PART V:
Public health

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Nutrigenomics: Use of personalized diet to prevent the onset of disease and optimize human health

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ABSTRACT

Purpose: Providing an insight into the nutrigenomics research concentrating on Europe for bringing: (1) Public understanding about changing food habits and lifestyle; (2) How nutrigenomics can contribute to making life healthier; (3) Support additional research in this area.

Methodology: Concentrating on Europe, a literature search on nutrigenomics was conducted by using different databases: PubMed, Web of Science, Science Direct, Springer, Scopus and views for the European Nutrigenomics Organisation (NuGO) reports, publications and newsletters.

Findings: Diet interrelates with the genotype to produce a phenotypical change. It has a significant effect on health and chronic disease. Functional genomic techniques could let the bioactivities of food ingredients to be described. Results showed the possibility of identifying gene polymorphisms, which predispose people to disease and adapt nutritional needs. Variances in genetic makeup (genotype) are causes in different diseases. Nutrigenomics explain why some people can control disease with diet, whereas others require drugs.

Practical implications: Training a new generation of European scientists to practice nutrigenomics.

Social implications: Enable targeting of nutritional advice and treatment to 'at risk' groups.

Originality/value: Nutrigenomics is expected to contribute significantly to personalized medicine.

Keywords: Nutrigenomics; Europe; Diet-gene Interaction; Personalized Nutrition

INTRODUCTION AND OBJECTIVES

Throughout the past few years, scientific and epidemiological research has specified numerous links among health plus nutrition. Relationships have been discovered between degenerative diseases and dietary habits. Examples of these diseases are cancer, cardiovascular diseases and type2 diabetes.

As traditional nutrition research focused on deficiencies of nutrients that affect health, it currently concentrates on improving health through diet. The relationship of unbalanced nutrient intakes with the development of chronic diseases demonstrates the direct effects of dietary substances on molecular genetic manners.

The complicated combination of foods with many distinctive constituents makes diet the highest efficient environmental element able to interact with the human biological system and molecular mechanisms. They do this by affecting the genotype to produce a phenotypical alteration, which make any disease related to nutritional constituents. Genetics might be directed to nutrigenomic examination so as to study the effect of dietary interference on the outcome.

Nutrigenomics is a subject that has definite methodologies to clarify the interaction between genes and the diet. It has a collective basic aim of improving health within diet personalization, and influential methods to unknot the complicated relationships concerning nutritional molecules and genetic polymorphism. The development of nutrigenomics has generated many opportunities of increasing the knowledge of the way that nutrients regulate expression of the gene and biosynthesis of protein metabolism.

The aim of the current review is to provide an insight on nutrigenomics, its definition, terminology, advanced experimental methods, and its effect on polygenic diseases. The present situation in nutrigenomics research, and its contribution in making life healthier by being the future for personalized nutrition for managing chronic diseases in Europe, is also discussed.

The review also describes the organizations, groups, networks and academic centres, in the field of nutrigenomics and activities related to nutrigenomics in EU programmes, and latest progress in nutrigenomics research. Ethical issues and expected benefits and nutrigenomics effects on health, dietary advising, commercial uses and business chances, and effect on Europe sustainability are discussed.

IMPORTANCE OF MOLECULAR NUTRITION

Knowing that nutrients are able to interrelate and regulate the molecular process underlying biological functions has stimulated an alteration in the nutrition field. The lack of genetic knowledge in nutritional epidemiological studies may result in inaccurate scientific conclusions and mislead nutritional recommendations. To avoid this, the nutrition field has initiated a focus on the technologies to bring out nutritional genomics. Nutrigenomics and nutrigenetics are the two main branches of molecular nutrition. Each branch has different approaches to clarify the genes and diet and interaction, but a shared final purpose to enhance health by the personalization of diets, giving influential approaches to clarify the complicated association between genetic polymorphisms and nutritional molecules (see **Figure 1**).

