REVIEW

Nutrigenetics of the lipoprotein metabolism

Antonio Garcia-Rios, Pablo Perez-Martinez*, Javier Delgado-Lista, Jose Lopez-Miranda and Francisco Pérez-Jiménez*

Lipids and Atherosclerosis Research Unit, IMIBIC, Reina Sofia University Hospital, University of Cordoba, CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos, Córdoba, Spain

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It is well known that lipid metabolism is a cornerstone in the development of the commonest important chronic diseases worldwide, such as obesity, cardiovascular disease, or metabolic syndrome. In this regard, the area of lipid and lipoprotein metabolism is one of the areas in which the understanding of the development and progression of those metabolic disorders has been studied in greater depth. Thus, growing evidence has demonstrated that while universal recommendations might be appropriate for the general population, in this area there is great variability among individuals, related to a combination of environmental and genetic factors. Moreover, the interaction between genetic and dietary components has helped in understanding this variability. Therefore, with further study into the interaction between the most important genetic markers or single-nucleotide polymorphisms (SNPs) and diet, it may be possible to understand the variability in lipid metabolism, which could lead to an increase in the use of personalized nutrition as the best support to combat metabolic disorders. This review discusses some of the evidence in which candidate SNPs can affect the key players of lipid metabolism and how their phenotypic manifestations can be modified by dietary intake.

Keywords:
Gene–diet interactions / Lipid metabolism / Nutrigenetics / Single-nucleotide polymorphisms (SNPs)

1 Introduction

Cardiovascular diseases (CVD) continue to be the major causes of morbidity and mortality in developed countries [1, 2] (http://dphpc.ox.ac.uk/bhfprg/stats/2003/). CVD are a paradigm of multi-factorial disorders related to genetic and modifiable risk factors. In this regard, lipid and lipoprotein metabolism is one of the areas in which the understanding of the development and progression of CVD has been studied in greater depth.

The relationship between lipid metabolism and the development of CVD has been clearly established. In the maintenance of lipid homeostasis there are complex interactions between binding proteins, enzymes and receptors that will determine the final phenotype (Fig. 1). In this context, it is known that genetic and environmental factors – particularly diet – play an important role in the development of atherosclerosis and in the maintenance of lipid homeostasis. Indeed, dietary modification continues to be the cornerstone in the prevention of metabolic disorders [3, 4]. In addition, it is known that in the maintenance of lipid homeostasis, numerous nuclear factors, binding proteins and receptors are involved, which act in a coordinated way and it has been demonstrated that genetic variability of those components influences the final plasma lipid levels.

Correspondence: Dr. Francisco Pérez-Jiménez, Hospital Universitario Reina Sofia, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC). Avda. Menéndez Pidal, s/n. 14004 Córdoba, Spain
E-mail: fperezjimenez@uco.es
Fax: +34-957218250

Abbreviations: apoE, apolipoprotein E; **CVD,** cardiovascular diseases; **HDL-C,** high-density lipoprotein cholesterol; **LDL-C,** low-density lipoprotein cholesterol; **MC4R,** melanocortin-4 receptor; **MetS,** metabolic syndrome; **PUFA,** polyunsaturated fat; **PPAR-α,** peroxisome proliferator-activated receptor α; **SCD,** stearoyl-coenzyme A desaturase; **SFA,** saturated fat; **TG,** triglycerides; **TRL,** triglyceride-rich lipoproteins

*These authors contributed equally in this work.

