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The Paradox of ApoA5 Modulation of Triglycerides: Evidences from Clinical and Basic Research

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Abstract

Apolipoprotein A5 (ApoA5) is a key regulator of plasma triglycerides (TG), although its plasma concentration is very low compared to other known apoproteins. Over the years, researchers have attempted to elucidate the molecular mechanisms by which ApoA5 regulates plasma TG *in vivo*. Though still under debate, two theories broadly describe how ApoA5 modulates TG levels: (i) ApoA5 enhances the catabolism of TG-rich lipoproteins and (ii) it inhibits the rate of production of very low-density lipoprotein (VLDL), the major carrier of TGs. This review will summarize the basic and clinical studies that have attempted to describe the importance of ApoA5 in TG metabolism. Population studies conducted in various countries have demonstrated an association between single nucleotide polymorphisms (SNPs) in ApoA5 and the increased risk to cardiovascular disease and metabolic syndrome (including diabetes and obesity). ApoA5 is also highly expressed during liver regeneration and is an acute phase protein associated with HDL which was independent of its effects on TG metabolism.

Conclusion—Despite considerable evidences available from clinical and basic research studies, on the role of ApoA5 in TG metabolism and its indirect link to metabolic diseases, additional investigations are needed to understand the paradoxical role of this important apoprotein shown modulated by diet and from its polymorphism variants.

Keywords

coronary artery disease; lipoproteins; atherosclerosis; ApoA5 polymorphism

ApoA5: An Important Modulator of Triglycerides

ApoA5 is an apoprotein that was independently discovered by Pennacchio et al. [1] and van der Vliet et al. [2] as a result of their investigations on new open-reading frames on chromosome 11q23 in the ApoA-I/ApoC-III/ApoA-IV gene cluster. This apoprotein is the

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newest member of the Apo A class of proteins. Apo A-V or ApoA5, an exchangeable apoprotein, is expressed in liver and secreted into plasma [3]. Since its discovery, ApoA5 has been shown to be a key regulator of plasma TG. For instance, van der Vliet and co-workers [4] demonstrated that mice with adenoviral overexpression of ApoA5 showed a remarkable 70% reduction in the level of TG when compared to wild type mice. This decrease in plasma TG was attributed to the lowering of TG in VLDL fraction [5]. On the contrary, ApoA5 knockout mice were shown to have a four-fold increased TG plasma levels relative to control mice [1]. These results strongly indicate an inverse relationship between ApoA5 and TG levels and hence, lack of normal functioning ApoA5 is a risk factor for hypertriglyceridemia.

It is important to note that the plasma concentration of ApoA5 is very low compared to other apoproteins, such as Apo A-I (e.g. mean value of 157 µg/L ApoA5 vs. ≈1 g/L Apo A-I [5] or < 0.1% of Apo A-I [6]). Despite its low concentrations, ApoA5 has profound effects on plasma TG levels [3, 4, 7] by modulating lipoprotein lipase (LPL) activity. Furthermore, ApoA5 is associated with chylomicrons, VLDL, high-density lipoprotein (HDL), but not low-density lipoprotein (LDL). Of particular interest is that the distribution of ApoA5 on lipoproteins is similar to that of Apo C-III [5], which is thought to inhibit LPL activity. Intriguingly, although the actions of ApoA5 and Apo C-III are opposite, they work independently to modulate triglyceride concentrations in an opposing fashion [7]. In both the double transgenic (overexpression of both ApoA5 and C-III genes) and double knockout (complete lack of both genes) mice models, the TG concentrations were found to be normal [7]. This suggests that the antagonistic effect of ApoA5/Apo C-III on TG favors neutrality, in the sense that the action of one protein modulates the other and vice versa.

Mechanism of Action of ApoA5

Since its discovery, researchers have attempted to elucidate the molecular mechanisms by which ApoA5 regulates plasma TG *in vivo*. Although ApoA5 mechanism of action is still debated, broadly there are two theories that describe how ApoA5 modulate TG: (1) ApoA5 enhances the catabolism of TG-rich lipoproteins by LPL or (2) it inhibits the rate of production of VLDL. In support of the first theory, Merkel et al. [8] asserted that reduction of TG was a result of ApoA5 increasing LPL-mediated hydrolysis of VLDL and/or chylomicrons. In their study, they found that ApoA5 did not have any effects on the hydrolytic rate of LPL in the absence of proteoglycans [8]. In addition, it was found that increase in LPL activity rectifies hypertriglyceridemia in ApoA5 deficient mice to normal TG levels; however, overexpression of ApoA5 had only slight modulation effects on TG levels when LPL was reduced [8].

The alternate theory by, Weinberg et al. [6] provided structural and chemical evidences that ApoA5 modifies TG levels via its alteration of the assembly rate and secretion of the VLDL particle rather than enhancing LPL hydrolysis of TG-rich lipoproteins. Surface chemistry analysis showed that ApoA5 displayed higher affinity, lower elasticity, and slower binding kinetics at hydrophobic interfaces [6]. These interfacial properties support the supposition that ApoA5 would retard production of VLDL particles [6]. In addition, transfected human ApoA5 COS-1 cells showed poor secretion of the protein from endoplasmic reticulum (ER) as well as its lack of trafficking to the Golgi apparatus, which further augments their assumption. This may be due to interference of secretory pathways of ER/Golgi by overexpression of ApoA5 proteins [9].

In another study carried out by Schaap et al. [9], the findings appeared to support both of the currently proposed theories of ApoA5 regulation of TG metabolism. Mice treated with adenovirus-mediated gene transfer of murine ApoA5 (Ad-apoa5) demonstrated a 29-37%

dose-dependent reduction in the rate of VLDL-TG production, but did not affect VLDL particle assembly [9]. Additionally, there was a 68-88% dose-dependent decrease in TG following postprandial intragastric load of fat in Ad-apoa5 treated mice indicating possible stimulation of LPL-mediated removal of TG-rich lipoproteins by ApoA5 [9]. Moreover, Ad-apoa5 treated mice were able to rapidly clear IV injected VLDL-like TG-rich emulsion simultaneously with increased uptake of emulsion TG-derived fatty acids [9]. Together, these results support ApoA5 reduction of plasma TG by inhibiting VLDL production and stimulation of LPL-mediated TG rich lipoprotein catabolism [9]. Insulin is reported to down regulate ApoA5 expression by inhibiting ApoA5 promoter activity; this may probably explain the association between hyperinsulinemia and hypertriglyceridemia [10].

ApoA5 has high affinity for heparin and heparin sulfate proteoglycans through its positive charge residue which enhances binding and hydrolysis of lipoproteins [11]. Xiao Shu et al. have reported that heparin injection resulted in rapid increases of plasma ApoA5 levels which reveals the potential function of heparin on mediating ApoA5 associated TG rich-lipoprotein hydrolysis [12]; nevertheless, it is shown that heparin significantly decreased ApoA5 binding to LRP and SorLA, the members of LDLR family, involved in ApoA5 associated chylomicron hydrolysis [11]. In addition to its role in TG metabolism, ApoA5 has also been recognized to be an acute phase protein, ApoA5 levels increased when mice were injected with endotoxin [13]. This acute phase response by ApoA5 however was independent of plasma triglyceride levels, thus highlighting the paradoxical behavior of ApoA5 [14] (Fig 1).

