NUTRITION

Nutrigenomics: *How your genes can tell you what to eat*

Nutrigenomics: *A promising future!*

Before long the idea of dietary guidance for the general population will be considered as old fashioned as counting bumps on one's head to determine intelligence. A revolution in the science of nutrition is about to occur and health professionals must decide what side they will be on. Maintaining the status quo of advising the entire population to avoid sodium, saturated fat and cholesterol will be hard to defend when individualized genetic counseling offers greater insight into who will be most affected by the nutrients in their diet and who, by luck of their parentage can eat these nutrients risk free.

After scientists were able to decipher the human genetic code we realized that our genes are not so different from those of other members of the animal kingdom. In the past, research studies depended on closely related animals to formulate nutrition policy. However, we now recognize that each human has a unique genotype and a lifetime of different environmental influences that make it difficult to justify human nutritional guidance based on animal research findings. Health professionals must adopt a new outlook on what had been considered nutritional dogma and determine if old research lacked sufficient sophistication to reach the conclusions that seemed acceptable a decade ago. Greater understanding of our genetic differences now makes it possible for many of us to disregard the "common sense" of past dietary guidance. Everyone can cite a relative who ate butter, eggs, bacon and sausage while drinking vast amounts of hard liquor and lived happily to be 100. Nutrigenomics will help to explain this paradox.

Benefits of Nutrigenomic research:

The ability of cells to adapt to environmental change by regulation of gene expression is essential for organism survival. Organisms vary their gene expression in the absence or presence of nutrients by increasing and decreasing production of cellular proteins necessary for life sustaining function. A perfect example of this evolutionary process is the development of a gene mutation that alters the ability to tolerate lactose (milk sugar). Adult mammals typically are unable to digest lactose. However, a mutation occurred ~9,000 years ago in Northern Europeans that allowed expression of the lactose-phlorizin hydrolase gene (LCH locus) to continue into adulthood. This mutation is thought to alter regulatory protein-DNA interactions which control genetic expression. The advantage that this mutation included improved nutrition, prevention of dehydration and improved calcium status for those who possessed the mutation. (Kaput et al., *Physiol Genomics*, 16:166-177, 2004)

Ultimately, the science of nutrigenomics promises to offer the health practitioner greater knowledge, enabling them to predict potential genetic responses to nutritional intake and to target and modify associated behavior. As described by Zeisel et al. (*J Nutr*, 135:1613-6, 2005), "Genes are important for determining

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function, but nutrition modifies the extent to which different genes are expressed and thereby modulates whether individuals achieve the potential determined by their genetic background. Nutrition modifies both the physical and cognitive aspects of performance. It also has an important effect on the risk of disease."

How Nutrients Affect Genes:

Nutrients from foods are considered bioactive ingredients when they pass through the cell membrane into the nucleus where they act as ligands with transcriptional factors, which bind to DNA to direct a pattern of transcriptional RNA, and ultimately direct the production of specific proteins. For example, retinoids from carrots and fatty acids from salmon, bind to specific genes resulting in the reduction of fatty acid synthesis and an increase in fatty acid oxidation. This simplistic example, where one process is turned on and another is turned off in the presence of a nutrient-transcriptional factor complex is only one of millions that occur between nutrients and genes daily. It will be important to remember, as we proceed along this path of genomic enlightenment, that research involving bioactive substances in human cell cultures, like associations drawn from epidemiological observations, are only preliminary until human clinical studies can verify the effects and mechanisms.

A major step will be to establish biomarkers needed to quantify a positive biological response to nutrient intake. This will be a valuable step that differentiates nutrigenomics from the general public health messages of the early 21st century, which led to punitive dietary restrictions unrelated to individual health outcomes. Once verifiable protocols, based on genomic biomarkers are established, nutrigenomics will revolutionize health care leading to the reduction of individual health risk.

Nutrigenomics-definitions

Genomics: The study of gene expression. Although living creatures look and behave in many different ways, all of their genomes consist of DNA, the chemical chain that makes up the genes that code for thousands of different proteins. Precisely which protein is produced by a given gene is determined by the sequence in which four chemical building blocks - adenine (A), thymine (T), cytosine (C) and guanine (G) - are laid out along DNA's double-helix structure.

Nutritional genomics: Covers nutrigenomics, which explores the effects of nutrients on the genome and metabolome, and nutrigenetics the major goal of which is to elucidate the effect of genetic variation as it relates to the role of diet and disease prevention.

