MCQ



* Head
  - Microcephally
  - Wide AF + Delayed closur Line
  - High past hair
  - Brachycephally -
* Eyes
  - Epicanthal fold
  - Hypertolirism
  - Depressed nasal bridge
* Eyes
  - Brush Field spots
  - Cataract
  - squint - myopia up
  - Lateral slanting Eyes
* Silky hair
* Low set ear + small Ears
* Mouth
  - Protruding tongue
  - High arched palate.
* Hypoplastic mandibule (Micrognathia)
* short Neck

* Hands
  - Short & broad Fingers
  - Simian crease
  - Clinodactyly ↘ (Hypoplastic middle phalanx)

* Foot
  - Sandal gap = Wide gap + Ape creases

General examination in Down syndrome (complication)
& late Manifestation & Medical problems

* CNS
  - Mental Retardation + Epilepsy
* Respiratory
  - Recurrent chest infection
* Hypotonia
* short Stature

* Heart ⇒ • CHD 40%
  - AVC = Endocardial cushion defect
* GIT ⇒
  - Doudenal atresia
  - Celiac disease.
  - Hirschsprung disease
  - Anal atresia
* Genetalia
  - small - undescended testes
  - infertility

* Musculoskeletal systeme.
  - ⇒ sudden atlantoaxial dislocation → Death.
* Endocrine systeme : ① Type IDM ② Hypothyriodism -
* Immune system & ass ē selective IgA Immunedeficiency
* Blood ⇒ ↑ Risk of Leukemia

* Diagnosis

* Antenatal diagnosis :-

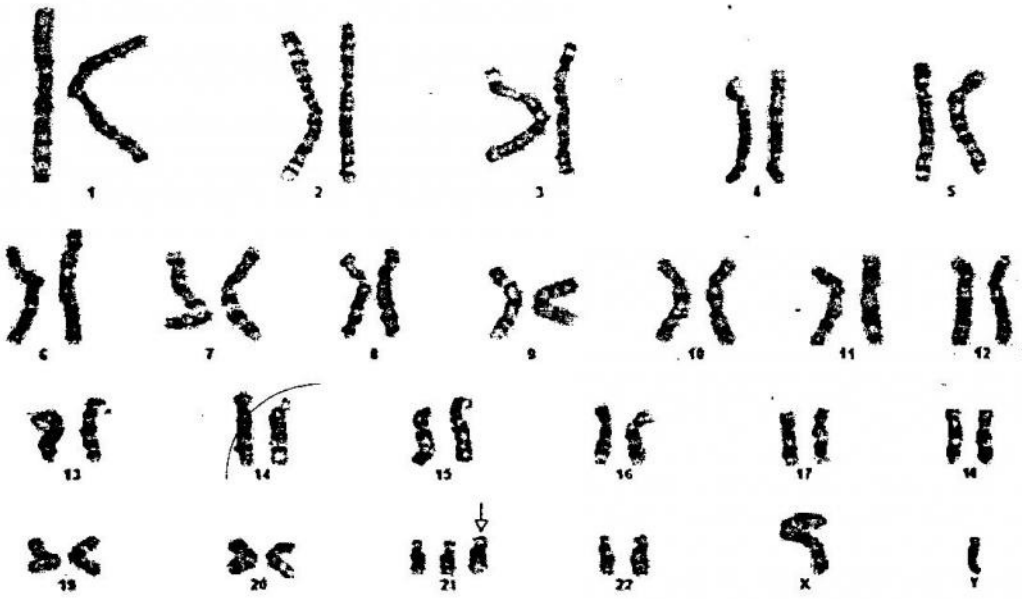
① Antenatal U/S screening ⇝ nachal pad thickness.

② Amniocentesis → Triple test ↑HCG
↓ α Fetoprotein
↓ Estradiol.

⇝ karyotyping

* postnatal diagnosis :-

Chromosomal Analysis (karyotyping)



* 47,XY,+21: Abnormal karyotype with trisomy 21, pt with Down syndrome

* 47XY+21 ♂

Q

* **Management** :- Needs Multidisciplenary team.

① Rx of complication as CHD - Atresia.

② Social & psychological support.

