Nutrigenetics and Nutrigenomics
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Volume Editors

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This is the third volume in the series *World Review of Nutrition and Dietetics* which is dedicated to the concept of genetic variation and nutrition in health and disease. The first volume published in 1989 was *Genetic Variation and Nutrition* (vol. 63) and the second volume published in 1997 was *Genetic Variation and Dietary Response* (vol. 80). The present volume bears the title, *Nutrigenetics and Nutrigenomics*, indicating the advances that have taken place in genetics using the methods of molecular biology and ushering functional genomics also known as systems biology. Genes define susceptibility to a disease or condition, and environmental factors, such as diet and exercise, determine who among the susceptibles will develop the disease or condition. The term ‘nutrigenetics’ was first used by Dr. R.O. Brennan in 1975 in his book *Nutrigenetics* with the subtitle ‘New concepts for relieving hypoglycemia.’ The term ‘nutrigenetics’ refers to an individual’s specific response to diet due to genetic variants or polymorphisms. Genetic variation is the hallmark of genetics. ‘Nutrigenomics’ refers to the role of nutrients in gene expression. There has been an enormous expansion in studying genetic variants (polymorphisms) and their association with chronic diseases such as cardiovascular disease, diabetes, hypertension, and cancer. These association studies have revealed that there is variability both in the type and frequency of the alleles, and the response to nutrients is influenced by other environmental factors, for example, smoking. An ambitious challenge for the next decade is to translate the nutrigenomics data into an accurate prediction of the beneficial or adverse health effects of dietary components. Both micronutrients and macronutrients can be potent dietary signals that influence the metabolic programming of cells, an important...
role in the control of homeostasis. In the relation between nutrition and health, it is necessary to develop a new concept of biomarkers.

Functional genomics provides the tools to generate new hypotheses on the mechanisms of action of nutrients. One of the goals for the application of genomics to nutrition science is the prevention of diet-related diseases. Nutrients are dietary signals that are detected by the cellular sensor systems that influence gene and protein expression, and subsequent metabolic products. Thus, new terms are being used such as ‘transcriptome,’ ‘proteome’ and ‘metabolome.’ The National Institutes of Health’s (NIH, Bethesda, Md., USA) NIH Roadmap states, ‘To better understand the proteome, innovative tools must be developed that will enable researchers to determine in real time the amounts, locations, and interactions of large numbers of individual proteins within a single cell.’ It goes on to say that ‘Researchers are eager for technologies that will enable them to measure local concentrations of carbohydrates, lipids, amino acids, and other metabolites within a single cell or even a specific part of a single cell.’

Molecular diagnostic tests eventually will have the potential to affect every area of health care, ranging from predicting who is at risk of developing disease, early diagnosis of disease, determining optimal treatment regimens, and monitoring the effectiveness of treatment.

Genomics, genotyping, transcriptomics, proteomics, and metabolomics along with bioinformatics constitute the discipline of functional genomics, which is also referred to as systems biology. The integration of systems biology into nutritional research has already started, as indicated by the papers in this volume.

This volume begins with the paper on ‘Genetic Variation: Nutritional Implications’ by Artemis P. Simopoulos. This paper discusses heritability; genetic diversity – ethnic differences and gene variants; genetic variation, dietary sodium and the response of blood pressure; genetic variation, omega–3 fatty acids and inflammation (omega–6 and omega–3 fatty acids and prostaglandin metabolism; omega–3 fatty acids, genetic variation and cytokines; genetic variation, interleukin-6 and cardiovascular disease); the future of genetic nutrition – nutrigenetics and nutrigenomics; and the potential for novel foods. The recent studies of genetic polymorphisms involving cytokines such as interleukin-1 (IL-1), IL-6, and 5-lipoxygenase indicate that the amount of omega–3 fatty acids necessary to suppress IL-1 is dependent on the polymorphic variant. Similarly, polymorphic variants of 5-lipoxygenase identify a subpopulation with increased atherosclerosis. This diet-gene interaction further suggests that dietary omega–6 fatty acids promote, whereas marine omega–3 fatty acids inhibit leukotriene-mediated inflammation that leads to atherosclerosis (as measured by carotid artery intima-media thickness) in the subpopulation (6%) carrying the variant.
Academia as well as industry are carrying out studies to define candidate genes because the technology is available to generate the data. What is lacking are models to interpret the data. Models are needed to be based on biological principles and not only on models based on mathematical and statistical principles. Disease is based on the interaction of genetic and many environmental factors. The frequency of variants and the environmental factors vary in different populations. There are already many association studies relating genes to risk factors for disease that cannot be reproduced and reconfirmed in other populations. Some scientists believe that increasing the number of subjects will take care of the problem. Others carry out meta analyses. But if genetics deals with individuals how can studies carried out in other populations, tell an individual’s risk? The ‘average individual,’ such a popular term with epidemiologists, really does not exist in genetics.

