REVISTA DE INVESTIGACIÓN CLÍNICA

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Rev Invest Clin. 2018;70:224-36 BRIEF REVIEW

Familial Combined Hyperlipidemia: Current Knowledge, Perspectives, and Controversies

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ABSTRACT

Familial combined hyperlipidemia (FCHL) is the most prevalent primary dyslipidemia; however, it frequently remains undiagnosed and its precise definition is a subject of controversy. FCHL is characterized by fluctuations in serum lipid concentrations and may present as mixed hyperlipidemia, isolated hypercholesterolemia, hypertriglyceridemia, or as a normal serum lipid profile in combination with abnormally elevated levels of apolipoprotein B. FCHL is an oligogenic primary lipid disorder, which can occur due to the interaction of several contributing variants and mutations along with environmental triggers. Controversies surrounding the relevance of identifying FCHL as a cause of isolated hypertriglyceridemia and a differential diagnosis of familial hypertriglyceridemia are offset by the description of associations with *USF1* and other genetic traits that are unique for FCHL and that are shared with other conditions with similar pathophysiological mechanisms. Patients with FCHL are at an increased risk of cardiovascular disease and mortality and have a high frequency of comorbidity with other metabolic conditions such as type 2 diabetes, non-alcoholic fatty liver disease, steatohepatitis, and the metabolic syndrome. Management usually requires lipid-lowering therapy directed toward reducing cholesterol and triglyceride concentrations along with cardiovascular risk protection. In recent years, the number of research studies on FCHL has been decreasing, mainly due to a lack of recognition of its impact on disease burden and comorbidity and the complexity in identifying probands for studies. This creates areas of opportunity to develop research for FCHL in epidemiology, genetics, pathophysiology, therapeutics, and cardiovascular risk management, which are discussed in depth in this review. (REV INVEST CLIN. 2018;70:224-36)

Key words: Familial combined hyperlipidemia. Genetics. Apolipoprotein B.

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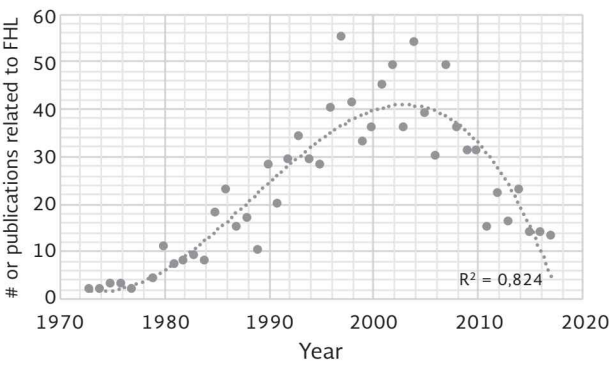
Received for publication: 02-05-2018
Approved for publication: 13-06-2018
doi: 10.24875/RIC.18002575

INTRODUCTION

Familial combined hyperlipidemia (FCHL) is the most prevalent primary dyslipidemia, occurring in up to 1-3% of the general population and in 20-38% of patients with previous history of myocardial infarction (MI)[1]. This disorder was simultaneously described by Goldstein et al.[2], Hazzard et al., and Kwiterovich et al., who independently described it in different cohorts[3]. FCHL is characterized by fluctuations in serum lipid profile and a rather heterogeneous clinical presentation which can be alternatingly identified with mixed hyperlipidemia, isolated hypercholesterolemia, or hypertriglyceridemia in combination with abnormally high levels of apolipoprotein B (apoB)[2,3]. Certain ethnic groups are particularly susceptible to FCHL, as demonstrated by Paramsothy et al. in a multiethnic cohort of 6814 participants in the United States, reporting a prevalence of 4.8% within Hispanics[4,5]. FCHL coexists with other metabolic diseases such as obesity, insulin resistance (IR), type 2 diabetes mellitus (T2D), hypertension, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome (MS)[6]. FCHL cases with metabolic comorbidities have remarkably higher apoB plasma levels compared to cases with a similar severity of IR. In addition, subjects with FCHL have a greater susceptibility to developing T2D and are thus at a higher cardiovascular risk in comparison to matched controls[3,6].

Notably, the number of research studies focused on understanding the epidemiology, genetics, pathophysiology, and treatment of FCHL has been decreasing over the years as demonstrated by the number of related articles cited in PubMed since 2007 (Fig. 1).

Figure 1. Publication rate related to studies focused on familial combined hyperlipidemia in the scientific database PubMed until December 2017.



This could be attributable to the complex nature of the disease, heterogeneous clinical definitions, and inconsistent consensus in its defining traits, which makes comparisons across reports largely unfeasible, complicating precise estimates of FCHL epidemiology and its metabolic burden. In this review, we will focus on the most recent advances in understanding FCHL. We will also evaluate gaps in available knowledge and areas that lack sufficient information and call for further studies to describe fully comorbidity and cardiovascular risk associated to FCHL.

EVOLUTION OF FCHL DIAGNOSTIC CRITERIA

Different diagnostic criteria have been proposed for FCHL over the years[7]. Classically, the phenotype to establish the diagnosis of FCHL comprised either isolated hypercholesterolemia or hypertriglyceridemia or a mixed lipid profile along with the first-degree family history of premature coronary artery disease (CAD), excluding other causes of dyslipidemia[3]. More recent criteria have also included elevated apoB levels as highly suggestive of FCHL (Table 1)[8].

