The Major Molecular Causes of Familial Hypercholesterolemia

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Abstract

Familial Hypercholesterolemia (FH) is a common dominant disorder of cholesterol metabolism characterized by elevated serum cholesterol level which results in increasing risk of many diseases. The major cause of FH is the loss-of-function in Low Density Lipoprotein Receptor (LDLR), Apolipoprotein B-100 (ApoB-100), Low Density Lipoprotein Receptor Adapter Protein (LDLRAP1), and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) gene that revealed to the defects in the uptake and degradation of Low Density Lipoprotein (LDL) via the LDLR pathway. In this review, we have highlighted the molecular disorder in LDLR, ApoB-100, LDLRAP1 and PCSK gene, leading to the possible accession on early diagnosis, screening of FH based on the clinical characteristics, family history, evaluated LDL-Cholesterol levels and recently genetic testing aided, hence molecular based therapy will be applied or recommended to FH patients.

Keywords: Apolipoprotein B-100 (ApoB-100), Familial Hypercholesterolemia, Low Density Lipoprotein Receptor, Low Density Lipoprotein Receptor Adapter Protein, Proprotein Convertase Subtilisin/Kexin Type 9

1. Introduction

Familial hypercholesterolemia (FH; OMIM#143890) was first described in 1930’s by Carl Müller, a Norwegian clinician. FH is a common dominant disorder of cholesterol metabolism characterized by highly elevated serum cholesterol bound to Low Density Lipoprotein (LDL) which promotes deposition of cholesterol in skin (xanthelasmas), tendons (xanthomas) and coronary arteries (atherosclerosis). In the mid 1960’s, Khachadurian studied and analyzed Lebanese FH pedigrees, he concluded that FH was inherited as a monogenic autosomal codominant trait- a dominant disorder with a gene-dosage effect. According to FH Foundation statistics, the frequency of FH in worldwide population is about 1 of 250-500 people. Many factors affect the manifestation of FH including age, gender, diet, and genetic disorders, such as a mutation in LDLR (Low Density Lipoprotein Receptor) (Chromosome 19), APOB-100 (Apolipoprotein B-100) (Chromosome 24). This review will describe the FH disease and the way in which the genetic basic of FH disorder, leading to the elucidation of LDL-receptor pathway, and how defects in different genes resulted in FH disease.

2. Genetic Counseling

FH is one of the most frequent monogenetic disorder, and inherited in an autosomal dominant hypercholesterolemia, meant that the affected parent with this disorder has 50% opportunity of passing the gene to each of his or her children. Because of the dominant, the inherited child will have this disorder (Figure 1). This disorder occurs in two clinical manifestations: Heterozygous Familial Hypercholesterolemia (HeFH) meant that the FH gene was inherited from one parent, and more severe Homozygous Familial Hypercholesterolemia (HoFH) the FH gene was inherited from each of parents. Recently, the prevalence of HeFH has been estimated to be about 1:250-500
making it were suspected to be more frequent, while the prevalence of HoFH has been reported in 1:1 million. FH could be caused by the mutations in four known genes. About 85% to 95% of FH cases are due to the inherited mutations in LDLR gene leading to functional reductions in the capacity to clear LDL Cholesterol (LDL-C) from circulation has been identified. Less commonly, the mutations in Apolipoprotein B (ApoB) gene that encoded protein recognizes LDL-C and leading to binding of LDL-C to the LDL receptor; and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) gene that mediates the degradation of the LDL receptor and Low Density Lipoprotein Receptor Adaptor Protein 1 (LDLRAP), a serine protease that degrades or destroys the LDL receptor.

2.1 LDLR Gene

The Low-Density Lipoprotein Receptor (LDLR), originally identified by Brown and Goldstein in 1973 during their research for the molecular basis of FH, is the cell surface receptor that plays an important role in cholesterol homeostasis that mediates the specific uptake of LDL from the circulation and transfer into cells via endocytosis. Brown and Goldstein showed that the mutation in LDLR was the cause of monogenic FH.

The LDLR gene is localized at 19p13.1-p13.3 spans 45 kb, includes 18 exons, encodes a glycoprotein of 839 amino acids that functions in cholesterol homeostasis. Till now, the six functional domains of the LDLR and the exons of LDLR gene is well understood (Figure 3).

