Conference Report

Sponsored by:

National Cancer Institute (NCI)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

National Heart, Lung, and Blood Institute (NHLBI)

NIH Office of Behavioral and Social Sciences Research

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Executive Summary

Obesity is a major public health problem that is associated with increased risk for chronic diseases, morbidity, and mortality. Specifically, obesity increases risk for cardiovascular disease and cancer, which remain the top two causes of death in the United States. Lifestyle factors, including poor diet and physical inactivity, are the primary agents contributing to increased risk of being overweight and obese. While there are a number of behavior-based weight loss strategies, the long-term efficacy of such programs is generally poor, and the prevalence of overweight and obesity remains high. Nevertheless, there is a wide range of response to weight loss interventions, and one explanation could be variation in the genetic underpinnings that drive both response and adherence to weight loss interventions. Emerging evidence suggests that certain obesity risk alleles are associated with greater energy intake, specific macronutrient selection/composition, reduced satiety, and positive affective response and tolerance to exercise interventions. Individual genetic variation in dietary intake and physical activity behaviors can influence response to weight loss intervention and impact the degree of weight loss and weight regained.

In May of 2014, the National Institutes of Health's (NIH's) National Cancer Institute (NCI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung, and Blood Institute (NHLBI), and the NIH Office of Behavioral and Social Sciences Research co-sponsored a Trans-NIH Conference titled, "Genes, Behaviors, and Response to Weight Loss Interventions." Research experts in obesity, genetics, and behavioral and social sciences were brought together to discuss whether individual genetic variation influences diet and physical activity behaviors and response to weight loss interventions. The conference highlighted the potential implications for personalized, gene-based interventions for successful weight loss and maintenance.

The goal of the conference was to help collectively identify scientific priorities and inform the research agenda in obesity and behavioral genetics. To this end, the presenting researchers were asked to identify at least one gap or research priority in the field of obesity and behavioral genetics prior to the conference. A list was compiled and conference attendees voted for the research gaps and priorities they believed were most important.

Researchers presented current findings related to five key areas:

- Obesity genetics and weight loss;
- How genes influence regulators of energy balance;
- Gene–environment interactions in response to weight loss interventions;
- Functional approaches to gene discovery and obesity; and
- Implications for personalized, gene-based interventions for successful weight loss, maintenance, and adherence.

The presentations in each key area provided important context for the discussion sessions that followed the last presentation given in each area. The conference concluded with a lengthy general discussion session that included input from all presenters as well as from researchers and NIH scientists in the audience. The five most important research gaps and priorities, as chosen by conference participants, were revealed. The research questions receiving the highest number of votes are listed below:

- Can we use genetic information to predict who will become obese or who will respond to a weight loss intervention?
- What are the mechanisms that might underlie gene–lifestyle interactions in obesity and how can we detect and validate these?
- Can models be built from large-scale genomic data to utilize polygenic risk to inform effective personalized interventions for obesity or to identify families with highly penetrant rare variants?

- Does epigenetics play a role in weight loss interventions, and if so, how dynamic are epigenetic modifications and how might they be targeted?
- How might individual variation in response to dietary interventions inform innovation in intervention research?

These questions will be used as a guide for future research into understanding the interplay between genetics, obesity, and weight loss and for informing policymakers.

Opening Remarks

Tanya Agurs-Collins, PhD, RD

Program Director
Health Behaviors Research Branch (HBRB)
Behavioral Research Program (BRP)

William Klein, PhD

Associate Director, BRP
Office of the Associate Director (OAD)
Behavioral Research Program (BRP)

Dr. Agurs-Collins welcomed the presenters and attendees to the Trans-NIH Conference titled, “Genes, Behaviors, and Response to Weight Loss Interventions.” She introduced Dr. William Klein, who spoke about the Behavioral Research Program (BRP) at NCI. Dr. Klein welcomed everyone to the NIH.

Dr. Klein noted that the conference will focus on how multiple factors and levels interact to produce important health outcomes. The meeting marries two NIH priorities: genetics and genomics and a better understanding of obesity and energy balance. As an example of how committed the NIH is to furthering research on these topics, Dr. Klein mentioned the Obesity Research Task Force, a group that includes members from multiple institutes and centers, which has produced a strategic plan to help guide the science with regards to obesity and energy balance.

Dr. Klein expressed a need to fill in the knowledge gaps between the role of genomics, the environment, and obesity. He anticipated that the presentations given at the conference would stimulate discussion, generate research questions, and provide some possible answers about how best to move the science of obesity and weight loss forward. He thanked all the people within and outside NIH who helped coordinate the meeting, as well as the speakers for their participation.

Dr. Agurs-Collins pointed out the three aims of the conference, which were to understand whether individual genetic variation influences diet and physical activity behaviors, response to weight loss interventions, and the degree of weight loss and weight regain; to provide the scientific background to inform future personalized, gene-based weight loss interventions; and to highlight potential implications for personalizing gene-based interventions for successful weight loss and maintenance.

Dr. Agurs-Collins indicated that all the speakers were asked to identify key research questions prior to the meeting, and attendees were asked to vote for the two research questions they thought were most important to address. Dr. Agurs-Collins also thanked the meeting planning committee.

Presentations

Session 1
Weight Loss and Maintenance: Can We Predict Who Succeeds?

The aim of this session was to provide a general overview of intervention strategies that have been utilized for weight loss in a variety of studies and populations.

Deborah Tate, PhD
Associate Professor
University of North Carolina at Chapel Hill Gillings School of Global Public Health

Weight Loss and Maintenance: Can We Predict Who Succeeds?

Dr. Tate presented an overview of the challenges related to behavioral weight loss interventions. She outlined the current model for effective behavioral weight loss programs and explained what is typically available to researchers and clinicians as part of the behavioral modification toolbox.

Results from a number of different weight loss intervention trials, including but not limited to the Diabetes Prevention Program (DPP), Power Trial, and Look AHEAD (Action for Health and Diabetes), were presented. Individual factors such as race and gender, treatment factors such as duration and amount of physical activity prescribed, adherence factors such as self-monitoring, and environmental factors such as the built environment and social support were all considered contributing factors to the variability observed with weight loss intervention outcomes, which makes it difficult to predict an individual's response to a weight loss intervention.

Session 2
Obesity Genetics and Weight Loss: Complexity of the Issues

The aim of this session was to discuss the complex nature of the issues that impact our understanding of genetics of obesity and weight loss.

Ruth Loos, PhD
Professor and Program Director
Genetics of Obesity and Related Metabolic Traits Program
Department of Preventative Medicine
Icahn School of Medicine at Mount Sinai, New York

The Genetic Epidemiology of Obesity: Are the Genes That Make You Gain Weight the Same as Those That Make You Lose Weight?

Dr. Loos reviewed three classic research studies conducted in monozygotic twins that have provided evidence for a genetic component to weight change. She stressed that a limitation of some weight loss studies was that they included only overweight and obese individuals, who likely have an increased genetic risk of gaining weight.

Dr. Loos stated that 78 obesity-susceptibility loci had previously been identified through different genome-wide association scan (GWAS) studies. These loci have been associated with a range of obesity-

associated phenotypes such as body mass index (BMI), waist-to-hip ratio (WHR), weight loss, and childhood obesity.

Results from the recent **G**enetic **I**nvestigation of **AN**thropometric **T**raits (GIANT) consortium GWAS study identified 56 new loci associated with BMI and 35 new loci associated with WHR. An issue with the study was that BMI, which is a heterogeneous phenotype, represented only one point in time for an individual. Since physical activity has been shown to attenuate obesity risk associated with some genetic variants, BMI associated loci likely represent a combination of genetic and gene–environment interactions.

BMI loci are more likely associated with weight gain rather than weight loss, but they cannot predict obesity. The strongest and most consistent associations with BMI have been with variants located within or near the fat mass and obesity-related transcript (FTO) gene. Variants of the FTO gene accurately predict obesity about 55 percent of the time, which is only 5 percent more than chance alone. Including additional single nucleotide polymorphisms (SNPs) in the prediction equation does not substantially increase the predictive power of the model.

