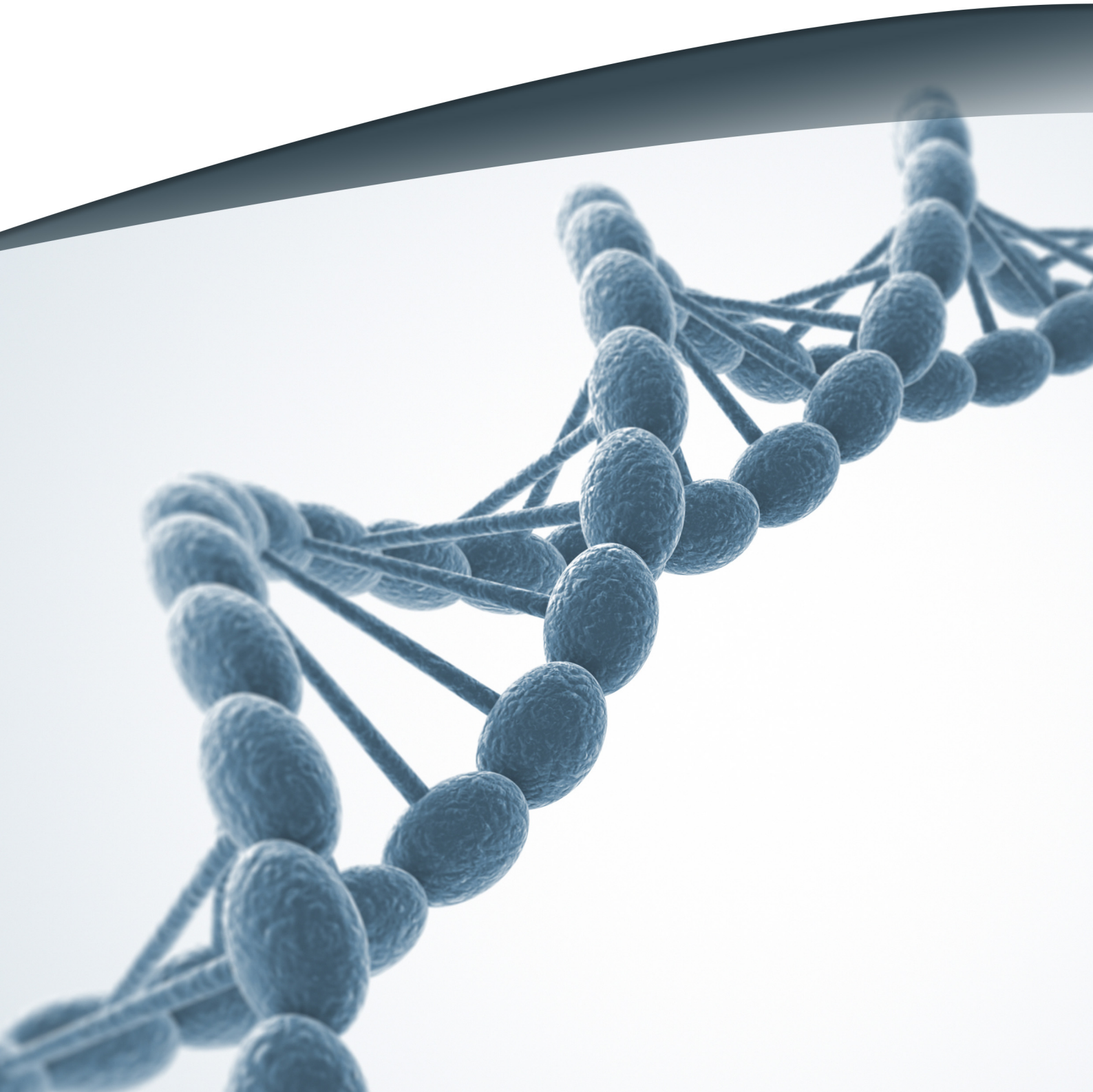


# Methylation Report



# Methylation

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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 essential bodily functions, including: detoxification, immune function, DNA integrity, regulation of gene expression, energy production, neurotransmitter balance, inflammation control and telomere protection.

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 B vitamins - B2, B3, 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 such as fertility issues, fatigue, cardiovascular disorders, neurodegeneration, allergies, anxiety and cancer.

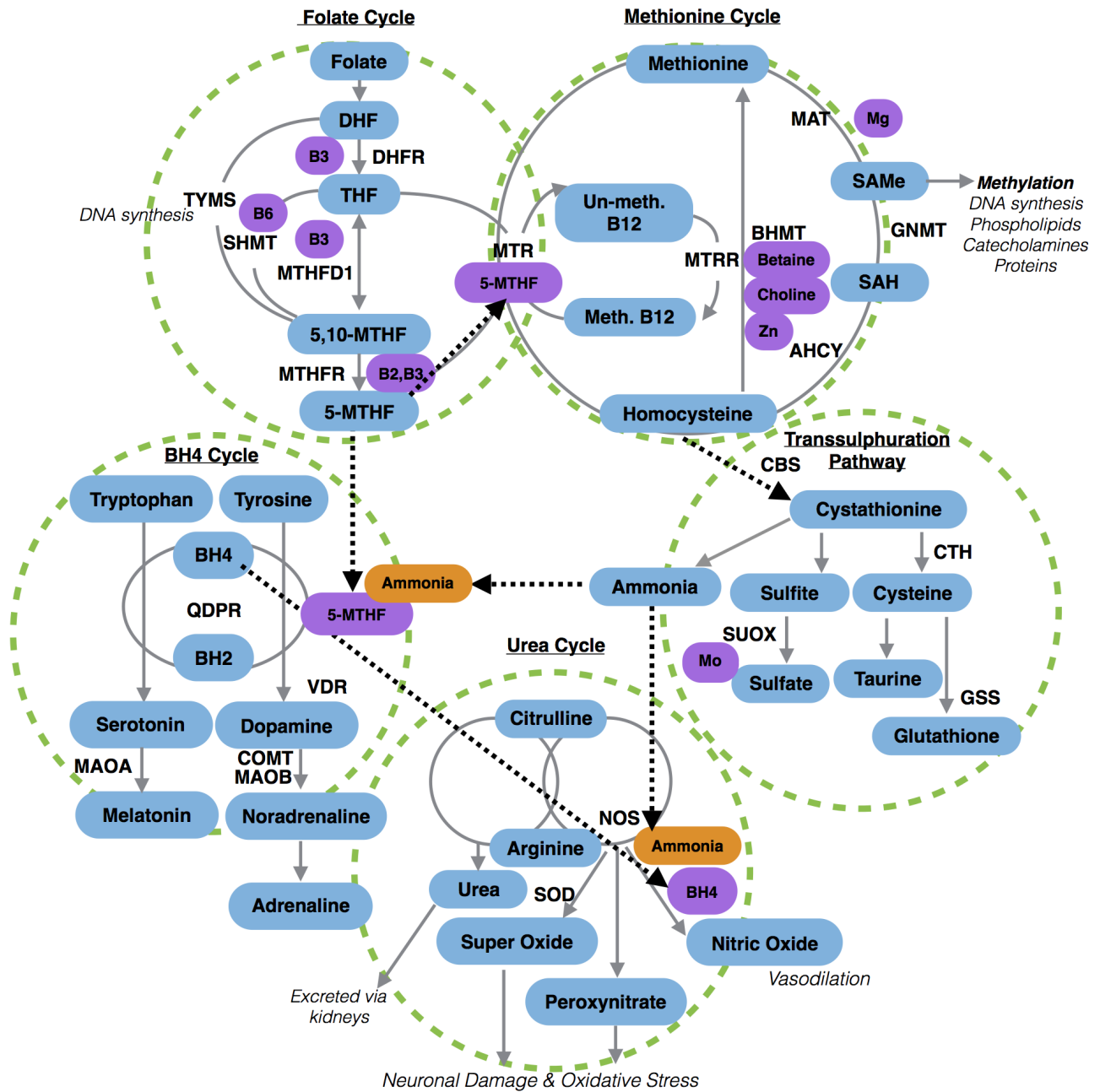
## **The role of genes in Methylation**

The purpose of analysing genetic variants (or single nucleotide polymorphisms (SNPs)) in the context of the methylation pathways 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 genetic code cannot be changed, the rate and manner of gene expression, protein synthesis, and function can be supported.

