NIH Working Group Report—Using Genomic Information to Guide Weight Management: From Universal to Precision Treatment

Molly S. Bray1, Ruth J.F. Loos2, Jeanne M. McCaffery3, Charlotte Ling4, Paul W. Franks4, George M. Weinstock5, Michael P. Snyder6, Jason L. Vassy7, Tanya Agurs-Collins8, and The Conference Working Group*

Objective: Precision medicine utilizes genomic and other data to optimize and personalize treatment. Although more than 2,500 genetic tests are currently available, largely for extreme and/or rare phenotypes, the question remains whether this approach can be used for the treatment of common, complex conditions like obesity, inflammation, and insulin resistance, which underlie a host of metabolic diseases.

Methods: This review, developed from a Trans-NIH Conference titled “Genes, Behaviors, and Response to Weight Loss Interventions,” provides an overview of the state of genetic and genomic research in the area of weight change and identifies key areas for future research.

Results: Although many loci have been identified that are associated with cross-sectional measures of obesity/body size, relatively little is known regarding the genes/loci that influence dynamic measures of weight change over time. Although successful short-term weight loss has been achieved using many different strategies, sustainable weight loss has proven elusive for many, and there are important gaps in our understanding of energy balance regulation.

Conclusions: Elucidating the molecular basis of variability in weight change has the potential to improve treatment outcomes and inform innovative approaches that can simultaneously take into account information from genomic and other sources in devising individualized treatment plans.
that a variant in the resistin gene (RETN, IVS2 + 39C>T) was associated with increases in both abdominal visceral and total fat following overfeeding in MZ twins, with individuals with the TC genotype having significantly higher values of both measures compared with TT homozygotes (11). Using a similar MZ twin design but inducing a daily energy deficit via a 400 kcal/day energy-restricted diet, Hainer et al. (12) observed 12.8 times more variation in weight loss between pairs than within twin pairs (r_within-pair = 0.85; F = 12.8). In another study of MZ and dizygotic twins, Keski-Rahkonen et al. (13) reported the heritability of intentional weight loss of ≥5 kg to be 38% (95% confidence interval [CI], 19%-55%) in men and 66% (95% CI, 55%-75%) in women. More recently, Hatoum et al. (14) found that a patient’s genetic makeup was a strong determinant in weight loss after gastric bypass surgery; first-degree relatives lost a similar amount of weight.

The ability of intentional weight loss of MZ and dizygotic twins, Keski-Rahkonen et al. (13) reported the heritability of intentional weight loss of ≥5 kg to be 38% (95% confidence interval [CI], 19%-55%) in men and 66% (95% CI, 55%-75%) in women. More recently, Hatoum et al. (14) found that a patient’s genetic makeup was a strong determinant in weight loss after gastric bypass surgery; first-degree relatives lost a similar amount of weight.

The genetic component contributing to the regulation of body mass/composition, only a limited number of genes (described later) have been associated with body weight change in response to changes in the environment.

Defining Weight Change Phenotypes

It is important to consider that changes in body weight and BMI, although commonly used in large epidemiologic and clinical trials because of their ease of measurement, may not fully capture genetic associations with weight-related phenotypes. For example, in a 1-year controlled trial of moderate exercise, variation in the cytochrome p19 (CYP19) gene was associated with significant decreases in total body fat (−3.1 kg vs. −0.5 kg, respectively for those with two vs. no copies of the CYP19 11-repeat alleles, P < 0.01) and percent fat (−2.4% vs. −0.6%, respectively, P < 0.001) but not change in BMI, suggesting that genes may act upon body fatness without significantly influencing body weight per se (25). Measures of body circumferences following weight loss may indicate important changes in fat distribution and lean body mass, and more refined measures of visceral versus subcutaneous fat using computed tomography or magnetic resonance imaging may also provide measures that are more closely correlated with gene function than BMI or body weight.

Weight change is a complex outcome, as both the degree and pattern of weight change impact health. For example, in the Diabetes Prevention Program (DPP, described in more detail later), both short- and intermediate-term weight loss were associated with reduced diabetes risk and intermediate cardiometabolic risk factor levels, whereas weight cycling (defined as number of 5 lb [2.25 kg] weight cycles) raised diabetes risk, fasting glucose levels, insulin resistance, and systolic blood pressure. Initial (baseline to 1 month) and late (last 6 months of the 2-year intervention period) weight loss had no discernable impact of diabetes risk (26). Similar results have been reported in people with pre-existing diabetes who underwent lifestyle intervention as part of the Look AHEAD (Action for Health in Diabetes) trial (27). These studies point to alternative phenotypes that may be informative for genetics studies of weight loss/maintenance/regain.

