



IUFOST Scientific Information Bulletin (SIB)
March 2012

Nutrigenomics

Summary

Nutrition and genetics both play an important role in human health as well as the development of chronic diseases such as cancer, osteoporosis, diabetes and cardiovascular disease. Nutrigenomics describes the scientific approach that integrates nutritional sciences and genomics and includes the application of other high-throughput 'omics' technologies such as transcriptomics, proteomics and metabolomics to investigate the effects of nutrition on health.

Dietary intake of a nutrient does not necessarily result in the same concentrations in the blood or tissue because substantial individual variability in the absorption, distribution, metabolism and elimination can exist. The mechanisms responsible for the between-person differences in dietary response are very complex and have been poorly understood. Research to date has indicated that diet-gene interactions play a significant role in this between-person variability, and has clarified some of these genetic differences.

The interaction between genetic and dietary influences can result in a higher risk of disease in certain individuals and populations. Currently, diet-gene association studies are revealing evidence on which to base gene-specific dietary intervention trials to confirm results.

Using examples of specific dietary factors such as alcohol, caffeine, fat, and fruits and vegetables, this bulletin highlights the importance of incorporating genetics into the field of nutrition and also address some of the questions and methods associated with the development of personalized nutrition.

Introduction

Nutrition and genetics both play an important role in human health as well as the development of chronic diseases such as cancer, osteoporosis, diabetes and cardiovascular disease. Nutrigenomics describes the scientific approach that integrates nutritional sciences and genomics and includes the application of other high-throughput 'omics' technologies such as transcriptomics, proteomics and metabolomics to investigate the effects of nutrition on health. The purpose of this bulletin is to describe the current state of knowledge using key examples and

assess the potential role of nutrigenomics in developing personalized dietary advice tailored to an individual's unique genetic profile.

Variability between individuals in response to dietary intervention is a well-known phenomenon in nutrition research and practice (Ordovas 2008). For example, the effect of dietary changes on phenotypes such as blood cholesterol, body weight and blood pressure can differ significantly between individuals (Ordovas et al. 2007). There are many factors that can influence the response to diet such as age, sex, physical activity, smoking and genetics. The goal of personalized nutrition is to identify individuals who benefit from a particular nutritional intervention (responders), and identify alternatives for those who do not (non-responders). Individuals should no longer be subjected to unnecessary diets they find unpleasant and ineffective when there may be an alternate dietary approach that is more effective. Personalized nutrition could be useful in both the prevention and treatment of chronic diseases by tailoring dietary advice to an individual's unique genetic profile.

The daily ingestion, absorption, digestion, transport, metabolism and excretion of nutrients and food bioactives involve many proteins such as enzymes, receptors, transporters, ion channels and hormones. Variations in genes encoding proteins that affect any of these processes can alter both the amount of the protein produced as well as how well that protein functions. If a genetic variation leads to altered production or function of these proteins then nutritional status might be affected. The study of the relationship between genes and diet is called nutrigenomics (or nutritional genomics), which is an umbrella term for two complimentary approaches: how nutrients affect gene function and how genetic variation affects nutrient response. The latter is sometimes referred to as nutrigenetics (El-Sohemy 2007), and includes the study of how genetic variations affect food intake and eating behaviours (Eny and El-Sohemy 2010; Garcia-Bailo et al. 2009).

Although the term nutrigenomics is relatively new, the concept has been around for some time. Perhaps the most familiar example is lactose intolerance, which is a condition resulting from an inadequate production of lactase in the small intestine due to genetic variation in the lactase gene (Swallow 2003). Individuals with lactose intolerance are unable to efficiently break down the primary milk sugar (lactose) from dairy products. Consequently, the dietary recommendation is to limit lactose-containing foods or to use lactase supplements or lactose-free dairy products to prevent gastrointestinal discomfort (Swagerty et al. 2002). Phenylketonuria (PKU) is an inborn error of metabolism, which represents another classic example of nutrigenomics. PKU can result from a genetic variation in phenylalanine hydroxylase (the enzyme needed to convert phenylalanine to tyrosine), which leads to a decrease in phenylalanine hydroxylase activity (DiLella et al. 1986). Individuals with PKU can develop neurological damage (severe mental retardation and seizures) from excess phenylalanine (Surtees and Blau 2000) unless they follow the recommended low-phenylalanine diet (National Institutes of Health Consensus Development Conference Statement: phenylketonuria: screening and management, October 16-18, 2000 2001).