Although not predictive of obesity, the variants associated with obesity and weight change can help provide insight about the biology of obesity. The next step is to identify other genes, possibly causal genes, responsible for weight change. The GIANT consortium results identified variants that were expressed in the nervous system, particularly the hippocampus and limbic system, which is something that needs to be explored further.

With regards to weight loss interventions, few genetic studies have been conducted. One GWAS study that included patients who had bariatric surgery reported one allele that was associated with decreased weight loss following surgery, but it was not predictive of weight loss overall. Dr. Loos pointed out the need for larger-scale genetic studies and meta-analyses of all available results.

Michael Snyder, PhD

Professor and Chair of Genetics
Director, Stanford Center for Genomics and Personalized Medicine

Personalized Medicine: Personal Omics Profiling for Healthy, Overeating, and Disease States

Dr. Snyder's presentation covered the topic of personalized "omics" and individualized medicine. "Omics" research extends beyond genomics to include epigenomics, transcriptomics, proteomics, lipidomics, and metabolomics, thereby generating billions of measurements for one individual over time.

Dr. Snyder stated that the cost of sequencing an entire human genome has dropped considerably (and now costs less than $2,000), although the interpretation of a healthy person's genome is still quite expensive at approximately $15,000. Genomics on an individual level can be used to help predict disease risk; diagnose, monitor, and treat diseases; and improve our understanding of physiological and disease states. Integrating other omics information can be used to better diagnose and understand disease and health states.

Dr. Snyder introduced the term "iPOP," or integrative Personal Omics Profiling, which entails analyzing an individual's genome, along with their epigenome, transcriptome (including mRNA and miRNAs), proteome, metabolomics, auto-antibody profiles, and more recently, their microbiome. Attempts are being made to follow numerous molecules in a person's body as comprehensively as possible in order to better understand their physiological state.

Dr. Snyder told a personal story about how sequencing his own genome revealed a predisposition to Type 2 Diabetes (T2D). Because he is thin and active, he had never been tested for T2D, but he monitored his glucose (along with thousands of other molecules) and eventually acquired the disease, which was quickly caught and managed. Dr. Snyder suggested that individual genome analysis can

provide a starting point for individuals to find out more about their family history of disease, since many people do not know everything about their family health history. In a small study of whole genome sequencing in 12 individuals, Dr. Snyder and his group were able to provide all participants with valuable information regarding their disease risk.

Dr. Snyder also explored the heritability of DNA methylation by looking at the epigenetics of his parents. Additionally, he examined his own microbiome to identify and monitor changes during times of viral or bacterial infection. Layered on top of this biologic information, he collected physical activity data using wearable monitors.

Dr. Snyder's team has enrolled 60 pre-diabetic study participants for an iPOP study and is following them for 3 years. A subset of 20 study participants is also part of an overfeeding study to track biologic changes that take place during weight gain and weight loss. The weight gain aspect of the study has shown that certain insulin sensitive genes are repressed during this process. Other results of the study are just becoming available.

Dr. Snyder concluded that disease susceptibility is multifactorial and an omics approach may identify predisposing factors. Nevertheless, because an external or environmental exposure is often the catalyst for the disease, stress and comorbidity monitoring are important for understanding disease onset.

Discussion

Moderator: Molly Bray

The University of Texas at Austin

Drs. Loos and Snyder fielded questions from the group after their presentations:

Expression patterns of obesity-risk alleles were mentioned, and the mechanisms through which these genes implement behavior was questioned. Dr. Loos stated that pathways for which these mechanisms occur must be analyzed for more information. Dr. Snyder highlighted the importance of interactions between alleles that influence obesity and/or diabetes. Many systems may not have been considered yet that are interacting to produce obesity risk factors.

Whether behavior plays more of a role in weight loss efforts versus one's genetic composition was also discussed. Dr. Loos stated that genetics may regulate behavior and added that the brain regulates metabolism. She also stated that one's willpower during weight loss efforts may be centrally regulated by their genetic composition.

Both Dr. Loos and Dr. Snyder emphasized the importance of studying a healthy cohort's genome sequence as a baseline control, and to determine baseline behaviors. Healthy molecular phenotypes should be studied in order to place individuals into categories of risk. These categories can then be further distinguished by their individual responses to different treatments and/or behaviors.

Dr. Snyder added that while studying blood tissue can be meaningful, fat, skin, and even exhaled breath are often underutilized. In addition to those types of subject samples, it may be beneficial to study fecal samples for more information on the influence of the gut microbiome and energy balance.

Lastly, the cost-effectiveness of studying one's family history versus their genomic composition was questioned. Dr. Snyder stated that both family history and genomic composition are complementary—acquiring both will provide a clearer picture of the possible diseases. Genomic information may be more useful for individuals who are not aware of their family history of a disease. It is important to note that having specific sequences does not guarantee that an individual will get that disease, which is why family history is also important.

Session 3
Genetics of Energy Balance

The aim of this session was to focus on how genes influence the regulators of energy balance, specifically dietary and physical activity.

Paul W. Franks, PhD

Professor of Genetic Epidemiology
Lund University Diabetes Center, Sweden
Adjunct Professor, Harvard School of Public Health

Do Genes Modulate the Effects of Non-Resting Energy Expenditure Body Weight Regulation?

Dr. Franks started with the premise that the genome is the conduit through which the environment conveys its effects on health. He also pointed out that although most gene–environment interaction research in the area of obesity tends to focus on physical activity, attention should be paid to multiple behaviors and not just physical activity. To illustrate the way gene–environment interactions contribute to disease, Dr. Franks highlighted a publication about the interaction between genetics and behavioral and environmental risk factors for T2D among the Pima Indians. The study found that the incidence rate of T2D among Pima Indians in Mexico (who are traditional, subsistence farmers) is much lower than the rate of this disease among the Pima of Arizona (who lead a sedentary lifestyle and have adopted a Western diet).

Dr. Franks reviewed the complexity of gene–environment interactions and how the environment can act as a trigger for disease through extracellular signals that cause cellular changes, including receptor interference, somatic mutations, epigenetic modifications, and transcriptional and post-transcriptional modulation. He noted that gene–environment interactions are dynamic, and therefore, it is important to obtain repeated measures over time. Empirical historical examples for gene–environment interactions in both animals and humans were also presented.

Dr. Franks discussed results of a systematic review of 212 studies that explored gene–environment interactions. The major findings from this review were that, for predominately GWAS-based studies, variants of the FTO gene were associated with obesity-related traits most often. Conversely, in predominately smaller biologic candidate gene-based studies, variants of the PPARG gene were the most frequently associated obesity-related loci. Dr. Franks presented results from several studies showing that increased physical activity attenuates one's genetic predisposition to obesity. Conversely, he presented results showing that low levels of physical activity accentuate the effect of the high-risk FTO gene variant on body fat accumulation. The study found that when people were active, the effect of the high-risk FTO gene variant was reduced by up to 30 percent.

Dr. Franks noted that BMI, rather than adiposity, was used as an outcome in many of these studies. BMI is typically used because it is an easy measurement to obtain from participants, but the limitations of BMI are well established. Dr. Franks commented that researchers should strive to obtain objective measures of body composition rather than rely solely on BMI. He also stated that there is a need for studies to be designed specifically to answer questions about genetics rather than depending on information collected as part of clinical trials or epidemiologic cohort studies.

Dr. Franks concluded that it is plausible that complex traits are caused to some extent by gene–environment interaction. There is evidence of gene–environment interactions with obesity, as shown by the attenuation effect of physical activity on high-risk variants of the FTO gene. He emphasized that even the better genetic studies that use sound statistical approaches often lack good replication data, and therefore, the results may be population specific, non-causal, or simply false signals of association.

Newer study methods and designs are emerging that will likely make it more feasible to detect gene–environment interactions; however, it will be necessary to identify interactions and confounding as part of the statistical analyses. Dr. Franks ended by saying that the major goal of the research on the genetics of obesity and weight loss is to be able to translate findings into meaningful clinical practice, and this should be kept in mind for current and future studies.

Lu Qi, PhD

Assistant Professor in the Department of Nutrition
Harvard School of Public Health
Boston, MA

Genes, Diet, and Obesity

Dr. Qi began by discussing the multiple risk factors for obesity, with a focus on dietary intake. He noted that genes associated with energy intake, such as those highly expressed in the hypothalamus region of the brain, are often involved in weight gain and obesity.

