NUTRIGENOMICS: A NON-CONVENTIONAL THERAPY

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Accepted on: 11-03-2011; Finalized on: 30-05-2011.

ABSTRACT

Nutrigenomics is a highly innovative and fast-growing interdisciplinary field of research linking genome research, plant biotechnology and molecular nutritional research and offering new applications for medicine and nutrition. Nutrigenomics aims at providing an understanding for how nutrition affects the balance between genome on a molecular and systemic level. The extent of influence of diet on balanced status of the body may depend on an individuals’ genetic makeup. Nutrigenomics involves identification and characterization of individual variants of genes and modifying the effect of gene expression and structure by food ingredients. It leads to tailor-made therapies for diseases like atherosclerosis, type-II diabetes, eye diseases, cancer and many more. This will open up new perspectives for the health services with the aid of advanced technologies like transcriptomics, proteomics and metabolomics. This article would give an insight to the future therapy with food instead of synthetic drugs.

Keywords: Nutrigenomics, Biomarkers, Transcriptomics, Proteomics, Metabolomics.

INTRODUCTION

The success of ‘HUMAN GENOME PROJECT’ and powerful tools of molecular biology have lead to the era of genetic nutrition. Nutrigenomics refers to the application of genomics in nutrition research, enabling associations to be made between the specific nutrients and genetic factors e.g. the way in which food ingredients influence gene expression. The basic idea is that there are genes that affect the risk of getting illnesses like heart disease, cancer, osteoporosis and diabetes; and the impact of those genes can be modified by what we eat. Everybody carries one version or another of each of these genes. So why not find out what gene versions we have and base dietary advice on that. The ultimate goal is to be able to prevent and potentially even treat diseases through targeted nutrition.\(^1\)

Consider what happens, biologically, when we eat a meal. Until quite recently, most scientists thought food had basically one job: it was metabolised to provide energy for the cell. Indeed, that is what happens to most dietary chemicals - but not all. Some don’t get metabolised at all; instead, the moment they’re ingested, they peel off and become ligands - molecules that bind to proteins involved in "turning on" certain genes to one degree or another. A diet that’s particularly out of balance, nutritional-genomics scientists say, will cause gene expressions that nudge us toward chronic illness unless a precisely-tailored "intelligent diet" is employed to restore the equilibrium.

How does diet affect our gene expression?

Virtually every day, researchers identify new genes that contribute to health and disease. Conditions like breast cancer (109 genes) and asthma (27 genes) and diabetes (114 genes) highlight how broad these genetic factors will become. At the same time, the new biotechnology methods are pinpointing how molecular nutrients shape genomic activity. For examples, Vitamin A changes activity in over 500 genes; calcium in over 145, zinc over 60. Cholesterol, which is made by the body, influences over 30 genes, which shows that molecular nutrients which might regulate cholesterol production are likely, in turn, to have important second order effects.\(^2\)

The four basic tenets of Nutrigenomics are:

i. Improper diets are risk factors for disease.

ii. Dietary chemicals alter gene expression and/or change genome structure

iii. The degree to which diet influences the balance between healthy and disease states may depend on an individual’s genetic makeup.

iv. Some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.

Genes express themselves through proteins. Enzymes are special proteins designed to get things started. Our genome instructs ribosomes to produce many enzymes that destroy toxins. Some foods such as cauliflower, broccoli and Brussels sprout contain chemicals that actually tell our genes to direct biosynthesis of these enzymes.

In some individuals, genes give unclear instructions for making an enzyme that metabolizes the amino acid, phenylalanine. As a result, this amino acid builds up, thereby causing brain damage. A diet restricting this amino acid will stop the damage if detected in early infancy.

Transfer of nutrients from gut to cells requires carrier and receptor proteins. Some individuals have genes that direct overproduction of iron carrying proteins. The
resulting iron overload is extremely toxic and may lead to death.

One gene that have received considerable attention and around which there has been a great deal of research is the gene for the enzyme methylenetetrahydrofolate reductase (MTHFR). Its relation to cardiovascular disease is confirmed.

Currently, several nutrition related issues benefit from genetic research. A number of conditions like phenylketonuria, caffeine intake and bone loss in post-menopausal women, folic acid and heart disease, obesity, anorexia nervosa, vitamin C supplementation to reduce cancer risk and low fat diet for high blood cholesterol levels, show the influence of genetic variation on nutrition advice.

The majority of practical applications of Nutrigenomics are just beginning to emerge. The trend appears to be that certain individuals with particular variations in their genes will have increased need of specific nutrients in their diet which will result in changes in translation of information in their genes. The impact of this dietary change on an individual’s gene expression may be an improvement in their projection disease trajectory over a life time.