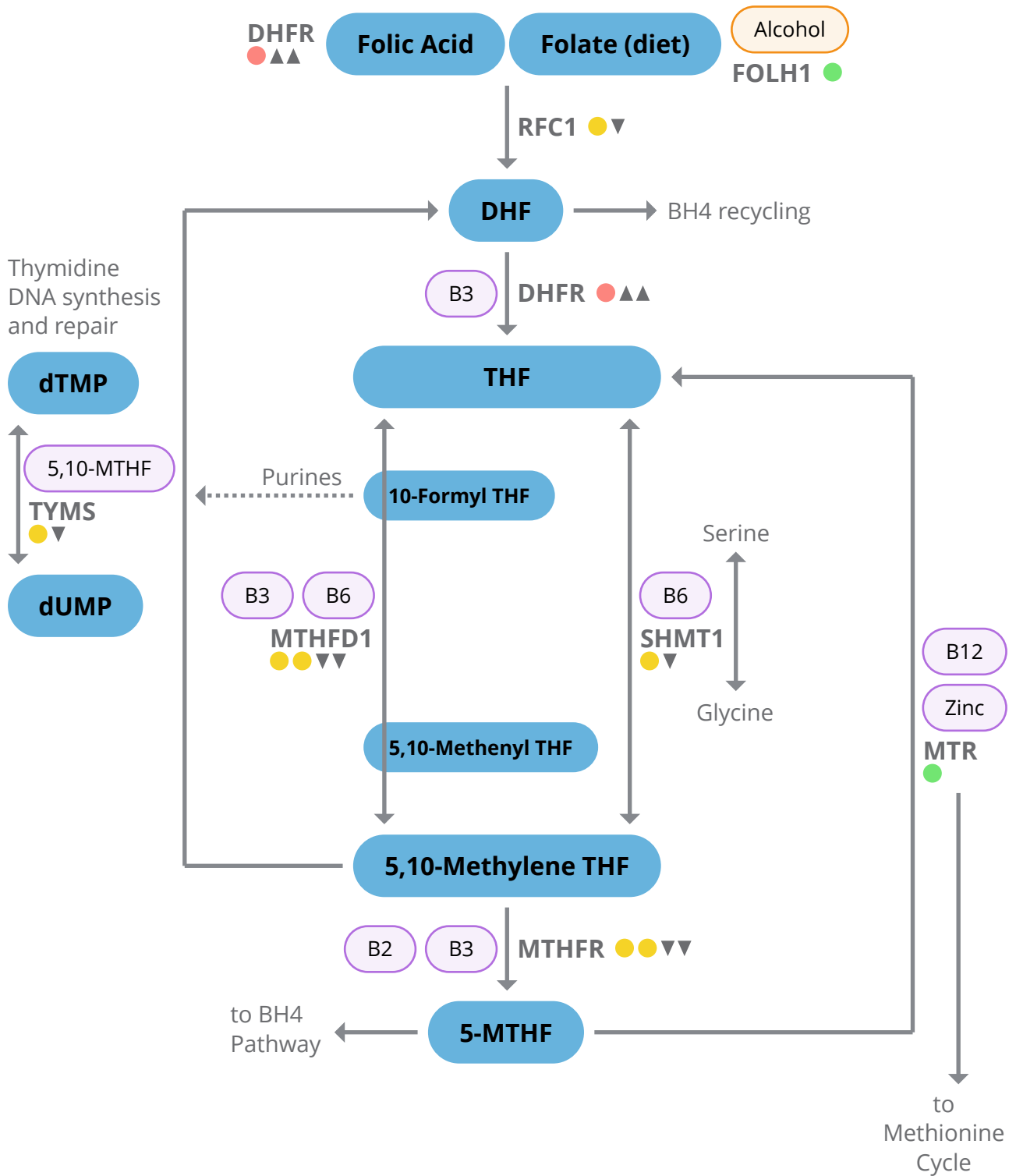
This report provides a personalised genotype analysis organised by the following methylation sub-cycles:

