

Nutrigenomics and Nutrigenetics

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Abstract

The nutrients are able to interact with molecular mechanisms and modulate the physiological functions in the body. The Nutritional Genomics focuses on the interaction between bioactive food components and the genome, which includes Nutrigenetics and Nutrigenomics. The influence of nutrients on gene expression is called Nutrigenomics, while the heterogeneous response of gene variants to nutrients, dietary components and developing nutraceuticals is called Nutrigenetics. Genetic variation is known to affect food tolerances among human subpopulations and may also influence dietary requirements and raising the possibility of individualizing nutritional intake for optimal health and disease prevention on the basis of an individual's genome. Nutrigenomics provides a genetic understanding for how common dietary components affect the balance between health and disease by altering the expression and/or structure of an individual's genetic makeup. Nutrigenetics describes that the genetic profile have impact on the response of body to bioactive food components by influencing their absorption, metabolism, and site of action.

In this way, considering different aspects of gene–nutrient interaction and designing appropriate diet for every specific genotype that optimize individual health, diagnosis and nutritional treatment of genome instability, we could prevent and control conversion of healthy phenotype to diseases.

Keywords: *Nutritional genomics, Nutrigenomics, Nutrigenetics, Genetic variation*

Introduction

With the completion of human genome sequencing and entering the-Omics area, the new term "Nutritional Genomics" tends to replace the former "nutrient-gene interactions" (1). It has been demonstrated that numerous genetic polymorphisms can influence protein structure function. The Nutritional genomic area includes two parts: first Nutrigenomics that is the study of interaction between dietary components and the genome, and the regulating changes in proteins and other metabolism; second Nutrigenetics that identify the response to dietary components with regard to genetic differences (2).

Nutrients as environmental factors can interact with genetic material. It has been clearly demonstrated that DNA metabolism and repair depend on a wide range of dietary factors that act

as cofactors or substrates in metabolic pathway, but much less is known about the impact of cofactors and/or micronutrients deficiency or excess on the fidelity of DNA replication and repair (3). Although the nutrients can influence the development of a particular phenotype, the response to a specific nutrient that determined by the individual genotype has also to be considered (Fig. 1).

The central role of genetic code in determining genome stability and related health outcomes such as developmental defects, degenerative diseases, and cancer is well-established (4). The etiology of complex chronic diseases obviously relates to both environmental and genetic factors (5). Specifically, the "fetal basis of adult disease" or "early origins hypothesis" postulates that nutrition and other environmental factors during prenatal and

early postnatal development influence gene expression and cellular plasticity, which can alter susceptibility to adult diseases (cardiovascular diseases, diabetes, obesity. etc) (6).

The concept of nutrients effects on DNA stability, repair and on the different gene expression processes, recently became more prominent in nutritional science (7). Numerous dietary components can alter genetic and epigenetic events and therefore influence health (8).

SNPs (single nucleotide polymorphisms) are the most common genetic variation, occur at about 500-2000 bp throughout the human genome, and normally found in at least 1% of the population

(5). Many human studies have demonstrated the evidence for interaction between SNPs in various genes and the metabolic response to the diet. Moreover, SNPs analysis provides a potential molecular tool for investigating the role of nutrition in human health, diseases and identification of optimal diets (9)

Nutrients and genome interact at two levels: 1) Nutrients can induce or repress gene expression thereby altering individual phenotype. 2) Conversely, single nucleotide polymorphisms can alter the bioactivity of important metabolic pathways and mediators and influence the ability of nutrients to interact with them (Fig. 1).

