REVIEW ARTICLE

Nutrigenomics and Nutrigenetics: Concepts and Applications in Nutrition Research and Practice

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ABSTRACT
Nutrigenomics refers to the application of genomic principles in nutritional research, enables us to formulate associations between specific nutrients and genetic factors, e.g. the way in which food or food ingredients influence gene expression. It aims to identify the genes that influence the risk of diet-related diseases and also helpful to solve the mechanisms that underlie these genetic predispositions. In contrast, nutrigenetics reveals the coordination of genetic makeup of individuals with their responses to various dietary nutrients. It clarifies different responses to same nutrient by different individuals. Interaction of genetic background and diet with regard to development of chronic conditions as obesity, cardiovascular disease, hypertension and cancer are discussed in present review. These two branches of nutrition resemble with two sides of a coin, facing towards opposite sides but simultaneously, they are intimately attached with each other. Collective efforts by the scientific community are needed to strictly follow guidelines put forth regarding experimental designs, analysis, and data storage for nutritional research. This strategy will be helpful to generate a sound database useful for clinicians and dietetic practitioners.

Keywords: Nutrigenomics, Nutrigenetics, Nutrition Research, Chronic diseases, Gene-diet interactions

Advancement of modern sciences realised us that not only are certain nutrients essential, but specific quantities of each nutrient were necessary for obtaining optimal health, thereby leading to such notions described by us as nutritional epidemiology, dietary recommendations and also, the realization that disease onset can be directly contributed by our diet.[1] Due to advancement in molecular techniques and nutritional researches, our understanding of diet and its effects on health status has evolved from just crude associations followed in past to today's well known conclusive facts.

In the field of nutrition, our ongoing efforts for understanding relationships between disease and diet through nutritional researches, leads us to find out the relationships between the genome and diet, currently termed nutritional genetics. Also, Nutritional genetics is a combination of two widely separable different areas of research and intervention-nutrigenomics and nutrigenetics.[2] Although these two concepts are intimately associated with each other, they describes fundamentally different approaches to understand the relationships between genes and diet.

NUTRIGENOMICS AND NUTRIGENETICS

Nutrigenomics describes that how your genes interact with nutrients. It clarifies that how our DNA and genetic code affect our need for certain nutrients and also within specific quantities and helps in maintaining optimal health throughout life. It establishes diet-gene interaction and identifies effects of diet producing beneficial or detrimental health effects.[2,3] It refers to the application of genomic principles in nutritional research, enables us to formulate associations between specific nutrients and genetic factors, e.g. the way in which food or food ingredients influence gene expression. Nutrigenomics facilitate greater understanding of how nutrition affects metabolic pathways and how this process is related to diet-related diseases.[4]

Nutrigenomics aims to identify the genes that influence the risk of diet-related diseases, and also helpful to solve the mechanisms that underlie these genetic predispositions.[5] It is helpful to determine the personalized diet that means individual nutritional requirements based on the genetic makeup of the person as well as clarifies some etiological perspectives of chronic diseases like type-2 diabetes, cancer, obesity and cardiovascular diseases (CVD) because of associations between diet and chronic diseases.[3,4] Nutrigenomics will also helpful to find out the associated genes that are involved in diet-gene interactions as well as detects polymorphisms, which may have significant nutritional consequences and the influence of environmental factors on genetic expression (Figure 1).[6]

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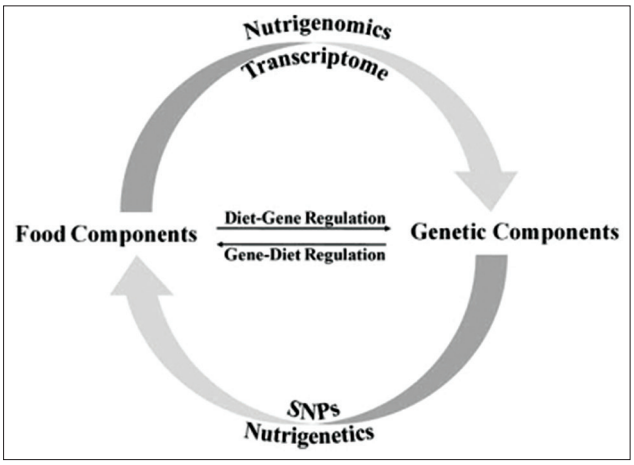

