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NUTRIGENOMICS: THE EMERGING FACE OF NUTRITION

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ABSTRACT

Nutrigenomics is the science that examines the response of individuals to dietary compounds, foods and diets using post-genomic and related technologies. It aims to determine the influence of common dietary ingredients on the genome. This new understanding of health and disease will lead to innovative developments in human medicine, agricultural biotechnology, food quality and safety, new food products, biomarker development and nutritional interventions. Unbalanced nutrient intakes are known to be associated with the development of chronic diseases demonstrating that dietary chemicals have direct effects on molecular genetic processes. Nutrigenomics is a potentially promising development in emerging functional food and nutraceutical research.

Keywords: nutrigenomics, nutrigenetics, diet, diseases

INTRODUCTION

Associations between diet and chronic disease have long been recognized through epidemiological studies. New genomic technologies have enabled to find out more about the basis of these associations through studies on the functional interactions of food with the genome at the molecular, cellular and systemic levels and, the ways in which individuals respond differently to different diets according to their individual genetic make-up. The completion of Human Genome Project, an effort to clone, map and sequence the entire human genome, has improved the understanding of nutrition. With the development of scientific and technological advances in the field of health and nutrition, much focus is now being directed towards the emerging field of Nutrigenomics which is being applied to agriculture (enhanced plants and animal food sources) and to human health[1]. Nutrigenomics explores how nutrients or bioactive dietary compounds can influence gene expression (Fig 1) and an individual's risk to certain diseases. It has the potential to impact various parts of the food chain including the genetic modification of crops and animal feeds, the development of nutrigenomic tests to monitor food safety and personalization of diets, as well as the identification of nutritional supplements and nutrigenomic based products which may offer potential health benefits. This new understanding of health and disease will lead to innovative developments in human medicine, agricultural biotechnology, food quality and safety, new food products, biomarker development and nutritional interventions. The long-term aim of

nutrigenomics is to understand how the whole body responds to real foods using an integrated approach termed ''systems biology''[2]. Over the past few decades, epidemiological and clinical studies have indicated many relations between nutrition and health. Links have been established between dietary habits and degenerative diseases like cardiovascular diseases; type 2 diabetes and cancer[3]. Unbalanced nutrient intakes are known to be associated with the development of chronic diseases demonstrating that dietary chemicals have direct effects on molecular genetic processes. From a Nutrigenomics perspective, food is enormously complex. Nutrigenomics looks beyond one gene at a time because most of the major health conditions involve tens and hundreds of genes.

Nutrigenomics and other 'omics technologies

Nutrigenomics is the science that examines the response of individuals to dietary compounds, foods and diets using post genomic and related technologies, i.e. genomics, transcriptomics, proteomics and metabolomics. It aims to determine the influence of common dietary ingredients on the genome, and attempts to relate the resulting different phenotypes to differences in the cellular and/or genetic response of the biological system[4]. More practically, nutrigenomics describes the use of functional genomic tools to probe a biological system following a nutritional stimulus that will permit an increased understanding of how nutritional molecules affect metabolic pathways and homeostatic control. Well-known examples of nutrigenomics research are the analyses of the huge array of gene polymorphisms relating to obesity and diabetes, the genetic polymorphism of enzymes for nutrient metabolism (e.g., enzymes for folate metabolism), and the genes involved in sodium sensitivity in hypertension[5].

Nutrigenetics examines the effect of genetic variation on the interaction between diet and disease or on nutrient requirements. It embodies the science of identifying and characterizing gene variants associated with differential responses to nutrients, and relating this variation to disease states[6]. Genetics has a pivotal role in determining an individual's risk of developing a certain disease[7].

The transcriptome is the complete set of RNA that can be produced from the genome. **Transcriptomics** is a very valuable way of beginning to understand how nutritional exposure influences gene expression on a genomic scale. It is possible to group genes of interest for particular metabolic processes and capture information from all of these at once to see how the cell is functioning at any given time or under certain conditions. Such techniques are aided by the commercial development of chips orientated around particular metabolic or functional systems.

Proteomics is the study of the proteome, and it addresses three categories of biological interest: protein expression, structure and function[8]. It attempts to characterize all proteins in a biological sample, including their relative abundance, distribution, posttranslational modifications, functions, and interactions with other biological molecules. Dietary components can also modify the translation of RNA to proteins and the posttranslational events, which can affect protein activity[9].The presence or absence of certain key proteins can give information about the early stages of disease. Currently, the most widely used technologies for proteomics are two dimensional (2D) gel electrophoresis to separate the proteins in a complex mixture isolated from cells or tissues, and specialized mass spectrometry techniques as protein identification tools [10,11].