Lactose intolerance and PKU are examples that involve a single genetic defect along with a single dietary exposure. A major challenge of nutrigenomics, however, is to identify gene-nutrient interactions that affect complex polygenic

disorders such as obesity, diabetes, cancer and cardiovascular disease that take several years – or even decades – to develop and have multifactorial etiologies. As such, it is often difficult to determine the role of specific dietary factors and gene variants in the development of these diseases. The concept of diet-gene interactions involves a genetic variant modulating the effect of a dietary factor on a specific phenotype or health outcome measure such as serum lipid concentrations, high blood glucose or obesity. Conversely, diet-gene interactions can refer to the dietary modification of the effect of a genetic variant on the phenotype or health outcome measure (Ordovas 2008).

A major goal of nutrigenomics is the prevention of the onset and progression of chronic disease. Research strategies currently contribute to this goal by building the body of evidence linking nutrients to metabolic pathways that affect disease outcomes. The incorporation of genetics into nutritional epidemiologic studies aims to improve their consistency. Current research could lead to the development of personalized nutrition guidelines for individuals and specific sub-populations, which could decrease the risk of chronic diseases.

Definitions and Principles

Nutrigenomics is both the examination of how nutrients affect genes (i.e. influence gene expression and function) and how genes affect diet (i.e. what an individual eats and how an individual responds to nutrients), with the latter sometimes being referred to as nutrigenetics. Nutrigenomics can include the full spectrum of research strategies from basic cellular and molecular biology to, clinical trials, epidemiology and population health. These different experimental approaches can be used to improve our understanding of how nutrition affects various health outcomes, and current trends in personalized nutrition have focussed on the role of genetic variation to understand why some individuals respond differently from others to the same nutrients consumed.

The gene is the functional and physical unit of heredity passed from parent to offspring. Genes are segments of DNA that contain the information for making a specific protein. When variations in the DNA occur the result can be changes to the structure and function of the protein. There are several different types of genetic variations, including single nucleotide polymorphisms (SNPs), which are alterations in a single nucleotide.

Alleles are the variant forms of a gene at a particular location on a chromosome. The genotype is the genetic identity of an individual for a genetic site, determined from the combination of maternal and paternal alleles. Genotypes do not necessarily show as outward characteristics, and as such are different from phenotypes. A phenotype is an observable trait in an individual such as hair color, high blood sugar concentrations, or the presence of a disease. Individuals with the same genotype may have different phenotypes, in part, because of their different environments. A haplotype is a group of alleles that are inherited together and, therefore, groups of genetic polymorphisms are often inherited together.

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into the field of nutrition and also address some of the questions and methods associated with the development of personalized nutrition.

Alcohol

Incorporating data on genetic variability into a nutrition study can clarify whether or not a specific dietary compound is linked to a particular health outcome. This diet-disease connection is made by the observation of whether the association between the disease and the dietary factor is influenced by functional variants in genes involved in the metabolism of the dietary factor. For example, moderate alcohol consumption has been associated with a lower risk of heart disease. The primary mechanism proposed for this association is the higher levels of high-density lipoprotein (HDL) cholesterol found among moderate drinkers. However, it is possible that the protective effect of moderate alcohol consumption is due to some confounding lifestyle factor associated with moderate alcohol intake that differs from abstainers or heavy drinkers.

