007 ADIPOSITY SIGNIFICANTLY MODIFIES GENETIC RISK FOR DYSLIPIDEMIA

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Background The Global Lipids Genetics Consortium identified 95 common loci that explained 12.2% (LDL-C), 12.1% (HDL-C) and 9.6% (triglycerides [TG]) of total variance in plasma lipid traits in the Framingham Heart Study. Since adiposity is associated with plasma levels of TG and HDL-C, we hypothesized that the predictive value of common risk variants for these lipid traits would differ for obese versus lean subjects.

Methods The study population consisted of two independent cohorts of subjects of European de-scent, genotyped on the Affymetrix 6.0 array with 1000G imputation. 1) OBLE: 959 obese/869 lean. 2) CC (healthy elderly subjects recruited as con-trols for a CAD study) 830 obese/1,044 lean. A genetic predisposition score was calculated for each individual as a sum across SNPs of the number of risk alleles at that SNP multiplied by the effect size of the SNP.

Results In the OBLE cohort, a genetic risk score explained a greater percentage of the total TG variance in obese vs lean (beta GRS=0.154 mmol/L (p<2e-16) vs 0.094 mmol/L (p=5.8e-10); adjusted R2=0.090 vs 0.042), a finding that was replicated in the CC cohort for obese vs lean (beta GRS=0.153 mmol/L (p=1.5e-7) vs 0.102 mmol/L (p=4.2e-6); adjusted R2=0.044 vs 0.024). A similar but less significant trend was noted for LDL-C. In addition, the genetic risk score predicted variability in TG better than sex/age for obese subjects. In contrast a genetic risk score for HDL-C was a better predictor of this trait in lean versus obese subjects in both the OBLE and CC cohorts. Genetic risk scores for each lipid trait showed no association with BMI (P>0.2) indicating that the above findings are not due to possible overlap between genetic loci for BMI and lipid traits.

Conclusions Genetic predisposition to elevated plasma triglycerides and LDL-C and low HDL-C is highly sensitive to extremes of BMI.