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Methylation Pathway

Dummy Persson

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How this works

On a chemical level, methylation is when a methyl group is transferred from one compound to another. Methyl groups are small backbones for organic compounds, the chemical compounds of all living beings that are found in every cell of your body.

Methyl groups are also switches that turn genes on or off based on environmental cues. This is called *epigenetics*. Additionally, methyl groups signal which hormones, brain chemicals, and amino acids need to be broken down and removed, maintaining a healthy balance in the body.

On a deeper level, the methylation cycle involves several steps outlined in the graph below.

Starting from the **MTHFR** enzyme and folate you take in with food, the methylation cycle produces the active vitamin methylfolate that circulates in your bloodstream (5-methyl THF). This step is crucial for turning harmful homocysteine into methionine [R].

This pathway also relies on vitamin B12 and enzymes, including **MTR** and **MTRR**.

The other pathway for clearing homocysteine uses betaine derived from choline. It relies on the **CHDH** and **BHMT** enzymes.

In the next step, methionine obtained via these pathways creates SAM-e (S-adenosyl-methionine), a compound that provides a methyl group for methylation [R, R].

Methionine also helps produce phosphatidylcholine via the **PEMT** enzyme. This cycle reveals a close connection between the genes and enzymes involved in choline, folate & vitamin B12 metabolism [R, R].

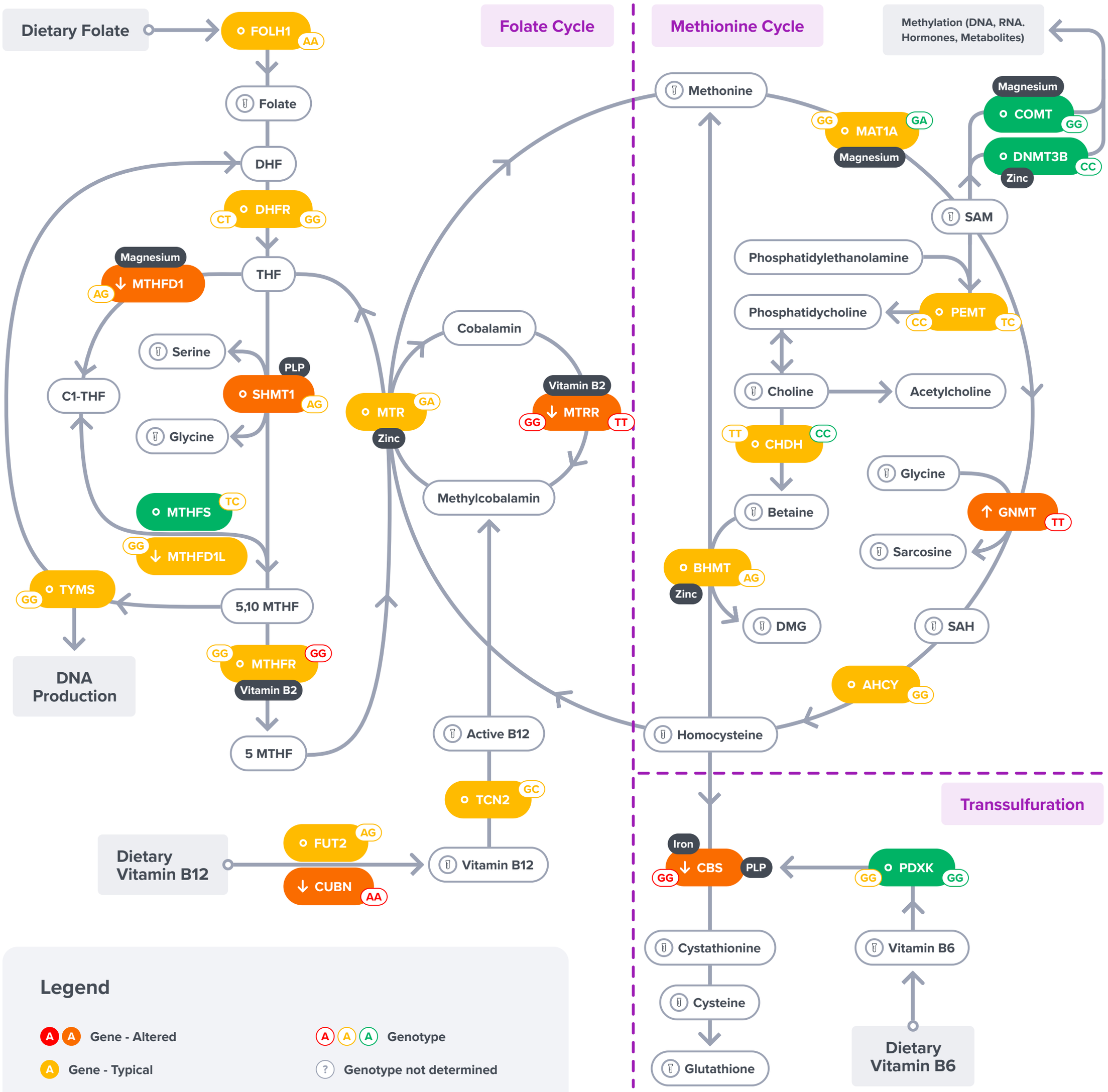
The third pathway for clearing homocysteine, the so-called *transsulfuration pathway*, helps produce glutathione, a.k.a the "master" antioxidant. This pathway relies on vitamin B6 and the **CBS** enzyme.

These reactions — collectively known as the **one-carbon metabolism** — are vital for many aspects of physical and mental health. Issues with the methylation cycle play a role in heart health, mental health, fertility problems, birth defects, cancer, and more [R, R, R].

The optimal function of the pathways discussed above depends on a number of enzymes that enable chemical reactions. Gene variants in some of those enzymes can alter their function and potentially compromise methylation.

Methylation Pathway

Methylation Pathway



Legend

- AA Gene - Altered
- A Gene - Typical
- A Gene - Better
- A Gene - Not determined
- ↑ Gene - Upregulating
- ↓ Gene - Downregulating
- ○ Gene - Neutral
- A Enhancer
- AAA Genotype
- ? Genotype not determined
- A Nutrient:
- ⚠ Significantly out of optimal
- ! Out of optimal
- ◇ Normal
- ✓ Optimal
- Missing lab result

Results Overview

Predisposed to typical methylation ability

Folate Cycle

Gene - SNP Summary

CUBN	rs1801222	↓ AA
SHMT1	rs1979277	○ AG
FOLH1	rs202676	○ AA
MTHFD1L	rs11754661	○ GG
TCN2	rs1801198	○ GC
MTHFS	rs6495446	○ TC

MTHFD1	rs2236225	↓ AG
DHFR	rs1650697	↓ GG
	rs408626	○ CT
MTHFR	rs1801133	○ GG
	rs1801131	↓ GG

MTRR	rs1801394	↓ GG
	rs1532268	↓ TT
FUT2	rs601338	○ AG
MTR	rs1805087	↑ GA
TYMS	rs2853533	○ GG

Labs Summary

Active B12 · Choline, Serum/Plasma · Folate · Folate, RBC · Glycine, Plasma · Homocysteine · Magnesium · Magnesium, RBC · Methionine, Plasma · Methionine/Homocysteine Ratio · Methylmalonic Acid, Blood · Serine, Plasma · Vitamin B12 · Vitamin B2 (Riboflavin), Plasma · Vitamin B6 · Zinc

Methionine Cycle

Gene - SNP Summary

GNMT	rs9296404	↑ TT
CHDH	rs12676	○ CC
	rs9001	○ TT
COMT	rs4680	↑ GG

AHCY	rs13043752	○ GG
MAT1A	rs7087728	↑ GA
	rs3851059	○ GG
DNMT3B	rs2424913	○ CC

BHMT	rs3733890	○ AG
PEMT	rs12325817	○ CC
	rs7946	○ TC

Labs Summary

Betaine (TMG), Serum | Betaine/Choline Ratio | Choline, Serum/Plasma | DMG, Serum | Glycine, Plasma | Homocysteine

Methionine, Plasma | SAH, Serum | SAM-e, Serum | Sarcosine, Plasma | Vitamin B6 | Zinc

Transsulfuration

Gene - SNP Summary

CBS	rs234706	↓ GG
PDXK	rs2010795	↑ GG
	rs147242481	o GG

Labs Summary

Copper | Cystathionine, Plasma | Cystine, Serum/Plasma | Homocysteine | Iron | SAM-e, Serum | Total Glutathione

Vitamin B6

CBS

CBS Report

The CBS gene encodes an enzyme called cystathionine beta-synthase that is part of the methylation cycle.

