

Review article

Nutrigenetics and nutrigenomics: A brief review with future prospects

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Corresponding author: **RajLaxmi Sarangi**. Email: drrajlaxmisarangi@gmail.com**ABSTRACT**

Individual's genetic makeup best describes the properties regarding its growth and development. It is stored and passed on to generations and is in dynamic equilibrium with the environmental and other non-living factors. The most predominant environmental stimuli are diet/nutrition. Diet/nutrition interacts and modulates varying underlying molecular mechanisms central to various physiological functions basically at three different levels: genome, proteome, and metabolome. Advances in genomic studies are paving the way to the development of scientific insights into nutritional sciences. Nutrigenetics and nutrigenomics are closely associated but two different areas of nutritional research. Both the fields involved the study of the implication between nutrition, metabolism, and genetic mechanism. The primary goal is to pinpoint nutrient-dependent health characteristics and nutrition dependent diseases. Another important area connected to these sciences concerns food composition and performance of quality assessment by studying proteomics and metabolic pathways. Nutrigenomics explains how the nutrients influences or effects the expression of the, while the response of different gene variants to nutrients or different dietary components is called Nutrigenetics. A personalized based diet can help us to know the right nutrient to take or avoid those who may potentially harm overall health. The goals are intended to alter or decrease the impact of hostile dietary changes that have occurred in since past in the developed world and more recently in the developing countries.

Keywords: Genome; metabolome; proteome; nutrigenetics; nutrigenomics.

INTRODUCTION

Etiopathogenesis of any disease is because of the interaction of genetics and the environment. Genetics defines the susceptibility of an individual to disease whereas environmental factors determine who among this susceptible will develop the disease.

One in five deaths globally is related to a poor diet. Diets high in sodium, low in whole grains and fruits have attributed to quite half of diet-related deaths globally in 2017, which incorporates 10 million deaths from cardiovascular disease (CVD), 913000 cancer death, and 339000 from Type2 Diabetes Mellitus (T2DM; 1). The burden of chronic diseases is increasing very rapidly throughout the world. In 2001 it contributed 60% of 56.5 million total reported deaths within the world which is nearly 46% of the worldwide burden of disease. This burden is expected to increase to 57% by 2020. Not only these chronic diseases like CVD, obesity, T2DM are in increasing trend but they have also started to appear much earlier in life. On a global basis, 60% of the burden of chronic diseases will occur in a developing country (2).

The amount of energy consumed with physical activity and quality of food (high in energy- sugar, starch, and or fat and low in essential nutrients) are the key determinants of nutrition-related chronic diseases (3). India is facing a burden of two divergent groups of diseases. On one hand, cardiovascular conditions are classically associated with overnutrition and on the other hand, diarrheal diseases and lower respiratory tract infections are associated with undernutrition (4).

Diet/nutrients are considered the most influential environmental stimuli. Though roots of nutrition are entrenched in centuries but with the advancement of modern sciences we have realized that nutrients are not only essential, but the specific quantity of each nutrient is necessary for optimal health. The development of molecular techniques and nutritional research has helped in our understanding of diet and its effect on health status.

The twentieth century has helped in a basic understanding of macro and micronutrients. One-size fits all approach and plans like My plate and Food Guide Pyramid was epitomized and was quite helpful in reducing malnutrition and diseases of nutritional deficiency. Genome-wide association study (GWAS) showed many genetic variants in association with specific nutrition related traits and are responsible for many diet gene interactions and the development of many human diseases. Several components of diet combined with the impact of diverse genetics affects the metabolism of many nutrients and can result in harmful diet gene interaction (5).

Response of the individuals to different lifestyle interventions like dietary, physical activity, alcoholism is different specifically those modulating the diet because the genetic variants influence nutrient absorption, metabolism, and utilization. Dietary reference intake values like Recommended Dietary Allowances (RDA) and other dietary reference intake values like safe upper limits established by the food and nutrition board of the National Academy of

medicine are specifically based upon the population rather than being individualized or for a group of individuals. But advances in personalized nutrition, precision nutrition, nutrigenetics dealt with individual-based tailored diets (6).

