Methylation Report

Lifecode GX
— Professional Genotype Analysis —

Methylation

Methylation, also referred to as one carbon metabolism, is a process by which methyl groups are added to molecules. It is involved in almost every biochemical reaction in the body, occurring billions of times every second in our cells and contributing to numerous crucial bodily functions, including:

- Detoxification
- DNA integrity
- Energy production
- Inflammation control
- Immune function
- Gene expression / suppression
- Neurotransmitter balance
- Telomere protection (ageing)

Environmental factors such as diet, chemical or drug exposure and stress are known to play a role in supporting or hampering methylation. Important dietary co-factors include vitamin B6, B9, B12, methionine, betaine(TMG), choline and S-adenosylmethionine (SAMe). Insufficiency or deficiency of any of these co-factors may also hinder methylation.

Impaired methylation may contribute to major chronic conditions, including:

- Cardiovascular disease
- Unexplained miscarriages
- Problems during pregnancy
- Mood and psychiatric disorders
- Cancer
- Free radical damage (premature ageing)
- Diabetes
- Infertility
- Neural tube defects
- Adult neurological conditions
- Chronic fatigue syndrome

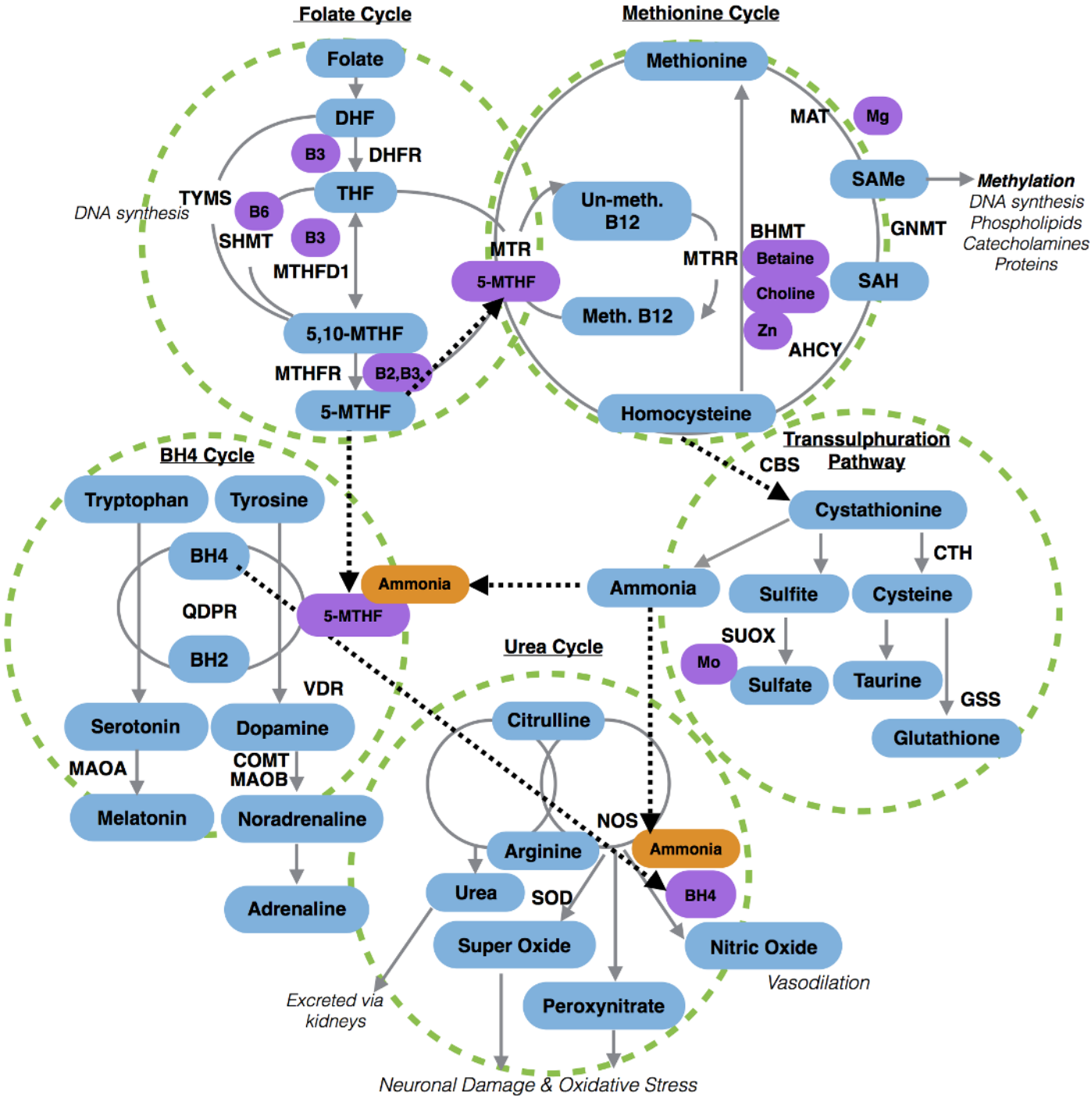
The Role of Genes in Methylation

The purpose of analysing genetic variants (or single nucleotide variants (SNVs)) in the context of the methylation pathway is to understand the likely effect, such as up or down regulation and subsequent impact on gene function, in order to provide guidance on how to support or bypass weaknesses or bottlenecks. Although an individual's genes cannot be changed, the rate and manner of gene expression, and therefore protein synthesis, can be regulated.

This report provides a personalised genotype analysis organised by the following methylation sub-cycles:

- The Folate Cycle
- The Methionine Cycle
- The Transsulphuration Pathway
- The BH4 Cycle / Neurotransmitter Metabolism
- The Urea Cycle

The Methylation Cycle Summary



Key:

- Co-factor
- Inhibitor

Folate Cycle

Folate, or vitamin B9, is the generic term for naturally occurring dietary folate and folic acid (the monoglutamate form of the vitamin found in supplements and fortified foods).

Folate is converted into dihydrofolate (DHF) in the presence of Vitamin B3. DHF is then converted to THF, also with the aid of B3.

The cyclical part of the process involves the conversion of tetrahydrofolate (THF) into 5,10-methylenetetrahydrafolate which in turn gets converted to 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is then converted back into THF.

5-MTHF is an important product of the folate cycle as it is required by the methionine cycle for the conversion of homocysteine to methionine and to drive the conversion of BH2 to BH4 to support the neurotransmitter cycle. Another folate-dependent reaction, the methylation of deoxyuridylate (dUMP) to thymidylate (dTMP) in the formation of DNA, is required for proper cell division. An impairment of this reaction initiates a process that can lead to megaloblastic anemia, one of the indicators of folate deficiency.

Genetics

Absorption of folate may be impacted by variants on the GCPII gene (food form) and on the RFC1 or DHFR genes (either form).

The MTHFR A1298C variant impacts the conversion of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4) leading to low levels of neurotransmitters. In addition to the strain on the BH4 cycle, the amount of BH4 will also affect the functioning of the urea cycle.

The MTHFR C677T variant slows down the production of 5-MTHF which not only affects the regeneration of THF in the folate cycle but also the transfer of methyl groups to regenerate methionine in the methionine cycle. A homozygous genotype (AA) has more impact than a heterozygous (AG).

Variants on the MTHFD1 and SHMT1 genes can also slow the conversion of THF to 5,10 Methylene and subsequently impact 5-MTHF levels. Variants on the SHMT1 gene can also affect the conversion of serine to glycine.

Variants on MTHFD1 can impact synthesis of purines and on TYMS can affect thymidine synthesis, both of which are important for cell proliferation and growth.

