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GENETICS (GVZ DEDOUSSIS, SECTION EDITOR)

Gene–Diet Interactions on Lipid Levels: Current Knowledge in the Era of Genome-Wide Association Studies

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Abstract Plasma lipids are important risk factors for cardiovascular disease. Both genetic factors and diet are known to regulate lipid levels, and there has been a longstanding interest in how genes may interact with diet to modulate changes in lipid levels. Genome-wide association studies have recently identified the genes most strongly associated with variation in lipids within a population. In this paper, the current knowledge on gene–diet interactions to regulate lipid levels is discussed in light of these studies. Future genome-wide studies are required that specifically identify genes that are important modulators of lipid levels in response to dietary change. Some methodologic challenges inherent in these studies are discussed.

Keywords Genome-wide association studies · GWAS · Gene–diet interactions · Lipids · Lipid metabolism · Variation · Cholesterol · Triglyceride · Dietary intervention

Introduction

An adverse lipid profile of high triglycerides, total and low-density lipoprotein (LDL) cholesterol, and low high density (HDL) cholesterol has been associated with atherosclerosis and cardiovascular disease [1–3]. At a population level, diet is an important determinant of the lipid profile, but a great degree of interindividual variation has been consistently noted, particularly in the lipid responses to dietary interventions. This variation has been attributed to differences in genetic background, in addition to age, gender, and ethnicity. In the past, a number of likely candidate genes have been explored, but no genes have been identified that can consistently account for a large number of these interindividual differences. In recent years, genome-wide association studies (GWAS) have shed light on genetic mechanisms underlying the regulation of lipid levels; however, it is becoming apparent that further research is required, with studies more specifically designed to assess diet–gene interactions in a more comprehensive way.

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Dietary Modulation of Lipids

Population-level effects of diet composition on lipid profile are well-established. Reductions in total fat, saturated fatty acids, and trans-fatty acids are all effective in reducing total cholesterol, LDL cholesterol, and triglycerides [4–6]. However, a reduction in total dietary fat intake achieved by replacement with carbohydrates has been associated with an unfavorable reduction in HDL cholesterol and increased triglycerides [5, 7]. Conversely, replacement of trans- or saturated fatty acids with monounsaturated fatty acids has been found to maintain HDL cholesterol [8]. Increased dietary intake of n-3 polyunsaturated fatty acids has been associated with lower triglycerides [9]. In addition to changes in dietary composition, a reduction in total energy leading to weight loss is associated with reductions in cholesterol and triglycerides, and an increase in HDL cholesterol associated with weight loss [10, 11].

While the effects of diet composition on the lipid profile are well-understood, the mechanisms by which diet can alter lipid levels are not fully elucidated. Thus far, mechanistic studies have shown that reductions in dietary saturated and trans-fatty acids involve changes in the activity of several

receptors and enzymes, in particular LDL receptor, apolipoproteins B and E, and cholesteryl ester transfer protein (Fig. 1) [12, 13]. Changes in the activity of these enzymes and receptors result in a change in circulating very low-density lipoprotein (VLDL), and a favorable redistribution of cholesterol between plasma and peripheral tissues (Fig. 1) [13]. The reduction in total cholesterol that results from an exchange of saturated with monounsaturated fatty acids appears to be a consequence of increased LDL clearance, most likely involving the LDL receptor [14], but also associated with reduced cholesteryl ester transfer protein activity [15]. The reduction in triglyceride associated with an increased n-3 polyunsaturated fatty acid intake is via decreased production and possibly increased clearance of

