Genetic Diseases
LEC. 2

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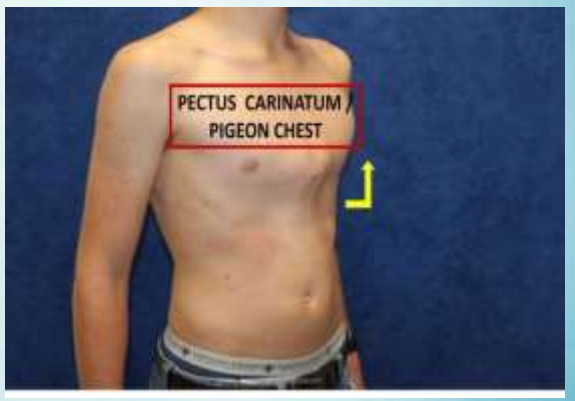
Diseases caused by mutation in structural proteins:

❖*Marfan"s syndrome:*

- Autosomal dominant disorder of connective tissue that affects **fibrillin 1** (a glycoprotein that is secreted by fibroblast) encoded by FBN1 gene (mapped on **chromosome 15).**
- **3 systems are mainly affected:**

1. Skeletal abnormalities

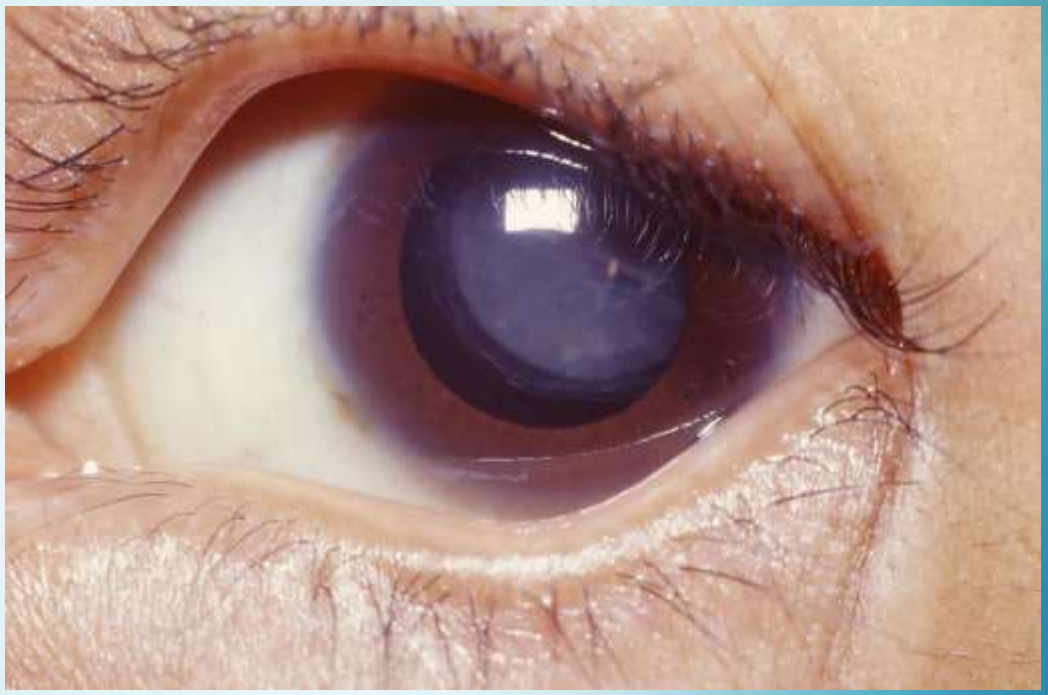
- Patients have a slender, elongated habitus with abnormally long legs, arms, and fingers (arachnodactyly).
- **Hyperextensibility** of joints.
- **A high arched palate.**
- A variety of spinal deformities, such as severe kyphoscoliosis, may be present.
- The **chest is deformed,** exhibiting either pectus excavatum (i.e., deeply depressed sternum) or a pigeon-chest deformity.