Nutritional research has led us to find our relationship between the genome and diet, currently termed nutritional genetics. It is a combination of two different areas of research that is nutrigenomics and nutrigenetics. Though both are intimately associated with each other, the basic approach to understanding the relationship between gene and diet are different.

The goal of nutritional research is basically to identify individuals who benefit from nutritional interventions and identify alternatives for those who do not respond to it. This is helpful both for the prevention and treatment of chronic diseases by adjusting dietary interventions with the genetic makeup of the individual (7).

There is direct impact of nutrients upon health by directly affecting the expression of the genes involved in regulation of various important metabolic pathways (8). Nutrigenomics describes how our gene interacts with nutrients. It helps in the establishment of diet gene interaction and identifies beneficial or detrimental effect of diet. It has facilitated for better understanding of the nutritional effect on the metabolic pathway and their relationship to diet related diseases. Clarification has been made regarding etiological perspectives of chronic diseases like Type 2DM, Obesity, and CVD (9).

Nutrigenetics has its roots within classical genetics and applies to the interaction of nutritional and genetic factors and their role in disease etiology. Personalized nutrition helps us to modify the diet based upon their genotype, so it will help in giving dietary advice that is more specified to a particular individual and will be more effective in preventing chronic diseases and improving health.

Our understanding of the human genome has progressed at an expeditious rate with the sequencing of a eukaryotic genome. Of the genes known so far 97% of human disease is because of monogenic diseases for example – galactosemia, phenylketonuria, etc. Modification in the consumption of certain dietary factors can prevent some of these monogenic diseases. Galactosemia arises due to recessive trait in galactose -1-phosphate uridyl transferase leading to accumulation of galactose in blood. Galactose free diet is the means to treat them nutritionally (10). Diseases like cancer, obesity, diabetes, and CVD which have reached epidemic proportions are polygenic diseases. Hence, dietary intervention in these diseases is complex and knowledge regarding diet and nutrition and their interaction modulating biological system is very much essential. Advances in genomic sequencing have helped us to find out the interrelationship

between genetic and epigenetic signatures with environmental factors like physical activity and its role in individuals' phenotypic expression (11). With the development of genomic sequencing and high throughput “omic” technologies, a better understanding is gained regarding the interaction of nutrients and genes depending on the genotype of an individual with the goal of optimal health and disease prevention (12).

Relationship between nutrigenetics and nutrigenomics

These nutritional sciences are defined as the effect of genetic variations on dietary response and the role of nutrients and bioactive compounds in gene expression (13).

Greater variance exists between the inherited genome of different ethnic groups and individuals this leads to difference in nutrient bioavailability and metabolism. Difference also exists in nutrient choices and nutrient availability based upon economic, geographical, cultural preferences and taste perception. Nutritional deficiency or excess also affects the expression of the genes and its stability, leading to mutations causing adverse phenotype (8). These factors have now led to nutrigenetics and nutrigenomics as an important science. Both nutritional studies hypothesizes that nutrition exerts its impact by directly affecting the expression of the gene involved in metabolic pathways and indirectly leads to genetic mutation. Genetic variation in nutrient uptake and its metabolism are mainly responsible for varied health effects of nutrients. Interaction of enzymes with nutrient cofactors and hence affecting the biochemical reaction, so by considering the inherited and acquired genetic characteristics better health outcomes can be accomplished.

Though Nutrigenetics and nutrigenomics are closely related to each other they deal with two different fields of research. Nutrigenetics specifically deals with the effect of inheritance in nutrition-related genes modifying the micronutrient uptake and the metabolism whereas, the field of nutrigenomics deals with multiple disciplines like the effect of diet on DNA damage at molecular and chromosomal level, epigenomic alteration, RNA and expression of micro-RNA, expression of protein, and metabolite changes. These independently or in a combined manner can help diagnose health status and reflects modifiable homeostatic response to change in nutritional exposure (14).

