GENETIC PREDICTORS OF WEIGHT LOSS AND WEIGHT REGAIN AFTER INTENSIVE LIFESTYLE MODIFICATION, METFORMIN TREATMENT, OR STANDARD CARE IN THE DIABETES PREVENTION PROGRAM

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RESEARCH DESIGN AND METHODS—Sixteen obesity-predisposing single nucleotide polymorphisms (SNPs) were tested for association with short-term (baseline to 6 months) and long-term (baseline to 2 years) weight loss and weight regain (6 months to study end).

RESULTS—Irrespective of treatment, the Ala12 allele at PPARG associated with short- and long-term weight loss (β = −0.63 and −0.93 kg/allele; P ≤ 0.005, respectively). Gene–treatment interactions were observed for short-term (LYPLAL1 rs2605100; Psubgroup×SNP = 0.032; GNPDA2 rs10938397, Psubgroup×SNP = 0.016; MTCH2 rs10838738, Psubgroup×SNP = 0.022) and long-term (NEGR1 rs2815752, Psubgroup×SNP = 0.028; FTO rs9939609, Psubgroup×SNP = 0.044) weight loss. Three of 16 SNPs were associated with weight regain (NEGR1 rs2815752, BDNF rs6265, PPARG rs1801282), irrespective of treatment. TMEM18 rs6548238 and KCTD15 rs29941 showed treatment-specific effects (Psubgroup×SNP < 0.05).

CONCLUSIONS—Genetic information may help identify people who require additional support to maintain reduced weight after clinical intervention.

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Genetics of weight regain

(Supplementary Table 3) (2). Genetic risk scores were constructed by summing effect alleles (see Supplementary Data) (7). Models are annotated in Supplementary Data.

Primary end points are 1) short-term WL (baseline to 6 months), 2) long-term WL (baseline to 2 years), and 3) average rate of WR (6 months to study end (range 2–4.5 years). WL analyses included all participants, whereas WR analyses included 1,411 participants who had achieved ≥3% WL at 6 months. Analyses were conducted in the pooled sample adjusting for self-reported ethnicity; sensitivity analyses were repeated in NHW only to rule out population stratification. Unless there was statistical evidence of gene x treatment interactions, data were pooled from the three study arms and models were adjusted for age, sex, ethnicity, treatment, and baseline value for the dependent variable. Where such interactions were observed, treatment-specific genetic effects were estimated. For general linear models assuming additive allele effects (except Pro12Ala, which was coded with Pro12Pro vs. Ala12×), nominal allele effects are reported here when allele effects differ in the three treatment groups. The empty cells correspond to cases for which SNP effects were observed, treatment-specific genetic effects were estimated. Listed P values are not adjusted for multiple comparisons. All P values for the same outcome are adjusted for multiple comparisons, and significant SNP effects are reported (8): for short-term WL, there are three significant SNP*treatment interactions (13 + (3*3) = 22 tests are corrected for); for long-term WL, there are two significant interactions (14 + (3*2) = 20 tests are corrected for); and for WR, there are six significant interactions (10 + (6*3) = 28 tests are adjusted for).

RESULTS—Baseline data are reported in Supplementary Tables 1 and 4. P values for self-reported ethnicity; sensitivity analyses were repeated in NHW only to rule out population stratification. Unless there was statistical evidence of gene x treatment interactions, data were pooled from the three study arms and models were adjusted for age, sex, ethnicity, treatment, and baseline value for the dependent variable. Where such interactions were observed, treatment-specific genetic effects were estimated. For general linear models assuming additive allele effects (except Pro12Ala, which was coded with Pro12Pro vs. Ala12×), nominal allele effects are reported here when allele effects differ in the three treatment groups. The empty cells correspond to cases for which SNP effects were observed, treatment-specific genetic effects were estimated. Listed P values are not adjusted for multiple comparisons. All P values for the same outcome are adjusted for multiple comparisons, and significant SNP effects are reported (8): for short-term WL, there are three significant SNP*treatment interactions (13 + (3*3) = 22 tests are corrected for); for long-term WL, there are two significant interactions (14 + (3*2) = 20 tests are corrected for); and for WR, there are six significant interactions (10 + (6*3) = 28 tests are adjusted for).
in Table 1 are obtained from the regressions; however, only SNPs that remain statistically significant after adjusting for multiple comparisons are reported in this section.

**WL**

Short- and long-term WL were greatest in the lifestyle intervention group, and both lifestyle and metformin groups had significantly greater WL than the placebo (control) group (4,5). Irrespective of treatment, the minor Ala12 allele at PPARγ was associated with short- and long-term WL (Table 1). Statistically significant gene–lifestyle interactions were observed for short-term (LYPLAL1 rs2605100; GPNPDA2 rs10938397; MTCH2 rs10838738) and long-term (NEGR1 rs2815752; FTO rs9939609) WL (Pinteraction < 0.05).

**WR**

The rate of WR (in kilograms per year) from 6 months to study end was greatest in the lifestyle group and least in the placebo group (Supplementary Table 1). Those who lost ≥3% body weight from baseline to 6 months had a mean (SD) WR of 0.94 (±4.68) kg/year. Three of 16 SNPs were associated with WR (NEGR1 rs2815752, BDNF rs6265, PPARγ rs1801282), irrespective of treatment. TMEM18 rs6548238 and KTCD15 rs29941 showed treatment-specific effects. In aggregate, the risk alleles associated with WR associated with faster WR (0.274 kg/year/allele [SE = 0.097]; P = 0.005), whereas these alleles had no detectable impact on WR in the control group (Supplementary Fig. 1). Sensitivity analyses performed in NHW participants, who are essentially free of admixture (9), yielded effect estimates of comparable magnitude, indicating that population stratification does not confound our findings (Supplementary Table 5).

**CONCLUSIONS**

Analyses were also performed assessing putative mediating roles of specific lifestyle factors (details in Supplementary Data). However, none explained a statistically significant amount of variance in the SNP-phenotype relationships.

**Mediator analyses**

Analyses were also performed assessing putative mediating roles of specific lifestyle factors (details in Supplementary Data). However, none explained a statistically significant amount of variance in the SNP-phenotype relationships.

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