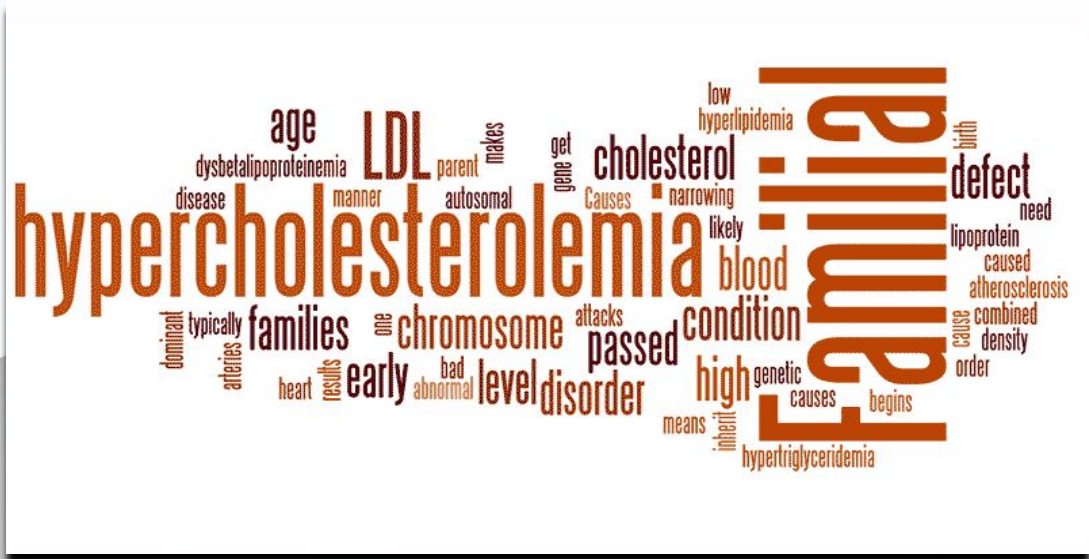


Familial Hypercholesterolemia



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INTRODUCTION

Familial hypercholesterolemia (FH) have raised cholesterol levels in blood with a significant risk of developing early CAD.

FH is an autosomal dominant disorder occurs in 1 in 500 individuals.

Usually due to mutations in LDL receptor gene that result in decreased clearance of LDL particles from plasma

Other mutations include those in the Apo B ,ARH and PCSK9 genes

CLINICAL MANIFESTATIONS

- ▶ High cholesterol level in blood.
- ▶ Heterozygotes may have premature cardiovascular disease at the age of 30 to 40.
- ▶ homozygous may cause severe cardiovascular disease in childhood.
- ▶ Accompanied by cholesterol deposition in tendons and skin (xanthomas) and in the eyes

- A- Xanthelasma
- B – Corneal arcus (Arcus senilis)
- C - Achilles tendon xanthomas
- D - Tendon xanthomas
- E - Tuberosus xanthomas
- F - Palmar xanthomas



