The association of a SNP upstream of INSIG2 with body mass index is reproduced in several but not all cohorts.

A SNP upstream of the INSIG2 gene, rs7566605, was recently found to be associated with obesity as measured by body mass index (BMI) by Herbert and colleagues. The association between increased BMI and homozygosity for the minor allele was first observed in data from a genome-wide association scan of 86,604 SNPs in 923 related individuals from the Framingham Heart Study offspring cohort. The association was reproduced in four additional cohorts, but was not seen in a fifth cohort. To further assess the general reproducibility of this association, we genotyped rs7566605 in nine large cohorts from eight populations across multiple ethnicities (total n = 16,969). We tested this variant for association with BMI in each sample under a recessive model using family-based, population-based, and case-control designs. We observed a significant (p<0.05) association in five cohorts but saw no association in three other cohorts. There was variability in the...
strength of association evidence across examination cycles in longitudinal data from unrelated individuals in the Framingham Heart Study Offspring cohort. A combined analysis revealed significant independent validation of this association in both unrelated (p = 0.046) and family-based (p = 0.004) samples. The estimated risk conferred by this allele is small, and could easily be masked by small sample size, population stratification, or other confounders. These validation studies suggest that the original association is less likely to be spurious, but the failure to observe an association in every data set suggests that the effect of SNP rs7566605 on BMI may be heterogeneous across population samples.