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Studying Gene–Behavior Interactions: Summary of Recommendations

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The workshop was designed to review the evidence on the role of gene–nutrition and gene–physical activity interaction effects in the etiology of obesity and the growing prevalence of obesity. One important goal was to produce a set of recommendations that would be helpful to the research community and to the sponsors of the meeting. As evidenced by the papers in this publication, all contributors to the workshop made recommendations concerning future research, and these were discussed extensively during the meeting. Our goal herein is not to generate an exhaustive list of all suggestions made by the speakers at the workshop, but rather to focus on the key recommendations that can have a significant impact on the research agenda of the field. We are grouping them under five headings.

However, one overarching issue needs to be raised first. The concept of gene–behavior interaction is one that is not always fully understood and appreciated. As was defined in the first paper of this supplement (1), one has to distinguish between the main effect of a gene from its potential contributions through interaction paths with behavioral or environmental factors or, perhaps more precisely, behavioral or environmental perturbations. The distinction is not always fully appreciated. For instance, some of the papers in this supplement deal with gene–behavior interaction effects only marginally. We will purposefully focus here only on recommendations that are relevant to the gene–behavior interaction research agenda.

Most of the genetic studies reported to date for human obesity and related traits have reported on the main effects of genes. The genetic architecture of obesity is obviously more complex than suggested by the majority of studies published to date (2). For example, the *FTO* gene has been shown in a good number of studies with large sample sizes to have a significant effect on body mass index (BMI) (Loos and Bouchard, submitted). Homozygotes for the risk allele are on average about 3–4 kg heavier than homozygotes for the wild-type allele. However, it appears that there is a strong interaction between the *FTO* genotype and physical activity level. Indeed the carriers of the risk allele are normal weight if they are physically active (3,4). It is only the sedentary individuals who are homozygotes for the risk allele who are heavier than the other genotypes.

Study Design

The ability to identify a gene–behavior effect is highly dependent on the study design. In this regard, a consensus emerged on several aspects of what productive study designs should include:

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1. Measure a phenotype of interest with precision and have true control over the exposure to the behavior or the environmental agent of interest
2. Prioritize controlled interventions, since they offer the best opportunity to identify the genes and alleles causally related to changes in a phenotype
3. Among observational studies, favor cohorts followed prospectively, since they have a better chance of identifying gene–behavior interaction effects when compared to cross-sectional observation studies
4. Identify genes through genome-wide association studies from large cohorts and subsequently test them as candidate genes in well-controlled intervention studies with appropriate control over the exposure to behavioral change
5. Pursue the quantification and characterization of the individual differences in the response to behavioral changes with a view of generating hypotheses for subsequent research

Specific Research Issues

1. Refine the phenotypes commonly used in studies focused on obesity by incorporating endophenotypes that will make it easier to identify specific gene–behavior interaction effects
2. Take advantage of findings on gene–nutrition or gene–exercise interaction effects to design human studies to verify whether the observations can be reproduced
3. Target candidate genes derived from animal studies for subsequent human testing
4. Compare gene–behavior interaction effects across ethnic groups
5. Design studies comparing obesity treatment responses across genotypes, using well-characterized genes associated with human variation in responsiveness to relevant behavioral exposure

Gene–Nutrition Interactions

1. Explore gene–macronutrients or –food groups interaction effects with respect to preference, overall consumption, and dietary restriction
2. Develop designs that will allow identification of the genes responsible for the genotype–overfeeding interaction effect in humans experiencing experimental weight gains
3. Identify the genes responsible for the differential responsiveness to weight loss protocols based on caloric restriction

Gene–Physical Activity Interactions

1. Identify the genes responsible for the variation in weight loss and the changes in body composition in exercise-based protocols designed to induce caloric deficits
2. Explore whether human variation observed in weight loss in response to an exercise regimen results from gene–fitness interaction effects
3. Design studies to examine whether there are gene–motivation trait interactions influencing physical activity behavior

Other Important Issues

1. Standardize the behavioral challenge in gene–behavior interaction effect studies such that it can be implemented at other sites
2. Undertake studies to understand whether genotype–behavior interaction effects result from lasting *in utero* programming or epigenetic events influencing gene expression
3. Study gene–drug interaction effects in weight loss treatment
4. Study gene–bariatric surgery interaction effects in the weight loss following the surgery and the weight loss retention over time

It should be apparent from the articles in this series that progress in the dissection of the gene–behavior interaction effects will necessitate combinations of informative animal models and human studies. We should continue to take advantage of existing large-scale population studies, which are generally characterized by more error variance in phenotype and exposure variable assessments. However, these population studies need to be complemented by smaller-scale experiments that offer an opportunity to measure phenotypes more precisely, to quantify the response to a standardized change in behavior, and to investigate mechanisms. Such small-scale experimental studies have the potential to define candidates that can be investigated further in larger cohorts.

In the end, efforts to fully understand the genetic architecture of a trait such as human obesity will require very large sample sizes so that many genes with significant main effects (that are likely to be small) together with many potential gene–behavior interaction effects can be tested simultaneously. Replication in independent cohorts will also be a requirement. Even though the conditions that are necessary for such an undertaking to be successful have not been fully defined, it is obvious that issues such as optimal sample size, statistical power, and analytical tools will be of prime importance.

Finally, a major challenge will remain as to how to translate advances in our understanding of gene–behavior interaction effects for public health consumption when promoting weight gain prevention and for clinical practice in the context of the treatment of obesity and its associated morbidities.

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