Genetic Predictors of Obesity Treatment Response

Given the small effects of BMI loci identified to date, it is possible that genetic effects may be more closely aligned with dynamic, rather than static, phenotypes. In a recent GWAS of weight change trajectories from age 1-17 years, Warrington et al. (28) identified a novel variant in the FAM120AOS gene and confirmed three known adult BMI-associated loci (FTO, MC4R, and ADcy3) and one childhood obesity locus (OLFM4) with significant genome-wide association (P_wald < 1.13 × 10−8) with BMI at 8 years and/or change over time. The analysis of short-term change in response to weight loss interventions may also reveal novel genes/loci and biology associated with treatment response.
Behavioral strategies for weight loss, involving kilocalorie restriction and physical activity, are currently the frontline treatment for common forms of obesity (29). Randomized controlled trials of lifestyle interventions for behavioral weight loss reliably produce initial weight losses of 7% or more, resulting in clinically important health benefits (30,31). Two of the largest obesity-treatment randomized controlled trials to date have focused on energy intake, dietary fat, and physical activity to support weight loss goals. The DPP randomized 3,234 individuals with obesity or overweight and at risk for diabetes to metformin treatment, lifestyle intervention, or a placebo control arm (30,32). In the Look AHEAD study, 5,145 individuals with obesity or overweight who had Type 2 diabetes (T2D) were randomized to intensive lifestyle intervention (ILI) or a diabetes support and education (DSE) control without an active weight loss program (33). Both weight loss interventions produced significant weight losses as compared with the control groups (e.g., Look AHEAD, Year 1 percent weight change, ILI: −8.6% + 6.9%, DSE: 0.7% + 4.8%) (6). Partial weight regain was nonetheless common (e.g., Look AHEAD, Year 4 percent weight change: ILI: −6.15% vs. DSE: −0.88%; percent weight change at a median of 9.6-year follow-up: ILI: −6.0% vs. DSE: −3.5% (31,34)).

The largest study to date to address the role of genetic variation in weight loss response examined the association between 91 established obesity-predisposing loci, derived from the comprehensive results of GWAS available in 2015 (15), and weight loss or weight regain in the DPP and Look AHEAD cohorts (35). The combined genetic sample included 5,730 participants randomly assigned to either behavioral weight loss treatment or a control condition. Of the 91 loci, one was consistently associated with weight loss over 4 years in meta-analysis. Each copy of the minor G allele for the rs1885988 variant at MTIF3 was significantly associated with a mean 1.14 kg lower weight in the lifestyle arm versus a nonsignificantly higher weight of 0.33 kg in the comparison arm. These effects produced a statistical interaction of gene × treatment arm reaching experiment-wide significance at Year 3 and nominal significance across the 4 years. Nevertheless, no other obesity-associated loci predicted weight loss, and no loci predicted weight regain. The MTIF3 gene encodes a protein that is essential for ATP synthesis and energy balance in the mitochondria (36). The minor G allele has previously been associated with higher BMI (37,38) and hip circumference (39). Thus, carriers of the MTIF3 obesity-inducing allele seem to benefit more from ILIs than noncarriers. This locus has also begun to emerge in epidemiologic gene × environment interactions studies of BMI, with MTIF3 genotype associated more strongly with BMI for those eating a healthy dietary intake pattern compared with those in the nonhealthy diet group (40).

No studies to date have searched for novel genetic loci associated with behavioral weight loss leveraging a genome-wide approach. The only exploratory study to date comes from Look AHEAD, in which single nucleotide polymorphism (SNP) variation across the IBC chip (Illumina, San Diego, CA), a gene-centric assay of roughly 50,000 SNPs covering early candidate genes for cardiovascular disease, was examined in relation to magnitude of weight loss after 1 year (41). Two novel regions of significant array-wide association with Year 1 weight loss in ILI were identified. ABCB11/G6PC rs484066 was associated with 1.16 kg lower weight loss per minor allele at Year 1, whereas TNFRSF11A, or RANK, rs17069904 was associated with 1.70 kg greater weight loss per allele at Year 1. ABCB11, or BSEP, is a bile salt export pump and the primary mediator of bile salt secretion and fat transport from the gut. G6PC is a primary regulator of glucose homeostasis with mutations related to hypoglycemia; this locus has previously been identified as a predictor of high density lipoprotein cholesterol and glucose in GWAS (42,43). RANK, along with the RANK ligand, are members of the tumor necrosis factor (TNF) family of genes and are expressed in adipose tissue (44). Although provocative, these exploratory analyses await confirmation in independent samples. Smaller trials have tested whether genetic variants may predict differential response to diets varying in macronutrient composition. For example, the Pounds Lost trial (45) found individuals carrying obesity-associated alleles at the FTO locus to differentially benefit from a high-protein, calorie-restricted diet in losing weight (46). Variation in the FTO locus has also been shown to be associated with weight loss following bariatric surgery (47,48). This interesting research awaits further replication.

Taken together, this emerging evidence indicates that genetic variation may impact the efficacy of behavioral weight loss interventions. Initial results indicate that agnostic genetic association studies focused on treatment response may yield new insights into genetic predictors of weight loss, but larger trials or a consortium of weight loss trial will be required to achieve the larger samples size necessary to test these hypotheses with statistical certainty.

