The genetic basis of familial hypercholesterolemia: inheritance, linkage, and mutations

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Abstract: Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism characterized by high plasma concentrations of low-density lipoprotein cholesterol (LDLc), tendon xanthomas, and increased risk of premature coronary heart disease. FH is one of the most common inherited disorders; there are 10,000,000 people with FH worldwide, mainly heterozygotes. The most common FH cause is mutations along the entire gene that encode for LDL receptor (LDLR) protein, but it has been also described that mutations in apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 genes produce this phenotype. About 17%–33% of patients with a clinical diagnosis of monogenic hypercholesterolemia do not harbor any genetic cause in the known loci. Because FH has been considered as a public health problem, it is very important for an early diagnosis and treatment. Recent studies have demonstrated the influence of the LDLR mutation type in the FH phenotype, associating a more severe clinical phenotype and worse advanced carotid atherosclerosis in patients with null than those with receptor-defective mutations. Since 2004, a molecular FH diagnosis based on a genetic diagnostic platform (Lipochip®; Progenika-Biopharma, Derio, Spain) has been developed. This analysis completes the adequate clinical diagnosis made by physicians. Our group has recently proposed new FH guidelines with the intention to facilitate the FH diagnosis. The treatment for this disease is based on the benefit of lowering LDLc and a healthy lifestyle. Actually, drug therapy is focused on using statins and combined therapy with ezetimibe and statins. This review highlights the recent progress made in genetics, diagnosis, and treatment for FH.

Keywords: LDLR, APOB, PCSK9, LDL cholesterol

Introduction

The object of this review is to update the status of familial hypercholesterolemia (FH, MIMN#143890), with special consideration on the genetics and diagnosis. Heterozygous FH (heFH) is presented with high prevalence around the entire world, thus supposing elevated costs in health care.1 Although this disease has been exhaustively studied, new locus and mutations associated with FH are described each year. Taking all things together, it is important to research about the FH causes, and the effectiveness in the diagnosis and treatment.

FH is an autosomal codominant inherited disorder of lipoprotein metabolism characterized by very high plasma concentrations of low-density lipoprotein cholesterol (LDLc), tendon xanthomas (TX), and increased risk of premature coronary heart disease (CHD).1 The penetrance of FH is almost 100%, which means that half of the offspring of an affected parent have a severely increased plasma cholesterol level from birth onwards, being both males and females equally affected.
FH was first described by Müller in 1938. Initially, the FH defect was long thought to be caused by cholesterol oversynthesis. In the middle 1970s, Brown and Goldstein found that FH defect was due to the absence of a high affinity receptor for uptake of serum low-density lipoprotein (LDL). These investigators characterized the LDL receptor (LDLR) pathway with its implications in other pathways and identifying the genetic defect that caused malfunction of the LDLr. Nowadays, FH has become one of the best known genetic diseases.

Although the vast majority of FH cases are caused by mutations in the LDL receptor gene (LDLR) gene, there are other causative genes such as apolipoprotein B (APOB) that codifies for the natural ligand of the LDLr protein And a third gene, proprotein convertase subtilisin/kexin type 9 (PCSK9) has been more recently identified as a cause of FH, however, mutations in this latter gene seems to be rare (PCSK9). Nowadays, FH has become one of the best known genetic diseases.

Epidemiology

FH is one of the most common inherited disorders with frequencies of heterozygotes and homozygotes estimated to be 1:500 and 1:1,000,000, respectively. In certain populations, a small number of mutations predominate due to founder effects and therefore, there is a high frequency in these populations including French Canadians, Christian Lebanese, Druze, Finns, South African Afrikaner, and Ashkenazi Jews of Lithuanian descent.

FH heterozygous patients display a twofold increase in plasma cholesterol (generally above the 95th percentile value for population). In patients with FH, the age–sex standardized mortality ratios are 4–5 times higher than in the general populations.

Due to the high incidence of premature (<55 years in men and <65 years in women) cardiovascular disease (CVD) and reduction in the life expectancy in many families with this disease, FH has been considered as a worldwide public health problem. Approximately, 85% of males and 50% of females will suffer a coronary event before the age of 65 years if they are not treated. It is noteworthy that up to 9% of the total premature CHD in eastern Finland and Germany is associated with FH.

