Nutrigenomics

A New Approach to Health & Nutrition

by Sylvia Onusic, PhD, CNS, LDN

Nutrition and biochemistry were new concepts in the 20th century, when vitamins and their value in the human and animal diet were discovered. Previously, Koch and Pasteur's germ theories had guided most scientific thinking about disease.[1] At the turn of that century, the leading causes of mortality were infectious diseases—pneumonia, influenza, diphtheria, and tuberculosis[2]—and the focus of medicine was on defeating and eradicating the "germs" causing illness and death.

The importance of nutrition in health was not generally recognized until nutrients were linked with deficiency diseases, which were very common until World War II. The early pioneers and "vitamin hunters" who found that vitamin deficiencies caused diseases such as scurvy, rickets, and pellagra were belittled and mocked. Even in the 1920s and 1930s, medical professionals in the US would not consider that a disease could be caused by diet.[3]

Current thinking regarding correct nutritional intake is expressed in the dietary reference intakes (DRIs), a set of reference values used to assess and plan the nutrient needs of the general population. The DRIs include recommended dietary allowances (RDAs), average daily intake levels that are believed sufficient to prevent disease in most healthy people. These figures do not take into account nutritional needs arising from individual genetic variations; some people, for optimal health, could require a hundred times the RDA of a specific nutrient.

Clinical medicine does not consider all the multifunctional roles of nutrients. For example, folate prevents macrocytic anemias and neural tube defects, and is key in preventing cardiovascular disease and various mental health problems, as well as certain cancers. A single nutrient may be involved in the processing of hundreds of biochemical reactions (300 or more in the case of magnesium). Suboptimal levels of nutrients may be a factor in long-latency (chronic) diseases, such as cancer, osteoporosis, immune disorders, and mitochondrial dysfunction.[4]

Recently, however, a different nutritional story has begun to take shape. The mapping of our genes has set the stage for new sciences focused on the importance of nutrition in the scheme of life. Scientists with the Human Genome Project completed the sequencing of the human genome (the full set of an individual's DNA) in 2003, giving us the ability to read nature's complete genetic blueprint for a human being. Our genomes are nearly (99.9 percent) identical,[5] but how the genes are expressed (what genetic products, generally proteins, they create in individual cells) makes each of us unique and very different from our neighbors.

The epigenome is a network of chemical compounds that surround the DNA and influence its activity without changing the DNA sequence. It is shaped, in part, by lifestyle, dietary, and other environmental factors. Genetics and epigenetics interact in determining our specific characteristics. The genome is the instrument, and the epigenome, the musician that makes the instrument sing. Epigenetics is the key driver that dictates genetic expression and the state of our health.[6]

Nutrigenomics combines a number of disciplines, including biochemistry, physiology, nutrition, genomics, and epigenomics, to study the reciprocal interactions between genes and nutrients at the molecular level. This is a new paradigm, one of precision or personalized medicine, where protocols that take into consideration biochemical individuality replace "one for all" drugs, surgeries, and regimens.[6]

BIOCHEMICAL INDIVIDUALITY

Coined by Roger Williams, PhD, in 1956, in his book of the same name, the term *biochemical individuality* refers to the product of the interaction between genetics and the environment.[7] This concept laid the basis for nutrigenomics.

Williams, who discovered vitamin B5 (pantothenic acid), attributed the anatomical and physiological variations among people to genetic interaction with environmental factors. He found that, starting in the uterine milieu, individuals developed in different environments, depending on maternal nutrition, physiology, and emotional status; transgenerational epigenetic inheritance; geographic location; and other factors. Williams suggested that the resultant differences in biochemical profiles led to different nutritional requirements. He also believed that the phenotype—the composite of a person's characteristics, including behavior, biochemical status, and physical appearance—could be modified by nutrition and diet.

