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Apolipoprotein A5 fifteen years anniversary: Lessons from genetic epidemiology

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Abstract

Apolipoprotein A5 (APOA5) is a small protein, expressed predominantly in the liver. In plasma, it is located on triglyceride rich lipoprotein particles (chylomicrons and VLDL) and on HDL. Plasma concentration of apolipoprotein A5 is very low, suggesting rather regulatory (activation of lipoprotein lipase, ...) than structural function. APOA5 is an important determinant of plasma triglyceride concentration; this effect has been confirmed both on animal models, as well as on human studies. Minor alleles of three commonly analysed variants within this gene (rs662799, rs3135506, rs2075291) are associated with higher plasma TG values and increased risk of myocardial infarction, with some important interethnic differences observed. Further roles of APOA5; determination of BMI, diabetes and last but not least nutri- and pharmaco-genetic interactions are suggested, but without the definitive conclusions.

Keywords

Apolipoprotein A5; Triglycerides; Polymorphism; Cardiovascular disease

1. Introduction

Plasma triglycerides (triacylglycerols, TG) are long time debated as a risk factor for not only cardiovascular disease (Miller et al., 2011) but also for another morbidities as cancer (Borena et al., 2011), renal disease (Navaneethan et al., 2012), suicide (Chang et al., 2012) and most importantly, also as an independent risk factor for all-cause mortality (Liu et al., 2013; Pikhart et al., 2015). It is interesting that despite these recent observations, international guidelines usually do not include plasma triglyceride values into risk calculators.

Plasma TGs are transported in blood mainly through the chylomicrons (the largest lipoprotein particles, transporting dietary triglycerides from intestine) and through the very low density particles (VLDL) (transporting triglycerides synthesised in the liver). The major enzyme participating on triglyceride degradation is lipoprotein lipase, which mediates lipolysis of triglycerides in very low density particles and chylomicrons (Hassing et al., 2012).

General variability of plasma TG values in population is relative high, in the vast majority of the individuals TG values are between 0,5 mmol/L (44 mg/dL) and 7 mmol/L (620 mg/dL). In some cases values can reach even 15 mmol/L (1330 mg/dL) or 20 mmol/L (1770 mg/dL). Hypertriglyceridemia could occur as a result of metabolic stressors, however the severe hypertriglyceridemia is usually rare monogenic disease (Johansen and Hegele, 2011).

Final level of plasma TG levels is a result of simultaneous effects of genetic predisposition (both polymorphisms and mutations are involved) dietary habits (negative effects of increased intake of dietary fat and alcohol) and physical activity (higher physical activity helps to reduce plasma TG levels) performed by each individual. Further, age (TGs are increasing with aging) sex (males have higher TG values than females) and smoking (smokers have higher plasma TG than nonsmokers) are significant factors influencing plasma TG levels.

It is still not clear, what proportion of final plasma TG levels is genetically determined. The heritability estimates range from 40% to even 60%, depending of the type of studies (Arsenault et al., 2011). So far, dozens of genes/variants have been associated with plasma levels of triglycerides (Schwarzova et al., 2015).

Through the era of association studies, major interest was focused on the gene cluster of apolipoproteins on chromosome 11. Common variants within apolipoprotein C1, apolipoprotein C3 and apolipoprotein A4 were intensively studied, but the obtained results have been controversial (summarised by Talmud, 2001; Vrablik and Hubacek, 2010; Hubáček et al., 2009a). This lead to the assumption, that analysed variants could be only markers for some (an)other, functionally more important variant(s) within (an)other gene(s), member(s) of the same cluster/in a close vicinity of the cluster.

2. Apolipoprotein A5 discovery

The gene for apolipoprotein A5 (*APOA5*, gene ID 116519, OMIM accession number – 606368) was originally found by comparative sequencing of ~200 kbp of human and mice DNA as a last member of the gene cluster of apolipoproteins *APOA1/APOC3/APOA4/APOA5*, located on human chromosome 11 at position 11q23 (Pennacchio et al., 2001). The creation of two mice models (*APOA5* transgenic and *APOA5* knock-out) confirmed the important role of this gene in plasma triglyceride levels determination. The transgenic mice had lower and the knock-out mice higher levels of plasma triglycerides, while plasma cholesterol levels remained unchanged in both animal models.