CBS is the key enzyme of the so-called *transsulfuration pathway*. It uses vitamin B6 and serine to convert homocysteine to a molecule called cystathionine. Another enzyme converts cystathionine to cysteine, which is used to build peptides and proteins. The final product of cysteine is glutathione, a.k.a the "master" antioxidant [R].

Blockers:

Lead | Excess sulfur | Excess ammonia

Enhancers:

PLP (active vitamin B6) | SAMe | Molybdenum | Selenium

SNP	Your Genotype
rs234706 C699T Alleles **A:** Increased CBS activity and methylation ability **G:** Relatively reduced CBS activity and methylation ability	↓GG **Your genotype is linked to relatively reduced CBS activity and methylation ability.**

Intro and Health Effects

The main CBS variant is rs234706. Its minor ‘A’ allele may boost CBS activity.

This variant has been linked to:

- Lower homocysteine levels (mixed evidence) [R, R]
- Lower odds of preeclampsia (high blood pressure in pregnancy) [R]
- Lower odds of venous thrombosis [R]

Some sources mention the potential of this variant to deplete methylation components (methyl donors) by favoring the transsulfuration pathway, but studies haven’t confirmed this yet.

CUBN

CUBN Report

Cubilin, the protein encoded by the CUBN gene, is essential for the intestinal **absorption of vitamin B12**. This vitamin is crucial for the conversion of homocysteine to methionine, a key process in the methylation cycle. For this reason, CUBN gene variants may affect methylation and homocysteine levels.

Blockers:

Heavy metals

Proton pump inhibitors

Enhancers:

Vitamin B12

Calcium

SNP

rs1801222 S253F

Alleles

A: Reduced CUBN activity and methylation ability

G: Normal CUBN activity and methylation ability

Your Genotype

↓AA

Your genotype is linked to reduced CUBN activity and methylation ability.

Intro and Health Effects

The main CUBN gene variant is rs1801222. Its “A” allele is linked to [R, R, R, R, R]:

- Lower vitamin B12 levels
- Increased homocysteine levels
- Pernicious anemia (B12 deficiency anemia)
- Megaloblastic (large cell) anemia

This variant seems to reduce CUBN activity, affecting vitamin B12 absorption.

GNMT

GNMT Report

The GNMT gene helps make glycine N-methyltransferase enzyme present in liver, kidney, and pancreas. It **turns SAM-e to SAH** (S-adenosylhomocysteine) and thus maintains their ratio within the cell. This ratio can be considered a “methylation potential” or indicator of functional SAM-e capacity [R].

During the SAM→SAH reaction, glycine is methylated into sarcosine.

Blockers:

Alcohol Methotrexate

Enhancers:

SAMe Glycine

SNP	Your Genotype
rs9296404	↑TT
Alleles **C:** Normal GNMT activity and methylation ability **T:** Increased GNMT activity and reduced methylation ability	**Your genotype is linked to increased GNMT activity and impaired methylation ability.**

Intro and Health Effects

Even though the GNMT enzyme plays a key role in the methylation cycle, the available research on GNMT variants is scarce.

One GNMT variant, **rs9296404-T**, may be linked to higher homocysteine levels in response to dietary methionine [R].

Another closely related GNMT variant (rs10948059-C) showed a link with liver damage and higher cholesterol levels. However, this variant may also be linked to better methotrexate (folate-targeting drug) response and its lower liver toxicity [R, R].

These variants are usually inherited together, meaning you likely carry either none or both of them. They may **increase GNMT activity**, shifting the SAM-e to SAH ratio towards the latter. As a result, the **methylation potential is reduced** [R].

MTHFD1

MTHFD1 Report

The *MTHFD1* gene encodes an enzyme (Methylenetetrahydrofolate dehydrogenase) that helps produce active folate and supports homocysteine methylation [R].

Vitamin B9 or folic acid needs to be “activated” to L-methylfolate to achieve its health effects. **MTHFD is one of the key enzymes in this process - it helps create methyl-THF**.

Folate and choline partake in a complex cycle of methylation reactions, known as the one-carbon metabolism. They both supply methyl groups for the production of methionine from homocysteine [R].

Blockers:

Pesticides | Air pollution | Processed foods

Enhancers:

Folate | Vitamin B3 (Niacin)

SNP

rs2236225 G1958A; Arg653Gln

Alleles

A: Reduced MTHFD1 activity and methylation ability

G: Normal MTHFD1 activity and methylation ability

Your Genotype

↓AG

Your genotype is linked to slightly reduced MTHFD1 activity and methylation ability.

Intro and Health Effects

One MTFD1 variant, **rs2236225**, is linked to increased choline and folate needs.

The presence of the “A” allele at rs2236225 changes one amino acid (Arg653Gln) in the MTHFD enzyme, making it less stable and more temperature-sensitive. Reduced MTHFD1 activity means less methyl-THF, which forces the body to use more choline for homocysteine methylation [R].

A 2014 meta-analysis concluded that white mothers carrying one or two "A" alleles were at an increased risk of having children with **neural tube defects** (NTDs) [R].

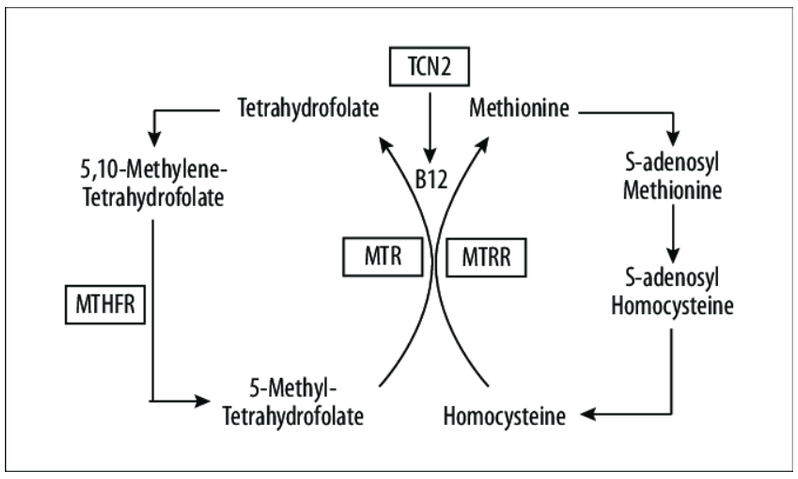
A study investigated the impact of this variant on choline dietary requirements. When placed on a low-choline diet, people with the “A” allele were seven times more likely to develop the signs of **choline deficiency, such as fatty liver** [R].

In another trial, this variant worsened the effects of folate deficiency on **homocysteine levels** [R].

MTRR

MTRR Report

The *MTRR* gene encodes an enzyme called methionine synthase reductase. This enzyme supports the function of methionine synthase (MTR), which turns homocysteine into methionine with the help of **active folate**. This pathway relies on active **vitamin B12** [R, R, R].



Blockers:

Mercury | Cadmium | Industrial solvents | Excessive EMF exposure

Enhancers:

Folate | Vitamin B12 | SAMe | Omega-3 | Flavonoids

SNP

rs1801394 A66G

Alleles

A: Normal MTRR activity and methylation ability

G: Reduced MTRR activity and methylation ability

Your Genotype

↓GG

Your genotype is linked to reduced MTRR activity and methylation ability.

Intro and Health Effects

The main MTRR variant is rs1801394 or A66G. The “G” allele changes one amino acid in the MTRR structure, reducing its ability to bind and activate MTR [R].

