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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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.

We recognize that, although the association of this SNP with BMI seemed clear in our OPERA study, this SNP showed only an association trend with WHR; and it did not associate at all with other obesity-related parameters such as plasma leptin and adiponectin levels in our study. Therefore, the association of this SNP with obesity cannot be assumed to be very strong. Of course, a false-positive result is always a possible explanation for the confusing results in genetic association studies. Another potential explanation for the different findings in OPERA compared with the current study may be that SNP −501A>C might be in linkage disequilibrium with a certain unidentified genetic factor or with a susceptibility locus that has impact on BMI and other obesity-related parameters. There is also a possibility that ghrelin promoter variant-environment interaction might exist. However, these possibilities are highly speculative; and to elucidate this, these possibilities should be further studied, for example, in linkage analysis or in studies of sib-pairs or twins.

We want here to remind that obesity is a complex trait with several environmental, genetic, and epigenetic factors —and yet to mention, their interactions—playing a role in its etiology. It is likely that genetic factors that affect obesity result from the additive effects of a combination of mutations in several genes at different loci rather than dominant or recessive effects of few genes or mutations. The role of one particular gene, such as gene coding for ghrelin, in the determination of BMI is likely to be very small.

More generally, the current study highlights many of the important problems in association studies of genetic variants and complex diseases. It is known that population-specific differences in reported associations exist. The Finnish population is isolated and genetically homogenous, offering many advantages for genetic studies [3]. We therefore conclude that more studies on this and other variants of ghrelin gene need to be performed in different populations to get a deeper understanding on the relationship of ghrelin gene and its variants to obesity.

Sincerely,

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