Due to the oligogenic nature of the disease, genetic testing is not yet a possibility[3], but diagnosis can be made based on a fluctuating lipid profile, increased apoB levels, and first-degree family history of mixed lipid disorders and premature cardiovascular disease (Fig. 2)[9-11]. Some limitations on these criteria include the low practicality of apoB measurements in everyday clinical settings in addition to interethnic differences in establishing the 90th percentile in both lipid and apoB measurements, which require population-specific percentiles that might not always be available.

GENETIC CHARACTERIZATION OF FCHL

Initial genetic characterizations of FCHL defined it as a primary lipid disorder with autosomal dominant inheritance[2]; however, recent data suggest that FCHL is an oligogenic entity with variable penetrance[11,12]. Establishing a unified causative genetic trait in FCHL is complex partly due to its clinical variability and the difficulties in comparing FCHL studies with inconsistent diagnostic criteria. Recent findings describe multiple genetic alterations contributing to the observed

Table 1. Changes in diagnostic criteria for FCHL throughout the years.

Year	Study/Author	TG (mmol/l)		CT (mmol/l)	ApoB (g/l)	Family history
1973	Goldstein	> 95th percentile	And	> 95th percentile	–	CAD < 60 years
1983	Brunzell	6.42 ± 1.19	And	2.53 ± 1.17	1.44 ± 0.36	CAD < 60 years
1999	EuroFam/ Pajukanta	> 90th percentile	Or	> 90th percentile	–	Mixed hyperlipidemia
1999	Dutch/Aouizerat	> 6.5	And	> 2.3	> 1.2	Differing hyperlipidemia in relative, CAD age < 60 years
2001	Consensus/ Sniderman	–	–	> 1.5	> 75th percentile	Hyperlipidemia in 1st degree relative
2003	British mapping/ Naoumova	> 95th percentile	And	> 90th percentile	-	Hyperlipidemia in 1st and 2nd degree relatives
2004	Dutch clinical/ Veerkamp	> 6.0	And	> 1.5	> 1.2	Hyperlipidemia in 1st degree relative
2004	Huertas-Vazquez	> 90th percentile	Or	> 90th percentile	> 90th percentile	CAD (MI) < 60 years in proband or 1st degree relative and One 1st degree relative TG or CT > 90th percentile
2004	Aguilar-Salinas	> 150 mg/dL	Or	> 200 mg/dL	> 90th percentile	CAD (MI) < 60 years At least three different family members: one with hypercholesterolemia, one with hypertriglyceridemia, and one with mixed hyperlipidemia
2005	GEM study/ Wyszynski	–	–	> 75th percentile	–	Index case and one relative with relevant profile
2014	Mata	> 200 mg/dL	And/or	< 240 mg/dL (LDL > 160 mg/dL)	–	Two or more family members with hypercholesterolemia, hypertriglyceridemia, or mixed hyperlipidemia

FCHL: familial combined hyperlipidemia, TG: triglycerides, CT: computed tomography, ApoB: apolipoprotein B, CAD: coronary artery disease, MI: myocardial infarction, LDL: low-density lipoprotein
*Adapted and modified from Wierzbicki AS (31).

clinical phenotype[2,3,11]. The fluctuating lipid profile characteristic of FCHL can be attributable to the interaction of cumulative large- and small-effect genetic variants that alter low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) concentrations and contributing environmental factors (Fig. 3). These genetic alterations usually have independent segregation on different chromosomes, which impacts the degree of expression in affected family members, thus leading to heterogeneous clinical presentations even within the same kindred[11].

Consistent susceptibility loci have been reported among individuals with FCHL from different ethnic backgrounds and have been mapped to chromosomes 1q21-23, 11p14.1-q12.1, and 16q22-24.1[13]. An association of FCHL with the region in chromosome 1q21-1q23[1,14] has been consistently reported. This region includes several genes which might contribute to FCHL phenotype, including the upstream transcription factor 1 gene *(USF1)*[1]. *USF1* encodes a transcription factor that regulates nearly 40 genes implicated in lipid and lipoprotein metabolism, as well as immune

Figure 2. Proposed updated diagnostic algorithm for FCHL. TC: total cholesterol; TG: triglycerides; apoB: apolipoprotein B-100; CAD: coronary artery disease, FCHL: familial combined hyperlipidemia.

