Homozygous Familial Hypercholesterolemia

Overview

Homozygous Familial Hypercholesterolemia (HoFH) is an ultra-rare lipid metabolism disorder characterized by profoundly elevated LDL-C levels and accelerated and premature atherosclerosis leading to major CV events, including sudden cardiac death.[1,2]

Prevalence of HoFH is estimated at 1 in 300,000 persons, but varies depending on region and data collection method.[3]

- EU: 1 in 160,000 (Denmark) to 1 in 860,000 (Germany)[1,4]
- Canada: 1 in 275,000 (higher frequency in French Canadians due to the founder effect)[5]

HoFH is often underdiagnosed and undertreated; consequently, delayed diagnosis of HoFH into the second decade of life allows for CV complications of the disease (eg, atherosclerosis, aortic supravalvular and/or valvular stenosis, and mitral regurgitation) to manifest.[1,3]

Early diagnosis (eg, systematic cascade or universal screening) is critical to promptly initiate lipid-lowering therapies for reducing CV morbidity and mortality.[1,2,6,7]

HoFH Pathophysiology

HoFH is primarily caused by variants in both alleles of the gene encoding the LDL receptor (*LDLR*; ≥90% of cases) and, to a lesser extent, by variants in other genes (*APOB*, *PCSK9*, and *LDLRAP1*) that reduce hepatic clearance of LDL-C.[1,2,8]

- Variants in the *APOB* gene impair ApoB-mediated LDL-C uptake by the LDLR[9]
- *PCSK9* gain-of-function mutations inhibit LDLR function and increase degradation of LDLRs[9]
- *LDLRAP1* genetic variants impair the ability to interact with LDL particles[9]

Patients with total (homozygous *LDLR*-deficient) loss of LDLR function have plasma LDL-C levels that are 4 times higher than normal; they are at the highest risk for experiencing a major CV event.[2]

Role of ANGPLT3 in Lipid Metabolism

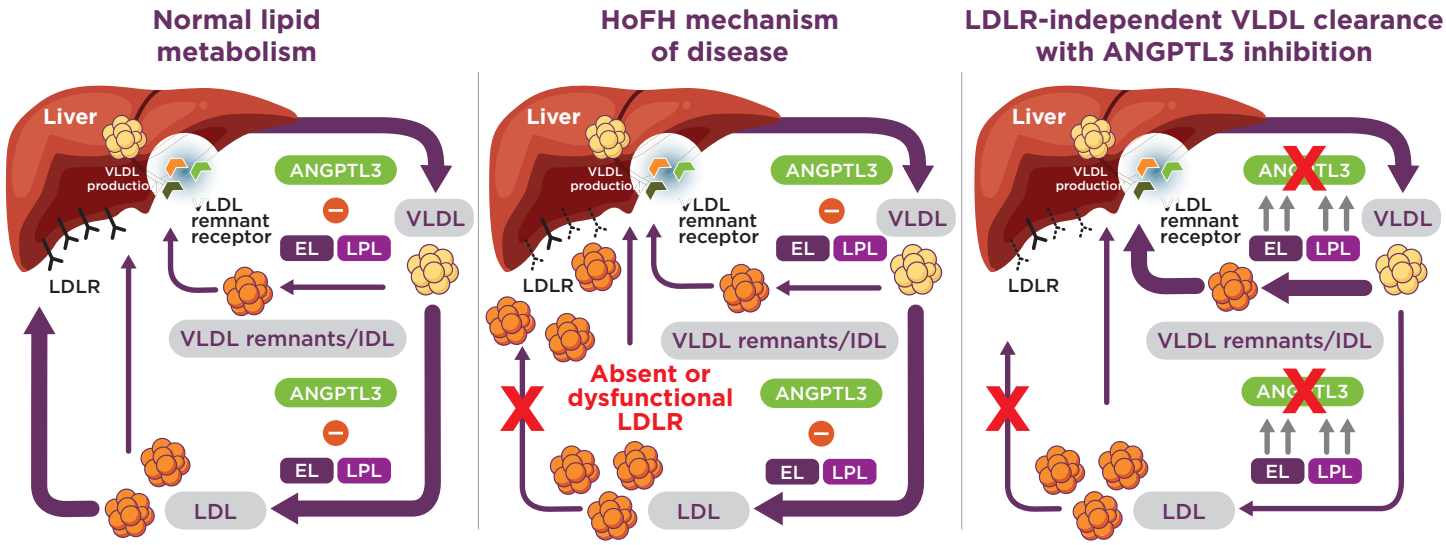
ANGPTL3 is a circulating protein predominantly synthesized in the liver that inhibits LPL and EL, thus regulating plasma levels of TG and LDL-C (**Figure 1**).[10]

