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8. Nutrigenomics – A Novel Way of Disease Diagnosis and Prevention

Vidya T. A., Sruthy P. M.

Research Scholar,
Department of Community Science,
College of Agriculture,
Kerala Agricultural University,
Vellanikkara, Thrissur.

Sharon C. L., Lakshmy P. S.

Assistant Professor,
Department of Community Science,
College of Agriculture,
Kerala Agricultural University,
Vellanikkara, Thrissur.

Aneena E. R.

Associate Professor,
Krishi Vigyan Kendra,
Thrissur.

Seeja Thomachan

Associate Professor and Head,
Department of Community Science,
College of Agriculture,
Kerala Agricultural University,
Vellanikkara, Thrissur.

Abstract:

Nutrigenomics is a study that combines genetic science and nutrition science. The emergence of nutrigenomics as a science opens up new avenues for better identifying individual dietary needs and the effect of food and its componentson gene expression, as well as understanding the nutrigenomics–disease interrelationship. Currently, nutrigenomics concentrates on Single Nucleotide Polymorphisms (SNPs) in genes. A SNP is a germline substitution of a single nucleotide at a specific position in the genome. SNPs are the most common type of human genetic variation and a valuable resource for mapping complicated genetic characteristics. The revelation of SNPs enabled us to diagnose numerous health conditions well before symptoms appeared. This can also help dieticians and health workers educate their patients with personalised nutrition and efficiently manage a healthier physique throughout their lifespan. However, because the tests are

primarily conducted at the laboratory level, the efficacy and feasibility of this are still in question. As a result, greater research on dietary components using tissue/cell model systems may aid in a better understanding of the interactions between nutrigenetics, nutritional epigenomics, nutritional transcriptomics, proteomics, and metabolomics.

Keywords:

Nutrigenomics, Personalised nutrition, Diabetes, Cancer, Disease diagnosis

8.1 Introduction:

Ever since the beginning of time, scientists have been working diligently to understand the etiology of human diseases. In recent decades, scientists could find that not only the nature and nurture of the human beings are the reason for disease conditions. The fact that even the presence of a gene or the mutation of the gene can be a cause of the diseases was recently unveiled. This has led to the development of various researches to understand the relation between genes and health. One such approach led way to the development of a branch of science named 'Nutrigenomics'.

Nutrigenomics is the study of integrating the genomic science and nutrition science. Initially, it was referred to the study of the effect of nutrients in the expression of a genetic makeup. Later on, the study was expanded to understand the nutritional factors which protected the genome from damage. It is more often termed as personalised nutrition, precision health care as it is a type of customised nutrition therapy that not only helps to combat diseases but also to maintain a healthy life[1].

The advent of nutrigenomics as a science, provides opportunities to better identify individual dietary demands and the effect of food and food components on gene expression, as well as to comprehend the nutrigenomics–disease interrelationship. It studies genetic differences, as well as the effects of epigenetic changes and transcriptome homeostasis on the response to individual bioactive dietary components. This concept is based on the notion that bioactive dietary components can alter the human genome, either directly or indirectly, and hence alter gene and gene product expression. As a result of this influence, dietary patterns and/or specific dietary components may alter many biological processes, including ageing, as well as the origin, incidence, progression, and/or severity of a variety of diseases. The health impacts of a diet are determined by the balance of health and disease in an individual's genetic makeup.

8.2 History of Nutrigenomics:

The history of nutrigenomics begins with the isolation of DNA. In 1869, the Swiss physician Friedrich Miescher, isolated DNA. He was researching the proteins in leucocytes when he discovered a material that was not a protein yet had special properties. Later in 1944, Avery, MacLeod and McCarty revealed that DNA is the hereditary material. Eventually, in 1953, Watson and Crick published the molecular structure of DNA. It was subsequently commercialised by 1980's. The first nutrigenomics company was launched in 1997. Nancy Fogg-Johnson and Alex Merolli renamed nutritional genomics as nutrigenomics in 1999 as

it provides a potent technique for uncovering genetic variables in disease. In 2003, the Human Genome Project was launched and the project contained the complete sequencing of the human genome which paved the way for the 'omics revolution'[2].

