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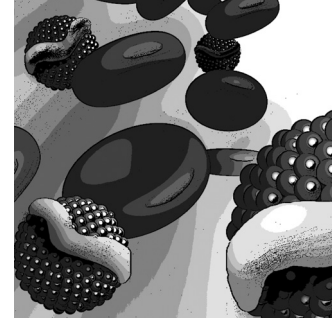
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Interaction between diets, polymorphisms and plasma lipid levels

Cardiovascular disease (CVD) is responsible for significant morbidity and mortality. Dietary guidelines that aim to manage fat intake reduce CVD, but an important interindividual variability in plasma lipid responsiveness is observed in individuals following these diets. This interindividual variability in response to diets may be attributable to several single nucleotide polymorphisms (SNPs) in genes encoding key proteins involved in lipoprotein metabolism. In this article, we discuss the effect of different diets, classified by type of dietary fats, on plasma lipid levels in relationship to various polymorphisms in key genes that may affect lipid and lipoprotein metabolism. In summary, various polymorphisms may predispose an individual to be more or less responsive to a specific dietary intervention; however, future studies need to be conducted to confirm the effect of these various SNPs. In conclusion, this article reinforces the importance of taking account genetic variability into account in order to personalize potential future dietary recommendations for the prevention and management of hyperlipidemia.

KEYWORDS: diet ■ genetic variation ■ HDL-C ■ LDL-C ■ low-fat diet ■ monounsaturated fat ■ n-3 polyunsaturated fat ■ polyunsaturated fat ■ total cholesterol ■ triglyceride

Cardiovascular disease, diets & polymorphisms

Cardiovascular disease (CVD) is the leading cause of death in adult men and women among all racial and ethnic groups. Epidemiological surveys have shown that plasma total cholesterol (TC) levels are correlated with CVD risk. Since plasma LDL-C levels correlate highly with TC in populations, the same relationship must exist between LDL-C concentrations and CVD risk [1]. In addition, there is increasing evidence that plasma triglycerides (TGs) are strong risk factors for CVD [2]. It has been demonstrated that the onset of most major diseases, including CVD, is modulated by the interaction between genetic and environmental factors, particularly diet. Several dietary approaches have reduced plasma lipid levels. For example, diets high in monounsaturated fat (MUFAs; e.g., the Mediterranean diet), diets high in polyunsaturated fats (PUFAs; including n-3 PUFA supplementation), low-fat diets (that are also low in saturated fatty acids [SFAs]) and low-cholesterol diets, have all been studied in relationship to CVD risk factors in numerous epidemiological and clinical trials [3]. Yet, even if these diets show beneficial effects on plasma lipids at the population level, there is a large interindividual variability in response

to a therapeutic diet [4]. A model example of interindividual variability is a study by Schaefer *et al.*, which demonstrates an overall reduction of LDL-C of 19 and 16% in men and women, respectively, with corresponding response ranges of +3 to -55% and +13 to -39% after feeding a National Cholesterol Education Program (NCEP) Step 2 diet [5]. Overall, the NCEP Step 2 diet was effective in reducing plasma cholesterol levels. However, the magnitude of plasma lipid response to changes in diet can vary greatly between individuals depending on baseline lipid levels, age and whether or not specific polymorphisms are carried. Several SNPs for key proteins in lipoprotein metabolism have been identified and linked to variable responses to diets, such as ApoE, A-I, A-IV, A-V, B and C-III, LDL receptor (LDLR), cholesteryl ester-transfer protein (CETP), lipoprotein lipase (LPL), hepatic lipase (LIPC), peroxisome proliferator-activated receptors- α (PPARA), - δ (PPARD) and - γ (PPARG), microsomal TG transfer protein (MTTP), intestinal fatty acid binding protein 2 (FABP2), cholesterol 7 α -hydroxylase (CYP7A1), scavenger-receptor class B type I (SCARB1), liver X-receptor- α (LXRA), ghrelin (GHRL), melanocortin 4 receptor (MC4R) and liver fatty acid-binding protein (LFABP)

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(Figure 1). In this article, we review studies to determine the effects of different diets (according to dietary fat composition) on plasma lipoproteins related to a variety of SNPs in genes encoding for proteins directly or indirectly involved in lipid metabolism. We end with the limitations of current nutrigenomic research, a future perspective and a summary of results of the studies on personalized nutrition therapies for lipid disorders.

High-monounsaturated fat diets & polymorphisms

Epidemiologic studies link Mediterranean-type diets to a low incidence of coronary heart disease (CHD) [6]. Olive oil, a rich source of MUFAs, is a main component of the Mediterranean diet. Numerous studies have established that diets rich in MUFA lower LDL-C, increases HDL-C and may modestly lower TC and TG, especially when compared with diets high in carbohydrates [3]. Furthermore, diets high in MUFA may have other potential antiatherogenic effects, such as decreasing the susceptibility of LDL to oxidation, improving endothelial function and reducing the level of inflammatory markers and platelet aggregation. Yet, there is variability in response of lipid levels to a high MUFA diet, which may be due to genetic variability of the population. In this section, we will review studies on the effects of high-MUFA diets or Mediterranean diets (defined as 20–25% MUFA in diet) and genetic variation on lipid levels.

Table 1 summarizes the effects of various polymorphisms and a MUFA-rich diets on plasma lipid and lipoprotein levels.

APOE E2/E3/E4 (rs7412) is the most intensively studied polymorphism in response to dietary interventions. ApoE acts as a ligand for a number of lipoprotein receptors located in the liver and other tissues and plays a part in the process of TG-rich lipoprotein uptake. It is also involved in the reverse transport of cholesterol from peripheral tissues to the liver, stimulates cellular efflux of cholesterol and regulates its absorption by the intestine and its excretion in bile [7]. Subjects with the *APOE* E4/E4 or *APOE* E4/E3 genotypes also appear to be more responsive to changes in the quality of dietary fat than those who have *APOE* E2 genotypes [8,9]. Yet, some studies show that the heterogeneity of lipoprotein responses to dietary intervention, such as high-MUFA diets, is unrelated to *APOE* phenotypes [10,11]. However, the shift from the SFA-rich to carbohydrate- or MUFA-rich diets decreased the plasma ApoE concentration in *APOE* E3/E2 and *APOE* E3/E3 subjects in women, but not in men, whereas no differences were observed in women with the *APOE* E4/E3 genotype [12]. Furthermore, the *APOE* genotype is a major genetic determinant of LDL size. Along with the carbohydrate diet, an increase in LDL particle size was noted with MUFA diet in *APOE* E4/E3 subjects, whereas a decrease was observed in the *APOE* E3/E3 individuals [13]. Overall, a diet high in MUFA may

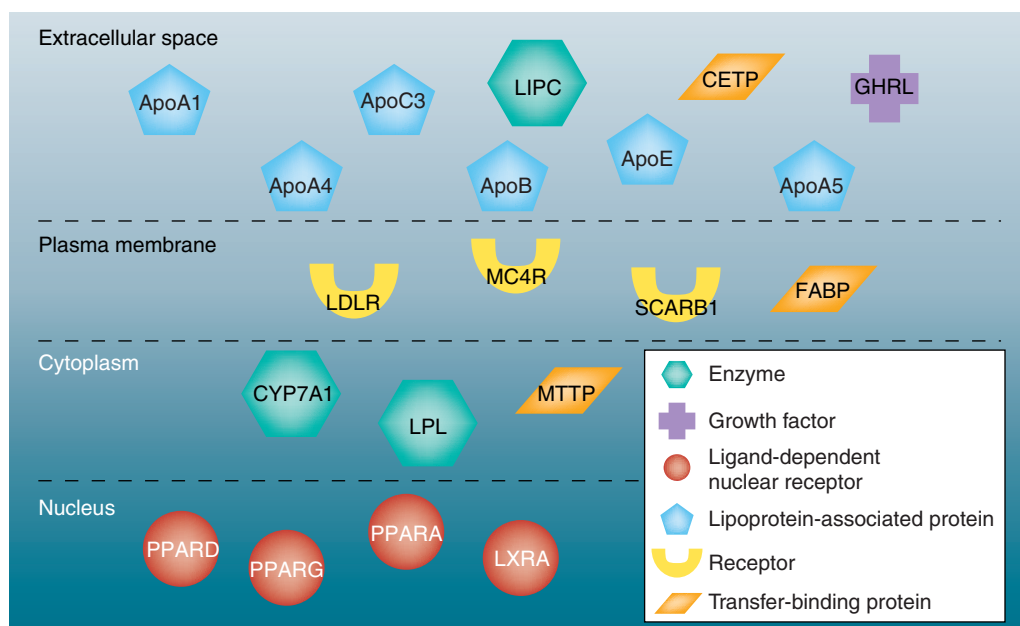


Figure 1. Location and function of genes involved directly or indirectly to lipid metabolism.

