SelfDecode Special Report:

Methylation Genes

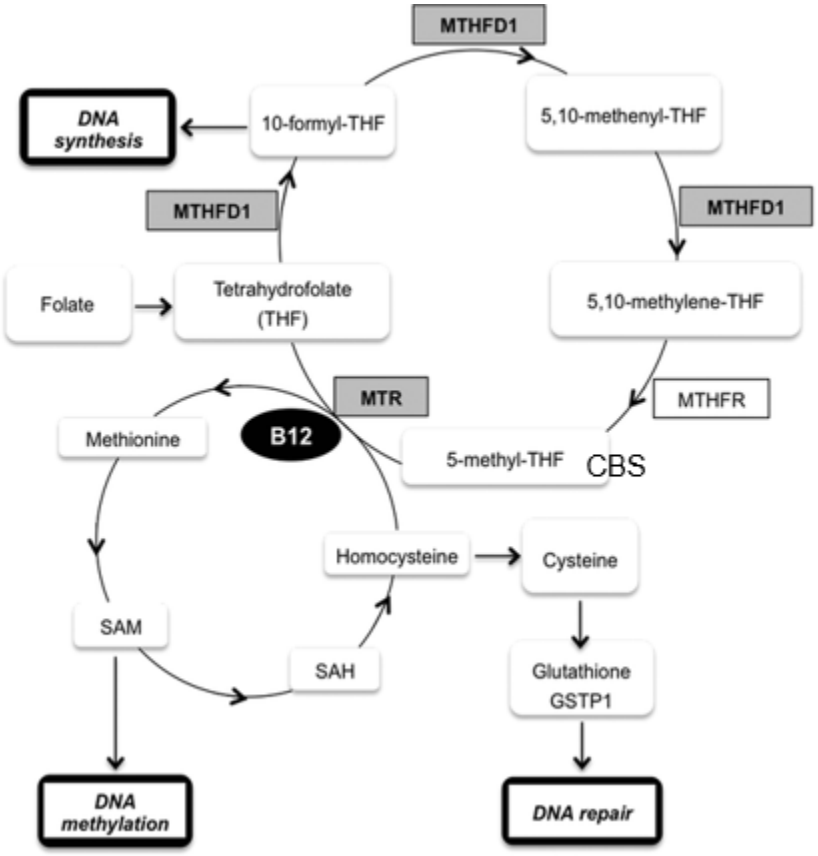
What is commonly called the methylation cycle is a biochemical pathway that is involved in the conversion of homocysteine to methionine through the use of folate. It is also involved in the processing of sulfur-containing amino acids and the production of glutathione.

MTHFR is the most studied gene for nutrigenomics. There have been many large-scale studies that connect the methylation process with some chronic health problems, which is why it has become such a popular topic. But it's also a very commonly misunderstood topic. We have come across numerous clients who think they have issues with their methylation cycles because of their mutations, and then reacted terribly to methylation supplements.

Joe himself is homozygous for the C677T, which is present in about 4% of the population. With this mutation, the enzyme function could be reduced by about 70%. It might explain some of the health issues that he has dealt with.

In this report, we cover each of the methylation genes and our take on it. Towards the end, we cover how Joe was able to overcome his methylation issues and helped many clients do the same.

The methylation cycle



[Top right] is what is called the folate pathway. Folic acid and folate is metabolized into MTHF or methyl tetrahydrofolate in steps involving many enzymes, including MTR, MTFD1, MTRR, and MTHFR.

10-formyl-THF is involved in DNA synthesis
[Bottom left] MTR, or methionine synthase, is the enzyme that converts homocysteine to methionine. It is dependent on vitamin B12 and 5-MTHF to function. **SAM has a methyl group attached to it and is used as a donor for DNA methylation. Adding a ''methyl'' group is one way of turning on and off of genes.**

[Bottom right] the CBS enzyme catalyzes the conversion of homocysteine, which can then be converted into cysteine and glutathione (which is involved in DNA repair).