The gene for apolipoprotein A5 is small, spans approximately 3 kbp, is constituted in a similar way to other apolipoprotein genes (with apolipoprotein B, which comprise from 29 exons, as an exception), is composed of 4 exons (start codone is localized within the second exon) and 3 introns and codes for the 366 amino acid protein (with the 23 amino acid signal peptide and the 343 amino acid of mature *APOA5*).

Interestingly, a Dutch group simultaneously described an identical gene as apolipoprotein which is associated with the early phase of liver regeneration, but failed to recognise its important role in the determination of plasma triglyceride levels (van der Vliet et al., 2001).

Another so far completely not understood and not extensively studied is the role of apolipoprotein A5 as an acute phase protein (Khovidhunkit et al., 2004; Ngaosuwan et al., 2015).

3. APOA5 expression and localisation

In humans, *APOA5* is expressed almost exclusively in the liver tissue (Pennacchio et al., 2001); some minor expressions have also been detected in the small intestine (Guardiola et al., 2012). Nothing is known about the existence of the potential alternative splicing variants of this gene.

APOA5 is associated predominantly with TG-rich lipoproteins (chylomicrons and VLDL) and has also been detected on HDL particles. In comparison with other apolipoproteins, plasma concentration of *APOA5* is very low (less than 1 µg/mL) (O'Brien et al., 2005) which is about 1000-time less than plasma concentration of the most common plasma apolipoprotein, apoB. This suggests that it has more catalytic than structural functions, since there is less than one APOA5 molecule per one lipoprotein particle. Some estimations refer to one APOA5 molecule per 20–25 TG rich particles (Merkel and Heeren, 2005).

4. Function

There are couple of possible explanations as to how APOA5 influences plasma triglyceride levels (summarised by Nilsson et al., 2011, Table 1).

The first suggested mechanism supposes that APOA5 functions as an activator of lipoprotein lipase (which is a key enzyme in triglyceride catabolism); APOA5 promotes lipolysis by the increasing the adherence of TG rich lipoproteins to cell surface through the heparin sulphate proteoglycans and/or glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 and, through this process, enhances the metabolism of TG-rich particles (Li et al., 2014). The second is the possible effect of APOA5 on the secretion of VLDL particles, since APOA5 reduces hepatic production by inhibiting VLDL-particle production and assembly by binding to cellular membranes and lipids (Beckstead et al., 2003).

Finally, the third possibility relates to the acceleration of the hepatic uptake of lipoprotein remnants and it has been shown that APOA5 binds to different members of the low-density lipoprotein receptor family (summarised by Nilsson et al., 2007, Forte et al., 2009).

Members of the LDL-receptor family have been described to bind APOA5 (reviewed by Nilsson et al., 2011). However, due to the very low plasma concentration of APOA5, these interactions are likely not a major intermediaries of APOA5 functionality. Rather they results from the general similarities between different apolipoproteins.

5. Gene variability

Within the *APOA5* gene, a couple of important SNPs with a widely confirmed effect on plasma TG levels as well as list of rare mutations have been described (Fig. 1).

In Caucasians, the common variants are inherited mostly in three haplotypes (Pennacchio et al., 2002), which are characterised by two SNPs, namely rs662799 (T-1131 > C; in almost complete linkage disequilibrium with A-3 > G, where the minor allele is associated with about 50% lower gene expression) and rs3135506 (Ser19 > Trp; C56³G; alters the signal peptide and influences APOA5 secretion into plasma). There are also a further three common variants (A-3 > G, IVS+476 G³A and T1259 > C) which are not necessary for haplotype characterisation.

Population frequencies of common APOA5 alleles exhibit large interethnic differences (Fig. 2). For example, there are about 15% of carriers of the – 1131C allele among Caucasians, but the frequency could reach even between 40% and 50% among Asians. In contrast, the Trp19 allele is very rare in the Asian population (less than 1% of carriers) but is common in Caucasians (about 15% of carriers).

Vice versa, important SNP influencing TG values (rs2075291, G553T, Gly185 > Cys) with a population frequency of about 5% has been detected among Asians, but it is extremely rare among Caucasians and carriers of this substitution were not detected in African-Americans or Hispanics (Pennacchio et al., 2002).

Minor allele frequency of the C-1131T polymorphism is slightly higher in African-Americans and Hispanics than in Caucasians and the strongest effect on plasma TG levels has been observed in Hispanics (Pennacchio et al., 2002).