Mutation in gene coding LDLR is the most common genetic cause of FH, to date, more than 1,600 mutations (including missense, nonsense, deletion, and insertion types) have been reported. Till now, a large of mutations have been catalogued from around the world on many websites, such as the LOVD database (Leiden Open (source) Variation Database: http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0/); UMD LSDBs (UMD Locus Specific Database: http://www.umd.be/LDLR), etc. According to LOVD database, total of 1741 variants of LDLR gene have been reported including substitutions, insertions, dele-
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In the literature, majority of these variants are nucleotide substitutions, counting for 73.5% (1280/1741) including missense substitutions: 72.9% (933/1280), nonsense substitutions: 13.8% (176/1280), other substitutions: 13.4% (171/1280). Mutations in LDLR gene are distributed along the full gene length, however, a high frequency of mutation in exon-4 coding central region of the ligand-binding domain have been reported19 (Figure 4). It could be explained that Exon 4 encodes three of seven cysteine-rich ligand binding repeats of the LDLR that plays an essential role which is required for LDL binding via Apolipoprotein B in receptor binding activity20. Therefore, mutations in this region leading to more severe FH than others. Based on the defects of LDLR, five major classes have been identified (Table 2)9,21,22.

2.2 ApoB Gene

In contrast to LDLR gene, mutation in Apolipoprotein B-100 gene (ApoB, #MIN 107730) is also associated with FH phenotype, but it is less common (< 8%)2,3,10,24. The clinical phenotype FH associated ApoB gene mutations is defined as “Familial Defective Apolipoprotein B-100” (FDDB). The ApoB gene is localized at 2p24.1 and consists 28 introns and 29 exons that codes for the protein component of LDL particles, plays a central role in human lipoprotein metabolism24,25. In human plasma, ApoB is existed in two different forms: ApoB-48 and ApoB-10025. ApoB-100 (2152 amino acids) is produced by the intestine, and identical to the amino-terminal 48% of ApoB-100, whereas ApoB-100 (4536 amino acids) is produced by liver. ApoB-100 is the protein component responsible for the cellular recognition and catabolism of LDL via the LDLR pathway. Therefore, ApoB-100 mediates the binding of LDL to LDLR, leading the clearance of LDL particles (Figure 2(a)). ApoB-100 has defined as five structural domains termed as βα, β, α, β, and α (β indicates β-sheet; α indicates α-helix structure) (Figure 5). Mutations in the ApoB-100 will drastically alter its functional activity leading to a decrease in its binding to LDLR, resulting in FH10. In contrast to LDLR, small mutations, such as R3500Q, R3500W, R3531C, and R3480W have been found only in residues 3130-3630 which are important for the binding of ApoB-100 to the LDL receptor26-29. According to

Figure 3. Domains organization of LDLR (Adapted from Human Protein Reference Database: http://www.hprd.org/). LA: Low-density lipoprotein receptor domain class A; EGF: Epidermal Growth factor-like domain; EGFC: Calcium-binding EGF-like domain; LY: Low-density lipoprotein-receptor YWTD domain; EGFL: EGF domain, unclassified subfamily; TM: Transmembrane domain.

Figure 4. Sequence variations in per exon of LDLR gene (Adapted from LOVD database).
Table 1. Criteria for diagnosis of familial hypercholesterolemia based on The Dutch Lipid Clinic criteria

| Criteria | Score | Patient score |
|----------|-------|---------------|
| LDL-cholesterol (mmol/L): | | |
| 4.0 – 4.9 (~ 155 – 189 mg/dl) | 1 | |
| 5.0 – 6.4 (~ 190 – 249 mg/dl) | 3 | |
| 6.5 – 8.4 (~ 250 – 329 mg/ml) | 5 | |
| ≥ 8.5 (~ 330 mg/ml) | 8 | |
| Physical examination: | | |
| Tendinous xanthamata | 6 | |
| Acruscornealis before 45 years old | 4 | |
| Clinical history: | | |
| Patients with premature coronary artery disease (men aged <55 years, women aged <60 years) | 2 | |
| Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years) | 1 | |
| Family history: | | |
| First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years), OR | 1 | |
| First degree relative with known LDL-cholesterol above the 95th percentile for age and gender | | |
| First degree relative with tendinous xanthomata and/or arcus cornealis, OR | | |
| Children aged <18 years with LDL-cholesterol above the 95th percentile for age and gender | 2 | |
| Total score | | |
| Diagnosis: | | |
| Definite FH: Total score > 8 | | |
| Probable FH: Total score 6 – 8 | | |
| Possible FH: Total score 3 – 5 | | |
| Unlikely FH: Total score < 3 | | |