Figure 1: Distinctions between nutrigenomics and nutrigenetics. The investigation of how food components modulate changes in gene expression profile or transcriptome is defined as nutrigenomics. One the other hand, nutrigenetics is defined as the study of how genetic variations such as single nucleotide polymorphism (SNP) among individuals affect their response to specific food components. Food pyramid image obtained from: http://openi.nlm.nih.gov/detailedresult.php?img=2682937_CG-9-239_F1&req=4

In contrast, nutrigenetics encompasses the study of individual differences at the genetic level that influences individual responses to diet. These individual differences may be at the level of single nucleotide polymorphisms rather than at the gene level.[4] It means that nutrigenetics reveals the coordination of genetic makeup of individuals with their responses to various dietary nutrients. It clarifies different responses to same nutrient by different individuals.[7] Nutrigenetics examines the effect of genetic variation on the interaction between diet and disease or on nutritional recommendations.[5]

DIET- DISEASE INTERACTION

Because of substantial individual variability in the dietary absorption, metabolism and elimination, intake of dietary nutrients doesn't acquire same concentrations in the blood or tissue. The underlying processes of these dietary responses between different individuals are complicated and poorly known till date. These variable interpersonal responses are a well known area of nutritional research. Effect of dietary responses and intervention on phenotypes such as body weight, blood pressure and blood cholesterol levels shows significant interpersonal differences.[8,9] As well as several factors except those mentioned above can be attributed that can influence dietary responses like gender difference, age, physical activity, genetic composition, smoking etc.

The goal of nutritional research in the field of nutritional genetics is to identify individuals who may benefit from a particular nutritional intervention, and identify alternatives for those who do not respond to it. Patients should no longer be subjected to unnecessary unpleasant ineffective diets when there may be possibility of an alternate effective approach available. It could be useful in both the prevention and treatment of chronic diseases by adjusting dietary intervention to subject's unique genetic makeup.

NUTRIGENETIC DISEASES: GENETIC BASIS

Pharmaceuticals approach for restoring health is usually a targeted approach, while dietary interventions are usually multi-parametric approach to optimize health. Literature review suggests that nearly 1000 genes that have so far been associated with human diseases, 97% times these results in monogenic diseases, i.e., a single dysfunctional gene in genomic scale is responsible for disease onset.[10]

Most well known and familiar example of such thing is lactose intolerance, in which genetic alteration in lactase gene occurs that results in inadequate lactase production in small intestine.[11] Affected individuals are unable to break down the lactose (primary milk sugar) obtained from dairy products. Therefore, limiting lactose-containing foods or to use lactose-free dairy products can be helpful to prevent gastrointestinal upset.[12]

Phenylketonuria is a metabolic genetic disorder characterised by mutations in the gene for the hepatic enzyme phenylalanine hydroxylase (PAH), rendering it non-functional. This enzyme is necessary to metabolize the amino acid phenylalanine to the amino acid tyrosine. In phenylketonuria (PKU), amino acid phenylalanine containing foods such as eggs, fish, chicken, milk, cheese etc. must be avoided.[13] Patients suffering from galactosemia (lack of a galactose digesting liver enzyme) should avoids diets which contain lactose or galactose, including all dairy products.[14] Therefore, dietary intake modifications can be helpful in some monogenetic diseases. It requires in-depth knowledge of such diseases in which a single nutrient may affect our biological system.[15]

