



Revisión

Genetic variation of apolipoproteins, diet and other environmental interactions; an updated review

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Abstract

This paper summarizes the recent findings from studies investigating the potential environmental modulation of the genetic variation of apolipoprotein genes on metabolic traits. We reviewed nutrigenetic studies evaluating variations on apolipoproteins-related genes and its associated response to nutrients (mostly dietary fatty acids) or any other dietary or environmental component. Most revised research studied single nucleotide polymorphism (SNP) and specific nutrients through small intervention studies, and only few interactions have been replicated in large and independent populations (as in the case of -265T > C SNP in *APOA2* gene). Although current knowledge shows that variations on apolipoprotein genes may contribute to the different response on metabolic traits due to dietary interventions, evidence is still scarce and results are inconsistent. Success in this area will require going beyond the limitations of current experimental designs and explore the hypotheses within large populations. Some of these limitations are being covered by the rapidly advance in high-throughput technologies and large scale-genome wide association studies.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, and its multifactorial etiology involves both genetic and environmental causes. Among environ-

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VARIACIONES GENÉTICAS DE LAS APOLIPOPROTEÍNAS Y SU INTERACCIÓN CON COMPONENTES DE LA DIETA Y OTROS FACTORES AMBIENTALES; UNA REVISIÓN ACTUALIZADA

Resumen

Este artículo resume los hallazgos recientes de estudios que investigan la potencial modulación, por parte de factores ambientales, del riesgo metabólico asociado a determinadas variantes genéticas de apolipoproteínas. Se han revisado estudios nutrigenéticos que evalúan variaciones en genes relacionados con apolipoproteínas y su asociación en respuesta a la ingesta de nutrientes (frecuentemente ácidos grasos) o cualquier otro componente de la dieta o del medio ambiente. La mayoría de la bibliografía revisada se centra en polimorfismos de un solo nucleótido (SNP) y nutrientes específicos a través de estudios de intervención de pequeña escala y pocas interacciones han sido replicadas en poblaciones independientes y de gran tamaño (como en el caso del SNP-265T > C en el gen *APOA2*). Aunque el conocimiento actual indica que ciertas variaciones genéticas de las apolipoproteínas pueden contribuir a la diferente respuesta sobre determinados factores metabólicos debido a las intervenciones dietéticas, la evidencia es todavía escasa y los resultados son inconsistentes. El éxito en esta área requiere superar las limitaciones de los diseños experimentales actuales y explorar estas hipótesis en poblaciones más amplias aprovechando el rápido avance de las tecnologías de alto rendimiento y la disponibilidad de datos del genoma completo.

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Palabras clave: *Apolipoproteína. Interacción gen-dieta. Ambiente. Intervenciones dietéticas.*

mental (or modifiable) causes, smoking, sedentary behaviors, and inadequate dietary habits, explain partially the high prevalence of intermediate CVD risk phenotypes (hypercholesterolemia, excess of body weight, hypertension, etc.).¹ Nowadays, however, and ever since the sequencing of the human genome, modern cardiovascular epidemiology also incorporates the genetic component of the disease aiming to integrate CVD genetic and environmental determinants.

As markers of CVD risk, lipoprotein concentrations are directly associated with environmental variables such as diet, and lifestyle in general, but genetics also play a significant role in modulating this association.

Several polymorphisms in genes encoding proteins related to lipid metabolism and etiologic factors of CVD have been found to increase CVD risk.^{2,3} Although there are a number of genes associated with CVD, the apolipoprotein (APO) loci (APOA1, APOA2, APOA4, APOC3, APOA5, APOB, APOE) are perhaps one of the best studied genetic variables because of its relevance to CVD in relation to dietary habits.³

The impact of single nucleotide polymorphisms (SNP) on CVD risk and the ability of environmental components to modulate genotype-phenotype associations is being increasingly recognized. Among environmental components, nutrients, and specifically fatty acids have been widely studied given the fact that dietary fat composition (quality and quantity) plays an important role in metabolic factors, including a marked effect on lipoproteins.⁴⁻⁶ Most current efforts are directed to understand these complex interactions in what have been called nutrigenetic studies. The ultimate goal of this research area is to tailor preventive recommendations, even treatments, based on individual genetic backgrounds. In order to achieve this, sound scientific evidence including replication studies, analyzing gene-environment interactions in large and varied populations is needed.

The number of scientific papers published on this field of research has increased considerably in the last few years. Given the fact that APO has been one of the most studied genes regarding lipid metabolism and dietary interventions, this paper aims to update the current knowledge on this topic by summarizing a selection of the literature that investigates the potential environmental modulation (not only diet but other components as well) of the genetic variation of APO genes on metabolic traits to summarize the scientific evidence available to provide personalized recommendations.