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

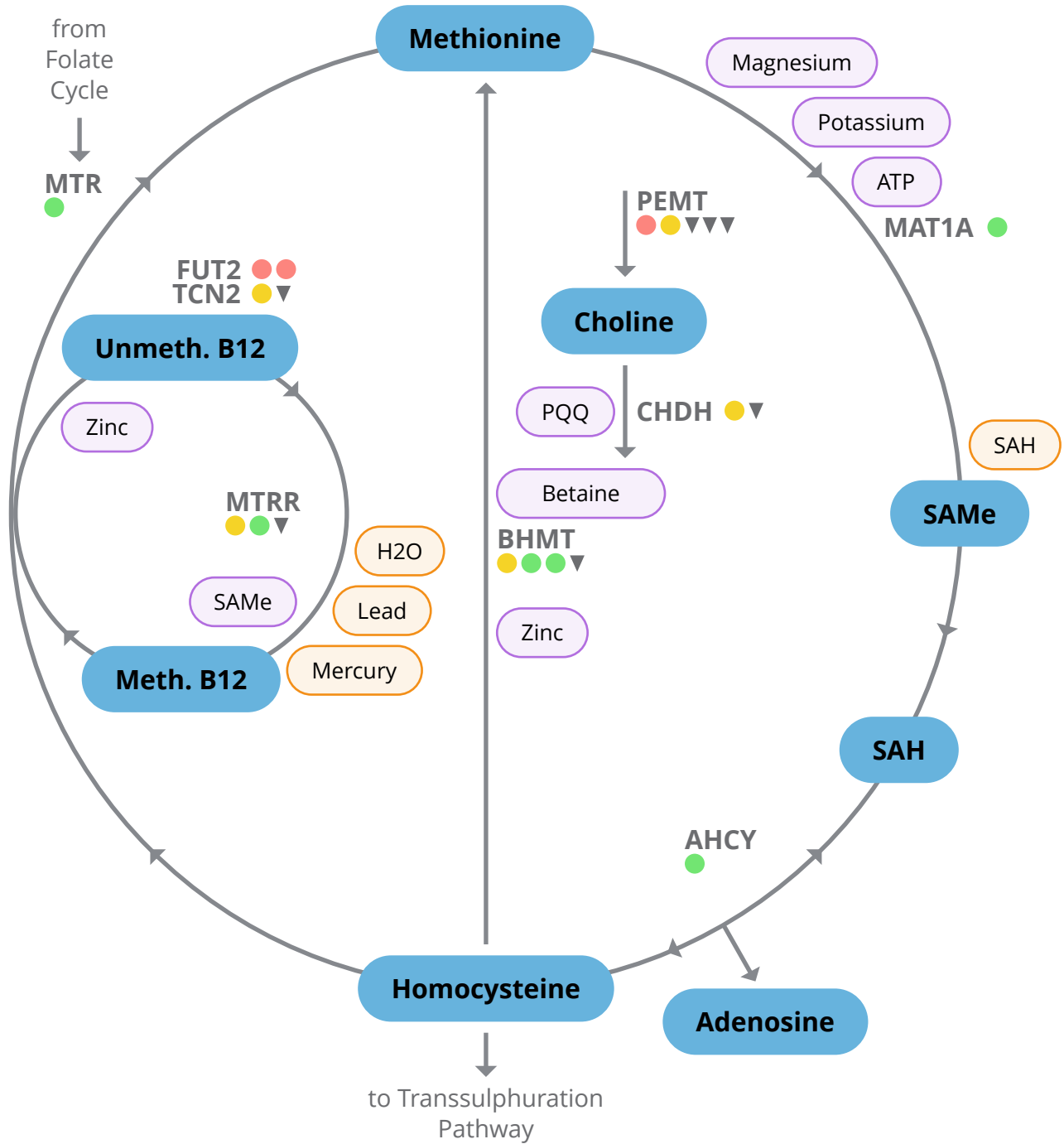
Overview



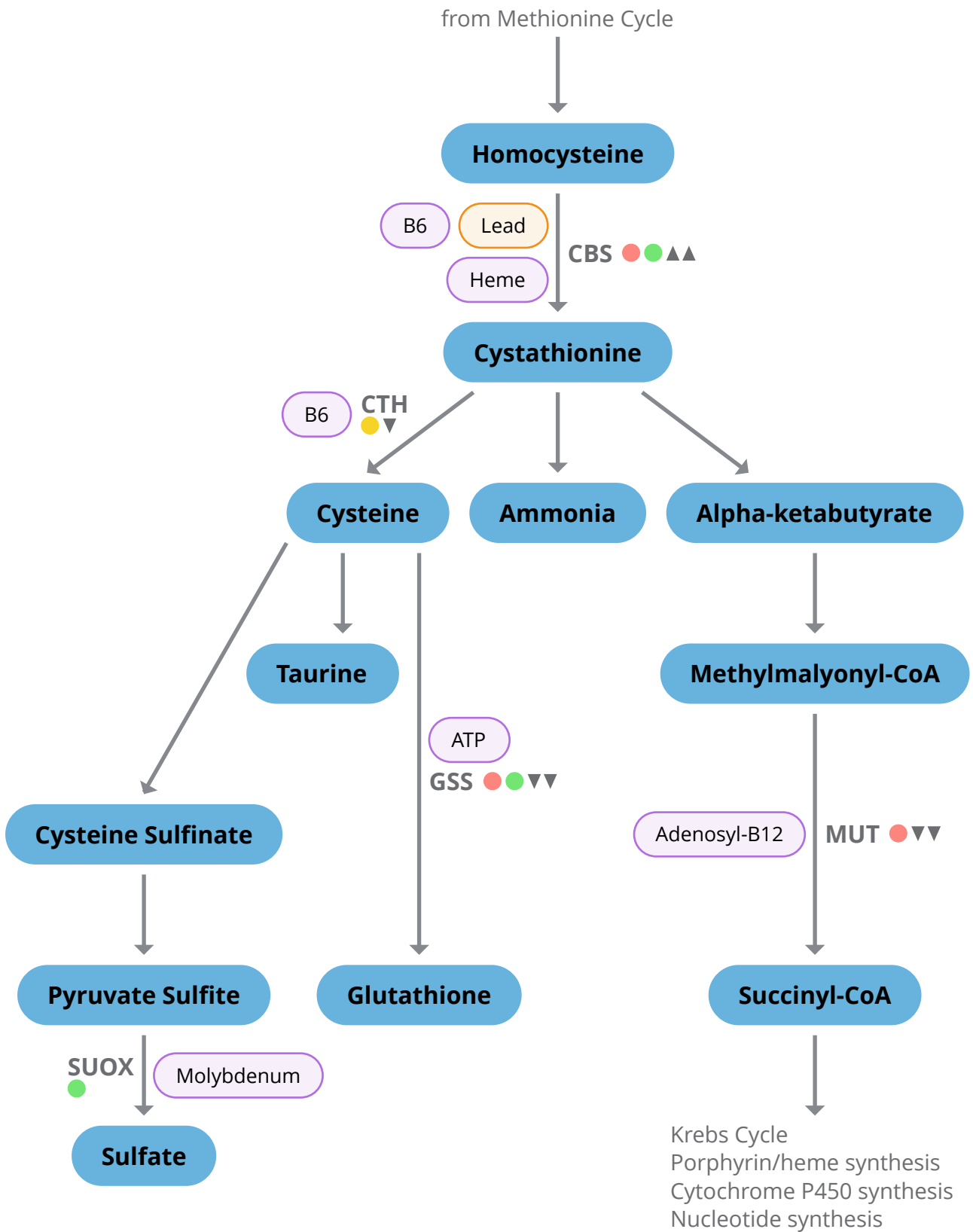
### Folate Cycle



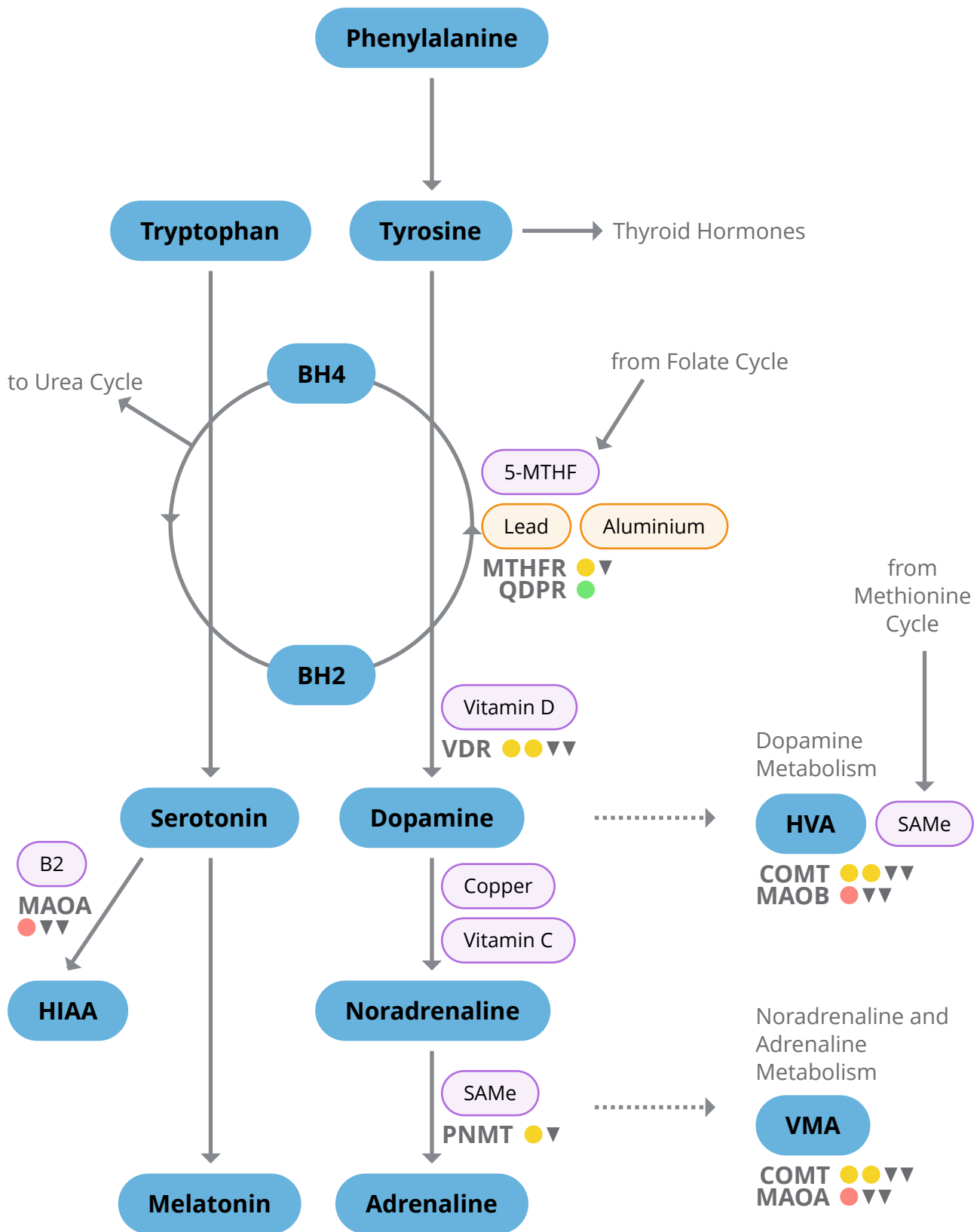
## Methionine Cycle



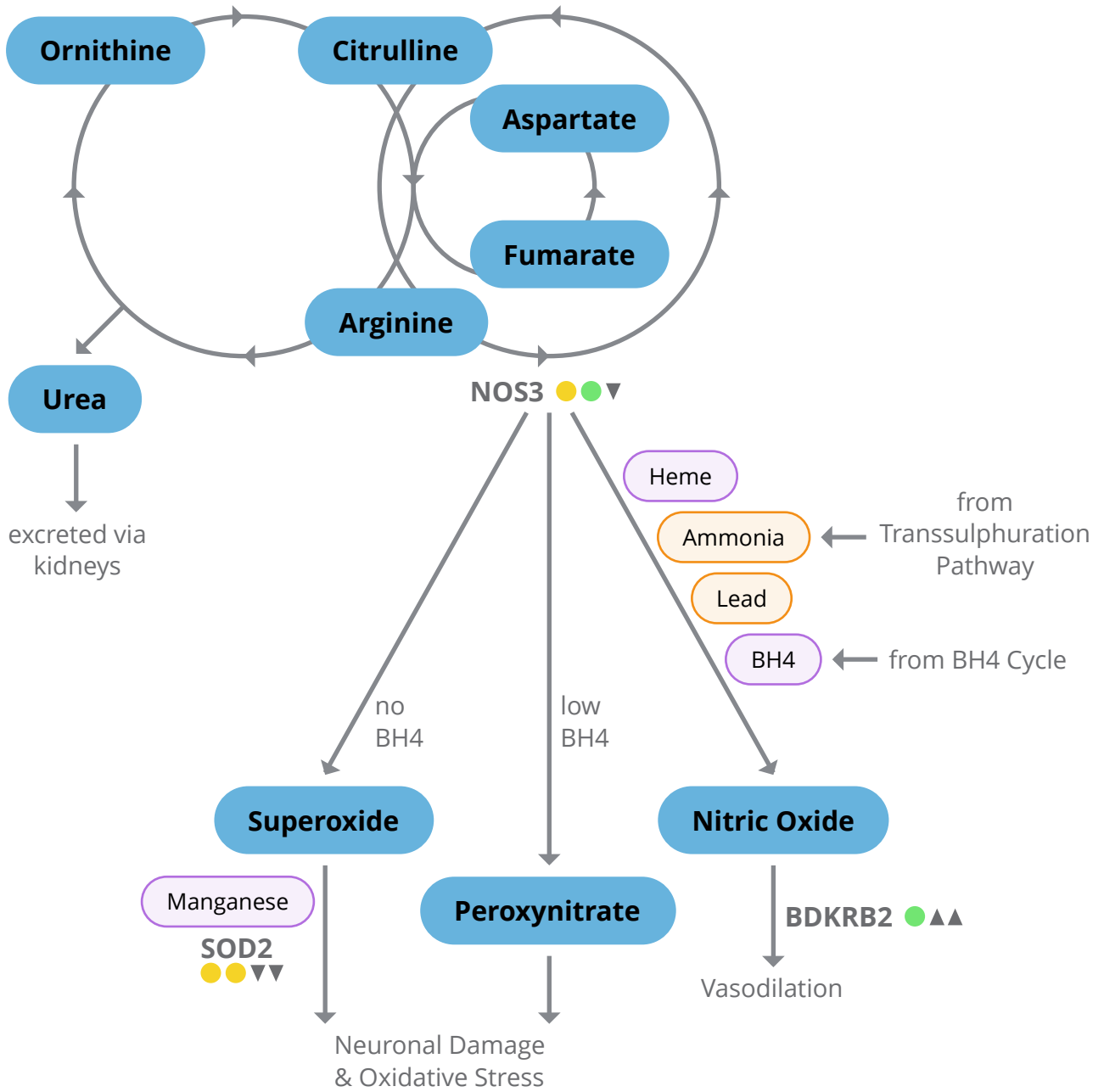
## Transsulphuration Pathway



BH4 Cycle / Neurotransmitter Metabolism



## Urea Cycle





## Detailed Results for Folate Cycle

<b>DHFR</b> rs70991108	DD▲▲	<p>Deletion genotype - a 19 base point sequence of the DHFR gene is deleted in both copies of the gene. Associated with up to 4.8x 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 4.6x) hepatic toxicity from methotrexate treatment. High intake of folic acid (synthetic folate has been linked to increased DHFR activity for this genotype.</p> <p>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).</p>
<b>FOLH1</b> rs202700	CC	<p>Normal intestinal absorption of dietary folate.</p> <p>Mono glutamate forms of folate may further improve folate status. Avoid alcohol to improve gut health.</p>
<b>MTHFD1</b> rs1076991	CT ▼	<p>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 to increased risk of neural tube defects and other developmental disorder.</p> <p>Possible 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.</p>
<b>MTHFD1</b> rs2236225	AG ▼	<p>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 to increased risk of neural tube defects.</p> <p>Possible increased 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 related infertility.</p>

## Detailed Results for Folate Cycle (continued)

<b>MTHFR</b> rs1801131	GT ▼	<p>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.</p> <p>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).</p>
<b>MTHFR</b> rs1801133	AG ▼	<p>Up to 40% reduction in gene function which may impact supply of methyl-folate (5-MTHF) needed for THF and homocysteine regeneration. Associated with a broad range of potential health impacts, although many people do not experience any symptoms. It is important to examine this variant in the context of the methylation cycle as a whole. Consider other genetic variants and environmental conditions that may affect 5-MTHF levels.</p> <p>Methylation can be supported through a diet rich in folate and other B vitamins (B2, B3, B12) and co-factors including magnesium and zinc.</p>
<b>MTR</b> rs1805087	AA	<p>Neutral genotype. No impact on recycling of methyl-folate (5-MTHF) to THF.</p> <p>MTR activity can be supported by ensuring adequate B12.</p>
<b>RFC1</b> rs1051266	CT ▼	<p>Reduced ability to take up, retain, and metabolise folate which could result in raised homocysteine levels.</p> <p>Associated with reduced transport of and poorer response to methotrexate treatment.</p> <p>Ensure folate intake and consider essential fatty acids for cell membrane health.</p>
<b>SHMT1</b> rs1979277	AG ▼	<p>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.</p> <p>This genotype may be supported by increasing intake of food folate/ reduced folate.</p>

## Detailed Results for Folate Cycle (continued)

**TYMS**  
rs2790

GA ▼








Potential risk of disruption to DNA synthesis or repair. Increased risk of some cancers including gastric cancer and multiple myeloma and poor response to chemotherapy.

Ensure more folate intake, and consider B2 for DNA stability.