Table 1. Summary of studies that have demonstrated interactions between diets, polymorphisms and plasma, lipids and lipoproteins.

Gene (OMIM gene symbol)	Polymorphism (rs no.)	Minor allele	After high-MUFA diet (including Mediterranean diet)	After high-PUFA diet	After high-n-3 PUFA diet	After low-fat diets	After high-fat, high-SFA and/or high-cholesterol diet	Ref.
Apolipoprotein E (APOE)	E2/E3/E4 (rs7412 or rs429358)	E4	8–10% higher response to dietary fat ↔ plasma ApoE ↑ LDL particle size; threefold ↑ reduction LDL-C	↑ baseline LDL-C	9% ↓ baseline HDL-C ↑ LDL-C levels ↓ trend HDL-C levels	↑ TG after low PUFA:SFA diet	[8,9,12,13, 28,37,51]	
		E2	12% ↓ plasma ApoE in women ↓ LDL particle size; fourfold ↑ reduction TG	↑ baseline TG and VLDL	28% ↓ incremental TG response ↑ Lipoprotein lipase activity		[12,13,28, 37,51]	
	-219G→T	T allele				14% ↑ LDL-C and 10% ↑ ApoB lowering	↑ baseline LDL-C and ApoB [57]	
Apolipoprotein A-I (APOA1)	-75 G/A (rs670)	A allele	↑ LDL-C (+10 mg/dl) and ApoB (+4 mg/dl)	↑ baseline TC, LDL-C and TG; ↑ TC and LDL-C lowering (-0.87 and -0.74 mmol/l); interaction with smoking		↓ baseline TC, LDL-C and ApoB Similar TC and LDL-C lowering to G allele	[14,32,58]	
Apolipoprotein C-III (APOC3)	SstI (rs5128)	S2 allele	↑ lowering by 1% TC, 7% LDL-C and 7% ApoB; interaction with smoking			↓ atherogenic ratio	[16,17]	
Apolipoprotein A-IV (APOA4)	Gln360His (Q360H) (rs5110)	360His	↑ HDL-C (9 vs 1 mg/dl) and ApoA-I (9 vs 2 mg/l) increases	↓ cholesterol absorption ↑ dense LDL-C		↓ baseline LDL-C and ApoB ↑ HDL-C lowering (-10 vs -1 mg/dl); ↑ ApoA1 lowering (-19 vs -8 mg/dl) ↓ reduction ApoB (6% vs 14%) ↔ LDL-C response 4% ↓ response to diet	[18,34,35, 59,66]	
	Thr347Ser (rs675)	Ser allele	5% ↑ TC and ApoB; fourfold ↓ LDL-C lowering	9% ↓ cholesterol absorption		↔ baseline or post-diet values in lipid; ↑ reduction by 37% TC, 50% LDL-C and 43% ApoB ↔ response; 17% ↓ TC response if Ser/Ser	[19,28,34, 59,66]	
	PvuII		Correlation between LDL-C levels and dietary MUFA				[62]	

Note: Approximate effect size as calculated from original manuscript when available.
 CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; TC: Total cholesterol; TG: Triglyceride.

Table 1. Summary of studies that have demonstrated interactions between diets, polymorphisms and plasma, lipids and lipoproteins (cont.).

Gene (OMIM gene symbol)	Polymorphism (rs no.)	Minor allele	After high-MUFA diet (including Mediterranean diet)	After high-PUFA diet	After high-n-3 PUFA diet	After low-fat diets	After high-fat, high-SFA and/or high-cholesterol diet	Ref.
Apolipoprotein A-V (APOA5)	-1131T>C (rs17120035)	C allele		↑ fasting TGs (34%), VLDL size and ↓ LDL size after high n-6 (but not n-3) PUFA diet			↑ 13% TG and 4% TC	[36,67]
	Ser19>Trp (S19W) (rs3135506)	Trp allele				5% ↓ baseline HDL-C; 21% ↑ TC lowering		[66,67]
Apolipoprotein B (APOB)	XbA1 (rs693)	X ⁻	↑ baseline TC and TG; ↑ TC and LDL-C levels; ↔ TG; ↓ changes in lipids response (39% TC and 49% LDL-C)			↑ TC and LDL-C levels; correlation between changes in TC and LDL-C and low-fat diet	↑ TC and LDL-C levels; ↓ increase LDL-C (11%)	[20–22,62,68]
	MSP1 (rs1801701)	M ⁺					↑ LDL-C and TG response (14%)	[68]
	ECOR1 (rs1042031)	R ⁻					↑ LDL-C increase (21%)	[68]
	signal peptide insertion/deletion, (rs1127910)	I/I				↔ responsiveness in ten studies		[68]
	1896 (His→Arg)	Arg allele				↑ responsiveness in two studies		[68]
	-516C/T	T allele	Unresponsive to diet			↑ LDL-C levels in men		[60]
						↔ risk factors at baseline		[23,61]
						Unresponsive to diet		[39]
Cholesteryl ester transfer protein (CETP)	I405V (rs5882)	V allele	↔ baseline lipids; ↑ ApoA-I and HDL-C lowering after low- PUFA-SFA diet					[40]
	TaqIB (rs708272)	B1 allele	0.44 mmol/l ↑ TC lowering					[40]
Lipoprotein Lipase (LPL)	S447X	X allele	0.45 mmol/l ↑ TC lowering					[40]
	HindIII	H ⁻ allele	↑ TC and TG response (13%)					[41]

Note: Approximate effect size as calculated from original manuscript when available.
 CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; TC: Total cholesterol; TG: Triglyceride.

Table 1. Summary of studies that have demonstrated interactions between diets, polymorphisms and plasma, lipids and lipoproteins (cont.).

