Genetics of Plasma LDL-c Levels (i): Monogenicity

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Changes in plasma low-density lipoprotein cholesterol (LDL-c) levels relate to a high risk of developing some common and complex diseases. LDL-c, as a quantitative trait, is multifactorial and depends on both genetic and environmental factors. In the pregenomic age, targeted genes were used to detect genetic factors in both hyper- and hypolipidemias, but this approach only explained extreme cases in the population distribution. Subsequently, the genetic basis of the less severe and most common dyslipidemias remained unknown. In the genomic age, performing whole-exome sequencing in families with extreme plasma LDL-c values identified some new candidate genes, but it is unlikely that such genes can explain the majority of inexplicable cases. Genome-wide association studies (GWASs) have identified several single-nucleotide variants (SNVs) associated with plasma LDL-c, introducing the idea of a polygenic origin. Polygenic risk scores (PRSs), including LDL-c-raising alleles, were developed to measure the contribution of the accumulation of small-effect variants to plasma LDL-c.

Keywords: plasma cholesterol levels ; autosomal dominant hypercholesterolemia ; hypocholesterolemia

1. Introduction

Based on evidence from epidemiological studies regarding the relationship between cholesterol and cardiovascular disease (CVD) [1], cholesterol, with nucleic acids and glucose, is one of the most cited organic molecules in the scientific literature and household conversations. A high plasma cholesterol level alone is not usually accompanied by clinical manifestations, but persistent hypercholesterolemia is strongly associated with an elevated risk of developing highly prevalent diseases like CVD—which includes myocardial infarction (MI), ischemic stroke, and peripheral vascular disease (PVD) [2]—and high blood pressure [3]. Hypercholesterolemia is negatively associated with other diseases, such as intracerebral hemorrhage [4], but the relationship between diabetes and cholesterol is controversial [5][6][7]. CVD is one of the leading causes of death in industrialized countries; for example, in Spain, where the prevalence of CVD is lower than in other Western countries [8], according to the Spanish National Statistics Institute, the leading causes of death in 2018 were ischemic heart disease in men and ischemic stroke in women [9]. Notably, hypercholesterolemia is a modifiable risk factor, so early diagnosis is crucial for decreasing cardiovascular morbimortality, and cholesterol-lowering treatments have been shown to dramatically reduce CVD risk in hypercholesterolemic subjects [10].

Cholesterol is a structural component of animal cell membranes, influencing membrane fluidity and cell signaling [11]. It is the precursor of steroid hormones, bile acids, fats, and lipophilic vitamins, but it also has a regulatory function in multiple processes, such as in the immune system, gene transcription, enzyme functions, protein degradation, signal transduction, and apoptosis [12][13]. Its multiple functions are due to its peculiar three-part structure, which has opposing hydrophilic and hydrophobic ends, and an extremely rigid four-ring central component [13].

Both a lack or excess of cholesterol can be dangerous for cells because the balance between membrane fluidity and rigidity in many cases determines important aspects of cell functions [14]. In humans, a limited ability to catabolize excess cholesterol can lead to serious health consequences, so scientific interest has focused mainly on mechanisms for regulating the uptake and synthesis of cholesterol, rather than eliminating it.

2. Genetic Determinants of Plasma LDL Cholesterol Levels in the Pregenomic Era

The first classification of plasma lipid disorders was Fredrickson and Lee's phenotypic classification [15]. This classification distinguished six basic phenotypes (HLP1, HLP2A, HLP2B, HLP3, HLP4, and HLP5) and was based on patterns of lipoprotein fractions observed in hyperlipidemic subjects. Notably, none of the phenotypes were characterized by alterations in HDL and, except for HLP2A, almost all phenotypes exhibited altered triglyceride-rich lipoproteins. For several years, this classification was clinically useful since different phenotypes were associated with different CVD risks [16]. The diseases associated with each phenotype were considered to be mainly caused by major-gene pathogenic

variants; therefore, studies on the association between lipoprotein levels and known targeted genes were the main methodology for the study of dyslipidemias.

