



DIGITAL ACCESS TO SCHOLARSHIP AT HARVARD

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

The Harvard community has made this article openly available. [Please share](#) how this access benefits you. Your story matters.

Citation	Delahanty, Linda M., Qing Pan, Kathleen A. Jablonski, Karol E. Watson, Jeanne M. McCaffery, Alan Shuldiner, Steven E. Kahn, William C. Knowler, Jose C. Florez, and Paul W. Franks. 2012. Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the diabetes prevention program. <i>Diabetes Care</i> 35(2): 363-6.
Published Version	doi:10.2337/dc11-1328
Accessed	February 19, 2015 11:57:55 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:11181096
Terms of Use	This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

(Article begins on next page)

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

LINDA M. DELAHANTY, MS, RD^{1,2}
 QING PAN, PHD³
 KATHLEEN A. JABLONSKI, PHD³
 KAROL E. WATSON, MD, PHD⁴
 JEANNE M. McCAFFERY, PHD⁵
 ALAN SHULDINER, MD⁶

STEVEN E. KAHN, MB, CHB⁷
 WILLIAM C. KNOWLER, MD, DRPH⁸
 JOSE C. FLOREZ, MD, PHD^{1,2,9,10}
 PAUL W. FRANKS, PHD, MPHIL, MS^{11,12}
 FOR THE DIABETES PREVENTION PROGRAM
 RESEARCH GROUP*

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, $P_{\text{lifestyle*SNP}} = 0.032$; *GNPDA2* rs10938397, $P_{\text{lifestyle*SNP}} = 0.016$; *MTCH2* rs10838738, $P_{\text{lifestyle*SNP}} = 0.022$) and long-term (*NEGR1* rs2815752, $P_{\text{metformin*SNP}} = 0.028$; *FTO* rs9939609, $P_{\text{lifestyle*SNP}} = 0.044$) weight loss. Three of 16 SNPs were associated with weight regain (*NEGR1* rs2815752, *BDNF* rs6265, *PPARG* rs1801282), irrespective of treatment. *TMEM18* rs6548238 and *KTC15* rs29941 showed treatment-specific effects ($P_{\text{lifestyle*SNP}} < 0.05$).

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

Diabetes Care 35:363–366, 2012

From the ¹Diabetes Research Center, Massachusetts General Hospital, Boston, Massachusetts; the ²Department of Medicine, Harvard Medical School, Boston, Massachusetts; ³The Biostatistics Center, George Washington University, Rockville, Maryland; the ⁴David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California; the ⁵Weight Control and Diabetes Research Center, The Miriam Hospital and Brown Medical School, Providence, Rhode Island; the ⁶Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, and Program in Genetics and Genomic Medicine, University of Maryland School of Medicine, Baltimore, Maryland; the ⁷Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, Washington; the ⁸National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona; the ⁹Center for Human Genetic Research, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; the ¹⁰Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts; the ¹¹Department of Clinical Sciences, Genetic and Molecular Epidemiology Unit, Lund University Diabetes Center, Skåne University Hospital, Malmö, Sweden; and the ¹²Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts. Corresponding author: Paul W. Franks, paul.franks@med.lu.se and dppmail@biostat.bsc.gwu.edu.

Received 25 July 2011 and accepted 23 October 2011.

DOI: 10.2337/dc11-1328. Clinical trial reg. no. NCT0004992, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1328/-DC1>.

*A complete list of centers, investigators, staff, additional methods, results, and list of Diabetes Prevention Program Research Group investigators (Genetics version) can be found in the Supplementary Data online. The opinions expressed are those of the investigators and do not necessarily reflect the views of the Indian Health Service or other funding agencies.

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

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 $\geq 3\%$ 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 \times 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 \times), 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 \times treatment interactions ($13 + (3 \times 3) = 22$ tests are corrected for); for long-term WL, there are two significant interactions ($14 + (3 \times 2) = 20$ tests are corrected for); and for WR, there are six significant interactions ($10 + (6 \times 3) = 28$ 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

Nearest gene	SNP	Effect (other allele)	6-Month WL (kg/allele; n = 3,085)		2-Year WL (kg/allele; n = 3,015)		WR (kg/year/allele; n = 1,411)	
			Coefficient (SE)	<i>P</i> value	Coefficient (SE)	<i>P</i> value	Coefficient (SE)	<i>P</i> 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 ($P_{\text{interaction}} < 0.05$).

