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Horizons in Nutritional Science

The case for strategic international alliances to harness nutritional genomics for public and personal health†

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Nutrigenomics is the study of how constituents of the diet interact with genes, and their products, to alter phenotype and, conversely, how genes and their products metabolise these constituents into nutrients, antinutrients, and bioactive compounds. Results from molecular and genetic epidemiological studies indicate that dietary unbalance can alter gene–nutrient interactions in ways that increase the risk of developing chronic disease. The interplay of human genetic variation and environmental factors will make identifying causative genes and nutrients a formidable, but not intractable, challenge. We provide specific recommendations for how to best meet this challenge and discuss the need for new methodologies and the use of comprehensive analyses of nutrient–genotype interactions involving large and diverse populations. The objective of the present paper is to stimulate discourse and collaboration among nutrigenomic researchers and stakeholders, a process that will lead to an increase in global health and wellness by reducing health disparities in developed and developing countries.

Strategic international alliances: Nutrigenomics: Gene–nutrient interactions: Health diaparities

Genomes evolve in response to many types of environmental stimuli, including nutrition. Therefore, the expression of genetic information can be highly dependent on, and regulated by, nutrients, micronutrients, and phytochemicals found in food. The study of how genes and gene products interact with dietary chemicals to alter phenotype and, conversely, how genes and their products metabolise nutrients is called nutritional genomics or 'nutrigenomics'. Unbalanced diets alter gene–nutrient interactions,

Abbreviations: NuGO, European Nutrigenomics Organization; PROGENI, Program for Genetic Interaction; SNP, single nucleotide polymorphism.

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thereby increasing the risk of developing chronic diseases. Differences in allele frequencies and DNA haplotype blocks within and between human subpopulations, together with the chemical complexity of food, make the study of nutrient–gene interactions highly complex. Genetic variation and numerous environmental influences put the study of these interactions beyond the scope and expertise of any one researcher, institute or programme. Additionally, systems biology approaches are necessary for analysing gene–environment interactions but they require discipline-specific expertise and are expensive. Hence, there is considerable justification for global sharing of knowledge. In the present paper we provide an overview of the field of nutritional genomics and specific recommendations regarding needs and requirements for methodological advances and comprehensive analyses of nutrient–genotype interactions in populations throughout the world. The need for well-designed experiments in model organisms and cell cultures is also discussed. The objective of the present paper is to initiate communication and collaboration among nutrigenomic researchers and stakeholders around the world. By sharing ideas, best practices, and datasets, we hope to identify synergies and create those breakthroughs needed to develop more effective nutritional interventions and genome-based dietary recommendations. Ultimately, an international consortium will probably be necessary. We suggest a roadmap for achieving this objective. This effort requires participation of populations in many geographically distinct areas of the world. We believe that developing collaborations and exchanging information will have a significant, positive impact on health and reduce health disparities in developed and developing countries.

Background

The shifting balance between health and disease states involves the complex interplay of genes and the environment, which includes diet. Most scientists acknowledge the importance of environmental influences on the expression of genetic information, yet many human, animal, and cell-culture studies overlook their influences in their experimental designs (Kaput, 2004). At least two factors contribute to the genome-centric view of current experimental strategies. First, in a 2001 report summarising genes known to cause disease, 97 % of 923 genes examined were found to be solely responsible for aberrant phenotypes (Jimenez-Sanchez *et al.* 2001). Advances in our understanding of the molecular mechanisms of monogenic diseases have led to the implicit, if not explicit, belief that mutations are responsible. However, even these monogenic diseases can vary in the age of onset and in severity, demonstrating that other genetic or environmental factors influence the expression of the causative gene or its mutation. The second factor that contributes to gene-centred research is the tremendous chemical complexity of food. The simplest plant- and animal-derived foods contain hundreds of chemical constituents, some of which are sources of energy (for example, glucose or certain fatty acids), while others serve as essential nutrients or regulators of cell functions (for example, certain fatty acids and phyto-oestrogens such as genistein). Consequently, diet is often overlooked as an important variable in experimental design even though dietary constituents can alter gene expression and/or gene structure. Two well-documented examples of how nutrient–gene interactions can affect gene expression are provided by hyperforin and genistein. Hyperforin, the active ingredient in St John's wort, binds to the ligand binding site of the pregnane X receptor (Watkins *et al.* 2003) and induces transcription of reporter genes in cell-culture systems (Tirona *et al.* 2004; for a review, see Rebbeck *et al.* 2004). Genistein, an isoflavone found in soya beans and other plants, binds to the active site of oestrogen receptor β (Pike *et al.* 1999) and induces oestrogen-specific gene expression in uteri of rats fed genistein-supplemented food (Naciff *et al.* 2002). Recent reviews discuss these and other molecular processes directly affected by nutrients and show that nutrient–gene interactions affect health (Jacobs & Lewis, 2002; Francis *et al.* 2003; Gillies, 2003; Davis & Milner, 2004; Kaput & Rodriguez, 2004; Simopoulos & Ordovas, 2004). Diet–gene interactions are complex and are likely to require large populations for adequate statistical power. Resolving experimental design issues that originate from complexities of gene–environment interactions will probably require pooling of information from several population groups.