PLASMA CHOLESTEROL LEVEL IN NORMAL AND FH INDIVIDUALS

NORMAL – 150 – 200 mg/dl

FH HETEROZYTOGE – 200 – 500 mg/dl

FH HOMOZYGOTES – 600 – 1000 mg/ dl

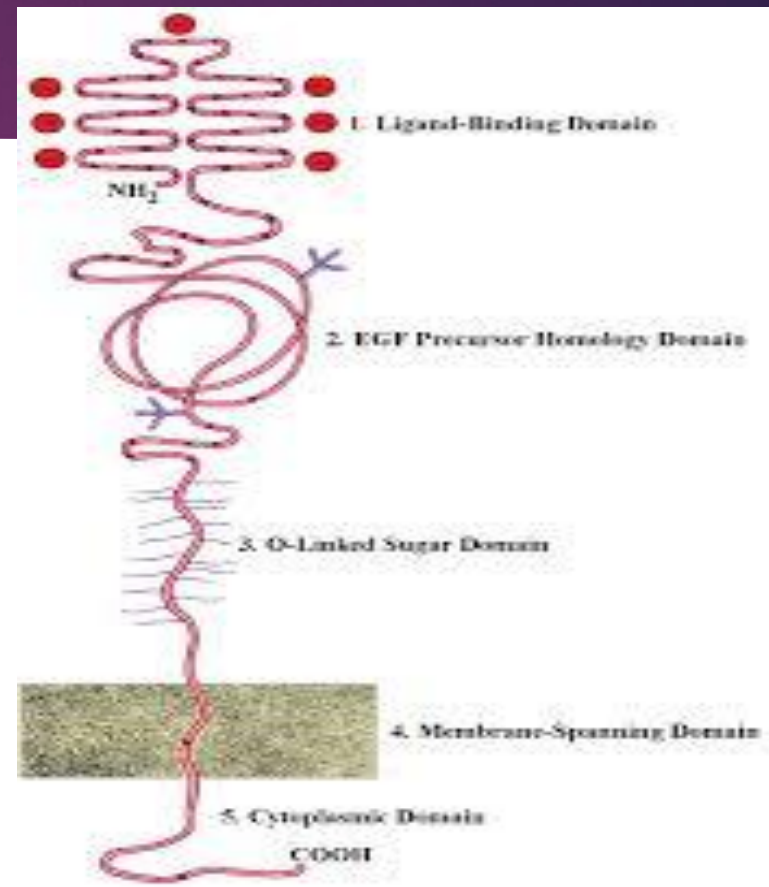
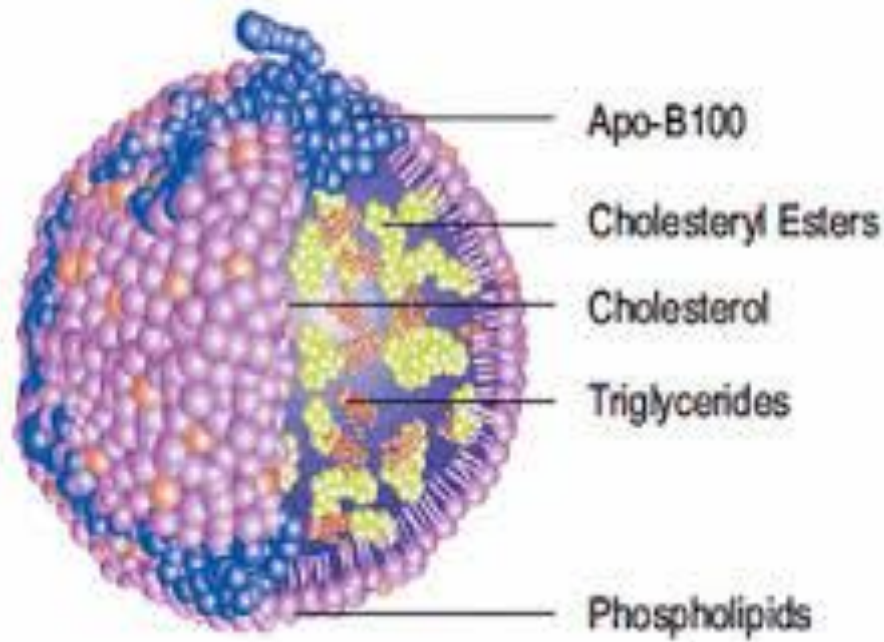
Function of LDLR gene

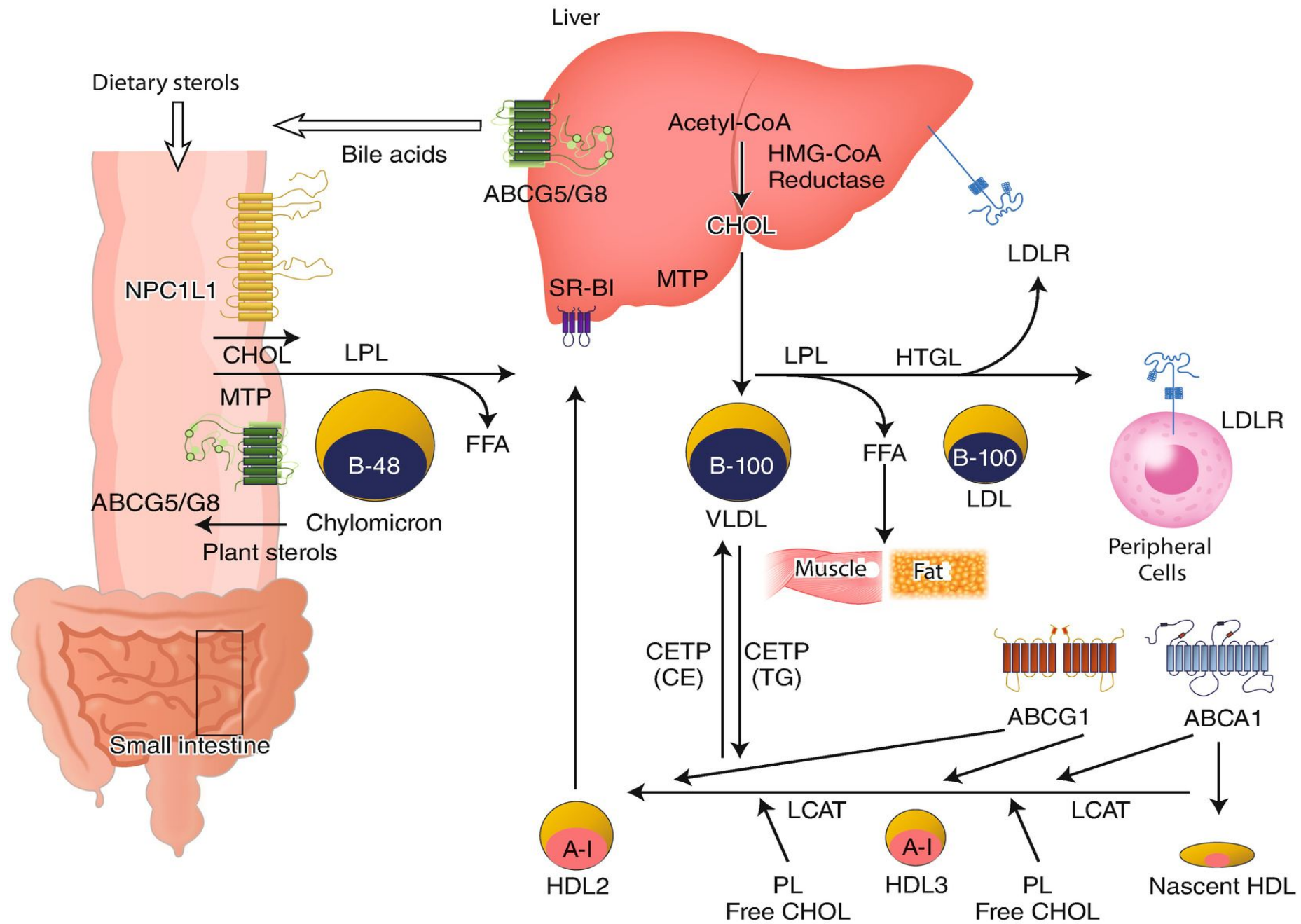
- ▶ The LDLR gene provides instructions for making a protein called low density lipoprotein receptor
- ▶ This receptor binds to particles called low-density lipoproteins, which are the primary carriers of cholesterol in the blood.
- ▶ They are particularly abundant in the liver, which is the organ responsible for removing most excess cholesterol from the body.