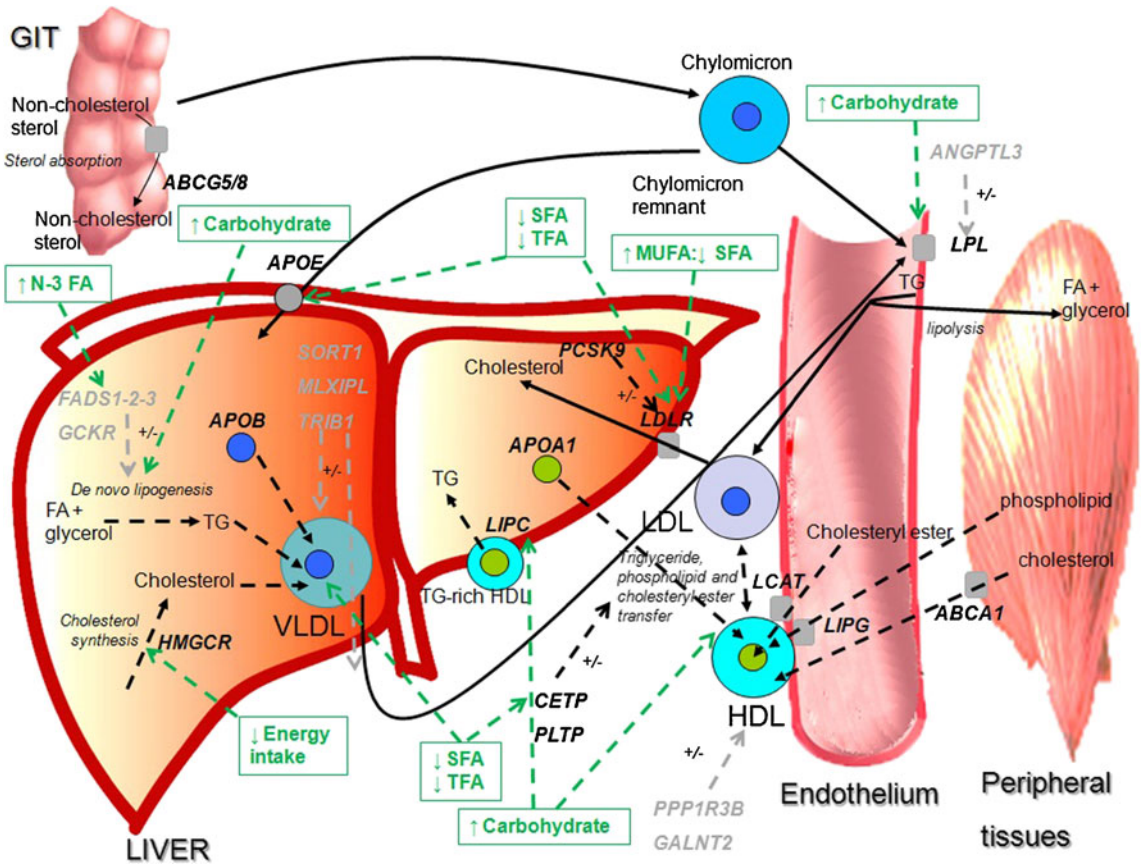

Fig. 1 Overview of lipid metabolic pathways, the role of key genes identified in genome-wide association studies (GWAS), and the effects of dietary changes. Gastrointestinal adenosine trisphosphate (ATP)-binding cassette subfamily G members 5 and 8 (*ABCG5/8*) transporters regulate selective sterol absorption. Dietary fats are packaged into chylomicrons for transport to peripheral tissues, where uptake of triglycerides is mediated by lipoprotein lipase (LPL). Angiopoietin-like 3 (*ANGPTL3*) contributes to the regulation of LPL. Chylomicron remnant uptake into the liver is regulated by apolipoprotein E (*APOE*). Triglycerides are synthesized in the liver, involving fatty acid (FA) desaturase (*FADS1-2–3*) enzymes and influenced by glycolytic flux and glucokinase regulatory protein (*GCKR*). Cholesterol is synthesized in the liver, regulated by 3-hydroxy-3-methyl-glutaryl-CoA reductase (*HMGCR*). Very low-density lipoproteins (VLDL) are assembled in the liver from apolipoprotein B (*APOB*), cholesterol, and triglyceride. Sortilin-1 (*SORT1*), carbohydrate response element binding protein (encoded by *MLXIPL*), and Tribbles homolog 1 (*TRIB1*) all contribute to the regulation of hepatic VLDL assembly and efflux. VLDL are processed by LPL, releasing triglyceride into peripheral tissues and resulting in low-density lipoprotein (LDL). High-density lipoproteins (HDL) are formed from apolipoproteins (*APOA1*) from the liver and phospholipids and cholesterol acquired from peripheral tissues by cholesterol efflux mediated by ATP-binding cassette A1 (*ABCA1*). Protein phosphatase 1, regulatory (inhibitor) subunit 3B (*PPP1R3B*) and polypeptide N-acetylgalactosaminyltransferase 2 (*GALNT2*) contribute to the regulation of HDL levels. Free cholesterol is esterified by the enzyme lecithin-cholesterol acyltransferase (LCAT), which is sequestered into the core of the particle. Continual remodeling of LDL and HDL particles, which involves triglyceride, phospholipid, and cholesteryl ester transfer, occurs via the enzymes cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP). VLDL and LDL laden with cholesteryl esters are taken up via the LDL receptor (LDLR) into the liver. Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) regulates degradation of LDLR. Triglycerides are removed and hydrolyzed from TG-rich HDL by hepatic lipase (encoded by *LIPC*). Endothelial lipase (*LIPG*) also contributes to HDL remodeling via phospholipase activity. Genes identified in GWAS are in *bold* and *italics*. Genes that have been implicated in the regulation of a pathway, but the mechanism has not been elucidated, are indicated in *gray* [2, 24, 37, 59]. The impact of diet, including changes in fat and carbohydrate content, FA composition, and energy intake, on the regulation of lipid metabolic pathways and the genes that regulate them is indicated. MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; TFA, trans-fatty acid

triglycerides regulated by several proposed mechanisms, particularly involving the desaturase enzymes encoded by fatty acid desaturase genes (Fig. 1) [16]. Hypertriglyceridaemia associated with increased dietary carbohydrate is a result of increased production and/or decreased clearance of triglyceride into peripheral tissues, particularly involving the enzyme lipoprotein lipase [17], as well as pathways regulating de novo lipogenesis (Fig. 1). Hypertriglyceridemia appears to be associated with a reduction in HDL cholesterol, possibly via cholesterol and triglyceride transfer mechanisms and subsequent catabolism of lipoprotein particles. This involves the enzymes hepatic lipase and cholesteryl ester transfer protein (Fig. 1) [18]. Acutely, energy restriction has been shown to inhibit cholesterol synthesis [19], but improvements are also seen as a longer-term consequence of weight loss, with reductions in cholesterol and triglycerides and an increase in HDL cholesterol [11, 20, 21]. The mechanisms behind sustained improvements in lipid profile are less clear and likely to involve additional factors associated with the weight loss, such as insulin sensitivity [20] and blood supply [22].