Complex Systems That Influence Energy Balance

Epigenetic mechanisms in energy homeostasis and obesity

Interactions between the environment and the genome that modulate the risk for obesity can happen through direct chemical alterations, including DNA methylation and histone modifications (49). Methylation, an epigenetic mechanism that can both positively and negatively regulate gene expression, plays a critical role in driving many cell-specific and tissue-specific functions. It is now well established that some epigenetic modifications of DNA may also occur in response to changes in the environment, including nutrition and exercise, which can alter gene expression in a stable and heritable manner that may influence metabolism, behavior, and ultimately overall health. These features make epigenetics a potentially important pathogenic mechanism in complex disorders, such as obesity.

Recent epigenome-wide association studies have shown that physical activity and high-fat diets may alter the DNA methylation pattern in tissues of importance for energy homeostasis such as skeletal muscle and adipose tissue (50-52); these epigenetic changes may affect weight loss and/or weight gain. In support of this hypothesis, a 6-month exercise intervention was associated with altered DNA methylation patterns of numerous candidate genes for obesity, such as FTO, GRB14, and TUB in adipose tissue, as well as of genes regulating adipogenesis, and was associated with decreased waist circumference in sedentary middle aged men (50). Additionally, obesity has been associated with altered DNA methylation compared to individuals without obesity in numerous human studies (49,53-55). HIF3A has shown consistent differential DNA methylation in relation to obesity in several studies (56,57). Epigenetic mechanisms may also affect a person’s response to weight increase, weight loss,
and maintenance by controlling genes that regulate energy homeo-
stasis. For example, Demerath et al. (55) found that the degree of
methylation of eight different CpG sites, including one site near
CPT1A, was associated with a change in BMI in participants who
gained weight over a 30-year period. Additionally, when Dahlman
et al. (58) compared the methylole in adipocytes from women who
formerly had obesity and had lost weight following gastric bypass
surgery with women who had never had obesity, they found differ-
ential DNA methylation of genes involved in adipogenesis.

Weight loss associated with roux-en-Y gastric bypass surgery, which
is commonly used to treat morbid obesity, was recently shown to
alter the epigenome in adipose tissue, skeletal muscle, and blood
(59-61). Interestingly, maternal weight loss by gastric bypass surgery
was also found to influence the methylation pattern of offspring
born after, versus before, weight loss (62). In a separate study, Nico
tetti et al. (63) compared epigenetic changes in relation to two dif-
f erent weight loss strategies: an energy-restricted diet and gastric
bypass surgery, and they reported that baseline methylation of SER
PINE1 may predict weight loss after gastric bypass surgery.
Together, these studies support an important role for epigenetic
mechanisms in controlling energy homeostasis and obesity. How-
ever, further studies are needed to fully dissect the role of epige-
netics in the growing incidence of obesity and to establish whether
epigenetic markers may be used to guide weight management.

The microbiome and weight change
The human microbiome may play a significant role in the etiology
of obesity in both humans and animal models (64). Hosted in the
gastrointestinal tract, the gut microbiome is part of a large endocrine
organ that regulates not only nutrient sensing and metabolism but
also satiety and energy homeostasis. The millions of microorganisms
comprising the complex intestinal “superorganism” perform a num-
ber of functions for host health, including food processing, break-
down and metabolism of indigestible nutrients, pathogen displace-
ment, synthesis of vitamins, and regulation of body weight (65).
They play such an important role that we now know that microbiota
disruptions in early life can have long-lasting effects on body weight
in adulthood (66). The host bacterial composition has been shown to
adapt in response to dietary factors and in response to weight loss.
Diet or surgically induced weight loss promote alterations in the gut
that can impact the efficacy of the treatment strategies (67,68). Spe-
cific bacterial species can have influences by themselves. For exam-
ple, the archaeon Methanobrevibacter smithii, has an enhanced abil-
ity to metabolize dietary substrates or end products of the metabo-
lolism of other bacteria, thereby increasing host energy intake
and weight gain (69).

Experiments in animal models, particularly rodents, show specific
reproducible changes in the microbiota because of the ability to con-
trol factors such as genetics, diet, and environment. However, in
humans, these effects have been less consistently demonstrated.
With weight loss, there is a decrease in the ratio of Firmicutes to
Bacteroidetes phyla (68). Damms-Machado et al. (70) demonstrated
that surgical weight loss interventions like laparoscopic sleeve gas-
trectomy seem to improve the obesity-associated gut microbiota
toward a lean microbiome phenotype. They described a reduction of
the energy-reabsorbing potential of the gut microbiota following sur-
surgery indicated by the Firmicutes/Bacteroidetes ratio. The interaction
of a community depends on a balanced microbial diversity, and
each group has different tasks and different qualities, which together
compose a “healthy” microbiome (71). Manipulation of gut micro-
biota could reduce intestinal low-grade inflammation and improve
gut barrier integrity, ameliorating metabolic balance and promoting
weight loss (71). The use of prebiotics and probiotics as potential
aids in weight loss/gain interventions has great potential, but further
evidence is needed to better understand the real clinical potential
of studies of the gut microbiome.