## Detailed Results for Methionine Cycle

<b>AHCY</b> rs121918608	TT	<p>Neutral genotype - no impact on conversion of SAH to homocysteine.</p>
<b>BHMT</b> rs3733890	AG ▼	<p>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).</p> <p>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.</p>
<b>BHMT</b> rs567754	CC	<p>No impact on BHMT and 'short cut' homocysteine to methionine conversion, or on homocysteine levels.</p> <p>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.</p>
<b>BHMT</b> rs651852	CC	<p>No impact on BHMT and 'short cut' homocysteine to methionine conversion, or on homocysteine levels.</p> <p>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.</p>
<b>CHDH</b> rs12676	CA ▼	<p>Slower oxidation of choline to betaine. Associated with an increased risk of choline deficiency among pre-menopausal women, and associated with increased risk of organ dysfunction (x20 when premenopausal women with low-choline diets). Associated with lower quality of sperm in men (increased tortuosity) which can lead to fertility issues.</p> <p>Ensure adequate intake of choline (found in eggs &amp; meat). Pyrroloquinoline quinone (PQQ), also called methoxatin, is a redox cofactor and antioxidant. It is found in soil and foods such as kiwifruit.</p>

## Detailed Results for Methionine Cycle (continued)

<b>FUT2</b> rs1047781	AA	 <p>Secretor genotype (Asian populations) - susceptibility to H. pylori infection and gastritis linked to reduced B12 absorption.</p> <p>Support GI system.</p>
<b>FUT2</b> rs601338	AG	 <p>Secretor genotype (non-Asian populations) - susceptibility to H. pylori infection and gastritis linked to reduced B12 absorption.</p> <p>Support GI system.</p>
<b>MAT1A</b> rs1985908	AA	 <p>Normal MAT activity and conversion of methionine to SAME.</p> <p>MAT activity can be supported by ensuring adequate intake of co-factors potassium and magnesium.</p>
<b>MTRR</b> rs162036	AA	 <p>Neutral genotype - does not impact Vitamin B12 or homocysteine levels.</p>
<b>MTRR</b> rs1801394	GA ▼	 <p>Reduced ability to re-methylate vitamin B12 which is needed for MTR conversion of homocysteine and can contribute to hyperhomocysteinemia.</p> <p>Supplementing methylated B12 may be beneficial to support methylation.</p>
<b>MTR</b> rs1805087	AA	 <p>Neutral genotype - no impact on MTR activity or B12 levels.</p> <p>Ensure adequate intake of B12.</p>
<b>PEMT</b> rs12325817	GC ▼	 <p>Potential for reduced choline synthesis, which can impact betaine levels needed to support the BHMT 'short cut' conversion of homocysteine to methionine, especially in premenopausal women.</p> <p>Dependency on PEMT activity can be reduced by ensuring adequate dietary intake of choline (found in eggs, beef, chicken and fish).</p>

## Detailed Results for Methionine Cycle (continued)

**PEMT**  
rs7946

TT ▼▼

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).

**TCN2**  
rs1801198

GC ▼

The G allele decreases the activity of the TCN2 gene and the cellular and plasma concentration of transcobalamin, the carrier protein which delivers vitamin B12 to cells. The variant has been associated with developmental disorders and pregnancy loss. It does not appear to impact homocysteine levels.

Support GI system/ heal the gut & consider B12.

