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Comment on "A Common Genetic Variant Is Associated with Adult and Childhood Obesity"

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Herbert *et al.* (Reports, 14 April 2006, p. 279) found that the rs7566605 genetic variant, located upstream of the *INSIG2* gene, was consistently associated with increased body mass index. However, we found no evidence of association between rs7566605 and body mass index in two large ethnically homogeneous population-based cohorts. On the contrary, an opposite tendency was observed.

Herbert *et al.* (1) tested 86,604 single-nucleotide polymorphisms (SNPs) for an association with obesity in 694 individuals of the National Heart, Lung, and Blood Institute–Framingham Heart Study. They found that minor-allele homozygotes (CC) of the rs7566605 variant, located 10 kb upstream of *INSIG2*, had an increased risk of obesity ($P = 0.0026$). This finding was replicated in four separate samples of different ethnicity. However, we found no evidence of association between this variant and obesity risk in two large ethnically homogeneous population-based cohorts ($n = 6599$) aged 35 to 79 years.

We genotyped the rs7566605 variant in 4916 individuals (BMI $26.0 \text{ kg/m}^2 \pm 3.7$, 12% obese) of the European Prospective Investigation of Cancer (EPIC) Norfolk study (EPIC5000) (2)

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and in 1683 individuals (BMI $27.2 \text{ kg/m}^2 \pm 4.8$, 22% obese) of the Medical Research Council (MRC) Ely study (3). All individuals were of Caucasian origin and unrelated. The association between BMI and the rs7566605 SNP genotype was tested using generalized linear models adjusted for age and sex. We first tested for association under an additive model, which assumes an additive effect for each additional minor allele. In post hoc analyses, we applied (i) the recessive model, which compares the CC homozygotes with G-allele carriers and (ii) the dominant model, which compares GG homozygotes with C-allele carriers. Analyses were performed for each cohort separately, as well as for the combined cohort (P value for heterogeneity between cohorts = 0.42). In the combined analyses, we adjusted for cohort in addition to BMI and sex and tested for genotype-by-cohort interaction. Sex-specific effects were tested by including a genotype-by-sex interaction term in the models.

The minor-allele frequency (C allele) is 32% in both cohorts. Genotype frequencies are in Hardy-Weinberg equilibrium ($P > 0.25$) and

similar to those reported for Caucasians in Herbert *et al.* (1). In contrast to Herbert *et al.*, however, we found a tendency ($P = 0.06$) for the C allele of the rs7566605 variant to be associated with a lower BMI in the EPIC5000 cohort (Table 1). The association was significant ($P = 0.02$) under the dominant model [GG: $26.1 \text{ kg/m}^2 \pm 0.08$ (mean \pm SEM); C-allele carriers: $25.8 \text{ kg/m}^2 \pm 0.07$]. No significant association ($P = 0.61$) was observed in the MRC Ely cohort (Table 2) or when both cohorts were combined (GG: $26.7 \text{ kg/m}^2 \pm 0.08$; CG: $26.5 \text{ kg/m}^2 \pm 0.08$; CC: $26.5 \text{ kg/m}^2 \pm 0.15$; $P = 0.09$). Also under a recessive model, as reported by Herbert *et al.* (1), no significant associations were observed (EPIC5000 $P = 0.87$, MRC Ely $P = 0.48$, combined $P = 0.57$). Furthermore, there was no evidence of sex-specific effects (genotype-by-sex interaction: EPIC5000 $P = 0.30$, MRC Ely $P = 0.28$, combined $P = 0.14$) or cohort-specific effects (additive model $P = 0.69$). Each cohort had sufficient power (>90%) to detect the genetic effects reported by Herbert *et al.* (1) under a recessive model and at a significance of 1%.

Despite replicated findings reported by Herbert *et al.* (1), we found no evidence of an increased obesity risk in minor-allele homozygotes in two large cohorts of Caucasian origin. On the contrary, we found a tendency toward a lower BMI in carriers of minor alleles, although the effect was small. We conclude that the rs7566605 variant is most likely not a major player in the genetic causes of obesity, at least not in Caucasian populations.

References

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Table 1. Association between BMI and rs7566605 genotype and prevalence by BMI category in women, men, and all individuals of the EPIC5000 cohort.

	<i>n</i>	Mean	SD	SE	<i>P</i> value	Proportion of individuals with:					
						BMI < 18.5;	18.5 ≤ BMI < 25;	25 ≤ BMI < 30;	30 ≤ BMI < 35;	35 ≤ BMI < 40;	BMI ≥ 40
<i>Females</i>											
CC	267	25.6	3.8	0.23	0.06	0.02;	0.49;	0.36;	0.12;	0.01;	0.00
GC	1189	25.5	4.0	0.12		0.01;	0.51;	0.35;	0.10;	0.02;	0.01
GG	1283	25.9	4.1	0.11		0.01;	0.47;	0.39;	0.11;	0.02;	0.01
<i>Males</i>											
CC	226	26.3	3.1	0.20	0.60	0.00;	0.34;	0.54;	0.10;	0.01;	0.00
GC	968	26.2	3.0	0.10		0.00;	0.34;	0.56;	0.09;	0.01;	0.00
GG	978	26.4	3.2	0.10		0.00;	0.35;	0.53;	0.10;	0.01;	0.00
<i>All</i>											
CC	493	25.9	3.5	0.16	0.06	0.01;	0.42;	0.44;	0.11;	0.01;	0.00
GC	2157	25.8	3.6	0.08		0.01;	0.43;	0.45;	0.10;	0.02;	0.00
GG	2261	26.1	3.7	0.08		0.00;	0.42;	0.45;	0.11;	0.02;	0.01

Table 2. Association between BMI and rs7566605 genotype and prevalence by BMI category in women, men, and all individuals of the MRC Ely study.

	<i>n</i>	Mean	SD	SE	<i>P</i> value	Proportion of individuals with: BMI < 18.5; 18.5 ≤ BMI < 25; 25 ≤ BMI < 30; 30 ≤ BMI < 35; 35 ≤ BMI < 40; BMI ≥ 40
<i>Females</i>						
CC	103	26.6	5.1	0.50	0.32	0.02; 0.39; 0.44; 0.09; 0.03; 0.04
GC	404	27.2	5.6	0.28		0.01; 0.37; 0.38; 0.15; 0.05 ;0.03
GG	404	27.3	5.2	0.26		0.01; 0.40; 0.35; 0.16; 0.07; 0.02
<i>Males</i>						
CC	77	27.6	4.1	0.47	0.60	0.00; 0.21; 0.58; 0.17; 0.03; 0.01
GC	306	27.3	3.6	0.20		0.00; 0.27; 0.52; 0.19; 0.02; 0.00
GG	389	27.3	4.2	0.21		0.01; 0.31; 0.47; 0.16; 0.04; 0.02
<i>All</i>						
CC	180	27.0	4.7	0.35	0.61	0.01; 0.31; 0.50; 0.12; 0.03; 0.03
GC	710	27.3	4.8	0.18		0.01; 0.33; 0.44; 0.16; 0.04; 0.02
GG	793	27.3	4.8	0.17		0.01; 0.35; 0.41; 0.16; 0.06; 0.02