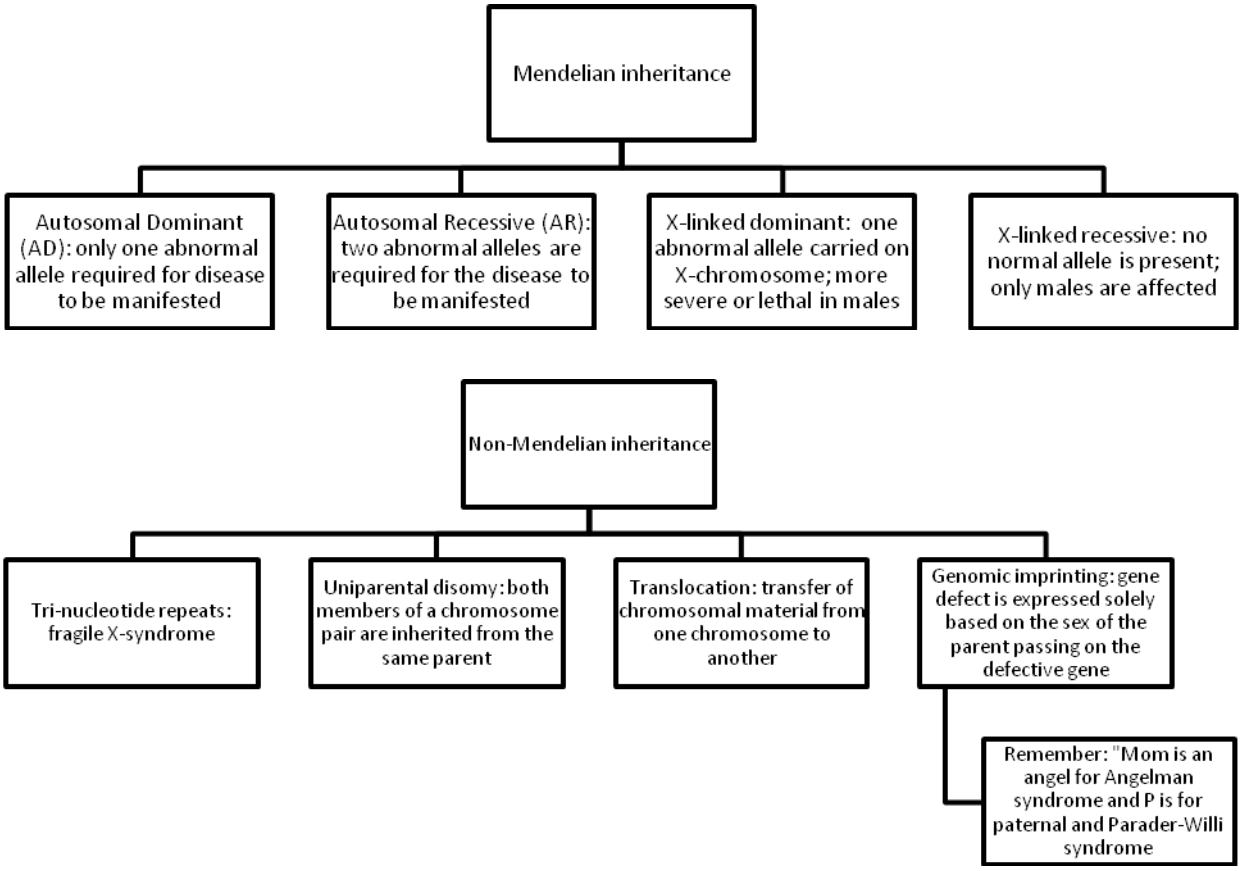


- **Abnormalities of morphogenesis:**
  - **Malformation**: intrinsically abnormal processes forming abnormal tissues.
  - **Deformation**: mechanical forces exerted on normal tissues and converting them to abnormal tissues.
  - **Disruption**: normal tissues become abnormal after being exposed to destructive forces.
  - **Syndrome**: a collection of what seem to be un-related abnormal features occurring in a familiar pattern.
- **Fetal evaluation and prenatal diagnosis:**
  - **Ultrasound**: used to assess for gestational age, fetal growth and fetal anomalies.
  - **Maternal serum markers:**
    - ✓ α-Fetoprotein (AFP):

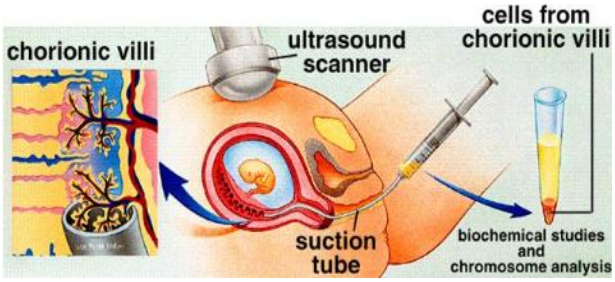
↑	• Gestational age error • Neural tube defect • Multiple gestation • Anterior abdominal wall defects
↓	• Gestational age error • Down or Edward's syndromes

