

## A Perspective on Systemic Nutrition and Nutritional Genomics

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## ABSTRACT

The brain and the gut work synergistically with each other and other organs. Reviewing nutrition systemically (rather than by single organs) is a holistic way for dietitians to evaluate their clients' health status. Nutrition influences the genetic onset and consequences of many chronic diseases. With identification of up to 500,000 single nucleotide polymorphisms (SNPs) in an individual, the population-level potential for nutrigenomic optimization is astounding (Ferguson, 2007.) The reader will be able to describe how several specific nutrients can maintain or improve health through supporting or suppressing gene expression.

**Key Words:** systemic nutrition, methylation, gene expression

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## SYSTEMIC NUTRITIONAL REVIEW

In the body, the brain and the gut work synergistically as part of a whole system. Applying a “systemic” review of genetics and nutrition is a new way to approach the onset and management of chronic diseases. While medical professionals are familiar with classic nutrient deficiencies such as beriberi (thiamin), goiter (iodine), iron deficiency anemia (iron), megaloblastic anemia (vitamin B12 and folate), pellagra (niacin), rickets (vitamin D) and scurvy (vitamin C,) they are not as aware of the nutritional and genetic origins of other disorders.

Genetic variation affects food tolerances among human subpopulations. In fact, the intake or absence of nutrients affects gene expression throughout life. Genetics may also influence dietary requirements, which has given rise to the field of nutritional genomics (Stover, 2006.) Knowledge of genetic variations that developed as a consequence of diet will help to identify genes and alleles that affect nutrient utilization (Stover, 2006.) The field of nutritional genomics will enhance both clinical nutrition and public health practices; that possibility is happening right now. Educated dietitians are applying genome-informed nutrient and food-based dietary guidelines for disease prevention and healthful aging, disease management, and public health interventions such as micronutrient fortification and supplementation (Stover and Caudill, 2008.)

As a result of studies of the human genome, the origins of many other disorders have been identified. Indeed, health and nutrition survey results point to the possibilities of using genetic information to help manage health more effectively (Chang et al, 2008). While the prevention of genetic errors is not currently applicable, dietitians are familiar with medical nutritional therapy for disorders such as phenylketonuria (PKU) and maple syrup urine disorder (MSUD.) These are conditions that can be identified at birth.

The intent of this article is to examine some of the disorders in which nutrition and genetics have been correlated. A closer look at some of the systemic effects of folate, vitamin B12, choline, betaine, amino acids (cysteine, methionine, tryptophan) and other nutrients is warranted.

## BACKGROUND

### Deoxyribonucleic acid (DNA) Sequence Variations and Single Nucleotide Polymorphisms (SNPs)

DNA provides the fundamental genetic instruction for all living things, including how to replicate cells for their specific purposes. DNA is made up of repeating strands of nucleotides. These nucleotides contain a sugar, a phosphate, and an adenine, cytosine, guanine or thymine base (abbreviated as A-C-G-T.) Bases form bonds with one base on the opposite strand (base pairing) where A bonds only to T, and C bonds only to G. The human genome contains 3 billion base pairs, neatly packaged within 46 chromosomes.

Each cell contains the chromosomes that make up its genome. One set of 23 chromosomes from each parent passes along during reproduction. The Human Genome Project (HGP) has identified these base pairs, and has shown how similar people really are to one another. When mutations occur in individuals, some of the bases are out of sequence within the DNA strands. DNA can be permanently by oxidizing agents, ultraviolet light, X-rays and other environmental factors. Sometimes these mutations are passed on to offspring.

All DNA requires protein for its structure, as chromatin, and for functioning, as histones. Genetic information moves between chromosomes and can make new combinations. This process promotes a “natural selection” process. When DNA coding changes occur, altered amino acid placement in the genome causes changes in the enzymatic or cellular function as well as in metabolism (Kauwell, 2008.) These changes are usually single nucleotide polymorphisms (SNPs.) An example of a SNP is the methylenetetrahydrofolate reductase (MTHFR) A222V (DNA: C677T) with its relationship to cardiovascular disease, migraines and some other neurological conditions.

Several new sciences have developed as a result of genetics research. Bioinformatics promotes mining of DNA sequence data; ecological genetics can be used to trace ancestry. Epigenetics identifies heritable changes in gene expression that do not involve a change in DNA sequence (Chuang and Jones, 2007.) These changes cause cells to behave differently (gene expression) where chromatin may either be silenced or activated.

Epigenetic changes can permanently alter an individual's genome. Waterland and Jirtle (2003) found that alterations in the intake of pregnant mice (folic acid, vitamin B12, choline, and betaine) influence the degree of DNA methylation in the *agouti* gene. This gene affects fur color, weight, and the tendency toward cancer. Research has linked prenatal human nutrition with adult susceptibility to cancer, autism, bipolar disease and schizophrenia. In short, if we are what we eat, then we are what our ancestors ate!

Nutrient deficiencies can be detrimental and may have long-range effects. Deficiencies of vitamins B-12, folic acid, B-6, C or E, iron or zinc mimic the effects of radiation on the body by damaging DNA through strand breaks and oxidative lesions (Ames, 2004.) Deficiencies of iron or biotin may cause mitochondrial decay and oxidant leakage, leading to accelerated aging and neural decay (Ames, 2004.) DNA damage and late onset disease seem to be consequences of a response to micronutrient scarcity during periods of human evolution (Ames, 2006.) Table 1 lists some micronutrient deficiencies that occur in the population in the U.S. with corresponding damage to DNA.

**Table 1 Population-Specific Micronutrient Deficiency, DNA Damage and Health Effects**

<b>%US Population Consuming &lt; half of the RDA</b>	<b>Micronutrient</b>	<b>DNA Damage</b>	<b>Health Effects</b>
20%	Vitamin E	Radiation mimic (DNA oxidation)	Colon cancer Heart disease Immune dysfunction
18%	Zinc	Chromosome breaks Radiation mimic	Brain & immune dysfunction Cancer
15%	Vitamin C	Radiation mimic (DNA oxidation)	Cataracts Cancer
10% (prior to supplementation in US)	Folic acid	Chromosome breaks	Colon cancer Heart disease Brain dysfunction
10%	Vitamin B-6	Uncharacterized	Same as folic acid
7% (19% women 12-50 years of age)	Iron	DNA breaks Radiation mimic	DNA breaks
4%	Vitamin B-12	Uncharacterized	Same as folic acid & neurological damage
2%	Niacin	Disables DNA repair (polyADP ribose)	Neurological symptoms Memory loss

Adapted from the University of California-Davis, NCMHD Center of Excellence for Nutritional Genomics, 2008. <http://nutrigenomics.ucdavis.edu/nutrigenomics/index.cfm?objectid=9688A280-65B3-C1E7-02E9FCDABDD84C68>, Website accessed 12/9/08.

## Folic Acid and Folate

Folate comes from foods and folic acid from supplements. Folic acid is absorbed in the proximal jejunum; it enters the enterohepatic circulation bound to albumin. Because serum folic acid levels reflect very recent dietary ingestion but not body stores, a normal serum level may not reflect cellular deficiency.

In the cells, folic acid is trapped in its inactive form until vitamin B<sub>12</sub> removes and keeps the methyl group. This step activates vitamin B<sub>12</sub> for its purposes. Once folic acid and vitamin B<sub>12</sub> are active, they are available for DNA synthesis. So with folate deficiency, DNA synthesis decreases and cell division suffers. This affects bone marrow. Megaloblastic anemia can occur at any age.

