NUTRITIONAL GENOMICS

Discovering the Path to Personalized Nutrition

Edited by

Jim Kaput
Raymond L. Rodriguez

A JOHN WILEY & SONS, INC., PUBLICATION

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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

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.
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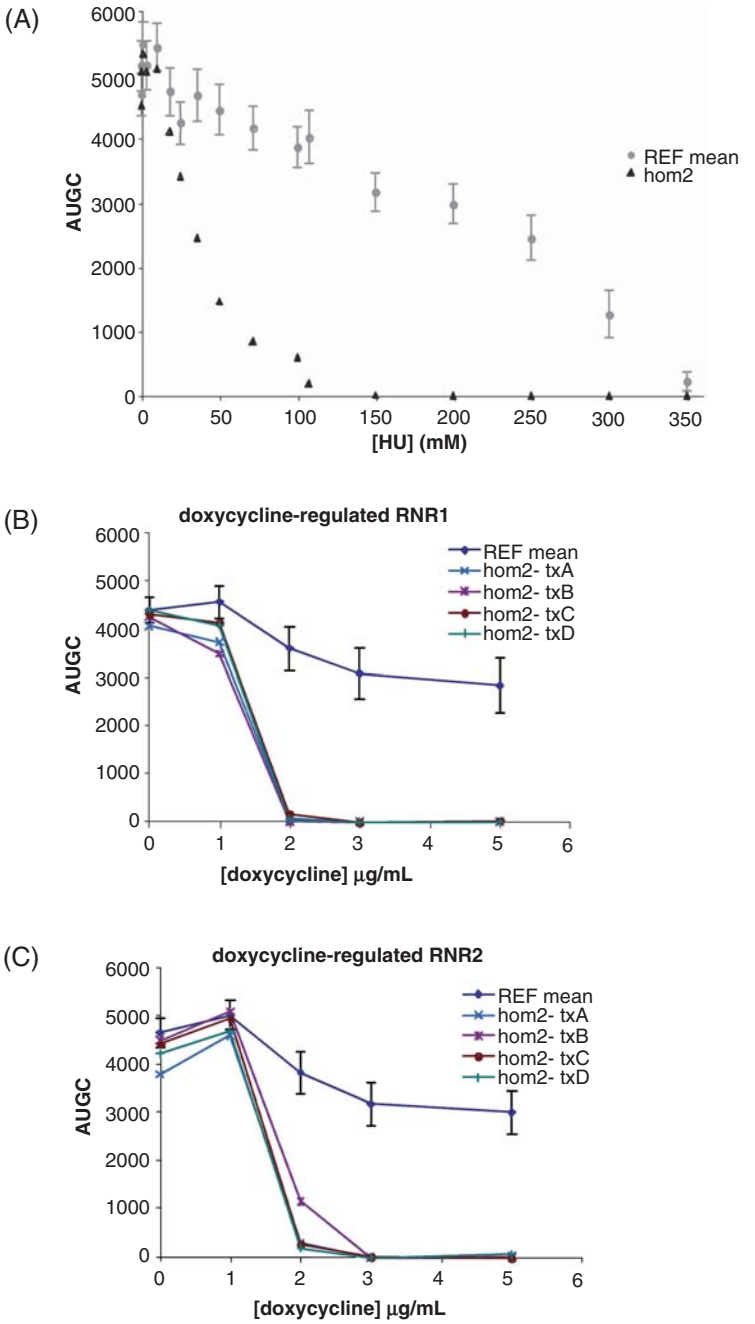


Figure 5.8. Tet-regulatable alleles of genetic drug targets are useful for validating chemical-genetic interactions. Panel A, buffering capacity of hom2 in response to HU perturbation. Panel B, depicts the average AUGC from multiple transformants of the reference strain. Panel C, similar data for tet-rnr2 deletion strain. See text page 119 for complete figure legend.

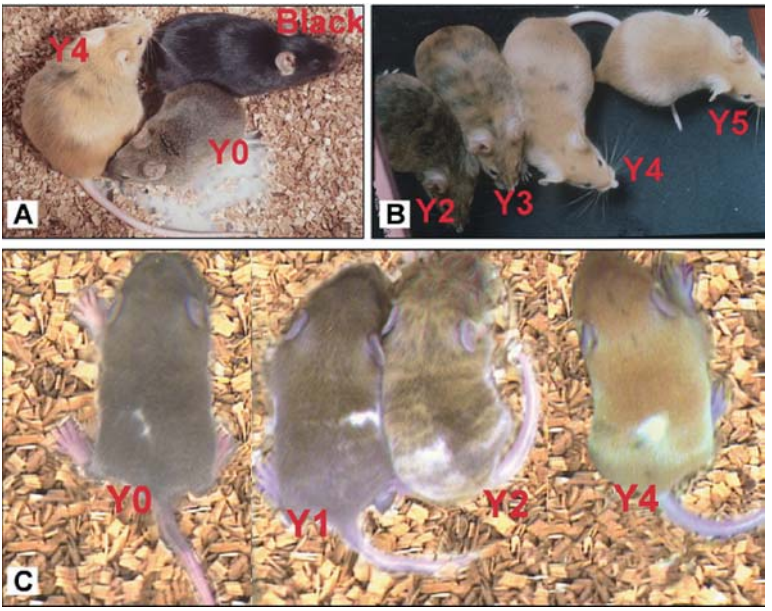


Figure 10.3. Examples of mice from viable yellow mouse model. (A) VY mice, (B) strain VY A^{vy}/a, (C) strain YS A^{vy}/a. See text page 228 for complete figure legend.