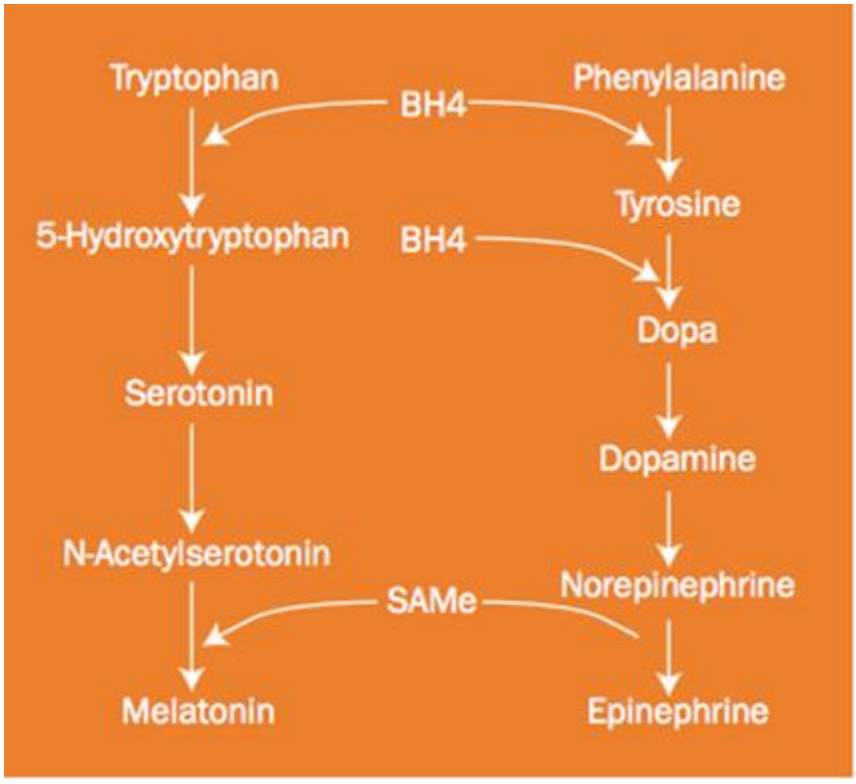
Methylation cycle

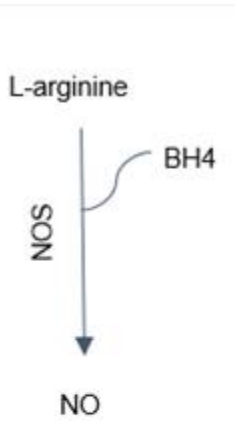
The methylation cycle mainly converts homocysteine to methionine.
It also:

- Generates methyl donor (SAMe) for methylation of other molecules, i.e. DNA, proteins, hormones, and neurotransmitters
- Produces BH4 (an important cofactor for enzymes that produce neurotransmitters and nitric oxide)
- Is important in the production of glutathione
- Folate metabolism (can affect fertility and tendency for gut issues, among others)
- Folate is important for cell division (affects cancer risks and the gut lining)

Note: In clinical studies we've evaluated, MTHFR mutation is only a problem when homocysteine levels are high or folate levels are low.