Genetic variation of apolipoproteins, cardiovascular risk phenotypes and environmental modulation

From table I to table VII, we present landmark studies as well as a selection of recent investigations on the APO gene-environment interaction on metabolic traits phenotypes, focusing on the genetic variation of *APOA1*, *APOA4*, *APOCIII*, *APOA2*, *APOA5*, *APOB* and *APOE* genes in relation to dietary interventions.

Apolipoprotein A1 (APOA1)

APOA1 is the major protein of HDL-C, a cofactor of lecithin-cholesterol acyltransferase (LCAT) and has a key role in the reverse cholesterol transport process.⁷ Genetic variation in this gene has been associated with premature coronary atherosclerosis.⁸ The most studied variant in this gene is -75 G > A, reported to be associated with HDL-C concentrations.^{2,9,10}

Most of the studies analyzed dietary interactions (table I), and only one analyzed training exercise as part of environmental modulation.¹¹ Data support that in dietary intervention studies using polyunsaturated fatty acids (PUFA) supplementation in normolipidaemic subjects, the A allele-carriers of the -75 G > A polymorphism appear to be associated with hyper-response to changes in the amount of fatty acids as well as high carbohydrate intake.¹²⁻¹⁴ Interestingly, women carrying the A variant, but no men, seem to be more susceptible to dietary fatty acids changes and high carbohydrate diet.^{12,14,15}

Apolipoprotein A4 (APOA4)

APOA4 plays an important role in dietary fat absorption and chylomicron synthesis⁸ and can serve as an activator of the LCAT.¹⁶ Several genetic variations in *APOA4* have been reported. The most studied (table II) SNPs have been those reporting changes in the amino acids Gln360His and Thre347Ser. Some of them suggesting that 360His allele to be a hypo-responsive isoform^{9,17} while others reported it as a hyper-responsive^{18,19} or with not effect at all.²⁰ It overall seems that 360Gln and 347Ser individuals, with higher genetic risk to high lipid levels, seem to benefit to changes on dietary fat.^{17,21-26}

Apolipoprotein CIII (APOCIII)

APOC3 is a component of chylomicrons, VLDL, and HDL, and inhibits the activity of lipoprotein lipase and delays VLDL clearance.¹⁶ Most of the genetic variants studied in *APOCIII* gene are localized in the promoter region. The C3238G with two alleles S1 and S2 has been associated with higher TG, TC, APOC3 concentrations, and other CVD markers.^{22,27} Polymorphisms in this gene are usually analyzed together with APOA1/APOA4 as they form a gene cluster,^{9,21} and isolated results are scarce and inconsistent (table III). For example, while Lopez-Miranda and co-workers²⁷ found that subjects carrying the S2 allele changing from low fat diet to a MUFA-rich diet showed a decrease in LDL-C,²⁷ more recently Herron and co-workers found that S2 carriers had smaller LDL peak particle independently of the dietary cholesterol intake,²² although differences in dietary intervention and characteristics of the population evaluated in the two studies have to be considered.

Apolipoprotein A2 (APOA2)

APOA2 is the second most important apolipoprotein of HDL-C. Some studies showed a positive relationship between APOA2 and synthesis of LDL-APOB in humans.²⁸ Although some studies have found an over-