Genetic Polymorphisms of ApoA5

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among individuals. It refers to DNA sequence variation in which a single nucleotide in the gene (or genome) differs between members of a biological species or paired chromosomes in an individual. There are several SNPs associated with the ApoA5 gene [1, 15-18]. The ApoA1/ApoC3/ApoA4/ApoA5 locus is one of the most significant loci in the genome-wide association studies (GWAS). It is associated with triglyceride, HDL-C, and total cholesterol plasma levels. The three most common haplotypes related to ApoA5 gene are APOA5*1, ApoA5*2, and ApoA5*3. These include five of the more typical ApoA5 SNPs: -1131T>C, -3A>G, 56C>G (also referred to as S19W), IVS+476G>A, and 1259T>C [19, 20]. ApoA5*1 represents the wild type haplotype as it is defined by the common alleles at all of the five SNPs [15, 21]. The second haplotype, ApoA5*2, comprises of one SNP with the common allele (56C>G) and four with the rare alleles (-1131T>C, -3A>G, IVS+476G>A, and 1259TC) [15, 21]. ApoA5*3 is the reverse form of ApoA5*2 in that the 56C>G SNP exhibits the rare allele and the other four common alleles [15, 21]. The frequencies of these haplotypes in the Caucasian population have been reported to be 69% for ApoA5*1 and 4% for ApoA5*2 and ApoA5*3 [22]. Of clinical importance and relevance to TG metabolism are the SNPs, ApoA5*2 and ApoA5*3; the rare alleles of both have been reported to elevate plasma TG levels [1, 17-25]. Changes in the nucleotide bases evidently result in alterations of the amino acid sequence of the ApoA5 molecule leading to morphological modifications. As a consequence, the functionality of the final ApoA5 product is altered giving rise to a dysfunctional or reduced activity protein. Several studies have investigated the effect of lipid modulators on SNPs, such as the interactions between dietary factors and SNPs in the ApoA1/ApoC3/ApoA4/ApoA5 cluster have been reported [19, 20]. In a recent study rs3135506-25OHD (vitamin D) interaction influences on HDL-C has been reported. The rs3135506 minor allele was found more strongly associated with low HDL-C in individuals with low dietary 25OHD. This finding provides an interesting function for ApoA5, showing a possible role beyond TG regulation. Several other clinical studies on ApoA5 SNPs have

demonstrated similar changes with dietary lipid intake [26], additional reports on ApoA5 SNPs can be seen below in the clinical studies sections.

ApoA5 Deficiency and hypertriglyceridemia

Animal and human studies have demonstrated that ApoA5 deficiency is associated with severe hypertriglyceridemia. Mutations in ApoA5 gene is the cause of severe hypertriglyceridemia. Early studies of Calandra et al in patients with primary hypertriglyceridemia, in whom mutations of the LPL and ApoC2 genes had been excluded, led to the identification of four families with two different mutations in this gene which was predicted to have resulted from shortened ApoA5 sequence [27]. These early findings which linked malfunctioned ApoA5 to hypertriglyceridemia has led to series of studies primarily focused on ApoA5 SNPs role on plasma TG disorders, some of which are discussed below. In a recently published study, a DNA sequence of the exons plus exon/intron boundaries of the ApoA5 gene of 291 patients with TG above the 95th percentile for age and sex (98 of whom had triglycerides above 875 mg/dl), 111 patients with ApoE2/2 genotype, of whom 100 had Type III hyperlipidemia and 108 probands with TG below the 25th percentile for age and sex in the studied cohort. Twenty four variants were detected; in this population nine patients had triglycerides above 875 mg/dl who were carriers of at least one deleterious mutation in the ApoA5 gene. Some of the patients with type III hyperlipidemia were carriers of rare variants [28, 29].

ApoA5 in Cardiometabolic Diseases

Population Studies

The association between ApoA5 and risk to cardiometabolic diseases comes from largescale SNP studies performed using population cohorts from various regions of the world (China, Japan, Brazil, Europe, Greek, and United States). Some of the SNPs with positive associations to cardiometabolic disease in these populations are described below:

Cardiovascular Disease

SNPs in ApoA5 increases risk to hypertriglyceridemia. A higher incidence of a T/C SNP (SNP3 or c.553G>T) in the 5' region of the ApoA5 gene was correlated to increased TG levels in Japanese adult population (n=481 male and n=412 female) and children (n=552) compared to Caucasian population [30, 31]. A similar association was seen between ApoA5 locus -1131T>C and high TG and low HDLc in all Caucasian population from Cooperative Health Research in the region of Augsburg (KORA) and the Salzburg Atherosclerosis Prevention Program in Subjects in High Individual Risk (SAPHIR) study (n=1,354) [32] and patient cohorts from the Hong Kong cardiovascular risk factor prevalence study and the Guangzhou Biobank Cohort Study [33].

The relationship between gene variants in ApoA5 and coronary artery disease (CAD) remains controversial. In patients with acute coronary syndrome (ACS), high plasma apoA5 levels correlated with increased presence of ACS, hCRP and high plasma TG but not plasma cholesterol levels [34]. In a case control study involving Korean male CAD patients (n=367) and controls (n=777), a decrease in plasma apoA5 levels were seen in patients with CAD. The lower ApoA5 levels correlated with increased TG and insulin levels and lower HDLc thus increasing risk to CAD [35]. In the Taiwanese Chinese population the presence of -1131C homozygous allele and c.553T heterozygous allele correlated to presence of CAD [36]. However, in the Vancouver selective coronary angiography cohort study (n=537), the presence of -1131T>C polymorphism predicted increased TG and FER (HDL) (fractional esterification rate in apoB depleted lipoproteins), but did not show any association with CAD [37]. Similarly, in an Italian population study, patients with CAD (n=669 CAD+ and

n=244 CAD-), there was an association between ApoA5-1131C allele and increased TG and Apo C-III variability but no association was observed with CAD. Interestingly, in the same patient population there was an association between Apo C-III-455C carriers and presence of CAD [38].

SNPs in ApoA5 correlated with severity of coronary atherosclerosis. In a case-control Italian study in patients with early onset MI, there was a strong association between ApoA5-1131C allele with increased TG and risk for early-onset MI [39]. In the Framingham Offspring study participants (n=2,273) who underwent carotid ultrasound, demonstrated that the presence of 56C>G showed a higher common carotid artery intimal medial thickness (IMT), i.e. increased atherosclerosis, compared to wild type carriers and the presence of -1131T>C variants were associated with increased IMT only in obese patients, even after adjusting for the TG levels [40]. In the Lipoprotein and Coronary Atherosclerosis (LCAS) study the S19W SNP in ApoA5 was independently correlated to minimal lumen diameter of the coronary atherosclerotic lesions and mean number of coronary artery occlusions [34]. Remnant lipoproteins that are generated during the partial hydrolysis of TG-rich lipoproteins are elevated during atherosclerosis. ApoA5 polymorphisms had no effect on the levels of these remnant lipoproteins [41].

