Plasma Methylation Profile

RESOURCE GUIDE
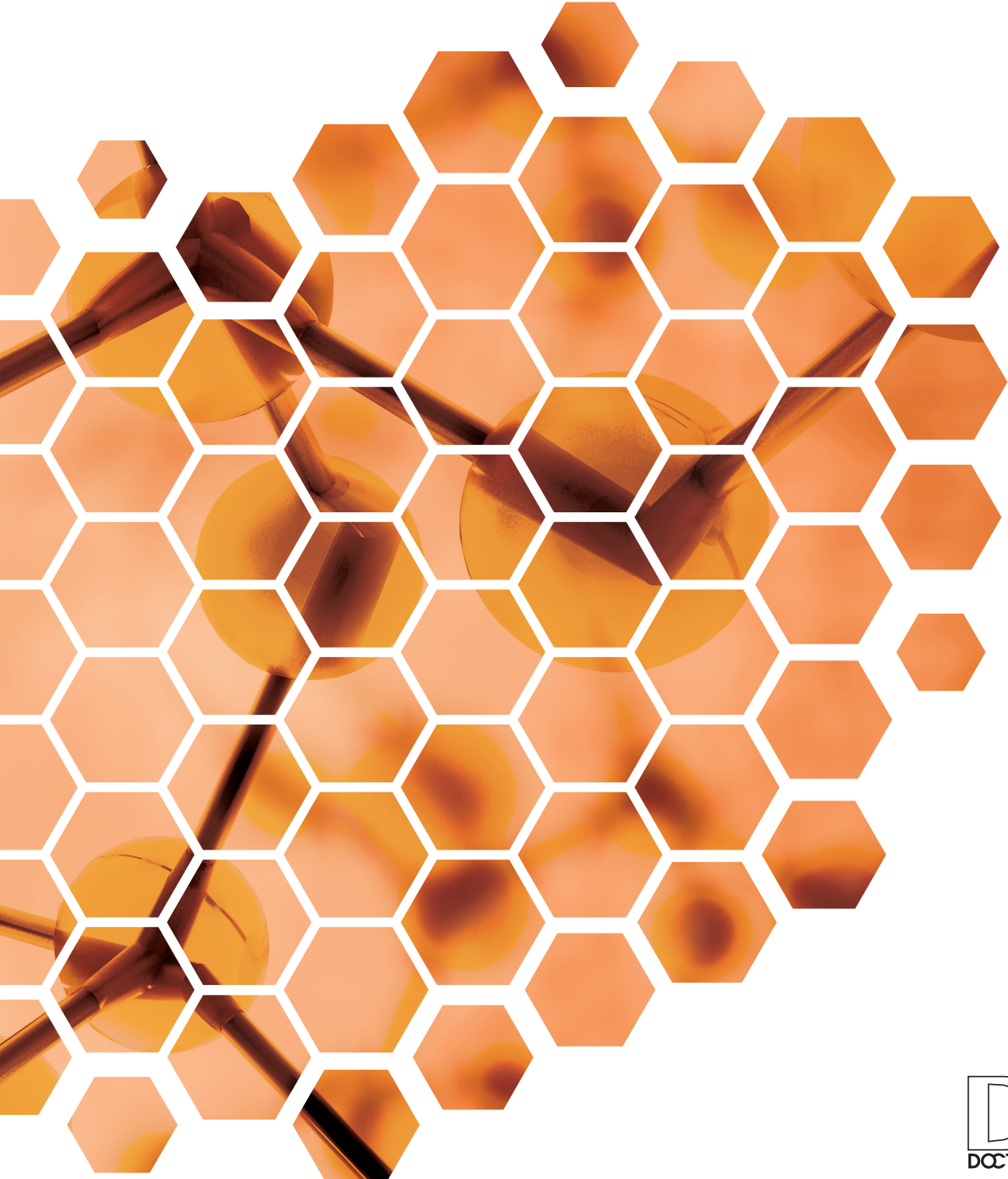
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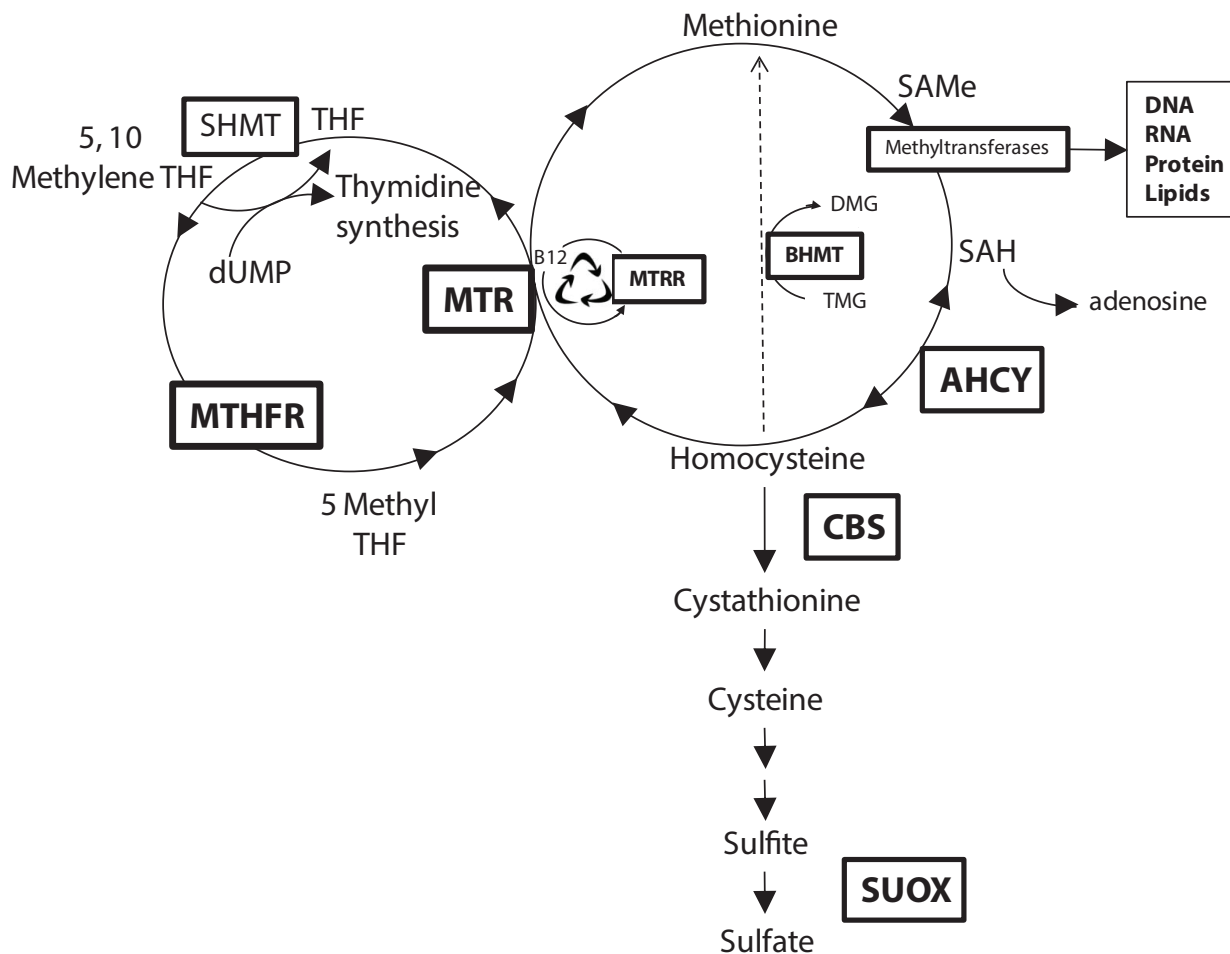
Introduction