8.3 Nutrigenomics – The Food Genome Interface:

The balance of human health is maintained by the adequate intake of all nutrients in a balanced way and the proper utilisation of these is required by each human being. The deficiencies can be reduced by slightly increasing the quantities and improving the quality of food taken. Eventhough a person's intake of nutrients is sufficient, he may have nutrient deficiencies. Hence,it is understood that beyond the intake of food and the metabolism of the food, there are even more factors affectingthe occurrence of a disease. Studies have concluded that the problem of deficiency is not only due to overt poverty, food choices, conditions or medications which alter nutrient utilisation and malabsorption disorders but also because of the genetic polymorphisms which modify the individual needs[3].

Researchers have evidently shown that the macronutrients (fatty acid and proteins), micronutrients (vitamins), bioactive compounds (phytochemicals) and certain zoo-chemicals (Eicosapentanoic acid and Decosahexanoic acid) regulate gene expressions. Most of these nutrients are also involved in the metabolic reactions which maintain things from hormonal balance, detoxification and immunity to even the utilization of macronutrients for energy and growth. Some bioactive compounds in food are ligands for transcription factors and some alter transduction pathways and chromatin structure. These can alter gene expression directly and indirectly. Studies have also pointed out that the deficiency or excess of nutrients plays a major role in determining genome health.

At present, nutrigenomics focuses much on Single Nucleotide polymorphisms (SNPs) of the genes. A Single Nucleotide Polymorphism (SNP) is a germline substitution of a single nucleotide at a particular point in a genome. SNPs are the most abundant form of human genetic variation and a resource for mapping complex genetic traits. Some of the essential nutrient gene interactions and their clinical manifestations are furnished below (Table 8.1).

Table 8.1: Essential Nutrient- Gene Interaction and Their Clinical Manifestations

Nutrient	Gene polymorphism	Effects on nutrient status	Clinical manifestations
Carbohydrates	Beta-2-adrenergic receptors Q27E	Unknown	Higher risk of obesity in female carriers with carbohydrate intake >49% of energy
Omega 3 and 6 fatty acids	Fatty acid desaturase, FADS SNP rs174537	Lower plasma arachidonic and eicosapentaenoic acids and higher plasma alpha	The minor allele homozygotes (TT) have lower plasma total cholesterol and

Nutrient	Gene polymorphism	Effects on nutrient status	Clinical manifestations
		linolenic and linoleic acids in carriers of the minor allele versus non carriers.	LDL-C compared with non-carriers
Vitamin A	β-carotene 15,15′-monoxygenase (BCMO1) R267S (rs12934922) and A379V (rs7501331)	Carriers of 267S or 267S + 379V have reduced activity in converting B-carotene to retinal	Increased risk for vitamin A deficiency, when B carotene is the major dietary source
Vitamin D	Vitamin D binding protein DBP-1 (rs7041, exon 11 T>G) and DBP-2 (rs4588, exon 11C>A)	SNPs for DBP-1 and DBP-2 are inversely related to levels of circulating 25(OH) vit D3 in premenopausal women	Unclear whether carriers would benefit from dietary supplementation or sun exposure
Vitamin K	Vitamin K epoxide reductase complex subunit 1 (VKORC1)j – +2255T>C	Associated with vitamin K recycling, vitamin K–dependent clotting factors and Warfarin resistance	Increased risk of arterial vascular disease such as stroke, coronary heart disease, and aortic dissection
Vitamin B12 (cobalamin)	Methionine synthase TCN2 776C>G and 67A>G	Causes hyperhomocysteine mia	Associated with birth defects
Folate	5,10-methylenetetrahydrofolate reductase (MTHFR) 677C>T	Causes a 70% reduction in MTHFR activity, hyperhomocysteine mia and reduced plasma folate concentration	Hyperhomocysteine mia is associated with increased risk of coronary heart disease, neural tube defects, occlusive vascular disease and breast cancer. In carriers, sufficient folate dietary intake decreases risk of colorectal cancer, and deficiencies increase risk of colorectal cancer
Calcium	Calcium sensing receptor (CASR) A986S	Loss of function for calcium, associated with higher serum calcium, and higher	Association with bone mineral density

