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Genetic determinants of plasma lipid response to dietary intervention: the role of the *APOA1/C3/A4* gene cluster and the *APOE* gene

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Polymorphisms at the *APOA1/C3/A4* gene cluster and the *APOE* gene have been extensively studied in order to examine their potential association with plasma lipid levels, coronary heart disease risk and more recently with inter-individual variability in response to dietary therapies. Although the results have not been uniform across studies, the current research supports the concept that variation at these genes explains a significant, but still rather small, proportion of the variability in fasting and postprandial plasma lipid responses to dietary interventions. This information constitutes the initial frame to develop panels of genetic markers that could be used to predict individual responsiveness to dietary therapy for the prevention of coronary heart disease. Future progress in this complex area will come from experiments carried out using animal models, and from carefully controlled dietary protocols in humans that should include the assessment of several other candidate gene loci coding for products that play a relevant role in lipoprotein metabolism (i.e. APOB, CETP, LPL, FABP2, SRBI, ABC1 and CYP7).

Dietary response: Lipoproteins: Polymorphisms: Coronary heart disease: Apolipoproteins

Introduction

To reduce low-density lipoprotein cholesterol (LDLC), a major risk factor for coronary artery disease (CAD), the National Cholesterol Education Program (NCEP) Expert Panel recommends for the general population a diet providing $<30\%$ of energy from fat, $<10\%$ of energy from saturated (SAT) fat and <300 mg/d of cholesterol (NCEP Step 1). For subjects who are still hypercholesterolaemic on this diet, the Expert Panel recommends further restriction of saturated fat to $<7\%$ of calories and cholesterol to <200 mg/d (NCEP Step 2) prior to use of drug therapy. Candidates for drug therapy after dietary treatment are those with LDLC values at or above 190 mg/dl, 160 mg/dl in the presence of two or more risk factors, or 130 mg/dl in the presence of coronary heart disease (CHD), with the goal of therapy being 30 mg/dl lower than the above values in each category.

The magnitude of plasma lipid responses to hypolipidaemic diet and drug therapies varies considerably among individuals (Ordovas, 1999; Ordovas & Schaefer, 1999*a*,*b*). These differences may be due to interactions among multiple genetic and environmental factors that affect the absorption of dietary fat or cholesterol, the bioavailability of drugs, or the regulation of the multiple metabolic pathways involved in lipoprotein synthesis and catabolism. During the past two decades numerous studies have examined gene–diet and gene–drug interactions in the response of plasma lipid concentrations to changes in dietary fat and cholesterol (Tall *et al.* 1997) or to different pharmacological therapies (Carmena *et al.* 1993; Nemeth *et al.* 1995; Ordovas *et al.* 1995; Nestel *et al.* 1997). In this paper we present the current knowledge regarding the association between alleles at the *APOA1/C3/A4* gene cluster on chromosome 11 and the *APOE* locus on chromosome 19, the most broadly studied candidate gene loci involved on individual variability in dietary response.

Apolipoprotein A-I (APOA1)

ApoA-I is the major protein of HDL, an *in vivo* activator of the enzyme lecithin : cholesterol acyl transferase (LCAT) (Fielding *et al.* 1972), and constitutes a key component of the reverse cholesterol transport process (Reichl & Miller, 1989). The gene for apoA-I (APOA1) is clustered with the APOC3 and APOA4 genes on the long arm of human chromosome 11 (Bruns *et al.* 1984; Karathanasis, 1985). This DNA region has been extensively analysed, resulting in the identification of several restriction fragment length polymorphisms (RFLPS). A number of studies have shown associations between some of these RFLPs and lipid abnormalities as well as increased CHD risk (Ordovas *et al.* 1991; Paul-Hayase *et al.* 1992; Tybjaerg-Hansen *et al.* 1993), but other studies have failed to do so (Marshall *et al.* 1994). Several rare genetic abnormalities at this locus have been associated with severe HDL deficiency and some of them with premature coronary atherosclerosis (Ordovas *et al.* 1989).

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A common variant due to adenine (A) to guanine (G) transition (G/A) has been described 75 bp upstream from the *apoA-I* gene transcription start site. Several studies have reported that individuals with the A allele, which occurs at a frequency of 0·15–0·20 in Caucasian populations, have higher levels of HDL-C and/or apoA-I than those subjects homozygous for the most common G allele (Juo *et al.* 1999; Ordovas, 1999). The magnitude of the effects and the gender–diet interactions reported have differed among studies. A recent meta-analysis has examined the associations of the −75 G/A polymorphism with plasma lipid profiles (Juo *et al.* 1999). This analysis concluded that there may be a mild association with apoA-I levels and that this is more apparent in men than in women. The associations between this polymorphism and response to diet are summarized in Table 1. Our own data (Lopez-Miranda *et al.* 1994*a*; Mata *et al.* 1998) (Table 1) support the notion that in well controlled dietary studies performed in normolipidaemic subjects, the A allele of this G/A polymorphism appears to be associated with hyper response to changes in the amount and saturation of dietary fat.

It is not clear whether the putative effect of this variant on HDL-C levels is due to the G to A substitution *per se*, or to linkage disequilibrium between the A locus and a distinct and as-yet-unidentified effector locus. *In vitro* analysis of the effects of this polymorphism on transcription has also yielded conflicting results. Smith *et al*. (1992) reported that the A allele decreased *in vitro* transcription by 30 %, consistent with their own *in vivo* turnover studies that showed decreased apoA-I synthetic rates in individuals with the A allele, although plasma HDL-C did not differ between GG and GA individuals. Tuteja *et al*. (1992) and Wang *et al*. (1998) reported that substitution of A for G decreased transcription about twofold, and Jeenah *et al*. (1990) reported a fourfold increase in transcription. Angotti *et al*. (1994) reported a five- to sevenfold increase in transcription associated to the A allele, and demonstrated that this may be due to reduced binding affinity of a nuclear factor to the A allele that results in increased transcription efficiency of the apoA-I promoter. More recently, Danek *et al*. (1998) have failed to find any direct effect of this polymorphism on transcriptional efficiency.

In summary, the mechanisms responsible for the observed effect are still unknown. This mutation may have a direct effect on liver and/or intestinal *apoA-I* gene expression, as suggested in previous studies, or it may be in linkage disequilibrium with a functional mutation in either of the neighbouring genes (*APOC3* and *APOA4*). Further studies are needed to demonstrate these hypotheses.

