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Familial Hypercholesterolemia: Three “under” (Understood, Underdiagnosed, and Undertreated) Disease

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Abstract

Familial hypercholesterolemia (FH) is one of the most prevalent genetic disorders leading to premature atherosclerosis and coronary heart disease. The main cause of FH is a mutation in the LDL-receptor gene that leads to loss of function of these receptors causing high levels of blood cholesterol. The diagnosis of FH is not very easy. Wide screenings are needed to reveal high levels of LDL cholesterol among “healthy” population. If the patient has MI or stroke at an early age, high levels of LDL cholesterol, and tendon xanthomas, the diagnosis of FH becomes much more clear. Genetic testing is a gold standard in the diagnosis of FH. There are several factors, influencing the time course of FH. Smoking males with low levels of HDL cholesterol have an extremely higher risk of death than nonsmoking females with high HDL cholesterol. Management of FH includes low cholesterol diet, statin and ezetimibe treatment, PCSK inhibitors, and LDL apheresis. Early and effective treatment influences much the prognosis in FH patients.

Keywords: prevalence of familial hypercholesterolemia (FH), diagnosis of FH, the time course of FH, treatment of FH

1. Introduction

Familial hypercholesterolemia (FH) is one of the most frequent inherited disorders caused mainly by a mutation of the gene encoding the low density lipoprotein receptor (LDLR). High concentrations of LDL result in uptake of LDL by extracellular matrix, including that of the arterial wall leading to premature atherosclerosis and coronary artery disease (CAD). CAD develops early with symptoms often manifesting in men in the fourth or fifth decade and women about 10 years later. Approximately 5% of all cases of premature myocardial infarction (MI) occur in patients with heterozygous FH [1, 2]. Before the development of statin therapy, at least 50% of FH male patients experienced MI by the age of 60. In homozygotes, symptomatic CAD can occur in childhood, and very few survive past the age of 30.

Brown and Goldstein are indisputably the fathers of FH. In 1972, they attributed the disorder to defective HMG-CoA reductase [3]. But, a year later they recognized that the main cause of the disease was the mutation in the LDLR gene [4]. The extremely rare homozygote with FH has two mutant alleles at the LDLR locus,

leaving a person with an absolute or nearly absolute inability to clear LDL from circulation [1]. Brown and Goldstein initially described homozygous FH (HoFH) as a condition in which an individual inherits a single and same mutation in the LDLR from each parent. Now we recognize this condition as “simple HoFH” [5]. Actually, this is a very rare event. Far more frequently, HoFH is a result of inheritance of two different pathogenic mutations in the same gene that is referred to as a “compound heterozygote.” Another type of HoFH is when an individual inherits a mutation of one gene (e.g., LDLR) from one of the parents and different gene (e.g., *apoB* or *PCSK9*) from another. This type of HoFH is a “double heterozygote.” It is important to know that the term “heterozygote” is used here to describe homozygote patients.

Heterozygotes with FH possess one normal allele, giving them approximately one half of the normal receptor activity. Actually, LDLR also contributes to the clearance of VLDL remnants from the plasma, so a deficiency of LDLR may lead to some accumulation of remnant lipoproteins as well.

Additionally, mutations of other genes such as *apoB*, *PCSK9*, and so on are now recognized to also cause FH [6–8].

The prevalence of heterozygous FH (HeFH) is about 1/200 [9] and HoFH—1/160,000 [10, 11]. Therefore, HeFH is a very frequent disorder, and it is more common than type 1 diabetes mellitus. Unfortunately, the diagnosis of FH is often unrecognized, leaving such individuals and members of their families undertreated and of greater risk of consequences of lifelong LDL-C elevations. Nevertheless, the prevalence of FH may differ greatly in different populations. For example, in French Canadians, South African Afrikaners, Ashkenazi Jews, or Christian Lebanese, which are the so-called founder populations, the prevalence of FH can be as high as 1/67 [12, 13]. So, it is important to “know your audience” and be on the lookout for such individuals in daily clinical practice.