2. Eyes:

- Bilateral dislocation or subluxation of the lens secondary to weakness of its suspensory ligaments **(ectopia lentis).**

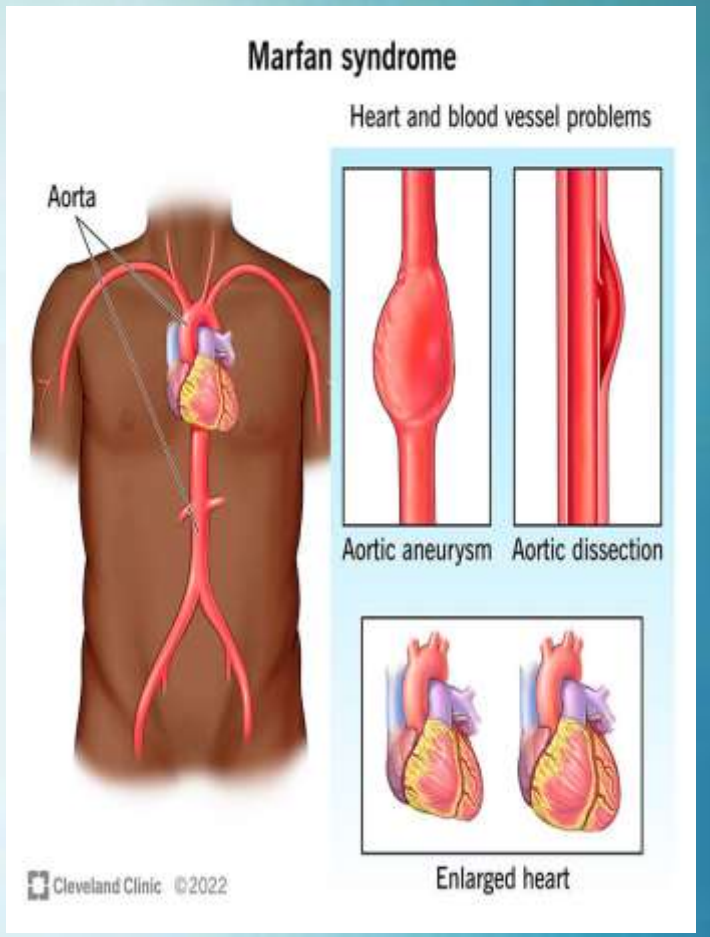
- Ectopia lentis, particularly if bilateral, is highly specific for Marfan syndrome and strongly suggests the diagnosis.



3. Cardiovascular system:

- Fragmentation of the elastic fibers in the tunica media of the aorta predisposes to **aneurysmal dilatation &aortic dissection.**
- Dilatation of aortic valve ring giving rise to **aortic incompetence.**
- **Mitral &tricuspid valves regurgitation** giving rise to congestive heart failure.
- **Aortic rupture is the most common cause of death and may occur at any age.**

➢Note: Variable expression of the features above between different patients.