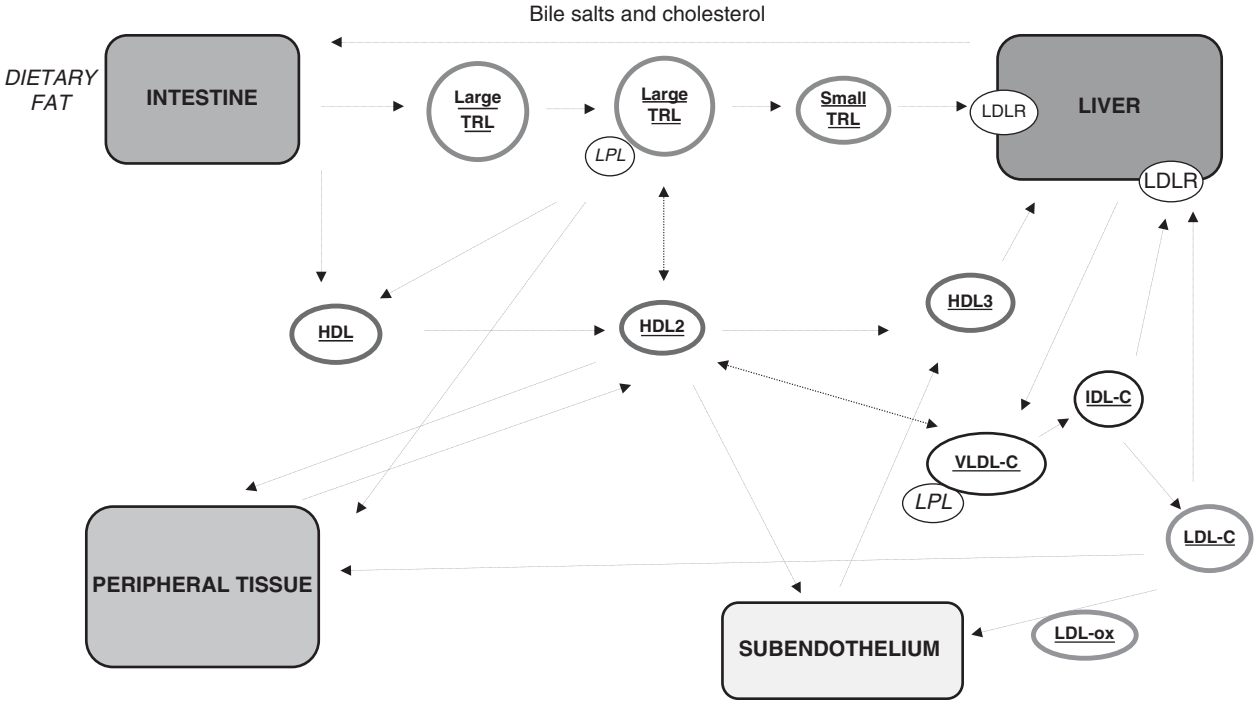

Figure 1. Human lipoprotein metabolism. Dietary fatty acids are absorbed and converted into TG to be incorporated into chylomicrons in the intestinal epithelial cells. Next, the triglyceride-rich apolipoprotein (apo) B48-containing chylomicrons (Large TRL) enter the plasma and LPL hydrolyzes the triglyceride in chylomicrons to fatty acids. The chylomicron remnants (Small TRL) are removed from the circulation by the liver through the LDL receptor (LDLR). The liver synthesizes very low-density lipoprotein-cholesterol (VLDL-C) particles which are also hydrolyzed by LPL. VLDL remnants or intermediate density lipoproteins (IDL-C) are taken up by liver receptors or converted to low-density lipoprotein-cholesterol (LDL-C). LDL is removed from the circulation by the liver through the LDLR. In addition, HDL is the key player in the reverse transport of cholesterol from peripheral tissue towards liver. HDL is synthesized in the liver and small intestine and in its core, across the lecythin cholesterol acyltransferase enzyme, transforms the cholesterol in cholesterol esters. Thus, the HDL becomes in HDL2 and HDL3 rich in cholesterol which completes the transport reverse of cholesterol in the liver.

Thus, interest in this area has increased over the last decade, with plentiful evidence from association studies with multiple lipid candidate genes in different populations [5–9].

However, it is important to recall that while general dietary recommendations can explain lipid changes for a group of people, it is not possible to predict the response for individual interventions. In this regard, the growing evidence from genetic factors and gene–diet interactions has helped to shed more light onto the understanding of this variability over the last few years, given that great advances have been made in the knowledge of the interactions between nutrients and individual characteristics, which may help us to know what the diet response for each individual could be [10–12]. In this area, nutrigenetics has emerged in the last decade to understand individual differences in the dietary response, which may be related to the presence of individual genetic markers – principally single-nucleotide polymorphisms (SNPs) – or through the interaction between these genetic markers and dietary components.

Therefore, with sufficient study about the interaction between some of the most important genetic markers or SNPs and diet, it may be possible to understand the variability in lipid metabolism. In the current review, we discuss the influence of some of the most important candidate genes that affect lipid metabolism (LDL-C, HDL-C, and triglycerides). In addition, we explained how interactions between those genes and environmental factors – particularly diet – can modify the final phenotype. With this point of view we explain that not only genetic factors or environmental factors such as diet but also gene–diet interactions explain the wide inter/intra-individual responses in lipid metabolism. The knowledge of the most important genetic variants in lipid metabolism and the understanding of gene–diet interactions could be used in the future to develop a personalized therapy or suitable guidelines of prevention according to the genotype of each individual.

2 Evidence from total cholesterol and low-density lipoprotein cholesterol (LDL-C)

LDL-C continues to be the primary target of lipid-lowering therapy [13]. However, it is known that there is a considerable heterogeneity in LDL-C concentrations and LDL-C size

among groups, probably as a result of a combination of gene and diet interactions.

The role of apolipoprotein E (apoE) in lipid metabolism and cholesterol transport is well established. In this context, apoE promotes efficient uptake of triacylglycerol-rich lipoproteins from the circulation and takes part in the cellular cholesterol efflux and it is found in HDL-C participating in cholesterol reverse transport. This apolipoprotein presents three major isoforms (*APOE2, APOE3* and *APOE4*) that modulate lipid levels and these isoforms differ in their affinity for binding to apoE and low-density lipoprotein receptors (LDL-R), and their affinity for other lipoprotein particles [14]. Indeed, a recent meta-analysis of 82 studies of lipid levels (86 067 healthy participants) and 121 studies of coronary outcomes (37 850 cases and 82 727 controls) found that there was a very consistent relationship of *APOE* genotypes and LDL-C and coronary risk [15]. Compared with individuals with the commonest *E3/E3* genotype, *E2* carriers had a 20% lower risk of coronary heart disease and *E4* carriers had higher risk. Indeed, subjects with the *E2/E2* genotype had about 31% lower mean LDL-C concentrations than those with the *E4/E4* genotype. Therefore, carriers of the *APOE4* allele have higher total and LDL-C plasma concentration and a greater coronary risk, particularly of myocardial infarction. Nevertheless, not everyone with the *E4* allele develops the disease, which suggests that other genetic or environmental factors could influence the final phenotype. In this context, it has been demonstrated that *APOE* gene promoter *−219G/T* polymorphism increases LDL-C concentrations and susceptibility to oxidation in response to a diet rich in saturated fat (SFA). In this study, carriers of the T allele showed higher concentrations of apoB and LDL-C after the SFA diet compared with GG subjects. However, in carriers of the T allele, the decrease in LDL-C and apoB was significantly higher when they changed from the saturated to the high-carbohydrate diet compared with GG subjects [16]. This particular SNP could explain individual differences in response to a diet. In addition, it has been demonstrated that the same *−219G/T* polymorphism determines insulin sensitivity in response to dietary fat in healthy young adults with *APOE3/E3* genotype [17]. Previously, Campos et al. had demonstrated that the *APOE2* allele could modulate the effect of habitual SFA on plasma lipoproteins in a population with an average habitual total fat intake of $<30\%$ [18]. This gene–diet interaction was confirmed later by the same group in a different population in which the *APOE2* and *APOE4* variants increased susceptibility to higher LDL-C levels and myocardial infarction in the presence of high SFA [19]. Therefore, based on the findings from intervention studies there is a clear evidence supporting the notion that the *APOE* locus could interact with dietary SFA, increasing LDL-C concentrations and also increasing CVD risk, which appears more evident in *E4* carriers. However, we need to be cautious before drawing general conclusions, given that the studies varied widely in the number and type of population, and also in the composition and duration of the dietary interventions used. Indeed, the previous meta-analysis ended by giving a warning about the heterogeneity between the findings of the different studies for the conclusions of gene–diet interactions.

