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IJPBS |Volume 3| Issue 4 |OCT-DEC|2013|193-197

Review Article
Biological Sciences

NUTRIENT–GENE INTERACTIONS IN PATHOLOGICAL CONDITIONS

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ABSTRACT

Nutrigenomics has emerged as a novel and multidisciplinary research field in nutritional science that aims to elucidate how diet influences human health. Adequate and proper amount of nutrients prevent us from developing chronic diseases. Nutrigenomics will also determine the individual nutritional requirements based on the genetic makeup of the person (personalized diet) as well as the association between diet and chronic diseases which will help to understand the etiologic aspects of chronic diseases. The nutrients should keep fundamental balance between total oxidation status and total antioxidant response of the genome to maintain a balanced level between these two variables and if this is achieved through the dietary habits, our genomic system by itself would prevent from the development of various pathological diseases. The present review will focus upon interaction of genetic milieu and diet with regard to development of life threatening chronic as well as pathological conditions such as cancer, celiac diseases, Phenylketonuria (PKU), bone diseases, Spina bifida, Cystic fibrosis, diabetes mellitus, alcoholic liver disease, obesity, depression, inflammatory bowel diseases, inflammation, cardiovascular disease (CVD), and hypertension which are most prominently found in the developed countries.

KEY WORDS

Nutrigenomics, Gene- diet interaction, Bio- active components, Transcriptomics, Proteomics, Metabolomics

INTRODUCTION

A few decades ago technological developments made it potential to spot mutations in single genes, which impede radically with metabolism and thus lead to nutrition related traits and disorders. Throughout our lifetime we are exposed to a complex mixture of foods with thousands of different compounds, and that makes diet the most important environmental factor challenging our biological system. Genetic unpredictability of metabolic pathways affects the biochemical and cellular processes involved in nutrition, thereby modifying nutritional requirements and susceptibility to diet- mediated diseases[1].

The interaction between food and genes is termed as Nutritional genomics, or nutrigenomics, also provides information regarding the effects of diet on an individual's genes and health. According to Müller & Kersten 2003, nutrigenomics attempt to study the genome wide influences of nutrition and identify the genes that influence the risk of diet related diseases on a genome wide scale, and to understand the mechanisms that trigger these genetic predispositions[2]. It is also understood that, nutrigenomics is a novel and multifaceted research domain in nutritional science and aims at elucidation of influence of bioactive compounds in the diet on human health[3]. This is done by studying interactions of bioactive food compounds with genes and their effect on transcription factors (transcriptome), protein expression (proteome) and metabolic profile (metabolome) as it is depicted in **figure No.1** as

Fig. 1: Genomics, Transcriptomics, Proteomics and Metabolomics as analytical tools in Nutrigenomics.

Source: Kussmann et al (2010)