Nutrient	Gene polymorphism	Effects on nutrient status	Clinical manifestations
		urinary calcium excretion	
Selenium	Missense mutation in selenium binding protein 2 (SBP2)	Causes defective selenocysteine insertion sequence (SECIS)-driven selenocysteine incorporation, downregulates expression of selenoproteins	Defective thyroid function
Iron	Human hemochromatosis protein (HFE) 187C>G or 845G>A	Both187C>G or 845G>A associated with iron overload (hemochromatosis)	Iron overload, liver cirrhosis, and cardiomyopathy, especially in diets high in iron
Sodium	Angiotensin gene (AGT) nucleotide −6 G>A,	The A substitution in AGT affects the interaction between at least one *trans*-acting nuclear factor and its promoter, resulting in increased gene transcription and increased angiotensin protein levels	Carriers of the A allele respond to low sodium diets with reductions in blood pressure; GG genotype is not salt-sensitive

In addition to the essential nutrients, there are several other factors dependent on the genetic expression and disease conditions. Other factors include diet composition, fibre, food structure and antioxidant capacity, environmental and metabolic regulation, including gut microbiota composition, prebiotics, metabolic phenotypeand physical activity[4]. Nutrients can affect gene expression via different mechanisms: (i) directly; (ii) through their metabolites and (iii) through signal transduction molecules. Nutrients present in food and diet can affect gene expression in a number of ways. They may directly act as ligands for transcription factors and change gene expression. Nutrients may be metabolized by different pathways, thereby modifying the concentration of substrates or intermediates that affect gene expression. Alternatively, the substrates or intermediates may act on or alter cell signaling pathways involved in gene expression. Moreover, nutrients may directly alter signal transduction pathways responsible for modifications in gene expression. Finally, the modifications in the signaling pathways, caused by nutrients, may modulate the metabolism of nutrients affecting gene expression. The modifications in gene expression may affect muscle, liver, pancreatic β cells, hypothalamus and adipose tissue, thereby regulating glucose homeostasis.

In short, Nutrigenomics involves the characterisation of gene products, their physiological function and interactions. By focusing on the effects of nutrients on genome, proteome, metabolome it explains the relationship between the nutrients and nutrient- regimes on human health. At the onset, nutrigenomics was concentrating on the genetics of the disease conditions such as obesity, diabetes mellitus and cardio vascular diseases. But advancements in researches, SNPs related to various other disease conditions like cancer, allergies, periodontitis, non-alcoholic liver diseases and many more were identified.

8.4 Nutrigenomics – Role in The Prevention of Diseases:

From several studies, it is understood that by examining the interaction of nutrients and their functions in the human body, the genetic changes occurring in them can be identified. This inturn helps to diagnose a disease in advance and thus helps to maintain good health. It is found that if there is a nutrient deficiency persisting in the body; it can lead to certain gene alterations. These gene alterations and the deficiency condition can together lead to certain disease conditions in thefuture. Some of such nutrient deficiencies, the gene alterations and the disease conditions are furnished below (Table 8.2).

Table 8.2: Nutrient Deficiencies, Gene Alterations and The Disease Conditions

Nutrients	Gene Alterations caused by deficiency	Deficiency diet and disease potential	Preventive foods
Protein	Alters gene expression	Kwashiorkor, Marasmus	Egg, milk, soya milk, tofu, yoghurt, cheese, broccoli, almonds, peanuts, cashew, poultry
Fatty acids	Alters gene expression	Obesity, CVD, Diabetes	Salmon, sardines, herring, mackerel, soyoil, sunflower oil, palm oil, flaxseeds, rapeseeds, peanuts, walnuts, almonds, mustard seeds, cloves, oregano, cauliflower, broccoli
Vitamin A(Retinol)	Repression of PEPCK gene	Termination of pregnancy and fetal death	Carrots, spinach, turnip, kale, apricots, Cantaloupe, bell pepper, Papaya, mango, peach, beef liver, chicken liver
Vitamin D (Calciferol)	Prevent gene variation	Colon, breast, prostate cancer	Beef liver, cod liver oils, salmon, mackerel, tuna, egg orange juice, cow milk, yogurt, cheese