Gene (OMIM gene symbol)	Polymorphism (rs no.)	Minor allele	After high-MUFA diet (including Mediterranean diet)	After high-PUFA diet	After high-n-3 PUFA diet	After high-fat, high-SFA and/or high-cholesterol diet	Ref.
Hepatic Lipase (LIPC)	-480 C/T (-514 C/T) (rs1800588)	T allele	Impaired adaptation to SFA and MUFA			↑ HDL-C, TG and ApoA-1 levels; ↑ atherogenic lipid profile	[24–26,63]
	G-250A	A allele	↑ baseline LDL-C; ↑ LDL-C lowering (-0.77 mmol/l)				[26]
	T1111	I1111		↑ HDL ₃ -C levels in women ↑ ApoA1 levels in women			[42]
Peroxisome proliferator-activated receptor γ (PPARG)	Pro12Ala (rs1801282)	12Ala	Interaction with dietary fat intake; ↑ HDL-C and TC		↑ TG lowering when n-3 PUFA added to high-fat or SFA diet		[27,53]
	XbaI (4.5 kb/8.6 kb)	8.6 kb				↑ TG levels	[72]
Peroxisome proliferator-activated receptor α (PPARA)	L162V (rs1800206)	V allele		↑ ApoB and TG levels; ↑ TG when PUFA intake was <4% but ↓ TG when PUFA intake was >8%; interaction with TC, ApoA1 and cholesterol concentrations in small LDL particles	↔ TG lowering ↑ CRP levels		[45–47,52]
	3'UTR G→A (rs6008259)	A allele		↓ TC and LDL-C levels			[48]
	3'UTR C→T (rs3892755)	T allele			↓ TC and LDL-C levels in African-American individuals only		[48]
Peroxisome proliferator-activated receptor δ (PPARD)	-87T→C	C allele				15% ↓ HDL-C levels; ↑ TC: HDL-C ratio	[70]
Microsomal triglyceride transfer protein (MTTP)	-493G/T	T allele	3-fold ↑ LDL-C and TG lowering ↓ CVD risk in men				[28,29]

Note: Approximate effect size as calculated from original manuscript when available.
 CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; TC: Total cholesterol; TG: Triglyceride.

Table 1. Summary of studies that have demonstrated interactions between diets, polymorphisms and plasma, lipids and lipoproteins (cont.).

Gene (OMIM gene symbol)	Polymorphism (rs no.)	Minor allele	After high-MUFA diet (including Mediterranean diet)	After high-PUFA diet	After high-n-3 PUFA diet	After low-fat diets	After high-fat, high-SFA and/or high-cholesterol diet	Ref.
Intestinal fatty acid binding protein (FABP or FABP2)	Ala54Thr (rs1799883)	T allele	↑ baseline TG-rich lipoprotein in men ↓ baseline TG-rich lipoprotein in women; fivefold ↑ TG lowering				↔ baseline lipids levels; ↑ TC, LDL-C and TG with greater SFA; ↓ HDL-C/TC ratio with greater SFA	[28,29,73]
Cholesterol 7 α -hydroxylase (CYP7A)	-278A→C	C allele				5–6% ↑ TG lowering		[64]
Scavenger receptor class B type 1 (SCARB1)	exon 1 variant (G→A) (rs4238001)	A allele				7% ↑ LDL-C lowering	Trend ↑ LDL-C levels with greater SFA	[65]
Liver X receptor α (LXRA)	-115G→A	A allele					↑ baseline 3% TC and 9% TG levels; ↑ 10% TC and 16% LDL-C after high cholesterol diet	[71]
Ghrelin (GHL)	-840C→A	A allele					↑ baseline 3% TC and 9% TG levels; ↑ 10% TC and 16% LDL-C after high cholesterol diet	[71]
	-1830T→C	C allele					↑ baseline 3% TC and 10% TG levels; ↑ 10% TC and 16% LDL-C after high cholesterol diet	[71]
Melanocortin 4 receptor (MC4R)	Leu72Met Val103Ile (rs2229616)	Leu allele Ile allele					↑ TG levels	[72]
Liver fatty acid binding protein (LFABP)	T94A	A allele					↓ Apob levels	[69]

Note: Approximate effect size as calculated from original manuscript when available. CRP: C-reactive protein; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein-cholesterol; MUFA: Monounsaturated fatty acid; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; TC: Total cholesterol; TG: Triglyceride.

influence plasma lipids, plasma ApoE levels, LDL particle size and this effect may be related to *APOE* genotypes.

ApoA1 is the major protein component of HDLs. Additionally, ApoA1 is an activator of the enzyme lecithin-cholesterol acyltransferase (LCAT), which is a key component of reverse cholesterol transport. Therefore, polymorphism-75 (G/A; rs670) within the *APOA1* gene may affect plasma lipid response to changes in amount of dietary fat. More precisely, a study demonstrated no differences at baseline in lipid levels between subjects with the G/G and the G/A genotypes. However, after consumption of the high-MUFA diet, increases were noted in LDL-C in the G/A subjects, but not in the G/G subjects [14]. Thus, subjects carrying the A allele may benefit more from other types of diets.

ApoC3 inhibits LPL and binding of ApoE-containing lipoproteins to their receptors. The SstI polymorphism (rs5128) of the *APOC3* gene distinguishes between two alleles: S1 and S2. The S2 allele has been associated with elevated plasma TG, TC and ApoC-III concentrations [15]. Lopez-Miranda *et al.* investigated the effect of this mutation on the response of LDL-C to dietary MUFA in 90 young men [16]. There were no differences in plasma cholesterol levels between subjects with the S1/S1 and S1/S2 genotypes. After consumption of the diet high in MUFA, increases in LDL-C were noted in the S1/S1 subjects whereas a decrease was observed in the S1/S2 subjects [16]. Furthermore, the researchers examined the interaction between this mutation and the *APOA1* -75 (rs670) polymorphism, which revealed an additive effect on changes in plasma TC, LDL-C and ApoB induced by diets [16]. In addition, Perez-Martinez *et al.* investigated whether this polymorphism had differential effects in smoking and nonsmoking volunteers [17]. Results demonstrate that smokers carrying the S1/S1 genotype were not influenced by any of the diets – SFA, MUFA or low-fat – but the atherogenic ratio decreased in the carriers of the S2 allele when they changed from the diet rich in SFA to a MUFA or low-fat diet. No difference was observed when the nonsmoking carriers of the S2 allele changed diet, but there was a decrease in the LDL-C:HDL-C ratio when the subjects with the S1/S1 genotype changed from the SFA diet to either the MUFA or the low-fat diet [17]. Overall, lipid responsiveness to the diet may also be explained, at least in part, by variation at the *APOC3* gene locus.

ApoA-IV (*APOA4*) has been related to fat absorption and to the activation of some of the enzymes involved in lipid metabolism. Jansen *et al.* aimed to investigate whether genetic mutation of *APOA4* Gln360His (rs5110) was accountable for the improvement in lipid profile when dietary SFA are replaced by carbohydrates or MUFA [18]. Briefly, the replacement of carbohydrates by MUFA produced a greater increase in plasma HDL-C and ApoA-I levels in carriers of the 360His mutation [18]. Furthermore, there also exists another polymorphism commonly described in the *APOA4* gene which causes substitution of Ser for Thr at position 347 (Thr347Ser, rs675). A study demonstrated that the change from the NCEP to MUFA diet resulted in a 5% increase in plasma TC and ApoB levels in the Ser allele compared with a 1% decrease in the T/T genotype [19]. In addition, when researchers combined the *APOA4* Thr347Ser and *APOA1* -75 polymorphisms, carriers of the A and the Ser alleles showed greater LDL-C responses to changes in dietary fat [19]. These results suggest that the response to dietary fat is influenced by the *APOA4* Gln360His and Thr347Ser polymorphisms, and this may be in combination.