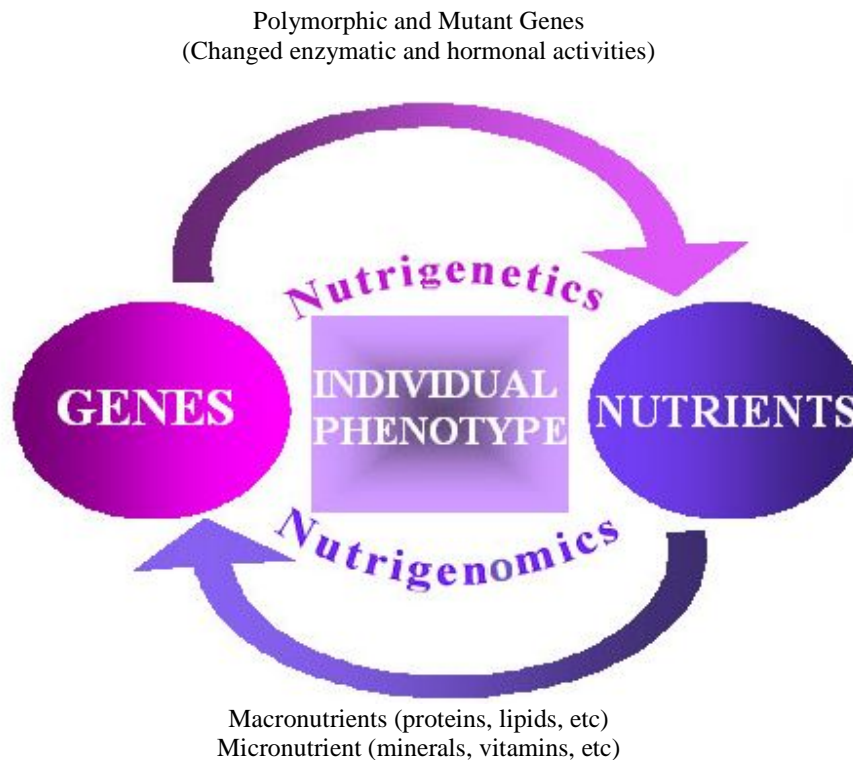


Fig.1: Nutrigenomics and Nutrigenetics are resulted from genes and nutrients interaction.

Genetic responses involve: effect on genome evolution, mutation, selection, programming, viability, gene expression, chromosome stability, signal transduction and metabolic pathways, protein synthesis and structure, epigenetic events, chronic diseases.

Nutritional responses involve: effect on nutrients absorption, nutrients utilization and requirement, food/nutrient tolerance, and food atopies

Nutritional Genomics

The interaction between the nutrients and cellular/genetic processes is being referred to as "nutritional Genomics" (10). This term describes the interface of biochemistry genomics, human nutrition, understanding of reactions and interactions at the molecular genomic levels (11). The conceptual basis for this genomic research can be summarized with the following five principles: 1) Common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression and/or structure. 2) Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases. 3) Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.

4) The degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic background. 5) Dietary intervention based on knowledge of individual nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used to prevent, relieve, or cure chronic disease.

Nutrigenetics

Nutrigenetics term was used first time by Dr R.O Brennan in 1975 in his book *Nutrigenetics* (12). Nutrigenetics points to understanding how the genetic background of an individual impact to the diet (13).

The study of gene-nutrient interaction is a developing area of science. This idea that adverse diet/genome interaction can cause disease is not new and the unsuitable diet for any individual genotype could be a risk factor for monogenetic and polygenetic disease (10, 14). Genetic polymorphisms can influence response to environmental elements, such as enzymatic activities changes that affect circulating concentrations and ultimately the effectiveness of chemicals and their metabolites (5). Furthermore, metabolic disorders are other examples of influence of the genetic variations to diet such as PKU, defects associated with long chain fatty acid oxidation, iron absorption (haemo-

chromatosis), which can be reasonably well managed with dietary restrictions (15).

As mentioned earlier SNPs study can be categorized in the field of Nutrigenetics. Some specific examples of the association between SNPs and specific food components such as enzymes deficiency are reviewed in this article. For example, different mutations in galactose-1-phosphate uridyltransferase (GALT) gene (14-18), phenylalanine hydroxylase gene (19, 20), and Glucose-6-phosphate dehydrogenase (G6PD) gene (21-24) 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 (25, 26).

Glutathione peroxide gene polymorphism is another example. The association between selenium supplementation and reduced incidence of liver, colon, prostate, and lung cancer in human has been shown. However, no individuals may respond equally. Glutathione peroxide is a selenium-dependent enzyme that acts as an antioxidant enzyme. Polymorphism at codon 198 of human glutathione peroxidase 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. The leucine-coding allele was less responsive to increased activity because of selenium supplementation as compared with the proline-containing allele (8).

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 (8).

