

# Folate Metabolism and MTHFR:


## Introductory Overview of an Essential Gene

Presenter:  
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I am President and CEO of Seeking Health, LLC

I am founder of MTHFR.Net



# Overview of this Presentation

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- What is Folate?

- Explain folate metabolism

- Explain the importance of folate metabolism

- Identify the necessary factors needed for folate metabolism

- Define MTHFR

- Identify the prevalence of MTHFR defects in the population and who is most at risk

- Identify common associated conditions and disorders which are linked to MTHFR

- Provide basic methods to support the MTHFR enzyme despite the defect

- Identify the commonly prescribed medications and supplements for bypassing the MTHFR enzyme.

- Identify the common side effects experienced by those supporting the MTHFR enzyme

- How to lessen the side effects commonly seen with MTHFR support

## What is Folate?

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 Folate comes from the Latin word 'folium' which means leaf

In 1946, folate was discovered by isolating the nutrient from 4 tons of spinach leaves.

Folate is Vitamin B9

Found in uncooked leafy greens in high amounts.

Cooking rapidly destroys folate.

Source: Herb, Nutrient and Drug Interactions by Stargrove et al *and* Advanced Nutrition and Human Metabolism by Groff and Gropper

## What is Folate? (cont'd)

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Generic Term for the over 150 different forms of food folate

Folate consists of three similar components

- 1) Pterin molecule
- 2) PABA
- 3) Glutamic acid residues



## Functions of Folate?

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“The **functions of folate** in human physiology are relatively simple, but the implications of their activity (and dysfunction) can be **profound and far reaching.**”

Functions:

- synthesis of nucleic acids (for DNA production and repair and tRNA)
- single carbon metabolism (methylation)
- interconversion of amino acids (for neurotransmitter production and detoxification)
- formation and maturation of RBC, WBC and platelet production

## Does Folic Acid = Folate?

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Folic acid does NOT equal Folate.

Folic Acid is only ONE type of Folate

Folic acid is not found in nature.

Folic acid must undergo various transformations prior to utilization.

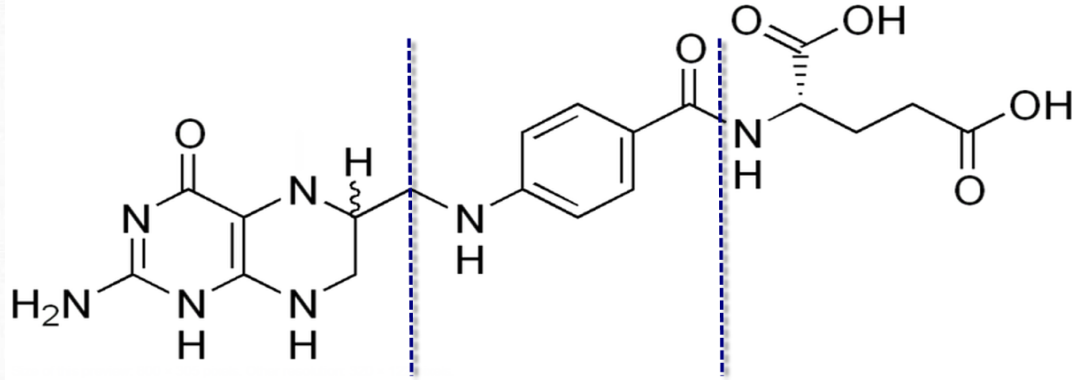


Must be specific when discussing folate. Use the appropriate term and form.

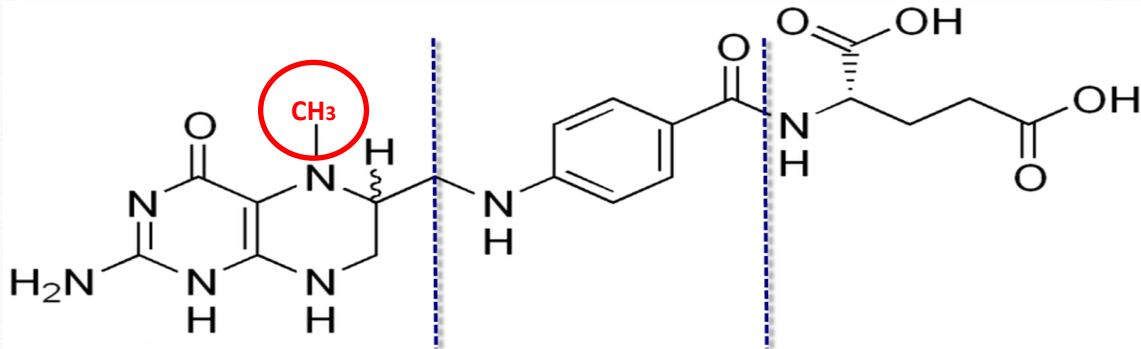
- Folic acid
- Folinic acid
- Methylfolate



