



Review article

Toward a new clinical classification of patients with familial hypercholesterolemia: One perspective from Spain



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HIGHLIGHTS

- There is a mismatch in clinical and genetic familial hypercholesterolemia diagnosis.
- Familial hypercholesterolemia is a syndrome including several entities.
- Monogenic and polygenic familial hypercholesterolemia determines high vascular risk.
- Familial hypercholesterolemia diagnosis has implications to access new therapies.
- A new classification including all FH genotypes and phenotypes is warranted.

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ABSTRACT

The introduction of singular therapies, such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), to lower high cholesterol levels requires better classification of patients eligible for intensive lipid lowering therapy. According to the European Medicines Administration, PCSK9i are recommended in primary prevention in familial hypercholesterolemia (FH) patients. Therefore, an FH diagnosis is not simply an academic issue, because it has many clinical implications. The bases of a diagnosis of FH are not entirely clear. The availability of genetic testing, including large genome-wide association analyses and whole genome studies, has shown that some patients with a clinical diagnosis of definite FH have no mutations in the genes associated with the disease. This fact does not exclude the very high cardiovascular risk of these patients, and an early and intensive lipid lowering therapy is recommended in all FH patients. Because an FH diagnosis is a cornerstone for decisions about therapies, a precise definition of FH is urgently required.

This is an expert consensus document from the Spanish Atherosclerosis Society.

We propose the following classification: familial hypercholesterolemia syndrome integrated by (1) heterozygous familial hypercholesterolemia: patients with clinically definite FH and a functional mutation in one allele of the *LDLR*, *ApoB:100*, and *PCSK9* genes; (2) homozygous familial hypercholesterolemia: mutations affect both alleles; (3) polygenic familial hypercholesterolemia: patients with clinically definite FH but no mutations associated with FH are found (to be distinguished from non-familial, multifactorial hypercholesterolemia); (4) familial hypercholesterolemia combined with hypertriglyceridemia: a subgroup of familial combined hyperlipidaemia patients fulfilling clinically definite FH with associated hypertriglyceridemia.

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1. Introduction

The bases for the diagnosis of familial hypercholesterolemia (FH) are not entirely clear. Until a few years ago, only clinical criteria were used, and this continues to be the only diagnostic method in many places. By definition, FH is a genetic condition; however, in many patients fulfilling the clinical criteria for definite FH, a causative genetic alteration cannot be found; on the other hand, patients with genetic mutations in the FH associated genes lack the expected phenotype [1]. This mismatch can range from 10% to 50% of all FH patients. Data from whole genome analyses suggest that any undiscovered gene could explain the disease in these patients. A more plausible explanation is that these families have a polygenic form of FH [2]. Furthermore, the clinical phenotype is highly variable among FH patients, even in those sharing the same pathogenic mutation, which suggests that FH is a complex syndrome rather than a single disease. The association between FH and cardiovascular risk was established before the genetic era and has been built on the basis of clinical diagnosis. Therefore, according to the latest clinical guidelines, in all FH patients, early and intensive lipid lowering therapy (LLT) should be considered [3,4]. This concept is essential considering the eruption of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) in the treatment plans. According to the European Medicines Administration, PCSK9i should be prescribed for patients with a previous major cardiovascular event and for FH patients, even as primary prevention, if they continue to have uncontrolled LDL levels after optimal LLT. Due to treatment costs, guidelines for defining the patients eligible for PCSK9i are strict and an FH diagnosis is a cornerstone for deciding on therapy [5,6].

Therefore, the FH diagnosis is not simply an academic issue but has many clinical implications. Because a precise definition of FH is urgently required, we propose the following classification system.

2. Familial hypercholesterolemia syndrome

The term “syndrome” (from the Greek “running together”) is applied to a group of signs and symptoms occurring together to characterize a particular condition or phenotype. This condition can have different aetiologies, or its origin can be poorly understood. Considering that FH is a clinical presentation characterized by very high LDL cholesterol levels with explicit familial aggregation and transmission, high cardiovascular risk and different causes, the use of the term FH syndrome is warranted. The FH syndrome includes genetically and clinically defined FH according the following entities (Table 1):

2.1. Heterozygous familial hypercholesterolemia (HFH)

HFH is the monogenic disease characterized by high LDL concentrations from birth, autosomal co-dominant heritage, presence of corneal arcus or tendon xanthomas in some patients, family history of premature cardiovascular disease and a single functional mutation in one allele of any of the following genes: *LDLR*, *APOB*, or *PCSK9*^{4,6}.

Occasionally, rare variants in genes such as *APOE*, signal transducing adaptor protein family 1 (*STAP1*) and patatin-like phospholipase-domain-containing family (*PNPLA5*) can also cause a heterozygous FH phenotype [7].