Figure 1: Migrating principles of pharmacogenomics (PGx) to nutrigenomics (NGx) to enable the practice of preemptive nutrition.

Biomarkers

Biomarkers are the genetic variants that predict the risk of disease and improve diagnosis and risk assessment. Genetic polymorphism may be partially responsible for variation in individual’s response to bioactive food component. Single nucleotide polymorphisms (SNP) are becoming increasingly recognized to have an important influence on disease risk, for example, inherited polymorphism in BRCA1 is the gene responsible for breast cancer susceptibility.

Women, who consume less fruits and vegetables were reported to be at the greatest risk of developing breast cancer because of a polymorphism that causes a valine to alanine change in the ninth position in the signal sequence for the enzyme manganese dependent superoxide dismutase.

Studies have shown correlations between mildly elevated homocysteine levels and cardiovascular disease risk. Methylene tetrahydrofolate reductase helps to convert homocysteine to methionine. Due to SNPs (C677T and A1298C) which reduce MTHFR activity it leads to increase in plasma concentrations of homocysteine and thereby to venous thromboembolic disease, ischemic arterial disease and neural tube defects. Treatment with folic acid supplementation helps to overcome the effects of these polymorphisms in MTHFR gene.

Similarly a number of polymorphic genes have been implicated to cancer development e.g. MCIR (melanocortin 1 receptor gene) have been associated with several types of skin and prostrate cancers. There are claims of dietary supplements that protects against diseases like cancer. New foods are developed as functional foods.

Obesity has become a major public health problem. Mutations in genes like leptin and leptin receptor genes have emerged as leading candidates towards predicting obesity. In addition, mutations in melanocortin 4 receptor and melanocortin 5 receptor gene and in the non -coding regions of the gene for neuropeptide Y (NPYY5R) receptor have also been shown to be strongly correlated with the...
risk of obesity. Once the mutations are detected in the family, the physician might be in a position to offer diet restriction/intervention at an early stage of life.\textsuperscript{8}

**Transcriptomics, Proteomics and metabolomics**

The inadequate success of single biomarkers in predicting chronic diseases attests to the need for other approaches like transcriptomics, proteomics and metabolomics. Nutrigenomics is the science that examines the response of individuals to food compounds using post-genomic and related technologies (e.g. genomics, transcriptomics, proteomics, metabolomics). The long-term aim of Nutrigenomics is to understand how the whole body responds to real foods using an integrated approach termed ‘systems biology’.

Transcriptomics by using DNA microarrays is presently the major approach to obtain gene-expression data in nutrigenomics. It is relatively mature technology to proteomics and metabolomics.

Bioactive ingredients directly from food pass through our cells into the nucleus where they interact with DNA to affect transcription of RNA and ultimately translation of proteins. It appears that transcription factors (TFs) are the main targets or nutrient sensors. For example peroxisome proliferator activator receptor -\(\alpha\) (PPAR\(\alpha\)) binds fatty acids.

Proteomics refers to all the studies related to structure of proteins, expression levels, biochemical activity, protein-protein interaction and cellular localization. Proteins can be analysed before and after diet intervention therapies. Plasma proteomics would be of great importance to nutrigenomic research. Progress in this area is likely to generate a wealth of information about important proteins like cytokines.

Metabolomics is emerging as a post-genomics science with applications that span the scope of biotechnology and medicine. It provides nutrition with an invaluable tool for determining the distribution of metabolite concentrations in humans, the relationship of these metabolite concentrations to diseases and the extent to which nutrition can modulate metabolite concentrations.

A global initiative on nutritional metabolomics has been already initiated by the NUGO, the European Nutrigenomics Society (http://www.nugo.org/everyone).\textsuperscript{9}

**APPLICATIONS OF NUTRIGENOMICS**

**In cancer**

It is believed that dietary habits as an important modifiable environmental factor, influence cancer risk and tumor behavior. It is estimated that diet influences about 30-40\% of all cancer cases, however, the actual percentage is not known and depends on the specific type of cancer and the specific components of diet. Many studies indicate that breast, prostate, liver, colon and lung cancers are linked to the dietary intakes.\textsuperscript{10-11}

Bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification. In-vitro studies and preclinical models have shown many constituents of plant foods can modulate detoxification enzymes; examples are flavonoids (e.g. quercetin, rutin, and genistein), phenols (e.g. curcumin, epigallocatechin-3-gallate and resveratrol), isothiocyanates, allyl sulfur compounds, indoles, and selenium.\textsuperscript{12-13}

