# Familial Hypercholesterolemia


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GROUP LA3_203(1)

# 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

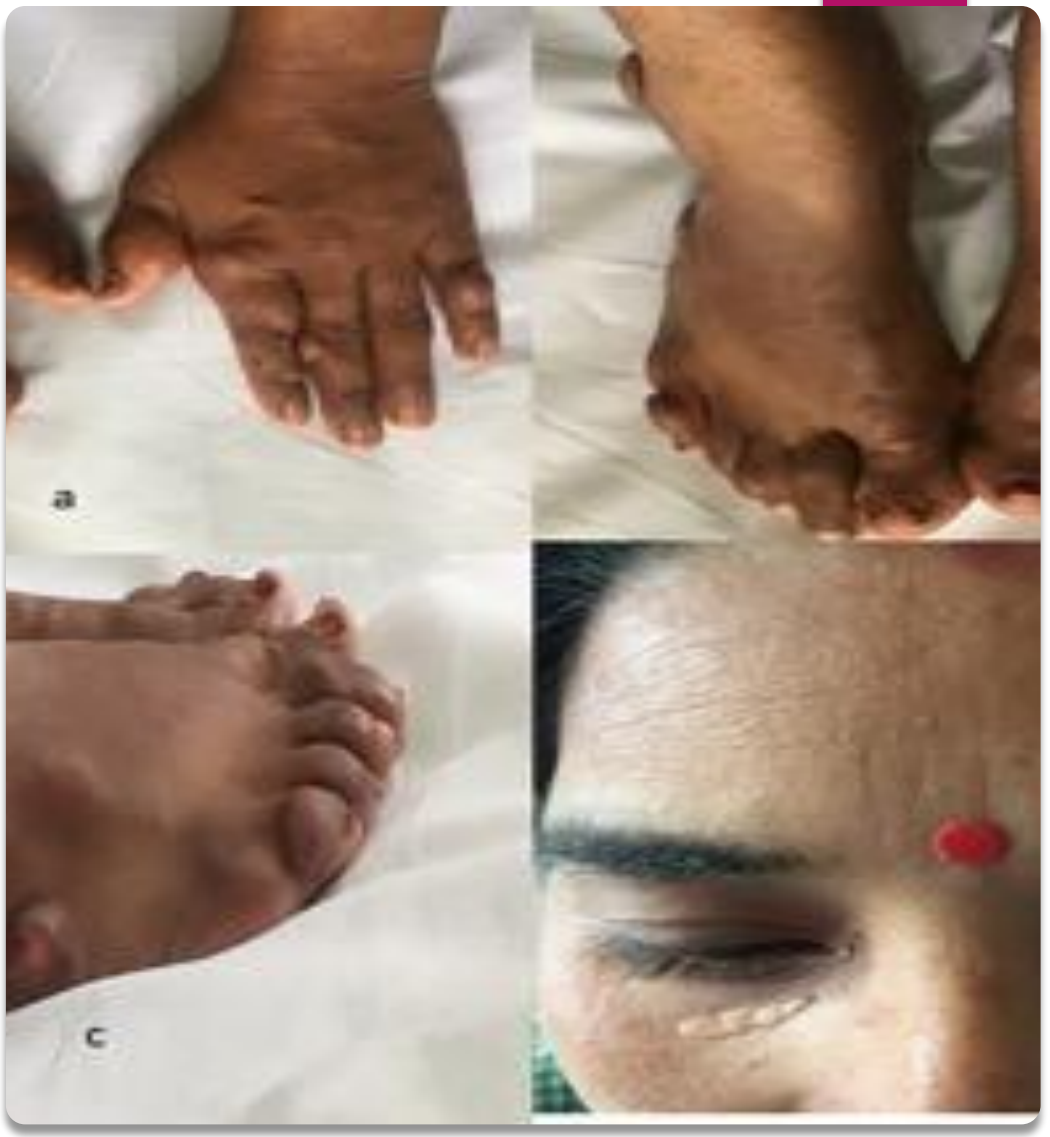
B – Corneal arcus (Arcus senilis)