NUTRIGENOMIC DISEASES: GENETIC BASIS

Nutrients, which are considered as the most influential environmental stimuli.[16] Genomes, are exposed to many types of environmental stimuli during lifetime, including nutrition. Therefore, the genetic expression are highly dependent and regulated by, nutrients and phytochemicals present in food.[17] Unbalanced diets can alter nutrient-gene interactions, thereby can increase the risk of developing chronic diseases. Dietary chemicals can alter genomic expression directly or indirectly.[18]

At the cellular level, nutrients may act in different ways like: 1) they can act directly as ligands for transcription

factor receptors; 2) can be metabolised by primary or secondary pathways of metabolism, thereby concentrations of substrates involved in gene regulation or cell signalling may be altered; or 3) alter signal transduction pathways. Transcription factors are the main agents through which nutrients influence gene expression. The most important group of nutrient sensors, involved as transcription factors are nuclear receptor superfamily with 48 members in the human genome. Receptors of this superfamily bind nutrients and their metabolites. Retinoic acid receptor (RAR) binds with retinoic acid, vitamin D receptor (VDR) binds with vitamin D, and peroxisome proliferator activated receptors (PPARs) binds fatty acids. By activation of these receptors, nutrients are able to influence a wide variety of specific genes.[19-21]

Disease conditions that are known to have genetic or nutritional components in etiology basis are considered for nutrigenomic studies. Nutrient imbalances are considered as factors in aging, cancer, substance abuse, behavioural disorders, cardiovascular disease (CVD), diabetes, immune disorders, chronic fatigue, multiple sclerosis, neurological disorders, Parkinson's disease and stroke etc. Differences in genetic makeup are factors in gastrointestinal cancers, digestive diseases, inflammatory conditions, osteoporosis etc.[20-22]

Therefore, both disciplines (nutrigenomics & nutrigenetics) aim to reveal genome-diet interactions; their approaches and immediate goals are distinct. Nutrigenomics will reveal the optimal diet to choose from series of nutritional alternatives available, whereas nutrigenetics will generate information that will useful for identifying the optimal diet for a given subject i.e. personalized nutrition.[22]

SINGLE NUCLEOTIDE POLYMORPHISM (SNP)

At the gene sequence level, 99.9 % identical genomic sequences are found in all human.[18] The remaining 0.1 % variations in genomic sequence, however, responsible for differences like phenotypic differences (height, weight etc.) and in an individual's susceptibility to disease conditions and health status.

Mostly, genes have differences in small sequences known as polymorphisms that are variable among different individuals. Single nucleotide polymorphisms (SNPs) are the most common genetic variations.[7] SNPs are single base variations within a genomic sequence; they forms approximately about 90% of all human genetic variations. Nutritional geneticists have identified over 3 million locations where single base human DNA differences occur and thus are potential sites for introducing alteration. SNPs in human populations change their dietary metabolic responses and can have an important effect on producing risks for disease onset. It is already known that there are many SNP's that influence chronic diseases related with nutrition like cardiovascular disease and diabetes mellitus. Single nucleotide polymorphism analysis provides a powerful tool for investigating the role of nutrition in disease and health status at molecular stage and its consideration in metabolic and epidemiological studies can contribute to define optimal diets.[23] Each genomic sequence is a recipe for a specific protein or group of proteins that regulates biological functions. Some SNPs change the recipe for the gene so that either a different quantity of the protein is produced or the structure is altered.[6]

These genetic polymorphisms influence absorption and metabolism of dietary components. Epigenetic variations can induce changes in DNA methylation pattern and thus influences overall genetic expression. Many dietary components affect post translational events and many account for at least part of the variation.[24]

