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Gene-Nutrition and Gene-Physical Activity Interactions in the Etiology of Obesity

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THE OBESITY EPIDEMIC

Obesity is a chronic disease that leads to personal suffering for affected individuals and major costs to public health systems and societies. In the United States alone, 66% of adults meet the definition of overweight (BMI ≥25 kg/m2) or obesity (BMI ≥30 kg/m2). Almost one-third of US adults are frankly obese. Even more alarming is the fact that the prevalence of overweight and obese children and adolescents is now about 17%. Large disparities have been observed among specific racial/ethnic groups (1).

By one estimate, obesity is currently responsible for the death of about 100,000 persons per year in the United States (2). Around the world, more than one billion people have a body weight high enough to have health implications. In countries where it is possible to quantify the costs of obesity, they have been reported to range from 2% to 7% of total health care costs (3).

A recent World Cancer Research Fund report, Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective, identified body fatness as a risk factor for cancers of the esophagus, pancreas, colorectum, breast (postmenopausal), endometrium, and kidney (4).

OBESITY IS MULTIFACTORIAL

Obesity is a complex multifaceted disease that is influenced by genetic, epigenetic, environmental, and behavioral factors. It results from long-term imbalance between energy intake and energy expenditure, favoring positive energy balance. When energy intake chronically exceeds energy expenditure, the resulting imbalance causes expansion of lipid storage and favors adipogenesis.

The past decade has seen a remarkable increase in our understanding of the molecular mechanisms that regulate energy homeostasis, the molecular mediators of energy homeostasis in the brain and the periphery, and the genetics of obesity. However, given the fact that the surge in the prevalence of obesity occurred within a short period of time, environmental and behavioral lifestyle factors clearly play a strong role. One convenient way to describe the prevailing situation is to group the potential contributors to this epidemic under four major

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headings: built environment, social environment, behavior, and biology (5). Factors in the built environment (e.g., transportation systems, reliance on the automobile, building design that minimizes the need for walking, lack of sidewalks) and the social environment (e.g., constant advertising, pressure to consume) are such that the global environment has become "obesogenic." Such an environment favors the adoption of obesogenic behavior (e.g., consumption of large portions of food, high-fat diets, high sugar intake, and many hours spent watching television, playing video games, or sitting at the computer). Obesogenic environments and behavior have the potential to account for the acute rise in the prevalence of overweight and obesity that the world is currently experiencing.

However, one should not omit biology from the discussion. A large number of biological factors have been implicated in animal and human studies. Common biological correlates of weight gain or obesity include low resting metabolic rate, low thermic effect of food, low lipid oxidation rate, high levels of adipose tissue lipoprotein lipase activity, low rates of lipid mobilization, abnormal biology of leptin and other hormones, poor regulation of appetite and satiety, and low skeletal muscle oxidative potential. Moreover, many genetic studies have concluded that there is in our genome a latent predisposition to achieve positive energy balance for long periods of time. Several lines of evidence support the contentions that there are individual differences in the predisposition to gain weight and that genetic variation has much to do with the risk of becoming obese, particularly the risk of severe obesity (6).

GENE-BEHAVIOR INTERACTIONS

In this context, the concepts of gene-behavior and gene-environment interactions are critical. There is a synergistic relationship among genes, behavior, and the environment. When individuals living in a "restrictive" environment evolve toward an obesogenic environment, such as that found in industrialized countries, most are likely to gain weight. However, those with a high genetic predisposition for obesity will gain the most weight, whereas those resistant to obesity will gain little, if any, weight. The findings reported to date and how to undertake more powerful studies of gene-behavior and gene environment interaction effects are the focus of the workshop papers published in this supplement issue of Obesity.

Knowledge of the human genome has grown exponentially in the past several years. Exploration of gene-gene, gene-behavior, and gene-environment interactions as they relate to health and disease can now be undertaken with more powerful tools than ever before. In 2006, the National Institutes of Health implemented the Genes, Environment, and Health Initiative, which promotes both genetic analysis and the development of new tools to measure environmental exposures that affect health (http://genesandenvironment.nih.gov). The development of innovative technologies to measure environmental exposures and behaviors such as diet and physical activity should be a priority, as they will greatly contribute to advancing gene behavior research.

The influence of genetic, environmental, and behavioral factors on the relationship between obesity and cancer has been identified as a priority scientific area for the National Cancer Institute (NCI). The 2008 NCI Strategic Plan highlighted the need to "increase our understanding of behavioral, environmental, genetic, and epigenetic causes of cancer and how they interact. " Using the plan as the impetus, in September 2007 the NCI Division of Cancer Control and Population Sciences (DCCPS) sponsored a workshop, Gene-Nutrition and Gene-Physical Activity Interactions in the Etiology of Obesity. Leading scientists representing various disciplines were convened to assess the state of the science and to evaluate the current understanding of gene-environment-behavior interactions as they relate to obesity risk and to identify research priorities and future directions.