The next three papers ‘Gene:environment interactions and coronary heart disease risk’ by Philippa J. Talmud and Steve E. Humphries; ‘Genes, diet and plasma lipids: The evidence from observational studies’ by Jose M. Ordonovas and Dolores Corella; and ‘Dynamic relationships between the genome and exposures to environments as causes of common human diseases’ by Charles F. Sing, Jari H. Stengard, and Sharon L.R. Kardia, extensively discuss the gene:environment interactions in cardiovascular disease and other common diseases, and they emphasize the need for more comprehensive association studies involving larger numbers of subjects, and the need to train scientists from the various disciplines to advance the field. Large-scale association studies are needed that examine many gene polymorphisms simultaneously before one can predict genetic risk for chronic disease. Today, we know more about genomics and about biological pathways. The problem is that as we learn more, it becomes obvious the daunting complexity of biology and biological systems.

Studies on the evolutionary aspects of diet indicate that Western diets are relatively deficient in omega–3 fatty acids, and a great effort has recently been made to return the omega–3 fatty acids into the food supply. Until now, the only way to enrich animal tissues with omega–3 fatty acids has been dietary provision because most animals including mammals cannot produce omega–3 from omega–6 fatty acids (which are excessive in Western diets) due to lack of a converting enzyme (omega–3 desaturase) gene found in some lower species such as Caenorhabditis elegans. Jing X. Kang, in his paper ‘Achieving balance in the omega–6/omega–3 ratio through nutrigenomics: Fat-1 transgenic mice convert omega–6 to omega–3 fatty acids’ shows that transgenic mice expressing the C. elegans fat-1 gene encoding an omega–3 fatty acid desaturase are capable of producing omega–3 from omega–6 fatty acids, leading to enrichment of omega–3 fatty acids with reduced levels of omega–6 fatty acids in almost all organs and tissues, including muscle and milk, with no need of dietary omega–3 fatty acid supply. This discovery
provides a unique tool and new opportunities for omega–3 research, and raises the potential of production of fat-1 transgenic livestock as a new and ideal source of omega–3 fatty acids to meet the human nutritional needs.

In the next paper ‘Nutrients and gene expression,’ Raffaele De Caterina and Rosalinda Madonna review the status of nutrients in gene expression with emphasis on omega–3 fatty acids, and conclude that control of gene expression by nutrients is providing clues to improve understanding of the human body’s physiology and the origin of complex polygenic disease.

Drs. Ben Van Ommen and John P. Groten in their paper ‘Nutrigenomics in efficacy and safety evaluation of food components’ state that unlike pharmacology, where usually a pronounced effect of a single compound on a single biological function during a short exposure period is pursued, both nutrition and toxicology deal with complex mixtures of nutrients and xenobiotics, chronically administered and with a multitude of biological effects. Since the majority of biological (both positive and adverse) responses are believed to be mediated through effector genes, and genomic technologies allow for the determination of an abundance of relevant genes/proteins and their effects on metabolism, functional genomics offers great opportunities in this research. Although hardly considered as closely related, nutrition and toxicology do have a number of shared features, and these common denominators will become of major importance for these two scientific disciplines, where efficacy and safety evaluation will slowly but steadily integrate to show the ‘specificity’ of a food chemical under study.