Folic acid helps to produce and maintain new cells, especially replication of DNA. Counseling about sufficient folic acid intake is important for pregnant and breastfeeding women. In studies of different populations, it has been noted that both Hispanic and Black women tend to use supplemental folic acid less often than Whites (Yang et al, 2007.) Table 2 identifies points to remember when counseling.

**Table 2. FOLIC ACID TRIVIA** (answers at the end of article)

1 µg food folate = how many µg folic acid from supplements and fortified foods?

What is the average daily intake of folate from unfortified foods?

When does the spinal column close in the fetus?

Pregnant women need how much folate?

Breastfeeding women need how much folate?

What is the UL for folic acid?

What are DFEs?

## Biochemistry, Structure and Forms

In the body, folate is reduced to dihydrofolate (FH<sub>2</sub>) and then to the biologically active form, tetrahydrofolate (FH<sub>4</sub>). Dihydrofolate reductase catalyzes both steps and facilitates conversion of dihydrobiopterin (BH<sub>2</sub>) to tetrahydrobiopterin (BH<sub>4</sub>) for production of serotonin and neutralization of ammonia.

5,10-Methylenetetrahydrofolate reductase (MTHFR) plays a key role in folate metabolism by channeling one-carbon units between nucleotide synthesis and methylation reactions (Schwan and Rosen, 2001.) The coenzyme forms of folic acid include tetrahydrofolate, methyl-THF, and methylene THF. Once taken up by cellular receptors, methyl THF is converted to tetrahydrofolate by the vitamin B<sub>12</sub> dependent enzyme, methionine synthase. Methylene tetrahydrofolate (CH<sub>2</sub>FH<sub>4</sub>) is formed from tetrahydrofolate by the addition of methylene groups from carbon donors in formaldehyde, serine, or glycine. Figure 1 shows the folic acid-methionine pathway and how vitamin B-12 works closely with folic acid.



### Methyl-tetrahydrofolate reductase (MTHFR) deficiency

MTHFR polymorphisms are technically “inborn errors of metabolism” on Chromosome 1, the longest human chromosome, and are related to many disorders (CDC, 2008). MTHFR polymorphisms affect 10% of the world’s population, especially Caucasians. When the MTHFR enzymes are ineffective or when dietary folate is inadequate, multiple changes occur. Inhibition of methionine synthase sets up a “methylfolate trap.” Variation in DNA methylation patterns and other epigenomic events influence the biological response to food components and vice versa (Milner, 2006.)

There are multiple MTHFR alterations. Two of the most common genetic polymorphisms of folate are C677T (cytosine displaced by thymine) and A1298C (adenine displaced by cytosine.) When there are disruptions in the folate pathway, serum tHcy may be elevated. Elevated tHcy levels, with or without the MTHFR alterations, may lead to undesirable health consequences (CDC, 2008; Devlin et al, 2006.) MTHFR deficiency symptoms are shown in Table 3.

**Table 3. MTHFR Deficiency Symptoms**

Congenital abnormalities such as cleft lip or palate	Mental retardation
Developmental delay	Neural tube defects or anencephaly
Gait abnormality	Pediatric stroke
Gastric cancer (Boccia et al, 2008; Dong et al, 2008)	Preeclampsia and thrombophilia (Bates et al, 2008; Mello et al, 2005)
Homocystinuria (rare)	Psychiatric manifestations
Infertility or miscarriage	Seizures

Sources: CDC, 2008; Boccia et al, 2008; Dong et al, 2008; Bates et al, 2008; Mello et al, 2005.

With the **MTHFR C677T (C>T) Allele**: serum tHcy and cholesterol levels may be increased; heart disease is more common; risks for diabetes, insulin resistance, inflammatory bowel disease increase; and neural tube defects occur more often, especially in males (Schneider, 2007.) MTHFR levels are only 40-50% of normal in autistic children with the C>T allele (Schneider, 2007.) Arsenic-related cancers, including skin, bladder, kidney or lung cancer, may be high in this population (Schneider, 2007; Marsit et al, 2006.) Table 4 shows the incidence of the C>T allele. Note that rates of spina bifida are highest in Ireland and Wales and their descendents around the world.

**Table 4. Incidence of C>T MTHFR Allele**

21% of US Latinos 20% of Italians 13% of British Caucasians 11% of Irish Caucasians	10-14% of other Caucasians 11% of Asians 8% of German Caucasians 1% of African Americans
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Source: Schneider, 2007

The **MTHFR A1298C (A>C) Allele** is not relevant for heart disease risk but appears to be related to autism, pediatric stroke, and schizophrenia (Schneider, 2007.) These alleles, with their pathways, can be seen in Figure 2.

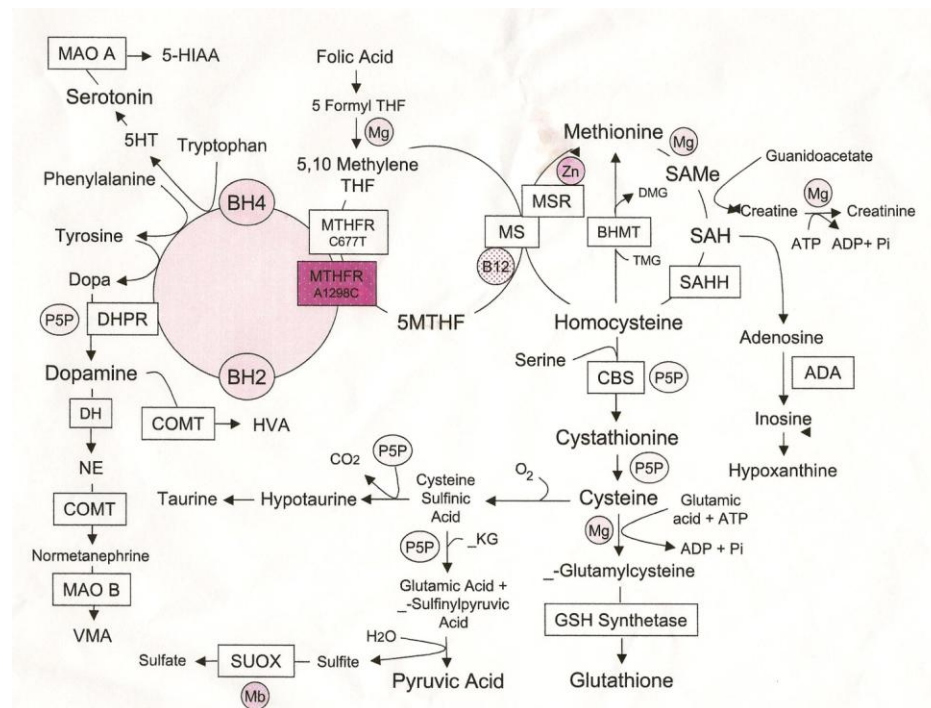


Figure 2. MTHFR Alleles and Pathways. Source: <http://www.autism.com/danwebcast/presentations/alexandria/Saturday/Schneider.pdf>

## Consequences of Folate Defects and Nutritional Transcription

Food components may increase or depress gene expression through nutritional transcription (Milner, 2006.) There are long-term implications for these changes. Insufficient intake of nutrients such as folic acid, choline, betaine, vitamin B12, omega 3 fatty acids, sulfur amino acids (methionine and cysteine), tryptophan (as precursor of serotonin and melatonin,) selenium and zinc may lead to undesirable



consequences over a lifetime. Genetic and environmental insults promote the development of cardiovascular disease, diabetes, cancer, infectious diseases, and neurological disorders. While the FDA mandate to fortify grain products with folic acid has reduced folate deficiency significantly in the general population (Dietrich et al, 2005; Pfeiffer et al, 2005,) there may be other nutrients in the food supply that could also reduce disease risk. These issues are being reviewed as potential public health measures.