2.1. Monogenic Forms of Hypercholesterolemia

The most frequent form of plasma cholesterol alteration is hypercholesterolemia, which is defined as a persistently high plasma cholesterol level (usually ≥4.9 mmol/L). Initially, familial hypercholesterolemia (FH) corresponded to Fredrickson's hyperlipoproteinemia type 2A phenotype (HLP2A) [15]—an autosomal dominant disorder. According to the Online Mendelian Inheritance in Man (OMIM) database, autosomal dominant hypercholesterolemia (ADH) involves phenotypes (see **Table 1**):

- FHCL1 (OMIM #143890) or defective cellular LDL receptor (LDLR) is an autosomal dominant disorder due to loss-of-function *LDLR* gene variants [17]—the most common genetic defect in FH [18][19]. Defective LDLR results in reduced LDL-c uptake by hepatocytes, with a consequent increase in blood cholesterol.
- FHCL2 or familial ligand-defective hypercholesterolemia (OMIM #144010) is an autosomal dominant disorder due to missense *APOB* variants [20] (mainly p.Arg3527Gln). Since each LDL particle contains only one molecule of apoB100, a ligand-defective apoB results in an inability of LDL to bind to the LDLR, impairing its clearance from the blood. Mutations of the *APOB* gene account for 6–10% of ADH cases in Europeans [19].
- FHCL3 (OMIM #603776) is an autosomal dominant disorder due to gain-of-function variants of LDLR catabolic regulator proprotein convertase subtilisin/kexin type 9 (PCSK9) [21]. PCSK9 is an enzyme involved in the regulation of the degradation of LDLR in the lysosome, and gain-of-function mutants increase the degradation of LDLR, reducing its quantity on the hepatocyte surface [22].
- There are also recessive forms of phenotype HLP2A—referred to as autosomal recessive hypercholesterolemia (ARH or FHCL4) (OMIM #603813)—mainly due to protein-truncated mutations of the low-density lipoprotein receptor adaptor-protein 1 gene (*LDLRAP1*) [23]—a cytosolic protein that interacts with the cytoplasmatic tail of the LDLR.

Table 1. Genes associated with primary monogenic dyslipidemias related to plasma LDL-c levels.

Gene	Chromosome	Phenotype [1]	Type	Inheritance [2]	OMIM
high LDL-c					
LDLR	**19p13.2**	**FHCL1**	**loss-of-function**	**AD**	**#143890**
APOB	**2p24.1**	**FHCL2**	**missense**	**AD**	**#144010**
PCSK9	**1p32.3**	**FHCL3**	**gain-of-funtion**	**AD**	**#603776**
LDLRAP1	**1p36.11**	**FHCL4**	**protein-truncated**	**AR**	**#603813**
Phenocopies					
ABCG5/8	**2p21**	**sitosterolemia**	**loss-of-function**	**AR**	**#618666/#210250**
APOE	**19q13.32**	**FCHL/dysB**	**p.Leu167del**		**#617347**
CYP7A1	**2q35**	**CTX**	**loss-of-function**	**AR**	**#213700**
LIPA	**10q23.21**	**CESD/WD**	**loss-of-function**	**AR**	**#278000**
LPA	**6q25-q26**			**AD**	**#618807**
low LDL-c					
APOB	**2p24.1**	**FHBL**	**protein-truncated**	**AD**	**#615558**
PCSK9	**1p32.3**	**FHBL**	**loss-of-function**	**AD**	**#615558**
ANGPTL3	**1p31.3**	**FHBL2**	**loss-of-function**	**AR**	**#605019**
MTTP	**4q23**	**ABL**	**loss-of-function**	**AR**	**#200100**
SAR1B	**5q31.1**	**CMRD**	**loss-of-function**	**AR**	**#246700**
Other genes					

Gene	Chromosome	Phenotype [1]	Type	Inheritance [2]	OMIM
NPC1L1	7p13	↓LDL-c	loss-of-function		#617966
MYLIP	6p22.3	↓LDL-c			*610082
SREBF1	17p11.2	CHL		AD	*184756

[1] FHCL, familial hypercholesterolemia; FCHL, familial combined hyperlipidemia; dysB, dysbetalipoproteinemia; CTX, cerebrotendinous xanthomatosis; CESD, cholesteryl ester storage disease; WD, Wolman disease; FHBL, familial hypobetalipoproteinemia; ABL, abetalipoproteinemia; CMRD, chylomicron retention disease; CHL, combined hypolipidemia. [2] AD, autosomal dominant; AR, autosomal recessive.

Linkage studies and/or exome sequencing in ADH-affected families have suggested other putative loci for ADH (Table 1). Linkage analysis in an ADH kindred without *LDLR*, *APOB* and *PCSK9* mutations, identified the gene for signal transducing adaptor family member 1 (*STAP1*)—a docking protein—as a candidate for ADH [43], initially describing it as FH4 (OMIM #604298). However, studies in Spanish families with a clinical diagnosis of ADH showed incomplete or lack of *STAP1* mutations cosegregation with the ADH phenotype [44,45]. A recent study failed to find *STAP1* associated with plasma LDL-c in mice or humans [46], so its exclusion from candidate genes has been proposed.