## Detailed Results for Transsulphuration Pathway

<b>CBS</b> rs1801181	GG	 <p>Wild genotype - typically exhibits normal CBS enzyme activity, normal homocysteine (hcy) conversion back to methionine.</p> <p>Ensure adequate intake of B6, B12 &amp; SAMe.</p>
<b>CBS</b> rs234706	AA ▲▲▲	 <p>Thought to be the strongest indicator of increased (up to 10x) CBS activity. This may prevent homocysteine (hcy) from being recycled back into methionine, decreasing synthesis of the vital methyl donor - SAMe, and depleting vitamins B6 and B12. Increased CBS activity may also lead to low glutathione production and generate high levels of ammonia and sulphites.</p> <p>Supporting the recycling of hcy to methionine via BHMT "short-cut" pathway may be beneficial. Limit sulphur-containing foods and supplements if sulphur levels are high. High ammonia levels can be reduced by limiting animal protein in the diet, taking probiotics which stop bacterial production of ammonia, and supplementing activated charcoal.</p>
<b>CTH</b> rs1021737	TG ▼	 <p>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.</p> <p>Consider increasing vitamin B6.</p>
<b>GSS</b> rs1801310	AA ▼▼	 <p>Low GSS enzyme activity - may lead to slow glutathione synthesis.</p> <p>This enzyme requires ATP as a co-enzyme to function optimally.</p>
<b>GSS</b> rs6088659	CC	 <p>Wild genotype - associated with normal GSS enzyme activity (uncompromised glutathione synthesis).</p> <p>Low ATP, an important co-enzyme, will slow GSS enzyme activity regardless of genotype</p>
<b>MUT</b> rs1141321	TT ▼▼	 <p>Associated with low circulating B12 levels and elevated homocysteine. Possible reduced ability to convert methylmalonyl-CoA to succinyl-CoA which may affect the Krebs cycle.</p> <p>Ensure adequate adenosyl-B12 to support enzyme function.</p>

## Detailed Results for Transsulphuration Pathway (continued)

**SUOX**  
rs705703

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.








## Detailed Results for BH4 Cycle

<b>COMT</b> rs4633	TC ▼	<p>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.</p> <p>Low SAME/ high SAH will further reduce COMT activity.</p>
<b>COMT</b> rs4680	AG ▼	<p>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.</p> <p>Low SAME/ high SAH will further reduce COMT activity</p>
<b>MAOA</b> rs6323	TT ▼▼	<p>Low MAOA enzyme activity and slower breakdown of monoamine neurotransmitters which can contribute to higher levels. This is sometimes known as the 'warrior' genotype.</p> <p>If symptoms such as anxiety and outward anger are experienced vitamin B2, magnesium and zinc may increase MAOA activity.</p>
<b>MAOB</b> rs1799836	CC ▼▼	<p>Reduced MAOB enzyme activity. Increased susceptibility to negative moods due to inefficient breakdown of neurotransmitters.</p> <p>Vitamin B2, magnesium and zinc may help to increase MAOB enzyme activity.</p>
<b>MTHFR</b> rs1801131	GT ▼	<p>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.</p> <p>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).</p>

## Detailed Results for BH4 Cycle (continued)

<b>PNMT</b> rs876493	AG ▼	 <p>Reduced PNMT activity and slower conversion of noradrenaline to adrenaline, which has been linked to hypertension.</p> <p>As SAME is a cofactor for PNMT, ensure sufficient B vitamins, zinc and magnesium to support SAME synthesis.</p>
<b>QDPR</b> rs1031326	CC	 <p>Wild genotype - typically exhibits normal recycling of BH4 from BH2.</p> <p>Low 5-MTHF will reduce the recycling of BH4 regardless of genotype.</p>
<b>VDR</b> rs1544410	TC ▼	 <p>Reduced dopamine synthesis. This is generally a negative trait, especially in combination with normal (high) COMT activity due to low levels of circulating dopamine increasing need for dopamine precursors and methyl donors.</p> <p>However, for those with variants on COMT, this is positive since dopamine will be broken down more slowly leading to normal circulating levels.</p>
<b>VDR</b> rs731236	GA ▼	 <p>Reduced dopamine synthesis. This is generally a negative trait, especially in combination with normal (high) COMT activity due to low levels of circulating dopamine increasing need for dopamine precursors and methyl donors.</p> <p>However, for those with variants on COMT, this is positive since dopamine will be broken down more slowly leading to normal circulating levels.</p>

## Detailed Results for Urea Cycle

<b>BDKRB2</b> rs1799722	TT ▲▲	 <p>Increased sensitivity to bradykinin. You need a smaller amount of bradykinin for its effects to be felt.</p> <p>This genotype is associated with the most efficient circulation and transport of oxygen and other nutrients.</p>
<b>NOS3</b> rs1799983	GT ▼	 <p>Reduced eNOS activity and nitric oxide linked to slower ammonia detoxification and higher free radical levels. Increased risk of hypertension and coronary artery disease.</p> <p>Ensure adequate levels of methyl-folate to support BH4 production. Increase antioxidants to reduce free radical damage. Moderate intake of ammonia generating foods (protein).</p>
<b>NOS3</b> rs2070744	TT	 <p>Wild genotype - normal eNOS activity and healthy production of nitric oxide.</p> <p>Low levels of BH4 will affect NOS activity regardless of genotype - ensure adequate levels of methyl-folate to support BH4 levels.</p>
<b>SOD2</b> rs2758331	AC ▼	 <p>Reduced SOD enzyme activity increasing risk of free radical damage.</p> <p>Ensure adequate intake of manganese to support SOD activity and increase antioxidant levels to reduce free radical damage.</p>
<b>SOD2</b> rs4880	GA ▼	 <p>Reduced SOD enzyme activity increasing risk of free radical damage.</p> <p>Ensure adequate intake of manganese to support SOD activity and increase antioxidant levels to reduce free radical damage.</p>

## Folate Cycle

Folate, or vitamin B9, is the generic term for naturally occurring dietary folate and synthetic folic acid (the monoglutamate form found in supplements and fortified foods). Foliates are converted (reduced) to dihydrofolate (DHF) with Vitamin B3 (NADH) as cofactor. DHF is then further reduced to tetrahydrofolate (THF), also with the support of Vitamin B3.

The folate cycle is in fact two linked cycles - tetrahydrofolate (THF) is converted into 5,10-methylene THF which then either i) supports the methylation of deoxyuridylate (dUMP) to thymidylate (dTMP) in the formation of DNA, required for proper cell division, or ii) converts to methylfolate (5-MTHF) whose folate component is recycled (back) into THF.

Methylfolate is an important product of the folate cycle as it is required to provide methyl (CH<sub>3</sub>) to the methionine cycle for the conversion of homocysteine to methionine and to drive the conversion of BH<sub>2</sub> to BH<sub>4</sub> to support the neurotransmitter cycle. Functional testing of serum and erythrocyte (red blood cell or RBC) folate levels may be considered. As serum folate levels are sensitive to recent dietary or supplementary intake, RBC levels may be more indicative of tissue folate stores.

Ensure adequate intakes of all B vitamins - particularly B9 (folates) B2, B3 and B6. Methylated or other forms of B vitamins may be appropriate depending on SNPs and environmental factors.

### Genetic Pathway

Assimilation of folate can be impacted by variants on the FOLH1 gene (food form) and on the RFC1 or DHFR genes (either form of folate).

FOLH1 (Folate Hydrolase1) codes for GPCII (Glutamate Carboxypeptidase II), which, as a metallothionein, requires zinc as a cofactor. GPCII is anchored to the intestinal brush border and facilitates the absorption of dietary folate by converting poly-glutamyl folate to mono-glutamyl forms. Folic acid is a monoglutamate, so does not require this conversion. Variants are

associated with impaired intestinal absorption of dietary folate and lower status.

RFC1 (Reduced Folate Carrier 1), also known as SLC19A1 (Solute Carrier Family 19A1), is a transporter of folate and is involved in the regulation of cellular folate. It has significantly higher affinity for reduced folates (DHF and THF) than for folic acid. RFC1 SNPs are associated with reduced ability to take up, retain, and metabolise folates.

