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Response to Comments on “A Common Genetic Variant Is Associated with Adult and Childhood Obesity”

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Identification of genetic variants affecting complex traits such as obesity is confounded by many types of bias, especially when effect sizes are small. Given our findings of a positive association between rs7566605 and body mass index in four out of five separate samples, a false positive finding cannot be ruled out with certainty but seems unlikely. Meta-analyses of multiple large studies will help refine the estimate of the effects of rs7566605 on body mass index.

We previously reported that rs7566605, a common genetic variant near the *INSIG2* gene, was associated with obesity in four separate study populations (1). The results presented by Loos *et al.* (2) from the British European Prospective Investigation of Cancer (EPIC) Norfolk study and by Dina *et al.* (3) from the French Données Épidémiologiques sur le Syndrome d'Insulino-Résistance (DESIR) study represent nonreplications of this finding, as did the results from the Nurses Health Study (NHS) in our original report. The analysis of German participants from the SHIP study by

Roskopf *et al.* (4) does not report a positive association in the entire sample and thus cannot be considered a replication. In this analysis, the authors report that within the subgroup of overweight and obese participants (≥ 25 kg/m²), obese individuals (≥ 30 kg/m²) have a higher frequency of the CC risk genotype than do overweight individuals. Interestingly, the KORA study from our original report (1) showed a similar trend: The effect of the CC risk genotype on body mass index (BMI) was stronger within the obese portion of the sample than in the lean individuals. As we noted, excluding the upper quartile from the analyses in the KORA data set to more closely mimic the NHS data set eliminated the association with rs7566605 (CC genotype mean BMI = 25.24 ± 2.99 , $n = 312$; in contrast with the GG genotype, $P = 0.67$). However, a subgroup analysis within NHS based on participants with BMI ≥ 25 kg/m² as suggested by Roskopf *et al.* did not demonstrate an increased risk of obesity (BMI ≥ 30 kg/m²) for individuals with the CC genotype.

Why is the association between rs7566605 and BMI seen in some but not all cohorts? Given the positive association findings in four out of five samples from our initial study, a false positive finding cannot be ruled out with certainty but has become increasingly unlikely. One contribution to the difference in outcomes reported here may arise from study design. For example, the minimum age of the EPIC-Norfolk population at the time of DNA collection was 58 years (5), suggesting that an older population was studied in this report, whereas the Medical Research Council (MRC) Ely study appears to use a retrospective collection of data because only 1122 individuals were studied prospectively (6), and the DESIR participants were not randomly ascertained (7).

Other legitimate reasons may explain the inconsistency in replication. Heterogeneity of effect

size may be contributing, because of unknown gene-gene interactions, gene-environment interactions, or an association that is largely limited to particular phenotypic subgroups. Heterogeneity is often invoked to explain a lack of replication, but such arguments only merit careful consideration if the likely source of heterogeneity can be identified or if very strong evidence in favor of association is balanced by careful and well-powered studies that fail to replicate. For this particular association, the preponderance of positive replications in (1) suggests that heterogeneity of effect might be a plausible hypothesis in the remaining studies for the lack of association. The finding that, in several cohorts, the association was strongest in the most obese individuals within those cohorts may provide a clue as to the nature of the heterogeneity. However, such a subgroup-specific effect remains a hypothesis at present, and careful studies of this variant in very well-characterized populations will likely be required to identify any phenotypic subclasses, genetic modifiers, or environmental factors that could influence the strength of the association between rs7566605 and BMI.

Finally, if the actual genetic effect were smaller than estimated in Herbert *et al.*, then subsequent studies would have lower power to replicate the association (8, 9). Modest effects might be even more difficult to detect if subtle population stratification were present in the negative studies (for example, if lean individuals were drawn from a population with a higher underlying frequency of the CC genotype than the population from which obese individuals were ascertained). Overestimation of genetic effect size may be a more general problem and has been described as the “winner’s curse” (8, 9). In any genome-wide association study, the distribution of effect sizes for a trait or disease may often be L-shaped, consistent with the existence of few genetic loci with large effects and numerous loci with small effects (10). Thus, the causal variants for which a study has only modest power will usually outnumber those for which there is excellent power. Some variants with more modest or heterogeneous effects will become prominently represented among the best results from a particular genome-wide screen, but only because the winner’s curse applies to those SNP alleles. Such associations may appear to be difficult to replicate consistently in subsequent studies despite convincing statistical evidence in the initial reports. Validating, refining, or refuting these associations will be important and will likely require larger sample sizes and/or meta-analyses of multiple large studies.

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