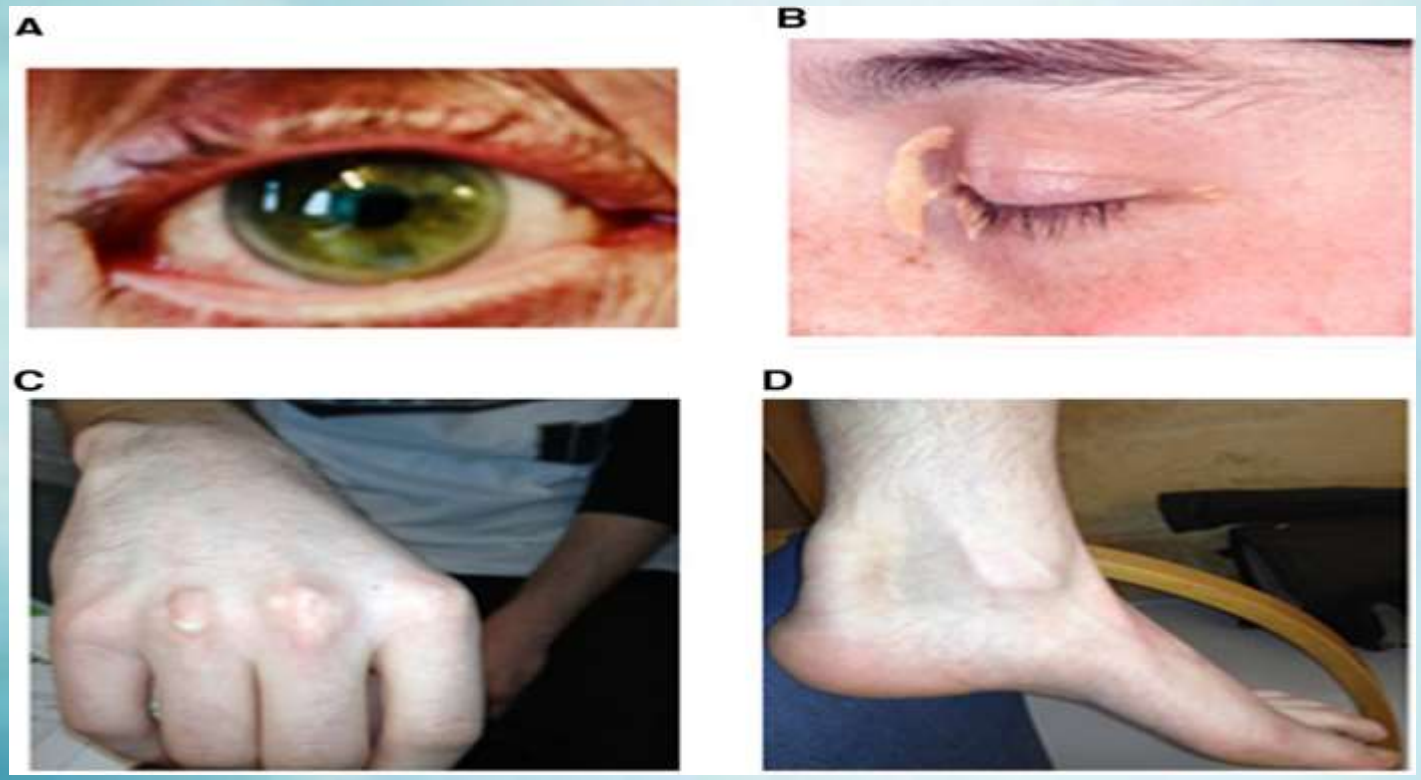


Diseases caused by mutation in receptor proteins:

❖*Familial hypercholesterolemia:*

- ➢Autosomal dominant disease caused by mutation in the gene that specifies the receptor for low density lipoproteins **LDL.**
- ➢**Heterozygotes** have 2-3 folds elevation of plasma cholesterol level
- Remain asymptomatic until adulthood when develop xanthoma along tendon sheaths & premature coronary artery diseases.
- While **homozygotes** are much more severely affected, cutaneous xanthoma in childhood &dying from myocardial infarction before the age of 20 years.

