FAST MOVING FRONTS - 2009

March 2009

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Jim Kaput talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Biology & Biochemistry. The author has also sent along images of their work.

Article: The case for strategic international alliances to harness nutritional genomics for public and personal health
Authors: Kaput, J, et al.
Journal: BRIT J NUTR, 94 (5): 623-632 NOV 2005
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SW: Why do you think your paper is highly cited?

More and more scientists are realizing that an understanding of complex biological systems cannot be achieved by analyzing merely one aspect of a particular problem. Nutritionists typically ignore genetic variation, and many genetic association studies do not measure environmental influences. This paper was a call to scientists of many disciplines to collaborate under the banner of nutrigenomics—although the more popular term used now is personalized nutrition.

The genesis of this paper was initiated at the 1st Bruce Ames Symposium on Nutritional Genomics that was held at the University of California, Davis, in October, 2004. A group of about 20 scientists at that multidisciplinary meeting met and agreed that understanding gene-nutrient (or gene-environment) interactions would require the knowledge and technologies of many disciplines and international alliances. This group formed the core that developed the concepts in the paper. These concepts were rooted in the studies in humans and laboratory animals conducted in the 1990s and early 2000s which demonstrated the need for analyzing multiple genotypes and multiple diets in order to understand biological processes.

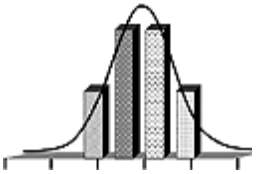
Since genotypes and cultures vary across the world, it was not a great leap to realize that the study of gene-nutrient-phenotype associations could only be done through international collaborations. To accomplish such an ambitious goal, we outlined the need for data sharing, improving the analyses and consistency of phenotypes (deep phenotyping), the need for genomic controls (population architecture analyses), ethical issues, other environmental variables, and more accurate nutritional assessments.

While some of these needs were the same ones for the International

Haplotype Mapping project, phenotyping and assessing nutritional intakes added to the complexity of the task. Our colleagues in nutrigenomics organizations in Europe: European Nutrigenomics Organization, New Zealand, Brazil, Canada, and other countries are all involved in meeting these challenges.

In addition, the human variome project is now collaborating with us on some aspects of our effort and we on their effort. Progress has been made on many of these topics, and many are focusing on various needs described in the paper, citing our publication in the process.

Figure 1:



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SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

The paper highlighted the re-awakening of long-known knowledge: that what an individual eats will affect one's health (Hippocrates: "Let medicine be your food and food your medicine.") The only difference from that ancient, but largely ignored, knowledge is the ability in the modern era to conduct high-throughput analyses of biological systems using various omic technologies. Many of us acknowledge that nutrigenomics sounds as if the only omic is genomic, when in reality, analyzing transcripts, proteins, and metabolites are required for a complete understanding of the effects of nutrients (and lifestyle) on an individual's genetic make-up.

This paper was actually one of many reviews of the early 2000s which began summarizing the need to study nutrient intakes and genetic variation. In one sense, its appeal and utility was needed to synthesize the knowledge of these scientific fields, along with the fact that 89 authors from 22 countries agreed to what was needed to make progress. Many of these authors are still working together, both formally and informally, to forge new initiatives in this area of research. It goes without saying that many of these authors could have produced the first draft of this article and that many contributed excellent edits which yielded the final version.

SW: Would you summarize the significance of your paper in layman's terms?

The general public knows that food is important for health, but many are confused by the nutritional epidemiological studies that yield conflicting conclusions about what to eat. The general hype surrounding genetic research has led to a deterministic view of disease susceptibility: the "It does not matter what I eat or how active I am, my genes dictate my health outcomes" syndrome.

Our paper acknowledged the limitations in current research methods and laid out a specific plan to improve the science. Our goal is to understand why an individual such as Jim Fixx died at age 52, even though he was a runner and ate a healthy diet, yet the English statesman Winston Churchill lived to age 90 while being overweight and smoking cigars throughout his life.