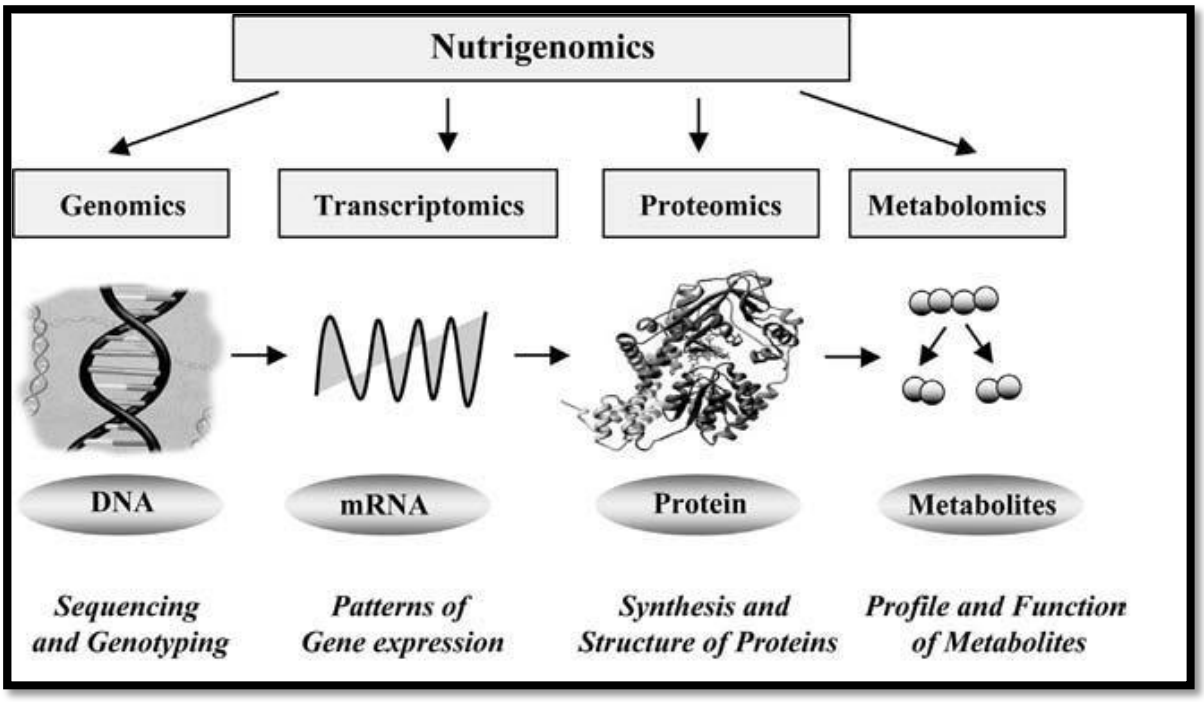
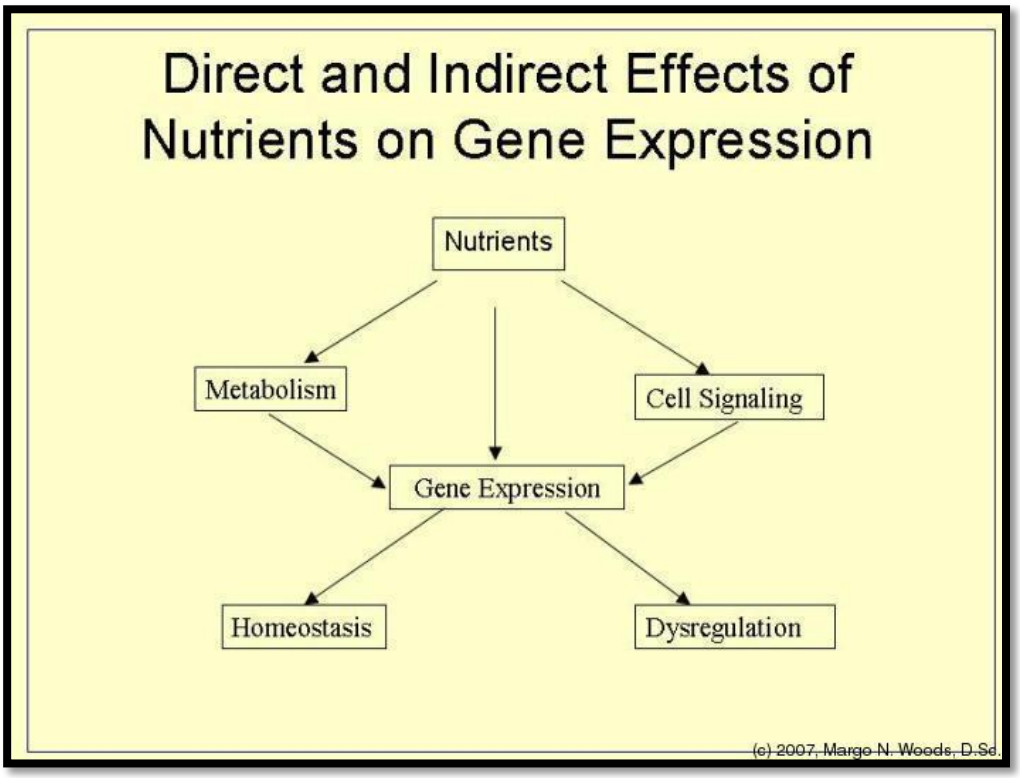


Figure 2: Effects of Nutrients on Gene Expression



Source: **Margo Woods, Tufts University School of Medicine, 2007**

Robert et al (2001) described the two strategies used in molecular nutrition research where the first strategy is used as a traditional hypothesis-driven approach in which the expression of specific genes and proteins influenced by nutrients are identified[5]. However, in this approach genomic tool such as transcriptomics, proteomics and metabolomics are used to discover specific regulatory pathways which are affected by diet[5, 6]. Apart from above tools, additionally transgenic mouse models and cellular models are also used which can allow new genes and pathways to be identified. In future, the use of such models may lead to better understanding of the interactions between metabolic and inflammatory signalling routes.