Dr. Qi reviewed research from his group showing the link between sugar-sweetened beverage consumption and the genetic risk for obesity as well as very recent findings demonstrating the effects of gene-diet interactions with fried food consumption and obesity.

For a study examining the relationships between fried food consumption, genetic susceptibility, and obesity, Dr. Qi's group utilized data collected as part of the DietGen consortium (which includes the Nurses' Health Study, Health Professionals' Follow-Up Study, and the Women's Genome Health Study). Subjects were grouped by their genetic risk score based on genotype at multiple obesity loci (high or low). An analysis of participants' weekly fried food consumption and BMI revealed a gene–diet interaction. In all three cohorts studied, BMI was higher in those who ate fried foods more often; however, the association between fried food consumption and BMI was stronger in those who had a high genetic risk score.

Given that fried food consumption is only one aspect of a person's diet and lifestyle, confounding with low physical activity and consumption of other high calorie foods such as sugar-sweetened beverages is likely. However, such influence has been carefully controlled in analyses. Furthermore, there may be important differences based on the type of oil used for frying. This was an observational study and the results may be also subject to other potential bias such as reverse causation, although prospective design of the included cohorts might partly lower such risk. As it was not possible to directly evaluate the participants' responses to different dietary and environmental exposures in observational settings, it is essential to test gene–diet interactions in the context of randomized clinical trials as well.

Dr. Qi finished by summarizing and comparing the results from the POUNDS Lost Trial (a 2-year intervention trial whereby 811 overweight adults were assigned to one of four diets with different macronutrient compositions) and the DIRECT Trial (also a 2-year intervention trial that assigned 322 overweight individuals to one of three diets that varied by fat composition). Both studies found significant interactions between diet and insulin levels with the high-risk genotype in the IRS1 gene. Dr. Qi concluded by saying that the results from these trials provide evidence that there are feasible applications for personalized nutrition in the future, and that additional research into the genetic basis of weight loss and weight gain will help shed light as to how best to use genetic information for tailoring personalized medicine.

Xifeng Wu, MD, PhD

Professor and Chair
Department of Epidemiology
Center for Translational and Public Health Genomics, University of Texas
MD Anderson Cancer Center

Energy Balance, Genetics, and Cancer Risk

Dr. Wu began her presentation by describing the epidemiologic roadmap and the efforts her research team is making with integrative risk assessment of cancer, which combines information about environmental exposures, genetics, lifestyle factors, clinical variables, and phenotypes to create personalized risk models. These models will help improve personalized medicine and therapies as well as influence public attitudes, practices, and policies in medicine and public health.

Dr. Wu reviewed research related to physical activity as a modifiable risk factor for disease. Very few people meet standard physical activity guidelines, but a recent study showed that just 15 minutes of physical activity per day reduced mortality by 14 percent, with each additional 15 minutes reducing mortality by an additional 4 percent, compared to sedentary individuals.

Dr. Wu's team adapted the MPOWER approach, typically used for smoking behavior modification, to physical activity. In their study, both energy intake and physical activity were associated with incidence of renal cell carcinoma (RCC). High-risk alleles in the mTOR pathway were found to be associated with RCC and bladder cancer risk, and this risk increased with obesity and low levels of physical activity.

Dr. Wu also described research in which a metabolic risk score was computed for individuals based on their L-proline, BHBA, and D-Mannose levels. A high metabolic risk score, combined with having a BMI greater than 30 kg/m^2, was found to be associated with an increased risk for esophageal adenocarcinoma. Additionally, when Dr. Wu's team measured 93 candidate miRNAs in both normal tissue and RCC tumor tissue, they found that 12 miRNAs were differently expressed in obese versus non-obese patients, and nine miRNAs were differently expressed in patients with recurring versus non-recurring cancers; four of the miRNAs were common to both comparisons.

Dr. Wu noted that single cross-sectional tissue images taken using computer tomography (CT) scans have been shown to correlate significantly with whole-body volumes of muscle and adipose tissue. She suggested that this information can be used to categorize body composition in a way that is much more informative and meaningful than BMI. Dr. Wu ended her presentation by stating that combining genetic and biomarker information with lifestyle factors and exposures can help inform and develop evidence-based personalized interventions for patients.

Discussion

Moderator: Jeanne McCaffery

Brown University

Questions were not taken for the sake of time; individuals were encouraged to discuss questions with colleagues prior to lunch.

Session 4
Gene–Behavior Interactions in Response to Weight Loss Interventions

The aim of this session was to examine the interaction between genes and behaviors including eating behaviors, exercise adherence, exercise tolerance, and weight regain.

Molly Bray, PhD

Professor and Susan T. Jastrow Chair for Excellence in Nutritional Sciences
Department of Nutrition Sciences
The University of Texas at Austin
Austin, TX

The Genetics of Physical Activity and Exercise Adherence

Dr. Bray started by explaining that both eating and physical activity are health behaviors, and that individuals who are either obese or exceedingly lean may engage in activities that are on the extremes of the spectrum of these health behaviors. Dr. Bray stated that many researchers believe that there is a genetic component involved with health behaviors. She went on to say that the spectrum of persistence in a behavior from non-adherence (no persistence in the behavior) to addiction (continual persistence in a behavior that may be psychologically and/or physically driven) could be driven by the same genes.

Health behaviors are known to aggregate in families, but this could be a result of a shared cultural and social environment rather than genetics. Physical activity in humans has been shown to be heritable, but the range of heritability in these studies is quite broad (ranging from .10 - .85). Additional proof of the heritability of physical activity can be found in the fact that animals can be bred for increased levels of physical activity, with the brain reward system and metabolic pathways having been found to be key elements in this process.

Dr. Bray presented the research she conducted in the Training, Interventions, and Genetics of Exercise Response (TIGER) study, which looked at how genes influenced response to a controlled physical activity protocol. Subjects were asked to do 30 minutes of high-intensity aerobic exercise three times per week, and each person's total exercise dose was calculated using information obtained from heart rate monitors. During the study, subjects were asked about changes in their mood, energy, depression, and anxiety levels. Those adherent to the exercise protocol experienced positive health changes in all categories. Exercise intensity was the best predictor of positive health outcomes. Some subjects experienced dramatic changes (both positive and negative) resulting from the exercise protocol, which Dr. Bray suggested may indicate a genetic basis for responses to exercise.

When the genetics of those in the TIGER study were analyzed, five variants in the FTO gene were associated with exercise non-adherence. In a replication study, one of these five SNPs was again found to be associated with exercise non-adherence. Furthermore, FTO methylation was found to differ by the number of risk-raising FTO alleles an individual had.

Dr. Bray summarized by saying that there is evidence from animal and human studies indicating that physical activity is heritable, but in no instance does genetics explain completely the variability in traits and behaviors observed in populations. With regard to weight loss interventions, it seems that the behavioral intervention component is key. Research in the area of obesity genetics has identified neural pathways involved in the reward system as well as metabolic pathways that are likely important in influencing weight loss adherence and tolerance to exercise and intervention treatments.

Jeanne McCaffery, PhD

Associate Professor
Department of Psychiatry and Human Behavior, Brown Medical School
Staff Psychologist, The Miriam Hospital
Providence, RI

Genetic Predictors of the Ability to Lose Weight: Evidence from the Look AHEAD Trial

Dr. McCaffery began by discussing the potential of personalized medicine leading to more accurate diagnoses and tailored treatments. To date, personalized medicine has focused primarily on pharmaceutical treatments, although behavioral treatments could also be personalized. Individuals differ in magnitude of weight loss and weight regain, even when enrolled in state-of-the-art interventions. More research is needed regarding the heritability of weight beyond the small twin studies that are often cited as the evidence base for there being a genetic component to weight gain. Dr. McCaffery explained the potential for using genetic testing to identify and motivate high-risk individuals, once more is known about the specific genetic factors that impact the ability to lose weight with behavioral interventions.

