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FTO predicts weight regain in the Look AHEAD Clinical Trial

Jeanne McCaffery[1], **George D. Papandonatos**[2], **Gordon S. Huggins**[3], **Inga Peter**[4], **Steven E. Kahn**[5], **William C. Knowler**[6], **Gina Evans Hudnall**[7], **Edward Lipkin**[8], **Abbas E. Kitabchi**[9], **Lynne E. Wagenknecht**[10], **Rena R. Wing**[1], and **The Genetic Subgroup of Look AHEAD and The Look AHEAD Research Group**

[1]Weight Control and Diabetes Research Center, Department of Psychiatry and Human Behavior, The Miriam Hospital and Brown Medical School, Providence, RI

[2]Center of Statistical Sciences, Brown University, Providence, R.I.

[3]MCRI Center for Translational Genomics, Molecular Cardiology Research Institute, Tufts Medical Center, Boston, MA

[4]Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, New York, NY

[5]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA

[6]National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ

[7]Baylor College of Medicine & Michael E. DeBakey VA Medical Center, Houston, TX

[8]Division of Endocrinology, Diabetes & Metabolism, University of Tennessee Health Science Center, Memphis, TN

[9]Department of Medicine, Division of Metabolism, Endocrinology and Nutrition, University of Washington, Seattle, WA

[10]Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC

Abstract

Background—Genome-wide association studies have provided new insights into the genetic factors that contribute to the development of obesity. We hypothesized that these genetic markers would also predict magnitude of weight loss and weight regain after initial weight loss.

Methods—Established obesity risk alleles available on the *Illumina CARe iSelect* (IBC) chip were characterized in 3,899 overweight or obese participants with type 2 diabetes from the Look

Corresponding Author: **Jeanne McCaffery, PhD**, Associate Professor, Weight Control and Diabetes Research Center, The Miriam Hospital and Brown Medical School, 196 Richmond Street, Providence, R.I. 02903, Phone: 401 793-8101, Fax: 401 793-8944, jeanne_mccaffery@brown.edu.

Disclosure

The authors have no conflict of interest to declare.

Supplementary information is available at IJO's website' at the end of the article and before the references.

AHEAD (Action for Health in Diabetes), a randomized trial to determine the effects of intensive lifestyle intervention (ILI) and Diabetes Support and Education (DSE) on cardiovascular morbidity and mortality. Primary analyses examined the interaction between 13 obesity-risk polymorphisms in 8 genes and randomized treatment arm in predicting weight change at year 1, and weight regain at year 4 among individuals who lost 3% or more of their baseline weight by year 1.

Results—No SNPs were significantly associated with magnitude of weight loss or interacted with treatment arm at year 1. However, *FTO* rs3751812 predicted weight regain within DSE (1.56 kg per risk allele, p = 0.005), but not ILI (p = 0.761), resulting in SNP×treatment arm interaction (p = 0.009). In a partial replication of prior research, the obesity risk (G) allele at *BDNF* rs6265 was associated with greater weight regain across treatment arms (0.773 kg per risk allele), although results were of borderline statistical significance (p=0.051).

Conclusions—Variations in the *FTO* and *BDNF* loci may contribute risk of weight regain after weight loss.

Keywords

type 2 diabetes; obesity; weight loss, diet, genetics

Introduction

Obesity is a major public health problem associated with increased risk of a number of diseases, including cardiovascular disease (CVD), type 2 diabetes and certain cancers. Behavioral weight loss is the treatment of choice for mild to moderate obesity1 as weight losses of 10% have repeatedly been documented to improve diabetes2 and cardiovascular disease risk factors3,4. At the same time, the long-term maintenance of these losses remains a critical issue in obesity treatment.

Obesity susceptibility loci identified through genome-wide association studies (GWAS) and replicated in multiple independent cohorts have provided new insights into the genetic factors that contribute to the development of obesity. The fat mass and obesity associated gene (*FTO*) was one of the first genes to be identified by this approach and it has emerged as an important gene associated with obesity and body mass in numerous cohorts 5–7. With increasing samples sizes in GWAS studies, the number of confirmed loci continues to increase 5–7.

The treatment implications of these obesity susceptibility loci remain unclear. In particular, it is not known whether obesity-risk genetic markers predict success with weight loss or weight loss maintenance. Previously, in the Diabetes Prevention Program, *FTO* rs9939609 predicted a greater increase in subcutaneous adipose tissue in the placebo group compared to lifestyle intervention at year 1, but no significant genotype×treatment interaction was observed for overall weight loss8. The obesity risk allele at rs6265 in *BDNF* was also associated with greater weight regain at two year follow-up among those who lost 3% or more of their initial weight at six-months9.