ApoB (APOB) is essential for the assembly and secretion of chylomicrons in the intestine and the VLDL in the liver. Moreover, APOB is a ligand for a number of lipoprotein receptors. Several polymorphic sites in the gene locus for APOB have been observed. A common polymorphism is the X⁺ allele of the XbaI restriction fragment polymorphism (rs693) of the *APOB* gene, which has been found to be associated with higher plasma TC and TG levels [20]. Similarly, another study demonstrated that X⁺ individuals had higher levels of TC and LDL-C after the consumption of a SFA, NCEP and MUFA diet in comparison with X⁻ individuals [21]. Furthermore, the Lopez-Miranda *et al.* study established a decrease in TG in the X subjects after the high intake of a MUFA diet, while no differences were observed in the X⁺ individuals [21]. In addition, Friedlander *et al.* examined the role of numerous polymorphisms in the *APOB* gene (signal peptide insertion/deletion, rs11279109; XbaI, rs693; MspI, rs1801701; and EcoRI, rs1042031), *LDLR* gene (AvaII, StuI and HincII), the *CYP7A1* gene (intron 2, intron 4) and the *APOE* genotypes (E2/E3/E4, rs7412) in relation to lipid and lipoprotein response to diet [22]. Briefly, investigators recruited 23 students who followed a high-MUFA diet

and were then switched to a high-PUFA diet. The researchers combined the analysis of data from both diets owing to similarities in the baseline characteristics and in the changes in both plasma TC and LDL-C levels after both diets [22]. There were no differences in dietary responsiveness among the *APOE*, *LDLR* and the *CYP7AI* genotypes [22]. However, the average reductions induced by diet in participants who were XX homozygous for the *APOB* gene were higher compared with those carrying the X⁺ allele. Furthermore, genetic variation in the *APOB* gene region, as defined by haplotypes, accounted for 9 and 24% of the phenotypic variance in TC and LDL-C response to diet, respectively [22]. Moreover, Perez-Martinez *et al.* tested whether the presence of another polymorphism in the *APOB* gene promoter (-516C/T) modified the lipid response in healthy subjects who consume either a carbohydrate or MUFA diet [23]. Results demonstrated no differences in plasma lipid response after changes in dietary fat intake in relation to the -516C/T polymorphism. Thus, several polymorphisms in the *APOB* gene may be associated with the dietary response of TC and LDL-C.

LIPC (also known as hepatic lipase [HL]) is a lipolytic enzyme that hydrolyzes TG and phospholipids on plasma lipoproteins, and is also a key determinant of HDL metabolism. The rare variant of the -480C/T (also called -514C/T; rs1800588) polymorphism has been associated with lower LIPC activity. Ordovas *et al.* reported an interaction between -514C>T polymorphism at the *LIPC* gene and dietary fat, SFA and MUFA intakes, on HDL-C metabolism in subjects participating in the Framingham Heart Study [24]. Specifically, T/T subjects demonstrated an impaired adaptation to higher animal SFA and MUFA intake [24]. Furthermore, Tai *et al.* examined this gene–nutrient interaction in a sample population of Singaporeans [25]. Data demonstrate that T/T subjects showed higher TG concentrations only when consuming a high-fat diet (>30% of total energy) without any differences in fat quality [25]. Another common G-250A polymorphism in the promoter of the *LIPC* gene has been recently examined. In a study by Lindi *et al.*, the A/A genotype of the *LIPC* gene was associated with high baseline LDL-C, but the MUFA-enriched diet reduced LDL-C concentrations, especially in these subjects [26]. In summary, *LIPC* polymorphisms may modify an individual's reaction to MUFA-rich diets.

Peroxisome proliferator-activated receptor- γ is a nuclear receptor that functions as a ligand-dependent transcription factor. The Pro12Ala polymorphism (rs1801282) in the *PPARG* gene has been demonstrated as an important factor in physiological responses to dietary fat. Memisoglu *et al.* demonstrated that intake of MUFA was not associated with BMI among homozygous Pro12 women, but was inversely associated with BMI among 12Ala-variant allele carriers [27]. Furthermore, the association between dietary fat intake and plasma lipid concentrations also differed according to *PPARG* genotype. In summary, polymorphisms in *PPARG* may be modified by dietary fat, with MUFA fats having beneficial effects on individuals who carry this particular polymorphism.

In addition, Vincent *et al.* carried out a large intervention study to examine the interactions between diets, normally the MUFA (Mediterranean type) or low-fat diet versus the Western diet [28]. They examined a large assortment of SNPs including: *APOE* (E2/E3/E4, rs7412), *APOB* (-516C/T, rs934197), *APOC3* (SstI, rs5128), *APOA4* (Ser347Thr, rs675), *MTTP* (-493, G/T), *FABP2* (Ala54Thr, rs1799883), *CETP* (TaqIB, rs708272) and *LIPC* (-480C/T, rs1800588). The investigators' preliminary findings demonstrate that some SNPs showed interactions with diets in relation to changes in particular variables, in particular: *APOE* (E2/E3/E4, rs7412) E4 and E2 had greater reduction in LDL-C and TG, and the T allele of *APOA4* (Ser347Thr, rs675) gene had a greater reduction in LDL-C [28]. The SNP (A54T) of the *FABP2* gene has been previously associated with hypertriglyceridemia, obesity, hyperinsulinemia and increased insulin resistance. Results of this study show that men and women with T/T allele presented an opposite pattern for TG-rich lipoprotein cholesterol at baseline, with the highest values observed in T/T men and the lowest values in T/T women. Nevertheless, the *FABP2* genotype did not impact the interindividual variability of response to the dietary intervention. Second, a number of polymorphisms in the *MTTP* gene, which plays an essential role in the assembly of VLDL in the liver and chylomicrons in the intestine, as well as regulating the transfer of TG and phospholipids to lipoproteins, have been described. Results demonstrate that subjects homozygous for the T allele displayed a more pronounced response to dietary intervention for plasma TC and TG, while the lowering of cardiovascular

risk was more pronounced in T/T men than T/T women. The follow-up analysis of this study by Lairon *et al.* indicated more interactions with diets regarding changes of these specific lipid parameters [29]. In particular, investigators looked at several other SNPs, such as: *APOE* (-219, G/T), *SCARB1* (exon1, G/A, rs4238001; exon8, C/T, rs5888; intron5, G/A), *LPL* (-93 G/T, rs1800590) and angiotensin I-converting enzyme 1 (*ACE*; insertion/deletion, rs1799752). The authors calculated that the overall SNP analyses could predict up to 23% of the change in blood biochemical pattern during the dietary intervention [29]. Overall, these results provide evidence of the interaction between some polymorphisms in genes coding for *APOE*, *APOA4*, *APOB*, *MTTP* and metabolic parameters, which indicate the importance of polymorphisms in modulating response to diets and controlling nutritional status and metabolic homeostasis.

In summary, the above studies provide evidence of an interaction between SNP and lipid and lipoprotein responses to diets. The strongest evidence of a gene–nutrient interaction includes *APOE*, *APOA1*, *APOC3*, *APOA4*, *APOB*, *LIPC*, *PPARG* and *MTTP*. However, possible polymorphisms in other genes, such as *CETP*, that may also impact an individual's response need to be confirmed. Overall, it is clear that an individuals' response to a high-MUFA diet is probably due to a combination of polymorphisms; yet, much research remains to be conducted in order to determine the particular genotypes and/or haplotypes that have the highest response to MUFA diets.

Diets high in polyunsaturated fats & polymorphisms

Dietary intervention trials using high-PUFA diets (defined as $\geq 4\%$ PUFA of total fat intake), including n-6 PUFA and n-3 PUFA, have been more effective than those using low-fat, high-carbohydrate diets in lowering TC and rates of CVD [30]. Furthermore, the PUFA:SFA ratio was strongly associated with a lower risk of CVD in the Nurses' Health Study [31]. In general, the literature shows clearly that n-6 PUFAs decrease LDL-C without changing HDL-C [3]. However, it has been suggested that high intakes of n-6 PUFAs may have a harmful effect on inflammatory processes, especially when the n-6:n-3 PUFA ratio is extremely high. On the contrary, n-3 PUFAs have strong anti-inflammatory properties and have been shown to lower TG in numerous studies. However, when

we examine the individual studies, a large discrepancy in lipid levels exist following the consumption of a high-PUFA diet. **Table 1** details the responses of plasma lipids and lipoproteins of subjects with various polymorphisms in pertinent genes after high-PUFA diets.