Dr. McCaffery presented results from genetic studies that were part of the Look AHEAD Trial. High-risk variants of the FTO and BDNF genes were associated with increased calorie intake, and FTO was specifically linked to an increased number of eating episodes and fat intake. Additionally, variants of the FTO, SH2B1, and QPCTL genes were associated with baseline BMI, although there were no statistically significant associations when looking at weight loss one year after baseline. A variant of the FTO gene was also associated with weight regain in the diabetes support and education arm but not in the intensive lifestyle intervention arm.

Dr. McCaffery also discussed results of a meta-analysis that combined data from Look AHEAD and the DPP. The meta-analysis found that the MT1F3 gene was associated with decreased weight loss during the intervention, although other high-risk genotypes for obesity were not associated with weight loss. Additional exploratory analysis was conducted using all available SNPs, not just those related to obesity, and several genes were identified as possibly being related to weight loss. These included the ABCB11, G6PC2, TNFRSF11A, and AANAT genes. None of the SNPs reached statistical significance for weight regain. Other genes were associated with HDL cholesterol changes including the CETP, LPL, and LCAT genes, which may be more predictive in diverse populations.

Dr. McCaffery ended by saying that personalized behavioral medicine is still a possibility but more work is needed to identify and characterize the genes, rare variants, and pathways involved in weight loss. Phenotypes related to obesity (e.g., cardiovascular disease) also need to be understood more fully. Communicating genetic information is also important as personalized medicine progresses.

Toni Pollin, MS, PhD

Associate Professor of Medicine, Epidemiology, and Public Health
Division of Endocrinology, Diabetes, and Nutrition
University of Maryland School of Medicine
Baltimore, MD

Genes, Diet, Exercise, Drugs, and Metabolic Syndrome: How Do They All Connect?

Dr. Pollin began with an overview of the DPP and a discussion of the genetic results of the study. First, the high-risk genotype for a SNP in the TCF7L2 was associated with increased cumulative incidence of

T2D. Second, a variant of the OCT1 gene was associated with an altered response to Metformin, and pre-diabetics who had the high-risk genotype had a shorter diabetes-free survival period.

Additionally, lifestyle interventions were found to attenuate the effect of the TCF7L2 risk allele, although variants of the TCF7L2 gene only explained a small amount of the differences observed with diabetes risk. However, testing pre-diabetics for this variant presents an additional set of challenges, as it is difficult to know how patients will perceive genetic risk information that isn't clearly defined. Conversely, genetics can also reduce the impact of lifestyle changes. Dr. Pollin presented research showing that individuals with a high genetic risk profile for dyslipidemia experienced a smaller decrease in small LDL particles following adherence to lifestyle interventions, compared to individuals with a low genetic risk profile.

Dr. Pollin also discussed the results from a longitudinal cohort consisting of Amish families. High levels of physical activity were shown to abolish the association of FTO gene variants and BMI. A variant of the APOC3 gene, R19X, was also found to be linked to lipoprotein metabolism, although it was unclear if this was due to a founder effect in this population. Selection could also have been a factor, given the large quantity of animal products in the Amish diet. Other findings from this cohort include the link between an APOC3 gene variant and decreased artery calcification as well as reduced dyslipidemia among those at risk for T2D. Furthermore, a diabetes risk allele in the GRB10 gene appeared to dampen the effect of lifestyle interventions to enhance insulin secretion.

In summary, Dr. Pollin stated that studying gene–diet and gene–activity interactions with obesity-related traits in different populations reveals differential responses that enhance the biologic understanding of the genetic basis for weight loss and weight gain. However, she warned that it is still too early to determine the extent to which individual genetic variance data will be used for personalizing diet and physical activity interventions.

Discussion

Moderator: Tanya Agurs-Collins

National Cancer Institute, NIH

Drs. Bray, McCaffery, and Pollin fielded questions from the group after their presentations:

Utilizing genetics for personalized medicine versus creating stratified medicine for subgroups was discussed. Stratified medicine created for subgroups was voted as more likely to be implemented. Genetics may also provide leads for characterizing adjunct biological systems. How personalized medicine applies to the population was also discussed: if access to individual genomic data increases, personalized medicine may be possible.

Personalized and/or stratified medicine may also be utilized to guide weight loss interventions. Researchers are hoping that genetics can shed more information about why individuals who do not adhere to diet and exercise interventions have not been well studied. Also, it appears that individuals are biologically driven to gain weight even though they do not want to. The perspective of psychiatry and psychology may be help to explain this phenomenon.

An additional question that was posed to the group was, why are people taking in more energy than they need? Researchers believe that food intake is imprinted within the genes in the brain at a very young age. If you overfeed an animal at an early age, those standards may be imprinted within the brain of that animal. It may be hard to alter that standard. However, there is promising technology that aims to alter certain cells and possibly reverse these imprints.

Questions were asked about the most important aspect of weight loss maintenance. According to the researchers who presented during the session, mechanisms that contribute to obesity, weight loss, and weight regain may be distinct—these should be investigated further. Behavioral components may also allow certain individuals to maintain their weight; however, this has not been studied in depth.

Session 5
Functional Approaches to Gene Discovery and Obesity

The aim of this session was to examine functional approaches to gene discovery. This included the effect of epigenetics, gene functional analysis, and the microbiome in weight loss.

George M. Weinstock, PhD

Professor
The Jackson Laboratory for Genomic Medicine
Farmington, CT

The Human Microbiome in Health and Disease

Dr. Weinstock began his presentation with an overview of the microbiome and emphasized that unlike genes, which are fixed, the microbiome changes. He pointed out that researchers should think about the microbiome ecologically, as microbes exist in communities that have adapted to the body's environment and to other communities of microbes.

Dr. Weinstock explained the two different methods in which metagenomic experimental designs are carried out. The first method involves sequencing 16s rRNA in a sample in order to obtain the taxonomy of the host's microbiome. Pairwise comparisons are computed for the presence or absence of certain microbes and the abundance of a specific type of microbe (essentially, 16s rRNA analysis groups the microbiome into different enterotypes). The second method uses shotgun sequencing, where different bacterial communities can be identified at each body site. The microbiomes from different body sites have been shown to be distinct (e.g., bacteria from a tooth sample can be differentiated from bacteria isolated from a tongue sample).

In addition to bacteria, individuals have different viral DNA present in their microbiome—in particular, herpes and human papilloma—but viruses are largely ignored despite the fact that they can trigger disease. An individual's microbiome can change based on changes to the community structure (biodiversity), concentration of a specific organism type, and gene expression in pathways that affect the microbiome.

Dr. Weinstock explained that it has become well accepted that the host's microbiome correlates with disease susceptibility; however, we don't know if this is a cause or an effect. It is still unclear if information about the microbiome can be useful as a diagnostic tool or as a target for treatment. Obesity has been shown to be associated with changes in composition of the gut microbiome. Obesity has been linked to a decrease in overall diversity in the gut and to changes in specific types of gut bacteria. In animal models, implanting an "obese type" microbiome in healthy mice makes them gain weight, and this effect is negated upon the subsequent introduction of a "lean type" microbiome, suggesting a direct causal relationship.

To date, human and animal studies have yielded conflicting results about the associations between the microbiome composition and obesity, likely due to many confounders. Dr. Weinstock concluded by saying that understanding the microbiome is a promising field of research but much still remains to be explored.

Charlotte Ling, PhD

Professor and Investigator
Epigenetics and Diabetes Unit
Lund University Diabetes Center, Sweden

Epigenetic Changes Associated with Exercise, Diet, and Disease: Implications for Energy Balance

Dr. Ling began by describing the risk factors for T2D, which include age, genetics, intrauterine environment, diet, obesity, low levels of physical activity, and epigenetic factors such as DNA methylation and histone modifications.

Dr. Ling talked about a study with monozygotic twins, discordant for T2D and obesity, who had subtly different epigenetic characteristics even though they shared the same gene sequences. Adipose tissue and blood samples were collected from the discordant monozygotic twins and tested for gene expression and methylation. Genes that showed a decrease in expression in the twins with diabetes were mainly involved in metabolism, whereas genes that showed an increase in expression in subjects with diabetes were involved in glycosylation and inflammation. Some of these gene expression patterns have also been replicated in non-twin studies among obese and non-obese individuals.