Regarding SNP's, one of the best-described examples is the relationship between folate and the gene for MTHFR – 5, 10-methylenetetrahydrofolate reductase. MTHFR has a role in supplying 5-MTHF, which is essential for remethylation of homocysteine for production of methionine. Methionine is crucial for many metabolic pathways including neurotransmitters production and genetic expression regulation. Folate is essential to the efficient functioning of MTHFR. When thymine replaces cytosine at base pair 677 in MTHFR gene, it leads to two forms of the protein: the wild type (C), which functions normally, and the thermal-labile version (T), which has a significantly reduced activity.[25] Individuals with two copies of the wildtype gene (CC) or one copy of each (CT) will have normal folate metabolism. Those persons with unstable version of both copies (TT) and low folate intake, will have higher plasma homocysteine levels, which increases their risk of cardiovascular disease and premature cognitive disturbances.[26] If supplemented with folic acid or increased folate intake, these individuals can restore their normal methionine levels through metabolising homocysteine. The beneficial effect of folic acid supplementation (1 mg/day for 3 months) on plasma homocysteine level has been shown in previous researches.[27]

Interrelationship between SNPs and associated specific food components also include Apolipoprotein E (apo E) of which three isoforms are found E2, E3 and E4. Individuals with apo E4 (approximately 25 % of the population) have a higher risk of CVD and usually higher levels of LDL cholesterol, and these persons responds better to a low fat diet. Several SNP's variations of vitamin D receptor (VDR) gene may affect the response to diet and possibly increases risk of

disease. Caffeine, a risk factor for bone loss in women with a variant of VDR and these individuals may need to cut down caffeine intake in their diet to reduce risk of osteoporosis. SNP's in angiotensinogen gene can affect individual's blood pressure responsiveness to dietary fibre component.

NUTRIGENOMICS AND CHRONIC DISEASE

With recent development of high-throughput -omics (genomic, transcriptomic, proteomic, and metabolomic) technologies, field of nutrigenomics has expanded. These advanced technologies helpful for identification and measurement of many molecules of each type at one point of time. We can now measure innumerable variations in DNA, including tens of thousands of SNP's as well as many RNA molecules. This is crucial in development of chronic diseases since in most cases, mutations in single genes are not responsible rather there are complex interactions occurs among variants of several genes.

Obesity is the commonest multifactorial disorder affected by multiple environmental and genetic factors. Expanding information of the genes involved in the obesity development is guiding for newer methods of obesity control. Nutrigenomics, may orientate development of new functional diets for control of obesity, based on the scientific knowledge of the effect of specific dietary components on the human body weight and their mechanisms of producing it. Obesity is the major element of a group of metabolic abnormalities (metabolic syndrome) which includes impaired glucose tolerance, insulin resistance, hypertension and noninsulin-dependent diabetes mellitus.[28] Obesity and associated metabolic abnormalities drastically increase the risk of development of various chronic diseases that includes CVD and cancer.[29-30] Dietary intake regulation may be affected by SNP's in the genes that encode taste receptors and a variety of peripheral signaling peptides such as cholecystokinin, insulin, ghrelin, leptin etc. Central regulators of energy intake include agouti-related protein, hypothalamic neuropeptide Y, melanocortin pathway factors and their receptors.[31]

In present scenario, CVD is primary chronic disease related to nutrition. CVD can be label as a group of multifactorial conditions and it is associated with obesity, hypertension, thrombosis and atherosclerosis. These pathologic conditions are related to both genetic and environmental factors. A strong association between dietary composition and risk for CVD is properly documented.[32-33] Atherosclerosis considered as core element in the CVD pathogenesis and it is an complex combination of metabolism disorder and lipid transport with chronic inflammation.[34] Genetic variations in genes that encodes for apolipoproteins and some hormones can alter individual susceptibility for CVD. Individuals with the E4 allele in the apolipoprotein E gene show higher LDL cholesterol. Specific polymorphism in genes encoding lipid-processing enzymes, lipid transport proteins, receptors, and proteins related to inflammation were associated with the remarkable changes in lipid levels of blood.[35-36]