Methylen tetrahydrofolate reductase (MTHFR) enzyme catalyzes the reaction that produces 5-methyl tetrahydrofolate. The one-carbon units are carried on N-5 or N10 of tetrahydrofolate. One-carbone metabolism is needed for the de-novo synthesis of purine nucleotides and thymidilate and for the remethylation of homocysteine to methionine. With methionine adenylation S-adenosylmethionine (SAM) is formed, which is a co-factor for numerous methylation reactions such as DNA methylation that affect gene regulation (27). For the *MTHFR* gene two 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). The C677T polymorphism is the most common variant that occurs as homozygous T/T in 5-10% of the and as heterozygous C/T genotypes up to 40% general population (28). 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 (2).

Another polymorphism of *MTHFR* gene is Ala222Val that affects folate metabolism. It increases the conversion of dUMP to dTMP and leads to more folate-dependent thymidine biosynthesis and folate deficiency (27). This polymorphism is a risk factor for spontaneous abortions and decreased fetal viability, thus maternal folate supplementation can be useful for individuals with this polymorphism (29).

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 (27).

Changes in the concentration of folate (the MTHFR substrate) and riboflavin (the MTHFR cofactor) can modulate the activity of *MTHFR* gene (28). Generally, folic acid supplementation can help

the negative health effect of these SNPs with decrease in plasma homocysteine levels (2, 27, 28).

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 (27).

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 (5).

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 (5, 30). Some components such as dietary isothiocyanates that are found in cruciferous vegetables are eliminated with GSTs enzymes. Indeed, protective effect of the GSTM1 null genotype on colon and lung cancer has been related to lower urinary excretion of glutathione-conjugated phytochemicals indicating they are not

rapidly excreted. GSTT1 plays a similar role to GSTM1 in eliminating beneficial phytochemicals found in cruciferous vegetables. Moreover, in vegetables rich in phytochemicals such as isothiocyanates the expression of GSTs is increased conjugating them to more water-soluble forms that are easily excreted (5).

Endothelial nitric oxide synthase (eNOS) is synthesized from the amino acid L-arginine by NO synthase (NOS). The eNOS is expressed in the endothelium and produces NO that diffuses to vascular smooth muscle cell, where it increases the concentration of cGMP, leading to vascular relaxation. NO has central role in the pathogenesis of coronary spasm and atherogenesis. Several polymorphisms of eNOS may be associated with specific phenotype. For example, a Glu298Asp polymorphism in the eNOS gene has been associated with ischemic heart disease, myocardial infarction, and coronary spasm (30).

Genetic polymorphisms in catechol-O-methyltransferase, sulfotransferase, and UDP-glucuronosyltransferase result in differences in enzymatic activity. These enzymes metabolize some of dietary compounds. For example, green tea was associated with a lower risk of breast cancer only in women with the low-activity allele for catechol-O-methyltransferase. This enzyme catalyzes the methylation of catechins (a polyphenolic antioxidant plant secondary metabolite) in green tea making them more quickly eliminated (5).

Apolipoprotein E (ApoE) gene has three different alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$). Persons with $\epsilon 4$ 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 (2). 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 (cardiovascular 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 a key component of high-density lipoprotein particles (HDL). The locus of gene encoding APOA-1 is on chromo-

some 11q and highly polymorph and has a specific SNP in its promoter region (19, 20). 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 (28, 30). APOA-5 gene is also an important regulator of triglyceride (TG)-rich lipoprotein (TRL) metabolism (30).

One of the Vitamin D receptor (VDR) polymorphism is Fok1. Individuals with F allele have three amino acids more than those without F allele in their VDR. The Ff or ff genotype is associated with 51% and 84% greater risk of colorectal cancer, respectively. Individuals that consumed low calcium and fat diet have more than double risk of colorectal cancer, specifically in persons with ff genotype rather than Ff genotype (8). VDR polymorphisms have been also associated with childhood and adult's asthma (27).

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor super 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. PPAR- 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 have 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 (31).

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 (20). 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 (32).

Nutrigenomics

Nutrigenomics aims to identify the effects of several nutrients, including macronutrients and micronutrients on the genome (13) and explores the interaction between genes and nutrients or food bioactives and their effects on human health (33). The influence of nutrients on the transcription activity, gene expression, and heterogeneous response of gene variants is also referred to as "Nutrigenomics".

