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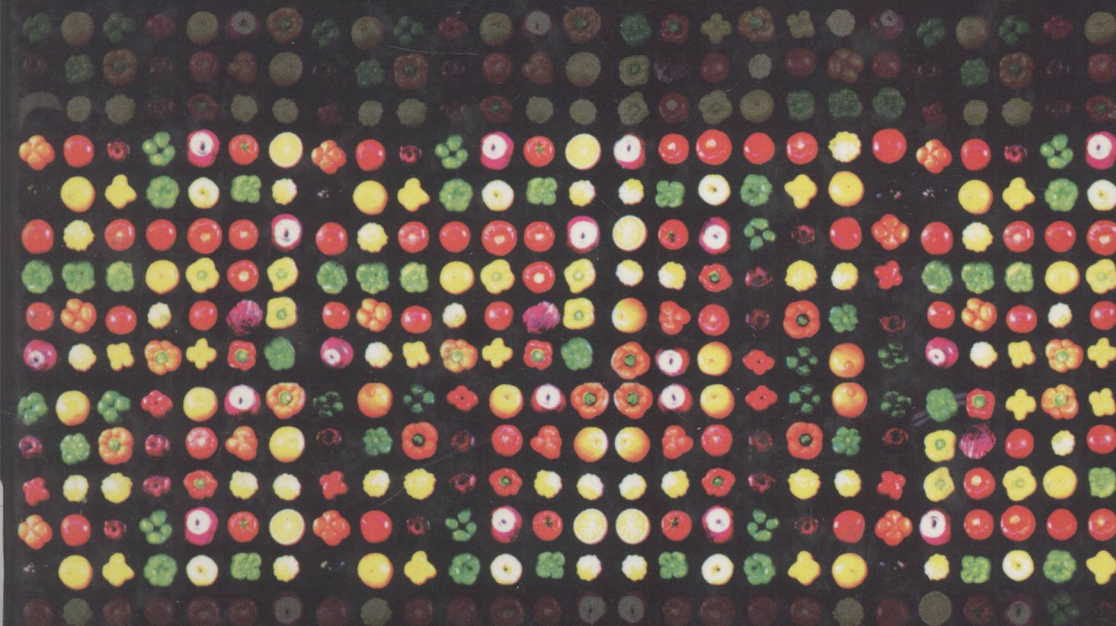
NUTRITIONAL GENOMICS

Discovering the Path to Personalized Nutrition

Edited by JIM KAPUT and RAYMOND L. RODRIGUEZ



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Discovering the Path to Personalized Nutrition

Edited by

Jim Kaput
Raymond L. Rodriguez

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CONTRIBUTORS

David B. Allison Department of Biostatistics, Section on Statistical Genetics, Comprehensive Cancer Center, and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Bruce N. Ames Nutrition and Metabolism Center, Children's Hospital Oakland Research Unit, Oakland, California and University of California–Berkeley, Berkeley, California

Stephen Barnes Departments of Pharmacology and Toxicology, Comprehensive Cancer Center, and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Mark Carpenter Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama and Department of Mathematics and Statistics, Auburn University, Auburn, Alabama

David Castle Department of Philosophy, University of Guelph, Guelph, Ontario, Canada

Sally Chiu Rowe Program in Genetics and Department of Pediatrics, University of California–Davis, Davis, California

Cheryl Cline Joint Centre for Bioethics, University of Toronto, Toronto, Ontario, Canada

Craig A. Cooney Department of Biochemistry and Molecular Biology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

Dolores Corella Genetic and Molecular Epidemiology Unit, School of Medicine, University of Valencia, Valencia, Spain

Abdallah S. Daar Joint Centre for Bioethics and Program in Applied Ethics and Biotechnology, University of Toronto, Toronto, Ontario, Canada

Kevin Dawson Section of Molecular and Cellular Biology, Bioinformatics Shared Resources Core, and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

Adam L. Diament Rowe Program in Genetics and Department of Pediatrics, University of California–Davis, Davis, California

Cora J. Dillard University of California–Davis, Davis, California

James S. Felton Biosciences Program, Lawrence Livermore National Laboratory, Livermore, California

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Erik Fernandez University of California–Davis, School of Medicine, Davis, California

Janis S. Fisler Department of Nutrition, University of California–Davis, Davis, California

Gary L. Gadbury Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama and Department of Mathematics and Statistics, University of Missouri, Rolla, Missouri

Alfredo Galvez Section of Molecular and Cellular Biology, Bioinformatics Shared Resources Core, and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