ARTICLES IN THIS ISSUE

The objective of this supplement is to summarize the major themes and ideas developed from the conference by highlighting the workshop presentations and discussions. Taken together, the papers provide a multidisciplinary perspective and raise important questions as to how to conduct gene-environment-behavior studies in obesity research. The supplement includes 16 articles that cover a range of topics, from genetics studies using animal models to prevention and treatment of obesity in humans. The final article (7) highlights the research recommendations discussed in the last workshop session. The first article, by Bouchard (8), defines gene-environment and gene-behavior interactions, discusses study design issues, and examines what is currently known about obesity and obesity-related genes. The second paper, by Lenard and Berthoud (9), is devoted to the pathways and genes involved in the central and peripheral regulation of food intake and physical activity.

The papers by Reed and Ordovas address gene-nutrition interaction. Reed (10) discusses how animal models can be used to examine genetic determinants of food preferences, and Ordovas (11) focuses on nutritional genomics and gene-nutrient interactions in the prevention of chronic diseases. Chung and Leibel (12) review human and animal studies relevant to the genetics of obesity. Specifically, they discuss the role of genes in regulating body weight and response to nutrient excess and deficiency. Levin (13) examines epigenetic influences on food intake and physical activity. Using an animal model, he illustrates how manipulations in the perinatal environment can permanently alter the system that regulates energy homeostasis.

Two articles address gene-physical activity interactions. Koch and Britton (14) describe the use of an animal model to explore mechanistic gene-environment interactions for aerobic capacity and risk for disease. Rankinen and Bouchard (15) discuss heterogeneity in responsiveness to standardized behavioral changes and how genotype may influence this response in humans.

Epidemiological study designs and strategies for investigating how gene-behavior interactions lead to weight gain are discussed by Wareham, Young, and Loos (16), who emphasize the importance of precise measurement tools to accurately assess the exposure and outcome of interest. Bray (17) explores the implications of gene-environment-behavior interactions in obesity prevention and intervention studies. She also discusses whether genes in pathways controlling energy balance and adipogenesis influence the results of weight-loss programs.

In the spirit of a broad and transdisciplinary approach to understanding gene-environment-behavior interactions, several leading researchers were asked to serve as discussants after the presentations. Those important perspectives are included in this supplement. The behavioral research discussants were Dishman and Faith. Dishman (18) discusses the importance of using motivational traits or social-cognitive mediators when studying physical activity behaviors. He also advocates using multilevel statistical modeling of personal, environmental, and genetic influences on physical activity. Faith (19) discusses opportunities for behavioral scientists to become involved in designing behavioral “challenges” in experiments, determining behavioral phenotypes for genetics studies, and identifying specific measures of the environment or environmental exposures for studies of gene-behavior interactions.

To complement the behavioral perspective, genetic research discussants were invited to provide comments. Warden and Fisler (20) summarize the conference presentations and the barriers that must be overcome before individual diet and exercise recommendations can be made on the basis of genotype. Shuldiner (21) summarizes the field’s current understanding of energy homeostasis and offers recommendations for translating our limited genetic knowledge into more effective modalities for treatment and prevention.

Finally, although the topic was not discussed during the workshop, Agurs-Collins and colleagues (22) discuss public health genomics as a framework for translating obesity genomics research into clinical and public health practice. Common challenges for gene-environment-behavior research, as outlined in the articles, include study design, measurement precision in assessing behavioral phenotypes, sample sizes large enough to achieve adequate statistical power, and technologies to accurately measure behavioral and environmental exposure.

CONCLUSION

The articles in this supplement present the major themes of state-of-the-science research focused on gene-environment behavior interactions and propose future research directions in obesity research. Fulfilling the research recommendations outlined in the last section will require transdisciplinary research teams representing behavioral science, genetics, nutrition, exercise science, epidemiology, and biostatistics. We believe that this collection of articles is critical for moving obesity research forward, demonstrates the need for collaborative and transdisciplinary approaches, and will serve as a catalyst for the development of partnerships and collaborations. It is our hope that the information provided will encourage researchers to strive to incorporate gene-behavior and gene-environment interaction components in their studies to improve our understanding of the complex network of factors that contribute to obesity risk, and in the process will aid in both control and prevention of lifestyle behaviors related to chronic diseases and cancer.

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