Nutrients	Gene Alterations caused by deficiency	Deficiency diet and disease potential	Preventive foods
Vitamin E (Tocopherols)	Mimics radiation damage	Colon cancer, heart disease, immune dysfunction	Tomato, spinach, broccoli, blueberries, mangoes, kiwi, papaya, almonds, hazelnuts, peanuts, wholegrain cereals and vegetable oils
Vitamin B6 (Pyridoxine)		Cancer, heart disease, brain dysfunction, male infertility, leukemia	Spinach, potato, bell peppers, turnip, mushroom, garlic, cauliflower, banana, chicken, pork, beef, salmon, tuna, turkey
Vitamin B3 (Niacin)	Hampers DNA repair	Nerve problem, memory loss	Pork, tuna, prawns, kidney, liver, poultry, carrots, turnips and celery, mushrooms, beans, almonds, wheat products, rice bran, as well as milk and other dairy products
Vitamin B6 (Pyridoxine)		Cancer, heart disease, brain dysfunction, male infertility, leukemia	Spinach, potato, bell peppers, turnip, mushroom, garlic, cauliflower, banana, chicken, pork, beef, salmon, tuna, turkey
Vitamin B12 (Cobalamin)	Chromosome break and hampers DNA repair/methylation	Cancer, heart disease, brain dysfunction, male infertility, leukemia, memory loss	Liver, sardines, salmon, clam, beef, milk, cheese, yoghurt
Folic acid	Chromosome break and hampers DNA repair/methylation	Cancer, heart disease, brain dysfunction, male infertility, leukemia	Liver, kidney, egg yolk, asparagus pea, cowpeas, lentils, peanuts, spinach, beetroot, broccoli, orange
Zinc	Chromosome breaks	Brain and immune dysfunction	Oysters, beef, crab, pork, lobster, chicken, spinach, broccoli, cashew nuts, almond, milk, cheese, yogurt

Nutrients	Gene Alterations caused by deficiency	Deficiency diet and disease potential	Preventive foods
Flavonoids	Alters gene expression	Cancer	Onion, green bean, broccoli, curly kale, endive, celery, cranberry, orange juice, grape fruits, lemons, red, blue and purple berries, peppers, tomatoes and eggplants

What is the source for the Table 2:

Nutrigenomics and its involvement in the diagnosis and prevention of various diseases are discussed further.

8.4.1 Diabetes Mellitus:

Diabetes mellitus (DM) is a group of metabolic diseases characterised by hyperglycemia, which results from defects in insulin secretion, insulin activity or both. It is associated with the dysfunction and failure of different organs, such as the blood vessels, heart and kidneys [5]and this disease is considered asa global burden[6]. Food intake is a key component that affects the incidence of DM. Thus, the identification and analysis of nutrient/gene interactions can assist in understanding the DM etiopathogenesis. Diabetic Mellitus is one of the first diseases, the nutrigenomics have intervent.

There are several factors which help to identify the incidence of DM. The intake of excess fat and calorie can increase the prevalence of diabetes. It was also reported that adinopection gene polymorphism can contribute to insulin resistance and can cause DM. This is said to aggravate in the persons consuming foods witha high glycemic index.

Likewise, the sufficient or insufficient intake of many bioactive compounds, amino acids, vitamins and other major or minor nutrients predispose to the exposition of genetic variations related to DM. The intake of dietary fibre in the diet is interrelated to the microbiota in the body. The activity of this microbiota is highly influential in the absorption of various nutrients. The deficiency caused because of the improper absorption or utilisation of the essential nutrients may cause gene polymorphism. This gene polymorphism may in turn increase the prevalence of diseases like DM[7]. It is found that apart from the absorption and utilisation of nutrients in the microbata, the change in the microbial activities may affect the gut immunity. The alterations in gut immunity can precipitate diabetes in DM prone persons.