- LPL and EL are key enzymes that hydrolyze VLDL and chylomicrons to release free fatty acids for uptake into the peripheral tissues for energy release or storage[10]
- Inhibition of LPL and EL by ANGPTL3 results in higher levels of circulating plasma TG-containing lipoproteins[10]

Inhibiting ANGPTL3 promotes lipolysis and VLDL remnant clearance via LDLR-independent uptake by the liver and/or extrahepatic tissues.[10]

- Loss-of-function *ANGPTL3* variants are associated with decreased TG and LDL-C levels[11-17]

Figure 1. Role of ANGPTL3 in lipid metabolism and elevated LDL-C in HoFH disease state[11-17]



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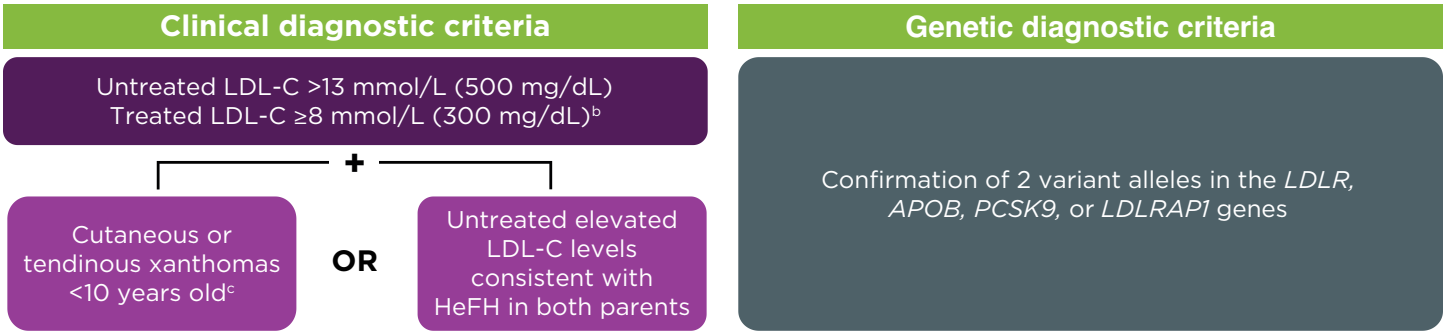
Diagnosis and Clinical Presentation

Diagnosis of HoFH (**Figure 2**) is based on LDL-C levels, physical signs and symptoms (xanthomas and CV complications, including supravalvular aortic stenosis and mitral regurgitation, due to cholesterol and calcium deposits in the vasculature[1]), family history, and genetic testing when available; there is no international consensus on diagnostic criteria.[1,18,19]

Figure 2. EAS/ESC diagnostic criteria for HoFH[1,3,a]



[a]The Canadian Cardiology Society's position statement on FH references the EAS/ESC HoFH diagnostic criteria.[19]
[b]These LDL-C levels are only indicative of HoFH, and lower levels, especially in children or in treated patients, do not exclude HoFH.
[c]Evidence of xanthomas in the eyes (corneal arcus) reinforces HoFH diagnosis.[1]

Current Management

EAS/ESC guidelines recommend combinatory pharmacologic treatment, principally high-intensity statins, ezetimibe, PCSK9 inhibitors (alirocumab and evolocumab), and microsomal transfer protein inhibitors (lomitapide).[1,20]

These pharmacotherapies either rely on a functional LDLR or require gradual dose escalation (in combination with a low-fat diet) to minimize the incidence and severity of gastrointestinal adverse events.[19,20]

Plasmapheresis and lipoprotein apheresis are utilized to great effect in removing LDL-C, but reductions are transient, and the frequency, duration, and cost of treatment greatly impact quality of life.[1,19,20]

Therefore, most patients with HoFH do not reach the recommended LDL-C target and remain at an increased risk of atherosclerotic CV disease.[21]

New therapies have the potential to change disease management of HoFH.[21]

Abbreviations

ANGPTL3, angiopoietin-like 3; APOB, apolipoprotein B; CV, cardiovascular; EAS, European Atherosclerosis Society; EL, endothelial lipase; ESC, European Society of Cardiology; EU, European Union; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia ; HoFH, homozygous familial hypercholesterolemia; IDL, intermediate density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adaptor protein 1; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low-density lipoprotein

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