## Comparing Folic Acid to 5-Methyltetrahydrofolate



Folic Acid



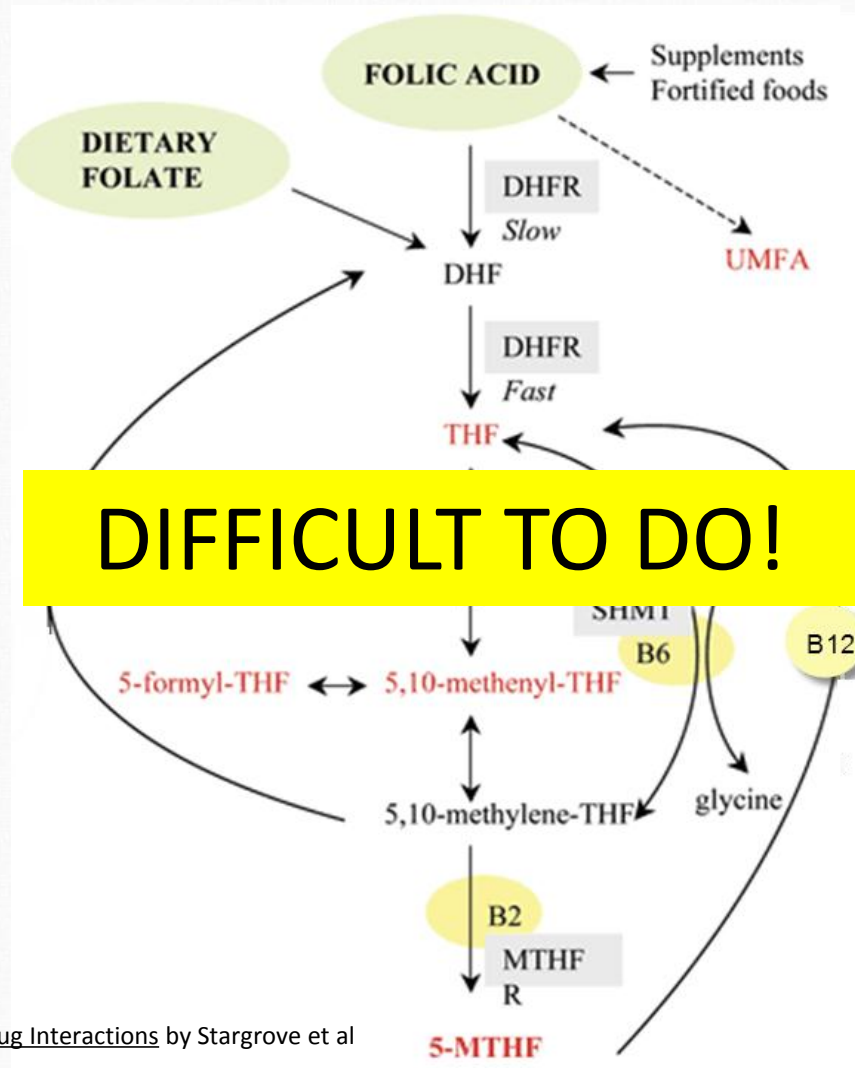
5-Methyltetrahydrofolate



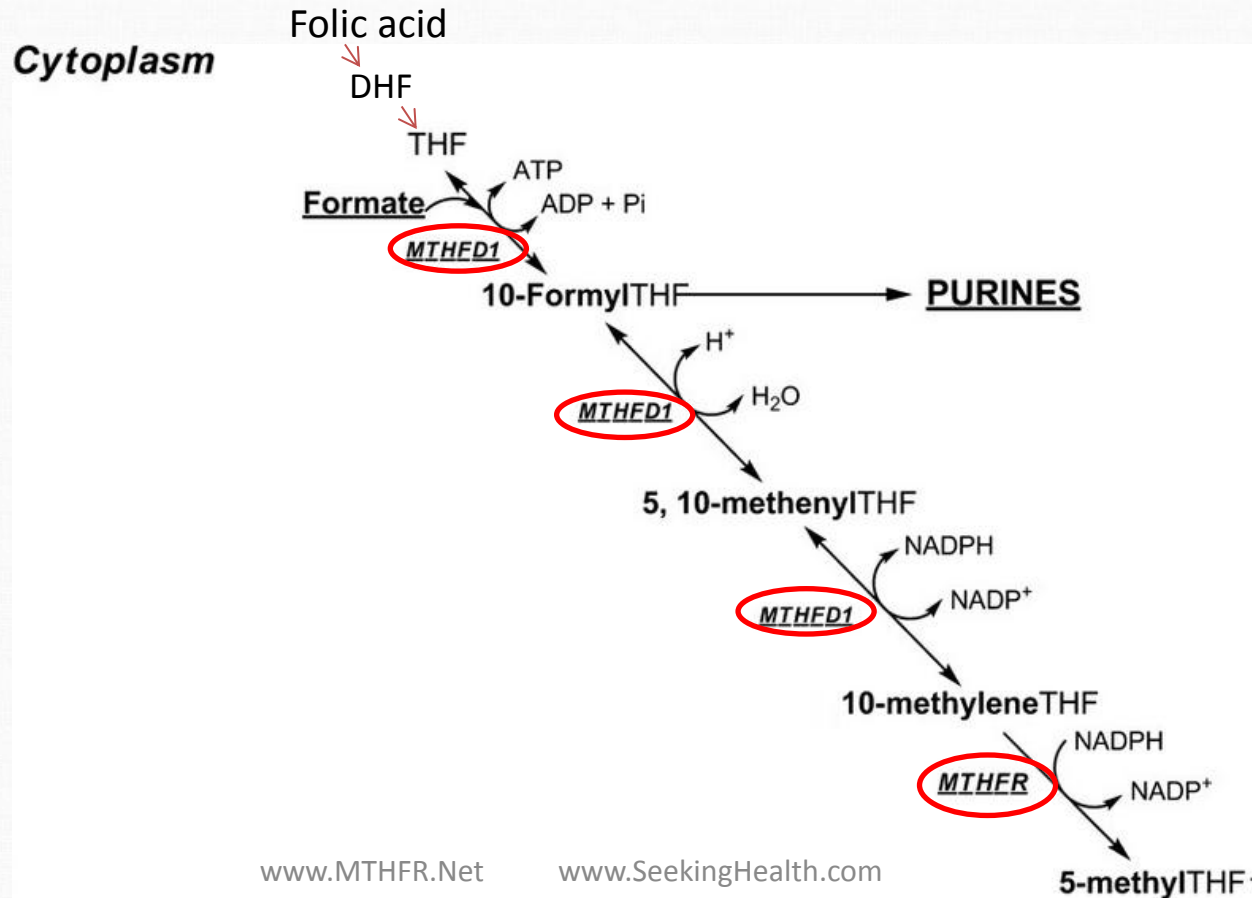
# Converting Folic Acid to 5-Methyltetrahydrofolate

Requires:

- 1) Two functioning enzymes
  - MTHFD1
  - MTHFR
- 2) Vitamins, Minerals and pH:
  - B2
  - B3
  - B6
  - B12
  - Vitamin C
  - Zinc (for absorption)
  - Acidic environment (for absorption)




## A Look at the Enzymes Needed for Conversion of Folic Acid to Methylfolate



## Recap

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1. Folate is vitamin B9
  2. Critical regulator of methylation
  3. Essential for DNA synthesis and repair
  4. Essential for neurotransmitter production
  5. Essential for WBC, RBC and platelet formation and maturation
  6. Essential for detoxification of homocysteine
  7. Folic acid is unnatural to the human body
  8. There are over 150 forms of folate in food
  9. Use the appropriate term – don't just say 'folate' – be specific
  10. Folic acid must undergo numerous steps in order for humans to utilize it
  11. Various nutrients and enzymes are needed to convert folic acid into methylfolate
  12. MTHFR is the last and final step from the conversion of folic acid into methylfolate





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# Terminology

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**Gene:** inheritable material (DNA) from parents which has encoded data that must be read and translated. Produces proteins and enzymes.