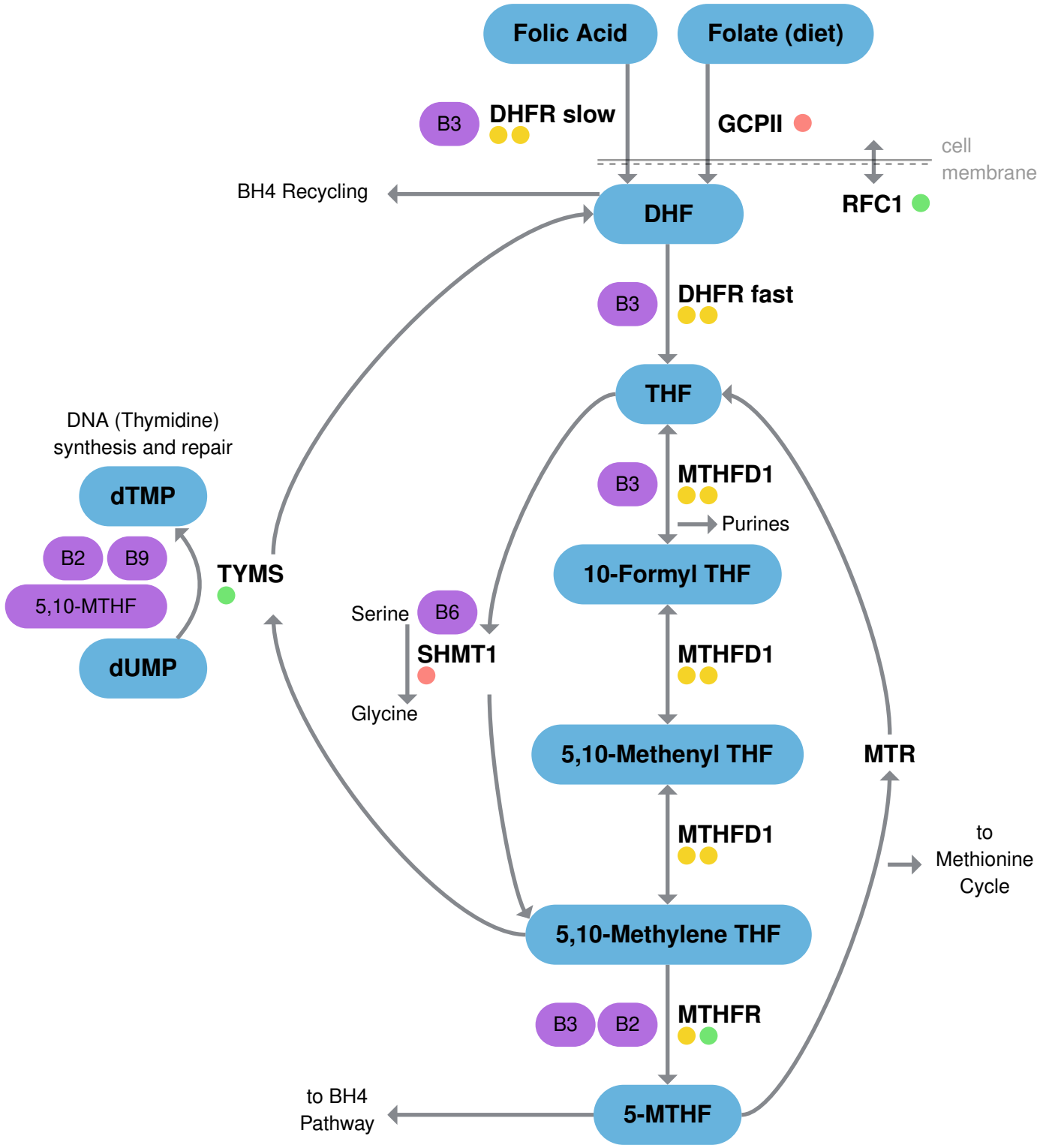
Further Investigation

Functional testing of serum and erythrocyte folate levels may be considered. As serum folate levels are sensitive to recent dietary intake, erythrocyte levels are more indicative of tissue folate stores.

Management and Lifestyle

Ensure adequate intakes of B vitamins - particularly B9 (folates) B2, B3 and B6. Methylated forms of B vitamins may be appropriate depending on variants.

Your Folate Cycle Results:



Key:

- Co-factor
- Inhibitor
- Protective - neutral
- Neutral - negative
- Negative

DHFR Dihydrofolate Reductase

SNV		Result	Description
rs1643649	A16352G	CT	Down regulation of DHFR which may result in reduced folate absorption and has been linked to neural tube defects (NTDs). DHFR function can be supported by increasing intake of food folate (green leafy veg, citrus fruit) and reduced form folate (folinic acid or methyl-folate).
rs70991108	19bp DEL	ID	Heterozygous genotype - a 19 base point sequence of the DHFR gene is deleted in one copy of the gene. Associated with up to 2.4 x higher expression of DHFR and increased enzyme activity. This can deplete the 5,10-methylene-THF pool, the critical substrate for both DNA synthesis and homocysteine re-methylation that provides the methyl donor (SAMe) for methylation reactions. This genotype has also been linked to increased (up to 2x) hepatic toxicity from methotrexate treatment. High intake of folic acid (synthetic folate has been linked to increased DHFR activity for this genotype. Ensure adequate intake of reduced form folate, which occurs naturally in foods (green leafy veg, citrus fruit, beans) and reduced form supplements (folinic acid or 5-MTHF/methyl-folate).

The enzyme dihydrofolate reductase catalyses the conversion of dihydrofolate (DHF) into tetrahydrofolate (THF), a methyl group shuttle required for the synthesis of purines, thymidine and nucleic acids - precursors to DNA and RNA. The action of DHFR on folic acid (synthetic folate) absorbed in the liver is slower than on dietary folate absorbed in the intestine.

Anti-folate drugs such as methotrexate target DHFR to deplete cells of reduced folate resulting in the suppression of purine and pyrimidine precursor synthesis.

Variants on the DHFR gene may down regulate or up regulate activity. Lower activity may protect against certain cancers (colorectal cancer and childhood leukaemia), similar to the action of methotrexate, however, the consequent deficiency of folate can increase susceptibility to megaloblastic anaemia, neural tube defects and spina bifida. Higher enzyme activity can deplete 5,10 Methylene-THF and 5-MTHF required for synthesis of SAMe (the master methyl donor) and may tilt the balance in favour of DNA synthesis at the expense of methyl supply which can lead to aberrant DNA methylation and instability. High intake of folic acid (synthetic folate) has been linked to higher DHFR activity and increased risk of breast cancer in DHFR 19-bp deletion carriers.

GCPII Glutamate carboxypeptidase II

SNV		Result	Description
rs202700	C1561T	TT	Impaired intestinal absorption of dietary folate and lower blood folate levels linked to miscarriage; and elevated homocysteine linked to coronary artery disease. Risk may be reduced by improving folate status by increasing intake of food form folate and/or supplementation, particularly if gut health is suboptimal.

GCPII, also known as FOLH1 (Folate Hydrolase), is anchored to the intestinal brush border and facilitates the transfer of dietary folate into the body by converting polyglutamylated folates to monoglutamyl folates. Folic acid (a synthetic form of folate) is a monoglutamate, so does not require this conversion.

Variants are associated with down regulation of the gene resulting in impaired intestinal absorption of dietary folate, resulting in lower blood folate levels and consequent hyperhomocysteinemia.

MTHFD1 Methylenetetrahydrofolate Dehydrogenase 1

SNV		Result	Description
rs1076991	C105T	CT	Possible reduction in gene activity which may limit the supply of methyl-folate (5-MTHF) to recycle homocysteine to methionine (via the 'long route'). Folate insufficiency has been linked risk of neural tube defects and other developmental disorder. Dependency on the short route (via BHMT) and betaine (as co-factor) and its substrate choline (found in eggs). Depletion of choline may increase risk of endometriosis and infertility.
rs2236225	G1958A	AG	Possible reduction in gene activity which may reduce the supply of methyl-folate to recycle homocysteine to methionine (via the 'long route'). Folate insufficiency has been linked risk of neural tube defects. Possible increased dependency on the short route (via BHMT) and betaine (as co-factor) and it's substrate choline (found in eggs). Depletion of choline may increase risk of endometriosis, and related infertility

MTHFD1 possesses three distinct activities which catalyse the sequential reactions in the interconversion of the carbon-1 derivatives of THF, which are substrates for methionine, thymidylate, and de novo purine synthesis. These are reversible reactions that can be directed towards 5-MTHF - and homocysteine re-methylation - or away from it and can, therefore, impact the methionine cycle.