Superimposed are technical challenges of clinical data collection from individuals of diverse cultures and ecosystems along with the expense of complex phenotypic assessments and genotype analyses. Nutritional genomics requires a systems biology approach, with the methods and technical skills ranging from genotyping (especially single nucleotide polymorphism (SNP) analysis), nutritional epidemiology, microarray analysis, proteomics, metabolomics, bioinformatics, pathology, and diverse clinical assessments, in models ranging from cell culture to experimental animals and human populations. Significant numbers of investigators are developing nutrigenomics programmes in various countries, and each of them will probably face similar problems in developing and adapting cutting-edge technologies for high-dimensional research efforts. The strategic and technical challenges of nutritional genomics justify the sharing of resources and knowledge to avoid duplication in developing experimental tools, software programs, and computational models.

Nutrition and human genetic diversity

Although there is a growing body of evidence demonstrating the influence of some food constituents on gene activity, nutrigenomics must address how individual genomes respond to the complex nutrient and chemical mixtures that comprise foods. The sequencing of the human genome laid the foundation for one of the most significant scientific contributions to humankind – an evidence-based understanding that while human individuals are genetically similar, each retains a unique genetic identity underlying the wide array of biochemical, physiological, and morphological phenotypes in human populations. However, genetic variation produces a continuum for each human trait, thus challenging dichotomous social groupings based solely on external phenotypes (Keita *et al.* 2004; Parra *et al.* 2004). Variation among individuals from Africa, Asia, and Europe ranges from 10 % (analyses of simple tandem repeats) to 14 % (analyses of Alu insertion polymorphisms). However, about 86–90 % of genetic variation in our species is shared by ancestral groups (Jorde & Wooding, 2004).

Genetic variation in populations confounds molecular epidemiology studies that seek to analyse gene–disease or nutrient–gene associations. For example, of the 603 gene–disease associations reported up to 2002, only six have been replicated more than three times (Hirschhorn *et al.* 2002). Meta-analyses of twenty-five different reported associations (data from 301 published studies) showed statistically significant replication for

eight gene associations (Lohmueller *et al.* 2003). Similarly, non-replicated results associating diet with candidate gene variants are the norm (for reviews, see Loktionov *et al.* 2000; Loktionov, 2003; Corella & Ordovas, 2004; Ordovas, 2004; Ordovas & Corella, 2004). In addition to population stratification, other confounders include sample sizes lacking statistical power, inappropriately matched controls, overinterpretation of data (Lander & Kruglyak, 1995; Risch, 1997; Cardon & Bell, 2001), and the influence of other environmental factors (see later; p. 629 of proof). There is a growing awareness that epistasis (i.e. gene on gene interactions) (Hartman *et al.* 2001; Moore, 2003; Carlborg & Haley, 2004), genotype–environment interactions particularly those involving diet (for reviews, see van Ommen & Stierum, 2002; Corella & Ordovas, 2004; Kaput & Rodriguez, 2004; Ordovas, 2004), and health status (for example, Stoehr *et al.* 2000; Lan *et al.* 2003) may alter associations of SNP or sets of SNP with disease processes. A lack of consistency in methods of estimating food composition often precludes comparisons between populations. For example, estimates of dietary fibre contents differ if they are defined and analysed as NSP, or according to one of the more recent definitions (for example, Ferguson & Harris, 2003; Devries, 2004). The combinations of study design issues, complex and interacting molecular processes, and diverse environmental influences demand a re-evaluation of how biomedical research is conducted.

