Nutritional genomics

Patrick J. Stover
Cornell University, Division of Nutritional Sciences, 315 Savage Hall, Ithaca, New York 14853
Submitted 5 December 2003; accepted in final form 8 December 2003

Stover, Patrick J. Nutritional genomics. Physiol Genomics 16: 161–165, 2004; 10.1152/physiolgenomics.00204.2003.—The integration of genomics into nutritional sciences has illuminated the complexity of genome responses to nutritional exposures while offering opportunities to increase the effectiveness of nutritional interventions, both clinical and population based. Nutrients elicit multiple physiological responses that affect genome stability, imprinting, expression, and viability. These effects confer both health benefits and risks, some of which may not become apparent until later in life. Nutritional genomics challenges us to understand the reciprocal and complex interactions among the human genome and dietary components in normal physiology and pathophysiology. Understanding these interactions will refine current definitions of benefit and risk and lead to the establishment of dietary recommendations that have a high predictive value, minimize the risk of unintended consequences, and account for the modifying effects of human genetic variation. Furthermore, nutritional genomics will enable the design of effective dietary regimens for the prevention and management of complex chronic disease. This review focuses on new perspectives that have been presented to the nutritional sciences by the advent of genomics, and new challenges that demand attention because of their potential impact on, and immediate translation into, current public health nutrition recommendations and interventions.

nutrition; genetic variation; recommended daily allowance; single-nucleotide polymorphism; haplotype; mutation; selection

Genomics encompasses knowledge related to “the study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors” (27, 43). The acquisition of whole genome sequences is the foundation from which this new discipline emerged, which seeks to understand fundamentally the origin and molecular basis of all life processes that are encoded by DNA sequence, processes that are hardwired and those that are modifiable by environment. “Nutritional genomics,” sometimes referred to as “nutrigenomics,” is a widely recognized term that has renewed interest in the benefits of nutrition research but has suffered from a lack of meaningful scientific identity. Definitions of nutritional genomics range from the application of high-throughput genomic technologies to nutrition research (13, 34, 50) to the genetic enhancement of plants for higher nutritional quality (8). Technological and theoretical advances in nanobiotechnology, robotics, genetics, mathematics, and computational biology, among others, unquestionably facilitate and in some cases enable research and discovery in genomics and all of the life sciences. However, definitions of nutritional genomics that exclusively accentuate the application of high-throughput and/or genomic technologies to accelerate the pace of traditional nutrition research and its applications fail to recognize the new science that has evolved at the interface of the disciplines of nutrition and genomics and the new opportunities for research, discovery, and application that it offers. This mini-review focuses on new perspectives that have been offered to the nutritional sciences by the advent of genomics, and new challenges that demand attention because of their potential impact on, and immediate translation into, current public health nutrition recommendations and interventions.

Nutrition is an integrative discipline. From its inception, nutritional science has been distinguished by its integration of knowledge and technology derived from the biological and physical sciences to understand the role of nutrients and other dietary components in human health and disease throughout the life cycle, and the translation of that information for the improvement of public health (1, 14). Basic nutrition knowledge is built upon research from many diverse disciplines including analytical chemistry for isolation and structural characterization of essential nutrients, biochemistry and physiology for elucidation of nutrient metabolic and signaling pathways and their role in homeostasis, and human genetics for the initial discovery of gene-nutrient interactions through the study of inborn errors of metabolism. However, these approaches are not sufficient to predict and quantify interactions among dietary components and human polymorphic alleles. This limitation has hindered efforts to achieve scientifically based dietary recommendations and effective nutrient interventions that faithfully maximize health benefit and minimize the risk of unintended consequences for all human populations. Nutritional genomics challenges us to understand, in molecular detail, the reciprocal and complex interactions within the human genome, including all genetic variation therein, and dietary components in normal physiology and pathophysiology (Fig. 1). These interactions, including the modifying influence of genetic variation on nutritional requirements, have been
appreciated for decades but not developed sufficiently to influence dietary recommendations or nutrition policy.