Behavioral Phenotypes Underlying BMI
and Body Weight Change
Of the known genes underlying Mendelian forms of severe obesity
(see Table 1), one consistent underlying feature is hyperphagia, sug-
gest ing that ingestive behavior may be the prime driver of weight
 gain or loss. Many of the loci associated with obesity in GWAS are
also expressed in the brain and often specifically in hypothalamic
eating regulatory pathways (15). Physical activity is a second promi-
ent health behavior known to prevent weight gain and promote
weight loss maintenance (72-75). Both eating and physical activity
behaviors have been shown to have substantial genetic underpin-
nings (76,77) and may directly or indirectly mediate the association
between genetic/genomic variation and measures of body mass/size.

Genetics of food preferences and ingestive
behavior
Many of the loci associated with obesity in GWAS are located in or
nearby genes expressed in brain eating regulatory pathways, high-
lighting a potential role in the central nervous system and eating
behavior for these genetic associations (78). Consistent with this
hypothesis, the FTO locus rs9939609, for example, has been shown
to predict preferences for and consumption of palatable, calorie-
dense foods (79,80) and reduced satiety (81) in laboratory para-
digms, and greater total caloric and total fat intake assessed by die-
tary recall (80,82). In recent GWAS of dietary intake, FTO emerged
as associated with a greater percentage of calories from protein
(83,84) and fat (85), although inconsistently so.

Although monogenic obesity is often associated with abnormal appetite
and excessive food consumption, more subtle types of feeding behavior,
such as food preferences, have also been shown to have a substan-
tial genetic component (86,87). The TAS2R38 gene is associated with
the perception of the bitter-tasting thiourea compounds, and genotype
at this locus defines three taster groups: supertasters, medium tasters,
and nontasters, with nontasters having a higher BMI compared with
the other taster groups; differences in dietary patterns were also
observed (88). Taster status at another locus, 6-n-propylthiouracil
(PROP), was associated with significantly greater reduction in energy
intake for super-tasters during two randomized control dietary inter-
ventions focused on lowering energy density or changing eating fre-
quency (89). Taken together, these studies suggest that genetic associa-
tions with body weight or BMI may be modulated by more direct links
between food preferences, eating behavior, and genes.

Genetics of physical activity
Multiple studies have demonstrated that physically active individuals
are less likely to gain weight over time (75,90,91), and physical
exercise has also been shown to facilitate both weight loss and weight maintenance (92). In studies of twins and other related individuals, physical activity has been shown to aggregate in families, with reported heritability estimates for physical activity behavior ranging from 9% to almost 80% (93-96). In animal models, the strongest genetic predictors of spontaneous physical activity include the dopamine receptor 1 (Drd1) and nescent helix loop helix 2 (Nhlh2) genes, which have also been implicated in feeding behavior (97-100). In humans, variation in the leptin receptor (LEPR) and melanocortin 4 receptor (MC4R) genes was associated with physical inactivity (101-103), which appears to be driven by genetic pathways that are distinct from those encoding activity. A limited number of genes have been identified that may influence exercise adherence and/or exercise tolerance, with small effects that await replication (104,105). Change in body weight, waist circumference, hip circumference, and BMI have been shown to be significantly associated with adherence status both before and after an aerobic exercise intervention (105), suggesting a plausible pathway by which genes that influence adherence may ultimately influence weight change.

### Personalizing Weight Loss Interventions

Although ongoing efforts are elucidating the genetic underpinnings of obesity and weight change, a different question is whether these discoveries can be implemented in the clinical setting to personalize weight loss interventions. The success of such interventions would rely not only on an understanding of the pathophysiological mechanisms linking genotype and weight but also on the ability to communicate a personalized strategy to patients and motivate behavior change.

A few studies have examined whether communicating genetic risk information to patients motivates weight-related health behavior change. In a recent trial, 1,016 university students were randomized to receive simple weight control advice with and without their FTO rs9939609 genotype (106). Of the 279 participants who completed the 1-month follow-up survey, those in the genotyped group were more likely to be in a contemplation or action stage of readiness to control weight, compared with those receiving advice only (odds ratio 1.77, 95% CI, 1.08-2.89, P = 0.023). The researchers observed an interaction of study group with body weight; the effect of FTO genotype information on readiness for change was greater among individuals with overweight/obesity (only 9% of the respondents) than among those of normal weight (106). Perhaps most relevant to the present discussion, the researchers also observed an interaction between study group and genotype; compared with control participants, participants learning they carried the higher-risk AT or AA FTO genotype, but not those learning they carried the low-risk TT genotype, were more likely to be in an advanced stage of change after 1 month (106). The groups did not differ, however, in the proportions reporting they had actually followed any of the weight control advice, suggesting that additional information may need to be given to motivate actual behavior change.