SNPs in ApoA5 were also linked to other vascular diseases. ApoA5, being a direct downstream target of upstream stimulatory factor-1 (USF-1), showed increased atherosclerotic risk in families with both variants (rs3135506 in Apo A5 and rs2516839 in USF1) [42]. USF 1 is a transcription factor controlling expression of several genes involved in lipid and glucose homeostasis and co-localizes with familial combined Hyperlipidemia (FCHL) and type 2 diabetes affected genes on chromosome 1q22-23. The -1131t>c and -3A>G haplotypes in ApoA5 were associated with familial combined hyperlipidemia in Hong Kong Chinese population [43]. The presence of the -1131T>C in the ApoA5 gene also increased risk to cerebrovascular atherosclerosis in patients with Type III hyperlipoproteinemia (Type III HLP) [44]. SNP S19W in ApoA5 was more prevalent in hypertriglyceridemic pancreatitis patients than in patients with severe hypertriglyceridemia alone [45].

Metabolic Syndrome (Obesity & Diabetes)

In patients with either metabolic syndrome (MS) or cardiovascular disease, a higher frequency of the -1131C allele in overweight subjects, with high BMI and TG levels was observed only in MS patients but not in CVD patients [46]. In the same patient cohort however, there was an association of Apo C-III genotypes, -482T and -455C with ApoA5-1131C allele in MS patients [47]. In addition to the -1131T>C variant, the presence of the common variant IVS3+476A allele and not T1259C variant increased risk to metabolic syndrome [48] due to its association with increased plasma TG [49]. In a cohort of European Caucasian population the presence of c.56C>G variant and not the -1131T>C variant of the ApoA5 was associated with MS [38]. There was also a significant association between polymorphisms in methylenetetrahydrofolate reductase (MTHFR) (c677C.T) and ApoA5 at (g-1131T>C) in MS patients with higher TG levels [50].

Plasma ApoA5 levels were lower in subjects with insulin resistance-related hypertriglyceridemia in obesity [51]. In contrast to the -1131T>C (rs662799) variant the c533G>T variants or T1259C allele had lower BMI and reduced risk to obesity [52, 53]. The Brazilian elderly longitudinal study identified that the GC haplotype of polymorphisms in ApoA1 (rs12721026) and ApoA5 (rs1729408) were associated with high risk to obesity [54]. Similar associations were also observed in children with obesity (148 obese children and 46 with normal body weight) were more than 68% of the obese children were positive for S19W ApoA5 allele along with G-75A allele in ApoA1 [55]. In obese individuals there

was also a significant interaction between ApoA5 S19W and LDL m107 polymorphisms [56]. Four polymorphisms in ApoA5 (SNP1, SNP2, S19W and SNP3) has been correlated with high TG levels in diabetic women [57].

Intervention Studies

For a better understanding of the association between ApoA5 variants and increased risk to hypertriglyceridemia, and cardiometabolic diseases, several intervention studies in populations with or without ApoA5 variants have been studied. The effect of 12 week of Diet Intervention and Regular Exercise (DIRE) on ApoA5 and TG levels were performed in hypertriglyceridemia patients with 1131T/T or 1131T/C carriers. Presence of T/T allele compared to the T/C allele had lowered TG and higher HDL levels after intervention [58] and higher body weights both before and after intervention [59]. In a smaller cohort of the Framingham offspring study (1,073 men and 1,207 women), and a Spanish population study, significant interactions between the presence of Apo A5-1131T major allele and not the minor allele or S19W SNP with increased BMI and increased fat intake was seen [60, 61]. When 88 ApoE3/3 volunteers with ApoA5*1 haplotype (n=76), ApoA5*2 haplotype (n=12), and ApoA5*3 haplotype (n=9) underwent a fat load test by consuming 1g/kg body weight and 60,000 IU of vitamin A there was an association between higher postprandial lipid response in subjects with ApoA5*2 and ApoA5*3 haplotypes and not ApoA5*1 haplotype, thus increasing risk to CHD [62, 63]. Short term fat restriction in hyperlipidemic and overweight men resulted in reduction in BMI in C allele carriers [64]. In Type 2 diabetics after ingestion of a lipid-rich cream, an elevated postprandial ApoA5 levels was seen compared to normolipidemic subjects, which did not correlate with increase in plasma TG or LPL dependent lipolysis [65]. Increased glucose load in subjects with variants of ApoA5 haplotype decreased LPL activity and alterations in NEFA concentrations [66].

SNPs in ApoA5 altered responses to various drug therapies. For example, presence of ApoA5 (rs662799) or ApoA5-ZNF259 variants in patients with or without metabolic syndrome contributed to the variations in response to the lipid lowering drugs, such as statins or fenofibrate therapy [67-69]. HIV-positive patients with -1131T>C ApoA5 genotype on protease inhibitors have severe hyperlipidemia compared to patients with wild type ApoA5 [70]. Polymorphisms in ApoA5 gene also modulated lipid levels and lipid-soluble antioxidants (alpha tocopherol) in children in the 4P study. In boys (6-8 years old), the presence of -1131T>C ApoA5 genotype increased circulating levels of TG and alpha tocopherol however in age matched girls the presence of the rare allele -S19W (mutation of this allele alters the endoplasmic reticulum signal peptide and thereby impairs apoAV secretion into the circulation) of ApoA5 increased TG and alpha tocopherol [71] (Table 1).

Animal Studies

Animal studies using ApoE^{-/-}/LDLR^{-/-} double knockout mice had lower ApoA5 and ApoA4 mRNA but no change in ApoA1, PPAR α , and LXR α gene expression. An increase in early atherosclerotic lesions and increase in serum TC, TG and LDLc was observed in these mice [72]. Human ApoA5 (*hApoA5*) overexpression in the ApoE^{-/-} mice decreased atherosclerotic lesion formation. Supplementation of these mice with a PPAR α agonist, fenofibrate, enhanced the atheroprotective effect of *hApoA5* overexpression [73]. In contrast, in the lean and obese Zucker rats receiving a PPAR γ agonist, rosiglitazone with fish oil diet or coconut oil containing diet, the hepatic ApoA5 levels were higher even at baseline levels in the obese Zucker rats. Rosiglitazone along with fish oil significantly increased ApoA5 liver mRNA levels but lowered both liver and plasma apoAV levels. Since no PPARE was identified on the ApoA5 promoter the effects of rosiglitazone was PPAR independent [74]. Transgenic mice that overexpressed *hApoA5* gene lacking endogenous mouse ApoA5 gene (ApoA5Tg mice) had very low VLDL [75]. ApoA5 transgenic mice on

the FVB/N background when fed diet rich in fat and sucrose for 18 weeks did not show an increase in plasma TG levels but showed high total cholesterol levels. The male A5tg mice had slightly larger inguinal fat pads and increased plasma glucose to insulin ratio compared to female A5tg mice [76]. In order to test the therapeutic feasibility of ApoA5 complexed with reconstituted HDL, it was intravenously injected either into the hypertriglyceridemic apoA5^{-/-} mice or gp1hbp1^{-/-} mice [77]. There was a 60% decrease in TG levels in apoA5^{-/-} mice which was attributed to VLDL catabolism and clearance. No such decrease was observed in gp1hbp1^{-/-} mice [78-83] (Table 2).