Studies revealed that not only dietary factors but other environmental factors also influence DM incidence and development. These factors primarily include the use of breast milk *vs.* infant formula, highly hydrolyzed infant formula *vs.* conventional infant formula, early/late exposure to gluten and vitamin D.

Identifying the SNPs related directly and indirectly to these changes in the body can thus diagnose the incidence of DM in people. Scientists working in the field of nutrigenomics have already pointedoutseveral SNPs associated with both Type 1 and Type 2 Diabetes Mellitus.

8.4.2 Cardiovascular Diseases:

Cardiovascular diseases include heart attacks, stroke, hypertension, rheumatic heart disease, congenital heart disease and heart failure[8]. Diet and exercise plays a major role in controlling these conditions to a great extent. In spite of the advances in the diagnosis and treatments of cardiovascular diseases, there were some lacunae[9]. These lacunae were addressed to some extent when genetics was employed to identify the gene-disease relationship.

There are several foods related factors linked with cardiovascular diseases starting with the increased intake of saturated fatty acids (SFA), andlower intake of dietary fibre. The potential molecular mechanisms for nutrigenomic interactions in CVD risk include (1) differential intestinal metabolism and uptake of nutrients depending on the gut microbiota, (2) differential absorption and nutrient binding, desponding of the genotype and phenotype, (3) modulation of gene expression through specific transcription factor binding, (4) effects on methylation and epigenetic modification and (5) modulation of metabolic signalling through lipids, metabolites and proteins. The interaction of genetic variants with the environment and specific dietary consumption can alter the overall risk of CVD. There are many genes and SNPs identified which is associated with cardiovascular diseases.

With sufficient knowledge on the connection between certain genetic variants, diet and CVD risk, it may be capable of giving individuals dietary counselling suited to their genotype, hence extending life expectancy and maintaining health.

8.4.3 Obesity:

The fraction of the global population that is overweight or obese is reaching epidemic proportions, with all of the associated health, social and economic consequences. Although there are several causes for the rise in obesity, the most plausible reason is the modern lifestyle's increased calorie consumption and decreasing exercise.

Most people who eat more and moveless will gain weight,but being overweight or obese is a gradual process that takes years of even little excess calorie consumption. Although weight reduction is challenging, sustaining weight loss is even more challenging.

In fact, just a few non-surgical therapies for obesity succeed in long-term weight loss. Long-term weight loss maintenance necessitates permanent lifestyle changes in exercise and food habits. One such approach paved the way for the inclusion of nutrigenetically personalised diets to such persons. A study conducted by Arkadianos *et al.* [10] on the patients who strived to reduce theirweight revealed that the adoption of nutrigenetically personalized diets resulted in improved long-term BMI reduction. The inclusion of such a diet also helped in maintaining the blood glucose levels in the persons.

Obesity susceptibility is influenced in part by hereditary factors, but "obesogenic" environment is often required for its phenotypic expression. As a result, while new evidence of genetic influence and neuroendocrine imbalance emerges on a daily basis, it is crucial to analyse a holistic model in which biological and psychological factors interact in a complex manner.

As a result of several studies, several genes and SNPs associated with obese phenotypes were discovered. The important genes associated with obesity are the FTO gene, INSIG2 Gene, MC4R gene and APO-A gene. Several SNPs connected with these genes were uncovered, and they had an impactonweight loss in a variety of ways[11].

8.4.4 Cancer:

According to WHO, cancer is a vast category of disease that can begin in practically any organ or tissue of the body when abnormal cells develop uncontrollably, invade neighbouring tissues, and/or spread to other organs. The latter phase is known as metastasizing, and it is a primary cause of cancer death. Cancer is also known as a neoplasm and a malignant tumour. Globally, cancer is the second most important reason for death.

As the incidence of cancer is rising day by day and the mortality increases because of the late diagnosis, an effective preventive strategy has to be developed. In such scenario, cancer is a disease which can be more benefitted with the advent of nutrigenomics. Dietary changes have the potential to be an effective approach of lowering cancer risk. Many studies have pointed out the relationship of nutrients and cancer.

