L-Methylfolate & Depression: The Folate Reductase/Methylation Cycle
With Respect to Genetic Variants in Individuals
(Originally Compiled by Mike Prestwich 5-12-2014 and Revised 07-07-2014)

(Also available at: http://www.mlprestwich.com/depression/ ) Contact me direct at misc@mlprestwich.com for PDF Copy that may be saved.

Clinical Depression is by far, the worst thing I have experience in my life. That is not an overstatement. The pain and darkness surpasses losing a parent, having cancer or anything else I have imagined or experienced in my lifetime. Clinical Depression is truly serious debilitating and often deadly disease; just as serious as Alzheimer's, heart disease, cancer or any similar illnesses.

“What is depression like?” he whispered.

“It’s like drowning.

Except you can see everyone around you breathing.”
Unfortunately, this appears to be present in my mother’s side of the family (some descendants of William J. Olsen). It appears to be genetically based to some extent as will become more evident below.

While there is significant technical information here, one can get the idea by reading the parts that you understand. In my case, although it took many doctors and over 10 years, I finally found a relatively simple treatment that works for me. If you, or one of your family members has any of these conditions, it may be something you wish to address with your doctor or mental health specialist.

I decided to compile the information below for my family and friends. I have researched and fought depression to various degrees for about 10 years now. I finally think I have found some answers to the question of “why” and how to treat my specific form of MDD (Major Depressive Order). I hope this information can help you or a loved one who may also suffer from this disease.

Depression is a disease – pure and simple! It is not about just having a bad day or “feeling down”. It is deep, real and debilitating in many cases. To tell a person suffering from clinical depression to “cheer up” is as meaningful as telling them to change the color of their eyes. Depression is real, and the worst pain I have ever personally experienced. I can last for years if not properly addressed and treated.

My personal interest in this field stems from my own depression that is related to colon cancer and the resultant chemotherapy I had almost 10 years ago.

I have long known that depression “runs” on my mother’s side of the family, and is evident in some of my children as well. This became clearly evident for me about 2/3 of my way through aggressive chemotherapy in 2005.

This has been a 10 year battle attempting to find a medication, or group of medications that would work for me and eliminate the episodes of depression. I was desperate many times for something that would allow me to feel “normal”; with energy and the desire to just perform daily routine functions – basically to enjoy life as I had before cancer and depression.

We have none of the “normal stresses” in our life. As I have told the medical experts I have worked with, our life is about as close to perfect as I can image. Yet, at times, there has been an overwhelming desire to just withdraw and do nothing; deep depression. Sleep was the only relief, often 18 or more hours a day.

I recently decided enough was enough. I was going to find an answer and solution or die - literally. In consultation with my wonderful family doctor, Dr. Danny Worwood, to whom I am eternally grateful, we decided a seek a higher level of expertise in the field – a psychiatrist. Heaven forbid that I should need the help of a “shrink”, but that is exactly what I needed.

After the initial steps and diagnosis of MDD – Major Depressive Disorder, Dr. Fatam Reda, a local psychiatrist prescribed two additional medication for me, and the deletion of two that I had been taking.

Because we are each so individual in our genetics and needs for the “right” medication(s) to control such diseases, I won’t go into details here about those medications specific to me, other than to identify and outline the single element that seems to have been a major factor in resolving my depression.

Interestingly, the compound, while available with or without prescription, is not a drug at all, but a food supplement! The compound I am referring to is L-Methylfolate!

I have detailed the compound and made an analysis of why and how this substance works (for me). I am convinced there is a genetic polymorphism, primarily on my mother’s side of the family with respect to the genes described below, more specifically the MTHFR gene and “C677T & A1298C”.

While some of the information I have collected below is rather technical, there are also portions that are written for the layman. Please feel free to use those parts that may be of benefit to you. I can’t overemphasize the value this has been to me. I truly has been like a “night and day” transformation.
I have revised this information as of 7-7-2014. The newest version begins with a typical case and treatment using L-Methylfolate as adjunct therapy. This first article provides a very good background on the number of people who suffer from depression and how a high percentage go partially or untreated.

Regards,

-mike prestwich – July 7, 2014

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**A Good Case Study & Overview using L-Methylfolate**


**Medical Food Aids in the Treatment of Major Depression**

Deborah Brauser

December 10, 2012

Adjunctive L-methylfolate is safe, effective, and "relatively well tolerated" for patients with major depressive disorder (MDD) who are resistant to selective serotonin reuptake inhibitors (SSRIs) alone, new research suggests.

A randomized controlled trial (RCT) of 75 adults with MDD showed that the participants who received 15 mg/day of L-methylfolate in addition to continued SSRI treatment showed significantly higher response rates and depression symptom score changes than those who received placebo plus continued SSRI therapy.

Dr. George Papakostas. Source: Massachusetts General Hospital

In this trial, "15 mg/day of adjunctive L-methylfolate appeared to result in a treatment outcome (efficacy) superior to continued SSRI therapy plus placebo in both primary outcome measures," write George Papakostas, MD, from the Center for Treatment-Resistant Depression at Massachusetts General Hospital in Boston and from Harvard Medical School, and colleagues.

The researchers note that this is the first randomized, double-blind, placebo-controlled trial to examine these outcomes in this particular patient population. Although the results were positive, replication is needed, they add.

Initially presented at the European Congress of Psychiatry in 2011 and reported by Medscape Medical News at that time, the study is published in the December issue of the American Journal of Psychiatry.

**Better Therapies Needed**
"According to the literature, only about 1 of every 3 patients with depression will achieve remission with standard antidepressant monotherapy," said Dr. Papakostas at the time.

"So it's clear that we need better therapies for depression," he added.

According to the investigators, previous research has suggested a link between low folate levels and an increased risk for MDD, as well as the possibility that "low folate levels in patients with major depression may predict poorer prognosis during treatment."

"These studies have in turn attracted the interest of the research community regarding the use of folate as a potential treatment for major depression," they write.

In the current journal article, the researchers report on 2 RCTs they conducted to examine the use of adjunctive L-methylfolate for treatment-resistant MDD.

In the first RCT, which was conducted at 11 sites, 148 outpatients (69.5% women) between the ages of 18 and 65 years with SSRI-resistant MDD were randomly assigned to receive either L-methylfolate for 60 days (7.5 mg/day for the first 30 days, 15 mg/day for the remaining 30 days), placebo for 60 days, or placebo for 30 days followed by 7.5 mg/day of L-methylfolate for 30 days.

"L-Methylfolate is the biologically active form of folate and the only form...that crosses the blood-brain barrier," report the investigators.

After randomization, follow-up visits occurred every 10 days.

The primary outcomes measures were differences in response rate and degree of improvement score, which were both measured by the 17-item Hamilton Depression Rating Scale (HAM-D).

Secondary measures included continuous change in scores on the Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR) and the Clinical Global Impressions (CGI) severity scale.

Higher Dose Better

Results showed that there were no significant between-group differences in the first trial.

Although it did not reach statistical significance, the response rate and change in depression symptom score were greater for the patients receiving adjunctive L-methylfolate when they switched over to the 15 mg/day dose compared with the patients who received adjunctive placebo only.