The primary goals of nutritional genomics research are: 1) to establish dietary recommendations that have a high predictive value with respect to disease prevention, minimize the risk of unintended consequences, and account for the modifying effects of human genetic variation; and 2) to design effective dietary regimens for the management of complex chronic disease (Fig. 1). The identification of alleles that contribute to polygenic chronic diseases such as obesity, diabetes, and hypertension is expected to catalyze organism-based research that will support the rational design of targeted dietary regimens for the prevention and/or management of disease phenotypes (48). Such expectations for achieving therapeutic nutrition through the application of genomics to nutrition research and practice are warranted. There exists a scant yet persuasive literature that demonstrates the potential for modifying the penetrance of deleterious genetic alleles by optimizing gene-nutrient interactions through dietary interventions. The prevention of severe cognitive dysfunction associated with phenylketonuria by dietary phenylalanine restriction is the classic example (3, 32). Yet, enthusiasm is tempered by an inability to identify low-penetrant contributing alleles in multigenic disorders (48), insufficient knowledge to accurately modify genome function and cell physiology through diet, and an inability to address and minimize the potential for unintended consequences resulting from the administration of nutrients at intake levels that cannot normally be achieved with a healthy and natural food-based diet (21).

**Reciprocal interactions between nutrition and the mammalian genome.** The primary sequence of the human genome and the genetic variation that exists within the human species are the result of molecular adaptation to evolutionary pressures that have been exerted through the processes of gene mutation and purifying selection as well as random drift (10). Throughout this process, nutrition has been perhaps the most persistent and variable of the environmental exposures that have challenged and thereby shaped the human genome and contributed to its variation (Fig. 1). Individual dietary components markedly affect gene mutation rates (15), and nutrients are one of several environmental factors that can influence fetal viability and modify the penetrance of deleterious genetic lesions; nutrition is in utero selective pressure that can contribute to the fixation of new mutations in human populations (Fig. 1) (4, 30, 45). Likewise, past decades of nutrition research have established that the function of the modern human genome, which is made manifest through its expression, is modified continuously in response to dietary exposures. Homeostatic mechanisms have evolved to permit adaptive genomic responses to nutritional milieu at the level of DNA transcription, mRNA translation, as well as protein and mRNA stability. These mechanisms permit cells to regulate rates of nutrient transport and nutrient status, alter nutrient storage capacity, fine-tune the flux of intermediates through metabolic branch points, dramatically restructure the cellular transcriptome and proteome, and trigger the cellular programs of differentiation, cell cycle, and apoptosis. A comprehensive understanding of the mechanisms that underlie the reciprocal interactions of dietary components with the genome, which is not attainable by genomic profiling approaches alone, will enable the manipulation of genome expression and stability for benefit through diet with high predictive value (Fig. 1).

**Genetic variation influences nutritional requirements.** The term “nutrient” has been most recently defined as a “fully characterized (physical, chemical, physiological) constituent of a diet, natural or designed, that serves as a significant energy yielding substrate or a precursor for the synthesis of macromolecules or of other components needed for normal cell differentiation, growth, renewal, repair, defense, and/or maintenance or a required signaling molecule, cofactor, or determinant of normal molecular structure/function and/or promoter of cell and organ integrity” (23, 54). A primary goal of the nutritional sciences is to establish scientifically based “recommended dietary allowance” (RDA) for each nutrient, which is defined as the level of dietary intake that is sufficient to meet the requirement of 97% of healthy individuals in a particular life stage and gender group (29). In the absence of sufficient data to calculate an RDA for a nutrient, an “adequate intake” (AI), which is an estimated recommended intake value, is established (Fig. 2). Some nutrients are toxic at elevated intake levels, and therefore a “tolerable upper intake level” (UL) may be established for an individual nutrient. A UL represents the highest level of nutrient intake that can be achieved without incurring risk for adverse health effects for most individuals in the general population (29).

Even prior to the sequencing of the human genome and initiation of haplotype mapping efforts (20), nutritional requirements were recognized to be complex traits that are subject to modification by both genetic background and by nutrient-nutrient interactions. Genetic background can alter both minimal nutrient requirements and tolerable upper intake levels. Single-nucleotide polymorphisms (SNPs) have been identified in genes that encode proteins that function in nutrient metabolism or storage and alter optimal nutritional requirements. A common polymorphism in the methylenetetrahydrofolate reductase (MTHFR) gene (A222V) generates an amino substitution in the protein that alters its stability and affinity for its riboflavin cofactor (24, 26). The MTHFR polymorphic allele encodes an enzyme with decreased enzymatic activity compared with the enzyme encoded by the normal allele and
impaired both folate accumulation and homocysteine remethylation (2, 18, 19). This polymorphism is a risk factor for neural tube defects and cardiovascular disease but decreases risk for colon cancer (2). The penetrance of this polymorphic allele is modified by dietary folate. Carriers of the A222V MTHFR polymorphism require higher intakes of folic acid to lower serum homocysteine and reduce their risk for folate-related pathologies (2).