Peroxisome proliferator-activated receptor α (*PPAR-α*) is a ligand-dependent transcription factor that plays a key role in lipid homeostasis. Indeed, activation of PPAR-α contributes to the clearance of triglyceride-rich lipoproteins (TRL), improves HDL-C concentrations, and reduces the oxidation of LDL-C across, influencing key players in lipid metabolism such as lipoprotein lipase (LPL), apoC-III and the induction of enzymes related to fatty acid oxidation [20]. Thus, specific genetic variants in this gene have shown to influence the final concentrations of lipids in the fasting state as well as during the acute postprandial response to dietary fat. Thus, one of the most frequently studied has been the *Leu162Val* variant of *Peroxisome proliferator-activated receptor α* (*PPARA*) gene in which minor allele was associated with higher fasting total cholesterol, LDL-C, and apolipoprotein B (apoB) after a single fat load composed of 60% calories as fat, 15% as protein, and 25% as carbohydrate. This suggests that *PPARA* variants may modulate the risk of CVD by influencing lipid concentrations [21]. Previously, this genetic variant had been studied extensively and associated with lipid metabolism and atherosclerosis [22–24]. Therefore, given the influence of the *PPARA* gene and the effect of specific variants on lipid concentrations, this gene could be a key candidate in the understanding of the variability in lipid metabolism.

Finally, it has been demonstrated that in plasma LDL-C response to changes in dietary fat influences genetic variants in the *apolipoprotein A1* (*APOA1*) and *apolipoprotein A4* (*APOA4*) genes, which codify two of the most important proteins in lipid metabolism. Thus, it has been demonstrated that the *−75G/A APOA1* SNP influenced the postprandial LDL-C response to a monounsaturated (MUFA) diet. After consumption of a high MUFA diet, carriers of the A allele showed significant increases in LDL-C concentrations, which were not noted in G/G subjects [25]. In addition, the postprandial LDL-C response to dietary fat is influenced by the presence of the *347Ser* variant of the *APOA4* gene. Thus, carriers of the *347Ser* allele presented a greater decrease in LDL-C when they were switched from the SFA to the NCEP type 1 diet than those with the homozygous *347Thr* allele [26]. Moreover, it has recently been demonstrated that the presence of *APOA1* and *APOA4* SNPs can even influence the effects of dietary fat on the LDL particle size and oxidation in healthy young adults [27]. Therefore, following the current evidence, apoA-I and ApoA-IV are key players in the metabolism of the major plasma lipids, mainly HDL-C but also LDL-C. The relationship of these two apolipoproteins with HDL-C is clear. However, the changes observed in LDL-C in response to dietary fat and cholesterol vary greatly among individuals and could be related to particular gene–diet interactions. One the one hand, the mechanism for the interaction between APOA1 gene variant and diet might involve the effect of this

interaction on VLDL-C clearance after the consumption of a fatty meal. Thus, the decreased uptake of VLDL-C and VLDL-C remnants leads to higher levels of TRL with an increased conversion into smaller LDL-C [28]. On the other hand, it has been demonstrated that apoA-IV can regulate cholesterol ester transfer mediated by cholesterol ester transfer protein between HDL-C and LDL-C [29]. Thus, the presence of genetic variants in APOA4 gene modifies plasma LDL-C concentrations after a dietary fat [26, 27]. Obviously, it is important to recall that in those studies gene–diet interactions were demonstrated and the main objective was not potential mechanistic explanations. However, the key role of these two apolipoproteins in lipid metabolism allows us to take into consideration these two genes in the understanding of variability in lipid metabolism; however, on the other hand, there is a lack of replication of the reported gene–diet interactions, and so we need to be cautious and these findings should be confirmed in the future.

Other important key players in LDL-C metabolism have been studied. Thus, apolipoprotein B (apoB) is an essential protein for the formation of chylomicrons in the small intestine and for the secretion of VLDL-C in the liver. In addition, apoB is the most important apoprotein for LDL-C. In this regard, it has been demonstrated that *apolipoprotein B* (*APOB*) *−516C/T* polymorphism has no effect on lipid and apolipoprotein response following changes in dietary fat intake in a healthy population [30], although the presence of the same SNP has proved to influence the postprandial response of healthy Caucasian subjects [31]. On the other hand, the association between polymorphisms in the *scavenger receptor class B type I* (*SCARBI*) gene and variations in basal plasma concentrations of cholesterol in humans has also been widely studied. This gene codifies an integral membrane protein implicated in the efflux of cholesterol from peripheral tissues towards liver for excretion. However, studies on SRB-I function in cultured cells showed that this receptor can also mediate the selective uptake of LDL-C, which suggests that SRB-I could participate in the metabolism of lipoproteins containing apo B [32, 33]. Thus, the polymorphism exon 1 variant at the locus of the *SCARBI* gene influences plasma LDL-C concentrations in healthy subjects during the consumption of diets with different fat contents [34]. These findings taken together with studies involving the manipulation of *SCARBI* expression in mice have suggested that the expression of *SCARBI* could protect against the development of atherosclerosis. Obviously, further studies will be necessary to confirm the previous results in mice but SRB-I activity could be considered as an attractive target for therapeutic interventions.

