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APOA5 variant Ser19Trp influences a decrease of the total cholesterol in a male 8 year cohort

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Abstract

Objectives: To evaluate whether the relationship between dietary composition and plasma lipid levels is genetically determined.

Design and methods: We have evaluated the influence of common apolipoprotein A5 (*APOA5*) variants (T-1131 > C, Ser19 > Trp and Val153 > Met) on plasma lipid concentrations in 117 males for whom dietary composition markedly changed and total cholesterol decreased (from 6.21 ± 1.31 mmol/L in 1988 to 5.43 ± 1.06 mmol/L in 1996) over an 8 year follow-up study.

Results: *APOA5* T-1131 > C and Val153 > Met variants did not influence the change in lipid measures over time. In Ser/Ser19 homozygotes, the plasma cholesterol was relatively stable over the years (6.1 ± 1.2 mmol/L in 1988 and 5.6 ± 1.0 mmol/L in 1996, − 8%, $P < 0.01$). In contrast, in the Trp19 carriers, the decrease of the plasma cholesterol was more than 20% (6.5 ± 1.6 mmol/L in 1988 and 5.1 ± 1.0 mmol/L in 1996) ($P < 0.001$). The difference of the changes is significant (8% vs. 20%, $P < 0.005$). Changes in other analyzed lipid parameters have not been significantly associated with *APOA5* variants.

Conclusions: Ser19 > Trp variant in the *APOA5* gene may play an important role in an individual's sensitivity to dietary composition.

Keywords: Apolipoprotein A5; Polymorphism; Cholesterol; Dietary change; Lipids

Introduction

To lower high plasma lipids (cholesterol and triglycerides), a major risk factor for coronary artery disease development, the reduction of dietary fat and cholesterol is the first expert recommendation. Still, despite the fact that many patients have changed their dietary habits, the response of plasma lipids to dietary cholesterol/lipids varies between the individuals—they could be roughly divided to hyper-, normo- and hypo-responders. However, within the individuals, the response is relatively stable [1] and there is no doubt that this will be regulated by the genetic background of the individual. Although intensively analyzed over the last few years, genetic determination of the response of plasma lipids to changes in diet is poorly understood.

The most broadly studied candidate gene locus (despite the apolipoprotein E gene variants) is the apolipoprotein (APO) gene cluster *APOA1/APOC3/APOA4* (reviewed by [2]). Results from different studies suggest that variants in *APOC3* and *APOA1* genes are in some part involved in dietary response for lipid parameters [2].

In the same gene cluster, the *APOA5* gene has been identified [3–5]. The creation of *APOA5* knock-out and transgenic mice [3] as well as creation of *APOA5–APOC3* double knock-out and double transgenic mice [6] showed that apoA5 and apoC3 could play an opposite role in regulation of plasma lipid levels (especially triglycerides). This means that behind the *APOC3* gene, the *APOA5* gene is also a candidate gene that could play an important role in the genetic determination of the dietary response of plasma lipids.

ApoA5 is located on TG rich particles (chylomicrons and VLDL) and on HDL and enhances the activity of lipoprotein lipase [7]. In comparison to other apolipoproteins, the plasma concentration of apoA5 is low in humans, ranging from ~ 25 to 400 μg/L [8]. In the *APOA5* gene, more that 10 variants have

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been described so far [9,10]. The most commonly analyzed variants T-1131 > C and Ser19 > Trp are associated in many populations with differences in plasma TG levels [3,9,11–17]. C-1131 and Trp19 alleles have been also described like risk factors for MI and CAD development [12,18].

The aim of this present study was to evaluate the role of common variations in the *APOA5* gene in response to dietary change in a male cohort of the Czech MONICA study, where dietary composition had significantly changed between 1988 and 1996 due to social and economic changes and lipid measures were available at these two time points.