However, population-level effects of diets on lipid levels conceal significant heterogeneity at an individual level [5]. This is often attributed (in part) to genetic variation [23, 24]. Previous genetic studies, in particular studies of monogenic lipid disorders, have helped characterize specific lipid metabolic pathways that may be modulated by diet [2, 24, 25]. Further advances in genetic analysis and in particular gene–diet interactions will help further elucidate these pathways and identify novel pathways.

Genetic Modulation of Lipids

Heritability estimates for variation in lipid levels within a population range from 30 % to 60 % [26]. In addition to the effect on the variation in lipids within a population, it is also assumed that genetic factors contribute to interindividual differences in response to dietary changes that cannot be explained by sex, age, and ethnicity [3, 23]. Over the past few decades, studies have been conducted to investigate candidate genes within specific lipid metabolic pathways (Fig. 1) in order to identify whether mutation or variation in these genes can explain the differences in lipid levels. Reviews of these candidate gene studies can be found elsewhere [2, 24]. In summary, gene variants have been identified in apolipoproteins, and genes involved in cholesterol synthesis and efflux, lipolysis, lipogenesis, and triglyceride and cholesterol transfer (Fig. 1). The genes that have most consistently been found to account for some of the variation in population lipid levels are *APOE*, *CETP*, and *APOA5* [24].

However, there are fewer data relating to the genetic influence on lipid changes in response to diet, and no genes have consistently been shown to account for a large proportion of the interindividual variation in lipid responses to dietary change. The *APOE* polymorphism, which has often been described as a genetic modifier of dietary lipid responses [27], has shown inconsistent results between studies. In a systematic review of studies that involved responses to a modification of dietary saturated fat, only 11 of the 46 intervention studies showed evidence of modification in response by *APOE* genotype [23]. In the same systematic review, variations in other genes previously found to be moderators of lipid responses to dietary change, including *APOB, APO A-I*, *C-III*, and *A-IV* gene cluster, LDL receptor and lipoprotein lipase, were also found to have inconsistent results. The majority of studies that found significant associations were small ($n<50$) studies and therefore possibly a result of false-positive chance [23].

GWAS Identified the Genes That Are Most Important in Variation of Lipids Within a Population

In the preceding 5 years, a number of genome-wide association studies (GWAS) have been conducted to identify several loci robustly associated with variation in lipid levels in (mostly white European) populations [28–32]. Most recently, a large meta-analysis of more than 100,000 individuals [33•] reported on 95 loci that were associated with lipid traits. The 25 loci most strongly associated with lipid traits from this study are shown in Table 1. Of these loci, 16 were located in or near genes whose proteins played a clear and defined role in lipid metabolic pathways (Fig. 1). These included pathways of cholesterol and triglyceride transfer, apolipoprotein formation, cholesterol synthesis and efflux, lipogenesis, and lipolysis, and in many cases, these genes had already been examined through a candidate gene approach. A further six loci identified in these GWAS, which had previously been unknown or thought to be unrelated to lipid metabolism, have since been shown to play novel roles in lipid metabolism (Table 1). Follow-up mechanistic studies on mice overexpressing the *SORT1* gene have established the product of this gene to play a novel regulatory role in reducing hepatic triglyceride and VLDL production and efflux [34•]. Although the exact mechanism remains unclear, this is one of the first examples of genes identified in GWAS leading to identification of novel lipid metabolic pathways [34•]. *GCKR*, which encodes glucokinase regulatory protein, was shown in mechanistic studies to increase hepatic glycolytic flux and glucose uptake, and was subsequently predicted to increase plasma triglyceride by a mechanism of increased malonyl CoA-activation of de novo lipogenesis and inhibition of fatty acid oxidation [35, 36]. In mice, TRIB1 expression was confirmed to be associated with a reduction in triglyceride and total cholesterol via a reduction in VLDL production, possibly mediated by

