# Genetic Predictors of Weight Loss and Weight Regain After Intensive Lifestyle Modification, Metformin Treatment, or Standard Care in the Diabetes Prevention Program

# 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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**OBJECTIVE**—We tested genetic associations with weight loss and weight regain in the Diabetes Prevention Program, a randomized controlled trial of weight loss–inducing interventions (lifestyle and metformin) versus placebo.

**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 (−0.63 and −0.93 kg/allele, $P \leq 0.005$, respectively). Gene–treatment interactions were observed for short-term (*LYPLAL1* rs2605100, $P_{lifestyle*SNP} = 0.032$; *GNPDA2* rs10938397, $P_{lifestyle*SNP} = 0.016$; *MTCH2* rs10838738, $P_{lifestyle*SNP} = 0.022$) and long-term (*NEGR1* rs2815752, $P_{metformin*SNP} = 0.028$; *FTO* rs9939609, $P_{lifestyle*SNP} = 0.044$) weight loss. Three of 16 SNPs were associated with weight regain (*NEGR1* rs2815752, *BDNF* rs6265, *PPARG* rs1801282), irrespective of treatment. *TMEM18* rs6548238 and *KTCD15* rs29941 showed treatment-specific effects ($P_{lifestyle*SNP} < 0.05$).

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

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Multiple obesity-predisposing gene variants are known (1,2), which may interact with lifestyle to modify obesity risk (3). It is unknown whether these variants influence weight regain (WR) after intentional weight loss (WL). We therefore tested associations of 16 obesity-predisposing variants with weight change in Diabetes Prevention Program (DPP) participants.

## RESEARCH DESIGN AND METHODS

The DPP is described elsewhere (4,5). In brief, 3,234 overweight/obese adults with impaired glucose tolerance were randomly assigned to placebo, 850 mg metformin twice daily, or intensive lifestyle modification aimed at ~150 min of physical activity per week and ~7% WL, to compare effects on diabetes incidence. Participants provided written informed consent, and institutional review boards of 27 DPP study centers approved the study.

### Participants

Of 3,597 participants with baseline and 1-year data available, 93.3% consented to genetic analyses. Of these, 56.1% were non-Hispanic white (NHW), 20.4% were African American, 16.7% were Hispanic, 4.4% were Asian American, and 2.5% were American Indian; on average participants were middle-aged and obese (see Supplementary Table 1 for participant characteristics).

### Genotyping

Sixteen obesity-predisposing variants reported elsewhere (1,2) or in the DPP (6) were genotyped as described previously (6); genotyping success rates exceeded 99% (Supplementary Table 2).

### Statistical analysis

Analyses were performed using SAS v9.2 (Cary, NC). Predictor variables were single nucleotide polymorphisms (SNPs), with effect alleles coded consistent with the association of each SNP with BMI or waist circumference in published meta-analyses

(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 two-sided *P* values are reported. 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

**Table 1—*Summary of association data for each of 16 known obesity loci and short-term (6 months) change in weight (kilograms per year), long-term (2 years) change in weight (kilograms per year), and rate of WR from 6 months through trial end (kilograms per year) in the overall DPP cohort and each treatment arm if significant SNP treatment interactions were detected***

| | | | 6-Month WL (kg/allele; *n* = 3,085) | | 2-Year WL (kg/allele; *n* = 3,015) | | WR (kg/year/allele; *n* = 1,411) | |
|---|---|---|---|---|---|---|---|---|
| Nearest gene | SNP | Effect (other) allele | Coefficient (SE) | *P* value | Coefficient (SE) | *P* value | Coefficient (SE) | *P* value |
| *MC4R* | rs17782313 | C(T) | 0.11 (0.14) | 0.433 | −0.10 (0.20) | 0.633 | −0.22 (0.18) | 0.241 |
| *FTO* | rs9939609 | A(T) | −0.12 (0.12) | 0.336 | | | 0.20 (0.16) | 0.207 |
| *MTCH2* | rs10838738 | G(A) | | | 0.02 (0.19) | 0.899 | −0.10 (0.18) | 0.580 |
| *NEGR1* | rs2815752 | A(G) | −0.20 (0.13) | 0.130 | | | −0.35 (0.16) | 0.034 |
| *TMEM18* | rs6548238 | C(T) | 0.11 (0.17) | 0.519 | 0.20 (0.24) | 0.408 | | |
| *SH2B1* | rs7498665 | T(C) | 0.01 (0.13) | 0.928 | −0.01 (0.18) | 0.934 | 0.06 (0.17) | 0.729 |
| *SEC16B* | rs10913469 | C(T) | 0.01 (0.15) | 0.938 | 0.08 (0.21) | 0.710 | 0.20 (0.20) | 0.330 |
| *BDNF* | rs6265 | C(T) | −0.04 (0.17) | 0.828 | 0.35 (0.24) | 0.140 | 0.55 (0.21) | 0.011 |
| *FAIM2* | rs7138803 | A(G) | 0.07 (0.13) | 0.625 | −0.07 (0.19) | 0.692 | 0.12 (0.18) | 0.504 |
| *KTCD15* | rs29941 | G(A) | −0.06 (0.14) | 0.639 | −0.16 (0.19) | 0.404 | | |
| *PPARG* | rs1801282 | Ala(Pro) | −0.63 (0.22) | 0.005 | −0.93 (0.31) | 0.003 | −0.79 (0.27) | 0.004 |
| *LYPLAL1* | rs2605100 | G(A) | | | 0.22 (0.20) | 0.272 | −0.16 (0.18) | 0.399 |
| *ETV5* | rs7647305 | C(T) | 0.05 (0.14) | 0.726 | −0.08 (0.20) | 0.675 | 0.17 (0.18) | 0.360 |
| *GNPDA2* | rs10938397 | G(A) | | | 0.08 (0.18) | 0.668 | 0.09 (0.16) | 0.577 |
| *TFAP2B* | rs987237 | G(A) | −0.05 (0.15) | 0.725 | 0.15 (0.21) | 0.483 | 0.12 (0.20) | 0.530 |
| *MSRA* | rs7826222 | G(C) | −0.05 (0.16) | 0.751 | −0.09 (0.23) | 0.691 | −0.14 (0.21) | 0.508 |
| Treatment-specific SNP effects | | | Lifestyle | | Metformin | | Placebo | |
| 6-Month WL (kg/allele; for lifestyle, *n* = 1,041; for metformin, *n* = 1,024; for placebo, *n* = 1,020) | | | | | | | | |
| *MTCH2* | rs10838738 | G(A) | −0.12 (0.28) | 0.666 | −0.02 (0.21) | 0.932 | 0.37 (0.21) | 0.079 |
| *LYPLAL1* | rs2605100 | G(A) | 0.35 (0.29) | 0.234 | 0.19 (0.22) | 0.389 | −0.11 (0.22) | 0.600 |
| *GNPDA2* | rs10938397 | G(A) | 0.11 (0.26) | 0.676 | 0.12 (0.19) | 0.544 | 0.40 (0.19) | 0.038 |
| 2-Year WL (kg/allele; for lifestyle, *n* = 999; for metformin, *n* = 1,004; for placebo, *n* = 1,012) | | | | | | | | |
| *FTO* | rs9939609 | A(T) | 0.56 (0.36) | 0.124 | −0.41 (0.27) | 0.134 | −0.29 (0.26) | 0.269 |
| *NEGR1* | rs2815752 | A(G) | −0.35 (0.37) | 0.346 | −0.79 (0.29) | 0.006 | 0.19 (0.28) | 0.496 |
| WR rate (kg/year/allele; for lifestyle, *n* = 808; for metformin, *n* = 409; for placebo, *n* = 194) | | | | | | | | |
| *TMEM18* | rs6548238 | C(T) | 0.62 (0.31) | 0.044 | 0.13 (0.40) | 0.745 | −0.78 (0.55) | 0.158 |
| *KTCD15* | rs29941 | G(A) | 0.50 (0.24) | 0.041 | −0.17 (0.31) | 0.592 | −0.36 (0.39) | 0.364 |

