Understanding MTHFR genetic mutation

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What is MTHFR?

Methylenetetrahydrofolate reductase (MTHFR) is an enzyme that activates and regulates folate metabolism in the body. Specifically MTHFR converts 5,10- methylenetetrahydrofolate into 5-methyltetrahydrofolate (5-MTHF), the active form of folate. 5-MTHF then plays a key role in the single carbon transfer (i.e. methylation) reactions involved in the synthesis of nucleotides for DNA and RNA production; manufacture of S-adenosylmethionine (SAMe); methylation of DNA, proteins, neurotransmitters (NTs), and phospholipids; and remethylation of homocysteine to methionine.[1] [2]

MTHFR SNPs

The Human Genome Project gave birth to the study of nutrigenomics—how nutritional status affects genetic expression and genes affect nutrient needs. Current research in nutrigenomics indicates that some individuals, due to their unique genetic patterns and expression, do not produce adequate or effective MTHFR. The genetic variations in DNA sequencing are known as single nucleotide polymorphisms (SNPs). When SNPs occur in genes, they produce variants or alleles of that gene. Single nucleotide polymorphisms in the gene that codes for MTHFR result in production of an enzyme with decreased activity, an anomaly that can have an impact on a myriad of biochemical processes. Ultimately MTHFR SNPs can cause hyperhomocysteinemia (especially if folate levels are low); affect nervous system, behavioral, and vascular health; contribute to birth defects, miscarriage, and preeclampsia; modulate cancer risk; and increase chronic disease risk.[3] [4] [5] [6] [7]

Although a number of MTHFR variants have been identified, currently the two most researched and understood are 677C>T (C667T also called rs1801133) and 1298A>C (A1298C also called rs1801131). Of course the final expression and influence of these variants can be affected by nutritional status, environment, genotype, and race/ethnicity.[8] [9]

The C677T allele is the most extensively studied variant. An estimated 50% of a population may have inherited one copy (heterozygous C/T) while up to 25% may have inherited two copies (homozygous T/T).10 C677T is considered “thermolabile;” individuals homozygous for C677T have at least a 50-60% reduction in MTHFR activity at body temperature (98.6°F/37°C).11 Severe MTHFR deficiency with 0-20% enzyme activity can cause early developmental delay, seizures, motor/gait dysfunction, and even schizophrenic disturbances.[12]

The prevalence of the C677T SNP varies significantly between ethnic populations. It appears to be considerably greater (up to 20%) in Italians, Hispanics, and Asians than in Caucasians and Africans.13 Population frequency of the

A1298C variant is not well documented at this time though it may be similar to that of the C667T variant.

The C677T allele (especially the homozygous genotype or the combination of C677T with other MTHFR variants such as A1298C) can contribute to hyperhomocysteinemia, increased risk of cardiovascular disease, migraine, depression, schizophrenia, bipolar disease, dementia, Alzheimer's disease, and fetal neural tube defects.[14] [15] [16] [17] [18] [19] Migraine with aura and several clinical symptoms of migraine were significantly associated with the C677T variant.[20]

The A1298C allele, though common, may not fundamentally affect disease risk unless present in homozygous form or if combined with other SNPs. The A1298C SNP alone may not have as profound an effect on homocysteine levels but can contribute to hyperhomocysteinemia if present along with the C677T allele and low folate levels.[21]

MTHFR SNPs, along with other SNPs that affect homocysteine metabolism, may even increase obesity risk.[22] Interesting research suggests that the C677T and A1298C variants and the resulting hypomethylation of DNA may contribute to an adaptive phenomenon affecting muscle cells and resulting in increased muscle mass.[23] The combination of C677T and A1298C alleles appears to contribute to male infertility as well.[24] Both the C667T and A1298C alleles appear to affect the metabolism and efficacy of medications (including methotrexate, nitrous oxide, and antidepressants). These genetic variations should be taken into account when considering drug dosing.[25]