In the second trial, the group that continuously received 15 mg/day of L-methylfolate plus continuous use of SSRIs had significantly greater response rates (32.3% vs 14.6%, \( P = .04 \)) and a higher degree of change in depression symptom scores (-5.58 vs -3.04, \( P = .05 \)), QIDS-SR scores (-4.7 vs -2.62, \( P = .04 \)), and CGI symptom severity (-0.92 vs -0.34, \( P = .01 \)) than the group that received adjunctive placebo.

No statistically significant differences were found between the groups in change in weight, standing heart rate, or standing diastolic and systolic blood pressure.

The most commonly reported treatment-related adverse event categories included gastrointestinal (16.7% of those receiving active treatment vs 14.8% of those receiving placebo), somatic (14.3% vs 29.6%, respectively), infectious (11.9% vs 13%), and psychological (9.5% vs 16.7%).
The only patient withdrawal was from the L-methylfolate group; the patient withdrew because of the development of manic symptoms.

"In summary, our results suggest that 15 mg/day, but not 7.5 mg/day, of adjunctive L-methylfolate may constitute an effective, safe, and relatively well tolerated augmentation strategy for patients with major depression who have had no response or partial response to SSRIs," write the investigators.

They add that replication is needed, "as well as additional research to further clarify the antidepressant role of L-methylfolate and other elements of the one-carbon cycle."

Medical Food

J. Craig Nelson, MD, from the Department of Psychiatry at the University of California, San Francisco, writes in an accompanying editorial that this study "adds to the growing literature suggesting that the one-carbon cycle may moderate antidepressant treatment response."

Dr. Nelson notes that L-methylfolate is a "medical food" and differs significantly from dietary supplements.

"Medical foods are prescribed by a physician and are intended for the dietary management of a disease or condition for which nutritional requirements are established," he explains, adding that 2 large pharmacy chains report costs of $90 to $94 for a 30-day supply of this product — charges that are not likely to be covered by insurance.

He goes on to note that although the side effects profile did not differ significantly between the treatment groups, this was a small and limited study. Past research has suggested a possible increased risk for cancer in those administered folate, although "this remains controversial," and increased mortality.

"If supplementation is used to treat a disorder for which efficacy is established, the benefit will likely outweigh the harm, but the data suggest that these compounds are not harmless," writes Dr. Nelson.

Nevertheless, he notes that L-methylfolate "may be particularly helpful in patients with the TT genetic variant."

"The potential value of long-term administration...in individuals with recurrent depression and the genetic enzyme deficiency is particularly intriguing," he concludes.

Both studies were funded by Pamlab. The study authors and Dr. Nelson have disclosed several possible conflicts, which are fully listed in the original articles.


A Good Overview

(from: http://holisticprimarycare.net/topics/topics-a-g/functional-medicine/1353-mthfr-mutation-a-missing-piece-in-the-chronic-disease-puzzle )

MTHFR Mutation: A Missing Piece in the Chronic Disease Puzzle
Methylenetetrahydrofolate reductase (MTHFR) is one of the most important enzymes in human physiology, having influence on at least as many biochemical processes as it has syllables in its nearly unpronounceable name.

Deficiencies in production or function of this enzyme have been associated with increased risk of myocardial infarction, stroke, venous thrombosis, several types of cancer, congenital defects, inflammatory bowel disease, and several neuropsychiatric conditions. In practice, MTHFR function is an important predictor of predispositions to chronic disease states, and interventions aimed at optimizing MTHFR function can often be preventive or therapeutic.

Put most simply, MTHFR converts 5,10-methylenetetrahydrofolate into the activated form, 5-MTHF or 5-methyltetrahydrofolate. Though this reaction plays a part in many biochemical pathways, it is probably best-known in the context of breaking down the amino acid homocysteine. This process produces methionine and eventually S-Adenosylmethionine (SAMe), a crucial DNA methylator.

Other significant roles of a properly functioning MTHFR enzyme include nucleic acid biosynthesis, neurotransmitter synthesis, and production of signaling molecules important for regulating embryonic development, all of which will be discussed in more detail in later sections.

The role of MTHFR in health and disease has been the subject of intense research in recent years, and this work is beginning to influence clinical practice. In many ways, MTHFR function provides important clues to the risk of developing particular diseases, and to the etiology of seemingly unexplained or unexpected symptom patterns.

Fortunately, it is now possible and practical to test for the presence of mutations in the gene coding for this important enzyme.

MTHFR Mutations

The normal wild type (CC) MTHFR gene gives instruction for production of the methylenetetrahydrofolate reductase enzyme. Currently, over 40 point mutations of this gene have been identified. Of these, mutations on the points at C677T and A1298C seem to have the most clinical significance.

In particular, the C677T polymorphism shows a wide regional and ethnic variation. Homozygosity (TT) among Whites is 6-14%. In African populations and in Blacks living outside of Africa such as in Brazil and in the United States, the frequency falls to less than 2% for the TT variant. The prevalence rises in Mediterranean and Hispanic population. For example, among Hispanics in prevalence ranges as high as 21%. Northern China and Japan show an 18 and 12% prevalence respectively (R. Castro, et al. J Med Genet. 2004;41:454-458).

The A1298C mutation, on the other hand, does not show as much population variance; its prevalence is more uniform within the currently studied groups. The table below notes the variant frequencies lumping the heterozygous and homozygous genotypes together. For the most part, the other MTHFR gene mutations are still under study and their effects are not completely understood.
Geneticists and evolutionary biologists hypothesize that, in the past, mutations in MTHFR may have conferred benefits for people living in areas with higher incidence of malaria and tuberculosis. Some mutations may also play a role in protection from colon cancer and acute lymphocytic leukemia. It is interesting to note, however, that geneticists have not been able to identify any clear evolutionary advantage for C677T nor A1298C, the two most relevant mutations for our current discussion.

A more in-depth look at the regional and ethnic variations, with subgroupings by wild type, heterozygotes and homozygotes, can be found in the *Journal of Medical Genetics* in an article authored by Wilcken and colleagues.

**MTHFR Mutations & Disease Risk**

The level of MTHFR enzyme activity in a given individual depends on the genotype variant he or she carries. For example, homozygotes for C677T have approximately a 70% reduction of normal MTHFR enzyme activity and heterozygotes have approximately a 40% reduction of normal enzyme activity, according to ARIP Laboratories/National Reference Laboratory. Impaired MTHFR function has multiple negative impacts on DNA synthesis and repair, embryonic development, neurotransmitter synthesis, and cardiovascular risk factors.

**Cardiovascular Disease:** The normal recycling of homocysteine to methionine relies on 5-MTHF. If there is a defect in the MTHFR enzyme, the result is lower levels of 5-MTHF and consequently, elevated levels of homocysteine. Hyperhomocysteinemia is an independent risk factor for cardiovascular disease including atherosclerosis, heart attack, stroke and venous thrombosis from increased blood clots (Varga, E. et al. *Circulation*; 2005; 111: e289-e293).

Currently, only the C677T mutation is thought to be associated with elevated homocysteine levels and thus a majority of the research has been done on this variant.