Nutrigenetics: Used for decades in certain rare monogenic diseases such as phenylketonuria and has the potential to provide a basis for personalized dietary recommendations based on the individual's genetic makeup in order to prevent common disorders long before their clinical appearance.

Proteomics: Study of proteins encoded by the genes.

Metabolomics: study of small molecular weight molecules within the spectrum of the biochemical pathway

Gene expression: Process by which genes are activated to make proteins that in turn carry out a range of functions within the body.

Genotype: The genetic identity of an individual that does not show as outward characteristics.

Phenotype: The observable traits or characteristics of an organism, for example hair color, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.

Polymorphism: A common variation in the sequence of DNA among individuals.

SNP: Single nucleotide polymorphism: Common, but minute, variations that occur in human DNA at a frequency of one every 1,000 bases. These variations can be used to track inheritance in families. SNP is pronounced "snip".

Allele: One of the variant forms of a gene at a particular location on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

Comparative genomics: Is a new field of biological research in which the genome sequences of different species: human, mouse and a wide variety of other organisms from yeast to chimpanzees are compared. By comparing the finished reference sequence of the human genome with genomes of other organisms, researchers can

identify regions of similarity and difference. This information can help scientists better understand the structure and function of human genes and thereby develop new strategies to combat human disease. Comparative genomics also provides a powerful tool for studying evolutionary changes among organisms, helping to identify genes that are conserved among species, as well as genes that give each organism its unique characteristics.

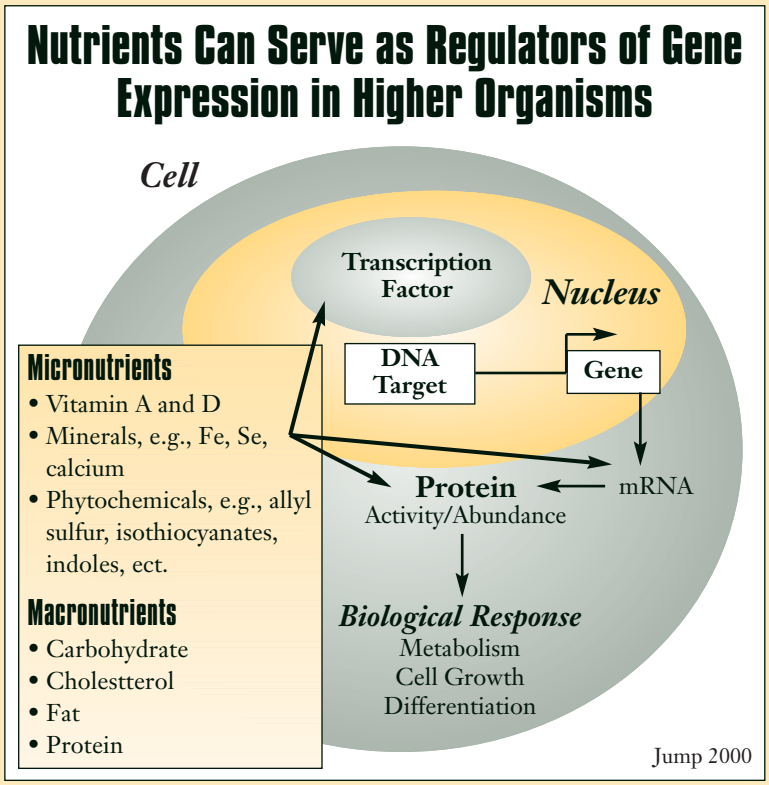
Ligands: an atom, molecule, group or ion that is bound to a central atom of a molecule, forming a complex.

Transcription factors: bind to specific DNA sequences in the promoter region of specific genes, thereby either enhancing or suppressing gene expression.

Microarray technology: A new way of studying how large numbers of genes interact with each other and how a cell's regulatory networks control vast batteries of genes simultaneously. The method uses a robot to precisely apply tiny droplets containing functional DNA to glass slides. Researchers then attach fluorescent labels to DNA from the cell they are studying. The labeled probes are allowed to bind to complementary DNA strands on the slides. The slides are put into a scanning microscope that can measure the brightness of each fluorescent dot; brightness reveals how much of a specific DNA fragment is present, an indicator of how active it is.

Nutrient Intake and Genetic Response

Kaput et al. (*Physiol Genomics*, 16:166-177, 2004) discusses what is currently known about suboptimal nutrient intake and genetic response.