5-MTHF

5-methyltetrahydrofolate is the active, circulating form of folate and the predominant form found naturally in food.26 27 Currently folic acid (the synthetic inactive form that has no biological function) is used to fortify foods due to its increased stability and resistance to oxidation.28 However, synthetic folic acid is not the preferred form of supplementation, particularly for individuals unable to process it effectively. Instead, 5-methytetrahydrofolate (also called L-methylfolate) is recommended.[29] [30] [31]

5-methyltetrahydrofolate plays a key role in methylation, the donation of a methyl group (CH3) to another molecule in the body. This action is a crucial step in several biochemical reactions including DNA repair, detoxification, monoamine neurotransmitter synthesis, and recycling of molecules such as homocysteine, methionine, and tetrahydrobiopterin (BH4). Insufficient methylation can sabotage the body's biochemistry and may contribute to cognitive impairment, mood and behavior disorders, immune dysfunction, cancer, cardiovascular disease, comprised detoxification, and susceptibility to addiction.[32] [33] [34] [35]

5-MTHF appears to have an independent and supportive effect on blood vessels[36] [37] [38] and on reduction of vascular and lipoprotein oxidation.39 Clearly, recognizing and addressing genetic variations in the MTHFR enzyme and

resulting alterations in folate metabolism is vital to supporting adequate methylation and overall health.

Homocysteine Metabolism

Homocysteine is a potentially toxic, sulfur-containing amino acid that must be kept in check; without proper processing, it can build up and cause tissue and organ damage. Increased homocysteine levels are observed in individuals who are homozygous for C677T and who also have compromised folate status. The combination of C677T and A1298C can contribute to hyperhomocysteinemia as well.[40]

Elevated blood levels and accumulation of homocysteine are associated with a variety of anomalies including birth defects, diabetes, renal disease, osteoporosis, and vascular, immune, neurodegenerative, and neuropsychiatric disorders.[41] [42]Elevated serum homocysteine (>~15 *u*mol/L) is considered an independent risk factor for vascular disease and related complications such as myocardial infarction, stroke, and venous thrombosis.[43] Although homocysteine levels of less than 13*u*mol/L are considered “normal,” 6-8 *u*mol/L is more likely to be an ideal or optimal level.[44]

Although MTHFR facilitates the conversion of homocysteine back to methionine, this conversion may be limited and ineffective in the event of methionine loading.45 In such cases homocysteine can be methylated by the compound betaine (trimethylglycine-a compound found in food or produced in the body from choline). Homocysteine can also be converted to cysteine via transsulfuration in the liver, a process dependent on the cofactor vitamin B6.[46] The Linus Pauling Institute Micronutrient Information Center provides a detailed diagram of homocysteine metabolism.[47]

Inadequate MTHFR activity also disrupts the overall metabolism of methionine and its byproduct S-adenosylmethionine (SAMe)—compounds crucial to protein synthesis, neurotransmitter metabolism, and methylation cycles in the body.[48]SAMe itself is a key methyl donor.

Conditions associated with MTHFR SNPs

There is a growing body of knowledge and awareness with regard to nutrigenomics, supporting the current premise in functional medicine that “genes load the gun, but environment pulls the trigger.” The recognition that genes and environment interact on such a fundamental basis is an important component of comprehensive healthcare. In view of this knowledge, hopefully testing for MTHFR SNPs will become routine.[49]

Autism Spectrum Disorders

One carbon metabolism, particularly DNA methylation, is believed to play a critical role

in the development, severity, and potential treatment of autism spectrum disorder (ASD).[50] The link between ASD, methylation, and the MTHFR variants is being closely studied, especially in view of the fact that C677T and A1298C variants occur at significantly higher rates in those with ASD compared to controls.[51] [52] [53] [54]

A 2013 meta-analysis reports that the C677T variant was significantly associated with an increased risk of ASD in countries where foods were not fortified with folic acid. The A1298C variant was actually associated with a reduced risk of ASD in the recessive model.[55]

The CHARGE (Childhood Autism Risks from Genetics and Environment) study (2003-2009) revealed that “mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy.”[56]Researchers concluded that taking prenatal vitamins prior to conception may reduce the risk of autism in the child, especially when mother and child are genetically susceptible to alterations in one carbon metabolism.