Dihydrofolate reductase (DHFR) converts dihydrofolate (DHF) into tetrahydrofolate (THF), a methyl group shuttle required for the synthesis of purines, thymidine and nucleic acids - precursors to DNA and RNA. Anti-folate drugs such as methotrexate target (block) DHFR to deplete cells of reduced folate and suppress purine and pyrimidine synthesis. A 19-bp deletion (variance) on DHFR is associated with higher activity, and stronger 'pull' of 5,10 Methylene-THF via TYMS to support DNA synthesis (TYMS cycle) at the expense of 5-MTHF (methyl folate). High intake (> 500 mcg) of folic acid has been linked to higher circulating (unmetabolised) folic acid levels, particularly in 19-bp homozygous (deleted) genotypes.

Variants on the MTHFD1 and SHMT1 (serine hydroxymethyltransferase 1) genes are both involved in the conversion of THF to 5,10 Methylene and subsequently impact 5-MTHF levels. SHMT1 is a vitamin B6 dependent enzyme which catalyzes the reversible conversion of serine to glycine and of tetrahydrofolate to 5,10-methylenetetrahydrofolate needed for DNA synthesis and repair. SHMT1 SNPs are associated with lower activity and availability of 5,10-MTHF, impacting both DNA synthesis and repair and availability of methyl folate to support methylation.

MTHFD1 catalyses three sequential reactions (hence three gene names - methylenetetrahydrofolate dehydrogenase, cyclohydrolase and formyltetrahydrofolate synthetase 1) in the interconversion of THF metabolites, which are needed for the synthesis of purine, thymidine (nucleotides) and methionine. These are reversible reactions that

can be directed towards 5-MTHF - and homocysteine re-methylation (methionine cycle) - or away from it. MTHFD1 variants can impact DNA synthesis and repair, and increase demand for choline as a methyl-group donor, in the methionine cycle. MTHFD1 SNPs have been linked to increased risk of folate sensitive neural tube defects, and endometriosis related infertility due to choline depletion.

Thymidylate synthase (TYMS) catalyses the methylation of deoxyuridylate to deoxythymidylate using 5,10-methylenetetrahydrofolate as a cofactor. This maintains the dTMP (thymidine-5-prime monophosphate) pool critical for DNA replication and repair. Functional genetic variants in TYMS may impact DNA stability which may increase the risk of certain cancers. It also produces DHF which is then reprocessed in the folate cycle.

The MTHFR gene codes for the protein methylenetetrahydrofolate reductase (also called 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, and the metabolism of neurotransmitters, phospholipids and proteins such as myelin. Variants on MTHFR 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% for heterozygotes and 70% for homozygotes. MTHFR activity can be supported by increasing the intake of folate (B9) and the cofactors riboflavin (vitamin B2) and niacin (vitamin B3). The A1298C variant has less impact on 5-MTHF levels but is associated with depletion of BH4 - vital for neurotransmitter synthesis, and affecting urea cycle function.

Also known as methionine synthase (MS), MTR (5-methyltetrahydrofolate-homocysteine methyltransferase) facilitates the transfer of methyl from methyl folate to B12. The folate (THF) is recycled (within the folate cycle). The methyl B12 is used to support the conversion of homocysteine to methionine in the next (methionine) cycle.

## Methionine Cycle

The methionine cycle, also known as the methylation cycle, is responsible for making SAME (S-Adenosyl-Methionine), referred to as the universal methyl donor, and for recycling homocysteine to methionine either via the 'long route' via B12 dependent MTR (5-methyltetrahydrofolate-homocysteine methyltransferase) or the 'short route' via BHMT (betaine dependent). Methionine is then converted (back) to homocysteine via intermediates SAME and SAH (S-Adenosyl-Homocysteine). Homocysteine may also be removed from the methionine cycle by conversion into cystathionine (see Transsulphuration cycle).

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.

Ensure sufficient intake of vitamin B9 (see Folate cycle), B12, choline (in eggs, fish and meats), betaine (in beetroot), zinc, potassium and magnesium.

### Genetic Pathway

At the 'top' of the cycle, methionine is converted to SAME in the presence of magnesium and ATP (universal energy donor) by the enzyme MAT1A. Variants in MAT1A may down regulate activity and lower the rate of SAME synthesis, impacting methylation status.

When it donates its methyl group to a substrate S-Adenosyl-Methionine (SAME) is converted to S-Adenosyl-Homocysteine (SAH). A high ratio of SAH to SAME may inhibit the conversion of SAME to SAH (by negative feedback). This may occur if SAH conversion to homocysteine is slow - either due to down-regulation of the AHCY (adenosylhomocysteinase) gene or if homocysteine levels are high. AHCY catalyses the reversible hydrolysis of SAH to adenosine and homocysteine. Metabolic effects of AHCY deficiency include elevated plasma SAH, SAME, and methionine. The same effects may result from high homocysteine stimulating the reverse reaction, and being converted to SAH.

The 'long route' for converting homocysteine to methionine involves the MTR mediated transfer of a methyl group from 5-MTHF (produced by the folate cycle) to form methylated B12. The B12 methyl group is then used to convert (methylate) homocysteine to methionine. Some of the resulting unmethylated 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 by insufficiency of cofactors - vitamin B12 or SAME, resulting in high homocysteine. MTRR activity can be significantly impacted by heavy metals (including mercury) and nitrous oxide (in anaesthetics and laughing gas), reducing availability of methyl B12.

The FUT2 gene regulates expression of H antigens on the gastrointestinal mucosa. FUT2 secretor status (SeSe) has been associated with both H. pylori infection and gastritis which would impact vitamin B12 malabsorption and serum vitamin B12 levels. However, SeSe (secretor) status is also associated with increased Bifido bacterium in the host. The FUT non-secretor status (sese) confers resistance to Norwalk/ Norovirus and resilience to H. Pylori and better absorption of B12. However non-secretor status is associated with lower Bifido bacteria and less diverse and populated commensal bacteria in general, as well as increased risk of coeliac disease and other autoimmune conditions. 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.

The TCN2 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).

The 'shortcut' pathway for conversion of homocysteine to methionine is not dependent on vitamin B12. The PEMT gene (phosphatidylethanolamine N-methyltransferase) converts phosphatidylethanolamine to

phosphatidylcholine by sequential methylation in the liver, providing a significant source of choline relative to dietary intake. Oestrogen induces PEMT gene expression and enables 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. CHDH (choline dehydrogenase) then locates choline to mitochondria where it is oxidised to betaine. Variants on CHDH lower activity and increase risk of choline deficiency with impacts on mitochondrial structure and function impacting sperm concentration and motility, fetal development, NAFLD, and (more broadly) cell membrane structure. CHDC can be supported by Vitamin B2 (cofactor) and PQQ (pyrroloquinoline quinone) found in kiwi fruit. BHMT (Betaine-homocysteine S-methyltransferase) catalyses the conversion of betaine (TMG, trimethylglycine) to DMG (dimethylglycine) by transfer of a methyl group to homocysteine to make methionine. This can be impacted by BHMT variants, and requires zinc as cofactor.

## Transsulphuration Pathway

The transsulphuration pathway involves the interconversion of cysteine and homocysteine, through the intermediate cystathionine, and generates the antioxidant glutathione, as well as the amino acids taurine and cysteine. Some unhelpful by-products may result including: ammonia - which depletes BH4 leading to low dopamine and serotonin (see BH4 cycle); sulphites - which stimulate cortisol, allergy type reactions, and result in brain fog; and glutamate - which can be excitotoxic.

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.

If the CBS (cystathionine beta-synthase) gene is upregulated, it is more important to support homocysteine recycling (see Methionine Cycle), and assess levels of toxic by-products such as ammonia, sulphur (if sensitive). Charcoal can be used to detoxify/ remove ammonia, probiotics

can help reduce bacterial production (of ammonia), and limiting animal protein can help reduce ammonia levels; sulphur-containing foods such as eggs, garlic, onions and broccoli, and supplements (such as cysteine), since sulphur sensitivity may occur (avoid completely if homozygous for SUOX). Vitamin B6 can support cysteine and glutathione synthesis, and molybdenum will support SUOX activity.

## Genetic Pathway

The CBS (cystathionine beta-synthase) gene converts homocysteine to cystathionine. This initial step in the transsulphuration pathway requires vitamin B6 and heme (iron) as cofactors. The C699T (A) variant is thought to have a strong up-regulating effect on CBS activity. A fast CBS can act as an 'open gate' between homocysteine and the transsulphuration pathway, draining homocysteine (from the Methionine Cycle) and reducing SAME synthesis and with potentially unbalancing effects on the Transsulphuration pathway. Less commonly, CBS deficiency may result in high homocysteine due to the blockage of the transsulphuration pathway.