Table I
Selected studies analyzing Apolipoprotein A1 gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Song et al., 2012 ¹⁴	-75 G/A	The ratios of TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, APOB100/APOAI	Intervention (cross-over): wash-out diet and high-CHO diet	N = 56, healthy	High-carbohydrate diet	Following the high-carbohydrate diet, significant decreases of TC/HDL-C were found in all the groups, regardless of sex and genotype (P < 0.01). LDL-C/HDL-C experienced significant decreases in both the genotypes in males (P < 0.05), while in females, significant decrease of LDL-C/HDL-C was only observed in A carriers (P < 0.01).
Phillips et al., 2011 ⁶⁴	-75 G/A	MetS risk	Nested case control study	N = 1,754	Dietary fat consumption	G allele homozygotes had increased MetS risk (p = 0.013). MetS risk was exacerbated among the habitual high-fat consumers (> 35% energy). While MUFA intake (> 14% energy) increased MetS risk (OR 1.57 [CI 1.10, 2.40], P = 0.014, low-fat consumers < 35% energy abolish this association.
Song et al., 2011 ¹⁹	+83C/T	Serum lipids, glucose, insulin and HOMA-IR	Intervention (cross-over): washout diet for 7 days followed by a high-CHO diet for 6 days	N = 56, healthy	High-carbohydrate diets	Triglyceride and insulin were found significantly increased in the subjects with the CC genotype, but not in the T carriers after the high-carbohydrate diet. Significant decreases of total cholesterol and LDL-C and a significant increase of HDL-C were observed after the dietary intervention of the high-carbohydrate diet.
Ruano et al., 2006 ¹¹	-75 G > A	HDL-C, HDL-C subfractions	Intervention: 6 months of supervised aerobic exercise	N = 75, normolipidemic	Exercise training	After exercise changes in total HDL-C did not reach statistical significance (0.8 ± 7.2 mg/dL (+1.7%), p < 0.005). However it is associated with HDL subfraction redistribution (G homozygotes increased the amount of large HDL subfraction and decreased small HDL subfraction in comparison with A carriers, p < 0.005).
Ordovas et al., 2002 ¹²	-75 G > A	HDL-C	Cross-sectional study	N = 1577	PUFA intake	In women carriers of the A allele, higher PUFA intakes were associated with higher HDL-cholesterol concentrations (13% higher, p < 0.05) than those of G/G subjects.
Mata et al., 1998 ¹⁵	-75A > G	LDL-C	Intervention: SFA diet for 28 days, followed by a diet rich in MUFA for 35 days and a diet rich in PUFA for 35 days	N = 50	Dietary fat saturation	As compared to the SFA diet, a PUFA diet induced significantly LDL-C decreases (P = 0.001) in G/A women (-1.62 and -1.32 mmol/l, respectively) than in G/G subjects (-0.87 and -0.74 mmol/l for plasma and LDL-C, respectively). In men the major determinant of this response was smoking (21.4%)
Lopez-Miranda et al., 1994 ¹³	-75G > A	LDL-C	Intervention (cross-over): low-fat diet during 25 days, followed by a diet rich in MUFA during 28 days	N = 50, young men with the same mutation	MUFA intake	They studied the influence of the LDL-C postprandial response to the intake of MUFA reporting significant diet-gene interaction (p = 0.015). After high intake of MUFA carriers of A allele had higher LDL-C (p = 0.035) but not the GG (p = 0.996).

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; PUFA: Polyunsaturated fatty acids; TRL-TG: Small TRL-triglyceride; VLDL: Very low density lipoprotein; MetS: Metabolic Syndrome; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; TG: Triglycerides; HOMA-IR: The homeostasis model assessment of insulin resistance.

Table II
Selected studies analyzing Apolipoprotein A4 gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Gómez et al., 2010 ²¹	APOA4 Thr347Ser APOA1 G-76A	Changes in LDL size	Intervention (cross-over): a SFA, low-fat and high-CHO diet or a MUFA diet, 4-weeks each	N = 97, healthy	Fat and CHO intakes	Interaction between the APOA1 and APOA4 genotypes revealed that individuals with the GA/ThrSer genotype had larger LDL particle size during consumption of the MUFA diet than when they consumed the CHO diet.
Hubacek et al., 2007 ⁹	Gln360His Thr347Ser	Plasma lipid levels: cholesterol	Cohort study (8-year follow-up study)	N = 133, men	Dietary intervention (changes in diets)	A better response to dietary changes in plasma cholesterol was detected in carriers of the common APOA4 haplotypes Thr- 347Thr/Gln360Gln and Thr347Ser/Gln360Gln (p=0.001)
Weggemans et al., 2000 ²⁰	Gln360His	LDL-C HDL-C	Intervention with two diets: 136 mg/d cholesterol or 948 mg/d of cholesterol during 29 days	N = 23	Dietary fat and cholesterol	Changes in lipids intake did not affect in lipids parameters in people with Gln360His polymorphism
Ostos et al., 2000 ¹⁸	Gln360His	Postprandial lipemia TRL-C, TRL-TG	Intervention: 1 g fat/kg body and 60,000IU of vitamin A for 11 hours	N = 51, healthy men	Fat and vitamin A intake	360His allele hyper responders to fat during the postprandial period regarding small triacylglycerol rich lipoproteins (TRL)-C (P < 0.02), small TRL-TG (P < 0.01) and large TRL-TG (P < 0.05) (greater postprandial levels)
Heilbronn et al., 2000 ⁷	Gln360His	HDL-C	Intervention: Energy restricted diet. 12 weeks	N = 186, overweight/obese	Hypocaloric diet	360His allele hypo-responsive isoform. Energy restriction for 12 weeks resulted in HDL-C increased 5.4% in subjects with the Gln360Gln genotype compared to a 2.6% decrease in Gln360His subjects (P = 0.035). ApoA-IV genotype was not related to change in total cholesterol, LDL-C or triglyceride concentrations
Jansen et al., 1997 ²⁵	Gln360His	HDL-C	Intervention: Three consecutive 4-week diets (diet rich in SAT, low fat diet (NCEP-I) and diet rich in MUFA	N = 41, healthy men	SFA intake	Switching from SAT to NCEP-I diet or MUFA, carriers of the 360His allele presented a greater decrease in HDL-C (P < 0.004, P < 0.003) and apoA-I levels (P < 0.037 and P < 0.036 respectively)
Carmena-Ramon et al., 1998 ¹⁹	Gln360His Thr347Ser	Lipid response	Intervention diet (National Cholesterol Education Program type I (NCEP-I) diet)	N = 67, FH heterozygotes	NCEP-I	Haplotype analysis suggested that in these FH subjects, the 360His (P = 0.036) allele was associated with lower plasma lipid levels during the NCEP-I diet period, whereas no significant effects were observed for the 347Thr allele
Jansen et al., 1997 ⁶¹	Thr347Ser	Total cholesterol and APOB	Intervention. Three consecutive 4-week diets (diet rich in SAT, low fat diet (NCEP-I) and diet rich in MUFA	N = 41, healthy men	SFA intake	Switching from NCEP type I to the MUFA diet, carriers of 347Ser resulted in greater increase in total cholesterol (0.18 vs -0.05 mmol/L, P < 0.028) and apo B (5 vs -1 mg/dL, P < .006) levels than in the 347Thr individuals
Ostos et al., 1998 ²⁶	Thr347Ser	LDL TG Lipoprotein fractions	Intervention: vitamin A-fat load test	N = 50, healthy men homozygous for APOE3	High saturated fat diets	Subjects with the 347Ser allele have a lower postprandial response in total TG (p < 0.025), TRL (P < 0.02), and small-TRL levels (P < 0.007), and a higher postprandial response in large-TRL, apoA-IV (P < 0.006) and apoB-100 (P < 0.041) levels than subjects homozygous for the 347Thr subjects.