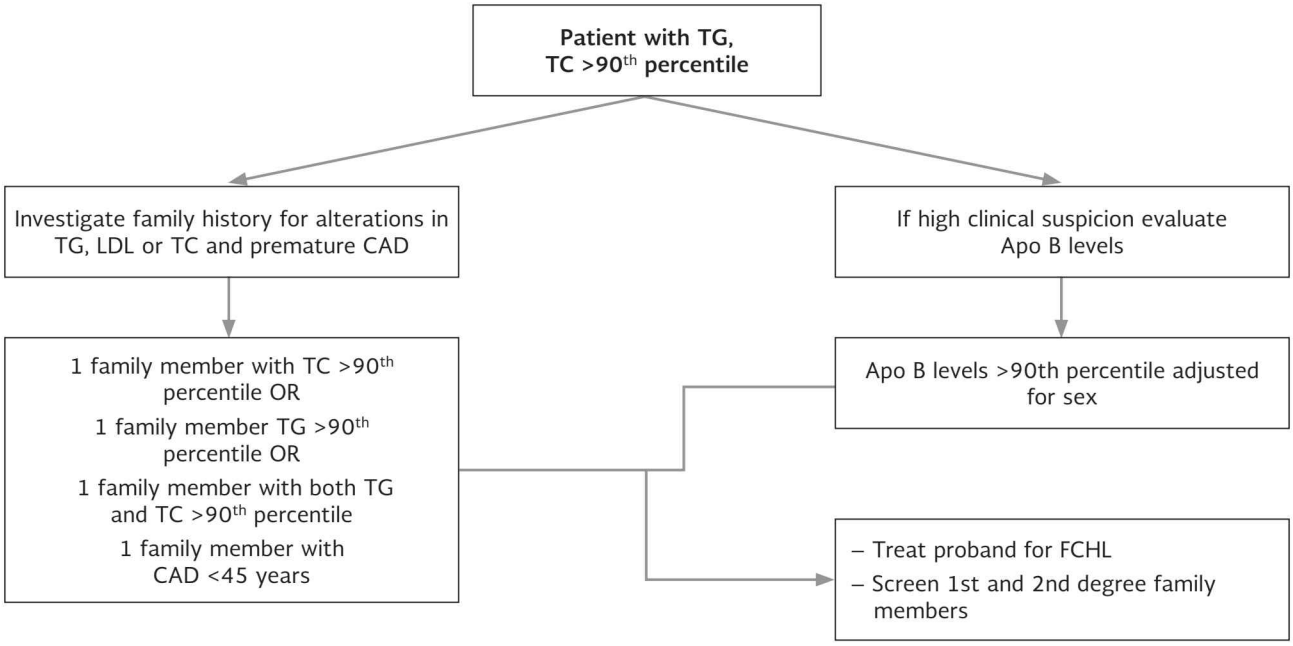
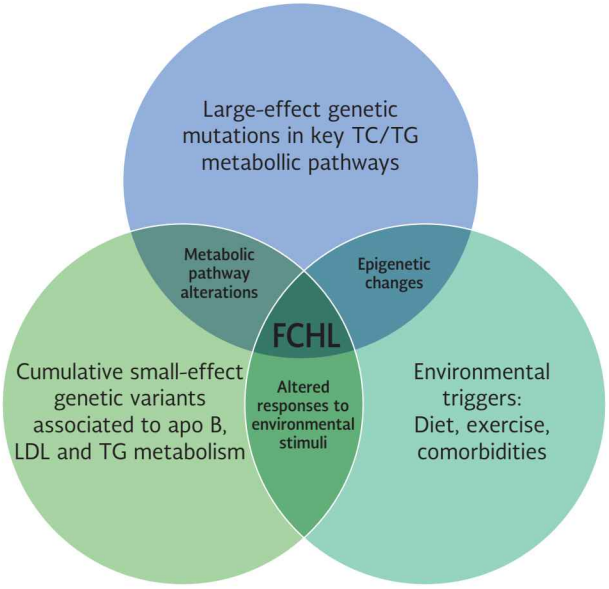


Figure 3. Genetics of familial combined hyperlipidemia (FCHL): The interplay of large-effect genetic mutations, cumulative small-effect genetic variants, and environmental triggers contribute to developing the FCHL phenotype.



response, and is located 1.5Mb away from *TXNIP,* a gene linked to mixed hyperlipidemia in mice[1,3]. *USF1* encodes for a basic helix-loop-helix leucine zipper transcription factor located in chromosome 1q23.3, which binds to a palindromic E-box sequence. *USF1* was first described by Sawadogo et al. as a key component in adenovirus replication[15] and its role as a regulator of lipid and glucose metabolism was later reported. USF1 has been shown to regulate expression of L-pyruvate kinase, fatty acid synthase, and glucokinase, as well as apoA-V, apoC-III, apoA-II, apoE, hormone-sensitive lipase, and other enzymes involved

in lipid and carbohydrate metabolism[16-19]. Pajukanta et al. characterized *USF1* as the major genetic trait of FCHL which was further demonstrated by Huertas-Vázquez et al. in Mexican population[1,20].

Several single-nucleotide polymorphisms (SNP) have been associated with FCHL. A haplotype for *USF1* associated with susceptibility for both FCHL and FHTG was identified in Finnish and Mexican families, with a stronger association for FCHL[20]. The SNP rs3737787 has been associated with differences in the expression of the target genes for *USF1* in adipose tissue and lymphoblasts, as well as higher TG concentrations in Mexican and Finnish populations, and is the SNP most consistently associated to FCHL. A comparison of the expression of USF1 in muscle and adipose tissue identified 13 genes that are regulated by *USF1,* including *FASD3, FABP2, FOLH1, MADD, NR1H3, CETP, LCAT, APOE,* and *PLTP*[21]. Overall, GWAS have confirmed that subjects with FCHL have a high polygenic lipid score for associated LDL-C and TG variants and confirm the polygenic nature of the disease[1,10].