Two trials in the field of T2D have assessed weight change in response to genetic testing. In the Genetic Counseling and Lifestyle Change for Diabetes Prevention Study (107), 177 patients with metabolic syndrome were randomized to receive genetic testing for T2D susceptibility based on 36 T2D-associated SNPs plus brief genetic counseling versus no genetic testing. Diabetes risk for genotyped
participants was summarized with a risk score categorizing their genetic risk as low, average, or high. All patients were then enrolled in a 12-week lifestyle medication program modeled on the evidence-based DPP (108). The lifestyle intervention was effective: the group overall lost a mean of 8.5 ± 10.1 pounds, with 31% losing at least 5% of their body weight. Communicating genetic risk did not change this effectiveness, however. The genotyped and control arms did not differ with respect to weight loss, attendance at the 12 DPP sessions, or motivation or confidence to make health behavior changes (107). In a second randomized trial, 601 patients with obesity or overweight received T2D risk estimates based on family history, BMI, and fasting plasma glucose, followed by either T2D genetic susceptibility results from four T2D-associated SNPs or eye disease counseling as a control (109). All participants received brief lifestyle counseling but were not otherwise enrolled in a weight loss program. Although the group receiving genetic risk information reported lower calorie and fat intake after 3 months, the two groups did not differ in these behaviors or in physical activity, weight loss, insulin resistance, or perceived risk after 6 months.

Personalizing genetic risk information is only one component of a genotype-informed approach to weight loss. A clear deficit of the trials to date is that the genetic risk information provided to participants was not connected to personalized weight loss strategies but, rather, to uniform interventions, be they simple advice or an intensive 12-week program. To advance the field of precision weight loss, the combination of an individual’s genotype, along with the unique underlying pathophysiology it suggests, should be used to develop dietary and physical activity recommendations that target the metabolic derangements specific to each person.

Future Directions

Although a genetic basis for obesity and even response to alterations in energy balance has been clearly established, few studies (24,110) have examined whether the same genes and/or processes that influence obesity when assessed cross-sectionally also influence weight loss, weight maintenance, and/or weight regain following weight loss interventions. By taking into account the influence of genetic variation on these disease processes, precision medicine in behavioral weight loss may present several new avenues to tackle the obesity epidemic. For example, identifying subgroups of populations with obesity who are genetically prone to respond well to a given weight loss intervention might be targeted accordingly. Similarly, genetic information might prove valuable when seeking to identify people who are unlikely to respond well to a given weight loss therapy or who might experience adverse events. There are many compelling examples of the use of genomic data in clinical settings, such as screening for BRCA1/BRCA2 gene mutations to aid treatment decisions for familial breast cancer and genetic screening for drug metabolizing genes like CYP2D6 to inform the prescription and dosing of codeine for pain relief. To optimize the use of genetic information, clinicians, patients, and their relatives would all benefit from an improved level of medical literacy when exchanging genetic information (111).

Although complex diseases and outcomes pose the biggest challenge for precision medicine, improving treatment for such outcomes also has the potential to impact the greatest number of people. Technology exists today to characterize individuals in a highly comprehensive manner that includes 24-h assessment of heart and respiratory rate, physical movement, exposure to changes in light/sound/temperature, sleeping patterns, eating patterns, and a host of other measures. Portable, wearable monitors can be used to upload patient data remotely and automatically, and Web-based, computerized devices, like scales and bioimpedance instruments, can monitor fluid balance and body composition without the need for the participant or patient to interact directly with researchers or health care providers. These devices can be linked to environmental monitors in the home, and GPS tracking systems can document the location and physical setting of the wearer. In addition to monitoring devices, it is now feasible and affordable to sequence an entire genome in as little as 10 days. Next-generation sequencing and advanced mass spectrometry have paved the way for the fast and complete characterization of the transcriptome, proteome, epigenome, and metabolome. Classic information about family and medical history can be combined with a
host of behavioral, psychological, and demographic data to completely account for a multitude of factors that may influence both disease processes and response to treatment.

Acquiring data is the easy part. What is direly needed are innovative approaches for mining multiple levels of “omics” and other data to discern patterns of data-disease relationships that may then be used for decision-making in clinical treatment. Although the statistical approaches lag behind the technology and our ability to gather data, the potential is great to make substantial progress in this area. This article highlights the importance of developing a model that combines genes with established phenotypes in order to bring us closer to personalized treatment. Table 2 outlines future research directions to advance the science and potentially inform personalized gene-based interventions for successful weight loss, maintenance, and regain.

With advances in technology comes a demand for more innovative studies. There are several large, multimillion-dollar prospective studies that have been recently initiated in Europe and the United States, including the Innovative Medicines Initiative DIRECT Study in Europe (112) and the Google Baseline Study in the United States (https://www.dtm1.duke.edu/news/duke-and-stanford-assist-google-x-defining-health); both studies involve repeated invasive phenotyping and objective long-term measures of behavior assessed with wearable devices, from which much will be learned about the genetic and environmental influences on weight change and metabolic health. Although interrogating existing trials for gene-intervention interactions is pragmatic and should be done, new trials that are specifically designed to assess the combined effects of genotypes and interventions are needed. Genotype-based recall trials, in which the power to detect differences in response to treatment between participants with a high and low degree of genetic burden is maximized, provide one such opportunity. With innovation at every level, from data acquisition to statistical analysis to study design, recent and future scientific discoveries may help move obesity prevention and treatment from universal to precision approaches.