Mutation in LDLR gene

- ▶ Mutations in the LDLR gene cause FH
- ▶ More than 1,000 mutations have been identified in this gene.
- ▶ Some genetic changes reduce the no. of low-density lipoprotein receptor and other mutations disrupt the receptor's ability to remove low-density lipoproteins from the blood.
- ▶ As a result, people with mutations in the LDLR gene have very high blood cholesterol levels.
- ▶ The excess cholesterol circulates through the bloodstream, is deposited abnormally in tissues such as the skin, tendons.
- ▶ And also arteries that supply blood to the heart (coronary arteries) results in heart attack.

Low Density Lipoprotein





CLASSES OF MUTATION IN LDLR

- ▶ Class 1 mutations affect the synthesis of the receptor in the endoplasmic reticulum (ER).
- ▶ Class 2 mutations prevent proper transport to the Golgi body needed for modifications to the receptor
- ▶ Class 3 mutations stop the binding of LDL to the receptor..
- ▶ Class 4 mutations inhibit the internalization of the receptor-ligand complex
- ▶ Class 5 mutations give rise to receptors that cannot recycle properly. This leads to a relatively mild phenotype as receptors are still present on the cell surface
- ▶ Class 6 Failure to localize receptor to the basolateral domain

Mutation in APOE gene

1. At least five mutations in the APOB gene are known to cause a form of inherited hypercholesterolemia.
2. Each mutation that causes this condition changes a single amino acid in a critical region of apolipoprotein B-100.
3. The altered protein prevents low-density lipoproteins from effectively binding to their receptors on the surface of cells.
4. As a result, fewer low-density lipoproteins are removed from the blood, and cholesterol levels are much higher than normal.

Function of LDLRAP1 Gene

- ▶ The LDLRAP1 gene is located on 1p36-p35.
- ▶ The LDLRAP1 gene is also known as ARH(Autosomal recessive hypercholesterolemia)
- ▶ The LDLRAP1 gene provides instructions for making a protein LDLRAP1 that helps remove cholesterol from the bloodstream.
- ▶ The LDLRAP1 protein interacts with a protein called a low-density lipoprotein receptor.
- ▶ The LDLRAP1 protein appears to play a critical role in moving these receptors, together with their attached low-density lipoproteins, from the cell surface to the interior of the cell.

Mutation in LDLRAP1 gene

- ▶ More than 10 mutations in the LDLRAP1 gene have been shown to cause a form of inherited high cholesterol called ARH
- ▶ These mutations lead to the production of an abnormally small, nonfunctional version of the LDLRAP1 protein or prevent cells from making any of this protein.
- ▶ Without the LDLRAP1 protein, LDL receptors are unable to remove LDL's from the bloodstream effectively.
- ▶ The receptors can still bind normally to low-density lipoproteins, but not properly transported into cells . As a result, more low-density lipoproteins remain in the blood.

FUNCTION OF PCSK9 GENE

- ▶ The PCSK9 protein appears to control the number of low-density lipoprotein receptors, which are proteins on the surface of cell
- ▶ the PCSK9 protein helps control blood cholesterol levels by breaking down low-density lipoprotein receptors before they reach the cell surface

TREATMENT

- ▶ Heterozygous FH is normally treated with statins—drugs that lower cholesterol level
- ▶ Bile acid sequestrants (hypolipidemic agents), Ezetimibe, Fibrates (such as gemfibrozil or fenofibrate) and nicotinic acid
- ▶ Also other hypolipidemic agents that lower cholesterol levels.
- ▶ Homozygous FH often does not respond to regular medical therapy and may require LDL-apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation.
- ▶ Dietary reduction of cholesterol, and healthy lifestyle

Thank
you!