

Chapter (6)
GENETIC VARIATION IN PLASMA HDL-C

INTRODUCTION

- Genetic factors accounts for approximately 50% of the variation in HDL-C level in general population.
- The lower the level of the HDL, the more likely is an underlying genetic etiology.
- Several genetic abnormalities have been identified and many of them occurred in mild or subclinical forms.
- Full blown genetic syndromes of HDL deficiency (see table) are quite rare.
- Several common mutations have been identified in genes involved in the regulation of plasma HDL-C concentration and, in some cases, the development of CAD.

GENETIC CAUSES OF LOW HDL-C

- **ApoA-I**
 - Complete apoA-I deficiency
 - ApoA-I mutations (eg, ApoA-I Milano)
- **LCAT**(lecithin cholesterol acyl transferase)
 - Complete LCAT deficiency
 - Partial LCAT deficiency (fish-eye disease)
- **ABC1**(ATP BINDING CASSETE PROTEIN)
 - Tangier disease
 - Homozygous
 - Heterozygous
 - Familial hypoalphalipoproteinemia (some families).
- **Hepatic Lipase Deficiency**
- **Unknown genetic etiology**
 - Familial hypoalphalipoproteinemia (most families)
 - Familial combined hyperlipidemia with low HDL-C
 - Metabolic syndrome.

GENETIC CAUSES OF HIGH HDL-C

- Deficiencies in the genes for cholesteryl ester transfer protein (CETP)
- Deficiencies in the genes for hepatic lipase.

GENETIC CAUSES OF LOW HDL-C

ApoA-I Deficiency

-Complete ApoA-I Deficiency

- Familial apolipoprotein A-I (apoA-I) defects may be caused by complete deficiency of the apoA-I gene or by mutations in the apoA-I gene.
- Genetic deficiency of apoA-I may be due to the deletion of the gene or to nonsense mutations that prevent the synthesis of apoA-I protein, which results in an absence of plasma high-density lipoprotein (HDL).
- Patients with this disorder sometimes display cutaneous xanthomas.
- The risk of premature cardiovascular disease in patients with apoA-I deficiency may be increased, but the onset of symptoms varies from the third to the seventh decade.

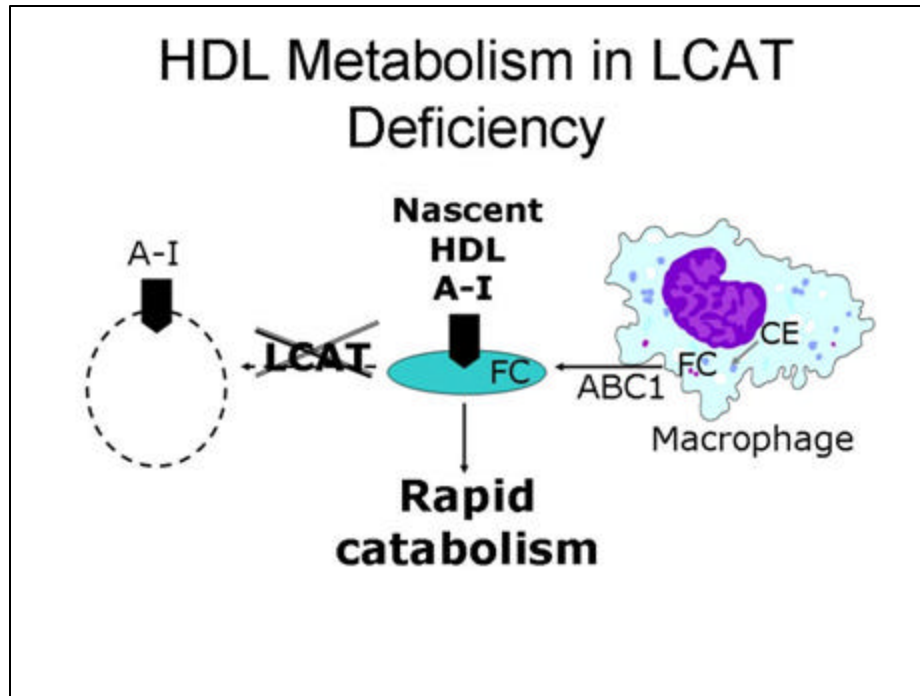
ApoA-I Mutations

- Mutations in the apolipoprotein A-I (apoA-I) gene may also lead to marked reductions in levels of high-density lipoprotein cholesterol (HDL-C) (usually 15–30 mg/dL) and apoA-I protein.
- Subjects with structural apoA-I mutations do not appear to have clinical sequelae, although a mutation in the apoA-I gene at the amino-terminus has been described in association with systemic amyloidosis.
- **ApoA-I structural mutations are rarely associated with premature atherosclerotic disease.**

LCAT Deficiency and Fish-eye Disease

- Both are due to mutations in LCAT gene:
 - LCAT deficiency**
 - Complete (Figure 6-1)
 - Partial LCAT deficiency (Fish-eye disease)

Figure (6-1)



Both types of LCAT deficiency result in

- Markedly reduced levels of high-density lipoprotein cholesterol (HDL-C) (< 10 mg/dL) and apolipoprotein (apo) A-I;
- Variable hypertriglyceridemia;
- Corneal opacities.
- Haemolytic anemia.
 - Complete LCAT deficiency, but not fish-eye disease, is characterized by progressive proteinuria and renal insufficiency.
 - Despite very low levels of HDL-C and apoA-I, these conditions rarely lead to premature atherosclerotic disease.