The Plasma Methylation Profile is a functional assessment of the enzymes involved in methionine metabolism and the trans-sulfuration pathway (commonly called the "Methylation Pathway").

The genomics revolution has made it possible to assess genetic information stored in the DNA code. An awareness of single nucleotide polymorphisms (SNPs) has made genetic testing for certain SNPs part of diagnostic patient assessment. While the identification of SNPs in a patient's genome is important, it is vital to remember that **functional** testing of enzymes should determine treatment decisions. There are many layers of translation between the genome and the enzyme. Enzyme function may be compromised not only by inheritance, but also by acquired epigenetic factors such as nutritional status, oxidative stress, autoimmunity or environmental exposures. There is mounting evidence that, especially within the folate and methylation pathways, multiple SNPs in multiple genes (haplotypes) may be necessary to alter metabolism or change health outcomes.

Gastrointestinal functions may influence absorption, physiology, metabolism and immunity; nutrient maldigestion or malabsorption may inhibit normal enzyme functions, and may have greater effects on enzymes with SNPs.

Methionine High

Methionine may be elevated for a variety of reasons. Several enzymes involved in the metabolism of methionine require magnesium and other nutritional cofactors. Elevated levels of methionine may occur due to:

- Methionine or SAMe supplementation
- Magnesium deficiency
    – Evaluate *RBC Elements* for Magnesium status
- Impaired liver function or liver disease
    – Evaluate *Hepatic Detox Profile* to assess liver Phase I and II functions and standard liver function tests
- Enzymatic defects

Three separate enzyme defects may be involved in the elevation of Methionine, none of them are available yet as SNP tests, but all should be considered if methionine levels are elevated:

- Methionine adenosyltransferase (MAT) – see section below
    – SAM will be low
- Methyltransferases
    – Some require a magnesium cofactor
    – SAM will be high
- Adenosylhomocysteinase (AHCY)
    – SAH and SAM will both be high
    – May be inhibited by iron or copper overload
    – Requires nicotinamide adenine dinucleotide (NAD) cofactor
        • Vitamin B-3 may support NAD synthesis; alternately consider NADH supplements

Supplements may support normal metabolism:
    – Vitamin C
    – B-3
    – B-2, B-6, folate and B-12 as indicated by *Plasma Methylation Profile* results

Methionine adenosyltransferase (MAT)

Methionine adenosyltransferase (MAT) converts methionine to SAM; it converts 50% of dietary methionine to SAM on the first pass through the liver.
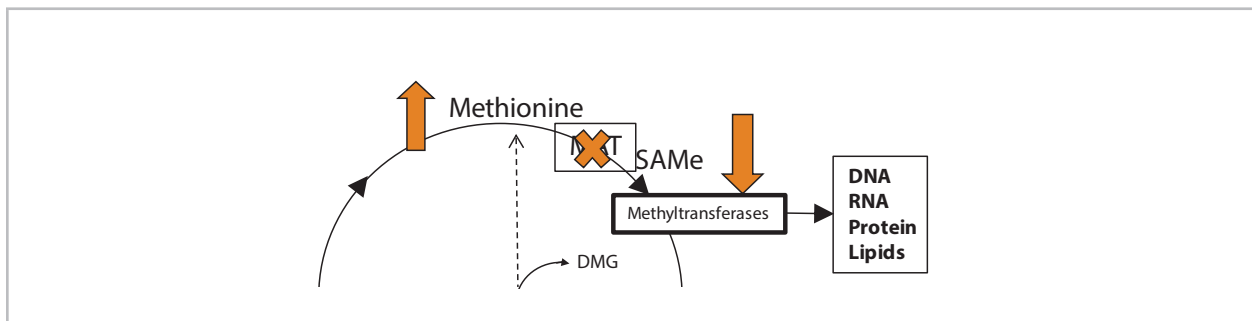
MAT is inhibited by:

- ↑ oxidative stress or nitrosative stress
  – Evaluate oxidative stress with *DNA Oxidative Damage Assay*
- Glutathione depletion (rats)
  – Evaluate GSH status with *RBC Glutathione.*
- Defective tyrosine metabolism
- ↑ bacterial LPS endotoxins in circulation
  – Evaluate GI functions with *Comprehensive Stool Analysis* and *Intestinal Permeability tests.*
- Inflammation – ↑ TNF-a, IL-6 depress MAT
- Mutations MAT III or isoform polymorphisms (SNPs)
- Liver cirrhosis or disease
- Pharmaceuticals such as methotrexate and other folate inhibitors

Methionine adenosyltransferase (MAT) is a critical enzyme in the methionine cycle. Two MAT isoforms catalyze the synthesis of S-adenosylmethionine, the primary methyl donor for biological methylation reactions. These reactions result in the methyl conjugation of many drugs, xenobiotics, hormones, and neurotransmitters as well as DNA, RNA, proteins and phospholipids. A mutation In MAT may cause methionine adenosyltransferase deficiency resulting in isolated hypermethioninemia. Most patients have no clinical abnormalities, although some neurologic abnormalities have been reported in rare cases with a severe loss of enzyme activity. SNPs or lack of nutritional cofactors may also affect MAT functions. MAT requires ATP and magnesium cofactors.