Variants in MTHFD1 are associated with down regulation of the gene activity and can impact availability of the various THF substrates required for nucleotide biosynthesis, DNA synthesis and repair and increase the demand for choline as a methyl-group donor (in the BHMT ‘short cut’ pathway of the methionine cycle). Variants have been linked to increased risk of folate sensitive neural tube defects and endometriosis related infertility due to choline depletion.

MTHFR Methylenetetrahydrofolate Reductase (NAD(P)H)

SNV		Result	Description
rs1801131	A1298C	GT	Reduced gene function which may result in lower 5-MTHF (methyl-folate) and slower conversion of BH2 to BH4 - needed for neurotransmitter synthesis. This genotype should be examined in the context of the BH4/ Neurotransmitter cycle. Methylation can be supported by adequate consumption of folate containing foods (such as green leafy vegetables, citrus fruits, beans and liver) and cofactors (vitamins B2 and B3).
rs1801133	C677T	GG	Neutral genotype. No impact on 5-MTHF and homocysteine levels.

The MTHFR gene is responsible for making the protein methylenetetrahydrofolate reductase (MTHFR), the rate-limiting enzyme in the methylation cycle which catalyses the conversion of folate to 'active' folate (5-MTHF) needed to support the re-methylation of homocysteine to methionine, DNA synthesis and repair (vital for healthy cell division), and the metabolism of neurotransmitters, phospholipids and proteins such as myelin.

Variants on the MTHFR gene usually result in lower enzyme activity. The C677T variant, which occurs in about 30% of people, can result in significantly reduced 5-MTHF levels - up to 40% reduction for heterozygotes and 70% for homozygotes (AA). MTHFR activity can be supported by increasing the intake of folate (B9) and the cofactors riboflavin (vitamin B2), niacin (vitamin B3), cobalamin (vitamin B12) and zinc. The A1298C variant has less direct impact on 5-MTHF levels but is associated with depletion of BH4 - vital for neurotransmitter synthesis.

RFC1 Reduced Folate Carrier 1

SNV		Result	Description
rs1051266	A80G	CC	Neutral genotype - no impact on intracellular folate transport

RFC1, also known as SLC19A1 (Solute Carrier Family 19), is a transporter of folate and is involved in the regulation of intracellular concentrations of folate. It has a higher affinity for reduced folate than folic acid.

Variants on this gene are associated with reduced ability to take up, retain, and metabolise folate resulting in reduced bioavailable folate (5-MTHF) which impacts DNA methylation, and impacts the methionine cycle - contributing to increased homocysteine levels, and the BH4/ neurotransmitter cycle - decreased BH4 levels.

SHMT1 Serine hydroxymethyltransferase 1 (Soluble)

SNV		Result	Description
rs1979277	C1420T	AA	Reduced activity of SHMT1 can deplete availability of 5,10-Methylene THF needed for synthesis of methyl-folate, purines, thymidine, needed for DNA synthesis and repair, and for conversion of serine to glycine (which fuels methylation), which can result in abnormal methylation patterns, slow conversion of homocysteine (higher levels) and DNA instability. This genotype may be supported by increasing intake of food folate/ reduced folate.

SHMT is a vitamin B6 dependent enzyme which catalyzes the reversible conversion of serine to glycine and of tetrahydrofolate to 5,10-methylene tetrahydrofolate needed for the synthesis of purine, thymidine and methionine. Variances causing disturbances in SHMT1 expression and activity lower the concentration of available 5,10-MTHF, leading to lower synthesis of purines and DNA and lower availability of 5-MTHF for methylation processes.

TYMS Thymidylate Synthetase

SNV		Result	Description
rs2790		AA	Neutral genotype - no impact on DNA synthesis or repair

Thymidylate synthase catalyses the methylation of deoxyuridylate to deoxythymidylate using 5,10-methylenetetrahydrofolate as a co-factor. This function maintains the dTMP (thymidine-5-prime monophosphate) pool critical for DNA replication and repair.

Functional genetic variants in TYMS may impact DNA stability and increase the risk of certain cancers.

Methionine Cycle

The methionine cycle is also known as the SAMe or methylation cycle. It is the cycle that is responsible for the process of methylation - adding or removing methyl groups from one chemical to another – by SAMe. SAMe is called the universal methyl donor as it is the primary source of methyl groups for most other biochemical reactions including methylation of DNA, RNA, proteins, creatine etc.

The major intermediates involved in this cycle are methionine, S-adenosylmethionine (SAM or SAMe), S-adenosylhomocysteine (SAH) and homocysteine. It involves the regeneration of methionine from homocysteine with the help of methylated vitamin B12 (methylcobalamin) and 5-MTHF, which is an important intermediate in the folate cycle. There is also an alternative 'short cut' conversion pathway that is catalysed by BHMT. Methionine is converted into the various intermediates such as SAMe, SAH and (back) to homocysteine.

Homocysteine may also be removed from the methionine cycle by conversion into cystathionine (see transsulphuration cycle).

Genetics

Methionine is converted to SAMe in the presence of magnesium (Mg) and ATP (universal energy donor) by the enzyme MAT. Variants in MAT may down regulate its activity and impact the rate of SAMe synthesis.

SAMe, once it donates its methyl group to the various reactions, gets converted to SAH. A high ratio of SAH to SAMe may inhibit the conversion of SAMe to SAH and therefore the rate of methylation. This may occur if the rate of SAH conversion to homocysteine is slowed either due to down-regulation of the AHCY gene or if homocysteine levels are high.

The 'long route' reaction that converts homocysteine back to methionine involves the MTR mediated transfer of a methyl group from 5-MTHF (from the folate cycle) to form methylated B12. The B12 methyl group is then used to re-methylate homocysteine to methionine. Some of the un-methylated B12 is re-methylated by the enzyme MTRR using SAMe as the methyl donor. This reaction can be impacted by variants in MTR, MTRR genes or in the folate cycle (particularly MTHFR) or by vitamin B12 or SAMe deficiency.

The 'short cut' pathway for conversion of homocysteine to methionine does not involve B12 or the folate cycle. The BHMT enzyme catalyses the conversion of betaine (TMG) to DMG by transferring a methyl group to homocysteine for it to become methionine. This pathway can be impacted by variants in the BHMT gene or betaine or choline deficiency.