One of the newest "omics" technologies in nutrition is **metabolomics**. It focuses on the analysis of metabolites, the metabolome. It tries to measure the level of all substances (other than

DNA, RNA or protein) present in a sample; the metabolome comprises the complete set of metabolites synthesized by a biological system[12]. Metabolomics examines global patterns of metabolites present in the cell or in body fluids in response to specific dietary exposures. Metabolomics is a useful tool for generating individual metabolite profiles, such as complete plasma lipid (ie, cholesterol, triglycerides) and vitamin profiles.

Epigenetics is the study of modifications to the genome which are copied from one cell generation to the next but which do not involve changes to the primary sequence. These changes, mediated through modification of chromatin proteins such as histones and through the methylation of DNA, contribute to the regulation of transcription and provide a way for the genome to "learn from experience", regulating gene expression in response to dietary and other exposures and leading to altered cellular phenotypes associated, for example, with chronic disease or ageing. All of these "-omics tools" have been used to study in detail the molecular responses to food substances or the early stages of disease in common diet-related conditions.

System biology

The long term aim of nutrigenomics is to understand how the whole body responds to real foods using an integrated approach termed 'systems biology'. Systems biology is an approach for studying biological systems that analyzes multiple macromolecular species (DNA polymorphisms, RNA, protein, metabolites, etc) in one experiment. It is a holistic approach to study biological systems.

NUTRIENT-GENE INTERACTION

Genes are turned on and off according to metabolic signals that the nucleus receives from internal factors, e.g. hormones, and external factors, e.g. nutrients, which are among the most influential of environmental stimuli. 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[13]. Unbalanced diets alter nutrient gene interactions, thereby increasing the risk of developing chronic diseases. Rare genetic differences are called mutations, and common genetic variations (occurring in more than 1% of a population) are called polymorphisms. One major initiative is cataloguing the simplest form of these variations (called single-nucleotide polymorphisms, or SNPs). A SNP (pronounced 'snip') occurs when only a single nucleotide (chemical letter) in the DNA sequence varies. There are thought to be some 100,000 to 300,000 SNPs in human genes, which may either influence phenotype directly or be used as markers by researchers when they look for important genetic variants[14]. Some SNPs directly alter a metabolic response to a nutrient, rather than changing the requirement for it. MicroRNA (miRNA) expression may be influenced by dietary manipulation[15], but little data are available describing miRNA-level modulation of genes of metabolism. Finally, genetic variation influences eating behaviors[16,17] but these effects have not been systematically explored. Other types of genetic variation include copy-number polymorphisms (CNPs).Numerous dietary components can alter genetic events, and thereby influence health. Dietary chemicals can affect gene expression directly or indirectly[18,19]. At the cellular level, nutrients may: 1) act directly as ligands for transcription factor receptors; 2) be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates involved in gene regulation or cell signaling; or 3) alter signal transduction pathways and signaling. From the molecular standpoint, nutrients are considered to

be signaling molecules that, through appropriate cellular sensing mechanisms, result in translation of these dietary signals into changes in gene, protein, and metabolite expression[20,21].

Methylene tetrahydrofolate reductase (MTHFR) enzyme catalyzes the reaction that produces 5-methyl tetrahydrofolate**.** MTHFR has a role in supplying 5methylenetetrahydrofolate, which is necessary for the remethylation of homocysteine to form methionine. Methionine is essential to many metabolic pathways including production of neurotransmitters and regulation of gene expression. Folate is essential to the efficient functioning of MTHFR. For the MTHFR gene tow important SNPs has been well recognized: C677T (cytosine to thymidine substitution resulting in the conversion of an alanine to valine) and A1298C (adenine to- cytosine substitution resulting in the conversion of an alanine to glutamic acid)[22]. The presence of C677T or A1298C mutations is associated with reduction in MTHFR enzyme activity and impairs folate accumulation, which may cause increases homocysteine concentration in plasma, a risk factor for venous thromboembolic and ischemic arterial diseases[23]. The beneficial effect of folic acid supplementation (1 mg/day for 3 months) on plasma homocysteine level has been shown in a geno type stratified, randomized, double-blind, placebo controlled trial[24]. MTHFR is also involved in maintenance genomic CpG methylation patterns and prevention of DNA strand breaks, these mutations are associated with increased risk of neural tube defects and some types of cancer[25].