**Enzymes:** produced by genes. Enzymes are actively moving and functioning proteins which do work. Enzymes require specific pH, substrates and cofactors in order to do work

**Cofactor:** typically a mineral or vitamin which enables an enzymes to function properly

**Substrate:** a molecule that is being converted into a different molecule by an enzyme

**Nucleotide:** building blocks of DNA bases.

**Codon:** comprised of three nucleotides and codes for a specific amino acid

**Mutation:** change in the nucleotide sequence which in turn alters the gene. It may or may not have an effect on the gene.

**SNP:** a single nucleotide base change in the gene. It may or may not have an effect on the gene. It may not change the codon due to redundancy of our genetic code. A SNP may cause a mutation.

**Redundancy:** our genetic code has multiple nucleotide combinations to produce a single codon. Example: GAG and GAA produce glutamic acid. If the last nucleotide base changes from a G to an A, the SNP has no effect.

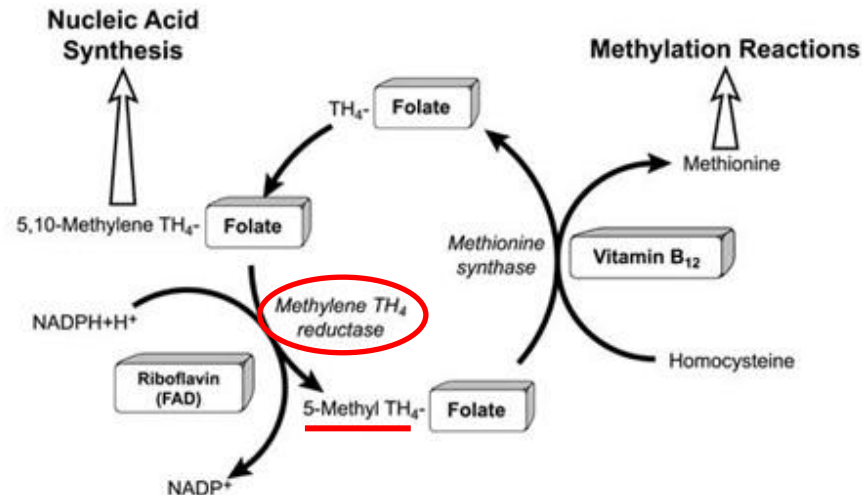


# MTHFR: Gene which produces the Methylene tetrahydrofolate Reductase Enzyme



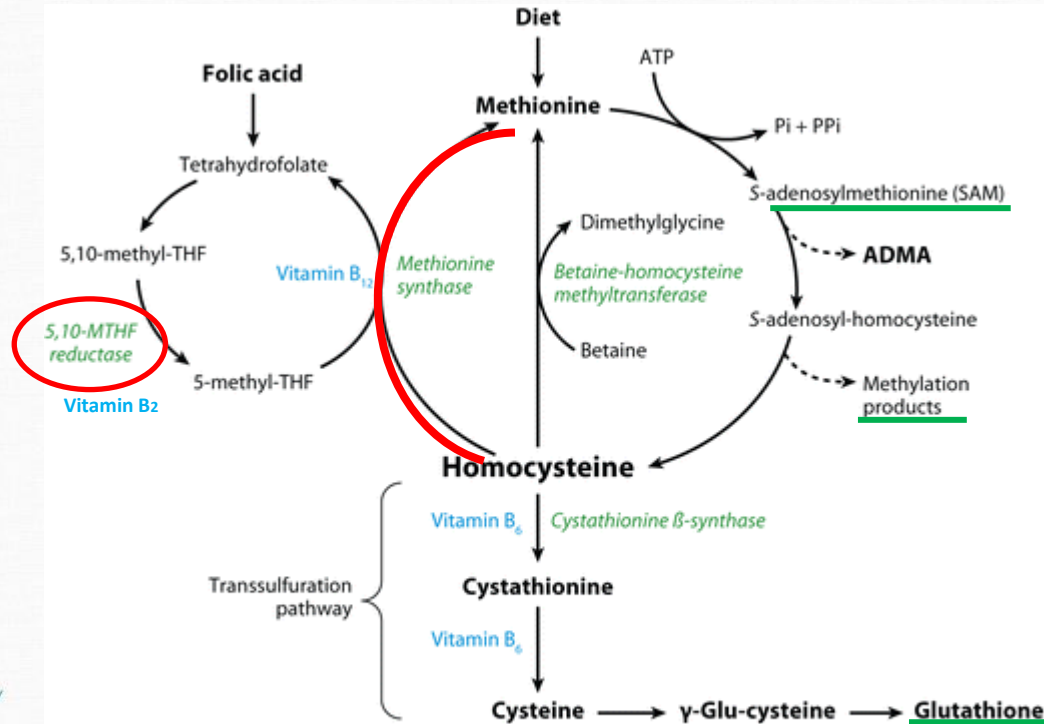
## MTHFR:

- 1) Produces the final form of folate – as 5-methyltetrahydrofolate (5-MTHF)
  - 5-MTHF is the most abundant form of folate in the plasma circulation.
- 2) Provides the substrate for the transmethylation cycle
- 3) Found inside each cell – more so in certain areas such as testis, brain, kidney.





# MTHFR: Gene which produces the Methylene tetrahydrofolate Reductase Enzyme



Without 5-MTHF, the transmethylation pathway suffers and puts pressure on the BHMT pathway. BHMT is only in liver, kidney and eye whereas MTHFR is in every cell – specifically the cytosol.

Source:

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515933/> and  
PMID: 11468972 and  
<http://www.ncbi.nlm.nih.gov/books/NBK6561/>



Maron BA, Loscalzo J. 2009.  
Annu. Rev. Med. 60:39–54



## MTHFR SNPs

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SNPs in the MTHFR enzyme cause it to not work as well

Two commonly known MTHFR defects:

- 1) MTHFR C677T – at nucleotide 677, the cytosine changes to a thymine causing alanine to switch to valine.
- 2) MTHFR A1298C – at nucleotide 1298, the adenine changes to a cytosine causing glutamate to switch to alanine.