The enzyme alcohol dehydrogenase 1C (ADH1C), also known as alcohol dehydrogenase type 3 (ADH3) oxidizes alcohol to acetaldehyde. It has two polymorphic forms with distinct kinetic properties. The *ADH1C*1* allele produces $\gamma 1$ and the *ADH1C*2* allele produces $\gamma 2$. The rate of alcohol metabolism (ethanol oxidation) in $\gamma 1\gamma 1$ individuals is more than twice as high as in $\gamma 2\gamma 2$ individuals, with heterozygous individuals metabolizing alcohol at an intermediate rate. Therefore, if there is a causal protective effect of moderate alcohol on risk of heart disease, this effect would be expected to be stronger in individuals with the slow *ADH1C* genotype compared to those with fast metabolism. An early gene-diet interaction study examined data from the Physicians Health Study and the Nurses Health Study to determine whether the effect of moderate alcohol consumption on HDL levels and the risk of myocardial infarction (MI) vary according to ADH3 genotype (Hines et al. 2001). The study reported evidence of a dose response decrease in heart disease as alcohol metabolism slows according to genotype, for a marked 86% reduction in heart disease risk in subjects with the slow-alcohol-metabolizing genotype who consumed at least 1 alcoholic drink per day (Hines et al. 2001). The polymorphism was also associated with higher levels of HDL (Hines et al. 2001). The finding of an effect of the functional *ADH1C* polymorphism on the relation between alcohol consumption and the risk of heart disease suggests that the protective effect is due to the alcohol and not some associated lifestyle factor since those with the slow-alcohol-metabolizing genotype who did not consume alcohol were not at a lower risk. A key step in nutrigenomics research is to identify the sub-set(s) of the population that have different reactions to dietary factors. In the case of alcohol, those groups were identified based on genetic differences in alcohol metabolism. The extent to which this knowledge is being or will be incorporated into nutrition practice remains unknown.

Caffeine

Knowledge gained by incorporating genetic variation into a nutrition study not only provides a more rational basis for giving personalized dietary advice, but will also improve the quality of evidence used for making population-based dietary

recommendations for the prevention of specific diseases. This can be illustrated by considering recent studies that explore the effects of caffeine on certain health outcomes (Cornelis et al. 2006). These studies have helped pinpoint caffeine as the bioactive in coffee that affects certain diseases. These studies have also identified how a response to coffee by a specific genotype can be beneficial or detrimental depending on the disease being examined.

Caffeine is metabolized primarily by the cytochrome P450 1A2 (CYP1A2) enzyme, and a polymorphism in the *CYP1A2* gene determines whether individuals are 'rapid' caffeine metabolizers (those who are homozygous for the -163 A allele) or 'slow' caffeine metabolizers (carriers of the -163 C allele). Intake of coffee is associated with an increased risk of MI only among individuals with slow caffeine metabolism (Cornelis et al. 2006), suggesting that caffeine increases risk of MI since it is the only major compound in coffee that is known to be detoxified by CYP1A2. Furthermore, a protective effect of moderate coffee consumption was observed among the fast metabolizers, suggesting that other components of coffee might be protective and their effects are 'unmasked' in those who eliminate caffeine rapidly. This coffee-*CYP1A2* genotype interaction has since been supported by a prospective study investigating the effect of coffee intake on the risk of developing hypertension in individuals stratified by *CYP1A2* genotype (Palatini et al. 2009). That study also measured epinephrine and norepinephrine in the urine of the subjects, because these catecholamines have been shown to increase after caffeine administration in humans. Urinary epinephrine was significantly higher in coffee drinkers than abstainers, but only among slow caffeine metabolizers, which is of interest because increased sympathetic activity is considered an important mechanism through which caffeine raises blood pressure.

A similar concept was utilized in an observational study of coffee and breast cancer (Kotsopoulos et al. 2007). By dividing subjects into *CYP1A2* genotypes, this study aimed to determine if caffeine was the compound in coffee that explains the protective effect that had previously been observed between coffee and risk of breast cancer (Nkondjock et al. 2006; Baker et al. 2006). Indeed, a diet-gene interaction was present. However, unlike the studies on risk of MI and hypertension in which slow caffeine metabolizers were at increased risk from drinking coffee, in this study coffee was associated with a lower risk of breast cancer among slow metabolizers (Kotsopoulos et al. 2007). No protective effect was observed among fast metabolizers, implicating caffeine as the protective component of coffee. This is consistent with findings from animal studies showing that caffeine inhibits the development of mammary tumors (Wolfrom et al. 1991; Yang et al. 2004).