The CHARGE research demonstrated that an average intake of ≥600 ug/day of folic acid in the first month of pregnancy was associated with a significantly reduced risk of ASD and risk declined further with increasing folic acid intake.[57] The association between folic acid and risk of ASD was greatest for mothers and children with the C677T SNP. A National Institutes of Health clinical trial is researching folinic acid intervention in ASD with a focus on language impairment.[58]

Increased blood levels of homocysteine have been associated with autism and may be an important clinical indicator and monitoring tool.[59] Although one 2012 meta-analysis did not confirm an association of ASD with elevated homocysteine, it did confirm an association with ASD with decreased blood levels of methionine which may indicate that disruption of methylation cycles could be at play. The study does confirm an association of homozygous C677T variants with ASD.[60]

Even if alterations in folate metabolism and MTHFR activity are overcome, delivery of active folate to the brain may be impaired in ASD. Receptors in the brain have a high affinity for 5-MTHF which must be transported across the blood-brain barrier.[61] Research suggests that for some children with autism, a defect in folate transport may lead to cerebral folate deficiency (CFD) and contribute to neurological deficits.[62] This premise is supported by research revealing that a subgroup of individuals with Rett syndrome (an ASD) have decreased levels of 5-MTHF in their cerebrospinal fluid, suggesting
anomalies in folate binding and/or transport.[63] [64]

Ongoing research suggests that in some cases of autism and cerebral folate deficiency, autoantibodies to folate receptors (in mother and in child) appear to be the cause of altered transport of folate into the brain.[65] [66] Autistic

children with folate receptor autoantibodies and decreased cerebrospinal 5-MTHF were found to favorably respond to folinic acid supplementation and experienced significant improvement in verbal communication, language, attention, and behavior.67

Attention Deficit Hyperactivity Disorder

Some research suggests that MTHFR SNPs may be associated with attention deficit hyperactivity disorder (ADHD), a condition now considered to be part of the autism spectrum. One study of Turkish children (40 with ADHD and 30 controls) suggested a possible association between the A1298C allele and attention deficit disorder.68 However, a larger study of Turkish children (100 diagnosed with ADHD and 300 controls) found no association between the C677T or A1298C MTHFR alleles.[69]

Another study focusing on the incidence of ADHD following acute lymphoblastic leukemia therapy revealed that children with the A1298C genotype had a 7.4 fold increase in ADHD diagnosis, while those with the C677T SNP had a 1.3 fold increase in ADHD diagnosis.[70] A study of 478 children suggested that ADHD symptoms in children with myelomeningocele (a neural tube defect) may be related to MTHFR SNPs, though not C677T or A1298T specifically.[71]

Cancer

The association between MTHFR SNPs and cancer is still being clarified; MTHFR SNPs may increase risk of some cancer while decreasing risk of others. Susceptibility to colorectal cancer for those with a MTHFR SNP appears to depend on homozygosity, gender, and presence of other MTHFR SNPs.[72] In some cases (e.g. in conjunction with high folate intake) the C677T variant may reduce risk of colorectal cancer, although further research is warranted.73

Vascular Health and Cardiovascular Disease

The degree to which the C677T SNP compromises cardiovascular health appears to be related to homozygosity, folate status, homocysteine status, and presence of other MTHFR SNPs (e.g. A1298C).[74] [75] Research suggests that the A1298C variant may be associated with cerebral venous thrombosis (CVT)76 as well as subclinical atherosclerosis in patients with rheumatoid arthritis.[77] Deep vein thrombosis was significantly associated with increased serum homocysteine levels due to the C677T MTHFR mutation.[78]

Homozygous C677T is considered to increase risk of premature cardiovascular disease by three fold.[79] A retrospective study suggested that SNPs in the MTHFR gene were an important risk factor for acute cerebral strokes in young adults studied.80 Another study, looking at a wide range of polymorphisms, associated the C677T MTHFR

SNP with advanced arterial stenosis in individuals under 45 years of age.[81]