Genetic variation can also influence ULs. An SNP in the hereditary haemochromatosis linked gene (HFE) increases risk for haemochromatosis, an iron storage disease, which can result in up to 50-fold increases in storage deposits (25). These examples have questioned the concept of generalized nutritional requirements and fueled a movement to personalize these recommendations. The degree to which common polymorphisms lower the UL or increase the RDA for a given nutrient and thereby narrow the window of optimal nutrient intake has not been established and depends on the criteria that are used to establish requirement and toxicity. The few SNPs that have been demonstrated to be penetrant with respect to their impact on metabolism and nutrient requirements were identified because of their obvious association with disease. However, highly penetrant monogenic alleles are expected to be the exception, because of the recognition that individual nutrient requirements are polygenic traits and modifiable by intake levels of other nutrients.

The impact of genetic variation on public health nutrition policy remains uncertain. Haplotype mapping efforts offer the possibility of “classifying humans” for personalized preventative and therapeutic medicine (6) and enable initiatives in pharmacogenomics that seek to optimize the efficacy of pharmaceutical agents to genetic background (47). Similar benefits have been anticipated for nutritional genomics, but may not be realized. Nutrition, unlike pharmaceuticals, is a lifelong exposure and a selective pressure during mammalian development. Nutrient availability selects against embryonic genotypes that confer nutritional requirements that cannot be met by the placenta. Mammalian genomes encode developmental termination programs, including embryo resorption in rodents and spontaneous abortion in primates, which can be activated by malnutrition and/or deleterious genetic lesions (33). Polymorphisms that escape this selection can be masked or buffered by compensatory alterations in genome expression that are set and memorized during early development (7). This phenomenon, referred to as canalization, has been observed in studies of mice with induced gene deletions (22, 31, 46). Therefore, it is not unreasonable to assume that RDAs and ULs can be generalized, with few exceptions, to entire populations because genomes that confer extreme nutrient requirements fail to develop or undergo adaptation. Screening for genetic minorities with exceptional nutrient requirements may prove to be advantageous, but this is not currently common practice.

Nutrient intakes influencing genome stability and genetic variation. The impact of dietary components on genome integrity and viability may provide new criteria for establishing both RDAs and ULs. Nutritional requirements have been defined historically as the level of intake required to prevent severe deficiency and the associated clinical symptoms (29). Because genomic mutation is the antecedent of certain developmental anomalies, degenerative diseases, and cancers and is a physiological event that can be quantified in a controlled experimental setting, it has been suggested that the effects of key minerals and vitamins on DNA mutation rates should be considered when establishing RDAs (15). Studies in cell cultures and animal models have established that marginal deficiencies in folate, vitamin B12, niacin, and zinc can influence genome stability, and antioxidants including carotenoids, vitamin C, and vitamin E may prevent the oxidation of macromolecules in vivo. Validation of these protective effects in controlled human trials may indicate benefits and lead to increased recommended intake levels for these nutrients for certain populations (Fig. 2), perhaps at levels not normally achievable from a natural food-based diet.

Other genomic outcomes, including embryo rescue, are emerging as criteria for establishing tolerable upper limits during reproductive ages. The concept of nutritional rescue of genetic mutations, or “good diet hides genetic mutations,” was recently publicized (44). Individual nutrients, when administered in supra-physiological levels during critical developmental windows, can rescue severe genetic lesions in mice. Maternal retinoic acid administration between 7.5 and 9.5 days postconception rescued deafness and inner ear development in Hoxa1−/− mice (42). Folic acid has also been demonstrated to rescue skeletal defects associated with deletion of a Hox gene, as well as neural tube defects in mice that have no evidence of disrupted folate metabolism (49). The prevalence of this rescue phenomenon is not established, but animal studies indicate that nutrients can modify the viability of genomes, including ge-

![Figure 2](https://www.physiolgenomics.org/images/figure2.png)
nomes that confer atypical nutrient requirements to the surviving fetus (16).

