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Clinical significance of apolipoprotein A5

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Abstract

Purpose of review—We have examined the evidence from recent human studies examining the role of apolipoprotein A-V in triglyceride-rich lipoprotein metabolism and cardiovascular disease risk. Special emphasis was placed on the evidence emerging from the association between genetic variability at the apolipoprotein A5 locus, lipid phenotypes and disease outcomes. Moreover, we address recent reports evaluating apolipoprotein A5 gene–environment interactions in relation to cardiovascular disease and its common risk factors.

Recent findings—Several genetic association studies have continued to strengthen the position of *APOA5* as a major gene that is involved in triglyceride metabolism and modulated by dietary factors and pharmacological therapies. Moreover, genetic variants at this locus have been significantly associated with both coronary disease and stroke risks.

Summary—Apolipoprotein A-V has an important role in lipid metabolism, specifically for triglyceride-rich lipoproteins. However, its mechanism of action is still poorly understood. Clinical significance at present comes largely from genetic studies showing a consistent association with plasma triglyceride concentrations. Moreover, the effects of common genetic variants on triglyceride concentrations and disease risk are further modulated by other factors such as diet, pharmacological interventions and BMI. Therefore, these genetic variants could be potentially used to predict cardiovascular disease risk and individualize therapeutic options to decrease cardiovascular disease risk.

Keywords

apolipoprotein A-V; cardiovascular disease; diet; gene–environment interaction; pharmacogenomics; plasma lipids

Introduction

Apolipoprotein A-V (APOA-V) was identified by two groups simultaneously in 2001. Since that time, studies conducted on rodents have implicated APOA-V in the physiology of

triglyceride-rich lipoprotein (TRL) metabolism. Animal experiments using different strategies of underexpression and overexpression indicated an inverse relationship between apolipoprotein A5 (*APOA5*) gene expression and plasma triglycerides. These initial studies were accompanied by data on humans demonstrating an association between single nucleotide polymorphisms (SNPs) at the *APOA5* locus and blood triglycerides, suggesting that this protein is also involved in TRL metabolism in humans.

In the present review, we have examined the data largely from human studies in an attempt to delineate the clinical relevance of *APOA5*.

Significance of apolipoprotein A-V in the plasma

Several individuals with rare mutations resulting in severe *APOA-V* deficiency have been studied [1]. The affected individuals exhibit type V hyperlipidemia with other clinical features of chylomicronemia. This phenotype is consistent with that observed in *APOA5* knockout mice.

Unlike the situation with severe *APOA-V* deficiency, despite earlier studies which showed a negative correlation between plasma *APOA-V* and triglyceride concentrations [2], accumulating data support a positive correlation between the two [3–7]. Two studies deserve special mention because of their size. *APOA-V* levels have been examined in 2490 men from the Northwick Park Heart Study II [6]. This study confirmed the positive correlation between plasma *APOA-V* and triglyceride concentrations. Interestingly, the authors in the study also found that the –1131T→C polymorphism at the *APOA5* locus, but not *APOA-V* concentrations, was associated with plasma triglycerides. As such, it would appear that this polymorphism did not exert its effect on plasma triglyceride concentrations through its effect on plasma levels of *APOA-V*. In a nested case–control study that included 997 cases and 2031 controls derived from the prospective European Prospective Investigation into Cancer and Nutrition (Epic)-Norfolk Population Study [7], no association was observed between plasma *APOA-V* concentrations and the risk of incident fatal or nonfatal coronary artery disease (CAD). Similar to the Northwick Park Heart Study II, plasma *APOA-V* and triglyceride levels were positively correlated. Furthermore, the –1131C→T polymorphism did show an association with increased risk of CAD providing further evidence that the effects of this polymorphism on the risk of CAD is not related to its effects on the plasma levels of *APOA-V*. In this regard, it is interesting that in mice expressing the human *APOA5* transgene, which lack an endogenous mouse *APOA5* gene, it was found that plasma *APOA-V* levels also showed a positive correlation with triglyceride concentrations [8*]. These findings recapitulate the findings in humans wherein extreme forms of *APOA-V* deficiency were associated with severe hyperlipidemia, but, in the absence of a severe deficiency, *APOA-V* concentrations were positively correlated with triglycerides.

The positive correlation between *APOA-V* and triglyceride concentrations is further supported by studies which show that changes in plasma triglycerides in humans parallel changes in *APOA-V* concentrations. Two studies have shown that, in type 2 diabetes mellitus (T2DM), postprandial hypertriglyceridemia is associated with an increase in *APOA-V* concentration [9*,10]. In patients with diabetes mellitus, this postprandial increase

in APOA-V is more pronounced in the presence of microalbuminuria [11*] and also parallels the postprandial increase in blood triglycerides. Dallinga-Thie *et al.* [3] reported that treatment with atorvastatin in patients with T2DM reduced APOA5 concentrations in tandem with reductions of triglycerides. Finally, in sepsis, APOA5 concentrations declined and increased upon recovery in parallel with triglycerides [12].