Nutrigenomics has helped us to identify new biomarkers for nutrition-related diseases and helped us to incorporate various diagnostic proprieties disease stage specific nutritional intervention or therapeutics. The study of the expression profile helped us to develop a biomarker which can help us to monitor the efficacy of the nutritional interventions.

Nutrigenomic research has given us knowledge regarding genes and molecular pathways in the pathogenesis of various diseases and helped us to bring forth a novel strategy for the prevention and progression of the disease. It has also helped us to develop functional foods to normalize the pathogenic gene expression profile. These functional foods or nutraceuticals play a role in disease state optimizing health and preventing disease (15).

Response to nutrition is managed by multigenic processes. Individuals respond differently to various nutrients. This is because of genetic variations. Nutrigenetics explains to what extent nutrition-related traits and disorders are influenced by genetic variation and the molecular basis behind it. The researcher in the “hypothesis-driven approach” tests the candidate genes for a trait or disorder and searches in those genes for sequence variation followed by association or linkage study. In another approach “holistic” search for genes responsible for risk of certain diseases for certain traits or disorders is found by total genome scan. Even there are extensive data on genetic polymorphism in human it was found its translation into medical practice is low because time is required to accumulate population data on single nucleotide polymorphism incidence. Examples of these SNP for the applicability of nutrigenetics are C 677 T cytosine to thymidine substitution resulting in a valine to alanine switch and A 1298C with adenine to cytosine substitution resulting in a glutamic acid to alanine switch in methylenetetrahydrofolate reductase (MTHFR) gene. This reduces MTHFR activity causing an increase in concentration of homocysteine in plasma. This increases the risk factor for neural tube defect, venous thromboembolic diseases, and ischemic heart disease. Folic acid supplementation helps to overcome negative health effects (16,17).

Potential genes related to obesity, leptin and leptin receptors, melanocortin 4 and 5 receptor genes and genes for neuropeptide Y, if mutation seen related to these genes dietary restrictions or interventions based upon nutrigenetic study is started early in life can combat obesity (18).

Genetic basis of nutrigenetic diseases and dietary influences

99.9% of our gene sequences are identical with only 1% variation, which is responsible for phenotypic differences, the susceptibility of an individual to the disease. Single nucleotide polymorphism (SNP) is the most common type of polymorphism characterized by replacement of one nucleotide base with another. SNPs can alter the nutritional requirement and nutrient metabolism by affecting the synthesis and function of various proteins. Similarly, genetic variations through structural DNA changes for example insertions or deletions, translocation, and copy number variants also play important role in human health (19,20). Research works investigating various genetic variants

with obesity risk and it's resistance to weight loss have clarified various molecular mechanisms involved in obesity. FTO gene (fat mass and obesity-associated) has two copies of common FTO variants are found in 60% of the individual way around 3 kg more than non-carrier and have 1.67fold increased risk of obesity (21). Variance in genes needed for the metabolism of lipids, for example, Lipoprotein lipase, Cholesteryl Ester Transfer Protein, LDL receptor, and apolipoprotein E increases the risk of coronary artery diseases (22). Disease risk can be reduced in a better way by dietary advices based upon the knowledge of genetic information compared to genetic counselling. New advances in technology like next-generation sequencing provides a rapid scan of these genetic variants between these individuals. Multiple variants can be scanned regarding effect on the function of a particular gene or multiple genes which may be responsible for the development and progression of disease (23). Through nutrigenetics, scientific advances are possible to predict individual risk for a particular disease, explain the aetiology behind the disease, and enabled personalization in nutritional management which in turn contributed to the prevention and treatment of chronic diseases. SNPs have been associated with common chronic diseases through interaction with intakes of micro or macronutrients. Genes regulating homocysteine like MTHFR and methionine synthase (MTR) have been linked to increase the risk for breast cancer in individuals who take low intake of folate, B6 & B12 (24). Genetic risk scoring has also been used in certain studies where they have examined the cumulative effect of SNPs on diet interaction and disease susceptibility. Augustench *et al.*, in their study found that micronutrient intake modifies the association of obesity genetic risk score (GRS) with greater values of adiposity (25). Similarly, lower GRS for type 2 DM had greater improvement in insulin resistance and beta-cell function by consumption of a low protein diet (26). SNPs have also been included in various nutrigenetic tests to evaluate their impact on changing an eating habit. It was seen that disclosure of genetic information (gene based personalized nutrition) was more useful compared to general population-based dietary advice, for example when genetic information was disclosed regarding Angiotensin 1 converting enzyme (ACE), personalized nutrition brought about marked change in intake of sodium compared to general population-based dietary advice (27).