3 Evidence from high-density lipoprotein cholesterol (HDL-C)

HDL-C is a protective factor for CVD that is independently and inversely linked to CVD risk [35]. The main function of HDL-C is the transport of cholesterol from peripheral tissues back to the liver for metabolism, for which HDL-C establishes complex interactions with other lipoproteins, enzymes and receptors. In this reverse transport of cholesterol, there are also several well-documented gene–diet interactions that influence the final HDL-C concentrations. Indeed, a major structural and functional component of HDL-C as *apolipoprotein A-1* (*APOA1*) gene supports well-documented evidence. A specific SNP in its promoter region, known as *−75G/A*, has been extensively studied in relation to apolipoprotein A-1 (ApoA-I) and HDL-C levels [36]. However, it has been demonstrated that interactions with dietary factors could modulate the effect of this genetic polymorphism. Thus, subjects carrying the A allele for that SNP showed an increase in HDL-C concentrations with increased intake of polyunsaturated (PUFA), whereas those homozygous for the more common G allele showed a predictable lowering of HDL-C levels with increased intake of PUFA [37]. In addition, the influence of gender has also been demonstrated in this specific interaction. Indeed, in women carriers of the A allele, higher PUFA intakes were associated with higher HDL-C concentrations, whereas the opposite effect was observed in G/G women in the Framingham Study. PUFA intake had no significant effect on either HDL-C or ApoA-I concentrations in men [38]. The influence of new gene–PUFA interactions continues to grow and recently, it has been demonstrated that genetic polymorphisms of *tumor necrosis factor-α* also modify the association between dietary PUFA and fasting HDL-C and ApoA-I concentrations [39].

To continue with the key players in the reverse cholesterol transport, we have recently demonstrated the effect of variations in the *APOA1/C3/A4/A5* gene cluster on postprandial lipid metabolism after an SFA-rich meal in which the main influence was on apoA-1 concentrations. Thus, *APOA1-2803* AA subjects (minor allele homozygotes) showed a smaller postprandial area under the curve (AUC) of triglycerides (TG), large TRL and apoB compared with GA and GG subjects. On the other hand, TT individuals of *A4A5_inter* (homozygotes for the common allele) showed a larger AUC of total TG compared with heterozygotes (CT) and a larger AUC of total cholesterol and apoB compared with CC subjects. On the other hand, heterozygotes for *APOA4 N147S* and *T29 T* showed a smaller AUC of apoA-I levels than homozygotes for the common allele (apoA4 N147S GG 69 531 $\pm$ 1562 versus GA 63 734 $\pm$ 2006; *T29T* AA 69 401 $\pm$ 1709 versus AG 64 408 $\pm$ 1930). In addition, repeated measures showed a higher concentration of apoA-I in homozygotes for the common allele versus heterozygotes for the two APOA4 SNPs [40]. In summary, this study identified new associations between SNPs in the *APOA1/C3/A4/A5* gene cluster and altered postprandial lipid metabolism. In this context, it is important to note that *apoA1* and *apoA4* are shown as two important key genes in lipid metabolism, influencing both LDL-C metabolism and lipoproteins of reverse cholesterol transport.

Variability in the *hepatic lipase* (*LIPC*) gene, which encodes a key enzyme involved in reverse cholesterol transport, is also associated with interactions between intake of fat and concentrations of HDL-C. This gene codifies an enzyme that can process the HDL-C when this molecule is enriched in triglycerides. Indeed, this enzyme can convert the phospholipid-rich HDL2 into HDL3. Thus, *−514C/T* SNP in that gene interacted with dietary fat in determining HDL-C levels and subclasses of HDL-C [41], in which the T allele was associated with significantly greater HDL-C concentrations and large HDL-C size only in subjects consuming $<30\%$ of energy from fat. This gene–nutrient interaction confirms previous findings in other populations [42], and could explain some of the findings showing no association between this particular SNP and HDL-C.

As we explained previously, the role of apoE in cholesterol transport is well established and this apoprotein or their three major isoforms (*APOE2, APOE3* and *APOE4*) can influence and modulate not only LDL-C metabolism but also final concentrations of HDL-C given that it is known that apoE is present in HDL-C and the content of apoE could influence the function of HDL-C in the reverse cholesterol transport. In this regard, important interactions have been shown between some of these genotypes of *APOE* gene and fat intake, which influence the final concentrations of HDL-C. Thus, dietary fat also influences *APOE* genotypes in which higher VLDL-C and lower HDL-C concentrations were demonstrated in *E2* carriers only with high SFA [18]. Therefore, as we explained previously for LDL-C, the *APOE* gene influences other key players in lipid metabolism such as HDL-C, for which a cornerstone in our knowledge of inter-individual variability is considered.

ATP-binding cassette (ABC) transporters are a family of proteins that act as trans-membrane carriers of molecules using ATP hydrolysis as the energy source [43]. ABCA1, a member of the ABC family, is a major regulator of HDL-C metabolism and is implicated in the reverse cholesterol pathway given that regulates the migration of lipid molecules through the cell membrane. Thus, ABCA1 family takes part in the formation of nascent HDL-C given that mediates the efflux of cholesterol towards lipid-poor lipoproteins [44]. To further characterize the effects of *ABCA1* variants in human postprandial lipid metabolism, we studied the influence of three SNPs (*i27943, i48168, R219 K*) in the postprandial lipemia of 88 normolipidemic young men who were given a fatty meal. This meal contained 60% of its energy in the form of fat (35% saturated, 19% monounsaturated fat, 6.3% polyunsaturated fat), 15% as protein, and 25% as carbohydrate. For *i27943* and *i48168* SNPs, fasting and postprandial values of apoA-I were higher and postprandial lipemia was lower in those who were homozygous for the major alleles. These volunteers also showed a higher apoA-1/apoB ratio. Major allele homozygous for *i48168* and *i27943* showed additionally higher HDL-C and lower postprandial apoB [45].

Finally, other gene–diet interactions that influence HDL-C metabolism have been demonstrated [46, 47]. In this regard, a common SNP of the *Peroxisome proliferator-activated receptor gamma (PPARG)* gene (*Pro12Ala*) has been widely studied and the total fat intake has been shown to be correlated with plasma HDL-C concentrations. Thus, among *Pro12Pro* homozygotes, the total fat intake was inversely correlated with HDL-C concentrations [46]. However, among *12Ala* variant allele-carriers, the intake of total fat was directly correlated with HDL-C concentrations.