Summary and Future Directions

The present review has summarized recent clinical and basic research studies on the physiological role of ApoA5 and exploring its various functions. Though one of the major biological roles of ApoA5 along with Apo C3 is modulation of plasma triglyceride concentrations in humans and rodents, this protein was also identified as an acute phase protein associated with HDL. We also have discussed the various SNPs associated with ApoA5 and their biological consequences in human populations. The presence of SNPs in ApoA5 has been linked to hypertriglyceridemia and cardiometabolic diseases. Though intervention studies using humans and animal models have attempted to investigate the association between diet or drug therapy to ApoA5 levels, more studies are needed to better understand these interactions. Our laboratory is currently investigating the effect of dietary fats on ApoA5 regulation of TG clearance, storage, and recycling. A better understanding of these pathways will help identify ApoA5 targets for hypertriglyceridemia and cardiometabolic diseases.

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Abbreviations

(ApoA5)	Apolipoprotein 5
(TG)	Plasma triglycerides
(VLDL)	Very low-density lipoprotein
(SNP)	Single-nucleotide polymorphism
(HDL)	High-density lipoprotein
(LPL)	Lipoprotein lipase
(ER)	Endoplasmic reticulum
(Ad-apoa5)	Adenovirus-mediated gene transfer of murine ApoA5
(LRP)	Lipoprotein receptor-related protein
L (DLR class)	Sortilin-related receptor
(SorLA)	A repeats-containing
(LDLR)	Low-density lipoprotein receptor
(FER)	Fractional esterification rate
(CAD)	Coronary artery disease
(IMT)	Intima-media thickness

(HDLc)	High-density lipoprotein concentration
(KORA)	Cooperative Health Research in the region of Augsburg
(SAPHIR)	Salzburg Atherosclerosis Prevention Program in Subjects in High Individual Risk
(LCAS)	Lipoprotein and coronary atherosclerosis study
(ACS)	Acute coronary syndromes
(hs-CRP)	High-sensitivity C-reactive protein
(USF-1)	Upstream stimulatory factor-1
(Type III HLP)	Type III hyperlipoproteinemia
(BMI)	Body mass index
(MS)	Metabolic syndrome
(CVD)	Cardiovascular disease
(MTHFR)	Methyletetrahydrofolate reductase
(CHD)	Coronary heart disease
(NEFA)	Non-essential fatty acid
(DIRE)	Diet intervention and regular exercise
(CETP)	Cholesteryl ester transfer protein
(PPAR-alpha)	Peroxisome proliferator-activated receptor alpha
(LXR-alpha)	Liver X receptor alpha
(LDL)	Low-density lipoprotein
(LDLc)	Low-density lipoprotein concentration
(hApoA5)	Human ApoA5
(rApoA5)	Recombinant ApoA5
(SDS-PAGE)	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
(LC/MS)	LC tandem mass spectrometry
(HRP)	Horseradish peroxidase
(ROR-alpha)	Retinoic acid receptor-related orphan receptor-alpha

References

- [1]. Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM. An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science*. 2001; 294:169–173. [PubMed: 11588264]
- [2]. van der Vliet HN, Samuels MG, Leegwater AC, Levels JH, Reitsma PH, Boers W, Chamuleau RA. Apolipoprotein A-V: a novel apolipoprotein associated with an early phase liver regeneration. *J Biol Chem*. 2001; 276:44512–44520. [PubMed: 11577099]
- [3]. Rensen PCN, van Dijk KW, Havekes LM. Apolipoprotein AV Low Concentration, High Impact. *Arterioscler Thromb Vasc Biol*. 2005; 25:2445–2447. [PubMed: 16306435]
- [4]. van der Vliet HN, Schapp FG, Levels JH, Ottenhoff R, Looije N, Wesseling JG, Groen AK, Chamuleau RA. Adenoviral overexpression of apolipoprotein A-V reduces serum levels of