③ Frequent Follow up & yearly screen For Endocrine disease

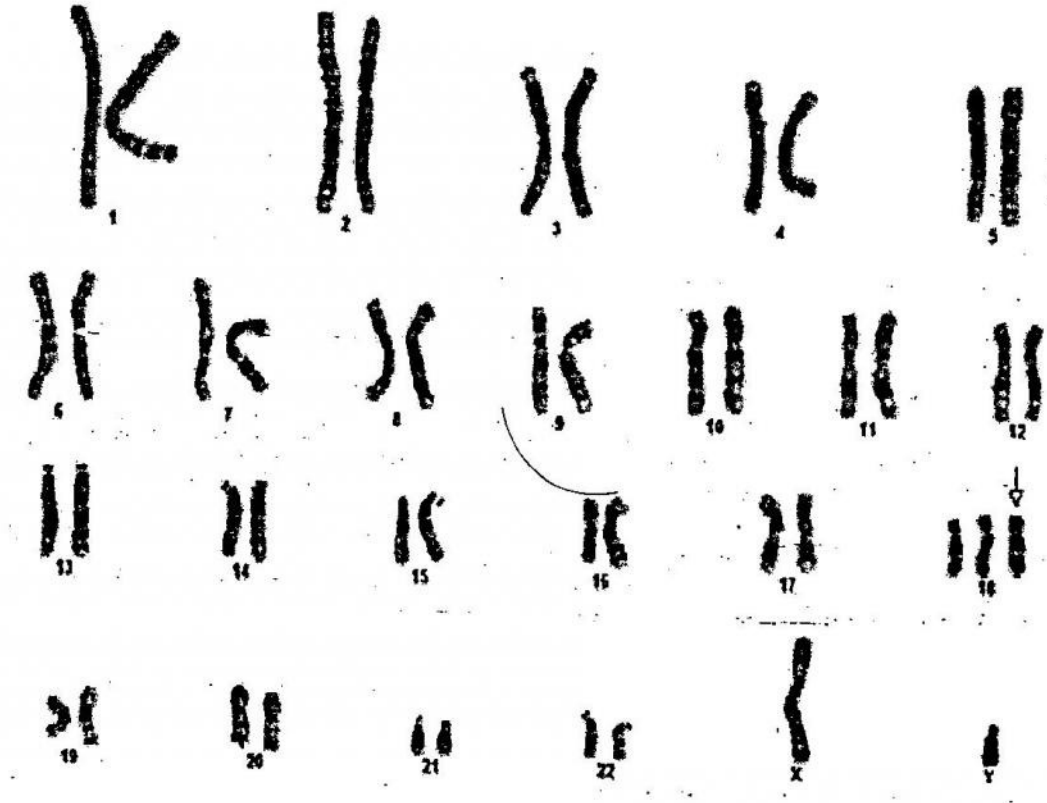
④ General health support → good Nutrition
• Immunization

⑤ Genetic counseling to parents & Education about down syndrome & posible progression

MCQ

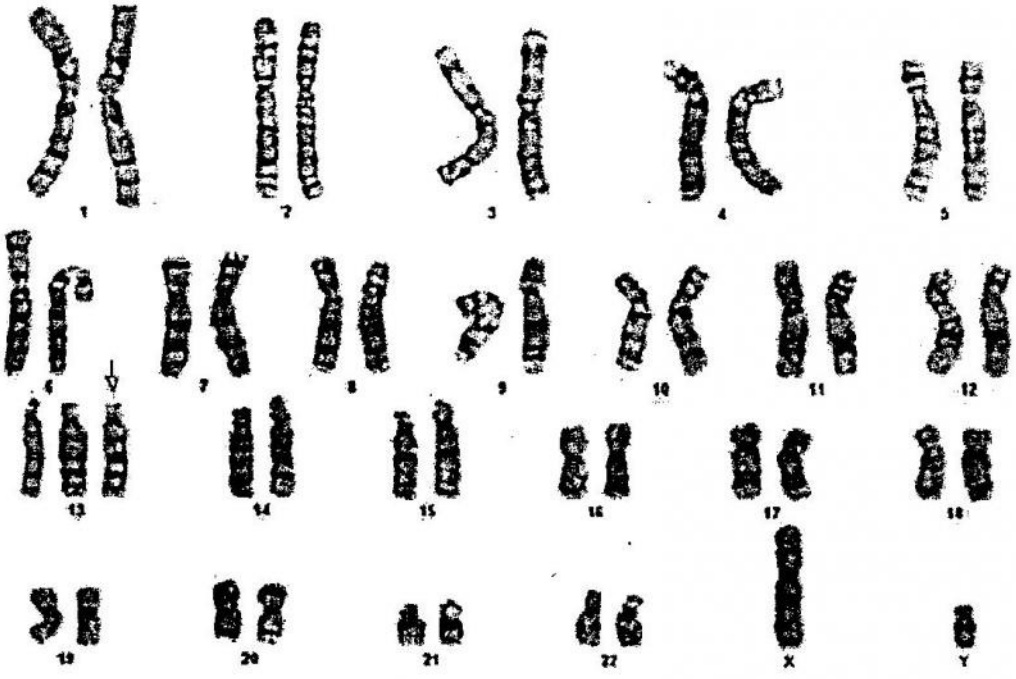
	Edward's Syndrome	Patau's Syndrome
Type	Trisomy "18"	Trisomy "13"
%	1:6000 - 8000 Live births	1:10000 - 14,000 live births.
Karyotyping	47XX+18 or 47XY+18	47XX+13 or 47XY+13
CIP	• LBW - IUGR. • prominant occiput* (small head - small mouth & chin) • Short sternum - * • Rocker botton Feet - clenched Fists* - overlapying Fingers - Hypoplastic Nails. • CHD ⇒ 80-90%. VSD* - ASD - PDA • Severe MR + develop-mental delay.	• LBW - IUGR • Scalp defects "cutis Aplasia" small head - cleft palate - polydactyly micro-ophtalmia. • Omphalocele - hernia • CHD 80-90%. VSD* - ASD - PDA • Renal Anomalies - • MR - developmental delay.
prognosis	⇒ 50% survival upto 2m Age. ⇒ Only 5-10% " " 1year. ⇒ Cause of death "CHD + Apnea"	⇒ up to 90% will die within the 1st month due to Complex CHD + Apnea.