Nutrigenomics also describes the use of functional genomic tools to study a biological system to understanding of how nutritional molecules affect metabolic pathways and homeostatic control. This branch of science will reveal the optimal diet form within a series of nutritional changes, whereas Nutrigenetics will yield critically important information that assist clinicians in identifying the optimal diet for a given individual, i.e. personalized nutrition (13). Transcriptomics, proteomics, and metabolomics are also technologies that apply in Nutrigenomics research (33).

According to numerous studies, nutrients can alter the expression of genes at the level of gene regulation, signal transduction, chromatin structure and protein function (33).

Epidemiological studies show association between food intake and the incidence and severity of chronic diseases (34, 35). A large number of nutrition related pathologies (obesity, metabolic syndromes, type 2 diabetes, CVD, and some types of cancers) are polygenic and multifactorial and their onset and progression are related to multiple genes and their variants as well as several environmental factors, especially the diet (30).

Dietary chemicals can affect gene expression directly or indirectly. At the cellular level nutrients

may act as ligands for transcription factor receptors (36, 37) or be metabolized by primary or secondary metabolic pathways, thereby altering concentrations of substrates or intermediates, and finally positively or negatively affect signal pathways (38-40).

Transcription factors (TFs) are one of the key molecules through with nutrients can alter the gene expression. One of the most important groups of nutrient sensors is PPARs TFs with 48 members in the human genome. The majority of receptors in this superfamily bind nutrients, their metabolites, and influences expression of specific genes involved in numerous metabolic process in the liver, including fatty acid oxidation, ketogenesis, gluconeogenesis, amino acid metabolism, cellular proliferation, and acute-phase response (41). For example, the fatty acids palmitic (16:0), oleic (18:1n9), linoleic (18:2n6), and arachidonic acid (20:4n6) (42-45), and the eicosanoids, 15deoxy- δ 12, 14prostaglandinJ2 and 8-(S) hydroxyeicosatraenoic acid, are ligands for PPAR- δ (46-48). These nuclear receptors act as sensors for fatty acids. Lipid sensors usually heterodimerize with retinoid receptor, whose ligand is derived from another dietary chemical, vitamin A, and hyperforin, bind directly to nuclear receptors and influence gene expression (Table 1). The liver X receptor- α (binding cholesterol metabolites), bind as a heteromers to specific nucleotide sequence (response elements) in the promoter regions of a large member of genes. During ligand binding, nuclear receptors undergo a conformational change that results in coordinated dissociation of corepressors and recruitment of coactivator proteins to prepare transcriptional activation (41). Thereby, a number of genes are induced such as those involved in fatty acid oxidation or fatty-acid storage, depending on the cellular metabolic state (31). In metabolically active organs, such as the liver, intestine, and adipose tissue, these TFs act as nutrient sensors by changing the level of DNA transcription of specific genes in response to nutrients changes (41).

Table 1: Nuclear receptors and dietary ligands. Umbers in parentheses indicate percent activity after ligand binding relative to estradiol (36, 37, 50, 52, 53)

Regulation	Receptor	Type	Endogenous ligand	Dietary ligand
Endocrine: hormonal lipids: feedback paradigm	Estrogen	ER α	17 β -Esteradiol (100)	Genisteine (4)
		ER β	17 β -Esteradiol (100)	
	Progesterone		Testoterone	Genisteine (87)
	Androgen		5 α -dihydrotestosterone	Endogenous metabolism cholestrol precursor
Androgen		Aldosterone		
Mixed paradigm	Retinoic acid		Glucocorticoid	Cortisol
		RAR α	All- <i>trans</i> retinoic acid	Vitamin A
		RAR β	All- <i>trans</i> retinoic acid	Vitamin A
		RAR γ	All- <i>trans</i> retinoic acid	Vitamin A
	Thyroid	TR α		Iodine
		TR β		Iodine
Lipid sensors: dietary lipids: feed-forward paradigm	Vitamin D		1,25-dihydroxyvitamin D	Vitamin D/Sunshine
	Ecdisone		Cholesterol derivatives	Cholesterol
	Retinoid X		<i>C is</i> -9-retinoic acid	Docsahexaenoic acid
	PPAR	PPAR α	FA	Pristinic/phytanic Pristinic/phytanic
		PPAR β	FA/eicosanoids	
		PPAR δ	?	
	Pregnan X		Estrogen	Hyperforin
		Progesterone Progesterone	Coumesterol	
			Genisteine	
Liver X			Oxysterols	Cholesterol metabolites
Famosoid X			Bile acids	