Autosomal recessive cholesteryl ester storage disease (CESD) is caused by mutations of the lysosomal acid lipase (*LIPA*) gene. One study associated a homozygous splice junction mutation of the *LIPA* gene with the ARH phenotype in a Dutch family [47], but another study of patients with a clinical diagnosis of FH detected an enrichment of heterozygous (but not homozygous) *LIPA* mutations [48,49].

Cytochrome P450 family 7 subfamily A member 1 (CYP7A1)—also known as cholesterol 7-alpha monooxygenase—is the rate-limiting enzyme that catalyzes the first step of the transformation of cholesterol into bile acids [50]. A homozygous *CYP7A1* frameshift mutation was associated with high levels of LDL-c in a UK family [51], and a promoter *CYP7A1* gene variant has been reported to influence the LDL-c-lowering response to atorvastatin, modulated by the *APOE* genotype [52].

The *APOE* mutation p.Leu167del was associated with ADH in a large French family [53]. This *APOE* variant was previously associated with splenomegaly, thrombocytopenia, and the Fredrickson HLP2B (familial combined hyperlipidemia) and HLP3 (dysbetalipoproteinemia) phenotypes [54], both characterized by mixed hyperlipidemia. A study of ADH subjects with this mutation showed that VLDLs carrying mutant *APOE* caused hypercholesterolemia by down-regulating *LDLR* expression in hepatocytes [55].

ABCG5 and *ABCG8* loss-of-function mutations are associated with sitosterolemia (OMIM #618666/#210250)—an autosomal recessive disease characterized by elevated plant-sterol plasma levels. Although sitosterolemia shares clinical features with ADH, such as the presence of tendon xanthomas and CVD risk, cholesterol plasma levels in affected subjects are typically normal or moderately elevated in adulthood [56]. A common *ABCG5/8* polymorphism was associated with plasma lipid concentrations in ADH and influenced CVD risk [57,58]. More recent studies reported a significantly higher frequency of carriers of pathogenic or likely-pathogenic ABCG5/8 mutations in mutation-negative ADH patients compared to the reference population [59,60,61,62]. However, although ABCG5/8 mutations may contribute to hypercholesterolemia in mutation carriers, it has not been proven to be sufficient to cause an ADH phenotype [62].

Patatin-like phospholipase domain containing 5 (PNPLA5) belongs to a patatin-like phospholipase family, which plays a key role in the hydrolysis of triglycerides and the regulation of adipocyte differentiation [63]. Exome sequencing of individuals with extreme LDL-c levels showed an association of rare *PNPLA5* variants with mainly high, but also low, plasma LDL-c levels [64].

Recently, a study has described the role of cyclase-associated protein 1 (CAP1) in cholesterol metabolism [65]. CAP1 is a binding partner of PCSK9 and plays an important role in LDLR catabolism by directing LDLR–PCSK9 complex to lysosomal degradation. To my knowledge, no studies have been performed to detect *CAP1* variants associated with plasma LDL-c levels.

Finally, it is noteworthy that patients diagnosed with ADH have elevated plasma levels of lipoprotein (Lp)(a)—an LDL-like particle with apolipoprotein(a) covalently bonding to apoB [66]. In the absence of hypertriglyceridemia, plasma LDL-c concentrations are usually calculated using the Friedewald formula [67], rather than by direct detection; thus, Lp(a) particles could be responsible for an increased likelihood of high LDL-c diagnosis, since the cholesterol within Lp(a) contributes to the estimated LDL-c. A recent study showed that the presence of Lp(a) cholesterol misclassified a

significant number of samples submitted for lipid testing as high LDL-c [68]. Lp(a) is an independent CVD risk factor, and 90% of circulating Lp(a) plasma levels are genetically determined [69], so studies must consider a possible interference of Lp(a) if plasma LDL-c concentrations are not directly measured.

2.2. Monogenic Forms of Hypocholesterolemia

A very low plasma cholesterol level, or hypocholesterolemia, is usually defined as persistent plasma total cholesterol, LDLc, and apoB concentrations below the 5th percentile of the reference population [24]. Hypocholesterolemia is a rare condition and, in the heterozygous form, usually does not have a clinical expression, so it is usually underdiagnosed. The main disorders related to low plasma cholesterol levels are as follows (**Table 1**):