J. Bruce German University of California–Davis, Davis, California and Nestlé Research Centre, Lausanne, Switzerland

Jeff Gregg Molecular Pathology Core, University of California–Davis Medical Center, and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

Shangqin Guo Department of Biochemistry and Women's Health Interdisciplinary Research Center, Boston University School of Medicine, Boston, Massachusetts

John L. Hartman IV Department of Genetics, University of Alabama–Birmingham, Birmingham, Alabama

Wayne Chris Hawkes Western Human Nutrition Research Center and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

S. Luke Hillyard University of California–Davis, Davis, California

Pamela Horn-Ross Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama and Northern California Cancer Center, Fremont, California

Liping Huang Western Human Nutrition Research Center and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

Jim Kaput Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California, NutraGenomics, Chicago, Illinois, and Laboratory of Nutrigenomic Medicine, University of Illinois, Chicago, Illinois

Warren A. Kibbe Director of Bioinformatics, Robert H. Lurie Comprehensive Cancer Center, Center for Genetic Medicine, and NIH Center for Neurogenomics at Northwestern University, Chicago, Illinois

Helen Kim Department of Pharmacology and Toxicology, Comprehensive Cancer Center, and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Ronald M. Krauss Children's Hospital Oakland Research Institute, Oakland, California, Department of Genome Science, Lawrence Berkeley National Laboratory, Berkeley, California, and Department of Nutritional Sciences, University of California–Berkeley, Berkeley, California

Matthew C. Lange University of California–Davis, Davis, California

Coral A. Lamartinere Department of Pharmacology and Toxicology, Comprehensive Cancer Center, and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Su-Ju Lin Section of Microbiology, College of Biological Sciences, University of California–Davis, Davis, California

Jiankang Liu Nutrition and Metabolism Center, Children's Hospital Oakland Research Unit, Oakland, California and University of California–Berkeley, Berkeley, California

Mark Jesus M. Magbanua Section of Molecular and Cellular Biology, University of California–Davis, Davis, California

Michael A. Malfatti Biosciences Program, Lawrence Livermore National Laboratory, Livermore, California

Wasyl Malyj Section of Molecular and Cellular Biology, Bioinformatics Shared Resources Core, and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

Sreelatha Meleth Comprehensive Cancer Center and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Jose M. Ordovas Nutrition and Genomics Laboratory, Jean Mayer–U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts

Grier P. Page Department of Biostatistics, Section on Statistical Genetics, Comprehensive Cancer Center, and Center for Nutrient–Gene Interaction, University of Alabama–Birmingham, Birmingham, Alabama

Raymond L. Rodriguez Section of Molecular and Cellular Biology, Bioinformatics Shared Resources Core, and Center of Excellence in Nutritional Genomics, University of California–Davis, Davis, California

Gertrud U. Schuster Nutrition Department, University of California–Davis, Davis, California

Peter A. Singer Joint Centre for Bioethics, University of Toronto, Toronto, Ontario, Canada

Patty W. Siri Children's Hospital Oakland Research Institute, Oakland, California

Jennifer T. Smilowitz University of California–Davis, Davis, California

Gail Sonenshein Department of Biochemistry and Women's Health Interdisciplinary Research Center, Boston University School of Medicine, Boston, Massachusetts

Jung H. Suh Nutrition and Metabolism Center, Children's Hospital Oakland Research Unit, Oakland, California and University of California–Berkeley, Berkeley, California

Melanie Tervalon Children's Hospital and Research Center at Oakland, Oakland, California

Charoula Tsamis Joint Centre for Bioethics, University of Toronto, Toronto, Ontario, Canada

Robert E. Ward University of California–Davis, Davis, California

Craig H. Warden Rowe Program in Genetics and Department of Pediatrics, and Section of Neurobiology, Physiology, and Behavior, University of California–Davis, Davis, California

Walter C. Willett Department of Nutrition, Harvard School of Public Health and Channing Laboratory, Department of Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts

Angela M. Zivkovic University of California–Davis Davis, California

FOREWORD

As director of the National Center for Minority Health and Health Disparities (NCMHD), I am pleased and honored to contribute this forward to *Nutrigenomics: Discovering the Path to Personalized Nutrition*. As one of the sponsors of the Bruce Ames International Symposium on Nutritional Genomics, from which many of the chapters of this volume were derived, it a reassuring to see innovative and multidisciplinary approaches being applied to address the problems of chronic disease and cancer. In 2002, NIH director Elias Zerhouni instituted the NIH Roadmap for the 21st Century which consists of the following three broad themes: new pathways to discover, research teams for the future, and re-engineering the clinical research enterprise. The Roadmap is designed to identify major opportunities and gaps in biomedical research by promoting high-risk, interdisciplinary research and public–private partnerships. I believe the editors and authors of this volume have captured the true spirit and highest aspirations of the NIH Roadmap. The volume's focus on diet–gene interactions is one that boldly crosses disciplinary, institutional, and organizational boundaries, to tackle complex biomedical problems and transform new scientific knowledge into tangible benefits for all people.