C - Achilles tendon xanthomas

D - Tendon xanthomas

E - Tuberous xanthomas

F - Palmar xanthomas



# PLASMA CHOLESTEROL LEVEL IN NORMAL AND FH INDIVIDUALS

NORMAL – 150 – 200 mg/dl

FH HETEROZYTOGE – 200 – 500 mg/dl

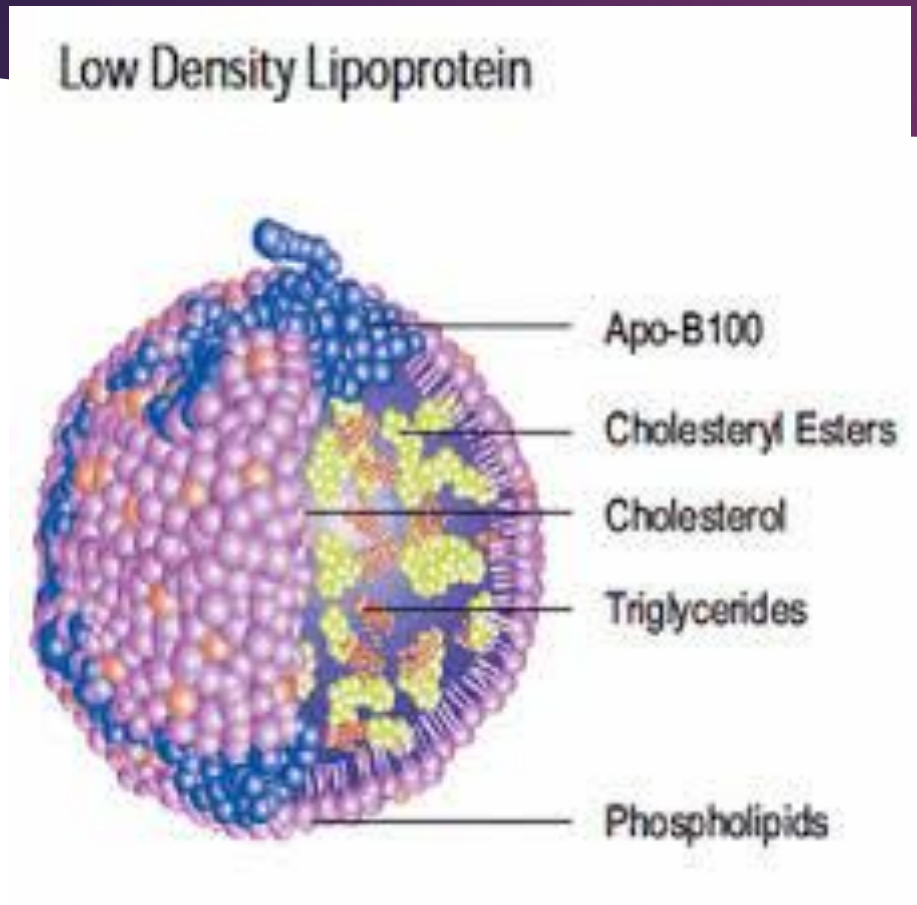
FH HOMOZYGOTES – 600 – 1000 mg/ dl

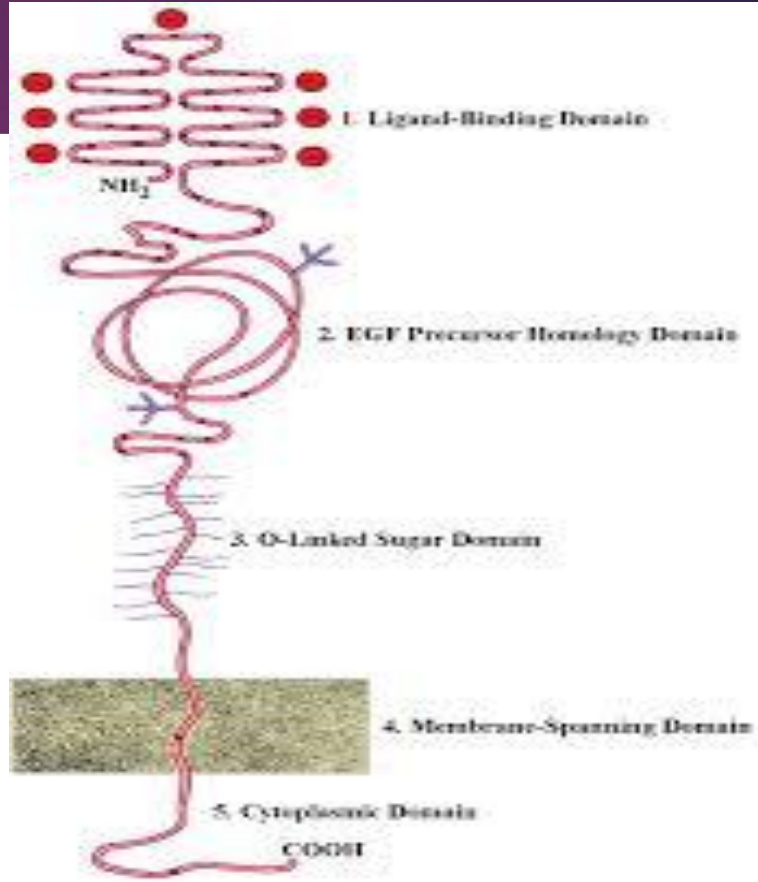
# Function of LDLR gene

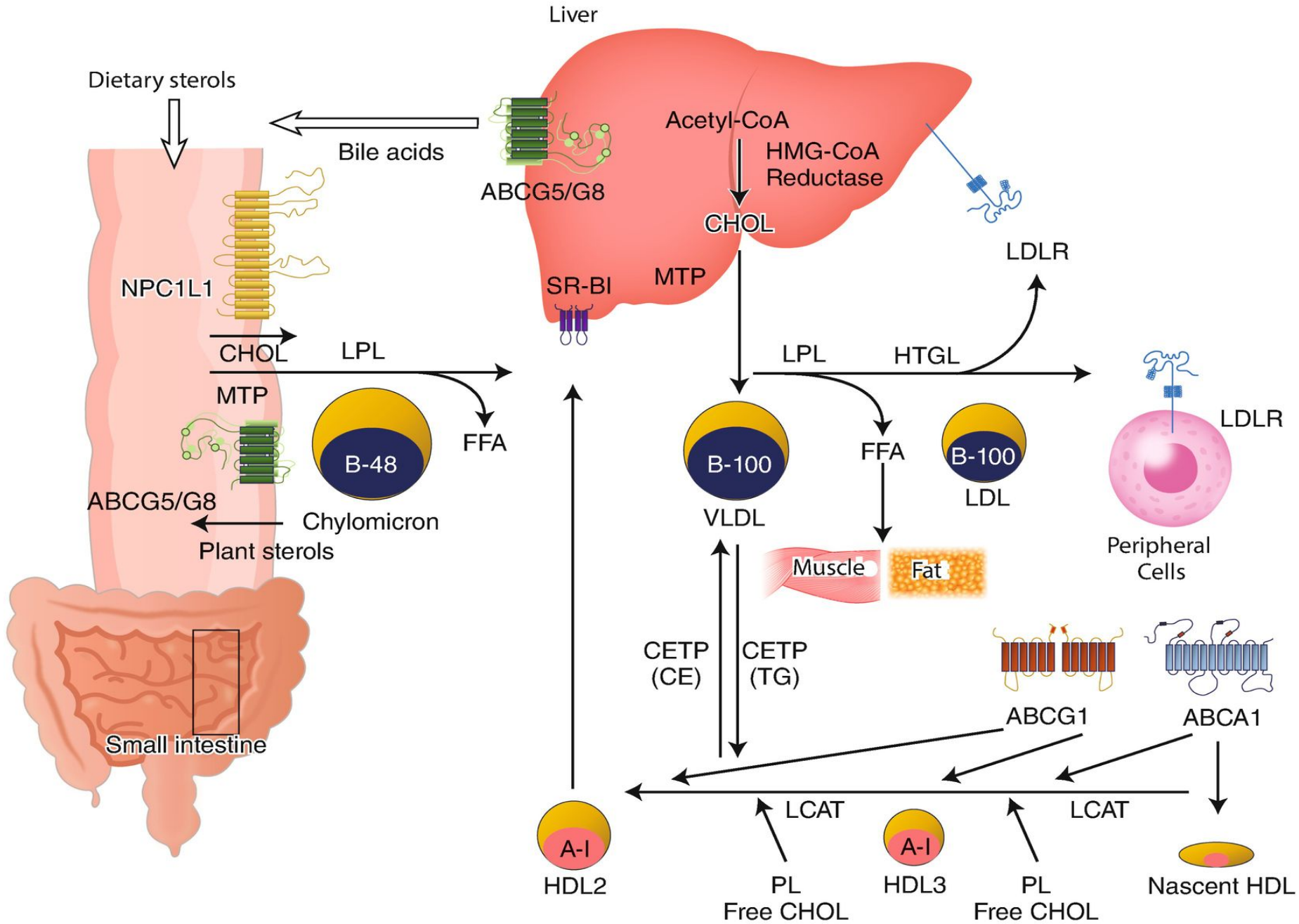
- The LDLR gene provides instructions for making a protein called low density lipoprotein receptor
- This receptor binds to particles called low-density lipoproteins, which are the primary carriers of cholesterol in the blood.
- They are particularly abundant in the liver, which is the organ responsible 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
Apo-B100
Cholesteryl Esters
Cholesterol
Triglycerides
Phospholipids


1. Ligand-Binding Domain
NH2
2. EGF Precursor Homology Domain
3. O-Linked Sugar Domain
4. Membrane-Spanning Domain
5. Cytoplasmic Domain
COOH


Liver
Dietary sterols
Bile acids
ABCG5/G8
Acetyl-CoA
HMG-CoA Reductase
CHOL
LDLR
NPC1L1
SR-BI
MTP
CHOL
LPL
LPL
HTGL
MTP
B-48
FFA
B-100
FFA
B-100
LDLR
ABCG5/G8
Chylomicron
VLDL
LDL
Plant sterols
Muscle
Fat
Peripheral Cells
CETP (CE)
CETP (TG)
ABCG1
ABCA1
Small intestine
LCAT
LCAT
A-I
A-I
HDL2
PL
Free CHOL
HDL3
PL
Free CHOL
Nascent HDL

# 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 effective.
- 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!
grammarly