Supplements may support normal function:

- Magnesium cofactor
  – Evaluate *RBC Elements* for magnesium status

Methionine Low

Methionine may be low for a variety of reasons. Defects in various enzymes may result in low methionine levels. Several enzymes involved in the recycling (regeneration) of methionine require magnesium and other nutritional cofactors. Levels of methionine may be decreased due to:

- Diet
  – Imbalanced or inadequate protein intake
- Gastrointestinal dysfunction
  – Hypochlorhydria; gastric or small intestine resections may decrease absorption
  – Pancreatic insufficiency (lack of digestive enzymes)
  – Evaluate GI function with *Comprehensive Stool Analysis*
- Methylation pathway defects
  – Acquired enzyme defects
    - Environmental toxicant exposures
      – Evaluate exposure to toxic metals *Urine Toxic Elements, Whole Blood Elements, Hair Elements or Urine Porphyrins*
    - Nutritional cofactors
      – *RBC Elements*

– Inherited enzyme defects

  • SNPs

  • Mutations
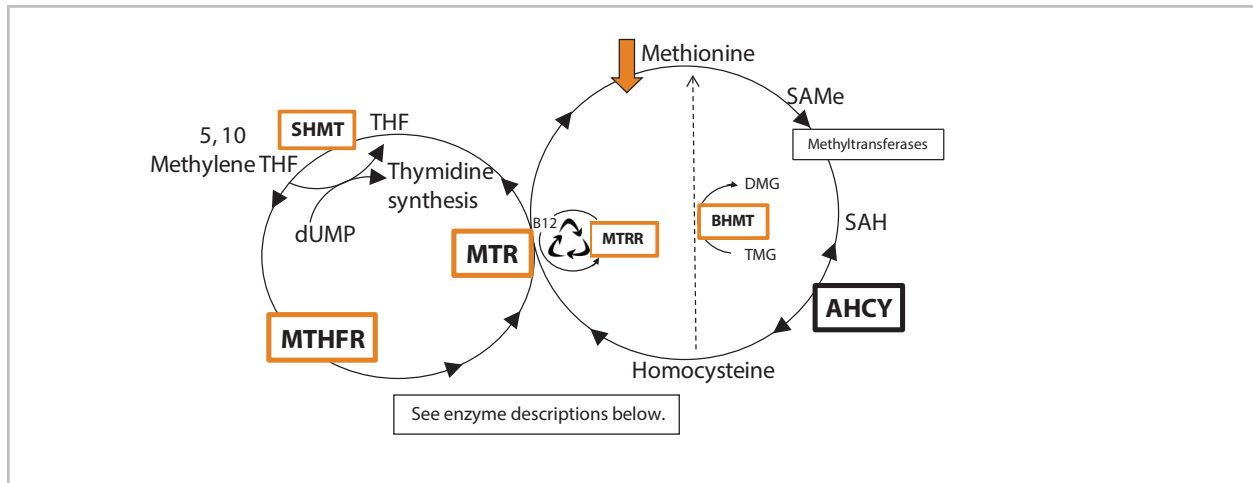
Regeneration of methionine from homocysteine (transmethylation) may be diminished during folate, B12 or methionine deficiency. As in methionine deficiency, the body responds to decreasing availability of SAM by diverting folate away from DNA biosynthesis towards the remethylation of homocysteine to methionine and SAM. This explains why administration of folic acid, which induces cell division and use of methionine in protein synthesis, impairs methylation of myelin and precipitates or exacerbates subacute combined degeneration (SCD). Folate should be last nutrient added to methylation support protocols.

Interventions, based on the cause, that may improve methionine levels, include improved nutrition and supplements:

- Cheeses, fish, poultry, meats and some nuts (e.g. Brazil nuts, almonds and cashews) are good dietary sources of methionine.

- Methionine supplementation and methylation pathway supports

  – Magnesium, B-2, B-6, folate, betaine and B-12

  – Selenocysteine

- Evaluate BHMT, MTHFR, MTR, MTRR SNPs with *DNA Methylation Pathway*.

Cysteine High

Cysteine levels may be elevated by a high protein diet, supplements (N-AC) or from enzymatic deficiencies on the pathways that convert cysteine to glutathione or taurine.

High levels of cysteine in circulation are considered toxic and increase oxidative stress. Low levels of glutathione may also result in increased oxidative stress.

Cysteine levels may be normalized by:

- Decreasing dietary cysteine and N-AC supplementation

- Evaluate Glutathione status with *RBC Glutathione*

- Evaluate taurine status with *Plasma Amino Acids*

- Support cysteine metabolic pathway with pyridoxal-5'- phosphate (vitamin B6/P5P)

- Evaluate iron status

Cysteine levels may also be elevated due to a genetic defect in cysteine dioxygenase (CDO). CDO is the pivotal enzyme that initiates the biochemical pathway from cysteine to taurine or glutathione.

Cysteine dioxygenase (CDO)

CBS, CTH, CDO
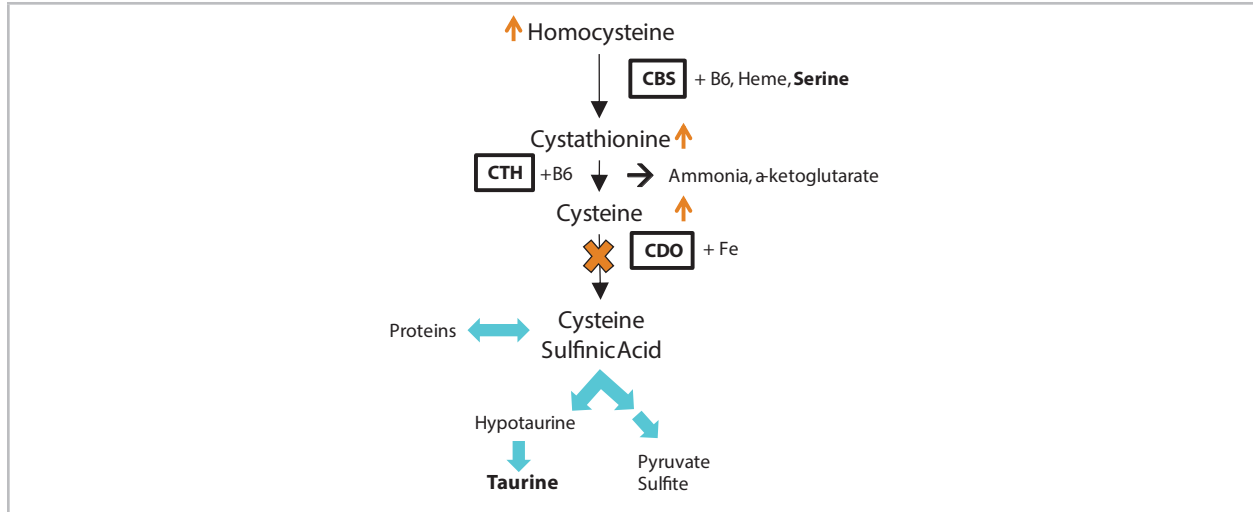
Cysteine dioxygenase (CDO) oxidizes cysteine to cysteine sulfinic acid. The enzyme is the first step to either sulfite/pyruvate or hypotaurine/taurine synthesis. Enzyme function may be sensitive to inflammatory cytokines. Mutations and SNPs in CDO have been associated with Rheumatoid arthritis, Parkinson's disease, Alzheimer's disease and motor neuron disorders. The enzyme requires an iron cofactor and vitamin B-6. Evaluate iron status

Cysteine Low

Cysteine levels may be low for a variety of reasons.