BH4 as a cofactor for neurotransmitter synthesis



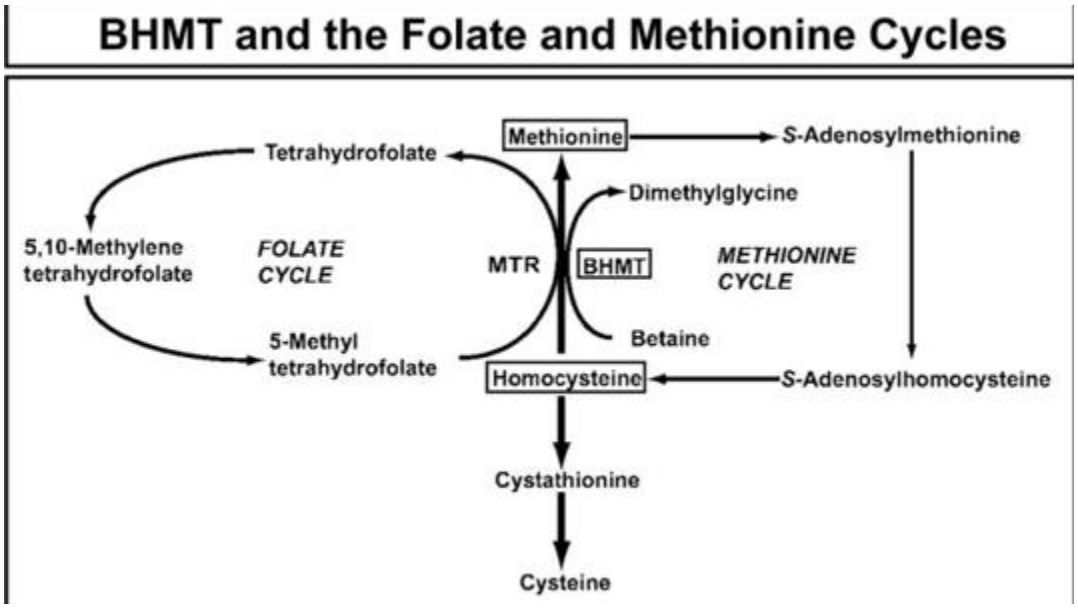


[left hand side] Tetrahydrobiopterin, or BH4, is a cofactor for the synthesis of catecholamine neurotransmitters, including serotonin, dopamine, epinephrine, and norepinephrine.

[right hand side] BH4 is also a cofactor in the production of nitric oxide.
BH4 is generated from the methylation of BH2. so many people who have low methylation also have BH4. Also, what could happen is that NO is a signalling molecule that is important in many processes , like mast cell activation or blood vessel dilation, so the lack of BH4 could have some widespread effect there.

BHMT (Betaine-Homocysteine-S-methyltransferase)

Converts betaine and homocysteine into dimethylglycine (DMG) and methionine. It appears mostly in the kidney and liver.