Discrete clinical manifestations of familial hypercholesterolemia

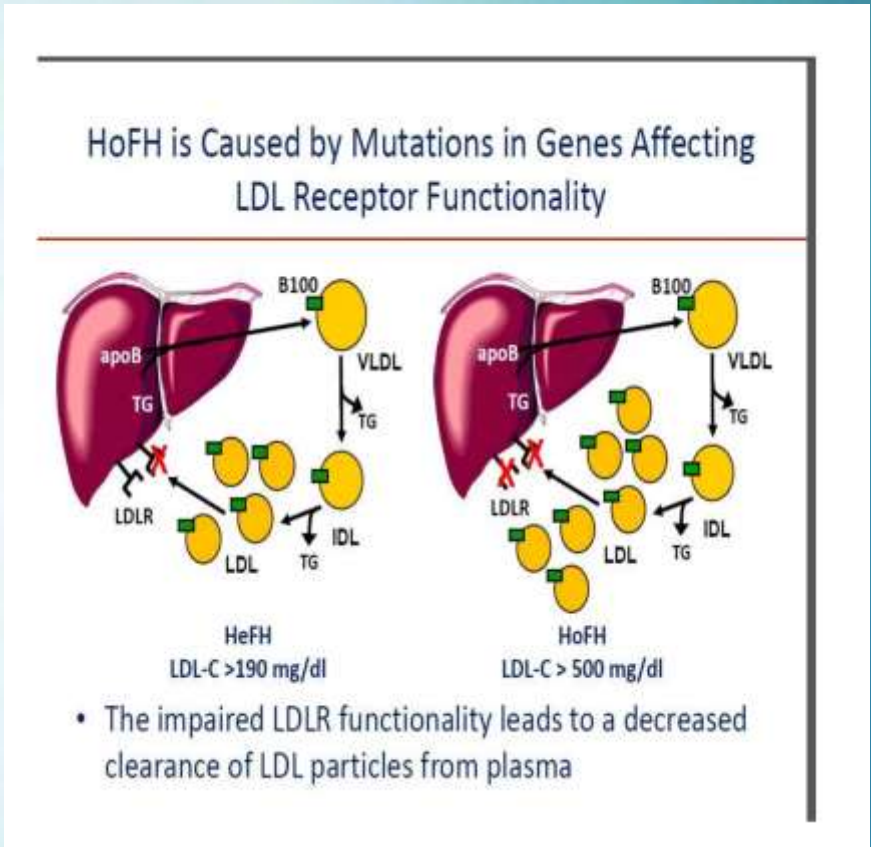


(A) Corneal arcus (B) xanthelasma (C) extensor tendon xanthomas
(D) Achilles tendon xanthomas.

- **Cholesterol** 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) by the liver and secreted to the blood. In the capillaries of adipose tissue and muscle, the VLDL particle undergoes lipolysis and converted to intermediate density lipoprotein (IDL) then taken up by the liver through the LDL receptor again.

- **Mutation** in LDL receptor gene impair the intracellular transport and catabolism of LDL, resulting in 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 so a greater proportion of plasma IDL is converted into LDL.



