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Letters to the Editor

No significant association between A-501C single nucleotide polymorphism in preproghrelin and body mass index or waist-to-hip ratio in central European population

To the Editor:

We read with interest the study by Vartiainen et al [1] that appears in one of the last issues of *Metabolism*. They described detailed analysis of the preproghrelin gene 5′ flanking region (promoter and possible regulatory elements) and detected altogether 11 single nucleotide polymorphisms (SNPs). One of the detected SNPs, namely, A-501C variant (rs26802), was associated with body mass index (BMI) in individuals with high and low plasma ghrelin concentrations (n = 50 in each group) and in individuals from the OPERA (epidemiologic case-control study addressing the risk factors and disease end points of atherosclerosis) study (N = 1045).

Preproghrelin gene codes for 2 short hormones, ghrelin and obestatine. Ghrelin is a short 28–amino-acid peptide, and its role in the long-term regulation of body weight has been suggested [2]. The associations between the preproghrelin SNPs (Arg51Gln, Leu72Met, and Gln90Leu) and BMI were found in some, but not in all, cohorts [3-6]. Recently, 2 authors independently described the association between the plasma levels of high-density lipoprotein cholesterol and Leu72>Met variant [6,7].

To confirm the association found by Vartiainen et al [1], we have analyzed the association between BMI, waist-to-hip ratio (WHR), and plasma lipid levels in a total of 1143 unrelated white men (age, 49.2 ± 10.8 years) and 1323 women (age, 48.8 ± 10.6 years) recruited as a representative 1% population sample in 9 Czech districts (post-MONICA study [8]). Furthermore, 94 unrelated, overweight, nondiabetic Czech women (mean age, 30.7 ± 3.7 years; BMI, >27.5 kg/m^2 [mean, 31.4 ± 3.7 kg/m^2]) were genotyped. These women underwent 9 weeks of lifestyle modification program consisting of a reduction of energetic intake to desirable values and exercise program (aerobic exercise 4 times a week, 60 minutes each) [9]. The achieved mean weight loss was 5.9 ± 2.5 kg (7% ± 3%), and biochemical and anthropometrical measurements were performed before and after intervention. The A-501C variant was genotyped by polymerase chain reaction–restriction fragment length polymorphism as described in detail elsewhere [1]. Analysis of variance was used for the statistical analysis.

The frequencies of individual genotypes in the population were in Hardy-Weinberg equilibrium and did not differ from the previously analyzed Finish population. The frequencies of the individual alleles were 66.4% for the A and 33.6% for the C in the whole population.

There were no significant associations between rs26802 genotypes and BMI or WHR regardless if the analysis was performed on unadjusted or adjusted variables (adjustment for age) under either the dominant (carriers of the A allele vs CC homozygotes), codominant (AA vs AC vs CC), or recessive model (carriers of the C allele vs AA homozygotes). Furthermore, we did not detect an effect of the preproghrelin A-501C variant on plasma lipids (total, low-density lipoprotein, and high-density lipoprotein cholesterol; triglycerides) or C-reactive protein.

No associations were observed in the whole population (Table 1) as well as if the men and women have been analyzed separately, despite the fact that a slight trend, similar to the results described originally [1], was observed.

In the interventional part of our study, of the women with BMI >27.5 kg/m^2, there were 42 homozygotes for the A allele, 41 heterozygotes (AC), and 11 homozygotes for the C allele. This genotype distribution of the preproghrelin genotype corresponds to the general population. Their average weight loss was not significantly associated with preproghrelin genotypes (data not shown).

Table 1
Preproghrelin gene A-501C variant and BMI and WHR in the Czech POST-MONICA study

	Men				Women			
	n	%	BMI	WHR	n	%	BMI	WHR
AA	508	44.4	28.16 (4.04)	0.931 (0.071)	569	43.0	27.70 (5.64)	0.811 (0.074)
AC	519	45.4	28.33 (3.97)	0.932 (0.070)	587	44.4	27.60 (5.38)	0.809 (0.076)
CC	116	10.2	27.73 (3.98)	0.922 (0.076)	167	12.6	27.23 (5.66)	0.802 (0.065)

Values are given as mean (SD). All differences not significant.