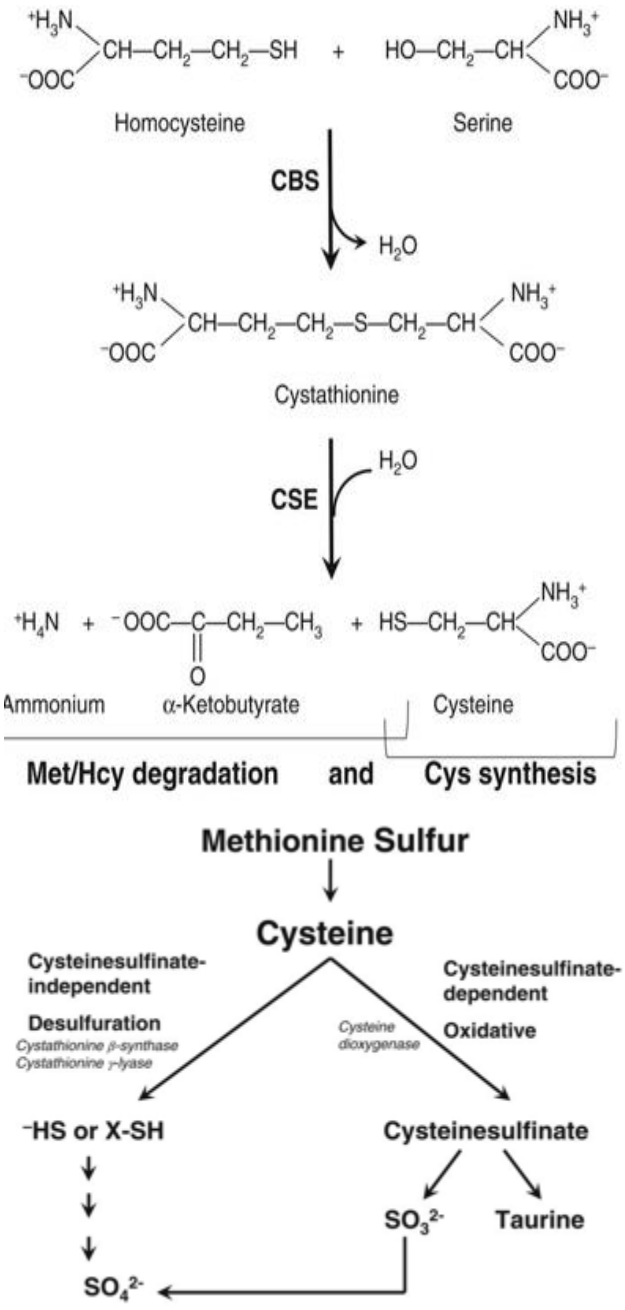
Important BHMT SNPs

Rs16876512 may reduce production of BHMT enzyme [1].

Rs651852 and rs657754 may reduce function of BHMT enzyme, but there is no biochemical data to confirm this.

Fix for low BHMT function: take betaine and increase foods that contain betaine.

Trans-sulfuration pathway



CBS catalyses the combination of homocysteine and serine into cystathione, before it is catalyzed into ammonia, alpha ketobutyrate, and cysteine by the enzyme CSF (cystathione gamma lyase).

The desulfurization of cysteine and methionine can result in hydrogen sulfides, other sulfide chemicals, sulfates, and taurines.

Hydrogen sulfides relaxes smooth muscle in the blood vessels and in the gut, and inhibits platelet aggregation as well as reduces the output of the heartbeats. It can also increase the sensitivity of NMDA receptors to glutamate in the hippocampus.

CBS (Cystathione-beta-synthase)

Converts homocysteine and serine into cystathionine, and subsequently cysteine, using vitamin B6 as a cofactor.

Important SNPs inside of CBS

rs234709 T allele increases selenium in blood, and homocysteine levels.
May affect arsenic levels and overall heavy metal [2].

rs2851291 G may increase homocysteine.

rs234706 (A) and rs1801181 (A) are said to increase activity of CBS, with the following effects:

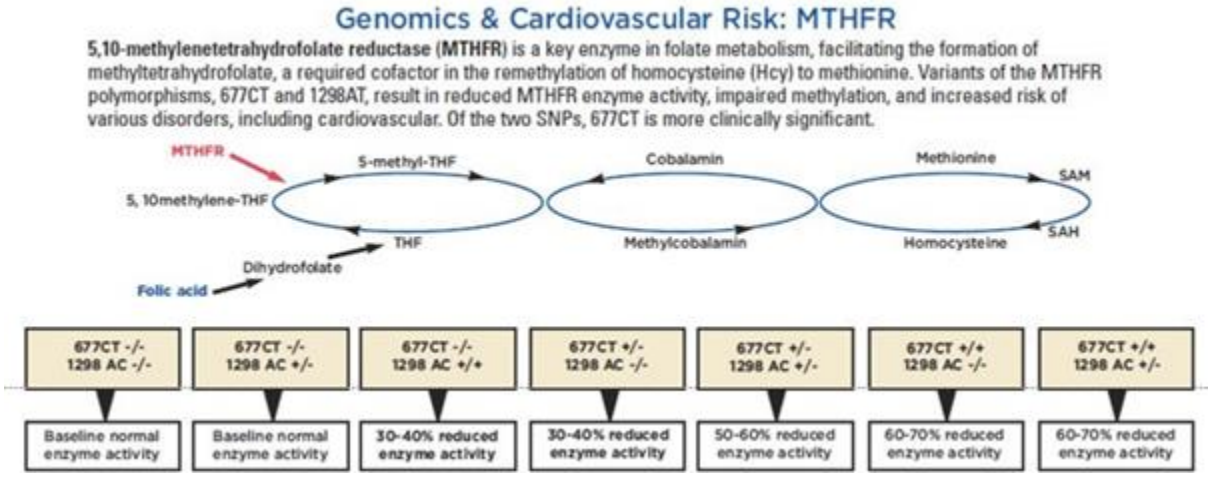
- AA=Increased responsiveness to homocysteine-lowering effects of folic acid
- Limited homocysteine in the body
- Possible increased risk of sulfur toxicity if too much sulfur is ingested due to lower homocysteine levels
- Increased risk for ammonia detoxification issues