Apolipoprotein C-III (APOC3)

ApoC-III is a component of chylomicrons, VLDL and HDL that is synthesized primarily in the liver and to a lesser extent in the intestine. *In vitro*, apoC-III inhibits LPL and also inhibits the binding of apoE-containing lipoproteins to the LDL receptor, but not to the LRP receptor. Several DNA polymorphisms have been reported in the *APOC3* promoter region. These mutations are in linkage disequilibrium with the *Sst*I site in the 3′ untranslated region (C3238G) (Dammerman *et al.* 1993). Preliminary results have mapped an insulin-response element to a 42 nt fragment located between −490 and −449 relative to the transcription start site, and *in vitro* studies have demonstrated that transcriptional activity of the *APOC3* gene was down-regulated by insulin only in the construct bearing the wild-type promoter, but not in those constructs containing the C^{-482} T and T^{-455} C variants (Li *et al.* 1995). The C3238G polymorphism distinguishes between two alleles, S1 and S2. The S2 allele has been associated with elevated triacylglycerol, cholesterol, apoC-III concentrations, high blood pressure and increased CAD risk. The linkage disequilibrium between this mutation and those at the 5′ region provide some suggestions toward understanding the molecular basis behind the increased levels of apoC-III found in subjects carrying the S2 allele and its association with hypertriglyceridaemia, and also suggest an active role of dietary fat in determining the effects associated with this polymorphism (Lopez-Miranda *et al.* 1997).

Several studies have examined the potential associations between some of the *APOC3* polymorphisms and variability in plasma lipid response. The results are summarized in Table 1. Overall, these data suggest that the *APOC3* gene locus is involved in dietary response for both fasting and postprandial parameters.

Apolipoprotein A-IV (APOA4)

ApoA-IV is synthesized primarily in the intestine. Although its physiological role has not been established with certainty, several lines of evidence involve this apolipoprotein in several key steps of lipoprotein synthesis and catabolism. ApoA-IV plays a significant role in dietary fat absorption and chylomicron synthesis (Ordovas *et al.* 1989) Moreover, *in vitro* studies have shown that the activation of lipoprotein lipase (LPL) by apoC-II is mediated by apoA-IV, and that apoA-IV can serve as an activator of lecithin : cholesterol acyl transferase (LCAT). ApoA-IV-containing lipoproteins promote cholesterol efflux from cultured fibroblasts and adipose cells *in vitro*, and some evidence shows that apoA-IV may be one of the ligands for the HDL receptor.

Several genetically determined isoforms of apoA-IV have been detected, with those at amino acid positions 360 and 347 of the mature protein being the most common. The apoA-IV*2 isoform, characterized by the presence of His at position 360, instead of the common Gln that characterize the apoA-IV*1 allele, has an allele frequency for Caucasians in the range of 0·05 to 0·12. In some population studies the apoA-IV*2 allele has been associated with higher levels of HDLC and/or lower TG levels, but no associations have been observed in others. The common mutation (Thr^{347} Ser) documented within subjects with the apoA-IV*1 isoform has been less studied in terms of lipid associations in populations; however several studies have implicated this isoform with individual variability of plasma lipid levels in response to diet intervention.

Table 1 shows a summary of those studies that have examined APOA4 gene–diet interactions, in the fasting and postprandial states. The combined information for the $Thr^{347} \rightarrow$ Ser and the $Gln^{360} \rightarrow$ His suggests that the responsiveness of LDLC to changes on dietary fat is as follows: ^{347}Ser/^{360}Gln > ^{347}Thr/^{360}Gln > ^{347}Thr/^{360}His. The

mechanisms by which these mutations may exert the observed effects are still unknown. The apoA-IV*2 allele binds to lipoproteins with higher affinity than apoA-IV*1 which may result in delayed hepatic clearance of chylomicron remnants as shown in metabolic studies. The substitution of Ser for Thr at position 347 induces changes in the secondary structure and a slight increase in hydrophilic profile at this position, which could result in a decrease in its affinity for lipids on the TRL particles. This could facilitate the exchange with apoC-II, thereby increasing LPL activity over those particles, which would in turn accelerate clearance of remnants. The increased influx of dietary cholesterol would down-regulate the LDL receptors with consequent increases in LDLC concentrations. Therefore, consumption of fat-rich diets would produce a greater increase in LDLC in Ser347 carriers.

Apolipoprotein E (APOE)

The *APOE* gene has been the locus more intensively examined in terms of its potential as a determinant of the individual variability in LDL-C response to diet interventions. This interest is obvious considering the pivotal role of apoE in lipoprotein metabolism.

ApoE in serum is associated with chylomicrons, VLDL and HDL, and serves as a ligand for the LDL receptor and the LRP (Beisiegel *et al.* 1989; Mahley, 1988). When apoE deficiency is present, there is marked accumulation of cholesterol-enriched lipoproteins of density $<1{\cdot}006$ g/ml containing apoB-48 and apoA-IV, as well as apoB-100 (Schaefer *et al.* 1986). Moreover, in this disorder there is delayed clearance of both apoB-100 and apoB-48 within TRL. The current data support the concept that apoE is important for the clearance of TRL and apoE containing HDL particles.

Genetic variation at the apoE locus results from three common alleles in the population, E*4, E*3 and E*2, with frequencies in Caucasian populations of approximately 0·15, 0·77 and 0·08, respectively (Davignon *et al.* 1988). Population studies have shown that plasma cholesterol, LDL cholesterol and apoB levels are highest in subjects carrying the apoE4 isoform, intermediate in those with the apoE3 isoform, and lowest in those with the apoE2 isoform (Ordovas *et al.* 1987; Schaefer *et al.* 1994). *ApoE* allelic variation may account for up to 7 % of the variation in total and LDL-C levels in the population (Davignon *et al.* 1988). The association of the apoE4 isoform with elevated serum cholesterol levels is greater in populations consuming diets rich in saturated fat and cholesterol than in other populations. These epidemiological data indicate that the higher LDL cholesterol levels observed in subjects carrying the *apoE4* isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies, and that the response to dietary saturated fat and cholesterol may differ among individuals carrying different *apoE* alleles.

Previous findings related to this locus have been extensively reviewed (Ordovas, 1999; Ordovas & Schaefer, 1999*a*,*b*) and those findings are summarized in this work (Table 2). It should be noted that despite the large number of studies examining the relation between *APOE* genetic variability and LDLC response to diet intervention, there is considerable inconsistency regarding the magnitude and significance of the reported associations, and this locus continues to be the subject of intense research.