This variant may be linked to:

- Higher homocysteine levels [R]
- Congenital disorders (mixed evidence) [R, R, R]
- Some types of cancer [R, R]
- Male fertility issues (mostly in Asians) [R, R]
- ADHD in children [R]

SNP	Your Genotype
rs1532268 C524T Alleles **C:** Increased MTRR activity and methylation ability **T:** Reduced MTRR activity and methylation ability	↓TT **Your genotype is linked to reduced MTRR activity and methylation ability.**

Intro and Health Effects

Another well-researched SNP in the MTRR gene is **rs1532268**. The **“T” allele** changes the enzyme structure and **reduces its activity** [R].

The effects of this variant may **depend on vitamin B12 status**. In one study, it was associated with increased homocysteine when B12 status was low. Other studies have linked it to [R]:

- Gastric cancer [R]
- Congenital heart disease [R]
- Neural tube defects (mixed evidence) [R, R]

SHMT1

SHMT1 Report

The SHMT1 gene helps make an enzyme serine hydroxymethyltransferase (SHMT), This enzyme plays a crucial role in balancing folate groups between the *methylation cycle* (SAM-e production and Hcy removal) and the *folate cycle* (nucleotide production) [R].

It uses serine and glycine to transfer methyl groups between tetrahydrofolate (THF) and 5,10-methylenetetrahydrofolate (5,10-MTHF), depending on the body's requirements.

Blockers:

Heavy metals

Enhancers:

Folate

PLP (active vitamin B6)

SNP

rs1979277 C1240T

Alleles

A: Altered SHMT1 activity and methylation ability

G: Normal SHMT1 activity and methylation ability

Your Genotype

AG

Your genotype is linked to slightly altered SHMT1 activity and methylation ability.

Intro and Health Effects

The main SHMT1 variant is rs1979277 or C1420T. It seems to reduce the ability of SHMT to produce 5,10-MTHF, leading to lower levels of active folate. This may have a detrimental effect on methylation. In other words, this variant may favor the folate cycle over the methylation cycle [R].

This variant may be linked to [R, R]:

- Liver cirrhosis
- Congenital problems with blood vessels
- Down’s syndrome

In one study, the link between the MTHFR gene variant and heart disease was stronger in people who also carried this SHMT1 variant [R].

AHCY

AHCY Report

The AHCY gene helps make the SAHH (S-adenosylhomocysteine hydrolase) enzyme. This converts S-adenosylhomocysteine (SAH) to adenosine and homocysteine. This reaction is a crucial step in the methylation cycle [R].

Blockers:

Heavy metals | Mercury | Oxidative stress

Enhancers:

Betaine (TMG) | SAMe

SNP

rs13043752 Arg38Trp

Alleles

A: Reduced AHCY activity and methylation ability.

G: Normal AHCY activity and methylation ability.

Your Genotype

GG

Your genotype is linked to typical AHCY activity and methylation ability.

Intro and Health Effects

The **rs13043752** variant is one of several rare AHCY variants that may change the enzyme structure and reduce its activity [R].

One paper has linked the **“A” allele** of this variant to **venous thrombosis**. However, the research on AHCY variants is scarce, so we can’t be sure about their potential effects on methylation and human health [R].

BHMT

BHMT Report

The BHMT gene encodes an enzyme called betaine-homocysteine methyltransferase, a crucial part of the methylation cycle.

The BHMT enzyme, which is most abundant in the kidneys and liver, participates in the betaine pathway. It uses betaine derived from choline to clear homocysteine by turning it into methionine [R, R, R, R].

Blockers:

Excess methionine | Stress | Oxidative stress | Excess fructose

Enhancers:

Betaine (TMG) | Zinc | Phosphatidylcholine (PC)

SNP

rs3733890 G742A

Alleles

A: Altered BHMT activity and methylation ability

G: Normal BHMT activity and methylation ability

Your Genotype

AG

Your genotype is linked to slightly altered BHMT activity and methylation ability.

Intro and Health Effects

The main *BHMT* variant is rs3733890. The **"A" allele** of this variant may be linked to [R, R]:

- Failure of folate therapy for high homocysteine [R, R]
- Pulmonary thromboembolism [R]
- Placental abruption [R]
- Congenital heart disease [R]
- Down's syndrome [R]
- Neural tube defects [R, R]
- Short telomeres [R]
- Liver toxicity from methotrexate [R]

However, it has also been associated with a decreased risk of:

- Cervical cancer [R, R]
- Breast cancer and death from this condition [R, R, R]
- Colorectal cancer [R]

The mechanism behind these conflicting findings is not entirely clear. One possibility is that the "A" allele reduces or impairs BHMT activity. Another possibility is that it increases BHMT activity too much and thus depletes choline.

The effects may also depend on folate status, other variants of the same gene, and variants of other methylation pathway genes [R, R, R, R, R].

CHDH

CHDH Report

The *CHDH* codes for choline dehydrogenase, an enzyme that turns choline into betaine (TMG). Betaine then supplies a methyl group needed for homocysteine clearance [R, R].

Blockers:

Alcohol

Enhancers:

Choline

Betaine (TMG)

SNP

rs12676 G432T

Alleles

A: Altered CHDH activity and methylation ability

C: Normal CHDH activity and methylation ability

Your Genotype

CC

Your genotype is linked to normal CHDH activity and methylation ability.

Intro and Health Effects

A CHDH gene variant rs12676 is linked to choline deficiency and may thus affect methylation. In one study, the **"A" allele** was associated with liver and muscle damage when dietary choline was restricted to <50 mg/day [R, R].

It also showed a link with higher odds of breast cancer in another study [R].

According to one potential explanation, this variant may favor the transformation of choline to betaine at the expense of phosphatidylcholine (PC) production. When dietary choline is low, this effect could contribute to organ damage due to choline deficiency [R, R].

SNP

rs9001 119A>C

Alleles

G: Improved CHDH activity and methylation ability

T: Typical CHDH activity and methylation ability

Your Genotype

TT

Your genotype is linked to typical CHDH activity and methylation ability.

Intro and Health Effects

The mentioned study identified another CHDH variant associated with liver and muscle damage when dietary choline was restricted to <50 mg/day. Those with the rare **“G” allele at rs9001** were 5x less likely to develop signs of choline deficiency [R].

Other authors have noticed that people with the protective SNP, rs9001-G, use more choline for phosphatidylcholine production, and less for betaine production [R, R].

This effect may preserve choline stores and phosphatidylcholine synthesis. In the absence of dietary choline, it may protect against organ damage due to choline deficiency [R].

DHFR

DHFR Report

The DHFR gene encodes an enzyme called **dihydrofolate reductase** with a key role in folate metabolism. Specifically, it converts dihydrofolate (DHF) into tetrahydrofolate (THF). THF is a methyl group shuttle required for methylation and DNA production [R, R].

Chemotherapeutic agents such as methotrexate inhibit DHFR to decrease DNA synthesis and cell proliferation. In line with this, increased DHFR expression in tumors is associated with resistance to methotrexate [R, R].

Blockers:

Methotrexate | Air pollution | Water pollution

Enhancers:

Folate | Vitamin C

SNP

rs1650697 473T>C

Alleles

A: Increased DHFR activity and altered methylation ability

G: Reduced DHFR activity and altered methylation ability

Your Genotype

↓GG

Your genotype is linked to reduced DHFR activity and altered methylation ability.

Intro and Health Effects

A common polymorphism is **rs1650697**. Its minor 'A' allele may be linked to increased DHFR levels. This variant has been associated with [R]:

- Decreased risk of methotrexate hepatotoxicity [R]
- Increased survival in non-small cell lung cancer patients [R]

However, one study linked this variant to an increased risk of pemetrexed toxicity [R].

The contradictory findings likely stem from varying treatment contexts and disease-specific conditions.

SNP	Your Genotype
rs408626 317A>G Alleles **C:** Reduced DHFR activity and methylation ability **T:** Increased DHFR activity and methylation ability	CT **Your genotype is linked to intermediate DHFR activity and methylation ability.**

Intro and Health Effects

One of the best-researched *DHFR* polymorphisms is **rs408626**. Its major 'T' allele may increase gene expression. This variant has been associated with [R]:

- Worse response to methotrexate in patients with rheumatoid arthritis [R]
- Lower event-free survival in children with acute lymphoblastic leukemia [R]
- Increased risk of methotrexate-induced leucopenia [R]

However, this allele has also been associated with:

- Decreased risk of acute lymphoblastic leukemia relapse [R, R]
- Better response to methotrexate in Crohn's disease [R]

The contradictory findings likely stem from varying treatment contexts and disease-specific conditions.