Goals and objectives of nutritional genomics research

The purpose here is to stimulate communication and collaboration among nutrigenomic researchers and stakeholders throughout the world. Stakeholders include representatives from academia, industry, government, and public interest groups. To help identify synergies and create the breakthroughs needed to develop more effective nutritional interventions and genome-based dietary recommendations, we are proposing discussions that will lead to sharing ideas, datasets, research results, reagents, samples, and best practices for conducting nutritional genomics research under high scientific standards and in an ethical, socially responsible, and culturally sensitive manner. The needs that have been identified for nutritional genomics research are presented (Muller & Kersten, 2003; Kaput, 2004; Ordovas & Corella, 2004).

Data federation

Development of a scalable database with semantic interoperability that will allow sharing anonymised genetic, phenotypic, dietary, nutritional status, and other environmental and cultural information must have the highest priority. Semantic interoperability will require agreements between independent database developers that all systems share common ‘meanings’ of data elements in a way that define a common ontology, mechanisms to share common data elements, and a means to ‘harmonise’ definitional disagreements. Several biobanks have developed such systems.

Larger study populations are needed

The statistical power of association studies needs to be increased with common phenotypic measurements and combining results from many studies. This can be a two-edged sword; in order to detect the subtle effects of gene variants, large numbers of study participants will be required. However, as the number of individuals in a study increases, the greater the likelihood that variance may be due to differences in environment and population stratification. Stratification occurs when individuals within the study population have different genetic architectures, which arise from their ancestral lineage (for example, African *v.* Asian ancestries). Analyses of genetic variance in human populations show a greater variation within populations than between populations (for a review, see Jorde & Wooding, 2004). Hence, combining data from multiple ancestral groups may reveal common genotypes and responses to diet. Stratification may be a confounder in standard statistical analyses because allele frequencies may differ between populations (Reich & Goldstein, 2001; Freedman *et al.* 2004). Genomic controls, such as analysing mitochondrial DNA, Y chromosome, or autosomal (Jorgenson *et al.* 2005; Tang *et al.* 2005) markers in participants, provide a measure of population stratification. Dimensionality reduction algorithms may identify clustering due to ancestral origins and associations with groups of SNP and dietary composition.

Improving analyses and consistency of phenotypes

Early molecular epidemiology studies attempted to link one SNP in a gene to a disease state such as cancer. However, variations in different molecular pathways may produce the same phenotype or disease. For example, type 2 diabetes mellitus is currently treated by changing diet or exercise habits and/or by drugs that target insulin secretion from the pancreas, glucose production by the liver, glucose absorption by the intestine, or insulin resistance by PPAR-targeted drugs in peripheral tissues (American Diabetes Association, 2005). Patients respond differently to these treatments or their combinations. Molecular epidemiologists include disease markers such as insulin, glucose, and/or HDL-cholesterol concentrations (rather than diabetes or atherosclerosis alone) to identify ‘subphenotypes’ of disease. Clinical studies should include repeated sampling and analyses that assess phenotypes more accurately (Pereira *et al.* 2004). Since the molecular basis for many diseases is lacking, the greater the number of accurate clinical measurements analysed, the more powerful the study. Since DNA samples may be shared across studies, common phenotypes for multiple diseases may be developed and measured that would facilitate measurements across studies. For example, serum HDL-cholesterol measurements could also be taken in breast or colon cancer studies.

