ICoLA 2019
The 8th International Congress on Lipid &Atherosclerosis(ICoLA)
The 58th Conference of the Korean Society of Lipid & Atherosclerosis
September 5(Thu.) ~ 7(Sat.), 2019, Conrad Hotel Seoul, Republic of Korea

# Lipoprotein metabolic derangements in FH

**Christoph J. Binder**[1,2]

[1] *Deparment of Laboratory Medicine, Medical Univeristy of Vienna, Vienna, Austria*

[2] *Research Center for Molecular Medicine, Austrian Academy of Sciences, Vienna, Austria*

*christoph.binder@meduniwien.ac.at*

## Abstract

Familial hypercholesterolemia (FH) results from delayed clearance of LDL from the plasma, resulting in hypercholesterolemia, physical signs and premature atherosclerotic cardiovascular disease (ASCVD). Elevated levels of LDL have multiple negative effects on vascular function, including impairement of the normal arterial response to vasodilatory stimuli, promotion of vascular inflammation, and pathological uptake by arteyl wall macrophages when LDL particles become oxidized, leading to the formation of foam cells – hallmark cells of atherosclerotic lesions. The majority of plasma cholesterol is transported within LDL particles, which are primarily cleared by cellular uptake via LDL receptors on hepatocytes. The increased LDL-C levels in FH result from impaired LDL-receptor activity, which is often caused by different classes of mutations that directly affect the receptor or receptor-mediated clearance. In most cases FH is an autosomal co-dominant disorder. Heterozygous FH (HeFH) is the most common inherited metabolic disorder causing ASCVD, affecting 1:200-250 individuals, while homozygous FH (HoFH) is thought to affect about 1:160,000 - 300,000 people. Most individuals with genetically confirmed HeFH and HoFH have one and two mutant alleles of the LDLR gene, respectively, conferring either defective or null LDL receptor functionality. More than 2,300 unique FH-causing mutations have been reported in the LDLR gene. Heterozygous mutations in other genes, including APOB and PCSK9 explain <10% of HeFH cases, and two mutant alleles of these genes and of LDLRAP1 also called ARH (autosomal recessive hypercholesterolaemia) produce a phenotype resembling HoFH. Notably, at least 20% of patients referred to a lipid clinic with suspected HeFH do not have a single gene mutation, but instead carry polygenic susceptibility to high LDL-C. Diagnosis of FH is commonly based on scores that include lipid values (total cholesterol and/or LDL-C levels); the presence of physical stigmata considered pathognomonic for FH, such as tendon xanthomas, xanthelasmas, or arcus cornealis; the family history of premature CVD; and the presence of pathogenic DNA variants. Two clinical scoring systems are in general use: the Simon Broome Register (SBR) and the Dutch Lipid Clinic Network (DLCN) criteria. The basic metabolic alterations in FH, the functional and genetic basis for it, as well as the diagnosis and clinical implications will be discussed.

***Keywords***

*Familial hypercholesterolemia, atherosclerosis, LDL-C, LDL receptor, diagnostic criteria*