Mutations in *LDLR* and *PCSK9* have been associated to increased LDL-C levels in FCHL; however, identification of these mutations is not specific of FCHL and demonstrates the difficulty of distinguishing mutations associated with the FCHL phenotype and those with increased LDL-C levels. Minocci et al. reported that up to 5% of cases with FCHL and predicted dysfunctional *LDLR* had to be reclassified as familial hypercholesterolemia with elevated TG levels, whereby additional genetic variants and environmental factors were responsible for the elevated TG concentrations[11,22]. An additional example of these interactions is the loss-of-function in lipoprotein lipase (LPL), APOA5 and GCKR, which have known to contribute to elevated TG levels, and which interact with additional genetic variants in other genes that increase LDL-C concentrations in FCHL[22]. Genome-wide scans have also demonstrated a strong link between the angiopoietin-like protein 3 gene *(ANGPTL3)* and plasma TG levels in FCHL[23]. ANGPTL3 is a secretory protein that affects plasma TG levels by reversibly inhibiting the catalytic activity of LPL; studies in both animal and human models have shown that inactivation of *ANGPTL3* leads to a decrease in TG, high-density lipoprotein-cholesterol (HDL-C), and LDL-C levels, which might diminish the risk of atherosclerotic cardiovascular disease[14]. However, the role of alterations in *ANGPTL3* in FCHL patients and its potential therapeutic role have not been determined[24].

Additional SNPs have been identified for specific populations in relation to FCHL and metabolic comorbidities. Huertas-Vázquez et al. demonstrated that the rs7903146 and rs12255372 variants in *TCF7L2* are associated with TG concentrations and T2D in Mexicans with FCHL as well as the 20q12-q131 locus, which is explained by *HNF4*α variants in Mexican and Finnish subjects with FCHL[25]. Two novel associations have been recently described for apoB levels at rs1424032 in 16q21, a highly conserved non-codifying region, and rs1349411 12p13.31, which included the *APOBEC1* gene, implicated in the edition of apoB mRNA in the small intestine[1]. Alterations in several metabolic pathways have been identified as potential candidates to further describe metabolic alterations in FCHL. Altered pathways in FCHL have been reported in the *APOA1-C3-A4-A5* gene cluster, which has been linked to HDL-c and TG levels, as well as *LPL, LCAT,* and *TNFRSF1B*[10,11,22]. SNPs in some of these loci have been linked to both TG and cholesterol fluctuations, with recent reports also suggesting a role for a highly disruptive p.Tyr125Cys SNP in *SLC25A40,* which encodes a mitochondrial solute transporter evaluated in Seattle kindred[26].

PATHOPHYSIOLOGY OF FCHL

FCHL comprises both hyperapobetalipoproteinemia and normal or elevated apoB synthesis[27,28]. Alterations in both secretion and degradation of apoB particles have been encountered in FCHL patients and have been linked to IR, decreased apoB clearance rate, and increased expression of molecules that downregulate the LDL receptor[2,12,30]. Imbalance between de novo lipogenesis and β-oxidation is a hallmark of FCHL, resulting in hepatic fat accumulation and very low-density lipoprotein (VLDL) overproduction[31]. Adipose tissue dysfunction has been linked with an increase in free-fatty acid (FFA) levels and efflux of FFA toward the liver, leading to an increased rate of lipoprotein synthesis[2,3]. It is known that increased levels and production of apoC-II and C-III are determinants of kinetics and plasma concentrations of TG-rich lipoproteins (TRLs), including VLDL1 and 2[32]. The *APOCIII* gene has also been linked to states of IR and T2D, both of which are frequent in FCHL

patients. FCHL has also been characterized by lower intestinal cholesterol absorption and higher cholesterol synthesis independent of body mass index (BMI) in comparison to primary hypercholesterolemia of genetic origin[33]. Unfavorable lipid profiles and increased postprandial lipemia have been linked to higher cardiovascular risk in FCHL[34]. A study by Almeda-Valdes et al. determined that the incremental area under the curve of postprandial lipemia in FCHL patients is determined by fasting apoB-48 levels[35,36] and potentiated by the presence of abdominal obesity. This study also proposed that apoA-V was associated with VLDL and chylomicron production in FCHL subjects.

The role of *USF1* in the pathogenesis of FCHL has not been completely explained. Inactivation of *USF1* in mice leads to protection for diet-induced dyslipidemia, obesity, NAFLD, and atherosclerosis; the proposed mechanism has been linked to increased TG uptake by brown adipose tissue through an LPL-dependent mechanism, which increases adrenergic response and thermogenesis[16]. *USF1* knockout mice *(USF1$^{-/-}$)* preserved a normal lipid profile when exposed to a high-fat and -carbohydrate diet; in addition, this group showed an enhanced insulin sensitivity and reduced liver steatosis compared with *USF1$^{+/+}$* type mice[16]. The findings of *USF-1* downregulation in animal models are similar to those observed in humans in whom improved insulin sensitivity, atheroprotective lipid profiles, and decreased atherosclerosis were associated with reduced *USF1* mRNA expression[16]. Plaisier et al. compared *USF1* expression patterns in subcutaneous adipose tissue from FCHL patients compared to healthy controls, demonstrating higher USF1 expression in affected subjects[1]. Wu et al. developed two overexpression *USF1* models in mice; both liver and systemic *USF1* overexpression models showed adverse metabolic phenotypes including obesity, worsened lipid profile, and higher glucose/insulin ratio[37]. These observations suggest a role for *USF1* in the pathophysiology of FCHL; however, identification of precise mechanisms requires functional studies on human subjects with FCHL with and without *USF1* variants that can be later confirmed in controlled studies in animal models.