Capturing and assessing accurate food intakes

Food surveys and dietary histories are often inaccurate because of differences in ability to recall specifics (type and amounts) of food intakes and differences in dietary assessment methods (for example, self-administered *v.* interviewed; food-frequency questionnaires *v.* diet diaries), and variations in their definitions and analyses. A major emphasis of this international effort will therefore focus on standardising and improving dietary assessment methodologies. Surveys will also have to capture self-described affiliations to religions, cultures, customs, or ethnic groups because of possible food restrictions and preferences. Confirmation of food intakes might also be accomplished by measuring plasma micronutrient concentrations, assuming funds were available. In addition to accurate food intake information, databases

are needed on the macro- and micronutrient content of local foods, a challenge for the diverse cultures and diets throughout the world. The FAO of the UN (Food and Agriculture Organization, 2005) and various national governments have compiled food composition tables for many countries worldwide, but data must often be extracted from unlinked flat files or from publications. A relational database of food composition must be developed through international collaborations.

Genomic controls

More diverse genetic analyses, that include not only genetic variants in nuclear DNA, but also analyses of mitochondrial DNA are needed. When high throughput methods are further developed, chromosome structure and DNA methylation analyses will also be needed.

Ethical and culturally sensitive recruitment

Ethical and culturally sensitive recruitment of study participants from diverse cultures (International HapMap Consortium, 2004) is needed. Some racial and ethnic populations and the poor suffer disproportionately from chronic diseases and are likely starting populations for nutrigenomic research. However, some cultures and populations may be sceptical of molecular and genetics disease research efforts, particularly because of colonial histories. Addressing the legitimate concerns of these populations will require the input of representatives from diverse communities and cultures to develop standards of collaboration and communication with study participants. To our knowledge, there are no precedents that allow for data sharing across national borders yet protect individuals' biological information (Austin *et al.* 2003; Maschke & Murray, 2004). Hence, among the first tasks of the international effort will be to develop protocols for five categories of ethical, legal, and social issues: study sponsorship and benefit sharing, public engagement, consent, and data protection (see Austin *et al.* 2003). The participation of the international nutrigenomic research community in addressing these issues may help facilitate development of regional, national, and international policies for such research. Such efforts are scientifically justified because comparative analyses among various ancestral populations with different macro- and micronutrient intake levels may be the critical approach to identify gene–nutrient interactions involved in health and disease. Results from comparing physiological and molecular responses between inbred strains of experimental animals fed different defined, reproducible diets identify gene–gene interactions and gene–environment interactions (for example, Park *et al.* 1997; Kaput *et al.* 2004) that cannot be revealed in homogeneous or genetically similar populations. Comparative analyses of different ancestral groups may therefore reveal common as well as population-specific nutrient–gene interactions (Tai & Tan, 2004).

Capturing the range of environmental variables

Capturing the range of environmental variables affecting expression of genetic information is an essential component of comprehensive gene–environment experiments and analyses. Although our primary focus is on nutrient–gene interactions, expression of genetic information is influenced by numerous environmental factors. For example, cytokine levels are unusually sensitive to environmental changes and serve as good markers of environmental influences that may alter protein and RNA expression. Some examples of non-nutrient environmental factors are:

1. Overall sleep time and sleep continuity (for example, Redwine *et al.* 2000; Irwin, 2002);
2. O_2 tension (Prabhakar & Peng, 2004), which is related to altitude;
3. Over-the-counter drugs, for example, non-steroidal anti-inflammatory drugs (Serhan *et al.* 2000);
4. Water intake relative to tea (Tomita *et al.* 2002) and other beverages;
5. Physical activity, including genetic fitness to activity (Nieman *et al.* 2003*a*,*b*, 2004; Gleeson *et al.* 2004);
6. Psychological factors such as stress (Irwin *et al.* 2003);
7. Exposure to allergens and pollutants (for example, Pandya *et al.* 2002);
8. Circadian rhythm and seasonal changes (Albrecht & Eichele, 2003);
9. Balance between energy intake and expenditure (for a review, see Seeley *et al.* 2004).

Each added variable may increase the need for larger populations since small studies may be unable to discriminate between all environmental effects. However, meta-analyses may be possible if studies record similar data elements for their populations. Although developing appropriate environmental survey instruments is challenging, a set of guidelines and suggestions would facilitate the development of common data elements for nutrigenomics studies.

