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Importance of nutrigenomics in human health: A review

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Abstract
Due to changes in lifestyle and food habits, people are more at risk of diet-related diseases. It is also established that dietary modifications significantly reduce the risk of diseases. Nutrigenomics is relatively fresh discipline, but possess an enormous potential that can apply for prevention and management of certain carcinomas and diseases. It influences health conditions of individuals and susceptibility of disease by defining the metabolic response and gene expression. Certain bioactive food compounds have a proven role in cancer prevention through an epigenetic mechanism. Dietary polyphenols substantially take part in prevention of oral, breast, skin, oesophageal, colorectal, prostate, pancreatic and lung cancers. Moreover, minerals and vitamins involve regulatory processes. Zinc, Selenium and folate involve in DNA repairing process have anticancer properties. Consumption of multivitamins prevents methylation of cancer cells. Nutrigenomics seeks to provide a genetic understanding for how common dietary chemicals (i.e., nutrition) affect the balance between health and disease by altering the expression or structure of an individual's genetic makeup. Nutrigenomics is establishing the effects of ingested nutrients and other food components on gene expression and gene regulation. It will also determine the individual nutritional requirements based on the genetic makeup of the person i.e. personalized diet.

Keywords: Lifestyle disease, carcinoma, personalized diet, nutrigenomics.

Introduction
It is well established that everyone responds to the same dietary treatment differently. Disparities in the likelihood of getting diseases may be due to genetic differences. All humans are 99.9 % identical at gene level, generally 0.1% variation in sequence produce differences in phenotype (Nicastro *et al*., 2012) [18]. Individual genetic variation manipulates how nutrients are assimilated, metabolised, stored and excreted by the individual body (Reen *et al.*, 2015) [19]. Single nucleotide polymorphism (SNP) accounts for over 90 per cent of all human genetic diversity, people contain between 5 million to 8 million SNP (Nicastro *et al.*, 2012) [18]. Food and nutrients affect genome evolution mutation hence susceptibility to a particular disease. A healthy diet provides ligands (special molecule) that turn on disease fighting gene and turn off those that cause disease.

Fenech originated the concept of "genome health nutrigenomics," the science of how nutritional deficiency or excess can cause genome mutations at the base sequence or chromosomal level. It includes nutrigenetics, epigenetics, and transcriptomics as well as other omic disciplines like proteomics, and metabolomics to explain vast disparities in same disease among people with roughly similar lifestyle (Mead, 2007) [25]. "The main goal of this particular research discipline is to define the optimal dietary intake and tissue culture medium concentration to maintain damage to the genome at its lowest (Fenech, 2007) [15]

"The studies that follow the effect of a certain diet often disregard the possible effect of genetic variability within the studied cohort, on the other hand, some studies analysing the effect of candidate gene polymorphism on the studied trait (for example blood pressure, obesity) do not include the diet interference, which can dramatically influence the resulting association. Nutritional genomics aims to resolve this evident discrepancy (Miggiano *et al*., 2006) [17].

Pharmacogenomics is the nutritional genomics which focuses on the phytochemicals found in regular food and how those substances affect the balance between health and disease via the interaction with the individual's genome (Srivastava *et al.*, 2022) [21].

This discipline nutrigenetics and nutrigenomics hold much promise for providing better nutritional advice to the public generally genetic subgroup and individuals.

It is often difficult for professionals to appreciate their relevance to the practice of preventive approaches for optimising health and delaying onset of diseases and diminishing its severity. So in this review the basic knowledge was conceptualized for its application in the optimization of health and treatment of disease.

Conceptual Framework

A nutrient is not merely a chemical component required for a particular metabolic function, but also that it plays an informational or signalling role in the cell which reveals following phenomenon.

a) Effect of dietary bioactive compounds on gene expression
b) The pathway of genetic action influenced by nutrient intake
c) Effect of nutrients on genes to prevent and treat diseases
d) Molecular relationship of genes and nutrient (Kaput, 2005) [13]

Fenech and his colleague identified nine key nutrients that may affect genomic integrity in various ways when consumed in increasing amounts in food, six of these nutrients (folate, vitamin B12, niacin, vitamin E, retinol, and calcium) are associated with a reduction in DNA damage, whereas three others (riboflavin, pantothenic acid, and biotin) are associated with an increase in DNA damage to the same extent observed with occupational exposure to genotoxic and carcinogenic chemicals. "These observations indicate that nutritional deficiency or excess can cause DNA damage on its own and that the effects are of the same magnitude as that of many common environmental toxicants (Mead, 2007) [25]

These are five basic principles of nutrigenomics (German, 2005) [12]:

1. Substances contained in the food (micro- and macro-nutrients) can directly or indirectly affect the human genome through changes in its structure and gene expression.
2. Under certain circumstances and in some individuals the diet can be an important risk factor for the development of the number of diseases.
3. Some genes regulated by active substances in the diet probably play a crucial role in the onset, incidence, progression and severity of the disease.
4. The degree to which diet influences the balance between health and disease may depend on individual's genetic makeup.
5. Nutritional intervention is based on the knowledge of individual's nutritional status and needs as well as genotype (individualized nutrition) and can be used for prevention, mitigation or healing the chronic diseases.