Dietary chemicals indirectly regulate some of TFs. The sterol regulatory element binding proteins (SREBPs), for example, are activated by protease cleavage, an event regulated by low levels of oxy sterols and changes in insulin/glucose and PUFAS (49). The carbohydrate-responsive element-binding protein (chREBP) is a large TF, activated in response to high glucose levels, and is regulated by reversible phosphorylation events (50). This DNA binding protein serves as an effector of lipogenic gene expression (51). 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 (50, 52, 53).

PUFAs such as n-3 and n-6 are other micronutrients, which are also referred to as omega-3 and omega-6 fatty acids, may influence gene expression. Animal studies have demonstrated that PUFA intake can modulate the gene expression of several enzymes involved in lipid and carbohydrate metabolism. A significant interaction has also been

shown for the PPARA Lue162Val polymorphism n-6 PUFA intake. Individuals with the less common V162 allele, increased n-6 PUFA intake is associated with a marked reduction in triacylglycerol concentration, whereas this association is not observed in L162 carriers. Conversely, in L162 and V162 carriers n-3 PUFA intakes results in triacylglycerol concentrations reduction (32). Approximately 40 micronutrients are needed in the human diet. Suboptimal intakes of specific micronutrients have been associated with CVD

(Vit B, E, and carotenoids), cancer (folate, carotenoids), neural tube defects (folate), and bone mass (Vit D) (54). B6, B12 and folate deficiencies, for example, are associated with increased serum homocysteine levels. Hyperhomocysteinemia is a risk factor and marker for coronary artery disease. Deficiency of Vit B12, folic acid, B6, niacin, C or E, iron or zinc appears to imitate radiation in damaging DNA by causing single and double-strand breaks, oxidative lesions, or both (55), (Table 2).

Table 2: Examples of the role and effect of specific micronutrients deficiencies on genomic stability (56, 57)

Micronutrients	Role in genomic stability	Consequence of deficiency
Vits C and E	Prevention of DNA and lipid oxidation.	Increased baseline level of DNA strand breaks, chromosome breaks, oxidative DNA lesions and lipid peroxide adducts on DNA.
Vit D	Antioxidant activity by increasing glutathione level in normal cell, induction apoptosis in cancer cells.	uracil misincorporation in DNA, increased chromosome breaks and DNA hypomethylation.
Folate and Vits B2, B6, B12	Maintenance methylation of DNA, synthesis of dTMP from dUMP and efficient recycling of folate.	Increased level of unrepaired nicks in DNA, increased chromosome breaks and rearrangement, sensitivity of mutagens.
Niacin, Nicotinic acid	Required as substrate for poly (ADP- ribose) polymerase which is involved in cleavage and rejoining of DNA and telomere length Maintenance and DNA repair.	
Zinc, Manganese and Selenium	Zn, required as a cofactor for Cu/Zn superoxid dismutase, endonuclease IV, P53 function, DNA replication and Zinc finger proteins such as poly (ADP- ribose) polymerase. Mn, required as a component of mitochondrial Mn superoxide dismutase. Se, required as a component of peroxidases e.g. glutathione peroxidase.	Increased DNA breaks and oxidation, elevated chromosomal damage rate.
Iron	Required as a component of ribonucleotide reductase and mitochondrial cytochromes.	Reduced DNA repair capacity, increased propensity for oxidative damage to mitochondrial DNA.
Magnesium, Calcium	Mg, required as a cofactor for a variety of DNA polymerases, in nucleotide excision Repaire, base excision repair and mismatch Repair, essential for microtubule Polymerization and chromosome segregation. Ca, plays an important role in chromosome Segregation and is required for apoptosis.	Reduced fidelity of DNA replication, reduced DNA repair capacity, chromosome segregation Errors, survival of genomically aberrant cells.

Nutrient deficiencies are more important than radiation because of constancy of exposure to milieu promoting DNA damage (58-60). For example, folate deficiency breaks chromosomes due to substantial incorporation of uracil in human DNA (4 million uracil/cell) (61).