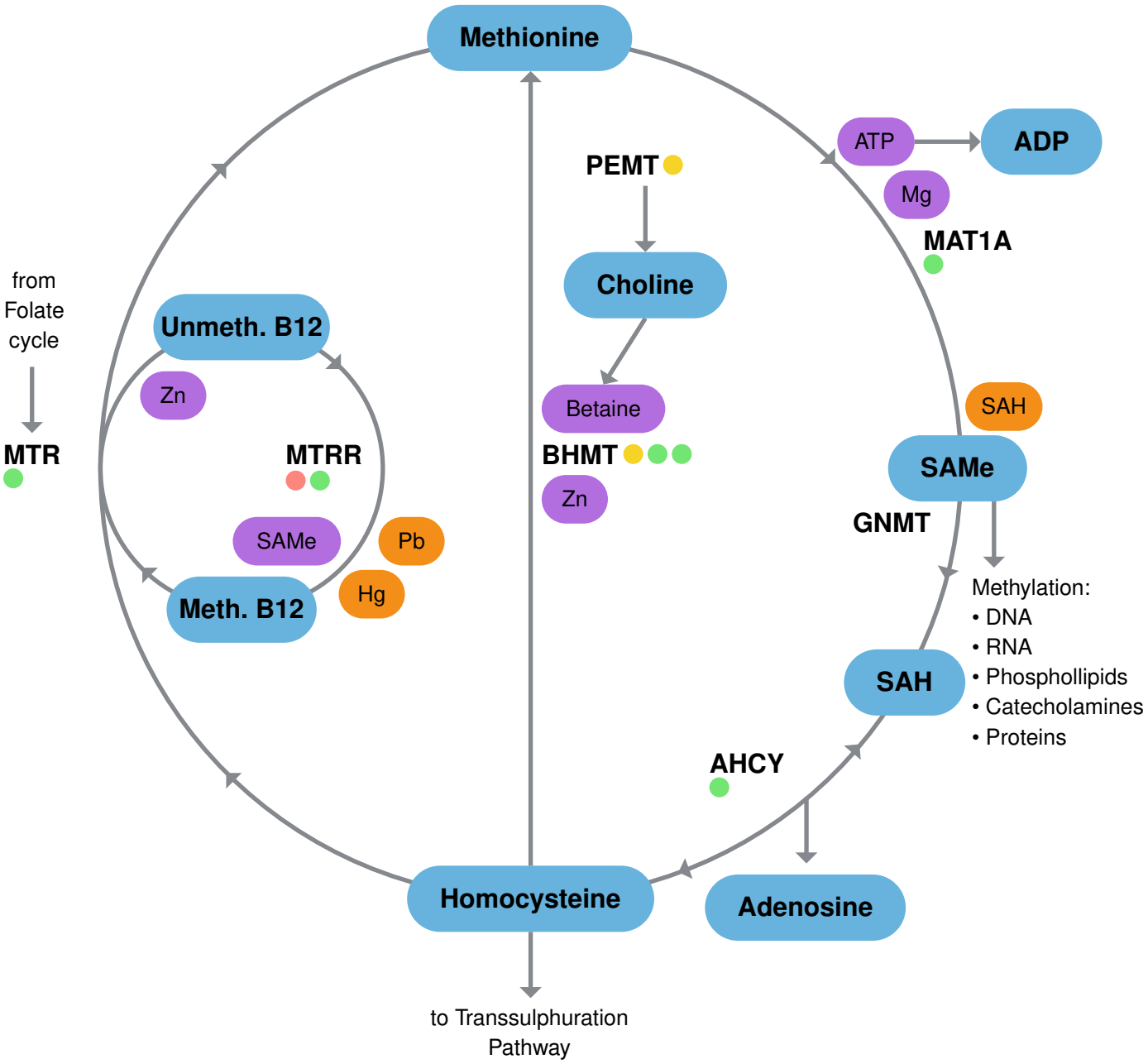
Further Investigation

Functional testing of homocysteine, methionine, B12 and SAMe levels may be considered. The ratio of SAH: SAMe is also a useful indicator of SAMe conversion.

Management and Lifestyle

Ensure adequate intakes of vitamin B9 (see Folate cycle), B12, betaine (found in beetroot) and choline. SAMe supplementation may be considered.

Your Methionine Cycle Results:



Key:

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- Negative

AHCY S-Adenosylhomocysteinase

SNV		Result	Description
i5000928	Tyr143Cys	TT	Neutral genotype - no impact on conversion of SAH to homocysteine.

AHCY, which is also known as SAHH, catalyses the reversible hydrolysis of S-adenosylhomocysteine (SAH) to adenosine and homocysteine.

Although genetic deficiency of AHCY activity in humans has been reported in only a few cases, metabolic effects of AHCY deficiency include elevated plasma SAH, SAMe, and methionine. The same effects may more likely result from high homocysteine levels triggering the reverse reaction metabolising and increasing levels of SAH. A high SAH to SAMe ratio can inhibit SAMe conversion and cause build up of methionine.

BHMT Betaine-homocysteine S-methyltransferase

SNV		Result	Description
rs3733890	R239Q	AG	This genotype is associated with down-regulated BHMT activity resulting in a less effective 'short cut' pathway for the conversion of homocysteine to methionine and risk of high homocysteine. It is also reported to increase the risk of NTDs (neural tube defects). BHMT can be supported by increasing intake of co-factors including foods containing zinc - such as beef, lamb, chicken, chickpeas, pumpkin seeds, cashews, betaine - from quinoa, spinach and beetroot, and choline (substrate of betaine) - found in eggs.
rs567754	BHMT/2	CC	No impact on 'short cut' homocysteine to methionine conversion, or on homocysteine levels.
rs651852	BHMT/8	CC	No impact on 'short cut' homocysteine to methionine conversion, or on homocysteine levels.

BHMT catalyses the transfer of a methyl group from betaine to homocysteine to form methionine. It uses a ‘short cut’ mechanism rather than the B12-dependent 'long route'. The BHMT pathway is zinc-dependent and requires adequate levels of TMG - trimethylglycine (betaine) to function properly. This reaction is also required for the irreversible oxidation of choline. BHMT activity can also be affected by cortisol levels (stress) and may play a role in ADD/ADHD by affecting norepinephrine levels.

Variants in BHMT may contribute to increased homocysteine levels particularly if there are also variants on the MTR or MTRR genes affecting the 'long route' re-methylation of homocysteine.

FUT2 Fucosyltransferase 2

SNV		Result	Description
rs1047781	A385T	AA	Secretor genotype (Asian populations) - susceptibility to H. pylori infection and gastritis linked to reduced B12 absorption
rs601338	W143X	GG	Secretor genotype (non-Asian populations) - susceptibility to H. pylori infection and gastritis linked to reduced B12 absorption

The classic human secretor locus (Se), FUT2 gene, encodes alpha-(1,2)fucosyltransferase which regulates the expression of the H antigen, a precursor of the blood group A and B antigens, on the gastrointestinal mucosa. Absorption of B12 requires the secretion of the glycoprotein intrinsic factor (IF) from the gastric cells, binding of IF to vitamin B12 and a functional gastrointestinal absorption system.

The FUT2 secretor status has been associated with both H. pylori infection and gastritis; patients with vitamin B12 malabsorption and low levels of serum vitamin B12 have higher prevalence of H. pylori infection.

The homozygous genotypes W143X (AA) in non Asian populations and A385T (TT) in Asian populations have been reported as reliable indicators of an inactive FUT2 gene and non secretor status. About 20% of people are non secretors.

MAT1A Methionine Adenosyltransferase I, Alpha

SNV		Result	Description
rs1985908	T1297C	AA	Normal MAT activity and conversion of methionine to SAMe

MAT catalyses a two-step reaction that involves the transfer of the adenosyl from ATP to methionine to form S-adenosylmethionine (SAMe) and tripolyphosphate. SAMe is the main source of methyl groups for most biological methylations and is known as the master methyl donor.

Variants on the MAT genes partially inactivate MAT activity and may lead to hypermethioninemia, low SAMe and therefore slow methylation.

MTR 5-Methyltetrahydrofolate-Homocysteine Methyltransferase

SNV		Result	Description
rs1805087	A2756G	AA	Neutral genotype - no impact on MTR activity or B12 levels

Also known as cobalamin-dependent methionine synthase (MS), MTR catalyses the final step in methionine synthesis from homocysteine. MTR eventually becomes inactive due to the oxidation of its cobalamin co-factor. Disruptions to the MTR conversion of homocysteine can result in high homocysteine levels which have been implicated as risk factors in a number of health conditions including heart disease as well as Alzheimer's disease.

Variants in MTR can result in significant up-regulation of gene activity and consequently increase usage and deficiency of methylcobalamin/ B12. MTR activity can be supported by supplementing the methylated form of B12. The MTR and MTRR composite status is also important as MTRR helps to recycle B12 for use by MTR.

MTRR 5-Metyltetrahydrofolate-homocysteine S-Methyltransferase Reductase

SNV		Result	Description
rs162036	K350A	AA	Neutral genotype - does not impact Vitamin B12 or homocysteine levels.
rs1801394	A66G	GG	Reduced ability to re-methylate vitamin B12 which is needed for MTR conversion of homocysteine and can contribute to hyperhomocysteinemia. Supplementing methylated B12 may be beneficial to support methylation.

MTRR (methionine synthase reductase) regenerates MTR via a methylation reaction that uses SAMe as donor. MTRR also supports MTR activity by recycling and converting vitamin B12 into its methylated form.

Variants in MTRR can result in down-regulation of the gene activity and reduce its effectiveness in supporting MTR and contribute to high homocysteine levels.