- Diet
  - Imbalanced or inadequate protein intake
- Gastrointestinal dysfunction
  - Hypochlorhydria; gastric or small intestine resections may decrease absorption
  - Pancreatic insufficiency (lack of digestive enzymes)
  - Evaluate GI function with *Comprehensive Stool Analysis*
- Methylation pathway defects
  - Acquired enzyme defects
    - Environmental toxicant exposures
      - Cysteine is the rate limiting amino acid in the biosynthesis of glutathione
        - Evaluate Glutathione status with *RBC Glutathione*
      - Evaluate exposure to toxic metals *Urine Toxic Elements, Whole Blood Elements, Urine Porphyrins or Hair Elements*
    - Nutritional cofactors
      - *RBC Elements*

– Inherited enzyme defects in cystathionine beta-synthase (CBS) or cystathionine gamma-lyase (CTH)

- SNPs
    - Evaluate *DNA Methylation Pathway* for CBS SNPs
- Mutations
    - Some homozygous CBS mutations (present in 4 out of 10,000 people) may be vitamin B6-resistant, and result in congenital cystathioninemia. Most patients with congenital cystathioninemia are asymptomatic, unless dietary assimilation of cysteine is compromised and cysteine deficiency results.

Interventions, based on the cause, which may improve cysteine levels, include improved nutrition and supplements:

- Dietary sources of cysteine include undenatured whey protein, legumes and eggs
- Supplement cysteine directly as N-acetyl cysteine (N-AC)
- Supplement CBS cofactors pyridoxal-5'-phosphate (vitamin B6/P5P) and serine
    - Evaluate serine status with urine or plasma *Amino Acids*
    - Evaluate heme (cofactor) synthesis with *Urine Porphyrins*

CBS, CTH, CDO
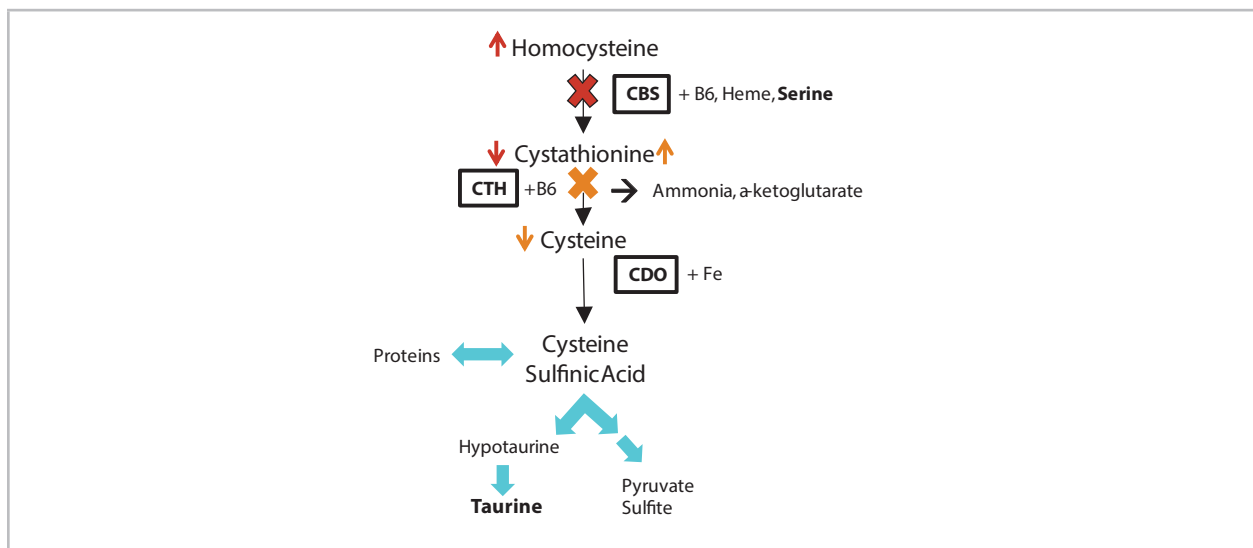
Cystathionine beta-synthase (CBS)

Cystathionine beta-synthase (CBS) catalyzes the vitamin B6–dependent transsulfuration reaction condensing serine and homocysteine to cystathionine before further synthesis to taurine, cysteine, sulfite and glutathione. Research indicates that heme may be an essential cofactor for proper enzyme conformation and the proper binding of pyridoxal-5'-phosphate (vitamin B6/P5P). Serine is also a cofactor for CBS. Poor CBS function may elevate homocysteine levels and decrease cystathionine and cysteine levels. Cystathionine levels are normally very low, but a disproportionately low cystathionine level in the presence of elevated homocysteine may be interpreted as an indication of compromised CBS activity. Low cysteine levels may inhibit glutathione and ultimately sulfate synthesis.

Some defects in CBS are responsible for homocystinuria and altered sulfur metabolism. CBS SNP 699TT may be especially sensitive to folate levels. CBS "up-regulation" is not commonly seen, however, the phenomenon is documented in Down 's syndrome populations.

- Supplement CBS cofactors pyridoxal-5'-phosphate (vitamin B6/P5P) and
    - Evaluate serine status with urine or plasma *Amino Acids*
    - Evaluate heme (cofactor) synthesis with *Urine Porphyrins*

Cystathionine gamma-lyase (CTH)

Cystathionine gamma-lyase (CTH) converts cysteine to cysteine sulfinic acid. This is the first step towards sulfite, pyruvate or taurine synthesis. (See image on Page 6.) Inflammatory cytokines may downregulate CTH activity. CTH requires a vitamin B6 cofactor. Mutations and SNPs in CTH are associated with Rheumatoid arthritis, Parkinson's disease, Alzheimer's disease and motor neuron diseases.

Supplements that may support normal enzyme function:

- Requires B6 cofactor

S-adenosylmethionine High

S-adenosyl methionine (SAM) is the primary methyl donor in the body. Elevated levels of SAM indicate either an inhibition of the methyltransferase enzymes that convert SAM to S-adenosylhomocysteine or over-supplementation of SAMe or methionine. There are about 50 methyltransferases; it is not yet practical to test all of these enzymes for single nucleotide polymorphisms (SNPs). One enzyme, however, is of particular interest; its product sarcosine may serve to regulate the methylation pathway. Glycine-N-methyltransferase converts glycine into sarcosine. The excretion of sarcosine serves to regulate the level of SAM in the body. Importantly, elevated SAM acts as a "switch," increasing the flux through transsulfuration and away from transmethylation.