In contrast to the original finding on the Finish population, we did not confirm the association between rs26802 preproghrelin SNP and BMI or WHR. Furthermore, we did not show any association between this variant and plasma levels of cholesterol and triglycerides either in men or in women. Finally, lifestyle changes leading to body weight loss in women did not suggest any differences in the responsiveness according to preproghrelin rs26802 genotypes.

In summary, we conclude that the rs26802 SNP in the preproghrelin gene is no major genetic determinant of BMI values.

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References

[1] Vartiainen J, Kesäniemi YA, Ukkola O. Sequencing analysis of ghrelin gene 5′ flanking region: relations between the sequence variants, fasting plasma total ghrelin concentrations, and body mass index. Metabolism 2006;55:1420-5.
[2] Ukkola O, Pöykkö S. Ghrelin, growth and obesity. Ann Med 2002;34: 102-8.
[3] Ukkola O, Ravussin E, Jacobson P, et al. Mutations in the preproghrelin/ghrelin gene associated with obesity in humans. J Clin Endocrinol Metab 2001;86:3996-9.
[4] Ukkola O, Ravussin E, Jacobson P, et al. Role of ghrelin polymorphisms in obesity based on three different studies. Obes Res 2002;10:782-91.
[5] Hinney A, Hoch A, Geller F, et al. Ghrelin gene: identification of missense variants and a frameshift mutation in extremely obese children and adolescents and healthy normal weight students. J Clin Endocrinol Metab 2002;87:2716-9.
[6] Hubacek JA, Bohuslavova R, Skodova Z, Adamkova V. Variants within the ghrelin gene—association with HDL-cholesterol, but not with body mass index. Folia Biol (Prague) 2007;53:202-6.
[7] Choi HJ, Cho YM, Moon MK, et al. Polymorphisms in the ghrelin gene are associated with serum high-density lipoprotein cholesterol level and not with type 2 diabetes mellitus in Koreans. J Clin Endocrinol Metab 2006;91:4657-63.
[8] Böthing S. WHO MONICA Project: objectives and design. Int J Epidemiol 1989;18(Suppl 1):S29-S37.
[9] Dvorakova-Lorenzova A, Suchanek P, Havel P, et al. The decrease in C-reactive protein concentration after diet and physical activity induced weight reduction is associated with changes in plasma lipids, but not interleukin-6 or adiponectin. Metabolism 2006;55:359-65.

Reply

To the Editor:

We were pleased to read that one of the single nucleotide polymorphisms (SNPs) that we described in the 5′ flanking area of ghrelin gene had inspired other scientists on the wide field of obesity research. Dr Hubacek and his coworkers had studied frequencies of this variant, −501A>C, in a middle-aged Czech district population consisting of 1143 men and 1322 women. In addition to this, it was studied in 94 overweight Czech women who underwent a weight loss program. Association of the SNP with obesity-related parameters body mass index (BMI), waist-to-hip ratio (WHR), and plasma lipids was studied. Although the allelic frequencies were quite similar to those observed in our population, only nonsignificant association trends were found between this SNP with BMI and WHR. This result differs from our preliminary finding in the OPERA study that showed clearly that this SNP was associated with BMI [1]. The author concludes his recent study with a rather strong statement that SNP −501A>C is not a major genetic determinant of BMI values.

We want here to point out that the study populations in Dr Hubacek's studies compared with ours can be assumed to share quite different gene pools. Finnish population is famous for its characteristic of being a genetic isolate. The signs of founder effect, genetic drift, and isolation have been well documented. Studies on Finns have revealed some rare genetic diseases, and it has been suggested that research on genetic isolates might be of the greatest importance also for genetic studies of polygenic and complex traits [2]. Czech population can be assumed to share more diversity in its gene pool compared with Finns; and therefore, it is not surprising that the association between the SNP and BMI in Dr Hubacek's studies was seen only as a trend. We believe that the slight discrepancy between this study and our results from the OPERA study is mainly explained by the different gene pools of the populations.