Nutrigenetics helps in identifying individuals who are a risk for alcohol dependence. Alcohol dehydrogenase 1B (ADH1B) encodes the protein involved in the first step of alcohol metabolism in the liver. Polymorphism has been identified in this gene. Heterozygous A/G and/or homozygous (A/A) carriers of a mutant allele from either SNP increase the risk of ethanol metabolism, resulting in a reduced rate of alcohol consumption and decrease dependence (28).

Effect of diet on gene expression profile

Nutrients directly or indirectly influences the gene activity by regulating the role of signalling pathway, or by acting as a ligand for transcription factors. Therefore, Nutrigenomics illustrates how dietary factors influence gene expression and affect the amount of protein and metabolites. Study in nutrigenomics involves gene expression analysis and biochemical profiles (29). Many studies have evaluated so far, the effect of a different dietary factor on gene expression profile associated with disease susceptibility. Individuals subjected to western dietary patterns with high refined grain products, desserts, sweet, processed meat resulted in a gene expression profile related to inflammatory response and cancer signaling (30). Similarly, a diet rich in high fat specifically saturated fatty acid induces gene expression profiles associated with inflammation, glucose intolerance, accumulation of lipid in the liver, and upregulation of neuropeptide expression (31). Choline and folate-deficient diet results in dysregulation of the gene in lipid metabolism increasing the susceptibility to Non-Alcoholic Fatty Liver Disease (NAFLD; 32). Beneficial effects are also seen in some studies regarding nutrient and bioactive food compounds and regulation of critical gene expression. High intake of MUFA is associated with low expression of a gene involved in inflammation and abnormal lipid storage. PUFA regulates the expression of the neuropeptide gene involved in energy homeostasis (33). Bioactive food compounds like theaflavin (Black tea), curcumin (turmeric), resveratrol (Grapes and red wine), genistein (Soybean) exerts anticancer properties by upregulation of tumor suppressor gene and downregulation of tumor promoting genes (34).

In the cancer cells there occurs altered metabolism to take care of its uncontrolled growth. Omega-3 & 6 PUFA differentially influence gene expression linked to inflammation, (example: TNF- α , IL-1 β , IL-6, IL-18), angiogenesis (VEGF, PDGF, IGF-1, MMP-2) and proliferation (example- cyclin, P53, Wnt, PTEN and, hence controlling tumorigenesis (35).

Detrimental diet gene interaction alongside environmental, biological, and genetic components due to alteration in the exposure of a particular nutrient may bring about several unfavorable outcomes. This was specifically observed when there was a marked shift in fatty acid exposure from saturated fatty acid (SFA) to PUFA to lower total cholesterol and LDL. It increased Linoleic acid LA (w 6) exposure with w3 and alpha-linoleic acid (ALA) being constant causing an altered ratio of dietary w6: w3 increasing from 2:1 to > 10:1. This change resulted in enhanced inflammation and inflammation-related disorders (36). Epigenetic alterations also are important ill effects of some diet- gene interaction. Epigenetics has

been defined as an inheritable and reversible process that can regulate gene expression with no concomitant change in the DNA coding sequence. One of the important epigenetic alterations like methylation of DNA in and around promoter region resulted in suppressed gene transcription. The complex interaction of nutritional factors with DNA methylation, covalent histone modification, and noncoding RNA including micro-RNA have been suggested in obesity, dyslipidemia, Type 2 DM, NAFLD, Cancer, and CVD (36). A low protein diet induces glucose and protein alteration by changes in NRIH-3 acetylation causing histone modification and hence increasing the Type-2 DM risk (37). Deficiency in choline and folate results in mi-RNA changes and causing progression to NAFLD (38). Vit- D, calcium, magnesium deficiencies result in changes in DNA methylation patterns of NF κ B1A, HSD 11B1, HSD 11B2 genes causing a potential risk of Type 2 DM (39,40).

