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RAPID COMMUNICATION

Apolipoprotein AV Variants Do Not Affect C-Reactive Protein Levels in Caucasian Males

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Summary

The important role of *APOAV* gene variants in determination of plasma triglyceride levels has been shown in many population studies. Recently, an influence of *APOAV* T-1131>C polymorphism on C-reactive protein (CRP) in young Korean males has been reported. We have therefore analyzed a putative association between T-1131>C, Ser19>Trp and Val153>Met *APOAV* variants (PCR and restriction analysis) and CRP concentrations in 1119 Caucasian males, aged between 28 and 67 years (49.2±10.8 years). The frequency of C allele carriers was lower in Caucasians than in Koreans (15.5 % vs. 46.2 %). CRP levels did not differ between T/T homozygotes (n=946, 1.61±2.05 mg/l) and carriers of the C allele (n=173, 1.67±1.95 mg/l). Thus, in contrast to Korean males, T-1131>C *APOAV* variant has no effect on plasma concentrations of CRP in a large group of Caucasian males. Other *APOAV* variants (Ser19>Trp and Val153>Met) did not also influence plasma concentrations of CRP. *APOAV* variants are unlikely to be an important genetic determinant of plasma CRP concentrations in Caucasian males.

Key words

Apolipoprotein AV • Polymorphism • Genetics • Triglycerides • Myocardial infarction • CRP

Introduction

Recently, an interesting association between the T-1131>C apolipoprotein AV (*APOAV*) variant and plasma concentrations of C-reactive protein (CRP) was described in 158 young non-obese Korean males (Jang *et al*. 2004). Carriers of at least one allele C-1131 had higher plasma levels of CRP when compared to carriers of the common T-1131T genotype.

APOAV plays an important role in modulating triacylglycerol metabolism not only in experimental animal models, but *APOAV* variants have been described as important genetic determinants of plasma lipids (mainly triglycerides but in some cases also HDL cholesterol concentrations) in humans (Pennacchio *et al.* 2001, 2002, Nabika *et al.* 2002, Talmud *et al.* 2002, Šeda

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and Šedová 2003, Hubáček *et al.* 2004a).

Interestingly, apoAV was also detected as positive acute-phase protein in mouse HDL **(**Khovidhunkit *et al.* 2004). An increase in hepatic mRNA levels of *apoAV* was detected after injection of endotoxins. *ApoAV* expression is also elevated in early phase of rat liver regeneration (van der Vliet *et al.* 2001). These changes suggested that APOAV, apolipoprotein whose activities are not yet fully understood, may serve functions other than just regulating lipid metabolism. While CRP levels are elevated through the acute phase, the finding of an association between *APOAV* variant and elevated CRP suggests a role which APOAV could play in host defense.

High plasma levels of CRP have been described as an independent risk factor of atherosclerosis. CRP is the acute phase serum protein produced by the liver. Serum levels of CRP can increase by even 1000 times over the baseline during the response to infection or inflammation. The exact physiological role of CRP remains unknown, but CRP is involved in host defense. Elevated plasma levels of CRP have been found in patients with cardiovascular disease or myocardial infarction, and it is believed that the CRP is an independent risk factor of cardiovascular disease development (Black *et al.* 2004). So far, the information about genetic determination of plasma CRP levels is very limited.

Using a previously described methods (Hubáček *et al.* 2004a,b), we have analyzed not just the T-1131>C, but also other (Ser19>Trp and Val153>Met) *APOAV* variants in a total of 1119 unrelated Caucasians males (aged 49.2±10.8 years) with known CRP levels recruited as a representative 1 % population sample [*Multinational monitoring of trends and determinants in cardiovascular diseases: MONICA Project,* Manual of operations WHO/MNC 82.2, Nov 1983]. The CRP was measured immunoturbimetrically by the WHO Regional Lipid Reference Center on a Roche COBAS MIRA autoanalyzer using ultrasensitive kit (Orion Diagnostica, Espoo, Finland).

Written informed consent was obtained from participants in the study before blood samples had been taken and the measurements were performed. CRP levels were logarithmically transformed before the analysis and statistical analysis was performed using the t-test.

In European Caucasian population the frequency of the less common allele C-1131 was much lower (15.5 vs. 46.2 %) compared to the Korean population, where the association between *APOAV* gene variant and CRP was initially described (Jang *et al.* 2004). The higher frequency of the allele C-1131 in Asians than in Europeans was already observed previously (Nabika *et al.* 2002, Baum *et al.* 2003, Lai *et al.* 2003). Usual associations between elevated levels of plasma triglycerides and the presence of the C-1131 allele were observed both in Czech (Hubáček *et al.* 2004a) and Korean males (Jang *et al*. 2004).

The plasma levels of CRP were almost twice as high in Caucasian males as in Korean males. In contrast to Jang *et al*. (2004), we found no association between the T-1131>C variant of the *APOAV* gene and CRP concentrations. CRP concentrations (mean ± C.D.) did not differ between T/T homozygotes (n=946, 1.61±2.05 mg/l) and C allele carriers (n=173, 1.67±1.95 mg/l). Also other two *APOAV* variants exhibited no significant effect on plasma levels of CRP (data not shown).

More than 1100 unrelated Caucasian males were included in this study. We believe that the design of the presented study reduces the chance of false positive or false negative results to a minimum. We conclude that the T-1131>C variant in the *APOAV* gene has no general effect on CRP concentrations and the association described by Jang *et al.* (2004) need not be generally valid.

We can only speculate about the causes of the differences. At first, the difference in ethnicity could play an important role. For example T-1131>C variant influence the triglyceride levels in Hispanics and Caucasians, but not in African-Americans (Pennacchio *et al.* 2002). The similar ethnic-specific effect could also be present in the case of associations between *APOAV* variants and plasma levels of CRP. We cannot exclude that the differences in age (Czech males were older) or BMI (Koreans had a lower BMI) between analyzed populations could also play a substantial role, because it is known that plasma levels of CRP are higher in obese and elderly subjects.

We summarize that in contrast to the study published by Jang *et al*. (2004), *APOAV* variants (not just T-1131>C but also Ser19>Trp and Val153>Met) were not found to play a role in the determination of plasma CRP concentrations in Caucasian males. If the *APOAV* T-1131>C (and eventually also Ser19>Trp and Val153>Met) variant can influence C-reactive protein concentrations in other ethnic groups needs to be analyzed in other studies.

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