Cognitive Function, Mood, and Behavior

The link between nutrition and cognition is highlighted when we observe the role that folate plays in neurotransmitter production. The active form of folate is required for the production of serotonin, epinephrine, and dopamine—monoamine neurotransmitters that orchestrate mood, behavior, and cognition.[82] The influence of active folate on the production of tetrahydrobiopterin (BH4) and SAMe further links it to cognitive function. A 2007 meta-analysis examining MTHFR variants and psychiatric disorders revealed an association between the C677T variant and depression, bipolar disorder, and schizophrenia, suggesting a role for supplemental folate in both treatment and prevention.[83]

Depression

Research suggests that folate deficiency may be present in up to one third of patients with severe depression,[84] [85] a statistic that is not surprising considering folate's intimate role in methylation, monoamine metabolism, and brain health. Without the presence of active 5-MTHF, SAMe and monoamine neurotransmitter levels can decrease in cerebrospinal fluid, setting the stage for biochemical imbalance and depressive disorder.[86]

Decreased serum and RBC folate has been observed in up to 38% of adults with depressive order, and is associated with a decreased response to selective serotonin re-uptake inhibitors (SSRIs).[87] [88] This association may in part be due to MTHFR variants as individuals with MTHFR deficiency appear to have decreased serotonin synthesis.[89] A 2013 meta-analysis supported the association between the C677T SNP and increased risk of depression.[90]

In a study of 46 severely depressed patients, 52% presented with elevated serum homocysteine and decreased levels of a number of parameters including red cell and cerebrospinal fluid (CSF) folate, CSF SAMe, and CSF metabolites of serotonin, dopamine, and norepinephrine. Researchers concluded that serum homocysteine was a sensitive marker for functional folate deficiency in severely depressed patients.[91]

A cross-sectional study of older men suggests that reducing total serum homocysteine by 0.19 mg/L in those individuals with the C677T variant and concomitant elevated homocysteine may reduced the odds of depression by 20%.[92]

High dose methylfolate (15 mg/d) was used successfully as adjuvant therapy in individuals major depressive disorder who previously had partial or no response to SSRIs.93 Not surprisingly, experts are calling for integration of folate (particularly active or "optimized" methylfolate94) and vitamin B12 supplementation into treatment for depressive

disorders.[95] [96]

Schizophrenia and Bipolar Disorder

Alterations in folate metabolism are suspected of affecting incidence of schizophrenia and bipolar disorder. The C677T variant is significantly associated with schizophrenia, bipolar disorder, and unipolar depressive disorder, while the A1298C was associated with only bipolar disorder.[97]

Research suggests that elevated serum homocysteine increases risk of schizophrenia, especially in those with the C677T SNP.98 99 One study of 88 patients with schizophrenia revealed an average homocysteine level of 11.94+/-5.6*u*mol/L versus 6.8 +/- 2.93 *u*mol/L for controls. Individuals with the highest homocysteine appeared to have the most severe illness, especially those heterozygous for C677T.[100]

A review of the literature suggests that “folate is one of the most widely used nutraceuticals for the treatment of mood disorders… The biologically active form of folate could potentially correct mood stabilizer-associated functional folate deficiency, help normalize monoamine synthesis, and improve outcomes.”101Although not all researchers recommend that general healthcare professionals test for MTHFR or provide nutrition support for individuals with psychiatric disorders,[102] the nutrition professional is already in a position to assess potential nutrigenomic influences and recommend nutrition support as part of a comprehensive, responsible care plan.

Neural Tube Defects

The link between folate status of the mother and neural tube defects in the fetus is well established. Folate deficiency or taking antifolate drugs during the first trimester of pregnancy increases risk of neural tube and cardiovascular defects in the developing fetus.103

Alterations in folate metabolism and teratogenesis may be related to overall decreased methylation, sustained elevated homocysteine, or outright folate deficiency. Ultimately the risk of neural tube defects (NTD) appears to be related to a complex interaction of maternal and fetal SNPs (ten SNPs in four genes) and maternal folate status.[104] [105] [106] [107]

Women with high homocysteine levels and a history of unexplained miscarriages experienced a significant decrease in serum homocysteine levels when supplemented with 0.5 mg of folic acid for two months. For women who were homozygous for C677T, the homocysteine-lowering effect was most dramatic, however increases in serum folate was least dramatic for this same group, likely due to their reduced capacity to convert folic acid into the active form of folate.[108]

Nutritional Implications and Recommendations

The nutrition professional may be the first healthcare practitioner to assess an individual's folate status and recognize possible links between folate status, blood chemistry anomalies, and clinical symptoms. Consideration of MTHFR SNPs is a vital part of that assessment.