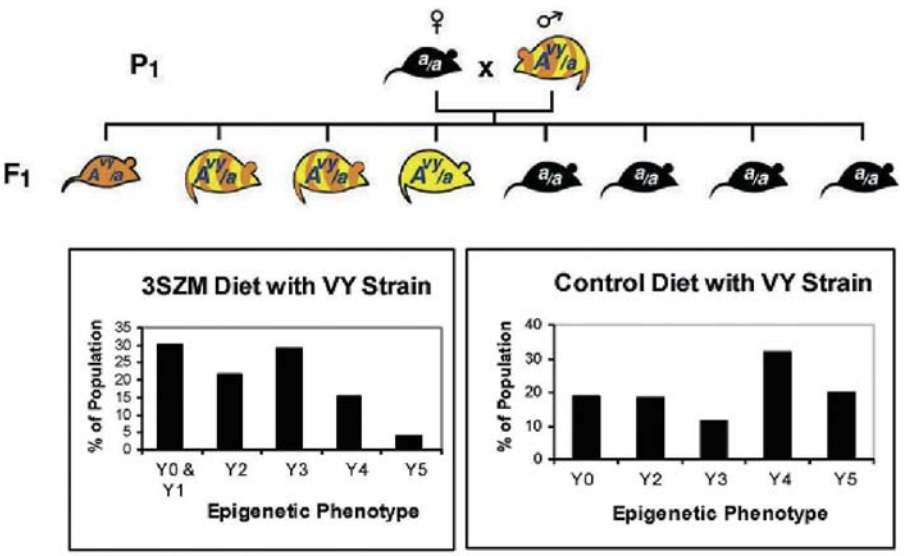


Figure 10.4. Mice mated a/a dam X A^{vy}/a sire. Dam is on 3SZM diet resulting in epigenetic phenotype shown in left panel or on control diet resulting in epigenetic phenotype shown in right panel. See text page 232 for complete figure legend.

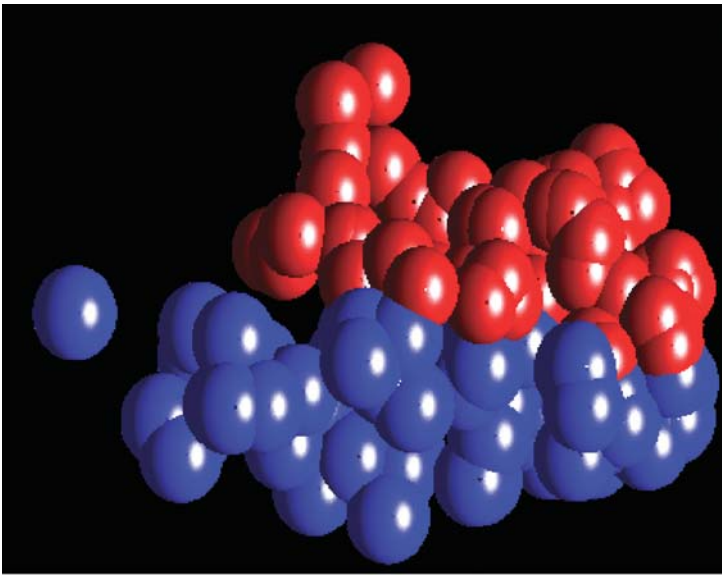


Figure 17.8. Isomap visualization of normal (red) and clear cell carcinoma (blue) cells isolated from kidney tissues. See text page 390 for complete figure legend.