In FCHL, there is an upregulation of thioredoxins, which are disulfide reductases responsible for regulating redox reactions, and confers an increased oxidative stress with reduced glutathione levels associated to IR. Both the increase in oxidative stress damage and IR contribute to atherosclerosis and potentially to increased cardiovascular risk in FCHL patients[38]. Most FCHL patients have increased sdLDL and apoB levels for all levels of IR in comparison to controls, adjusted by HOMA-IR and BMI[9]; this supports the concept that the etiology of the lipid phenotype in FCHL is a result of additive effects of genetic determinants with modulation by BMI and IR. Cardiovascular risk has also been associated to IR in FCHL. Subjects with FCHL have been reported to have increased vascular inflammation and metabolic activity in spleen, bone marrow, and liver as measured by ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography imaging[39]. In addition, Carratala et al. showed that subjects with FCHL had increased plasminogen activator inhibitor type 1 (PAI-1) levels, which correlated with IR, MS components and increased carotid intima thickness, all of which are markers of increased cardiovascular risk[17,39-42].

Along with TRL, diminished lipoprotein clearance associated to IR-mediated decreased LPL activity, leads to sdLDL and intermediate-density lipoprotein particle accumulation, both of which are highly atherogenic and easily oxidized, contributing to its entry into subendothelial pathways[3,43]. Decreased adiponectin levels in the setting of IR have been linked to higher levels of apoB and VLDL particles, further contributing to atherogenesis[44], which might be feasible in the setting of FCHL. Fibroblast growth factor 21 (FGF-21) is also implicated in the metabolism and kinetics of TRLs, causing an increase in insulin-induced CD36 and LPL-mediated catabolism of TRLs in white and brown adipose tissue and a reduction of serum TG concentrations. It could be hypothesized that the FGF-21 physiologic activity may be decreased in FCHL, but this has not been shown in animal or human subjects[45]. There is also evidence that PCSK9 concentrations are elevated in FCHL and contribute to the impaired catabolism of apoB[12]. PSCK9 induces degradation and downregulation of the LDL receptor through resistin and other pro-inflammatory cytokines[2,12] and is as well one of the factors contributing to the hyperapolipoproteinemia in FCHL and a possible target for therapies as discussed later.

COMORBIDITIES AND CARDIOVASCULAR RISK IN FCHL

Metabolic comorbidities in FCHL

FCHL has been associated to numerous metabolic diseases and comprises metabolic and biochemical abnormalities not unlike T2D, NAFLD, and the MS. FCHL has also been linked to an increased cardiovascular risk, particularly with CAD[3]. MS shares several pathophysiological alterations with FCHL, including elevated TG levels, impaired glucose tolerance, increased cardiovascular risk, and the comorbid presence of obesity and hypertension. However, in contrast to MS, FCHL subjects consistently show apoB levels > 90th percentile, while in patients with MS apoB may be high, normal, or even decreased. FCHL onset occurs earlier and hereditary traits are more evident, while for MS lifestyle plays a more prominent role than genetics[3]. In a recent study, Skoumas et al. examined the relationship between FCHL and MS, demonstrating that apoB levels were higher for FCHL patients, despite many similar features in both[11].

FCHL has been shown to carry an increased risk of incident T2D, conferring a higher metabolic and cardiovascular burden for patients with the disease. However, FCHL studies that evaluate cardiovascular risk often omit population with comorbid T2D, making excess risk estimations unfeasible[1,40]. The shared genetic background in FCHL has also been suggested by the evidence of association of FCHL with variants in *HNF4*α and *TCF7L2*[1,25,40,46]. FCHL has been shown to share common pathophysiological mechanisms with T2D including muscle and adipose tissue IR, as well as impaired insulin-mediated suppression of hepatic VLDL production[40].

An increased risk of hepatic steatosis has been observed in FCHL, with consistent associations for both NAFLD and non-alcoholic steatohepatitis (NASH) and up to 20-37% of the variability in intrahepatic fat content attributable to genetic factors in FCHL[40,47,48]. Increased hepatic visceral fat explains the change in serum TG levels in relation to changes in alanine aminotransferase levels for FCHL patients[48]. Brouwers et al. described that fatty liver occurrence was significantly higher for FCHL patients and their normolipidemic family members when compared to their spouses, who were used as control subjects, and determined that subcutaneous and intravisceral fat were predictors of intrahepatic fat content[2]. Recent studies suggest that genetic polymorphisms in *USF1* (rs6427573 and rs2516839), which have been linked to FCHL, have an increased independent risk of NAFLD when compared to controls in Chinese population[49]. Due to the role of *USF1* in the transcriptional regulation of hepatic lipogenesis, mice with *USF1* overexpression could be used to understand the role of USF1 in the setting of hepatosteatosis and IR and epigenetic studies could contribute to the understanding of the role of post-translational modifications in the setting of hepatosteatosis in FCHL patients[17]. Identification of additional mutations that explain intrahepatic fat accumulation, NAFLD, and NASH in FCHL patients remains largely unexplored and requires further evaluation and validation in other ethnic groups.