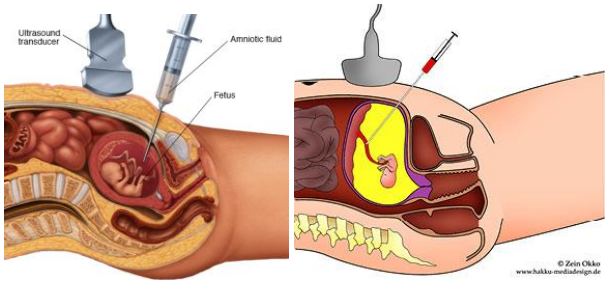
    - ✓ Triple marker:

Syndrome	AFP	Unconjugated estriol	B-HCG
Down syndrome	↓	↓	↑
Edward's syndrome	↓	↓	↓

✓ Genetic evaluation of fetus:

Chorionic Villous Sampling (CVS)	• Done between 10-12 weeks • A sample of placental tissue is taken. • Risk of pregnancy loss: 0.7%
Amniocentesis	• Done > 15 weeks. • A sample of amniotic fluid is taken. • Risk of pregnancy loss: 0.5%
Percutaneous Umbilical Blood Sampling (PUBS)	• Done after 20 weeks. • A sample of blood from umbilical vein is taken.

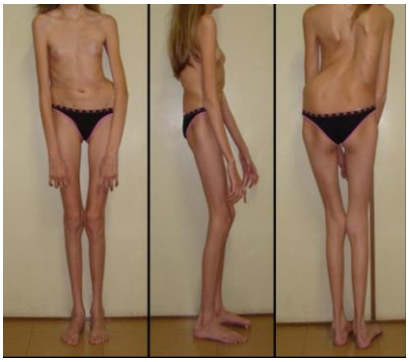


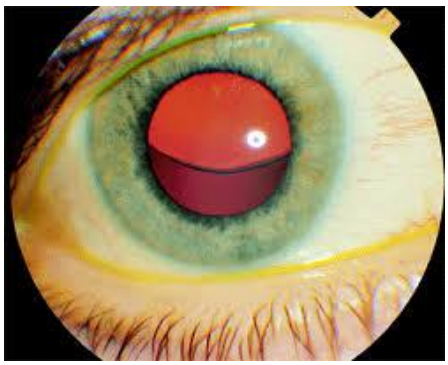


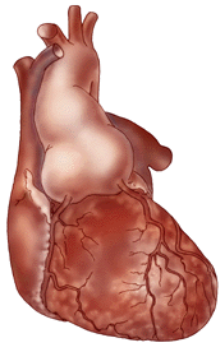
- **Common genetic disorders:**
  - **Marfan syndrome:**
    - ✓ It is an AD disorder of connective tissue due to abnormality in chromosome 15 (that coder for febrillin).
    - ✓ Clinical features:

Skeletal	Tall stature with elongated extremities and long fingers, ↓ U/L segment ratio, joint laxity, pectus excavatum and scoliosis or kyphosis
Ocular	Upward lens sublaxation
Cardiovascular	Aortic root dilation (±aortic dissection)

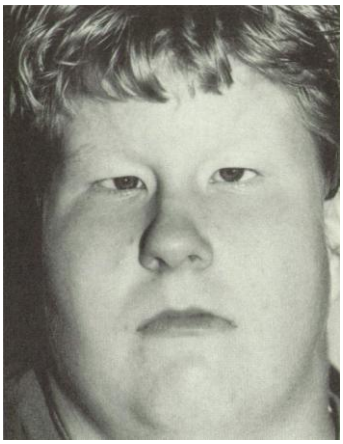
    - ✓ Diagnosis: based on clinical features. Notice that you have to differentiate it from homocytinuria (because both have similar features).
    - ✓ Complications: endocarditis, sudden death due to aortic dissection (↑risk with HTN and trauma) and retinal detachment.

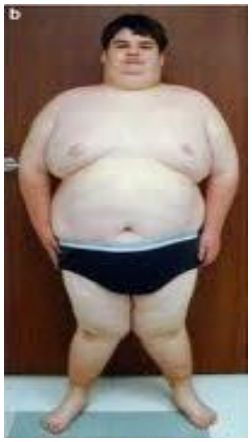






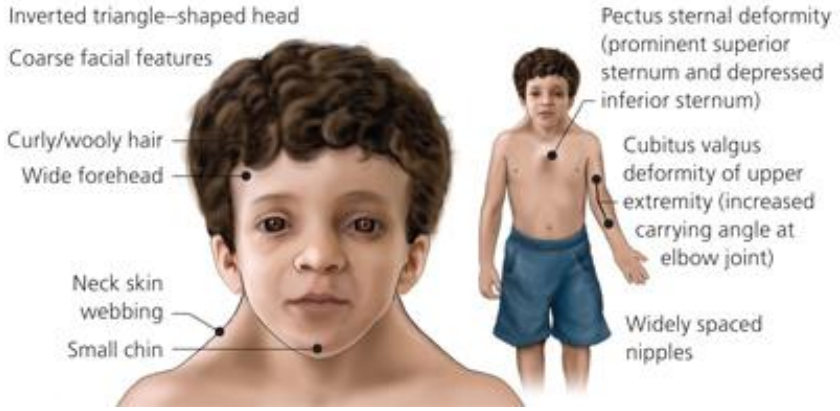
  - **Prader-Willi syndrome:**
    - ✓ It is an example on genomic imprinting in which there is a deletion involving paternally derived chromosome 15.
    - ✓ Clinical features: almond-shaped eyes, fish-like mouth, short stature, obesity/hyperphagia, small hands and feet, hypotonia, mental retardation and small penis/testes.
    - ✓ Diagnosis: FISH probes detecting deletion on chromosome 15.
    - ✓ Complications: obstructive sleep apnea due to obesity (in childhood); cardiac diseases and type-II DM (in adulthood).