Manganese super oxide dismutase (MnSOD) is a mitochondrial enzyme that plays a key role in detoxification of reactive oxygen species. A polymorphism valine to alanine substitution in this enzyme alters its transport into mitochondria, which has been associated with increased risk of breast cancer[9].

Enzymes that utilize and metabolize vitamin B12 have been associated with NTDs, increased risk of Down syndrome and colon cancer. For example, a common polymorphism in the HFE gene (Cys282Tyr) is associated with iron storage disease hereditary haemochromatosis, leading to an iron accumulation in the liver, heart and endocrine glands. This protein is an important regulator of cellular iron homeostasis and has role in intestinal iron absorption by regulating the interaction of the transferrin receptor with transferrin[25].

Cytochrome P450s (CYPs) enzymes play a central role in the oxidative biotransformation of steroids, prostaglandins, nutrients, drugs, chemicals and carcinogens. Several dietary factors can alter the expression of CYP isoforms. CYP1A2 plays an essential role in the metabolism of wide range of drug and chemical substances. For example, CYP1A2 activates dietary carcinogens such as aromatic amines, but also detoxifies compounds such as caffeine. Low-activity CYP1A2 genotype with an increased risk of myocardial infarction suggests that this enzyme detoxify a substance, which may be an important risk factor in the population. Indeed, individuals with a low-activity CYP1A2 genotype are at a greater risk of coffee- associated heart disease. As caffeine is the main substance in coffee and is detoxified by CYP1A2, it may be an important risk factor for heart disease in certain population[26].

Glutathione S transferase (GST) enzyme is a superfamily of enzymes that play an important role in the detoxification of several dietary compounds. GSTM1, GSTT1 and GSTP1 are isoforms of this enzyme. The GSTM1 and GSTT1 null genotype have been associated with both an increased and a decreased risk of some types of cancers such as breast cancer[26,27]. Some components such as dietary isothiocyanates that are found in cruciferous vegetables are eliminated with GSTs enzymes.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor supper family that plays an essential role in fatty acid oxidation, glucose, and extracellular lipid metabolism. PPARs are the best-known fatty-acid-regulated nuclear receptors. One of the three members of the PPARs family regulates many genes involved in fatty acid metabolism. PPR-α (PPARA) plays a central role in lipid oxidation and inflammation, whereas PPAR-γ is involved in adipocytes differentiation, glucose and lipid storage, and inflammation. PPAR-δ (also known as PPAR-β), may has a crucial role in development, lipid metabolism, and inflammation. These receptors bind to fatty acid and regulate the expression of genes involved in fatty acid transport and metabolism. PPARs family also involve in activation of about 300 genes[28]. The PPAR-α gene has a polymorphism at codon 162 (Lue162Val) that has been associated with changes in total cholesterol, LDL-associated cholesterol, and Apo B concentrations. The less common V162 allele is associated with significantly higher serum concentration of total cholesterol, LDL cholesterol, Apo B, and Apo C-III than in carriers of L162 allele, especially in men. For individuals with the common L162 allele, increased intake of polyunsaturated fatty acids (PUFAs) had little effect on fasting triacylglycerol concentrations. In those with the less common V162 allele, however, fasting triacylglycerol concentrations fell abundantly with increasing PUFA intake[29].

Moreover, dietary chemicals can directly affect signal transduction pathways. For example, green tea contains the polyphenol, 11-epigallocatechin-3- gallate (EGCG) that EGCG inhibits tyrosine phosphorylation of Her-2/neu receptor and epidermal growth factor receptor that reduces signaling via the phosphatidyl inositol 3-kinase (PI- 3)-AKt kinase-NF-kB pathway. Activation of the NF-kB pathway is associated with some types of breast cancer[30,31,32].

Approximately 40 micronutrients are needed in human diet and each has specific role to play in maintaining genomic stability (Table 1).