Table 2. The five major LDLR defects

| Class 1: LDL receptor is not synthesized at all. |
| Class 2: LDL receptor is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface. |
| Class 3: LDL receptor does not properly bind LDL on the cell surface because of a defect in either Apolipoprotein (APO) B-100 (R3500Q) or in the LDL receptor. |
| Class 4: IV: LDL receptor bound to LDL does not properly cluster in Clathrin-coated pits for receptor-mediated endocytosis. |
| Class 5: LDL receptor is not recycled back to the cell surface |

Figure 5. Schematic diagram of ApoB-1100.
the study of Borén et al. (2001), they investigated that the molecular mechanism of the normal receptor binding in ApoB-100 depends on the interaction of Arginine 3500 (R3500) and Tryptophan 4369 (W4369). The interaction between R3500 and W4369 is important and essential for the correct folding of the carboxyl terminal of ApoB-100 which permits normal interaction between LDL and LDLR. Additionally, W4369 interacts not only the R3500, but also with R3480 and R3531. Therefore, the mutation in those sites could disrupt the binding of LDL to its receptor leading to FH. They proposed that Arginine-Tryptophan interactions are crucial during the conversion of VLDL to LDL for positioning ApoB-100 carboxyl tail which functions as a modulator element that inhibits VLDL from interacting with LDL receptor to permit ApoB-100 on LDL to bind normally to the receptor. The disrupted folding process gives rise to the forming of FDB. The mutations in ApoB-100 have been found to be linked to the defective LDLR binding and hypercholesterolemia: Exon 26: R3500Q, R3500W, R3480W; Exon 29: W4369Y. The most common mutation in ApoB-100 is R3500Q which leads to the autosomal dominantly inherited clinical disorder FDB.

2.3 LDLRAP1 Gene

LDLRAP1 protein encoded by LDLRAP1 gene also known as ARH is mapped to chromosome 1p35, includes 9 exons, encoded a 32-kDa endocytic adaptor protein of 308-amino acid protein that interacts with the cytoplasmic tail of LDLR, results in LDLR endocytosis. Mutation in gene coding LDLRAP1 has been reported to be associated with the Autosomal Recessive Hypercholesterolemia (ARH) which is considered as an extremely rare inherited hypercholesterolemia. LDLRAP1 protein contains the conserved Phosphotyrosine-Binding (PTB) domain, and reported to function as an accessory adaptor protein which binds the consensus sequence NPXY presents in the cytoplasmic domains of several cell-surface proteins, and mediates its cellular internalization via the clathrin machinery. Up to now, there are few published documents about the mutation on LDLRAP1 as well as the clinical characteristics of LDLRAP1 heterozygous mutations carriers due to the rarity of this disorder. The phenotype of ARH is similar to that of patients with HoFH caused by mutated LDLR, but it is somewhat milder in terms of serum total cholesterol and LDL cholesterol levels, and shows the better response to treatment with lipid-lowering drugs or without LDL apheresis. According to the LOVD database, a high frequency of mutation in exon-1 have been reported (Figure 6). In the study of Gracia et al., they identified six mutations in ARH, including 1 frameshift was found in homozygosity in the Sardinian families, 1 nonsense mutation was found in the Lebanese family, and other mutations were missense resulting in the high plasma LDL level. Notably, all the affected individuals were homologous for a frameshift mutation at nucleotide 432 of LDLRAP1 resulting appearance of termination codon at residue 170 leading to the coronary artery disease with 8 relatives in this family died at an age of less than 33 years old.

2.4 PCSK9 Gene

The heterozygous mutation on PCSK9 Proprotein Convertase Subtilisin/Kexin type 9 located at 1p32 contains 12 exons, first found in 2003 by Abifadel et al., have since shown to be associated with FH. This is the least common cause of FH accounting less than 5% of cases. Abifadel et al., reported that PCSK9 cDNA also known as Neural Apoptosis-Regulated Convertase-1 (NARC1), yields 3.617 bps and encodes a protein of 692 amino acids, that mediates the degradation of the LDLR. PCSK9 is belonged to the subtilisin family of kexin-like proconvertases has defined as three structural domains, including signal sequence, prodomain, catalytic domain followed by C-terminal (Figure 7).
According to LOVD database (Leiden Open (source) Variation Database, total of 163 variants have been reported, and a high frequency of mutation was observed in exon 1 (Figure 8). Functional defects have been studied to be associated with two forms of function mutations of PCSK9 in human, including loss-of-function and gain-of-function mutation\(^{35}\). Gain-of-function mutation in PCSK9, including S127R, D129N (in prodomain); R215H, F216L, R128S (in catalytic domain); R469W, R496W (in C-terminal) degrades the LDLR in the liver resulting in increase of plasma LDL level and susceptibility to coronary heart disease\(^{12}\), whereas the loss-of-function mutations, such as R46L, ΔR97, G106R, Y142X (in prodomain); L253F (in catalytic domain); A443T, C679X (in C-terminal), lead to the reduction of plasma levels of LDL cholesterol via reduces PCSK9 mediated degradation\(^{35,36}\). Therefore, PCSK9 has become an insight into the discovery of new target drug for cholesterol-lowering therapy\(^{2,47}\).