PEMT Phosphatidylethanolamine N-methyltransferase

SNV		Result	Description
rs7946	G5465A	TC	Potential for reduced choline synthesis, which can impact betaine levels needed to support the BHMT 'short cut' conversion of homocysteine to methionine. As PEMT activity is stimulated by oestrogen, this variant may have more impact on males and post-menopausal females. Dependency on PEMT activity can be reduced by ensuring adequate dietary intake of choline (found in eggs, beef, chicken and fish).

PEMT encodes an enzyme which converts phosphatidylethanolamine to phosphatidylcholine by sequential methylation in the liver, a significant source of choline relative to dietary intake. Choline is a major source of methyl groups via its metabolite betaine - which catalyzes the methylation of homocysteine to form methionine. Oestrogen induces expression of the PEMT gene and allows premenopausal women to make more of their required choline endogenously compared to postmenopausal women, and men.

Polymorphisms in the PEMT gene alter the endogenous synthesis of choline which can impact the 'short cut' re-methylation of homocysteine to methionine by BHMT and may therefore increase susceptibility to high homocysteine levels particularly in combination with variants on MTHFR, MTR or MTRR genes.

TCN2 Transcobalamin II

SNV		Result	Description
rs1801198	C776G	CC	Neutral genotype - no impact on ability to absorb cobalamin (vitamin B12)

This gene encodes transcobalamin II (TCII), a member of the vitamin B12-binding protein family. This plasma protein binds cobalamin and mediates its transport from the intestine into blood cells.

Variants on the gene may reduce ability to absorb cobalamin (vitamin B12).

Transsulphuration Pathway

The transsulphuration pathway is a metabolic pathway involving the interconversion of cysteine and homocysteine, through the intermediate, cystathionine. This pathway generates the antioxidant glutathione, as well as the amino acids taurine and cysteine. The negative by-products: ammonia - which depletes BH4 leading to low dopamine and serotonin (see BH4 cycle); sulphites - which stimulate cortisol and produce brain fog; and glutamate - which leads to excitotoxicity, are also generated in this process.

Genetics

CBS regulates the enzyme that converts homocysteine to cystathionine and its downstream metabolites. The majority of variants on this gene cause up-regulation, making the enzyme work too fast, pulling homocysteine at a high rate from the methionine cycle, preventing it from being recycled via MTR and BHMT and compromising our ability to recycle homocysteine back to SAMe, the universal methyl donor. Homocysteine is then rapidly converted into taurine, cysteine and ammonia leading to high levels of sulphites and low levels of glutathione. Excess ammonia floods the urea cycle, weakening NOS activity (see urea cycle) and decreases BH4 which disrupts neurotransmitter metabolism (see BH4 cycle). The CBS C699T variant has the strongest effect, thought to increase CBS activity by up to 10 times.

Variants in BHMT aggravate and frequently co-exist with CBS variants.

CTH and GSS mediate the conversion of cysteine and glutathione respectively. Variants on either gene will lead to low glutathione synthesis.

Variants on SUOX will exacerbate high sulphite levels caused by up-regulated CBS due to slow degradation and detoxification of sulphites. This can result in sulphite sensitivity and neurological abnormalities.

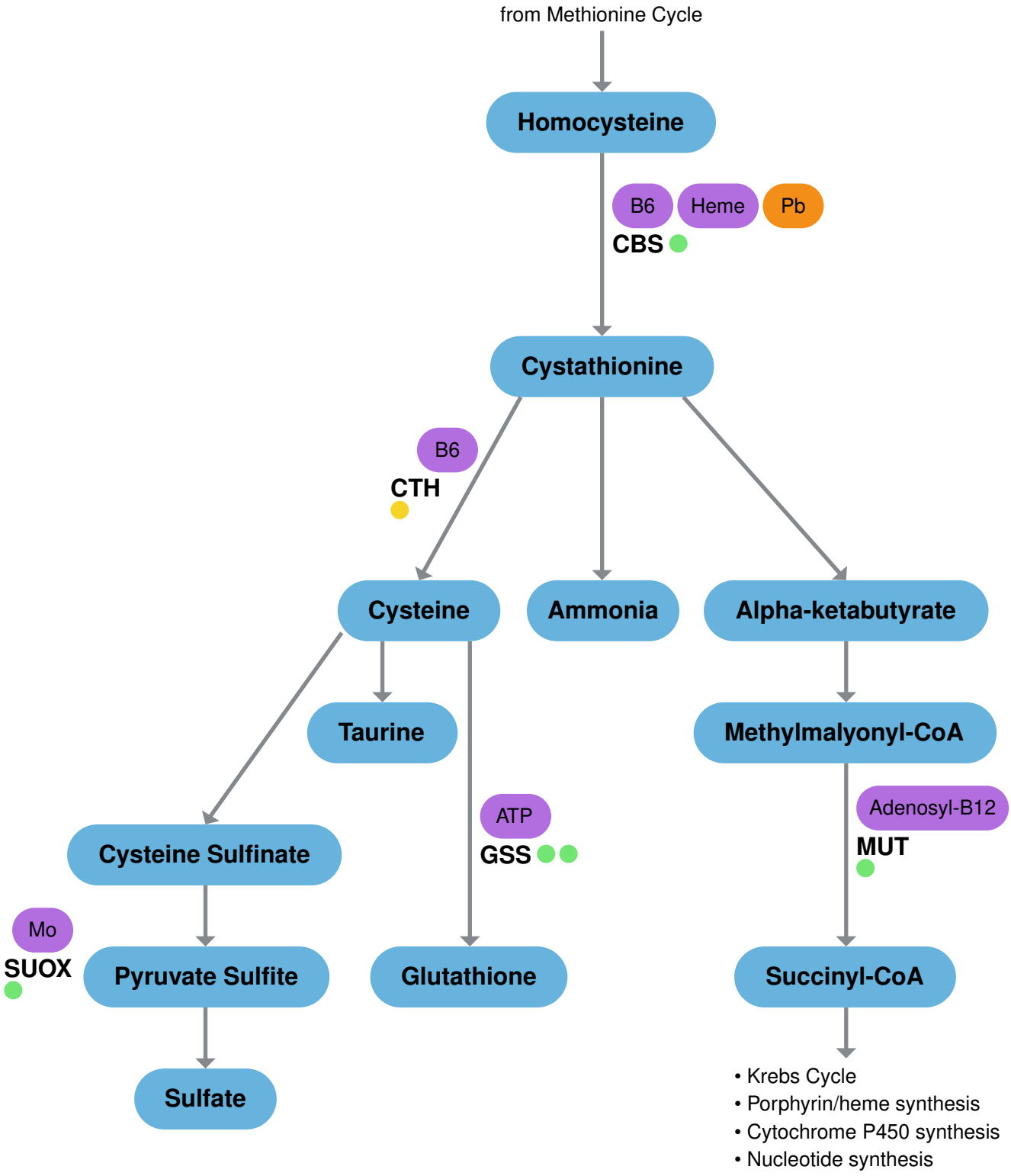
Further Investigation

A urine or plasma amino acid profile will identify homocysteine, taurine, glutathione, ammonia and sulphur-containing amino acids: cysteine and methionine. A urine dipstick test will identify sulphur in the urine.

Management and Lifestyle

Support BHMT to balance CBS up-regulation (TMG, phosphatidylserine, phosphatidylcholine and zinc). Neutralise ammonia (charcoal, probiotics to stop bacterial production of ammonia, limit animal protein). Limit sulphur-containing foods such as eggs, garlic, onions and broccoli, and supplements, e.g. cysteine, since sulphur sensitivity may occur (avoid completely if homozygous for SUOX). Supplementing B6 (P5P) will ensure proper functioning of the pathway and molybdenum will support SUOX activity.