Table 1 Top 25 genes most strongly associated with lipid traits in GWAS

Gene[a]	Trait	Lipid metabolic pathways	Mechanism[b]	*P* for lead trait[c]
CETP	HDLC, TC, LDLC, TG	Cholesteryl ester/triglyceride exchange	Known	$P<10^{-380}$
APOA1	TG, TC, HDLC, LDLC	Major lipoprotein component of HDL, promotes cholesterol efflux	Known	$P<10^{-240}$
SORT1	LDLC, TC	Hepatic VLDL efflux	Novel	$P<10^{-170}$
APOE	LDLC, TC, HDLC	Major lipoprotein in chylomicrons and important in clearance of TG-rich lipoproteins	Known	$P<10^{-147}$
GCKR	TG, TC	Improved glycemic regulation at the expense of high hepatic TG production [36]	Novel	$P<10^{-133}$
LDLR	LDLC, TC	Cell surface receptor for apo B, which regulates endocytosis of cholesterol-rich LDL	Known	$P<10^{-117}$
LPL	TG, HDL	Endothelial protein that promotes uptake of cholesterol-rich lipoproteins into peripheral tissues	Known	$P<10^{-115}$
APOB	LDLC, TC	Major lipoprotein of LDL, docks to LDLR for cholesterol delivery to peripheral tissues	Known	$P<10^{-114}$
LIPC	HDLC, TC, TG	Hepatic protein that hydrolyzes triglyceride and catalyzes receptor-mediated lipoprotein uptake	Known	$P<10^{-96}$
MLXIPL	TG, HDLC	Transcription factor that binds carbohydrate response elements to increase transcription of genes involved in glycolysis, lipogenesis, and VLDL secretion	Novel	$P<10^{-58}$
TRIB1	TC, LDLC, HDLC	Scaffold protein with high hepatic expression. Affects lipogenic gene expression, hepatic lipogenesis, VLDL formation, and plasma lipids [37]	Novel	$P<10^{-55}$
LIPG	HDLC, TC	Endothelial lipase that hydrolyzes HDL	Known	$P<10^{-49}$
ABCG5/8	LDLC, TC	Selective sterol absorption in GIT and hepatic sterol excretion	Known	$P<10^{-47}$
HMGCR	TC, LDLC	Rate-limiting enzyme in cholesterol synthesis pathway	Known	$P<10^{-47}$
ANGPTL3	TG, TC, LDLC	Hepatic secretory factor that inhibits LPL and endothelial lipase	Known	$P<10^{-43}$
CILP2	TC, TG, LDLC	Scaffold protein (role in lipid metabolism unknown)	Unknown	$P<10^{-38}$
ABCA1	HDLC, TC	Catalyzes cholesterol efflux from peripheral tissues and HDL formation	Known	$P<10^{-33}$
LCAT	HDLC	Conversion from cholesterol to cholesteryl ester for f ormation of HDL	Known	$P<10^{-33}$
PCSK9	LDLC, TC	Regulates LDLR activity	Known	$P<10^{-28}$
TIMD4	TC, LDLC, TG	Receptor protein involved in engulfment of apoptotic cells (role in lipid metabolism unknown)	Unknown	$P<10^{-28}$
PPP1R3B	HDLC, TC, LDLC	Protein of high hepatic expression that can reduce HDL levels [33•]	Novel	$P<10^{-25}$
FADS1–2–3	TG, HDLC, TC, LDLC	Fatty acid biosynthesis	Novel	$P<10^{-24}$
HPR	TC, LDLC	Plasma protein (role in lipid metabolism unknown)	Unknown	$P<10^{-24}$
PLTP	HDLC, TG	Phospholipid transfer protein; plasma protein that transfers phospholipids from triglyceride-rich lipoproteins to HDL	Known	$P<10^{-22}$
GALNT2	HDLC, TG	GalNAc-transferase involved in o-linked oligosaccharide biosynthesis, which can regulate HDL levels [33•]	Novel	$P<10^{-21}$

[a] Genes in which there is existing evidence for gene–diet interactions on lipid levels are indicated in bold

[b] When the mechanism by which the gene regulates lipid traits is known, prior to GWAS, it is marked as known; if the gene was not previously implicated in the regulation of lipid traits prior to GWAS and a pathway of regulation has been targeted by subsequent analysis/experiments, it is marked as novel; if the gene was not previously implicated in the regulation of lipid traits and a mechanism has not yet been identified, it is marked as unknown

[c] *P* value for the association with the lead trait from the meta-analysis by Teslovich et al. [33•]

GIT gastrointestinal tract; *GWAS* genome-wide association study; *HDL* high-density lipoprotein; *HDLC* HDL cholesterol; *LDL* low-density lipoprotein; *LDLC* LDL cholesterol; *LDLR* LDL receptor; *TC* total cholesterol; *TG* triglyceride; *VLDL* very low-density lipoprotein

regulation of lipogenic genes [37]. Functional roles for GALNT2 and PPP1R3B proteins were also shown in murine models [33•]. Overexpression of both GALNT2 and PPP1R3B was associated with reduced HDL cholesterol, although the mechanism by which they act remains unknown [33•]. The functions of the remaining 3 loci in Table 1 and many of the other 70 loci reported in this meta-analysis [33•] remain unknown.

Loci identified in GWAS now account for about 25 % to 30 % of genetic variance in each trait (or 10 %–13 % of total variance in the trait) [33•]. There are likely to be more SNPs with small effect sizes that have not yet been identified with current GWAS methods [33•]. Rare SNPs of larger effect size will also not have been captured by GWAS and will contribute to the estimate of genetic variance [38]. Variations in loci do not occur in isolation, and combinations of polymorphisms are likely to act together to modulate lipid levels. It has been demonstrated that SNPs identified in GWAS have a cumulative effect on lipid traits, such that a linear increase in the number of risk alleles for a given trait corresponded with an increasingly more adverse lipid profile [39•, 40, 41]. However, this simple additive approach does not explore the potentially multiplicative effects of two or more SNPs. A simple example is seen for the *APOE* polymorphism, which has been identified in GWAS to be associated with all lipid traits [29–31, 33•], but with an effect size of 0.18 mM per risk allele for LDL cholesterol [33•]. However, two SNPs define the common *ApoE*, and when combined, the difference between individuals of the lowest risk isoform compared with those of the highest risk isoform was greater than 1 mM for LDL cholesterol [42]. Variance in a number of SNPs, in a number of genes, and of a number of different lipid metabolic pathways is likely to have complex and interacting effects. To fully explore these interactions in a comprehensive and systematic way will require novel data analytical methods and possibly increased computing power.