Overall, a significant diet by *apoE* gene interaction was reported in studies with men alone. In those studies including men and women, significant effects were noted only in men, suggesting a significant gene–sex interaction. Another difference between the negative studies and those reporting significant *apoE* gene–diet interactions related to the baseline lipid levels of the subjects. Frequently, those studies reporting significant associations included subjects who were moderately hypercholesterolaemic and/or had significant differences in base TC and LDLC among the apoE genotype groups, suggesting that the significant gene × diet interaction is apparent only in subjects who are susceptible to hypercholesterolaemia. Concerning differences in dietary interventions, significant interactions were more commonly observed among studies in which total dietary fat and cholesterol were modified. It is possible that dietary cholesterol may play a significant effect in gene–dietary fat interaction.

Several mechanisms have been proposed to explain these *apoE*-related differences in individual response to dietary therapy. Some studies have shown that intestinal cholesterol absorption is related to apolipoprotein E phenotype, with apoE4 carriers absorbing more cholesterol than non-apoE4 carriers. Other mechanisms, such as different distribution of apoE on the lipoprotein fractions, LDL apoB production, bile acid and cholesterol synthesis, and postprandial lipoprotein clearance, may also be involved.

Conclusions

Evidence accumulated during the past few years supports the concept of gene–diet interactions in humans in plasma lipid response to dietary intervention. Several candidate genes (*APOA1*, *APOC3*, *APOA4* and *APOE*) have been extensively examined under different experimental conditions, and some consensus is starting to emerge regarding their relative contribution to variability in response. However this is still a controversial area, and future studies need to be carefully designed in terms of sample size and dietary interventions. It is also important to emphasize that some of the genetic effects appear to influence primarily the postprandial state; consequently studies should be designed to test gene–diet interactions, both in the fasting and fed states. Furthermore, the genetic heritability of dietary responsiveness has not been carefully studied in humans. Therefore future dietary studies should include siblings and families. This will serve two purposes. Firstly, it will allow us to obtain more accurate estimates of the heritability of these traits. Secondly, a family structure will allow us to take advantage of the new powerful genetic techniques based on wide genome scans to search for responsiveness loci. In this regard, the use of animal models will play a crucial role to test the feasibility of this approach and to lead us to new gene loci that could be involved in dietary responsiveness across different species before embarking on more costly and difficult human experiments. Once a substantial number of responsiveness loci are mapped, we will be able to

Table 1. Summary of studies examining polymorphisms at the *APOAI*/*C3*/*A4* gene cluster, plasma lipid levels and dietary response

Polymorphism	Subjects	Experimental design	Y/N	Gene/diet effects
APOAI (−75 G/A)				
(Xu *et al.* 1993)	204 Italian boys and girls (8–11 years old)	Population. Diet intervention (LF/LC diet) in a subset	N	The A allele was associated with higher levels of TC, LDLC, apoB and apoA-I, with the effects being more marked in boys. No significant gene–diet interaction was observed
(Lopez-Miranda *et al.* 1994*a*)	50 Spanish young men	Diet intervention (LF vs high MUFA)	Y	After consumption of the high-MUFA diet, significant increases were noted in LDLC in the G/A subjects but not in the G/G subjects
(Meng *et al.* 1997)	86 men and women	Low-fat, low-cholesterol dietary intervention study. Two-week baseline period, 8-week intervention period, 8-week switchback period	N	HDL-C responses to dietary change did not differ significantly between genotypes
(Mata *et al.* 1998)	50 men and women	Diet intervention. SAT fat diet for 28 days, MUFA-rich for 35 days and PUFA-rich for 35 days	Y	A PUFA diet induced significantly greater TC and LDL-C decreases in G/A than in G/G women
(Carmena-Ramon *et al.* 1998*b*)	44 women, 25 men heterozygotes FH	Diet intervention. Baseline (35 %, fat, 10 % saturated, 300 mg/d cholesterol for 1 month and an NCEP-1 diet for 3 months	N	FH subjects carrying the A allele have significantly lower total and LDL-C and apo B baseline levels, but respond to a low-fat diet with similar reductions in total and LDL-C when compared with homozygotes for the G allele at this polymorphic site
APOC3				
(Lopez-Miranda *et al.* 1997)	90 young men	Subjects were fed a low-fat diet for 25 d, followed by a MUFA-rich (22 % MUFA, 38 % total fat) diet for 28 d	Y	After consumption of the MUFA-rich diet, significant increases in LDL-C were noted in the S1/S1 subjects whereas a significant decrease was observed in the S1/S2 subjects. Significant genotypic effects were seen for diet-induced changes in LDL-C, TC and apo B
(Salas *et al.* 1998)	41 males	Dietary intervention. The first was a SAT-rich diet, the second was an NCEP-1 diet, the last a MUFA-rich diet. At the end of each dietary period subjects received an oral glucose-tolerance test (OGTT)	Y	*APOC3* genotype significantly affected basal glucose concentrations and insulin concentrations after the OGTT. Carriers of the S2 allele ($n=13$) had higher insulin concentrations after the OGTT than S1/S1 subjects ($n=28$) in the three periods
(Waterworth *et al.* 1999)	Male offspring whose fathers had had early MI (cases, $n=407$) and age-matched controls ($n=415$)	Postprandial lipid levels following an oral fat load test (OFTT)	Y	The *APOC3* variations examined were C3238G (*Sst*I) in the 3′-UTR, C1100T in exon 3, C-482T in the IRE, and T-2854G in the apoCIII-AIV intergenic region. The postprandial response was regulated by variation at the T-2854G and C3238G sites. After the OFTT, carriers of the rare alleles had significantly delayed clearance of TG levels; G-2854 carriers showed the largest effect on TG, and G3238 carriers showed a lesser response. However, after adjustment for fasting TG levels, only the effect with the T-2854G remained significant. Variation at the C-482T (IRE) determined response to the OGTT, with carriers of the rare T-482 having significantly elevated glucose and insulin concentrations
APOA4				
(Mata *et al.* 1994)	153 men and women	HF/HC versus LF/LC diets Retrospective controlled and counseling protocols (4–24 weeks)	Y	The ApoA-IV*2 ($Gln^{360} \rightarrow His$) allele (apoAIV*2) is associated with hyporesponsiveness of LDL-C to dietary therapy consisting of reductions in total fat and cholesterol
(McCombs *et al.* 1994)	23 men and women 12 apo A-IV 1/1 and 11 apo A-IV 1/2	Step 1 diet for 2 weeks followed by step 1 diet plus four egg yolks/d for 3 weeks	Y	The hyporesponsiveness associated with the apoA-IV*2 allele may be due exclusively to the reduction in dietary cholesterol

