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

Dieter Roskopf,1* Alexa Bornhorst,1 Christian Rimmbach,1 Christian Schwahn,2 Alexander Kayser,1 Anne Krüger,1 Grietje Tessmann,1 Ingrid Geissler,1 Heyo K. Kroemer,1 Henry Völkle2

Contrary to the findings of Herbert et al. (Reports, 14 April 2006, p. 279), homozygous carriers of the C allele of the rs7566605 variant near the INSIG2 gene did not exhibit a significantly increased risk for obesity in a large population-based cross-sectional German study. A subgroup analysis, however, revealed that this allele significantly increased the risk for obesity in already overweight individuals.

Obesity is a leading health problem in many countries and results from a complex and dynamic interaction of social, environmental, and genetic factors. Herbert et al. (J) recently reported the association of the C allele in the rs7566605 polymorphism located near the INSIG2 gene with obesity in four different human samples. In a fifth sample, however, a large cohort of the Nurses Health Study (NHS), no such association was detectable (J).

Therefore, we examined this association in the Study of Health in Pomerania (SHIP), a cross-sectional population-based health survey from the northeastern area of Germany comprising 4310 unrelated German individuals, collected in 12 five-year age strata from 20 to 79 years (2–4).

SHIP was designed to address general health and community medicine issues, with obesity as a main focus. In SHIP, 66.1% of all participants were overweight [body mass index (BMI) ≥25 kg/m²] and 25.4% were obese (BMI ≥30 kg/m²).

Genotyping of the rs7566605 polymorphism was successful in 4089 of 4304 individuals (in six subjects, data sets were incomplete). Excluded individuals and the entire study sample did not differ with respect to age, gender, and BMI. Genotype frequencies (45.5% GG, 44.4% GC, 10.1% CC) were compatible with a Hardy-Weinberg equilibrium (P = 0.6769) and similar to the Caucasian samples reported in (J).

Logistic regression analyses (dependent variable, obesity) and linear models (dependent variable, BMI) were performed on adjustments for age and gender. Table 1 details BMI stratified by genotype, gender, and the genotype distribution in predefined SHIP strata.

Mean adjusted BMI for the whole sample amounted to 27.38 ± 0.22 kg/m² (means ± SE; linear model), 27.16 ± 0.11 kg/m², and 27.18 ± 0.10 kg/m² for CC, GC, and GG genotypes, respectively, and rs7566605 genotypes were not associated with BMI [P = 0.6531; 2 degrees of freedom (df)]. Odds ratios (ORs) for obesity were 1.13 (95% CI 0.97 to 1.31) and 1.20 (95% CI 0.94 to 1.54) for carriers of the GC and GG genotypes compared with GG genotypes, and thus were not significantly different (P = 0.1782, 2 df, logistic regression). This observation for obesity did not change in a recessive model (CC versus GC + GG), as pursued by Herbert et al. (J), with OR of 1.13 (95% CI 0.90 to 1.43; P = 0.2916). Likewise, the age- and gender-adjusted mean BMI of CC carriers did not differ significantly (difference from GC + GG carriers, 0.21 ± 0.23 kg/m²; mean ± SE; P = 0.3593). Taken together, our data indicate that the rs7566605 variant is not associated with the overall risk for obesity in SHIP.

The current scenario suggests that the rs7566605 variant affects the function of the INSIG2 protein in a hitherto unknown manner (I). INSIG2 controls the synthesis of fatty acids and is itself regulated by insulin (3, 6). Therefore, we hypothesized that conditions of increased insulin stimulation, for example in already overweight subjects, are especially suited to unmask disorders in the INSIG2 system.

Based on this assumption, we performed a subgroup analysis among the 2701 overweight individuals in SHIP. Adjusted mean BMI amounted to 29.53 ± 0.11 kg/m² (means ± SE, linear model), 29.72 ± 0.11 kg/m², and 30.35 ± 0.24 kg/m² for GG, GC, and CC genotypes, respectively, and were significantly different between homozygous carriers (P = 0.0068, 2 df).

In a recessive model, mean BMI of CC homozygotes was 0.73 ± 0.25 kg/m² higher than for GC and GG genotypes combined (P = 0.0034). ORs for overweight subjects to be obese were 1.21 (95% CI: 1.02 to 1.43; P = 0.0253; logistic regression) and 1.45 (95% CI: 1.10 to 1.91; P = 0.0081) for GC and CC versus GG genotypes. In a recessive model (CC versus GC + GG combined), the respective OR was 1.32 (95% CI: 1.02 to 1.72; P = 0.0378). Adjustment for further environmental factors, including school education, occupation, marital status, nutrition, physical activity, and smoking status, changed these results only marginally.

Taken together, our data do not support a statistically significant association of the rs7566605 polymorphism with obesity for the entire SHIP sample. However, based on a large number of individuals, our findings suggest that the rs7566605 C allele is associated with an increased risk for obesity in a subgroup analysis of already overweight subjects, a notion that requires verification in independent samples (7).

A disease-modifying action of the rs7566605 polymorphism, as postulated here, is compatible with current evidence suggesting that INSIG2 is a regulator of insulin-mediated fatty acid synthesis and their subsequent storage (5, 6). Our findings of a predominant effect of the rs7566605 variant in already overweight subjects may explain the lack of replication in the NHS (I) given their lower mean BMI and the lower frequency of obese individuals.

Table 1. BMI values and distribution of the SHIP sample stratified by gender and rs7566605 genotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>Proportion of individuals with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &lt; 18.5; 18.5 ≤ BMI &lt; 25; 25 ≤ BMI &lt; 30; 30 ≤ BMI &lt; 35; 35 ≤ BMI &lt; 40; BMI ≥ 40</td>
<td>Females</td>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>26.9</td>
<td>5.6</td>
<td>0.38</td>
<td>0.03; 0.44; 0.26; 0.19; 0.06; 0.03</td>
</tr>
<tr>
<td>GC</td>
<td>27.1</td>
<td>5.3</td>
<td>0.18</td>
<td>0.02; 0.40; 0.34; 0.16; 0.06; 0.02</td>
</tr>
<tr>
<td>GG</td>
<td>26.8</td>
<td>5.3</td>
<td>0.17</td>
<td>0.02; 0.40; 0.34; 0.16; 0.06; 0.02</td>
</tr>
<tr>
<td>CC</td>
<td>28.0</td>
<td>4.5</td>
<td>0.32</td>
<td>0.01; 0.23; 0.53; 0.20; 0.03; 0.01</td>
</tr>
<tr>
<td>GC</td>
<td>27.5</td>
<td>4.1</td>
<td>0.14</td>
<td>0.01; 0.23; 0.53; 0.20; 0.03; 0.01</td>
</tr>
<tr>
<td>GG</td>
<td>27.8</td>
<td>4.0</td>
<td>0.13</td>
<td>0.01; 0.23; 0.53; 0.20; 0.03; 0.01</td>
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</table>

*To whom correspondence should be addressed. E-mail: dieter.rosskopf@uni-greifswald.de

References

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