Long-term follow-up studies have shown that the main cause of death in FH patients is CHD. With adequate long-term pharmacological treatment, many FH patients could achieve substantial reductions in LDLc, and probably increase their life expectancy by 10–30 years.

Intervention studies in FH

Scientific evidences, coming from large clinical trials, have demonstrated the benefit of LDLc reduction in the prevention of CVD in a broad spectrum of populations, especially in subjects with symptomatic CHD or with absolute high risk. As mentioned earlier, FH patients should be considered high risk subjects due to the prevalence of CHD, and they should benefit as a group at least as much as other high risk groups. According to the presence of major risk factors and/or clinical or subclinical atherosclerosis, three categories of risk for heFH are suggested (Table 2): (1) low 10-year risk, with no major risk factors; (2) moderate 10-year risk, with one major risk factor; and (3) high 10-year risk: (a) with ≥2 major risk factors, (b) subclinical atherosclerosis, or (c) clinical CVD.

In the last 15 years, different studies have used well-established surrogates of CVD to study the effects of aggressive LDLc reduction in FH. These studies demonstrate...
that coronary lesions measured by coronary angiography in SCOR,28 LARS,29 L-CAPS,30 LAARS and FHRS,31,32 or by intracoronary ultrasonography in LACMART,33 aortic lesions evaluated by transesophageal echocardiography,34 carotid intima-media thickness measured by quantitative B-mode ultrasound in ASAP,35 endothelial dysfunction measured by flow mediated dilatation and E-selectin;36 myocardial ischemia detected by exercise test in LAARS,31 and myocardial perfusion abnormalities assessed by digital angiography in LAARS;37 all improve with aggressive LDLc reduction obtained with LDL apheresis and/or lipid lowering drugs.

Consistent with these findings, the use of lipid lowering drugs, especially methylglutaryl coenzyme A (HMGCoA) reductase inhibitors, has been shown to be associated with improved cardiovascular prognosis without any change in noncardiovascular mortality in FH subjects on the Simon Broome Register in the United Kingdom.18

The LDL receptor
The LDLr is synthesized as a 120 KDa precursor protein. The glycosylated mature receptor reaches the cell surface and is directed towards clathrin-coated pits where it binds to Apo B-enriched and apolipoprotein E (Apo E)-enriched lipoproteins via its extracellular domain (Figure 1).38 The complex is endocytosed and migrates to the endosomes. Upon acidification of the endosomal pH, the LDL particle is released and later degraded in lysosomes. The LDLr returns to the membrane and enters in a new cycle. There is extensive evidence that plasma PCSK9 raises LDLc levels by binding to cell surface LDLr and targeting the receptor to lysosomes for degradation.39,40

The LDLR is mapped to 19p13.1–13.3, spans 45,000 base pairs (bp), and codifies for an ubiquitous transmembrane glycoprotein of 839 amino acids that mediates the transport of LDL into cells via endocytosis.41 It contains 18 exons and 17 introns encoding the six functional domains of the mature

Figure 1 The LDL receptor pathway.
Notes: The low-density lipoprotein receptor (LDLr) is synthesized as a 120 KDa precursor protein and processed in the golgi apparatus (GOLGI) producing the glycosylated mature receptor that is transported to the cell surface and is directed towards clathrin-coated pits through interactions involving LDL particle, enriched with apolipoprotein B (APOB) where it binds to LDL particle. The complex is transported to endosomes where the acidic pH causes a dissociation of the receptor–ligand complex, releasing the LDLr to its recycling so the LDL is degraded in the lysosomal compartment. The proprotein convertase subtilisin/kexin type 9 (PCSK9) and Idol protein participate in a decreasing of receptor recycling and increasing the LDLr degradation.
mutations were associated with this disease.43,45,46

Other two regions, named as FP1 and FP2 and located between −281 to −269, contain important cis-acting elements that have been described as essential for maximal induction of transcription.50 Repeat 2 contains a sterol regulatory element (SRE) that enhances transcription when the intracellular sterol concentration is low through interaction with a transcriptional factor designated as sterol regulatory element binding protein-1.49