- triglycerides and cholesterol in mice. *Biochem Biophys Res Commun.* 2002; 295:1156–1159. [PubMed: 12135615]
- [5]. O'Brien PJ, Alborn WE, Sloan JH, Ulmer M, Boodhoo A, Knierman MD, Shcultze AE, Konrad RJ. The Novel Apolipoprotein A5 Is Present in Human Serum, Is Associated with VLDL, HDL, and Chylomicrons, and Circulates at Very Low Concentrations Compared with Other Apolipoproteins. *Clin Chem.* 2005; 51:351–359. [PubMed: 15528295]
- [6]. Weinberg RB, Cook VR, Beckstead JA, Martin DD, Gallagher JW, Shelness GS, Ryan RO. Structure and interfacial properties of human apolipoprotein A-V. *J Bio Chem.* 2003; 278:34438–34444. [PubMed: 12810715]
- [7]. Baroukh N, Bauge E, Akiyama J, Chang J, Afzal V, Fruchart JC, Rubin EM, Fruchart-Najib J, Pennacchio LA. Analysis of apolipoprotein A5, c3, and plasma triglyceride concentrations in genetically engineered mice. *Arterioscler Thromb Vasc Biol.* 2004; 24:1297–1302. [PubMed: 15117734]
- [8]. Merkel M, Loeffler B, Kluger M, Fabig N, Geppert G, Pennacchio LA, Laatsch A, Heeren J. Apolipoprotein AV Accelerates Plasma Hydrolysis of Triglyceride-rich Lipoproteins by Interaction with Proteoglycan-bound Lipoprotein Lipase. *J Biol Chem.* 2005; 280:21553–21560. [PubMed: 15774484]
- [9]. Schaap FG, Rensen PC, Voshol PJ, Vrins C, van der Vliet HN, Chamuleau RA, Haveskes LM, Groen AK, van Dijk KW. ApoAV reduces plasma triglycerides by inhibiting very low density lipoprotein-triglyceride (VLDL-TG) production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. *J Biol Chem.* 2004; 279:27941–27947. [PubMed: 15090553]
- [10]. Nowak M, Helleboid-Chapman A, Jakel H, Martin G, Duran-Sandoval D, Staels B, Rubin EM, Pennacchio LA, Taskinen MR, Fruchart-Najib J, Fruchart JC. Insulin-mediated down-regulation of apolipoprotein A5 gene expression through the phosphatidylinositol 3-kinase pathway: role of upstream stimulatory factor. *Mol Cell Biol.* Feb; 2005 25(4):1537–48. [PubMed: 15684402]
- [11]. Nilsson, Stefan K.; Lookene, Aivar; Beckstead, Jennifer A.; Gliemann, Jørgen; Ryan, Robert O.; Olivecrona, Gunilla. Apolipoprotein A-V Interaction with Members of the Low Density Lipoprotein Receptor Gene Family. *Biochemistry.* 2007; 46(12):3896–904. [PubMed: 17326667]
- [12]. Shu X, Nelbach L, Ryan RO, Forte TM. Apolipoprotein A-V associates with intrahepatic lipid droplets and influences triglyceride accumulation. *Biochim Biophys Acta.* May; 2010 1801(5): 605–8. [PubMed: 20153840]
- [13]. Khovidhunkit W, Duchateau PN, Medzihradsky KF, Moser AH, Naya-Vigne J, Shigenaga JK, Kane JP, Grunfeld C, Feingold KR. Apolipoproteins A-IV and A-V are acute-phase proteins in mouse HDL. *Atherosclerosis.* Sep; 2004 176(1):37–44. [PubMed: 15306172]
- [14]. Becker, Steffi; Schomburg, Lutz; Renko, Kostja; Tölle, Markus; van der Giet, Markus; Tietge, Uwe J.F. Altered apolipoprotein A-V expression during the acute phase response is independent of plasma triglyceride levels in mice and humans. *Biochemical and Biophysical Research Communications.* 2006; 20:833–839. [PubMed: 16325772]
- [15]. Hodogluligil U, Tanyolac S, Williamson DW, Huang Y, Mahley RW. Apolipoprotein A-V: A potential modulator of plasma triglyceride levels in Turks. *J Lipid Res.* 2006; 47:144–153. [PubMed: 16258166]
- [16]. Lai CQ, Tai ES, Tan CE, Cutter J, Chew SK, Zhu YP, Adiconis X, Ordovas JM. The APOA5 locus is a strong determinant of plasma triglyceride concentrations across ethnic groups in Singapore. *J Lipid Res.* 2003; 44:2365–2373. [PubMed: 12951359]
- [17]. Kao JT, Wen HC, Chien KL, Hsu HC, Lin SW. A novel genetic variant in the apolipoprotein A5 gene is associated with hypertriglyceridemia. *Hum Mol Genet.* 2003; 19:2533–2539. [PubMed: 12915450]
- [18]. Pennacchio LA, Olivier M, Hubacek JA, Krauss RM, Rubin EM, Cohen JC. Two independent apolipoprotein A5 haplotypes influence human plasma triglyceride levels. *Hum Mol Genet.* 2002; 11:3031–3038. [PubMed: 12417524]
- [19]. Chen SN, Cilingiroglu M, Todd J, Lombard! R, Willerson JT, Gotto AM Jr. et al. Candidate genetic analysis of plasma high-density lipoprotein-cholesterol and severity of coronary atherosclerosis. *BMC Med Genet.* 2009; 10:111. [PubMed: 19878569]

- [20]. Chien KL, Hsu HC, Chen YC, Su TC, Lee YT, Chen MF. Association between sequence variant of c.553 G > T in the apolipoprotein AS gene and metabolic syndrome, insulin resistance, and carotid atherosclerosis. *Transl Res*. 2009; 154:133–41. [PubMed: 19665689]
- [21]. Elosua R, Ordovas JM, Cupples LA, Lai CQ, Demissie S, Fox CS, Polak JF, Wolf PA, D'Agostino RB Sr, O'Donnell CJ. Variants at the APOA5 locus, association with carotid atherosclerosis, and modification by obesity: the Framingham Study. *J Lipid Res*. 2006; 47:990–996. [PubMed: 16474174]
- [22]. Talmud PJ, Palmen J, Putt W, Lins L, Humphries SE. Determination of the Functionality of Common APOA5 Polymorphisms. *J Bio Chem*. 2005:28215–28220. [PubMed: 15941721]
- [23]. Lai CQ, Demissie S, Cupples LA, Zhu Y, Adiconis X, Parnell LD, Corella D, Ordovas JM. Influence of the APOAT locus on plasma triglyceride, lipoprotein subclasses, and CVD risks in the Framingham Heart Study. *J Lipid Res*. 2004; 45:2096–2105. [PubMed: 15342688]
- [24]. Ribalta JL, Fernandez-Ballart J, Vilella E, Castro M, Masana L, Joven J. Newly identified apolipoprotein AV predisposes to high plasma triglycerides in familial combined hyperlipidemia. *Clin Chem*. 2002; 48:1597–1600. [PubMed: 12194944]
- [25]. Aouizerat BE, Kulkarni BE, Heilbron M, Drown D, Raskin S, Pullinger CR, Malloy MJ, Kane JP. Genetic variants of a polymorphism in the human apoA-V gene: effect on plasma lipids. *J Lipid Res*. 2003; 44(6):1167–73. [PubMed: 12671030]
- [26]. Shirts BH, Howard MT, Hasstedt SJ, Nanjee MN, Knight S, Carlquist JF, Anderson JL, Hopkins PN, Hunt SC. Vitamin D dependent effects of APOA5 polymorphisms on HDL cholesterol. *Atherosclerosis*. May; 2012 222(1):167–74. [PubMed: 22425169]
- [27]. Calandra S, Priore Oliva C, Tarugi P, Bertolini S. APOA5 and triglyceride metabolism, lesson from human APOA5 deficiency. *Curr Opin Lipidol*. Apr; 2006 17(2):122–7. [PubMed: 16531747]
- [28]. Grosskopf I, Baroukh N, Lee SJ, Kamari Y, Harats D, Rubin EM, Pennacchio LA, Cooper AD. Apolipoprotein A-V deficiency results in marked hypertriglyceridemia attributable to decreased lipolysis of triglyceride-rich lipoproteins and removal of their remnants. *Arterioscler Thromb Vasc Biol*. Dec; 2005 25(12):2573–9. [PubMed: 16166565]
- [29]. Charlton-Menys V, Durrington PN. Apolipoprotein A5 and hypertriglyceridemia. *Clin Chem*. Feb; 2005 51(2):295–7. [PubMed: 15681559]
- [30]. Nabika T, Nasreen S, Kobayashi S, Masuda J. The genetic effect of the apoprotein AV gene on the serum triglyceride level in Japanese. *Atherosclerosis*. 2002; 165:201–4. [PubMed: 12417270]
- [31]. Endo K, Yanagi H, Araki J, Hirano C, Yamakawa-Kobayashi K, Tomura S. Association found between the promoter region polymorphism in the apolipoprotein A-V gene and the serum triglyceride level in Japanese schoolchildren. *Hum Genet*. 2002; 111:570–2. [PubMed: 12436249]
- [32]. Grallert H, Sedlmeier EM, Huth C, Kolz M, Heid IM, Meisinger C, et al. APOA5 variants and metabolic syndrome in Caucasians. *J Lipid Res*. 2007; 48:2614–21. [PubMed: 17768309]
- [33]. Jiang CQ, Liu B, Cheung BM, Lam TH, Lin JM, Li Jin Y, et al. A single nucleotide polymorphism in APOA5 determines triglyceride levels in Hong Kong and Guangzhou Chinese. *Eur J Hum Genet*. 2010; 18:1255–60. [PubMed: 20571505]
- [34]. Huang XS, Zhao SP, Zhang Q, Bai L, Hu M. Association of plasma apolipoprotein AV with lipid profiles in patients with acute coronary syndrome. *Atherosclerosis*. 2009; 204:e99–102. [PubMed: 19150068]
- [35]. Hyun YJ, Jang Y, Chae JS, Kim JY, Paik JK, Kim SY, et al. Association of apolipoprotein AS concentration with serum insulin and triglyceride levels and coronary artery disease in Korean men. *Atherosclerosis*. 2009; 205:568–73. [PubMed: 19185864]
- [36]. Hsu LA, Ko YL, Chang Q, Hu CF, Wu S, Teng MS, et al. Genetic variations of apolipoprotein A5 gene is associated with the risk of coronary artery disease among Chinese in Taiwan. *Atherosclerosis*. 2006; 185:143–9. [PubMed: 16054149]
- [37]. Lee KW, Ayyobi AF, Frohlich JJ, Hill JS. APOA5 gene polymorphism modulates levels of triglyceride, HDL cholesterol and FERHDL but is not a risk factor for coronary artery disease. *Atherosclerosis*. 2004; 176:165–72. [PubMed: 15306190]
- [38]. Martinelli N, Trabetti E, Bassi A, Girelli D, Friso S, Pizzolo F, et al. The –1131 T>C and S19W APOA5 gene polymorphisms are associated with high levels of triglycerides and apolipoprotein