To our knowledge, the early detection of FH gene mutation carrier allows primary prevention of FH and coronary heart disease, thus, it is essential for simple diagnosis tools for the genetics analysis. The detection of mutations in the LDLR, ApoB, LDLRAP1 or PCSK9 has been considered to be the criteria for the diagnosis of monogenic causes of FH. For the detection of mutations of FH gene, several genetic methods have been established, including sequencing, Single-Strand Conformation Polymorphism (SSCP) analysis, Denaturing Gradient Gel Electrophoresis (DGGE), melting analysis, Denaturing High Performance Liquid Chromatography (DHPLC), Multiplex Probe Amplification (MLPA), etc. Recent approaches include target exon sequencing, Array-based resequencing, or Next Generation Sequencing (NGS), Whole Genome Sequencing (WGS), have been identified in a number of numerous mutations on FH-related genes.

### 4. Novel Therapies for FH

In current therapies a number of guidelines for FH therapies have been reported in order to reduce the LDL-C levels below 2.5 or 1.8 mmol/L without increased risk of Cardiovascular disease\(^{37}\). According to NLA recommendations, the NCEP ATP III guidelines, and the NICE guidelines, statins, also known as HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors therapy was suggested to be the corner-stone and first-line therapy for FH patients. Statins, including lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, pitavastatin, rosuvastatin, supported by FDA, act by competitively block the HMG-CoA reductase in the liver, the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor, then making for cholesterol (Figure 9)\(^{38,39}\). Other different kinds of medicines to control cholesterol includes Bile acid sequestrants, Fibrates, Niacin, Cholesterol absorption inhibitors, Omega-3 fatty acid, etc.

Over the past few years, many studies have been afforded led to the emergence of a number of novel therapies for lowering LDL-C levels based on the genetic disorders such as PCSK9, ApoB-100 served as potential therapeutic targets. Mipomersen (FDA approval) is an antisense oligonucleotide of 20 nucleotides that targets ApoB-100 in liver for treatment of HoFH. Mipomersen acts by hybridizing within the coding region of apoB-100 mRNA resulting in activation of RNase H, an enzyme

![Figure 8. Sequence variations in per exon of PCSK9 gene (Adapted from LOVD database).](image-url)
that catalyzes the RNA cleavage, and selective causes the degradation of ApoB-100 mRNA. This result inhibits the cessation of ApoB protein translation and thereby the production of atherogenic lipids, includes LDL, VLDL, and lipoprotein is decreased\textsuperscript{40,41}. The MTP (Microsomal Triglyceride Transfer) protein that is required for the assembly and secretion of VLDL-Lipoprotein by the liver\textsuperscript{42}. After VLDL is secreted, VLDL is converted to LDL. Lomitapide, developed by Aegerion Pharmaceuticals, approval by US FDA, used as an orphan drug in treatment of HoFH blocks the MTP activities resulting in reduction of plasma LDLC levels\textsuperscript{43}. PCSK9i (PCSK9 inhibitor), the kind of monoclonal antibodies, a new therapeutic class represents a novel and promising approach to reducing of LDL-C levels by using a mechanism at LDLR level\textsuperscript{44}. PCSK9i binds to PCSK9, resulting in inhibits the binding of PCSK9 to LDLR, thereby blunting PCSK9-mediated LDLR degradation, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone\textsuperscript{45,46}.

5. Conclusion

FH is an inherited disorder characterized by a high concentration of serum LDL cholesterol, which has been identified to be significant to the cardiovascular disease. FH is an autosomal, dominant genetic disorder associated with the mutation in FH-related genes, including LDLR, ApoB-100, LDLRAP1 and PCSK1 gene. Screening typical by the evaluation of the level of Cholesterol as well as using The Dutch Lipid Clinic criteria, confirmed by the genetic analysis of FH-related genes, give the well diagnosis of FH. The early identification and initial of treatment is paramount to make a huge impact on the prevention of CHD and related detrimental squeal.

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Figure 9. Inhibition of the cholesterol biosynthesis pathway acted by statins.
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