Repeats 1 and 3 contain binding sites for Sp1 transcription factor, and contribute to the basal expression of the gene requiring the contribution of the repeat 2 for a strong expression.48 Repeat 2 contains a sterol regulatory element (SRE) that enhances transcription when the intracellular sterol concentration is low through interaction with a transcriptional factor designated as sterol regulatory element binding protein-1.49

The LDLr production is tightly regulated by a sophisticated feedback mechanism that controls the transcription of the LDLR in response to variations in the intracellular sterol concentration and the cellular demand for cholesterol.47 DNA motifs are essential for the transcriptional regulation of the LDLR and are located within 280 bp of the proximal promoter (Figure 3). This region contains all the cis-acting elements for basal expression and sterol regulation and includes three imperfect direct repeats of 16 bp each, repeats 1–3. Repeats 1 and 3 contain binding sites for Sp1 transcription factor, and contribute to the basal expression of the gene requiring the contribution of the repeat 2 for a strong expression.48

Repeat 2 contains a sterol regulatory element (SRE) that enhances transcription when the intracellular sterol concentration is low through interaction with a transcriptional factor designated as sterol regulatory element binding protein-1.49 Other two regions, named as FP1 and FP2 and located between −281 to −269, contain important cis-acting elements that have been described as essential for maximal induction of transcription.50 To date, several naturally occurring mutations have been mapped to the transcriptional regulatory elements of the LDLR.51–59

Figure 2 The LDLR gene.
Notes: Exons are shown as dark bars numbered underneath. Arrows indicate exons encoding the different domains of the low-density lipoprotein receptor (LDLr) protein: the signal peptide (exon 1), ligand-binding domain (exons 2–6), EGF precursor-like domain (exons 7–14), the domain named as OLS, O-linked carbohydrate chains (exon 15), transmembrane (TM) domain (exons 16 and 5′ part of exon 17), and the cytoplasmic domain (3′ region of exon 17 and 3′ region of exon 18).
The third domain of the LDLr is a region of 58 amino acids rich in threonine and serine residues that is encoded by exon 15. The function of this domain is unknown, but has been observed that this region serve as attachment sites for O-linked carbohydrate chains.

Class 2 mutations are transport defective alleles which encode for proteins that do not have an adequate three-dimensional structure after being synthesized and kept blocked, complete or partially (2A and 2B, respectively) in transport process between endoplasmic reticulum and golgi apparatus. This defect is caused, normally, by missense mutations or small deletions in LDLr avoiding partial or completely the folding protein. These mutations are located within exons that encode ligand-binding domain and EGFP-like domain.

Class 3 mutations are binding defective alleles which encode for LDLr that are synthesized and transported to cell surface but are not able to bind LDL particles. This is a heterogeneous group, because LDL binding activity goes from 2% to 30% of normal. This defect is due to rearrangements in repeat cysteine residues in binding ligand domain or repeat deletions in EGFP-like domain.

Class 4 mutations are known as internalization-defective alleles which produce proteins that are not able to group into clathrin-coated pits; therefore, LDLr are not internalized (4A: only cytoplasmic domain is affected and 4B: also affected transmembrane domain).

Finally, recycling-defective alleles are also named as class 5 mutations, such as missense mutations in EGFP-like domain, which encode for LDLr that are not able to release LDL particles in endosomes avoiding receptor return to cell surface.