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; TRL-C: Small triacylglycerol-rich lipoprotein; PUFA: Polyunsaturated fatty acids; TRL-TG: Small TRL-triglyceride; VLDL: Very low density lipoprotein; BMI: Body mass index; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; RFLP: Restriction Fragment Length Polymorphism; TG: Triglycerides; HOMA-IR: The homeostasis model assessment of insulin resistance.

Table III
Selected studies analyzing Apolipoprotein CIII gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Lin et al., 2011 ⁴¹	-482C > T	TRL-TG	Intervention (cross-over) (wash-out diet for 7 days, and HC/LF diet for 6 days)	N = 56, healthy young adults	Carbohydrate intake	APOC3-482T carriers had higher TRL-TG levels following the wash-out and HC/LF diets, but these were not directly attributable to a single gender
Herron et al., 2006 ²²	C3238G (S1/S2)	Plasma lipids and LDL size	Intervention (cross-over) (640 mg/d cholesterol) or placebo for 30 days)	N = 91, healthy	Dietary cholesterol intake	Carriers of the S2 allele had smaller LDL peak particle diameter, higher APOCIII and TG than those having the common APOC3 independently of dietary cholesterol (p < 0.05)
Olivieri et al., 2005 ⁶⁶	-455T > C	APOC-III concentrations	Cross-sectional	N = 848, heart disease patients	Erythrocyte n-3 PUFAs	Patients homozygous for the -455C APOC3 variant are poorly responsive to the apo C-III lowering effects of n-3 PUFAs.
López-Miranda et al., 1997 ²⁷	C3238G (S1/S2)	LDL-C	Intervention (cross-over) (low-fat diet for 25 days, MUFA-rich diet for 28 days)	N = 90, young men	MUFA	After MUFA-rich diet intervention, S1/S1 subjects showed significant increases in LDL cholesterol (0.13 mmol/L, P < 0.027) whereas a significant decrease was observed in the S1/S2 subjects (-0.18 mmol/L, P < 0.046).

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; PUFA: Polyunsaturated fatty acids; TRL-TG: Small TRL-triglyceride; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; HC/LF: High-carbohydrate/low-fat diet

Table IV
Selected studies analyzing Apolipoprotein A2 gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Smith et al., 2012 ⁶⁶	-265 T > C	Behavioral (patterns of eating) and plasma ghrelin	Cross-sectional study	N = 1,225, overweight and obese	SFA intake	CC subjects with low SFA intake displayed lower plasma ghrelin than CC subjects with high SFA intake (all P < 0.05). CC subjects were more likely to exhibit behaviors that impede weight loss (P = 0.008) and less likely to exhibit the protective behavior (P = 0.034)
Corella et al., 2011 ³²	-265 T > C	BMI and obesity and IR	Cross-sectional study (SFA: <or> = 22 g/d)	N = 4,602	SFA intake	Interaction of -265CC with SFA intake modulating risk of obesity. Mediterranean individuals with CC genotype and high SFA intake had 6.8% greater BMI and higher prevalence of obesity in in Chinese and Asian Indians (P = 0.036). Moreover, significant APOA2-saturated fat interaction in determining IR (P = 0.026).
Corella et al., 2009 ³¹	-265 T > C	BMI, obesity	Cross-sectional follow-up (20 years) and case-control analyses	N = 3,462	SFA intake	C carriers that had high intake of SFA had higher prevalence of obesity (mean increase of 6.2% BMI)
Corella et al., 2007 ³⁰	-265 T > C	Obesity	Intervention (postprandial study): Cholesterol content = 240 mg and PUFA/SFA = 0.06	N = 1,078	Food consumption	The -265C allele is associated with food consumption (higher energy intake (P = 0.005), total fat and proteins (P = 0.002 and P = 0.005, respectively) and obesity.