Mechanism of action

Cellular proteins that receive and transmit information are termed "receptors." The receptors then must relay this information via a transducing mechanism to the part of the cell that is capable of reprogramming the cell to adapt to the new environmental conditions. This reprogramming can occur in the cell nucleus or cytoplasm. It can involve changes in the expression of genes (transcription and translation), the stability of messenger RNA and protein, or the activity of proteins. The key principle behind nutrient control of gene expression is specificity. Each receptor must have the capability of binding a nutrient-signalling molecule with specificity and should initiate an adaptive change. It is reported that until recently, the regulation of gene expression in response to changes in nutritional environment was thought to be mediated primarily by hormones and/or the nervous system. However, the last decade has provided evidence that major (glucose, fatty acids, and amino acids) or minor (e.g., iron, vitamin) nutrients, or their respective metabolites, regulate gene expression in a hormone in dependant manner (Walker, 2004) [1].

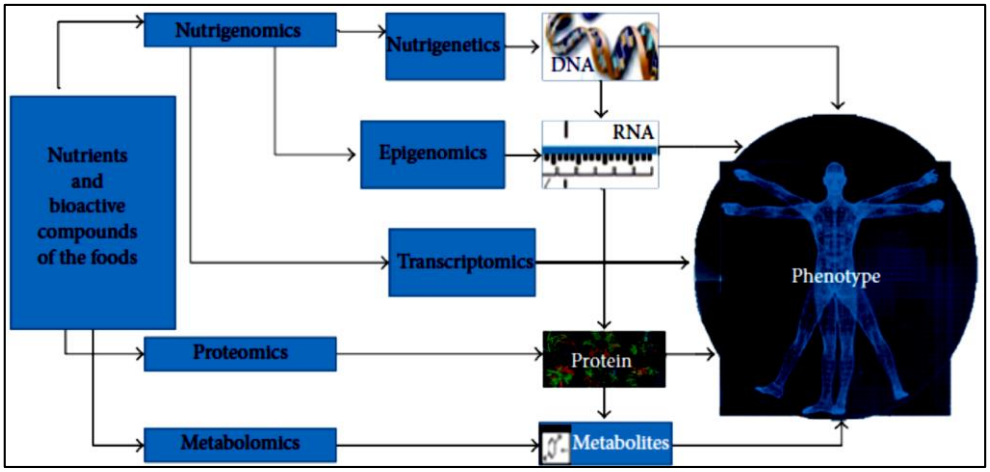

Fig 1: "Omics" sciences used in understanding the relationship between nutrition versus health versus disease (Adapted from Sales *et al.* (2014) [20], Lorenzo (2008) [14], Costa and Rosa (2011) [6].

The nutritional state of an individual is the result of the interaction between various factors, such as genetic background, physical body, and emotional and social state (Costa and Rosa, 2011, Damiel, 2012) [6, 7]. Diet is a key role factor, once those nutrients and other bioactive compounds present in food can either be beneficial or initiate several diseases (Liew and Qian, 2011) [3]. Among the illnesses related to food consumption, there are the celiac disease, phenylketonuria, and NTCDs (Non Transmissible Communicable Diseases) such as cancer, diabetes, and dislipidemies (Damiel, 2012) [7]. In this way, the health state of a person will depend on the interaction between their genes and their food (Liew and Quian, 2011) [3].

Nutrients Genes Interactions

Glucose also has been shown to play a key role in transcriptional regulation (Reen *et al.*, 2015) [19]. It is the most abundant monosaccharide in nature, provides a very good example of how organisms have developed regulatory mechanisms to cope with a fluctuating level of nutrient supply. In mammals the response to dietary glucose is complex because it combines effects related to glucose metabolism itself and effects secondary to glucose-dependent hormonal modifications, mainly pancreatic stimulation of insulin secretion and inhibition of glucagon secretion. In the pancreatic - cells, glucose is the primary physiological stimulus for the regulation of insulin synthesis and secretion. In the liver, glucose, in the presence of insulin, induces expression of genes encoding glucose transporters and glycolytic and lipogenic enzymes. Although insulin and glucagon were long known as critical in regulating gene expression, it is only recently that this function of glucose has been recognised.