2. Discussion

The diagnosis of FH is simple and complicated at the same time. First of all patients with FH should have a very high LDL (>95% for age/gender matched controls) with typically normal TG and HDL. For patients with HoFH, LDL is >500 mg/dl (13 mmol/l) when untreated and >300 mg/dl (7.7 mmol/l)—on lipid-lowering therapy (LLT) [14–16]. The cut point for HeFH in adult had similarly been >190 mg/dl (5 mmol/l). Recent genotyping studies showed great difference in LDL levels among FH patients. To date, the lowest LDL level in untreated FH patient was 170 mg/dl (4.4 mmol/l) [9]. Still, there is no question that the higher the LDL-C, the more aggressive the vascular disease.

The second thing is that patients should have a family history of premature atherosclerotic cardiovascular disease (ASCVD), very high cholesterol, or both. Premature ASCVD in a patient is often a clue to FH. In fact, 20% of all myocardial infarctions (MI) in people under the age of 45 are a consequence of FH [17, 18].

The third thing is that the expected response to lipid-lowering therapy is often blunted in FH patients, and their LDL levels are falling less robustly than would normally be anticipated. This occurs because standard medications such as statins and ezetimibe are concentrated on LDLR upregulation. As these receptors by definition defective, their upregulation is less effective at internalizing LDL from plasma.

Physical signs of FH depend greatly on type of the mutation, age, gender, and other factors.

This is an example of one of our FH patient, a 26-year-old woman, who had tendon xanthomas at the age of 1. She have been examined in different clinics (mainly, dermatological), but the diagnosis of FH was suspected only at the age

of 10 when concentration of total cholesterol was measured (total cholesterol level = 21 mmol/l) (**Figure 1**).

Unfortunately, LLT (statins, ezetimibe, and LDL-apheresis) has been started in this patient only at the age of 19. She represents positive stress-echo test, and coronary angiography reveals 50% stenosis of the right coronary artery. A 50% stenosis of both common carotid arteries according to an ultrasound was also revealed. At present time, this patient receives 80 mg of atorvastatin, 10 mg of ezetimibe, and LDL-apheresis procedures (each 2 weeks). She also takes part in a randomized placebo-controlled international clinical study on a new PCSK9 inhibitor—Inclisiran.

You can see a pedigree of this patient in **Figure 2**. It is seen that the index patient (marked with red arrow) with very high cholesterol level has two still young

Figure 1.
Corneal arcus (both the eyes) and tendon xanthomas (hands, Achilles tendon, elbow, and knee) in a 26-year-old woman with FH.

Figure 2.
Pedigree of a 26-year-old female (23 at entry).

parents without clinical signs of ASCVD, but having high total cholesterol levels (9.5–12.2 mmol/l). Parents of proband are divorced, and both of them have new families. The father's daughter from the second marriage who is 11 years of age has also high cholesterol level (8.5 mmol/l). It is seen that the grandfather of the proband died at the age of 54 of acute myocardial infarction (MI).

This patient has undoubtedly homozygous FH phenotype due to a very high cholesterol level, premature atherosclerosis, tendon xanthomas, family history of hypercholesterolemia, and premature ASCVD. Nevertheless, it was interesting to perform genetic testing in this family.

This test was performed in Health-In-Code genetic laboratory (Spain) using Next Generation Sequencing (NGS). Patient specimen (blood) was subjected to automated genomic DNA purification (QIAasymphony SP®, Qiagen). Library preparation was carried out using the Agilent SureSelect library preparation kit for Illumina paired-end multiplexed sequencing according to the manufacturer's instructions. Enrichment of regions of interest was performed using a SureSelect probe kit (Agilent) that selectively captures the coding regions and adjacent intronic areas of the selected genes. After cluster generation, captured DNA was sequenced on the Illumina HiSeq 1500 platform. Sequencing data analysis was done using a proprietary bioinformatics pipeline that includes sample demultiplexing as well as all the steps necessary to obtain a report of annotated variants together with their coverage and corresponding quality parameters.