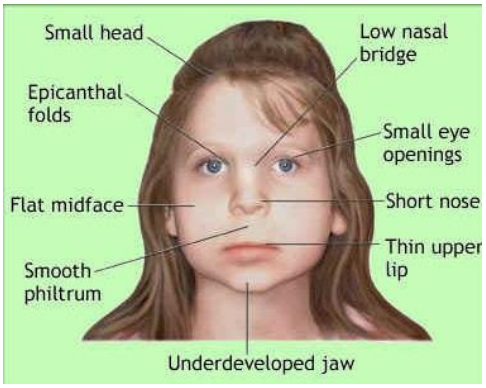


- **Angelman syndrome (happy puppet syndrome):**
  - ✓ It is an example on genomic imprinting in which there is a deletion involving maternally derived chromosome 15.
  - ✓ Clinical features: puppet-like gait, frequent laughter and smiling, mental retardation, blond hair, blue eyes, large mouth with protruding tongue and widely-spaced teeth.
  - ✓ Diagnosis: FISH probes detecting deletion on chromosome 15.

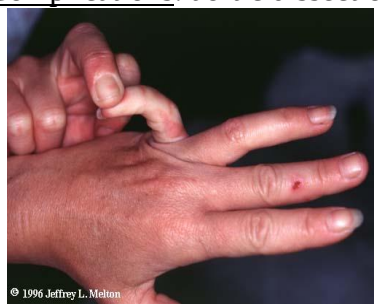
- **Noonan syndrome (male version of Turner's syndrome):**
  - ✓ It is an AD disorder involving chromosome 12.
  - ✓ Clinical features: short stature, shield chest with widely-spaced nipples, webbed neck, low hairline, right-sided heart lesions (pulmonary valve stenosis) and mental retardation (in 25% of patients).
  - ✓ Diagnosis: based on clinical features.

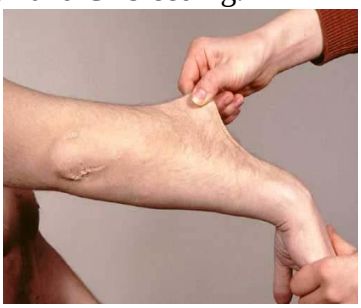


- **DiGeorge syndrome:**
  - ✓ It is characterized by a deletion on chromosome 22 resulting in defects in structures derived from 3rd and 4th pharyngeal pouches (thymus and parathyroid gland).
  - ✓ CATCH-22:
    - ❖ *C*: Cardiac anomalies.
    - ❖ *A*: Abnormal facies.
    - ❖ *T*: Thymic hypoplasia.
    - ❖ *C*: Cleft palate.
    - ❖ *H*: Hypocalcemia.
  - ✓ Diagnosis: FISH probes detecting deletion on chromosome 22.
  - ✓ Complications: infections (due to cell-mediated immunodeficiency resulting from thymic hypoplasia) and seizures (due to hypocalcemia resulting from hypoparathyroidism).

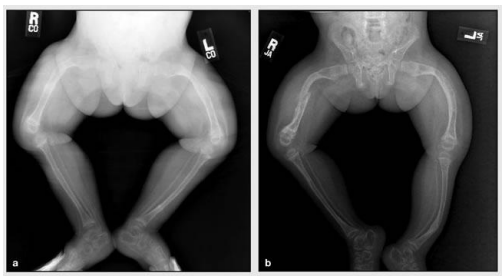


- **Ehlers-Danlos syndrome:**
  - ✓ It is an AD in which there is defective type V collagen.
  - ✓ Clinical features: loose fragile skin, hyperextensible joints and fragile blood vessels. Other features include constipation, hernias and rectal prolapse.
  - ✓ Diagnosis: based on clinical features.
  - ✓ Complications: aortic dissection and GI bleeding.

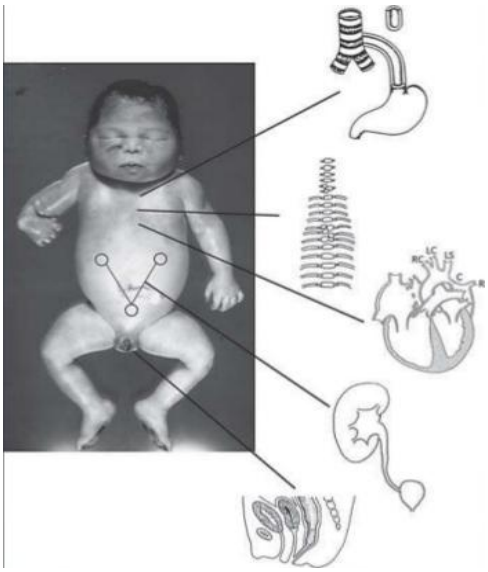


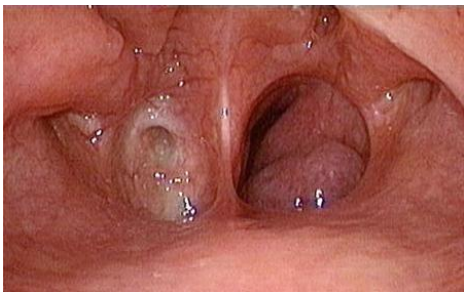


- **Osteogenesis imperfecta:**
  - ✓ It is characterized by a defective type-I collagen.
  - ✓ Clinical features: blue sclera, gray-blue teeth, fragile bones resulting in frequent fractures and easy bruisability.
  - ✓ Diagnosis: based on clinical features + ↓ type-I collagen synthesis in fibroblasts.
  - ✓ Complications: skeletal deformities due to multiple fractures and early conductive hearing loss.