NUTRIGENETICS AND DIET RELATED DISEASES

Nutrigenetics and Galactosemia, PKU and Favism

Different mutations in galactose-1-phosphate uridyltransferase (GALT) gene[35],[36], phenylalanine hydroxylase gene[37], and Glucose-6-phosphate dehydrogenize (G6PD) gene [38],[39,40] resulted in Galactosemia, Phenylketonuria (PKU), and Favism diseases, respectively. Other examples of enzymes polymorphisms include Lactase-phlorizin hydrolase gene (LPH) polymorphisms that show how SNPs alter gene expression. This polymorphism is in the upstream of the lactase-phlorizin hydrolase gene (LPH) associated with hypolactasia and changes tolerance to dietary lactose (milk sugar, LPH hydrolyzes lactose into glucose and galactose) and allows different expression of the LPH[41].

Nutrigenetics and Cardiovascular diseases

Cardiovascular diseases are a group of multifactorial conditions associated with atherosclerosis, thrombosis and hypertension. The link between genetic variations in the APOE gene and heart disease has been found to be significant. Apolipoprotein E (ApoE) gene has three different alleles (ε2, ε3, ε4). Persons with ε4 variant respond to a high-fat diet negatively with an increased risk for coronary heart disease (CHD). In these individuals, low-fat diet should be useful[23]. Moreover, there is an important relationship between allelic variants in the ApoA1/C3/ A4/A5 genes and the effect of dietary fats on lipoprotein metabolism and CVD (cardio vascular diseases) risk. Linkage disequilibrium within Apo A1/C3/A4/A5 cluster has been represented to affect plasma lipid

concentration and CVD risk. Apolipoprotein A-1 is and is a key component of high-density lipoprotein particles (HDL). The locus of gene encoding APOA-1 is on chromosome 11q and highly polymorph and has a specific SNP in its promoter region[37]. An Adenin/Guanin substitution in the promoter region (-75bp) of the ApoA1 gene is common in different populations. The presence of A allele (A/A and A/G) has been associated with increased HDL cholesterol. Moreover, mild increase in APOA-1 concentrations in subjects with the G/G genotype was observed[22,42]. APOA-5 gene is also an important regulator of triglyceride (TG) - rich lipoprotein (TRL) metabolism[27].

Nutrigenetics and Diabetes II

Diabetes is a group of disorders that result in high blood sugar levels (hyperglycemia). The body either lacks the ability to make the hormone insulin or does not use it properly. Diabetes also increases the risk of other diseases such as heart disease, blindness, nerve damage and kidney damage. Type 2 diabetes develops over time as the body gradually stops producing enough insulin (abnormal 'insulin secretion') or the cells in the body stop using it properly (called 'insulin resistance'). A rare inherited form of type 2 diabetes, called Maturity-Onset Diabetes of the Young (MODY) can result from mutations in any one of at least six different genes[43]. In addition, mutations in genes in the mitochondria (inherited via the mother's egg) can cause another rare form of diabetes (accounting for about 1% of cases)[44]. To date, over 250 genes have been studied for their role in type 2 diabetes and the majority of studies have failed to find any association. A common genetic variation in the KCNJ11 gene appears to slightly increase risk[45],[46]. The CAPN10 gene[47] and the IRS-1 gene may also have a small effect but results are very inconsistent.

Nutrigenetics and Cancer

Cancer is a complex disease and how it develops and spreads is not fully understood. However, it is thought to be caused by damage to the DNA inside a person's cells, including mutations and other types of damage, which then cause some cells (cancer cells) to grow out of control. Most mutations are thought to arise during a person's lifetime (called 'somatic' mutations) but some people can be born with mutations ('germ line' mutations) that increase their risk of cancer, often at an unusually early age. Diet plays an important role in increasing or decreasing the risk of developing some cancers. However, there are significant uncertainties about the role of diet in cancer and the effects depend on the type of cancer.

Mutations in genes which increase the risk of breast and ovarian cancer and of colorectal cancer are some of the best studied. Mutations in either of two genes called BRCA1 and BRCA2 have been associated with a lifetime risk of breast cancer of between 45% and 87%. Mutations in these genes are thought to account for about 5% of breast cancer cases, and also increase the risk of ovarian cancer. Also it has been reported that women who consume less fruits and vegetables than required reported to be at greater risk of developing breast cancer because of a polymorphism that causes a valine to alanine (Val to Ala) change in the ninth position in the signal sequence for the enzyme manganese dependent superoxide dismutase[48]. Familial adenomatous polyposis (FAP) is a largely inherited form of colorectal cancer. About 0.5% to 1% of colorectal cancer is thought to be due to mutations in the BRCA1 and BRCA2 genes. Lynch Syndrome is a form of hereditary colorectal cancer (called 'hereditary nonpolyposis colorectal cancer' or HNPCC) associated with mutations in the family of MMR genes (including four genes: hMSH2, hMLH1, PMS1, PMS2). About 3-5% of