### **Hypomethylation**

Hepatic folate, methyl group, and tHcy metabolism are interrelated. Pathology occurs when these pathways are disrupted (Williams and Schalinske, 2007.) Inadequate dietary intake of methyl groups leads to hypomethylation, disturbed hepatic methionine metabolism, elevated plasma tHcy, altered SAM concentrations, inadequate hepatic fat metabolism and even dyslipidemia. Maintenance of normal methyl group and tHcy homeostasis requires a balance between SAM-dependent transmethylation (which produces tHcy,) remethylation of tHcy back to methionine by folate mechanisms, and tHcy catabolism via the transsulfuration pathway (Williams and Schalinske, 2007; van der Linden et al, 2006.)

### **Methylation and the Blood Brain Barrier**

Neuronal connections during development are finely tuned and regulated through environmental interactions (diet, proteins, drugs, and hormones) along with changes in gene expression and epigenetic DNA methylation (Abdolmaleky et al, 2004.) Indeed, DNA methylation affects psychiatric disorders. Methionine metabolism is regulated by folate; folate deficiency and abnormal hepatic methionine metabolism need to be corrected. L-methionine treatment may exacerbate psychosis, while valproate hypomethylates DNA and reduces symptoms (Abdolmaleky et al, 2004.)

Dietary folate and folic acid supplements compete with L-methylfolate at the blood-brain barrier. Unmetabolized folic acid is unable to cross the blood brain barrier and may become bound to folate binding receptors on the membrane, blocking absorption of the active form, L-methylfolate (Zajecka, 2007.) Conditions with genetic-nutritional implications are described in the remainder of this article.

## **DISEASES WITH NUTRITIONAL-GENETIC IMPLICATIONS**

### **ALCOHOLIC LIVER DISEASE (ALD)**

Folate deficiency may promote the development of ALD by accentuating abnormal methionine metabolism, lipid oxidation, and liver injury (Halsted et al, 2002; Schalinske and Nieman, 2005.) A national symposium held in 2005 summarized the role of SAM, betaine, and folate in the treatment of ALD (Purohit et al, 2007). The scientists reported that these components decrease oxidative stress through up-regulation of glutathione and interleukin-10 synthesis; they also reduce inflammation via down-regulation of tumor necrosis factor-alpha (TNF- $\alpha$ .) These changes increase levels of SAM, inhibit apoptosis of normal hepatocytes, and stimulate apoptosis in liver cancer cells. Betaine may attenuate ALD by increasing the synthesis of SAM and glutathione, decreasing hepatic concentrations of tHcy (Song et al, 2008.)

### **AMYOTROPHIC LATERAL SCLEROSIS**

Environmental exposure to arsenic depletes SAM, especially in a state of folate insufficiency (Dubey and Shea, 2007.) In a study involving 62 amyotrophic lateral sclerosis (ALS) patients and 88 age-matched controls, elevated tHcy was found to damage motor neurons (Zoccolella et al, 2008.) This factor

suggests that a higher tHcy may be linked to faster progression of ALS. While folate deficiency seems to play a role in amyotrophic lateral sclerosis (ALS,) whether the MTHFR defect is present in ALS patients has yet to be elucidated.

## AUTISM SPECTRUM DISORDERS (ASDs)

Autism includes a spectrum of disorders related to developmental and behavioral criteria. Genetic underpinnings have been elusive; both genetic sensitivity and environmental issues reduce the capacity to clear toxins or repair damage at key developmental times. Unfortunately, autism prevalence has increased significantly (Muhle et al, 2004.) With higher rates, environmental factors must be enhancing genetic factors (Deth et al, 2007.)

Children with autism often have had higher use of oral antibiotics or higher mercury exposure during fetal/infant development (Adams et al, 2007.) Mercury intoxication causes increased oxidative stress and decreased detoxification capacity, leading to decreased plasma levels of methionine, glutathione (GSH), cysteine, SAM, and sulfate (Geier et al, 2008; James et al, 2004.) Therefore, a methylation problem is likely (Deth et al, 2007.)

Nutritional status affects immune resistance to toxins including heavy metals, Streptococcal infection, and other viruses. Autistic children often have IgA deficiency and a decrease in natural killer (NK) cell numbers and functionality (Vojdani et al, 2008.) They may also have antibodies against serotonin receptors, and a tumor necrosis factor (TNF) response to casein, gluten, and soy (Schneider, 2007.) Nutritional intervention with folinic acid, betaine, and methylcobalamin may be needed to normalize metabolic imbalances and to treat cerebral folate deficiency (Moretti et al, 2005; James et al, 2004.)

Finally, gluten-casein-soy free diets that have been proposed for parents of autistic children should be tested for effectiveness. Clinical trials are needed to verify these dietary suggestions. Because multiple genes, SNPs, receptors and enzymes seem to be involved in ASDs (see Table 5,) genome screening from affected families is also warranted. Studies suggest interactions of at least 10 genes (Muhle et al, 2004.)

**Table 5. Relevant Genes, Enzymes and Receptors Under Study in Autism**

Adenosine Deaminase (ADA)	Methionine Synthase Reductase (MSR)
Cystathionine -B-Synthase (CBS)	MTHFR C677 T and A1298C
Catecholamine-O-Methyltransferase (COMT 472G > A)	Paraoxonase (PON1)
FOXP2, RAY1/ST7, IMMP2L	Reduced folate carrier (RFC 80G > A)
GABA(A) receptor	Reelin and RELN genes at 7q22-q33
Glutathione-S-transferase (GST M1).	Serotonin transporter gene (5-HTT)
MET Receptor Tyrosine Kinase (MET)	Transcobalamin II (TCN2 776G > C)
Methionine Synthase (MS)	UBE3A genes

*Sources: James 2007; Schneider, 2007; Campbell et al, 2006; Muhle et al, 2004.*

## BONE DISEASE

Cysteine (Cys) is formed from tHcy. Cys is involved in bone metabolism as part of collagen and cysteine protease enzymes. High tHcy levels are associated with higher bone turnover, poor physical performance, lower bone mineral density (BMD,) frailty, and increased mortality among women (Gerdhem et al, 2007.) After menopause, the C>T or T>T genotype risk doubles risk when compared with the C>C genotype regardless of age, physical activity, occupation, passive smoking, height, weight, years since menopause, or total hip BMD (Hong et al, 2006.) Interestingly, low serum levels of B-vitamins (B-12, B-6 and riboflavin) may also increase fracture risk (Yazdanpanah, 2008.) Therefore, elevated tHcy is a risk factor for developing osteoporosis and should be corrected (Shiraki et al, 2008; Baines et al, 2007.)