The design of the custom capture library includes the following six genes related to familial hypercholesterolemia: *APOB*, *APOE*, *LDLR*, *LDLRAP1*, *PCSK9*, and *SLCO1B1*.

The genes included in this test have been selected on a clinical basis according to their relation to a particular phenotype and classified on the basis of evidence supporting this association into priority, secondary, and candidate genes.

Probes were designed to adequately cover all coding exons and 10 base pairs (bp) of flanking intronic sequences; therefore, this test is unable to identify genetic variants located in intronic zones far from splice sites or UTR regions.

Analysis of SNVs and INDELs: This test can identify single-nucleotide variants (SNVs) and insertions/deletions (INDELs) of up to 20 bp. Genetic variants are reported following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org).

Genetic variants that are selected because of their potential association with the patient's phenotype or constitute relevant incidental findings are reported in the main table of the report on the first page. Please note that a variant's pathogenicity may be subject to change as new scientific evidence appears.

Confirmation studies: Variants included in the main table meeting the conditions below are confirmed by orthogonal testing:

- point variants (SNVs) and insertions, deletions, and/or INDELs of ≤ 4 bp that meet at least one of the following criteria: called by only one variant caller, suboptimal quality (QUAL < 100), depth of coverage $< 30\times$, variants in low-mappability, or multiple alignment regions and
- insertions, deletions, and/or INDELs of > 4 bp.

Similarly, low-coverage regions in priority genes that may be of clinical interest are resequenced by the Sanger method.

Analysis of CNVs: Health-In-Code has developed an alternative bioinformatics pipeline that is also able to identify gross insertions/deletions affecting one or more exons of a gene/s included in the panel (CNVs: copy number variations). This complementary analysis is possible when bioinformatics data are adequate (evaluable CNVs) and may not be available in all studies (nonevaluable CNVs).

CNV confirmation studies: Variants identified using this technique will be confirmed by an adequate alternative method.

Analytical specifications of the test: Both analytical sensitivity and specificity of this test are greater than 99% for single-nucleotide variants (SNVs) and insertions/deletions (INDELs) of ≤ 20 bp.

Average coverage values of the tested gene/s and other quality parameters specific to this patient's study are detailed in each study report.

Technical limitations that can be in any study report: Despite the high sensitivity and specificity of this test, some genotyping errors may occur in specific situations:

- contamination of samples before they arrive at our laboratory;
- mosaic variants;
- monosomies and trisomies;
- genetic paternity problems;
- genetic variants producing allelic drop-outs;
- studies performed on paraffin-embedded tissues;
- presence of pseudogenes (homologous regions);
- incorrect identification of variants in homopolymer or high GC-content zones; and
- errors in the reference sequence

This study is usually not able to identify the phase (same/different alleles) of more than one variant affecting the same gene. This limitation should be considered in cases of recessive disorders, which occur only when both alleles are mutated.

Unequivocal traceability: Health-In-Code developed in-house software NextLIMS that efficiently identifies and tracks samples in the laboratory and allows to unequivocally trace the steps a sample has already gone through.

As you can see in **Figure 3**, two different mutations in the LDLR gene were revealed. First mutation (Val806Glyfs*11) has been previously described and was also found in the mother of proband. Second mutation (Asp569Val) was a new one

RESULT: POSITIVE

Two genetic variants associated or very likely associated with familial hypercholesterolemia have been identified in the LDLR gene. Therefore, in the case that each variant affects a different copy of the gene (a condition called compound heterozygosis), the expected phenotype is clinical homozygous familial hypercholesterolemia (HoHF). We suggest including both of them in the familiar screening to identify other likely to be affected family members. The identification of either variant can be used as a diagnostic criterion for FH in the case that Dutch Lipid Clinic Network or Simon Broome diagnostic criteria are used for evaluation.