FOLH1

FOLH1 Report

The FOLH1 gene encodes an intestinal enzyme called **folate hydrolase** that regulates folate levels. Dietary folate mainly exists as polyglutamyl-folate, which has to be broken down by this enzyme to free folate for absorption [R].

Another, better-known function of this enzyme is the breakdown of N-acetyl-L-aspartyl-L-glutamate (NAAG) to N-acetylaspartate (NAA) and glutamate. By controlling the levels of these neurotransmitters, FOLH1 influences nerve health and function [R].

Blockers:

Alcohol

Processed foods

Enhancers:

Folate

Vitamin B12

SNP

rs202676 484T>C

Alleles

A: Normal FOLH1 activity and methylation ability

G: Altered FOLH1 activity and methylation ability

Your Genotype

AA

Your genotype is linked to typical FOLH1 activity and methylation ability.

Intro and Health Effects

The best-researched FOLH1 polymorphism is rs202676. Its minor 'G' allele alters FOLH1 activity and negatively affects methylation [R].

Studies have linked this variant to:

- Increased risk of neural tube defects such as anencephaly [R, R]
- Lower IQ and visual memory performance [R]
- Impaired arsenic metabolism through methylation [R]

It's worth noting that some of the negative effects of this variant might not be related to folate metabolism. As mentioned, the enzyme produced by this gene affects nerve health through NAAG metabolism.

FUT2

FUT2 Report

The FUT2 gene encodes an enzyme named galactoside 2-alpha-L-fucosyltransferase 2. This enzyme is involved in the production of ABO blood group antigens that are released (secreted) into saliva, mucus, and other fluids of the gut [R].

Depending on their ability or inability to secrete ABO blood group antigens into gut fluids, carriers of FUT2 variants are categorized respectively as “secretors” or “non-secretors” (“secretor status”) [R].

ABO antigens found in mucus that lines the guts of **secretors** can act as attachment sites for both harmful and beneficial bacteria. The attachment of harmful bacteria such as Helicobacter pylori (H. pylori) can cause complex inflammatory reactions in the gut lining and reduce stomach acid levels. This ultimately **reduces vitamin B12 absorption** [R, R].

However, scientists still don’t fully understand the mechanism behind ABO antigen secretion and vitamin B12 levels.

Blockers:

Alcohol

Enhancers:

Folate

Vitamin B12

SNP

rs601338 461G>A

Alleles

A: Reduced FUT2 activity and higher methylation ability

G: Increased FUT2 activity and higher methylation ability

Your Genotype

AG

Your genotype is linked to intermediate FUT2 activity and higher methylation ability.

Intro and Health Effects

A study looked at the **rs601338** SNP of FUT2 in over 1,200 people from Europe and West Africa [R].

According to the study, those with the ‘AA’ genotype (the non-secretor variant) have significantly higher vitamin B12 levels. Those with the heterozygous genotype (AG) had intermediate B12 levels [R].

Given the crucial role of vitamin B12 in methylation and homocysteine clearance, people with the ‘secretor’ variant (GG) may have slightly impaired methylation.

MAT1A

MAT1A Report

The *MAT1A* gene provides instructions for producing the enzyme **methionine adenosyltransferase (MAT)**. The enzyme helps turn methionine to S-adenosylmethionine (SAM-e), making it a key component of the methylation cycles [R].

Blockers:

Alcohol Mold

Enhancers:

Magnesium Methionine

SNP

rs7087728 3U1510A

Alleles

A: Increased MAT1A activity and methylation ability

G: Typical MAT1A activity and methylation ability

Your Genotype

↑GA

Your genotype is linked to increased MAT1A activity and methylation ability.

Intro and Health Effects

In one study, people with an MAT1A variant, **rs7087728-A**, were less likely to have high blood pressure and stroke. They also had lower rates of DNA damage, especially if their vitamin B6 levels were high [R].

SNP

rs3851059 d18777A

Alleles

A: Reduced MAT1A activity and methylation ability

G: Normal MAT1A activity and methylation ability

Your Genotype

GG

Your genotype is linked to typical MAT1A activity and methylation ability.

Intro and Health Effects

Research has linked one MAT1A variant, rs3851059 or d18777A, with methylation issues. People with the “A” allele may have **higher homocysteine levels if their folate status is low**. The same study also found over 4x higher odds of **stroke** in people with this variant [R].

This variant likely reduces MAT1A activity and SAM-e production [R].

Interestingly, another study found a link between rs3851059-A and high homocysteine only in people with **higher fat intake** [R].

MTHFD1L

MTHFD1L Report

The MTHFD1L gene helps make an enzyme with a crucial role in the mitochondrial folate pathway. It is responsible for the reaction between 10-formyltetrahydrofolate (C1-THF) and 5,10-methenyltetrahydrofolate (5,10-MTHF) [R].

This conversion is vital for DNA production, methylation, and more.

Blockers:

Alcohol | Heavy metals

Enhancers:

Folate | Vitamin B12

SNP

rs11754661

Alleles

A: Reduced MTHFD1L activity and methylation ability

G: Normal MTHFD1L activity and methylation ability

Your Genotype

GG

Your genotype is linked to typical MTHFD1L activity and methylation ability.

Intro and Health Effects

The main MTHFD1L variant is rs11754661. Studies have linked its “A” allele to [R, R, R, R]:

- Alzheimer’s disease
- Parkinson’s disease
- Depression

Folate is necessary for homocysteine clearance. Folate deficiency and elevated homocysteine are related to both depression and cognitive issues [R, R, R].

This variant likely reduces MTFD1 activity, leading to impaired methylation and homocysteine removal. However, the available evidence is limited [R].

On the other hand, increased MTHFD1 activity may play a role in cancer development [R, R].

MTHFR

MTHFR Report

The *MTHFR* gene helps make an enzyme called methylenetetrahydrofolate reductase (MTHFR). It produces the active form of folate, methylfolate, and helps clear homocysteine [R].

The whole methylation cycle depends on MTHFR, which is why it is called a "*rate-limiting enzyme*". Low MTHFR activity can make methylation as a whole much less productive [R].

Two of the most widely studied variants—**rs1801133 and rs1801131**—reduce MTHFR enzyme activity [R, R, R, R].

Blockers:

Alcohol | Heavy metals | Excess sulfur

Enhancers:

Folate | Vitamin B6 (Pyridoxin) | Vitamin B12 | Betaine (TMG) | Magnesium

SNP

rs1801133 C677T

Alleles

A: Reduced MTHFR activity and methylation ability

G: Normal MTHFR activity and methylation

Your Genotype

GG

Your genotype is linked to typical MTHFR activity and methylation ability.

Intro and Health Effects

MTHFR **rs1801133 or C677T** variant at nucleotide 677 substitutes a valine for an alanine at amino acid 222. This variant is associated with reduced enzyme activity, elevated total homocysteine levels and lower folate levels [R].

People heterozygous for this mutation present a 35% decrease of the normal enzyme activity and homozygous individuals a 70% decrease [R].

Studies found links between this variant, higher homocysteine, and [R, R, R, R, R, R]:

- Cognitive problems
- Heart disease and stroke
- Asthma and allergies
- Fertility and pregnancy issues
- Birth defects
- Mental health issues

- Migraines

SNP	Your Genotype
rs1801131 A1298C Alleles **G:** Slightly reduced MTHFR activity and methylation ability **T:** Normal MTHFR activity and methylation	↓GG **Your genotype is linked to reduced MTHFR activity and methylation ability, especially if combined with another MTHFR variant.**

Intro and Health Effects

MTHFR **rs1801131 or A1298C** variant causes Glu429-to-Ala substitution.

It also decreases MTHFR enzyme activity, but less so than rs1801133. The effects of this variant may only be meaningful in people who also have the “AA” genotype at rs1801133 [R, R, R, R, R].