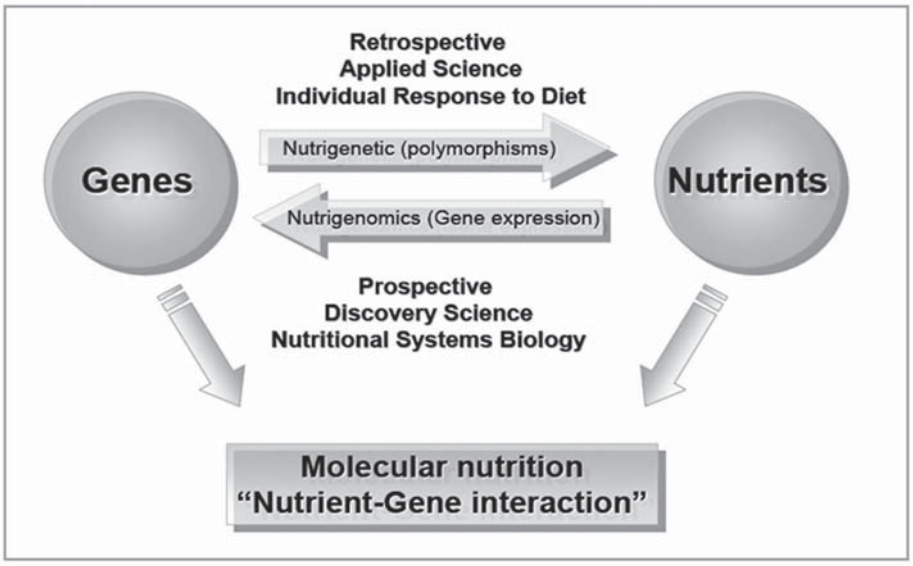

Figure 1 Nutrient – Gene Interaction

Source: Dikutip dari Gillies PJ, *J Am Diet Assoc.*, 103:S51

Nutrigenomics and nutrigenetics are the developing faces of nutrition that, when studied with more standard approaches, will provide the basic stepping stones to attain the determined goal of augmenting an individual's health through nutritional intervention (Mutch et al., 2005).

NUTRIGENOMICS

Nutrigenomics is a combination of the two words 'nutrition' and 'genomics'. It studies the connections of bioactive dietary constituents with regard to the genome. The word '"nutrigenomics'" was initially defined in 2001 by Peregrin (2001) and later in 2002 in a publication by Van Ommen and Stierum (2002). It targets the recognition of the impact of diet on an individual's healthiness and genes. Müller and Kersten (2003) reported that nutrigenomics challenges were to analyse the genome's broad effects on nutrition, recognizing the genes that affect the risk of diseases related to diet on a genome wide scale, and to recognize the ways that result in these genetic predispositions. Recently Sales *et al*. (2014) defined nutrigenomics as an emergent science that inspects a definite zone of nutrition that utilizes molecular tools to investigate, access and understand the numerous reactions gained through a definite diet applied between population and individual.

THE IMPORTANCE OF NUTRIGENO MICS

To identify the best diet from a sequence of nutritional choices and to communicate the resulting dissimilar phenotypes to changes in the genetic and cellular response of the living system which give analytically significant knowledge that will help clinicians to identify the ideal diet for a certain singular personalized diet (Mutch *et al*., 2005)

The opinions on the approaches and outcomes of using personalized medicine to patients stimulate the need for personalized nutrition, which is clearly seen at the end of the Human Genome Project. To date, there have been many areas in nutrigenomics that have not been examined comprehensively. Sales *et al*. (2014) emphasize that the metabolic process resulted in the gene response, which influenced people's health. Therefore the genotype and the nutrient (environmental factor) interaction should be studied in detail. Nutrigenomics defines the functional genomic tool used to investigate a living system's changes resulting from a nutritional stimulus, which will document an improved understanding of the way that nutritional molecules affect homeostatic mechanisms and metabolic pathways. Nutrigenomics studies the reaction of individuals to foods, dietary compounds and diets using various advanced 'omics' techniques, including proteomics, genomics, metabolomics and transcriptomics, to study the genome-wide effects of dietary compounds or nutrition on the proteomics, metabolomics and transcriptomics of organisms, cells or tissues at a known time, and its application for personalized nutrition (**Figure 2**).