The diagnostic requirement is the presence of a functional mutation in one of the abovementioned genes.

2.2. Homozygous familial hypercholesterolemia (HoFH)

HoFH is the severe form of the previous disease [8]. Cardiovascular complications, including aortic valve and coronary heart disease, appear before the age of twenty years. This condition can be classified as:

- Real homozygous: when the same mutation affects both alleles of

Table 1 Classification of familial hypercholesterolemia syndrome.

Clinical entity	Usual lipoprotein phenotype ^a	Genetic alteration	Heritage pattern	Dyslipidemia family history	CVD family history	Cholesterol deposits	CVD disease risk
Heterozygous familial hypercholesterolemia	LDL > 5 mmol/L	Functional mutation in the <i>LDLR</i> , <i>ApoB</i> or <i>PCSK9</i> genes ^b	Autosomal dominant	1 parent affected. Several first degree relatives are usually affected	Frequently CVD in first degree relatives	Frequent (about 50% of affected)	High
Homozygous familial hypercholesterolemia	LDL > 12 mmol/L	Homozygous functional mutation in <i>LDLR</i> , <i>ApoB</i> , <i>PCSK9</i> , <i>ARH</i> genes. Compound heterozygous or combined heterozygous (see text)	Autosomal dominant (autosomal recessive in <i>ARH</i>)	Both parents affected. Other first-degree relatives with HeFH. (ARH: No affected parents or relatives)	Frequently, CVD in parents and other first-degree relatives. ARH relatives: general population risk	Almost constant	Extremely high
Polygenic familial hypercholesterolemia	LDL > 5 mmol/L	High hypercholesterolemia GS	Polygenic, but suggesting Mendelian autosomal dominant heritage pattern	1 parent affected. Several first degree relatives are usually affected	Frequently CVD in first degree relatives	Can be observed (about 15% of affected)	High
Familial hypercholesterolemia combined with hypertriglyceridemia	LDL > 5 mmol/L + TG > 3.5 mmol/L	High hypercholesterolemia GS plus high hypertriglyceridemia GS	Polygenic, but suggesting Mendelian autosomal dominant heritage pattern	Several members of the family affected, including parents with hypercholesterolemia or hypertriglyceridemia. Variable phenotype	Frequently CVD in first degree relatives	Can be observed	High

ARH: autosomal recessive hypercholesterolemia; CVD: cardiovascular disease; HDLc: high density lipoprotein cholesterol; LDL: low density lipoprotein; PCSK9: proprotein convertase subtilisin/kexin type 9; TG: triglycerides; GS: genetic score.

^a Orientate values.

^b Other minority genes have also been involved.

one of the major FH-related genes (*LDLR*, *ApoB*, or *PCSK9*).

- Compound heterozygous: when different mutations affect two alleles of one of the major FH-associated genes.
- Combined heterozygous: when different mutations affect two different FH-related genes.
- Autosomal recessive hypercholesterolemia (ARH). This condition presents with the same HoFH phenotype; however, it is transmitted as an autosomal-recessive disease. Therefore, the parents of the affected child have normal LDL concentrations. These patients have both LDLR adaptor protein 1 (*LDLRAP1*) gene alleles affected. The severity of the illness falls between the other HoFH forms, and a better response to statins has been observed [9].

2.3. Polygenic familial hypercholesterolemia (PFH)

PFH includes patients with a definite FH diagnosis (according to Simon Broom (SB), Dutch Lipid Clinics Network (DLCN), World Health Organization (WHO) indexes or others), but monogenic alterations associated with FH are not found. PFH accounts for 10–50% of all clinically definite FH patients depending on the clinical setting [1,10].

These families usually have several members with very high cholesterol levels (LDL above 5 mmol/L) suggesting vertical transmission, some with tendon xanthomas or corneal arcus, and a high burden of cardiovascular disease, thereby fulfilling the FH clinical criteria.

An extensive search for alternative candidate genes to explain this lipid disorder, including whole exome sequencing, yielded no new mutations [11].

Several lines of evidence show that these patients have a polygenic form of hypercholesterolemia since they carry a high number of gene variants associated with high LDL levels [2,12] and/or major genetic determinants of high cholesterol levels such as apo E4.

These patients have a high cardiovascular risk because they have a genetically driven high LDL-C concentration, sometimes observed from a young age. Although the risk is probably lower than that of genetically proven heterozygous FH, according to recent data [13], these patients must be managed clinically and treated as FH according to international guidelines [1,3].

The diagnostic requirement is a definite FH classification according any of the abovementioned clinical indexes (the yield of either DLCN or SB indexes is similar [10]), despite negative genetic testing. If available, an LDL cholesterol genetic risk score can help to support the diagnosis [12], although it is not formally recommended.