Dr. Ling pointed out that, although there were no differences in global methylation by disease type within the discordant monozygotic twin pairs, the degree of methylation varied in different regions of the genome. The average methylation level was high within the gene body, 3' untranslated region (UTR), and intergenic regions, while it was low within CpG islands and intermediate within shores.

Although methylation was highly correlated across the entire genome within monozygotic twins, the data suggested that small differences in methylation patterns at specific loci were associated with disease. In fact, dizygotic twins and unrelated individuals have more differences in their methylation patterns than monozygotic twin pairs. Although methylation differences were observed between the discordant (for diabetes) twin pairs at more than 23,000 specific CpG sites, none remained significant after adjusting for multiple testing. In a separate T2D case-control cohort of unrelated individuals, methylation patterns were analyzed in human skeletal muscle and adipose tissues, and 50 percent of the more than 14,000 CpG sites were found to have altered methylation in the diseased individual compared to the control.

Extensive analysis was also done on pancreatic islet cells in diabetic and non-diabetic subjects, and the differences observed were not due to altered cell composition, but rather to differences in epigenetic methylation patterns. In this study, more than 50 percent of T2D-related SNPs either introduced a new CpG site or removed an existing CpG site, which led to changes in DNA methylation in islet cells.

Dr. Ling summarized by stating that there is a genetic basis for altered DNA methylation as shown in the study of monozygotic twins discordant for T2D who exhibited differential DNA methylation in their skeletal muscle and adipose tissue. Additionally, altered DNA methylation has been observed in the pancreatic islets of subjects with T2D. Furthermore, a high-fat diet and exercise have been shown to alter DNA methylation in human skeletal muscle tissue, and exercise has been associated with altered DNA methylation in adipose tissue. Dr. Ling finished by saying that there exists a strong interaction between genetics and epigenetics.

George Argyropoulos, PhD

Staff Scientist
Geisinger Health System
Weis Center for Research
Danville, PA

Genes and Mechanisms Modulating Weight Loss and Diabetes Remission After Bariatric Surgery

Dr. Argyropoulos began by describing characteristics of a large cohort of more than 3,200 individuals who have undergone bariatric surgery, in particular the diabetes remission associated with weight loss following surgery. Electronic health records were available for all participants in this cohort, and these records provided a wealth of individual variables to include in outcomes prediction models designed to determine factors associated with response to surgery (e.g., comorbidities, body metrics, and perioperative condition).

The bariatric surgery cohort provided the unique opportunity to perform functional studies in multiple tissues that might predict surgical response. The results of gene expression assays conducted using samples collected from the study subjects revealed differences in adipose gene expression by type of adipose tissue: epigastric, visceral, or subcutaneous. There were a number of unique genes and pathways associated with each adipose tissue type, although the epigastric and visceral adipose tissues appear to share more genes and pathways compared to subcutaneous. The functional importance of the unique genes in adipose tissue types remains to be determined; however, there is speculation that if expressed in circulating leukocytes, these genes could be used to help determine an individual's adiposity and/or disease state.

Dr. Argyropoulos then discussed the role of fibroblast growth factor 19 (FGF19) and bile acids in diabetes remission following Roux-en-Y gastric bypass (RYGB) surgery. Attenuation of fibroblast growth factor signaling in mouse beta cells has been associated with diabetes. Bile acids (whose synthesis from cholesterol in the liver is modulated by the enzyme CYP7A1) induce enteric FGF19 gene expression, which in turn leads to increased release of bile acids. Before RYGB surgery, FGF19 circulating levels are lower and hepatic CYP7A1 gene expression is higher in diabetic patients. After surgery, however, both bile acids and FGF19 increase, especially in people who experience diabetes remission. Diabetes remission after RYGB surgery is likely due to the intestinal realignment that takes place, which prevents bile acids from mixing with food, making the bile acids more potent and better able to stimulate FGF19 expression. Increasing FGF19 expression appeared to be beneficial as it re-equilibrated the FGF19-CYP7A1-BA pathway in the liver, and sensitized the liver to insulin. FGF19 could be increased by using pharmacologic or natural agonists; for example, meal replacement drinks and coffee have been shown to up-regulate FGF19.

Dr. Argyropoulos also reported the development of the DiaRem score, which is a method for predicting, preoperatively, the probability that a patient has for remitting diabetes after RYGB surgery. Patients who were responsive to metformin, preoperatively, were more likely to experience diabetes remission after RYGB surgery. Patients that had to use insulin, however, had the lowest probabilities for remitting diabetes, but addition of a glucagon-like peptide 1 agonist to their therapy significantly improved their diabetes remission rates.

Discussion

Moderator: Cashell Jaquish
National Heart, Lung, and Blood Institute, NIH

Researchers discussed mutations in the microbiome, but stated that no specific SNP-chip is available currently. When shotgun sequencing is conducted, SNPs may be identified. Variation analysis is conducted on hundreds of microbial species in parallel. After bariatric surgery is conducted, the microbiome in the GI tract is radically altered; studies have been conducted on mice to demonstrate this is the case.

Researchers were asked whether fecal transplants could ever become a treatment for obesity. Researchers do not believe so, as it is not clear how or why they work, but they do have a high success rate. For obesity, it is not clear what the drivers are. The goal is to acquire precise definitions of the interactions of the microbiomes.

Session 6
Implications for Tailoring Gene-Based Interventions for Successful Weight Loss, Maintenance, and Adherence

This session focused on the use of genetic information when tailoring weight loss intervention studies.

Colleen M. McBride, PhD
Chief and Senior Investigator
Social and Behavioral Research Branch
National Human Genome Research Institute
Bethesda, MD

Using Genomics to Improve the Effectiveness of Dietary Interventions

Dr. McBride introduced her presentation by asking how emerging genomic knowledge can improve behavior change interventions. She then discussed issues related to translating genomic information to the public and patients as new knowledge is acquired about the role of genes in disease and tailoring or targeting information to individuals based on their own genetic profile. Early studies showed that when genetic information was provided to patients, it had only a small effect on diet change, although those studies were small. These studies illustrate that more must be known about how best to communicate the effect of gene–environment interactions on health outcomes, especially when the genetic variants are single variants that, individually, contribute little to risk for disease. Dr. McBride questioned whether metaphors could help communicate information about gene–environment interactions, specifically if metaphors could enhance coherence of interventions or increase engagement with interventions.

Dr. McBride explained that family history is the “first genetic test,” and obtaining family history information has been shown to create communication processes within families. However, there is a lack of sufficient evidence to assess the effect family health history has on health behaviors and behavior change.

Dr. McBride talked about a study showing that patients had more concern for their health when they were given genetic information as part of a family health history compared to the same information being presented as a genetic test. Another study showed that when mothers were given different types of information about food and then asked to select foods in a virtual cafeteria, the mothers who were obese and received family history information had the highest levels of “genetic guilt” and chose lower calorie foods.

Dr. McBride presented additional examples to demonstrate that genetics can provide information about individual variation and can help shed light as to why some people have difficulties adhering to behavioral interventions. She also mentioned that obtaining blood samples during interventions to monitor epigenetic and other biomarkers will help provide more information about genes that are associated with obesity. Dr. McBride added that she would ideally like to see clinical trials that were randomized based on genotype.

Dr. McBride concluded that tailoring dietary and weight loss information can result in better long-term outcomes and can lead to interventions that are a better fit for the individual; however, more investigation into the comparative benefits of targeting versus tailoring interventions is needed.

Jason Vassy, MD, PhD, SM

Instructor in Medicine
Brigham and Women's Hospital
Division of General Internal Medicine
Jamaica Plain, MA

Motivating Behavior Change with Genetic Testing: The Genetic Counseling/Lifestyle Change Study for Diabetes Prevention

Dr. Vassy reviewed the components of the DPP for prevention of T2D and pointed out that poorer results are observed in the general population compared to study participants. Personalized genetic information has been proposed to be a strong motivator for behavior change but the clinical impact of this information is still not well known. In some cases, there is a concern that individuals who have a low genetic risk profile may become less motivated if they do not perceive they are at risk, while those who have a high genetic risk profile may become less motivated if they think their predisposition to disease has already been determined by their genes and behavior change will not make a difference.