**Cancer Risk:** Appropriate DNA methylation is important for proper DNA replication. A disruption in methylation may occur due to a reduction 5-MTHF, which leads to a buildup of homocysteine. This eventually results in a drop in production of S-adenosylhomocysteine (SAMe) - an inhibitor of several methyltransferases.

Individuals with MTHFR mutations have altered DNA methylation, which is associated with changes in gene expression and could potentially influence oncogenic processes. One example is the 2.8-fold increased risk for endometrial cancer in women with the C677T homozygous genotype (Crott, J. et al. *Carcinogenesis*. 2004; 22(7): 1019-1025).

**Defects in Developing Embryos:** The mechanism for this concern actually comes from multiple consequences of a mutated MTHFR enzyme. Developing embryos may be adversely affected by toxic levels of homocysteine that result from MTHFR mutations. Altered DNA methylation may also have direct negative effects on gene expression and DNA synthesis. The main concerns here are neural tube defects and other midline defects such as cleft palate, although they are not the only ones. Noteworthy research includes a study from Ireland showing that 26% of all neural tube defects were related to either the homozygous or heterozygous MTHFR mutations (Kirke, P. et al. *BMJ*. 2004;328:1535-1536)

Additionally, a 2.6-fold increase in the frequency of the MTHFR C677T polymorphism has been observed in the mothers of Down Syndrome patients in South India (Cyril, C. et al. *Indian J Hum Genet*. 2009; 15(2): 60-64).

A very recent meta-analysis supports the association between recurrent pregnancy loss (RPL) and the C677T genotype in Asians, although this association was not found in Caucasians (Wu, X. *Genet Test Mol Biomarkers*. 2012 Feb 7).

Congenital heart disease (CHD) in children has also been linked to MTHFR gene mutations in either the mother or the child, although a complete analysis and conclusion is still unclear. One of the more recent studies however, did find a clear relationship between CHD and MTHFR mutations (Garcia-Fragoso, L. et al. *Int J Genet Mol Biol*. 2010; 2(3): 43–47).

The authors note that “The prevalence of the TT polymorphism was higher in mothers (22%) than in controls (10%). Compound heterozygosity for both polymorphisms was 3.7 times more common.
An interesting question in relation to embryonic development is whether it is the MTHFR mutation in the mother or in the developing child that is the critical determinant in the development of congenital defects. It is certainly possible that both mutations play a role. Further research is certainly needed to shed light on this very important area of prenatal and pregnancy health.

Neuropsychiatric & Neurological Conditions: MTHFR mutations have been linked to neuropsychiatric conditions due to the indirect effects of MTHFR activity on the production of serotonin, dopamine and norepinephrine, as well as the potentially toxic effect of hyperhomocysteinemia. Schizophrenia-like syndromes, bipolar disorder, Parkinson’s disease, Alzheimer’s disease and vascular dementia have all been associated with one or more mutations of the MTHFR gene (Lewis, X. *Molecular Psychiatry.* 2006;11, 352–360).

Insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy and restless leg syndrome are all also mentioned in the literature as potentially being influenced by this enzyme deficiency. The MTHFR C677T homozygous genotype has also been associated with an increased risk for migraine with aura in most ethnic groups except for Caucasian populations (Schurks M., et al. *Headache.* 2010; 50(4):588-99).

In a recent metanalysis, there was a relationship between the C677T mutation and increased susceptibility for depression (Lewis, X. *Molecular Psychiatry.* 2006;11, 352–360).

Understanding the indirect connection between MTHFR mutation and neurotransmitter production opens up the possibility of using folate supplementation alone or as an adjunct to medications as a treatment for depression.

Some studies indicate a connection between the C677T MTHFR mutation and increased risk of autism and ADHD. Case-control comparisons revealed significantly higher frequency of homozygosity as well as heterozygosity for both the C677T and A1298T genotypes among autistic versus non-autistic children (Liu X. et al. *J. Autism Dev Disord.* 2011;41(7):938-44). Interestingly, it is the A1298C genotype which may be associated with increased rates of ADD/ADHD, and not the C677T genotype (Gokcen, C. et al. *Int J Med Sci.* 2011; 8(7): 523–528).

Other Chronic Health Concerns: Other areas of recent study include the association between MTHFR mutation and epilepsy, Turner’s syndrome, infertility and inflammatory bowel disease. With regard to the latter, researchers have reported a 2.7 and 2.8-fold higher risk for Crohn’s disease and ulcerative colitis, respectively, in people who are homozygous for the C677T variant (Crott, J. et al. *Carcinogenesis.* 2004; 22(7): 1019-1025).

Therapeutic Implications

No number of medications or surgeries can "fix" a deficient enzyme. This is not to say the situation is hopeless, and patients must simply live with the risks and predispositions inherent in their genes.

Corrective treatment must move in the direction of optimizing each individual’s genotype expression. In the context of MTHFR mutations, the goal is to optimize as far as possible the production and function of this enzyme, to counterbalance the individual’s natural tendency for under-expression. This can be done through a nutrigenomics approach.

Some clinicians treat patients with MTHFR mutations by supplementation with 5-MTHF, the end product of MTHFR’s main catalytic reaction. Other vitamins and minerals that affect methylation cycles can also be helpful.

Before effective protocols can be designed, however, one must know what one is treating. MTHFR genetic tests are now readily available, but to date, there are no firm guidelines on who should be tested for MTHFR mutations.

My view is that it is wise to be vigilant when working with patients who fall into any of the above-mentioned chronic disease categories, or who have family members with known MTHFR mutations, or histories suggestive of this possibility. I also consider it when working with patients interested in preventative health programs and/or family planning.
You can learn a lot from a simple blood screening for MTHFR mutation at the C677T and A1298C points. Any patient who is positive for any form of MTHFR genotype mutation should be counseled on the importance of replening 5-MTHF. It’s usually a good idea to give information about MTHFR testing to other family members who may also carry mutations.

There is no advantage to waiting until a patient shows signs or symptoms of one of the MTHFR mutation-associated chronic diseases states; if there is a suspected family history or if a patient is not responding as would be expected to your usual therapeutic approaches – test and treat appropriately. What you discover could have big impact on someone’s future health.

END

Dr. Bianca Garilli is a former US Marine turned Naturopathic Doctor. She is the Director of Lifestyle Medicine at the Institute for Restorative Health in Davis, CA. In addition to her clinical practice, she also consults for nutritional supplement companies, teaches holistic nutrition at Hawthorn University, is active in writing for the professional and public audiences and routinely lectures on a wide variety of medical and wellness topics. Dr. Garilli specializes in natural and nutritional approaches to chronic disease with a focus on CFS, fibromyalgia, GI conditions, migraines, and ADD/ADHD. For further information, visit www.drbiancagarilli.com

Association of Low Folate with Depression

Since the early 1960s, reports have shown a correlation between low folate levels and MDD (Major Depressive Disorder). Since these initial findings, community studies have strengthened the association between low folate and depressive illnesses. Whether measuring serum, plasma, or RBC folate, patients diagnosed with MDD have been shown to have significantly lower folate levels when compared to non-depressed controls. RBC folate levels will generally reflect CNS folate levels, and have been demonstrated to be low in as many as 56% of depressed patients. Folate deficiency has also been linked to courses of depressions that are more severe, longer in duration, and treatment resistant. Suboptimal folate may also predict non-responders and partial responders, as patients with low RBC folate are 6 times more likely not to respond to antidepressant therapy and are less likely to achieve and maintain remission. The connection between folate and MDD is believed to be L-methylfolate, a necessary cofactor in the synthesis of monoamine neurotransmitters. Thus, a deficiency may result in inadequate CNS synthesis of serotonin, norepinephrine, and dopamine.