However, according to some authors, the GG genotype results in 30-40% reduction in MTHFR enzyme activity, regardless of the other MTHFR variant [R].

Studies found links between these two variants, higher homocysteine, and [R, R, R, R, R, R]:

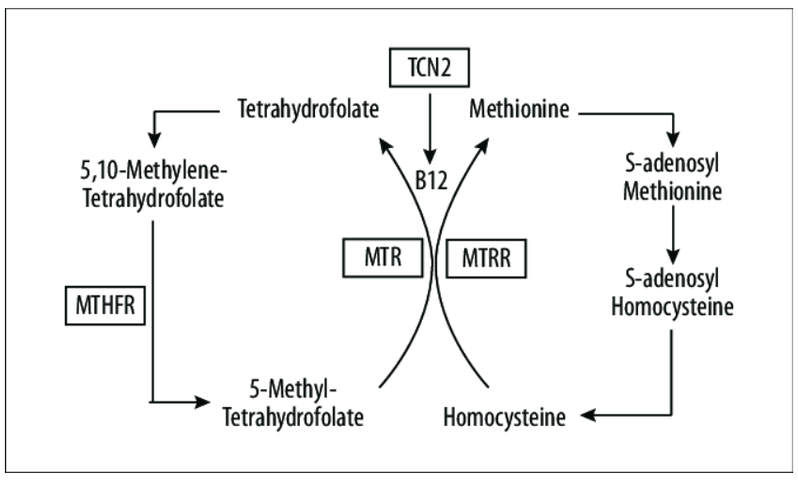
- Cognitive problems
- Heart disease and stroke
- Asthma and allergies
- Fertility and pregnancy issues
- Birth defects
- Mental health issues
- Migraines

MTR

MTR Report

The *MTR* gene provides instructions for making an enzyme called **methionine synthase**. This enzyme plays a key role in methylation—it helps convert homocysteine to methionine [R].

To work well, methionine synthase requires methylcobalamin (a form of vitamin B12) and another enzyme, encoded by the MTRR gene [R].



Blockers:

Nitrites/nitrates (processed meat) | Excess copper | Oxidative stress

Enhancers:

Folate | Vitamin B12 | Zinc | Rhodiola

SNP

rs1805087 A2756G

Alleles

A: Normal MTR activity and methylation ability

G: Increased MTR activity and altered methylation ability

Your Genotype

↑GA

Your genotype is linked to slightly increased MTR activity and altered methylation ability.

Intro and Health Effects

The main MTR gene variant is **rs1805087 or A2756G**. The “G” allele changes the enzyme structure and appears to increase MTR activity, judging by its link with **lower homocysteine levels** [R, R, R, R, R].

However, studies have also linked this allele to:

- Fertility problems [R]
- Autism [R]
- Depression and stress [R, R]
- Cognitive impairment [R]

Assuming a higher activity, the “G” allele should increase methylation, and some studies have confirmed this. The mechanism behind the negative associations of this allele is not clear, but it may involve **excessive or altered DNA methylation**. Overactive MTR might “spend” too much folate for methylation and deplete it in other crucial pathways [R, R].

Finally, studies have found **negative or mixed results** for the link between rs1805087 and:

- Cancer [R, R]
- Neural tube defects [R]
- Congenital heart disease [R]

PEMT

PEMT Report

The PEMT gene encodes an enzyme (phosphatidylethanolamine N-methyltransferase) that produces phosphatidylcholine (PC) in the liver. This pathway supplies choline and thus plays a key role in the methylation cycle [R, R].

This pathway is your only source of choline if you don't get it from food. It has played a critical evolutionary role by supplying choline and PC during periods of starvation [R, R].

PEMT is mainly expressed in the liver and accounts for 30% of liver PC production. Choline and PC are essential for [R, R, R]:

- Cell membranes
- Signaling
- Fat transport and metabolism
- Brain health

Blockers:

Alcohol Trans fats

Enhancers:

Choline Betaine (TMG)

SNP

rs12325817 G774C

Alleles

G: Reduced PEMT activity and methylation ability

C: Normal PEMT activity and methylation ability

Your Genotype

CC

Your genotype is linked to typical PEMT activity and methylation ability.

Intro and Health Effects

Certain PEMT variants, like **rs12325817**, make the gene less responsive to estrogen stimulation. This prevents estrogen from binding to this gene and boosting its expression. As a result, **PEMT activity drops** and the liver doesn't make enough choline [R, R].

A study identified one PEMT variant, rs12325817, strongly associated with choline deficiency [R].

As a result, this variant is linked to higher homocysteine levels, which may affect heart health and mental health [R].

SNP

rs7946 G5465A; V175M

Alleles

C: Normal PEMT activity and methylation ability

T: Reduced PEMT activity and methylation ability

Your Genotype

TC

Your genotype is linked to typical PEMT activity and methylation ability.

Intro and Health Effects

The best-researched PEMT variant **rs7946** may reduce PEMT function. In one lab test, the “TT” genotype resulted in a 30% loss of PEMT function. This causes lower phosphatidylcholine production in the liver [R].

This variant may be linked to:

- Choline deficiency
- Fatty liver
- Heart disease

TCN2

TCN2 Report

The TCN2 gene encodes transcobalamin, a carrier protein that binds vitamin B12 and facilitates its transport into cells. Once inside the cells, vitamin B12 acts as a cofactor in critical methylation reactions like the conversion of homocysteine to methionine. These reactions are essential for DNA synthesis, red blood cell formation, and proper neurological function [R].

Given the key role of vitamin B12 in the methylation cycle,TCN2 gene variants may affect methylation ability [R].

Blockers:

Alcohol | Heavy metals | Cadmium

Enhancers:

Folate | Vitamin B12

SNP

rs1801198 C776G, R259P

Alleles

G: Reduced TCN2 activity and methylation ability

C: Increased TCN2 activity and methylation ability

Your Genotype

GC

Your genotype is linked to typical TCN2 activity and methylation ability.

Intro and Health Effects

The main TCN2 variant is **rs1801198 or C776G**. According to a large review of 34 studies, the “GG” genotype is linked to [R]:

- Lower levels of active vitamin B12 (holotranscobalamin)
- Higher homocysteine levels (in European descendants)

On the other hand, the review found **no link** between this variant and health conditions like birth defects, cancer, or Alzheimer’s disease.

The “G” allele most likely reduces TCN2 activity, leading to impaired vitamin B12 uptake.

TYMS

TYMS Report

The TYMS gene is crucial for producing thymidylate synthase, an enzyme that converts deoxyuridylate (dUMP) to deoxythymidylate (dTMP), an essential nucleotide for DNA synthesis and repair. This reaction is vital for maintaining DNA integrity and ensuring proper cell division [R].

Folate, or vitamin B9, is a key nutrient that supports this process. The active form of this vitamin (5,10-methylenetetrahydrofolate) supplies a methyl group needed for TYMS function [R].

Blockers:

Alcohol

Methotrexate

Enhancers:

Folate

Vitamin B12

SNP

rs2853533 184C>G

Alleles

G: Normal TYMS activity and methylation ability

C: Altered TYMS activity and methylation ability

Your Genotype

GG

Your genotype is linked to typical TYMS activity and methylation ability.

Intro and Health Effects

One TYMS gene variant, rs2853533, seems to alter its activity. It may be linked to [R, R, R]:

- Colorectal cancer
- Chemotherapy (5-FU) toxicity
- Spina bifida (unclear)

The available information about this variant is scarce, so we can't be sure about its associations and underlying mechanisms. It most likely involves depletion of active folate or impaired DNA production.

COMT

COMT Report

The COMT gene helps make an enzyme called catechol-O-methyltransferase. The COMT enzyme helps break down chemical messengers in the body by **methylating** them. These include [R, R, R]:

- Dopamine
- Norepinephrine (noradrenaline)
- Epinephrine (adrenaline)

COMT also helps methylate and deactivate other crucial components such as estrogen metabolites. In turn, estrogen reduces COMT activity [R].