The goal of the present study was to define the effects of obesity genetic risk markers available on the *Illumina CARe iSelect* IBC chip10 (within or in the region of *FTO, SH2B1, MC4R, BDNF, TNNI3K, MTIF3, QPCTL/GIPR, and TFAP2B)* on weight loss at 1 year in response to gold standard behavioral weight loss intervention, and weight regain from year 1 to 4 among those who lost 3% or more of their initial weight at year 1. The Look AHEAD trial, a randomized controlled trial designed to determine the effects of intensive lifestyle intervention, including diet and physical activity, on cardiovascular morbidity and mortality among overweight individuals with type 2 diabetes, provides a unique opportunity to conduct such analyses.

Material and Methods

Study cohort

The Look AHEAD study enrolled 5,145 ethnically diverse overweight and obese subjects with type 2 diabetes and aged 45 to 76 years. Of these, 1,038 did not provide genetic consent to be included in a genetic ancillary study, including all participants from three Southwest American Indian sites, 10 withdrew consent for genotyping and 60 were identified to have no or a low concentration of DNA. This left 4,037 individuals, of which 3,899 contributed genetic data on at least one of the 13 markers of interest that passed genotyping quality control procedures. These subjects form the basis for the present analyses. Overall, relative to those who provided genetic consent, those who did not were more frequently African-American, Hispanic, female, more highly educated and not dyslipidemic. Consent rates did not differ by BMI11.

The design and methods of the Look AHEAD trial have been reported elsewhere, as have the baseline characteristics of the randomized cohort12. Briefly, at baseline participants were randomized to either an Intensive Lifestyle Intervention (ILI) or a Diabetes Support and Education (DSE) arm. Both the ILI and DSE groups were provided one session of education on diabetes and cardiovascular risk factors. In addition, ILI patients received an intensive lifestyle program, combining diet modification and increased physical activity, designed to produce an average of 7% weight loss and maintain these weight losses. The ILI included one individual and three group meetings per month for six months, followed by one individual and two group meetings per month through one year. From years 2–4, participants were seen individually at least once a month, contacted another time each month by telephone or email, and offered a variety of ancillary classes. These sessions focused on behavioral weight loss strategies, such as self-monitoring, goal setting and stimulus control, to achieve and maintain weight loss. The DSE group received the option of attending three sessions per year on nutrition, physical activity and social support with no explicit weight loss goals. In the full trial3,4, maximal difference in average weight loss across intervention arm occurred at 1 year follow-up (8.6% in ILI vs. 0.7% in DSE, $p < 0.001$), with an average weight loss of 4.7% in ILI and 1.1% in DSE at year 4 follow-up.

The Look AHEAD trial was approved by local Institutional Review Boards, including genetic analyses.

Anthropometric Measures

Weight was measured in duplicate at baseline and year 1 and 4 follow-ups using a digital scale and height was measured at baseline and year 4 using a standard wall-mounted stadiometer. Weight regain was defined as weight change from year 1 – year 4 among individuals initially losing at least some weight (>=3%) at year 1 following methods used in the Diabetes Prevention Program9. As can be seen in Table 1a, among those who lost 3% or more weight at year 1, women regained 3.7±8.2 and men regained 4.8±7.8 from year 1 – 4 on average. It is important to note, however, that only 72.5% of women and 78.5% of men in this subgroup regained weight, as defined by a weight at year 4 greater than their weight at year 1, while the remaining individuals either maintained or continued to lose weight.

Genotyping

The genomic DNA extraction was based on the use of FlexiGene DNA Kit (Qiagen Inc., Valencia, CA) as described by the manufacturer and DNA quantitation was performed using the PicoGreen dsDNA Quantitation Reagent (Invitrogen, Inc., Carlsbad, CA). Genotyping was carried out at the Children's Hospital of Philadelphia using the *Illumina CARe iSelect* (IBC) chip, a gene-centric 50,000 single nucleotide polymorphism (SNP) array designed to assess relevant loci across a range of cardiovascular, metabolic and inflammatory syndromes 10. Taqman Applied Biosystems (ABI) Assays-On-Demand were used to genotype the *MC4R* polymorphism rs17782313 (ABI catalogue number C_32667060_10)) using an Applied Biosystems 7900HT.