Carbohydrates: Most of the research has focused on the differential effects of simple vs. complex carbohydrate intake through the use of glycemic index (GI). The GI is a quantitative measure of foods based upon their effect on postprandial blood glucose response compared to a single portion of white bread or glucose. Nearly all cohort studies of type 2 diabetes and GI intake show an association between high GI food intake and type 2 diabetes and increased risk of coronary artery disease and colon or breast cancer in case controlled studies.

Fats: The association between the intake of saturated fat and increased levels of LDL production is fairly well established. In addition to cardiovascular disease, elevated LDL levels are associated with obesity and diabetes. Human studies have shown an association between the amount and type of fat consumed and prostate, colorectal and breast cancers but are not conclusive.

Protein: Determining an effect of protein intake on health is complicated by the confounding factors of preparation method, fat and micronutrient content. Broiling, frying and baking produce different effects on the protein source and in some cases creates nitrosamines and other carcinogens. Dietary intake of meat has been linked with bowel and colorectal cancers and type 2 diabetes. Research has identified certain genes, for example glutathione-S-transferase, may be able to modify the effect of meat on disease risk. Excessive protein intake increases the production of urea containing ionized ammonia which has been shown in animals to disrupt metabolic pathways, alter gastro-intestinal mucosa and promote cancer.

Micronutrients: Certain micronutrient deficiencies seem to mimic radiation in their damaging effects to DNA. In fact, nutrient deficiencies are thought to be more hazardous to cells than radiation because in their absence, genetic materials are continuously exposed to intermediary products. This can explain why the quarter of the US population that eats less than five servings of fruit and vegetables daily has twice the rate for most cancers compared with the quarter of the population that has the highest consumption. Other examples of these associations are:

1. **Cardiovascular Disease:** B vitamins, vitamin E, carotenoids
2. **Cancer:** folate, carotenoids
3. **Neural Tube Defects:** folate
4. **Bone Mass:** Vitamin D
5. **Hyperhomocysteinemia:** B6, B12, folate

Ongoing research continues to seek the mechanisms between mineral intake and disease states.

Disease states associated with genetic profile

An association between dietary intake and chronic disease was first recorded in 1908. Ignatovski found that rabbits fed meat, milk and eggs developed arterial lesions resembling atherosclerosis in humans. As modern day nutrigenomic research confirms associations between specific nutrients and health, refinement of dietary guidance should follow. Some examples of new relationships that have come to light are:

Cardiovascular Health:
In the past dietary guidance to lower cardiovascular disease risk recommended a low fat, low cholesterol intake for the general population as well as those with a history of cardiovascular disease risk factors. Genetic research has shown that the Apo-A1 gene is instrumental in lipid metabolism and coronary heart disease. The guanine to adenosine (A-G nucleotide bases) transition in the APOA1 gene is associated with increased high density lipoprotein (HDL) cholesterol concentrations. The A allele variant appears to be associated with decreased serum HDL levels in women. Those women who eat more polyunsaturated fat relative to saturated and monounsaturated fat have increased serum HDL. Interestingly, this effect is only seen in men when alcohol consumption and tobacco smoking are contributing variables. (Kaput et al. *Physiol Genomics,* 16:1666-177, 2004)

In 1999 it was demonstrated by Dreon et al. (*Am J Clin Nutr,* 69:411-8) that individuals with small, dense LDL particles (phenotype B) have an increased risk of coronary artery disease relative to individuals who exhibit large, less dense LDL particles (phenotype A). In fact, those men who exhibited this phenotype A received no lipoprotein benefit by reducing dietary fat intake from 20% to 10%. In addition, earlier research by the same group found that one third of the men with the heart healthy phenotype A who changed from a high fat to a low fat diet, converted to the more dangerous phenotype B.

More recently, Herron et al. (*J Nutr,* 134: 187-190, 2004) found that the consumption of a high cholesterol diet does not negatively affect the size of the LDL particle. They reached this conclusion after conducting a crossover intervention study of 27 premenopausal women and 25 men fed either an egg or placebo for 30 days. Those who exhibited an increase of serum cholesterol >2.5 mg/dl for each 100 mg of additional cholesterol consumed, were categorized as hyper-responders. Results showed no association between dietary cholesterol intake from eggs and cardiovascular disease risk because LDL particle diameter was unchanged and the subjects considered hyper-responders had the larger LDL particle size after egg intake. This led to the conclusion that an increase in dietary cholesterol intake of 200 mg from an egg did not contribute to increase risk for heart disease.