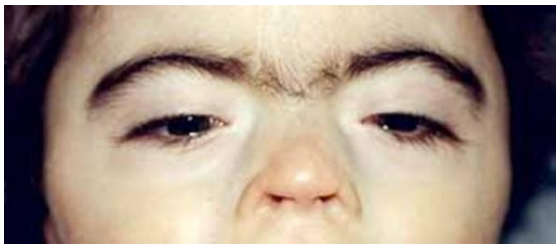
- **VACTERL association:**
  - ✓ V: Vertebral defects.
  - ✓ A: Anal atresia.
  - ✓ C: Cardiac anomalies (VSD).
  - ✓ TE: Tracheo-Esophageal fistula.
  - ✓ R: Renal and genital defects.
  - ✓ L: Limb defects.
- **CHARGE association:**
  - ✓ C: Colobomas (absence of ocular tissue).
  - ✓ H: Heart defects (TOF).
  - ✓ A: Atresia of nasal choanae.
  - ✓ R: Retardation (mental and growth).
  - ✓ G: Genital anomalies.
  - ✓ E: Ear anomalies.



- **William's syndrome (cocktail party personality):**
  - ✓ It is and AD disorder in which there is deletion on chromosome 7 (involving gene for elastin).
  - ✓ Clinical features:
    - ❖ *Elfin facies*: small palpebral fissures, round cheek and flat nasal bridge.
    - ❖ Mental retardation and talkative personality.
  - ✓ Diagnosis: FISH probes detecting deletion on chromosome 7.

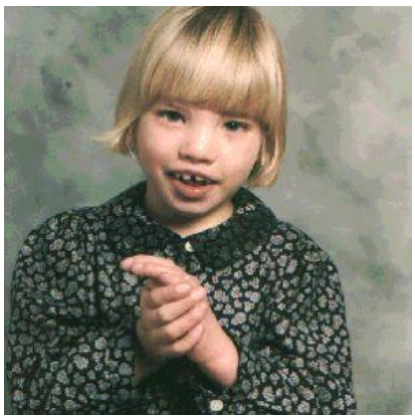
- **Cornelia de Lange syndrome:**
  - ✓ Clinical features: single eyebrow and very short stature without skeletal abnormalities.



- **Russell-Silver syndrome:**
  - ✓ Clinical features: short stature with skeletal asymmetry. Other features include: prominent forehead, small triangular face but head circumference if normal.
  - ✓ Diagnosis: based on clinical features.

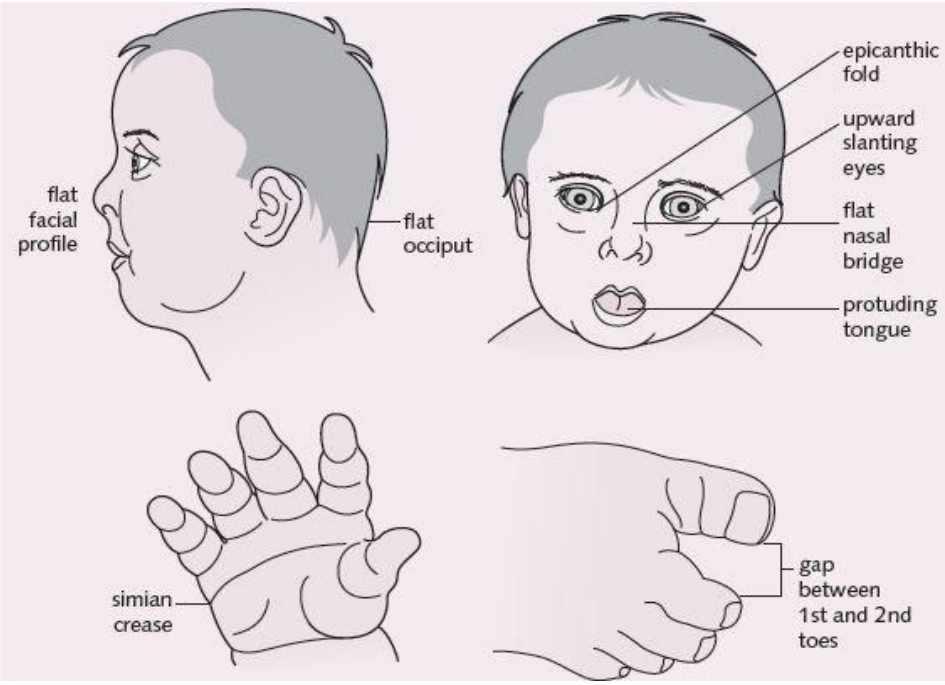
- **Pierre Robin syndrome:**
  - ✓ Clinical features: micrognathia, cleft lip/palate, protruding tongue and feeding is often difficult.
  - ✓ Diagnosis: based on clinical features.
  - ✓ Complications: recurrent otitis media and upper airway obstruction.