The heterogeneity observed in FH patients in relation to plasma LDLc levels and CHD has been suggested due to differences in the nature of the mutation in the LDLr and several studies have been published in support of this. Even HMGCoA reductase inhibitors may depend on the nature of the mutation in the LDLr gene. Recently, a study carried out by our group, with 436 Spanish FH patients with known LDLr mutations classified as null alleles or defective alleles, has demonstrated that patients with a molecular diagnosis of

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**Notes:**

- Low-density lipoprotein receptor gene (LDLR) 5’ promoter region of 300 bp is represented, numbered the A of the ATG codon as +1. The major regulatory regions are indicated with different colors: FP2 (from −280 to −268); FP1 (−238 to −217); repeat (REP) 1 (−196 to −181); REP 2 (−161 to −146); REP 3 (−145 to −128); and TATA box (from −116 to −110 and −107 to −101). Interaction between cis-element and trans-element at the proximal promoter drives high levels transcription when sterol level becomes deficient. The sterol regulatory element (SRE) binding protein transcription factor interacts with the SRE-1 of REP 2, whereas SP1 transcription factors interact with REP 1 and REP 3 to promote high levels of LDLr gene transcription in response to low intracellular sterol concentrations. SP1 also involved with constitutive, basal-level expression of the LDLr gene. The TATA boxes recruit and direct the assembly of general transcription factors at the promoter.

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**Figure 3** The LDLr promoter regulation.

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<td>FP2</td>
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**LDLR PROMOTER BOX**

- FP1 (−238 to −217)
- REP 1 (−196 to −181)
- REP 2 (−161 to −146)
- REP 3 (−145 to −128)
- TATA box (−110 to −101)
FH characterized by null allele mutations of LDLR show a more severe clinical phenotype and worse advanced carotid atherosclerosis than those with receptor-defective mutations, independently of age, gender, lipid, and nonlipid risk factor.76

Other genes associated with FH

Apolipoprotein B
In 1986, Vega and Grundy77 showed that some patients (5 of 15 studied) with hypercholesterolemia have reduced clearance of LDL not because of decreased activity of LDLr but because of a defect in structure or composition of LDL that reduces its affinity for receptors. Innerarity et al78 found that moderate hypercholesterolemia, presented in the five subjects previously studied, could be attributed to a defective receptor binding of a genetically altered Apo B-100 to the LDLr.77,78 The inherited nature of this disease was indicated by the findings of the same defect in proband’s first-degree relatives. These findings resulted in referring this disease as Familial Defective Apo B-100 (FDB).78

The first mutation found as a FDB cause was demonstrated by Soria et al79 who sequenced the two alleles of APOB from patients of three families. They observed the mutation R3500Q.79 Two new mutations were described in 1995 as cause of FDB: R3500W and R3531C.80,81 For the classical mutation, R3500Q, frequency was estimated in 1:500–1:700 in several Caucasian populations in North America and Europe (Table 1).82 On the other hand, R3500W and R3531C have been found in a minor frequency.

Recently, a novel mutation H3543Y in APOB associated with FDB has been described with a high prevalence (4 times R3500Q) in a German population.83 Recent data reveal that compared with FH patients with LDLR mutations, FDB patients have lower LDLc levels by 20%–25% (Table 3),84 respond better to statins and have lower risk of CHD.86 This difference could be due to normal clearance of very low-density lipoprotein remnants through Apo E-mediated uptake in FDB.86

Proprotein convertase subtilisin/kexin type 9 gene
In 1999, Varret et al87 identify a new autosomal dominant hypercholesterolemia (ADH) locus in 1q34.1-p32 chromosome (Tables 1 and 2). PCSK9 was first identified as a member of proprotein convertase family with hepatic, intestine, and kidney expression.88 Mutations in PCSK9 gene (S127R, P216L, and D374Y y N157K) that produce gain of function were associated with a decrease in LDLr number and ADH.89 Initially, it was thought the hypothesis of a PCSK9 role in LDLr degradation in the cell surface.89 Nowadays, as we have described earlier, there are enough evidence to think that PCSK9 participates in LDLr lysosomal degradation (Figure 1).39,40,90 Recently, it has been proposed that PCSK9 may induce internalization and degradation of LDLr by leading receptor to ubiquitination by Idol.91

PCSK9 mutations have been also classified into five classes, including “null alleles”, mutations that affect autocatalytic scission avoiding the protein transport through endoplasmic reticulum or from the endoplasmic reticulum to cell surface, alleles that affects PCSK9 stability and finally mutations that produce gain of function because of gene overexpression.82-94 Some mutations in PCSK9 (Y142X, C679X, and R46L) produce a loss of function and are associated with low LDLc.95,96