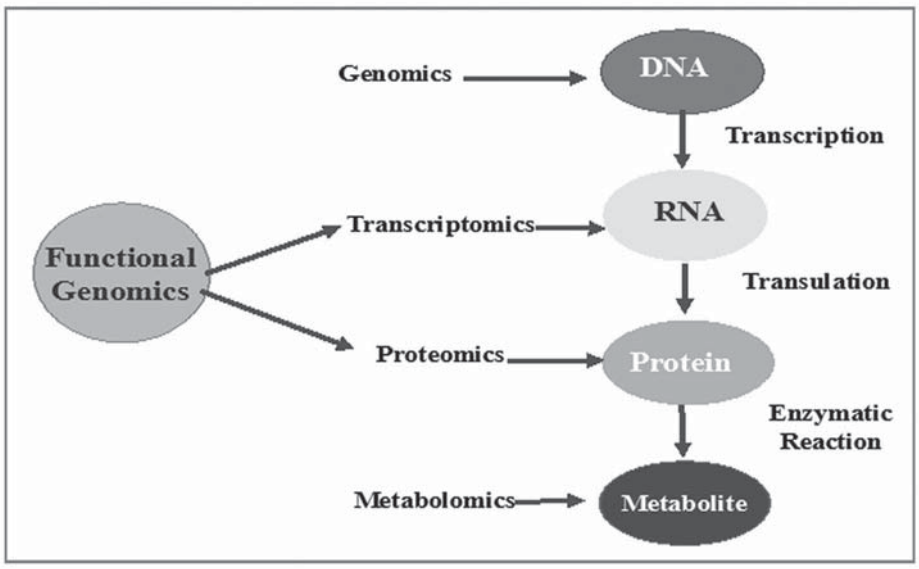

Figure 2 Diet, Gene Expression and the Functional Genomics Techniques

Source: Khalifa, 2016 (Unpublished work)

GENOMICS

Genomics is the organized genome study of an organism: the genome is described as the total DNA of a cell or an organism. The human genome has 3.2 billion cores (Baltimore, 2001).

TRANSCRIPTOMICS

Transcriptome is defined as the total mRNA in an organism or a cell, and the template for protein formation in the translation process: the transcriptome reflects the actively expressed genes at any given moment. The packaged mRNA was measured by gene expression microarrays as a conclusion of gene activity (Szabo, 2014).

PROTEOMICS

Proteome is recognized as the set of the total expressed proteins in an organism, tissue or cell. Proteomics goals are to describe the information flow inside the organism and the cell via protein networks and pathways, with the ultimate aim of recognizing the protein's functional relevance (Vlahou and Fountoulakis, 2004).

METABOLOMICS

Metabolomics is generally defined as the analysis of total metabolite shapes in a system that might be cell, tissue or organism, under a particular set of circumstances (Goodacre *et al*., 2004).

FOOD GENE INTERACTION

Many dietary constituents have the ability to change genetic incidents and thus affect health. Food has gene expression regulators that include essential nutrients such as carbohydrates, amino acids, fatty acids, folate, selenium, calcium, zinc, and vitamins A, C and E, and non-essential nutrients such as phytochemicals, isoflavones, metabolites of food components, etc. These essential and non-essential bioactive food constituents are recognized to affect the genetic and epigenetic cellular incidents; these include inflammatory response, cell differentiation, carcinogen metabolism, DNA repair, hormone regulation, Apoptosis and cell growth cycle (Corthésy-Theulaz *et al*., 2005).

Recent studies done by Ortega-Azorín *et al*. (2012) showed a gene-diet interaction; this was because two of the very recognized genes (MC4R and FTO) were examined, putting into concern the Mediterranean adherence for two polymorphisms (rs17782313 and rs9939609 respectively. Another study conducted by Luczynski *et al*. (2014) found that diabetic children's bodies might be affected by the presence of the A allele of the FTO rs9939609.

DIET DISEASE INTERACTION

Nutrition-related health problems start to change, from vitamin and mineral deficiency diseases to over-nutrition, type-2 diabetes and obesity. The nutrition studies were transferred from physiology and epidemiology to genetics and molecular biology, and the focus was directed to nutrigenomics to prevent the increase of chronic diseases that were moderately mediated by chronic exposure to special food constituents. They investigated in what way nutrition can improve and keep the homeostasis of the cell and the whole body, which need recognizing how nutrients perform at the molecular level, which include interactions related to nutrients at the metabolic, protein, and gene levels.