- **Cri du cht syndrome:**
  - ✓ It is caused by deletion involving chromosome 5.
  - ✓ Clinical features: slow growth, microcephaly, hypertelorism (widely-spaced eyes), mental retardation and cat-like cry.
  - ✓ Diagnosis: FISH probes detecting deletion on chromosome 5 and clinical features.

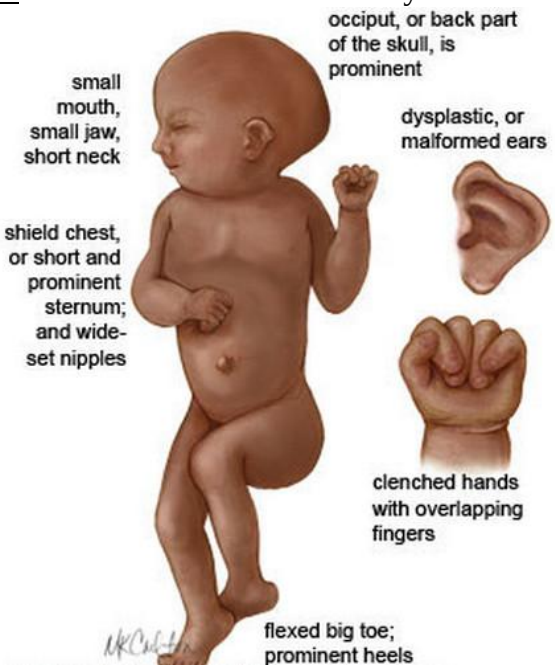


- **Down syndrome:**
  - ✓ It is the most common trisomy syndrome in which there is trisomy 21 caused by: non-disjunction, Robertsonian translocation or mosaicism.
  - ✓ Incidence increases with advanced maternal age (> 35 years).
  - ✓ Diagnosis: karyotyping

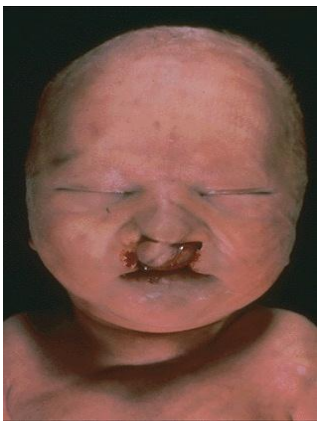
Clinical features	Complications
Craniofacial features	Leukemia (X20 times)
• Brachycephaly الـ رأس الـ عريـ ض • Epicanthal skin folds • Upslanting palpebral fissures • Brushfield spots • Protruding tongue	Early alzheimer's disease
Hypotonia and mental retardation	Obstructive sleep apnea
Musculoskeletal features	Hypothyroidism
• Clindodactyly (fingers are curved at an angle). • Single palmar crease. • Wide space between 1st and 2nd toes	Cataracts and glaucoma
Gastrointestinal features	
• Duodenal atresia. • Anal atresia.	
Endocardial cushion defects	



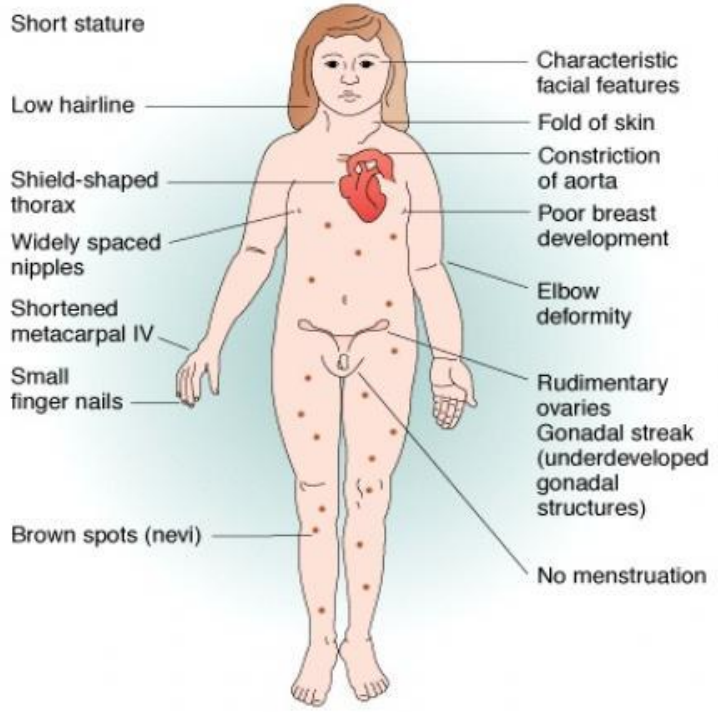
- **Edward's syndrome:**
  - ✓ It is trisomy 18 which is more common in females.
  - ✓ Clinical features: microcephaly, mental retardation, low-set ears, micrognathia, cardiac defect, clenched fist with overlapping of digits, rocker bottom feet.
  - ✓ Diagnosis: karyotyping
  - ✓ Prognosis: 95% will die within the first year of life.