SNP: Single Nucleotide Polymorphism; PUFA: Polyunsaturated fatty acids; BMI: Body mass index; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; RFLP: Restriction Fragment Length Polymorphism; TG: Triglycerides;

expression of APOA2 in hypertriglyceridemic, obese and insulin-resistant subjects,²⁹ its role in humans is still controversial. The -256C > T polymorphism in the APOA2 gene promoter is one of the most studied, and

CC genotype has been associated with increased Body Mass Index (BMI) or obesity in different populations and on those following a saturated fatty acid (SFA)-rich diet³⁰⁻³² (table IV). This gene-SFA interaction

Table V
Selected studies analyzing Apolipoprotein A5 gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Shirts et al., 2012 ²⁷	S19W,-1131T>C	HDL-C	Cross-sectional study	N = 1,060 N = 2,890 (for replication)	Vitamin D	The 19W minor allele was more strongly associated with low HDL-C in individuals with low winter dietary vitamin D in initial and replicate samples (p = 0.0003 Utah, p = 0.002 Family Heart). A 25OHD receptor binding site modifying APOA5 promoter polymorphism is associated with lower HDL-C in vitamin D deficient individuals
Sánchez-Moreno et al., 2011 ⁴⁰	-1131T>C	TG-rich lipoprotein, Anthropometric measures	Cross-sectional study	N = 1,465, overweight/obese	Dietary Fat Intake	Genotype-dietary fat interactions for TG-rich lipoproteins (P < 0.001). -1131TT showed positive association between fat intake and obesity, whereas in those carrying the APOA5-1131C minor allele and higher fat intakes were not associated with higher BMI
Jang et al., 2010 ³⁷	-1131T>C	APOA5, TG, HDL-C	Intervention (12-week DIRE (replacing 1/3 of refined rice with legumes, increasing vegetable intake, and regular walking)	N = 283, hypertriglyceridemic patients	Dietary intervention and regular exercise (DIRE)	1131TT may benefit more from the DIRE than C allele carriers on lower serum TG (P = 0.009), higher HDL cholesterol (P = 0.036) and free fatty acid (P < 0.01)
Corella et al., 2007 ³⁴	-1131T>C 56C>G (S19W)	Body weight: BMI and obesity risk	Cross-sectional study	N = 2,280	Fat intake (MUFA)	APOA5-1131C minor allele carriers with high fat intake (mostly from MUFA), had a lower obesity and overweight risk (P = 0.032 and P = 0.031 respectively) compared with TT subjects but not when fat intake was low (P = 0.47 and P = 0.48, respectively)
Lai et al., 2006 ⁴²	-1131T_C 56C>G,	TG, RLP, and lipoprotein particle size	Cross-sectional study	N = 2,148	Dietary fat intake, n-6 Fatty Acids	APOA5 1131C carriers with higher n-6 (but not n-3) PUFA intake showed an increase in TG and RLP concentrations (P < 0.01), and VLDL size and decreased LDL size (P < 0.01). No interactions for the 56C>G SNP.
Aberle et al., 2005 ³⁹	-1131T>C	Lipid traits and BMI	Intervention (Short-term fat restriction)	N = 606, hyperlipidemic and overweight men	Fat restriction	The reduction of BMI was significantly higher in C allele carriers (p = 0.0021) after following a fat restriction diet.

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; TRL-C: Small triacylglycerol-rich lipoprotein; PUFA: Polyunsaturated fatty acids; TRL-TG: Small TRL-triglyceride; VLDL: Very low density lipoprotein; BMI: Body mass index; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; TG: Triglycerides; RLP: Remnant-like particle; DIRE: Dietary intervention and regular exercise.

determining BMI on this SNP is the first gen-diet interaction consistently replicated in large and independent populations.³⁰⁻³² Based on this, it could be of interest to further explore the possible modulation of this association by specific dietary or physical activity patterns that will lead to wider recommendations, or if this polymorphism also influences other cardiovascular risk factors such as the ratio APOA1/APOA2 or the development of atherosclerosis.³³

Apolipoprotein A5 (APOA5)