The MTHFR enzyme is functional with these SNPs; albeit less so proportionately to the number of SNPs

## Loss of Function

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The MTHFR enzyme is functional with these SNPs; albeit less so proportionately to the number of SNPs

Heterozygous = 1 copy of the gene from either parent

Homozygous = 1 copy of the gene from each parent (most commonly – some exceptions)

MTHFR C677T Heterozygous = 40% loss of function

MTHFR C677T Homozygous = 70% loss of function

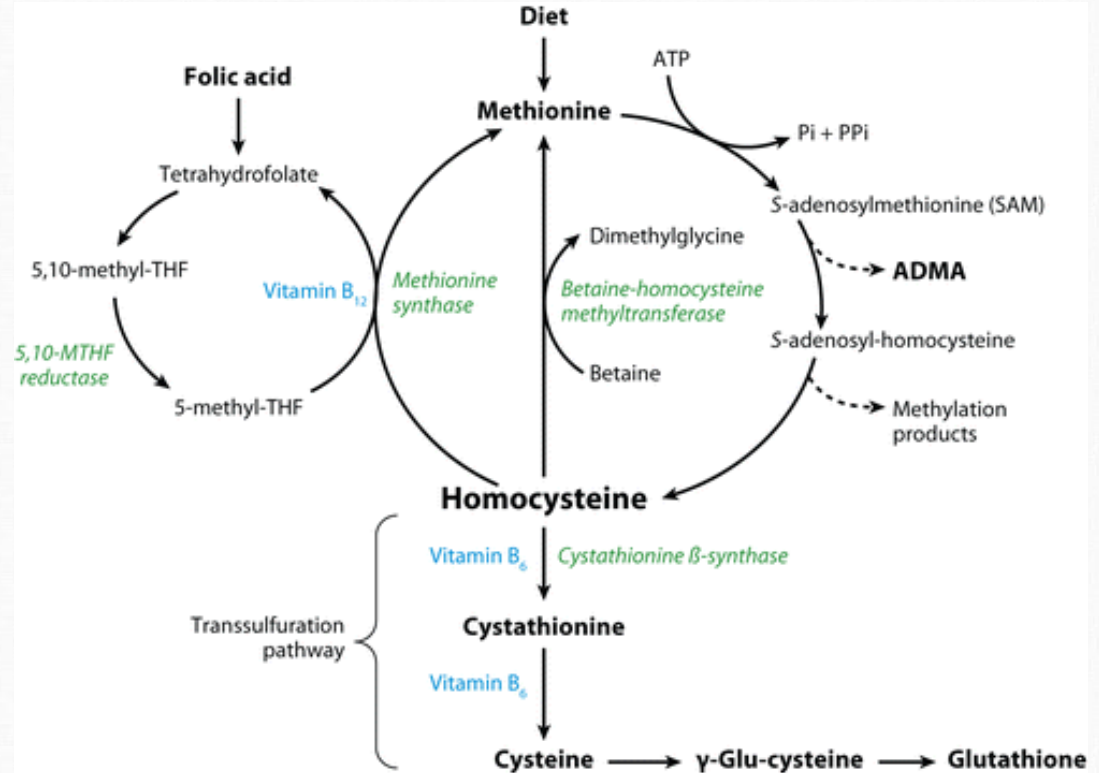
MTHFR A1298C Heterozygous = No loss of function (debatable)

MTHFR A1298C Homozygous = No loss of function (debatable)

MTHFR C677T & MTHFR A1298C Compound Heterozygous = 50% loss of function

## What happens if we don't have enough MTHFR activity?

1. 5-MTHF levels go down
2. Transmethylation cycle slows
3. BHMT enzyme activity increases but this only supports liver and kidney
4. All tissues except liver and kidney begin to suffer the effects of decreased methylation
5. Decreased methylation leads to:
  1. Deficient neurotransmitter production
  2. Deficiency in glutathione
6. As BHMT become depleted in choline:
  1. Homocysteine levels rise
  2. Methylation in liver and kidneys decrease
  3. Phosphatidylcholine production drops causing cell membrane and myelin instability



Maron BA, Loscalzo J. 2009.

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## MTHFR Defects: *Some* Conditions They Cause

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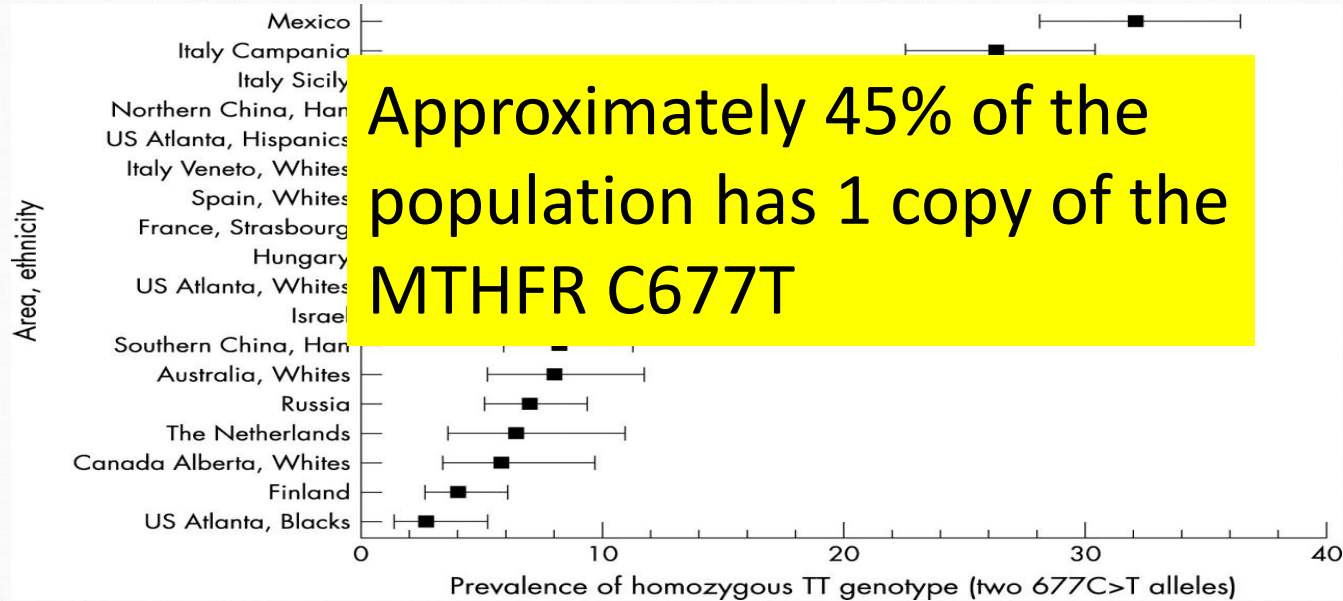


- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>• Diabetes</li><li>• Cancer</li><li>• Pulmonary Embolisms</li><li>• Cleft Palette</li><li>• Spina Bifida</li><li>• Autism</li><li>• Parkinson's</li><li>• Neural Tube Defects</li><li>• Atherosclerosis</li><li>• Immune Deficiency</li><li>• ADD/ADHD</li><li>• Multiple Sclerosis</li><li>• Alzheimer's</li><li>• Dementia</li><li>• Chemical Sensitivity</li><li>• Congenital Heart Defects</li></ul> | <ul style="list-style-type: none"><li>• Fibromyalgia</li><li>• Chronic Fatigue Syndrome</li><li>• Depression</li><li>• Alcoholism</li><li>• Addictive Behaviors</li><li>• Insomnia</li><li>• Down's Syndrome</li><li>• Chronic Viral Infection</li><li>• Thyroid Dysfunction</li><li>• Neuropathy</li><li>• Recurrent Miscarriages</li><li>• Infertility</li><li>• Anxiety</li><li>• Schizophrenia</li><li>• Bipolar</li><li>• Allergies</li></ul> |
|--|--|

## Who are at risk for MTHFR mutations?



**Prevalence of homozygous TT genotype (two 677C>T alleles) among newborns by area and ethnic background, ICBDS 2003**



[Wilcken B et al. J Med Genet 2003;40:619-625](#)

## Testing for MTHFR

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MTHFR Genetic Testing is available through:

- Spectracell
- Quest
- LabCorp
- [Baylor Research Institute](#) – excellent out of pocket option if insurance does not cover
- 23andMe - (provides only raw data which must be interpreted. Interpretation done by [www.MTHFRSupport.com](http://www.MTHFRSupport.com) )



Insurance **may** cover MTHFR testing if one has experienced:

- Drug sensitivity – especially to methotrexate or nitrous oxide
- Recurrent blood clots
- Elevated homocysteine
- Recurrent miscarriage



### MTHFR Genotype Test Result

<u>Test</u>	<u>Result</u>
C677T Mutation	Homozygous
A1298C Mutation	Negative

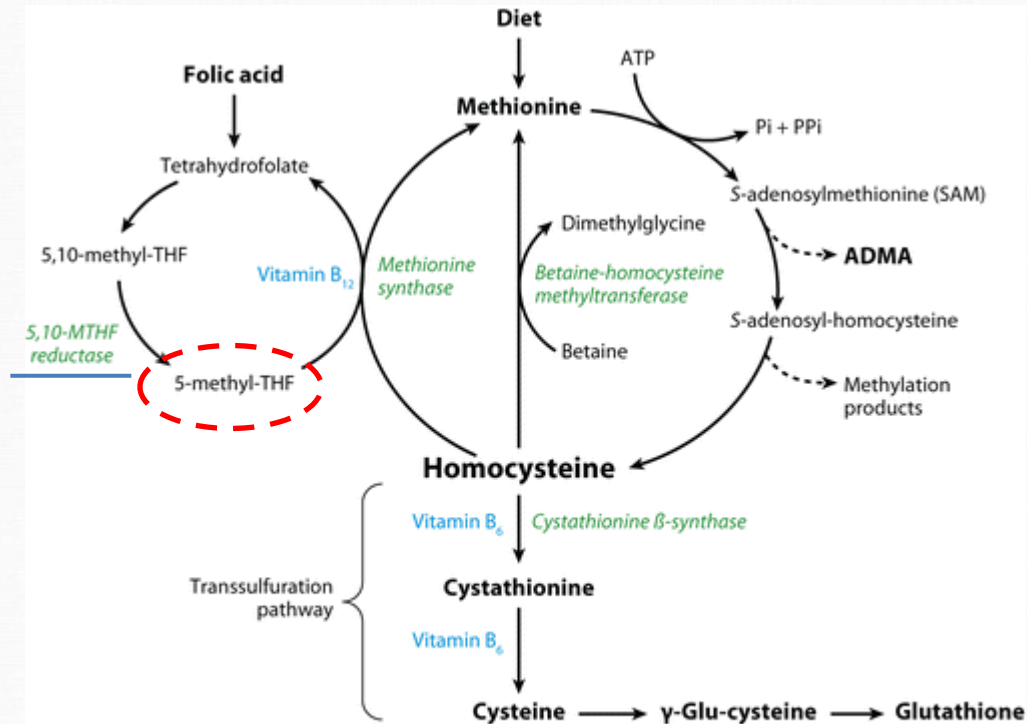
This sample has two copies of the C677T mutation and is negative for the A1298C mutation.

This genotype

- is associated with decreased enzyme activity (approximately 30% of normal activity).
- is associated with increased homocysteine levels.
- is correlated with increased risk of cardiovascular disease or thrombosis.
- is associated with potential methotrexate intolerance and patients may require dosage adj