Folate and L-methylfolate

Folate is a water soluble B vitamin (B9), considered one of the 13 essential vitamins. The primary function of folate is the transfer of methyl and formyl groups, thus, it is essential for cell growth and reproduction, the breakdown and utilization of proteins, the formation of nucleic acids, red blood cell maturation, and a variety of CNS reactions. Dihydrofolate is the dietary form found in orange juice, spinach, asparagus, beans, liver, yeast, whole grain cereals, and eggs. Folic acid is the synthetic form of folate in over-the-counter vitamins and used to fortify the food supply (to help prevent neural tube defects, the FDA mandated folic acid fortification of flour in 1998). Folic acid is also the predominant form used in prescription strength prenatal vitamins. Both folic acid and dihydrofolate are not biologically active forms of folate, but are essentially pro-drugs, and must undergo enzymatic transformation to L-methylfolate in order to be used by cells, and unlike other forms of folate, L-methylfolate readily crosses the blood-brain barrier for use in the CNS.

Almost 85% of dietary folate and nearly all supplemental folic acid is absorbed into the venous system in the proximal small intestine. The enzymatic conversion begins in the intestinal wall—it is a three step process for dihydrofolate, and a four step process for folic acid (Slide 3). Folic acid is converted to dihydrofolate (DFH) by dihydrofolate reductase enzyme (DHFR), and DHF is then
converted to tetrahydrofolate (THF). The conversion of THF to 5,10-methyleneTHF follows. Finally, the conversion of 5,10-methyleneTHF to L-methylfolate is achieved by the methylenetetrahydrofolate reductase enzyme (MTHFR). This last step completes the four step transformation process by which the bioactive cofactor, L-methylfolate, is made available to the brain to be used in the synthesis of monoamine neurotransmitters associated with mood regulation (serotonin, norepinephrine, and dopamine).

**Genetic Factors & “Mechanics” of**

For many, dietary folate will result in adequate delivery of L-methylfolate to the brain, however, inhibition of any of the above enzymes, or having defective, less functional forms of enzymes could result in inadequate CNS L-methylfolate levels. There are over 40 identified mutations of the MTHFR gene that codes for the enzyme responsible for the last step in the conversion of folate to L-methylfolate,

C677T polymorphism is characterized by a mutation at position 677 of the MTHFR gene resulting in a single amino acid substitution, rendering the MTHFR enzyme thermolabile, thus significantly reducing its activity (Slide 4). Numerous studies indicate an association between the C677T polymorphism and depression. In one study, 70% of depressed individuals were positive for either the heterozygous or homozygous form of the C677T polymorphism (14% T/T, 56% C/T). The C/T, or heterozygous polymorphism reduces the MTHFR activity by 35%, while for the homozygous, T/T form, enzyme activity is decreased by more than 70%. Thus depressed patients may be at significant risk for inadequate levels of CNS L-methylfolate, and thus, lower synthesis of serotonin, norepinephrine, and dopamine.

Note: Also see [http://en.wikipedia.org/wiki/Methylenetetrahydrofolate_reductase](http://en.wikipedia.org/wiki/Methylenetetrahydrofolate_reductase) for additional detail of the polymorphism of the gene that reduces certain people’s ability to properly metabolize Folates and biologically create L-Methylfolate internally.

### In Plain Terms:

from: [http://www.bioactivhealth.com/methylfolate.htm?gclid=CM68h6vrm74CFQpgfodBFkAiaA](http://www.bioactivhealth.com/methylfolate.htm?gclid=CM68h6vrm74CFQpgfodBFkAiaA)

**Are you converting Folic Acid to L-Methylfolate?**

Folic acid is allowed to be labeled folate or folicin. However, none of these are the active form of folate known as L-Methylfolate (or L-5-MTHF) which your body can put to work. It takes four separate biochemical reactions for your body to turn folic acid into active folate:
Medical studies have shown that the conversion of folic acid into L-Methylfolate is frequently disrupted by genetic factors, age-related problems, medications and metabolic obstacles.\(^1,2\)

- Up to 40% of adults are affected by genetic flaws that limit the amount of folic acid converted to the active folate (L-Methylfolate) that neutralizes homocysteine.\(^3-10\)
- Transformation of folic acid into active folate (L-Methylfolate) falls off after ingesting 200 mcg, and is saturated at doses in the region of 400 mcg. Higher doses result in unabsorbed folic acid circulating in the blood, and we do not know the long term biological effects of a lifetime of exposure to unmodified synthetic folate.\(^1,10\)

**The Methylation Cycle Explained in Simple Words**

From: [http://www.ceu-usa.com/courses/Wc001/test_drive/methylation_cycle.htm](http://www.ceu-usa.com/courses/Wc001/test_drive/methylation_cycle.htm)

**The Methylation Cycle**

The second Key. So far we have reviewed some specific supplements that help relieve depression. We discussed each in isolation. But we haven't talked about that second Golden Key yet. This Key brings many of the puzzle pieces solidly together, making things simpler. It explains why certain vitamins, minerals, and other nutrients can reduce depression.

What is this concept? It's called the Methylation Cycle, and it's a rather complex topic. Fortunately, we can vastly oversimplify it and still gain all the understanding we need! With the goal of simplification in mind we now present...

A Mickey Mouse explanation of the Methylation Cycle. As we have seen, the body makes different neurotransmitters out of particular amino acids. To do this, it usually changes the amino acid slightly. It does this mostly by sticking one or more methyl groups onto the amino acid. This is called Methylation.

A methyl group is one carbon (C) atom with two hydrogen (H) atoms stuck on it. The result looks a bit like Mickey Mouse -- a big round thing (the face) with two smaller round things (the ears) at the top. The body can't make methyl groups out of nothing. So it has to have a supply of these units to work with. The Methylation Cycle is the body's way of supplying these methyl groups. The diagram below is a simplified view of the Methylation Cycle. Let's see how it works.

From A to B. The Methylation Cycle carries methyl groups around the body like railcars on a circular track. Because the track goes around in a circle, we could start anywhere. But let's start at the bottom, at point A. There a methyl group is
attached to a molecule called SAM. The SAM molecule carries the methyl group to the place where it will be used -- point B. When it gets there methylation happens. Methylation is just a word meaning that the methyl group is popped off the SAM molecule and stuck on an amino acid to make a neurotransmitter.

**From B to C.** What happens to the SAM molecule when the methyl group is taken off? When the methyl group is gone, the molecule is not SAM anymore. It turns into a different molecule called Homocysteine. Now we've moved from point A all the way to point C.