Evidences suggest that foods offer advantages over their isolated constituents in treatment of cancer. This may be due to presence of multiple bioactive compounds within the food that exert additive or synergistic effects. For example, in treatment of human lung cancer cells which undergo apoptosis, whole green tea is more effective than the individual constituents of the green tea in inhibiting TNF-\(\alpha\) release. These effects appear to be mediated through enhanced incorporation of the tea polyphenols into the cells. In a rat study in which prostate carcinogenesis was induced by N-methyl-N-nitrosourea (NMU) - testosterone, tomato powder was shown to inhibit carcinogenesis. These effects were suspected to be at the levels of absorption, retention, or metabolism.\textsuperscript{14-15}

In another study a fat-soluble extract from vegetable powder was found to be more efficacious than \(\beta\)-carotene in inhibiting cell proliferation in a lung cancer cell line. There have been also cases wherein, the foods were found not to be as effective as their isolated components, suggesting that the food may contain constituents that inhibit the cellular response. Although the mechanisms involved in these processes are not known yet, it may be due to modification of components involved in absorption, metabolism, or site of action of the bioactive food constituent in the body. An example for this may be the reduced ability of soy flour and full fat soy flakes to inhibit aberrant crypt foci compared to isolated genistein. At the present time, there is not much known about the food matrix and the bioactive components in them and how they influence cancer prevention. Cancer prevention studies have shown that all of the major signaling pathways deregulated in different types of cancer, are affected by nutrients. Pathways studied include: carcinogen metabolism, DNA repair, cell proliferation/ apoptosis, differentiation, inflammation, oxidant/antioxidant balance and angiogenesis.\textsuperscript{16-18}

Rodent models offer opportunities for identifying targets: Recent developments with mouse strains containing cancer related genes that are overexpressed or inactivated provided investigators with new models for studying the carcinogenesis process and testing preventive strategies. For example, a mutation of the p53 tumor suppressor gene is one of the most frequently observed genetic lesions in human cancer, accounting for; 50\% of all human tumors examined to date. Hursting et al. observed in p53-knockout (p53\(^{-}\)) mice that energy
restriction (60% of the control intake of carbohydrate energy) increased the latency of spontaneous tumor development by 75%, decreased serum insulin-like growth factor-1 and leptin levels, and significantly slowed thymocyte cell cycle traverse and induced apoptosis in immature thymocytes. Still, other research demonstrates the effect of the tumor suppressor gene p21 in determining the response to a diet high in fat and low in vitamin D and calcium and how the allele from each parent can influence the size of the response in terms of longevity. Collectively, both animal and human studies provide evidence that genetic background can profoundly influence the way that bioactive food components are absorbed, are metabolized, and influence molecular targets. Unquestionably, more information is needed to examine how genetic profiles influence the ability of specific dietary components to bring about phenotypic changes. Understanding the dynamic interactions between food components and genetic pathways leading to cancer is the basis of a recent request for application (RFA 03-001) and its soon-to-be released reissuance. It is believed that enhanced emphasis on genetic pathways and molecular targets will energize the nutrition community to explore sites of action of many bioactive food components across various tissues.\textsuperscript{19-20}

**In cardiovascular diseases**

Hyperlipidemia is usually associated with atherosclerosis and coronary heart disease. Therapy includes lifestyle changes as alterations in the patient's diet, physical activity and treatment with pharmaceuticals such as statins. However, individuals respond differently to the treatment. This was attributed to genetic variations within the population. Genetic variations in genes encoding for apolipoproteins, some enzymes and hormones can alter individual sensitivity to developing cardiovascular diseases. Some of these variants are susceptible for dietary intervention, for example: Individuals with the E4 allele in the apolipoprotein E gene show lower low-density lipoprotein-cholesterol (bad cholesterol) levels with increased dietary fat intake compared with those with the other (E1, E2, E3) alleles receiving equivalent amounts of dietary fat. One single nucleotide polymorphism (-75 G/A) in the apolipoprotein A1 gene in women is associated with an increase in High density lipoprotein-cholesterol levels with the increase in the dietary intake of polyunsaturated fatty acids (PUFA). Individuals with the A variant showed an increase in the protective HDL (good cholesterol) levels following an increased consumption of PUFA compared with those with the G variant taking similar amounts of PUFA. One polymorphism (-514 CC) in the hepatic lipase gene is associated with an increase in protective HDL levels compared with the TT genotype (common in certain ethnic groups such as African-Americans) in response to high fat diet.\textsuperscript{21}