Table 1. (*Continued*)

Polymorphism	Subjects	Experimental design	Y/N	Gene/diet effects
(Jansen *et al.* 1997*b*)	41 healthy males	Dietary intervention (high-SAT, low-fat and high-MUFA diets) for 4 weeks each	Y	Carriers of the ^{347}Ser allele presented a greater decrease in TC, LDL-C, and apo B levels when they were switched from the SFA to the NCEP1 diet than homozygous carriers of the ^{347}Thr allele. The change from the NCEP1 to the MUFA diet resulted in a greater increase in total cholesterol and apo B levels in the ^{347}Ser than in the ^{347}Thr individuals
(Jansen *et al.* 1997*a*)	41 healthy males	Dietary intervention (high-SAT, low-fat and high-MUFA diets) for 4 weeks each	Y	After consuming the saturated fat diet, carriers of the APOA4*2 allele had a greater decrease in HDLC and apoA-I. In these subjects, replacement of a high carbohydrate diet by MUFA fat resulted in a greater increase in HDLC and apoA-I as compared with homozygotes for the APOA4*1 allele
(Ostos *et al.* 1998)	50 healthy male subjects homozygous for the APOE3 allele	Vitamin A–fat load test	Y	Subjects with the A-IV-^{347}Ser allele ($n=14$) had a lower postprandial response in total TG, large and small TRL-TG levels, and a higher postprandial response in large-TRL apoA-IV and apoB-100 levels than subjects homozygous for the A-IV-^{347}Thr subjects ($n=36$)
(Carmena-Ramon *et al.* 1998*a*)	67 women and men heterozygotes FH	Diet intervention. Baseline (35 %, fat, 10 % saturated, and 300 mg/d cholesterol for 1 month and an NCEP-1 diet for 3 months	Y	The apoA4*2 allele was associated with lower LDLC and apoB levels independent of diet effects. No differences in TC, LDLC, HDLC and apoB levels were observed between subjects homozygous for the APOA4^{347}Thr allele and those carriers of the APOA4^{347}Ser allele. After dietary intervention, Ser/Ser subjects showed significant reductions in plasma triglycerides and VLDLC levels, but no changes were found in carriers of the Ser allele
(Fisher *et al.* 1999)	EARSII study	Oral fat load test	Y	After consumption of an oral fat load, carriers of His^{360} who were most obese had significantly reduced postprandial lipaemia

Table 2. Summary of studies examining *apoE* genotype–diet interactions with changes in dietary fat and/or cholesterol

Study	Subjects	Experimental design* (diet period)	Y/N	Observed effects
(Fisher *et al.* 1983)	9 normolipidaemic males	Corn oil versus coconut oil plus low versus high cholesterol Combination (9 d)	N	No effect on TC, LDLC, HDLC or TG levels
(Miettinen *et al.* 1988)	16 men	Low-fat/low-cholesterol versus low-fat/high cholesterol (6 weeks)	Y	E4 allele associated with greater TC, LDLC and HDLC response. E2 associated with increased HDLC response
(Tikkanen *et al.* 1990)	110 men and women	Baseline (high-fat, high-cholesterol) versus low-fat high-P/S diet Controlled (6 or 12 weeks)	Y	Significant apoE allele effect on plasma lipid levels. Greater reductions in TC occurred in subjects homozygous for the apoE4 allele
(Boerwinkle *et al.* 1991)	71 men	Low-cholesterol versus high-cholesterol Counselled (3 weeks)	N	The average responses in lipid levels were not significantly different among apo E genotypes
(Gaddi *et al.* 1991)	20 FH men and women	Low-fat/low-cholesterol versus soy protein diet Controlled (4 weeks)	Y	The plasma cholesterol reduction was higher in patients with apolipoprotein E3/E3 or E3/E4 versus an almost negligible effect on E3/E2
(Manttari *et al.* 1991)	117 dyslipidaemic middle-aged men (placebo group Helsinki Heart Study)	Diet therapy counselling (15 months)	Y	Baseline lipid levels were not affected by the E allele. E4 subjects exhibited a greater reduction in TC and LDLC
(Savolainen *et al.* 1991)	44 healthy middle-aged men and women	Low-fat/low-cholesterol versus high-fat/high-cholesterol Controlled (4 weeks)	N	The absolute and percentage lipid changes on the two diets were equal in E3 and E4 subjects
(Cobb *et al.* 1992)	67 normolipidaemic men and women	One a 'western' diet, with a low polyunsaturated to saturated (p:s) fatty acid ratio and the other a 'therapeutic' diet with a high P : S ratio Retrospective pooled analysis of six controlled studies	Y	Women of the ApoE3/2 phenotype stand to benefit the least from a high P : S diet because of reduction in the more 'protective' HDL-C, whereas men of the 4/3 phenotype showed the greatest improvement in the LDL/HDL ratio
(Lehtimaki *et al.* 1992)	36 healthy students	Usual (no eggs) versus usual plus eggs Counselling (3 weeks)	Y	The increases were similar in groups E3/2, E3/3, and E4/3. Stronger responses were observed in E4/4 subjects
(Miettinen *et al.* 1992)	29 middle-aged men	Normal diet versus a diet low in fat and cholesterol. Counselled (5 weeks)	Y	The apoE subscript (e.g. E2/2 = 1, E2/3 = 2, etc.) was positively associated with cholesterol absorption and the LDL apoB and cholesterol levels and negatively with cholesterol synthesis and FCR for LDL apoB
(Uusitupa *et al.* 1992)	19 subjects	High-fibre diets (oat versus wheat bran) (8 weeks)	Y	Only E3 subjects had hypocholesterolaemic response to oat bran. No change was found in E4 subjects
(Jenkins *et al.* 1993)	67 men and women	High-fibre diet (oat versus wheat bran) (2 weeks)	Y	Carriers of the E2 allele appear to be more responsive than non-carriers to a dietary change involving increased fibre intake
(Cobb & Risch, 1993)	67 normolipidaemic men and women (as above) Design as above	Low P : S ratio, and the other had a high P : S ratio.	N	apoE phenotype was not a significant predictor of responsiveness
(Hunninghake *et al.* 1993)	97 male and female patients with moderate hypercholesterolaemia	High in fat and cholesterol versus low-fat diet Counselled (9 weeks)	N	apoE phenotype was not a significant predictor of responsiveness
(Martin *et al.* 1993)	30 young normal male subjects	Low-cholesterol versus high-cholesterol controlled (35 d)	Y	The LDL-C response to dietary cholesterol did not differ among the *apoE* genotypes. *ApoE* genotype has significant and opposite effects on plasma CETP and HDL-C responses to dietary cholesterol in men
(Lopez-Miranda *et al.* 1994*b*)	128 men and women	HF/HC versus LF/LC diets. Retrospective-controlled and counselling protocols (4–24 weeks)	Y	The plasma LDLC reduction was higher in male subjects with the E4 allele