Acquired defects in the methyltransferase enzymes may occur due to environmental exposures. Bisphenol A (BPA), lead or other toxic metals may inhibit methytransferases. Polyphenols or cholorgenic acid from tea or coffee may also inhibit methyltransferases.

- Evaluate the bioaccumulation of toxic elements with *Urine Toxic Elements*
- Evaluate chronic or recent toxic elements exposure with *Hair Elements, Whole Blood Elements or Urine Porphyrins*
- Evaluate history of exposure to BPA

Nutritional deficiency may also affect the activity of methyltransferase enzymes. All methyltransferase activities require magnesium. Magnesium supplementation may support normal methyltransferase activity.

- Evaluate intracellular magnesium status with Red Blood Cell (RBC) Elements

Glycine N-methyltransferase (GNMT)

GNMT catalyzes the reaction that converts glycine and S-adenosylmethionine (SAM) to N-methylglycine and S-adenosylhomocysteine (SAH). The SAM:SAH ratio is important in many body processes, including the regulation of other genes by the addition of methyl groups to DNA (global methylation).

GNMT
Glycine N-methyltransferase
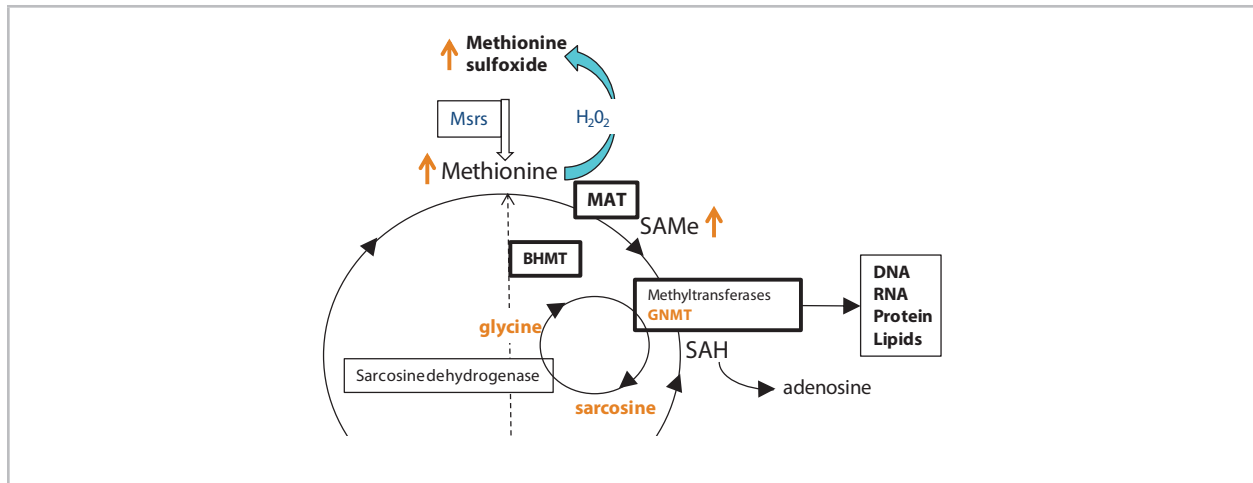
The GNMT enzyme is also involved in processing toxic compounds in the liver. Studies performed using laboratory animals demonstrate that the hepatic activity of GNMT was significantly elevated in a dose-dependent fashion when diets contain excess methionine. Excess SAM is converted into sarcosine and either metabolized by sarcosine dehydrogenase into glycine and methylene-tetrahydrofolate or excreted as sarcosine. An enzyme defect in sarcosine dehydrogenase will result in <u>elevated urinary sarcosine</u> levels if the intake of methyl groups (e.g. SAMe) exceeds physiological need.

Animal studies indicate that GNMT is inhibited by folate, low methionine, and low SAM levels. GNMT expression may be induced by high methionine, high SAM, Vitamin A, glucocorticoids and glucagon (animal studies).
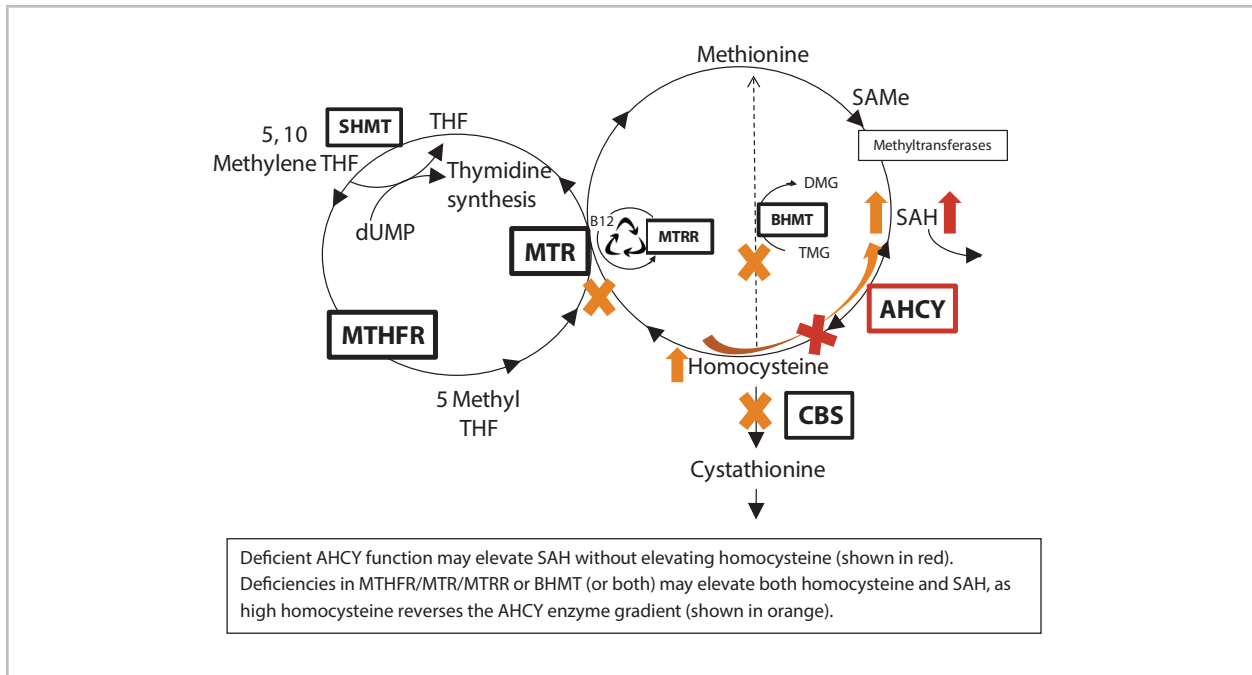
S-adenosylmethionine Low

S-adenosylmethionine (SAM) may be low if the level of the precursor amino acid methionine is low. See **Methionine Low** section for more information and treatment options. SAM levels may also be low due to a defect in the enzyme methionine adenosyltransferase (MAT), which converts methionine to SAM. A defect in MAT will cause elevated methionine levels and low SAM levels. See the **Methionine adenosyltransferase (MAT)** section for more information and treatment options.