Interactions between academia and industry

In the spirit of creating a truly integrated research initiative in nutrigenomics, the interaction of partners from agriculture, food processing, biotechnology, and pharmaceutical industries with academic centres would accelerate technology development and dissemination of nutrigenomic information to the public. Examples include the development of new crop varieties with enhanced nutritional value, novel food formulations and dietary supplements that promote health and prevent disease, and the development of chip-based diagnostic tests for monitoring genome-specific dietary interventions. An excellent model for this type of interaction is the recently awarded Freedom to Discover grant from Bristol-Myers Squibb Company to the Program in International Nutrition at the University of California (Davis, 2005). The goal of this grant is to explore the implications and applications of nutrigenomics and other 'omics' technologies in developing countries. Establishing productive and mutually beneficial relationships with industry for societal benefits and the greater good is a goal shared by the members of the nutrigenomics research community. Addressing the issue of revenue sharing among stakeholders, particularly study participants, will be a high priority for the international nutrigenomics network. One of many possible concepts is to develop novel agreements that ensure revenue sharing with participants or communities (Austin *et al.* 2003; Maschke & Murray, 2004) and, perhaps more importantly, investments for economic development in developing countries (Sachs, 2005).

Integration of nutrigenomics research

Nutrigenomic research depends upon robust and reliable methods for discovering candidate genes for association analyses, and

results of epidemiological associations that must be understood at the molecular level. Reliable model systems are essential for the development of an effective and successful international nutrigenomics effort. Examples of model systems that can provide valuable insights into molecular mechanisms underlying nutritional genomics research are now described.

Cell culture

Nutrient interactions have been analysed in model systems such as glucose deprivation (a model of energy restriction) in *Saccharomyces cerevisiae* (for example, Lin *et al.* 2002; Lin & Guarente, 2003) to human cells exposed to purified phytochemicals (for example, Pianetti *et al.* 2002) or micronutrients (for example, folate (Kimura *et al.* 2004). Although genetic variation is not typically analysed in such studies, cells in culture allow the dissection of molecular pathways influenced by dietary chemicals. Identifying diet-regulated or diet-influenced genes (and their products) using cell cultures allows for the analyses of gene variants in human or animal studies.

Animal models

Cell cultures do not have livers, microflora in an alimentary tract, nor the full metabolic repertoire of their complementary *in vivo* counterparts. That is, metabolism and regulation of nutrient and bioactive components of food are often affected by metabolism and products in other organs. Animal studies are often necessary to verify the results from cell-culture experiments. A distinct advantage of using animal models is the array of genetically defined mouse strains, the result of a 100-year effort to produce and characterise inbred strains for biomedical research (Jackson Laboratory, 2005). Laboratory animals are excellent models for biomedical research. Comparative genomic analyses (for example, Linder, 2001) have demonstrated that mice and rats share genes and diseases that are similar in other mammals. For example, 99 % of mouse genes have human homologues (Waterston *et al.* 2002) and obesity-induced diabetes occurs in mice (for example, Hribal *et al.* 2002; Rossmeisl *et al.* 2003) and dogs (Fleeman & Rand, 2001). Molecular responses to dietary chemicals can be analysed or compared in strains of known genotypes with differing susceptibility to diet-induced disease, enabling previously unsuspected contributors to the disease process to be identified (for example, Park *et al.* 1997; Kaput *et al.* 2004). Breeding strategies permit identification of epistatic interactions likely to influence gene–disease (Reifsnyder *et al.* 2000; Cheverud *et al.* 2004) and nutrient–gene interactions (for example, Cooney *et al.* 2002). Defined diets, which are reproducible, are critical for diet–gene studies in experimental animals (for example, Park *et al.* 1997; Kaput *et al.* 2004).

Studies in humans subjects

Ultimately, candidate genes from cell-culture systems or laboratory animals must be verified in human subjects. The two most common methods are large-scale molecular epidemiological studies and dietary cross-over trials. Ordovas & Corella (2004) critically reviewed the methodology and progress of molecular nutrigenomic epidemiological studies. Although such studies do not prove causality, they provide statistical associations between gene variants and disease, subphenotypes of disease, or changes in physiology caused by diet. Since statistical association studies are based on the analysis of groups or populations, the presence or absence of a particular SNP in an individual may or may not be linked to disease or response to diet. As mentioned previously, dietary surveys or histories fail to accurately determine food intake. Nevertheless, such association studies provide valuable information linking genotype to phenotype. It is likely that panels of SNP in different genes will be needed to improve the probability that a set of gene variants is associated with a physiological process or disease. Randomised double-blind (where possible) cross-over studies may be of value to confirm the validity of nutrigenomics findings reported in genetic epidemiological studies (for example, Dreon *et al.* 1999).