Note: we have not been able to find peer-reviewed research that confirms that this allele really increases the activity of CBS. There is one piece of really weak evidence, that Down's syndrome patients have increased urinary thiosulfate.

But the activity of the CBS enzyme with this particular mutation has never been directly measured. In addition, these practitioners make many questionable claims that can't be reasonably supported by scientific evidence.
Confirmed by ref #3.

MTHFR (methyl-tetrahydrofolate reductase)

MTHFR generates 5-MTHF, important for conversion of homocysteine to methionine, and the generation of SAM
rs1801131 A1298C and rs1801133 C677T reduce MTHFR function and are associated with many



MTR

Reduced function of any of genes that function in the methylation cycle (MTR, MTRR, MTFD1) may increase homocysteine.

MTR: Methionine Synthase converts homocysteine to methionine

rs1805087 (G) increases homocysteine and the risks of health issues from folate deficiency and elevated homocysteine
rs2275565 (T) is associated with increased homocysteine measurements

MTRR

MTRR (5-methyltetrahydrofolate-homocysteine transferase reductase)
Helps regenerate vitamin B12 to keep MTR working

Rs1532268 (C) increases the risks of colorectal cancers
Rs1801394 (G) can help MTR function less well and may increase homocysteine level

MTHFD1

This enzyme produces purines and thymidylate, which are bases of DNA, and also help with the regeneration of methionine from homocysteine.

Important SNP: rs2236225 (A) makes the enzyme less stable and therefore reduces its function to 38% of the G allele, thus increases the need for choline. Fix: increase choline intake.

Things that may help with methylation SNPs

- Choline and betaine [4].
- Vitamin B6
- Methyl B12
- Methylfolate, or, preferably, whole-food sources of folate and B-vitamins
- Sufficient protein intake but less [5].
- Reducing alcohol consumption
- Reducing toxic load

If you have methylation SNPs it does not immediately mean that you have low methylation. Most studies that demonstrate if these SNPs are problematic only when homocysteine is elevated.

If you are concerned about methylation issues here are some things that can help.
Choline and betaine can help break down homocysteine to BHMT.

Vitamin B6 increases the activity of the CBS enzyme, while B12 increases the function of MTR enzyme. You also want to make sure you eat enough proteins, but focus on proteins that have more glycine and less methionine, like gelatin and tougher cuts of meat.

When you introduce these B vitamins, you should start from really low doses as many people who already have inflammation react to these vitamins. The B vitamins are stimulants, which can trigger reactions in some people. If you can get the vitamins from whole food sources, like chicken liver or green vegetables, that's even better.

It will also be very important to reduce toxic load in general, including reducing alcohol consumption.

How Joe overcame his MTHFR issues

- Reducing oxidative stress and inflammation, also by supporting other antioxidant pathways like SOD2 and NRF2
- Managing stress
- Eating low-inflammatory diet with enough proteins
- Having whole-food sources of B vitamins, i.e. dark leafy greens that he tolerates and red meat
- Including organ meats, and cuts of meats that have more glycine
- Supplementation with glycine
- Including methylfolate supplementation along with other B vitamins

Joe was able to fix most of health problems not by taking methylfolate but by addressing oxidative stress and inflammation and making sure that he is not nutrient deficient.

References

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