Materials and methods

Population sample

The 117 unrelated males included in this study represented a part of an 8 year cohort selected in 1988 at age 25–64 years and reinvestigated in 1996 according the protocol of the MONICA study (*Multinational monitoring of trends and determinants in cardiovascular diseases: "MONICA Project"*, Manual of operations WHO/MNC 82.2, Nov 1983). Out of 131 individuals, only males with all lipid parameters in both years and all genotypes characterized were included in the study. Information about the dietary changes in the population was obtained by personal communication from the Czech Institute of Agriculture Economy (partially published in [19], the details were published only in Czech [20]).

Genetic and biochemical analysis

DNA was isolated by a standard method [21] and the *APOA5* gene polymorphisms were genotyped as described in detail elsewhere [12,22]. The lipoprotein parameters were measured enzymatically by the WHO Regional Lipid Reference Centre, IKEM, Prague on the Roche COBAS MIRA autoanalyzer, using conventional enzymatic methods with reagents from Boehringer Mannheim Diagnostics and Hoffmann-La Roche, as described previously [23]. LDL was calculated by the Friedewald formula [24]. Body mass index (BMI) was calculated as weight in kilograms divided by square height in meters.

Statistical analysis

Statistical analysis was performed using the ANOVA method to estimate the difference among genotypes. Data are presented as means ± SD. Written informed consent was obtained from the study participants and the local ethic committee approved the design of the study.

Results

Dietary composition and plasma lipid parameters

Dietary composition changed dramatically in the Czech Republic between 1988 and 1996. Briefly, the consumption of meat, eggs, butter and animal fat greatly decreased, while the consumption of vegetables, fruits and vegetable oils increased (for example red meat 80 → 68 kg/person/year, animal fat 16 → 9 kg/person/year, fruits and vegetables 133 → 150 kg/person/year) [20]. Reflecting these dietary changes, total cholesterol levels decreased in the population by 0.54 mmol/L ($P < 0.001$, [19]). In this cohort, significant differences in the levels of total (6.23 ± 1.33 mmol/L vs. 5.44 ± 1.08 mmol/L, $P < 0.001$) and LDL cholesterol (3.77 ± 0.98 mmol/L vs. 3.30 ± 0.89 mmol/L, $P < 0.01$) between 1988 and 1996 were observed [25].

Table 1
Distribution of the *APOA5* genotypes

	N	%
T/T-1131	91	77.8
T/C-1131	24	20.5
C/C-1131	2	1.7
Ser/Ser19	94	80.3
Ser/Trp19	22	18.8
Trp/Trp19	1	0.9
Val/Val153	113	96.6
Val/Met153	4	3.4
Met/Met153	0	0

Population frequency and effects of the APOAV genotypes

Genotype distributions (the frequencies of the genotypes are in Hardy–Weinberg equilibrium) of the *APOA5* gene are summarized in Table 1. There is a slightly higher frequency of the less common alleles C-1131 and Trp19 in this cohort than in the other Caucasian population samples described before [9,11,12]. The *APOA5* genotype distribution and lipid measures of the sample, taken at the two time points (1988 and 1996), are summarized according to genotypes in Table 2.

Variations in the *APOA5* gene were not associated with statistically significant effects on the plasma traits if examined individually in 1988 or 1996. However, the change in total and LDL cholesterol over the 8 year period was considerably influenced by the *APOA5* Ser19 > Trp polymorphism ($P = 0.003$ and $P = 0.09$ by ANOVA). While individuals homozygous for the Ser19 allele lowered total cholesterol levels in response to dietary change only by 8% (Δ − 0.54 ± 1.04 mmol/L), a marked lowering in total cholesterol was observed in Trp19 carriers (Δ − 1.31 ± 1.37 mmol/L) (Table 2).

LDL cholesterol levels showed the same trend with Trp19 carriers having the larger difference in LDL cholesterol levels over time but the differences did not reach statistical significance (3.71 ± 1.01 mmol/L vs. 2.93 ± 0.59 mmol/L and 3.78 ± 1.12 mmol/L vs. 3.39 ± 0.91 mmol/L).

The other *APOA5* variants did not influence the changes in plasma lipid parameters significantly.

Discussion

Evidence that has accumulated in recent years gives further support to the theory of gene–nutrition interactions of the plasma lipid response to dietary changes. It is known that those responses to diet intervention (as well as for example response