![Figure 2: Drugs (Rx) and nutrients (Nx) have (A) common sites of intervention and (B) can share common response modifying SNPs in their regulation of lipid and lipoprotein metabolism.](image-url)
In diabetes

Type-2 diabetes is a metabolic disorder associated with impaired carbohydrate, protein, and lipid metabolism. This is further linked to inactive lifestyle and consumption of ‘wrong’ foods. We know that certain foods that are high in sugar and white starches can make the symptoms of diabetes worse. However, people with diabetes will have different responses to particular foods because of their different genes. For example, a study found that physicians recommend changes to diet and an increase in physical activity for type 2 diabetes patients, but only 20% of patients can actually control symptoms through these interventions.

This is where nutrigenomics can help manage type-2 diabetes. Nutrigenomics can come to aid through clinical diagnostics for phenotypes such as insulin level and glucose tolerance, as well as through metabolomic diagnostics in which diabetes biomarkers (biochemical substances viz. glucose, cholesterol, creatine, and fatty acids that indicate the susceptibility and progress of the disease) are assessed. Researches have shown that ‘over expression’ of SREBP -1a and SREBP -1c (t-RNAs that activate genes involved in the synthesis and uptake of cholesterol, fatty acids, and triglycerides) play an important role in the development of diabetes. Another research has suggested that presence of certain gut microbes increased fat reserves and insulin resistance, and thus may have an influence on the development of type-2 diabetes. Similarly, certain fibers modulated cholesterol absorption in the gastrointestinal tract, thus playing an important role in defining nutrient bioavailability.

This would help experts understand the complex relationship of diet-gene interaction of the diabetic person and provide more efficacious dietary recommendations. In the same way, nutrigenomics can also help in developing treatments for type-2 diabetes through personalized diet. And they have proven to be more effective than certain drugs. For example, the drug, rosiglitazone, commonly used by type-2 diabetics, is known to alter lipid metabolism in liver tissues and adipose tissues leading to liver toxicity with prolonged use. On the other hand, nutrients found in certain diets have the same metabolic pathway as the said drug, but without its side effects. 22

Typical nutritional studies analyzing the response of an intervention group to controls provided the same diet lacking a specific nutrients or nutrients. Simple examples analyzed serum lipid changes in response to a high fat vs control diet or determined differences in nutrient intakes between groups of individuals who have a disease (cases) versus those that do not (i.e., controls). Results of such studies are averages of all members of the control and all members of the intervention group. While population attributable risk yields useful guidelines, it does not provide information for individual members of the group nor can it be confidently applied to individuals not in the study. Low intakes of vitamin D have also been associated with an incidence and pathogenicity of Type 2 diabetes mellitus. 23,25

In eye diseases

There has been a recent finding on the implication of nutritional and genetic factors in age-related eye diseases: age-related macular degeneration (AMD; a degenerative disease of the retina) and cataract (opacification of the lens). Because of direct exposure to light, the eye is particularly sensitive to oxidative stress. Antioxidants, such as vitamin E, C or zinc, clearly have a protective effect in AMD and probably in cataract.

In addition, two carotenoids, lutein and zeaxanthin, may play a more specific role in the eye: they accumulate in the retina, where they form the macular pigment, and in the lens. Finally, docosahexaenoic acid (an omega-3 polyunsaturated fatty acid) is particularly important for the retina, where it exerts structural, functional and protective actions. Besides, these diseases are strongly influenced by genetics, as demonstrated by familial and twin studies. The apolipoprotein E4 allele is associated with a reduced risk of AMD, while an association of AMD with complement factor H polymorphism has recently been demonstrated. 26

CONCLUSION

The knowledge of Nutrigenomics would spawn a revolutionary way of viewing the food just not for sustenance, but as a pharmaceutical capable of reversing disease and stalling the rigors of ageing. Although Indian ayurvedic medicine and traditional Chinese medicines have already documented effects of plants on human disease since generations.

The real challenge for Nutrigenomics research is to target the genes involved in the major human diseases like cancer, heart disease, arthritis and obesity. In fact, many of the genes involved in these polygenic, chronic diseases are yet to be identified. The bioactive ingredients of food may turn ON some genes and simultaneously turn OFF other set of genes involved in a disease. The success of this science will require meaningful biomarkers and completion of clinical trials that monitors biomarkers.

The ultimate aim of this emerging field of science is PREVENTION rather than cure. This is not very different from the opinion of Hippocrates- Father of medicine (460-360BC) who said "Leave your drugs in the chemist’s pot if you can heal the patient with food."

REFERENCES