SAM may also be low if choline synthesis is compromised or dietary choline sources are insufficient. Choline deficiency may inhibit the re-methylation of homocysteine and decrease methionine and SAM levels. Inherited genetic variations in phosphatidylethanolamine-N-methyltransferase (PEMT) and/or 5,10-methylenetetrahydrofolate dehydrogenase (MTHFD1) may alter the daily nutritional requirements for choline. Post-menopausal women may require choline, as PEMT activity, in women, is regulated by estrogen levels.

S-adenosylhomocystine High

S-adenosylhomocystine (SAH) may elevate due to an enzyme deficiency in adenosylhomocysteinase (AHCY). SAH may elevate if homocysteine and/or adenosine levels are high. It is also possible for SAH to elevate and homocysteine levels to be normal, if the AHCY enzyme deficiency is severe.

Deficient AHCY function may elevate SAH without elevating homocysteine (shown in red). Deficiencies in MTHFR/MTR/MTRR or BHMT (or both) may elevate both homocysteine and SAH, as high homocysteine reverses the AHCY enzyme gradient (shown in orange).

Elevated levels of SAH increase oxidative stress and may contribute to vascular disease, renal disease, neural tube defects and dementia. High levels of SAH inhibit the methyltransferase enzymes that use SAM, and may result in elevated SAM levels. AHCY has no nutritional cofactors, but the enzyme does use nicotinamide adenine dinucleotide (NAD) as a cofactor. NAD is synthesized from Vitamin B3 (niacin) in the body. Supplements that may support normal metabolism:

- Vitamin B3 or NADH supplements
  - Recheck Plasma Methylation Profile 1-2 months after initiating therapy; better AHCY function may uncover additional functional defects and elevate homocysteine

Adenosylhomocysteinase (AHCY)

Adenosylhomocysteinase (AHCY) is found in the cytoplasm and is the only enzyme known in mammals to convert S-adenosylhomocysteine (SAH or AdoHcy) to homocysteine. The reaction is reversible, and driven by substrate to elevate availability. SAH may elevate if homocysteine and/or adenosine levels are high. It is also possible for SAH to elevate and homocysteine levels to be normal, if the AHCY enzyme deficiency is severe. AHCY has no nutritional cofactors, but the enzyme does use nicotinamide adenine dinucleotide (NAD) as a cofactor. NAD is synthesized from Vitamin B3 (niacin) in the body. AHCY activity may be inhibited by iron overload, excess copper or viral infection.

- Evaluate iron status
- Supplement B-3

S-adenosylhomocystine Low

S-adenosylhomocystine levels may appear low if methyltransferase function is suboptimal or inhibited. The inhibition of methyltransferase enzymes may occur due to toxic exposures such as lead or bis-phenol A (BPA). Methyltransferase enzymes require magnesium. Plant polyphenols from green tea and coffee may also downregulate methyltransferase expression.

- Evaluate intracellular magnesium status with *Red Blood Cell (RBC) Elements*
- Evaluate the bioaccumulation of toxic elements with *Urine Toxic Elements*
- Evaluate chronic or recent toxic elements exposure with *Hair Elements, Whole Blood Elements*
- Recent damage from toxic exposures may be evaluated with *Urine Porphyrins*

Homocysteine High

Homocysteine levels may elevate due to a variety of enzymatic defects:

- Betaine homocysteine methyltransferases
- Methylene-tetrahydrofolate reductase
- Methionine synthase
- Methionine synthase reductase
- Serine hydroxymethyltransferase
- Cystathionine beta-synthase (See **cystathionine beta-synthase (CBS)** and **Cysteine Low** sections.)

BHMT = Betaine homocysteine methyltransferases; MTHFR =Methylenetetrahydrofolate reductase; MTR = Methionine synthase; MTRR Methionine synthase reductase; SAM = S-adenosylmethionine; SHMT = Serine hydroxymethyltransferase
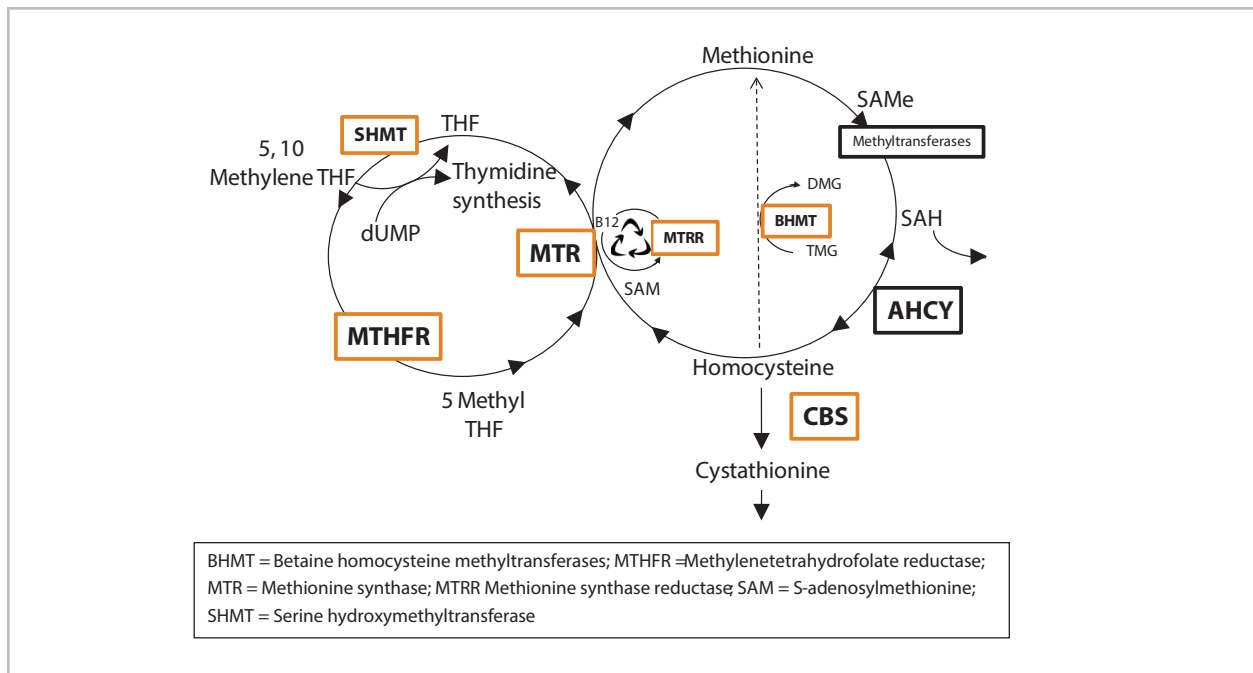
Betaine-homocysteine methyltransferase (BHMT)

Betaine homocysteine methyltransferase (BHMT) is the first enzyme defect that may elevate homocysteine. The BHMT enzyme transfers a methyl group from betaine (trimethylglycine or TMG) to homocysteine, synthesizing methionine and dimethylglycine (DMG). The enzyme may be downregulated by oxidative stress.