Your Transsulphuration Pathway Results:



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CBS Cystathionine Beta-Synthase

SNV		Result	Description
rs1801181	C1080T	Uncallable	No result
rs234706	C699T	GG	Wild genotype - typically exhibits normal CBS enzyme activity

The CBS gene converts homocysteine (generated from methionine from the methionine cycle) to cystathionine, the first step in the transsulphuration pathway requiring vitamin B6 and heme as co-factors. The CBS enzyme acts as an "open gate" between homocysteine and the transsulphuration pathway, draining homocysteine, preventing it from being recycled into methionine, depleting B6 and B12, and preventing the synthesis of SAMe. Instead, homocysteine is diverted and converted into cysteine and taurine, a process which generates ammonia. High ammonia puts pressure on the urea cycle and causes low BH4, disrupting neurotransmitter metabolism. High cysteine creates toxic sulphites putting pressure on the SUOX gene. Glutathione synthesis is also negatively affected by the flooding of this pathway. CBS enzyme deficiency is less common but can occur and causes high homocysteine levels due to the blockage of the transsulphuration pathway.

The C699T (A) variant is thought to have the strongest up-regulating effect on the CBS enzyme. CBS should be assessed together with variants on MTHFR, MTR , BHMT and MUT.

CTH Cystathionine Gamma-Lyase

SNV		Result	Description
rs1021737	G1112T	TG	Slow CTH enzyme activity leading to slow conversion of cystathionine to cysteine. Studies show that this genotype in combination with variants on CBS could lead to high levels of homocysteine. Consider increasing vitamin B6

CTH encodes an enzyme that converts cystathionine into cysteine. This is the second step in the transsulphuration pathway requiring vitamin B6 as a co-factor. Glutathione synthesis in the liver is dependent upon the availability of cysteine and is important for healthy detoxification.

Variants on this gene cause compromised conversion of cystathionine to cysteine

GSS Glutathione Synthetase

SNV		Result	Description
rs1801310	59270A>G	GG	Wild genotype - associated with normal GSS enzyme activity (uncompromised glutathione synthesis). Low levels of the co-enzyme, ATP, will slow GSS enzyme activity regardless of genotype.
rs6088659	A5997G	CC	Wild genotype - associated with normal GSS enzyme activity (uncompromised glutathione synthesis). Low ATP, an important co-enzyme, will slow GSS enzyme activity regardless of genotype

GSS controls the second step of glutathione biosynthesis, the ATP-dependent conversion of gamma-L-glutamyl-Lcysteine to glutathione. Glutathione is important for a variety of biological functions including protection of cells from oxidative damage by free radicals, detoxification of xenobiotics, and membrane transport.

Variants on this gene may cause low synthesis of glutathione leading to possible deficiency.

MUT Methylmalonyl-CoA Mutase

SNV		Result	Description
i6060254	G1595A	CC	Wild genotype - associated with normal MUT enzyme activity, normal plasma B12 and homocysteine levels, and ability to convert methylmalyonyl-CoA to succinyl-CoA provided levels of adenosyl-B12 are adequate

MUT is a mitcochondrial enzyme that converts methylmalonyl Co-enzyme A to succinyl-Co-enzyme A requiring adenosylcobalamin (adenosyl-B12) as co-factor. Succinyl-CoA is an important enzyme in the Krebs cycle and is crucial for the synthesis of heme, cytochrome P450s and nucleotides.

Mutations in this gene may lead to various types of methylmalonic acuduria.

SUOX Sulfite Oxidase

SNV		Result	Description
rs705703	C5444T	CC	Wild genotype - typically indicates normal SUOX enzyme activity leading to normal conversion of sulphites to sulphates. Molybdenum insufficiency will lead to reduced enzyme function regardless of genotype

SUOX catalyses the oxidation of sulphite to sulphate, the final molybdenum-dependent reaction in the oxidative degradation of the sulphur amino acids cysteine and methionine. This gene product helps to detoxify sulphites in the body.

Variants on SUOX may result in sulphite sensitivity and neurological abnormalities, and should be regarded in combination with up-regulated CBS. Sulphites are generated as a natural byproduct of the methylation cycle as well as ingested from foods we eat and give off the gas sulphur dioxide, which can cause irritation in the lungs, severe asthma attack in those who suffer from asthma; nausea, hives and, in rare cases, more severe allergic reactions.

BH4 Cycle / Neurotransmitter Metabolism

Tetrahydrobiopterin, or BH4, is a naturally occurring chemical compound requiring active folate (5-MTHF) and S-adenosylmethionine (SAMe) to help convert several amino acids such as phenylalanine, tyrosine and tryptophan into the neurotransmitters norepinephrine, dopamine, serotonin, melatonin and thyroid hormones. Without the participation of 5-MTHF in this process, SAMe and neurotransmitter levels decrease in the cerebrospinal fluid, contributing to depression.

BH4 is crucial for neutralising ammonia and for generating nitric oxide from arginine in the urea cycle (without BH4, the free radical superoxide, is created instead). BH4 also protects nerve cells from heavy metal toxicity and glutathione depletion.

Low levels of crucial neurotransmitters can cause mood imbalances, poor memory and concentration, sleep disturbances and aggressive behaviour.

Genetics

BH4 deficiency can occur as a result of variants on QDPR, the gene responsible for converting BH2 to BH4 with the help of active folate from the folate cycle. Variants on CBS, BHMT and MTHFR A1298C can also cause BH4 deficiency due to high ammonia and low active folate.

Variants on COMT, MAOA & MAOB result in poor breakdown of neurotransmitters and may lead to imbalances causing mood disorders. SAMe and SAH compete for the SAMe binding site on the COMT molecule (think of the SAMe binding site as the 'on-off' switch for COMT). A build up of SAH will thus reduce COMT activity.

Variants on VDR TaqI, BsmI and ApaI lead to lower vitamin D levels causing low dopamine production. COMT variants can be beneficial as there will be less circulating dopamine in need of being broken down. Those with VDR variants but without COMT variants will have low dopamine levels and increased need for methyl donors and dopamine precursors. Conversely those with COMT variants but without VDR variants will have the highest levels of dopamine and low need for and tolerance of methyl groups and dopamine precursors.