GWAS do not take into account environmental modifiers (eg, diet) in the identification of genes associated with a given trait. A number of different methods for analyzing the data are beginning to emerge to address this. Manning and colleagues [43] have proposed a joint meta-analytical method for simultaneously testing gene and gene–environment interactions in cross-sectional data in order to identify genetic loci that are impacted upon by a given environmental exposure on a trait of interest. These analyses could be conducted in studies in which data on dietary exposures are available in very large cohorts, along with GWAS data. However, this method is limited to testing a single dietary exposure at a time, and it remains to be seen how effective this approach will be in identifying gene–diet interactions that modify lipid levels. In a separate approach, Igl and colleagues [44•] performed a GWAS with a lifestyle-adjusted model that included certain dietary covariates (eg, game meat, non-game meat, fish and milk products) in their models to identify SNPs associated with lipid levels. This approach identified SNPs that were sensitive to the inclusion of environmental factors into the model (gene + diet) but did not assess how diet could interact with genes (gene × diet) to modify blood lipids.

Diet–Gene Interactions to Modify Lipids for Individual Genes Identified in GWAS

The effect of a number of genes that were identified in GWAS to modify lipid responses to diets has been studied previously from a candidate gene approach. These include *CETP*, *APOA1*, *APOE*, *LDLR*, *LPL*, *APOB*, *LIPC*, *LIPG*, *ABCG5/8*, and *LCAT* (Table 1, Fig. 1), and these findings have been comprehensively reviewed elsewhere [23, 24]. Although there is some evidence of gene–diet interactions, there is considerable heterogeneity in response, and it is noted that these gene–diet interaction studies were generally of short duration, with a small sample size, and from studies not designed for this purpose. Therefore, these findings need to be replicated in further studies, including well-designed, adequately powered randomized controlled trials. However, for some of the top genes identified in GWAS, in which the roles in lipid metabolism have been clearly established (Table 1, Fig. 1), there have been surprisingly few reports of gene–diet interactions. For example, despite the clearly defined role that *HMGCR* plays in the regulation of cholesterol synthesis, there has been a scarcity of reports on variation in this gene interacting with dietary factors to modulate lipid levels. In one cross-sectional analysis of interactions between dietary fat and a variant of the *HMGCR* gene, carriers of the variant appeared to have higher serum triglyceride levels to greater saturated fat intake but no effect on other lipids [45]. There has also been a scarcity of reports on effects of dietary interactions with *ANGPTL3*, *PLTP*, *PCSK9*, and *ABCA1* (Table 1).

Of the genes identified in GWAS that had not been implicated previously in the regulation of triglyceride and cholesterol levels (Table 1), some preliminary studies into possible gene–diet interactions have been conducted. In observational, cross-sectional studies, variants in the *FADS* genes (which encode desaturase enzymes in long-chain fatty acid biosynthesis) have been reported to interact with different levels of dietary n-3 and n-6 polyunsaturated fatty acids to alter serum cholesterol levels. In people who consumed a high proportion of n-3 polyunsaturated fatty acids (compared with the population median), the variant allele was associated with lower serum total and non-HDL cholesterol, translating to a protective effect [46, 47]. However, as these findings were cross-sectional, the impact of these gene variants on lipid concentrations over time or in response to changes in diet remains to be determined. Also, in a cross-sectional analysis in a small cohort (n=379), there was no interaction observed between variants of the *GCKR* gene and the level of polyunsaturated, saturated, or monounsaturated fat in the diet on plasma triglycerides [48]. In an intervention trial, variation in the *GCKR* gene was shown to modify triglyceride responses to an intensive lifestyle intervention of increased physical activity, weight loss, and a

low-fat diet such that there was a greater reduction in carriers of the variant [49]. However, it cannot be determined from this study whether diet, physical activity, or the effects of weight loss (or all factors) are important determinants. In acute postprandial studies, individuals who carry the *GCKR* risk variant were found to have an elevated postprandial triglyceride response to a high-fat meal (in combination with another variant in the apolipoprotein A-V [*APOA5*] gene) [50, 51], indicating a probable cumulative effect of high-fat diets to increase triglyceride levels in individuals with variants in these genes.

For many of the novel loci recently identified to be associated with lipids, the gene within the loci underlying the mechanistic effect may not have been identified, and the mechanism underlying the regulation of lipid levels is unknown (Table 1). These loci have not yet been studied in terms of gene–diet interactions to determine the modulation of effect on lipid levels.

There are some notable examples of genes that have been identified through candidate gene studies as important moderators of diet to modulate lipid levels, but that were not identified in GWAS. These include the transcription factors peroxisome proliferator-activated receptor (*PPAR*) alpha and gamma, which regulate the expression of several genes involved in lipid metabolism [13]. Variants in the *PPAR* alpha gene have previously been shown to interact with polyunsaturated fatty acid intake to enhance improvements in total and LDL cholesterol [52] and triglycerides [53] among people with a higher proportional intake of n-3 and n-6 polyunsaturated fatty acids. A *PPAR* gamma SNP was also found to enhance the reduction in serum triglyceride in response to a dietary intervention to increase n-3 polyunsaturated fat intake [54]. It is likely that these genes become important modifiers of lipid levels in response to particular dietary exposures, and were therefore not identified in GWAS that did not take into account diet. More examples of such genes are likely to be discovered when dietary factors are included.