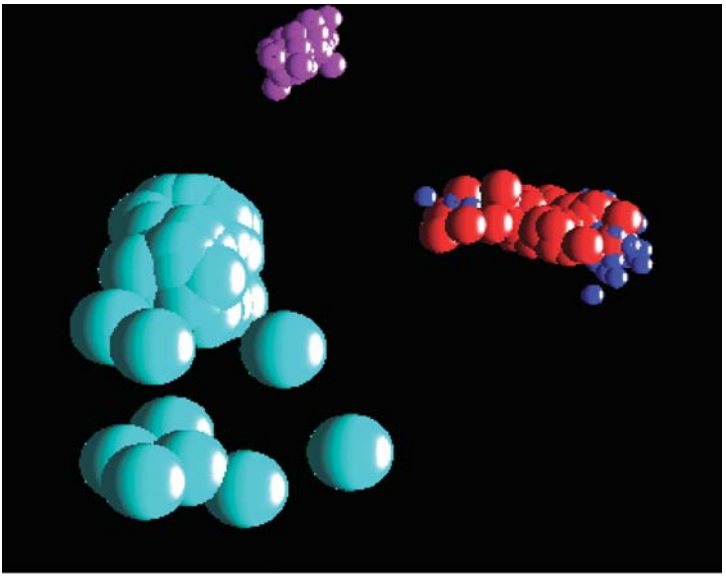
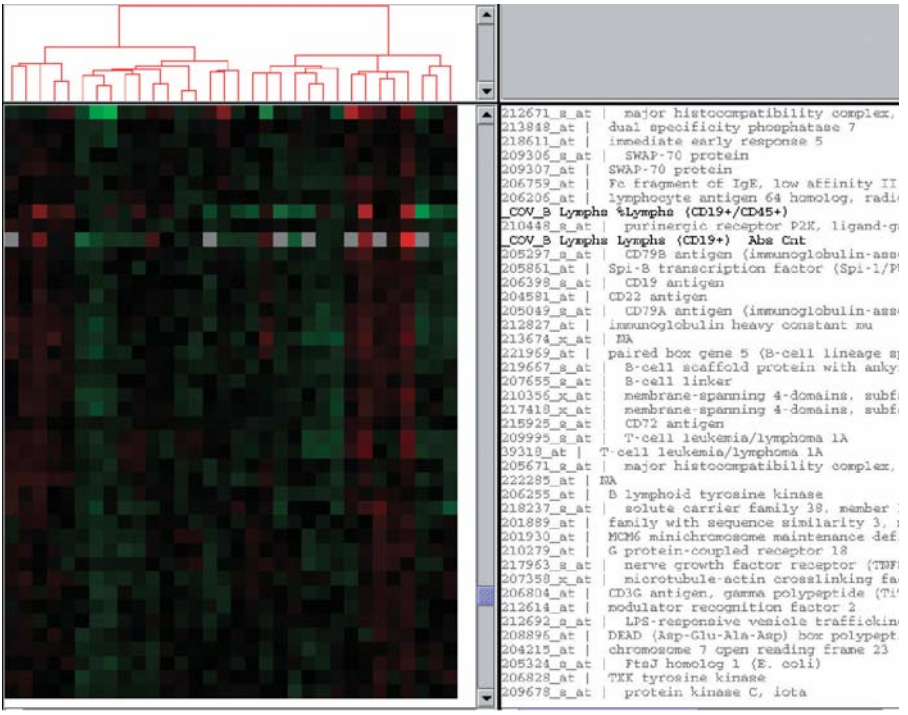
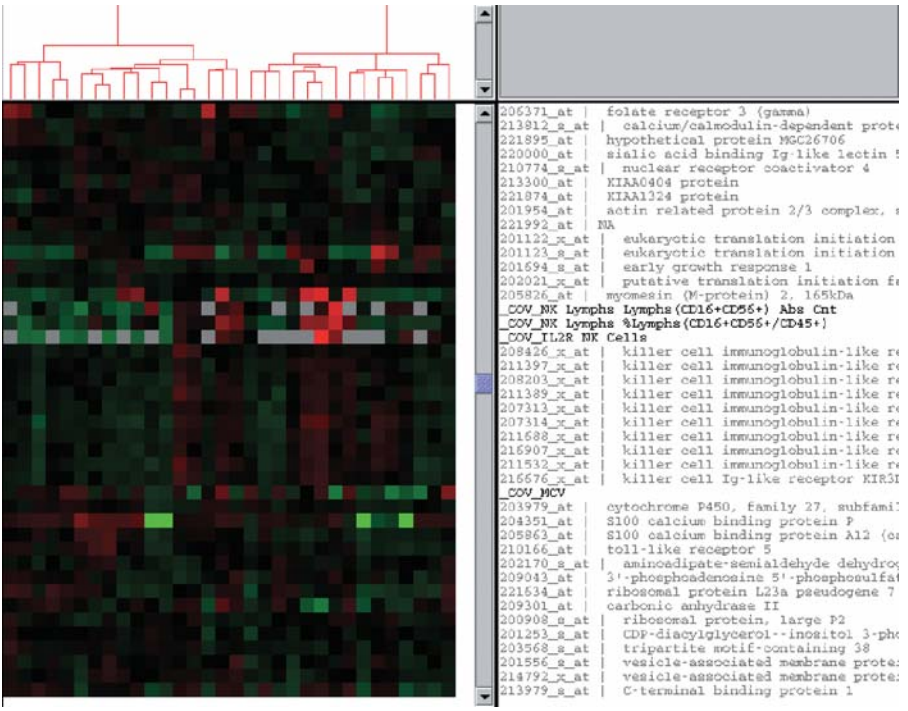


Figure 17.9. Principal component analysis (PCA) identifies three clusters in single nucleotide polymorphism (SNP) dataset. Asians (magenta), Yoruba Africans (dark blue), African-Americans (red) and European-Americans (light blue). See text page 391 for complete figure legend.



(A)



(B)

Figure 17.11. Expression values of genes expressed in particular cell types. (A) CD19+/CD45+, (B) CD16+/CD56+. See text page 397 for complete figure legend.