Next with regard to the second strategy, systems biology approach is used where the gene, protein and metabolite signatures that are linked with specific nutrient or dietary protocols are systematically organized to serve as molecular biomarkers for early detection of diseases in response to nutrient induced changes in the body. The first strategy covers detailed molecular data on the interaction between genome and nutrition. The second strategy will potentially furnish various biomarkers to establish and trail the health of an individual at any point of time during the course of her/his lifespan[7].

PROTOCOLS INVOLVED IN NEUTRIGENOMICS

There are several techniques used to analyze the genomes, of which the following are the widely used studies.

Transcriptomics

The transcriptome is the complete set of RNA that can be produced from the genome. Transcriptomics is the study of the transcriptome, i.e. gene expression at the level of the mRNA[8]. Bunney et al, 2003 used several methods to contour gene expression, including differential display and various types of microarrays and macroarrays which would be followed by validation method, including real time quantitative polymerase chain reaction [9]. These technologies can be used independently or in parallel, where they investigate mRNA transcripts quantitatively by amplification of RNA from disease and control samples, with detection of specific complementary DNA (cDNA) or antisense RNA (aRNA) species[10]. Microarrays have been described as "the hottest thing in biology and medicine since the advent of the polymerase chain reaction"[11]. The best practices and standard operating procedures for microarray analyses in nutrigenomic studies such as RNA extraction, RNA amplification, Microarray construction have been well defined by Garosi et al (2005)[12].

Proteomics

Proteins are the key actors in virtually all biological processes in the human body—they are the ‘‘molecular robots’’ that do all the work [13]. Proteomics refers to all the studies related to structure of proteins, expression levels, biochemical activity, protein- protein interaction and cellular localization [14]. Kussmann et al(2006), described proteomics as the central platform in elucidating molecular events in nutrition as it can identify and quantify bioactive proteins and peptides and addresses questions of nutritional bioefficacy [15].

A number of techniques are involved in testing the proteins produced during a particular disease, which helps to diagnose the disease quickly. Techniques include western blot, immunohistochemical staining, enzyme linked immunosorbent assay (ELISA) or mass spectrometry[16, 17]. According to Hathout et al (2007), Secretomics is a subfield of proteomics that studies secreted proteins and secretion pathways using proteomic approaches and has recently emerged as an important tool for the discovery of biomarkers of disease [18]. Breikers et al. (2006) identified 30 proteins differentially expressed in colonic mucosa of healthy mice group when they increased vegetable intake, in which expression levels of 6 proteins changed, these proteins played a protective role in colorectal cancer[19].

Metabolomics

Metabolomics is the scientific study of chemical processes involving metabolites. Daviss et al (2005) described metabolomics as the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind", the study of their small-molecule metabolite profiles[20]. According to Riitta et al (2005), metabolomics would examine the whole metabolism, which ultimately reflects the behaviour of different patterns of genes and also it investigates the metabolic regulation as well as fluxes in individual

cells or tissues, in response to specific environmental changes[8]. From the study of Dunn et al (2005), it is found that the quantitative analysis of the metabolome requires expensive equipment such as gas-chromatographs linked to mass spectrometers and nuclear magnetic resonance instruments [21].

GENE- DIET INTERACTION

Variability between individuals in response to dietary intervention is a well known phenomenon in nutrient research and practise. Gene- diet interaction involves a genetic variant modulating the effect of a dietary factor on a specific phenotype or health outcome measures such as serum lipid concentrations, high blood glucose or obesity. Nagwa (2011) reported that ninety seven percent of the genes are known to be associated with human diseases resulting in monogenic diseases and from the paper "Public Health Nutrition" it is understood that the dietary intake can prevent some monogenetic diseases[22]. Ordovos and Corella, 2004 described that the main objective of gene- diet interaction is to generate the recommendations regarding the risk and benefits of specific diet on dietary components for the individual[23]. 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. At this juncture, it may be imperative that a qualified nutrigenomic nutritionist is the need of the day. Also, it suggests that the curriculum for qualifying as nutritionist should indispensably include nutrigenomics as one of their core subjects.