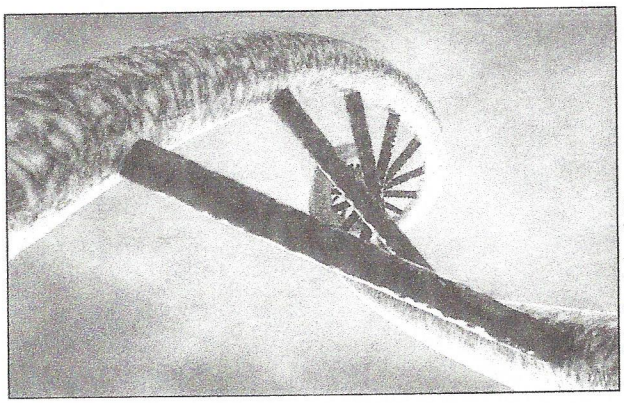
METHYLATION FACTORS

There are several ways that epigenetic factors change gene expression, but the most widely researched is DNA methylation, which involves the addition of a methyl group (CH_3) to a DNA strand. Methylation occurs in every cell of the body (except mature red blood cells, which do not contain DNA) many times each second and is crucial in hundreds of chemical reactions that regulate cell energy, healing, and immunity. All of these reactions are responsive to environmental conditions, including nutrient status.[8] Methyl groups are transferred from specific nutrients to kick-start or decommission molecules that control many vital functions in the nervous, detoxification, cardiovascular, and immune systems, among others.

Nutrigenomics is key to methylation because nutrients such as folate, betaine, and vitamins B12, B6, and B2 supply the raw materials for the methylation cycle. The major steps in the cycle involve a form of folate donating a methyl group to homocysteine to create methionine. Vitamin B12 is a cofactor in this process. Methionine is then used to generate the body's primary methyl donor, S-adenosylmethionine (SAMe), which is found in almost every tissue and fluid in the body. Most of the SAMe is used to make phosphatidylcholine for cell membranes, glutamine and creatine for energy supply to the muscles, and carnitine for energy production. Over 250 enzymes use SAMe for processing, including MAO (monoamine oxidase), which is a key regulator of brain function.[9,10]

When there is an excess or deficiency of methyl groups, due to factors such as cigarette smoking, alcohol ingestion, inadequate nutrition, and/or exposure to toxins, methylation is affected. Deficiencies of methyl donors can result in hypo- or hypermethylation, which can lead to chronic disease and premature aging. In terms of brain health, hypermethylation can result in excessive levels of dopamine, norepinephrine, and serotonin, potentially leading to anxiety, depression, and chemical and food sensitivities. Hypomethylation, which is associated with low serotonin, can cause conditions such as obsessive-compulsive disorder and seasonal depression.[11]

These epigenetic changes—and their associated health effects—are potentially reversible,



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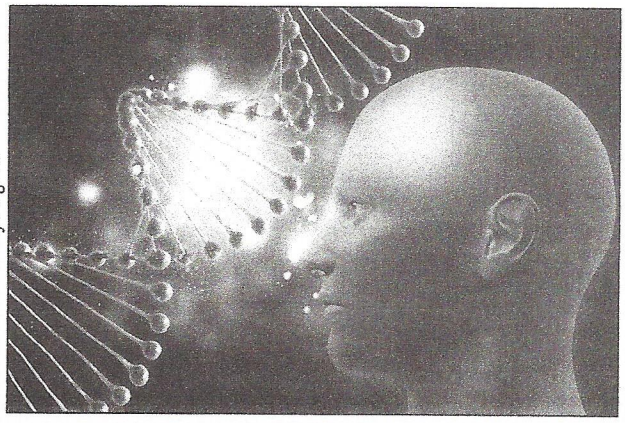
and various substances in plants show promise due to their methylating capabilities. Curcumin, a polyphenol in the spice turmeric, modulates DNA methylation and is associated with the increased apoptosis (death) of cancer cells. Apigenin, another polyphenol, found in parsley and chamomile, also has methylation effects, as do other plant compounds, including sulforaphane in cruciferous vegetables, allicin and other allyl compounds in garlic, and lycopene in tomatoes.