Gene	Variant	Result	Pathogenicity	Population frequency	Number of references
LDLR	NP_000518.1:p.Val806Glyfs*11 NM_000527.4:c.2416_2417insG NC_000019.9:g.11240215_11240216insG	Heterozygosis	Pathogenic or disease-causing (+++)	Rare variant (found in <1% of controls)	20
	NP_000518.1:p.Asp569Val NM_000527.4:c.1706A>T NC_000019.9:g.11227535A>T	Heterozygosis	Very likely to be pathogenic or disease-causing (++)	Variant of unknown frequency	0

Other genetic variants possibly not related to the disease have been identified (see Appendix: Other identified variants).

Clinical interpretation

The mutation Val806Glyfs*11 has been previously described in association with FH. This mutation affects the protein synthesis and is also called “null allele,” or class 1 mutation. This kind of variants are associated with a more severe phenotype and with a poorer response to lipid-lowering drugs compared with other kind of mutations. The mutation Asp569Val has not been previously published, but neither has it been reported in individuals of the general population. It affects a very important region of the LDLR gene where a number of mutations have been clearly associated with FH.

Technical aspects of the study

This sample has been studied by a massive parallel sequencing method using a library that included 6 genes related to familial hypercholesterolemia. Both sensitivity and specificity are above 99% for SNVs and small INDELs (≤20 bp).

Figure 3. Results of genetic testing in a 26-year-old female, performed in Health-In-Code genetic laboratory (Spain).

(never described in the literature previously). The same mutation was found in a father’s daughter from the second marriage. Therefore, in case that each variant affects a different copy of the gene (we call this condition as compound heterozygote), the expected phenotype is homozygous familial hypercholesterolemia.

This clinical case shows difficulties in the diagnosis of FH despite of the presence of obvious facts that actually led to the late onset of LLT and marked atherosclerotic lesions of coronary and carotid arteries in a young patient.

Another patient is a female, 42 years of age with high total cholesterol level (11–12 mmol/l) known for 10 years with no signs of ASCVD. Stress test is negative, intima-media thickness of carotid arteries is 0.8 mm, and no tendon xanthomas or corneal arcus.

It is seen that the father of the proband died at the age of 56 of MI, her aunt at the age of 69 has high cholesterol and angina pectoris, and her cousin at the age of 45 has high cholesterol and underwent CABG (Figures 4 and 5).

This clinical case is an example of mutation of *apoB* gene that also leads to hypercholesterolemia. Familial ligand defective apolipoprotein B (FDB) was first described in 1986 by Vega and Grundy [19]. In lipoprotein kinetic studies, it was observed that LDL from some donors was cleared more slowly from circulation in individuals with normal LDL receptor function. Genomic DNA analysis revealed a point mutation in Apo B: CGG-to-CAG mutation at the codon for amino acid 3500 resulting in an arginine to glutamine substitution. The prevalence of this disorder is unknown but is estimated to be 5–10% that seen in FH. Hypercholesterolemia in FDB is usually less severe than in FH. Patients with FDB do respond to statin drug therapy, probably reflecting increased removal of Apo E-containing remnant particles through upregulated hepatic LDL receptors. Our patient was treated with rosuvastatin 40 mg/day + ezetimibe 10 mg/day. Her total cholesterol is 4.9 mmol/l; LDL cholesterol is 2.3 mmol/l; HDL cholesterol is 1.8 mmol/l; and TG is 1.6 mmol/l.

Figure 4.
Pedigree of a 42-year-old woman with high cholesterol level.

Figure 5.
Results of genetic testing in a 42-year-old woman with high cholesterol level.

Physical signs of FH can occur but not needed for the diagnosis. Extensor tendon xanthomas, typically affecting the Achilles or the hands, could appear at the age of 20 and may be present in 70% of older patients. Because xanthomas are subtle, careful examination of the dorsal hand tendons and Achilles tendon is required for their detection. Thus, it is important to always examine the Achilles tendon when performing physical exam. Xanthelasma (cutaneous xanthomas on the palpebra) is common in patients with FH after the age of 30; however, it is not specific for FH. With regard to corneal arcus, it does not have to be circumferential. In fact, it often starts in the superior and inferior aspects of the cornea where the blood supply is greatest. Also, a corneal arcus in someone under 45 years of age is pathognomic for FH [20]. It is important to recognize that because of the prevalent use of lipid-lowering therapy xanthomas, and other clinical signs of FH are uncommon findings nowadays.