Obesity:
The global increase in overweight and obesity appears to be the product of many influences unique to the 21st Century. The fact that human genetic response has not adapted to a changed environment which includes highly restricted motion coupled with continuous eating and unrestricted access to an unlimited variety of food sources, is without a doubt at the root of this growing epidemic. According to Loos and Bouchard *(J Inter Med,* 254:401-25, 2003) humans possess a genetic susceptibility for obesity in which the environment plays a permissive role in the severity of the expression of the obesity phenotype. At least 5% of the obesity cases represent genetic obesity minimally impacted by the environment. The more common forms of obesity are impacted more heavily by environmental conditions that allow the expression of the obesity phenotype.

A study by Williams et al. (*Am J Clin Nutr,* 82:181-7, 2005) attempted to determine the contribution of genes to body weight and lipoprotein response when 28 pairs of monozygotic twins ate a high carbohydrate diet for six weeks then switched to a high fat diet. In the study, one twin was sedentary and the other ran an average of 50km/wk which allowed researchers to assess the interaction of diet and exercise on genetic response. Results showed that decreasing dietary fat intake significantly decreased HDL and plasma Apo A-I levels in both the sedentary and running twin. The size and concentration of large, buoyant LDL particles also decreased significantly. The authors make the observation that "The lipoprotein responses to the diets were not significantly different between the running and sedentary twins" which indicates that genetic rather than environmental influences may have greater impact on blood lipids. In addition, genetic control of body weight, even when activity levels were divergent among twins, was noted by body weight fluctuations that were significantly correlated within twin pairs and in light of the fact that increased dietary fat did not significantly change body weight within twin pairs.

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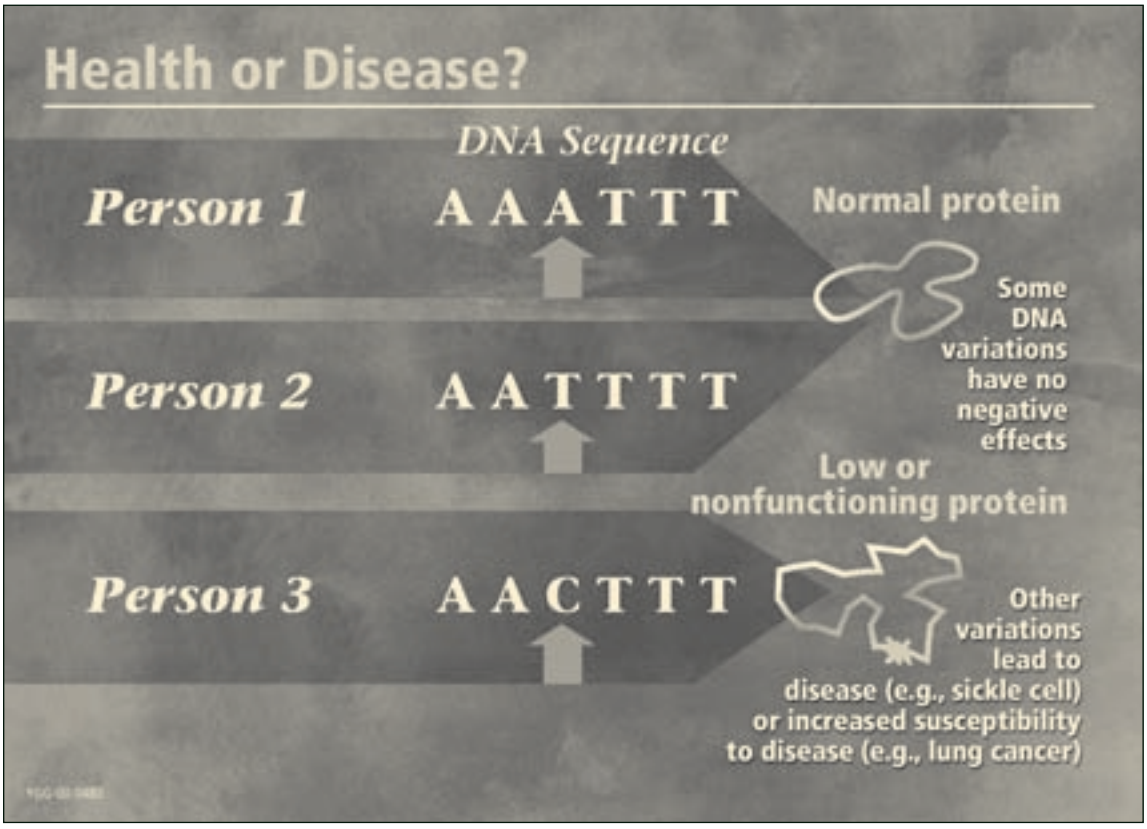
Other research into the relationship between nutrigenetics and weight control concerned the interaction between hormones such as leptin and ghrelin and macronutrient intake. Weigle et al. (*Am J Clin Nutr,* 82: 41-8, 2005) found that a higher protein content of the diet (30% of calories) has an anorexic effect mediated by leptin and insulin secretion which appears to potentiate the satiating effect of a higher protein intake leading to weight loss and significant loss of visceral fat tissue.