**From C back to A.** Here's where things get tricky. The body normally recycles Homocysteine back into SAM -- from point C back to point A. A new methyl group is added to turn the molecule back into SAM again. Then the cycle is complete. The molecule goes round and round -- A-B-C-A-B-C-A-B-C, etc -- carrying methyl groups where they are needed. That's why we call it a Cycle. But that can happen only if there's enough of certain vitamins and nutrients around -- vitamin B12, folic acid, and a nutrient called TMG. These things enable the recycling. They have to be present, or the Homocysteine can't be changed back into SAM.

**A depressing shortage.** So what happens if the required nutrients just aren't there? Look at the diagram to the right. The Homocysteine doesn't get recycled. Instead, it simply piles up at point C unchanged. Big dollops of it accumulate. Because Homocysteine isn't being changed back into SAM, a shortage of SAM soon develops. And when there is a shortage of SAM, not as many neurotransmitters are made. So soon there is a shortage of neurotransmitters, too. The shortage includes Serotonin and Norepinephrine, those anti-depression neurotransmitters. A "chemical imbalance" -- the very kind the antidepressant ads talk about -- has appeared. The individual gets depressed.

**Insight!** Now we see why deficiencies of specific vitamins and minerals can lead to depression. The shortages tied to depression are of the very nutrients required to keep SAM circulating. When they aren't there, the SAM dries up. That's why supplementing with those vitamins and minerals can help with depression.

**Why SAMe works.** Understanding the Methylation Cycle also helps us understand why the supplement SAMe can help relieve depression.
SAMe is a special form of SAM designed to be taken orally. Taking SAMe increases the available supply of SAM in the body. That leads to increased methylation, and so to increased production of neurotransmitters. It quickly revs up the methylation process to bring neurotransmitter production back up. That can quickly relieve depression.

SAMe doesn't help with recycling Homocysteine, though. That substance continues to build up. Even so, supplementing with SAMe can provide a band-aid solution. It can power up methylation until something can be done to bring Homocysteine recycling back to normal.

**The real fix.** If SAMe is just a band-aid solution, what's the real fix? The only way to restore the Methylation Cycle to normal is to provide adequate vitamins and nutrients to recycle all the homocysteine that's lying around. Is this hard to do? Not at all! The individual just needs to take therapeutic amounts of vitamins B-12, Folic Acid, and TMG. There is no particular hazard associated with use of these supplements. Improvement may take a couple of months, but that's how it's done.

**Ethics** Is this the end of the methylation story? Hardly. There are weighty ethical issues at play here. One of them flows from this fact: Neurotransmitters are not the only things impacted by poor methylation. It's a basic process that affects the functioning of the body in multiple areas. Low methylation levels are associated not only with depression, but with cardiovascular disease, arthritis, and several other serious health problems. Some of these can be debilitating and/or life-threatening. For example, high levels of Homocysteine have been associated with increased risk of heart attack and stroke. Many experts think Homocysteine itself is toxic. Others feel it's just a marker for poor methylation. But either way it signals trouble. High Homocysteine levels need to be fixed, not covered up.

Suppose our client's depression is rooted in poor methylation. Her health is already impaired. In this case an antidepressant medication will at best cover up the symptom. It will do nothing to improve her methylation. Failure to address the basic problem may well lead to a further decline in her health. In some cases it will lead to serious health problems.

Our clients rightly regard us as experts in mental and emotional dysfunction. Are we providing the best service when we fail to recognize the true source of our client's suffering? Do we have a responsibility to gain a basic understanding of methylation, this common cause of depression? Can we conscientiously participate in covering up a serious physical problem by masking symptoms with antidepressants?
A second ethical issue relates directly to our responsibility to provide effective treatment. If a client is suffering from depression due to inadequate methylation, it is unlikely that counseling or psychotherapy (or pharmaceuticals, for that matter) will provide lasting benefit. Are we on shaky ethical ground when we provide services we have reason to believe will not be very helpful?

**NOTE:** For purposes of our discussion we have drastically simplified the Methylation Cycle. We kept the basic idea, but eliminated all the messy details. In fact, we left out most of the steps in the Cycle! If you're interested, you can view a more realistic diagram of the Methylation Cycle [here](http://www.ceu-usa.com/courses/Wc001/test_drive/depression_cause_3.htm). Readers who wish to go beyond our "Mickey Mouse" presentation may find the following book helpful.

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**Too Much Of A Good Thing?**

From: [http://www.ceu-usa.com/courses/Wc001/test_drive/depression_cause_3.htm](http://www.ceu-usa.com/courses/Wc001/test_drive/depression_cause_3.htm)

**Depression Cause 3: Excessive Neurotransmitter Levels**

**Discussion:** Some researchers believe overmethylation can cause depression too. An overmethylated person produces too many neurotransmitters. In such cases taking a serotonin-enhancing agent like Prozac or a methylation agent like SAMe just makes the problem worse. Bill Walsh of the Pfeiffer Treatment center says

Many persons who suffer from anxiety and depression are over-methylated which results in excessive levels of dopamine, norepinephrine and serotonin. Typical symptoms include chemical and food sensitivities, underachievement, upper body pain, and an adverse reaction to serotonin-enhancing substances such as Prozac, Paxil, Zoloft, St. John’s Wort, and SAMe. They have a genetic tendency to be very depressed in folates, niacin, and Vitamin B-12, and biochemical treatment focuses on supplementation of these nutrients. These persons are also overloaded in copper and methionine and supplements of these nutrients must be strictly avoided.²⁶

**Nutritional Approaches**

1. **Slow down methylation.** If a client has tried pharmaceutical antidepressants and has experienced a worsening of the depression, overmethylation could be considered as a possible cause. Dr. Walsh outlines nutritional approach as follows:

   Treatment focuses on B3, C, and B12 with about 2-4 months required for correction of the imbalance. Also DMAE, choline, manganese, zinc, omega-3 essential oils, C and E. They should avoid methionine, SAMe, inositol, TMG and DMG.²⁷

   Remember that it's no longer necessary to guess whether neurotransmitter levels are too high or too low. Specific testing for neurotransmitter levels is available at reasonable cost.²⁷
Do you have a genetic defect in the MTHFR gene??

Maybe you've have a family history of heart attack or stroke... maybe you've suffered through multiple miscarriages. Or maybe you struggle with chronic migraine headaches or irritable bowel syndrome or depression. Perhaps your child or a sibling has autism. What do all these things have in common? Well, these are just some of the conditions liked to a faulty enzyme called MTHFR.

**What’s up with MTHFR?**

MTHFR stands for methyl-tetrahydrofolate reductase, an enzyme that is responsible for the process of methylation in every cell in your body. MTHFR is a common genetic variant that causes this key enzyme in the body to function at a lower than normal rate. This can lead to a variety of medical problems. Although there are over fifty known MTHFR variants, the two primary ones are called C677T and A1298. Your doctor can order a blood test to determine if you have these genetic variants. Better yet, you can order a complete genetic profile yourself through 23andMe.