Cardiovascular risk in FCHL

FCHL is strongly associated with premature CAD, with up to 10-14% of patients with premature CAD having comorbid FCHL[22]. A patient diagnosed with FCHL has 1.7-10-fold higher risk of CAD compared to the average population 20 years after the initial diagnosis[22,50]. Wiesbaue et al. demonstrated that 38% of premature MI survivors had FCHL, and a similar study including 706 participants with FCHL reported a CAD prevalence of 15.3%, describing that disease presentation was independent of age, sex, or presence of T2D[6]. Cardiovascular risk in patients with hypertriglyceridemia is also increased, especially in the setting of older age, tobacco use, and hypertension and decreased HDL-C levels[11]. Among FCHL patients, males are more susceptible to inherit and develop the lipid disorder independent of lipid profile, which might also account for the increased risk[24]. Elevated expression of CD11b, a marker of fasting and postprandial leucocyte activation, has been previously reported for FCHL subjects and has been associated to increased cardiovascular risk in subjects with FCHL and comorbid T2D[51-55].

THERAPEUTIC APPROACH IN FCHL

As of the writing of this review, no specific clinical trials, guidelines, or algorithms have been developed for the management of FCHL. However, some

guidelines such as the 2016 ESC/EAS Guidelines for the Management of Dyslipidemias suggest that it would be managed as a particular primary lipid disorder and an atherogenic dyslipidemia[56,57]. However, the recommendation is lacking since it considers the oligogenic nature of the disease but does not offer specific comments regarding the particular cardiovascular risk in FCHL and how it might interact with metabolic comorbidities which also increase CV risk; furthermore, the guideline does not offer precise recommendations regarding family studies and early initiation of treatment in susceptible individuals.

A reasonable initial step in the management of a patient with FCHL includes controlled interventions targeting modifiable cardiovascular risk factors including smoking, alcoholism, overweight, and obesity[12]. Mateo-Gallego et al. showed that a weight loss of 5% of total weight in overweight adults with FCHL significantly reduces TG and non-HDL cholesterol levels at 3 and 6 months[58]. This justifies the role of weight loss in overweight patients with FCHL to complement lipid-lowering therapy in FCHL[59]. Evidence and recommendations regarding management of specific risk factors in FCHL are insufficient and call for the development of intervention-based evaluations aiming at describing the role and magnitude of these treatments and their impact on lipid profile and metabolic burden.

The decision of using either a statin, a fibrate, or a combination of both as the first-line therapy in FCHL is highly dependent on the predominant lipid alteration at diagnosis. However, it has been shown that the use of statins in comparison to fibrates as the first-line therapy significantly improves the lipid profile and increases the likelihood of reaching lipid targets in patients with FCHL[60,61]. Furthermore, statins have been shown to decrease significantly the levels of total cholesterol, LDL-C, apoB, non-HDL-C, and VLDL particles and remnants in comparison to fibrates, which are more effective at decreasing TG and increasing HDL-C levels in FCHL patients[61]. The effect of statin therapy on lipoprotein kinetics was evaluated by Le et al., who demonstrated that rosuvastatin significantly decreases LDL-C, apoB-100, and TG levels and increases the fractional catabolic rate of LDL and apoB-100 in a dose-dependent manner and thus cholesterol biosynthesis but does not have effect on apoB-100 production or HDL kinetics. This indicates that high-intensity statins in FCHL patients are effective at decreasing LDL apoB-100 levels and thoroughly modify lipoprotein profile[62]. As mentioned earlier, the inhibition of apoB production may also have beneficial roles in preventing hepatosteatosis and improving beta-oxidative pathways, which suggests a potential role to investigate the therapeutic effect of VLDL reduction in FCHL patients[42].

FCHL confers an increased risk of premature cardiovascular disease partly due to a rise in the accumulation of atherogenic particles, which may require the use of moderate- to high-intensity statin. Rosuvastatin increases the catabolism of sdLDL apoB-100 levels without changes in the conversion of TRL apoB-100 to sdLDL, though at a lower rate than large buoyant LDL-C[63]. Additional cardiovascular risk has been associated to increased postprandial lipemia in FCHL patients; despite its efficacy in sdLDL and LDL-C reduction, statin therapy has not shown modifications on postprandial lipemia for most FCHL patients, except for MTP-493G/T carriers, in whom a greater reduction of postprandial lipemia has been associated with the use of atorvastatin in comparison to non-carriers[36]. A particular concern of statin therapy in FCHL patients is the associated increase in incident T2D risk with statin use. Skoumas et al. showed that the risk of incident T2D did not increase with statin use or statin intensity in FCHL patients; these findings were confirmed by their group after a 10-year follow-up in which no significant differences in T2D incidence with statin use were observed between subjects with FCHL and controls. These observations suggest that the risk/benefit analysis for statin use in FCHL should have considerations similar to the rest of the population in terms of the statin-associated incident T2D risk[45,36].