Blockers:

BPA (plastics) | Excess caffeine | Xenoestrogens | Excess copper

Enhancers:

SAMe | Magnesium | Vitamin C | EGCG (green tea) | Omega-3

SNP

rs4680 Val158Met

Alleles

A: Lower COMT activity and methylation ability

G: Higher COMT activity and methylation ability

Your Genotype

↑ GG

Your genotype is linked to higher COMT activity and methylation ability.

Intro and Health Effects

The main COMT variant is **rs4680 (Val158Met)**, sometimes called the “worrier or warrior” variant [R, R].

People with two copies of the “A” allele (AA) may have lower COMT enzyme activity. They have been nicknamed the “worriers.” They break down stress-related chemical messengers more slowly in the brain. For this reason, they may be more vulnerable to stress but tend to have enhanced cognitive performance under relaxed conditions [R, R, R, R].

Some studies suggested a potential link between this variant and estrogen-related conditions like breast cancer. However, a large meta-analysis of 56 studies didn’t confirm this [R].

People carrying two copies of the “G” allele (GG) are at the opposite extreme. They tend to thrive under stress and have thus been nicknamed “warriors”. Those with both alleles (AG) tend to be in between the described extremes [R, R].

DNMT3B

DNMT3B Report

The DNMT3B gene helps make an enzyme called DNA Methyltransferase 3B. This enzyme performs DNA methylation, using SAM-e as a methyl donor. SAM-e gets converted to SAH and later to homocysteine [R].

Blockers:

BPA (plastics) | Cigarette smoke | UV radiation | Air pollution

Enhancers:

Folate | SAMe | Vitamin C | Selenium

SNP	Your Genotype
rs2424913 -149C>T Alleles **C:** Normal DNMT3B activity and methylation ability **T:** Altered DNMT3B activity and methylation ability	CC **Your genotype is linked to better DNMT3B activity and methylation ability.**

Intro and Health Effects

One DNMT3B variant, **rs2424913-T**, has shown links with several traits related to methylation [R, R]:

- Folate deficiency anemia
- Increased toxicity and reduced effectiveness of methotrexate
- Liver disease
- High blood sugar

The mechanism behind these findings is unclear. One possibility is that the variant increases DNMT3B activity, thus spending too much SAM-e for DNA methylation and depleting it from other pathways. Another possibility is that the variant reduces DNMT3B activity, thus impairing DNA methylation [R].

MTHFS

MTHFS Report

The MTHFS gene is essential for the proper function of the folate cycle, which has a central spot in methylation. The enzyme produced by MTHFS converts 5-formyltetrahydrofolate (5-FTHF) to 5,10-methenyl-tetrahydrofolate (5,10-MTHF).

Efficient folate metabolism is necessary for maintaining adequate methylation, and certain MTHFS variants may affect this process.

Blockers:

Oxidative stress

Enhancers:

Folate

Vitamin B12

SNP

rs6495446

Alleles

C: Increased MTHFS activity and altered methylation ability

T: Normal MTHFS activity and methylation ability

Your Genotype

TC

Your genotype is linked to typical MTHFS activity and methylation ability.

Intro and Health Effects

The main MTHFS variant is rs6495446. A large study has found a link between the “C” allele of this variant and higher odds of kidney disease [R].

This finding is not surprising, given the various benefits of folate for kidney function. However, scientists are not sure if this variant has a causal effect and what the underlying mechanism is. Interestingly, they found that the “C” allele may increase MTHFS activity [R].

A study on people with type 2 diabetes found no link between this variant and diabetic kidney disease [R].

PDXK

PDXK Report

The PDXK gene helps make pyridoxal kinase, an enzyme that produces pyridoxal-5'-phosphate (PLP), the active form of vitamin B6. PLP is crucial for the function of methylation-related enzymes such as SHMT and CBS [R, R].

Blockers:

Stress Antibiotics

Enhancers:

Vitamin B6 (Pyridoxin) Magnesium

SNP

rs2010795

Alleles

A: Reduced PDXK activity and methylation ability

G: Increased PDXK activity and methylation ability

Your Genotype

↑ GG

Your genotype is linked to increased PDXK activity and methylation ability.

Intro and Health Effects

A PDXK variant, **rs2010795-A**, may be linked to higher odds of Parkinson's disease. PLP supports the production of dopamine, which is depleted in people with Parkinson's disease. However, two smaller studies didn't find this association [R, R, R].

SNP

rs147242481

Alleles

A: Reduced PDXK activity and methylation ability.

G: Normal PDXK activity and methylation ability.

Your Genotype

○ GG

Your genotype is linked to typical PDXK activity and methylation ability.

Intro and Health Effects

One rare PDXK gene variant, rs147242481-A, is linked to higher homocysteine levels [R].

This variant likely reduces PDXK activity, leading to lower PLP levels. This may compromise key enzymes involved in homocysteine clearance: SHMT and CBS.

Your recommendations

Your recommendations are prioritized according to the likelihood of it having an impact for you based on your lab results, along with the amount of scientific evidence supporting the recommendation.

You'll likely find common healthy recommendations at the top of the list because they are often the most impactful and most researched.

		DOSAGE
1	Dietary Folate	
2	Methylfolate	400 mcg
3	Dietary Pyridoxine (Vitamin B6)	
4	Betaine (TMG)	500 mg
5	Dietary Choline	
6	Pyridoxal-5-Phosphate (PLP)	20 mg
7	Vitamin B12	100 mcg
8	Avoid Mercury Exposure	
9	Avoid Smoking	
10	Dietary Iron	
11	Dietary Magnesium	
12	Dietary Zinc	
13	Glutathione supplements	
14	L-Serine	500 mg
15	Limit Copper Intake	
16	Riboflavin (Vitamin B2)	25 mg
17	SAM-e	400 mg

Dietary Folate

How to implement

Increase your intake of folate-rich foods such as leafy green vegetables, fruits, nuts, and legumes. Aim to consume these foods daily, incorporating them into various meals throughout the day to meet the recommended dietary allowance of 400 micrograms for adults.

How it helps

L-methylfolate is a biologically active form of folate. People use it as a supplement to support methylation, mental health, and more. L-methylfolate may be a better choice for people with methylation problems, but the research is still limited [R, R].

Personalized to Your Genes

↓ MTHFD1	People with your variant may not be able to produce enough methylfolate [R].
SHMT1	Your variant may deplete active folate and worsen the effects of the main MTHFR variant [R].
DHFR	Your variant (rs1650697-GG) may reduce the production of active folate [R].
MTHFR	People with your variant (rs1801131-G) may produce less active folate (methyl-folate) [R].

Methylfolate

How to implement

Take an L-methyl folate supplement (400-800 micrograms daily), ideally with a meal, to improve absorption. This dosage is recommended for adults, including pregnant women, to support overall health, especially to reduce the risk of neural tube defects in developing fetuses. Continue daily use as part of your regular supplement routine.

TYPICAL STARTING DOSE

400 mcg

How it helps

Folate is a crucial nutrient for methylation and homocysteine removal. Supplementation with folate may lower homocysteine levels in healthy people and those with different health conditions. A dose of 0.8 mg/day may be most effective. L-methylfolate may be a superior form, especially for people with methylation issues, but the research is ongoing [R, R, R, R, R].

Personalized to Your Genes

↓ MTHFD1	Your variant may worsen the effects of folate deficiency on homocysteine levels [R].
SHMT1	Your variant may deplete active folate and worsen the effects of the main MTHFR variant [R].
DHFR	DHFR helps make active folate, so folate may compensate for your low-activity variant (rs1650697-GG) [R].
MTHFR	People with your variant (rs1801131-G) may require more folate to support methylation [R].

Dietary Pyridoxine (Vitamin B6)

How to implement

Increase your intake of vitamin B6 by eating more foods rich in this nutrient, such as bananas, chickpeas, tuna, salmon, chicken breast, and spinach. Aim for a balanced diet that includes these foods regularly, about 2-3 servings of B6-rich foods per day, to help meet the general daily requirement of 1.3mg for adults.

How it helps

People with methylation issues may have increased needs for B vitamins, especially folate, B12, and B6. Vitamin B6 is crucial for transsulfuration, one of the three main methylation pathways [R].