About 17%–33% of patients with a clinical diagnosis of monogenic hypercholesterolemia based on Simon Broome Register Group (SBRG) criteria do not harbor any genetic cause in the known loci suggesting a possibility of additional hypercholesterolemia loci (Table 1).9,10

FH diagnosis
Clinical criteria used to identify patients with FH include high plasma levels of total and LDLc (>250 mg/dL or >7 mmol/L), family history of hypercholesterolemia especially in children, deposition of cholesterol in extravascular tissues such as TX or corneal arcus, and personal and family history of premature CVD.1 Heterozygous FH (heFH) patients have LDLc levels approximately twice those of the normal population, ranging from 190 to 400 mg/dL (4.9–10.3 mmol/L). Triglycerides (TG) levels are usually in the normal range. However, some patients with FH have increased TG levels, explained in part by the interaction with other genes (ie, E2/E2 genotype) or environmental factors (ie, alcohol, overweight, and diabetes mellitus).

TX are pathognomonic of FH; however, their identification is not always easy and they are considered insensitive diagnostic markers. A high variability of xanthoma presence in FH patients has been reported.97 Xanthelasmas occur commonly in heterozygotes, but are rare in homozygotes. Xanthelasmas are not specific for FH and can appear in subjects with normal lipid levels.1 TX may appear in patients with cerebrotendinous xanthomatosis and are indistinguishable from those FH. This kind of xanthomas also occur in subjects affected by FDB, dysbetalipoproteinemia, and sitosterolemia (Table 3).1

Variability in the frequency observed in different studies depends in part on the clinical criteria used for FH (some of
them included the presence of xanthomas), as well as the methods used for the identification of xanthomas.\textsuperscript{15}

There are no absolutely predictive clinical criteria for the diagnosis of FH, and arbitrary criteria must be used. Several criteria have been proposed (Table 4) by SBRG,\textsuperscript{18} the USA Make Early Diagnosis to Prevent Early Death (MEDPED) Program,\textsuperscript{98} and the Dutch MEDPED Program.\textsuperscript{99} Our group demonstrated that MEDPED programs resulted in high sensitivities and specificities being more accurate as more complex is the scoring system.\textsuperscript{100} The best approach in most populations is to determine LDLc in all first degree of a FH proband and it is recommended that all second-degree family members are also screened.\textsuperscript{101}

Although clinical diagnosis criteria have been extensively used for FH,\textsuperscript{18} the genetic testing is the preferred method for FH because it provides an unequivocal diagnosis.\textsuperscript{1,10,19} Since 2004, a genetic diagnostic platform for FH called Lipochip\textsuperscript{\textregistered} (Progenika-Biopharma, Derio, Spain) has been developed, which includes a microarray for the detection of common point mutations and small deletions in the \textit{LDLR} and \textit{APOB} genes, the diagnosis of large rearrangements, and a full LDLR coding sequence analysis when the former are negative.\textsuperscript{102} By providing either a positive (presence of \textit{LDLR} or \textit{APOB} mutations) or negative (absence of defects in these genes) diagnosis, this platform has allowed the genetic characterization of 5,000 Spanish patients.\textsuperscript{100,103} Even though the diagnosis of FH based on the detection of a functional mutation on a causative gene is the recommended procedure in most suspicious cases but it cannot be recommended for all cases of hypercholesterolemia because the genetic testing is still complex, expensive, and require specific families for microarray analysis. For those reasons, clinical diagnosis is still very important and in the FH

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Table 3 Common hypercholesterolemia and hypertriglyceridemia

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Abbreviations: CHD, coronary heart disease; LDLr, low-density lipoprotein receptor protein; LPL, lipoprotein lipase; TC, total cholesterol; TG, triglycerides; TX, tendon xanthomas.
FH based on age, TX presence, and LDLc levels have been genetic confirmation in subjects with clinical suspicions of FH. Together, a new set of criteria has been developed to maximize the likelihood of making an accurate diagnosis. These criteria are particularly useful in distinguishing familial combined hyperlipidemia (FCH) from FH patients, when the presence of TX is highly specific of FH. Mutations that are responsible for most FH cases; the most frequent causative mutations are known; or in subjects with known mutations with an uncertain clinical presentation can produce a misclassification, which can be solved by finding mutations that prove the molecular diagnosis. These criteria include: Familial history, Hypercholesterolemia, Family history of hypercholesterolemia, Premature vascular disease, Children < 18 yo with LDLc > 95th percentile, TX presence, Arcus cornealis (< 45 yo), and Physical exam showing premature vascular disease (1–2 points).99