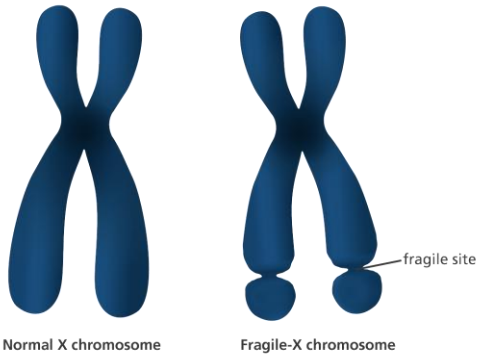
- **Patau syndrome (trisomy 13):**
  - ✓ Clinical features: microcephaly, mental retardation, severe cleft lip/palate, microphthalmia (and rarely a single eye).
  - ✓ Diagnosis; karyotyping
  - ✓ Prognosis: death usually within first month of life.



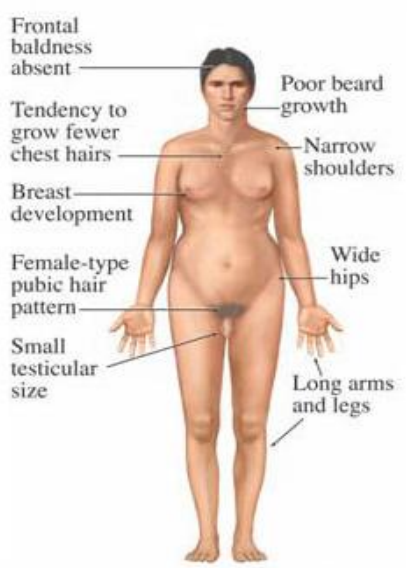
- **Turner's syndrome (XO: only one X chromosome is present):**
  - ✓ Clinical features: short stature, webbed neck, low hair line, shield chest with widely spaced nipples, streak ovaries and left-sided heart lesions (coartication of aorta).
  - ✓ Diagnosis: karyotyping.



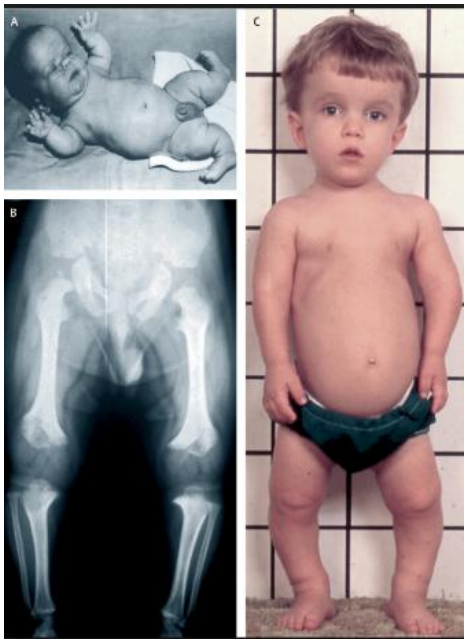
- **Fragile X syndrome:**
  - ✓ It is an X-linked disorder which is considered as an example on anticipation and is characterized by trinucleotide repeats (CGG). As the disorder passes from generation to generation, there is an increase in the number of CGG repeats which will cause increased severity and earlier onset.
  - ✓ Clinical features: severe mental retardation, macrocephaly, large ears and large testes develop during puberty.
  - ✓ Diagnosis: karyotyping



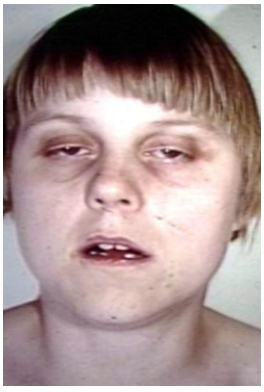
- **Klinefelter syndrome (XXY):**
  - ✓ It is the most common cause of male hypogonadism and infertility. Risk increases with advancing maternal age.
  - ✓ Clinical features: tall stature, long extremities, gynecomastia, small penis/testes with infertility and excessive shyness or aggression.
  - ✓ Diagnosis: karyotyping.



- **Achondroplasia:**
  - ✓ It is an AD disorder which is characterized by rhizomelia (abnormalities of proximal long bones such as femur and humerus) and is considered as the most common skeletal dysplasia. Incidence increases with advancing paternal age.
  - ✓ Clinical features: megalencephaly, mid-face hypoplasia, foramen magnum stenosis, rhizomelic limb shortening, lumbar lordosis and trident-shaped hand.
  - ✓ Diagnosis: clinical features and radiographs.
  - ✓ Complications: Foramen magnum stenosis can lead to hydrocephalus, cord compression or obstructive sleep apnea. Development of severe bowed legs is also a complication.



- **Inborn errors of metabolism:**
  - **Amino acid disorders:**
    - ✓ Phenylketonuria:
      - ❖ It is an AR disorder. Normally, phenylalanine is converted to tyrosine in the liver via the enzyme phenylalanine hydroxylase. In classic phenylketonuria, there is deficiency of this enzyme thus accumulation of phenylalanine.
      - ❖ *Clinical presentation*: mousy urine odor, developmental delay, mental retardation, blond hair/blue eyes, eczema and hypotonia.