## Test Positive for MTHFR? Now What?



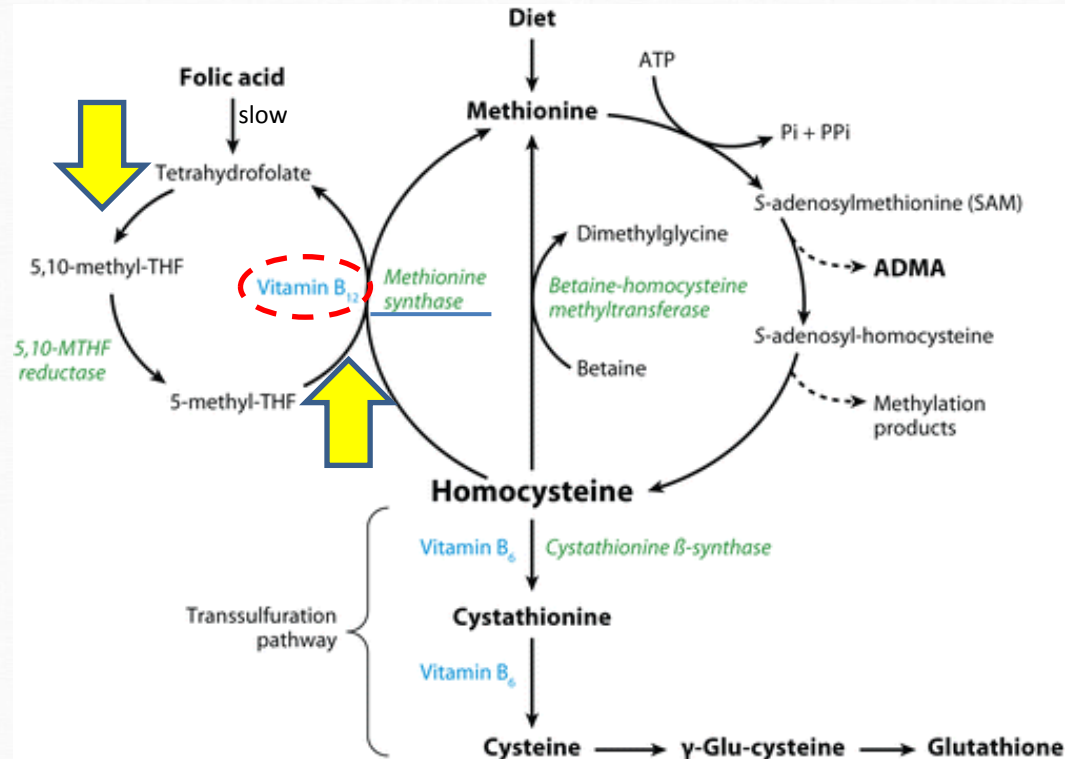
**Supplement with:**  
**L-5-MTHF**

That's enough right?



Maron BA, Loscalzo J. 2009.  
Annu. Rev. Med. 60:39–54

# Methyl Trapping: Why more than L-Methylfolate is Needed



## Supplement:

L-5-MTHF and  
Methylcobalamin  
(or Hydroxocobalamin)

Lozenge or Liposomal  
Preferred for Best  
Absorption

Those with digestive disorders  
may not absorb or transport  
either nutrient well.



Maron BA, Loscalzo J. 2009.

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[www.MTHFR.Net](http://www.MTHFR.Net)

[www.SeekingHealth.com](http://www.SeekingHealth.com)

# Unmetabolized Folic Acid

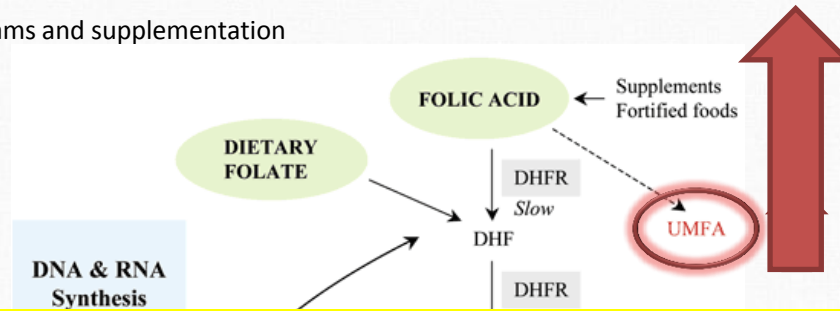


Increased levels may decrease NK cell activity. PMID: 16365081

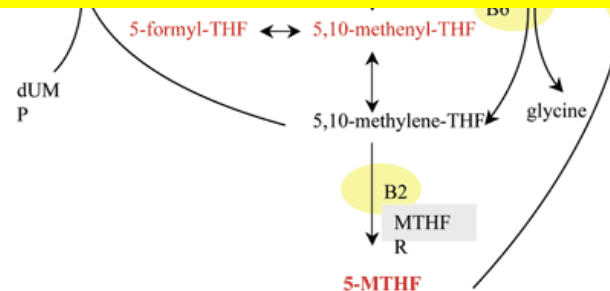
Caused by excessive fortification programs and supplementation

May mask a vitamin B12 deficiency

Avoid Folic Acid



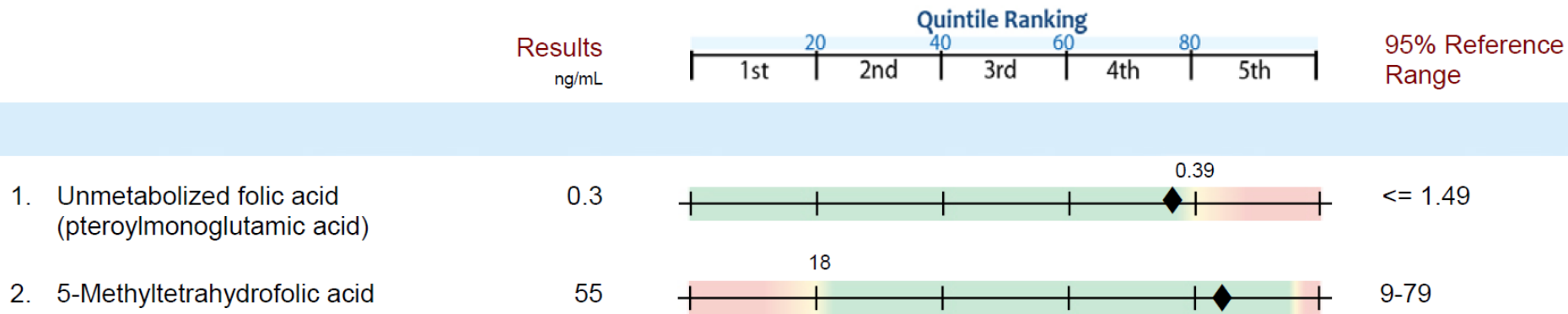
“Following absorption of physiological amounts of folic acid into the enterocytes, a certain percentage undergoes reduction.”



# Testing Levels of Methylfolate and UMFA

## 0030 Unmetabolized Folic Acid - Serum

LC/Tandem Mass Spectroscopy



Unlike folate which is found naturally in food, folic acid (pteroylmonoglutamic acid) is the synthetic form of the vitamin used commercially in fortified foods and supplements.<sup>1</sup> Excess folic acid supplementation can lead to a build-up of folic acid in serum, termed unmetabolized folic acid (UMFA). Folic acid supplementation has been associated with cancer progression<sup>1</sup> and this may be due to high UMFA. Monitoring of UMFA has been recommended by researchers from the National Institutes of Health, Office of Dietary Supplements.<sup>2</sup>

Test available through Metamatrix Labs

# Drugs to Avoid with MTHFR

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## Common Drugs to Avoid with MTHFR