Diabetes:

It is widely recognized that the genetic basis for diabetes mellitus (DM) type 1 differs significantly from that of type 2. Australian researchers working with mice appear to have identified a genetic variation in the IL-12B '3UTR gene responsible for type 1 DM. This gene variant produces IL-12B which is common in type 1 diabetics and seems to accelerate the onset of diabetes by stimulating the immune system to attack pancreatic cells. Research is now being sought which will identify ways to reduce the IL-12B levels.

Type 2 DM is considered more likely attributed to many genetic determinants including defects in one or more molecular pathway. Although the concordance rate of diabetes is consistently higher in monozygotic than in dizygotic twin pairs, the influence of environment and lifestyle can not be overlooked including diet, physical activity and prenatal and early postnatal nourishment. Current research into the genetic cause of type 2 DM focuses on minor rather than major mutations in specific genes such as peroxisome proliferators-activated receptor gamma (PPAR) which has shown an association with an increased diabetes risk of 25% or Glu23Lys which encodes for a potassium channel and also increases diabetes risk by about 25%. (O'Rahilly et al., Science, 307:5708, 370-3, 2005). However, it is generally agreed that until there are case controlled studies that have measured lifestyle factors over a sufficient length of time, understanding the mechanism between genetic factors and environmental influences that lead to increased incidence of type 2 DM will be only a futuristic goal.



Some variations in a person's genetic code will have no effect on the protein that is produced others can lead to disease or an increased susceptibility to a disease.

image credit: U.S. Department of Energy Human Genome Program

Emerging Biomarkers of Nutritional Health to Watch in Cardiovascular Disease:

Lecithin: Cholesterol Acyltransferase Activity (LCAT): An enzyme that reversibly transfers an acyl residue from a lecithin to cholesterol, deficiency of this enzyme leads to an accumulation of unesterified cholesterol in plasma.

Interleukin-1 (IL-1): gene that is actively involved in the nflammatory process

C- Reactive Protein (CrP): C-reactive protein (CRP) is one of the plasma proteins known as acute- phase proteins: proteins whose plasma concentrations increase (or decrease) by 25% or more during inflammatory disorders.

High Density Lipoprotein (HDL): Low levels (men <40 mg/dl and women <50 mg/dl) have been associated with increased risk of cardiovascular disease

Triacylglycerol (TG): Storage form of fat also found in the bloodstream with normal blood levels between 10-150 mg/dl. Elevations of the triglyceride level (particularly in association with elevated cholesterol) have been correlated with the development of atherosclerosis, the underlying cause of heart disease and stroke.

Low Density Lipoprotein Peak Diameter: A predominance of small, dense LDL particles are considered to be more atherogenic than the larger more buoyant particles.

Homocysteine: An amino acid that at high levels of in the blood (hyper-homocysteinemia) can damage the inner surface of blood vessels, promote blood clotting, and accelerate atherosclerosis.

Peroxisome Proliferator-activated Receptor (PPAR): regulator of fatty acid metabolism.

Apolipoprotein A-1: (Apo A-1) gene codes for the major protein in HDL cholesterol and plays a major role in promoting transport of cholesterol from extrahepatic tissue to the liver where it is metabolized and excreted from the body.

Summary

The future looks bright. As associations between dietary intake and genetic response become clearer we should all benefit from a reduction in chronic disease and lower healthcare costs. No longer will health practitioners be asked to promote dietary recommendations that reduce population health risk while leaving the individual unprotected. As we gain an understanding of nutrient-gene interactions and quantify their influence on health outcome, dietary recommendations can be tailored to reduce the individual's health risk beginning at conception. Nutrition and dietary intake will once again be seen as a valid commitment to improved quality of life.

NUTRITION realities

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