In Africans Americans the frequencies of minor alleles of the rs3135506 are analogues to the Caucasians, with the similar effect on plasma TG levels. Among Hispanics is almost 30% of carriers of the minor allele, and the effect on plasma TG is only borderline (Pennacchio et al., 2002).

Sporadic publications refer to some other common polymorphisms, e.g. Val150 > Met (rs3135507, G448A) where they suggest significant sex-dependent associations (Hubacek et al., 2005a) with plasma lipids, namely HDL-cholesterol levels.

Rare variants within the *APOA5* gene have been described in a couple of different populations. Among the “common mutations/rare SNPs”, one of the most characterised on a population level is the Ala315 > Val (C944 > T, Hubacek et al., 2008a) exchange. Originally detected in patients with extreme TG levels over 10 mmol/L, it was also found in about 0.7% of the general population (mostly in individuals with normal TG values), which suggests a low penetrance of this variant.

More than twenty other rare variants (mutations) have been described within the human *APOA5* gene. They cover a wide spectrum that includes preliminary stop codons, amino acid changes as well as insertions and deletions. These mutations are generally associated with hypertriglyceridaemia, but penetration is usually not 100%. Individual mutations have been found mostly in one pedigree only and have been very well summarised by Melegh et al. (2012).

6. Health conditions/diseases associated with *APOA5*

6.1. Plasma concentrations of *APOA5* as a CVD risk factor

Even though plasma concentration of *APOA5* is very low, some studies have focused on the analysis of the potential association of this biochemical parameter with cardiovascular disease (CVD). This relationship remains controversial, as higher plasma levels of *APOA5* in individuals with CVD disease have been found in some, but not in all studies (Manpuya et al., 2001; Hyun et al., 2009; Yang et al., 2012).

In contrast, correlation between plasma *APOA5* concentration and triglycerides was described consistently, and seems to be stronger in individuals with high plasma TG levels (Schaap et al., 2006; Hyun et al., 2009; Talmud et al., 2006). Interestingly individuals with higher plasma TG levels have also higher concentration of *APOA5*. This is in contrast with animal experiments, where inverse correlation between *APOA5* concentration and plasma TG concentrations was detected. No explanation exists at this moment to explain these inconsistencies between *APOA5* plasma concentration and plasma TG levels in different settings, but such discrepancies between the animal models and human subjects are common (Langley, 2009; Marti -Kehl et al., 2012).

6.2. *APOA5* polymorphisms and plasma lipids

The major effect of the apolipoprotein A5 gene (and its variants) is on plasma triglyceride levels. Minor alleles (C1131 and Trp19) are primarily associated with the elevation of plasma triglyceride levels. The most extensive information available has been drawn from Caucasian populations, particularly in relation to the rs662799 SNP. Here, one minor allele is associated with an approximate 0.25 mmol/L increase of plasma TG levels based on the analysis of more than 300,000 individuals (Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration et al., 2010).

A similar effect is associated with the Trp19 allele, even though it has not been confirmed by a huge number of studies. Original studies have further described that the strongest effect of *APOA5* polymorphisms on plasma TG levels is observed among Hispanics, with only minor effects detected among Africans. Among Asians, the effect on plasma TG levels is similar that found among Caucasians. Generally, studies have suggested significant interethnic differences and in some cases sex-dependent associations as well (Pennacchio et al., 2002; Hubacek, 2005; Lai et al., 2003; Ken-Dror et al., 2010; Ferreira et al., 2013).

Importance of *APOA5* common polymorphisms for determination of plasma triglyceride levels has been confirmed also by potent genome wide association studies (Kathiresan et al., 2008; Chasman et al., 2008; Waterworth, et al., 2010). All these powerful studies have described an association between the minor *APOA5* alleles and enhanced plasma TG values.

Sporadic publications have also mentioned a weak but nonetheless significant effect of *APOA5* variants on plasma HDL-cholesterol and non-HDL cholesterol levels (Hubacek et al., 2008b). These slight effects have been for C-1131T confirmed by a large collaboration study (Triglyceride Coronary Disease Genetics Consortium et al., 2010). Despite the fact, that effects have been statistically significant, the biological importance is in this case

questionable, as it represents for example 0,053 mmol/L per allele difference in the case of HDL cholesterol levels.

6.3. APOA5 polymorphisms and risk of cardiovascular disease and myocardial infarction

A large meta-analysis of 101 studies (more than 300,000 with no history of CVD and almost 13,000 cases) (Triglyceride Coronary Disease Genetics Consortium et al., 2010) confirmed a risk associated with the presence of the minor *APOA5* allele –1131C and coronary heart disease. The odds ratio was 1.18 for every C allele.