- ❖ *Diagnosis*: it is usually detected in neonatal screening via neonatal heel prick (but this is not done in Bahrain because the disease is not common). The disorder can be diagnosed by ↓tyrosine and ↑phenylalanine in serum (> 6mg/dL).
- ❖ *Management*: low phenylalanine diet (fruits and vegetables).

✓ Homocystinuria:

- ❖ It is an AR disorder which is characterized by deficiency in cystathionine synthase enzyme.
- ❖ *Clinical presentation (compare it to Marfan syndrome):*

Skeletal	Tall stature, long extremities and fingers, scoliosis and pectus excavatum/carinatum
Ocular	Downward lens subluxation
Cardiovascular	Aortic/mitral regurgitation (no aortic root dilation)
Hypercoagulable state	Predisposing patients to MI, stroke and DVT

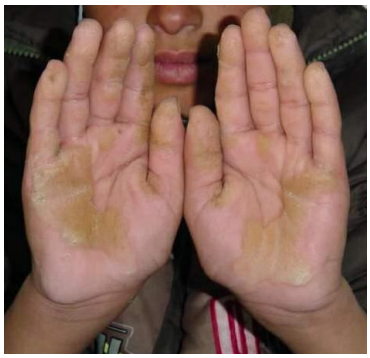
- ❖ *Diagnosis*: ↑homocyteine and methionine in serum and urine; (+) urinary cyanide nitroprusside test.
- ❖ *Management*: methionine-restricted diet, aspirin (to decrease the risk of thrombosis), folic acid and vitamin B6.

✓ Tyrosinemia type-I:

- ❖ It is an AR disorder in which there is deficiency of fumarylacetoacetase resulting in accumulation of toxic metabolites in liver and renal tubules. Severe liver disease will result in ↑tyrosine.
- ❖ *Clinical features:*

Liver	Liver failure, bleeding disorders, hypoglycemia, hypoalbuminemia and tyrosinemia
Renal	Dysfunction of proximal renal tubules, cabbage-odor urine

- ❖ *Diagnosis*: ↑tyrosine in blood, ↑succinylacetone in urine.
- ❖ *Management*: phenylalanine and tyrosine restricted diet + NTBC.
- ❖ *In tyrosinemia types II and III*: no succinylacetone is produced; patients present with hyperkeratosis of palms of the hand and soles of the feet with keratitis; condition managed by phenylalanine and tyrosine restricted diet

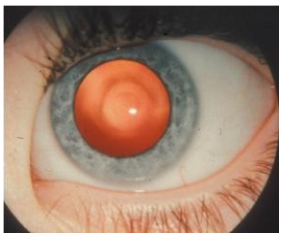


✓ Maple Syrup Urine Disease (MSUD):

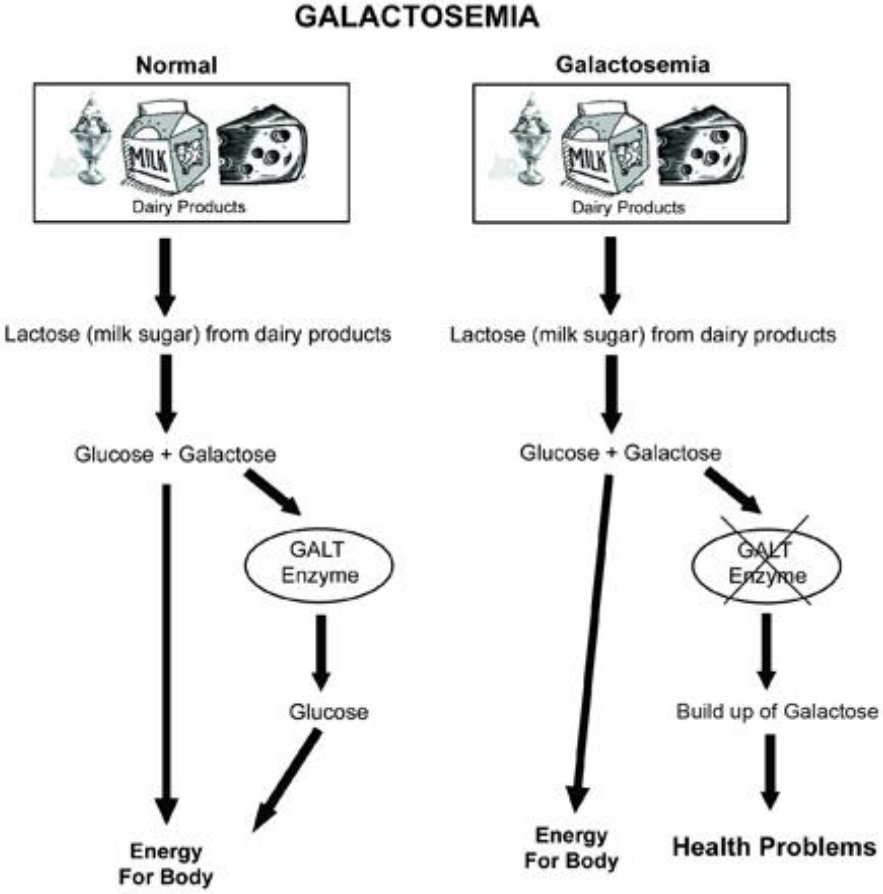
- ❖ It is an AR disorder in which there is deficiency of decarboxylase that is involved in degeneration of branched chain amino acids: valine, leucine and isoleucine.
- ❖ *Clinical presentation*: vomiting and poor feeding, lethargy and hypotonia, maple syrup odor in urine and hypoglycemia with metabolic acidosis during episodes.