The specific quest of discovering the impact of common genetic variation on nutritional requirements and risk of adverse medical events has generated considerable interest, including nutritional researchers, educators and public health specialists. In this respect, the vitamin folate has served as a prototype in demonstrating how genetic profile can influence an individual’s achievable nutrient status and consequently, influence the risk of developing certain diseases. Dr. Anne M. Molloy, in her paper ‘Genetic variation and nutritional requirements’ points out that the volume of published literature on all aspects of folate research has quadrupled within a decade. Consequent to this expanding wisdom, the traditional view of cut-off biochemical blood levels defining a clinical deficiency when signs and symptoms of disease start to emerge, has given way to a new science where the markers of inadequate status are defined in terms of increased risk of disease and the predominant evidence is derived from population studies and clinical trials. Within this context, small alterations in the function of folate binders, receptors, and enzymes due to relatively common polymorphisms in their encoding genes have become essential considerations in determining the factors that control the optimum achievable folate status of any individual. The 677C→T polymorphism in the enzyme
methylene tetrahydrofolate reductase (MTHFR) is the most widely researched. New variants emerge on a daily basis and the impact of genetic factors on folate status is constantly being updated. The model presented by folate is unquestionably valid for other micronutrients and there is no doubt that the future will bring new challenges for nutritionists in designing effective dietary strategies to maintain lifelong health, aimed ultimately at the individual and his or her unique genetic profile.

In mammals, including humans, vitamins are essential nutrients. In addition to their well known roles as substrates and cofactors, in the last decades an increasing number of vitamin-mediated effects are being discovered at the level of gene expression. Drs. Antonio Velázquez and Cristina Fernández-Mejía, in their paper ‘Vitamin metabolism, genetics and the environment’ discuss new approaches, like microarrays, SAGE, etc., as essential for exploring the complex networks in which vitamins intervene, and for identifying specific genes and proteins whose expression is influenced by nutrients. These techniques promise to lead to precise definitions of genotypes that are risk factors for the development of diet-related human diseases. The authors present aspects on both the metabolism and the metabolic effects of selected vitamins, especially on vitamin A and biotin, and on how they are affected by the environment and genetic variation.

The next paper ‘Gene-nutrient interactions in type I diabetes’ by Sergio Muntoni and Sandro Muntoni is a review of the dietary components in the development of type I diabetes mellitus. Gene-nutrient interactions modulate the diabetogenicity associated with type I diabetes. The great majority of cases of type I diabetes result from autoimmune destruction of pancreatic beta-cells. Its incidence varies worldwide by more than 350 times, reflecting interaction of genetic and environmental factors. More than 50% of genetic susceptibility to type I diabetes is conferred by HLA on chromosome 6 and insulin gene on chromosome 11.

Genetic factors and dietary factors, each account for about one-third of the cancer risk. Drs. Claudine Junien and Catherine Gallou in their paper on ‘Cancer nutrigenomics’ present an extensive review of the cancer nutrigenomics, using the colorectal cancer paradigm, which provides an excellent model for describing the complex genetic basis of cancer, the mechanisms, and the level of alterations by nutrients and their metabolites on genes and their products and on the epigenetic processes.

The next paper is on ‘Genetic variation and physical performance’ by John Payne and Hugh Montgomery. The authors review the heritability of musculoskeletal, cardiovascular and more complex ‘integrated’ phenotypes. Subsequently, the authors examine the data to tease out the specific loci that contribute to variations in physical performance ability. Over several years a
large body of evidence has accrued attempting to associate a common variant of angiotensin-converting enzyme (ACE) gene with physical performance. The authors review these data and suggest possible implications for disease states such as heart failure and osteoporosis.

Systems biology (or functional genomics) is using new terminology that does not appear in many clinical journals, nutrition journals, dietetics journals, or agriculture and nutrition policy journals. Therefore, in order to help the reader, Appendix I consists of the definitions of new terms in systems biology as well as other commonly used terms in genetics. Appendix II contains the recommendations from the 1975 book Genetic Screening, Programs, Principles and Research, edited by Simopoulos and Childs for the Committee for the Study of Inborn Errors of Metabolism, Division of Medical Sciences, Assembly of Life Sciences, National Research Council, National Academy of Sciences in Washington, D.C. This book, considered a classic in the field, emphasizes the ethical, legal, social, scientific, and economic aspects that need to be taken into consideration in genetic screening of populations. The recommendations provide procedural guidance for genetic screening, which is considered an appropriate form of medical care when certain criteria are met. As is made clear in the first four papers in this volume, we are not ready to carry out genetic screening programs for common diseases at the population level or to estimate individual risk based on genetic variation. It might take another 10 years, but for the time being, knowledge of the evolutionary aspects of diet and family history should guide dietary advice for the prevention and management of chronic diseases.

Bringing together vital information on nutrigenetics and nutrigenomics for the first time, this book is important reading for physicians, nutritionists, dietitians, geneticists, physiologists, molecular biologists, anthropologists, food technologists, policy makers, ethicists and educators.

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