To a certain extent, this volume reflects the generous increase in the funding of biomedical and behavioral research at the National Institutes of Health over the past two decades. This era of "doubling" the NIH budget has resulted in a multitude of scientific advances and programs contributing to improved health and quality of life for many Americans. At the same time, this national focus on biomedical research has heightened our awareness that many individuals, both at home and abroad, still suffer disproportionately from a number of diseases such as cardiovascular disease, Type 2 diabetes, hypertension, asthma, and cancers of various kinds. These health disparity populations are typically characterized by higher incidence, earlier onset, and greater severity of a particular disease, as well as lower responsiveness to treatment and thus, lower survival rates than the general population. Moreover, health disparities are often most apparent among ethnic/racial groups, women, the poor, and the uninsured. As evidenced by the numerous articles in the popular press and scientific literature, it is clear that the American people, from patients to policy makers, are deeply concerned about these health inequities. Health disparities by definition are counter to our shared sense of fairness and our belief in equal access. But while health disparities may present a formidable challenge to the biomedical research community, they may also hold the key to the next scientific breakthrough or blockbuster drug. So whether its the Pima Indians of Arizona, coal miners in West

Virginia, or the Kosraeans of Micronesia, health disparities are both a challenge and opportunity that will require not only new technologies but new ways of thinking about how biological systems interface with lifestyle and culture.

Lastly, although the NIH is charged with the responsibility of addressing national health needs first and foremost, we cannot forget or ignore our responsibility to promote human health and wellness around the world. According to 2003 World Health Report, approximately 80% of all deaths from cardiovascular (CVD) disease occurred in low to middle-income countries and by 2010, CVD will be the leading cause of death in developing countries. In 1998, the World Health Organization (WHO) declared obesity a global epidemic, with more than one billion adults with BMIs greater than 25 and at least 300 million adults with BMIs greater than 30. At least 171 million people worldwide suffer from Type 2 diabetes and this figure is expected to more than double by 2030. Clearly health disparities are a global problem that must be viewed through the wider lens of "inclusion." I hope that the authors and readers alike will bear this in mind as they move forward in the development of new conceptual and methodological frameworks for reducing health disparities. By working locally, partnering nationally, and thinking globally, we can bring the benefits of cutting-edge biomedical, behavioral, and social science research and research training to the question of nutrition *and* genomics as risk factors for disease.

John Ruffin
Director, NCMHD

PREFACE

The link between food and health is a long and a well documented one. With over 24,000 people worldwide dying from hunger each day and obesity reaching epidemic proportions in developed counties, the consequences of too little or too much food are easily seen. While the tragedy of world hunger is beyond the scope of this volume, new scientific insights into how nutritional and genetic factors contribute to obesity, chronic disease, and cancer, will be addressed.

The focus and timing of this volume reflect a paradigm shift in the way people look to nutrition for its short- and long-term impacts on health and disease. People no longer view food as merely a source of calories but rather as a complex mixture of dietary chemicals, some of which are capable of preventing, mitigating, or treating disease. With the sequencing of the human genome, a new genetic dimension as been added to the equation linking the foods we eat to the good health we all hope to enjoy. This new genomic perspective on nutrition and health can be seen in recent marketing campaigns for drugs that address the "two sources of cholesterol—food and family history." Americans are beginning to understand that we bring two things to the dinner table—our appetite and our genotype. As we begin to understand the genetic diversity that makes each of us uniquely different, we are also beginning to understand why we respond to our nutritional environment differently and how these differences can, over time, lead to health or disease.

Genomic analysis reveals that humans are 99.9% identical at the DNA level. This implies that the remaining 0.1% of the human genome (or about three million single nucleotide polymorphisms (SNPs)) is responsible for all the morphological, physiological, biochemical and molecular differences between any two individuals. As will be discussed in this volume, common genetic variation in the form of SNPs in enzyme-encoding genes (or their promoters) can affect reaction rates in metabolic pathways that in turn, can create individual differences in the way we absorb, metabolize, store, and utilize nutrients. According to Bruce Ames to whom many of the chapters are dedicated; "single nucleotide polymorphisms provide a powerful tool for investigating the role of nutrition in human health and disease and . . . can contribute to the definition of optimal diets."