Participants in the Genetic Counseling/Lifestyle Change (GC/LC) Study were randomized to receive diabetes genetic susceptibility testing versus no testing prior to starting the DPP intervention. Following the intervention, patients were surveyed about their attitude, confidence, and motivation in order to evaluate if prior genetic information had an effect on behavior or adherence to the intervention and if it led to better health outcomes. Adherence to the intervention and amount of weight lost were similar across the genetic risk groups. However, participants who were told prior to the intervention that they had a high genetic risk for developing diabetes were more motivated to change their diet. Subjects who were told they had a low genetic risk were less motivated to increase their physical activity.

Dr. Vassy concluded that, in the GC/LC Study, prior knowledge about genetic risk neither added nor detracted from the DPP intervention results. Questions still remain as to which subgroups of patients might still benefit from being provided with genetic information prior to an intervention. Additional questions need to be addressed, such as whether interventions can be tailored to specific genotypes and if more precise genetic tests would be helpful to patients.

Deborah Tate, PhD

Associate Professor
University of North Carolina at Chapel Hill
Gillings School of Global Public Health

Methods for Pooling Weight Loss Interventions: To Pool or Not to Pool?

Dr. Tate proposed the types of questions that could potentially be answered by pooling weight loss intervention data. Specifically, do people with different genes respond differently to different types of weight loss interventions? Personalized medicine already relies on subgroup characteristics that influence response to different treatments. This approach could be applied to weight loss interventions as well.

Most weight loss or weight maintenance clinical trials typically include only 100 to 200 participants and are limited to one experimental arm. Pooling study data may provide larger sample sizes for analysis and allow more diverse interventions to be evaluated. In order to pool data, each study needs to be well characterized so overlapping versus unique interventions can be identified. The studies also need to have common outcome measures and control variables. The statistical methods used also need to control for certain variables while exploring others. As behavior change techniques are standardized and linked to specific theories, pooling data across studies will be more feasible.

Dr. Tate presented results from the Early Adult Reduction of Weight through Lifestyle Interventions (EARLY) Trials, which took place at seven different sites. Each site had its own study population and a unique set of hypotheses, interventions, and outcomes. In order to pool the data from these seven sites, a set of common data elements was identified. Identifying variables a priori to be uniformly measured enabled pooled analysis for at least a subset of the data. Dr. Tate concluded by saying that interventions have to be more accurately defined in terms of diet, exercise, and behavior prescribed and received in order for data to be pooled. To this end, an NHLBI and NIH Working Group is in the process of developing a behavior change taxonomy that will help classify the key or active components of behavior change interventions.

Discussion

Moderator: Erica Spotts

Office of Behavioral and Social Science Research, NIH

Dr. Vassy was asked whether there was a specific level or threshold of genetic risk that might encourage people to respond to the information. He stated that this might be the case but, because the study did not examine the effect of using different levels of risk, this could not be determined from the study as it was conducted. Including more than one level of risk might be an informative next step in future studies.

Whether patients with metabolic syndrome should have been included was discussed. Dr. Vassy stated that other trials have studied the general population; patients with metabolic syndrome were studied as the researchers felt that they were a high-risk group. They wanted to test the hypothesis on a high-risk population and determine whether genetic risk counseling would affect this population. Genetic risk was based on 36 SNPS.

It was found that weight loss in low-risk groups was similar to weight loss in high-risk groups. Dr. Vassy felt that low-risk individuals were less worried and concerned and more willing to engage in healthy behaviors, ultimately leading to weight loss. He added that the low-risk group was very motivated to pay attention to their lifestyle as they realized their risk was not dependent upon their genes.

High- and low-risk individuals also did not differ in terms of BMI and fasting glucose. The groups did not differ greatly in their motivation to change their diet and physical activity habits, although more precise measurements such as food frequency questionnaires or pedometers were not used.

One researcher stated that it may be misleading to characterize an individual as high risk, because the full spectrum of alleles (e.g., non-risk alleles, protective alleles) that that individual might carry was not determined. Unless the study genotypes the entire individual and all of the alleles that might contribute to disease progression, one cannot make a true inference about that individual's risk of the disease.

Dr. Vassy agreed and stated that every patient is different and that this study focused on how patients respond to qualitative genetic risk (high versus low) instead of absolute numeric risk.

Researchers felt that genetic risk communication and information delivery should be considered further. Thus far, the genetic counseling model has been followed; however, risk information may not be sufficient to invoke a response. The genetic counseling model should be reconsidered.

Dr. Vassy added that heritability was not conveyed in the study as they were not stratifying risk—the study was testing motivation. Time spent completing interventions and affect should be studied further as interventions may need to be individually tailored.

Conclusions
Determining Gaps and Priorities for Future Research

The aim of this session was to identify research gaps and priorities to advance the science on genes, behaviors, and response to weight loss interventions. This session was moderated by Dr. Philip Smith, NIDDK. All speakers, as well as members of the audience, were invited to participate in this discussion.

Philip Smith, PhD

Deputy Director, Division of Diabetes, Endocrinology, and Metabolic Diseases
Co-Director, Office of Obesity Research
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institutes of Health (NIH)

Gaps in the Scientific Knowledge Regarding Genetics and Weight

Dr. Smith laid out the pros and cons of using common genetic variation to personalize therapeutic approaches. Genetic markers are incredibly stable over time and the cost of genotyping is low. Genetic testing also does not require *a priori* knowledge of function. The downside of identifying common genetic variants, however, is that the information must be considered in the context of all of the other variants in an individual. It is also challenging to know which genetic markers to use when creating interventions and knowing what to do for those individuals who do not respond to the intervention.

Currently, there is a very rudimentary knowledge base of gene function with regard to genes associated with obesity and weight loss. There is also little basis for assuming obesity risk genes are related to pathways involved in adherence and response to interventions. Few studies have examined the genetics of individuals who adhere to an intervention.

Meeting presenters and attendees discussed whether the response to weight loss interventions or one's persistence during weight loss interventions is similar. Some believe that persistence ultimately leads to a response, but that persistence itself may be influenced by genetic variation. There were also questions regarding whether some individuals are resistant to losing weight, or if these individuals are simply not compliant with the intervention. Markers associated with compliance need to be identified. It was also suggested that there may be an interaction between genes and response to an intervention, and that response to an intervention may also drive compliance. Since quantifying the response to weight loss interventions is difficult, markers, such as gene variants, blood biomarkers, microbiome classifications, behaviors, prior history with weight loss attempts, taste preferences, and family health history, are needed to distinguish responders from non-responders.

Also discussed was how cognitive issues (i.e., impulsivity) impact response to weight loss interventions. For example, if researchers can prove that impulsivity is biologically plausible, then this variable might influence response in some individuals. The possibility of conducting GWAS on impulsivity and whether GWAS-derived loci were likely to interact with environmental factors was discussed.

Methodological Issues

Several methodological approaches that can be utilized to determine which genetic variants to test were discussed. Since GWAS requires a large number of samples for associations to have statistical significance, family studies may be an acceptable alternative because they require thousands rather than hundreds of thousands of individuals. Dr. Smith suggested a crowd-sourcing option for people to provide their genetic information as a way to increase the number of available samples. Also, researchers agreed that a candidate pathway approach has not panned out as well as GWAS studies, but that the candidate pathway approach should be explored further.

Positive trial design needs to be utilized where those at the extremes of the distribution are included and multiple interventions are tested to observe which subjects respond to which strategies the best. Developing markers for subgroups is also critical to determining the optimal intervention approach. It was suggested that researchers include more discovery-based capabilities into clinical trials and re-examine existing data. Dr. Smith also pointed out that statistical methods are needed for layering different types of omics information with multiple other types of information (e.g., demographic and behavioral).

Future Directions

The research gaps and priorities that received the most votes from conference presenters and attendees were the following:

- Can we use genetic information to predict who will become obese or who will respond to a weight loss intervention?
- What are the mechanisms that might underlie gene-lifestyle interactions in obesity and how can we detect and validate these?
- Can models be built from large-scale genomic data to utilize polygenic risk to inform effective personalized interventions for obesity or to identify families with highly penetrant rare variants?
- Does epigenetics play a role in weight loss interventions, and if so, how dynamic are epigenetic modifications and how might they be targeted?
- How might individual variation in response to dietary interventions inform innovation in intervention research?