SW: How did you become involved in this research and were any particular problems encountered along the way?

A well-known and highly respected nutritionist, Dr. Willard Visek, M.D., Ph.D., of the University of Illinois, Urbana-Champaign, passed by my office each day, often entreating me to teach him about molecular biology. In his view, the discipline of nutrition needed more concrete answers to questions of how nutrients influence health. Although I was reluctant to change fields as a young assistant professor in the Biochemistry Department, I realized that the emerging tools of high-throughput molecular biology could be used to analyze nutrient–gene interactions.

Although the molecular methods we started using on this project in 1986 were crude by today's standards, emerging technologies and ideas were transforming how biological systems were being analyzed. Some rather brave graduate students (Tim Elliot, Deborah Swartz, Liz Paisely, Eric Park) and one of the best research associates, Heather Mangian, started a series of studies that helped developed a mouse model for studying gene-nutrient interactions.

> Our strategy for identifying these gene-nutrient interactions was to compare gene expression—which could be at the metabolite or protein levels—among two or more strains of mice that (i) differ in response to the same diets and (ii) had different genetic susceptibility to disease. Only the differences in gene expression could produce a different phenotype (disease or not) based on diet.
>
> We proposed (see Kaput J, *et al*., "Diet-disease interactions at the molecular level: An experimental paradigm," *J. Nutr.* 124: 1296S-1305S, 1994) that genes regulated by diet and mapping to genetic loci involved in disease would identify the likely causal genes, i.

"The list of potential implications and applications of this science are quite lengthy and extensive."

e., within quantitative trait loci, (see Park EI, *et al*., "Lipid level and type alter stearoyl CoA desaturase mRNA abundance differently in mice with distinct susceptibilities to diet-influenced diseases," *J. Nutr.* 127: 566-73, 1997, and Kaput J, *et al*., "Identification of genes contributing to the obese yellow Avy phenotype: caloric restriction, genotype, diet x genotype interactions," *Physiological genomics* 18: 316-24, 2004). Subsequent studies by others called these "expression quantitative trait loci," or eQTLs.

Our work unknowingly was consistent with the research of pioneers such as Charles Scriver, the eminent Canadian pediatrician and biochemical geneticist, and others, who demonstrated that the avoidance of phenylalanine prolonged life and also reduced symptoms for those with phenylketonuria—that gene-environment interactions contribute to health and disease processes.

Others were showing that different fat intakes in humans produced different serum lipid levels in individuals with polymorphisms in apolipoproteins (see Corella and Ordovas, "Single nucleotide polymorphisms that influence lipid metabolism: Interaction with dietary factors," *Annu. Rev. Nut.,* 25:341-90, 2005). Even with the work of many in humans and laboratory animals, nutrigenomic ideas , concepts, and experiments (and our grant applications) were not well accepted in the 1980s and 1990s.

Where do you see your research leading in the future?

The goal of the authors on this paper, and our new colleagues and collaborators around the world, is to produce more complete answers about how nutrients influence health in the individual. That latter statement is still not well understood by all scientists or the general public.

Our current experimental designs for nutritional or genetic epidemiology are based on population studies. These studies yield the population's attributive risk (see Kaput J, "Nutrigenomics research for personalized nutrition and medicine," *Current Opinions in Biotechnology* 19: 110-20, 2008) and not individual risk factors.

While the population-attributable risk (PAR) provides useful guidelines for what to eat or which genes and their variants may contribute to health or disease, epistatic interactions and other gene-environment interactions may alter the effect of a single nucleotide polymorphism (SNP) in different individuals. One approach that is based on the concept of challenging homeostatic systems (e.g., the oral glucose tolerance test, measuring glucose but also other serum metabolites—see van Ommen B, *et al.* "Challenging homeostasis to define biomarkers for nutrition related health," Molecular Nutrition and Food Research, in press).