; 47,XY,+18: Abnormal
karyotype with trisomy
onsistent with Edwards
ome



karyotyping → 47XY+18

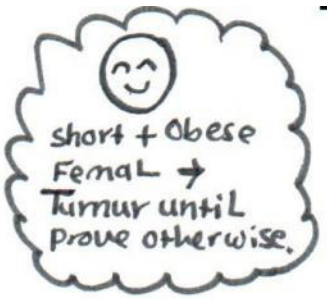
13: Abnormal
with trisomy
ith Patau



karyotyping → 47XY+13

- MCQ
- Clinic
- Diagnostic

Turnur's Syndrome.

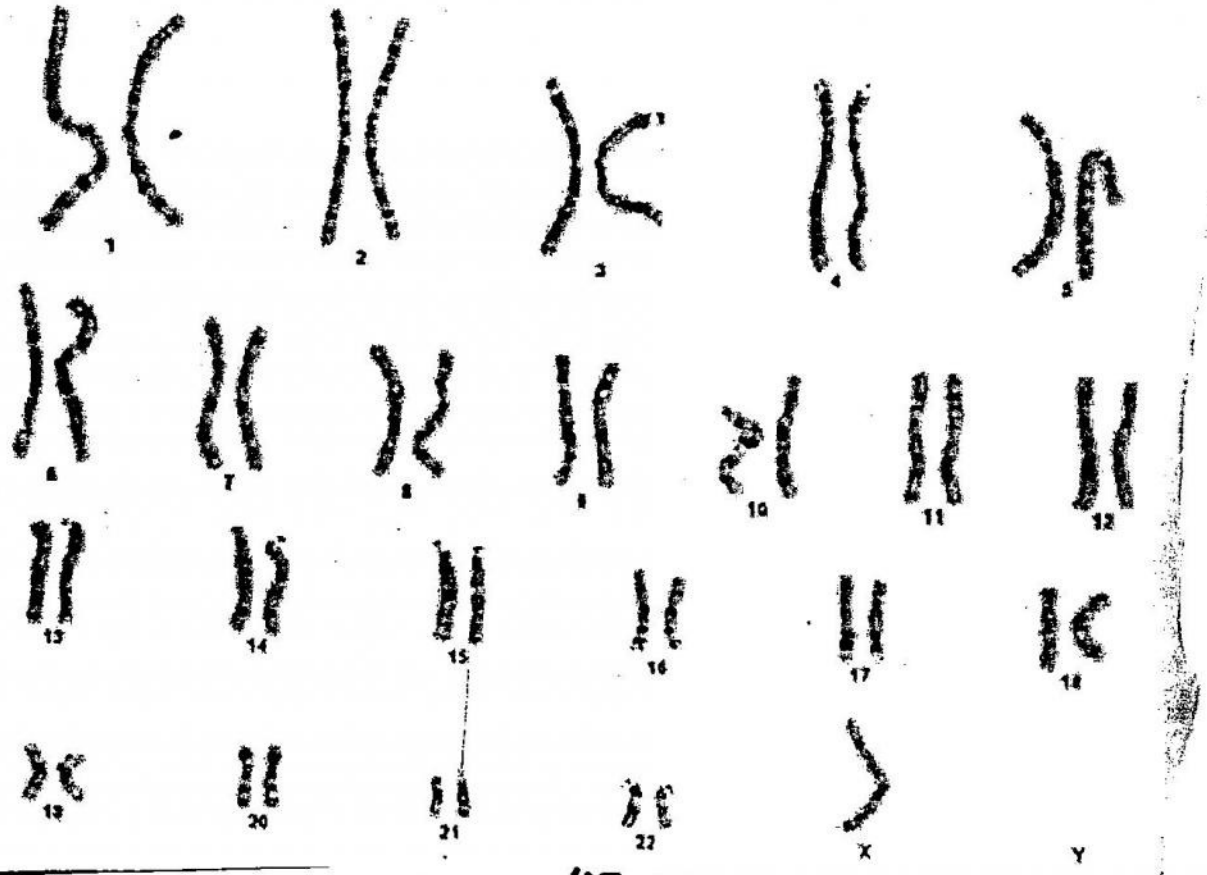


* % → 1:2500 Live Femal births.
* karyotyping ⇝ 45XO
* C/P :-
  1. Newborn ♀ + lymphedema (hand + Feet odema) !! at birth
  2. Head + Face ⇝ . webbing neck.
     - low posterior hair Line.
     - High arched palate.
     - Eyes → ptesis + cataract
     - Ears → otitis media.
     - ☺ ⇝ good IQ (No MR)
  3. Skeletal ⇝
     - Short Stature ***
     - cubitus valgus + spoon shaped nails.
     - short 4th metacarpal or metatarsal bone
     - Scoliosis (10%)
  4. Chest & heart ⇝
     - widly spaced nipples. + shieled chest.
     - CHD ⇝ CoA & bicusped aortic valve 15-20%.
  5. Renal System ⇝ . horse shoe kidneys & Renal anomalies 30%.
  6. Ovarian Failure ⇝ . Delayed puberty ⇝ Amenorrheq ↗14y ↘12y
     - x NO breast enlargment
     - & but pubic hair present.
     - x ↑ LH & FSH.
     - & infertility.
  7. Endocrine system ⇝
     - Hypothyriodism (Hashimoto's)
     - DM type (I)
  8. Skin ⇝ CaFe alait Spots.

* Diagnosis ⇝ antenatal ⇝ amniocentesis or chorionic villus sampling.
  ⇝ karyotyping ⇝ 45XO.
  other Ix ⇝ Echo – U/S Abdomen – LH & FSH level.
  TFT

* Rx :-
  1. GH therapy ⇝ SS.
  2. Oestrogen replacment therapy ⇝ 12-15 years.
  3. TFT / 2 years.
  4. Counsling & support may be required.

Abnormal karyotype, sex chromosome, Turner syndrome