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 $\geq 3\%$ 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.

Acknowledgments—This work was funded by R01 DK-072041-02 to J.C.F., K.A.J., and A.S. (P.W.F. and W.C.K. are coinvestigators). P.W.F. was supported by grants from Novo Nordisk, the Swedish Research Council, the Swedish Heart-Lung Foundation, and the Swedish Diabetes Association. S.E.K. is supported in part by the Department of Veterans Affairs. J.C.F. is supported by a Doris Duke Charitable Foundation Clinical Scientist Development Award. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National

Institutes of Health funded the clinical centers and the Coordinating Center for the design and conduct of the study and the collection, management, analysis, and interpretation of the data. The Southwestern American Indian Centers were supported directly by the NIDDK and the Indian Health Service. The General Clinical Research Center Program, National Center for Research Resources, supported data collection at many of the clinical centers. The Office of Research on Minority Health, the National Institute of Child Health and Human Development, the National Institute on Aging, the Centers for Disease Control and Prevention, Office of Research on Women's Health, the Department of Veterans Affairs, and the American Diabetes Association funded data collection and provided participant support. This research was also supported, in part, by the intramural research program of the NIDDK. The Henry M. Jackson Foundation provided support services under subcontract with the Coordinating Center.

LifeScan, Health O Meter, Hoechst Marion Roussel, Merck-Medco Managed Care, Merck and Co., Nike Sports Marketing, Slim Fast Foods Co., and Quaker Oats Co. donated materials, equipment, or medicines for concomitant conditions. Bristol-Myers Squibb and Parke-Davis provided medication. McKesson BioServices Corporation and Matthews Media Group provided support services under subcontract with the Coordinating Center. No other potential conflicts of interest relevant to this article were reported.

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.

The investigators acknowledge the commitment and dedication of all participants in the Diabetes Prevention Program Research Group, without whom this work would not have been possible.

References

1. Lindgren CM, Heid IM, Randall JC, et al.; Wellcome Trust Case Control Consortium; Procardis Consortia; Giant Consortium. Genome-wide association scan

- meta-analysis identifies three Loci influencing adiposity and fat distribution. *PLoS Genet* 2009;5:e1000508
- Willer CJ, Speliotes EK, Loos RJ, et al.; Wellcome Trust Case Control Consortium; Genetic Investigation of ANthropometric Traits Consortium. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* 2009;41:25–34
 - Li S, Zhao JH, Luan J, et al. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. *PLoS Med* 2010;7:e1000332
 - Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
 - Rubin RR, Fujimoto WY, Marrero DG, et al.; DPP Research Group. The Diabetes Prevention Program: recruitment methods and results. *Control Clin Trials* 2002;23:157–171
 - Franks PW, Jablonski KA, Delahanty L, et al.; Diabetes Prevention Program Research Group. The Pro12Ala variant at the peroxisome proliferator-activated receptor gamma gene and change in obesity-related traits in the Diabetes Prevention Program. *Diabetologia* 2007;50:2451–2460
 - Hivert MF, Jablonski KA, Perreault L, et al.; DIAGRAM Consortium; Diabetes Prevention Program Research Group. Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes* 2011;60:1340–1348
 - Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist* 1979;6:65–70
 - Jablonski KA, McAteer JB, de Bakker PI, et al.; Diabetes Prevention Program Research Group. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes* 2010;59:2672–2681
 - Nicklas BJ, van Rossum EF, Berman DM, Ryan AS, Dennis KE, Shuldiner AR. Genetic variation in the peroxisome proliferator-activated receptor- γ 2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain. *Diabetes* 2001;50:2172–2176
 - Goyenechea E, Dolores Parra M, Alfredo Martínez J. Weight regain after slimming induced by an energy-restricted diet depends on interleukin-6 and peroxisome-proliferator-activated-receptor-gamma2 gene polymorphisms. *Br J Nutr* 2006;96:965–972
 - Vogels N, Mariman EC, Bouwman FG, Kester AD, Diepvens K, Westerterp-Plantenga MS. Relation of weight maintenance and dietary restraint to peroxisome proliferator-activated receptor gamma2, glucocorticoid receptor, and ciliary neurotrophic factor polymorphisms. *Am J Clin Nutr* 2005;82:740–746