While nutriomic research provides the technologies and concepts, we need to develop novel research strategies for developing individual risk factors, while taking into account gene variants, epistatic interactions resulting from differing genetic ancestries, and influences of different environments—quite a challenging task.

Do you foresee any social or political implications for your research?

The results of nutrigenomic research have significant implications for society, from food fortification programs that account for the majority genotype in a region (see Darnton-Hill *et al.*, "Public health nutrition and genetics: implications for nutrition policy and promotion," *Proc. Nutr. Soc.* 63: 173-85, 2004), to how drugs are developed and used. For example, agribusinesses interested in developing plants with improved nutrient profiles will need to know which populations will benefit from their products and which populations may be harmed.

Some dietary chemicals which alter drug metabolism pathways and basic dietary profiles are rarely considered in drug treatments, although specific drug-diet interactions are well known. Food manufacturers may adopt research results to create healthy, stable, and economical foods based on health-related evidence rather than relying only on taste and shelf life. The list of potential implications and applications of this science are quite lengthy and extensive.

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Figure 1:

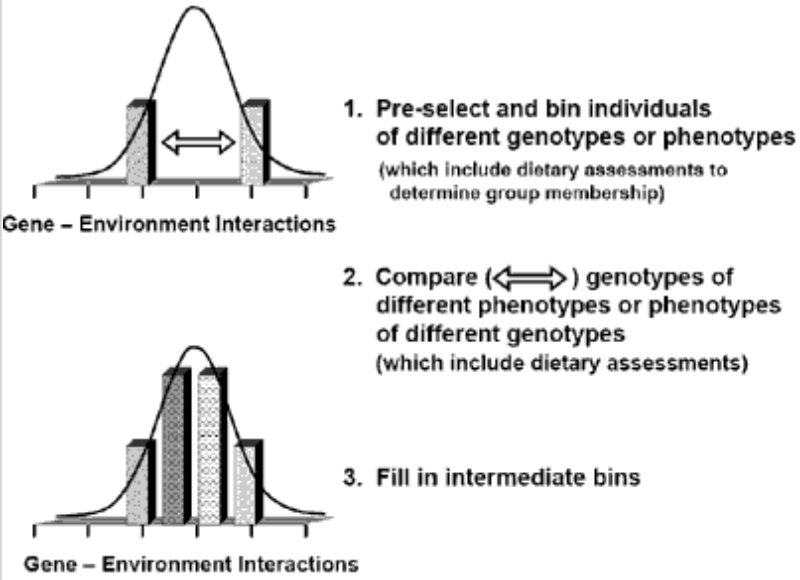

Figure 1:

Many nutritional or genetic epidemiology studies analyze a population of (largely) one ancestral group (e. g., Europeans - such as the group represented by the column on the right in the top graph) and apply those results to the rest of the human population (the bell shaped curve). Only a small sampling of the total genetic variation, phenotypic variation, or lifestyle (diet) variation is accounted for in such studies. International collaborations are needed to find populations with the greatest differences in gene - environment interactions. That is, instead of examining the statistical main effect of genetic variation differences between populations or the statistical main effect of different nutrient intakes, the statistical main effect that is most important is the interaction term (gene - environment). The first step, therefore, is to conduct a harmonized protocol so that gene - environment interactions can be analyzed to find those of greatest difference. While one may predict these to correspond to difference between different ancestral groups, variables such as gene - gene interactions may confound simplistic experimental designs. Once these extremes are found, the intermediate bins can be filled in using standard statistical concepts (quintiles, quartiles etc). The goal of this design is to discover the full range of human gene - environment interactions by finding and then defining metabolic groups that respond most differently. (see *Current Opinions in Biotechnology* 19: 110 – 20, 2008) for more details.

KEYWORDS: STRATEGIC INTERNATIONAL ALLIANCES; NUTRIGENOMICS; GENE-NUTRIENT INTERACTIONS; HEALTH DISPARITIES.

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