Table 2. (*Continued*)

Study	Subjects	Experimental design* (diet period)	Y/N	Observed effects
(Sarkkinen *et al.* 1994)	40 hypercholesterolaemic men and women	High SAT versus high MUFA, counselled (6 months)	N	apoE phenotype was not a significant predictor of responsiveness
(Clifton *et al.* 1995)	120 normolipidaemic men and women	LF versus LF plus two liquid supplements (one that contained HF/HC and one that was fat free) (2 and 3 weeks) Counselled and supplement	Y	The plasma LDLC reduction was higher in male subjects with the E4 allele
(Dreon *et al.* 1995)	102 normal men	High-fat versus low fat. Counselled (6 weeks)	Y	The plasma LDLC reduction was higher in subjects with the E4 allele
(Schaefer *et al.* 1995)	32 men and women	High-fat/high-cholesterol versus NCEP step II. Controlled (6 and 24 weeks)	Y	The plasma LDLC reduction was higher in male subjects with the E4 allele
(Zambón *et al.* 1995)	122 hypercholesterolaemic men and women	High-MUFA versus LF, counselled (12 weeks)	N	apoE phenotype was not a significant predictor of responsiveness
(Park *et al.* 1996)	17 subjects	High-fat diets containing different proportions of specific saturated fatty acids (4 weeks)	N	Apo E phenotype was not a significant predictor of responsiveness
(Dixon *et al.* 1997)	125 children aged 4–10 years	LF dietary intervention. Counselled (3 months)	N	The magnitude of the changes in TC and LDLC were not dependent on *apoE* genotype
(Lefevre *et al.* 1997)	103 men and women	HF/HC versus AHA Step I versus low-SAT (no changes in dietary cholesterol) Controlled (8 weeks)	N	apoE phenotype was not a significant predictor of responsiveness
(Lehtimaki *et al.* 1997)	58 healthy men and women	Fasting. Controlled (1 week)	Y	In men, the changes in plasma LDLC during fasting differed significantly between apoE genotypes
	488 healthy women	LF dietary intervention. Counselled (6 months)	N	The magnitude of the changes in TC and LDLC were not dependent on apoE genotype
(Pasagian-Macaulay *et al.* 1997)	36 type 1 diabetes mellitus subjects	Long-term response to a low-cholesterol diet (1 year)	Y	The *APOE4* group had a significantly higher decrease in LDL-C than those in the E3 group
(Blaauwwiekel *et al.* 1998)	65 healthy men and women aged 20–73 years	Tea (six mugs of black tea/d) and then a crossover of placebo (consisting of water, caffeine, milk and sugar) (4 weeks)	Y	Tea drinking was associated with significant decreases in HDLC levels of E3/3 subjects as well as decreases in TG levels and PAI-1 activities of apoE2/3 subjects
(Loktionov *et al.* 1998)	Middle-aged and mildly hypercholesterolaemic	Modification of dietary fat and cholesterol.	Y	The TC lowering effect of an NCEP diet was significantly greater in APOE4 carriers. This group also experienced the greatest TC increase following the addition of 300 mg of cholesterol to the diet
(Sarkkinen *et al.* 1998)	36 healthy premenopausal women	HF diets containing different proportions of specific saturated fatty acids. Controlled (4 weeks)	Y	Responsiveness regulated in part by apoE polymorphism

develop simple genetic tests that will allow the clinician to implement the most successful therapy for each individual, and therefore to increase the success and reduce the long-term cost of preventive and therapeutic interventions.

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References

Angotti E, Mele E, Costanzo F & Avvedimento EV (1994) A polymorphism (G → A transition) in the −78 position of the apolipoprotein A-I promoter increases transcription efficiency. *Journal of Biological Chemistry* **269**, 17371–17374.

Beisiegel U, Weber W, Ihrke G, Herz J & Stanley KK (1989) The LDL-receptor-related protein, LRP, is an apolipoprotein E-binding protein. *Nature* **341**, 162–164.

Blaauwwiekel EE, Beusekamp BJ, Sluiter WJ, Hoogenberg K & Dullaart RPF (1998) Apolipoprotein E genotype is a determinant of low-density lipoprotein cholesterol and of its response to a low-cholesterol diet in type 1 diabetic patients with elevated urinary albumin excretion. *Diabetic Medicine* **15**, 1031–1035.

Boerwinkle E, Brown SA, Rohrbach K, Gotto AM Jr & Patsch W (1991) Role of apolipoprotein E and B gene variation in determining response of lipid, lipoprotein, and apolipoprotein levels to increased dietary cholesterol. *American Journal Human Genetics* **49**, 1145–1154.

Bruns GA, Karathanasis SK & Breslow JL (1984) Human apolipoprotein AI-CIII gene complex is located in chromosome 11. *Arteriosclerosis* **4**, 97–104.

Carmena R, Roederer G, Mailloux H, Lussier-Cacan S & Davignon J (1993) The response to lovastatin treatment in patients with heterozygous familial hypercholesterolemia is modulated by apolipoprotein E polymorphism. *Metabolism* **42**, 895–901.

Carmena-Ramon RF, Ascaso JF, Real JT, Ordovas JM & Carmena R (1998*a*) Genetic variation at the *ApoA-IV* gene locus and response to diet in familial hypercholesterolemia. *Arteriosclerosis, Thrombosis and Vascular Biology* **18**, 1266–1274.

Carmena-Ramon RF, Ordovas JM, Ascaso JF, Real J, Priego MA & Carmena R (1998*b*) Influence of genetic variation at the *apoA-I* gene locus on lipid levels and response to diet in familial hypercholesterolemia. *Atherosclerosis* **139**, 107–113.

Clifton PM, Abbey M, Noakes M, Beltrame S, Rumbelow N & Nestel PJ (1995) Body fat distribution is a determinant of the high-density lipoprotein response to dietary fat and cholesterol in women. *Arteriosclerosis, Thrombosis and Vascular Biology* **15**, 1070–1078.