Dietary Fat

Considerable research efforts have been devoted to studying dietary fat in relation to biomarkers of chronic disease such as concentrations of blood lipids. There is growing evidence that the optimal amount and type of dietary fat intake depends, in part, on an individual's unique genetic profile (Ordovas 2008). A major focus has been placed on the epidemiological diet-gene interaction studies, but clinical dietary trials that examine the difference in response to treatment among genotypes have also been conducted based on the findings from observational

studies. For example, plasma omega 3 fatty acid response to an omega 3 fatty acid supplement was found to be modulated by apoE ϵ 4, but not by the common *PPAR- α* L162V polymorphism (Plourde et al. 2009). After supplementation, only non-carriers of E4 had increased omega-3 in their plasma (Plourde et al. 2009). After 3 months of supplementation with 3.6 g of omega 3 fatty acids/day (containing 2.4 g of EPA and DHA) or placebo capsules containing olive oil, changes in cholesterol, including HDL cholesterol concentrations, were similar among the *PPAR- α* L162V genotypes (Lindi et al. 2003). In another study, subjects followed a low-fat diet for 8 weeks and then were supplemented daily with 5 g of fish oil for 6 weeks, and the decrease in plasma triglyceride concentrations was comparable for both *PPAR- α* L162V genotype groups, although a significant diet-gene interaction was observed for plasma C-reactive protein (Caron-Dorval et al. 2008). Such clinical studies are often limited by small sample sizes and short durations to assess physiological changes. However, such limitations could be overcome with partnerships and collaborations among researchers (McCabe-Sellers et al. 2008). The replication of diet-gene interactions is an important step towards personalized nutrition because it strengthens the evidence that will be used to design clinical trials and subsequent nutrition recommendations based on genotype.

It is widely recognized that nutrigenomics provides industry with an incentive to develop functional foods and novel nutritional products (Kaput 2007). Concern exists that functional foods created for prevention of chronic diseases may incorporate bioactive compounds, such as PUFAs, without considering the interaction with genetic polymorphisms (Ferguson 2009). Even where diet-gene interactions are well established there may be a lag between the science and the evidence-based development and promotion of functional foods optimized to certain genotypes. For example, the consumption of a food containing added PUFA could lead to a range of responses in individuals, from significant benefit, to an adverse effect (Ferguson 2009).

Fruits and Vegetables

Fruits and vegetables can affect multiple pathways and biological processes in the human body because they are sources of water, fibre, vitamins, minerals, and numerous phytochemicals. Evidence derived from epidemiological studies has suggested that high fruit and vegetable intake is associated with a reduced risk of a variety of cancers (Kim and Park 2009) as well as cardiovascular disease (He et al. 2006). However, a protective role has not been established conclusively in clinical studies. This may be due to general challenges associated with conducting long-term clinical trials, or to differences in dietary treatments and controls. However, human genetic variation could also be one of the factors modifying response to plant foods and their constituents. It has been observed that dietary intake of a phytochemical might not necessarily result in comparable exposure levels in the circulation or target tissues of interest (Lampe 2009). This variation in individual response may explain, in part, the observed heterogeneity across different study populations. Characterizing how genetic factors modify the effects of a high plant-based diet or specific components in plant foods on human health outcome could clarify how plant foods influence disease risk and help to identify populations that might benefit most from high fruit and vegetable intake.

Variations in genes affecting phytochemical absorption, distribution, utilization, biotransformation and excretion potentially influence nutrient exposure at the tissue level (Lampe 2009). For example, the protein expression and activity of many nutrient metabolizing enzymes are modulated by several compounds, including the substrates they act on. Therefore, genetic variations in the pathways that these compounds act could alter biological response to dietary factors. Although few studies have addressed these potential genetic differences (Lampe 2009), some studies have explored the effects of genetic variation in biotransformation enzymes such as glutathione S-transferases (GSTs) (Probst-Hensch et al. 1998) (Lampe et al. 2000b) (Lampe et al. 2000a).