Personalized to Your Genes

↓ CBS	Active vitamin B6 (PLP) supports CBS function and may thus lessen the impact of your lower-activity variant [R].
SHMT1	Active Vitamin B6 (PLP) supports SHMT enzyme function, which may counteract your low-activity variant [R].
MAT1A	The link between rs7087728 and DNA damage may depend on adequate vitamin B6 intake [R].

Betaine (TMG)

How to implement

To take Betaine (TMG) as a supplement, consume 500-2000 mg daily, preferably with a meal to enhance absorption. It is recommended to start at the lower end of the dosage range and adjust based on personal tolerance and effectiveness. This supplement can be taken indefinitely for ongoing support of heart health and liver function.

TYPICAL STARTING DOSE

500 mg

How it helps

TMG or betaine helps turn homocysteine into methionine. For this reason, it plays a key role in the methylation cycle. People with poor methylation may have reduced betaine production. Supplementing with TMG (1.5-4 g/day for 6-24 weeks) may lower homocysteine levels [R, R].

Personalized to Your Genes

BHMT — The BHMT enzyme uses betaine (TMG) to clear homocysteine. Take special care to get enough betaine because of your variant [R, R].

MTHFR — According to preliminary results, betaine may help people with MTHFR deficiency [R, R].

Dietary Choline

How to implement

Increase your intake of choline-rich foods such as eggs, beef liver, chicken liver, fish, peanuts, and dairy products. Aim for an adult intake of about 425 mg to 550 mg of choline per day through these food sources, as part of your regular diet.

How it helps

Choline is a crucial nutrient in the methylation cycle. It provides betaine (TMG), which helps clear homocysteine. People with methylation issues may have increased choline needs. Insufficient choline can disrupt this cycle, leading to a range of health issues [R].

Personalized to Your Genes

↓ MTHFD1 — Your variant is linked to choline deficiency, so take special care to get enough of this nutrient [R, R, R].

BHMT — Choline provides betaine (TMG) and thus indirectly supports BHMT function. Take special care to get enough choline because of this variant [R].

Pyridoxal-5-Phosphate (PLP)

How to implement

Take 20-50 mg of pyridoxal-5-phosphate daily, with or without food, preferably at the same time each day. Swallow with water, and if you experience stomach discomfort, take it with a meal. Consult your healthcare provider for personalized dosing, especially if pregnant, breastfeeding, or on medications, and avoid exceeding the recommended dose unless advised.

TYPICAL STARTING DOSE
20 mg

How it helps

Vitamin B6 is crucial for transsulfuration, one of the three main methylation pathways. Pyridoxal-5'-phosphate (PLP, P-5-P) is an active form of vitamin B6, but the research behind this vitamin B6 form is limited [R, R].

Personalized to Your Genes

↓ CBS — Active vitamin B6 (PLP) supports CBS function and may thus lessen the impact of your lower-activity variant [R].

SHMT1 — Active Vitamin B6 (PLP) supports SHMT enzyme function, which may counteract your low-activity variant [R].

Vitamin B12

How to implement

Take a 50 mcg vitamin B12 supplement daily, preferably with a meal to enhance absorption.

TYPICAL STARTING DOSE
100 mcg

How it helps

People with methylation issues may have increased needs for vitamin B12. Supplementation with vitamin B12 (1 mg/day) may lower homocysteine levels. **Methylcobalamin** is the active form that might be more suitable for people with reduced methylation [R, R, R, R].

Personalized to Your Genes

↓ CUBN

Your variant is linked to lower levels of vitamin B12. Since it may affect B12 absorption in the gut, consider alternative supplement forms such as **sublingual** [R, R].

↓ MTRR

Active vitamin B12 is crucial for people with reduced MTRR activity. In one study, rs1801394-G was linked to birth defects but only in mothers deficient in vitamin B12 [R, R, R, R, R].

Active vitamin B12 is crucial for people with reduced MTRR activity. In one study, rs1532268-T was associated with increased homocysteine when B12 status was low [R, R, R, R, R].

Avoid Mercury Exposure

How to implement

Limit consumption of large fish such as shark, swordfish, king mackerel, and tilefish, which are known to have higher mercury levels. Opt for smaller fish like salmon, shrimp, pollock, and catfish, and limit seafood intake to 8-12 ounces (two to three servings) per week. Check and follow local advisories regarding the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas.

How it helps

Heavy metals can interfere with the activity of enzymes involved in methylation, potentially leading to impaired methylation of essential molecules like DNA and proteins. Some heavy metals can be methylated by the body, which increases methylation demand [R].

Personalized to Your Genes

MTHFR

Mercury may worsen the impact of your variant (rs1801131-G) on methylation [R].

Avoid Smoking

How to implement

Try not to smoke cigarettes. If you are a smoker, seek support for smoking cessation through programs or products designed for this purpose.

How it helps

Smoke contains toxic compounds like arsenic, cadmium, and nickel, which can inhibit the activity of enzymes involved in methylation. It can also deplete folate and other B vitamins essential for the one-carbon cycle [R, R].

Personalized to Your Genes

↓ CBS

Cigarette smoke may worsen the effects of your variant by inhibiting CBS [R].

Dietary Iron

How to implement

Incorporate iron-rich foods into your daily meals, such as red meat, chicken, turkey, fish, beans, lentils, tofu, cooked spinach, and fortified cereals. Aim for at least 18 mg of iron per day for adult women and 8 mg per day for adult men. It's also beneficial to pair these foods with vitamin C-rich foods like oranges, strawberries, or bell peppers to enhance iron absorption.

How it helps

Dietary iron benefits methylation-related conditions like anemia and cognitive impairment [R].

Personalized to Your Genes

↓ CBS

Iron helps support CBS function, which is crucial for your lower-activity variant [R].

Dietary Magnesium

How to implement

Increase your intake of magnesium-rich foods such as leafy green vegetables, nuts, seeds, and whole grains. Aim to include these foods in your diet daily, following the recommended dietary allowance of 320 mg per day for women and 420 mg per day for men.

How it helps

Magnesium acts as a cofactor in many enzymatic reactions in the methylation cycle. It supports key enzymes like MTHFD and MAT.

Personalized to Your Genes

↓ MTHFD1 Your variant makes the MTHFD enzyme less stable, but magnesium might reduce this effect [R, R, R].

Dietary Zinc

How to implement

Incorporate foods high in zinc, such as beef, poultry, seafood (especially oysters), beans, nuts, and whole grains, into your daily diet. Aim for the recommended dietary allowance of zinc, which is 11 mg per day for adult men and 8 mg per day for adult women.

How it helps

Zinc is important for folate absorption and healthy methylation. If you are deficient in zinc, your gut enzymes can’t break down folate into the form you can absorb. It also helps folate carry out its role in the body [R, R].

Personalized to Your Genes

BHMT Zinc supports BHMT enzyme function. Make sure to get enough zinc because of this variant [R].

Glutathione supplements

How to implement

Take glutathione supplements orally, usually in pill or powder form, with a recommended dose ranging from 500mg to 1000mg daily, divided into two doses. It's best taken on an empty stomach or as directed by a healthcare professional. Continuous use is advised for sustained benefits, but consulting with a healthcare provider for personalized advice and duration is important.

How it helps

Glutathione acts as an antioxidant, protecting cells from damage and ensuring that the methylation cycle functions efficiently. This is essential for DNA synthesis, repair, and cellular health.

Personalized to Your Genes

↓ CBS

CBS enables the first step of a chain reaction that helps produce glutathione. Your variant might slow this process down.

L-Serine

How to implement

Take l-serine supplements orally, starting with a dose of 500 mg per day. If well tolerated and based on the desired effect, the dose can be gradually increased, but it should not exceed 2,000 mg per day without medical advice. It's best taken with meals to enhance absorption.

TYPICAL STARTING DOSE

500 mg

How it helps

Dietary L-serine may reduce the homocysteine-raising effects of methionine. Adding this amino acid to methionine-containing meals may reduce post-meal homocysteine levels [R].

Personalized to Your Genes

SHMT1

SHMT1 uses L-serine to produce active folate, making this nutrient crucial for your low-activity variant [R].