Gene and SNP Selection

We performed a search of published literature and selected SNPs that had been associated with obesity by GWAS 5–7,13–19 and appeared on the IBC chip 10 or, in the case of *MC4R* rs17782313, had been genotyped by Taqman. References for the selection of each SNP are provided in Table 2. As multiple markers have showed the strongest association with obesity in the *FTO* region6,13,16,18 and two distinct loci have been identified in the *BDNF* region6, we retained multiple SNPs in each of these regions. *FTO* rs1421085, rs3751812 and rs9939609, *BDNF* rs6265 and rs10767664 and *TFAP2B* rs2272903 were assayed directly on the IBC chip. GWAS obesity SNPs not on the IBC chip were replaced by proxies where possible using the SNP Annotation and Proxy Search tool (SNAP) 20 based on haplotype maps of individuals of European ancestry (CEU) and Yoruba people of Ibadan (YRI) as follows: *FTO* rs9930506 was replaced by rs9922708 (distance 681 bp r2=1.00, D'=1.00 in both CEU and YRI); *BDNF* rs925946 was replaced by rs1401635 (distance 26,789 bp r2=0.96, D'=1.00 in CEU; no proxy was available in YRI), *SH2B1* rs7498665 was replaced by rs4788099 (distance 27,514 bp r2=1.00, D'=1.00 in CEU and D'=1.00 and r2=0.94 in YRI), *TNNI3K* rs1514175 was replaced by rs1514176 (distance 48 bp, r2=1.00, D'=1.00 in CEU and r2=1.00, D'=1.00 in YRI), *MTIF3* rs4771122 was replaced by rs7988412 (distance 19898, r2=0.83, D'=1.00 in CEU; no proxy was available in YRI), and *QPCTL/GIPR* rs2287019 was replaced by rs11672660 (distance 21988 bp, r2=0.83, D'=1.00 in CEU, r2=0.89, D'=1.00 in YRI).

The four *FTO* SNPs selected for inclusion were in strong linkage disequilibrium in non-Hispanic Whites (r^2=0.78–0.97), but differed in the degree of disequilibrium among

African-Americans (rs3751812, rs1421085: r2=0.98; rs3751812, rs9922708: r2=0.70; rs1421085, rs9922708: r2=0.67; rs9939609 with other SNPs: r2<0.36). In contrast, two *BDNF* SNPs, rs6265 and rs10767664, were in strong linkage disequilibrium in both non-Hispanic Whites (r2=0.88) and African-Americans (r2=0.81).

Observed genotype frequencies were compared with those expected under Hardy Weinberg Equilibrium (HWE) using stratified X^2 tests within the two largest racial/ethnic groups (non-Hispanic White and African-American). All SNPs under study conformed to HWE ($p > 0.001$).

Statistical Analysis

To control for admixed study population, all IBC SNPs were examined by principal component analysis (PCA) using the EIGENSTRAT algorithm 21 as implemented in Golden Helix version 7.1 (Bozeman, Montana, USA). PCA results indicated that the majority of the variance among the Look AHEAD cohort was accounted for by the first two principal components, which agreed with self-reported ethnicity (Supplemental Figure 1). Accordingly, the first two principal components were included as covariates in our analyses to adjust for population stratification in the multi-ethnic Look AHEAD cohort.

As the primary adiposity outcome in the Look AHEAD clinical trial is weight (not body mass index), we focus on baseline weight (in kg) and change in weight (in kg) as primary outcomes. Longitudinal linear mixed models were used to model the effect of SNP on weight change by treatment arm over time. As baseline weight as well as treatment response can be associated with the SNPs, baseline was modeled as the first time point in longitudinal analyses as recommended by McArdle & Whitcomb, 200922. Within this model, differential SNP effects on year 1 weight change or by treatment arm are detected through SNP (0,1 or 2 copies of the minor allele) × time (baseline, year 1) × treatment arm (ILI, DSE) interaction. An additive genetic model was used for all markers, with genotype coded by the number of minor alleles. Therefore, all our SNP effects can be interpreted as the effect on the outcome of interest of one additional copy of the corresponding minor allele. Models were estimated in Splus 8.2 23 using restricted maximum likelihood. Longitudinal outcomes were additionally adjusted for age, gender, study site, and the first two ancestry informative marker principal components.