- FHBL or familial hypobetalipoproteinemia (OMIM #615558) is an autosomal codominant disorder caused mainly by protein-truncated *APOB* gene mutations [25], but also by loss-of-function *PCSK9* gene mutations [26];
- FHBL2 or familial hypobetalipoproteinemia type 2 (OMIM #605019)—also known as familial combined hypolipidemia—is an autosomal recessive disorder caused by loss-of-function mutations of the angiopoietin-like 3 (*ANGPTL3*) gene [27]. ANGPTL3 is an inhibitor of the lipases LPL and LIPG (endothelial lipase), reducing the clearance of triglyceride-rich particles [28];
- ABL or abetalipoproteinemia (OMIM #200100) is an autosomal recessive disorder caused by mutations of the microsomal triglyceride transfer protein (*MTTP*) gene [29]. MTTP is a chaperone and the major lipid transfer protein of triglyceride, cholesteryl esters, and phospholipid to nascent apoB-containing lipoproteins [30];
- Chylomicron retention disease (CMRD; OMIM #246700)—also known as Anderson's disease—is an autosomal recessive disorder caused by mutations of the secretion-associated Ras-related GTPase 1B (*SAR1B*) gene [31]. SAR1B plays a central role in the specific prechylomicron transport vesicles within the Golgi apparatus, as a component of coat protein complex II [32].

Other candidate loci for hypocholesterolemia have been proposed. Apolipoprotein C-III (apoC-III) reduces the clearance of triglyceride-rich particles by inhibiting lipoprotein (LPL) and hepatic (LIPC) lipases [33]. Loss-of-function *APOC3* variants have been associated with low LDL-c and reduced CVD risk [34][35], but the results of a multi-ethnic study failed to detect any association with low LDL-c [36]. The reduction in CVD risk seems to be related to reduced remnant cholesterol, rather than low LDL-c [37].

Myosin regulatory light chain interacting protein (MYLIP)—an E3 ubiquitin ligase—promotes the degradation of LDLR. A loss-of-function *MYLYP* mutation was associated with low plasma LDL-c in a Dutch cohort [38]; however, a *MYLIP* common missense mutation (p.Asn342Ser) was recently associated with hypercholesterolemia in Han Chinese people [39].

As we mentioned previously, enterocytes in the intestine incorporate dietary sterols via the NPC1L1 transporter. Targeted sequencing of *NPC1L1* identified loss-of-function mutations associated with low cholesterol absorption, low plasma LDL-c, and a lower risk of CVD [40][41]. Notably, the NPC1L1 transporter is the target for the lipid-lowering drug ezetimibe.

Sterol regulatory element-binding transcription factor 1 gene (*SREBF1*) codifies SREBP1—a transcription factor that regulates cholesterol and fatty acid synthesis in the liver. An *SREBF1* missense mutation (p.Pro111Leu) was identified in a family with severe combined hypolipidemia [42], alongside reduced transcriptional activation of *LDLR*, *ABCA1*, fatty acid synthase (*FAS*), *MTTP*, and *HMGCR*.

Rare mutations in these genes may explain extreme cases at both ends of the plasma LDL-c distribution, but not the less severe and more common LDL-c-related dyslipidemias. The inheritance of moderate conditions does not follow a clear Mendelian pattern; thus, the next section aims to identify the genetic basis of the population variance in LDL-c.

3. The Future

GWAS studies have uncovered a large number of genes associated with plasma levels of LDL-c. Some of these genes encode proteins involved in well-known metabolic pathways related to cholesterol metabolism. However, other genes encode proteins involved in metabolic pathways whose connection to cholesterol metabolism is unknown. Thus, high-performance techniques, such as hypothesis generators, have suggested new metabolic pathways connected with cholesterol metabolism. Further functional studies are needed to determine if the identified associations are causal since identifying new therapeutic targets depends on this relationship. On the other hand, there is a bias in the published

studies towards European populations. Performing GWASs in different ethnic groups is necessary to determine to what extent the genetic determinants of plasma LDL-c levels are population-specific or can be generalized.

Plasma LDL-c levels, as a complex trait, depend on both genetic and environmental factors. Usually, genetic and environmental influences on a quantitative trait are measured independently. As shown by this review, the percentage of LDL-c-related dyslipidemias that can be explained by genetic causes has been increasing over time, mainly due to the continuous development of new analytical methods. However, a significant proportion of the population variance in plasma LDL-c and many other complex traits remains unexplained by genetic inheritance and environmental effects, which has led to the concept of “missing” heritability. Gene–environmental interactions are not usually considered in association analysis, despite the evidence that the effect on the phenotype of some common variants markedly depends on the environment: for example, the *APOE* genotype influences the lowering of LDL-c in response to dietary changes in fatty acids consumption [43], and common SNVs in *ABCG5/G8* modulate plasma lipid concentrations that depend on the smoking status of ADH patients [44]. Another study showed some evidence of an interaction between a weighted PRS constructed with 32 SNVs associated with LDL-c and diet quality in a Swedish cohort [45]. Gene-gene interactions must also be considered.

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