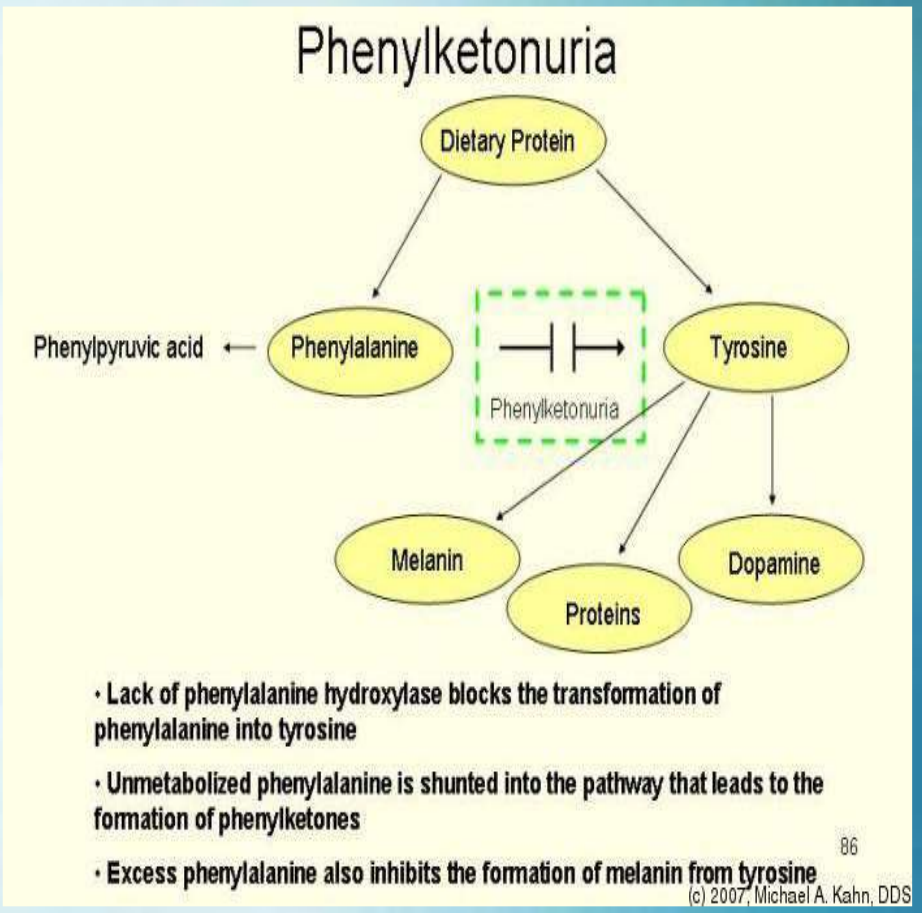
Diseases caused by mutation in enzymes proteins:

❖*Phenylketonuria (PKU)*

- PKU is an **autosomal recessive disorder** caused by a lack of the enzyme phenylalanine hydroxylase and a consequent inability to metabolize phenylalanine.
- **Homozygotes** have severe lack of phenylalanine hydroxylase leading to hyperphenylalaninemia & PKU
- The affected infants are **normal at birth** but **within few weeks to 6 months** exhibit a **rising plasma phenylalanine level** with severe mental retardation, inability to walk, inability to talk, seizures, decrease pigments of the skin &hair, eczema, musty odor of sweat.

- **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.

➢ **Treatment:** restriction of phenylalanine intake early in life.



- Many clinically normal PKU female patients treated with diet early in life &reach child bearing age, most of them have high serum phenylalanine because dietary treatment is discontinued after reaching adulthood, children born to them are mentally retarded &have many congenital abnormalities results from the **teratogenic** effects of phenylalanine --- This syndrome, termed **maternal PKU.**
- The presence and severity of the fetal anomalies directly correlate with the maternal phenylalanine level, so it is mandatory that maternal dietary restriction of phenylalanine be initiated before conception and continued throughout pregnancy.

❖Glycogen storage disorders (Glycogenoses):

- 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.
- Most glycogenoses are inherited as autosomal **recessive** diseases.
- On the basis of **pathophysiology** they grouped into **3 categories**:

1- Hepatic form: liver contains several enzymes 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 disease