karyotyping ⇒ 45XO

Syndromes recognised by 'Gestalt' (clinical recognition)

Figure 8.17 Noonan's syndrome affects males and females. There are some similarities to the phenotype in Turner's syndrome, but it is caused by a faulty autosomal dominant gene and the chromosomes are normal.

Figure 8.18 Williams' syndrome is usually sporadic.

Figure 8.19 Prader–Willi syndrome.

Box 8.11 Clinical features of Noonan's syndrome MCQ

- Characteristic facies
- Occasional mild learning difficulties
- Short webbed neck with trident hair line
- Pectus excavatum
- Short stature
- Congenital heart disease (especially pulmonary stenosis, atrial septal defect)

Box 8.12 Clinical features of Williams' syndrome MCQ

- Short stature
- Characteristic facies
- Transient neonatal hypercalcaemia (occasionally)
- Congenital heart disease (supravalvular aortic stenosis)
- Mild to moderate learning difficulties

Box 8.13 Clinical features of Prader–Willi syndrome MCQ

- Characteristic facies
- Hypotonia
- Neonatal feeding difficulties
- Failure to thrive in infancy
- Obesity in later childhood
- Hypogonadism
- Developmental delay
- Learning difficulties

* Fragile X Syndrome :-


Normal X chromosome

Fragile x chromosome

* XLR disorders.
* Most common cause of inherited mental retardation in male.
* C/P ⟶ ① Face ⟶ Elongated Face
prominant ears (larg)
Larg head.
prominent mandible & Forehead.

② ⟶ low IQ mental retardation.

③. CVS ⟶ CHD (Mitral valve prolapse).

④. Genital ⟶ macro-orchidism.

⑤. Others ⟶ Joint laxity - Autism - ADHD.