Other polyphenols may also be able to mediate DNA methylation, activating the genes that prevent tumor growth. Resveratrol, found in grapes and knotweed, has antitumor activity. Polyphenols in green tea have been shown to reverse hypermethylation of tumor-suppressing genes.[12,13] However, some green teas contain high levels of fluoride, which is a toxin and negatively affects methylation.[14,15]

Thus, methylation is a central feature of adaptation to the ever-changing physical and chemical conditions of life. Methyl group donations enable cells to maintain homeostasis and ensure genomic stability.

TALE OF THE YELLOW AND BROWN MICE

In 2003, Randy Jirtle, PhD, and his team at Duke University showed that they could change the phenotype of mouse pups by giving the mothers "methylation factors"—nutrients that support healthy methylation, such as folate, choline, betaine, and vitamin B12.[16] The agouti mothers (who had a gene mutation that made them yellow and obese) gave birth to slim, brown pups. The nutrients silenced the agouti gene expression in the pups. Moreover, these changes in the first generation of offspring could be passed down to subsequent generations. This widely read study suggests that nutrition affects infant health and DNA inheritance in a very big way. In another agouti mouse study, Jirtle found that the effects of the endocrine disruptor bisphenol A were reversed with maternal supplementation of nutrients that promote healthy methylation.[17]



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EPIGENETICS AND THE MIND

Central nervous system structures are formed in the first trimester of pregnancy, and epigenetic changes underlying mental illness, impaired appetite regulation, or age-related declines in cognitive function likely occur during this period.[18]

In the winter and spring of 1944, after a railway strike, the German occupation limited rations for the entire population, including pregnant women, to as little as 400-800 calories per day in the western region of The Netherlands, including Amsterdam. Approximately 20,000 persons died because of the famine. Research co-authored by Ezra Susser, MD, DrPH, determined that children who had been exposed to malnutrition and stress in the second or third trimesters of gestation during the Dutch Hunger Winter were more likely to develop major affective (mood) disorders than those who were not exposed.[19] The risk was greater for subjects who were in utero in the third trimester during the famine.

Another study coauthored by Susser demonstrated that exposure to severe famine during the first trimester of gestation was associated with a twofold increase in risk of schizophrenia.[20] The Dutch famine studies also found an increased rate of central nervous system anomalies, including neural tube defects, from maternal starvation.

Researchers have also linked prenatal deficiencies of vitamin D, folate, and iron to increased risk of schizophrenia.[21] Recent studies indicate that lead exposure in utero increases the risk of developing this condition, due to hypermethylation.[22]

BEHAVIORAL EPIGENETICS

According to new insights into behavioral epigenetics, traumatic experiences in our past,

or in our recent ancestors' past, leave methylation "scars" (methyl groups) fixed to our DNA.[23] These scars—stemming, perhaps, from the stress experienced when our grandparents left their homes to journey across the Atlantic Ocean or when mom grew up with abusive parents—are heritable, and may cause depression, dysfunctional handling of cortisol, abnormal brain activity, and other effects of impaired DNA methylation.

A landmark paper in 2004 showed that the mothering habits of mice can cause epigenetic changes that alter the levels of stress hormones (including corticosteroids) in their offspring as adults. The more the mothers licked and groomed the pups, the lower their stress in adulthood.[24] Mothering style and attention to offspring did indeed influence future metabolism.

GENE MUTATIONS AND SNPS

With each roll of the reproductive dice, the genes of two human parents—about 20,000 from each parent—can combine in trillions of ways to build a separate individual. The child's genome is composed of all the inherited genes, organized into 23 pairs of chromosomes, with one chromosome in each pair coming from each parent. These chromosomes, found in every cell of the body (except red blood cells), each contain a molecule of DNA, which provides instructions the body needs to develop, function, and reproduce.