Dietary components are believed to be important predictors of cancer risk in humans. Genetic variations influence absorption and metabolism, resulting in altered response to dietary components. Epigenetic processes can alter DNA methylation patterns, affecting overall gene expression, which can be modified in response to diet components.

Many dietary constituents influence post-translational events and may contribute for some of the variances in response to dietary components. Bioactive food components have the potential to influence cellular and molecular activities that are crucial in cancer prevention.

Covalent adducts with individual nucleic acids of DNA or RNA is produced as a result of carcinogen activation. It has also been discovered that reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, and hydroxyl radicals damage DNA bases, potentially resulting in DNA sequence mistranscription. Such interruptions can affect DNA replication, resulting in alterations in oncogenes and tumour suppressor genes.

ROS can also cause DNA strand breaks, resulting in mutations or deletions of genetic material. There are certain DNA repair mechanisms in the body such as base excision repair, direct repair, nucleotide excision repair and double strand break repair, which helps in maintaining the genome stability which will help in cancer prevention[12]. Deficiency in the dietary components such as flavonoids, vitamin E and C; isothiocyanates can disrupt the mechanisms of DNA repair. The interactions of food with these actions can be clearly estimated with the help of nutrigenomics.

8.5 Other Disease Conditions:

Non Alcoholic Fatty liver disease (NAFLD) is a liver disease where the fat accumulation exceeds 5% other liver weight which is not attributed to alcohol intake. NAFLD develops with a complex interaction between genetic susceptibility and other environmental factors such high calorie diet and physical inactivity[13]. Epigenetic factors such as liver specific DNA methylation and microRNAs, which regulate liver transcriptome also contributeto the NAFLD development and progression.

Esterification in the form triglycerides, excess hepatocellular triglycerides, oxidative stress, inflammation triggered by endotoxin, activation of hepatic stellate cells, insulin resistant and altered profile of adipokines are some of the factors which aggravates the disease incidence. There are various genes which are related to these and identifying the genetic variations can thus help in the early diagnosis of the disease condition. Periodontics is an area where nutrigenomics has intervent very recently. Periodontics is the study of supporting structures of teeth and the disease conditions related to it. Zinc deficiency is said to have an increased susceptibility to periodontal disease progression. Disease like DM, insulin resistance can also contribute to the periodontal diseases. The SNPs related to zinc absorption and utilisation is also associated with periodontal diseases. There are even other factors like this, to be estimated to completely identify the condition.

8.6 Nutrigenomics and Personalized Diet:

The identification of certain genes in the body which may be the potent reason for the cause of a specific disease can be a great advent in managing the disease condition as well as in reducing the mortality rates. The ultimate aim of personalized diet is to provide a diet by identifying those differences that are due to the heritable genetic sequence variation which can be evidently portrayed by nutrigenomics. The goals of nutrigenomics in determining a personalized diet can be summarized as: 1. Identification of transcription factors (as nutrient targets) and the genes they target; 2. Identification of signaling pathways involved at the cellular level and characterization of the main dietary signals; 3. Measurement of specific micronutrients and macronutrients inducing cell and organ specific gene expression signatures; 4.Identification of interactions between nutrient related regulatory pathways and pro-inflammatory stress pathways for a better understanding of diet related diseases; 5.Identification of genotypes which can be risk factors for the development of diet related human diseases (such as diabetes, hypertension or atherosclerosis); 6.Use of nutritional systems biology to discover biomarkers for early detection of disease and susceptibility (stress signatures) that are changed in response to diet. Nutrigenomics is an upcoming branch of science which reveals the relationship betweengenes and nutrients. The identification of Single Nucleotide Polymorphism (SNPs) helps us to diagnose the incidence of various disease conditionsfar before the symptoms are portrayed. This can also help the dieticians and health workers to guide their patients with personalised nutrition and helps to maintain a healthier body throughout the lifetime effectively. But since, the studies are only done atlaboratory levels, the efficiency and practicality of this is yet in vain. Hence, more studies of dietary components employing tissue/cell model systems may aid in a better understanding of the interrelationships between nutrigenetics, nutritional epigenomics, nutritional transcriptomics, proteomics and metabolomics.

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