APOA5 enhances the activity of lipoprotein lipase and inhibits VLDL-triglyceride (TG) production.^{34,35} Multiple studies have shown consistent associations

between genetic variants in this gene and fasting TG concentrations^{34,36,38} but gene-environment interactions have not been yet fully addressed. Among the few studies that have examined the influence of environmental factors on possible genetic variations, the most important are those that contemplate possible gene-diet interactions.^{34,37,39-42} Only the Dietary Intervention and Regular Exercise (DIRE) study contemplates regular exercise as part of the intervention.³⁷ Most of the cross-sectional studies analyzing gene-diet interactions in large populations agreed that those with higher genetic risk (C carriers in -1131T>C SNP) may modulate that risk controlling the content and quality of fat^{34,39,40,42} (table V). The evidence however is still poor and each study reports different phenotypes and interactions.

Table VI
Selected studies analyzing Apolipoprotein B gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Hammoud et al., 2010 ⁶	-516C/T	Lipids: APOB48, TG, TRL	Intervention: three-month diet (advised to reduce total energy and fat intakes and replace SFA by MUFA and PUFA)	N = 169, moderate CVD	Healthy diet as defined in intervention	APOB-516 TT subjects are unresponsive to a healthy diet that improves cardiovascular risk status in the whole population
Pérez-Martínez et al., 2007 ⁴	-516C/T	TG, LDL-C, HDL-C, CT	Intervention (cross-over): (SFA-rich diet, CHO-rich diet or a MUFA-rich diet, 4 weeks each)	N = 97, healthy	Amount and quality of dietary fat	Changes in dietary fat intake in relation to the -516C/T did not produce any plasma lipid and apolipoprotein response
Pérez-Martínez et al., 2007 ⁶	-516C/T	Insulin sensitivity	Intervention (cross-over): (SFA-rich diet, CHO-rich diet or a MUFA-rich diet, 4 weeks each)	N = 59, healthy	Dietary fat	After consumption of all diets, -516T male carriers showed a significant increase in insulin resistance being this difference more detectable after the SFA diet compared with the MUFA- and CHO-rich diets (P = 0.001)
López-Miranda et al., 1997 ⁷	XbaI RFLP	RP and apoB-48, large and small TRL	Intervention: postprandial lipemia (Vitamin A-fat load test)	N = 51, healthy young men APOE3 homozygous	Fatty meal	Subjects with the X- genotype had significantly RP and apoB-48 postprandial responses on both the large and the small TRL lipoprotein fractions.
Friedlander et al., 1993 ⁸	XbaI	RFLP Plasma-lipid and lipoprotein	Intervention (cross-over) 5-week (Low SFA-cholesterol diet and high SFA-cholesterol)	N = 37	SFA intake-cholesterol	Significant changes in total cholesterol, LDL-C, and apoB were observed in subjects with high SFA-cholesterol. However, the differences between the genotypic classes were not statistically significant.
Tikkanen et al., 1990 ⁹	XbaI RFLP	LDL-C, APOB, HDL-C, CT	Intervention (low-fat, low-cholesterol diet)	N = 103	Fat and cholesterol intake	Reductions in total (p = 0.036) and LDL-C (p = 0.049), apoB (p = 0.012) and HDL-C (p = 0.008) were greater in subjects homo- or heterozygous for the presence of the XbaI cutting site (X1X2 or X2X2 genotype, designated X2+)

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; PUFA: Polyunsaturated fatty acids; VLDL: Very low density lipoprotein; BMI: Body mass index; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; RFLP: Restriction Fragment Length Polymorphism; TG: Triglycerides; HOMA-IR: The homeostasis model assessment of insulin resistance; RP: Retinyl palmitate; RLP: Remnant-like particle; TF: Total fat; SF: Saturated fat; LSF: Low SFA-cholesterol; H/CLF: High-carbohydrate/low-fat diet; NCEP: National Cholesterol Education Program.

Apolipoprotein B (APOB)

APOB is the primary apolipoprotein of chylomicrons and LDL-C. Through a mechanism that is not yet fully understood, high levels of APOB can lead to atherosclerotic plaques and heart disease.⁴³ A number of SNPs have been studied in this gene (-516C > T, XbaI, EcoRI, Msp1, signal peptide I/D, BsP). Regarding -516C > T SNP non-significant gene-diet interactions have been found modulating plasma lipids levels.^{44,45} Only one study found that male carriers of the minor allele had higher insulin resistance when followed intervention with SFA-rich diet⁴⁶ (table VI). Evidence for an interaction between the XbaI SNP and diet is inconsistent.⁴⁷⁻⁴⁹ No other environmental-associated interactions have been studied.