Amino acids can play the role of nutritional signals in the modulation of expression of particular genes. Studies have shown that cells can detect variants in amino acid levels and respond by mechanism as control of transcription, mRNA stabilization ,as well as by up or down regulation

of translation initiation (62). For example, in human cells amino acid L-tryptophan in supra-physiologic concentrations is a powerful inducer of collagenase gene expression at a transcriptional level. The increase in collagenase mRNA levels was reversible, time and L-tryptophan dose-dependent (63).

Simple and complex carbohydrates have differential effects on blood glucose concentrations. Foods with a high glycemic index (GI) would increase insulin production and, decrease synthesis of insulin receptors. High glucose concentration also induces the transcription of several genes of the glycolytic and lipogenic pathways (64).

Therefore, dietary chemicals are regularly ingested and are involved indirectly and directly in regulation gene expression, it follows that a subset of genes regulated by diet must be involved in disease initiation, progression, and severity (65, 66).

Nutritional epigenetics

The term "epigenetics" is used to gene expression that occurs without changes in the DNA sequence. Epigenetic regulation plays an important role in development and is needed to gain stable expression or repression of genes in specific cell types or at defined developmental stages (67). Epigenetic changes may influence cell cycle control, DNA damage, apoptosis, invasion, imprinting, and aging (8).

Epigenetic events can be modified by bioactive food components (Table 3).

Table 3: Some nonessential nutrients and bioactive food components that can alter genetic and epigenetic events (8)

Nutrient group	Example
Phytochemicals	Isothiocyanates, allyl sulfur Carotenoids, flavonoids, indoles,
Zoochemicals	Conjugated linoleic acid, n-3 fatty acids
Fungochemicals	β -glucans, lentinan, schizophylan, and other compounds in mushrooms.
Bacteriochemicals	Equol, butyrate, and other compounds formed from gastrointestinal flora fermentation

A majority of regulatory proteins including DNA methyltransferases, methyl-cytosine guanine dinu-

cleotide binding proteins, histon-modifying enzymes, chromatin-remodeling factors, and their multi-molecular complexes are involved in the overall epigenetic process (8). The best studied epigenetic modification is DNA methylation and in the mammals genome occurs at many of cytosine residues that are followed by guanine residue (CpG islands) and in most cases methylation in these regions induces gene repression. However, this phenomenon can lead to the expression of neighboring genes (67). Studies identify that DNA methylation is dependent on bioactive food components ranging from alcohol to zinc (8) (Table 4).

Table 4: Nutrients and chemicals involved in DNA methylation (8, 68)

Micronutrients	
Alcohol	Genistein
Arsenic	Methionine
Betaine	Nickel
Cadmium	Polyphenol
Choline	Selenium
Coumestrol	Vitamin A
Equol	Vitamin B6
Fiber	VitaminB12
Folate	Zinc

Several dietary factors may influence the provision of methyl groups available for the formation of S-adenosylmethinine. Moreover, dietary factors may modulate the use of methyl group by processes including change in DNA methyltransferase activity. The methyl groups' status depends on B vitamins as cofactors including folate, Vit B12, and Vit B6 (29). The folate-dependent biosynthesis of nucleotide precursors for DNA synthesis and of SAM for genome methylation is dependent on the availability of many vitamins including B12, B6, niacin, riboflavin and minerals (zinc, cobalt). Therefore, folate-mediated one-carbon metabolism mediates communication between the cellular nutrient environment and regulation of the genome. Impairments in one-carbon metabolism and the SAM cycle induced by nutritional deficiencies and/or SNPs in genes that encode folate-dependent enzymes, alter genome methylation patterns and gene expression levels. Disruptions in folate metabolism are common and increase risk cancers, cardiovascular disease, neu-

rological disorders and developmental anomalies such as spina bifida, cleft palate, and spontaneous abortion. Therefore, folate supplementation can reduce the risk of these disorders developing (69). DNA methylation patterns may effect on the response to bioactive food components and thereby account for differences in response in normal and neoplastic cells (70).

Genome health and disease prevention

It is clear that even the small damages in the genome can cause crucial effects in whole human life. DNA metabolism and repair is depending on a variety of dietary factors that act as cofactors or substrates. Nutritional requirements is important for the prevention of DNA oxidation (i.e. antioxidants such as carotenoids, Vit E and C), prevention of uracil incorporation into DNA (i.e. folate), maintenance methylation of CpG in DNA (methionine, cholin, folate and vitamin B12), as cofactors or as components of DNA repair enzymes (Zn, Mg), maintenance of telomere length (niacin, folate) (56, 69, 70).