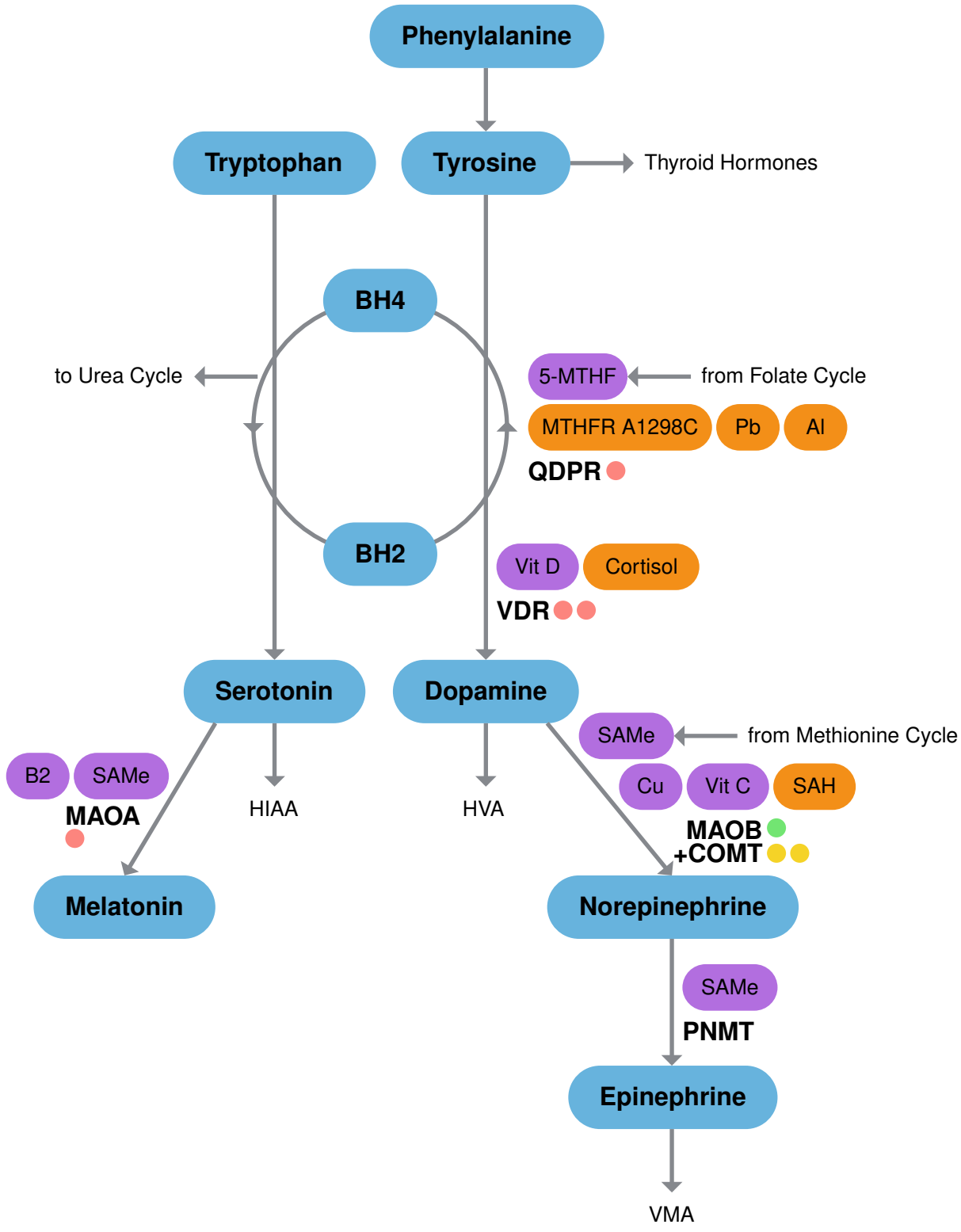
Further Investigation

Investigate neurotransmitter balance and SAH: SAMe ratio (since SAH inhibits COMT).

Management and Lifestyle

Focus on removing any heavy metals (especially mercury, lead and aluminium). Consider supplementing BH4 and 5-MTHF, however, avoid supplementing methyl donors if there are variants on VDR and COMT as these will not be well tolerated and may lead to irritability and mood disorders. Avoid foods rich in tyrosine (dopamine precursor) as it competes with tryptophan (serotonin precursor) for uptake and may cause a high dopamine / low serotonin imbalance. Instead, emphasise foods rich in tryptophan. Individuals with COMT variants should avoid coffee/caffeine as it releases catecholamines, leading to adrenalin overload.

Your BH4 Cycle / Neurotransmitter Metabolism Results:



Key:

- Co-factor
- Inhibitor
- Protective - neutral
- Neutral - negative
- Negative

COMT Catechol-O-Methyltransferase

SNV		Result	Description
rs4633	H62H	TC	Reduced COMT activity causing slower breakdown of catecholamines. This is mostly a negative trait, however, in combination with variants in VDR (low activity) this can be positive since dopamine synthesis and break down is slow leading to normal circulating levels. Those with normal (higher) VDR activity will have higher dopamine levels and low need for and tolerance of methyl donors and dopamine precursors, and the greatest susceptibility to mood swings. Low SAMe/ high SAH will further reduce COMT activity.
rs4680	V158M	AG	Reduced COMT activity causing slower breakdown of catecholamines. This is mostly a negative trait, however, in combination with variants in VDR (low activity) this can be positive since dopamine synthesis and break down is slow leading to normal circulating levels. Those with normal (higher) VDR activity will have higher dopamine levels and low need for and tolerance of methyl donors and dopamine precursors, and the greatest susceptibility to mood swings. Low SAMe/ high SAH will further reduce COMT activity

COMT is responsible for breaking down and inactivating the catecholamines: dopamine, adrenalin, and noradrenalin by transferring a methyl group from SAMe to the catechol molecule, preparing it for excretion. COMT is also involved in oestrogen metabolism, converting active oestrogen to inactive/ less active oestrogen. SAMe and SAH compete for the binding site on the COMT molecule, therefore a build up of SAH will reduce COMT activity.

Variants in COMT may lead to reduced enzyme function and excess methyl groups causing irritability, heightened stress response, hyperactivity, abnormal behaviour, heightened pain sensitivity and reduced detoxification of oestrogen.

MAOA Monoamine Oxidase A

SNV		Result	Description
rs6323	R297R	GG	Wild genotype - typically exhibits high MAOA enzyme activity leading to lower levels of neurotransmitters in the brain and associated with inward anger, depression, risk aversion and sleep disturbances (one of the worrier genotypes). Curcumin and quercetin have been shown to reduce MAOA enzyme activity and may be beneficial for this genotype.

MAOA is a member of the monoamine oxidase gene family whose enzymes catalyse the deactivation of monoaminergic neurotransmitters: serotonin, melatonin, noradrenalin and adrenalin. It also metabolises dopamine, tyramine and tryptamine, equally with MAOB. MAOA is located on the X chromosome, so males only carry one allele, inherited from their mother. We report results for males as homozygous as they will not inherit a 'balancing' allele.

MAOA is nicknamed the “warrior gene” because variants are associated with anger and aggression due to slower neurotransmitter breakdown - effects which may be amplified if COMT variants are also present. Conversely, a combination of wild alleles has been labelled the "worrier" genotype, associated with low mood due to rapid breakdown of neurotransmitters.

MAOB Monoamine Oxidase B

SNV		Result	Description
rs1799836	A118723G	TT	Wild genotype - typically exhibits normal MAOB enzyme activity, efficient breakdown of substrates including neurotransmitters and reduced susceptibility to negative moods

MAOB is a member of the monoamine oxidase gene family whose enzymes catalyse the deactivation of monoaminergic neurotransmitters. It is the main catalyst for the breakdown of phenethylamine (PEA), benzylamine and histamine. It also metabolises dopamine, tyramine and tryptamine, equally with MAOA. MAOB is located on the X chromosome, so males only carry one allele, inherited from their mother. We report results for males as homozygous as they will not inherit a 'balancing' allele.

Variants on the MAOB gene are associated with reduced enzyme activity and slower breakdown of neurotransmitters and some pharmaceuticals.

QDPR Quinoid Dihydropteridine Reductase

SNV		Result	Description
rs1031326	A690G	TT	Reduced recycling of BH4 from BH2 resulting in decreased synthesis of neurotransmitters serotonin, melatonin, dopamine, noradrenaline and adrenaline, and decreased nitric oxide production affecting the urea cycle. Low 5-MTHF (particularly variants on MTHFR A1298C) will compound reduced QDPR enzyme activity

QDPR, also known as DHPR, catalyses the regeneration of tetrahydrobiopterin (BH4) from quinonoid dihydrobiopterin (BH2), a reaction requiring active folate (5-MTHF). BH4 is an important co-factor for the biosynthesis of the neurotransmitters serotonin, melatonin, dopamine, noradrenaline, adrenaline and nitric oxide production.

Variants may result in BH4 deficiency. CBS up-regulation creates excess ammonia further depleting BH4.

VDR Vitamin D (1,25- dihydroxyvitamin D3) Receptor

SNV		Result	Description
rs1544410	BsmI	TT	Reduced dopamine synthesis. This is generally a negative trait, especially in combination with normal (high) COMT activity due to very low levels of circulating dopamine increasing need for dopamine precursors and methyl donors. However, for those with variants on COMT, this is a positive trait since dopamine will be broken down more slowly leading to normal circulating levels
rs731236	TaqI	GG	Reduced dopamine synthesis. This is generally a negative trait, especially in combination with normal (high) COMT activity due to very low levels of circulating dopamine increasing need for dopamine precursors and methyl donors. However, for those with variants on COMT, this is a positive trait since dopamine will be broken down more slowly leading to normal circulating levels

VDR encodes the nuclear hormone receptor for vitamin D3 (the active form of vitamin D in the body). This receptor belongs to the family of trans-acting transcriptional regulatory factors and shows sequence similarity to the steroid and thyroid hormone receptors and mediates an increase in dopamine production in response to Vitamin D requiring less methyl groups. Vitamin D3 is also crucial for bone formation, modulation of the immune system, and cell proliferation and differentiation.