A review of the literature has revealed that LDL apheresis is over 60%, and similar values were observed in Lp(a). LDL apheresis is an invasive and expensive but safe procedure. The inconvenience of this method is that it has to be performed at 1-weekly or 2-weekly intervals.108

A statin is the drug of first choice in the majority of cases. The safety and efficacy of statins as LDLc lowering drugs and their demonstrated performance in preventing CVD morbidity and mortality in primary and secondary prevention trials have been amply demonstrated. In addition, statins can be safely combined with either resins or ezetimibe. Furthermore, the LDLc-lowering effect of these drugs is not modified by the concomitant use of plant sterols/stanols that can be recommended also to these patients.109

Considering that < 100 mg/dL (2.6 mmol/L) is the optimal LDLc concentration defined by ATPIII guidelines,26 it would be necessary to achieve mean reductions between 50% and 75% to reach that goal. Based on published data from both heFH and other high-risk populations, three different LDLc goals can be recommended for heFH (Table 5). An important aspect of FH treatment with many benefits beyond LDLc lowering is a healthy lifestyle, which includes a healthy diet, ideal body weight, no smoking, and moderate physical activity. Although LDLc is the main CVD risk factor in FH patients, other risk factors such as smoking habit or low HDLc concentration are great modifiers of the CVD development.110

### Table 4: Familial hypercholesterolemia diagnostic criteria

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### Notes:
- **Clinical criteria proposed for genetic testing.**100
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  - SBRG, Simon Broom Register Group from United Kingdom;
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### Treatment
The standard of care for patients with homozygous FH has been LDL apheresis.106,107 The LDLc reduction observed with LDL apheresis is over 60%, and similar values were observed in Lp(a). LDL apheresis is an invasive and expensive but safe procedure. The inconvenience of this method is that it has to be performed at 1-weekly or 2-weekly intervals.108

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  - SBRG, Simon Broom Register Group from United Kingdom;
  - MEDPED, Make Early Diagnosis to Prevent Early Death program in the United States;
  - DLCN MEDPED: Dutch Lipid Clinic Network MEDPED group criteria scoring system for the diagnosis of heterozygous FH patients ('Definitive' diagnosis > 7 points, "Probable" 5–7 points).99
Several intervention studies have clearly demonstrated that a healthy diet reduce cardiovascular risk factors independently of classic risk factors (Table 2). Moreover, this kind of diet can increase the LDLc-lowering power of drugs. The beneficial effect is probably mediated by a variety of mechanisms including improved carbohydrate metabolism, lower blood pressure, greater antioxidant protection, and regulating inflammatory and thrombogenic processes.

### Summary

In this manuscript, we have reviewed the recently genetic and molecular mechanisms described as target for hypercholesterolemia and updated FH diagnosis and treatment.

FH has been studied widely since its first description in 1938. Despite this knowledge, new mutations and genes implicated in cholesterol pathway, as PCSK9 or Idol, have been recently associated with hypercholesterolemia. In fact, over 17% of ADH is caused by unknown mechanisms, because of that an exhaustive research in this way has to be done.

Moreover, an accurate FH clinical diagnosis combined with genetic testing allows physicians to discriminate FH from other dyslipemias. The treatment goal in FH for decreasing CHD risk is LDLc levels but not denying the benefits obtained with lifestyle changes that reduce the environmental risk factors.

### Acknowledgments

This work has been partially funded by grants FIS PS09/00665, P106/1238, and PSE 010000-2008-5.

### Disclosure

The authors report no conflicts of interest in this work.

### References


39. De Castro-Orós et al. 2010;3