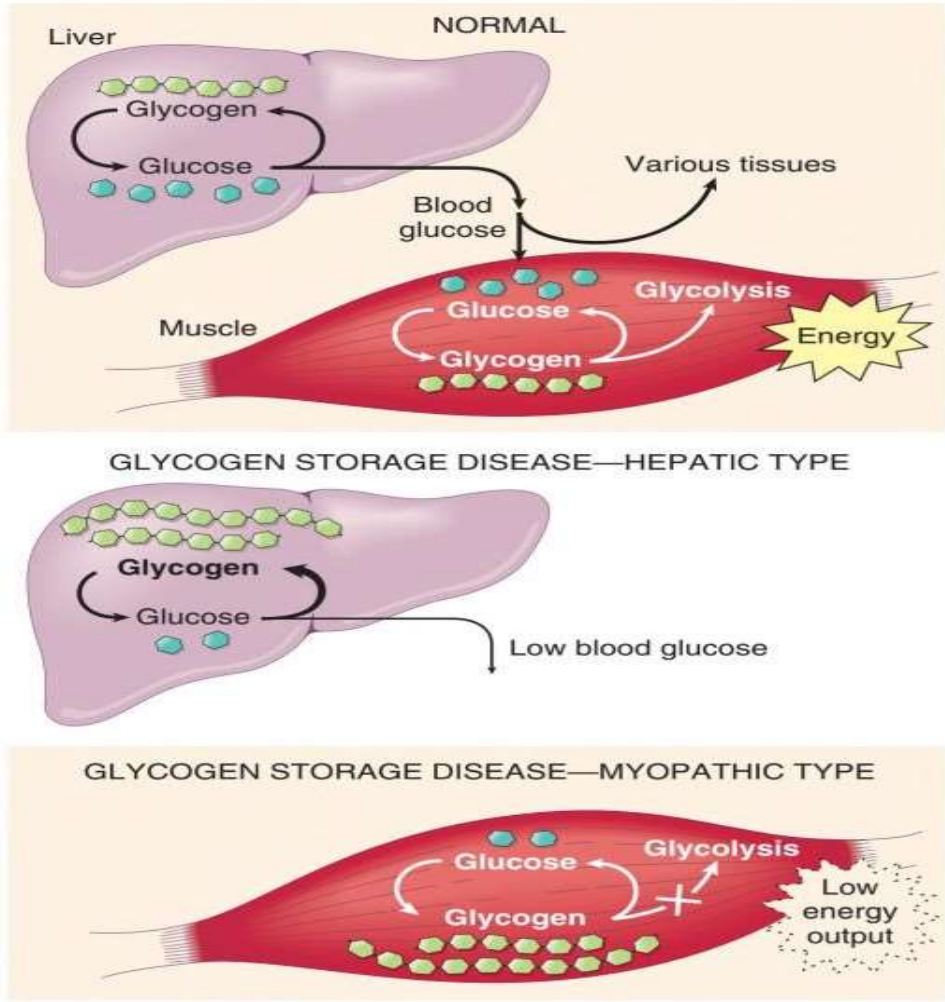


Fig. 7.12 *(Top)* A simplified scheme of normal glycogen metabolism in the liver and skeletal muscles. *(Middle)* The effects of an inherited deficiency of hepatic enzymes involved in glycogen metabolism. *(Bottom)* The consequences of a genetic deficiency in the enzymes that metabolize glycogen in skeletal muscles.

2- **Myopathic form**: In striated muscles glycogen is an important source of energy, derived **by glycolysis,** When enzymes that are involved in glycolysis are **deficient, glycogen storage occurs in muscles** and there is an associated muscle weakness due to impaired energy production. Typically, the myopathic forms of glycogen storage diseases are marked by muscle cramps after exercise, myoglobinuria, and failure of exercise to induce an elevation in blood lactate levels because of a block in glycolysis. ***McArdle disease***, resulting from a deficiency of muscle phosphorylase.

3- **Pompe disease** due to deficiency of lysosomal acid maltase and is associated with deposition of glycogen in virtually every organ, but cardiomegaly is most prominent.

Diseases caused by mutation in protein that regulate cell growth:

- Two classes of genes that regulate cell growth:

  protooncogenes & tumor suppressor genes.
- Mutation affecting these genes **most often in somatic cells,** are involved in the pathogenesis of tumor.
- In **5% to 10% of all cancers**, however, mutations affecting certain tumor suppressor genes are present in all cells of the body, **including germ cells,** and hence can be transmitted to the offspring. These mutant genes predispose the offspring to **hereditary tumors.**

❖Neurofibromatoses type 1 &2

➢Neurofibromatoses type 1:

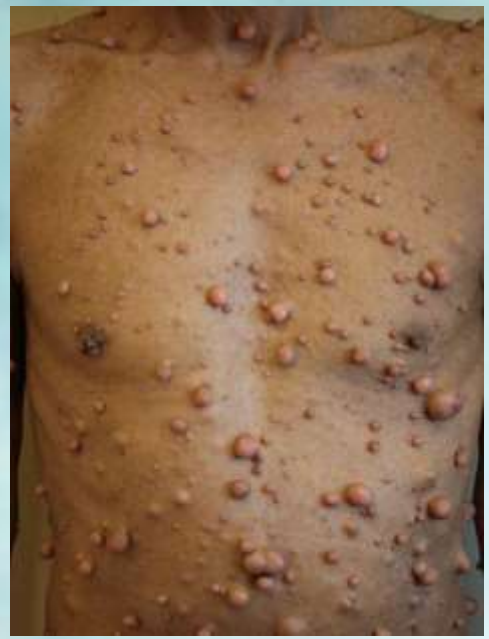
- A counts for **90%** of the cases.
- Caused by autosomal dominant mutation in in the tumor suppressor gene **(neurofibromin) encoded on chromosome 17;** act as negative regulator of RAS oncoprotein.
- Characterized by:

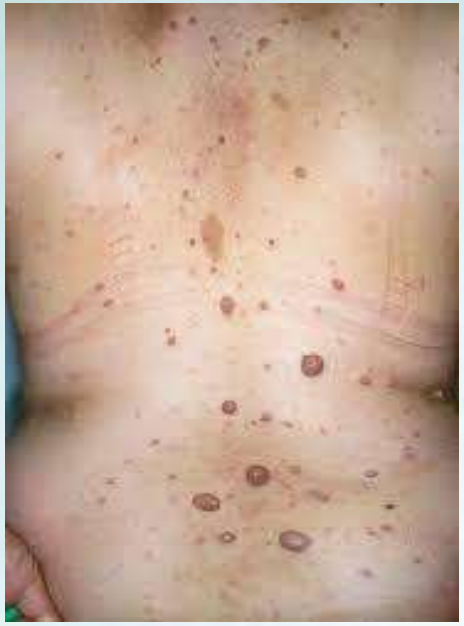
1- Multiple neurofibroma in the form of **pedunculated nodules** protruding from the **skin** , they are discrete, unencapsulated, soft, sometimes the tumor form large multilobar masses (plexiform NF). They are derived from schwan cells, similar tumors may occur along nerve trunk, cauda equine, cranial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

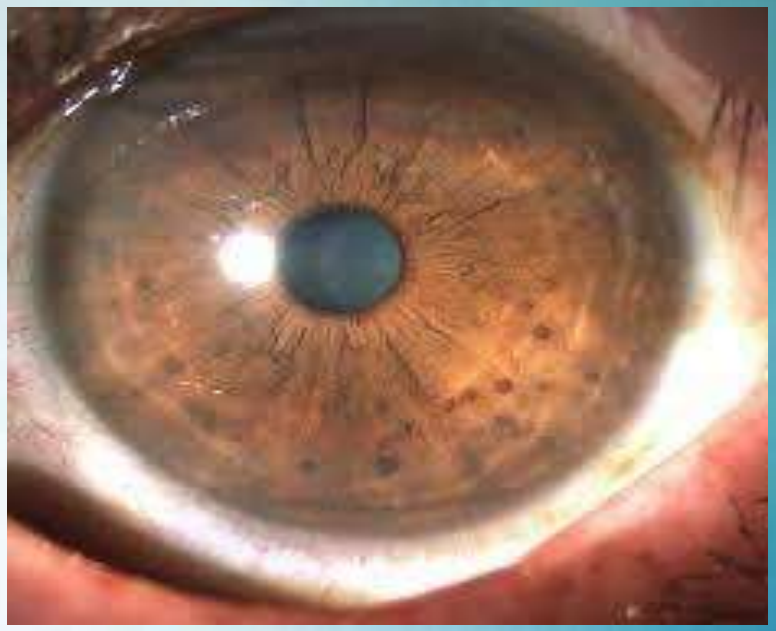
2- Pigmented skin lesions (café-au-lait spots), sometimes overlie a NF.