- C-III, but not with coronary artery disease: an angiographic study. *Atherosclerosis*. 2007; 191:409–17. [PubMed: 16682041]
- [39]. De Caterina R, Talmud PJ, Merlin PA, Foco L, Pastorino R, Altshuler D, et al. Strong association of the APOA5-1131T>C gene variant and early-onset acute myocardial infarction. *Atherosclerosis*. 2011; 214:397–403. [PubMed: 21130994]
- [40]. Elosua R, Ordovas JM, Cupples LA, Lai CQ, Demissie S, Fox CS, et al. Variants at the APOA5 locus, association with carotid atherosclerosis, and modification by obesity: the Framingham Study. *J Lipid Res*. 2006; 47:990–6. [PubMed: 16474174]
- [41]. Hubacek JA, Kovar J, Skodova Z, Pit'ha J, Lanska V, Poledne R. Genetic analysis of APOAV polymorphisms (T-1131/C, Ser19/Trp and Val53/Met): no effect on plasma remnant particles concentrations. *Clin Chim Acta*. 2004; 348:171–5. [PubMed: 15369751]
- [42]. Laurila PP, Naukkarinen J, Kristiansson K, Ripatti S, Kauttu T, Silander K, et al. Genetic association and interaction analysis of USF1 and APOA5 on lipid levels and atherosclerosis. *Arterioscler Thromb Vase Biol*. 2010; 30:346–52.
- [43]. Liu ZK, Hu M, Baum L, Thomas GN, Tomlinson B. Associations of polymorphisms in the apolipoprotein A1/C3/A4/A5 gene cluster with familial combined hyperlipidaemia in Hong Kong Chinese. *Atherosclerosis*. 2010; 208:427–32. [PubMed: 19732897]
- [44]. Evans D, Bode A, von der Lippe G, Beil FU, Mann WA. Cerebrovascular atherosclerosis in type III hyperlipidemia is modulated by variation in the apolipoprotein AS gene. *Eur J Med Res*. 2011; 16:79–84. [PubMed: 21463987]
- [45]. Coca-Prieto I, Valdivielso P, Olivecrona G, Ariza MJ, Rioja J, Font-Ugalde P, et al. Lipoprotein lipase activity and mass, apolipoprotein C-II mass and polymorphisms of apolipoproteins E and AS in subjects with prior acute hypertriglyceridaemic pancreatitis. *BMC Gastroenterol*. 2009; 9:46. [PubMed: 19534808]
- [46]. Niculescu LS, Fruchart-Najib J, Fruchart JC, Sima A. Apolipoprotein A-V gene polymorphisms in subjects with metabolic syndrome. *Clin Chem Lab Med*. 2007; 45:1133–9. [PubMed: 17635078]
- [47]. Niculescu LS, Vladica M, Sima AV. Association of APOA5 and APOC3 gene polymorphisms with plasma apolipoprotein A5 level in patients with metabolic syndrome. *Biochem Biophys Res Commun*. 2010; 391:587–91. [PubMed: 19932084]
- [48]. Kisfali P, Mohas M, Maasz A, Hadarits F, Marko L, Horvatovich K, et al. Apolipoprotein AS IVS3+476A allelic variant associates with increased triglyceride levels and confers risk for development of metabolic syndrome in Hungarians. *Circ J*. 2008; 72:40–3. [PubMed: 18159097]
- [49]. Ong KL, Jiang CO, Liu B, Jin YL, Tso AW, Tarn S, et al. Association of a genetic variant in the apolipoprotein AS gene with the metabolic syndrome in Chinese. *Clin Endocrinol (Oxf)*. 2011; 74:206–13. [PubMed: 21054477]
- [50]. Vasilopoulos Y, Sarafidou T, Bagiatis V, Skriapa L, Goutzelas Y, Pervanidou P, et al. Association between polymorphisms in MTHFR and APOA5 and metabolic syndrome in the Greek population. *Genet Test Mol Biomarkers*. 2011; 15:613–7. [PubMed: 21473680]
- [51]. Huang XS, Zhao SP, Hu M, Bai L, Zhang Q, Zhao W. Decreased apolipoprotein A5 is implicated in insulin resistance-related hypertriglyceridemia in obesity. *Atherosclerosis*. 2010; 210:563–8. [PubMed: 20047745]
- [52]. Wu CK, Chang YC, Hua SC, Wu HY, Lee WJ, Chiang FT, et al. A triglyceride-raising APOA5 genetic variant is negatively associated with obesity and BMI in the Chinese population. *Obesity (Silver Spring)*. 2010; 18:1964–8. [PubMed: 20134407]
- [53]. Horvatovich K, Bokor S, Barath A, Maasz A, Kisfali P, Jaromi L, et al. Haplotype analysis of the apolipoprotein AS gene in obese pediatric patients. *Int J Pediatr Obes*. 2011; 6:e318–25. [PubMed: 20883102]
- [54]. Chen ES, Furuya TK, Mazzotti DR, Ota VK, Cendoroglo MS, Ramos LR, et al. APOA1/A5 variants and haplotypes as a risk factor for obesity and better lipid profiles in a Brazilian Elderly Cohort. *Lipids*. 2010; 45:511–7. [PubMed: 20480398]
- [55]. Shcherbakova M, Sinitsin PA, Poriadina GI, Larionova VI, Khmyrova AP, Petriakina EE, et al. Correlation of metabolic syndrome clinical signs and genetic determinants at children with obese. *Eksp Klin Gastroenterol*. 2010; 7:6–11. [PubMed: 21033077]