The proportion of variance in lipid responses to dietary change that can be explained by variation in a single gene is not likely to be greater than 10 % [23]. We have examined the potential cumulative effect of SNPs identified in GWAS to modify lipid responses to a dietary intervention of reduced dietary saturated fat. We showed that a cumulative genetic predisposition score composed from simple addition of these SNPs did not modify the response to changes in dietary saturated fat [39•]. We had insufficient power to explore the effects in individual SNPs, but a preliminary analysis revealed no obvious modifying effect of any of the individual SNPs [39•]. A similar approach was used to examine the combined effects of nine common genes on the change in lipid responses to statin therapy [55•]. In this analysis, the combined genetic score appeared to modify the response to statin therapy such that the response was greater—the higher the genetic predisposition to low HDL cholesterol and high LDL cholesterol—in women only [55•]. Although this study was not diet related, it illustrates that the modifying effect of the interaction between genes and environmental modifiers will depend on the mechanism by which the environmental factor acts to alter plasma lipids. Because different dietary factors act to regulate lipid levels via different metabolic pathways, the effect of SNPs on the change in lipids is likely to be complex, with different combinations of SNPs responding differently to various dietary exposures. New analysis and modeling techniques are required to comprehensively investigate interactions of multiple SNPs and multiple dietary components.

Studying the effects of genes that modify lipid responses to diets in a controlled intervention setting, by its nature, means the cohort is limited to a small size, which can limit power to detect gene–diet interactions. The use of large, longitudinal, population-based studies may offer an alternative. Following GWAS that identified the SNPs most strongly associated with body mass index (BMI), a study was conducted that used the cumulative score of these SNPs to test gene–lifestyle interactions [56]. This study effectively demonstrated that physical activity (assessed by a self-administered questionnaire) attenuated the genetic predisposition to BMI in a cross-sectional, population-based sample of 20,430 individuals, and furthermore limited the change in BMI over time [56]. A similar approach could be used with lipid-associated genes identified in GWAS in which measures of dietary intake are also available. Dietary exposures such as total fat, saturated fat, and high carbohydrate, which are known to impact upon lipid levels, could be used to test the effect on the cross-sectional association between genetic predisposition and an unfavorable lipid profile, and the change in lipids over time.

GWAS on Interventions

The majority of GWAS to date have been conducted in cross-sectional data; it is therefore unsurprising that the loci identified as most important for variation of population lipid levels may have less of a moderating effect on changes in plasma lipids in response to diet [39•]. Some small GWAS have been performed on dynamic lipid responses to lipid-lowering drugs [55•, 57, 58]. A combined analysis of such studies has shown that there was no overlap between the SNPs associated with variation in the lipid levels of the cohort at baseline or after treatment compared with those that associated with the change in lipid levels [58]. This illustrates that the genes that are most important in modifying changes in lipids in response to lipid-lowering drugs are likely to be different from those that underlie differences in

population lipid levels. Likewise, dietary-induced changes are likely to act via different mechanisms to pharmaceutical agents. Due to the nature of highly controlled dietary intervention trials, the size of the cohort is small in terms of genetic analyses. To combat this, it is likely that data from a number of similar studies would need to be combined to achieve the required power to assess diet–SNP interactions. Challenges to be encountered by this approach will be the heterogeneity in trial design with regard to changes in diet, participant characteristics, duration, and rigor.

Conclusions

GWAS have been central to recent advances in the understanding of genetic mechanisms underlying variation in blood lipid levels. However, as of yet, these studies have done little to enhance our understanding of gene–diet interactions and their modifying effect on blood lipids. Data analytical tools are being developed to incorporate dietary factors into GWAS studies in order to identify genes that interact with dietary factors to modify lipids. It is emerging that SNPs identified in cross-sectional GWAS may not be the most important modifiers of lipid changes in response to changes in diet or other environmental factors, and GWAS are now beginning to be conducted to identify the SNPs related to change in measured traits. These methods applied to large, controlled dietary intervention trials will help identify SNPs that interact with particular dietary exposures, although it is likely that data from many trials will need to be combined to obtain adequate power. The SNPs identified may differ, depending on the nature of the dietary exposure (eg, energy reduction, saturated fat reduction, increase in carbohydrate), and this in turn will increase our understanding of how these different diets alter blood lipids and the pathways involved. It is clear that advances will be required in the way data are analyzed in order to handle the vast amount of data that will take into account the complex interactions between different dietary exposures and different genes.