FUNCTION OF NUTRIGENOMIS IN VARIOUS DISEASES

Cancer

Davis et al (2004), reported that the dietary habits as one of the most important amendable environmental factor which influence cancer risk and tumour development [24]. Similarly, from the same study it is found that the diet influences about 30-40% of all cancer cases, however, the actual percentage is not known and depends on the specific type of cancer and the specific components. Keum et al, (2004) and Milner et al, (2001) conducted *in-vitro studies* and demonstrated that the many constituents of plant foods can modulate detoxification enzymes; examples are flavonoids (e.g. quercetin, rutin, and genistein), phenols (e.g. curcumin, epigallocatin- 3-gallate and resveratrol), isothiocyanates, allyl sulfur compounds, indoles, and selenium[25, 26]. Several dietary compounds such as selenium, epigallocatechin-3-gallate, phenylethyl isothiocyanate, retinoic acid, sulforaphane, curcumin, apigenin, quercetin and resveratrol have their cancer preventive effect by apoptosis inhibition [27, 28]. Many studies exist now demonstrate that selected dietary components, including conjugated linoleic acid, long chain omega-3 fattty acids such as those in fish oil, butyrate, epigallo-catechin-3-gallate, curcumin, resveratrol, genistein, luteolin, quercetin, and vitamins A and D, may influence the inflammatory process at various sites [29-34]. Dietary supplementation with cooked carrots have been shown to increase the repair of 8-oxodG (an indicator of oxidative DNA damage)in white blood cells.

Ordovas, 2006 similarly states that more than 1000 different phyto-chemicals with cancer preventive activities have been identified [35]. Most beneficial foods for the prevention of developing cancer includes green tea, grapes, and cruciferous vegetables and also efforts are being made to extract these bioactive compounds and apply them in cure of chronic degenerative diseases including cancer by boosting defensive mechanism against free radical damage and lipid peroxidation [36].

Bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification.

Celiac Disease

Celiac disease (CD) is a chronic, immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults precipitated by the ingestion of gluten-containing foods[37]. From the study of Van et al (2006) and Wieser et al (2008) it could be concluded that the prolamin (gluten) fractions in cereal grains (gliadin in wheat and similar alcohol-soluble proteins in other cereals, secalin in rye, hordein in barley) are the environmental stimuli responsible for the development of intestinal damage associated with celiac disease[38, 39]. Dietary components such as plant polyphenols, carotenoids and fatty acids, have the

potential to modulate predisposition to intestinal chronic inflammatory conditions and also have role in nutritional therapy of celiac disease as these components act through a variety of mechanisms including decreasing inflammatory mediator production through effects on cell signalling and gene expression on NF-κB activation , reducing the production of damaging oxidants and promoting gut barrier function and anti-inflammatory responses [40,41]. Bernardo *et al.* (2011) have recently reported that administration of vitamin C in small-bowel mucosal biopsy organ culture system prevents the augmented secretion IFN-γ, TNF-α, and IL-6 and increases the expression of IL-15 triggered by gliadin, suggesting that vitamin C supplementation might be beneficial for celiac patients[42].

Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive metabolic genetic disorder characterized by a mutation in the gene (chromosome 12) for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it non-functional. It is considered one of the best examples of gene-diet interactions because the mental retardation in subjects with mutations in the PAH gene is easily preventable with dietary modification[44]. Phenylalanine is an essential amino acid found in all protein foods, and current treatment of PKU consists of a Phenylalanine -restricted diet (well-adjusted to the tolerance) supplemented with a tyrosine-, vitamin-B12 and chromosome 6 oligoelement-enriched amino acid mixture or with a specific formulation high in all the other amino acids necessary for protein synthesis[45].

Bone Disease

Bone is a critical component of the musculoskeletal system. Gerdhem et al, (2007) conducted an study on "Associations Between Homocysteine, Bone Turnover, BMD, Mortality, and Fracture Risk in Elderly Women" and from the study results he concluded that High tHcy levels were associated with higher bone turnover, poor physical performance, lower bone mineral density (BMD,) frailty, and increased mortality among women[46]. From the study of Hong et al, 2006 it is evident that after menopause, the C>T or T>T genotype risk doubles risk when compared with the C>C genotype regardless of age, physical activity, occupation, passive smoking, height, weight, years since menopause, or total hip BMD[47]. Yazdanpanah, 2008 described that low serum levels of B-vitamins (B-12, B-6 and riboflavin) may also increase fracture risk[48].