These research questions can serve as a guide for creating research initiatives designed to increase understanding of the interplay between genetics, obesity, and weight loss, and for informing policymakers about these issues.

Speaker Biographical Descriptions

George Argyropoulos, Ph.D.

Dr. Argyropoulos complete his graduate studies (MS and Ph.D.) on “mouse genetics of gonadal development” at the University of Essex, England U.K. He completed his post-doc at St. Mary’s Hospital, Imperial College and then moved in 1995 to the Medical University of South Carolina, in Charleston, SC. In collaboration with Tim Garvey and Mark Reitman of NIH, he identified the human UCP3 and reported associations of UCP3 with fat oxidation in African Americans. While he remained involved in human genetics projects, he turned his attention to genes involved in the central regulation of energy homeostasis and in particular the neuropeptide agouti related protein. At the Geisinger Clinic, Dr. Argyropoulos joined a group of clinical investigators that use Roux-en-Y gastric bypass (RYGB) as a means of treating obesity. He turned a big component of his research towards exploring mechanisms that mediate diabetes remission after RYGB surgery, which is one of the few interventions that lead not only to weight loss but also to diabetes remission. The group has shown that the FGF19-CYP7A1-bile acids (BA) pathway is dysregulated in T2D but becomes normalized after RYGB surgery. The group has performed several other studies along the same lines of research and also pioneered a scoring system (the DiaRem score) for predicting preoperatively the probability of diabetes remission following RYGB surgery. His research interests continue to be centered on the BA-FGF19/21-GLP1-insulin pathway which he considers to be a major integrator of the pathogenesis of diabetes and its remission following RYGB surgery.

Molly S. Bray, Ph.D.

Dr. Bray is a nationally recognized expert and a featured speaker on the genetics of obesity, energy balance, and exercise response with a master’s degree in Exercise Physiology and a PhD in Human and Molecular Genetics. She is a professor and holds the Susan T. Jastrow Endowed Chair in the Department of Nutritional Sciences at the University of Texas at Austin. She also served as the former Director of the Heflin Center for Genomic Science Genomics Core Laboratory at the University of Alabama at Birmingham and the Children’s Nutrition Research Center/Baylor College of Medicine Genetics Core Laboratory. Dr. Bray’s research focuses on the relationship between energy balance and lifestyle factors such as exercise, nutrition, and circadian patterns of behavior. Her findings related to how the timing and quality of energy intake affect weight gain and metabolic health have been featured on national and international news programs and a myriad of websites and popular news media. Dr. Bray currently leads one of the largest genetic studies of exercise adherence established to date, the Training Interventions and Genetics of Exercise Response (TIGER) study, with a total planned cohort of more than 5,000 individuals. Dr. Bray's research has included investigations of aerobic fitness and resting and exercise energy expenditure in children and adolescents, circadian studies of feeding and metabolic response, and clinical studies of morbidly obese adolescents undergoing bariatric surgery. Dr. Bray has published extensively in a wide range of peer-reviewed journals and her work has been featured in national and international scientific meetings.

Paul Franks, Ph.D.

Dr. Franks trained in genetic epidemiology and biostatisitcs at Cambridge University in the UK under the guidance of Dr. Nicholas J. Wareham and with Dr. William C. Knowler at the Phoenix Epidemiology and Clinical Research Branch of the National Institutes of Diabetes and Digestive and Kidney Disease (NIDDK) in the US. In 2010, Paul was appointed full professor in genetic epidemiology and the head of the Genetic & Molecular Epidemiology Unit at Lund University Diabetes Center in Malmö, Sweden. Paul is also an adjunct professor at Harvard University in Boston, MA and a professor of molecular epidemiology at Umeå University in Sweden. He is internationally recognized for his research on gene-environment interactions in type 2 diabetes, obesity and CVD, having authored more than 200 publications in a range of high impact journals. He has been the Principal Investigator on more than 40 awarded grants, including those funded by the Swedish Research Council, the National Institutes of

Health, and the EU's Innovative Medicines Initiative (IMI). Paul currently leads the epidemiology work package of the EU- funded IMI DIRECT Project, which in 2011 received one of the largest grants of all time for diabetes research (approximately $50,000,000).

Charlotte Ling, Ph.D.

Dr. Charlotte Ling is a lecturer at Lund University and a principle investigator of the Epigenetics and Diabetes Unit at Lund University Diabetes Centre (LUDC) in Sweden. She obtained her PhD in Endocrinology at University of Gothenburg, Sweden in 2002. After a post-doc at Lund University, where she studied the genetics of type 2 diabetes, she dedicated her research to the study of epigenetic mechanisms causing type 2 diabetes and metabolic disease. Her research group has contributed to novel epigenetic discoveries in type 2 diabetes. The group has identified epigenetic modifications in patients with type 2 diabetes and they have shown that genetic and environmental risk factors alter the epigenetic pattern in human pancreatic islets, skeletal muscle and adipose tissue.

Ruth Loos, Ph.D.

Dr. Ruth Loos is Director of the Genetics of Obesity and Related Metabolic Traits Program in The Charles Bronfman Institute of Personalized Medicine of the Icahn School of Medicine at Mount Sinai. Her primary research interests focus on the identification of genes and genetic loci contributing to the risk of obesity and related metabolic traits. She has been involved in gene-discovery since 2005, when 'genome-wide association' was introduced**,** and has since actively contributed to many consortia that use this approach to identify genetic loci for a large number of metabolic traits. Increasingly, her gene-discovery work also focuses on the identification of low-frequency variants through the implementation exome-chip genotyping and sequencing projects, not only in individuals of white European descent, but also in those of African and Hispanic de**s**cent. Besides gene-discovery, Dr. Loos uses epidemiological methods to follow-up on established loci with the aim to elucidate the pathways through which they increase risk of metabolic disease. Furthermore, her work also assesses the public health implications of the established loci by examining their predictive value and their interaction with lifestyle factors such as diet and physical activity.

Colleen McBride, Ph.D.

Dr. Colleen McBride is Chief and Senior Investigator of the Social and Behavioral Research Branch in the National Human Genome Research Institute's Division of Intramural Research. Dr. McBride received her doctorate in behavioral epidemiology from the University of Minnesota. She is a recognized leader in the field of behavioral epidemiology and an expert in the development and evaluation of behavior change interventions for use in public health settings. Dr. McBride's research focuses on the development of innovative public health interventions to promote risk-reducing behaviors and on understanding how genetic information can best be used to motivate people to behave in more healthful ways. In 2005, Dr. McBride and colleagues launched the Multiplex Initiative, a multi-disciplinary research collaboration to explore healthy young adults' interest in "multiplex testing". The prototype multiplex test assessed an individual's genetic susceptibility to eight common health conditions: type 2 diabetes, coronary heart disease, hypercholesterolemia, hypertension, osteoporosis, lung cancer, colorectal cancer and malignant melanoma based on 15 genetic variants. Dr. McBride also studies the potential of genetic risk information to motivate parents to positively influence their children's health behaviors and is evaluating public health models for using genetic information to categorize populations according to risk level. Dr. McBride has authored more than 100 peer-reviewed articles.

Jeanne M. McCaffery, Ph.D.

Dr. Jeanne McCafferry is Associate Professor of Psychiatry and Human Behavior at The Warren Alpert School of Medicine at Brown University and a Clinical Psychologist at the Weight Control and Diabetes Research Center at The Miriam Hospital. Her research interests are in the interaction of genetic and environmental/behavioral factors in cardiovascular behavioral medicine, obesity and weight loss. She has served as PI or Co-PI of multiple NIH grants, including the genetic ancillary studies to Look AHEAD, a

16-center trial of the health benefits of weight loss among individuals with type 2 diabetes. She has published over 70 peer-reviewed manuscripts.

Toni Pollin, Ph.D.