The nutritional intervention has also been done aiming at revering these epigenetic changes. A Mediterranean diet specifically results in hypermethylation of proinflammatory genes with the potential health effects of being anti-inflammatory (41). Diet-epigenetic modification have also helped in the nutritional treatment of various diseases by changes in various metabolic profile.

Prospects

It is now increasingly evident that nutrigenetics and nutrigenomics are taking the future stage of nutritional research on health outcomes via various “omic” technology and biomarkers. Although some of the innovations are recent and distinct in their validation status for health results, these studies are now bringing us new insights and becoming increasingly obvious.

Nutrigenetics is a rapidly developing budding field and is riding on the wave of personalized medicine that offers many opportunities for nutraceuticals to grow.

Specific nutraceuticals targeting specific metabolic sites by the various nutrigenetic study can be developed. Future study may differentiate which component or combination of components can produce a particular molecular effect by modulation of a biological process that plays a critical role in tumorigenesis, protein metabolism, intra cellular protein trafficking, and protein phosphorylation modulating various cancer prognosis. There can be the integration of pharmacogenomics with nutrigenomics and can be applied for the prevention of various diseases by individual prescription and lifestyle modification. Gene-based designer diet can be developed various chronic and inflammatory diseases, for example, Coronary artery diseases, Type-2 DM, asthma, etc., These nutritional studies help to discover different genetic variants for diseases that have a

genetic predisposition, which can help improve dietary advice for prevention and management in addition to age, gender, health status, ethnicity, and all other characteristics that affect dietary responses.

We can predict the responsiveness of a particular population to nutrient and drug intervention. As responses between individuals to dietary changes differ even within the genetic subgroup, it is necessary to combine nutrigenetic-based advised with “omic” biomarkers to check if the personalized recommendation produces expected nutritional change and health benefit. Better interpretation of data from epidemiological and clinical interventional studies regarding health impact of dietary factor may further help us to revise recommendation for personalized nutrition.

CONCLUSION

Genomic and epigenomic processes may not entirely account for the ability of dietary factors to influence phenotypic changes as rate of transcriptomics can also lead to various cellular processes. Multiple pathways including genomic and epigenomic processes, transcriptomics etc., may be responsible for the ability of the dietary factors to cause various disease processes. Knowing these pathways by “omic” profiling may provide us with various important clues regarding individual based disease risks. Hence, extensive study on nutrient-gene interaction and their phenotypic influence are needed to recognize and prioritize various dietary interventions. Knowledge of the individual genome via sequencing and various new emerging techniques have generated interest in the field of personalized medicine. Replication and validation of these nutrigenomic and nutrigenetic studies is a priority before personalized nutrition is implemented improving human health. There is need of appropriate translation of these nutritional research to effectively implement dietary strategies to improve health. Various largescale initiatives and programs are needed to complement the requirements. Strengthening of nutritional sciences by creating reliable bank of polymorphism, development of new bioinformatics tool for analysis of data and identification of valid biomarker.

Limitations

Genetic tests and its interpretation, assessment of disease susceptibility based on test result and formation of basic components of nutrigenetic research, all raises serious ethical and legal issues. As there is translation of in vitro studies of cultured cell, tissue specific cell lines, the result obtained should interpreted with care or tested for their relevance. As the results obtained from animal studies cannot be translated directly to human, some of the scientists even argued that human should be the main subject for this research. Public acceptance of these technologies is influenced by estimation of benefits and costs, or

risk involved. Legal issues may arise as there is utilization of genetic information of an individual. So, implementation of these personalized goals basically is collective effort by the scientific committee, analysis, data storage and the individual and sound strategy, useful databases can be generated for clinicians and dietetic practitioner.

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CONFLICT OF INTEREST

Authors do not have any conflict of interest.

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