Next, we examined the extent to which the genetic markers predicted weight regain at year 4. As weight regain implies initial weight loss, we limited analyses to those who lost 3% or more of their initial weight at year 1, consistent with prior analyses focusing on weight regain in the Diabetes Prevention Program9. Interest centered on whether SNP effects, if present, could be averaged across treatment arms or should be presented in a treatment-specific fashion (SNP × treatment arm interaction). The same covariates were employed as above, with the addition of year 1 weight.

To adjust for multiple comparisons, we calculated the effective number of independent genetic loci using principal component analysis as recommended by Li and Ji24. Principal component analysis of the genotypic correlation matrix of the 13 markers of interest identified 10 independent loci in the full and non-Hispanic White samples. Therefore, one

can maintain the family-wise error rate at 0.05 via Sidak's adjustment for multiplicity by declaring as significant only those markers with a nominal significance level of 0.05/10=0.005. However, as the markers were selected *a priori*, we also discuss results with p values less than 0.05 not adjusted for multiple testing. All analyses were performed at Brown University.

Results

Descriptive statistics

Participant characteristics of the sub-cohort of Look AHEAD used in these analyses are shown in Table 1. Individuals were evenly distributed between the ILI and DSE intervention arms, and had comparable age, gender and ethnicity as in the entire cohort (data not shown). No baseline differences in demographic or clinical characteristics across ILI and DSE were observed. Similar to the larger Look AHEAD trial3, participants assigned to ILI lost significantly more weight at year 1 and 4 than those assigned to DSE. SNP characteristics, including the obesity risk allele identified in the prior literature, are presented in Table 2.

Genetic associations with baseline weight

Genetic associations of SNP markers with baseline weight are listed in Table 3. Obesity risk alleles in *FTO*, *SH2B1* and *QPCTL/GIPR* regions predicted baseline weight in directions consistent with prior research. Risk alleles for the markers in these 3 genes were associated with elevated baseline weight of 1.01–1.29 kg per copy. Similar associations were found for baseline BMI (Table 3), with BMI effects per risk allele in the 0.38–0.46 range.

Genetic associations with weight loss at year 1

Genetic associations of the full set of SNP markers with year 1 weight change in ILI and DSE are listed in Supplemental Table 1. No SNPs were significantly associated with the magnitude of weight change in either ILI or DSE or interacted with treatment arm in predicting the degree of weight change

Weight regain

Participant characteristics for those who lost 3% or more at year 1 of their weight at baseline are presented in Table 1a. Genetic associations of the full set of SNP markers with weight at year 4 in this subgroup is presented in Table 4. The obesity risk (A) allele at *FTO* rs3751812 was significantly associated with weight regain in DSE (1.559 kg per risk allele, p = 0.005), but not ILI (-0.092 kg per risk allele, p = 0.761), resulting in SNP×treatment arm interaction (p = 0.009). Similar effects were seen for *FTO* rs1421085 and rs9922708.

A regional plot of the association of *FTO* with differential change in weight regain across ILI and DSE is depicted in Supplemental Figure 2. Of interest, rs3751812 and SNPs in linkage disequilibrium do not show the strongest association with differential weight change across ILI and DSE. One SNP, rs8061397, in a distinct linkage disequilibrium block is associated with differential change in weight across ILI and DSE ($p = 6.4 \times 10^{-5}$), suggesting a possible additional signal in the region.

In a possible replication of prior research, the obesity risk (G) allele at *BDNF* rs6265 was associated with greater weight regain across treatment arms (0.773 kg per risk allele), although results were of borderline statistical significance (p=0.051). When combined, the *FTO* and *BDNF* SNPs accounted for R^2 = 1.43% of year 4 weight across treatment arms.

Discussion

This paper presents the results of the largest study to date examining whether SNPs previously associated with obesity predict weight loss in response to behavioral treatment or weight regain after successful weight loss treatment. We found no significant SNP associations with magnitude of weight loss at year 1 or SNP × treatment arm interactions in predicting year 1 weight change, suggesting behavioral factors, such as adherence to weight loss recommendations, may predominate in predicting initial weight loss. However, the obesity risk region within *FTO* was significantly associated with weight regain in the control group, but not in the lifestyle intervention group, resulting in SNP × treatment arm interaction. Further, variation within *BDNF* was associated with weight regain across treatment arms in replication of prior results in the Diabetes Prevention Program9. Overall, these results suggest that the obesity risk alleles do not appear to be strongly predictive of the magnitude of weight loss in response to behavioral intervention but may instead be associated with weight regain after weight loss.