- [56]. Smith CE, Tucker KL, Lai CO, Parnell LD, Lee YC, Ordovas JM. Apolipoprotein A5 and lipoprotein lipase interact to modulate anthropometric measures in Hispanics of Caribbean origin. *Obesity* (Silver Spring). 2010; 18:327–32. [PubMed: 19629056]
- [57]. Qi L, Liu S, Rifai N, Hunter D, Hu FB. Associations of the apolipoprotein A1/C3/A4/A5 gene cluster with triglyceride and HDL cholesterol levels in women with type 2 diabetes. *Atherosclerosis*. 2007; 192:204–10. [PubMed: 16781717]
- [58]. Jang Y, Chae JS, Kim OY, Park HJ, Kim JY, Paik JK, et al. APOA5-1131T>C genotype effects on apolipoprotein A5 and triglyceride levels in response to dietary intervention and regular exercise (DIRE) in hypertriglyceridemic subjects. *Atherosclerosis*. 2010; 211:512–9. [PubMed: 20392444]
- [59]. Suchanek P, Lorenzova A, Poledne R, Hubacek JA. Changes of plasma lipids during weight reduction in females depends on APOA5 variants. *Ann Nutr Metab*. 2008; 53:104–8. [PubMed: 18946207]
- [60]. Corella D, Lai CO, Demissie S, Cupples LA, Manning AK, Tucker KL, et al. APOA5 gene variation modulates the effects of dietary fat intake on body mass index and obesity risk in the Framingham Heart Study. *J Mol Med (Berl)*. 2007; 85:119–28. [PubMed: 17211608]
- [61]. Sanchez-Moreno C, Ordovas JM, Smith CE, Baraza JC, Lee YC, Garaulet M. APOA5 gene variation interacts with dietary fat intake to modulate obesity and circulating triglycerides in a Mediterranean population. *J Nutr*. 2011; 141:380–5. [PubMed: 21209257]
- [62]. Moreno R, Perez-Jimenez F, Marin C, Moreno JA, Gomez P, Bellido C, et al. A single nucleotide polymorphism of the apolipoprotein A-V gene –1131T>C modulates postprandial lipoprotein metabolism. *Atherosclerosis*. 2006; 189:163–8. [PubMed: 16386743]
- [63]. Moreno-Luna R, Perez-Jimenez F, Marin C, Perez-Martinez P, Gomez P, Jimenez-Gomez Y, et al. Two independent apolipoprotein AS haplotypes modulate postprandial lipoprotein metabolism in a healthy Caucasian population. *J Clin Endocrinol Metab*. 2007; 92:2280–5. [PubMed: 17356049]
- [64]. Aberle J, Evans D, Beil FU, Seedorf U. A polymorphism in the apolipoprotein AS gene is associated with weight loss after short-term diet. *Clin Genet*. 2005; 68:152–4. [PubMed: 15996212]
- [65]. Pruneta-Deloché V, Ponsin G, Groisne L, Fruchart-Najib J, Lagarde M, Moulin P. Postprandial increase of plasma apoAV concentrations in Type 2 diabetic patients. *Atherosclerosis*. 2005; 181:403–5. [PubMed: 16039297]
- [66]. Kovar J, Adamkova V. Lipoprotein lipase activity determined in vivo is lower in carriers of apolipoprotein A-V gene variants 19W and –1131C. *Physiol Res*. 2008; 57:555–61. [PubMed: 17705673]
- [67]. Feitosa MF, An P, Ordovas JM, Ketkar S, Hopkins PN, Straka RJ, et al. Association of gene variants with lipid levels in response to fenofibrate is influenced by metabolic syndrome status. *Atherosclerosis*. 2011; 215:435–9. [PubMed: 21324458]
- [68]. Brautbar A, Covarrubias D, Belmont J, Lara-Garduno F, Virani SS, Jones PH, et al. Variants in the APOA5 gene region and the response to combination therapy with statins and fenofibric acid in a randomized clinical trial of individuals with mixed dyslipidemia. *Atherosclerosis*. 2011; 219:737–42. [PubMed: 21889769]
- [69]. Cardona F, Guardiola M, Queipo-Ortuno MI, Murri M, Ribalta J, Tinahones FJ. The –1131T>C SNP of the APOA5 gene modulates response to fenofibrate treatment in patients with the metabolic syndrome: a postprandial study. *Atherosclerosis*. 2009; 206:148–52. [PubMed: 19344899]
- [70]. Guardiola M, Ferre R, Salazar J, Alonso-Villaverde C, Coll B, Parra S, et al. Protease inhibitor associated dyslipidemia in HIV-infected patients is strongly influenced by the APOA5-1131T>C gene variation. *Clin Chem*. 2006; 52:1914–9. [PubMed: 16887900]
- [71]. Guardiola M, Ribalta J, Gomez-Coronado D, Lasuncion MA, de Oya M, Garces C. The apolipoprotein A5 (APOA5) gene predisposes Caucasian children to elevated triglycerides and vitamin E (Four Provinces Study). *Atherosclerosis*. 2010; 212:543–7. [PubMed: 20688329]