DNA is made up of units called nucleotides, each of which contains a phosphate group, a sugar group, and a nitrogen base. These nucleotides are attached together and form two long strands that spiral, creating a double helix. The structure of the double helix resembles a ladder, with linked pairs of bases forming the rungs. Among the billions of pairs of nucleotides in each cell are the genes—distinct stretches of DNA that contain information that will be used by the cell to manufacture proteins. This information is coded into sequences of the four nitrogen bases: adenine (A), guanine (G), cytosine (C), and thymine (T). The order of these bases determines which proteins will ultimately be made by the cell.

Changes in the order of these bases can alter the gene's "instruction manual." The body makes about one million proteins based on instructions from the genes, and there is plenty of room for error. A variation in only one base at a specific position in a gene is known as a *single nucleotide polymorphism* (SNP, pronounced "snip"), if it is present in one percent or more of the population. A SNP may result in the manufacture of a protein with altered shape, activity, or stability or may affect the amount of protein produced. Such a protein may act differently than usual or have a low affinity for its receptor or for binding its cofactors. If not repaired by innate mechanisms, the change becomes permanent—a mutation. Although mutations can occur at any time during the lifecycle, it is most likely that humans are born with them, will carry them throughout life, and will pass them down to offspring. All humans carry 100-200 mutations in their genetic code.[25]

Over half the population has SNPs that reduce the activity of at least one enzyme by up to 70 percent.[26] As many as one-third of mutations result in the enzyme having a decreased binding ability.[27] Bruce Ames, PhD, a leading nutritional biochemist, believes that various diseases stem from this type of gene mutation and that nutritional supplementation can remedy them by increasing the binding affinity of the enzymes.[27,28] Many enzymes use a vitamin or mineral cofactor, such as zinc, magnesium, or vitamin B12. Ames says that about 50 genetic diseases can be treated with high-dose B vitamins. Other nutrients that he suggests may prove effective in treating specific genetic diseases include vitamin K, SAMe, lipoic acid, carnitine, and various minerals and amino acids.[27]

THE MTHFR GENE

One gene that is receiving a great deal of press—and whose SNPs are posing a major public health problem—is MTHFR.* This gene provides instructions for making an enzyme, also called MTHFR (methylenetetrahydrofolate reductase), which is an essential cog in the methylation

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* Ben Lynch, ND, offers much information about the MTHFR gene at his website mthfr.net.

cycle. Specifically, this enzyme is important for methylation involving forms of folate. It plays a vital role in converting the amino acid homocysteine to methionine, which the body uses to make proteins and other necessary compounds.

Several variations in the MTHFR gene have been associated with an increased risk of neural tube defects, including anencephaly (in which parts of the brain are missing) and spina bifida (a spinal cord malformation). At least 40 mutations in this gene have been identified in people who cannot process homocysteine and methionine properly. Such individuals may develop eye problems, abnormal blood clotting, skeletal abnormalities, and cognitive problems. Variations in this gene have also been suggested as risk factors for heart disease, stroke, high blood pressure, preeclampsia, glaucoma, psychiatric disorders, and some types of cancer.[29]

GENETIC TESTING

Genetic testing is becoming increasing popular as a way of identifying gene variations that may increase one's risk of disease. Some tests for SNPs are available to the public, while others require a physician's prescription. The three listed here can be ordered directly through consumer websites. There may be other companies on the Internet that offer similar services.

1. DNA Methylation Pathway with Methylation Pathway Analysis: a test for 30 methylation SNPs, designed by Amy Yasko, PhD, NHD.* This blood spot test comes with lancets and a blood card. A full explanation of results is included. Available at www.holisticheal.com/dna-methylation.html.