Therefore, although PPARG is a critical transcriptional regulator of adipogenesis, it has been proposed that may be a mediator of physiological responses to lipids given that promotes the HDL-induced cholesterol efflux in adipocytes [48]. On the other hand, recently, a common SNP in the *angiopoietin-like 4* gene interacts with carbohydrates in determining plasma HDL-C concentrations. In men, the inverse association between carbohydrate and HDL-C was stronger in A allele carriers than in non-carriers [49]. Authors hypothesized that those findings could be due to that angiopoietin-like 4 regulate fatty acid transport among tissues via inhibition of LPL, a key enzyme in HDL-C and triglyceride metabolism. However, this new evidence should be confirmed in the future in other independent studies.

4 Evidence from triglyceride metabolism

Accumulating evidence suggests that elevated plasma TG concentrations, in both the fasting and the postprandial states, are a significant independent risk for CVD [50, 51]. However, it is known that both fasting and postprandial lipoprotein concentrations vary substantially among individuals. This inter-individual variability is driven by genetic factors, the environment and by the complex interactions between gene and diet [52, 53]. In order to elucidate the variability in TG metabolism, numerous evidences have been accumulated with multiple lipid candidate genes in both the fasting and in the postprandial state.

4.1 Evidence from the fasting state

As previously explained for LDL-C, the *PPARA* gene regulates the transcription of genes involved in lipid metabolism [54]. Indeed, the activation of *PPAR-α* can lead to increased LPL expression, which is driven towards plasma clearance of triglycerides and an increase in HDL-C levels. For this reason, this receptor had been widely studied as an important key target for the pharmaceutical industry due to its influence on TG metabolism. Thus, it has been demonstrated that a very common polymorphism (*L162 V*) at *PPARA* gene interacts with dietary PUFA intake in determining fasting TG and apoC-III concentrations. The *162 V* allele was associated with greater TG and apoC-III levels only in subjects consuming a low-PUFA diet [55]. In contrast, when the consumption of PUFA was higher *162 V* was related with the opposite effect on apoC-III. This

particular SNP takes a great importance given that the substitution of a common leucine to valine has been considered functional. However, the study of this particular SNP has had controversial results about its influence on plasma TG and apoC-III concentrations. The previous findings suggest that a habitual dietary PUFA intake can modulate the effects of this SNP on lipid metabolism in humans and this interaction may help to explain both the conflicting results about this particular SNP on lipid metabolism and may help to explain the intra-individual differences in the plasma TG in response to PUFA intake in the diet.

Apolipoprotein A-V (ApoA-V) is an important determinant of plasma triglycerides concentrations. In addition, ApoA-V is a component of lipoproteins such as HDL-C and chylomicrons and plays a role in the activation of LPL. In this regard, a common SNP in the *APOA5* gene (*−1131T>C*) has been clearly related with greater TG concentrations in carriers of the C allele. In addition, with this SNP it is possible to understand how gene–diet interaction can modulate the effect of a genetic polymorphism [56–58]. Thus, in the Framingham study, the consistent association was also demonstrated between the *−1131T>C* and fasting TG concentrations. However, when the potential contribution of the dietary intake in these findings was examined, the authors demonstrated a significant interaction between this SNP and PUFA intake. In this context, the *−1131C* allele was associated with an increase in fasting TG and in remnant-like particle–TG concentrations only in subjects consuming >6% of energy from PUFA.

On the subject of fasting TG variability, another gene–nutrient interaction has recently been demonstrated between *nitric oxide synthase* (*NOS3*) gene and plasma *n*-3 PUFA status. Thus, carriers of the minor allele for *rs1799983* SNP showed higher plasma TG concentrations in those with low plasma *n*-3 PUFA status compared with subjects homozygous for the major allele. In addition, those subjects had a better response to changes in plasma *n*-3 PUFA after supplementation, than major allele homozygotes [59]. This is of great importance given that those individuals might show greater beneficial effects of *n*-3 PUFA consumption to reduce plasma TG concentrations. NOS3 is essential for the regulation of vascular function and blood pressure. However, this enzyme has also been related with atherogenic lipid profile. The mechanism for which this enzyme is associated with lipids could be related with an increase in the L-arginine transport protein in the endothelial caveolae, which play a major role in lipid metabolism and in the development of atherosclerosis [60, 61]. Obviously, this potential relation needs to be confirmed with further mechanistic studies.

4.2 Evidence from the postprandial state

Nowadays, the postprandial period is considered the physiological state in the human metabolism where the assessment of the postprandial lipemic response is the best way to identify disturbances in lipid metabolism [62]. Accumulating evidence points to a role for postprandial lipemia in the pathogenesis of metabolic diseases such as obesity, CVD, and metabolic syndrome (MetS) [50, 51]. Thus, the postprandial state following a fatty meal, especially when the meal is rich in SFAs, induces ''physiological'' postprandial hypertriglyceridemia that may play a pivotal role in the control of atherogenesis. Regarding the genetic component, multiple lipid candidate genes have been investigated in order to explain the enormously wide variability in postprandial response.