FTO was the first gene to show replicated association with obesity in GWAS13,16,18,25 and continues to show the strongest association with obesity and body mass index across a variety of populations5. This region also shows strong evidence for gene×behavior interaction as the interaction of obesity-risk alleles at *FTO* with physical activity in predicting body weight has been confirmed by replication and meta-analysis in epidemiologic studies26. In the context of randomized, controlled trials, *FTO* rs9939609 predicted a greater increase in subcutaneous adipose tissue in the placebo group compared to lifestyle intervention at year 1, but no significant genotype × treatment interaction was observed for overall weight loss in the Diabetes Prevention Program8. In the POUNDS LOST trial27, the minor allele at *FTO* rs1558902 predicted greater free fatty mass in response to a low-protein diet but less free fatty mass in response to a high fat diet at two year follow-up, again with no effect on weight change. The present results extend this gene × behavior interaction to the context of a combined caloric restriction and physical activity intervention arm in a longitudinal randomized, controlled clinical trial with four year follow-up. Taken together, these results indicate that behavioral strategies may blunt *FTO* effects on weight gain and weight regain after weight loss. However, the detection of effects of the *FTO* region on weight loss may require detailed measurements of body fat, such as with dual energy X-ray absorptiometry scan.

Previously in the DPP, the obesity risk allele at rs6265 in *BDNF* was associated with greater weight regain over 2 years among those who had initially lost 3% at or more at six months. The effect occurred across all three treatment arms: a lifestyle intervention promoting weight loss and physical activity, 850 mg metformin twice daily, and placebo9. In Look AHEAD, we provide some evidence, albeit of marginal significance (p = 0.051), for association of the obesity risk allele at rs6265 with weight regain at four-year follow-up

among those who had lost 3% at one-year follow-up across two treatment arms. *BDNF* and its primary receptor TrkB are widely expressed in the brain, including key regions of the hypothalamus and dorsal vagal complex related to body weight and energy homeostasis28,29. In these regions, infusion of *BDNF* produces appetite suppression and weight loss30,31. Conversely, targeted disruption of *BDNF* in transgenic models results in hyperphagia and obesity 32–36. In a prior Look AHEAD study, *BDNF* rs6265 was associated with greater total caloric intake and more servings from the dairy and the meat, eggs, nuts and beans food groups37. At least one case study also links rare mutations in *BDNF* to severe obesity in an 8-year-old girl38.

This study has several strengths, including a randomized clinical trial design, a highly effective behavioral weight loss intervention and inclusion of multiple genetic markers previously associated with obesity. The sample size of the study is both a strength and limitation. While this is the largest study to examine genetic predictors of weight loss and weight maintenance, it is smaller in size than samples used to discover the obesity risk SNPs under consideration. It is plausible that the inclusion of more obesity risk polymorphisms would have identified additional associations with weight loss or regain. However, we did include markers reflecting several of the strongest associations with obesity, including those within *FTO*, *MC4R* and *BDNF*. Although we sought to define the role of obesity risk SNPs in weight loss and weight regain, it is possible that genetic factors associated with weight loss and regain may derive from different pathways than those influencing obesity per se. An agnostic approach, such as GWAS or exome sequencing, may be required to identify such pathways. Finally, this cohort was selected for type 2 diabetes and overweight and the generalization of these results to other populations remains to be determined.

Overall, our findings advance existing knowledge on the treatment implications of obesity susceptibility loci derived from GWAS. No significant SNP associations with magnitude of weight loss at year 1 or SNP×treatment arm interactions in predicting year 1 weight change were observed. However, we identify *FTO* and *BDNF* as possible predictors of weight regain after weight loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Centers for Disease Control and Prevention: Edward W. Gregg, PhD; David F. Williamson, PhD; Ping Zhang, PhD

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[1] Principal Investigator

[2] Program Coordinator

[3] Co-Investigator

All other Look AHEAD staffs are listed alphabetically by site.