THE POSSIBILITY OF NUTRIGENOMICS IMPLEMENTATION

It is becoming progressively marked that people do not respond similarly to diet. Nuno and Heuberger (2014) reported that genetic poly-

morphisms in fatty acid desaturase, apolipoprotein E, peroxisome proliferator-activated receptors, lipoxygenase-5, apolipoprotein A1, apolipoprotein A5, apolipoprotein A2, and methylenetetrahydrofolate reductase, have been related to cardio-vascular disease.

Crohn's disease and ulcerative colitis are two inflammatory disorders of the gastrointestinal tract. They have a complicated cause; a genetically definite susceptibility interrelating with environmental causes, gut microbiota and nutrients. Up to now, genome broad association research has involved more than 160 single-nucleotide polymorphisms, which are linked to disease susceptibility. The development of inflammatory bowel disease has been connected to genetic variants, which support inflammation. In this environment, the doco-sahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and the long chain polyunsaturated omega-3 (n−3) fatty acids from fish oil supplements and oily fish, can partially inhibit many aspects of inflammation (Ferguson, 2013). Also there is an indication that signalling of vitamin D can directly stimulate NOD2 expression, which suggests that vitamin D deficiency or insufficiency might have a contributory part in Crohn's disease (Wang *et al*., 2010). It is likely that this deficiency interrelates with polymorphisms of the vitamin D receptor in developing the susceptibility of inflammatory bowel disease.

Thousands of genes have been found to be related to the occurrence of some diseases. Of these genes, 97% are single genes resulting in monogenic diseases such as phenylketonuria and lactose intolerance. Prevention of these diseases can be achieved by modifying the dietary intake of some nutrients or food items. On the other hand, many common diseases such as celiac disease, cardio-vascular diseases, obesity and diabetes are polygenic, occurring due to the dysfunction of more than one gene; this makes the prevention of these diseases by dietary intervention complicated. Specific dietetic research found that the health effects of food constituents are linked mostly to certain interactions at the molecular level: this helps in the prevention of polygenic diseases. Dietary constituents contribute to gene expression regulation by modulating the activity of transcription factors (Mitroi and Mota, 2008).

Lactose intolerance, phenylketonuria, and celiac disease are disorders resulting from nutrient-gene interactions. Lactose intolerance occurs as a result of insufficient lactase production in the small intestine due to genetic change in the lactase gene (Swallow, 2003). As a result, the milk sugar (lactose) found in all dairy products cannot be effectively catabolized down. Accordingly, limitation of the foods containing lactose is recommended, in addition to using lactose free dairy products or lactase supplements to inhibit gastrointestinal distress (Swagerty *et al*., 2002).

Another example of nutrient gene interactions is Phenylketonuria (PKU), which occurs as a result of hepatic phenylalanine hydroxylase deficiency and therefore the failure of converting phenylalanine to tyrosine. Genetic changes on the human phenylalanine hydroxylase gene lead to a decrease in the enzyme's activity, an excess of serum phenylalanine resulting in hyperphenylalaninemia. The dietary recommendation of phenylalanine and protein restriction is essential to prevent postnatal neurological damage (DiLella *et al*., 1986).

Lactose intolerance and PKU are considered to be examples of single genetic disorders, which require a single dietary treatment. On the other hand, celiac disease has a complicated interaction between nutrients and genetics. Celiac disease is a public genetic chronic inflammatory disorder of the small intestine, which occurs as a result of gluten/gliadin permanent intolerance. The function and structure of the intestinal cell may be affected by modulating gene expression (pro-inflammatory cytokines, adhesion molecules, and enzymes whose gene expression is controlled by oxidative stress (PPARγ receptor) and (NF-κB). Therefore, the dietetic recommendation is gluten restriction (Ludvigsson *et al*., 2014).

Plant flavonoids, carotenoids and long chain ω − 3 fatty acids have been determined to reduce production of inflammatory mediators, oxidative stress and gene expression. Therefore, they could protect against gliadin peptides toxicity, maintain integrity of the intestinal barrier, and function in celiac disease nutrition therapy (Ferretti *et al*., 2012).

METHODOLOGY

Searching for the literature

Aimed search

The literature was gained by searching library databases (MEDLINE (PubMed), Google Scholar, CINAHL, PsycINFO, Cochrane Library databases and Quertile databases). It is a summary of both conceptual and empirically published literature on the molecular nutrition, functional genomic techniques and uses of nutrigenomics in the prevention and treatment of diseases.