Acknowledgments

The authors acknowledge the following NIH collaborators who convened the working group and made important contributions to the meeting: Cashell E. Jaquish, Ph.D., NHLBI; Catherine Loria, Ph.D., NHLBI; Philip Smith, Ph.D., NIDDK; Erica Spotts, Ph.D., OBSSR; and Sharon Ross, Ph.D., NCI. Special thanks to Diana Gutierrez for her valuable comments on the manuscript.

© 2015 The Obesity Society

References

1. World Health Organization. World Health Statistics 2015. Geneva, Switzerland: World Health Organization; 2015.
2. Allison DB, Heshka S, Neale MC, Heymsfield SB. Race effects in the genetics of adolescents' body mass index. Int J Obes Relat Metab Disord 1994;18:363-368.
3. Chagnon YC, Perusse L, Bouchard C. Familial aggregation of obesity, candidate Pediatr 4. Chung WK. An overview of mongenic and syndromic obesities in humans. Genet 5. Goran MI. Genetic influences on human energy expenditure and substrate metabolism. Am J Clin Nutr 6. Speakman JR, Levitsky DA, Allison DB, et al. Set points, settling points and some obes Metab 7. Bray et al. Using Genomic Information to Guide Weight Management

7. Tabery J. Debating interaction: the history, and an explanation. Int J Epidemiol 2015;44:1117-1123.
8. Barsh GS, Farooqi IS, O’Rahilly S. Genetics of body-weight regulation. Nature 2000;404:644-651.
9. Bouchard C, Tremblay A, Despres J, et al. The response to long-term overfeeding in identical twins. N Engl J Med 1990;322:1477-1482.
10. Bouchard C, Tremblay A, Despres JP, et al. The response to exercise with constant energy intake in identical twins. Obes Res 1996;2:400-410.
11. Ukkola O, Kesanen Y, Tremblay A, Bouchard C. Two variants in the resistin gene and the response to long-term overfeeding. Eur J Clin Nutr 2004;58:654-659.
12. Hainer V, Stunkard AJ, Kunesova M, Parizkova J, Stich V, Allison DB. Intrapair resemblance in very low calorie diet-induced weight loss in female obese identical twins. Int J Obes Relat Metab Disord 2000;24:1051-1057.
13. Keski-Rahkonen A, Neale BM, Bulik CM, et al. Intentional weight loss in young adults: sex-specific genetic and environmental effects. Obes Res 2005;13:745-753.
14. Hatoum JJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the weight loss response to gastric bypass surgery. J Clin Endocrinol Metab 2014;99:1630-1636.
15. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197-206.
16. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose tissue to insulin biology and body fat distribution. Nature 2015;518:187-196.
17. Chen CY, Chang IS, Hsuing CA, Wasserman WW. On the identification of potential regulatory variants within genome wide association candidate SNP sets. BMC Med Genom 2014;7:34.
18. Spisak S, Lawrenson K, Fu Y, et al. CAUSEL: an epigenome- and genome-editing pipeline for establishing function of noncoding GWAS variants. Nat Med (in press). Please update Refs. 18, 19, 35, 63, 109, and 111, if possible.
19. Rask-Andersen M, Almen MS, Schioth HB. Assessing the ZOLO locus: compelling evidence for a complex, long-range regulatory context. Hum Genet (in press).
20. Waalen J. The genetics of human obesity. Transit Res 2014;164:293-301.
21. Yang J, Manolio TA, Pasquaule LR, et al. Genome partitioning of genetic variation for complex traits using common SNPs. Nat Genet 2011;43:519-525.
22. Llewellyn CH, Trzaskowski M, Plomin R, Wardle J. Finding the missing heritability in pediatric obesity: the contribution of genome-wide complex trait analysis. Int J Obes (Lond) 2013;37:1506-1509.
23. Winkler TW, Justice AE, Graff M, et al. The influence of age and sex on genetic associations with adult body size and shape: a large-scale genome-wide interaction study. PLoS Genet 2015;11:e1005378.
24. Delahanty LM, Pan Q, Jablonski KA, et al. Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the Diabetes Prevention Program. Diabetes Care 2012;35:363-366.
25. Tworoger SS, Chabak J, Aiello EJ, et al. The effect of CYP19 and COMT polymorphisms on exercise-induced fat loss in postmenopausal women. Obes Res 2004;12:972-981.
26. Delahanty LM, Pan Q, Jablonski KA, et al. Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the Diabetes Prevention Program. Diabetes Care 2014;37:2738-2745.
27. Nebirgh RH, Wing RR, Bray GA, et al. Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors in the Look AHEAD Study. Obesity (Silver Spring) 2012;20:2048-2056.
28. Warrington NM, Howe LD, Patemoster L, et al. A genome-wide association study of body mass index across early life and childhood. Int J Epidemiol 2015;44:700-712.
29. Jensen MD, Ryan DH, Donato KA, et al. Guidelines (2013) for managing overweight and obesity in adults. Obesity 2014;22(S2):S1-S410.
30. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
31. Look ARG, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. Arch Intern Med 2010;170:1566-1575.
32. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care 1999;22:623-634.
33. Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabet 34. Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610-628.
35. Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145-154.
36. Papandonaos GD, Pan Q, Paisiwicki NM, et al. Genetic predisposition to weight loss & regain with lifestyle intervention: analyses from the Diabetes Prevention Program & the Look AHEAD randomized controlled trials. Diabetes (in press).
37. Behrouz B, Vilarino-Guell C, Heckman MG, et al. Mitochondrial translation initiation factor 3 polymorphism and Parkinson’s disease. Neurosci Lett 2010;486:228-230.
Obesity