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Table 1

Population Characteristics in Look AHEAD Genetic Sub-Cohort

Characteristic	Total (N= 3,899)	DSE (N=1,964)	ILI (N=1,935)
Women (%)	2,192 (56.2)	1,096 (55.8)	1,096 (56.6)
Ethnicity (%)			
African American	618 (15.8)	305 (15.5)	313 (16.2)
American Indian/Alaskan Native[a]	20 (0.5)	9 (0.5)	11 (0.6)
Asian/Pacific Islander	41 (1.1)	19 (1.0)	22 (1.1)
Hispanic/Latino	307 (7.9)	159 (8.1)	148 (7.7)
Non-Hispanic White	2,835 (72.7)	1,430 (72.8)	1,405 (72.6)
Other (multiple)	78 (2.0)	42 (2.1)	36 (1.9)
Age (years)	59.1±6.8	59.2±6.8	59.0±6.9
BMI (kg/m^2)			
Women	36.8±6.2	36.9±6.1	36.7±6.3
Men	35.3±5.5	35.1±5.2	35.5±5.8
Waist circumference (cm)			
Women	111.4±13.7	111.5±13.6	111.3±13.8
Men	118.8±13.4	118.5±12.9	119.2±13.9
Weight at Y0 (kg)			
Women	96.7±17.5	96.6±17.4	96.8±17.7
Men	109.6±18.5	109.4±17.8	109.8±19.2
Weight at Y1 (kg)			
Women	92.1±17.8	95.6±17.5	88.7±17.3
Men	104.1±18.9	108.7±17.9	99.4±18.8
Weight at Y4 (kg)			
Women	93.3±17.8	94.4±17.7	92.3±17.9
Men	106.1±19.1	108.4±18.2	103.7±19.7
Weight Change Y1-Y0 (kg)			
Women	−4.6±7.1	−0.9±5.1	−8.1±7.1
Men	−5.6±8.4	−0.9±5.2	−10.5±8.3
Weight Change Y4-Y0 (kg)			
Women	−3.3±9.0	−2.2±9.4	−4.5±8.5
Men	−3.3±8.8	−0.9±7.8	−5.8±9.0

a. Population Characteristics among individuals who lost 3% or more of baseline weight at year 1

Characteristic	Total (N= 2,022)	DSE (N=477)	ILI N=1,545)
Women (%)	1,151 (56.9)	287 (60.2)	864 (55.9)

a. Population Characteristics among individuals who lost 3% or more of baseline weight at year 1

Characteristic	Total (N= 2,022)	DSE (N=477)	ILI N=1,545)
Ethnicity (%)			
African American	300 (14.8)	64 (13.4)	236 (15.3)
American Indian/Alaskan Native[a]	8 (0.4)	2 (0.4)	6 (0.4)
Asian/Pacific Islander	21 (1.0)	3 (0.6)	18 (1.2)
Hispanic/Latino	145 (7.2)	39 (8.2)	106 (6.9)
Non-Hispanic White	1,511 (74.7)	360 (75.5)	1151 (74.5)
Other (multiple)	37 (1.8)	9 (1.9)	28 (1.8)
Age at Y1 (years)	61.0±6.9	61.1±6.8	61.0±6.9
BMI at Y1 (kg/m^2)			
Women	33.2±5.9	34.9±6.0	32.6±5.8
Men	31.7±5.5	33.2±5.0	31.3±5.5
Waist circumference at Y1 (cm)			
Women	103.6±13.4	107.4±13.3	102.4±13.2
Men	109.3±14.0	114.1±12.9	107.9±14.1
Weight at Y1 (kg)			
Women	87.4±16.5	91.3±17.3	86.1±16.0
Men	98.5±18.0	104.2±17.0	96.9±18.0
Weight at Y4 (kg)			
Women	91.1±17.4	91.8±17.2	90.8±17.4
Men	103.3±19.1	106.6±17.6	102.4±19.4
Weight Change Y4-Y1 (kg)			
Women	3.7±8.2	0.5±9.1	4.7±7.6
Men	4.8±7.8	2.4±7.0	5.5±7.8
Weight Regain Y4-Y1 (%)[b]			
Women	834 (72.5)	157 (54.7)	677 (78.4)
Men	684 (78.5)	123 (64.7)	561 (82.4)

[a]The number of American Indian participants included in this study is less than that of the parent Look AHEAD trial due to limitations in genetic consent.

[b]Percentage of individuals who gained weight (>0 kgs) from year 1 – year 4.

Table 2

SNP characteristics in the full genetic sample and two most common racial groups: Non-Hispanic Whites and African-Americans.