## CANCER

Folate helps prevent changes to DNA that may lead to cancer (Powers et al, 2007.) A major clinical trial found that folic acid, B-12 and B-6 supplementation did not prevent or treat cancer effectively (Zhang et al, 2008.) Genetic testing for MTHFR alleles and clinical trials using methylated folate and vitamin B-12 may be warranted.

Oncogenes are silent with adequate DNA methylation; loss of methylation can induce their aberrant expression (van Vliet et al, 2007.) DNA methylation and methylation or acetylation of histone proteins bound to chromosomal DNA are being studied. Medications such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors can re-regulate the epigenetic signaling in the cancer cell (van Vliet et al, 2007.)

### Acute Leukemia

Acute lymphocytic leukemia (ALL) is the most common pediatric cancer worldwide. Because ALL has an association with MTHFR polymorphisms, especially in males, C>T and A>C can be good markers (Reddy and Jamil, 2006.) There is also evidence for MTHFR gene variants in adults who have acute lymphoblastic leukemia, especially the C>T allele (Pereira et al, 2006.) However, risks may vary from one population to another; MTHFR polymorphisms are not significant in Koreans who have ALL, for example (Oh et al, 2007.) More research is needed to clarify population-specific risks.

### Breast Cancer

Folate and defective methionine metabolism have a role in breast tumorigenesis. The presence of MTR A2756G and MTHFR C>T mutant allele in BRCA carriers is associated with increased breast cancer risk (Beetstra et al, 2008.) Estrogen receptor/progesterone receptor status modifies the association between the MTHFR C>T polymorphism and survival (Xu et al, 2008.) Interestingly, MTHFR A>C alleles have been associated with a decreased risk in breast cancer (Chou et al, 2006.) Medications that affect one-carbon metabolism should be targeted to improve breast cancer survival (Xu et al, 2008.)

Dietary changes can be recommended, such as sufficient B-complex vitamin intake (Chen et al, 2005.) While vitamin D3 has been linked to inflammatory conditions such as multiple sclerosis (Kimball et al, 2007,) vitamin D and calcium supplements do not protect against breast cancer (Chlebowski et al, 2008.)

### Colon Cancer

Elevated tHcy levels, DNA hypomethylation, and low levels of SAM as a precursor for methylation reactions play a key role in colon carcinogenesis (Burrin and Stoll, 2007; Martinez et al, 2006.) Individuals

having at least one mutant allele have a higher risk of colorectal cancer (Osian et al, 2007.) Interestingly, there may be a slightly protective role of the MTHFR C>T genotype in women and A>C in men and women (Sohn et al, 2008; Murtaugh et al, 2007.) However, individuals with the A>C allele may have shorter survival when they have metastatic colon cancer (Zhang et al, 2007.)

Chronic alcohol ingestion produces hypomethylation of DNA in the colonic mucosa during early colorectal neoplasia (Mason and Choi, 2005.) Genetic polymorphisms in MTHFR A > C, interacting with low folate or methionine intake and high alcohol use, promote this cancer (Curtin et al, 2007.) Alcohol intake redirects folate toward serine synthesis instead of thymidine synthesis (Mason and Choi, 2005.)

Low folate intake, low methyl donor status, and MTHFR polymorphisms play independent roles in the etiology of rectal cancer (Murtaugh et al, 2007.) In addition, inadequacies of riboflavin, vitamins B6 and B12 amplify aberrations of the p53 gene that are induced by folate depletion (Liu et al, 2008.) Studies must identify how much of each specific nutrient is needed. For example, folic acid supplements are NOT better in all circumstances (Ulrich, 2007.) Specific nutrient forms, such as methylated B12 and L-methylfolate, should be evaluated.

### **Gastric Cancer (GC)**

Folate plays a role in gastric carcinogenesis. In a meta-analysis, researchers found a 27% increase with the C>T allele in gastric cancer compared with the A>C allele, mainly in East Asians (Zintzaras, 2006a.) A more recent meta-analysis confirmed that C>T is more relevant (Boccia et al, 2008.) Indeed, different tumors seem to evolve from different genes and MTHFR relationships (Dong et al, 2008; Mao et al, 2008.) Inhibition of the over-expression of MTHFR is one possible treatment (Sun et al, 2008.)

## **CARDIOVASCULAR DISEASE**

Essential hypertension (EH) and cardiovascular disease are influenced by multiple genes (Ilhan et al, 2008.) C>T variants have been associated with an increased risk of cardiovascular disease and stroke in adults, as well as the risk of high blood pressure in pregnancy as preeclampsia (Genetics Home Reference, 2008.) Individuals with the MTHFR polymorphism have an independent risk factor for EH (Ilhan et al, 2008.)

Elevated tHcy levels (> 6 µmol/L) promote an increased incidence of stroke (thrombosis), cardiovascular disease, myocardial infarction (MI) and other cardiac effects. C>T genotypes tend to have a higher tHcy level (Genetics Home Reference, 2008.) However, in the NORVIT trial, researchers concluded that folic acid supplements used to lower risk of myocardial infarction may cause more harm than good, especially if given with B-12 supplements (Bonaa et al, 2006.)

Betaine given in high doses (6 g/d and higher) acutely reduces increased tHcy after methionine loading by up to 50%, whereas folic acid has no effect (Olthof and Verhoef, 2005.) Folic acid lowers plasma tHcy by 25% maximally, because 5-methyltetrahydrofolate is a methyl donor in the remethylation of tHcy to methionine (Olthof and Verhoef, 2005.) This fact may have played a role in the outcome of recent folic acid trials. Albert (2008) and Ebbing (2008) and their colleagues reported that long-term studies for lowering tHcy with folic acid, B-12 and B-6 supplements failed to prevent cardiac events. If tHcy plays a causal role in the development of cardiovascular disease, a diet rich in betaine and choline might benefit cardiovascular health through a tHcy-lowering effect (Olthof and Verhoef, 2005.) It is plausible that genetic testing is needed in high-risk population groups.

Elevated tHcy levels, hypomethionemia, and MTHFR alleles are risk factors for cardiovascular disease (Wiltshire et al, 2008; Koo et al, 2007; Klerk et al, 2002.) In the C>T mutation, individuals have a higher height, weight, body mass index, obesity index, arm circumference, fat mass, fat distribution, carotid IMT, and tHcy level than individuals with a normal genotype. MTHFR genotype may be useful in predicting the development of premature coronary artery disease, especially in hypertensive adolescents (Koo et al, 2007.)

## **Inflammation**

Genes affect inflammation. Lifelong antigenic burden leads to chronic inflammation, with increased lymphocyte activation and pro-inflammatory cytokine production (Vasto et al, 2007.) Cytokine genes may have polymorphisms that are associated with age-related diseases including atherosclerosis. Intake of nutrients such as zinc may be protective (Vasto et al, 2007.) Essential fatty acids, especially omega-3 sources, should also be considered; see Focus on EFAs.

While the EFAs cis-linoleic acid (LA) and alpha-linolenic acid (ALA) are needed by humans, deficiency is rare in humans because they are easily available in the diet. EFAs are metabolized to their respective long-chain metabolites: dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA) from linoleic acid, eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) from alpha linolenic acid. The two most recognized groups are Omega-3 (n-3) and Omega-6 (n-6) fatty acids. The n-3 fatty acids reduce the inflammatory process. The n-6 fatty acids promote the inflammatory process for wound healing, to fight infections, and to induce fever in the presence of foreign bodies.