Some of our contributors discuss well-documented evidence that certain genotypes are more severely affected by specific types of dietary factors than other genotypes (although no genotype is completely immune to the deleterious effects of poor diet). However, it is unlikely that a single gene, SNP, mutation, biomarker, or

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risk factor will have the positive predictive value needed to show a predisposition for chronic disease or cancer. This is because diet–gene interactions are strongly influenced by epigenetic, environmental, socio-economic, and lifestyle filters that modify or potentiate genetic effects. For this reason, multidisciplinary approaches will be needed to develop accurate and reliable nutritional interventions using genome-based dietary recommendations.

The notion that interactions between dietary factors and genes (or their variants) can promote health or cause disease is perhaps best captured by the term "nutrigenomics" (a contraction of nutritional genomics). As one of the latest "omic" technologies to emerge from the post-genomic era, nutrigenomics adhere to the following precepts: (1) poor nutrition can be a risk factor for diseases; (2) common dietary chemicals can act on the human genome, either directly or indirectly, to alter gene expression and/or gene structure; (3) the degree to which diet influences the balance between health and disease depends on an individual's genetic makeup; (4) some diet-regulated genes (and their common variants) play a role in the onset, incidence, progression, and/or severity of chronic diseases, and (5) dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype can be used to prevent, mitigate, or cure chronic disease.

For nutrigenomics to grow and mature as a discipline, much research is needed to answer several important questions. For example, will the cost of omic technologies come down to a level that will make nutrigenomic testing affordable to everyone? How will researchers integrate dietary and medical histories with genotype, gene expression, and metabolomic datasets from large, diverse human populations? Can we assure human subjects and consumers of nutrigenomic services that these data will be secure, safe, and not exploited for legal/political reasons or financial gain? What are those genetic variants that keep us from deriving full benefit from our nutrition, versus those that will increase our risk of disease? What role will genetically modified foods play in dietary interventions and will the benefits of these genetically enhanced foods outweigh real or perceived risks? Can the health benefits of bioactive compounds in food be confirmed clinically and what are the safe upper limits for these bioactives? These are just a few of the challenges facing nutrigenomic researchers today. This volume should provide the conceptual and technical basis from which to tackle these difficult questions.

In closing, I would like to remind readers that good nutrition has been, and will continue to be, the cornerstone of good health and disease prevention—but good nutrition comes at a price. This is particularly true as new nutrigenomic tests come to market. Dietary interventions, including those using genetic tests, will play an important role in disease prevention and treatment, especially as populations around the world grow increasingly older and more obese. As we learn more about the health-promoting dietary chemicals we eat and how they interact with nutrient-regulated and disease-associated genes, we should be able to achieve optimal health and wellness earlier, maintain it longer, and at a lower cost. Just as pharmacogenomics has led to the development of "personalized drugs," so will nutrigenomics open

the way for "personalized nutrition." This may be the single most important outcome to emerge from 100 years of nutrition research and the sequencing of the human genome.

Raymond L. Rodriguez, Ph.D.
Director, Center of Excellence in Nutritional Genomics
University of California, Davis

ACKNOWLEDGMENTS

This volume is largely an outgrowth of the Bruce Ames International Symposium on Nutritional Genomics held on the campus of the University of California, Davis on October 22–24, 2004. The purpose of the symposium, and, hence the focus of this volume, is to bring together the leading experts in the emerging discipline of nutritional genomics to discuss recent breakthroughs and future directions for the field. It became apparent to the symposium organizers and presenters after the first day that the symposium proceedings represented a unique and valuable educational resource and that the proceeding should to be documented for the future edification and benefit of a wider audience. Many individuals were involved in making this critical decision and the subsequent preparation of this volume. We would to thank first and foremost, Ms. Heather Bergman, Associate Editor at John Wiley and Sons for providing this opportunity to publish these proceeding as *Nutrtgenomics: Discovering the path to personalized nutrition.* Her vision and patience throughout this project were a tremendous encouragement to us. Of course, we owe a special debt of gratitude to the contributing authors who took time out of their busy schedules to share with the readers of this volume, their knowledge and insights on nutritional genomics. Lastly, we want to thank Ms. Liga Bivina who worked long and tirelessly on the preparation of this volume. Thanks to her exceptional skill and professionalism, this volume is more than just a collection of interesting scientific articles, but rather, it a carefully organized and highly readable compilation of chapters that will inform and enlighten both the student and practitioner of nutritional genomic research.

J.K.
R.L.R.

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