**What's the big deal about methylation?**

Methylation is a core process that occurs in all cells to help your body make biochemical conversions. When people with genetic mutations is MTHFR are exposed to toxins, they have a harder time getting rid of them which can cause some very serious illnesses. The methylation process is responsible for:
- **Cellular Repair**: synthesis of nucleic acids, production & repair of DNA & mRNA
- **Detoxification and Neurotransmitter Production**: interconversion of amino acids
- **Healthy Immune System Function**: formation & maturation of red blood cells, white blood cells & platelet production

The 677T variant is most commonly associated with early heart disease and stroke and the 1298C variant with a variety of chronic illnesses, but either anomaly can cause a wide variety of health problems. The MTHFR anomaly is reported out as heterozygous or homozygous. If you are heterozygous that means you have one affected gene and one normal gene. Your enzyme activity will run at about 60% efficiency compared to a normal.

If you are homozygous or have 2 abnormal copies, then enzyme efficiency drops down to 10% to 20% of normal, which can be very serious. The worst combination is 677T/1298C in which you are heterozygous to both anomalies. Many chronic illnesses are linked to this anomaly. Fibromyalgia, irritable bowel syndrome, migraines, chemical sensitivity, frequent miscarriage and frequent blood clots are all conditions associated with MTHFR anomaly. For a great diagram of more methylation related health problems, check this out:

**MTHFR Related Health Problems**

Glutathione is the body's primary antioxidant and detoxifier. One of the ways that MTHFR gene mutation can make you susceptible to illness is by lowering your ability to make glutathione. People with MTHFR anomalies usually have low glutathione, which makes them more susceptible to stress and less tolerant to toxic exposures. Accumulation of toxins in the body and increased oxidative stress, which also leads to premature aging.

Some conditions that may be associated with MTHFR gene mutations

- Autism
- Addictions: smoking, drugs, alcohol
- Down’s syndrome
- Frequent miscarriages
- Male & female infertility
- Pulmonary embolism and other blood clots
- Depression & anxiety
- Schizophrenia
- Bipolar disorder
- Fibromyalgia
- Chronic Fatigue Syndrome
- Chemical Sensitivity
- Parkinson’s disease
- Irritable Bowel Syndrome
- Stroke
- Spina bifida
- Migraines
- Hyperhomocysteinemia
- Breast cancer
- Atherosclerosis
- Alzheimer’s
- Multiple Sclerosis
- Myocardial Infarction (Heart Attack)
- Methotrexate Toxicity
- Nitrous Oxide Toxicity

**Treatment for MTHFR**

Fortunately, you can easily be tested for the MTHFR mutation. If you find out that you have one or more of the gene mutations, you can supplement with methyl-folate and methyl B12, the active forms of these B vitamins. You can also supplement with liposomal or acetyl-glutathione, the end product of the pathway. Glutathione is poorly absorbed so either the liposomal form or a precursor, called n-acetylcysteine (NAC) may be used. Some of my favorites are Thorne Research Methyl Guard Plus and 5-MTHF 1mg and 5mg.

There are prescription medicines, that also contain methyl-folate: Deplin, MetanX, CerefolinNAC are a few. Methyl B12 can also be given as shots, nasal sprays, and sublingually. The intramuscular shots are by far the most effective method and must be prescribed by your physician. The choice of nutrients will vary from patient to patient and should be done under a doctor's supervision. There is a bell-shaped optimal curve so you may not feel well with too much or too little of the appropriate supplements. Other B vitamins, such as riboflavin and vitamin B6 also play an important role. As you may have surmised, this can be quite complex and I suggest you find a functional medicine trained physician to help you sort through your needs for the different nutrients if you have a chronic health condition related to the gene mutations. It is not uncommon for patients with these genetic polymorphism's to be very sensitive to supplementation.

**Patients who I recommend screen for MTHFR mutations:**

- Pre-conception care: test both man and woman
- Mental dysfunction including but not limited to depression, anxiety, irritability, mood swings, schizophrenia, bipolar
- Infants and children of parents with MTHFR mutations
- Family members related to someone with MTHFR mutations
- Elevated folate (not processing to active 5-MTHF due to inability to methylate)
- Elevated homocysteine (due to low active 5-MTHF and methylcobalamin)
- Elevated s-adenosylhomocysteine (due to low active 5-MTHF and methylcobalamin)
- Elevated serum cobalamin (due to inability to methylate cyanocobalamin to methylcobalamin)
- Elevated methylmalonic acid (due to methylcobalamin deficiency)
- Patients with syndromes: IBS, Chemical sensitivity, Fibromyalgia, Down Syndrome, Chronic fatigue syndrome
- Neurological disorders: Multiple sclerosis, Autism, Alzheimer’s, Epilepsy, Parkinson’s to name a few
- Cancer: family history of cancer or undergoing cancer treatment
- Cervical dysplasia
- Infertility
- Cardiovascular risk: family history of strokes, embolisms, heart attacks, clots, essential hypertension
- Birth defects: cleft palate, tetralogy of Fallot, spinal bifida, midline defects
- Drug sensitivities: methotrexate, anti-epileptics, nitrous oxide, anesthesia

If you are interested in knowing more about your genes, the 23andme gene test will be the best $99 investment you've ever spent!

Check out Health Tips for Dealing with MTHFR Gene Mutations...

For more reading
Holistic Primary Care
Genetics Home Reference
Molecular Biology of MTHFR
Genetics of Homocysteine Metabolism
Homocysteine and MTHFR mutation
23andMe Gene Test

Posted by Jill Carnahan, MD at 5:15 PM

More Detail About The Associated Genetics

From: http://genetics.thetech.org/ask/ask425

What are the A1298C mutation and C677T mutation?

August 25, 2011

Since we wrote this, scientists have found that these variants may not be as worrisome as previously thought.

Given that these DNA differences are so common, it probably should come as no surprise that scientists are starting to rethink their effects on health. In fact, the American College of Medical Genetics and Genomics (ACMG) released a statement in early 2013 that in most cases there is not a medical reason to be tested for the C677T and A1298C variants of MTHFR.

The reason they came to this conclusion is that accumulating evidence seems to show no difference in risk for disease in people in the United States with and without the C677T and A1298C polymorphisms. In fact, the A1298C does not appear to affect the gene function at all. Keep in mind, though, that this is still an active area of research and none of this is definitive yet.

Good question! A1298C and C677T each refer to differences (or "variants") in a gene in our DNA named MTHFR. Having one of these variants means that you have a slightly different version of the MTHFR gene.
People talk about them because they sometimes (but not always) can cause problems. For example, having one or both of them can put you at a higher risk for heart problems or having a child with birth defects. You could also be at a slightly increased risk for nerve defects and even schizophrenia.

But like I said, not everyone with these variants has problems. And this is a good thing, considering how common they are!

Around 30% of Europeans, 10% of Africans, and 50% of Chinese people have the C677T version of the MTHFR gene. The A1298T variant is similar.

This all might sound scary – but not to worry. As I said before, most people that have these variants are perfectly fine, with no symptoms.

One reason is that to have a chance at ending up with problems, you need a double dose of these variants. Remember, you have two copies of each of your genes - one from your mom and one from your dad. So both the copy from mom and the copy from dad have to be the C677T and/or A1298C versions for there to be a risk for problems.

Now the chance of having problems is much lower. For example, only around 10% of Europeans have two copies of the C677T version of the MTHFR gene.

Even if a person ends up with two copies of these different gene versions, it doesn't mean that they will definitely have symptoms. For instance, a person with two copies of the C677T version of the gene has only a 10-20% higher chance of getting heart disease than someone with two non-C677T copies. And as far as scientists can tell, the A1298C version usually only causes problems if a person's other gene copy is the C677T version.