As precursors to prostaglandins, thromboxanes, leukotrienes, lipoxins and resolvins, EFAs have significant clinical implications in obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer (Das, 2006.)

## **CYSTIC FIBROSIS (CF)**

Cystic fibrosis is a genetic defect (CF transmembrane conductance regulator) located on chromosome 7. There are multisystem clinical effects from increased proinflammatory mediators and oxidant stress (Innis et al, 2008.) Children with CF tend to have liver triacylglycerol accumulation, steatosis and fat malabsorption; high plasma tHcy, SAH, and adenosine levels; and lower levels of DHA, methionine, SAM, and GSH (Innis et al, 2008; Innis et al, 2007; Chen et al, 2005.)

Trials of supplementation with lecithin, choline, or betaine can significantly increase plasma methionine, SAM, and glutathione while decreasing tHcy levels (Innis et al, 2008; Innis et al, 2007.) While more clinical trials are needed, foods rich in lecithin, choline, betaine and DHA can safely be recommended to reduce the effects of oxidative stress in CF.

There may also be a relationship for using n-3 fatty acids for managing elevated lipids in cystic fibrosis, but more research is needed (Innis et al, 2008.) Currently, goals include normalizing altered (n-6) to (n-3) fatty acid balance and decreasing production of (n-6) fatty acid-derived inflammatory mediators (Innis et al, 2008.) Dietitians will want to monitor nutritional plans accordingly.

## DEPRESSION

Major depressive disorder (MDD) is debilitating and has a high morbidity rate (Farah, 2009.) The lifetime risk is 10-25% in women, 5-12% in men (Fava, 2007.) Even with treatments of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), a majority of patients never achieve symptom relief. Folate and its derivatives seem to have a causal relationship in depression (Lewis et al, 2006.) When there are lower red blood cell folate levels, episodes of depression are longer and more severe; folate may reduce symptoms when used with antidepressants (Fava, 2007.)

Elevated tHcy levels and depression have been identified among the elderly. Individuals with the C>T allele may be at higher risk for depression (Almeida et al, 2008.) It can be useful to test for MTHFR levels and to augment therapy with methylfolate and omega-3 fatty acids (Fava, 2007; Shelton, 2007). Deplin® contains 7.5 mg L-methylfolate and may help in managing depressive episodes. It unmasks vitamin B-12 anemia whereas folic acid masks vitamin B-12 anemia. After 4-week trials of Deplin®, if patients are not feeling better, psychiatrists often recommend doubling the dose to 15 mg/day (Zajecka, 2007.)

## DEMENTIA and ALZHEIMER'S DISEASE (AD)

The apolipoprotein E (APOE) epsilon4 allele is the primary gene that has been confirmed in AD. While DNA methylation usually increases with age, hypomethylation of the amyloid A4 precursor gene and hyperhomocysteinemia may contribute to the pathophysiology of AD (Aisen et al, 2008; Abdolmaleky et al, 2004.) Aggressive behavior, depression, and psychosis often occur in AD from imbalanced neurotransmitters levels.

Folate deficiency can also promote age-related neurodegeneration and depression (Chan et al, 2008.) Folic acid and vitamin B12 supplements do not slow cognitive decline in dementia patients but can lower tHcy levels (Malouf et al, 2003.) In another multicenter, randomized, double-blind controlled clinical trial, a regimen of high-dose (5 mg/d) folate, 25 mg/d of vitamin B6, and 1 mg/d of vitamin B12 found similar results (Aisen et al, 2008.) Where there are MTHFR polymorphisms, the active form of folate (methyltetrahydrofolate) may be more effective (Mischoulon and Raab, 2007.) Cerefolin® contains N-acetylcysteine (NAC) and L-methylfolate. SAM as a supplement can facilitate glutathione and acetylcholine utilization (Chan et al, 2008.) Longer trials are needed to determine efficacy of these products.

## DIABETES COMPLICATIONS

Hormonal imbalance controls key proteins that regulate the folate-SAM-homocysteine pathways (Williams and Schalinske, 2007.) Poor folate status has been associated with endothelial dysfunction in adolescents with type 1 diabetes (Wiltshire et al, 2008.) The MTHFR A>C genotype may confer protection against early nephropathy with lower tHcy levels, whereas MTHFR 677 TT genotypes may have earlier onset of retinopathy (Wiltshire et al, 2008.) The MTHFR C>T polymorphism has a significant association with diabetic neuropathy in Caucasians and in persons with type 2 diabetes (Zintzaras et al, 2007.) More rigorous studies are needed to define the role of genotypes in diabetes complications and management.

## DOWN SYNDROME (DS)

Folic acid has been implicated as a contributor to DS. For maternal risk for DS, Biselli et al (2008) found that the presence of 3 or more polymorphic MTHFR alleles increases the risk 1.74 times. Elevated maternal risk for DS was also observed when plasma tHcy concentration > 4.99 micromol/L (Biselli et al, 2008.) Other studies have reported conflicting results from genetic testing (Patterson, 2008.)



## HIGH RISK PREGNANCY

MTHFR polymorphisms may be a risk factor for recurrent implantation failure. When thrombophilic gene polymorphisms were compared among women with unexplained infertility and fertile control women, women with a history of unexplained infertility displayed a higher prevalence of MTHFR C>T polymorphisms than control women (Coulam et al, 2008.) Neevo® is a prescription available for the dietary management of women who are unable to fully metabolize folic acid as it contains 1 mg of L-methylfolate (Neevo, 2008).

## INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease (IBD) is associated with the inheritance of a number of specific SNPs and variants of other genes which disrupt bacterial homeostasis mechanisms (Ferguson et al, 2007.) In addition, the GI tract is a site of net tHcy release; production of tHcy within the intestinal mucosa may contribute to the inflammatory response and endothelial cell dysfunction (Peyrin-Biroulet et al, 2007.)

Patients with Crohn's disease (CD) and ulcerative colitis (UC) have a three- to fourfold greater risk of venous thrombosis compared with the general population (Bernstein et al, 2006.) Thromboembolism seems to develop as a result of interactions between genetic risk factors and acquired factors (Nagano et al, 2003.) It is important to screen for and treat folate and vitamin B12 deprivation as well as MTHFR polymorphisms, especially for those who have active disease, history of intestinal resection, or treatment with methotrexate (Peyrin-Biroulet et al, 2007.) In vulnerable individuals, use of sulfur amino acids (methionine and cysteine) may also be needed. See Focus on Sulfur Amino Acids: Methionine and Cysteine.

### FOCUS ON Sulfur Amino Acids: Methionine and Cysteine

Sulfur amino acid metabolism in gastrointestinal tissues may be linked to human health and gut disease. The gastrointestinal tract metabolizes 20% of dietary methionine; its metabolic fate is transmethylation to tHcy and transsulfuration to cysteine. Cysteine impacts redox status and regulates epithelial intracellular signaling, proliferation and survival (Burrin and Stoll, 2007.) Because methionine transsulfuration, a constituent of antioxidant systems, and local production of tHcy, S-adenosylmethionine and antioxidants contribute to the development of gastrointestinal diseases, dietary intervention with folate and cysteine may have a role in prevention and treatment (Burrin and Stoll, 2007.)