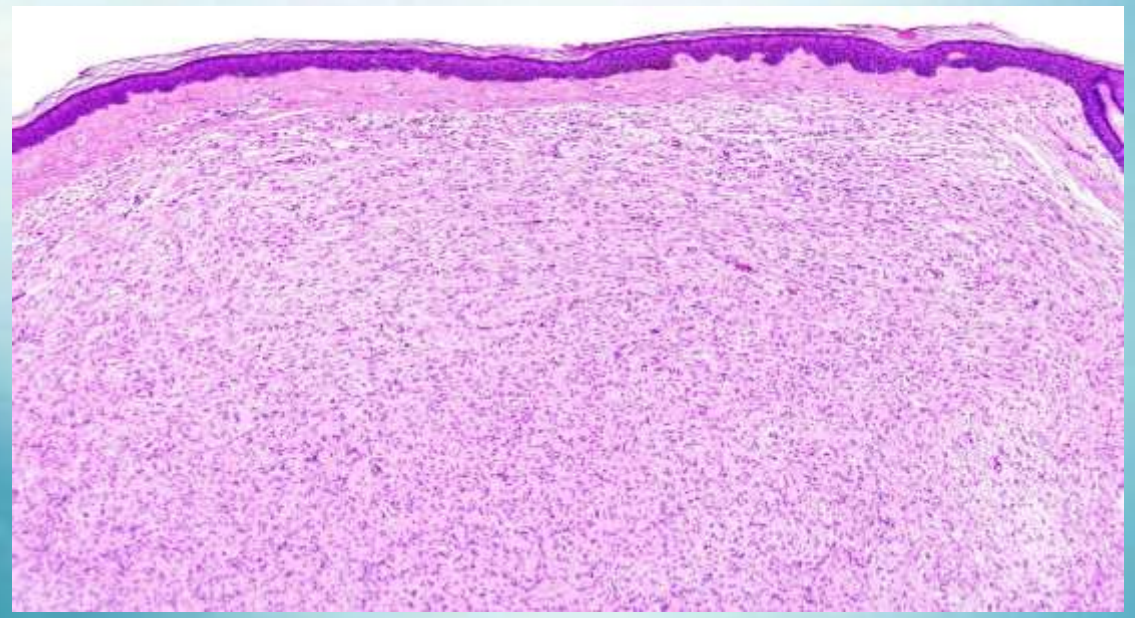
3- Pigmented iris hamartomas (Lisch nodules), no clinical symptoms but helpful in the diagnosis.

Neurofibromatoses type 1:









➢ Neurofibromatoses type 2:

- Caused by autosomal dominant mutation in the tumor suppressor gene **(merlin)** on **chromosome 22.**
- The hallmark of NF2; is the presence of **bilateral vestibular schwannomas** **(bilateral acoustic 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, meningioma & pheochromocytoma.**

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

2- Disorders with multifactorial inheritance:

- Also called complex or polygenic inheritance.
- Multifactorial inheritance disorders are **caused by a combination of** environmental factors and mutations in in multiple genes (genetic factor).

- The following features characterized multifactorial inheritance:

1- The **risk** of expressing the disease is **conditioned by the number of mutant genes inherited.** Also the greater the number of affected relatives, the higher the risk for other relatives.

2- The rate of recurrence is the same **for all first- degree relatives** of the affected individual between **2-7%.**

3- **Identical twins** will be affected less than 100% (**about 20-40%)** but is much greater than the chance of non-identical twins.

➢Examples of disorders with multifactorial inheritance:

- Hypertension
- Diabetes type II
- Gout
- Cleft lips, Cleft palates
- Congenital heart diseases
- Cancer


Thanks