Although most FH specialists diagnose FH on clinical grounds, three systems are also available: Make Early Diagnosis to Prevent Early Death (MEDPED), the Dutch Lipid Clinic Network (DLCN), and Simon Broom. Each has its own pros and cons, and none is essential to make the diagnosis. Nevertheless, it is useful to utilize them in clinical practice.

As it is clear from **Table 1**, if a patient has LDL-C level ≥ 8.5 mmol/l and premature coronary artery or cerebral artery disease, he/she already has more than eight points that means definite FH. It is important to know that if a person has positive results of genetic testing, he/she has only eight points and it is not enough to make a diagnose of definite FH.

Once the diagnosis of FH has been made, he/she is dubbed the proband or the index case. As FH is an autosomal dominant disorder, and early diagnosis and treatment dramatically reduce the risk of future ASCVD events, it is important for physicians to identify other members of the family. Screening relatives of the proband is called “cascade screening.”

There are two methods of cascade screening, active and passive. Passive screening employs the index case as the messenger to inform the other family members and recommend further testing. Passive screening is usually not very successful. In contradistinction, active cascade screening—a system in which clinicians rather than patients seek out affected family members—is extraordinarily effective.

	Points
Criteria	
Family history	
First-degree relative with known premature* coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C ≥ 330 mg/dL (≥ 8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>apo B</i> or <i>PCSK9</i> gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6 – 8
Possible Familial Hypercholesterolemia	3 – 5
Unlikely Familial Hypercholesterolemia	<3

*Premature = <55 years in men; <60 years in women.
LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; apoB, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 1.
Dutch Lipid Clinic Network Score for FH [21–23].

It was successfully performed in the Netherlands. This active cascade screening system sets the bar for the world, identifying nearly 75% of the Netherlands' FH population and adding eight additional FH patients for every single-index case identified [9].

The time course of FH depends on a lot of genetic and environmental factors. Previously, we have identified mutations of the LDLR gene in 45 families in St. Petersburg [24]. Our aim was to follow the development of dyslipidemia in children of probands with verified mutations of the LDLR gene as these children were growing up, to compare severity of atherosclerotic complications in patients with different LDLR gene mutations, and to compare atherosclerotic disease progress in males and females with FH. We were following probands with FH and their available relatives with LDLR gene mutations, including children, during 10 years. In all patients, total blood plasma cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were monitored, and clinical manifestations of ASCVD were documented.

As it is seen in **Table 2**, there were 26 original mutations of the LDLR gene, and 7 were not original but revealed in different families. Due to high heterogeneity of FH-causing mutation in St. Petersburg, we failed to establish interrelations between type of LDLR gene mutation and severity of atherosclerosis manifestation. As a rule, complications of coronary artery disease (CAD) were found less commonly and tend to be less severe in females rather than in males (**Table 3**).

As you can see in **Table 3**, CAD was revealed in three-fourth of males with LDLR gene mutations and only in half of females. Thus, mean age of healthy persons was 34 ± 3.1 years in males and 41 ± 2.6 years in females. Mean age of patients with CAD clinical manifestations was 45 ± 1.9 and 53 ± 2.9 , respectively. Otherwise, males suffer from atherosclerotic complications more frequently and much earlier than females. Apparently, females are defended of ASCVD anyway in cases of FH. Some authors explain this by protective function of estrogens. Not infrequently, this protection still remains in the menopause period. To our mind, this protective effect could be explained by the level of HDL cholesterol. Thus, we followed up a mother and her two daughters with genetically verified diagnosis of FH. Mother and her younger daughter had severe clinical manifestations of CAD, while older daughter had no clinical manifestations of ASCVD and did not take LLT. LDL levels did not differ

Number of probands with LDLR gene mutations	Number of members of families of probands with LDLR gene mutations	Number of original mutations (revealed only in one family)	Number of families with the same type of LDLR gene mutation in two families	Number of families with the same (only one) mutation (G197del)
45	78	26	6 (12 probands, 6 variants of the LDLR gene mutation)	7 probands with 1 variant of mutation

Table 2.
Number of probands and their relatives with LDLR gene mutations.