Review

37. Spielotes EK, Miller CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* 2010; 42:937-948.

38. Hong KW, Oh B. Recapitulation of genome-wide association studies on body mass index in the Korean population. *Int J Obes (Lond)* 2012;36:1127-1130.

39. Goumidi L, Cotter D, Dallogeveille J, Amouyel P, Meirhaega A. Effects of established BMI-associated loci on obesity-related traits in a French representative population sample. *BMC Genet* 2014;15:62.

40. Nettleton JA, Follis JL, Ngwa JS, et al. Gene × dietary pattern interactions in obesity: analysis of up to 68 317 adults of European ancestry. *Hum Mol Genet* 2015;24:4728-4735.

41. McCaffery JM, Papandonatos GD, Huggins GS, et al. Human cardiovascular disease IBC chip-wide association with weight loss and weight regain in the look AHEAD trial. *Hum Hered* 2013;75:160-174.

42. Kraja AT, Vaidya D, Pankow JS, et al. A bivariate genome-wide approach to novel methylation loci associated with body mass index and waist circumference. *Diabetologia* 2011;54:1329-1339.

43. Bouatia-Naji N, Rocheleau G, Van Lommel L, et al. A polymorphism within the G6PC2 gene is associated with fasting plasma glucose levels. *Science* 2008;320:1085-1088.

44. An JJ, Han DH, Kim DM, et al. Expression and regulation of osteoprotegerin in expression of genes influencing metabolism and inflammation in adipose tissue. *Yonsei Med J* 2007;48:765-772.

45. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* 2009;360:859-873.

46. Zhang X, Qi Q, Zhang C, et al. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST/HeBeFit study. *Diabetologia* 2012;61:3005-3011.

47. Liou TH, Chen HH, Wang W, et al. ESR1, FTO, and UCP2 genes interact with bariatric surgery affecting weight loss and glycemic control in severely obese patients. *Obes Surg* 2011;21:1758-1765.

48. Sarzynski MA, Jacobson P, Rankinen T, et al. Associations of markers in 11 obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. *Int J Obes (Lond)* 2011;35:676-683.

49. Renn T, Volkov P, Gillberg L, et al. Impact of age, BMI and HbA1c levels on the genome-wide DNA methylation and mRNA expression patterns in human adipose tissue and identification of epigenetic biomarkers in blood. *Hum Mol Genet* 2015;24:3793-3813.

50. Renn T, Volkov P, Davegardh C, et al. A six months exercise intervention influences the genome-wide DNA methylation pattern in human adipose tissue. *PLoS Genet* 2013;9:e1003572.

51. Nitert MD, Dayeh T, Volkov P, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes* 2012;61:3322-3332.

52. Jacobsen SC, Gillberg L, Bork-Jensen J, et al. Young men with low birthweight exhibit decreased plasticity of genome-wide DNA methylation by high-fat overfeeding. *Diabetologia* 2014;57:1154-1158.

53. Nilsson E, Janson PA, Periliev Y, et al. Altered DNA methylation and differential expression of genes influencing metabolism and adipose tissue in subjects with type 2 diabetes. *Diabetes* 2014;63:2962-2976.

54. Aslibekyan S, Demerath EW, Mendelson M, et al. Epigenome-wide study identifies multiple replicated loci. *Nat Genet* 2012;44:1277-1287.

55. Vitart F, Demir A, Tybjaerg-Hansen A, et al. DNA methylation of adipogenesis genes. *Hum Mol Genet* 2013;22:1493-1501.

56. Demerath EW, Guan W, Grove ML, et al. Epigenome-wide association study identifies multiple loci associated with body mass index and waist circumference. *Int J Obes (Lond)* 2013;37(Suppl 5):v5.

57. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine position stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc* 2009;41:459-471.

58. Zhang X, Qi Q, Zhang C, et al. FTO genotype and 2-year change in body composition and fat distribution in response to weight-loss diets: the POUNDS LOST/HeBeFit study. *Diabetologia* 2012;61:3005-3011.

59. Liou TH, Chen HH, Wang W, et al. ESR1, FTO, and UCP2 genes interact with bariatric surgery affecting weight loss and glycemic control in severely obese patients. *Obes Surg* 2011;21:1758-1765.