Hypertension considered as an important element in CVD pathogenesis. Some genetic patterns are responsible for increase in blood pressure (BP). It is well known fact that the weight loss in obese hypertensive individuals usually leads to decrease BP.[37] BP responses to variable dietary salt intake (more or less) may be heterogeneous, as only about 15% individuals suffers from sodium-sensitive hypertension. For the remaining 85%, eliminating salt intake has no effect on BP.[38] Polymorphic genes responsible in BP regulation include those encoding angiotensinogen (AGT), aldosterone synthetase (CYP11B2) and angiotensin converting enzyme (ACE). Sodium transport related genes like those encoding epithelial sodium channel (ENaC) subunits, 11B-hydroxysteroid dehydrogenase and adducing are also found responsible.[38-39] That's why nutrigenomics can answer the question that why some people can control their BP with dietary recommendations, while other people require medicinal treatment. Increased homocysteine levels is now considered as an independent risk factor in the development of cerebrovascular and coronary heart disease.[40]

Arterial thrombosis regarded as chief factor leading to acute coronary and cerebrovascular syndromes. Altered levels of multiple coagulation factors can produce hypercoagulative state. Excessive fat intake can enhance postprandial hypercoagulative state. Genes encoding platelet surface glycoproteins, and coagulation factors can affect hemostasis. Coagulation of blood is counterregulated by the anticoagulant and fibrinolytic systems. Polymorphic variations can also affect anticoagulation and fibrinolysis.[41-42]

NUTRIGENOMICS AND CANCER

Cancer is a complex process composed of aberrantly operated multiple stages of gene expression, and protein and metabolite function.[43] Scientific evidence suggests that many cancers are preventable. Diet and nutrition are key factors held responsible in the modulation of risk of cancer.[44] Dietary habits are considered to contribute for 35% of all human cancers and for some cancers, association is approximately 70%.[45-46] In the absence of overt exposure of genotoxins, genome and epigenome damage biomarkers are sensitive indicators of deficiency in nutrients required as cofactors of DNA repair enzymes, prevention of DNA oxidation and/or uracil incorporation into DNA and for maintenance methylation of CpG sequences.[47] Polymorphisms affecting carcinogen metabolism may

alter probability of contact between carcinogens and target cells, thereby acting at the cancer initiation stage. Influences of polymorphisms of Alterations of gene encoding factors involved in hormonal regulation are most strongly associated in hormone dependent tumours like breast, ovarian, endometrial and prostate cancers. SNP's in sex hormone receptor genes encoding estrogen, progesterone and androgen receptor have been associated with modification of cancer risk.[31]

Excessive consumption of red meat is found to be associated with increased risk of colorectal cancer. Several polymorphisms exist for N-Acetyl transferase (NAT) enzyme that exists in two forms: NAT1 and NAT2. NAT found in well cooked red meat, is involved in acetylation of the heterocyclic aromatic amines. During cooking of meat at high temperature, heterocyclic aromatic amines (HAA) are produced by reaction of some aminoacids with creatinine. Acetylation of HAA may form reactive metabolites which can bind DNA and produce cancers. Only NAT2 fast acetylators can perform this activity. Therefore, NAT fast acetylator genotype is susceptible for higher risk of developing colon cancer. Excess body weight combined with sedentary lifestyle are estimated to account for one fifth to one third of many of the most common cancers, esp. cancers of the breast in postmenopausal women, endometrium, esophagus, colon, endometrium and kidney.[48] Specific dietary components like salts and preservatives have been suggested as possible carcinogens for gastric cancer.[49]

Previous studies regarding prevention of cancer have established the fact that all of the major signalling pathways deregulated in different cancers, are affected by specific dietary intake. Till date, greater than 1000 different phytochemicals have been identified with cancer-preventive activities.[50] Long chain polyunsaturated fatty acids (LC-PUFA) are shows beneficial effects in cancer prevention. They affect physiological bodily processes including growth, lean and fat mass accretion, reproduction, neurological development, innate and acquired immunity and affects incidence and severity of all chronic and degenerative diseases such as cancer, stroke, arthritis, atherosclerosis, diabetes, neurodegenerative, inflammatory, osteoporosis.[51-53] Omega-3 fatty acids inhibits growth of colonic tumours in both invitro and invivo systems. Fruits and vegetables which contains various bioactive components can prevent carcinogenesis through increasing detoxification process.[54-55]