If CBS activity is high there is more opportunity for homocysteine to be converted via cysteine to ammonia. Excess cysteine can generate toxic sulphites putting pressure on the SUOX gene. Glutathione synthesis is also negatively affected by the flooding of the Transsulphuration pathway. High ammonia can put pressure on the urea cycle (inhibiting NOS activity) and, additionally, cause low BH4 (impacting neurotransmitter synthesis).

CTH (cystathionine gamma-lyase) and GSS (glutathione synthetase) mediate the conversion of cysteine and glutathione respectively. Variants on either gene can lower synthesis of glutathione. CTH conversion of cystathionine into cysteine requires vitamin B6 as a cofactor. Variants on CTH can compromise conversion of cystathionine to cysteine, with downstream effects on glutathione synthesis.

The GSS gene controls the second step of glutathione synthesis, the ATP-dependent conversion of gamma-L-glutamyl-L-cysteine 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 impact synthesis of glutathione and result in deficiency.

MUT (methylmalonyl-CoA mutase) is a mitochondrial enzyme that converts methylmalonyl-CoA to succinyl-CoA requiring adenosyl-cobalamin (B12) as cofactor. Succinyl-CoA is an important enzyme in the Krebs cycle and is crucial for the synthesis of heme, cytochrome P450s and nucleotides. SNPs on MUT gene may lead to various types of methylmalonic aciduria.

Finally, SUOX (sulphite oxidase) 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 considered 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 which helps to convert amino acids such as phenylalanine, tyrosine and tryptophan into the neurotransmitters noradrenaline, dopamine, serotonin (and subsequently to melatonin) and thyroid hormones. BH4 is recycled (from BH2) with the help of methylfolate (5-MTHF).

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 or high levels of, or different sensitivities to, neurotransmitters can result in mood imbalances (low or high), aggressive behaviours, poor memory and concentration and sleep disturbances.

Assess nutrients that impact neurotransmitter synthesis including amino acids (tryptophan and tyrosine), vitamin D, methylfolate and vitamin B6, alongside those that support neurotransmitter breakdown such as vitamin B2, SAME (methionine cycle), zinc and magnesium. Environmental factors such as stress, diet (particularly stimulants, such as caffeine), and heavy metal toxicity can have significant effects on neurotransmitter balance.

## Genetic Pathway

BH4 (tetrahydrobiopterin) is an important cofactor for the synthesis of the neurotransmitters serotonin and dopamine, and for nitric oxide production (see Urea cycle). In the process of neurotransmitter synthesis BH4 donates two hydrogens and is converted to BH2. BH4 deficiency can occur as a result of variants on QDPR, the gene responsible for recycling BH2 to BH4 with the help of methylfolate (from the folate cycle). Variants on CBS and MTHFR A1298C can also cause BH4 deficiency due to excess ammonia and insufficient methylfolate respectively.

Vitamin D Receptor (VDR) variants (called TaqI and BsmI) are associated with lower vitamin D sensitivity which can lower serotonin and dopamine production. Whilst consideration should be given to balancing synthesis and metabolism, as VDR (vitamin D) is essential for a very broad range of functions, it is important to consider that optimum Vitamin D levels for individuals with VDR SNPs may be higher, than for those without SNPs.

The PNMT (phenylethanolamine N-methyltransferase) enzyme methylates noradrenaline to form adrenaline and therefore plays a key role in regulating adrenaline production. During environmental or physiological stress such as exercise, the

secretion of glucocorticoids that induce PNMT. Variants on PNMT are reported to reduce its activity and slow down the conversion of noradrenaline to adrenaline, and has been linked to hypertension. As SAME is a cofactor for PNMT, ensure sufficient B vitamins, zinc and magnesium to support SAME synthesis.

Variants on COMT (catechol-O-methyltransferase) and on MAOA and MAOB (monoamine oxidase genes) indicate slow breakdown of neurotransmitters which may contribute to imbalances (high levels). As 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), buildup of SAH will thus inhibit COMT activity. COMT variants are associated with lower activity and symptoms such as irritability, heightened stress response, hyperactivity, heightened pain sensitivity, as well as slower detoxification of other catecholamines, such as oestrogen.

MAOA helps to break down the monoaminergic neurotransmitters serotonin, melatonin, noradrenaline and adrenaline, whereas MAOB is the main catalyst for the breakdown of phenethylamine (PEA), benzylamine, histamine, dopamine, tyramine and tryptamine. The MAO genes are 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 have been 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 associated with low mood due to rapid breakdown of neurotransmitters. MAOB is a target for MAO inhibitor drugs used to raise dopamine levels and to improve motor function in Parkinson's disease patients.



## Urea Cycle

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

With the support of BH4 (cofactor), Nitric Oxide Synthase (NOS) converts arginine to nitric oxide, a reactive free radical which acts as a biologic mediator in several processes, including cardiovascular, neurotransmission and antimicrobial and antitumoral activities. BH4 insufficiency can result in higher levels of damaging superoxide or peroxy-nitrate instead of nitric oxide.

As BH4 is depleted by ammonia, assess the ammonia burden, and ensure adequate methylfolate for BH4 regeneration. Antioxidants including vitamin C and glutathione, can help to reduce oxidative stress including neutralising NOS and SOD metabolites.

### Genetic Pathway

NOS3 (nitric oxide synthase 3) codes for endothelial NOS (eNOS) one of three NOS enzymes that synthesise nitric oxide (NO) from L-arginine and molecular oxygen with the cofactor BH4 (tetrahydrobiopterin). The citrulline formed as a by-product of the NOS reaction can be recycled to arginine. eNOS is primarily responsible for the generation of NO in the vascular endothelium, regulating vascular tone (vasodilation), cellular proliferation, leukocyte adhesion, and platelet aggregation, and is therefore essential for cardiovascular function - lowering blood pressure and supporting transport of oxygen and other nutrients around the body. The NOS variants result in dysfunctional eNOS enzymes which are less effective in breaking down ammonia and generating nitric oxide. In addition, insufficiency of the BH4 can tip the 'pendulum' of the urea cycle away from nitric oxide production towards superoxide - the highly reactive free radical with deleterious effects on cardiovascular health. Impaired NO production is a risk factor for several diseases including hypertension,

preeclampsia, diabetes mellitus, obesity, erectile dysfunction, and migraine.

SOD (superoxide dismutase) are a family of enzymes that dismutate (partitions) superoxide into oxygen and hydrogen peroxide, protecting cells from superoxide toxicity. There are three major families of SOD which bind to different metal cofactors (copper, manganese or zinc). The SOD2 form binds to a manganese cofactor, hence is also known as mnSOD (manganese SOD) and is active in mitochondria. The A16V SNP on SOD2 is associated with lower activity and increased susceptibility to oxidative stress.

Bradykinin is released upon activation by pathophysiologic conditions such as trauma and inflammation, and binds to its kinin receptors, B1 and B2. It causes blood vessels to dilate (widen), and blood pressure to fall, and also stimulates uptake (storage) of glycogen by skeletal muscle. Variants on the Bradykinin Receptor Beta 2 (BDKRB2) gene increase sensitivity to bradykinin, so less bradykinin is needed to stimulate vasodilation, and improve blood circulation, transport of oxygen and other nutrients.

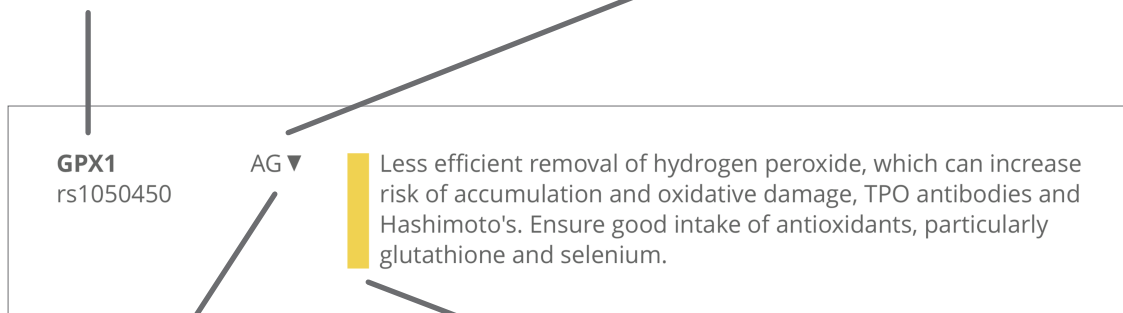
## How to Read the Report

### Genes

Results are listed in order of the gene short name. The 'rs' number is the reference sequence number that identifies a specific location on the genome. It is also known as a SNP (Single Nucleotide Polymorphism) pronounced 'snip', polymorphism or mutation.