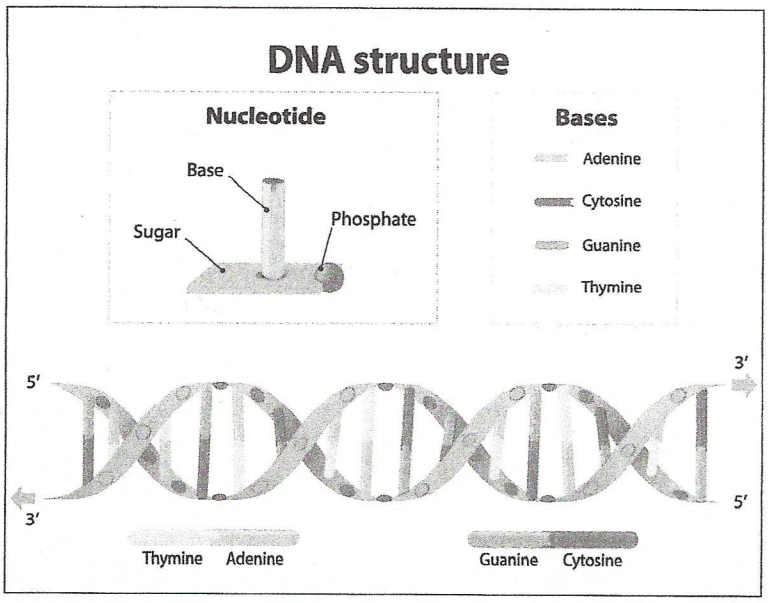
2. 23andMe: over 60 reports based on testing of a saliva sample. The results include the raw data (the genome), ancestry reports, and limited genetic reports. Available at www.23andme.com.

3. Ancestry: raw data and a more extensive ancestral report, based on a saliva sample. This service may not test for all the genes that are included in the 23andMe reports. Available at dna.ancestry.com.

Numerous laboratories offer genetic testing of blood samples, usually requiring a doctor's prescription. Such labs include Doctor's Data, Genova Diagnostics, SpectraCell Laboratories, Quest Diagnostics, The Great Plains Laboratory, and others. The costs are higher than those of direct-to-consumer tests, and results may or may not come with a full report.

GENOME REPORTS

Four to eight weeks after submitting your sample to a testing service such as 23andMe or Ancestry, you will receive an email with instructions for downloading your raw genome data from their website. You can then load your data into one or more apps online to get an in-depth report of many SNPs, organized into systems. Several apps are available: Genetic Genie (free), LiveWello, Promethease, and Sterling's App (MTHFR Support). Most, but not all, will accept the raw data from either of the two sources mentioned.



*Amy Yasko, PhD, NHD, offers extensive educational resources, including a free book download, about nutrigenomics at dramyyasko.com. She also offers a free genome analysis at www.knowyourgenetics.com.

I mainly work with Sterling's App, which was developed by Sterling Hill Erdei and is available at the MTHFR Support website (mthfrsupport.com). I recommend this app to those who are new to nutrigenomics. It can be used with 23andMe or Ancestry raw data to generate a report that is one of the most comprehensive and easy to use. The MTHFR Support website also contains video tutorials on getting your raw data from your source.

MTHFR Support offers both a Variant Report and an Excipient Report. The Variant Report provides a comprehensive list of SNPs, along with charts that explain the relevant enzyme pathways. The Excipient Report lists SNPs that affect the metabolization of various excipients—adjuvants in vaccines or inactive substances in drugs or supplements. Some of the excipients tested are cellulose, magnesium stearate, FD&C yellow, aluminum lake dyes, formaldehyde, thimerosol, polysorbate 80, monosodium glutamate, and phenol red. Many other apps offer reports similar to those available from MTHFR Support.

READING THE GENETIC REPORTS

These reports indicate whether one or both copies, or alleles, of each listed gene have a mutation at a specific location. For example, one of MTHFR's major SNPs appears at location C677T on the DNA strand. On the MTHFR Support Variant Report, this may be listed as indicated below:

SNP Name	Risk Allele	Your Alleles	Your Results
MTHFR C677T	A	AG	+/-

If both copies are in the normal, or "wild," form at a specific location (in other words, if there is no mutation), the gene is normal at that location, and the result will be shown as -/-. The minus sign indicates that there is no change from the norm. A heterozygous SNP (only one copy of the gene carries the mutation) is shown as +/-, as seen above. A homozygous SNP appears as +/+, indicating that both copies carry the mutation.