* Kinefelter syndrome

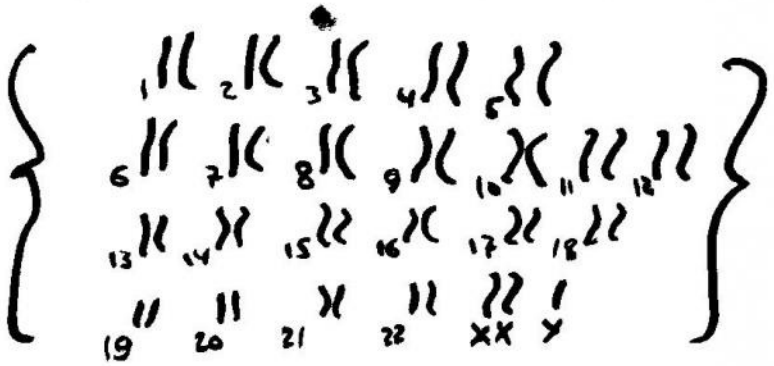
* karyotyping "47 XXY" (٪ 1: 600 live born males)
* is the most common chromosomal disorder ass ē male hypogonadism & infertility.

C/P

- Tall stature
- Hypogonadism** ē delayed 2ry sexual caracheter.
- infertility Azoospermia*** - small penis - subnormal lipido.
- Gynecomastia* - Fat ḡ distribution.
- Mild developmental & behavioral proplems.
- ↑ Risk of breast carcinoma * ☹ ōطبية

* Ix → low serum testesterone - ↑ LH & FSH.

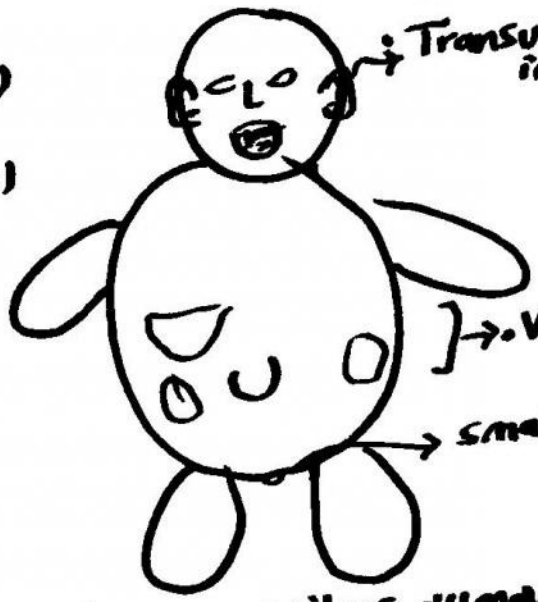
47 XXY



Beckwith-Wiedemann syndrome :-

C/P :-

- Larg wt (macrosomia)
- Larg tongue (macroglosia)



- Small head.
- Transverse creases in the ear.
- Visceromegaly (Liver & Kidney)
- small genetalia
- omphalocele or umbilical hernia

↑ * Risk of Tumour wilms tumor.
* Risk of Hypoglycemia

* Angelman Syndrome:-

* 100% ⇝ . Developmental delay.
. Speech impairment الكلام
. Frequent Laughter / Smiling (appear happy 😊)

* other Features ⇝ • Microcephally.
• Seizures.
• sever MR.
• Fair hair & skin.

. pedigrees & inheritance .

Normal male .
diseased = .
carrier = .

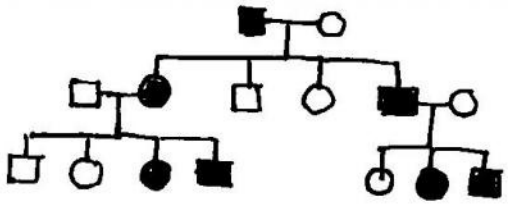
Normal Femal .
diseased = .
carrier = .

Dizygous twins

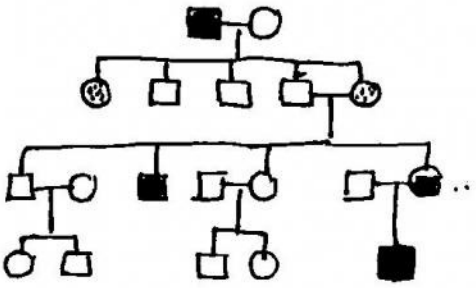
Monozygous twins.

parents
(unrelated)

Consangeous parents
(Related)



- Mode of inheritance ?
- Example ?



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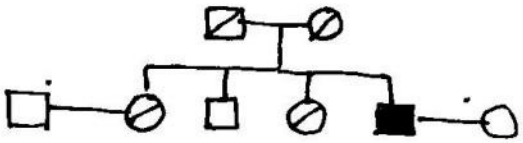

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