## NEURAL TUBE DEFECTS

The etiology of neural tube defects (NTDs) is related to environment and genetics. Spina bifida occurs by the 28<sup>th</sup> day of gestation (Li et al, 2006.) In anencephaly, the upper end of the neural tube fails to close and the brain either never completely develops or is totally absent, resulting in spontaneous loss, stillbirth or neonatal death. Folic acid supplements help to prevent NTDs, yet many women still do not take them (Cena et al, 2008.) While supplementation prevents the majority of NTDs, the MTHFR polymorphism is a risk factor where diets deficient in folate do not influence the incidence or severity of NTDs. Inborn errors of folate metabolism include congenital folate malabsorption, severe MTHFR deficiency, and formiminotransferase deficiency (Whitehead, 2006.)

There is also the need to investigate the folic acid and methionine cycle genes for SNP genotyping and the effects of diet (Boyles et al, 2007.) For example, the MTRR 66GG genotype is a maternal risk factor for NTDs, especially when vitamin B12 status is low (van der Linden et al, 2006.) In a study that recruited

Hispanics of Mexican descent and North American Caucasians of European descent, the maternal C>T allele was a strong risk factor for NTDs (Au et al, 2008.) Different populations have different results, so studies are needed in multiple population groups. Finally, choline and betaine may play a role in NTDs; see Focus on Choline and Betaine.

#### **FOCUS ON CHOLINE AND BETAINE**

Choline is involved in one-carbon metabolism for methylation of tHcy to methionine. Inadequate choline intake may contribute to NTDs, liver triacylglycerol accumulation, and oxidative stress (Innis et al, 2007; Shaw et al, 2004.) Phospholipids and fatty acids require choline via betaine to acquire the methyl groups to regenerate SAM for GSH production.

Betaine (trimethylglycine) is formed from choline, or from the diet. It is mostly found in the liver and kidney (Holm et al, 2007) and provides methyl groups for the tHcy-methionine cycle. Betaine attenuates a rise in tHcy after meals (Olthof and Verhoef, 2005) and is a strong determinant of plasma tHcy in subjects with low serum folate, especially in the C>T genotype who have an inadequate B-vitamin status (Holm et al, 2007.) Low levels of betaine-tHcy methyltransferase (BHMT) may be associated with NTDs (Boyles et al, 2007); see Figure 1.

In the diet, betaine is widely distributed in animals and plants, especially seafood, wheat germ, bran, and spinach. Betaine intake from foods is estimated at 0.5-2 g/d (Olthof and Verhoef, 2005.) Because betaine treatment increases plasma low-density-lipoprotein (LDL) cholesterol, these changes in blood lipids may have an undesirable effect (Zeisel, 2006.) Results may also vary from one population to another. Studies are needed to clarify how different populations respond to betaine and choline from diet or supplements.

#### **PARKINSON'S DISEASE (PD)**

Increased plasma tHcy accelerates the selective dopaminergic cell death underlying PD (De Lau et al, 2005.) Todorovic et al (2006) conducted a prospective, population-based cohort study with 5,920 participants aged 55 and older. They found the TT variant of the MTHFR C>T polymorphism connected with increased risk for PD among smokers.

Elevated plasma tHcy levels have been observed in PD patients treated with levodopa. New approaches have been evaluated for management of PD in persons who have MTHFR alleles (Caccamo et al, 2007; Todorovic et al, 2006.) Serum tHcy levels do not seem to affect global measures of cognition, mood, dyskinesias, fluctuations, or freezing, but higher serum vitamin B12 levels are associated with lower dyskinesia risk (Camicoli et al, 2009.) Adequate B-complex intake and measurement of serum levels of B-12 may be an important measure.

#### **RENAL DISEASE**

Elevated tHcy levels are common in patients with chronic kidney disease (Sunder-Plassman, 2006.) Supplemental folic acid, B-12 and B-6 are often recommended. One major study using folic acid supplementation found no improvement in mortality rates in this population (Jamison et al, 2007.) In another randomized, prospective study with 341 hemodialysis patients, one group received 50 mg of 5-MTHF intravenously and the other took 5 mg/day folic acid. Both groups received intravenous vitamins B6 and B12. High-dose supplemental 5-MTHF reduced inflammation (CRP levels) regardless of tHcy levels, and improved overall patient survival (Cianciolo et al, 2008.) ESRD patients who enter chronic dialysis with a previous cardiovascular event (CV), high total tHcy levels, or MTHFR 677TT genotype must be



considered at high risk for more cardiovascular events (Pernod et al, 2006.) The use of L-methylfolate should be evaluated individually.

## **RHEUMATOID ARTHRITIS (RA)**

Methotrexate (MTX) is often prescribed in RA. It inhibits dihydrofolate reductase and folate-dependent enzymes (Kurzawski et al, 2007.) Research has examined the association of folate-dependent gene polymorphisms with methotrexate (MTX) toxicity; pharmacogenetic associations seem to be race-specific (Ranganathan et al, 2008.) Well-designed studies are needed to clarify the role of MTHFR polymorphisms in varying patient genotypes and ethnicity (Tottoli and DeMattia, 2008; Ranganathan et al, 2008.)

The C>T and A>C polymorphisms influence the cytotoxic effect of fluoropyrimidines and antifolates and have a role in predicting efficacy and toxicity in RA patients (Tottoli and DeMattia, 2008.) The C>T and A>C alleles yield higher rates of RA remission in patients treated with MTX if they also receive high doses of folic acid (Kurzawski et al, 2007.) The A>C polymorphism protects against overall MTX toxicity without minimizing efficacy of the drug (Bohanec Grabar et al, 2008.)

## **SCHIZOPHRENIA (SCZ)**

Evidence implicates methylation of genes in schizophrenia and mood disorders (Abdolmaleky et al, 2004.) SCZ is characterized by neuron pathology, mediated by hypermethylation of gamma-amino butyric acid (GABA) and reelin (Guidotti et al, 2009; Grayson et al, 2006.) Working memory impairment is associated with abnormal dopamine signaling in the prefrontal cortex, which is under complex genetic control (Roffman et al, 2007.)

In a Pub Med review, Frankenburg (2007) studied associations between folate, cobalamin (B-12), tHcy, and MTHFR polymorphisms in both SCZ and depression. Folate supplementation alone exacerbates cobalamin deficiency; therefore, both folate and cobalamin deficiencies should be identified. Screening for tHcy, methylmalonic levels, and MTHFR polymorphisms should be considered. Folate supplementation alone is not sufficient to manage symptoms, but SAM may be useful (Frankenburg, 2007.) Clearly, clinical trials are needed.

MTHFR C>T is often found in depression, SCZ, and bipolar disorder (Gilbody et al, 2007.) It has been associated with reduced dopamine signaling and executive function impairment (Roffman et al, 2007.) Roffman and associates (2007) tested 200 outpatients with SCZ for the MTHFR genotype along with serum folate and tHcy. Results of the Positive and Negative Syndrome Scale (PANSS) showed that individuals with the A>C allele had a slight correlation with positive symptoms (hallucinations, hearing voices.) The C>T allele seems to promote negative symptoms (depression, dysthymia) but actually protects against positive symptoms (Roffman et al, 2007.) In another meta-analysis, A>C polymorphisms were found to be mildly related to both depression and SCZ among East Asians (Zintzaras, 2006b.)