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References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. 1998;97:1837–47.
2. Weissglas-Volkov D, Pajukanta P. Genetic causes of high and low serum HDL-cholesterol. J Lipid Res. 2010;51:2032–57.
3. Ordovas JM. Nutrigenetics, plasma lipids and cardiovascular risk. J Am Diet Assoc. 2006;106:1074–81.
4. Keys A, Parlin RW. Serum Cholesterol Response to Changes in Dietary Lipids. Am J Clin Nutr. 1966;19:175–81.
5. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta- analysis of 27 trials. Arterioscler Thromb Vasc Biol. 1992;12:911–9.
6. Mozaffarian D, Clarke R. Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils. Eur J Clin Nutr. 2009;63:S22–33.
7. Poppitt SD, Keogh GF, Prentice AM, et al. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. Am J Clin Nutr. 2002;75:11–20.
8. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr. 2003;77:1146–55.
9. Skulas-Ray AC, Kris-Etherton PM, Harris WS, et al. Dose-response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy persons with moderate hypertriglyceridemia. Am J Clin Nutr. 2011;93:243–52.
10. Dattilo A, Kris-Etherton P. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56:320–8.
11. Poobalan A, Aucott L, Smith WCS, et al. Effects of weight loss in overweight/obese individuals and long-term lipid outcomes – a systematic review. Obes Rev. 2004;5:43–50.
12. Abbey M, Nestel PJ. Plasma cholesteryl ester transfer protein activity is increased when trans-elaidic acid is substituted for cis-oleic acid in the diet. Atherosclerosis. 1994;106:99–107.
13. Fernandez ML, West KL. Mechanisms by which Dietary Fatty Acids Modulate Plasma Lipids. J Nutr. 2005;135:2075–8.
14. Gill JMR, Brown JC, Caslake MJ, et al. Effects of dietary monounsaturated fatty acids on lipoprotein concentrations, compositions, and subfraction distributions and on VLDL apolipoprotein B kinetics: dose-dependent effects on LDL. Am J Clin Nutr. 2003;78:47–56.
15. Jansen S, Lopez-Miranda J, Castro P, et al. Low-fat and high–monounsaturated fatty acid diets decrease plasma cholesterol ester transfer protein concentrations in young, healthy, normolipemic men. Am J Clin Nutr. 2000;72:36–41.
16. Shearer GC, Savinova OV, Harris WS. Fish oil- How does it reduce plasma triglycerides? biochim biophys acta 2011; Epub ahead of print (PMID:22041134).
17. Roberts R, Bickerton AS, Fielding BA, et al. Reduced oxidation of dietary fat after a short term high-carbohydrate diet. Am J Clin Nutr. 2008;87:824–31.
18. Williams CM. Postprandial lipid metabolism: effects of dietary fatty acids. Proc Nutr Soc. 1997;56:679–92.
19. Di Buono M, Hannah JS, Katzel LI, Jones PJH. Weight Loss Due to Energy Restriction Suppresses Cholesterol Biosynthesis in Overweight, Mildly Hypercholesterolemic Men. J Nutr. 1999; 129:1545–8.