Apolipoprotein E (APOE)

One of the most studied apolipoprotein is the APOE given its key role in lipid metabolism. The most studied

genetic variation in *APOE* gene results from three common alleles in the population: E2/E3/E4.⁵⁰ There is consistent evidence that APOE4 is associated with hypercholesterolemia and 40-50% higher risk of CVD whereas APOE2 prevents from high cholesterol levels.⁵¹⁻⁵³ However, when analyzing gene-diet interactions some discrepancies are found (table VII). There are more than 40 interventions studies analyzing *APOE* gene variation, a selection of them are presented in table I. The individual variability of *APOE* phenotype in response to diet appears to be determined by a genetic variant (E2/E3/E4). Some studies found that APOE4/E4 individuals respond to dietary fat content (especially SFA) with greater responses in the LDL phenotype.^{51,52,54,55} However, other studies did not find such interaction or any other gene-diet interaction,⁵⁶⁻⁵⁸ which suggest that intense research in this area is needed. Similarly, results support that on a low-fat/low-cholesterol diet, the effect of lowering LDL-C is twice as great in men than women, suggesting an *APOE*-mediated gen-gender interaction.⁵¹

Table VII
Selected studies analyzing Apolipoprotein E gene variation and its interaction with any environmental component

Author	SNPs	Phenotypes evaluated	Design	Sample	Interaction	Main outcomes
Petkeviciene et al., 2012 ⁵⁷	E2/E3/E4	TC, LDL-C	Cross-sectional study	N = 996	SFA intake	No statistically significant interactions between APOE genotype and SFA intake regarding TC and LDL-C level (all $p > 0.05$)
Corella et al., 2011 ⁶²	E2/E3/E4	CHD risk	Nested case-control study in the Spanish-EPIC	N = 534 incident CHD cases and 1,123 controls	Dietary fat, alcohol consumption	Gene-alcohol interactions in determining LDL-C were detected and SFA intake modified the effect of the APOE polymorphism in determining CHD risk. When SFA intake was low, there was no association between the APOE sNP and CHD risk was observed ($P = .682$), however when SFA was high the SNP was significant ($p = 0.005$) having E3 higher detrimental effect
Moreno et al., 2009 ⁵¹	E2/E3/E4	APOE levels	Intervention (cross-over: 3 dietary periods, 4-weeks each (SFA, CHO or a MUFA-rich diet)	N = 84, healthy	Quantity and quality of dietary fat	ApoE2 carriers have the highest ApoE levels, whereas apoE4 individuals show the lowest concentration after the SFA, CHO and MUFA diets. Women had significantly higher ApoE concentration than men only after the consumption of the SFA diet.
Moreno et al., 2005 ⁴⁸	-219G/T	Insulin Sensitivity response	Intervention (cross-over: 3 dietary periods, 4-weeks each (SFA, CHO or a MUFA-rich diet)	N = 43, healthy	Dietary fat intake	Significant gene-MUFA/CHO interaction for steady-state plasma glucose and plasma nonesterified fatty acids concentrations where only carriers of the -219G allele have improved insulin sensitivity when MUFA or CHO-rich diets were consumed ($P < 0.05$)
Moreno et al., 2004 ⁴⁹	-219G > T	LDL-C, APOB	Intervention (cross-over: 3 dietary periods, 4-weeks each (SFA, CHO or a MUFA-rich diet)	N = 55, healthy men	Content and quality of dietary fat	Carriers of the T allele had higher LDL-C ($P < 0.05$) and APOB ($P < 0.05$) plasma concentrations after the SFA diet than did GG subjects. However, when they changed to CHO had a significantly ($P < 0.05$) greater decrease in LDL-C and APOB
Hubacek et al., 2003 ⁵⁶	E2/E3/E4	TC, LDL-C	Cohort study (changes in dietary intake over an 8 year	N = 131, men	Dietary composition	APOE variation did not influence the change in TC and LDL-C over time
Campos et al., 2001 ⁵²	E2/E3/E4	VLDL, HDL-C	Intervention (two groups, low SFA, and high SFA)	N = 420	SFA intake	Significant interactions between APOE genotype and SFA were found for VLDL ($P = 0.03$) and HDL cholesterol ($P = 0.02$). Higher SFA intake was associated with higher VLDL cholesterol and lower HDL cholesterol in E2 carriers, while opposite effects were observed in E4 carriers
Corella et al., 2001 ⁷⁰	E2/E3/E4	LDL-C	Cross-sectional	N = 2,147	Alcohol intake	E2 carriers had lower LDL-C in those with moderate consumption of alcohol than in non-consumers. However, carriers of E4 allele that had a moderate consumption of alcohol had higher LDL-C ($P < 0.05$)
Erkkilä et al., 2001 ⁵³	E2/E3/E4	TG	Cross-sectional EUROASPIRE study	N = 414, CVD	Dietary sucrose intake	CVD patients with the E2 allele had a greater TG response to high dietary sucrose intakes than E3 or E4 allele
Loktionov et al., 2000 ⁵⁴	E2/E3/E4	LDL-C, TC	Cross-sectional study in EPIC population	N = 132, healthy	Energy from SFA	APOE3/E4 genotype displayed a stronger positive correlation between LDL cholesterol level and SFA intake ($r = 0.436$; $P = 0.043$) while no significant associations were found for E3E3 and E2E2. Positive correlation between alcohol consumption and HDL cholesterol level was present in E2 individuals
Lefevre et al., 1997 ⁵⁸	E2/E3/E4	Cholesterol, LDL-C, HDL-C	Intervention (cross-over) Three diets, an average American diet, an AHA Step 1 diet, and a low SFA 8 weeks each	N = 103, normolipidemic	SFA reduction	In a heterogeneous, normolipidemic study population, apoE genotype does not predict the magnitude of lipid response to reductions in dietary saturated fat.