Several genetic association studies have continued to strengthen the position of *APOA5* as a major gene that is involved in postprandial lipoprotein metabolism. In this context, Moreno et al. [63] evaluated whether the *APOA5* gene promoter SNP −1131T>C could be involved in the interindividual variability observed during postprandial lipemia. Thus, 51 healthy apo E3E3 male volunteers underwent a Vitamin A fat-load test consisting of 1 g of fat/kg body weight and 60 000 IU of Vitamin A (the meal contained 60% of energy as fat, 15% protein, and 25% carbohydrates and was eaten in 20 min). Blood samples were taken at time 0 and every hour until the 6th and every 2 h and 30 min until the 11th. They demonstrated that healthy men carrying the *−1131C* allele presented higher postprandial TG levels and markedly higher postprandial responses in both large and small TRL. Additionally, these results have been reinforced recently in other independent studies [64, 65]. This fact could be related with the higher risk of coronary artery disease associated with the −1131C allele [66]. In the same line, we studied the combined effects of the GCKR rs780094C→T, APOA5 −1131T→C, and APOA5 56C→G SNPs on postprandial response to a high-fat meal and fenofibrate treatment in two intervention studies in US whites ($n = 1061$). According to previous findings, the results showed that subjects in the risk group had greater postprandial TG response to a high-fat meal. Moreover, subjects in the risk group had greater fenofibrate-induced reduction of fasting TG compared with the other groups. This is of major importance, since it could help us to understand the inter-individual variability in response to fenofibrate treatment [67].

LPL is one of the key enzymes in the metabolism of TRL. We investigated whether the association of LPL *Hind*III (H1/H2) and serine447-Stop (S447X) SNPs explained the inter-individual variability observed during the postprandial state [68]. For that, 51 healthy apo E3E3 male volunteers underwent a Vitamin A fat-load test consisting of 1 g of fat/kg body weight and 60 000 IU of Vitamin A. The fatty meal consisted of two cups of whole milk, eggs, bread, bacon, cream, walnuts, and butter, which was consumed within 20 min. The meal provided 1 g fat and 7 mg cholesterol/kg body weight and contained 60% fat, 15% protein, and 25% carbohydrates. After the meal, subjects were not allowed to consume any calorie-containing food for 11 h. Blood

samples were drawn before the meal, every hour until the 6th hour, and every 2nd hour and 30 min until the 11th hour. We found that carriers of the H1 allele (H1S447 and H1X447 genotypes) presented a lower postprandial lipemic response than subjects with the H2S447 genotype (homozygotes for the H2 allele of the LPL *Hind*III SNP and S447 allele). This is extremely significant, since the modifications observed in postprandial lipoprotein metabolism might be involved in the increased prevalence of coronary artery disease observed in subjects homozygous for the H2 allele of the Hindlll SNP [69, 70] and the lower risk of myocardial infarction associated with H1X447 genotype [71]. Recently, we have shown that two genetic variations at the LPL gene (rs328 and rs1059611) influence plasma lipid concentrations, mainly TRL, and interact with plasma *n*-6 PUFA to modulate lipid metabolism. The understanding of these gene–nutrient interactions could help us learn more about pathogenesis in the MetS [72, 73].

It is known that hepatic lipase is regulated by the synthesis of cholesterol in the liver. However, it is known that this enzyme also influences the hydrolysis of triglycerides and monoglycerides and acts in the catabolism of chylomicrons, which will facilitate the captation by the liver. As we previously commented, the *−514C/T* polymorphism located in the promoter region of the *hepatic lipase* (*LIPC*) gene mediates changes in the plasma levels of the enzyme and lipids. In this regard, we studied whether the presence of this polymorphism modifies the postprandial clearance of lipoproteins of intestinal origin in 51 normolipemic subjects who underwent a vitamin A fat-loading test. Carriers of the T allele showed significantly lower postprandial levels of apoB, total TG in plasma, small TRL, large TRL, and small TRL-cholesterol when compared with subjects homozygous for the C allele. Our data suggested that the T allele of the *−514C/T* polymorphism in the promoter region of the hepatic lipase gene is associated with a lower postprandial lipemic response [74].

Finally, very recently, we have investigated a new candidate gene for TG metabolism – the *melanocortin-4 receptor* (*MC4R*) [75]. This gene codifies MC4R protein, which is expressed in the central nervous system and has a role in regulating feeding behaviour, energy homeostasis, and blood pressure. Variations in this gene have been reported to be linked with common forms of obesity [76, 77]. Previously, an independent genome-wide association study identified four variants (*rs12970134*, *rs477181*, *rs502933*, and *rs4450508*) in high linkage disequilibrium downstream of *MC4R* associated with obesity-related quantitative traits, of which the most strongly associated variant was *rs12970134* SNP [78]. In addition, previous data from Bronner et al. suggest an influence of MC4R activity on triglyceride levels in cardiovascular patients [79]. Looking for additional physiological pathways underlying MC4R effects on lipoprotein metabolism, we explored whether the presence of the *rs12970134* polymorphism near the *MC4R* gene could modulate postprandial lipid metabolism in a healthy population. Thus, after a 12-h fast, volunteers were given a fatty meal enriched with 60 000 IU of vitamin A/m^2 of body surface area. The amount of fat given was 1 g of fat and 7 mg cholesterol/kg body weight. The meal contained 65% of energy as fat, 15% as protein, and 25% as carbohydrates, and was consumed in 20 min. The foods provided were bread, whole milk, eggs, and butter. After this meal, subjects fasted for 11 h, but they were allowed to drink water. Blood samples were drawn before the meal, every hour until the 6th hour, and every 2 h and 30 min until the 11th hour. Interestingly, individuals carrying the G/G genotype displayed a higher postprandial response of large triacylglycerol-rich lipoproteins (large TRL) than carriers of the minor A-allele and they also presented higher concentrations of plasma TG and total cholesterol during the postprandial period than carriers of the A-allele. Furthermore, G/G subjects showed greater postprandial response of small TRL-apo B48 than carriers of the A-allele.

In this regard, this study proposes a link between MC4R, expression of stearoyl-coenzyme A desaturase 1 (SCD 1) in the liver, and plasma TRL [80, 81]. This link has been hypothesized given that it has been demonstrated that modulation of MC3/4R activity in animal models can affect the mRNA expression of SCD 1 in the liver, an enzyme required for fatty acid desaturation and TG synthesis. Therefore, we hypothesised that a more active form of the MC4R linked with the minor A-allele entails a reduced SCD 1 activity, resulting in reduced TG synthesis and a more efficient postprandial response. Previous studies have also reported the relationship between TG plasma levels and MC4R variations [79]. These results suggest that the *rs12970134* polymorphism near the *MC4R* gene may partly explain the inter-individual differences in postprandial lipoprotein response in healthy subjects. Interestingly, increased knowledge of how these and other genes influence postprandial response should increase our understanding of personalised nutrition.