20. Purnell JQ, Kahn SE, Albers JJ, et al. Effect of Weight Loss with Reduction of Intra-Abdominal Fat on Lipid Metabolism in Older Men. J Clin Endocrinol Metab. 2000;85:977–82.
21. Wing R, Jeffery R. Effect of modest weight loss on changes in cardiovascular risk factors: are there differences between men and women or between weight loss and maintenance? Int J Obes. 1995;19:67–73.
22. McQuaid SE, Hodson L, Neville MJ, et al. Downregulation of Adipose Tissue Fatty Acid Trafficking in Obesity. Diabetes. 2011;60:47–55.
23. Masson LF, McNeill G, Avenell A. Genetic variation and the lipid response to dietary intervention: a systematic review. Am J Clin Nutr. 2003;77:1098–111.
24. Corella D, Ordovas JM. Single nucleotide polymorphisms that influence lipid metabolism: interaction with dietary factors. Annu Rev Nutr. 2005;25:341–90.
25. Hegele RA. Plasma lipoproteins: genetic influences and clinical implications. Nat Rev Genet. 2009;10:109–21.
26. Hunt SC, Hasstedt SJ, Kuida H, et al. Genertic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. Am J Epidemiol. 1989; 129:625-638.
27. Lopez-Miranda J, Ordovas JM, Mata P, et al. Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. J Lipid Res. 1994;35:1965–75.
28. Saxena R, Voight BF, Lyssenko V, et al. Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels. Science. 2007;316:1331–6.
29. Kathiresan S, Manning A, Demissie S, et al. A genome-wide association study for blood lipid phenotypes in the Framingham Heart Study. BMC Med Genet. 2007;8:S17.
30. Willer CJ, Sanna S, Jackson AU, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nature Genet. 2008;40:161–9.
31. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nature Genet. 2008;40:189–97.
32. Aulchenko Y, Ripatti S, Lindqvist I, et al. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. Nature Genet. 2009;41:47–55.
33. • Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 2010;466:707–13. *This meta-analysis of GWAS identified 95 loci of importance for the regulation of lipid traits in more than 100,000 individuals. This study also examined whether loci identified in white European populations are applicable to other ethnicities. Finally, mechanistic studies in murine models were performed on three novel genes*.
34. • Musunuru K, Strong A, Frank-Kamenetsky M, et al. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. Nature. 2010;466:714–9. *This study used human cohort plus mechanistic studies in human hepatocytes and murine models to investigate the functionality of SORT1, a novel gene identified in GWAS of population lipid levels*.
35. Beer NL, Tribble ND, McCulloch LJ, et al. The P446L variant in GCKR associated with fasting plasma glucose and triglyceride levels exerts its effect through increased glucokinase activity in liver. Hum Mol Genet. 2009;18:4081–8.
36. Sparsø T, Andersen G, Nielsen T, et al. The GCKR rs780094 polymorphism is associated with elevated fasting serum triacylglycerol, reduced fasting and OGTT-related insulinaemia, and reduced risk of type 2 diabetes. Diabetologia. 2008;51:70–5.
37. Burkhardt R, Toh S-A, Lagor WR, et al. Trib1 is a lipid- and myocardial infarction-associated gene that regulates hepatic lipogenesis and VLDL production in mice. J Clin Invest. 2010;120:4410–4.
38. Gloyn AL, McCarthy MI. Variation across the allele frequency spectrum. Nat Genet. 2010;42:648–50.
39. • Walker CG, Loos RJF, Olson AD, et al. Genetic predisposition influences plasma lipids of participants on habitual diet, but not the response to reductions in dietary intake of saturated fatty acids. Atherosclerosis. 2011;215:421–7. *This study examined whether genetic predisposition scores, calculated from SNPs identified in GWAS associated with fasting lipid concentrations, could modify lipid responses to dietary interventions*.
40. Kathiresan S, Melander O, Anevski D, et al. Polymorphisms Associated with Cholesterol and Risk of Cardiovascular Events. N Engl J Med. 2008;358:1240–9.
41. Kathiresan S, Willer CJ, Peloso GM, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nature Genet. 2009;41:56–65.
42. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of Apolipoprotein E Genotypes With Lipid Levels and Coronary Risk. JAMA. 2007;298:1300–11.
43. Manning AK, LaValley M, Liu C-T, et al. Meta-analysis of gene-environment interaction: joint estimation of SNP and SNP×environment regression coefficients. Genet Epidemiol. 2010;35:11–8.
44. • Igl W, Johansson Ãs, Wilson JF, et al. Modeling of Environmental Effects in Genome-Wide Association Studies Identifies SLC2A2 and HP as Novel Loci Influencing Serum Cholesterol Levels. PLoS Genet. 2010;6:e1000798. *This study used a novel approach of including both environmental and genetic factors into the GWAS analysis in order to identify novel loci susceptible to environmental covariates*.
45. Freitas RN, Khaw K-T, Wu K, et al. A single nucleotide polymorphism in the 3-hydroxy-3-methylglutaryl-coenzyme A reductase gene (HMGCR) influences the serum triacylglycerol relationship with dietary fat and fibre in the European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) study. Br J Nutr. 2010;104:765–72.
46. Dumont J, Huybrechts I, Spinneker A, et al. FADS1 Genetic Variability Interacts with Dietary alpha-Linolenic Acid Intake to Affect Serum Non-HDL-Cholesterol Concentrations in European Adolescents. J Nutr. 2011;141:1247–53.
47. Lu Y, Feskens EJM, Dolle MET *et al.* Dietary n-3 and n-6 polyunsaturated fatty acid intake interacts with FADS1 genetic variation to affect total and HDL-cholesterol concentrations in the Doetinchem Cohort Study. Am J Clin Nutr 92:258-265.
48. Perez-Martinez P, Delgado-Lista J, Garcia-Rios A *et al.* Glucokinase Regulatory Protein Genetic Variant Interacts with Omega-3 PUFA to Influence Insulin Resistance and Inflammation in Metabolic Syndrome. PLoS ONE 6:e20555.
49. Pollin TI, Jablonski KA, McAteer JB, et al. Triglyceride Response to an Intensive Lifestyle Intervention Is Enhanced in Carriers of the GCKR Pro446Leu Polymorphism. J Clin Endocrinol Metab. 2011;96:E1142–7.
50. Shen H, Pollin T, Damcott C, et al. Glucokinase regulatory protein gene polymorphism affects postprandial lipemic response in a dietary intervention study. Hum Genet. 2009;126:567–74.
51. Perez-Martinez P, Corella D, Shen J, et al. Association between glucokinase regulatory protein (GCKR) and apolipoprotein A5 (APOA5) gene polymorphisms and triacylglycerol concentrations in fasting, postprandial, and fenofibrate-treated states. Am J Clin Nutr. 2009;89:391–9.
52. Volcik KA, Nettleton JA, Ballantyne CM, Boerwinkle E. Peroxisome proliferator-activated receptor alpha genetic variation interacts with n-6 and long-chain n-3 fatty acid intake to affect total cholesterol and LDL-cholesterol concentrations in the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2008;87:1926–31.
53. Tai ES, Corella D, Demissie S, et al. Polyunsaturated Fatty Acids Interact with the PPARA-alpha Polymorphism to Affect Plasma

Triglyceride and Apolipoprotein C-III Concentrations in the Framingham Heart Study. J Nutr. 2005;135:397–403.
54. Lindi V, Schwab U, Louheranta A, et al. Impact of the Pro12Ala polymorphism of the PPAR-gamma gene on serum triacylglycerol response to n-3 fatty acid supplementation. Mol Genet Metab. 2003;79:52–60.
55. • Hamrefors V, Orho-Melander M, Krauss RM, et al. A gene score of nine LDL and HDL regulating genes is associated with fluvastatin-induced cholesterol changes in women. J Lipid Res. 2010;51:625–34. *This combined analysis of three GWAS of lipid changes in response to statin therapy was one of the first studies to identify SNPs important for change in lipid traits rather than cross-sectional lipid levels*.
56. Li S, Zhao JH, Luan Ja, et al. Physical Activity Attenuates the Genetic Predisposition to Obesity in 20,000 Men and Women from EPIC-Norfolk Prospective Population Study. PLoS Med. 2010;7: e1000332.
57. Thompson JF, Hyde CL, Wood LS, et al. Comprehensive Whole-Genome and Candidate Gene Analysis for Response to Statin Therapy in the Treating to New Targets (TNT) Cohort/CLINICAL PERSPECTIVE. Circ Cardiovasc Genet. 2009;2:173–81.
58. Barber MJ, Mangravite LM, Hyde CL, et al. Genome-Wide Association of Lipid-Lowering Response to Statins in Combined Study Populations. PLoS One. 2010;5:e9763.
59. Gurr M, Harwood J, Frayn KN, et al. Lipid Biochemistry - 5th Edition. Blackwell Sciences LTD; 1980.