Numerous functions have been ascribed to APOA-V including the activation of lipoprotein lipase (LPL) either directly or by facilitating the binding of lipoproteins to heparan sulfate proteoglycans. These have been reviewed in a previous issue of *Current Opinion in Lipidology* [13]. However, at least in patients with T2DM, plasma concentrations of APOA-V were not correlated with LPL activity either in the fasting [9*] or in the postprandial state [10]. In addition, Chan *et al.* [14] investigated the associations between APOA-V and apolipoprotein C-III (APOC-III) levels and the kinetics of VLDL-triglycerides and apolipoprotein B-100 (APOB-100). They observed that the concentrations of APOC-III on VLDL were inversely correlated with the fractional catabolic rate of both VLDL-triglycerides and VLDL APOB-100, consistent with the belief that increased APOC-III in plasma inhibits the lipolysis of VLDL-triglycerides by LPL and interferes with the hepatic uptake of TRL remnant by LDL receptors. In contrast, no association was observed between VLDL APOA-V concentration and any of the VLDL kinetic parameters, despite the evidence from in-vitro and animal studies that APOA-V enhances LPL activity and enhances the uptake of TRLs by the liver.

Taken together, except in the instance of severe APOA-V deficiency, APOA-V concentrations in the plasma appear to reflect hypertriglyceridemia and provide little information with regard to the pathophysiology of hypertriglyceridemia. It also does not appear to be a strong predictor of either diabetes mellitus or CAD. One possible explanation of these findings is that APOA-V may play an intracellular role, modulating VLDL production. Animals overexpressing APOA-V show a reduced VLDL production. This would be consistent with the findings that plasma APOA5 levels are very low [15] as well as the lack of association between plasma APOA-V concentrations and either VLDL kinetics or cardiovascular disease (CVD), despite the evidence from genetic association studies that this genetic locus is important in the pathogenesis of dyslipidemia and CVD. A recent study has confirmed that APOA-V is expressed intracellularly in hep3B cells [16*]. In these cells, APOA-V was associated with lipid droplets rather than with VLDL. The function of APOA-V in this cellular context is as yet unknown. Nevertheless, these studies suggested that the association of APOA-V with VLDL was a postsecretory event signifying that APOA-V may not have a major role in modulating VLDL assembly. As such, the clinical relevance of APOA5 to cardiovascular and metabolic disease relate to the associations between genetic variants at the APOA5 locus and these clinical phenotypes.

Apolipoprotein A5 single nucleotide polymorphisms and association with triglyceride concentrations

The association between the APOA5 locus and plasma triglyceride concentration remains mostly undisputed, and, thus, APOA5 has emerged as one of the most solid candidate genes affecting plasma triglycerides in the general population. Recent reports continue to support

this concept in the fasting [17–20] and the postprandial states [21,22] as well as in different ethnic groups [17–20,23–25]. It should be noted that whereas all studies find significant associations between triglyceride concentrations and APOA5 polymorphisms, the strength of the association for different SNPs (mainly the –1131T→C and the C56G polymorphisms) varies between studies and remains an interesting topic for further investigation.

Apolipoprotein A5 single nucleotide polymorphisms and association with disease endpoints

The association between variants at this locus and clinical outcomes, particularly CVD, has been examined in several recent studies. As described in the preceding section, Vaessen *et al.* [7] reported an increased risk of incident CAD with the –1131T→C polymorphism. Yu *et al.* [26] examined the genotype and allele distribution of the APOA5 –1131T→C SNP in a northern Chinese Han population consisting of 140 patients with premature coronary heart disease and 156 healthy controls. According to these investigators, the minor allele was associated with increased serum triglyceride levels and with the development of premature coronary heart disease. Data from the Framingham Heart Study ($n=2273$) [27] show that the haplotype defined by the presence of the rare allele of the 56C→G variant was significantly associated with a higher common carotid artery (CCA) intima–media thickness (IMT) than the wild-type haplotype. However, the rare allele of each of the –1131T→C, –3A→G, IVS3+476G→A and 1259T→C variants and the respective haplotype were each significantly associated with CCA IMT only in obese participants. In contrast, van der Vleuten *et al.* [28] in The Netherlands reported in a population enriched with familial combined hyperlipidemia (FCH) that despite the expected association of the two APOA5 SNPs examined (–1131T→C and S19W) with triglycerides, HDL cholesterol (HDL-C) and small LDL size, no association of the APOA5 gene with IMT and CVD was evident. However, this was a small study and included only 22 cases of CVD.