Dietary fats: Fatty acids, in addition to their important role as energy-yielding nutrients, may exert a significant influence on the regulation of gene expression (Jump *et al.*., 1999). At the cellular level, the physiological response to fatty acids will depend on: (a) The quantity, chemistry, and duration of the fat ingested; (b) Cell-specific fatty acid metabolism (oxidative pathways, kinetics, and Competing reactions); (c) Cellular abundance of specific nuclear and membrane receptors (d) Involvement of specific transcription factors in gene expression. Nutrients impact gene expression mainly by activating or suppressing specific transcription factors (Desvergne *et al*., 2006) [8]

PUFA: Lipogenic enzymes in liver decreased as result of feeding a diet containing 60 % linoleic acid (Flick *et al*., 1977). Fatty acids stimulated the expression of adipocyte fatty acid binding protein. Adipocyte cell line, arachidonic acid (n-6) decreased m RNA stability in a dose dependent manner (80% maximum repression), as did linoleic and eicosapentanoic acids.

Protein: Protein is very essential for growth, to develop immunity, normal maintenance of body function and structure apart from reproduction and production. The function of protein in body is not only at macro level but it also functions at gene level. A variety or number of genes responds to dietary protein both protein quantity as well as quality influences gene expression. Insulin secretion was reduced in rats, which are fed with low protein diet (Reen *et al.*, 2015) [19].

Feeding low protein diet decreases insulin level, it also acts through decreased movement of intracellular calcium. They or their derivatives function as coenzymes, cellular antioxidants, and/or regulators of gene expression. Various vitamins are recognized in human nutrition (Vitamins A, D, E, K, B1, B2, B6, B12, C, niacin, folacin, pantothenic acid, biotin, choline), with deficiencies or excesses in intake leading to changes in protein, nucleic acid, carbohydrates, fat and/or mineral metabolism. Thus, the integrity of physiological systems, including those associated with detoxification, cellular repair, immune processes, and neural and endocrine function, depends upon the nutritional and vitamin status of the host. For these reasons, it may be anticipated that the adequacy of the vitamin supply to cells and tissues would affect the development, progress and outcome of cancers. Suboptimal intakes of specific micronutrients have been associated with CVD (B vitamins, vitamin E, carotenoids), cancer (folate, carotenoids), neural tube defects (folate), and bone mass (vitamin D) (Fairfield *et al*., 2002) [10].

B6, B12, serum homocysteine levels. Hyperhomocysteinemia is a risk factor and marker for coronary artery disease, but the mechanism(s) is not understood at the molecular level (Falk *et al*., 2001). Deficiency of vitamins B12, folic acid, B6, niacin, C, or E, or iron or zinc appears to mimic radiation in damaging DNA by causing single- and double-strand breaks, oxidative lesions, or both (Ames, 2001) [2]. Nutrient deficiencies are orders of magnitude more important than radiation because of constancy of exposure to milieu promoting DNA damage (Ames, 2001) [2].

Zinc is an essential trace element with cofactor functions in a large number of proteins of intermediary metabolism, hormone secretion pathways and immune defence mechanism. It is involved in regulation of small intestinal, thymus and hepatocytes gene expression. (Tako *et al*., 2003) [3]. Biotinylation of histones appears to play a role in cell proliferation, gene silencing, and the cellular response to DNA repair (Zempleni, 2005) [24].

Vitamin A dependent enzyme involved in conversion of oxaloacetate to phosphoenolpyruvate, one of the important steps in gluconeogenesis. Vitamin A deficiency condition leads to changes in chromosomal structure of RARE (Retinoic Acid Responsive Element), which further leads to change in co regulator binding and activity (Reen *et al.*, 2015) [19].

Nutrigenomics offers the potential of important health benefits for some individuals. Primary care physicians have minimal training in nutrition and genetics, and medical geneticists are in high demand and short supply. Dietetic practitioners are experts in nutrition science and interest in nutrigenomics is growing among members of this professional group. However, as with physicians, dietetics practitioners would require considerable training to bring nutrigenomics into their practice capacity (Castle and Ries, 2007) [5].

Advanced genetic analysis in combination with twin studies may provide opportunities to understand the basis of complex traits and the role of individual genotypes on the development of polygenic diet-related diseases such as cancer and CVS (Boomsma *et al*., 2002) [4].

Thus nutrigenomics treats food as a major environmental factor in the gene–environment interaction, with the final aim to personalize food and nutrition and ultimately individualize strategies to preserve health, by tailoring the food to individual genotype (Iacoviello *et al*., 2008) [26]

But today's biologists concede that neither nature nor nurture alone can explain the molecular processes that ultimately govern human health. The presence of a particular gene or mutation in most cases merely connotes a predisposition to a particular disease process. Whether that genetic potential will eventually manifest as a disease depends on a complex interplay between the human genome and environmental and behavioral factors. This understanding has helped spawn numerous multidisciplinary gene-based approach (Srivastava *et al.*, 2022) [21]