Treatment :

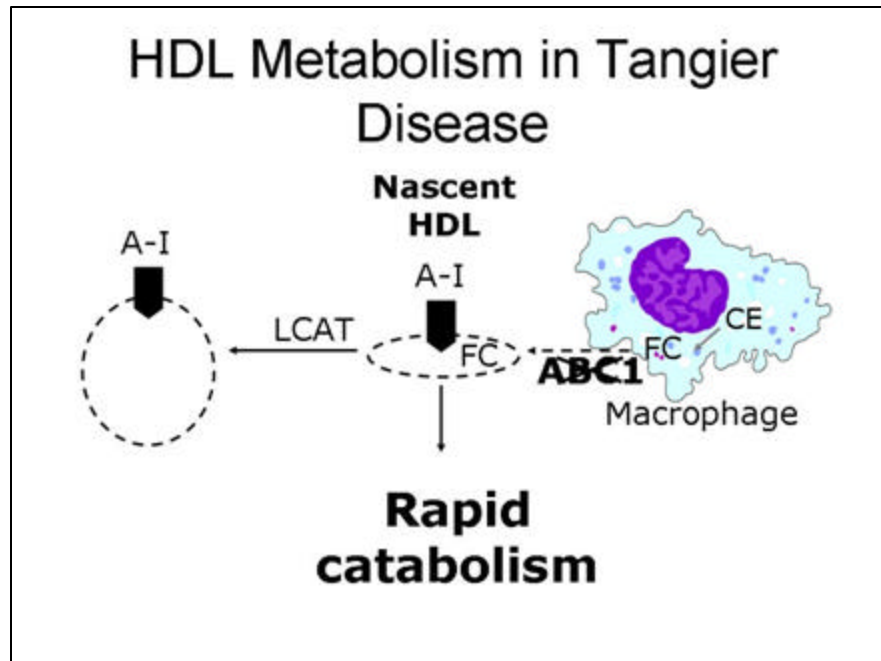
- 1- Renal transplantation
- 2- Fat restricted diet

ABC1(ATP BINDING CASSETE PROTEIN)

Tangier Disease

Tangier disease is a **very rare** autosomal codominant condition due to mutations in both alleles of the cellular receptor **ATP-binding cassette protein 1 (ABC1) gene.** (Figure 6-2)

Figure (6-2)



Patients with Tangier disease have

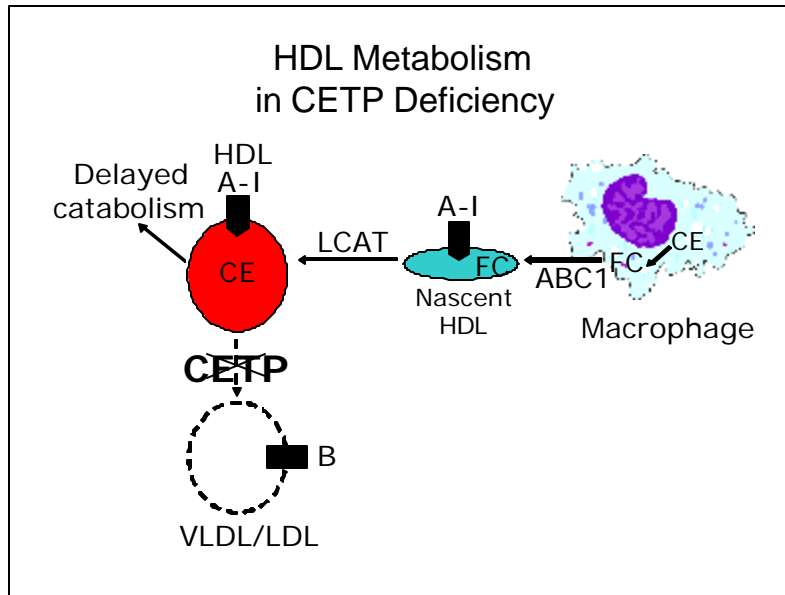
- High-density lipoprotein cholesterol (HDL-C) levels < 5 mg/dl.
- Extremely low levels of apolipoprotein A-I (apoA-I) due to markedly accelerated catabolism of apoA-I and apoA-II (Figure 6-1).
- Cholesterol accumulation in the reticuloendothelial system results in enlarged orange tonsils and hepatosplenomegaly.
- Intermittent peripheral neuropathy can also be seen due to cholesterol accumulation in Schwann cells and can develop corneal opacity.

Familial Hypoalphalipoproteinemia

- Primary or familial hypoalphalipoproteinemia is the most common genetic form of low high-density lipoprotein cholesterol (HDL-C).
- It is an autosomal dominant disorder and is the result of mutations in one allele of the ATP-binding cassette transporter 1 (ABC1) gene in some families; in other families, the nature of the genetic defect has not been established.
- Individuals with this condition have
 - Relatively normal triglyceride levels.
 - Moderate reductions in HDL-C (15–35 mg/dL) and apolipoprotein A-I.
- Most kindreds with this syndrome have an increased incidence of premature atherosclerotic cardiovascular disease.