				Full Sample (N = 3,899)		American Non-Hispanic Whites (N = 2,835)		African American (N = 618)		
Chr	**Positional candidate gene**	**SNP**	**Risk allele**	**Major/ Minor Allele**	**MAF[a]**	**Major/ Minor Allele**	**MAF[a]**	**Major/ Minor Allele**	**MAF[a]**	**Reference PMID; year**
1	*TNNI3K*	rs1514176[b]	G	A/G	0.48	A/G	0.43	G/A	0.34	20935630; 2010
6	*TFAP2B*	rs2272903	G	G/A	0.14	G/A	0.11	G/A	0.28	20935630; 2010
11	*BDNF*	rs6265	G	G/A	0.16	G/A	0.18	G/A	0.05	19079260; 2009
11	*BDNF*	rs1401635[c]	C	G/C	0.29	G/C	0.31	G/C	0.26	19079260; 2009
11	*BDNF*	rs10767664	A	A/T	0.19	A/T	0.21	A/T	0.07	19079260; 2009
13	*MTIF3*	rs7988412[d]	A	G/A	0.18	G/A	0.17	G/A	0.20	20935630; 2010
16	*SH2B1*	rs4788099[e]	G	A/G	0.37	A/G	0.38	A/G	0.29	20935630; 2010
16	*FTO*	rs1421085	C	T/C	0.39	T/C	0.46	T/C	0.14	17496892; 2007
16	*FTO*	rs3751812	A	C/A	0.38	C/A	0.45	C/A	0.13	19079260; 2009
16	*FTO*	rs9939609	A	T/A	0.44	T/A	0.45	T/A	0.49	17434869; 2007
16	*FTO*	rs9922708[f]	A	G/A	0.43	G/A	0.49	G/A	0.24	17658951; 2007
18	*MC4R*	rs17782313	C	T/C	0.25	T/C	0.25	T/C	0.29	18454148; 2008

Chr	Positional candidate gene	SNP	Risk allele	Full Sample (N = 3,899)		American Non-Hispanic Whites (N = 2,835)		African American (N = 618)		Reference PMID; year
				Major/ Minor Allele	MAF[a]	Major/ Minor Allele	MAF[a]	Major/ Minor Allele	MAF[a]	
19	*QPCTL/GIPR*	rs11672660[g]	G	G/A	0.18	G/A	0.21	G/A	0.10	20935630; 2010

[a] MAF – minor allele frequency

[b] *TNNI3K* rs1514175 was replaced by rs1514176 (distance 48 bp, r^2=1.00, D'=1.00 in CEU and r^2=1.00, D'=1.00 in YRI).

[c] *BDNF* rs925946 was replaced by rs1401635 (distance 26,789 bp r^2=0.96, D'=1.00 in CEU; no proxy was available in YRI).

[d] *MTIF3* rs4771122 was replaced by rs7988412 (distance 19898, r^2=0.83, D'=1.00 in CEU; no proxy was available in YRI).

[e] *SH2B1* rs7498665 was replaced by rs4788099 (distance 27,514 bp r^2=1.00, D'=1.00 in CEU and D'=1.00 and r^2=0.94 in YRI).

[f] *FTO* rs9930506 was replaced by rs9922708 (distance 681 bp r^2=1.00, D'=1.00 in both CEU and YRI).

[g] *QPCTL/GIPR* rs2287019 was replaced by rs11672660 (distance 21988 bp, r^2=0.83, D'=1.00 in CEU, r^2=0.89, D'=1.00 in YRI).

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Table 3

Genetic predictors of baseline weight (in kg; N = 3,899). Age, gender, ancestry principal components and study site statistically adjusted.

				Weight (in kgs)			Body mass index (kg/m^2)		
Chr.	**Gene**	**SNP**	**Minor allele**	**Value**	**Std. Error**	**P Value**	**Value**	**Std. Error**	**P Value**
1	*TNNI3K*	rs1514176	G	−0.054	0.398	0.892	−0.016	0.134	0.906
6	*TFAP2B*	rs2272903	A	−0.862	0.577	0.135	−0.212	0.194	0.274
11	*BDNF*	rs6265	A	−0.739	0.547	0.177	−0.231	0.183	0.207
11	*BDNF*	rs1401635	C	−0.173	0.429	0.687	−0.038	0.144	0.794
11	*BDNF*	rs10767664	T	−0.642	0.511	0.209	−0.188	0.171	0.272
13	*MTIF3*	rs7988412	A	0.009	0.520	0.986	−0.115	0.175	0.511
16	*SH2B1*	rs4788099	G	1.014	0.404	**0.012**	0.191	0.135	0.159
16	*FTO*	rs1421085	C	1.263	0.415	**0.002**	0.463	0.139	**0.001**
16	*FTO*	rs3751812	A	1.143	0.416	**0.006**	0.432	0.139	**0.002**
16	*FTO*	rs9939609	A	1.013	0.394	**0.010**	0.381	0.132	**0.004**
16	*FTO*	rs9922708	A	1.245	0.405	**0.002**	0.440	0.136	**0.001**
18	*MC4R*	rs17782313	C	0.550	0.459	0.230	0.550	0.459	0.230
19	*QPCTL/GIPR*	rs11672660	A	−1.282	0.510	**0.012**	−0.461	0.171	**0.007**