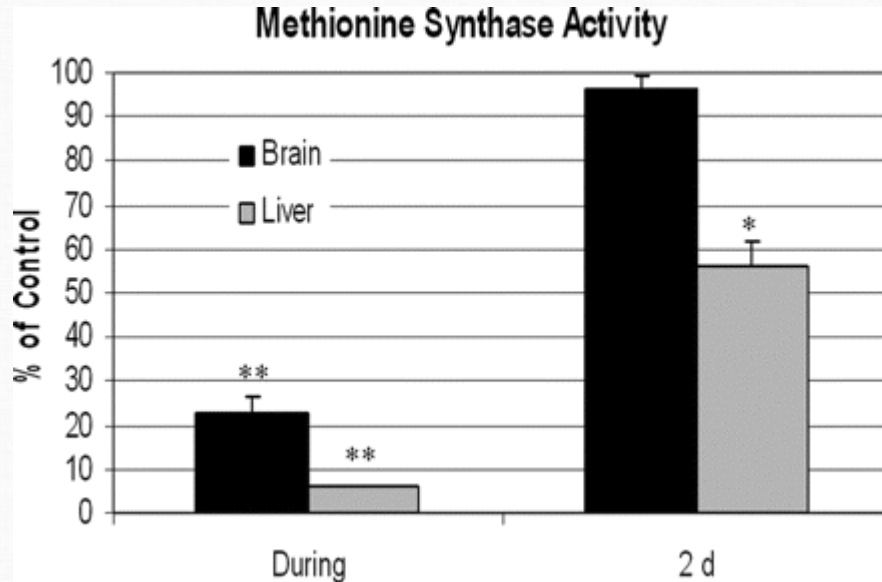
- Antacids (deplete B12)
- Cholestyramine (deplete cobalamin and folate absorption) – common in gallbladder issues during pregnancy!
- Colestipol (decrease cobalamin and folate absorption)
- Methotrexate (inhibits DHFR)
- Nitrous Oxide (inactivates MS)
- High Dose Niacin (depletes SAME and limits pyridoxal kinase = active B6) Small doses are great.
- Theophylline (limits pyridoxal kinase = active B6)
- Cyclosporin A (decreases renal function and increases Hcy)
- Metformin (decreases cobalamin absorption)
- Phenytoin (folate antagonist)
- Carbamazepine (folate antagonist)
- Oral Contraceptives (deplete folate)
- Antimalarials JPC-2056, Pyrimethamine, Proguanil (inhibits DHFR)
- Antibiotic Trimethoprim (inhibits DHFR)
- Ethanol
- Bactrim (inhibits DHFR)
- Sulfasalazine (inhibits DHFR)
- Triamterene (inhibits DHFR)

Source: Fischbach, Laboratory Diagnosis and BMJ <http://heart.bmj.com/content/83/2/127/T1.expansion.html>

www.MTHFR.Net

www.SeekingHealth.com

## Nitrous Oxide and MTHFR



Nitrous oxide inhibits MTR enzyme.

Those with MTHFR and methylation defects already have limited MTR enzyme function so further reducing it may cause significant neurological or cardiovascular damage.



# Common Meds used for MTHFR

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## Common Meds used with MTHFR

- Cerefolin
- CerefolinNAC
- Neevo
- NeevoDHA
- Metanx → personal favorite out of all of them but still don't like it
- Deplin
- Folbee
- Folplex
- Folgard
- Foltx
- FABB



## Common 'Other Ingredients' in MTHFR Meds

Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose 90, Microcrystalline Cellulose HD 90, Pyridoxal-5'-Phosphate, Opadry II Purple 40L10045 (Polydextrose, Titanium Dioxide, Hypromellose 3cP, Hypromellose 6cP, Glycerol Triacetate, Hypromellose 50cP, FD&C Blue #2, FD&C Red #40, Polyglycol 800), Microcrystalline Cellulose 50, Opadry II Clear Y-19-7483 (Hypromellose 6cP, Maltodextrin, Hypromellose 3cP, Polyglycol 400, Hypromellose 50cP), Lmethylfolate Calcium, Magnesium Stearate, Methylcobalamin, and Carnauba Wax.

Source: <http://mthfr.net/comparison-of-homocysteine-support-products/2011/09/13/>

www.MTHFR.Net

www.SeekingHealth.com



# Which Methylfolate to use for MTHFR?

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## Quality forms of Methylfolate

- L-5-MTHF (L is important to avoid racemic R forms)
- Quatrefolic (glucosamine form)
- Metafolin (calcium form)
- L-Methylfolate
- (6S)-5-Methylfolate

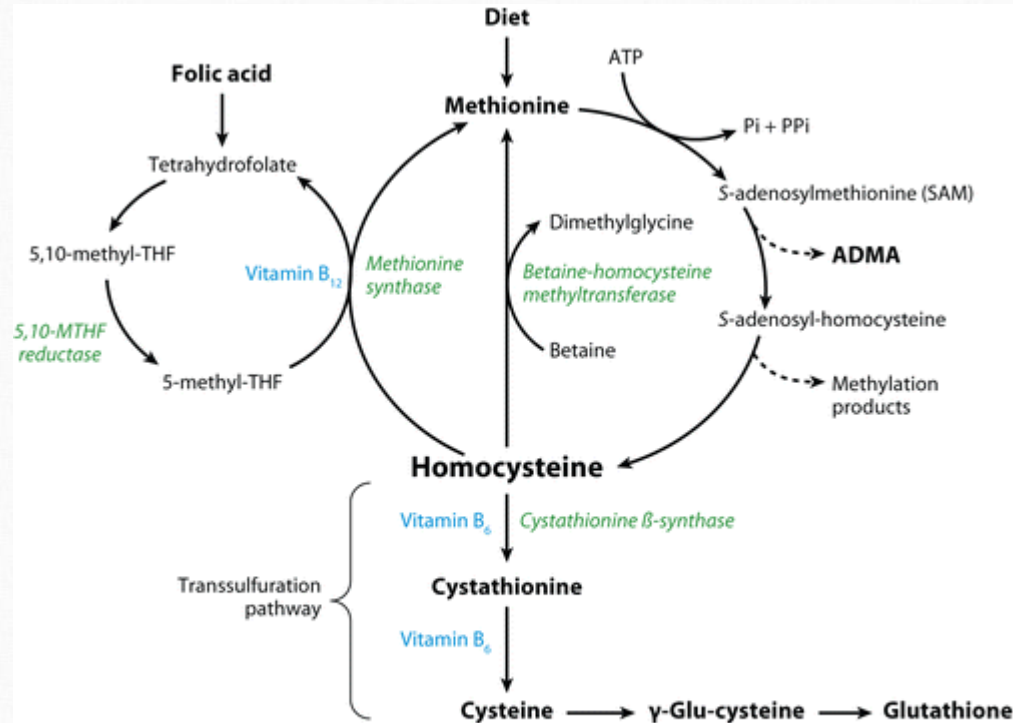


## Issues to Understand about Methylfolate

1. Maximum of 1,000 mcg of L-Methylfolate may be used solo
2. Maximum of 800 mcg of L-Methylfolate may be used in a formula
3. If no 'L' or (6S) or Quatrefolic or Metafolin is used on the label, avoid it!