5 Future directions

It is well known that lipid metabolism is a cornerstone in the development of the commonest chronic diseases worldwide, such as obesity, CVD or MetS. Nowadays, all these chronic diseases are approaching epidemic proportions, and this is why our knowledge of the possible control mechanisms in lipid metabolism is a major concern for the future.

In the maintenance of lipid homeostasis, there are complex interactions between binding proteins, enzymes, and receptors that will determine the final phenotype (Fig. 1). Both environmental and genetic factors influence the control of this complex schedule, and diet is the most important external factor. In this regard, it is well known that while general dietary recommendations could be sufficient for a group of people, we must clarify what contributes

to the inter-individual variability in plasma lipid profiles. In this context, of growing evidence of genetic factors and gene–diet interactions, nutrigenetics has helped us to understand this variability over the last few years, since the influence of the interactions between nutrients and individual characteristics has been demonstrated. Indeed, lipid and lipoprotein metabolism are areas in which the understanding of development and progression of CVD has been studied in greater depth and the growing evidence about key players in lipid metabolism has shifted our priorities from general recommendations towards personalised nutrition. Thus, in the field of lipid and lipoprotein metabolism, almost 30 different genes that encode key proteins have been implicated, and over 200 different SNPs have been identified in those genes. In the current review, we have explained the evidence about some of these genes, which is summarized in Tables 1–3.

Nowadays, we know more about the variability in lipid metabolism inter-individuals as well as the variability in other cardiometabolic factors [82–86]. These clues have come from a greater understanding of genetic factors and the study of the complex genotype–phenotype interactions. Our knowledge of how these and other genes influence lipid metabolism response should increase the understanding of personalised nutrition, which in turn could help with current cardiovascular prevention and treatment at this time. However, for the future it is necessary to reach a consensus in order to avoid greater bias over the current growing evidence. Therefore, although the basis of this complex knowledge has been clearly established thanks to the current evidence, we need this basis to be strong and well established. The effective use of therapeutic objectives will require a much more profound knowledge of the role of each relevant target before we will be able to design truly effective nutritional as well as pharmacological therapies in the field of lipid metabolism and other metabolic disorders. Thus, the following considerations must be taken into account for the future:

(i) Replication studies are badly needed in order to achieve higher consistency in the conclusions of the findings, mainly in the study of the interactions between nutritional and genetic factors in dietary intervention studies. Although it is important to stress the difficulty of carrying out an intervention study with a large number of subjects, an effort must be made in the future here, since it has been demonstrated that the same genotype may have different effects on intermediate phenotypes, depending on dietary intakes. Therefore, this issue will help to clarify the reasons for inconsistencies of genetic association studies as well as to understand the intra-individual differences in the plasma lipid response and will help to support a mechanistic relationship between genetic and nutritional factors on which preventive nutritional strategies may be based.

(ii) Large sample sizes and varying ethnicities. These have been one of the most important limitations in nutrigenetics, with very different conclusions depending on the sample size and ethnicity.

(iii) To standardize the design of future studies, so they are mainly focused on intervention studies in which it is necessary to homogenize nutritional information and the measure of potential confounding factors that could have an influence such as gender, age, body mass index, smoking, or physical activity. These potential confounding factors should be added to the statistical analyses, since the influence of those covariables in the final findings has been clearly demonstrated.

(iv) To identify what the real functional genes could be. This is essential in order to understand the variability in lipid metabolism and in the advance of personalised

Table 1. Gene–diet interaction studies into LDL-C

Genes/proteins	SNPs (references)	Results
APOE/ApoE	rs405509 [16]	Carriers of the T allele showed higher concentrations of apoB and LDL-C after the SFA diet compared with GG subjects
PPARA/PPAR-α	rs1800206 [21]	Minor allele is associated with higher fasting total cholesterol, LDL-C, and apoB after a single fat load composed of 60% calories as fat, 15% as protein, and 25% as CHO
APOA1/ApoA-I	rs670 [25]	After a high MUFA diet, carriers of the A allele showed significant increases in LDL-C compared with G/G subjects
APOA4/apoA-IV	rs675 [26, 27]	Carriers of the *347Ser* allele presented a greater decrease in LDL-C when they were switched from the saturated to the NCEP type 1 diet compared with *347Thr* homozygous [26]. *ApoA-1/apoA-4* SNPs influenced the effects of dietary fat on LDL particle size and oxidation [27].
SCARB1/SRB-I	rs4238001 [34]	Exon 1 variant at the locus of the *SCARB-I* gene influences plasma LDL-C in healthy subjects during the consumption of diets with different fat contents. Carriers of the minor allele were more susceptible to the presence of SFA diet because of a greater increase in LDL-C

APOE/Apo-E: apolipoprotein E. *PPARA*/PPAR-α: Peroxisome proliferator-activated receptor α. *APOA1*/ApoA-I: apolipoprotein A1. *APOA4*/ApoA-IV: apolipoprotein A4. *SCARB1*/SRB-I: scavenger receptor class B type I. CHO: carbohydrate. MUFA: monounsaturated. SFA: saturated. CVD: cardiovascular disease.