Genes for bipolar disorder and depression are different (Zintzaras, 2006b,) but there may be some relationship within families. Catechol-O-methyltransferase (COMT) is a key enzyme for regulating dopamine transmission in the prefrontal cortex (Woodward et al, 2007.) A SNP (val108/158met) in the gene that codes for COMT decreases cognitive function but is corrected with atypical antipsychotic drugs (Woodward et al, 2007.) Valproate

Recent advances in schizophrenia (SZ) research indicate that the telencephalic gamma-aminobutyric acid (GABA)ergic neurotransmission deficit associated with this psychiatric disorder probably is mediated by the hypermethylation of the glutamic acid decarboxylase 67 (GAD(67)), reelin and other GABAergic promoters. A pharmacological strategy to reduce the hypermethylation of GABAergic promoters is to induce a DNA-cytosine demethylation by altering the chromatin remodeling with valproate (VPA). When co-administered with VPA, the clinical efficacy of atypical antipsychotics is enhanced. This prompted us to investigate whether this increase in drug efficacy is related to a modification of GABAergic-promoter methylation via chromatin remodeling. Our previous and present results strongly indicate that VPA facilitates chromatin remodeling when it is associated with clozapine or sulpiride but not with haloperidol or olanzapine. This remodeling might contribute to reelin- and GAD(67)-promoter demethylation and might reverse the GABAergic-gene-expression downregulation associated with SZ morbidity.

### **Metabolic Syndrome in SCZ**

Metabolic syndrome and insulin resistance are 2-4 times higher in the SCZ population than the general population (Ellingrod et al, 2008.) Both decreased MTHFR activity and elevated tHcy can increase risk of cardiovascular disease. The C>T allele carriers are at greater risk for insulin resistance with increased central adiposity, independent of age, gender, BMI, or metabolic syndrome diagnosis (Ellingrod et al, 2008.)

### **Reelin and SCZ**

A secretory protease that supports neurodevelopment and synaptic plasticity, Reelin is necessary for neuronal migration and synaptogenesis (Suzuki et al, 2008.) Levels are reduced in SCZ and bipolar disorder, suggesting hypermethylation of the promoter region (Abdolmaleky et al, 2004.) Reelin is more heavily methylated in brain regions in patients diagnosed with SCZ as compared to non-psychiatric control subjects (Grayson et al, 2005.) Methyl donors may actually worsen symptoms (Schneider, 2007.)

Viral infections reduce Reelin levels; second trimester influenza may trigger SCZ in susceptible populations (Schneider, 2007.) In this respect, autism and SCZ have similar connections; prenatal infections including rubella, measles, herpes, and cytomegalovirus account for some cases of autism (Schneider, 2007; Muhle et al, 2004.) If the pathogenesis of SCZ is related to the Reelin-VLDLR/ApoER2 signaling pathway, peripheral VLDLR mRNA levels may become reliable biological markers of SCZ (Suzuki et al, 2008.)

## **SLEEP DISORDERS**

### **Serotonin**

Serotonin (5-hydroxytryptamine, or 5HT) is synthesized in neurons and in the gastrointestinal tract. The GI tract produces 80-90% of total body serotonin. It is part of the folic acid pathway (see Figure 2.) While serotonin is found in walnuts, mushrooms, fruits (bananas, papaya, dates, pineapple, kiwifruit, tomatoes, plantains) and vegetables, the dietary form does not cross the blood-brain barrier (BBB.) Increasing diets rich in precursor tryptophan from meat, fish, poultry and protein foods does not help unless the ratio of tryptophan to phenylalanine and leucine is raised because these amino acids compete at the BBB. Eating a carbohydrate-rich meal releases insulin, causing any amino acids in the blood to be absorbed except

for tryptophan. Tryptophan remains in the bloodstream at high levels following a carbohydrate meal, which means it can freely enter the brain and cause serotonin levels to rise.

In the central nervous system, serotonin is a neurotransmitter and helps to regulate body temperature, appetite, metabolism, anger, and aggression. It is important for circadian rhythms and sleep. The 5-HT(2A) serotonin receptor plays an active role in regulating slow wave sleep, important for restful sleep. There are studies underway to identify more purposes of serotonin, such as inhibition of bone formation. One study has also linked cases of sudden infant death syndrome (SIDS) with low levels of serotonin (Lesurtel et al, 2006.)

### **Melatonin (MT)**

Melatonin is an indole formed enzymatically from L-tryptophan (Konturek et al, 2007.) MT is found in the pineal gland, retina, lens, bone marrow, GI tract, and skin (Pandi-Perumal et al, 2008.) The production of MT by the pineal gland shows high night-time surge, especially at younger age, followed by a drop during the daylight (Konturek et al, 2007.) Production is inhibited by light, permitted by darkness, and decreased by artificial lighting, especially blue light. MT analogues have a rapid onset of action, improve sleep quality, and enhance mood. Agomelatine has 5-HT(2c) antagonist properties that may be used in treating patients with major depression, insomnia and some other sleep disorders (Pandi-Perumal et al, 2008.)

Much more MT is generated in the GI tract than in the pineal gland. In the GI tract, MT is partly released into portal circulation. In the liver, it has cytoprotective, anti-inflammatory properties that have healing potential in disorders such as esophagitis, gastritis, peptic ulcer, pancreatitis and colitis (Konturek et al, 2007.) Studies are also evaluating MT for treating migraines and cluster headaches (Stillman and Spears, 2008.)

MT is a powerful antioxidant that protects mitochondrial DNA. Unlike serotonin, it easily crosses blood-brain barrier. Studies suggest a role in Parkinson's, Alzheimer's disease, autism, ADHD, seasonal affective disorder, and bipolar disorders. MT also helps to regulate food intake by lowering leptin secretion at night. As a highly lipophilic substance, MT reaches all body cells within minutes (Konturek et al, 2007.) In conditions such as night eating syndrome (NES,) evening hyperphagia and frequent awakenings with ingestion of food yield higher levels of glucose, insulin, and ghrelin (Allison et al, 2005.) The effects of melatonin on obesity management are not yet clear.

Circulating CT decreases with age. MT stimulates the production of progenitor cells for granulocytes, macrophages, NK cells and CD4+ cells; it also inhibits CD8+ cells (Srinivasan et al, 2005.) MT regulates intracellular glutathione levels and has the potential to enhance immune function (Srinivasan et al, 2005.) There is a potential use for MT in cancer by strengthening T-cell lymphocytes (Linton and Thoman, 2001.)

MT, when taken with calcium, acts as an immunostimulator. Because this could aggravate conditions such as rheumatoid arthritis, use MT supplements with caution.

### **VISION: AGE-RELATED MACULAR DEGENERATION (AMD)**

AMD is a cause of vision loss in older Americans. In AMD as well as glaucoma, tHcy levels are often elevated. Taking a combination of folic acid (2.5 mg per day), pyridoxine hydrochloride (50 mg per day) and cyanocobalamin (1 mg per day) appears to decrease the risk of age-related macular degeneration in women (Christen et al, 2009.) This recent study suggests that improved antioxidant effects and blood

vessel functioning in the eye result from this treatment. A follow-up evaluation of MTHFR and other genes in this population would be a worthwhile study.