Gender	Number of patients	Patients with CAD	Mean age of patients with CAD	Patients without CAD	Mean age of patients without CAD
Male	26	20	45 ± 1.9	6	34 ± 3.1
Female	38	19	53 ± 2.9	19	41 ± 2.6

Table 3.
Number of males and females with the LDLR gene mutations, their age, and the presence of coronary heart disease.

Groups of patients (see text)	Number of patients	LDL/HDL
Group 1	15	10.4 ± 0.78
Group 2	8	7.7 ± 0.89
Group 3	10	5.2 ± 0.45

Difference between Groups 1 and 2 and Groups 2 and 3 is statistically significant (p<0.05).

Table 4.
LDL/HDL ratio in the three groups of patients with LDLR gene mutations.

greatly in the members of this family (326 mg/dl—mother, 322 mg/dl—younger daughter (24-year-old), 277 mg/dl—older daughter (30-year-old)), while HDL-C was 44 mg/dl and 49 mg/dl in the first two woman and 65 mg/dl—in the third.

We divided patients with LDLR gene mutations into three groups (**Table 4**). 1 with progressive CAD, 2 with stable disease, 3 without clinical manifestation of CAD and measured LDL/HDL ratio.

It is seen that high level of HDL is the only one proved lipid factor preventing atherosclerosis development in patients with genetically verified familial hypercholesterolemia.

3. Conclusion

Management of FH must always begin with therapeutic lifestyle changes (TLC); therefore, TLC is the foundation of all ASCVD prevention [25]. A healthful diet limited in saturated fats and simple sugars, daily aerobic exercise, avoidance of tobacco and alcohol, maintenance of an optimal blood pressure and weight, and reduction of stress are all important. The mainstay of therapy in FH is to lower the LDL-C as much and as soon as possible. One must remember that all patients with FH are considered high cardiovascular risk, and for this reason, formal risk stratification with Framingham or Score systems is never advised when guiding treatment. According to the European Guidelines, the goal of lipid-lowering therapy is <1.4 mmol/l if the patient has CAD, diabetes mellitus or >50% stenosis of carotid or peripheral arteries, and <1.8 mmol/l—without clinical manifestations of ASCVD [26]. It is recommended in adult patients to use high intensive statin therapy (atorvastatin 80 mg or rosuvastatin 40 mg). In cases where the goal is not achieved on statin therapy, it is recommended to add ezetimibe 10 mg. If the goal is not achieved, you should think about adding PCSK9 inhibitors (alirocumab 75/150 mg each 2 weeks, evolocumab 140 mg each 2 weeks or 420 mg once a month).

Drug therapy in children with FH should be started at the age of 8–10 years. The LDL-C goal is <4.0 mmol/l (8–10 years) and <3.5 mmol/l (10 years and more). Treatment should be started with statins. In case of homozygous FH when LDL-C levels are more than 13 mmol/l and ASCVD appears in childhood, the treatment should be started from a maximal doses of statins with the addition of ezetimibe and evolocumab (in children >12 years). In severe cases of HoFH, extracorporeal methods of treatment (LDL apheresis, HELP, etc.) are recommended.

Despite of the fact that pathogenesis and clinical manifestations of FH are well understood, this disease still remains underdiagnosed and undertreated. All FH patients are to be considered high risk. Some, however, are unfortunately even higher risk than rest. It depends on age, gender, or some biochemical and environmental risk and antirisk factors. Early diagnosis and management of FH can significantly improve lifespan and quality of life in these patients.

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