Source: <http://mthfr.net/l-methylfolate-methylfolate-5-mthf/2012/04/05/>

# Primary Nutrients to Support MTHFR



1. L-5-MTHF
2. Riboflavin (B2)
3. Methylcobalamin or Hydroxocobalamin
4. Zinc
5. DHA
6. Choline
7. TMG
8. Healthy Protein
9. Magnesium
10. SAMe
11. Pyridoxine (B6)
12. NAC
13. Vitamin E
14. Selenium
15. Glutathione
16. Vitamin C
17. Potassium
18. Probiotics
19. Molybdenum
20. Milk Thistle



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# Starting Supplementation

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## **Start Slow and Evaluate**

- One supplement or medication at a time – ideally one nutrient at a time vs formulations
- If sensitive to sulfur foods or sulfur supplements, do not start with L-5-MTHF.
  - Use Molybdenum
- Increase slowly in dosage – don't start high unless directed.
- Evaluate how you are feeling. Some days you need more support than other days. Adjust accordingly.
- More is not necessarily better
- Faster is not necessarily better
- More Methylation support is not necessarily better: BALANCE

# Common Side Effects with Methylfolate

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## Side Effects / Signs to Look For When Starting Methylfolate Meds or Supplements

- Muscle Pain
- Irritability
- Anxiety
- Depression
- Joint Pain
- Nausea
- Headache
- Insomnia
- Seizures
- Vomiting
- Stomach Pain
- Sweating
- 'Herxheimer Reaction'
- Rash
- Hypokalemia
- Palpitations

Source: <http://mthfr.net/methylfolate-side-effects/2012/03/01/>

## Dealing with Side Effects from Methylfolate

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### Neutralize Side Effects from Methylfolate ASAP

**There are two things to quickly quench most of the methylfolate side effects:**

1. Consider 50 to 100 mg of nicotinic acid OR niacinamide every 30 minutes to 1 hour. Use as needed only.



2. Consider 250 mg of liposomal curcumin to help quench inflammation.

**Note:** Curcumin is a dose dependent MAO inhibitor so use caution in those with MAO snps.

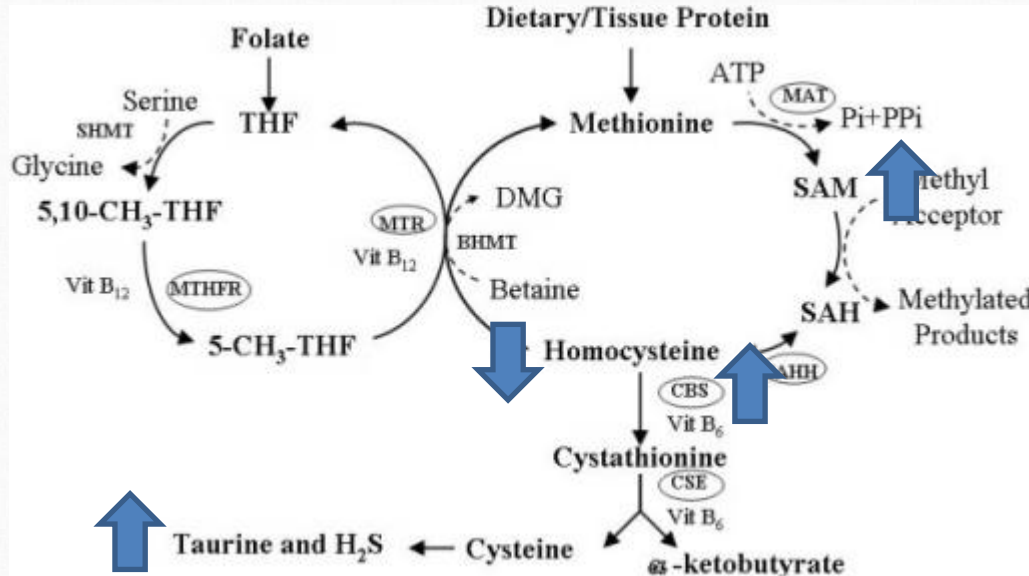


3. Lowered potassium levels. Why? Increased folate increases DNA production which requires higher K<sup>+</sup> demand.

Use Potassium Chloride powder or Potassium Gluconate or Neutralize. Consider 700 mg twice daily or as needed. Safest is supplementing with high potassium foods (apricots, avocados, dates, carrot juice, almonds, baked beans, lima beans, potatoes).

Source: <http://mthfr.net/methylfolate-side-effects/2012/03/01/> and <http://www.whfoods.com/genpage.php?tname=nutrient&dbid=90> and <http://www.ncbi.nlm.nih.gov/pubmed/18766332>

## Zero Tolerance to Methylcobalamin and/or Methylfolate?



MethylB12 and Methylfolate combined support SAM levels.

High SAM levels increase transulfuration (CBS activity) ~ 5 fold which reduces the transmethylation cycle thus depleting methylation production.

This leads to imbalanced SAM:SAH ratio which induces DNA methylation problems.

Combined with CBS 699 – even worse.

Source: <http://www.ncbi.nlm.nih.gov/pubmed/16275737>



## High Dose Folic Acid Affects SAM:SAH Ratio

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“Exposure of normal human cells to supra-physiological folic acid concentrations present in commercial cell culture media perturbs the intracellular SAM:SAH ratio and induces aberrant DNA methylation.”

Source: <http://www.ncbi.nlm.nih.gov/pubmed/22617627>


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## Positive Ending: Epigenetic Influence on the MTHFR Mutation

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 “....data are consistent for Mexico and northern China, which not only have a very high frequency of the TT genotype but also high rates of neural tube defect.”

“...In the United States, the rates of neural tube defects historically have been higher among Hispanics, intermediate among non-Hispanic whites, and lower among African-Americans, a trend that follows the relative frequency of the TT homozygous genotype.”

 **There are, however, notable exceptions.**

“In southern Italy, the TT genotype is common, but the rate of neural tube defects is not particularly high. Nevertheless, such exceptions are not entirely unexpected, because ***environmental and nutritional factors are likely to modulate considerably the genetic risk.***”

# Thank You

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