In addition to determining how an individual responds to an ingested amount of a specific dietary bioactive, genetic variation can also influence our food preferences and ingestive behaviours. Flavor including taste is an important determinant of how much a food is liked or disliked and subsequently eaten or not. Common polymorphisms in genes involved in flavor perception may account for differences in food preferences and dietary habits (Eny and El-Sohemy 2010). This variability could affect food choices, which may influence health status and the risk of chronic disease (Garcia-Bailo et al. 2009). For example, there are several vegetables that are disliked by many because they are experienced as tasting extremely bitter, yet many of these vegetables are rich sources of nutrients that have been associated with improved health outcomes. The *TAS2R38* receptor is known to detect two bitter substances called phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) (El-Sohemy et al. 2007; Kim et al. 2003), which are not found in foods, but have structural similarities to bitter compounds in certain foods. Carriers of the PAV haplotype have been classified as “super-tasters” because they have a higher sensitivity to PTC and PROP in comparison to individuals homozygous for AVI (Wooding et al. 2004; Drayna 2005). *TAS2R50* has been associated with risk of MI, which has been hypothesized to be due to differences in dietary preferences for bitter foods that appear to offer cardiovascular protection (Shiffman et al. 2005).

Establishing a genetic basis for food likes and dislikes may partially explain some of the inconsistencies among epidemiologic studies relating diet to risk of chronic diseases because the genetic makeup of a group of individuals could be a confounder to the nutritional exposure of interest. Additionally, polymorphisms strongly associated with taste perception may potentially be useful as surrogate markers of dietary exposure in gene–disease association studies where information on dietary habits is not available. Finally, an understanding of the genetics of taste perception may lead to the development of realistic personal and public health strategies for providing dietary advice.

Fruit and vegetables are generally regarded as healthy foods to be consumed by all. However, it may be beneficial for certain individuals, based on genetics, to focus on specific fruits and vegetables. For example, genotypes associated with more favourable metabolism of carcinogens may be associated with less favourable metabolism of phytochemicals (Lampe 2009). Research findings to date suggest a complex association between consumption of several vegetables and biotransformation enzyme activities in humans (Lampe et al. 2000b). Genetic variation in pathways affecting nutrient absorption, transport, utilization and excretion, taste preference, and food tolerance all potentially influence the effect of plant-based diets on risk of disease.

Conclusions

Dietary intake of a nutrient does not necessarily result in the same concentrations in the blood or tissue because substantial individual variability in the absorption, distribution, metabolism and elimination can exist. The mechanisms responsible for the between-person differences in dietary response are very complex and have been poorly understood. Research to date has indicated that diet-gene interactions play a significant role in this between-person variability, and has clarified some of these genetic differences.

The interaction between genetic and dietary influences can result in a higher risk of disease in certain individuals and populations. Currently, diet-gene association studies are revealing evidence on which to base gene-specific dietary intervention trials to confirm results. Replication of current findings and further research in the form of genotype-specific nutritional intervention studies are necessary. The future of nutrigenomics research promises to provide additional knowledge of biological function and individual response to diet. This iterative approach to health research is paving the road towards personalized nutrition.

Nutrigenomic practices for specific monogenic conditions such as PKU are currently being successfully used in health care interventions in the form of newborn screening programs. The application of nutrigenomics by healthcare professionals for the prevention and treatment of complex chronic diseases, however, has not yet been widely adopted. Whether such practice will be feasible for the population-at-large in the immediate future remains to be determined, but the principles and tools of nutrigenomics are expected to soon allow for earlier and more targeted interventions than currently exist (DeBusk 2009). As the current research in nutrigenomics often focuses on how diet-gene interactions influence phenotypes found to be predictive biomarkers of disease (Kaput et al. 2007), it is likely that the path from research to applications will proceed into clinical practice using these markers of chronic disease as outcome measures. Recent developments in genome-wide approaches have already identified many susceptibility alleles for common complex diseases (Office of Population Genomics et al.), including several previously unknown etiologic pathways in disease pathogenesis (Ding and Kullo 2009), and have the potential to identify novel targets for prevention or treatment with dietary factors.

Diet is an important environmental factor that interacts with the genome to modulate disease risk. A clear understanding of these interactions has the potential to support disease prevention through optimization of dietary recommendations. The extent to which nutrigenomics will be incorporated in nutrition therapy and promotion remains unknown. However, nutrigenomics has emerged as a rapidly developing research area with great potential to yield findings that could change the way dietary guidelines for populations and recommendations for individuals are established and advised in the future.

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