Baseline age, sex, and ethnicity are adjusted for in all analyses. Allele effects are in the pooled sample of three treatment groups. The empty cells correspond to cases with significant treatment and allele interactions, and treatment-specific allele effects are estimated. Listed *P* values are not adjusted for multiple comparisons. Treatment-specific allele effects are reported here when allele effects differ in the three treatment groups.

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 *PPARG* was associated with short- and long-term WL (Table 1). Statistically significant gene-lifestyle interactions were observed for short-term (*LYPLAL1* rs2605100; *GNPDA2* rs10938397; *MTCH2* rs10838738) and long-term (*NEGR1* rs2815752; *FTO* rs9939609) WL ($P_{interaction} < 0.05$).

### 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, *PPARG* 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).

### 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.

**CONCLUSIONS**—This is, to our knowledge, the first report of effects of validated obesity-predisposing genotypes on long-term WR after successful intentional WL. We found that three SNPs (*NEGR1* rs2815752, *BDNF* rs6265, *PPARG* rs1801282) predicted WR, irrespective of type of WL therapy, two of which (*BDNF* rs6265, *PPARG* Pro12Ala) were robust to correction for multiple hypothesis testing. Two other variants (*TMEM18* rs6548238, *KTCD15* rs29941) interacted with treatment modality to influence WR. We also replicated several associations reported previously with baseline obesity metrics (Supplementary Table 4).

Our WR findings are perhaps most clinically relevant, since these might help target susceptible individuals and thus improve long-term effects of WL interventions. One of few published genetic association studies on WR found that the minor allele at the Pro12Ala locus associated with greater regain 1 year after a 6-month hypocaloric diet intervention ended, also noting reductions in the rate of fat oxidation in Ala12 allele carriers but not in Pro12 homozygotes (10), findings supporting those reported here. A second small study (11) found a similar association between the Pro12Ala genotype and WR, whereas a third small study (12) reported no effect.

Despite plausible mechanisms by which the genetic effects reported here are expressed, we were unable to detect statistically significant mediators. Although the genetic variants we studied may act independently of the selected mediators, it is also possible some of our findings are false-negative, owing to the relatively small sample and indirect measures. Our study is also limited by the absence of information on lifestyle behaviors after 12 months of intervention, which may have hampered the detection of mediators. Finally, the hyperglycemic nature of the DPP cohort may limit generalizability of our findings.

In summary, our findings offer novel insights into the mechanisms influencing the propensity for WR after intentional WL. This information may help target individuals who require additional support to maintain reduced weight in intervention settings.

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L.M.D. conceived the analysis, designed the analysis plan, interpreted the results, wrote the manuscript, and provided critical input on the manuscript revisions. Q.P. designed the analysis plan, conducted the statistical analyses, interpreted the results, wrote the manuscript, and provided critical input on the manuscript revisions. K.A.J. designed the analysis plan, conducted the statistical analyses, and provided critical input on the manuscript revisions. K.E.W., J.M.M., and A.S. provided critical input on the manuscript revisions. S.E.K. and W.C.K. conducted the clinical trial, provided the phenotypic data, and provided critical input on the manuscript revisions. J.C.F. designed the analysis plan, coordinated the genotyping, and provided critical input on the manuscript revisions. P.W.F. conceived the analysis, designed the analysis plan, interpreted the results, wrote the manuscript, and provided critical input on the manuscript revisions and is the guarantor of this article.

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