Variants in VDR lead to lower vitamin D levels causing low dopamine production. This is good for those with COMT variants since there will be less circulating dopamine in need of breaking down. Individuals with variants on COMT but normal VDR activity will have higher dopamine levels and low need for and tolerance of methyl donors and dopamine precursors, and have the greatest susceptibility to mood swings.

Urea Cycle

The urea cycle (also known as the ornithine cycle) is a cycle of biochemical reactions occurring primarily in the liver, and to a lesser extent in the kidney whereby ammonia is converted to less toxic urea.

In the presence of BH4, Nitric Oxide Synthase (NOS) converts arginine to nitric oxide, a reactive free radical which acts as a biological mediator of the cardio vascular system by helping to resist plaque formation, vasospasm and abnormal clotting. In the brain and peripheral nervous system nitric oxide displays many properties of a neurotransmitter, and has been implicated in neurotoxicity associated with stroke and neurodegenerative diseases and neural regulation of smooth muscle, including peristalsis and penile erection. Nitric oxide also has antimicrobial and anti-tumoral properties.

NOS is also important for the detoxification of ammonia (from the transsulphuration pathway) - a process that uses up BH4 which may compromise serotonin and dopamine production. If there is insufficient BH4 arginine is converted into the damaging free radicals superoxide or peroxynitrate instead of being converted to nitric oxide.

Genetics

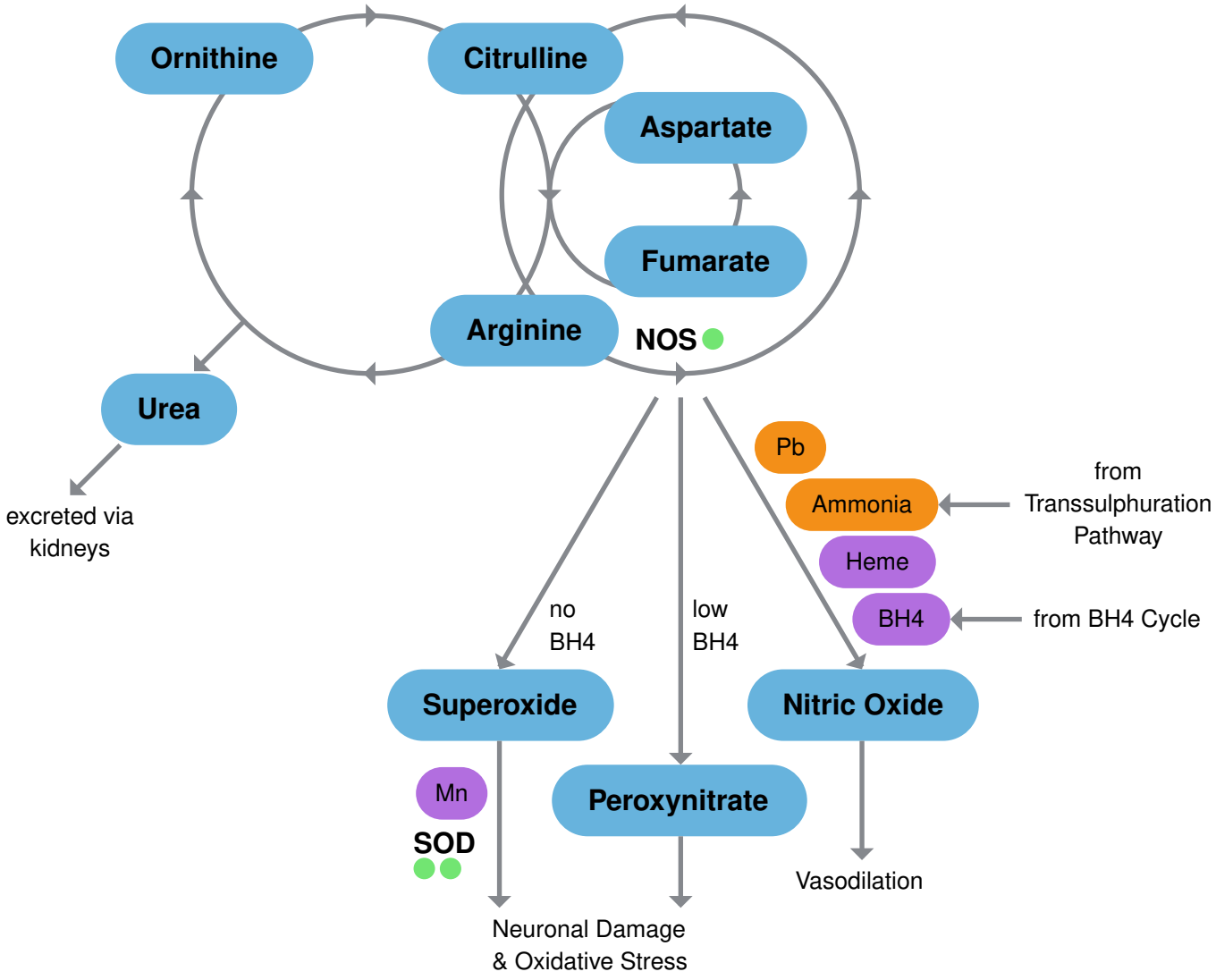
The NOS D298E and C19635A variants result in dysfunctional NOS enzymes which are less effective in breaking down ammonia and generating nitric oxide. This creates higher levels of the free radicals, superoxide and peroxynitrate.

Variants on SOD2 result in low superoxide dismutase activity (neutralisation of mitochondrial superoxide to hydrogen peroxide) and therefore susceptibility to oxidative stress.

Management and Lifestyle

Focus on decreasing the ammonia burden and increasing antioxidant intake to counteract free radical damage. BH4 supplementation may improve the generation of nitric oxide. Consider supplementing vitamin C or SOD to support break down of superoxide and 5-MTHF to address peroxynitrate.

Your Urea Cycle Results:



Key:

- Co-factor
- Inhibitor
- Protective - neutral
- Neutral - negative
- Negative

NOS3 Nitric Oxide Synthase 3

SNV		Result	Description
rs1799983	D298E	GG	Wild genotype - typically associated with normal NOS enzyme activity and normal production of nitric oxide. Low levels of BH4 will affect NOS enzyme activity regardless of genotype. Ensure adequate levels of 5-MTHF to support natural BH4 production
rs3918188	C19635A		No result

NOS is responsible for synthesising nitric oxide (NO), an important atheroprotective mediator that helps control endothelium-dependent vasodilatation, from L-arginine with the help of BH4. Without adequate BH4, NOS generates the free radicals peroxynitrate and superoxide instead of NO, compromising cardiovascular function. NOS also assists in the detoxification of ammonia by converting it into less toxic urea.

Variants on NOS cause low enzymatic activity. Increased CBS enzyme activity and variants on MTHFR A1298C will have an additive effect due to likelihood of low BH4 levels and excess ammonia.

SOD2 Superoxide Dismutase 2, Mitochondrial

SNV		Result	Description
rs2758331	G816T	CC	Wild genotype - associated with normal SOD enzyme activity and ability to neutralise superoxide. Low manganese levels will reduce SOD activity regardless of genotype, ensure adequate levels to support SOD activity
rs4880	A16V	AA	Wild genotype - associated with normal SOD enzyme activity and ability to neutralise superoxide. Low manganese levels will reduce SOD activity regardless of genotype, ensure adequate levels to support SOD activity

SOD2 is a member of the iron/manganese superoxide dismutase family and encodes a mitochondrial protein that is one of the body's major antioxidant defense system against oxidative damage.

Variants decrease superoxide dismutase activity and therefore the ability to break down the free radical, superoxide, potentially resulting in predisposition to oxidative stress. Ensure adequate levels of the co-factor manganese and increase antioxidants.

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BHMT Betaine-homocysteine S-methyltransferase

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CBS Cystathionine Beta-Synthase

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CTH Cystathionine Gamma-Lyase

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DHFR Dihydrofolate Reductase

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GSS Glutathione Synthetase

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MTHFD1 Methylenetetrahydrofolate Dehydrogenase 1

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TCN2 Transcobalamin II

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TYMS Thymidylate Synthetase

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VDR Vitamin D (1,25- dihydroxyvitamin D3) Receptor

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