60. Benton MC, Johnstone A, Eccles D, et al. An analysis of DNA methylation in women is characterized by global hypomethylation and differential DNA methylation in glucoregulatory genes of offspring born before vs. after maternal overfeeding. *Diabetes (Silver Spring)* 2014;63:1859-1873.

61. Nilsson EK, Ernst B, Voisin S, et al. Roux-en Y gastric bypass surgery induces differential methylation of obesity candidate genes with maximal weight loss and weight regain in the SOS bariatric surgery cases. *Int J Obes (Lond)* 2011;35:676-683.

62. Kwan GC, Billion Y, Zhao X, et al. Impact of high-fat diet on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes* 2012;61:3322-3332.

63. Nicoletti CF, Nonino CB, de Oliveira BA, et al. DNA methylation and overfeeding. *Obes Surg (in press).*
93. Maia JA, Thomis M, Beunen G. Genetic factors in physical activity levels: a twin study. *Am J Prev Med* 2002;23:87-91.

94. Mitchell BD, Rainwater DL, Hsueh WC, Kennedy AJ, Stern MP, Maccluer JW. Familial aggregation of nutrient intake and physical activity: results from the San Antonio Family Heart Study. *Ann Epidemiol* 2003;13:128-135.

95. Moore LL, Lombardi DA, White MJ, Campbell JL, Oliveria SA, Ellison RC. Influence of parents’ physical activity levels on activity levels of young children. *J Pediatr* 1991;118:215-219.

96. Pittaluga M, Casini B, Parisi P. Physical activity and genetic influences in risk factors and aging: a study on twins. *Int J Sports Med* 2004;25:345-350.

97. Lightfoot JT. Current understanding of the genetic basis for physical activity. *J Nutr* 2011;141:526-530.

98. Roberts MD, Gilpin L, Parker KE, Childs TE, Will MJ, Booth FW. Dopamine D1 receptor modulation in nucleus accumbens lowers voluntary wheel running in rats bred to run high distances. *Physiol Behav* 2012;105:661-668.

99. Garcia-Tornadu I, Perez-Millan MI, Recouvreux V, et al. New insights into the endocrine and metabolic roles of dopamine D2 receptors gained from the Drd2 mouse. *Neuroendocrinology* 2010;92:207-214.

100. Jing E, Nilini EA, Sanchez VC, Stuart RC, Good DJ. Deletion of the Nhlh2 transcription factor decreases the levels of the anorexigenic peptides alpha melanocyte-stimulating hormone and thyrotropin-releasing hormone and implicates prohormone convertases I and II in obesity. *Endocrinology* 2004;145:1503-1513.

101. Cai G, Cole SA, Butte N, et al. A quantitative trait locus on chromosome 18q for physical activity and dietary intake in Hispanic children. *Obesity (Silver Spring)* 2006;14:1596-1604.

102. Loos RJ, Rankinen T, Tremblay A, Perusse L, Chagnon Y, Bouchard C. Melanocortin-4 receptor gene and physical activity in the Quebec Family Study. *Int J Obes (Lond)* 2005;29:420-428.

103. Stefan N, Vozarova B, Del Parigi A, et al. The Gln233Arg polymorphism of the leptin receptor in Pima Indians: influence on energy expenditure, physical activity and lipid metabolism. *Int J Obes Relat Metab Disord* 2002;26:1629-1632.

104. Thompson PD, Tsongalis GJ, Or dovas JM, et al. Angiotensin-converting enzyme genotype and adherence to aerobic exercise training. *Prev Cardiol* 2006;9:21-24.

105. Herring MP, Yailors MH, Bray MS. Genetic factors in exercise adoption, adherence and obesity. *Obes Rev* 2014;15:29-39.

106. Meisel SF, Beeken RJ, van Jaarsveld CH, Wandle J. Genetic susceptibility testing and readiness to control weight: results from a randomized controlled trial. *Obesity (Silver Spring)* 2015;23:303-312.

107. Grant RW, O’Brien KE, Waxler JL, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. *Diabetes Care* 2013;36:13-19.

108. Diabetes Prevention Program Research G. The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 2002;25:2165-2171.

109. Voils CI, Coffman CJ, Grubber JM, et al. Does type 2 diabetes genetic testing and counseling reduce modifiable risk factors? A randomized controlled trial of veterans. *J Gen Intern Med* (in press).

110. Franks PW, Jablonski KA, Delahanty LM, et al. Assessing gene-treatment interactions at the FTO and INSIG2 loci on obesity-related traits in the Diabetes Prevention Program. *Diabetologia* 2008;51:2214-2223.

111. Eccles DM, Mitchell G, Monteiro AN, et al. BRCA1 and BRCA2 genetic testing: pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol* (in press).

112. Kovula RW, Heggie A, Barnett A, et al. Discovery of biomarkers for glycaemic deterioration before and after the onset of type 2 diabetes: rationale and design of the epidemiological studies within the IMI DIRECT Consortium. *Diabetologia* 2014;57:1132-1142.