Models of scientific consortia

Interdisciplinary research is being fostered within institutions (Cech & Rubin, 2004) and through national and international collaborations. Four of these multi-institutional and national initiatives are examples of collaborative efforts for nutritional genomics research. The Pharmacogenetics and Pharmacogenomics Knowledge Base, also known as PharmGKB, developed by Stanford University, is funded by the National Institutes of Health and is part of a nationwide collaborative research consortium called the Pharmacogenetics Research Network (National Institute of General Medical Services, 2005; Pharmacogenetics and Pharmacogenomics Knowledge Base, 2005). PharmGKB is building a knowledge base with accurate and detailed definitions of genotypes and phenotypes involved in individual responses to different medications. Data are generated by the US National Institutes of Health-funded projects in twelve individual laboratories.

A second collaborative project is the Program for Genetic Interaction (PROGENI; Program for Genetic Interaction, 2005). PROGENI is the Administrative and Data Coordinating Center for the 'Interaction of Genes and Environment in Shaping Risk Factors for Heart, Lung, Blood, and Sleep Disorders' Study. Five separate National Heart, Lung and Blood Institute-funded studies at different locations (GET READI, GeneSTAR, GOLDN, GenSALT and HAPI Heart) are coordinated through PROGENI, which also pools data from the centres. Communication between subcommittees are maintained and core issues shared by all studies are addressed through the coordinating activities of the Center. The subcommittees include Recruitment, Protection of Human Subjects/Data Sharing, Phenotyping, Laboratory/DNA, Analysis and an overarching Steering Committee. A Data Safety Management Board, which is independent of and external to the Center, was formed to critique protocols, oversee recruitment goals and study progress. Biannual analysis workshops are held to bring together statisticians, and experts in analytic techniques foster cross-study collaboration and sharing of methods, tools, and software.

Scientists from twenty-two organisations in the European Union have formed the European Nutrigenomics Organization (NuGO; www.nugo.org). Approximately 650 scientists belong to this organisation with the key objective of development and promotion of mechanistic nutrition and health research through the application of 'omics' technologies. This is achieved through the development of joint research programmes and stimulation of facility sharing, facilitating education, communication, commercialisation, and dissemination of information. Development, data warehousing, and exploitation of nutrition- and health-related

bioinformatics for European nutrition and nutrigenomics researchers and communities are key issues. The formation of NuGO is funded by the European Union. NuGO is fostering collaborations among members through targeted funding and an interactive website, which hosts discussion groups on subjects related to nutrigenomics research methods and results.

A fourth model of a collaborative project is the International HapMap project (International HapMap Consortium, 2003, 2004), which is analysing SNP patterns (haplotypes) of human genetic variations within chromosomal regions. Each haplotype block will be tagged or identified by one or more SNP. A use for this resource will be association studies; candidate disease genes are found within haplotype blocks more frequently associated with subphenotypes of disease (for example, insulin levels or HDL-cholesterol concentrations, etc) in individuals with symptoms compared with individuals who are symptom-free. The HapMap Consortium consists of committees dealing with: ethical, legal, and social issues; population studies; community engagement and public consultation; sample collection; genotyping and SNP analysis; SNP discovery; scientific management and methods; initial planning (International HapMap Consortium, 2004).