Cobb MM, Teitlebaum H, Risch N, Jekel J & Ostfeld A (1992) Influence of dietary fat, apolipoprotein E phenotype, and sex on plasma lipoprotein levels. *Circulation* **86**, 849–857.

Cobb MM & Risch N (1993) Low-density lipoprotein cholesterol responsiveness to diet in normolipidemic subjects. *Metabolism* **42**, 7–13.

Dammerman M, Sandkuijl LA, Halaas JL, Chung W & Breslow JL (1993) An apolipoprotein CIII haplotype protective against hypertriglyceridemia is specified by promoter and 3′ untranslated region polymorphisms. *Proceedings of the National Academy of Sciences, USA* **90**, 4562–4566.

Danek GM, Valenti M, Baralle FE & Romano M (1998) The A/G polymorphism in the −78 position of the apolipoprotein A-I promoter does not have a direct effect on transcriptional efficiency. *Biochimica et Biophysica Acta* **1398**, 67–74.

Davignon J, Gregg RE & Sing CF (1988) Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis* **8**, 1–21.

Dixon LB, Shannon BM, Tershakovec AM, Bennett MJ, Coates PM & Cortner JA (1997) Effects of family history of heart disease, apolipoprotein E phenotype, and lipoprotein(a) on the response of children's plasma lipids to change in dietary lipids. *American Journal of Clinical Nutrition* **66**, 1207–1217.

Dreon DM, Fernstrom HA, Miller B & Krauss RM (1995) Apolipoprotein E isoform phenotype and LDL subclass response to a reduced-fat diet. *Arteriosclerosis and Thrombosis* **15**, 105–111.

Fielding CJ, Shore VG & Fielding PE (1972) A protein co-factor of lecithin:cholesterol acyltransferase. *Biochemical & Biophysical Research Communications* **46**, 1493–1498.

Fisher EA, Blum CB, Zannis VI & Breslow JL (1983) Independent effects of dietary saturated fat and cholesterol on plasma lipids, lipoproteins, and apolipoprotein E. *Journal of Lipid Research* **24**, 1039–1048.

Fisher RM, Burke H, Nicaud V, Ehnholm C & Humphries SE (1999) Effect of variation in the *apoA-IV* gene on body mass index and fasting and postprandial lipids in the European Atherosclerosis Research Study II. *Journal of Lipid Research* **40**, 287–294.

Gaddi A, Ciarrocchi A, Matteucci A, Rimondi S, Ravaglia G, Descovich GC & Sirtori CR (1991) Dietary treatment for familial hypercholesterolemia – differential effects of dietary soy protein according to the apolipoprotein E phenotypes. *American Journal of Clinical Nutrition* **53**, 1191–1196.

Hunninghake DB, Stein EA, Dujovne CA, Harris WS, Feldman EB, Miller VT, Tobert JA, Laskarzewski PM, Quiter E, Held J, Taylor AM, Hopper S, Leonard SB & Brewer BK (1993) The efficacy of intensive dietary therapy alone or combined with lovastatin in outpatients with hypercholesterolemia. *New England Journal of Medicine* **328**, 1213–1219.

Jansen S, Lopez-Miranda J, Ordovas JM, Zambrana JL, Marin C, Ostos MA, Castro P, McPherson R, Lopez Segura F, Blanco A, Jimenez Pereperez JA & Perez-Jimenez F (1997*a*) Effect of 360His mutation in apolipoprotein A-IV on plasma HDL-cholesterol response to dietary fat. *Journal of Lipid Research* **38**, 1995–2002.

Jansen S, Lopez-Miranda J, Salas J, Ordovas JM, Castro P, Marin C, Ostos MA, Lopez-Segura F, Jimenez-Pereperez JA, Blanco A & Perez-Jimenez F (1997*b*) Effect of 347-serine mutation in apoprotein A-IV on plasma LDL cholesterol response to dietary fat. *Arteriosclerosis, Thrombosis & Vascular Biology* **17**, 1532–1538.

Jeenah M, Kessling A, Miller N & Humphries SE (1990) G to A substitution in the promoter region of the apolipoprotein AI gene is associated with elevated serum apolipoprotein AI and high density lipoprotein cholesterol concentrations. *Molecular Biology & Medicine* **7**, 233–241.

Jenkins DJA, Hegele RA, Jenkins AL, Connelly PW, Hallak K, Bracci P, Kashtan H, Corey P, Pintilia M, Stern H & Bruce R (1993) The apolipoprotein E gene and the serum low-density lipoprotein cholesterol response to dietary fiber. *Metabolism* **42**, 585–593.

Juo SHH, Wyszynski DF, Beaty TH, Huang HY & Bailey-Wilson JE (1999) Mild association between the A/G polymorphism in the promoter of the apolipoprotein A-I gene and aplipoprotein A-I levels: a meta-analysis. *American Journal of Medical Genetics* **82**, 235–241.

Karathanasis SK (1985) Apolipoprotein multigene family: tandem organization of human apolipoprotein. *A-I*, *C-III* and *A-IV* genes. *Proceedings of the National Academy of Sciences, USA* **82**, 6374–6378.

Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Roheim PS, Ramakrishnan R, Derr J, Gordon DJ & Reed R (1997) ApoE genotype does not predict lipid response to changes in dietary saturated fatty acids in a heterogeneous normolipidemic population. The DELTA Research Group. Dietary Effects on Lipoproteins and Thrombogenic Activity. *Arteriosclerosis, Thrombosis & Vascular Biology* **17**, 2914–2923.

Lehtimaki T, Moilanen T, Solakivi T, Laippala P & Ehnholm C (1992) Cholesterol-rich diet induced changes in plasma lipids in relation to apolipoprotein E phenotype in healthy students. *Annals of Medicine* **24**, 61–66.

Lehtimaki T, Frankberg-Lakkala H, Solakivi T, Koivisto A, Laippala P, Ehnholm C, Jokela H, Koivula T & Nikkari T (1997) The effect of short-term fasting, apolipoprotein E gene polymorphism, and sex on plasma lipids. *American Journal of Clinical Nutrition* **66**, 599–605.

Li WW, Dammerman MM, Smith JD, Metzger S, Breslow JL & Leff T (1995) Common genetic variation in the promoter of the human apo CIII gene abolishes regulation by insulin and may contribute to hypertriglyceridemia. *Journal of Clinical Investigation* **96**, 2601–2605.