A study examined the response to dietary fat saturation as a function of the *APOA1* -75 G/A (rs670) mutation [32]. Subjects were first fed a SFA-rich diet, followed by a MUFA- and PUFA-rich diet. Subjects carrying the A allele had higher TC, LDL-C and TG levels than those homozygous for the G allele. A PUFA diet induced greater plasma TC and LDL-C decreases in G/A women than in G/G subjects when compared with the SAT diet [32]. Furthermore, Odorvas *et al.*, [33] studied a population-based sample from the Framingham Offspring Study for the *APOA1* -75 G/A polymorphism [33]. At baseline, no differences were observed between G/G subjects and carriers of the A allele for any lipid variables. However, G/G subjects had approximately 14% higher HDL-C levels than carriers of the A allele when PUFA intake was less than 4% of energy intake. On the other hand, HDL-C concentrations in carriers of the A allele were 13% higher than those of G/G subjects when PUFA intake was less than 8%. Overall, the *APOA1* -75 G/A polymorphism appears to have an effect on plasma TC, LDL-C and HDL-C responsiveness to increase PUFA in diet, especially in women.

In addition, Weinberg *et al.* investigated the effect of the *APOA4* (Q360H (Gln360His), rs5110) and dietary fat on cholesterol absorption in humans [34]. After a high-SFA diet or a low-fat diet, there was no difference in cholesterol absorption between the two genotype groups. However, cholesterol absorption was higher in Gln/Gln subjects than in Gln/His subjects on high-PUFA diet. Furthermore, the analysis of the effect of the *APOA4* T347S (rs675) polymorphism showed a Q360H \times T347S interaction on cholesterol absorption and suggested that the Q360H only lowers cholesterol absorption in subjects with the 347 T/T genotype [34]. Furthermore, the Wallace *et al.* group investigated the impact of polymorphisms in the genes for *APOB* signal peptide ins/del (rs11279109), *APOA4* T347S (rs675) and Q360H (rs5110), *LPLR* S447X (rs328) and *CETP* (TaqlB, rs708272) variation in changes in plasma concentrations of dense LDL between a high-SFA and a high-PUFA diet [35]. Of the polymorphisms studied only variation in *APOA4*

Gln/His individuals demonstrated a greater change in cholesterol within dense LDL particles than Gln/Gln individuals [35]. An increase in PUFA observed in individuals with the *APOA4* Gln360His variant suggests that they may benefit most from a PUFA-rich lipid-lowering diet.

The *APOA5* gene encodes a protein that is an important determinant of plasma TG levels and variations may be associated with worse plasma TG levels. Lai *et al.* demonstrated significant gene–diet interactions between the -1131T>C (rs17120035) polymorphism of *APOA5* and PUFA intake for fasting TGs, remnant-like particle concentrations and particle size, but these interactions were not observed for the 56C>G polymorphism of *APOA5* [36]. In more detail, the higher n-6 PUFA intake increased fasting TGs, remnant-like particle concentrations and VLDL size, and decreased LDL size in *APOA5* -1131C carriers [36]. This study suggests that n-6 PUFA-rich diets are related to a more atherogenic lipid profile in individuals with the *APOA5* -1131T>C polymorphism.

More recently, a study by Paula *et al.* investigated the impact of a variety of SNP including *APOE* (E2/E3/E4, rs7412), *APOA5* (-1131T>C, rs17120035) and *APOB* (XbA1, rs693), together with dietary intake on lipid profile in elderly women in Brazil [37]. There was no association of the *APOA5* and *APOB* genotypes with lipid levels and diet [37]. At baseline, individuals carrying the *APOE* E2 allele demonstrated higher TG and VLDL compared with *APOE* E4 carriers, whereas LDL-C levels were considerably elevated in *APOE* E4 compared with *APOE* E2 carriers. Yet, in the presence of a high intake of total fat or a low ratio of PUFA:SFA, *APOE* E4 carriers lost protection against hypertriglyceridemia [37]. Therefore, these results emphasize the importance of a low-fat or high-PUFA:SFA diet for individuals with *APOE* E4.

Cholesteryl ester-transfer protein facilitates the transport of cholesteryl esters and TGs between the lipoproteins. Rare mutations leading to the increased function of *CETP* have been linked to accelerated atherosclerosis [38]. Thus, Darabi *et al.* investigated whether the *CETP* I405V (rs5882) polymorphism modifies the response to changes in the dietary ratio of PUFA:SFA [39]. At baseline, lipid or lipoprotein concentrations were not significantly different among *CETP*I405V genotype groups. Yet, after the low-PUFA:SFA diet, subjects carrying the V allele had greater reduction in plasma ApoAI and HDL-C levels than subjects with I genotype [39]. Furthermore, Wallace

et al., [40] examined free-living individuals, who followed two dietary regimens: a high SFA diet and a high PUFA fat diet. They investigated the influence of *APOC3*- C1100T (rs4520), *APOB* signal peptide ins/del (rs11279109), *CEPT*TaqIB (rs708272), *APOE* (E2/E3/E4, rs7412) and *LPL* HindIII (rs320) and S447X polymorphisms on lipid parameters. Only, individuals with the *CETP* B1B1 genotype and the *LPL* X447+ allele showed a greater change in TC than those with one or more *CETP* B2 alleles or homozygous for the *LPL* S447 allele when comparing high- and low-SFA diets [40]. Furthermore, Humphries *et al.* examined the role of common genetic variations in the *APOB* (signal peptide, rs11279109), *APOC3* (C1100-T, rs4520) and *LPL* genes (HindIII, rs320) in order to determine the consistency of response and magnitude of change in lipid levels in response to change from a SFA to a high-PUFA diet [41]. Yet, neither *APOB* nor *APOC3* genotypes affected the magnitude of this response to dietary intervention. However, individuals with the *LPL* HindIII genotype H+ H+ had a smaller change in mean TC and TG in response to diet than those with one or more H- alleles [41]. Various mutations in the *LPL* gene have been associated with type 1 hyperlipoproteinemia in numerous studies [7]; thus, beneficial effects of a high-PUFA diet in individuals who carry a *LPL* gene variation are encouraging. These results suggest that these two genes, *CEPT* and *LPL*, are determinants of variation in cholesterol response to dietary change.

The promoter of the *LIPC* gene contains several SNPs, including the T111I polymorphism. Results of a study by Paradis *et al.* demonstrate that plasma HDL3-C levels of I111I homozygote women were higher compared with those of women carrying the common allele [42]. Furthermore, a diet rich in PUFA was associated with increased plasma ApoAI levels among women carriers of the I111 allele and with decreased plasma ApoAI among women homozygous for the common allele [42]. The gene–diet interaction among women, however, suggests that the T111I mutation may be beneficial against the lowering effect on plasma ApoAI and HDL-C levels with a high dietary PUFA intake.

Peroxisome proliferator-activated receptor α is a nuclear transcription factor regulating multiple genes involved in lipid metabolism. It was shown that a common leucine to valine (L162V, rs1800206) substitution at the *PPARA* is functional and affects transactivation activity of *PPARA* ligands, such as PUFA, on a

concentration-dependent basis [43,44]. Robitaille *et al.*, determined that the carriers of the V162 were characterized by higher plasma ApoB and TG levels [45]. In a model including the *PPARA* L162V polymorphism, fat or SFA, its interaction and covariates, the interaction explained a significant percentage of the variance observed in waist circumference [45]. Similarly, Tai *et al.* further examined this gene–nutrient interaction in relation to plasma lipid parameters in the Framingham cohort [46]. These researchers found gene–nutrient interactions between the L162V polymorphism and total PUFA intake, which modulated plasma TG and ApoC-III concentrations [46]. In more detail, when PUFA intake was less than 4%, V allele carriers had approximately higher plasma TG than did L/L. On the other hand, when PUFA intake was more than 8%, plasma TG in V allele carriers was 4% lower than in L/L [46]. Paradis *et al.* tested this hypothesis in a clinical trial by recruiting carriers of the V allele matched according to age and BMI to subjects with the L/L genotype [47]. After a high-PUFA:SFA ratio diet, a gene–diet interaction was observed for changes in plasma TC, ApoAI and cholesterol concentrations in small LDL particles. Furthermore, Volcik *et al.* determined an interaction between 3'UTR G→A (rs6008259) in the *PPARA* gene, n-6 PUFA intake and TC and LDL-C in white subjects [48]. Taken together, the *PPARA* polymorphisms may contribute to interindividual variability in plasma lipid response.