Genes are critical for determining function, nutrition modifies the extent to which different genes are expressed and thereby modulates whether individuals attain the potential established

by their genetic background. Therefore nutrigenomics is concerned with the impact of dietary components on the genome, the proteome (the sum total of all proteins), and the metabolome (Sales, 2014) [20]. As in pharmacogenomics, where a drug will have diverse impacts on different segments of the population, researchers recognize that only a portion of the population will respond positively to specific nutritional interventions, while others will be unresponsive, and still other could even be adversely affected. Macronutrients (e.g., fatty acids and proteins), micronutrients (e.g., vitamins), and naturally occurring bioreactive chemicals (e.g., phytochemicals such as flavonoids, carotenoids, coumarins, and phytosterols; and zoochemicals such as eicosapentaenoic acid and docosahexaenoic acid) regulate gene expression in diverse ways. Many of the micronutrients and bioreactive chemicals in foods are directly involved in metabolic reactions that determine everything from hormonal balances and immune competence to detoxification processes and the utilization of macronutrients for fuel and growth. Some of the biochemicals in foods (e.g., genistein and resveratrol) are ligands for transcription factors and thus directly alter gene expression. Others (e.g., choline) alter signal transduction pathways and chromatin structure, thus indirectly affecting gene expression.

Nutritionists have long understood that the optimal requirements for many nutrients fall within a range between deficiency and toxicity. In an environment of vitamin fortification and supplementation, (Fenech, 2007) [15]

Defining the optimal concentration of micronutrients required to maintain cells in a genomically stable state remains one of the main challenges for nutrigenomics researchers. This challenge becomes magnified in the context of requirements for diverse genetic backgrounds (Mead, 2007) [25].

There are thousands of DNA alterations in each human cell daily; if not efficiently repaired, our genome would rapidly be destroyed. Diet and lifestyle are major mediating factors in this equation. For example, DNA damage is accelerated by oxidative stressors such as tobacco smoke, strenuous exercise, and a high-fat diet, according to a study in the September 2002 issue of Carcinogenesis. On the flip side, diets low in fat and/or high in cruciferous vegetables have been shown to lower the oxidative DNA damage rate in humans (Fenech, 2005) [16].

All diseases can be reduced to imbalances in four overarching processes: inflammatory, metabolic, oxidative, and psychological stress. Diseases arise because of genetic predispositions to one or more of these stressors. Nutrigenomics represents a major effort to improve our understanding of the role of nutrition and genomic interactions in at least the first three of these areas, says Kaput (Mead, 2007) [25]

It has been shown that genetic factors determine susceptibility to disease and environmental factors determine which genetically susceptible individuals will be affected. Nutrition is an environmental factor of major importance.

Conclusion

Genetically speaking, humans today live in a nutritional environment that differs from that for which our genetic constitution was selected. Nutrigenomics is the science which helps to understand the role of nutrients gene interaction which ultimately affects the progression of disease in an individual. Diet has certain functional bioactive components which influence at molecular level. A high omega-6/omega-3 ratio, as is found in today's diets, promotes the pathogenesis of many chronic diseases, including cardiovascular disease, diabetes, asthma, and possibly cancer. Increased dietary intake of linoleic acid (LA) leads to oxidation of low-density lipoprotein (LDL), platelet aggregation, and interferes with the incorporation of essential fatty acids (EFA) in cell membrane phospholipids. Both omega-6 and omega-3 fatty acids influence gene expression. Omega-3 fatty acids have strong anti-inflammatory effects, whereas omega-6 fatty acids tend to be pro-inflammatory. Because inflammation is at the base of many chronic diseases, including coronary heart disease, dietary intake of omega-3 fatty acids plays an important role in the manifestation of disease. The diet-gene interaction further suggests that dietary omega-6 fatty acids promote, whereas marine omega-3 fatty acids EPA and DHA inhibit inflammation that leads to atherosclerosis.

Chronic diseases are multifactorial, it is quite possibly that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. Knowing who is at risk would be useful if it meant that one could avoid the environmental triggers that convert susceptibility to disease. The prospect of targeting specific dietary treatment to those predicted to gain the most therapeutic benefit clearly has important clinical and economic consequences, particularly in diseases of high prevalence such as coronary artery disease, hypertension, diabetes, osteoporosis, and possibly cancer. There is no single universal approach for what we are calling the "lifestyle" approach to diseases with genetic predisposition. Therefore, it will be necessary to promote lifestyle patterns that will be compatible with a healthier phenotypic expression of genotypes evolved under different conditions, which means individualized prescriptions and gene-based designer diets

Nutrigenomics therefore initially referred to the study of the effects of nutrients on the expression of an individual's genetic makeup. More recently, this definition has been broadened to encompass nutritional factors that protect the genome from damage. This particular research discipline defines the optimal dietary intake and tissue culture medium concentration to maintain damage to the genome at its lowest.

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