CETP DEFICIENCY

Figure (6-3)

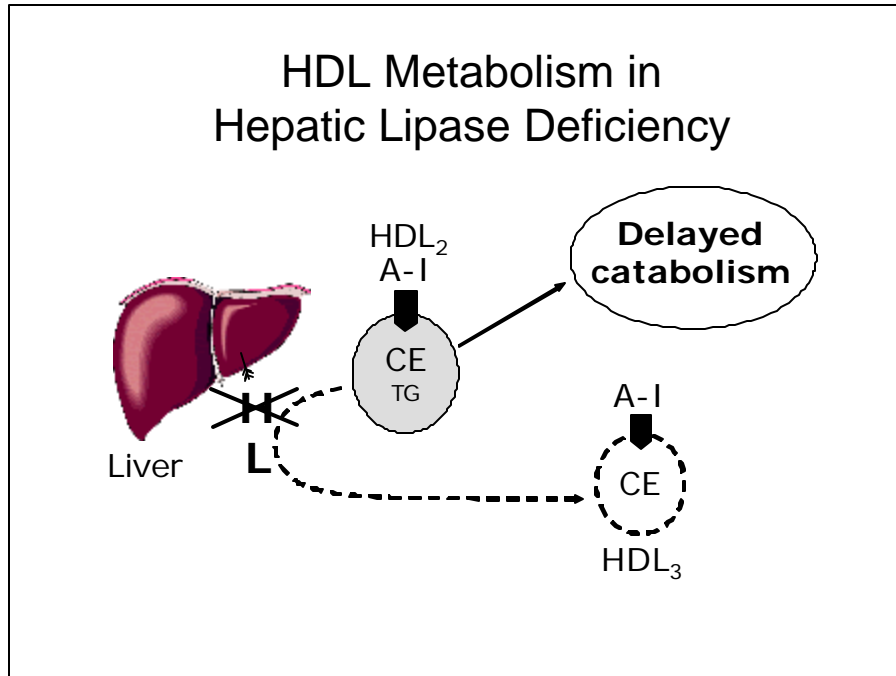


- Factors regulating the exchange of high-density lipoprotein (HDL) cholesteryl ester (CE) with very-low-density lipoprotein (VLDL) triglycerides, and the subsequent catabolism of HDL triglycerides, play an important role in regulating HDL levels.
- CE transfer protein (CETP) facilitates the transfer of CEs among lipoproteins (Figure 6-3)
- Deficiencies in the gene coding for CETP have been described.
- CETP deficiency results in delayed catabolism of CE in HDL and of apoA-I. This leads to the production of large HDL particles enriched in CE.

Hepatic Lipase Deficiency

Total deficiency of hepatic lipase is a rare autosomal recessive disorder due to mutations in both alleles of the hepatic lipase gene.

Figure (6-4)



The condition results in impairment in the final catabolism and/or remodeling of small very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). As a result, individuals with hepatic lipase deficiency show

1. Modestly elevated levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I and
2. Variable elevations in total cholesterol, triglycerides, and lipoprotein remnant particles (eg, chylomicron remnants).

Hepatic lipase deficiency does not protect against atherosclerosis; some subjects may have an increased risk for premature atherosclerotic vascular disease.

Familial Hyperalpha-lipoproteinemia

- Familial hyperalpha-lipoproteinemia is inherited as an autosomal dominant disorder, but its molecular etiology is currently unknown.
- It is characterized by modest to marked elevations in high-density lipoprotein (HDL)-cholesterol and apolipoprotein (apo) A-I.
- Epidemiologic studies have suggested that this syndrome may be associated with increased longevity and a decreased risk of atherosclerotic vascular disease.

SUMMARY

Table (6-1): Genetic Disorders associated with Low HDL-C Levels

Genetic Disorder	Molecular Defect	Lipoprotein Findings	Clinical Findings	Premature Atherosc.
Familial apoA -I deficiency	apoA -I absence	HDL<5mg/dl, TG normal	Planar xanthomas, corneal opacities	++
Tangier disease	ABCA I mutants	HDL<5mg/dl, TG Usually increased	Corneal opacities; enlarged, orange tonsils; hepatosplenomegaly; peripheral neuropathy	+
Familial apoA -I Structural mutants	Abnormal apoA- I	HDL 15-30 mg/dl, TG normal or increased	Often none; sometimes corneal opacities	No
Familial LCAT def	LCAT deficiency	HDL<10 mg/dl, TG normal or increased	Corneal opacities, anemia, proteinuria, renal insufficiency	No
Fish-eye disease	LCAT deficiency (partial)	HDL<10 mg/dl, TG normal or increased	Corneal opacities	No
Familial hypoalphalipoprotein	Unknown	HDL 15-35 mg/dl. TG normal	Often none; Sometimes corneal opacities	No to ++

Risk of premature atherosclerosis: +, moderate ++, marked