Table 2. Gene–diet interactions studies into HDL-C

Genes/Proteins	SNPs (references)	Results
APOA1/ApoA-I	rs670 [38]	PUFA intake modulates the effects of this SNP on HDL-C concentrations in a sex-specific manner. In female carriers of the A allele, higher PUFA intakes were associated with higher HDL-C levels. The opposite effect was observed in G/G women. These interactions were not demonstrated in men
TNFA/TNF-α	rs361525, rs1800629 [39]	PUFA intake was positively associated with HDL-C levels in carriers of the −238A allele, but negatively in those with the −238GG genotype. However, the intake of PUFA was inversely associated with HDL-C in carriers of the −308A allele, but not in those with the -308GG genotype
APOA1_A4_A5/ ApoA-I_A-IV_A-V	rs2727784/rs5104, rs5092/rs1263177 [40]	*ApoA1 -2803* (rs2727784) homozygous for the minor allele and *A4A5*_inter (rs1263177) carriers showed a limited degree of postprandial lipemia. Moreover, carriers of the rare alleles of *apoA4 N147S* (rs5104) and *apoA4 T29T* (rs5092) had lower apoA1 levels during this state
LIPC/HL	rs1800588 [41]	T allele was associated with significantly greater HDL-C concentrations and large HDL-C size only in subjects consuming <30% of energy from fat
ABCA1/ABC-1	rs2575875, rs4149272, rs2230806 [45]	For rs2575875 and rs4149272 SNPs, fasting and postprandial values of apoA-1 were higher and postprandial lipemia was lower in homozygous for the major alleles. These subjects also showed a higher apoA-1/apoB ratio, higher HDL-C and lower postprandial apoB concentrations
PPARG/PPAR-γ	rs1805192 [46]	Among *Pro12Pro* homozygotes, total fat intake was inversely correlated with HDL-C levels. In contrast, among *12Ala* carriers the intake of total fat was directly correlated with HDL-C levels

TNFA/TNF-α: tumor necrosis factor-α. *LIPC*/HL: hepatic lípase. *ABCA1*/ABC-1: ATP-binding cassette A1. *PPARG*/PPAR-γ: Peroxisome proliferator-activated receptor γ. PUFA: Polyunsaturated.

Table 3. Gene-Diet Interactions Studies into Triglycerides (TG)

Genes/Proteins	SNPs (references)	Results
PPARA/PPAR-α	rs1800206 [55]	The 162V allele was associated with greater TG and apoC-III levels only in subjects consuming a low-PUFA diet
APOA5/ApoA-V	rs662799 [56]	The *-1131C* allele was associated with an increase in fasting TG and in remnant-like particle-triglyceride concentrations only in subjects consuming >6% of energy from PUFA
NOS3/NOSIII	rs1799983 [59]	Carriers of the minor allele at rs1799983 in NOS3 have plasma TAG concentrations which are more responsive to *n*−3 PUFA
APOA5/ApoA-V	rs662799 [63]	Healthy men carrying the −1131C allele presented higher postprandial TG levels and markedly higher postprandial responses in both large and small TRL
APOA5_GCKR/ApoA-V_Glucokinase Regulator	rs662799, rs3135506_ rs780094 [67]	Subjects in the risk genotype group had significantly higher fasting TG and higher prevalence of hypertriglyceridemia than subjects in the protective genotype group across all population
LPL/LPL	rs320 [68]	Carriers of the H1 allele (*H1S447* and *H1X447* genotypes) presented a lower postprandial lipemic response compared with *H2S447* subjects
LIPC/HL	rs1800588 [74]	Carriers of the T allele showed lower postprandial levels of apoB, total TG in plasma, small TRL-TG, large TRL-TG and small TRL-cholesterol when compared to C/C subjects
MC4R/MC4-R	rs12970134 [75]	Subjects carrying the G/G genotype displayed a higher postprandial response of large-TRL TG than did carriers of the minor A-allele and also presented higher concentrations of plasma TG and total cholesterol during the postprandial period than did carriers of the A-allele

GCKR/Glucokinase Regulator: glucokinase regulatory protein. NOS3: nitric oxide synthase. IL1β/IL-1 β: interleukin 1B. LPL: lipoprotein lipase. *LIPC*/HL: hepatic lipase. *MC4R*/MC4-R: melanocortin receptor 4.

nutrition. Moreover, this could open the door to the study of new gene–gene interactions. Therefore, it is clear that personalised therapies will only prosper when we are able to transform the findings of the studies into suitable functional information through the study of the best key players in metabolic disorders.

(v) At present, the postprandial period is considered the physiological state in the human metabolism in which

the assessment of the postprandial lipemic response could be the best way to identify disturbances in lipid metabolism. However, large prospective studies assessing the magnitude of genetic factors on lipid metabolism are lacking. Increased knowledge about personal variability in postprandial lipemia would increase our understanding of personalised nutrition.

(vi) As with other gene-based sciences, epigenetics may play an important role in nutrigenetics. The final assembly of the coded proteins and its functionality is critically important, and the posttranscriptional changes applied to them may influence their final effects. The discovery and further study of genes and micro-RNAs (apparently unrelated with the lipid metabolism but which epigenetically control the final activity of species involved in this metabolism) will be essential in order to reveal the interindividual nutrigenetics differences.

(vii) Transcription factors emerge, on the other hand, as important players in lipid metabolism, especially in the postprandial responses from adipocyte and other cells. These factors usually act at various points of the metabolic chain, causing coordinated activation of different enzymes and proteins involved in lipid management. Our knowledge of their exact functions, as well as the consequences derived from variations in their coding genes, may be important to our understanding of the lipid physiology.

6 Concluding remarks

It has been demonstrated clearly that lipid metabolism is an important determinant of the growing metabolic disorders, which indicates that understanding its homeostasis is a matter of concern for both therapy and prevention targets in the future. Although the lipid response can be modified by diet, it is well known that this response is highly complex with high variability between subjects. Over the last few years, we have progressed in our knowledge and understanding of this variability, but it is now time to consolidate all this evidence with replications and standardised studies, as well as to continue discovering new factors involved in lipid metabolism. Such studies may be useful in identifying the mechanisms through which dietary components influence lipid levels, and this will facilitate the identification of subjects with a risk of developing metabolic disorders with whom preventive measures or suitable personalised dietary interventions can be started.

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