Surprisingly, there are far fewer studies on the second common *APOA5* polymorphism, Ser19>Trp, even though available studies have detected that its effect on plasma triglycerides is similar to C-1131>T. Nevertheless, the minor Trp allele is also associated with increased risk of CVD, and it seems that especially homozygotes and carriers of more minor alleles (both – 1131C and 19Trp) are at higher risk of CVD (Hubacek et al., 2004a).

Very recently Do et al. (2015), have described, that not only common polymorphisms, but also rare *APOA5* mutations increases risk of myocardial infarction.

6.4. BMI, metabolic syndrome, diabetes

Obesity and metabolic syndrome are both closely related to plasma triglyceride levels. Therefore, the focus on an association between *APOA5* and BMI or metabolic syndrome is understandable (Zaki and Amr, 2014). Recent meta-analyses suggested that the effect on metabolic syndrome development is stronger for rs662799 in Asian population and for rs3135506 for Europeans (Xu et al., 2013; Liu et al., 2012). However these differences can easily reflex the different allelic frequencies of analysed SNPs, and lower power of some studies. These studies also discuss the possibility that that minor *APOA5* alleles could be associated with an enhanced risk of obesity development.

However, genome wide studies have failed to prove that *APOA5* is a gene associated with BMI values and/or obesity, so the effect could be far from clinically significant or at least significantly context-dependent.

Meta-analysis focused on rs662799 and risk of type 2 diabetes mellitus has suggested a significant association in Asian (Lee et al., 2010), but not in European populations (Yin et al., 2014). Another polymorphisms within the *APOA5*, Val150 > Met (rs3135507) was suggested to be associated with insulin responses/possibly influence Beta-cell function (Chiu et al., 2005).

7. Nutri-, acti- and pharmacogenetic associations with apolipoprotein A5

Dozens of studies have focused on changes of anthropometrical (body weight, BMI, WHR, ...) or biochemical parameters (mostly plasma lipid levels) as a result of the interactions between common *APOA5* variants and dietary habits (polyunsaturated fatty acid intake, n-3 and n-6 fatty acid intake, total fat and total energy intake, alcohol intake), dietary (lowering the energy intake) and/or physical activity interventions or dyslipidemic (using statins or fenofibrate) treatment. Due to the high heterogeneity of the examined populations,

differences in protocol and/or interventions used, the studies are difficult to directly compare and draw definitive conclusions (Aberle et al., 2005; Lai et al., 2006; Hubacek et al., 2006; Suchanek et al., 2008; Liu et al., 2009; Mattei et al., 2009; Hubacek et al., 2009b; Sánchez-Moreno et al., 2011; Hishida et al., 2012; Zlatohlavek et al., 2012; Hubacek et al., 2014). The highest variability of results could be observed, if interactions with different dietary patterns are analysed.

As selected examples the following studies could be mentioned in details.

Rs662799 was suggested influencing weight loss decrease of BMI after short term fat restriction in adult males (Aberle et al., 2005). In contrast, no association with weight loss was detected in females on intensive dietary/physical activity intervention (Suchanek et al., 2008) or if children and adolescents have been examined (Zlatohlavek et al., 2012).

TT-1131 homozygotes seem to profit more from statin treatment (Hubacek et al., 2009b) but not from fibrate treatment (Lai et al., 2006).

However, with caution, it could be concluded that carriers of the minor C-1131, Trp19, or T553 alleles are in some cases less prone to the positive effects of environmental interventions.

8. Gene-gene interactions

Some papers suggest the importance of the interactions between *APOA5* and other genes, especially with common *APOE* (OMIM acc. no. 107741) three allelic (E2, E3, and E4) polymorphism, in the modulation of plasma lipids. In these cases, the interaction between minor alleles of both genes seems to be of importance. In the general population, *APOE4* seems to have the potential to diminish the effect of minor *APOA5* rs662799 and rs3135506 alleles, especially in females (Hubacek et al., 2008c). Interaction between *APOE* and *APOA5* Ser19 > Trp has been suggested (but not confirmed by all) to play some role in the development of type III hyperlipidaemia (Schaefer et al., 2004; Hubacek et al. 2005b, Martín-Campos et al., 2006).