In-depth assessment of folate status and MTHFR competence should be completed in individuals presenting with the following:

- Coronary artery disease
- Acute myocardial infarction
- Peripheral vascular artery disease
- Stroke
- Venous thromboembolism
- Elevated homocysteine
- Migraines
- Depression
- Bipolar disorder
- Schizophrenia
- Autism spectrum disorders
- History of preeclampsia, recurrent miscarriages, offspring with neural tube defects

It is important to assess an individual's current folate intake using a detailed history and food intake evaluation. Although some individuals may need additional folate supplementation, it is equally important to promote intake of folate from food sources. Healthful folate sources include dark leafy greens, spinach, asparagus, legumes (e.g.lentils, chick peas, lima beans, black beans, kidney beans, pinto beans, green peas), Brussels sprouts, avocadoes, and broccoli.[109] [110] [111]

Initial clinical evaluation should assess for folate deficiency which may manifest as macrocytic anemia, fatigue, depression, irritability, weakness, shortness of breath, mouth ulcers, swollen tongue, and even DNA damage.[112] [113] [114] [115] [116] [117]

A review of potential folate-depleting medications should be conducted as well. These include acid blockers, analgesics, antacids, antibiotics, anti-inflammatories, antivirals, blood pressure drugs, hormone replacement/oral contraceptives, and diabetes medications just to name a few of the most popular.[118]

Testing for the MTHFR Gene Mutation

Comprehensive testing to address folate status and MTHFR capacity should include a blood chemistry evaluation of

unmetabolized folic acid, homocysteine levels (using appropriate lab technique),[119] serum folate and red blood cell folate,[120] and a complete CBC (assess for macrocytic anemia). Serum folate is considered reflective of short-term folate status, while red blood cell (RBC) folate reflects long-term folate status.[121]

Research suggests that RBC folate distribution varies depending on MTHFR SNP; C677T promotes a drop in RBC folate while A1298C is associated with an increase in RBC folate.[122]

According to the Mayo Clinic, testing for the C677T and/or A1298C MTHFR variants "should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test."[123]

However, in view of recent research, it may be practical to test patients with migraines, psychiatric disorders (i.e. depression, bipolar disorder, schizophrenia), autism spectrum disorders, and those with a history of preeclampsia, recurrent miscarriages, and those bearing offspring with neural tube defects.

Supplementation

Groundbreaking research reveals that at least 50 different diseases may be due to suboptimal binding of vitamin-based coenzymes with their corresponding enzymes.[124] Providing high doses of vitamin cofactors can overcome these metabolic deficits. Currently functional medicine practitioners recommend providing active/methylated B vitamins in order to provide the bioavailable, coenzyme form.[125] [126] [127]

Individuals with MTHFR variants may need exogenous supplementation to normalize folate status, especially if homozygous for C677T or those with both C677T and A1298C variants. Ideally those with MTHFR SNPs should be supplemented with methylfolate
(not folic acid) over and above the Recommended Dietary Allowance which is currently 400 mcg dietary folate equivalents (DFE) for a non-pregnant/non-lactating adult. The RDA for pregnancy is 600 mcg DFE; the RDA during lactation is 500 mcg DFE. Originally the DFE was based on the premise that synthetic folic acid may be better absorbed than folate found naturally in foods, however current research has challenged that premise.[128]

One DTE is equivalent to 1 mcg folate from food; 0.6 mcg folic acid from fortified foods or supplements taken with food; or 0.5 mcg folic acid from supplements taken on an empty stomach.[129] However, the DTE system does not take into account individuals with MTHFR SNPs who are unable to efficiently or safely convert folic acid into active 5-MTHFR.