Overall, the studies demonstrate that variants of some genes (e.g., *APOA1*, *APOA4*, *APOA5*, *APOE*, *CEPT*, *LPL*, *LIPC* and *PPARA*) play an important role in changes in plasma lipid levels in response to dietary intervention.

High in n-3 polyunsaturated diets & polymorphisms

A low rate of CVD in populations with a high intake of fish, such as Alaskan Native Americans, Greenland Eskimos and Japanese living in fishing villages, suggest that fish oil may be protective against atherosclerosis [49]. Subsequent prospective cohort studies have found an inverse association between fish consumption and the risk of cardiovascular mortality in diverse populations [30]. A meta-analysis of 65 studies by Harris *et al.* demonstrated that n-3 PUFAs lowered TG levels in a dose-dependent manner, with the TG lowering being proportional to baseline levels [50]. In trials of subjects with high TG levels taking n-3 PUFAs in dosages of 3.4–4 g/day,

TG levels decreased by 16, to 45% [50]. The large heterogeneity in response to TG within studies with n-3 PUFA supplementation is likely to be attributable to genetic variability within the study population. Possible genetic variants that may impact the response to treatment include *APOE*, *PPARA* and *PPARG*. Studies describing the effects of n-3 PUFA on plasma lipid and lipoprotein levels in subjects with genetic variations have been included in **Table 1** in the high n-3 PUFA diet section.

The impact of the common *APOE* polymorphism on responsiveness to the dietary intervention has been established in numerous trials, as described previously [8,9]. Minihane *et al.* conducted a randomized crossover study of fish oil with 55 hyperlipidemic men looking at the effect of the *APOE* (E2/E3/E4, rs7412) polymorphism [51]. Data showed that baseline HDL-C levels were lower in *APOE* E4 carriers. Furthermore, an increase in TC and a trend toward a reduction in HDL-C were observed in the *APOE* E4 individuals, relative to those with the common E3/E3 polymorphism [51]. Thus, the *APOE* genotype may influence the response to an n-3 PUFA supplementation.

In the same way to previous studies with PUFA diets [46,47], a gene–diet interaction effect could be observed with intake of n-3 PUFAs and *PPARA*. First, Volcik *et al.* determined a significant interaction in African Americans between the *PPARA* 3'UTR C→T (rs3892755) polymorphism and n-3 PUFAs on TC and LDL-C levels [48]. Secondly, Caron-Dorval *et al.* examined whether n-3 PUFA induced changes in CVD risk factors are influenced by the *PPARA* L162V (rs1800206) polymorphism [52]. The results demonstrated that the extent of the decrease in TG concentrations was comparable for both genotype groups; yet, a gene–diet interaction effect was observed for plasma C-reactive protein concentrations [52]. Overall, it seems these polymorphisms in *PPARA* can instigate differences in the response of n-3 PUFA on cholesterol levels and inflammation parameters.

Furthermore, Lindi *et al.* investigated the influence of the Pro12Ala polymorphism (rs1801282) of the *PPARG* gene on plasma lipid and lipoprotein responses to n-3 PUFA supplementation [53]. Carriers of the Ala12 allele presented a greater decrease in TG concentration in response to n-3 PUFA supplementation than did subjects with the Pro12Pro genotype when the total dietary fat intake was low (<37% of energy intake) or the intake of SFA was low (<10% of

energy intake) [53]. Thus, this polymorphism may influence the response to n-3 PUFA supplementation.

Overall, there are no definitive explanations as to why individuals respond differently to dietary change in n-3 PUFA. However, the polymorphisms in *APOE*, *PPARA* and *PPARG* may partially explain the interindividual variability in the response of the CVD risk factors to n-3 PUFAs. Further studies are needed to determine if there exist specific genotypes that may benefit, to a greater extent, from n-3 PUFAs for hypotriglycerolemic effects.

Low-fat diets & polymorphisms

For many years, the American Heart Association (AHA) has recommended a low-fat diet of 55% of total calories from carbohydrates, 30% from fat and 15% from protein, with cholesterol restricted to less than 300 mg/day in the dietary treatment of hypercholesterolemia [54]. Similarly, the NCEP expert panel has recommended the consumption of the NCEP step I or II diets to lower TC and LDL-C. These diets are restricted in total fat (defined as 30% or less of total calories), SFA (defined as 8–10% of calories for Step I and <7% of calories for step 2) and cholesterol (defined as <300 mg/d for step I and <200 mg/d for Step 2) [55]. Studies report that populations consuming diets high in SFA and cholesterol have higher levels of LDL-C and higher age-adjusted rates of CHD and prospective dietary intervention studies demonstrate CHD risk reduction with restriction of dietary SFA and cholesterol [56]. As described previously by Schaefer *et al.*, an interindividual variation exists following the intake of a low-fat diet [5]. A summary of the results of the effects of a low-fat diet on plasma lipids and lipoproteins in individuals with various polymorphisms has been included in **Table 1**.

The *APOE* gene promoter polymorphism (-219G→T) has been associated with increased risk of myocardial infarction, premature coronary artery disease and decreased plasma ApoE concentrations. Moreno *et al.* determined that after the SFA diet, carriers of the T allele had higher plasma LDL-C and ApoB concentrations than did G/G subjects [57]. Carriers of the T allele had a greater decrease in plasma LDL-C and ApoB concentrations when they changed from the SFA to the carbohydrates diet compared with G/G subjects [57]. The -219G→T polymorphism of *APOE* may partially explain differences in individual responses to diet.

Previous studies show that polymorphisms in *APOA1* after certain diets are related to plasma lipid levels. Carmena-Ramon *et al.* examined the effect of the -75 (G/A) and +83 (MspI⁺) polymorphisms at the *APOA1* gene locus for associations with plasma lipid levels and response to an NCEP-I diet in subjects with familial hypercholesterolemia (FH) [58]. At baseline, individuals who carried the *APOA1* -75 polymorphism demonstrated lower plasma TC, LDL-C and ApoB concentrations than G/G individuals [58]. Following the NCEP-I diet, similar reductions in TC and LDL-C were observed between FH subjects carrying the A allele with subjects homozygous for the G allele [58]. The MspI⁺ allele at the *APOA1* +83 polymorphism was not associated with baseline lipids levels or with dietary response to the NCEP-I diet. In summary, consumption of a low-fat diet may not have supplementary beneficial effects in individuals with *APOA1* polymorphisms.