BHMT is found primarily in the kidney and liver. Defects in BHMT may affect detoxification capacity. The enzyme is most active under fasting or low methionine conditions; patients with defects may not tolerate fasting well. BHMT activity requires zinc; this enzyme pathway is folate-independent. Supplements that may support normal metabolism:

- Zinc
- Selenium
    – Evaluate RBC Elements for essential element insufficiency
- Betaine (trimethylglycine or TMG)

Serine hydroxymethyltransferase (SHMT)

SHMT1

Homocysteine/cysteine High
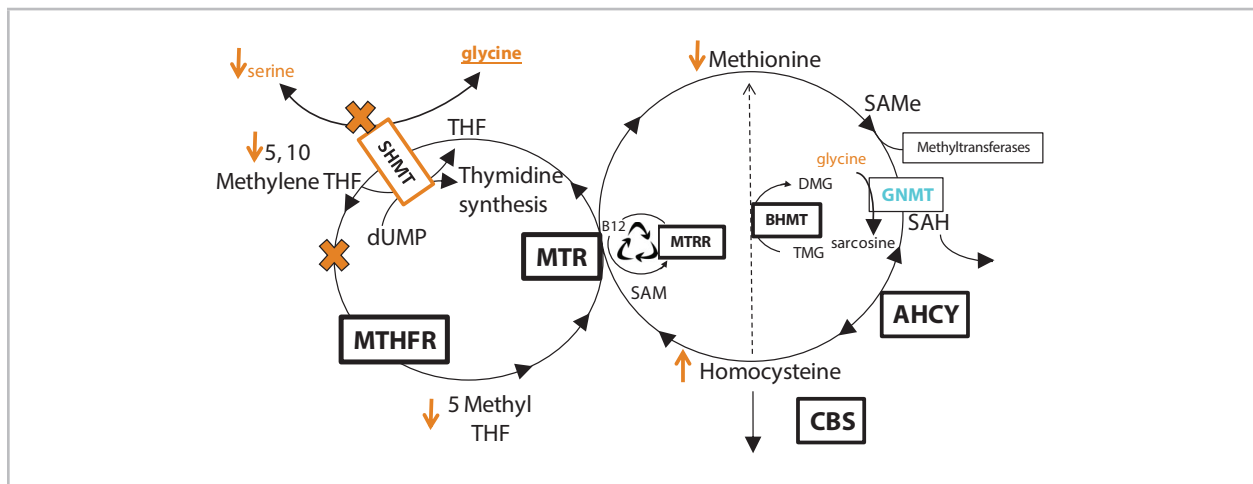
Serine hydroxymethyltransferase (SHMT) converts tetrahydrofolate into 5,10-methylenetetrahydrofolate, the substrate molecule for methylene-tetrahydrofolate reductase (MTHFR). The reaction simultaneously converts glycine into serine. Serine is a required cofactor for cystathionine beta-synthase (CBS). The SHMT enzyme reaction is reversible.

Cytoplasm SHMT (cSHMT) expression and activity is regulated by a number of factors, including retinoic acid (Vitamin A) and ferritin. SHMT activity requires vitamin B6 and may be an important regulator of the methylation pathway. Studies indicate that cSHMT competes with methylene-tetrahydrofolate reductase (MTHFR) for 5,10-methylenetetrahydrofolate and competes with methionine synthase (MTR) for 5-methyltetrahydrofolate (*in vitro*). Further *in vitro* studies on cells cultured from patients with MTR or MTHFR SNPs provides evidence of competition between MTHFR and cSHMT for 5,10-methylenetetrahydrofolate. Increases in cSHMT expression and/or elevated cellular glycine concentrations decrease the availability of folate for homocysteine remethylation, which may decrease S-adenosylmethionine (SAM) synthesis. Supplements that may support normal metabolism:

- Pyridoxal-5'-phosphate (vitamin B6/P5P)
- Dietary folate from leafy green vegetables for synthesis into tetrahydrofolate

MTHFR/MTR/MTRR Triad

The action of the three enzymes methionine synthase (MTR), methionine synthase reductase (MTRR) and methylene-tetrahydrofolate reductase (MTHFR) are tightly linked; at present there is no way to discern between them on functional laboratory tests. Deficient function of multiple enzymes in the triad may have cumulative effects on the transmethylation pathway, elevating homocysteine levels and inhibiting the re-methylation of homocysteine to methionine.

Methylene-tetrahydrofolate reductase (MTHFR)

Methylene-tetrahydrofolate reductase (MTHFR) converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a necessary cofactor for the recycling of homocysteine to methionine. Folate deficiency inhibits enzyme function.

MTHFR incorporates a flavin cofactor and uses NAD(P)H, which is synthesized from niacin. Supplements that may support normal enzyme function:

* Vitamin B2 (riboflavin)
* Vitamin B3 (niacin)
* L-5MTHF or L-methylfolate calcium (levomefolic acid) are supplemental forms of 5-methyltetrahydrofolate; they may be used to bypass an enzyme defect in MTHFR

Methionine synthase (MTR)

Methionine synthase (MTR) transfers the methyl group from methylcobalamin (methyl-B12) to homocysteine to regenerate methionine. Studies indicate that normal methionine synthase reductase (MTRR) may be necessary for proper MTR function. Ethanol, and its metabolic product acetalaldehyde, have been shown to inhibit MTR function in the brain (animal and in *vitro studies*). The enzyme incorporates zinc into its structure; homocysteine is bound to the enzyme by the zinc atom. Supplements that may support normal enzyme function:

* Methylcobalamin (methyl-B12)
* Zinc if deficient; evaluate with *Red Blood Cell (RBC) Elements*
* Minimize alcohol intake

Methionine synthase reductase (MTRR)

Methionine synthase reductase (MTRR) uses S-adenosylmethionine (SAM) to form methylcobalamin from the cobalamin generated by methionine synthase (MTR). MTRR provides MTR with a necessary cofactor. Studies indicate that normal MTRR may be necessary for proper methionine synthase function. MTRR requires flavin cofactors derived from vitamin B2. The enzymes that convert B2 into flavin cofactors require magnesium and zinc. Supplements that may support normal enzyme function:

* Hydroxycobalamin provides substrate for MTRR
* SAMe if *Plasma Methylation Profile* indicates low SAM levels and SAH is normal.
* Magnesium and zinc if deficient; evaluate status with *Red Blood Cell (RBC) Elements*
* Vitamin B2

Homocysteine Low

Homocystine levels may be low if there is a defect in adenosylhomocysteinase (AHCY). See the **S-adenosylhomocysteine High** and **Adenosylhomocysteinase (AHCY)** sections. Low levels of homocysteine are not documented to cause health problems **if** the methylation pathway is functional and there are normal levels of all other biomarkers on the *Plasma Methylation Profile* results.