- ❖ *Diagnosis*: ↑valine, leucine and isoleucine in serum and urine.
- ❖ *Management*: leucine-restricted diet (it is found in fish, eggs, red meat and cheese). Liver transplantation teats MSUD.

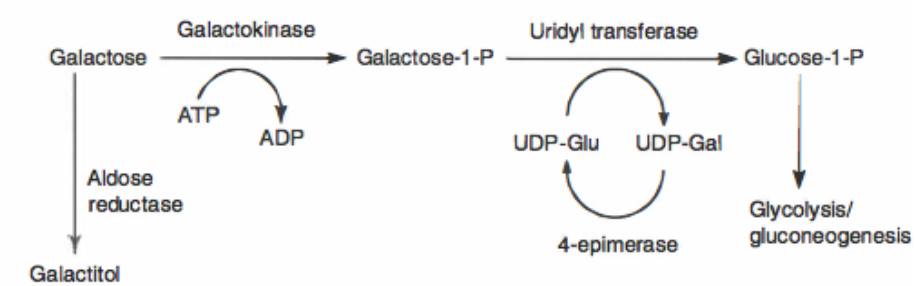
- **Carbohydrate disorders:**
  - ✓ Galactosemia:
    - ❖ It is an AR disorder in which there is deficiency of galactose-1-phosphate uridyltransferase.
    - ❖ *Clinical presentation*: vomiting. diarrhea and FTT; hepatomegaly; hypoglycemia; oil-droplet appearance cataract and renal tubular acidosis.



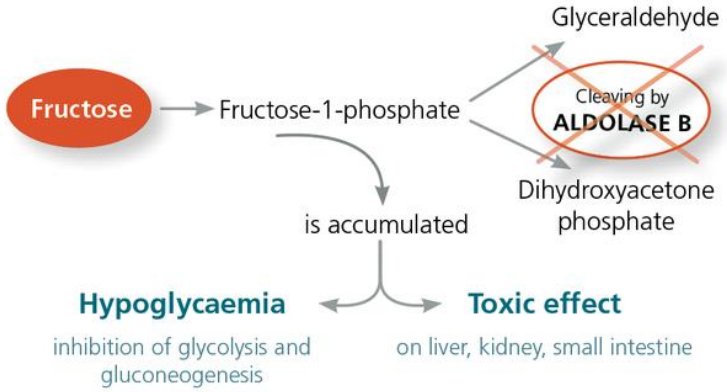
    - ❖ *Diagnosis*:
      - ➢ Clinitest: detecting non-glucose reducing substance in the urine (galactose).
      - ➢ This is confirmed by ↓galactose-1-phosphate activity in RBCs.
    - ❖ *Management*: galactose-free diet for life.



  - ✓ Galactokinase deficiency:
    - ❖ It is an AR disorder in which there is deficiency of galaktokinase resulting in accumulation of galactose that will be converted to galactitol via aldose reductase enzyme.
    - ❖ Galactitol is an osmotic agent which drags water into tissues thus resulting in cataracts and increased intracranial pressure.



- ✓ Hereditary fructose intolerance:
  - ❖ In this condition, there is a deficiency of fructose-1-phosphate aldolase B which results in accumulation of fructose-1-phosphate. The condition usually manifests when fruits and fruit juices are introduced into the infant's diet.
  - ❖ *Clinical features*: severe hypoglycemia, vomiting, diarrhea and FTT.
  - ❖ *Management*: avoidance of fructose, sucrose and sorbitol.



- ✓ Glycogen storage diseases:
  - ❖ They are AR disorders in which there are different enzyme defects leading to defective mobilization of glucose from glycogen. This will result in abnormal glycogen storage in liver and muscles.
  - ❖ *Clinical presentation:*
    - ➢ Types I and III (liver storage): hepatomegaly, hypoglycemia, hyperuricemia, hyperlipidemia, myopathy and heart diseases.
    - ➢ Types II and V (muscle storage): skeletal muscle weakness.
  - ❖ *Management:*
    - ➢ Type I: maintain blood glucose by frequent feeding with a high-complex carbohydrate diet.
    - ➢ Type-II: enzyme replacement (myozyme) early in life.
    - ➢ Type-III: high protein diet.

TYPE	ENZYME DEFECT	CLINICAL FEATURES
Type I (Von Gierke's disease)	Glucose-6-phosphatase deficiency.	Hypoglycemia, enlarged liver and kidneys, gastro-intestinal symptoms, Nose bleed, short stature, gout
Type II (Pompe's disease)	Acid maltase deficiency	Diminished muscle tone, heart failure, enlarged tongue
Type III (Cori's disease,Forbe disease)	Debranching enzyme deficiency	Hypoglycemia, enlarged liver, cirrhosis, muscle weakness, cardiac involvement
Type IV (Andersen's disease)	Branching enzyme deficiency	Enlarged liver & spleen, cirrhosis, diminished muscle tone, possible nervous system involvement
Type V (Mcardle's disease)	Muscle phosphorylase deficiency	Muscle weakness, fatigue and muscle cramps