Further studies, in which interaction with *APOA5* has been described, have included, for example, variants within *FTO* (Wang et al., 2014), lipoprotein lipase (Smith et al., 2010), *USF-1* (Laurila et al., 2010) and *FEN-1* (Park et al., 2010). They have also focused not only on plasma lipids, but on BMI values or hypertension as well.

9. Minor focus

Some other possible roles of *APOA5* variants have been discussed, but generally these reports comprise only one or two papers – and first original papers with positive findings are usually not confirmed in second publications. These papers focus on the possible effect of different *APOA5* variants on maternal height (Ward et al., 2003; Hubacek et al., 2004b), longer foetal birth length (Ward et al., 2003), putative associations with plasma levels of C-reactive protein (Jang et al., 2004; Hubáček et al., 2005c), LDL particle size (Jang et al., 2004, Austin et al., 2004) and haemostatic markers (Novotny et al., 2014).

10. Apolipoprotein A5 and intracellular triglyceride accumulation

The effect of the apolipoprotein A5 on plasma TG values and risk of cardiovascular disease in human beings is undoubted. As the plasma concentration of this apolipoprotein is very low, the mechanism of the effect is still not completely understood and different aspects of apoA5 effects have been analysed on animal models and on different cells.

Despite the fact, that substantial proportion of the results obtained on animal models and/or cell lines cannot be undoubtedly applied to the human subjects (Langley, 2009, Akhtar, 2015) there are some interesting findings pointing on possible general mechanisms of apoA5 functioning, as briefly summarised below. The detailed and extensive reviews about the role of this protein especially on intracellular levels have been published recently (Forte et al., 2009, Forte and Ryan, 2015).

Both cell line models as well as animal models; suggest that apoA5 plays an important role also in lipids accumulation within the cells. Experiments performed on human hepatoma Hep3B cells show that apoA5 secretion is lower, than expected and pointed on the low secretion efficacy of this protein. Further, apoA5 intracellular overexpression has no effect on apoB-containing lipoproteins secretion, and most of the apoA5 is secreted from the cells on HDL particles (Shu et al., 2007). Additional experiments on rat hepatic cells (McA-RH7777) further exclude the colocalisation of the apoA5 and apoB and suggest (Shu et al., 2007), that significant part of apoA5 is localized on intracellular lipid droplets. This association between apoA5 and lipid droplets was later confirmed on APOA5 transgenic mice (Shu et al. 2010). Here, the proportion of within-the-cell retained apoA5 was estimated to be cca 20% of the totally expressed apoA5. This intracellular apoA5 hamper the escape of the lipid droplets from the secretory pathway and help to accumulate the triglycerides within the cells (Shu et al. 2010). This mechanism could have the healing effect in the case of liver injury – apoA5 expression is significantly enhanced due to the liver regeneration in a rat animal model (van der Vliet et al., 2001), but can have in contrast the deleterious effect on the development of the non-alcoholic fatty liver disease, as hypothesised by Forte and Ryan (2015).

Finally, an in vivo study suggests that apoA5 can be internalized also by human adipocytes (Zheng et al., 2012), however, as association between APOA5 and BMI/obesity was not confirmed, the clinical significance of this process needs to be further examined.

11. Conclusions

Despite the very low plasma concentration, variants within apolipoprotein A5 are potent determinants of plasma triglyceride levels. Minor alleles of three SNPs (rs662799, rs3135506, rs3135507) are associated with the higher risk of cardiovascular disease.

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Abbreviations

Apo	apolipoprotein
CVD	cardiovascular disease
HDL	high density lipoprotein
SNP	single nucleotide polymorphism
TG	triglycerides
VLDL	very low density lipoprotein

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* Tagging SNPs

Fig. 1. Schematic structure of the human apolipoprotein A5 gene, with localisation of the tagging polymorphisms.

T-1131>C

C56>G (Ser19>Trp)

Fig. 2. Population frequencies of the tagging apolipoprotein A5 polymorphisms. Significant ethnic differences are detectable both for the T-1131>C (2a) and for C56>G (2b) polymorphism. Third tagging variant, G553>C, was detected just in Asians.

Table 1

How apolipoprotein A5 influences plasma triglyceride levels.

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- APOA5 is a an activator of lipoprotein lipase
 - APOA5 increase the lipolysis of TG rich lipoproteins
 - APOA5 accelerates the hepatic uptake of lipoprotein remnants
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