Spina Bifida - Neural Tube Defects

Spina bifida is a congenital disorder, affecting the central nervous system which is caused due to the incomplete closure of embryonic neural tubes[49]. Similarly, a large epidemiological study on Spina bifida was carried out by the MRC study research group in 1991 and their results eventually showed that the diet enriched with B vitamins was able to prevent the occurrence and recurrence of Spina bifida in humans with more than 50%[50].

Likewise, Dixon, 2007 conducted landmark studies on neural tube defects (NTD) and showed that the risk of neural tube defects (NTD) in the embryo ca n be significantly reduced

up to a 70% by increasing the intake of folate by wom en before and during the first 28 days aafter fertilisati on[51]. Naushad et al. (2010) observed high incidence of neural tube defects in South India where consanguinity is common and vitamin deficiencies were sceptical, which indicate the role of genetic and nutritional factors as the possible etiological factors specifically pointing towards folate metabolism and the result indicates significant gene-gene interactions between different loci and thus, highlights the importance of multiple loci in folate pathway for predicting the risk of NTD[52].

Inflammation

According to Vasto et al (2007), lifelong antigenic burden leads to chronic inflammation, with increased lymphocyte activation and pro-inflammatory cytokine production. From the study on "Zinc and inflammatory/immune response in aging", it was found that the cytokine genes may have polymorphisms that are associated with age-related diseases including atherosclerosis and the Intake of nutrients such as zinc may be protective against inflammation[54.] Das, 2006 suggested that as precursors to prostaglandins, thromboxanes, leukotrienes, lipoxins and resolvins, EFAs have significant clinical implications in obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer[55].

Cardiovascular Disease

Cardiovascular disease is a complex multifactor disease which is influenced by diet and genetic factors. Cardiovascular diseases (CVD) include congestive cardiac failure, cerebrovascular diseases (stroke with transitory ischemic attack), deep vein thrombosis and cardiac ischemic disease (CHD) which includes acute myocardial infarction (AMI), angina pectoris and sudden death [56].

From the study of Donald (2000), it is evident that the Apolipoprotein A-1 gene in women is linked with an increase in HDL cholesterol levels with the increase in polyunsaturated fatty acid (PUFA) intake from diet and this would reduce the CVD risk as compared to those who have GG genotype taking similar amounts of PUFA. Studies performed on role of olive oil components (lignans, hydroxyl tyrosol, secroids and tyrosol) in activation of t-PA(Tissue plasminogen activator) release and inactivation of PAI-1(Plasminogen activator inhibitor-1) gene expression have shown that they can be applied for control of cardiovascular diseases[57]. Oxidative stress is linked with inflammation and chronic inflammation which is associated with carcinogenesis. Similarly pro-inflammatory cytokines and chemokines also play their role in tumorgenesis. Borish et al (2003), described many cytokines that induce the synthesis of novel genes products once bound to their receptors. They are important positive or negative regulators of mitosis, cell survival, differentiation, migration, apoptosis and transforming oncogenes[58]. According to Perusse et al,(2005) , Excess Hcy level (>12 _mol/l) has toxic effect on the endothelium, promotes formation of thrombi, enhances oxidation of LDL-cholesterol and helps in enhancement of smooth muscle proliferation[59] and also the higher concentration is a marker of oxidation of membrane lipoproteins and DNA which finally result in tissue damage[60]. Insulin resistance syndrome linked with inflammation, high level of visceral fat and C-reactive protein (CRP) exert their role in these abnormalities[61]. *In vitro* experiments have suggested that both alleles of 4G/5G polymorphism and 5G are transcription repressors of PA-I-1[62]. Therefore, the 4G allele of the PAI-1 gene is associated with increased gene transcription and 4G4G homozygotes have higher activities linked with ischemic heart disease and AMI[63]. However, ample intake of fruits and vegetables possessing high levels of antioxidants would mitigate lipid peroxidation and manifestations due to high CRP[64]

Cystic Fibrosis (CF)

Cystic fibrosis is an autosomal recessive disease caused by mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene[65]. From the study of Innis et al, 2008; Innis et al, 2007; Chen et al, 2005 revealed that children with CF tend to have liver triacylglycerol accumulation, steatosis and fat malabsorption; high plasma tHcy, *S*-Adenosyl-L-homocysteine (SAH), and adenosine levels; and lower levels of DHA, methionine, S-adenosyl methionine (SAM), and GSH [66,67]. Trials of supplementation with lecithin, choline, or betaine can significantly increase plasma methionine, S-adenosyl methionine (SAM), and glutathione while decreasing tHcy levels [66]. The same author also in 2008 suggested that normalizing altered (n-6) to (n-3) fatty acid balance and decreasing production of (n-6) fatty acid-derived inflammatory mediators would also control cystic fibrosis.

