December 2, 2016

Trans-NIH Consortium: Randomized Controlled Trials of Lifestyle Weight Loss Interventions for Genome-wide Association Studies: Executive Summary

Meeting Dates: August 30-31, 2016

Background

The trans-NIH Working Group on Genes, Behaviors and Weight Loss is interested in understanding the genetic contribution to variability in weight loss treatment response. As a way to leverage existing resources, the Working Group issued RFI NOT-CA-15-042: *Randomized Controlled Trials (RCTs) of Lifestyle Weight Loss Interventions for Genome-Wide Association Studies* (https://grants.nih.gov/grants/guide/notice-files/NOT-CA-15-042.html) to explore genetic variants associated with intentional weight loss in trials of weight loss interventions. Investigators who responded to the RFI were invited to attend the *Trans-NIH Consortium Meeting: Randomized Controlled Trials of Lifestyle Weight Loss Interventions for Genome-wide Association Studies*, which took place August 30-31, 2016 in Rockville, Maryland. The objectives of the meeting were as follows:

1. To determine the feasibility of developing a consortium for collaborative genome-wide studies to explore the contribution of genetics to variation in intentional weight loss and weight maintenance
2. To discuss challenges and strategies for pooling existing resources; and
3. To discuss potential approaches for harmonizing phenotypes of interest.

The ultimate goal is to develop precision medicine approaches to improve treatment response to behavioral weight loss interventions through the integration of new genetic discoveries.

Summary

The first session reviewed the "state of the science for genetics of weight loss," which highlighted the fact that there are currently no GWAS for intentional weight change in RCT interventions. Large-scale GWAS for obesity traits, not including intentional weight loss, have identified more than 300 associated loci from observational studies. However, attempts to identify associations between established obesity-associated loci and weight loss/regain outcomes in intervention studies have proven largely unsuccessful so far. This lack of success could be due to small sample sizes or differences in the biology underlying weight loss/regain compared to cross-sectional studies of obesity. Large-scale GWAS studies for weight loss are needed to expand beyond the known obesity-associated traits, as the biology involved is likely different.

In the second session, each investigator provided a short overview of the RCT weight loss trials, including study objectives, methodology, biospecimens collected and phenotypes investigated. Seventeen trials represented approximately 18,000 individuals and provided insights into the variability in weight loss response as well as sample availability and consent for data sharing.

During the next session, challenges and methods for analyzing genetic associations were reviewed, including the importance of consent and data sharing in these types of studies. This was followed by a review of challenges specific to combining data from heterogeneous intervention trials and presentation of one potential solution—to code details of the interventions using behavior change techniques to create taxonomies that are common across studies. The second day began with a presentation on the use of the National Weight Control Registry as an alternate research design to examine weight maintenance. This was followed by an open discussion about the study design that might be used for this consortium, which highlighted the importance of identifying the hypotheses that could be tested. Next, there was a discussion of the phenotypes that are common across studies. The final session reviewed additional measures and phenotypes, such as the microbiome, epigenetic, and metabolomics, each of which could be incorporated into future studies or used with appropriately stored specimens.

Considerations for Genetic Association Studies (Study design) and Discussion

There are different treatment options for obesity (including behavioral, pharmacological, and surgical interventions). The ability to predict the likelihood of success in behavioral weight loss interventions would be an important scientific contribution. It is important to increase our understanding of the biology of weight loss and the genetic pathways implicated in this process to improve weight loss and maintenance. There is a need for more discovery in the area of genetics in the context of weight loss and response to weight loss interventions.

Study Design

Complex traits are typically polygenic, with variation defined by both genetic (many genes with variants of equal and small effect) and non-genetic factors. Therefore, it is important to identify the main goals and objectives. If the goal is to identify genes that predict weight loss, then it is possible to conduct GWAS in the intervention arm only (subgroup effect). However, if the goal is to test for gene-intervention interactions, then GWAS will need to be performed in both the intervention and non-intervention (control) arms. It is also possible to detect genetic variants associated with weight loss accounting for possible heterogeneity due to gene-environment interactions (omnibus testing for association and interaction). Researchers have to decide if they are interested in prediction, biological insights or both. Furthermore, if weight loss is biologically different from weight gain, researchers need to consider whether they should include all participants, or limit their analysis to only those who have lost weight.

For typical GWAS (with SNPs having minor allele frequency (MAF) > 5%) and typical effect size (OR ~ 1.2), in a case-control design, the sample size required for 80% power is in the 2K case/3K control range. Another study design option is to examine the extremes of the phenotypic distribution (e.g., hyper vs. hypo-responders). Examining the extremes may be generated by variants with larger effects, which permits detection with the same power and MAF but with smaller sample sizes. However, recent evidence from the NHLBI Exome Sequencing Project (focused on coding region variants that are suspected of having large effect in phenotypic extremes) and many studies using the extreme sampling design has found that the effect sizes remain comparable to GWAS. Further, caution is needed when defining the extremes, as

creating a pool of "resistant" individuals could be problematic if there are no objective assessments of behavior.

Meta-analysis is a tool for analyzing data across different studies. Meta-analyses are useful because they enable researchers to account for heterogeneity and employ standard statistical methods. It is also important to note that while combining individual-level data from these kinds of studies may be more difficult but allows participant-level covariates to be modeled. Each consortium investigator will need to have their methods plan and designated place in which data can be shared.

Sample Size

While sample size depends on the structured analytic plan, the minimum sample size needed is usually about 5,000-10,000 subjects. However, it is important to look for opportunities to expand the sample size whenever possible. For improved power, it might be important to model weight change trajectories.