colorectal cancer is thought to be due to Lynch Syndrome. Also variants of melanocortin1 receptor gene (MCIR) have been found to be associated with several types of skin and prostrate cancers[49]. Glutathione peroxide is a selenium-dependent enzyme that acts as an antioxidant enzyme. Polymorphism at codon 198 of human glutathione peroxides results in a substitution of proline to leucine amino acid, and has been associated with an increase risk of lung cancer. Investigators shown that persons with (Pro/Lue) genotype were at 80% greater risk for lung cancer and (Lue/Lue) genotypes were at 130% greater risk compared risk those with the (Pro/Pro) genotype.

Nutrigenetics and Obesity

Obesity has become a major public health problem. Mutations in the genes like leptin and leptin receptor genes have emerged as leading factors towards predicting obesity. In addition to this, mutations in melanocortin 4 receptor and melanocortin 5 receptor gene and in the noncoding regions of the gene for neuropeptide Y (NPYY5R) receptor has also shown to be strongly correlated with the risk of obesity[50].

PERSONALIZED DIET AS A HEALTH STRATEGY

In its simplest form, nutrigenomics is based on the idea that diet should be tailored to an individual's genetic make-up or genotype (this is sometimes called nutrigenetics). A person's genome is the inclusive set of all their 25,000 or so genes. The genes are the parts of the DNA sequence that contain the cell's instructions for making proteins. The study of the genome is called genomics. Nutrigenomics research may also include other biological measurements (not just a person's genetic make-up). In the future, some of these other measurements may also be used to 'personalize' nutrition or to help design new functional foods. To the food industry, nutrigenomics provides an opportunity to design new products, attempt new 'personalized' marketing strategies (based on genetic test results, or, in the longer term, on other biological measurements) and to claim that it is responding to public concern about the growing epidemic of diet-related disease. The aim is to prevent disease and improve quality of life through functional foods and tailored diets.

CONCLUSION

Nutrigenomics is a potentially promising development in emerging functional food and nutraceutical research. The ability of bioactive food components to influence gene expression patterns (nutrigenomics effects) is also a factor in determining the overall response. Finally, bioactive food components may influence protein synthesis, degradation, and posttranslational modification. Nutrigenomic studies involving calorie restriction, specific carbohydrate and fat features, and exercise interventions have uncovered mechanisms that up-regulate and down-regulate gene expression toward a beneficial state of health, especially in patients with metabolic syndrome, obesity, and type II diabetes. Understanding the interrelationships among human genetics diversity, genome function, and dietary components will enable precise manipulation of genome function and stability throughout the life cycle for optimal human health and disease prevention. Nutrigenetics is only beginning to claim its potential. One can visualize the development of beverages and foods either as preventive agents or for the treatment for individuals, families, or subgroups predisposed to a particular disease. Increased physical activity and recommended diets balanced in omega-3/omega-6 ratios can be the pillars for health promotion and prevention of multiple chronic diseases. As we advance our knowledge of gene-nutrient interactions, society will need to create or utilize appropriate social, ethical, legal,

educational, and economic frameworks to gain the benefits of such knowledge.

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Table 1 Role of specific micronutrients on genomic stability[33,34]

Micronutrients	Role in genomic stability
Vitamin C, vitamin E	Prevention of oxidation to DNA and lipid oxidation
Vit D	Antioxidant activity by increasing glutathione level in normal cell, induction apotopsis in cancer cells
Folate and Vit B2, B6 and B12	Maintainance & methylation of DNA, synthesis of dTMP from dUMP and efficient recycling of folate
Niacin, Nicotinic acid	Required as substrate for poly (ADP-ribose) polymerase which is involved in cleavage and rejoining of DNA and telomere length, maintainance & DNA repair
Zinc, manganese and selenium	Required as a cofactor for superoxide dismutase, endonuclease and glutathione peroxidase
Iron	Required as a component of ribonucleotide reductase and mitochondrial cytochromes
Magnesium and calcium	Mg is required as a cofactor for DNA polymerases, in nucleotide excision, repair, essential for microtubule polymerization and chromosome segregation. Calcium plays an important role in chromosome segregation and is required for apoptosis

Fig 1 Schematic representation of the steps involved in gene expression, the stages at which diet can modulate these processes and the functional genomics techniques used to analyze each stage