So having two copies of C677T (or one copy of C677T and one copy of A1298C) really only increases the risks for certain problems. And sometimes, taking extra B vitamins can help to lower that risk. What I'll do for the rest of the answer is talk about why these DNA differences can lead to such problems. To do this, though, we need to take a step back and talk about genes in general.

**Genes and MTHFR**

Our DNA is like a cookbook – it gives all the instructions for making us. Just like a cookbook has instructions for how to make bread and cookies, our DNA tells us how to make things like our hair and our eyes.

Our DNA cookbook is more thorough than a regular cookbook, though. It also gives the instructions for making all the tools that we need for cooking – like our pots, our pans, and our stove.

The recipes and instructions in our cookbook are called genes. The recipe for making chocolate chip cookies is in one recipe, or gene. The instruction manual for the microwave is in another.

Rather than explaining how to make cookies or how to put together a microwave, each gene explains how to make something that does some important job inside of our bodies. That something is called a protein.
The gene we're talking about in this article gives the instructions for making a protein called MTHFR. This protein is important for making sure that the right ingredients go into our recipes.

These ingredients are called amino acids, and they are the basic building blocks of every protein described by our genes. The job of the MTHFR protein is to help to change one type of amino acid, or ingredient, into another one. *(If you're curious about which ones, MTHFR helps to change the amino acid homocysteine into the amino acid methionine.)*

You can think of the MTHFR protein like a microwave, which can turn solid butter into liquid butter. Both ingredients are used in lots of recipes. Some recipes, like cookies, need solid butter. Other recipes, like a cake, need melted butter. The microwave is important so that we can use either ingredient when we need them.

**Small Change, Big Effect**

Now let's get back to the C677T and A1298C variants. Again, people with these variants have differences in the DNA of their MTHFR gene. In other words, they have different instructions for making their microwaves.

You can think of a gene with a variant as an instruction manual with one word changed. For example, the instructions for a microwave with a variant might read "put on the door with the handle facing *inwards*" instead of "handle facing *outwards*.”

So, different instructions can mean a microwave that works a bit differently. And that is why potential problems can arise.

The C677T variant is a change in the instruction manual that makes the MTHFR protein less able to deal with heat. The C677T version of the MTHFR protein is like a microwave with a glitch that causes it to sometimes spark and short-circuit if the weather gets too hot.

So, someone with the C677T variant has a MTHFR protein that doesn't work all of the time because of the glitch. And so, they have a microwave that can't always do its important job of melting butter.

But as I said before, we have two copies of each set of instructions – one from mom, and one from dad. So fortunately, most people with this version of the MTHFR gene have another MTHFR gene, or set of microwave instructions, that is just fine. The other working microwave can take over to melt the solid butter when the C677T microwave can't.

But problems can happen if both instruction manuals have the change. For example, a person with two faulty microwaves will be less able to make the important recipes with melted butter in them. Having too much solid butter lying around can also cause problems.

So, this is why having two C677T versions of the MTHFR gene can increase the chance of symptoms, like heart disease, that we mentioned before. But remember – not everyone with two C677T variants has symptoms. Some people manage just fine not being able to melt butter or having too much extra butter lying around.

And in fact, a person can deal with many of the symptoms of having two C677T variants by taking extra B vitamins. In a way, this is like using pre-melted butter, or maybe vegetable oil,
to make the recipes needing melted butter. B vitamins can help the C677T version of the MTHFR protein do its job.

The second variant we mentioned, A1298C, has been studied a little bit less. It can cause problems too, although it seems that it only does when it comes along with the C677T variant. If one of the person’s instruction manuals has the C677T variant, and the person’s other manual has the A1298T variant, there isn’t a fully working microwave to take over.

These two variants aren’t the only ones that have been found in people’s MTHFR genes, either. People have many other differences in their MTHFR instruction manuals. However, most of them probably don’t change the microwave that much. And since they are not as common, we don’t know as much about them.

There are lots of variants in the other genes of our DNA, too. These variants are what make us all unique! By studying them, scientists can better understand how all of our genes work together to make us who we are.

The Name Game

Want to understand what those complicated variant names (C677T and A1298C) mean? Instead of being made up of words like a recipe or instruction manual, our DNA is made up of the letters A, T, C and G.

A variant is often when one letter of a person’s DNA is different from most other people’s. Maybe they have a T in the place where most people have a C in their DNA. This difference at one letter is called a single nucleotide polymorphism, or SNP.

The first letter in the name of the variant is the original letter in the DNA. In the case of the C677T variant, it is the letter C. Can you guess what the T means? That’s right – it is the letter found in the person with the variant, or the difference in their DNA.

And the numbers? Since a gene (and our DNA) is a string of letters, the numbers tell us where in the gene the variant is. For the C677T variant, the name tells us that the variant is at the 677th letter of the gene.

So, a person with the C677T variant has a T instead of a C at the 677th letter of the MTHFR gene in their DNA. Can you work out on your own what the A1298C mutation means?

What Are Your Chances?

From http://genetics.thetech.org/ask-a-geneticist/mthfr-a1298c-c677t

Diseases

I was diagnosed with heterozygous MTHFR mutations C677T and A1298C. Did I inherit this from one or both parents and could I have passed it on to my children? Thanks.

-A curious adult from New Jersey

October 9, 2013
Odds are that you inherited C677T from one parent and A1298C from the other. There are exceptions where you could have gotten both from one parent but these are extremely rare.

If you got one from each parent, then most likely you will pass one (but not both) down to your kids. Each child will have a 50% chance to get a C677T and a 50% chance for getting an A1298C.

Before getting into the nuts and bolts of how you inherited these, I wanted to make a couple of points. First off, most scientists wouldn’t call these differences mutations.

A mutation is a recent change in your DNA. Neither of these changes is recent.

Thousands of years ago, there was a C677T mutation in one person, and an A1298C mutation in someone else. Those mutations were passed down and spread around the world. Now, people all around the world carry these two mutations.

When a mutation goes on to be common, it becomes known as a ‘polymorphism’. This just means it is one of the relatively common possible DNA differences or variants at that specific spot in the DNA. And these differences are definitely common.

Around 12% of MTHFR genes in the African American population have the C677T mutation, while that number is even higher for white Americans in the U.S. at 31%. A1298C is just as common. (Click here and scroll to the bottom to learn more about why they are called C677T and A1298C.)

Given that these DNA differences are so common, it probably should come as no surprise that scientists are starting to rethink their effects on health. In fact, the American College of Medical Genetics and Genomics (ACMG) released a statement in early 2013 that in most cases there is not a medical reason to be tested for the C667T and A1298C variants of MTHFR.

The reason they came to this conclusion is that accumulating evidence seems to show no difference in risk for disease in people in the United States with and without the C667T and A1298C polymorphisms. In fact, the A1298C does not appear to affect the gene function at all.

Keep in mind, though, that this is still an active area of research and none of this is definitive yet. The best recommendation is to consult a genetic counselor before and after getting a genetic test.

**Gene Inheritance**

We have two copies of most genes. One copy comes from each parent.