Statistical Considerations

It is important to define exposure, effect size and to calculate dose-response curves. Additional analytic complexities can be handled with robust statistical methods. For example, statistical adjustments such as for disease management/treatment effects, or a common set of covariates (e.g. gender, race/ethnicity, age) can be incorporated into the model. Missing data also will need to be handled in comparable ways across the trials.

Consent and Data Sharing

It is important to obtain copies of all the consent forms to ensure compliance with the NIH Genomic Data Sharing Policy. For whole exome or whole genome sequencing studies, it is important to consider study policies regarding the detection (and return of) incidental findings. Researchers need to consider how to share data and results, both within the consortium and throughout the community.

Considerations for Combining Phenotypes and Other Study Variables

The effectiveness of interventions may vary based on the characteristics of the interventions. Accounting for intervention characteristics that influence outcomes may require attention in the analysis of pooled data. Pooling data from diverse interventions permits study of gene-intervention interactions. The goal is to identify a well-defined phenotype (e.g., a common definition of intervention success) that is biologically significant. It will take thought to identify commonalities and deconstruct the intervention in a meaningful way.

Phenotypes and Macronutrients

- Consider a common definition of weight loss intervention success. A >=5% weight loss at 6 months is often used to indicate success but other criteria might be used, e.g., at least 3-5% (as recommended by the Obesity Society). Considering the variability across interventions, it will take work to identify a specific standard/definition for weight loss success.

- Consider developing an adherence score that is focused on high-level categories or critical domains. An adherence index would allow the examination of the genetic profile of those who adhere and do not adhere to the intervention.
- Consider characterizing the intensity of the intervention. For example, if self-regulatory genes play a role, then the "dose" of the intervention is needed to understand how these genes impact success.
- Consider characterizing the interventions as to the behavior change techniques that were included or other method for accurate description of the intervention to study gene x intervention interactions.
- Consider designing studies to address specific questions in subsets of the trials. An example is whether there are certain genetic profiles that do better with different macronutrient compositions.

Replication sets/pilot work with existing GWAS and weight loss data could advance the science by showing that existing GWAS data can be combined and demonstrating effect sizes for power analysis of proposed sample sizes.

Additional Measures/Outcomes/Phenotypes for Consideration

There is a strong argument for collecting microbiome samples. There are some striking findings, with many complications, but storing those samples would be relatively low-cost. Interest in understanding the influence of epigenetic mechanisms in weight loss was also expressed. Some of the RCTs performed epigenetic/epigenome analysis while others had plans to do so in the future. It would be important to know whether the epigenetics is blood-based, tissue-based (e.g., adipose), chip-based (e.g., Illumina 850K) or through sequencing. The various methods have cost implications.

Recommended Next Steps

- Refine the hypotheses/key compelling questions to be tested by a GWAS weight loss consortium. Possibilities include
    - Identify genetic predictors of successful weight loss (e.g., >=5% at 6 months)
    - Examine gene x intervention interactions
        - Are there genetic predictors of adherence? (e.g., might use an index based on session attendance, self-monitoring of weight, diet, and physical activity)
        - Gene x macronutrients profiles (e.g., low carbohydrate diet, low fat diet)
- Operational steps
    - Review study consent forms to ensure data sharing is possible and determine if re-consent is needed/feasible
    - Determine a model for sharing/storing data within the consortium
    - Review study aims, study populations, and covariate data to identify commonalities across studies
- Consider sources of possible replication data now rather than wait until they are needed
- Conduct pilot or replication studies with existing GWAS data to demonstrate feasibility

Consortium Participants

Lydia Bazzano, MD, PhD, School of Public Health and Tropical Medicine
Steve Belle, PhD, University of Pittsburgh
Phillip Brantley, PhD, Pennington Biomedical Research Center
Nilanjan Chatterjee, PhD, Johns Hopkins University School of Medicine
Julio Chirinos, MD, PhD, University of Pennsylvania, Perelman School of Medicine
Rebecca Clifton, PhD, George Washington University
Dolores Corella, PhD, University of Valencia and CIBERobn
Wendy Demark-Wahnefried, PhD, RD, University of Alabama at Birmingham
Christopher Gardner, PhD, Stanford University School of Medicine
Gang Hu, MD, PhD, MPH, Pennington Biomedical Research Center
William Knowler, MD, DrPH, National Institute of Diabetes and Digestive and Kidney Diseases
Ruth Loos, PhD, Icahn School of Medicine at Mount Sinai
Jeanne McCaffery, PhD, Brown University
Anne McTieman, MD, PhD, Fred Hutchinson Cancer Research Center
Lu Qi, M.D., PhD, Tulane University
Stephen Rich, PhD, University of Virginia School of Medicine
Sue Shapses, PhD, Rutgers University
Deborah Tate, PhD, University of North Carolina at Chapel Hill

Trans-NIH Working Group on Genes, Behaviors and Weight Loss

Tanya Agurs-Collins, PhD, RD; (Chair) National Cancer Institute
Susan Czajkowski, PhD; National Cancer Institute
Cashell Jaquish, PhD; National Heart, Lung, and Blood Institute
Robert W. Karp, PhD; National Institute of Diabetes and Digestive and Kidney Diseases
Catherine Loria, PhD; National Heart, Lung, and Blood Institute
Leah Mechanic, PhD, MPH; National Cancer Institute
Sharon Ross, PhD, MPH; National Cancer Institute
Susan Yanovski, MD; National Institute of Diabetes and Digestive and Kidney Diseases