Limit Copper Intake

How to implement

Do not include copper supplements in your daily vitamin or supplement routine. Check the labels of any multivitamins or dietary supplements you are currently taking to ensure they do not contain copper. Ideally, you should also check copper levels in your tap water. If they are excessive, consider using a reliable water filter or drinking spring water.

How it helps

High copper and homocysteine levels have been linked to heart disease. However, copper deficiency can also be detrimental to methylation, so it's important to maintain optimal levels [R, R].

Personalized to Your Genes

↓ CBS Copper is one of the most potent CBS inhibitors; excess levels may worsen the impact of your variant [R].

Riboflavin (Vitamin B2)

How to implement

Take a riboflavin (vitamin B2) supplement daily, with a dose ranging from 5mg to 400mg, depending on the specific health concern or advice from a healthcare provider. Swallow the supplement with water, preferably with a meal to enhance absorption. This regimen can be continued long-term or as directed by a healthcare professional.

TYPICAL STARTING DOSE

25 mg

How it helps

Riboflavin supports the function of several crucial enzymes involved in methylation and homocysteine clearance. The research on riboflavin supplementation for lowering homocysteine has yielded mixed results [R, R, R, R, R].

Personalized to Your Genes

↓ MTRR

Riboflavin helps make a substance (FAD) that supports MTRR function. You may have reduced MTRR activity, so take special care to get enough riboflavin [R].

SAM-e

How to implement

Take 400-1600 mg of SAM-e as a supplement daily, preferably on an empty stomach to enhance absorption. It is often recommended to start with low dosage and observe how your body responds over a few weeks, adjusting as necessary under the guidance of a healthcare provider.

TYPICAL STARTING DOSE

400 mg

How it helps

S-adenosylmethionine or SAM-e provides methyl groups for methylation reactions and helps clear homocysteine. It also boosts glutathione and may help support liver health, mood, and more [R, R, R].

Personalized to Your Genes

↑ GNMT

Overactive GNMT caused by your variant may deplete SAM-e [R, R].

Lab markers to check

Active B12

Personalized to Your Genes

↓ CUBN — Your variant is linked to lower vitamin B12 levels, so pay special attention to your levels.

↓ MTRR — Vitamin B12 is crucial for homocysteine clearance by MTRR, so make sure to check your levels.

Vitamin B12 is crucial for homocysteine clearance by MTRR.

MTR — Vitamin B12 is required for MTR function.

Betaine (TMG), Serum

Personalized to Your Genes

BHMT — BHMT is a key enzyme that turns betaine into DMG.

Betaine/Choline Ratio

Personalized to Your Genes

BHMT — Betaine is crucial for BHMT function. Choline helps make betaine, so it's important to monitor their ratio.

Choline, Serum/Plasma

Personalized to Your Genes

↓ MTHFD1 — Your variant indirectly increases choline needs by putting an extra burden on the methylation cycle.

BHMT — Choline is a major source of betaine, which is required for BHMT function.

Copper

Personalized to Your Genes

↓ CBS — Excess copper can inhibit the CBS enzyme. Make sure your levels are not too high.

Cystathionine, Plasma

Personalized to Your Genes

↓ CBS — CBS is a key enzyme that turns homocysteine into cystathionine.

Cystine, Serum/Plasma

Personalized to Your Genes

↓ CBS — CBS helps create cysteine. You can monitor your status by measuring the levels of a similar compound, cystine.

DMG, Serum

Personalized to Your Genes

BHMT — BHMT is a key enzyme that turns betaine into DMG.

Estradiol

Folate

Personalized to Your Genes

↓ MTHFD1	Your variant may increase folate needs by impairing its activation.
SHMT1	SHMT1 is one of the key enzymes that help produce active folate.
DHFR	DHFR plays a key role in folate metabolism, so pay special attention to your folate levels.
MTHFR	Your variant (rs1801131-GG) may be linked to lower levels of active folate [R].
MTR	MTR uses active folate (methyl-THF) to clear homocysteine.

Folate, RBC

Personalized to Your Genes

↓ MTHFD1	Your variant may increase folate needs by impairing its activation.
SHMT1	SHMT1 is one of the key enzymes that help produce active folate.
DHFR	DHFR plays a key role in folate metabolism, so pay special attention to your folate levels.
MTHFR	Your variant (rs1801131-GG) may be linked to lower levels of active folate [R].
MTR	MTR uses active folate (methyl-THF) to clear homocysteine.

Glycine, Plasma

Personalized to Your Genes

↑ GNMT	GNMT transfers the methyl group to glycine during SAM-e clearance
○ SHMT1	SHMT1 produces active folate by turning serine to glycine.

Homocysteine

Personalized to Your Genes

↓ CBS	CBS is one of the key enzymes that help clear homocysteine.
↓ CUBN	Your variant is linked to higher homocysteine, so pay special attention to your levels.
↑ GNMT	By enhancing SAH production, GNMT may raise homocysteine levels
↓ MTHFD1	Your variant is linked to elevated homocysteine due to impaired folate activation.
↓ MTRR	MTRR helps clear homocysteine indirectly, by supporting the function of MTR.
○ BHMT	BHMT is one of the key enzymes that clear homocysteine.
○ MTHFR	Due to impaired MTHFR activity, your variant (rs1801131-GG) may have a link with elevated homocysteine levels [R].
○ MTR	MTR is a key enzyme that helps clear homocysteine.

Iron

Personalized to Your Genes

↓ CBS	Iron supports the CBS function, to make sure to monitor your levels.

Magnesium

Personalized to Your Genes

↓ MTHFD1 Magnesium may help reduce the impact of your variant by stabilizing the MTFD enzyme.

Magnesium, RBC

Personalized to Your Genes

↓ MTHFD1 Magnesium may help reduce the impact of your variant by stabilizing the MTFD enzyme.

Methionine, Plasma

Personalized to Your Genes

↓ MTRR MTRR helps turn homocysteine into methionine by supporting the function of MTR.

BHMT BHMT is one of the key enzymes that turn homocysteine into methionine.

MTR MTR is a key enzyme that helps turn homocysteine into methionine.

Methionine/Homocysteine Ratio

Personalized to Your Genes

↓ MTRR MTRR helps turn homocysteine into methionine by supporting the function of MTR.

Methylmalonic Acid, Blood

Personalized to Your Genes

↓ CUBN	Elevated MMA levels may indicate vitamin B12 deficiency.
↓ MTRR	Elevated MMA levels may indicate vitamin B12 deficiency. Vitamin B12 is crucial for homocysteine clearance by MTRR.
○ MTR	Elevated MMA levels may indicate the lack of vitamin B12, which is required for MTR function.

SAH, Serum

Personalized to Your Genes

↑ GNMT	GNMT is a key enzyme that turns SAM-e to SAH

SAM-e, Serum

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↓ CBS	Adequate levels of SAM-e support the transsulfuration pathway and spare methyl donors.
↑ GNMT	GNMT is a key enzyme that turns SAM-e to SAH

Sarcosine, Plasma

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↑ GNMT	Sarcosine is produced when GNMT turns SAM-e to SAH

Serine, Plasma

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SHMT1 — SHMT1 uses serine to produce active folate.

Total Glutathione

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↓ CBS — CBS enables the first step of a chain reaction that helps produce glutathione.

Vitamin B12

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↓ CUBN — Your variant is linked to lower vitamin B12 levels, so pay special attention to your levels.

↓ MTRR — Vitamin B12 is crucial for homocysteine clearance by MTRR, so make sure to check your levels.

Vitamin B12 is crucial for homocysteine clearance by MTRR.

MTR — Vitamin B12 is required for MTR function.

Vitamin B2 (Riboflavin), Plasma

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↓ MTRR — Riboflavin helps make a substance (FAD) that supports MTRR function.

Vitamin B6

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↓ CBS	Vitamin B6 supports the CBS function, so make sure to monitor your levels.
SHMT1	Active vitamin B6 (PLP) supports SHMT enzyme function.
MAT1A	The link between rs7087728 and DNA damage may depend on optimal vitamin B6 status [R].

Zinc

Personalized to Your Genes

BHMT	Zinc supports BHMT enzyme function.
MTR	Zinc helps support MTR structure and function.