One study compared a single administration of 5-MTHF (5 mg) to folic acid (5 mg) in coronary artery disease patients homozygous for C677T (12 C677T variants and 12 controls). The study indicated that supplemental 6 [R,S] 5-MTHF resulted in a peak folate concentration nearly seven times greater than that achieved with folic acid in all patients

tested. Incidentally, those with the C677T SNP had higher fasting homocysteine and lower serum folate than those without the SNP. Folate levels increased following 5- MTHF administration though homocysteine levels remained unchanged over the one week study period.[130]

Individual folate requirements may vary depending on type of MTFHR mutation, biochemical parameters, and potential nutrient depletions.[131] [132] [133] Some drugs may block folate (e.g. birth control, methotrexate, etc.) or increase homocysteine (e.g. nitrous oxide).[134]

Supplementation needs may vary depending on current folate intake from food. Common supplement doses range from 0.8-1 mg (800-1000 mcg) per day, while doses up to 2.4mg may be indicated for drug-induced nutrient depletions. Some healthcare practitioners may supplement with 5 mg per day on a short-term basis. Because providing folate can mask a vitamin B12 deficiency, supplementing active B12 along with folate is recommended. 5-MTHF is less likely to mask a B12 deficiency.[136]

Remember many nutrients work together, for example, vitamins B6, B12, and folate are all cofactors in homocysteine metabolism. The MTHFR enzymes requires riboflavin as a cofactor, so providing high dose riboflavin to those with the C677T SNP can assist in methylation and reduction of homocysteine as well.137 138 139

Although folate supplementation is clearly beneficial for a number of individuals, folic acid is not well tolerated by those with the C677T mutation (whether heterozygous or homozygous) and circulating unmetabolized folic acid may be detrimental. Doses above 200 mcg may generate unmetabolized folic acid in the circulation.140 Unfortunately synthetic folic acid is the form that is currently used in lower quality supplements and in fortification of processed foods.

Methylated and bioactive forms of B vitamins, especially methylfolate, are the preferred form of supplementation,141 142 143 however some individuals may experience negative effects. Initiate methylfolate supplementation slowly, at a low dose, and observe closely for side effects. According to Dr. Ben Lynch, both healthcare practitioner and patient should be aware of these potential side effects:[144] [145]

- irritability
- insomnia
- sore muscles
- achy joints
- acne
- rash
- severe anxiety
- palpitations

- nausea
- headaches
- migraines

The take away for nutrition professionals regarding MTHFR is:

- Recognize the role that MTHFR SNPs can play in a wide range of conditions and disease states, especially in the presence of hyperhomocysteinemia.
- Assess folate status in individuals at risk for altered folate metabolism.
- Obtain MTHFR SNP data on individuals at increased risk or displaying associated complications.
- Monitor levels of homocysteine, serum and RBC folate, unmetabolized folic acid, and CBC
- Encourage intake of healthful food sources of folate; may need to recommended limited intake of synthetic folic acid in some individuals.
- Consider supplementation as needed with the bioactive forms of B vitamins, especially methylfolate.
- Be sure to monitor patients' response and tolerance once nutrition care plan is implemented.

What are the Variants?

C677T
• There is a mutation from cytosine to adenine at position 677 within gene.
A1298C
• There is a mutation from adenine to cytosine at position 1298 within gene.

These variants lead to amino acid differences in the protein that reduces its ability to function.

What are the possible genotypes?

677 - CC, CT, or TT

- CC - homozygous normal
  - Approximately 45% of the population
  - No increased risk associated
- CT - one variant copy
  - Approximately 45% of the population
  - Some reduced enzyme activity, but not alone associated with increased risk.
- TT - two variant copies
  - Approximately 10% of the population
  - Increased risk for hyperhomocysteinemia and associated complications

1298 - AA, AC, CC

- AA - normal homozygous
- AC or CC - one or two variant copies
  - Approximately 30% of the population
  - Not associated with increased risk
  - Associated with increased risk if found together with a 677 variant.