SNP: Single Nucleotide Polymorphism; CHO: Carbohydrates; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TC: Total cholesterol; TRL-C: Small triacylglycerol-rich lipoprotein; PUFA: Polyunsaturated fatty acids; TRL-TG: Small TRL-triglyceride; VLDL: Very low density lipoprotein; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; RFLP: Restriction Fragment Length Polymorphism; TG: Triglycerides; HOMA-IR: The homeostasis model assessment of insulin resistance; AHA: American Heart Association.

Conclusions and future directions

There are a number of studies analyzing the response of metabolic traits via modulation of the APO genetic variability after dietary intervention. Although scientific evidence is accumulating, the area of consensus is still limited. This is mostly due to different study conditions, design, including very different sample sizes, characteristics of the population, duration, nature of the dietary intervention, phenotypes analyzed, post-prandial or fasting state of the individuals, as well as to the inter-variability in lipid response due to polygenic regulation. Conclusions are therefore difficult to draw, more so when information is often derived from small intervention trials in which the usually small size of the group carrying the allele frequency for the particular SNP of interest, hinders a well-powered analysis of the gene-environment interaction. Either larger, well-standardized intervention trials, or smaller trials with prospective recruitment according to genotype are needed to fully establish the impact of diet on genotype-metabolic traits association to establish personalized dietary recommendations. In the past, genetic studies were carried out with conventional techniques; however, the introduction of high-throughput techniques has boosted the information available on nutritional genomics. In this line, Genome Wide Association studies (GWAs) carried out by large international consortia are delivering fundamental data on genetic variants that contribute to complex diseases. However, the area of nutrigenetics still faces the problem of the lack of standardizing procedures to study the biological complexity of phenotypes, dietary intake, study design, and background of the population genotyped, as mentioned above. To increase the validity of individual nutrigenetic studies, replication of results in different populations is crucial to control for potential information and selection bias. To avoid limitations in the conventional methods for measuring dietary and recognizing the need for standard phenotypic and exposure measures, particularly as related to Genome Wide Association studies, the National Human Genome Research Institute (NHGRI) initiated the PhenX Toolkit in 2006, "High-Priority Phenotype and Exposure Measures for Cross-Study Analysis in Genome-Wide Association Studies. The project, PhenX (<https://www.phenx.org/>) produces a toolkit that facilitates use of the selected consensus measures in GWAS and other large scale genomic efforts (www.phenxtoolkit.org).

Summarizing the current knowledge, it seems that variations in *APOA1*, *APOA4*, *APOB*, *APOA5*, and *APOE* genes may contribute to the different response to dietary interventions on metabolic traits.^{9,11,12,14,19,21,25,34,37,40,47,51,52,59-63} Specifically *APOA1* -75A, *APOA4* Gln360, *APOB* -X (XbaI), *APOA5* -1131C, *APOE4* tend to induce different lipids concentrations depending dietary fat^{9,11,12,14,19,21,25,34,37,40,47,51,52,59-63} despite not all studies being in agreement.^{22,24,45,46} To this date, the only SNP that has

been replicated in different populations (Framingham Offspring Study (whites),³¹ the Genetics of Lipid Lowering Drugs and Diet Network Study (whites),³¹ Boston-Puerto Rican,³¹ Mediterranean³² and Asian populations)³² following the criteria above mentioned is the *APOA2* -265T > C. In conclusion from these studies, CC individuals with *a priori* higher genetic risk to obesity, seem to modulate their BMI only when they have a low SFA dietary intake.

Derived from the literature reviewed, it seems evident that although advances in gene-nutrient interactions have been made, there is a need of studies that analyze dietary patterns, instead of isolated nutrients to address large population behavioral changes. Furthermore, the study of other environmental components (physical activity, smoking habits, stress, sleep deprivation) should be contemplated in future recommendations based on the individual genetic risk given that there is a lack of studies analyzing this environmental components.

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