Diabetes Mellitus

The World Health Organization estimates that type 2 diabetes mellitus (T2DM) afflicts ~200 million people worldwide and its prevalence will nearly double within 30 years. Type-2 diabetes is a metabolic disorder associated with impaired carbohydrate, protein, and lipid metabolism[14]. Universally, there has been an understanding that diet is the integral part of modalities of treatment in diabetes. However, people with diabetes will have different responses to particular foods because of their different genes.

Prentki et al 2002 suggested that diets high in sugar and saturated fatty acids elicit a condition termed “glucolipotoxicity” which negatively impacts the ability of the β-cell to adequately secrete insulin, resulting in hyperglycemia and hyperlipidemia[68]. Many of the effects of sugars and fats are mediated through transcriptional regulation of β-cell gene expression. Moreover, as the fat mass of obese individual’s increases, the concentration of inflammatory mediators produced by adipo-cytes rises and these mediators, termed adipokines, may

also influence insulin secretion directly and *via* genomic changes[14].

Sterol Regulatory Element-Binding Proteins (SREBPs) are the transcriptional factor that binds sterol regulatory element DNA sequence[69]. In isolated islets and β-cells, glucose treatment is strongly linked with SREBP-1c activation [70] mediated through, insulin- dependent 71' [72] and insulin-independent[73] mechanisms. Furthermore, insulin has been shown to upregulate SREBP-1c in other cell types[74- 76]. These effects are likely to be attributable to induction of lipogenic pathways and subsequent β-cell lipid accumulation [77.] Low intakes of vitamin D have also been associated with an incidence and pathogenicity of Type 2 diabetes mellitus[78- 80].

Depression

Farah, 2009 described depression as a major disorder which is debilitating and has a high morbidity rate[81]. The first major study of the incidence of folate deficiency in psychiatric patients was described by Carney (1967), who measured serum folate levels in 423 patients admitted to a psychiatric ward and found that a high incidence of folate deficiency occurs in patients with depression (29 – 30%), organic psychosis (24%), and schizophrenia (20%) [82]. Similarly from the study of Fava, 2007 it is evident that when the red blood cell have low folate levels, ultimately the episodes of depression would be longer and more severe[83]. Lewis et al, 2006 concluded from his experimental study that there is a causal relationship between folate and depression[84]. With reference to alleles, individuals with the C>T allele may be at higher risk for depression[85.] It can be useful to test for MTHFR (Methylenetetrahydrofolate reductase) levels and to augment therapy with methylfolate and omega-3 fatty acids[83, 86].

Obesity

Obesity is the most common nutrition-related disorder and is the core element for various metabolic abnormalities (metabolic syndrome) such as insulin resistance and hyper-insulinemia, hypertension, impaired glucose tolerance, and noninsulin- dependent diabetes mellitus[87]. Also obesity and associated metabolic anomalies dramatically increase the risk of developing a variety of chronic degenerative diseases including CVD and cancer [88, 89]. However, individual susceptibility to obesity strongly depends on the genetically determined patterns of energy balance regulation [90]. According to Loktionov 2003, food intake control may be affected by polymorphisms in the genes encoding taste receptors and a number of peripheral signaling peptides such as insulin, leptin, ghrelin, cholecystokinin, and corresponding receptors [90]. From the same study it is also evident that the polymorphic central regulators of energy intake include hypothalamic neuropeptide Y, agouti-related protein, melanocortin pathway factors, CART (cocaine- and amphetamine regulated transcript), additionally some other neuropeptides, and receptors for these molecules. Moreover, potentially important polymorphisms in the genes encoding energy expenditure modulators (alpha and beta-adrenoceptors, uncoupling proteins, and regulators of adipocyte growth and differentiation) were also recognized by the same author.

