Homozygous Familial Hypercholesterolemia (HoFH)

HoFH is a rare and severe genetic disorder characterized by extremely high levels of low-density lipoprotein cholesterol (LDL-C) in the blood.

Here are the key points about HoFH:

Inheritance:

- HoFH is an **autosomal codominant** disorder, meaning that both copies of the LDLR (low-density lipoprotein receptor) gene are affected.
- Individuals with HoFH inherit one mutated allele from each parent.

Clinical Features:

- **Severe Hypercholesterolemia: LDL-C levels are markedly elevated, often** exceeding 500 mg/dL.
- **Xanthomas**: These are cholesterol deposits in the skin, tendons, and other tissues.
- **Premature Atherosclerosis**: HoFH patients develop atherosclerotic plaques at an early age, leading to cardiovascular complications (often before the age of 20).
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- **Accelerated Coronary Artery Disease (CAD)**: HoFH patients are at high risk for heart attacks and other cardiovascular events.

Genetic Basis:

- Mutations in the LDLR gene are the most common cause of HoFH.
- Other genes involved include ApoB, PCSK9, and LDLRAP1.
- **The genetic basis can be two different mutations of one gene or two different mutations of 2 cholesterol metabolism genes (a compound heterozygote).**

Treatment:

- **Lifestyle Modifications**: Dietary changes, exercise, and weight management are necessary but cannot be sufficient

- **Medications**:
  - **High-Dose Statins**: In HoFH, it is often deficient due to the lack of functional LDLRs.
  - **Ezetimibe**: Inhibits cholesterol absorption.
  - **Bile Acid Sequestrants**: Help reduce LDL-C levels.
  - **LDL Apheresis**: A blood purification technique to remove LDL-C.
  - PCSK-9 inhibitors: Evolocumab or Alirocumab
  - **Lomitapide or Evinacumab**: Novel therapies for severe cases.
  - **Liver Transplantation**:**can replace the function of its own LDL receptors**
  - Only a combination of multiple treatments can lead to the achievement of the treatment goal

Prognosis:

- Without treatment, HoFH leads to premature cardiovascular disease and early mortality.
- Early diagnosis and aggressive management are crucial to prevent complications.

Remember that HoFH requires specialized care, genetic counseling, cascade screening

and a multidisciplinary approach involving cardiologists, lipid specialists, and geneticists. Genetic testing is essential for accurate diagnosis and to guide treatment decisions.

When to consider HoFH

When evaluating patients for the homozygous form of familial hypercholesterolemia (HoFH), clinicians consider both clinical and genetic criteria. Here are the key points to consider:

Clinical Features:

- **Early Onset**: Symptoms typically appear early in life, often in the first or second decade.
- **Physical Examination Findings**:
  - **Cutaneous or Tuberous Xanthomas**: These are fatty deposits under the skin.
  - **Tendon Xanthomas**: Especially interdigital xanthomas between the thumb and index finger.
  - **Xanthelasma**: Yellowish cholesterol deposits around the eyes.
  - **Arcus Corneae**: A white or gray ring around the cornea.
- **Elevated LDL-C Levels**: Untreated LDL-C levels >500 mg/dL or treated LDL-C levels ≥300 mg/dL.
- **Age of Onset**: Cutaneous or tendon xanthomas before 10 years of age
- Family history of HeFH in both parents or untreated elevated LDL-C levels consistent with heterozygous FH (HeFH) in both parents.

Genetic Criteria (Endorsed by the European Atherosclerosis Society):

- **Genetic Confirmation:** Two mutant alleles of the LDLR, Apo (b), PCSK9, or LDLR adaptor protein 1 gene locus.
- **Untreated LDL-C Levels:** LDL-C >500 mg/dL or >400 mg/DL with aortic valve disease or xanthomas at <20 years of age.
- **Compound Heterozygosity: two nonidentical mutations of one gene or two mutations of two LDL-C–raising gene defects.**

Simpler Classification for HoFH (Proposed by the American Heart Association):

- **LDL-C ≥400 mg/dL**: Genetic testing performed, confirming mutations in LDLR, Apo (b), or PCSK9.
- **LDL-C >500 mg/dL or LDL-C >400 mg/dL with aortic valve disease or xanthomas at <20 years of age**.

Remember that HoFH is a high-risk condition, and early detection and treatment are crucial to prevent cardiovascular events. Screening for elevated levels of lipoprotein (a) (Lp [a]) is also recommended due to its association with atherosclerotic cardiovascular disease (ASCVD) independent of LDL-C.