There are significant differences between these model collaborative projects and nutrigenomics research. Nutrigenomics will require nutritional, cultural, and other environmental data that may influence nutrient–gene interactions. Populations linked to those variables also need to be identified. For example, food intake and activity levels in urban areas may be significantly different from those in rural areas. Macro- and micronutrient intake levels may vary widely in rural populations because of customs and seasonal availability of different foods. Furthermore, allele frequencies may differ between rural and urban populations within the same country. Although it has been argued that SNP associated with nutrient intakes have low penetrance and are unlikely to be predictive of disease susceptibility (Haga *et al.* 2003), others contend that combinations of SNP in multiple disease-linked genes will be predictive of a range of susceptibility to chronic diseases (for example, Kaput, 2004). Nutrigenomic studies will eventually resolve these conflicts. Nevertheless, the identification of populations and the possibility of discovering disease susceptibilities linked to genes, environment, and their interactions bring into question ethical issues not faced by the HapMap project, which seeks mainly to catalogue variations rather than to link them with disease susceptibilities. It is our view that these ethical issues can be resolved with appropriate participation of individuals from different ethnicities and cultures in conjunction with scientists and ethicists associated with this nutrigenomics effort.

Roadmap

Ultimately, an international consortium will be necessary to effectively harness the power of a large collaborative network of nutritional genomics researchers with expertise, samples from populations, experimental models, data, resources, and knowledge of environment–gene interactions that affect health. Nutrigenomic initiatives are underway at many institutions and companies throughout the world, many with disease- or nutrient-specific foci. Hence, we recognise that additional stages of communication and coordination are necessary for forming the working consortium that harmonises plans and objectives to avoid unnecessary replication of efforts.

The steps (Fig. 1) for developing an international effort for nutritional genomics are the identification of researchers and groups who define needs and resources at the local, national, and regional efforts. NuGO is an example of a regional organisation that may be emulated by national (for example, USA or Canada) or regional efforts (North America or Africa or Asia). Interested individuals from these organisations or laboratories would then be organised into committees similar to those developed for the International HapMap Project. Parallel to this functional grouping, regional nutrigenomics societies can be founded to functionally stimulate and disseminate the science of nutrigenomics. No barriers are foreseen in collaborating with other national, regional, or international consortia focusing on parallel scientific efforts. An international nutrigenomics consortium would be a natural outgrowth of the coordinating group. The resulting organisation would then hone goals, seek research funding, develop research projects, educational tools and workshops, coordinate activities such as conference foci and dates, and develop common data warehousing (Fig. 1).

Those of us involved with the development of the Pharmacogenetics Research Network (R. K.) or of NuGO (B. vO.) emphasise the complexity of establishing strategic alliances at national (USA) or regional (European) levels. These organisations required approximately 4 years to develop and formalise, with significant amounts of funding either from the US National Institutes of Health or from the European Union, before reaching their current productive state. International collaborations or the formation of a nutrigenomics consortium will require time and funding. Some of the steps that may be necessary are summarised in Fig. 1.

Conclusion

Nutritional genomics is a multi-disciplinary approach for the comprehensive investigation of the influence of diet and individual genetic variation as risk factors for chronic disease. We understand that certain genotypes are more severely affected by specific dietary factors than others (no genotype is free from the deleterious effects of inadequate diet). Partnerships with academia, industry, and government offer hope for identifying and characterising diet-regulated or

Fig. 1. Roadmap to an international nutrigenomics consortium. For details, see p. 628.

diet-influenced genes and genetic markers associated with chronic diseases. Such knowledge is necessary, but not sufficient, to address health disparities among all racial and ethnic populations throughout the world. Social, economic and cultural factors are critical in selecting foods and designing studies to identify causative genes and interacting environmental factors. A comprehensive nutritional genomics approach will yield short- and long-term benefits to human health by: (i) revealing novel nutrient–gene interactions; (ii) developing new diagnostic tests for adverse responses to diets; (iii) identifying specific populations with special nutrient needs; (iv) improving the consistency of current definitions and methodology related to dietary assessment; (v) providing the information for developing more nutritious plant and animal foods and food formulations that promote health and prevent, mitigate, or cure disease. Achieving these goals will require extensive dialogue between scientists and the public about the nutritional needs of the individual *v.* groups, local food availability and customs, analysis and understanding of genetic differences between individuals and populations, and serious commitment of funds from the public and private sectors. Nutritional genomics researchers are seeking collaborations of scientists, scholars, and policy makers to maximise the collective impact on global poverty and health by advancing our knowledge of how genetics and nutrition can promote health or cause disease.

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