The association between stroke and APOA5 polymorphism has been repeatedly examined by the same group of investigators using case–control designs [29,30]. Their first report by Havasi *et al.* [30] identified a significant increase in the risk of stroke associated with the presence of the C allele at the –1131T→C SNP. More recently, Maasz *et al.* [29] reported that the G allele at the APOA5 C56G confers a higher risk for the development of large-vessel-associated ischemic stroke. In both cases, the minor alleles at these APOA5 SNPs were associated with higher plasma triglyceride concentrations, regardless of their case–control status. It should be noted that these authors did not include triglyceride concentrations in the models for stroke and risk, and it is not possible to conclude that the association observed was independent of plasma triglyceride concentrations.

Along similar lines, Li *et al.* [31] reported that the minor allele at the APOA5 –12238T→C SNP was associated with both higher plasma triglyceride concentrations and increased atherosclerotic cerebral infarction risk. Overall, the current information does not provide mechanistic evidence supporting these findings; moreover, it is not possible to conclude whether these effects may be the reflection of higher plasma triglyceride levels associated with the minor alleles at these APOA5 SNPs.

Metabolic syndrome and diabetes-related diseases

The consistent association observed between the APOA5 locus and hypertriglyceridemia and the more sporadic findings in support for associations with other metabolic syndrome-related traits (low HDL-C and increased BMI) make the APOA5 locus an obvious target to investigate its potential impact on the metabolic syndrome. Initially, a Japanese case-control study found that the -1131T→C SNP was associated with metabolic syndrome. More recently, several studies have examined such association in whites more in detail. Maasz *et al.* [32] using a case-control design demonstrated that the C allele at the -1131T→C SNP was associated with an approximately three-fold increase in the risk of metabolic syndrome as compared with homozygosity for the major T allele. Moreover, the C allele was associated with hypertriglyceridemia in cases and controls. Although these findings strongly suggest that this APOA5 variant is a risk factor for the development of hypertriglyceridemia and metabolic syndrome, it is not possible to conclude the independence of these findings. A more comprehensive study, in terms of both gene coverage and sample size, was conducted by Grallert *et al.* [33]. Ten polymorphisms were analyzed in two relatively large studies in southern Germany (KORA, $n = 1\,354$) and in Austria (SAPHIR, $n = 1\,770$). Minor alleles of variants -1131T→C, -3A→G, c.56C→G, 476G→A and 1259T→C were significantly associated with higher plasma triglyceride levels. Moreover, the minor G allele at the 56C→G SNP was associated with an approximately 50% higher risk for metabolic syndrome in both studies. However, unlike in the Japanese study, no such association was observed for the -1131T→C SNP. In contrast with these findings in Germans and Austrians, Niculescu *et al.* [34] in urban Romanian individuals found that the risk of metabolic syndrome was significantly associated with the minor allele of the -1131T→C SNP but not so with the 56C→G SNP.

Additional support for the role of this locus on the risk of metabolic syndrome has come from Japan, where Yamada *et al.* [35] examined 44 SNPs at 31 candidate genes in almost 2500 cases and controls and demonstrated that the minor alleles at two of the APOA5 SNPs examined [-3A→G and 553G→T (Gly185Cys)] were significantly associated with increased metabolic syndrome risk. Moreover, serum levels of triglycerides and HDL-C differed significantly ($P < 0.05$) between individuals with different APOA5 genotypes.

Patients with diabetic nephropathy have increased plasma fasting triglyceride levels, and most prospective studies report that elevated triglyceride levels precede diabetic nephropathy. Baum *et al.* [36] tested the hypothesis that elevated triglyceride levels, perhaps mediated by the APOA5 locus, contribute to the development of diabetic nephropathy. These authors genotyped the APOA5 -1131T→C SNP in a case-control study involving 367 Chinese patients with T2DM with diabetic nephropathy and 382 without diabetic nephropathy, as well as 198 individuals without diabetes. Mean fasting triglyceride levels were consistently higher in C homozygous (CC) than in T homozygous (TT) carriers in each of the three groups. However, the genotype distributions did not differ between patients with and without diabetic nephropathy. Therefore, these results do not support the hypothesis that a high level of fasting triglycerides *per se* causes diabetic nephropathy, and the strong association between triglyceride level and diabetic nephropathy may be due to a factor that is usually closely linked to triglyceride level but that is not affected by the APOA5 SNP.

Interactions with environmental factors

Most of the classical candidate genes involved in lipid metabolism have shown an evidence of significant gene–diet interactions [37]. The modulating effect of the diet over the effect of genetic variants has an important translational value as it may help to elaborate more personalized dietary recommendations. In addition, these interactions may shed some light over the habitual controversial findings involving genetic association studies. Although, in general, the overall association of the APOA5 locus with hypertriglyceridemia tends to be consistent across populations studied, the effect size associated with different APOA5 SNPs remains more contentious. These differences may be due to the fact that the two most commons SNPs in this locus (–1131T→C and 56C→G) are differently modulated by diet and other nongenetic factors. Evidence for APOA5–diet interaction has been demonstrated in the past [27,38,39] and further supported by more recent reports [40,41*].