The term PFH must be differentiated from Polygenic Hypercholesterolemia. The latter has been broadly used to define patients with high cholesterol, usually with lower concentrations than those of FH patients, and generally without family aggregation. Polygenic Hypercholesterolemia is by far the most frequent cause of hypercholesterolemia; however, its pathophysiology is not fully understood. Both increased apoB-LDL production and reduced fractional catabolic rates have been observed [14]. Polygenic Hypercholesterolemia is considered to be the product of a polygenic and environment interaction. Therefore, we suggest using the term “Multifactorial Hypercholesterolemia” instead of “polygenic” to avoid confusion.

2.4. Familial hypercholesterolemia combined with hypertriglyceridemia (FHcTG)

Familial combined hyperlipidaemia (FCH) was described by Goldstein et al. as a highly prevalent inherited metabolic disorder characterized by both high cholesterol and triglycerides with a variable phenotype [15]. The presence of tendon xanthomas or corneal arcus has also been reported. These patients have a very high cardiovascular risk, and the genetic transmission again suggests an autosomal-dominant pattern. However, after decades of an intense search for the causal gene or genes, none has been detected to date, and FCH is currently considered a polygenic disease.

These families carry a collection of genes causing high cholesterol and another set determining high triglycerides [16,17]. Since the hypercholesterolemic component in some families cannot be distinguished from that of the abovementioned polygenic FH, these families should also be considered as having the FH syndrome. According to the Spanish Arteriosclerosis Society registry, approximately 10–20% of clinically definite FH patients have high triglycerides. In fact, approximately 1 in 5 patients classified as FCH have *LDLR* mutations [18]. We propose the term FHcTG to designate a subgroup of FCH patients fulfilling FH criteria; therefore, including patients with very high cholesterol levels (LDL above 5 mmol/L) despite concomitant high triglyceride levels.

The diagnostic requirement for this category is to fulfil the diagnostic criteria for definite clinical FH according to the SB, DLCN, and WHO indexes or others, despite high triglycerides and negative genetic testing.

3. Conclusions

The intense and differential management of FH, including the introduction of singular therapies such as PCSK9i to lower high cholesterol levels, demands a better definition of this concept. This definition should not exclude patients with severe hypercholesterolemia and familial aggregation because we are not able, at this time, to diagnose the cause of their metabolic defect. On the other hand, the availability of genetic testing, including large genome-wide association analyses and whole genome studies, has shown that about one in three patients with a clinical diagnosis of definite FH have no mutations in the genes associated with the disease. This fact does not exclude the very high cardiovascular risk of these FH patients with negative genetic tests. Data from extensive genetic studies suggest that there are no hidden genes accounting for this condition. These affected families probably carry a collection of gene variants giving rise to high cholesterol levels. A different aetiology is no reason to exclude these patients from effective therapies aimed at genetically caused hypercholesterolemia.

On the other hand, classical FCH is currently considered a polygenic disease, with the concurrence of a set of gene variants associated with hypercholesterolemia and another associated with hypertriglyceridemia. There is no reason to exclude FCH patients when hypercholesterolemia is severe and constant from highly efficient therapies simply because they, or their family members, also have high triglycerides.

The term Familial Hypercholesterolemia Syndrome includes all these different conditions characterized by high cholesterol levels, family aggregation, a genetic cause, and increased cardiovascular risk.

We are not challenging the FH definition, screening pathways nor clinical management recommendations. Our aim is to help clinicians to properly classify FH patients by providing a clear-cut definition of various clinical conditions.

The novelty of this classification will probably open up the debate and the exchanges of opinion that we would like to result in a better definition of the relevant individual categories within the framework of familial hypercholesterolemia.

We consider that an official statement on the definition of FH will have an important impact on both physicians and health authorities when designing ASCVD prevention strategies.

Conflicts of interest

Dr. Civeira reports personal fees from Amgen, Sanofi, FERRER, Merck, during the conduct of the study. Dr. Guijarro reports personal fees from MSD, Amgen, Sanofi, FERRER (advisory panels and lectures). Dr. Lopez-Miranda reports personal fees from Amgen, Sanofi, FERRER, Laboratorios Dr. Esteve, Boehringer Ingelheim-Lilly, outside the submitted work (advisory panel and lectures). Dr. Masana reports personal fees from Amgen, Sanofi, MSD, outside the submitted work. Dr.

Mostaza reports personal fees from Sanofi, Amgen, outside the submitted work. Dr. Pinto reports personal fees from Amgen, Sanofi, FERRER, RUBIO, ESTEVE, MYLAN, outside the submitted work. The other authors have nothing to disclose.

Author contributions

LM has written the manuscript. All authors have read, reviewed and equally contributed to the design and content of the paper.

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