Search Strategy:

The keywords and phrases used in searching were Nutrigenomics; Europe; Diet-gene Interaction; Obesity and personalized nutrition. The reference lists from published studies and reports were searched for additional sources. A number of electronic journals specializing in molecular nutrition, Nutrigenomics, were searched. The overall search

method showed discussion papers and information from consultation papers, which were examined to abstract evidence related to the present literature review objectives.

Selecting the articles and review resources

Inclusion criteria: The inclusion criteria include articles (reviews, population, and intervention of Nutrigenomics in non-transmissible chronic diseases (NTCDS)).

Topics of interest: The use of Nutrigenomics and personalized nutrition in controlling chronic diseases.

Evaluating the evidence: The last selection of articles was carried out by a comprehensive review of each article; this was done by two people to prevent errors and omissions.

DISCUSSION, CONCLUSIONS AND IMPLICATIONS

Biological and genetic information affects nutrition and its relationship to the multifactorial disease risk factors. Nowadays the genetic variants that affect nutrient metabolism have been identified. However, the individual variants are not decisively joined to risk factors of multifactorial diseases. Moreover the multiple variants effect on health outcomes and nutrient metabolism is well known.

Nutrigenomics aims to focus on how human's genetic variations can clarify why some people respond inversely to the same beverage, foods, and supplements. This area of research is altering and updating nutrition science, and leading to the discovery of the inter-individual diversity in the body's capability to process and respond to nutrients; this will eventually result in the concept of personalized nutrition and dietary advice. Nutrigenomics was created as a result for a need to move from physiology and epidemiology to genetic molecular biology. In order to study the effect of nutrients on gene/protein expression, it is importance to assess the genes and the gene/protein network (Neeha and Priyamvadah, 2013).

The difference between personalized medicine and personalized nutrition was explained by Gibney and Walsh (2013), who reported that data of the genotype of the personalized medicine are connected to the increasing possibility of a disease, while in personalized nutrition genetic data must be linked to the best diet for a definite genotype so as to decrease the risk of the disease.

The combined analysis of metabolomic, genetic and proteomic characteristics, and the complicated interaction between the nutrients and genome, should symbolize the assessment foundation of the

nutritional status of the individual. Nutrigenomics will increase understanding of how nutrients affect homeostasis and metabolic pathways, which will help to avoid the progress of chronic diseases related to nutrition. The demonstration of effect of bioactive food compounds through nutrigenomics will lead to functional foods development; this will make the people's health depend on their individual requirements. Therefore there is a need for multidisciplinary scientists and cooperative powers of the scientific society such as nutrition bioinformatics, agenesis, molecular biology, etc., to establish an inclusive dataset for nutrigenomic research.

Although the future possible benefits of nutrigenomics are well known, a number of ethical issues arise. For example, incorporating the use of novel food products designed and fitted to people's genotypes and needs, and the existence of a certain medical nutritional therapy such as using only one definite product planned specially for this polymorphism. Therefore, the scientific connection between nutrigenomics, bioethics, and personalized nutrition as a way of treating or preventing disease and nutrigenomics implementation in the most ethical way is very important (Patrinos and Prainsack, 2014).

Diet has a considerable effect on health and chronic disease, and the technique of functional genomics might define the food constituents' bioactivities. This will make improvements in health by fortification, dietary modification and novel foods.

The application of 'omics' to nutrition will point to the detection of biomarkers for immediate diagnosis, in addition to the plan of personalised diets that include bioactive food constituents of excessive health advantage.

The European Nutrigenomics Organisation (NuGO) linking genomics, nutrition and health research, has developed from a European-funded Network of Excellence. A Network of Excellence (NoE) does not perform research *per se*. Its aim is to overpower the break-up of research, giving investigators throughout Europe the opportunity to work with each other, share experience and their facilities.

CONCLUSION

Well known about Nutrigenomic are:

- Personalized nutrition
- A triple 'omic' approach
- Future for the science of nutrition

Not known about Nutrigenomics are:

- More research is required
- Gene-disease association to be explained
- Gene-food intake interaction must be simulated
- The consideration of environmental factors

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BIOGRAPHICAL NOTES

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