Loktionov A, Bingham SA, Vorster H, Jerling JC, Runswick SA & Cummings JH (1998) Apolipoprotein E genotype modulates the effect of black tea drinking on blood lipids and blood coagulation factors: a pilot study. *British Journal of Nutrition* **79**, 133–139.

Lopez-Miranda J, Ordovas JM, Espino A, Marin C, Salas J, Lopez-Segura F, Jimenez-Pereperez J & Perez-Jimenez F (1994*a*) Influence of mutation in human apolipoprotein *A-1* gene promoter on plasma LDL cholesterol response to dietary fat. *Lancet* **343**, 1246–1249.

Lopez-Miranda J, Ordovas JM, Mata P, Lichtenstein AH, Clevidence B, Judd JT & Schaefer EJ (1994*b*) Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *Journal of Lipid Research* **35**, 1965–1975.

Lopez-Miranda J, Jansen S, Ordovas JM, Salas J, Marin C, Castro P, Ostos MA, Cruz G, Lopez-Segura F, Blanco A, Jimenez-Pereperez J & Perez-Jimenez F (1997) Influence of the *Sst*I polymorphism at the apolipoprotein C-III gene locus on the plasma low-density-lipoprotein-cholesterol response to dietary monounsaturated fat. *American Journal of Clinical Nutrition* **66**, 97–103.

Mahley RW (1988) Apolipoprotein E : cholesterol transport protein with expanding role in cell biology. *Science* **240**, 622–630.

Manttari M, Kosninen P, Enholm C, Huttunen JK & Manninen V (1991) Apolipoprotein E polymorphism influences the serum cholesterol response to dietary intervention. *Metabolism* **40**, 217–221.

Marshall HW, Morrison LC, Wu LL, Anderson JL, Corneli PS, Stauffer DM, Allen A, Karagounis LA & Ward RH (1994) Apolipoprotein polymorphisms fail to define risk of coronary artery disease: results of a prospective, angiographically controlled study. *Circulation* **89**, 567–577.

Martin LJ, Connelly PW, Nancoo D, Wood N, Zhang ZJ, Maguire G, Quinet E, Tall AR, Marcel YL & McPherson R (1993) Cholesteryl ester transfer protein and high density lipoprotein responses to cholesterol feeding in men: relationship to apolipoprotein E genotype. *Journal of Lipid Research* **34**, 437–446.

Mata P, Ordovas JM, Lopez-Miranda J, Lichtenstein AH, Clevidence B, Judd JT & Schaefer EJ (1994) ApoA-IV phenotype affects diet-induced plasma LDL cholesterol lowering. *Arteriosclerosis and Thrombosis* **14**, 884–891.

Mata P, Lopez-Miranda J, Pocovi M, Alonso R, Lahoz C, Marin C, Garces C, Cenarro A, Perez-Jimenez F, De Oya M & Ordovas JM (1998) Human apolipoprotein A-I gene promoter mutation influences plasma low density lipoprotein cholesterol response to dietary fat saturation. *Atherosclerosis* **137**, 367–376.

McCombs RJ, Marcadis DE, Ellis J & Weinberg RB (1994) Attenuated hypercholesterolemic response to a high-cholesterol diet in subjects heterozygous for the apolipoprotein A-IV-2 allele. *New England Journal of Medicine* **331**, 706–710.

Meng QH, Pajukanta P, Valsta L, Aro A, Pietinen P & Tikkanen MJ (1997) Influence of apolipoprotein A-1 promoter polymorphism on lipid levels and responses to dietary change in Finnish adults. *Journal of Internal Medicine* **241**, 373–378.

Miettinen TA, Gylling H & Vanhanen H (1988) Serum cholesterol response to dietary cholesterol and apoprotein E phenotype. *Lancet* **2**, 1261

Miettinen TA, Gylling H, Vanhanen H & Ollus A (1992) Cholesterol absorption, elimination, and synthesis related to LDL kinetics during varying fat intake in men with different apoprotein E phenotypes. *Arteriosclerosis and Thrombosis* **12**, 1044–1052.

Nemeth A, Szakmary KA, Kramer J, Dinya E, Pados G, Fust G & Huettinger M (1995) Apolipoprotein E and complement C3 polymorphism and their role in the response to gemfibrozil and low fat low cholesterol therapy. *European Journal of Clinical Chemistry and Clinical Biochemistry* **33**, 799–804.

Nestel P, Simons L, Barter P, Clifton P, Colquhoun D, Hamilton-Craig I, Sikaris K & Sullivan D (1997) A comparative study of the efficacy of simvastatin and gemfibrozil in combined hyperlipoproteinemia: predicition of response by baseline lipids, *apoE* genotype, lipoprotein(a) and insulin. *Atherosclerosis* **129**, 231–239.

Ordovas JM (1999) The genetics of serum lipid responsiveness to dietary interventions. *Proceedings of the Nutrition Society* **58**, 171–187.

Ordovas JM & Schaefer EJ (1999*a*) Genes, variation of cholesterol and fat intake and serum lipids. *Current Opinion In Lipidology* **10**, 15–22.

Ordovas JM & Schaefer EJ (1999*b*) Treatment of dyslipidemia: genetic interactions with diet and drug therapy. *Current Atherosclerosis Reports* **1**, 16–23.

Ordovas JM, Litwack-Klein L, Wilson PWF, Schaefer MM & Schaefer EJ (1987) Apolipoprotein E isoform phenotyping methodology and population frequency with identification of *apoE1* and *apoE5* isoforms. *Journal of Lipid Research* **28**, 371–380.

Ordovas JM, Cassidy DK, Civeira F, Bisgaier CL & Schaefer EJ (1989) Familial apolipoprotein A-I, C-III, and A-IV deficiency and premature atherosclerosis due to deletion of a gene complex on chromosome 11. *Journal of Biological Chemistry* **264**, 16339–16342.

Ordovas JM, Civeira F, Genest J, Jr, Craig S, Robbins AH, Meade T, Pocovi M, Frossard PM, Masharani U, Wilson PW *et al.* (1991) Restriction fragment length polymorphisms of the apolipoprotein A-I, C-III, A-IV gene locus. Relationships with lipids, apolipoproteins, and premature coronary artery disease. *Atherosclerosis* **87**, 75–86.

Ordovas JM, Lopez-Miranda J, Perez-Jimenez F, Rodriguez CR, Park J, Cole T & Schaefer EJ (1995) Effect of apolipoprotein E and A-IV phenotypes on the low density lipoprotein response to HMG-CoA reductase inhibitor therapy. *Atherosclerosis* **113**, 157–166.