ETHICAL CONSIDERATIONS

Goal of nutritional genetics is the prevention of the onset and progression of chronic disease. Nutrigenetics information should be relevant for health promotion, prevention of chronic diseases and treatment. Nutritional genetics is not only useful for patients and at risk individuals, but for all healthy individuals. For global health, world is facing a growing epidemic of the same chronic diseases. We need to concentrate more upon nutritional research for curing or prevention of these diseases.

Rapidly evolving science stream of nutritional genetics holds great promise for the detection of susceptibilities to disease and for health promotion and prevention that link genes to nutrition; it is still an emerging science that lacks evidences necessary to validate the results for claims of health benefits and disease prevention. In this perspective, a selection of participants for nutritional and epidemiological studies that is representative of whole populations is crucial. Selection of participants contributing for research may be a challenging task that raises both methodological and ethical issues. Researchers should always exclude those individuals who could bias the study results or decrease statistical power of study otherwise this strategy if not followed, can compromise the validity and usefulness of their findings. This field raises certain ethical, legal and social issues particularly with respect to how the general population may access nutrigenetic tests and associated nutritional and lifestyle advice for health promotion and prevention of diseases. Points that needs to be considered when nutritional research is undertaken or application of knowledge for commercialisation are managing nutritional genetics information, health claims benefits, nutritional genetics products, delivery methods followed for nutritional genetics services and its equitable accessibility to public.[56-57] Nutritional genetics will likely always remain a science of probabilities because it detects disease susceptibility arising from low penetrance polymorphisms.

Researchers should be wary of about the ethical and regulatory issues associated with nutritional genetics are somewhat pertinent on the nature and strength of the science. As the science unfolds the mysteries or it answers the curiosity of human brain, so too should the ethical and regulatory appraisal of that science. Further we need to inquire more about latest opportunities and limitations of nutrigenomics and its clinical and commercial applications in order to foster greater public awareness, prevention strategies and understanding of the potential risks and benefits of this rapidly evolving field.

CONCLUSION

Recent advancement in molecular biology techniques and the mapping of the human genome are fueling a revolution in a variety of sciences including nutrition. Nutrigenomics is sciencewhich focus upon identifying and understanding

molecular-level interactions between dietary components with the genome. With the help of nutrigenomics research, better dietary regimens may be designed or novel treatment of chronic diseases can be accomplished. It utilizes approaches like single nucleotide polymorphisms (SNPs), microarrays and genomics, proteomics and bioinformatics to improve nutrition and overall health status of population. Nutrigenetics reveals that how genetic makeup of an individual coordinates to various dietary nutrients. This branch investigates effect of genetic variation on the interaction between diet and disease or on nutritional recommendations. However, immediate goals are different to each other, the long-term goal of nutritional research of improving health and preventing disease requires the amalgamation of both disciplines. These two branches of nutrition resemble with two sides of a coin, facing towards opposite sides but simultaneously, they are intimately attached with each other.

Currently, with tools of nutritional genetics, diet-gene association studies are revealing evidence on which to base gene-specific dietary intervention trials are carried out to confirm results. Nutrigenomics research provides us additional knowledge of biological function. The application of information by physicians for the prevention and treatment of complex chronic diseases, however, has not yet been widely adopted. In future, application of information should be used to large population, however, feasibility is yet to be determined, but the principles of nutrigenomics are expected to soon allow us for more targeted interventions.[58] Collective efforts by the scientific community are needed to strictly follow guidelines put forth regarding experimental designs, analysis, and data storage for nutritional research. This strategy will be helpful to generate a sound database useful for clinicians and dietetic practitioners.

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