Table 4

Genetic predictors of year 1–4 weight change (in kg) among those who lost 3% or greater of initial weight (Total N = 2022; ILI N = 1545; DSE N=477). Age, gender, ancestry principal components, study site and year 1 weight statistically adjusted.

Chr	Gene	SNP	Minor allele	Effect	Beta	Std. Error	P value
1	*TNNI3K*	rs1514176	G	ILI[a]	0.204	0.292	0.486
				DSE[b]	0.334	0.501	0.512
				Avg[c]	0.269	0.294	0.360
				ILI-DSE[d]	−0.130	0.586	0.825
6	*TFAP2B*	rs2272903	A	ILI	0.122	0.417	0.769
				DSE	0.095	0.800	0.906
				Avg	0.109	0.451	0.810
				ILI-DSE	0.028	0.902	0.976
11	*BDNF*	rs6265	A	ILI	−0.397	0.399	0.320
				DSE	−1.150	0.685	0.094
				Avg	−0.773	0.397	0.051
				ILI-DSE	0.753	0.793	0.343
11	*BDNF*	rs1401635	C	ILI	0.055	0.316	0.862
				DSE	−0.864	0.567	0.128
				Avg	−0.405	0.325	0.213
				ILI-DSE	0.919	0.649	0.157
11	*BDNF*	rs10767664	T	ILI	−0.288	0.377	0.445
				DSE	−0.504	0.657	0.443
				Avg	−0.396	0.379	0.296
				ILI-DSE	0.216	0.758	0.776
13	*MTIF3*	rs7988412	A	ILI	0.243	0.386	0.531
				DSE	−0.916	0.663	0.167
				Avg	−0.334	0.384	0.381
				ILI-DSE	1.158	0.768	0.132

Chr	Gene	SNP	Minor allele	Effect	Beta	Std. Error	P value
16	*SH2B1*	rs4788099	G	ILI	0.072	0.297	0.809
				DSE	−0.480	0.521	0.358
				Avg	−0.204	0.301	0.498
				ILI-DSE	0.552	0.600	0.358
16	*FTO*	rs1421085	C	ILI	−0.137	0.300	0.649
				DSE	1.173	0.553	**0.034**
				Avg	0.518	0.315	0.100
				ILI-DSE	-1.310	0.629	**0.037**
16	*FTO*	rs3751812	A	ILI	-0.092	0.301	0.761
				DSE	1.559	0.551	**0.005**
				Avg	0.734	0.314	**0.020**
				ILI-DSE	−1.651	0.628	**0.009**
16	*FTO*	rs9939609	A	ILI	0.054	0.289	0.851
				DSE	1.029	0.522	**0.049**
				Avg	0.541	0.299	0.070
				ILI-DSE	−0.975	0.596	0.102
16	*FTO*	rs9922708	A	ILI	0.031	0.295	0.916
				DSE	1.382	0.551	**0.012**
				Avg	0.707	0.312	**0.023**
				ILI-DSE	−1.351	0.625	**0.031**
18	*MC4R*	rs17782313	C	ILI	−0.275	0.341	0.420
				DSE	0.252	0.619	0.685
				Avg	−0.012	0.354	0.973
				ILI-DSE	−0.527	0.707	0.456
19	*QPCTL/GIPR*	rs11672660	A	ILI	0.131	0.373	0.726
				DSE	−0.850	0.694	0.221
				Avg	−0.359	0.394	0.362

Chr	Gene	SNP	Minor allele	Effect	Beta	Std. Error	P value
				ILI-DSE	0.980	0.787	0.213

[a] SNP effect within the intensive lifestyle intervention arm

[b] SNP effect within the diabetes support and education arm

[c] SNP effect averaged across treatment arms

[d] SNP × treatment arm interaction