Ostos MA, Lopez-Miranda J, Ordovas JM, Marin C, Blanco A, Castro P, Lopez-Segura F, Jimenez Pereperez JA & Perez-Jimenez F (1998) Dietary fat clearance is modulated by genetic variation in apolipoprotein A-IV gene locus. *Journal of Lipid Research* **39**, 2493–2500.

Park S, Snook JT, Bricker L, Morroco M, Van Voorhis R, Stasny E & Lee MS (1996) Relative effects of high saturated fatty acid

levels in meat, dairy products,and tropical oils on serum lipoproteins and low-density lipoprotein degradation by mononuclear cells in healthy males. *Metabolism* **45**, 550–558.
Pasagian-Macaulay A, Aston CE, Ferrell RE, McAllister A, Wing RR & Kuller LH (1997) A dietary and behavioral intervention designed to lower coronary heart disease. Risk factors are unaffected by variation at the APOE gene locus. *Atherosclerosis* **132**, 221–227.
Paul-Hayase H, Rosseneu M, Van Bervliet JP, Deslypere JP & Humphries SE (1992) Polymorphisms in the apolipoprotein (apo) *AI-CIII-AIV* gene cluster: detection of genetic variation determining plasma apo AI, apo CIII and apo AIV concentrations. *Human Genetics* **88**, 439–446.
Reichl D & Miller NE (1989) Pathophysiology of reverse cholesterol transport: insights from inherited disorders of lipoprotein metabolism. *Arteriosclerosis* **9**, 785–797.
Salas J, Jansen S, Lopez-Miranda J, Ordovas JM, Castro P, Marin C, Ostos MA, Bravo MD, Jimenez Pereperez JA, Blanco A, Lopez-Segura F & Perez-Jimenez F (1998) The *Sst*I polymorphism of the apolipoprotein C-III gene determines the insulin response to an oral glucose tolerance test after consumption of a diet rich in saturated fats. *American Journal of Clinical Nutrition* **68**, 396–401.
Sarkkinen ES, Uusitupa MIJ, Pietinen P, Aro A, Ahola I, Penttilä I, Kervinen K & Kesäniemi YA (1994) Long-term effects of three fat-modified diets in hypercholesterolemic subjects. *Atherosclerosis* **105**, 9–23.
Sarkkinen E, Korhonen M, Erkkila A, Ebeling T & Uusitupa M (1998) Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *American Journal of Clinical Nutrition* **68**, 1215–1222.
Savolainen MJ, Rantala M, Kervinen K, Jarvi L, Suvanto K, Rantala T & Kesaniemi YA (1991) Magnitude of dietary effects on plasma cholesterol concentration: role of sex and apolipoprotein E phenotype. *Atherosclerosis* **86**, 145–152.
Schaefer EJ, Gregg RE, Ghiselli G, Forte TM, Ordovas JM, Zech LA, Lindgren FT & Brewer HB, Jr (1986) Familial apolipoprotein E deficiency. *Journal of Clinical Investigation* **78**, 1206–1219.
Schaefer EJ, Lamon-Fava S, Johnson S, Ordovas JM, Schaefer MM, Castelli WP & Wilson PWF (1994) Apolipoprotein E phenotype affects plasma lipoprotein levels in a gender- and menopausal status-dependent manner. *Arteriosclerosis and Thrombosis* **4**, 1105–1113.
Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Rasmussen H, McNamara JR & Ordovas JM (1995) Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. *Arteriosclerosis, Thrombosis and Vascular Biology* **15**, 1079–1085.
Smith JD, Brinton EA & Breslow JL (1992) Polymorphism in the human apolipoprotein A-I gene promoter region. Association of the minor allele with decreased production rate *in vivo* and promoter activity *in vitro*. *Journal of Clinical Investigation* **89**, 1796–1800.
Tall A, Welch C, Applebaum-Bowden D & Wassef M (1997) Interaction of diet and genes in atherogenesis. Report of an NHLBI working group. *Arteriosclerosis, Thrombosis and Vascular Biology* **17**, 3326–3331.
Tikkanen MJ, Huttunen JK, Enholm C & Pietinen P (1990) Apolipoprotein E4 homozygosity predisposes to serum cholesterol elevation during high fat diet. *Arteriosclerosis* **10**, 285–288.
Tso TK, Park S, Tsai YH, Williams G & Snook JT (1998) Effect of apolipoprotein E polymorphism on serum lipoprotein response to saturated fatty acids. *Lipids* **33**, 139–148.
Tuteja R, Tuteja N, Melo C, Casari G & Baralle FE (1992) Transcription efficiency of human apolipoprotein A-I promoter varies with naturally occurring A to G transition. *FEBS Letters* **304**, 98–101.
Tybjaerg-Hansen A, Nordestgaard BG, Gerdes LU, Faergeman O & Humphries S (1993) Genetic markers in the apo AI-CIII-AIV gene cluster for combined hyperlipidemia, hypertriglyceridemia, and predisposition to atherosclerosis. *Atherosclerosis* **100**, 157–169.
Uusitupa MIJ, Ruuskanen E, Mäkinen E, Laitinen J, Toskala E, Kervinen K & Kesäniemi YA (1992) A controlled study on the effect of beta-glucan-rich oat bran on serum lipids in hypercholesterolemic subjects: relation to apolipoprotein E phenotype. *Journal of the American College of Nutrition* **11**, 651–659.
Wang XL, Badenhop RB, Sim AS & Wilcken DEL (1998) The effect of transcription efficiency of the apolipoprotein AI gene of DNA variants at the 5′ untranslated region. *International Journal of Clinical and Laboratory Research* **28**, 235–241.
Waterworth DM, Ribalta J, Nicaud V, Dallongeville J, Humphries SE & Talmud P (1999) *ApoCIII* gene variants modulate postprandial response to both glucose and fat tolerance tests. *Circulation* **99**, 1872–1877.
Xu C-F, Angelico F, Del Ben M & Humphries S (1993) Role of genetic variation at the apo AI-CIII-AIV gene cluster in determining plasma apo AI levels in boys and girls. *Genetic Epidemiology* **10**, 113–122.
Zambón D, Ros E, Casals E, Sanllehy C, Bertomeu A & Campero I (1995) Effect of apolipoprotein E polymorphism on the serum lipid response to a hypolipidemic diet rich in monounsaturated fatty acids in patients with hypercholesterolemia and combined hyperlipidemia. *American Journal of Clinical Nutrition* **61**, 141–148.