- [72]. Du, Ha; Yin, M.; Ye, HY.; Shang, YJ.; Dai, XD.; Jing, W., et al. Expression profiles of lipid metabolism related genes in liver of apoE(−/−)/LDLR(−/−) mice. *Zhonghua Bing Li Xue Za Zhi*. 2007; 36:751–5. [PubMed: 18307880]
- [73]. Mansouri RM, Bauge E, Gervois P, Fruchart-Najib J, Fievet C, Staels B, et al. Atheroprotective effect of human apolipoprotein A5 in a mouse model of mixed dyslipidemia. *Circ Res*. 2008; 103:450–3. [PubMed: 18658049]
- [74]. Dorfmeister B, Brandlhofer S, Schaap FG, Hermann M, Fornsinn C, Hagerty BP, et al. Apolipoprotein AV does not contribute to hypertriglyceridaemia or triglyceride lowering by dietary fish oil and rosiglitazone in obese Zucker rats. *Diabetologia*. 2006; 49:1324–32. [PubMed: 16570166]
- [75]. Nelbach L, Shu X, Konrad RJ, Ryan RO, Forte TM. Effect of apolipoprotein A-V on plasma triglyceride, lipoprotein size, and composition in genetically engineered mice. *J Lipid Res*. 2008; 49:572–80. [PubMed: 18056685]
- [76]. Pamir N, McMillen TS, Li YI, Lai CM, Wong H, LeBoeuf RC. Overexpression of apolipoprotein A5 in mice is not protective against body weight gain and aberrant glucose homeostasis. *Metabolism*. 2009; 58:560–7. [PubMed: 19303979]
- [77]. Shu X, Nelbach L, Weinstein MM, Burgess BL, Beckstead JA, Young SG, et al. Intravenous injection of apolipoprotein A-V reconstituted high-density lipoprotein decreases hypertriglyceridemia in apoav−/− mice and requires glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1. *Arterioscler Thromb Vase Biol*. 2010; 30:2504–9.
- [78]. Lind U, Nilsson T, McPheat J, Strömstedt PE, Bamberg K, Balendran C, Kang D. Identification of the human ApoAV gene as a novel RORα target gene. *Biochem Biophys Res Commun*. Apr 29; 2005 330(1):233–41. [PubMed: 15781255]
- [79]. Garelnabi M, Selvarajan K, Litvinov D, Santanam N, Parthasarathy S. Dietary oxidized linoleic acid lowers triglycerides via APOA5/APOCIII dependent mechanisms. *Atherosclerosis*. Aug; 2008 199(2):304–9. [PubMed: 18243209]
- [80]. Mansouri RM, Bauge E, Gervois P, Fruchart-Najib J, Fiévet C, Staels B, Fruchart JC. Atheroprotective effect of human apolipoprotein A5 in a mouse model of mixed dyslipidemia. *Circ Res*. Aug 29; 2008 103(5):450–3. [PubMed: 18658049]
- [81]. Huang XS, Zhao SP, Hu M, Bai L, Zhang Q, Zhao W. Decreased apolipoprotein A5 is implicated in insulin resistance-related hypertriglyceridemia in obesity. *Atherosclerosis*. Jun; 2010 210(2): 563–8. [PubMed: 20047745]
- [82]. Zhang X, Wang J, Chen B. Effect in vitro of apolipoprotein A-V on the structure and functions of recombinant high density lipoprotein. *Biochem Biophys Res Commun*. Oct 22; 2010 401(3): 473–9. [PubMed: 20869952]

Highlights

Apolipoprotein A5 (ApoA5) is a key regulator of plasma triglycerides

SNPs in ApoA5 associated with risk for cardiovascular disease and metabolic syndrome

ApoA5 is an acute phase protein associated with HDL independent of its effects on TG

Figure 1.

Increased ApoA5 levels can significantly decrease plasma triglyceride level by modulating VLDL secretion and/or enhance its clearance. ApoA5 also found to increase TG loading on lipid droplet which leads to lipids accumulation in liver. Heparin induces ApoA5 release in plasma. ROR-α increase both ApoA5 and ApoC3 gene expressions and influences the overall TG metabolism.

Table 1

Summary of Selected Clinical Studies

Study	Polymorphism Variant	Cohort	Outcome	references
The ApoA5 gene on the serum triglyceride levels in Japanese	ApoA5 SNP3: -1131T>C	Participants (481 male and 412 female) were recruited at a health examination	Multiple regression analysis indicated that SNP3 had a significant independent effect on the serum TG level in Japanese	Nabika et al. Ref 30
Association of promoter region polymorphism in the ApoA5 gene and the serum triglyceride level in Japanese schoolchildren	ApoA5 SNP3: -1131T>C	552 schoolchildren	Promoter region polymorphism of the APOA5 gene is a genetic risk factor for hypertriglyceridemia in Japanese	Endo et al. Ref. 31
APOA5 gene polymorphism is not a risk factor for coronary artery disease	ApoA5 SNP3 -1131T>C & SNP (C/G) c.56C>G	The Vancouver SCA Cohort individuals referred for angiography between 1993 and 1995. DNA was extracted from 537 patients	No association between APOA5 gene polymorphisms or haplotypes and coronary artery disease as determined by angiography	Lee et al. Ref. 38
Genetic variations of apolipoprotein A5 gene is associated with the risk of coronary artery disease among Chinese in Taiwan	-1131C & c.553T	The subjects included 211 CAD patients and 677 unrelated controls	The -1131C homozygous carriers and c.553T heterozygous carriers were found more frequently in 211 patients with CAD than in the 317 age/sexmatched controls	Hsu et al. Ref. 37
Associations of polymorphisms in the apolipoprotein A1/C3/A4/A5 gene cluster with familial combined hyperlipidaemia in Hong Kong Chinese	-1131T > C (rs662799) and -3A >G (rs651821)	56 Chinese FCH patients and 176 unrelated controls were studied	Some polymorphisms and in APOA5 are closely associated with FCH in Hong Kong Chinese, they are different from those found in Caucasians	Liu et al. Ref. 43
Decreased apolipoprotein A5 is implicated in insulin resistance-related hypertriglyceridemia in obesity	n/a	682 participants including 340 nonobese and 342 obese subjects	Plasma apoA5 levels were inversely correlated with TG, body mass index and HOMAIR in humans	Huang et al. Ref. 52

Table 2

Summary of Selected ApoA5 Basic Research Studies

Study	Outcome	references
Associations of ApoA5 with infection and inflammation	ApoA5 is a positive acute-phase protein that increases in the serum during inflammation in mouse HDL. An increase in hepatic mRNA levels of ApoA5 was induced by injection of endotoxin. ApoA5 mRNA levels in Hep3B cells was up-regulated by Interleukin-6.	Khovidhunkit W, et al., 2004 [13].
Associations of ApoA5 with Retinoic acid receptor-related orphan receptor-alpha(RORalpha)	The endogenous expression of ApoA5 upregulated by overexpression of ROR- α in HepG2 via adenovirus-mediated. The activity of an ApoA5 promoter construct was enhanced by ROR- α in transiently transfected HepG2 cells. In the ApoA5 promoter that mediate ROR- α transactivation, three AGGTCA motifs were identified, one of which overlaps with the binding site for PPAR α .	Lind U, et al., 2005 [78].
Association of ApoA5 with the reduction of triglycerides induced by dietary oxidized linoleic acid	A significant increase in the expressions of ApoA5 and acetyl-CoA oxidase genes as well as a significant decrease in the expression of APOCIII gene and the levels of plasma TG in the mice fed by oxidized fatty acids was reported.	Garelnabi M, et al., 2008 [79].
ApoA5 in mixed dyslipidemia	Decreased plasma triglyceride levels were induced by hApoA5 a significant decrease in the development of atherosclerotic lesion was reported in the hApoA5 transgenic mice.	Mansouri RM, et al., 2008 [80].
Association of ApoA5 with insulin resistance-related hypertriglyceridemia	Fructose-fed rats showed a decrease in hepatic and plasma ApoA5; however there was no significant change in the expression of apoA5 in obese Zucker rats.	Huang XS, et al., 2010 [81].
Association of ApoA5 with the structure and functions of recombinant high density lipoprotein	Increased ApoA5 in rHDL enhanced lipidbinding ability was reported.	Zhang X, et al., 2010. [82].