Hubacek *et al.* [40] analyzed the effect of variation in the APOA1/C3/A4/A5 gene cluster on decreases in plasma cholesterol levels over an ecological 8-year follow-up study involving 133 Czech men. During this period, the dietary composition in the participants involved changed markedly, with decreases in red meat and animal fat and increases in fruits and vegetables. Their data showed that participants homozygous for the Ser19 allele at the APOA5 locus maintained stable plasma cholesterol concentrations over the years, whereas Trp19 carriers experienced a decline in plasma cholesterol concentrations. These findings support the notion that APOA5 variants may play an important role in interindividual differences in the sensitivity of blood lipid parameters to changes in the dietary composition in men.

Using a cross-sectional design, Lai *et al.* [38] examined the interactions between dietary fat and plasma lipids in the Framingham Heart Study. It was found that the –1131T→C, but not the 56C→G, polymorphism modulated the association between dietary polyunsaturated fatty acid (PUFA) intake and fasting plasma triglyceride concentrations. Individuals who carried the –1131C allele exhibited increased levels of plasma triglyceride, which was not observed in those who did not carry this variant. These interactions were extended to include the levels of remnant lipoproteins as well as VLDL and LDL particle sizes. In this study, it appeared that the n-6 and not the n-3 PUFAs were involved in this interaction. In the same population, Corella *et al.* [41*] tested the hypothesis that dietary macronutrient intake modulates the association between APOA5 gene variation and body weight in the Framingham Heart Study. This study reported a significant interaction between the –1131T→C SNP, but not the 56C→G, and the total fat intake for BMI. Specifically, in participants homozygous for the –1131T major allele, BMI increased as total fat intake increased. Conversely, this increase was not present in carriers of the –1131C minor allele. Therefore, the APOA5 –1131T→C SNP appears to modulate the effect of fat intake on BMI and obesity risk in both men and women participating in the Framingham Heart Study.

There is emerging evidence that genetic variants at the APOA5 locus have been implicated in the modulation of the effects of drugs that raise or lower blood lipids. This has been most convincingly demonstrated in relation to fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist that is known to regulate APOA5 gene transcription. In the

Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study, Lai *et al.* [42*] reported that the G allele for the C56G polymorphism was associated with fasting and postprandial levels of plasma triglyceride that were higher and HDL-C that were lower than in those who were homozygous for the C56 allele. Fenofibrate therapy had a greater triglyceride-lowering and HDL-C-raising effect in carriers of the 56G allele than in those who were homozygous for the 56C allele such that, following the treatment, the differences between genotype groups were no longer significant. Similar gene–drug interactions were not observed for the –1131T→C polymorphism.

More recently, in the Swiss HIV Cohort Study [43*], the –1331T→C polymorphism at the APOA5 locus was associated with an increase in plasma triglyceride. Hypertriglyceridemia was particularly pronounced in those who carried the C allele and were treated with protease inhibitors, particularly those treatment regimes that included ritanovir. In another study that included 229 patients with HIV [44], the presence of the –1131C allele was associated with an elevation of the plasma triglyceride level following the initiation of protease inhibitors, which was significantly greater than that occurring in either those who were homozygous for the wild-type allele or those who did not receive protease inhibitors or both. Unfortunately, although both studies suggested the possibility that the APOA5 genotype might be useful to identify individuals at increased risk of developing dyslipidemia when receiving specific antiretroviral therapies, neither of the studies was adequately powered to detect statistically significant interactions between drug and genotype. These findings require additional confirmation in larger studies. Another recent study reported a significantly higher fasting plasma cholesterol level and higher BMI in individuals with schizophrenia who were treated with a first-generation antipsychotic, an effect that was not observed in those treated with other antipsychotics, including clozapine, olanzapine or risperidone [45].

Conclusion

The physiologic role of APOA-V in humans remains to be fully elucidated. At present, plasma levels of APOA-V appear to have a limited clinical significance as they vary in parallel with plasma triglyceride levels and predict neither diabetes mellitus nor CAD. On the contrary, genetic variants at the APOA5 locus show strong, stable associations with plasma triglyceride levels and emerging evidence for associations with CVD. They also appear to modulate the association between blood lipids and the environment including dietary fat and some drugs including fibrates, antiretroviral therapy and anti-psychotics. Potentially, this means that genetic variants at this locus could be useful for incorporation into genetic risk scores for the prediction of CVD events, such as has been carried out recently for LDL-associated and HDL-associated genetic variants [46*]. Finally, there is the potential that these genetic variants could be used to individualize therapeutic options to optimize the risk–benefit ratio for therapies that may increase or decrease the CVD risk.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 414).

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