Many chronic diseases are polygenic and result from interaction between genes and environmental factor. Dietary intervention based on nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition"), can be used to prevent, control or treatment of chronic disease such as cardiovascular diseases (CVD), metabolic syndromes, and cancer (41). These disorders are partly mediated by chronic exposure to certain food components. Fore example, the association between amount of calories (35), the levels and types of vitamins (71), fat (72), and carbohydrates with atherosclerosis, diabetes, obesity, cancer, hypertension, and other chronic diseases is demonstrated (73).

Genome damage and nutritional deficiency

As mentioned earlier, nutritional status influences genome stability and deficiency of certain micronutrients can result in critical damages in the genome. Studies have shown that at least nine micronutrients (Vit E, Ca, folate, retinol, nicotinic acid, β -caroten, riboflavin, pantothenic acid,

and biotin) affect genome stability in human *in vivo* (4). Folate and vitamin B12 are need for DNA replication, repair and maintenance of DNA methylation patterns. Both *in vivo* and *in vitro* studies with human cells clearly show that folate and vitamin B12 deficiencies and elevated plasma homocysteine are associated with the expression of chromosomal fragile sites, chromosomal breaks, excessive uracile in DNA and DNA hypomethylation. Nicotinic acid (niacin) also plays a fundamental role in chromosome integrity and reduction of cancer risk (Table 2) (70).

Reactive oxygen species (ROS) such as highly reactive hydroxyl radical and superoxide radical contributes to DNA damage. Antioxidants (Vit C and E) and enzymes such as superoxid dismutase, catalase and glutathionperoxidase may control lipid and protein oxidation induced by ROS (3). Since developmental, degenerative diseases and aging are partly caused by DNA damage, defining optimal requirements of key minerals and vitamins for preventing nuclear and mitochondrial DNA damage is important (70).

Infertility is another consequence of genome damage on human health. Genome damage results from specific micronutrient deficiencies may cause developmental defects in the fetus or increased risk of cancer in the child. For example, inadequate Vit C intake results in increased oxidation of sperm DNA; folate deficiency increases risk of NTDs and genome damage. Increased risk of childhood leukemia in children with mothers who did not intake enough folic acid supplementation during pregnancy has demonstrated. Additionally, zinc deficiency induces oxidative damage to DNA and impairs DNA repair, which has a teratogenic effects (70, 74).

Telomere and nutritional status

Telomeres are nucleoprotein structures that cap the ends of chromosomes, and maintain chromosome stability. Degeneration of telomeres leads to whole chromosomal instability, and chromosomal fusion and therefore gene amplification, an important risk factor for cancer (3). Folate and nicotinic acid deficiency increased oxidative

stress and telomere dysfunction. Under folate deficiency uracil is incorporated into DNA instead of thymidine, leading to chromosome breakage. Similarly, oxidative stress causes telomere shortening. Folate and other methyl donors such as Vit B12, cholin, and methionin have an important role in maintenance methylation of cytosine. Defects in the DNA methylation can cause excessive telomere elongation and homologous recombination between telomeres and telomeres fusion. Hypomethylation or hypermethylation of the CpG islands is in the promoter of telomerase may cause excessive expression of telomerase or silence the gene respectively (3).

Telomere shortening has been observed in number of conditions including obesity, psychological stress, immune dysfunction, cancer, and CVD. In vitro studies antioxidant treatment has been found to prevent telomere damage (3).

Conclusions

Nutritional genomics elucidate the interaction among nutrients, metabolic intermediates, and the mammalian genome. The response to bioactive food components is dependent on genetic background (Nutrigenetics effects) that can influence absorption and metabolism targets or sites of action. Likewise, the response to food components depends on DNA methylation and other epigenetic events. 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. 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.

With greater insight in to the gene-nutrient interaction, alterations in diet and single nutrient interventions may help us to better protect against cancer, decrease the occurrence of cardiovascular and

other chronic diseases, and perhaps increase human longevity.

Ethical Considerations

All ethical issues including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc have been completely observed by the author.

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