## DRUGS AND MEDICATION ISSUES

MTHFR polymorphisms influence the tHcy-lowering effect of folates. Alleles modify the pharmacodynamics of antifolates and drugs whose metabolism, biochemical effects, or targets require methylation (Schwan and Rosen, 2001.) With these genetic issues, medication management can be a challenge. Drug interactions often include altered appetite, changes in intake, and nutrient interactions.

Folic acid will not correct changes in the nervous system that result from vitamin B<sub>12</sub> deficiency. Permanent nerve damage could occur if vitamin B<sub>12</sub> deficiency is not treated. Supplemental folic acid should not exceed the UL of 1000 mcg (1 mg) per day to prevent masking symptoms of vitamin B<sub>12</sub> deficiency. Older persons should test first for serum B-12 levels before folic acid supplementation.

Folic acid supplements are not the same as "Folinic acid." Leukovorin (folinic acid) is a form of folate that "rescues" or reverse toxic effects of methotrexate. Follow medical advice on the use of folic or folinic acid supplements when methotrexate is prescribed. Table 5 lists common medications that interfere with folic acid metabolism. More succinct applications of pharmacogenetics are needed to tailor drug therapies for individuals.

**Table 5. DRUGS THAT INTERFERE WITH FOLIC ACID METABOLISM**

Alcohol and tobacco	Methotrexate (MTX)*
Anticonvulsants	Oral contraceptives
Antacids	Sulfonamide (inhibits PABA in the reactions of dihydropteroate synthetase)
Aspirin	
Dihydrofolate reductase inhibitors: pyrimethamine and trimethoprim	

\*MTX is used for cancer, rheumatoid arthritis, lupus, psoriasis, asthma, sarcoidosis, primary biliary cirrhosis, inflammatory bowel disease. Low doses of methotrexate can deplete folate stores and cause side effects. High folate diets and supplemental folic acid may reduce toxic side effects of low dose MTX without decreasing effectiveness.

There are significantly different allele frequencies between populations (Hughes et al, 2006.) In the future, physicians may want to prescribe an L-methylfolate supplement in individuals with MTHFR alleles. Table 6 lists some available forms of L-methylfolate.

**Table 6. Available Forms of L-Methylfolate**

<u>Metagenics</u>
Fola-Pro® (800 mcg L-5-methylfolate)

PamLabs – prescription only

Cerefolin ® (5.6 mg L-methylfolate, 2 mg methylcobalamin, 600 mg N-acetylcysteine)

Deplin ® (7.5 mg L-methylfolate)

Metanx ® (2.8 mg L-methylfolate; 2 mg methylcobalamin; 25 mg pyridoxal 5-phosphate)

Neevo® for pregnant women (1 mg L-Methylfolate )

## IMPLICATIONS FOR DIETETIC PROFESSIONALS

Some genetic variations arise as a consequence of diet. Dietitians must understand the molecular mechanisms underlying gene-nutrient interactions; understand their modification by genetic variation; provide dietary recommendations and nutritional interventions that optimize individual health (Stover, 2006.) Individualized dietary interventions should be based upon knowledge of nutritional requirements, nutritional status, and genotype to optimize health and to prevent or mitigate chronic diseases (Castle and DeBusk, 2008.) Table 7 lists four key principles of nutrigenomics.

**Table 7. Four Principles of Nutrigenomics (Kaput, 2005)**

Common dietary chemicals alter gene expression and/or genome structure

The influence of diet on health depends upon an individual's genetic makeup

Genes or normal common variants are regulated by diet

Improper diets in some individuals may promote some chronic diseases under the right conditions

An emerging goal of medical nutrition therapy is to tailor dietary advice to an individual's genetic profile (Vakili and Caudill, 2007.) The supermarket of today will be the pharmacy of tomorrow (Ferguson, 2006.) While a multivitamin-mineral supplement is one low-cost way to ensure intake of the RDA of micronutrients throughout life (Ames, 2006,) current standardized nutritional guidelines may be ideal for only a small proportion of the population.

The development of nutritionally novel foods to support the health of specific populations is on the horizon (Ferguson et al, 2007.) Specific food enhancements may be needed for the micronutrients commonly lacking in diets (such as iodine, iron, zinc, selenium, magnesium, calcium and B-complex vitamins.) With these enhancements, it will be important to recognize that not all persons need fortified foods, and that many are also taking multivitamin-mineral supplements. Identifying individual genetic variations and dietary intakes will have a significant effect on disease-protective dietary counseling (Ferguson, 2006.)

The American Dietetic Association supports the use of standardized language for nutritional care. While the terms may be standardized, the care of individuals remains unique and personalized. Using the Nutrition Care Process of the American Dietetic Association, two examples of individualized nutrition management are shown in Table 8.

**Table 8. Nutrition Care Process Examples**

***Nutrition Diagnosis Example #1***

Problem: Altered nutrient utilization

Etiology: related to inability to metabolize dietary and supplemental folic acid

Signs/Symptoms: as evidenced by C>T polymorphism of MTHFR, elevated tHcy, normal serum folate

**Suggested Intervention:** Nutrient delivery or medication management with L-methylfolate.

***Nutrition Diagnosis Example #2***

Problem: Excessive intake of vitamins (folic acid)

Etiology: related to excessive use of supplemental folic acid medical diagnosis of vitamin B-12 anemia

Signs and Symptoms: as evidenced by use of a multi vitamin-mineral supplement 3 x daily and folic-acid fortified cereals 2x daily.

**Suggested Intervention:** Nutrition education and counseling about appropriate intake of folate from foods and reduction of excessive supplement use.

Dietitians are uniquely trained to manage the counseling for individuals with metabolic and genetic disorders and may wish to acquire subspecialty knowledge in genetics. This counseling work is highly rewarding as people explore their options for prenatal and lifelong decisions. This work is also challenging, as some ethical decisions have to be discussed. Dietitians should review genetic test results with their patients and individualize their counseling accordingly.

In summary, dietitians need to ask good questions and learn about genetics to understand systemic nutrition. Edward Bulwer Lytton suggests that, to find what you seek in the road of life, “leave no stone unturned.” The knowledge base is new, and there is an urgent need to deepen it. We must seek the evidence and understand the genetic basis before we can explain the effects of nutrition throughout the life cycle. Albert Einstein advised that “if you can’t explain it simply, you don’t understand it well enough.” Because of the need to understand this new science, our continuing education assignment is clear and compelling.

**Recommended Websites**

CDC, genomics. [www.cdc.gov/genomics](http://www.cdc.gov/genomics).

Deplin®, Metanx®, Cerefolin®, Neevo®: Pan Am Labs, <http://www.pamlabs.com/>

Fola-Pro®: Metagenics: <http://www.metagenics.com/>

NCMHD Center of Excellence for Nutritional Genomics. <http://nutrigenomics.ucdavis.edu>

National Society of Genetic Counselors: [http://www.nsgc.org/consumer/familytree/tree\\_images.cfm](http://www.nsgc.org/consumer/familytree/tree_images.cfm)

**Answers to Folate Trivia**

1 µg food folate = 0.8 µg folic acid from supplements and fortified foods

Average daily intake of folate from unfortified foods= 200 mcg

Fetal spinal column closes between 17-28 days

Pregnant women need 600 mcg folate/day

Breastfeeding women 500 mcg folate/day

The UL for folic acid is 1000 mcg

Dietary Folate Equivalents ("DFEs") measure the differences in the absorption of naturally occurring food folate and the more bioavailable synthetic folic acid.

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