Heterozygous mutations (+/-) may differ from homozygous mutations (+/+) in terms of disease risk because a person with a heterozygous mutation will often still have one fully functioning copy of the gene. It is also important to understand that having a gene with a SNP mutation does not mean that the gene is defective or nonfunctioning, only that it is working at an altered rate of efficiency—either lower or higher than normal—or that the gene is lacking regulatory mechanisms normally involved in its expression.[30]

Because the definition of the norm can vary from lab to lab, the call letter (the letter indicating the nitrogen base present in the SNP) is also provided. This tells you what base was seen at that location by the testing lab. In the example above, the mutation being tested for (the risk allele) has adenine at that precise location of the gene. The results indicate that mutation on one copy of the gene, and the normal base (guanine) on the other.

Once your SNPs have been identified, it is important to know what physiological processes they may impact. This can tell you which pathways or systems in the body may require support. The MTHFR Variant Report groups SNPs according to pathways, and for each grouping on the report, there is a chart that shows how the relevant genes are involved in the process. The following groupings are among those that may be included in the report:

- Liver detox: phase I and phase II enzymes. These enzymes transform substances such as vitamins and drugs into water-soluble compounds that can be metabolized and, when necessary, eliminated from the body. They are also involved in the removal of toxins. When taking drugs or undergoing chemotherapy, it is important to know whether you have a SNP that can interfere with metabolism of the drug, in which case that therapy may do little good.
- Yeast/alcohol metabolism. SNPs affecting this pathway can lead to methylation inhibition, leaky gut, and low energy production.
- Methylation and methionine/homocysteine pathways (previously discussed).

- Transulfuration pathway. This pathway works as an arm of the methylation pathway to make sulfite, sulfates, taurine, ammonia, and glutathione.
- Neurotransmitter pathways. These involve the formation and breakdown of serotonin, dopamine, glutamate, GABA, and COMT.

Other pathway groupings in your report may include mitochondrial enzymes, immunoglobulins (IgE , IgG, and IgA), celiac disease / gluten intolerance, and others.

PRACTICAL APPLICATION

The conclusion that genes are destiny has been disproven, and the medical model of disease causation is outdated. Genetic mutations tend to be irreversible, but epigenetic changes that cause such problems as hypo- or hypermethylation are inherently reversible. Diet and nutritional supplementation have the potential to restore normal epigenetic status, and research suggests that diseases caused by epigenetic aberrations may be treatable and preventable.

Nutrigenomics is the new tool for promoting health and understanding disease. As it turns out, sound nutritional support and healthy lifestyle factors are major epigenetic forces and major players in this powerful new science. Not many physicians are informed about or even aware of epigenetics and nutrigenomics, but nutrigenomics professionals are learning how to support your journey to health and empower you to become the steward of your well-being.

Here are some ways that you can use principles of nutrigenomics to decrease your overall risk of disease:

- Know your genome and your risk SNPs. Genome testing and online tools are readily available and easy to understand.
- Control and manage stress—this is extremely important to cellular stability.
- Eat a healthy diet that includes whole foods, good fats, proteins, and unrefined carbohydrates and is free of artificial additives, GMOs, and other toxins.
- Avoid folic acid in foods and supplements. Rather, look for activated forms of methylfolate, such as Metafolin or Quatrefolic.[31] Unmetabolized folic acid can block folate receptors and adversely affect methylation.[32] Leafy greens, lentils, and organ meats are good dietary sources of folate.
- Get regular exercise daily, even if it's only a short walk or jump on the rebounder.
- Be happy! 🕮

More information about topics in this article can be found at the author's website, www.drsylviaonusic.com.

ABOUT THE AUTHOR

Sylvia Onusic, PhD, CNS, LDN, is a food and genetics researcher, board-certified nutritionist in private practice, and published author who is very interested in the exciting new field of nutrigenomics. Her degrees in nutritional dietetics and public health education provide her with a solid background for understanding the current dilemmas in health and nutrition. Her website, "Nutrition Power," may be found at www.drsylviaonusic.com.

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* There are many papers available on this subject. For a comprehensive bibliography, please contact the author.

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