APOA4 has been related to fat absorption and activation of some of the enzymes involved in lipid metabolism, as described previously. Jansen *et al.* demonstrated no difference in plasma lipid and APO levels of both groups of the *APOA4* Gln360His (rs5110) genotype of individuals after consuming the SFA diet; however, when switching from SFA to the NCEP-I diet, carriers of the 360His allele demonstrated a greater decrease in HDL-C and ApoA-I levels [18]. Another mutation described in the *APOA4* gene is Thr347Ser (rs675), and has been associated with dietary fat intake. The Ser allele was associated with increased responsiveness of TC and LDL-C levels when subjects switched from a high SFA diet to NCEP-I diet comparative to homozygotes for the 347Thr allele [19]. Furthermore, Carmena-Ramon *et al.* studied the effect of the combination of two genetic variants (Gln360His [rs5110]) and Thr347Ser [rs675] of the *APOA4* gene on the lipid response to the NCEP-I diet in subjects with FH [59]. After consuming a NCEP-I diet, carriers of the *APOA4* His allele demonstrated a lower reduction in ApoB concentrations than G/G subjects; however, no differences in response were noted for LDL-C. Individuals with the *APOA4* Thr347Ser mutation had no differences in baseline or post-NCEP-I diet values in lipid or lipoprotein parameters. After dietary intervention, S/S individuals demonstrated reductions in plasma TG and VLDL-C levels; no changes were found in carriers of the T/T allele. Haplotype

analysis suggested that, in these FH subjects, the *APOA4* 360His allele was associated with lower plasma lipid levels during the NCEP-I diet period, whereas no effects were observed for the *APOA4* Thr allele [59]. Taken as a whole, the *APOA4* gene may modify the responsiveness of plasma lipids following a low-fat diet.

In previous studies, *APOB* polymorphisms have been shown to modify plasma lipid responses to changes in dietary fat intake. Therefore, Ilmonen *et al.* considered the effect of the *APOB* 1887 (Asn→Ser) and *APOB* 1896 (His→Arg) polymorphisms on plasma lipid levels and responses to changes in dietary fat intake in healthy free-living subjects [60]. Results demonstrate that the *APOB* 1896 Arg allele was associated with a higher LDL-C level during a low-fat, low-cholesterol diet in men [60]. Furthermore, Hammoud *et al.* examined the effect of the -516C/T polymorphism in the *APOB* gene [61]. Results demonstrated that carriers of the *APOB* 516T allele did not demonstrate any increase of risk factors at baseline when compared with other groups [61]. However, subjects homozygous for the *APOB* 516T allele were unresponsive to a healthy diet, which includes a reduction in total energy and fat intakes and the replacement of SFA dietary fat by MUFA and PUFA [61]. Overall, individuals with *APOB* polymorphisms may not benefit to the same extent from a low-fat diet.

Furthermore, Talmud *et al.* examined the impact of a variety of genetic variations at the *APOE* (E2/E3/E4, rs7412), *APOB* (XbaI, rs693, EcoRI, rs1042031 and MspI, rs1801701), *APOA1* (PstI, SstI and XmnI), *APOA2* (MspI), *APOC3* (PvuII) and *APOA4* (PvuII) genes on the relationship between dietary intake and plasma lipid traits in individuals who had participated in dietary intervention, changing from a basal high-fat diet to a low-fat diet followed by a return to their natural diet [62]. A heterogeneous effect was seen among genotypes of the *APOA4* PvuII on the correlation of plasma LDL-C levels and dietary MUFA during both dietary changes. A heterogeneous effect on the correlation between changes in TC and LDL-C was observed among individuals with the *APOB* XbaI (rs693) genotype during the change from high- to low-fat diet [62]. As previously mentioned, both the *APOA4* and *APOB* genes may affect the interindividual variability to diets.

Other less commonly examined polymorphisms have also been related to plasma lipids and dietary fat intake. For example,

polymorphisms in the *LIPC* gene have been also associated with variability in plasma HDL-C concentrations. Riestra *et al.* demonstrated that dietary fat intake modifies the effect of the *LIPC* gene (C-514T, rs1800588) polymorphism in pre-pubescent children [63]. In more detail, higher levels of HDL-C and ApoAI were only observed when fat intake is high in children carrying the *LIPC* polymorphism. In addition, the *CYP7A1* gene is of critical importance for bile acid and cholesterol metabolism. Barcelos *et al.* demonstrated a greater reduction in TG for subjects with the A/C and C/C genotypes compared with subjects with the A/A genotype (*CYP7A1* -278A>C) after reduced-fat diet in a dyslipidemic men [64]. Finally, several studies have associated polymorphisms in the *SCARB1* gene with variations in plasma concentrations of cholesterol. Perez-Martinez *et al.* determined whether the exon 1 variant (G->A; rs4238001) at the *SCARB1* gene is associated with the lipid response to quantity and quality of dietary fat in healthy subjects [65]. The results reveal that carriers of the A allele are more susceptible to the presence of SFA in the diet because of a greater increase in LDL-C and greater decrease in LDL-C after switching to a carbohydrate diet [65]. These results show that both dietary components and genetic variation in *LIPC*, *CYP7A1* or *SCARB1* genes affect the response of plasma lipid, lipoprotein and APO levels to dietary change in fat.

Overall, the intake of a low-fat diet may be more beneficial in certain individuals compared with others owing to common polymorphisms in the *APOE*, *APOA1*, *APOA4*, *APOB*, *LIPC*, *CYP7A1* and *SCARB1* genes.

High fat, saturated fat & cholesterol diets & polymorphisms

In general, high-fat intake (defined as ≥30% of energy intake), particularly of SFAs (defined as ≥20% SFA of total fat intake), increases LDL-C, especially if the unsaturated fatty acid intake is low, but also produces an apparent increase in HDL-C [3]. High LDL-C levels have been demonstrated in subjects carrying *APOE* E4, and this association is especially prominent in populations consuming diets rich in SFA and cholesterol [10,11].

Furthermore, Hubacek *et al.* analyzed the effect of variation in the *APOA1/C3/A4/A5* gene cluster on the decrease in TC over an 8-year follow-up study, where subjects naturally decreased their intake of SFA and cholesterol [66]. In particular, *APOA1* (-75G>A rs670 and

83C>T), *APOC3* (-482C>T and 3238C>G), *APOA4* (Thr347>Ser rs675 and Gln360His rs5110) and *APOA5* (T-1131>C rs17120035, Ser19>Trp rs3135506 and Val153>Met) variants were analyzed. In *APOA5* S/S subjects, plasma TC concentrations were relatively stable over the years, but the decrease was much higher in Trp19 carriers. Similarly, improved response to dietary changes was detected in carriers of the common *APOA4* haplotypes, Thr-347Thr/Gln360Gln and Thr347Ser/Gln360Gln. TC was relatively stable over time in carriers of at least one His360 allele and/or two Ser alleles. Other variants analyzed did not influence the change in lipid measurements over time [66]. Furthermore, Mattei *et al.* determined the association of *APOA5* -1131T>C (rs17120035) and S19W with plasma lipids, alone and in interaction with total fat intake, as a percentage of total energy intake in Puerto Ricans [67]. *APOA5* S19W (rs3135506) was associated with plasma HDL-C; minor allele carriers had lower HDL-C than those with the common variant, even after adjustment for plasma TG. Neither polymorphism was associated with TG or other lipids. Interaction of the -1131T>C SNP with total fat intake was observed for plasma TG and TC [67]. Overall, *APOA4* and *APOA5* variants may play an important role in the individual sensitivity of lipid parameters to dietary composition.

In addition, Rantala *et al.* examined the effects of *APOB* polymorphisms after a high-fat diet. Subjects with X/X genotype (XbaI, rs693) have greater LDL-C responses than X⁺/X⁺ or X⁺/X subjects [68]. The high-fat diet also induced a larger increase in plasma LDL-C in subjects with the R/R genotype than in those with the R⁺/R⁻ or R⁺/R⁺ genotype. *APOB* (MspI, rs1801701) M⁺/M⁺ subjects had a greater LDL-C and TG response than M⁺/M⁻ subjects. Further authors conducted a meta-analysis looking at published trials with *APOB* in all types of diets combined, and demonstrated the role of the EcoRI and TC, LDL-C and ApoB levels (greater in R/R⁻ than R⁺/R⁺ subjects), MspI and LDL-C, TG and ApoAI (greater in M⁺/M⁺ than M⁺/M⁻), but not that of the XbaI (rs693) or signal peptide (rs1127910) polymorphisms confirmed a diet-induced alterations in plasma lipid levels [68]. The study indicated that the *APOB* EcoRI and MspI polymorphisms are associated with responsiveness to diet.