Dr. Toni Pollin is an associate professor in the Departments of Medicine and Epidemiology & Public Health and the Program in Personalized and Genomic Medicine at the University of Maryland School of Medicine, and the leader of the PhD training track in Human Genetics and Genomic Medicine. She holds a PhD in human genetics and a master's degree and board certification in genetic counseling. Her NIH-funded research focuses on the identification and clinical translation of genetic factors in type 2 diabetes and dyslipidemia. She discovered the first *APOC3* gene null mutation and is currently characterizing the metabolic and cardioprotective effects of inborn heterozygous apoC-III deficiency in the Amish. Dr. Pollin studies the role of genetic factors in differential response to lifestyle and metformin interventions in the Diabetes Prevention Program and the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) Study. She also leads the Personalized Diabetes Medicine Program, a translational research study designed to implement, disseminate and assess the impact of a protocol which provides screening, genomic diagnosis and personalized treatment for highly penetrant genetic forms of diabetes. She has authored or co-authored over 60 peer reviewed research papers and several reviews and book chapters.

Lu Qi, Ph.D.

Dr. Qi's research has focused on genetic, nutrition, biochemical risk factors and gene-environment interactions in relation to obesity, type 2 diabetes and cardiovascular complications in diabetic patients. Dr. Qi is the Principal Investigator on the NIH R01 grant 'Obesity Genes, Energy Regulation in Response to Weight-Loss Diets' (NIDDK), a study in large cohorts (the NHS and HPFS) and randomized intervention trials (the Pounds Lost trial and DIRECT trial), as well as the Principal Investigator of the NIH R01 grant on the genome-wide association study of coronary heart disease among diabetic patients in the NHS and HPFS (NHLBI). He is also the Principal Investigator of the American Heart Association Scientist Development Grant on the biochemical and genetic predictors for cardiovascular disease in diabetes and Co-Principal Investigator of European Foundation for the Study of Diabetes (EFSD)- funded lifestyle intervention trial on prevention of metabolic risk in women with a history of gestational diabetes (GDM). As Principal Investigator, he is also leading a metabolomic study in two diet intervention trials funded by the U.S. – Israel Binational Science Foundation. Dr. Qi serves as Editor-in-Chief for the World Journal of Diabetes, Associate Editor for BMC Medical Genetics, and editorial board member for the Journal of Nutrition, Nutrition Reviews, the International Journal of Molecular Epidemiology and Genetics, and Frontiers in Nutrigenomics. Dr. Qi is a fellow of the American Heart Association (FAHA), American College of Nutrition (FACN), and The Obesity Society (FOS).

Michael Snyder, Ph.D.

Dr. Michael Snyder is the Stanford Ascherman Professor, Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine. He received his PhD from the California Institute of Technology and postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics, and one of the major participants of the ENCODE project. His laboratory study was the first to perform a large-scale functional genomics project in any organism, and has launched many technologies in genomics and proteomics. These include the development of proteome chips, high resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes and regulatory networks. Seminal findings from the Snyder laboratory include**:** the discovery that much more of the human genome is transcribed and contains regulatory information than was previously appreciated, and that a high diversity of transcription factor binding occurs both between and within species. He has also combined different state-of–the-art omics technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of person and used this to assess disease risk and monitor disease states

for personalized medicine. He is a co-founder of several biotechnology companies including; Protometrix (now part of Life Technologies), Affomix (now part of Illumina), Excelix, and Personalis, and he presently serves on the board of a number of companies.

Deborah Tate, Ph.D.

Dr. Deborah Tate is an Associate Professor at the University of North Carolina at Chapel Hill in the Gillings School of Global Public Health. She holds appointments in the Department of Health Behavior, Department of Nutrition and the Lineberger Comprehensive Cancer Center. She received her PhD and MS degrees in Clinical Psychology and completed her internship and an ADA post-doctoral fellowship at Brown University. Her research program focuses on two main areas: (a) strategies for improving weight loss and maintenance; and (b) the translation of evidence-based obesity prevention and treatment programs using alternatives to clinic-based care with a particular emphasis on eHealth and mHealth. Dr. Tate is nationally known for her pioneering work in eHealth as she has conducted programmatic research studies to determine the features of technology-delivered weight control programs that contribute to efficacy and cost-efficiency. She is currently the Principal Investigator or a co-Investigator on several ongoing NIH funded studies that use Internet and mobile technologies for weight control in special populations including young adults, low-income mothers, and primary care patients. In addition, she is the director of an NIH funded Core that helps researchers develop and evaluate behavioral interventions emphasizing health communications and technology. She serves as a standing member of the PRDP study section.

Jason Vassy, M.D.

Dr. Jason Vassy is an Instructor of Medicine at Harvard Medical School, Associate Physician at Brigham and Women's Hospital, and clinician-investigator in the Veterans Affairs Boston Healthcare System, where he practices primary care medicine. His research focuses on the clinical application of novel genomic technology to primary care patient populations, with a particular focus on type 2 diabetes. He is a co-investigator for the Genetic Counseling and Lifestyle Change for Diabetes Prevention (GC/LC) Study, a randomized trial of diabetes genetic susceptibility testing and counseling among primary care patients at risk of developing type 2 diabetes. He is also a co-investigator for the MedSeq Project, a randomized trial of integrating whole genome sequencing into the primary care of patients at Brigham and Women's Hospital.

Dr. George Weinstock, Ph.D.

Dr. George Weinstock, a pioneer in the genomic analysis of the microbiome, joined The Jackson Laboratory (JAX) in September 2013 as Professor and Associate Director for Microbial Genomics. He came to JAX from Washington University in St. Louis where he was Associate Director of The Genome Institute and a professor in the Departments of Genetics and Molecular Microbiology. He established a microbial genetics and metagenomics division at WUSTL, devoted to the study of infectious disease and the human microbiome and to the application of genomics in the clinic. Prior to that, Dr. Weinstock served as co-director of the Human Genome Sequencing Center at Baylor College of Medicine in Houston where he was one of the leaders of the National Institute of Health's Human Genome Project. As a scientist dedicated to exploring how the microbiome interacts with the host genotype to influence health and disease, Dr. Weinstock's ultimate goal is to elucidate genomic mechanisms that could one day inform the development of new diagnostic and therapeutic approaches to promote health as well as treat infectious diseases and other dire medical conditions. Dr. Weinstock's research spans human, mammalian, metazoan and microbial genetics, leveraging high-throughput DNA sequencing, genome-wide analysis, bioinformatics and other genetic methods to address important challenges in biology. Dr. Weinstock co-led one of the first personal genome projects, sequencing James Watson's genome using next-generation sequencing technology. In 1998, he guided one of the first bacterial genome projects, sequencing *Treponema pallidum*, the causative agent of syphilis, helping to usher in a new era of genomic exploration in microbes, microorganisms and humans.

Xifeng Wu, MD, Ph.D.

Dr. Wu is Professor and Chair of the Department of Epidemiology, Director of the Center of Translational and Public Health Genomics, and Epidemiology Program Leader for the Cancer Center Support Grant at The University of Texas MD Anderson Cancer Center. She also holds the endowed Betty B. Marcus Chair in Cancer Prevention. She earned her medical degree from Fudan University in 1984 and her PhD from The University of Texas School of Public Health in 1994. Dr. Wu's multifaceted, highly interactive and multidisciplinary molecular epidemiology program bridges field epidemiology, laboratory study and clinical research. Her team has developed or adapted an array of phenotypic and genotypic assays to identify, study, and validate inherited susceptibility biomarkers for cancer risk assessment and clinical outcome prediction. Her vision is to incorporate epidemiological, clinical and genetic information to develop personalized risk prediction models for cancer etiology, prevention, clinical outcomes, and survivorship. She constructed the first risk prediction model for bladder cancer and recently published a hepatocellular carcinoma risk prediction model that can be used for the general population. Dr. Wu is a highly productive cancer epidemiologist with more than 331 publications, many in highly acclaimed journals. Dr. Wu has received many awards, including MD Anderson's Faculty Scholar Award, The University of Texas Ashbel Smith Professorship, the Margaret and James A. Elkins Jr. Faculty Achievement Award in Cancer Prevention, the Julie and Ben Rogers Award for Excellence in Research, and the Robert M. Chamberlain Distinguished Mentor Award. She is frequently invited to present at workshops, deliver lectures and seminars, and chair conference sessions.