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is associated with the inheritance of a number of specific SNPs and variants of other genes which disrupt bacterial homeostasis mechanisms (Ferguson et al, 2007.) Peyrin - Biroulet et al, 2007 reported that as the GI tract is a site of net tHcy release; production of tHcy within the intestinal mucosa would also contribute to the inflammatory response and endothelial cell dysfunction[91].

Patients with Crohn's disease (CD) and ulcerative colitis (UC) have a three- to four fold greater risk of venous thrombosis compared with the general population (Bernstein et al, 2006.) Nagano et al, 2003 from his study stated that thrombo embolism seems to develop as a result of interactions between genetic risk factors and acquired factors[92]. Peyrin- Biroulet et al, 2007 on conducting a study on Vascular and cellular stress in inflammatory bowel disease suggested that it is important to screen folate and vitamin B12 deprivation as well as MTHFR polymorphisms, especially for those who have active disease, history of intestinal resection, or treatment with methotrexate[91].

Alcoholic Liver Disease

Alcoholic liver disease encompasses the hepatic manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis

with hepatic fibrosis or cirrhosis[93]. A national symposium held in 2005 summarized that the Betaine would pacify ALD by increasing the synthesis of SAM (S-adenosylmethionine) and glutathione, which eventually decrease the hepatic concentrations of homocysteine and SAH, and increase the SAM- SAH (S-adenosylhomocysteine)ratio, which would trigger the activation of phosphatidylethanolamine methyltransferase, increased phosphatidylcholine synthesis, and formation of VLDL for the export of triacylglycerol from the liver to the circulation. Additionally, decreased concentrations of homocysteine can down - regulate endoplasmic reticulum stress, which leads to the decrease of apoptosis and fatty acid synthesis[94]. Halsted et al, 2002; Schalinske and Nieman, 2005 reported that the Folate deficiency may promote the development of ALD by accentuating abnormal methionine metabolism, lipid oxidation, and liver injury[95].

Hypertension

Hypertension or high blood pressure is a common disease which is found worldwide. Major risk factors for its pathogenesis include genetics, nutrients (such as sodium, chloride, low potassium and low calcium, low omega-3 fatty acid) and other environmental factors (such as obesity). Polymorphic genes implicated in blood pressure regulation include renin-angiotensin system genes including those encoding angiotensinogen (AGT), angiotensin converting enzyme (ACE), and aldosterone synthetase (CYP11B2)[96]. Sodium transport/metabolism-related genes such as those encoding epithelial sodium channel (ENaC) subunits, adducin, and 11B-hydroxysteroid dehydrogenase are certainly of interest, given well-proven association between dietary salt intake and hypertension[97]. E-selectin, also known as endothelial-leukocyte adhesion molecule 1 (ELAM-1), or leukocyte-endothelial cell adhesion molecule 2 (LECAM2), is a cell adhesion molecule expressed only on endothelial cells activated by cytokines[98]. And that E-selectin is rapidly formed in response to certain some proinflamatory stimuli and is regarded as a biomarker of the activated endothelial phenotype. In order to explain the role of the genetic variation of E-selectin gene (T1880C, C602A and T1559C) in essential hypertension, a case-control pilot study in a Chinese population has been performed and their study result revealed that T1880C was not an independent risk factor for essential hypertension while other two polymorphisms (C602A and T1559C) were risk factors for this disease [99].

CONCLUSION

Adequate dietary nutrients not only prevent or delay chronic diseases but also decrease the progression and severity of chronic illness that is associated with abnormality of gene(s). The real challenge for nutrigenomics study is to target the genes involved in such major human diseases. Assessing for genotype of an individual would give us direction to rule out the aetiology of any such diseases. If the genotype is of nutrient oriented, a well balanced menu devoid of particular nutrient, for example abstaining from phenyl alanine in phenylketonuria would enhance better life quality. Another classical example may be Betaine which would attenuate homocysteine and down-regulate endoplasmic reticulum stress, which leads to the decrease of apoptosis and fatty acid synthesis. Similarly, several nutrients may be identified and controlled, if it is associated with genotype. However, in case of polymorphism alternative modality may be engaged. Nevertheless, eventually based on the knowledge of nutritional requirements, nutritional status and genotype, the nutrigenomic researcher may provide information on the nutrigenomic interaction and qualified nutritionists can provide “Personalized Nutrition” and diet recommendation that would enable for a healthy life as well as for the prevention and control of various pathological diseases.

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