However, to be relevant, the rescue of more subtle yet deleterious genetic mutations (i.e., SNPs) by less extreme ranges of nutrient intakes must be demonstrated rigorously, and the mechanisms whereby nutrients override developmental termination programs must be established. Nutritional rescue of deleterious genomes is suggested but has not been demonstrated conclusively in human populations. SNPs in the MTHFR (A222V) and MTHFD1 (R653Q) genes, which encode folate-dependent enzymes, are associated with increased risk for neural tube defects. These polymorphisms are not in Hardy-Weinberg equilibrium (5, 35, 45), consistent with evidence that the MTHFR A222V polymorphism is a risk factor for spontaneous miscarriage and decreased fetal viability (36–41). A recent study (45) indicated that maternal folate supplementation has increased the prevalence of the normally under-represented A222V allele in a Spanish population, suggesting that folate may be rescuing human embryos as observed in animal studies, although such findings have been challenged (53). The percentage of fetal loss that can be prevented by optimizing maternal nutrition is unknown. However, nearly 62% of all human conceptions are lost before the 12th week of gestation (11, 12), and therefore rapid genotypic shifts may be enabled through maternal vitamin supplementation as indicated (45). Although the long-term health consequences, if any, for embryos that result from nutritional rescue are unknown, confirmation of this effect in both human populations and experimental animal studies is warranted.

Maternal nutritional status can also alter the epigenetic state of the fetal genome and imprint gene expression levels with lifelong consequences (51). Epigenetic alterations of the fetal genome do not affect the primary sequence of DNA, but rather alter gene expression, and may explain subtle phenotypic differences observed in identical twins (9). DNA methylation of cytosine nucleotides is the best-established mechanism for nutrient imprinting of fetal gene expression, because methylation regulates gene expression. Methylation patterns are established very early in development and can remain metastable throughout life. The methyl groups that modify DNA are derived from one-carbon metabolism, a metabolic pathway that is dependent on B vitamins as enzymatic cofactors including folate, vitamin B12, and vitamin B6. Cytosine methylation is highly sensitive to cellular folate status, and DNA methylation density varies proportionately with folate status (17). Maternal supplementation with folate and other methyl donors alters the methylation status of targeted alleles in the embryo, and these methylation patterns are retained into adulthood (52). Genes that neighbor retroviral elements have been indicated to be preferred targets for epigenetic regulation by B vitamins (52), and such epigenetic genomic alterations are associated with and may underlie common diseases (9). Other studies have demonstrated culture-induced alterations in the methylation and expression of selected genetically imprinted genes in pre-implantation embryos (28, 30), indicating that permanent genomic alterations can result from in vitro fertilization procedures. Nutrient modification of epigenetic programs may begin to provide a mechanistic foundation for observational studies that associate risk for adult chronic disease with maternal malnutrition (51) and provide a sound scientific justification for investigating the long-term consequences of maternal undernutrition and overnutrition on fetal viability and lifelong disease risk.

Conclusions. The integration of genomics into nutritional sciences has illuminated the complexity of genomic responses to nutritional exposures while offering opportunities to increase the effectiveness of nutritional interventions, both clinical and population based. Basic research, facilitated by high-throughput technologies, will continue to elucidate mechanisms that underlie the effects of nutrients on genome stability, imprinting, expression, and viability. Quantifying the magnitude of these effects and their relevance and application to nutrition policy will prove to be more challenging. Definitions of benefit and risk associated with dietary exposures are likely to include effects on genome function, stability, and/or viability. However, nutrients elicit multiple genomic effects that confer both health benefits and risks that may not become apparent until later in life. Therefore, recommendations that encourage elevated intakes of individual nutrients at levels not normally achievable in healthy food-based diets, as present in common dietary supplements, may be justified, but will require rigorous validation so that their safety is established. Furthermore, nutritional interventions that target entire populations must consider adverse consequences to genetic minorities that may accrue risk while others benefit. The considerations raised in this review, which are not intended to be exhaustive, illustrate that the new science of nutritional genomics presents many more opportunities and challenges to the field of nutrition than it provides solutions.

REFERENCES