When we pass genes down to our kids, we give them one of the two copies. Which copy they get is determined by random chance. The other parent also gives one copy of each gene.

Let’s imagine the other parent of your children has neither of the MTHFR polymorphisms. A diagram of your situation might look like this:
In this cartoon example, the color of the stick figure indicates the MTHFR variant that person has. Gray is the standard MTHFR gene, red the C677T version and black A1298C.

Each of your parents, Parent 1 and Parent 2, has a different variation of the MTHFR gene in addition to the standard version. By chance, each gave you the non-standard version of the gene. The odds of this happening were 1 in 4.

Each of your kids would only get one copy of the MTHFR gene from you. Therefore, each child will have only one of the MTHFR polymorphisms, they are very unlikely to get both (or neither). Which one of the two they end up with is random.

**Why C677T/A1298C in the Same Gene is Rare**

For the last part of the answer, I thought I would focus on why A1298C and C677T aren’t usually both in the same copy of MTHFR. As you’ll see, it has to do with the history of these mutations, and how DNA is passed down to the next generation.

For starters, geneticists have looked at thousands of people for these two DNA polymorphisms. What they discovered was that if one copy of the MTHFR gene had C677T, it would rarely have A1298C also. To think of why, imagine the gene MTHFR as a grid of colors:
A long time ago, there was a spontaneous mutation in someone’s DNA at the MTHFR gene. Since they passed it on to the next generation, the mutation probably happened in a sperm or an egg. So, they had a slightly different MTHFR gene:

The black square represents the mutation in the gene.

Someone else, in a different time and place also had a mutation in the MTHFR gene. But this one was at a different location:

Notice that this person didn’t have the C677T mutation. This is why these two are usually separate. They each happened independently in different copies of the gene.

This is almost certainly what happened in our past (although of course we can’t know for sure). But it didn’t have to happen this way.

Imagine that the A1298C mutation happened after C677T was already starting to become common. And, let’s also suppose that a person who already had the C677T mutation got the A1298C mutation. This would have been the result:
So you see, the grid has both the yellow and black squares, representing both mutations. However, that is not what happened. Instead, people walked around having one of the first three possibilities: regular MTHFR, MTHFR with C677T, or one with A1298C.

Future mutations that might have occurred in the MTHFR gene now happen on the ‘background’ of one of these three. Imagine we had two more mutations (in gray) happen in someone’s DNA that already had the C677T mutation:

These three mutations now come as one block, so somebody that inherits the two gray mutations, will also receive the C677T polymorphism. Over time, more and more mutations build up in this way.

The result is that if you have the gray mutations, you probably have the black one (C677T) too. But this applies to all genes, not just MTHFR.

These mutation ‘blocks’ tend to be passed down from one generation to the next. Overtime, they become common in the population. At this point, scientists call these blocks ‘haplotypes’. If you know your haplotype at a region of DNA like where the MTHFR gene is, you can make a pretty good guess as to which common DNA polymorphisms you have without actually measuring them.

Of course nothing in genetics is 100%! Through something called recombination, haplotypes can mix and match before entering the sperm or egg. If they happened in just the right way, you’d end up with both differences in the same gene.

**Another Way to get A1298C and C677T in the same copy: Recombination**

One very important and interesting thing your DNA does is to mix up some of the genes you inherited from your mom and dad. That way, you’re not giving your kid only your mom’s genes, or only your dad’s. This is called ‘**recombination**’.
To go back to our grid example, let’s say that half of the gene you got from your mom was swapped with half the gene you got from your dad like this:

After the pieces got swapped, one of the gene copies has both DNA polymorphisms and the other now has neither. If this happened in the DNA of your parents’ or one of their ancestors’, then you might have inherited both C677T and A1298C from a single parent. That might actually be a good thing, because the other parent gave a copy of the MTHFR gene that works perfectly normally.

By Glenn Markov, *Stanford University*

**More Information**

- DNA is mixed and matched with each generation
- How DNA mutations happen
- What MTHFR does in the body
- Health concerns with MTHFR variants

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**The Chemistry of the Methylation Cycle:**

Methylenetetrahydrofolate reductase (MTHFR) is the rate-limiting enzyme in the methyl cycle, and it is encoded by the *MTHFR* gene. Methylenetetrahydrofolate reductase catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a cosubstrate for homocysteine remethylation to methionine. Genetic variation in this gene may influence susceptibility to occlusive vascular disease, neural tube defects, dementia, colon cancer, and acute leukemia, because mutations in this gene are associated with methylenetetrahydrofolate reductase deficiency.

Notice in the diagram below, the production of Dopamine & Serotonin

Exactly What my Doctor (Psychiatrist) Prescribed and what I take:

- **CELEXA/CITALOPRAM HBR - 40 mg QD** - MDD - Depression
- **ESCITALOPRAM/LEXAPRO - 10 mg BID** - MDD - Depression
- **LEVOMEFOLATE CALCIUM/ L-METHYLFOLATE - 15 mg QD** - MDD - Depression
**What is L-Methylfolate: Names and Definitions?**

- **Rx:** levomefolate calcium 15 mg tablet, 1 tablet, Oral, QD (daily)
- **Quantity:** ***30*** {thirty} tablet
- **Refill:** ***0*** {zero}
- **Substitutions:** Use generic substitution
- **Comments:** take one tablet by mouth in AM with food

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**Technical Name: Levomefolate Calcium**

In the US, Levomefolate Calcium is a member of the drug class \textit{vitamins} and is used to treat \textit{Dietary Supplementation}.

**Scheme**

- **USAN**

**CAS registry number (Chemical Abstracts Service)**

0151533-22-1

**Chemical Formula**

C20-H23-Ca-N7-O6

**Molecular Weight**

497

**Therapeutic Categories**

- Treatment and prevention of folate deficiency
- Antidote against folic acid antagonists

**Chemical Names**
L-Glutamic acid, N-[4-[[[(6S)-2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl][methyl]amino]benzoyl]-, calcium salt (1:1) (USAN)

N-[4-[[[2-Amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-6-pteridinyl]methyl]amino]benzoyl]-L-glutamic acid calcium salt

Calcium N-[4-{{[(6S)-2-amino-5-methyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl][methyl]amino}benzoyl]-L-glutamate (USAN)

Calcium (2S)-2-[[4-[[[(6S)-2-amino-5-methyl-4-oxo-1,6,7,8-tetrahydropteridin-6-yl][methylamino]benzoyl]amino]pentanedioate (IUPAC)

Calcium (6S)-5-Methyltetrahydrofolate

Foreign Name

- Calcium mefolinat (German)

Generic Names

- Levomefolate Calcium (OS: USAN)
- 5-MTHF, Calciumsalt (IS)
- AC-7457 (IS)
- BAY 86-7660 (IS)
- Calcium L-methylfolate (IS)
- Calcium L-methyltetrahydrofolate (IS)
- Calcium mefolinate (IS)
- Levomefolinate Calcium (IS)
- LMCA (IS)
- UNII-A9R10K3F2F (IS)

Brand Name

- Prefolic
  Zambon Italia, Italy

Glossary

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I will add to this as additional information becomes available.

-mike (Revised July 7, 2014)