Novel polymorphisms have also been studied in relation to dietary fat consumption and their impact on plasma lipid levels. First, Robitaille

et al. verified whether dietary fat intake interacts with the T94A polymorphism of the *LFABP* gene to modulate plasma ApoB levels [69]. The results demonstrated that T/T exhibit higher ApoB levels, whereas carriers of the A94 allele appear to be protected against high ApoB levels when consuming a high-fat and SFA-rich diet. Furthermore, the same research group investigated the influence of PPARD, a transcription factor involved in lipid metabolism. These results demonstrate that HDL-C and the TC:HDL-C ratio was modulated by a gene-diet interaction between total fat intake and -87T>C polymorphism [70]. In addition, the same investigators identified variations (-115G>A, -840C>A and -1830T>C) in the gene encoding LXRA and examined their effects on the plasma lipoprotein/lipid profile. At baseline, plasma TC and TG concentrations were higher in carriers of the -115A, -840A and -1830C alleles, compared with the -115G/G, -840C/C and -1830T/T homozygotes. In addition, when subjects were divided into four groups according to the median intake of cholesterol and *LXRA* genotypes, high cholesterol intake was associated with higher TC and LDL-C levels in -115A, -840A and -1830C allele carriers [71]. Finally, these researchers also determined that ghrelin (*GHRL*) Leu72Met, *MC4R* Val103Ile (V103I, rs2229616) and *PPARG* XbaI polymorphisms interact with dietary fat to influence TG concentrations [72]. Furthermore, Chamberlain *et al.* examined the cross-sectional associations of the *FABP2* gene with lipid levels [73]. No difference in baseline lipids levels was found between *FABP2* genotypes. However, in the presence of a high-SFA diet, the carriers of the T allele of *FABP2* had higher levels of TC, LDL-C and TG and a lower HDL-C:TC ratio compared with the Ala54 homozygotes [73]. In addition, the lipid levels did not vary by genotype with low SFA intake. Limiting dietary SFA intake may be particularly important among carriers of the A allele of *FABP2*. These results suggest that several polymorphisms in novel genes may interact with dietary fat intake to modulate well-known CVD risk factors.

Overall, the intake of a high-fat diet may have diverse effects on plasma lipids in individuals that carry certain polymorphisms. In particular, polymorphisms in *APOE*, *APOA4*, *APOA5*, *APOB*, *LFABP*, *PPARD*, *LXRA*, *GHRL*, *MC4R*, *PPARG* and *FABP2* may predispose individuals in having a more atherogenic lipid profile when consuming a diet high in fat, SFA and cholesterol.

Conclusion

Clearly, lipid response to dietary fat is, to a large extent, genetically controlled. The beneficial effects of a particular diets, such as MUFA, PUFA, n-3 PUFA or low-fat, may be more pronounced in an individual that carry, certain polymorphisms because there is more opportunity for improvement. In the same way, other polymorphisms may make some individuals nonresponsive to certain diets. A summary of the significant results is shown in **Table 1**. However, studies showing no significant or conflicting results should not be ignored, especially because they may outnumber the studies demonstrating significant effects, in addition to the numerous unpublished studies that have nonsignificant and uninteresting results. Furthermore, the studies reviewed may have some major limitations, such as sample size and assessment of diet composition. The majority of clinical studies reviewed have relatively small sample sizes, which may result in a small number of individuals homozygous for rare allele. Therefore, these studies have limited statistical power to detect modest gene–nutrient interactions. Future clinical trials should be based on power calculations derived from rare allele frequencies and effect size. Secondly, observational studies may have errors in measurement of diet. Researchers will have to increase the required sample size in order to compensate for exposure misclassification or will have to invest in better dietary assessment tools and biomarkers. For that reason, intervention studies have the greatest potential to reveal gene–diet interaction effects; however, large controlled clinical trials are costly, labor-intensive, time-consuming and have a higher burden for participants. These studies must also adjust for factors such as age, gender, BMI, menopausal status, medication use, smoking/tobacco use, physical activity and baseline lipid values of participants, which could contribute to the inconsistencies between the studies. However, it is imperative to conduct these large controlled dietary intervention trials, which accurately measure exposure and outcome variables in order to confirm the findings of this review article.

With the current knowledge in nutrigenomics, nutritional recommendations based on genetic information are not yet ready to be implemented; therefore, future research should be conducted in this area to develop adequately personalized nutrition therapies

for hyperlipidemia. Overall, diet is an important environmental factor interacting with the genetic background to modulate the likelihood of developing lipid disorders and, consequently, CVD risk.

Future perspective

The alternative to present diets, which are geared to the general public, are recommendations based on the specific responses to particular dietary patterns, which are modulated by various gene polymorphisms and/or their combinations. This can support the concept of ‘personalized nutrition’, which aims to provide targeted dietary advice to specific groups of people or even individuals. However, the findings on interactions between diets, plasma lipids levels and genetic polymorphisms need to be replicated in more studies, which will provide evidence for the use of nutrigenomics for CVD prevention. In general, more controlled clinical studies must be conducted to be able to replicate the interaction between polymorphisms with dietary fat on lipids parameters. These studies should measure compliance of subjects to diets as well as assess precise dietary intake. For now, the evidence is incomplete, but suggests and justifies the need for more studies with large sample sizes, with carefully controlled dietary interventions and that investigate the effects of polymorphisms in single genes as well as multiple genes. Since the relative contribution of a single polymorphism is small (probably 5–15%), the multiple interactions with other polymorphisms (either synergistically, additive or antagonistic interactions) may be potentially larger (20–25% or greater) or less significant. Therefore, each individual would have an exponential increase in the possible combination of the various genetic polymorphisms. Moreover, this genetic complexity would be increased when CVD risk factors, such as clinical biomarkers, as well as other risk factors are also taken into account, including diet, physical activity and smoking. Consequently, health professionals would need to create a gene risk-factor model to be able to predict response of an individual to a particular diet therapy. Overall, nutrigenomics has tremendous potential to impact the future of personalized medicine in the next 10–20 years; yet, more work is required for the basic research on nutrigenomics as well as the ability to use these data for nutritional recommendations in the general population.

Executive summary

Dietary guidelines that aim to manage fat intake reduce the risk of CVD

- High- monounsaturated fat, high-polyunsaturated fat or low-fat (including low-saturated fat) diets have been associated with beneficial effects on plasma lipid profile.

Interindividual variability in plasma lipid responsiveness is observed in individuals following these diets

- Interindividual variability in response to diets may be attributable to several SNPs in genes encoding key proteins involved in lipoprotein metabolism.
- Polymorphisms in *APOE*, *A-I*, *A-IV*, *A-V*, *B* and *C-III*, *LDLR*, *CETP*, *LPL*, *LIPC*, *PPARA*, *PPARG*, *PPARD*, *MTTP*, *FABP2*, *CYP7A1*, *SCARB1*, *LXRA*, *GHRL*, *MC4R* and *LFABP* may predispose an individual more or less responsive to a specific dietary intervention that aims to modify fat intake.
- An individual's response to a diet is probably the result of a combination of polymorphisms; yet, much research still needs to be conducted in order to determine the particular genotypes and/or haplotypes that have the highest responsiveness to diets.

Conclusions

- Lipid response to dietary fat is, to a large extent, genetically controlled.
- These findings on interactions between diets, plasma lipids levels and polymorphisms need to be replicated in more studies.
- Future research must be conducted in this area to develop adequately personalized nutrition therapies based on genetic knowledge for hyperlipidemia.

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