Current guidelines suggest that FCHL patients should be managed according to LDL levels to decrease cardiovascular risk as recommended by European guidelines, by which these levels are considered a condition of high CV risk[64-66] (Table 2). However, patients with FCHL often present hypertriglyceridemia, which may decrease the reliability of LDL-C estimation by the Friedewald equation; thus, alternative goals focusing on non-HDL cholesterol and apoB levels are required. Sniderman et al. conducted a meta-analysis to investigate whether apoB or non-HDL-C increased the predictive power of LDL-C. They reported that during a

Table 2. 2016/European Society of Cardiology/European Atherosclerosis Society for treatment of lipid disorder recommendations.

CV risk	Features	LDL-C target concentration
Low risk	SCORE < 1% for 10-year risk of fatal CVD	<190 mg/dL lifestyle intervention, consider drug if uncontrolled
Moderate risk	SCORE is > 1% and < 5% for 10-year risk of fatal CVD	100-<155 mg/dL, Lifestyle intervention, consider drug if uncontrolled
High risk	Markedly elevated single risk factors, in particular cholesterol > 8 mmol/L (> 310 mg/dL) (e.g., in FH and FCHL) or BP > 180/110 mmHg. Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). Moderate CKD. SCORE > 5% and < 10% for 10-year risk of fatal CVD	70-< 100 mg/dL Non-HDL-C < 130 mg/dL, ApoB < 90 mg/dL
Very high risk	Documented CVD, clinical or unequivocal on imaging, previous myocardial infarction, coronary revascularization, coronary artery bypass graft surgery, stroke and transient ischemic attack, and peripheral arterial disease. DM with target organ damage, severe CKD. SCORE > 10% for 10-year risk of fatal CVD	< 70 mg/dL Non-HDL-C < 100 mg/dL

CV: cardiovascular, CVD: cardiovascular disease, HDL-C: high-density lipoprotein cholesterol, T1D: type 1 diabetes, T2D: type 2 diabetes, CKD: chronic kidney disease, SCORE: systematic coronary risk estimation, FH: familial hypercholesterolemia, FCHL: familial combined hyperlipidemia.

10-year period, a strategy focused on controlling non-HDL-C could prevent 300,000 more cardiovascular events than one directed to LDL-C; and a strategy focused on controlling apoB could prevent 500,000 more cardiovascular events than one directed to LDL-C[67]. Therefore, targets focused on non-HDL cholesterol < 130 mg/dL and apoB < 90 mg/dL should be considered in patients with FCHL[65].

Evidence beyond the use of statins for cholesterol management in FCHL patients has not been extensively evaluated. Ezetimibe can be added to treatment in cases where LDL-C decrease is refractory to statins monotherapy to improve the prognosis in endpoint CAD event as shown in the IMPROVE-IT study[68]. Recent analyses suggest to reconsider the use of ezetimibe and bile acid sequestrants in primary prevention in patients with true statin intolerance and in those patients in whom the goal levels of LDL-C cannot be achieved with maximum statin doses[69]. Evidence from large trials has shown that iPCSk9 is highly effective at reducing LDL-C and non-HDL-C levels; they are currently indicated for patients who do not reach lipid target after receiving maximum statin doses and with additional therapy, or patients who have statin intolerance[70,71]. Despite its promising role, the effect of additional LDL-C reduction with iPCSk9 should be evaluated in terms of its effect in cardiovascular risk reduction for FCHL patients and its impact on specific lipoprotein metabolism and kinetics.

Because FCHL is also characterized by hypertriglyceridemia, specific measures to control TG concentrations should be taken for adequate management (Table 3). Non-pharmacologic therapy includes glycemic control, avoidance of medication that increases lipid levels, limitation of alcohol intake, avoidance of simple carbohydrates, low-fat diet (< 30% of total daily caloric intake), and weight loss in patients who are overweight or obese[66,72]. With regard to pharmacological therapy, the efficacy of fibrates, Ω-3 fatty acids, and statins has been demonstrated in clinical trials for the management of FCHL patients[73-75]. A meta-analysis by Guo et al. demonstrated that the concomitant use of a fibrate and a statin is recommended for the management of FCHL subjects[76], and an algorithm proposed by Ellis et al.[12] suggests that pharmacologic treatment for elevated TG levels in FCHL patients with levels > 180 mg/dL should be started after reaching targets of LDL-C and apoB by statin treatment with or without ezetimibe.

Evidence from randomized, controlled clinical trials should be generated in FCHL population to assess the

Table 3. Therapeutic goals and treatment strategies in hypertriglyceridemia with FCHL.

TG level	Therapeutic goal	Therapeutic strategies
Borderline high (150-199 mg/dL)	Achieve LDL-C target, and apoB levels	Non-pharmacologic strategies
High (200-499 mg/dL)	Achieve LDL-C and apoB target, non-HDL-C goal	Non-pharmacologic strategies
		If treatment for LDL-C (statin) does not achieve goal, consider:
		Fibrate, niacin, Ω-3 fatty acids
Very high (> 500 mg/dL)	Reduce triglycerides to prevent acute pancreatitis. Achieve LDL-C target and non-HDL-C. Investigate secondary causes of elevated TG levels, elevated TG unlikely due to FCHL	Pharmacologic treatment
		Fibrates are preferred or Niacin, Ω-3 fatty acids, and non-pharmacologic therapy

TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, FCHL: familial combined hyperlipidemia, TG: triglycerides

Table 4. Areas of opportunity to improve recognition, standards of care, and research in familial combined hyperlipidemia.