Cystathionine High

Cystathionine is an intermediary metabolite in the transsulfuration pathway; it is found between homocysteine and cysteine and is formed by the enzyme cystathionine beta-synthase (CBS). Cystathionine may elevate due to an enzyme deficiency in cystathionine gamma-lyase (CTH) or cysteine dioxygenase (CDO). See image below.

Cystathionine gamma-lyase (CTH)

Cystathionine gamma-lyase (CTH) converts cysteine to cysteine sulfinic acid. This is the first step towards sulfite, pyruvate or taurine synthesis. (See image below.) Inflammatory cytokines may downregulate CTH activity. CTH activity requires vitamin B6. Mutations and SNPs in CTH are associated with Rheumatoid arthritis, Parkinson's disease, Alzheimer's disease and motor neuron diseases.

*   Requires B6

CBS, CTH, CDO
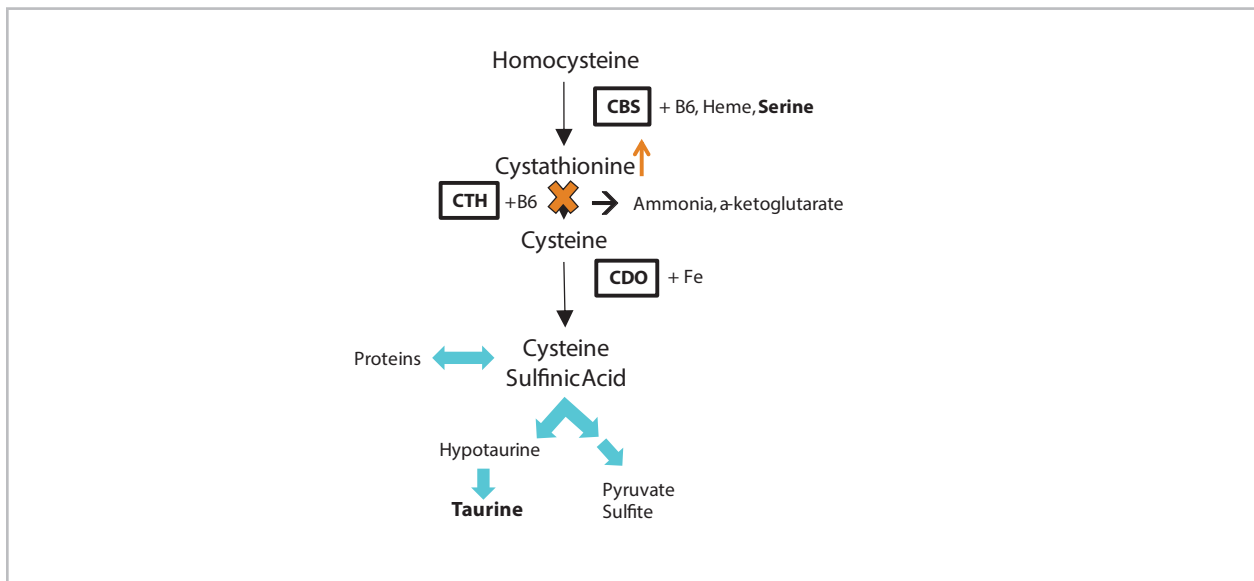
Cysteine dioxygenase (CDO)

Cysteine dioxygenase (CDO) is the primary enzyme that lowers excessive levels of cysteine. CDO oxidizes cysteine to cysteine sulfinic acid. The enzyme is the first step to either sulfite/pyruvate or hypotaurine/taurine synthesis. Enzyme function may be sensitive to inflammatory cytokines. Mutations and SNPs in CDO have been associated with Rheumatoid arthritis, Parkinson's disease, Alzheimer's disease and motor neuron disorders. CDO activity requires iron and vitamin B-6.

- Evaluate iron status

Cystathionine Low

Cystathionine is an intermediary metabolite in the transsulfuration pathway, and is normally detected at very low levels in plasma. It is found between homocysteine and cysteine and is formed by the enzyme cystathionine beta-synthase (CBS). A defect in CBS may elevate homocysteine and decrease both cystathionine and cysteine levels. Cystathionine levels are normally very low, but a disproportionately low cystathionine level in the presence of elevated homocysteine may be interpreted as being indicative of compromised CBS activity. Low cysteine levels limit the biosynthesis of glutathione. Elevated homocysteine is an oxidative stressor and may contribute to renal disease. See **Cysteine Low** and **Cystathionine beta-synthase (CBS)** sections.

S-adenosylmethionine : S-adenosylhomocysteine (SAM : SAH) Ratio

S-adenosylhomocysteine (SAH) is a by-product of all methylation reactions in the body and is normally metabolized to homocysteine. Increased levels of SAH may be exhibited when the intracellular concentration of homocysteine or adenosine increases, or due to defects in adenosylhomocysteinase (AHCY). SAH is a high affinity inhibitor of methyltransferase reactions. The ratio of SAM to SAH is often used as an index of methylation potential.

S-adenosylmethionine (SAM) is the methyl donor for methylation reactions that synthesize or metabolize proteins, DNA, phospholipids and neurotransmitters. Decreased levels of SAM commonly occur with folate and cobalamin (vitamin B12) deficiency (or oxidation of the cobalt moiety of cobalamine). Low SAM levels have been associated with depression, dementia, vacuolarmyelopathy and liver disease.

Research has demonstrated an association between altered SAM and SAH levels and several conditions, including HIV-positive patients, MTHFR deficiency, MAT II deficiency and with low cobalamin levels (lowest quartile).

Accurate interpretation of the SAM:SAH ratio presumes normal renal function, as serum SAM:SAH has been shown to be dependent upon renal status.

Methylation Index Low (SAM : SAH ratio)

A low value for the methylation index indicates limited capacity for methylation. SAH has a very high affinity for methyltransferase enzymes for which it is a very potent inhibitor. Evaluate the results of the *Plasma Methylation Profile* for evidence of enzyme defects, and apply nutritional interventions as indicated in each section, and in the *Plasma Methylation Profile* interpretive paragraphs, to normalize individual analyte levels.

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