Areas of opportunity in FCHL
1. Lack of recognition of FCHL and its associated comorbidities by primary care physicians
2. Lack of recognition of associated cardiovascular risk and measures to decrease risk burden
3. Imprecise diagnosis often leads to a lack of family screening, which, in turn, delays treatment in affected individuals
4. Under treatment associated to lack of precise diagnosis or unrecognized possible metabolic and cardiovascular complications
5. Patients are not thoroughly followed, which impairs the ability to influence outcomes and decrease morbidity
6. Studies lack consistent definitions, which makes comparisons across studies difficult
7. Comparative studies of combined treatment strategies are required to improve outcome-oriented treatment algorithms
8. GWAS and EWAS are required to investigate common and rare genetic variants for FCHL in other populations
9. Metabolomics, proteomics, systems biology, and epigenetic studies are required to further the understanding of the pathophysiology of FCHL
10. Follow-up studies are required to evaluate cardiovascular and metabolic risk and assess methods for risk prediction in FCHL

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efficacy of new treatments and determine the specific role of statin treatment intensity and fibrate use to improve therapeutic indications. Treatment evaluations should also focus on prevention of metabolic and cardiovascular complications in prospective long-term follow-ups. Given the shared genetic and pathophysiological features between FCHL and T2D, the role of insulin-sensitizing therapy should be evaluated in physiological assessments for human subjects and randomized, controlled clinical trials to determine its utility[40].

In summary, FCHL is a common disorder and the most prevalent primary dyslipidemia in the western world. Despite the extensive accumulated knowledge, FCHL is not usually considered as a first diagnostic choice because of a lack of awareness of its existence among primary care physicians. Therefore, FCHL is frequently undiagnosed, mostly due to its shifting clinical variability and the heterogeneity of diagnostic criteria, which leads to underreporting of its prevalence in epidemiological studies. This is significant since treatment is often delayed in affected family members that have not been evaluated. Areas of opportunity to improve recognition, standards of care, and research related to genetics, pathophysiology, cardiovascular risk, and management abound and call for further studies to confirm previous findings and increase awareness of this often neglected lipid disorder (Table 4). FCHL is a well-defined oligogenic

Table 5. Comparison between FCHL and familial hypertriglyceridemia as differential diagnosis of primary lipid disorders with elevated TG levels.

Features	FCHL	Familial hypertriglyceridemia
Former designations	Familial mixed hyperlipidemia, familial combined hyperlipoproteinemia, familial combined hypercholesterolemia-hypertriglyceridemia	Type 4 hyperlipidemia
Main lipoprotein disturbances	Elevated LDL-C and VLDL	Elevated VLDL
Typical onset	Adolescence	Adult age
Clinical features	Family history of coronary artery disease, cholesterol and triglyceride levels > 90th percentile, ApoB > 90th percentile, one family member with TC > 90th percentile, one family member with TG > 90th percentile, one family member with TC and TG > 90th percentile	TG levels > 200 mg/dL, Normal or decreased LDL levels, decreased HDL levels, Normal or decreased apoB levels, cholesterol:triglyceride ratio 1:5 when TGs reach 1000 mg/dL
Association with CVD	+++	++
Prevalence	1/40	1/20
Contribution of secondary factors	Obesity, IR, Metabolic Syndrome, T2D, NASH	Obesity, T2D, hypertension, pancreatitis, hyperuricemia, IR
Genetic features	Oligogenic	Variable
Genetic causes	*TXNIP, RXRA, CRABP2, ATF6, USF1, ANGPLT3, TCF7L2, APOA5, APOE*	*LPL, APOCII, APOA5, GPIHBP1, LMF1*
Current treatment	Statins, ezetimibe, fibrates	Fibrates, niacin, omega-3 fatty acids, fish oil
Future treatments	PCSK9 inhibitors, mipomersen	

HDL: high-density lipoprotein, LDL-C: low-density lipoprotein cholesterol, FCHL: familial combined hyperlipidemia, TG: triglycerides, VLDL: very low-density lipoprotein, ApoB: apolipoprotein B, TC: total cholesterol, T2D: type 2 diabetes, NASH: non-alcoholic steatohepatitis, IR: insulin resistance.

primary lipid disorder with a fluctuating lipid profile, increased cardiovascular risk, and comorbidity with other metabolic conditions such as T2D, NASH, and MS. It is unlikely that a similar phenotype could be found by chance in all patients who have been diagnosed with FCHL, thus, making the case for FCHL as an isolated lipid disorder. FCHL is a critical differential diagnosis in the setting of hypertriglyceridemia or a mixed dyslipidemia, particularly in distinguishing between common hypertriglyceridemia, mixed dyslipidemia, FCHL, and FHTG (Table 5).

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