### Personalised Result

Your genotype result is shown as two letters (A,G,T or C) which represent the DNA bases present at that location.



### Arrow Direction

The direction of the arrow indicates the potential effect of the SNP on gene expression, where applicable - it can increase or decrease activity, or neither.

- ▲ up-regulates or increases the activity and effect on the gene
- ▼ down-regulates or decreases the activity and effect on the gene

No arrow - no effect on the activity of the gene

### Highlight Colour

The genotype result highlight indicates the potential effect of the SNP on gene function in a particular context.

- RED** the effect of the variant is negative
- AMBER** the effect of the variant is somewhat negative
- GREEN** no variation, or the effect of the variant is positive

### Pathway Diagram Key

Cofactor

Inhibitor

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Shahid, Saleem & Saleem, Shabana & Cooper, Jackie & Rehman, Abdul. (2016). Association of ACE and NOS3 Gene Polymorphism with Blood Pressure in a Case Control Study of Coronary Artery Disease in Punjab, Pakistan. *Pakistan journal of zoology.* 48. 1125-1132. (<http://web.a.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=00309923&AN=116811458&h=TgE1PVq7H0E2i4Qc4FOPsxvzywA8o9jVpnTTfognMOFoD7wLqcrqgcMyp6u0VQuve6rtQc7msrdKvgDRlquKA%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d00309923%26AN%3d116811458>)

### PEMT Phosphatidylethanolamine N-methyltransferase

Ivanov A, Nash-Barboza S, Hinkis S, Caudill MA. (2009). Genetic variants in phosphatidylethanolamine N-methyltransferase and methylenetetrahydrofolate dehydrogenase influence biomarkers of choline metabolism when folate intake is restricted. *J Am Diet Assoc.* Feb;109(2):313-8. (<http://www.ncbi.nlm.nih.gov/pubmed/19167960>)

Zeisel SH. A Conceptual Framework for Studying and Investing in Precision Nutrition. *Front Genet.* 2019 Mar 18;10:200. doi: 10.3389/fgene.2019.00200. PMID: 30936893; PMCID: PMC6431609. (<https://pubmed.ncbi.nlm.nih.gov/30936893/>)

### PNMT Phenylethanolamine N-Methyltransferase

Rodríguez-Flores JL, Zhang K, Kang SW, et al. Conserved regulatory motifs at phenylethanolamine N-methyltransferase (PNMT) are disrupted by common functional genetic variation: an integrated computational/experimental approach. *Mammalian Genome*. 2010;21(3-4):195-204. doi:10.1007/s00335-010-9253-y. (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844968/>)

### QDPR Quinoid Dihydropteridine Reductase

Shi J, Badner JA, Hattori E, Potash JB, Willour VL, McMahon FJ, Gershon ES, and Liu C. (2008). Neurotransmission and Bipolar Disorder: A Systematic Family-based Association Study, *Am J Med Genet B Neuropsychiatr Genet*; 147B(7): pp. 1270–1277 (<http://europemc.org/articles/PMC2574701>)

### RFC1 Reduced Folate Carrier 1

Imbard A, Benoist JF, Blom HJ. (2013). Neural tube defects, folic acid and methylation. *Int J Environ Res Public Health*. Sep 17;10(9):4352-89 (<http://www.ncbi.nlm.nih.gov/pubmed/24048206>)

### SHMT1 Serine hydroxymethyltransferase 1 (Soluble)

Guerrero CS, Carmona B, Gonçalves S, Carolino E, Hidalgo P, Brito M, Leitão CN, and Cravo M. (2008). Risk of colorectal cancer associated with the C677T polymorphism in 5,10-methylenetetrahydrofolate reductase in Portuguese patients depends on the intake of methyl-donor nutrients. *Am J Clin Nutr* November 2008 vol. 88 no. 5 1413-1418 (<http://ajcn.nutrition.org/content/88/5/1413.full>)

Ilan J. N. Koppen, Frederik J. R. Hermans and Gertjan J. L. Kaspers. (2010). Folate related gene polymorphisms and susceptibility to develop childhood acute lymphoblastic leukaemia. *British Journal of Haematology* Volume 148, Issue 1, pages 3–14, January 2010. (<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2009.07898.x/full>)

Locasale JW. Serine, glycine and the one-carbon cycle: cancer metabolism in full circle. *Nature reviews Cancer*. 2013;13(8):572-583. doi:10.1038/nrc3557. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3806315/>)

### SOD2 Superoxide Dismutase 2, Mitochondrial

Bastaki M, et al. Genotype-activity relationship for Mn-superoxide dismutase, glutathione peroxidase 1 and catalase in humans. *Pharmacogenet Genomics*. 2006;16(4):279–86. (<https://www.ncbi.nlm.nih.gov/pubmed/16538174>)

Gallagher CJ, Ahn K, Knipe AL, Dyer AM, Richie JP Jr, Lazarus P, Muscat JE. (2009) Association between haplotypes of manganese superoxide dismutase (SOD2), smoking, and lung cancer risk. *Free Radic Biol Med*. 2009 Jan 1;46(1):20-4. doi: 10.1016/j.freeradbiomed.2008.09.018. (<http://www.ncbi.nlm.nih.gov/pubmed/18930810>)

Holley AK, Bakthavatchalu V, Velez-Roman JM, and St. Clair DK. (2011). Manganese superoxide dismutase: guardian of the powerhouse. *Int J Mol Sci*; 12(10): pp. 7114–7162 (<http://europemc.org/articles/PMC3211030>)

Wang P, Zhu Y, Xi S, Li S, Zhang Y. Association between MnSOD Val16Ala Polymorphism and Cancer Risk: Evidence from 33,098 Cases and 37,831 Controls. *Dis Markers*. 2018;2018:3061974. Published 2018 Sep 2. doi:10.1155/2018/3061974 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6139213/>)

### SUOX Sulfite Oxidase

Garrett RM, Johnson JL, Graf TN, Feigenbaum A, Rajagopalan KV. (1998). Human sulfite oxidase R160Q: identification of the mutation in a sulfite oxidase-deficient patient and expression and characterization of the mutant enzyme. *Proc Natl Acad Sci USA*; 95(11): pp. 6394-8 (<https://www.ncbi.nlm.nih.gov/pubmed/9600976?dopt=Abstract>)

### TCN2 Transcobalamin II

Guéant, J., Chabi, N. W., Guéant-Rodriguez, R., Mutchinick, O. M., Debard, R., Payet, C. Namour, F. (2007). Environmental influence on the worldwide prevalence of a 776C→G variant in the transcobalamin gene (TCN2). *Journal of Medical Genetics*, 44(6), 363–367. (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2740879/>)

Namour F, Olivier J, Abdelmouttaleb I, Adjalla C, Debard R, Salvat C, Guéant J L. (2001). Transcobalamin codon 259 polymorphism in HT-29 and Caco-2 cells and in Caucasians: relation to transcobalamin and homocysteine concentration in blood. *Blood*. 97(4), 1092–1098. (<http://www.ncbi.nlm.nih.gov/pubmed/11159542>)

### TYMS Thymidylate Synthetase

Shen R, Liu H, Wen J, Liu Z, Wang LE, Wang Q, Tan D, Ajani JA, Wei Q. (2015). Genetic polymorphisms in the microRNA binding-sites of the thymidylate synthase gene predict risk and survival in gastric cancer. *Mol Carcinog*. Sep;54(9):880-8. (<http://www.ncbi.nlm.nih.gov/pubmed/24756984>)

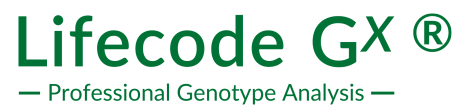
Simeon V, Todoerti K, La Rocca F, et al. Molecular Classification and Pharmacogenetics of Primary Plasma Cell Leukemia: An Initial Approach toward Precision Medicine. Angelini S, ed. *International Journal of Molecular Sciences*. 2015;16(8):17514-17534. doi:10.3390/ijms160817514. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4581206/>)

Xu J, Tian S, Yin Z, Wu S, Liu L, Qian Y, Pei D, Gao W, Xu J, Yin Y, Liu P, Shu Y. (2014) MicroRNA-binding site SNPs in deregulated genes are associated with clinical outcome of non-small cell lung cancer. *Lung Cancer*. Sep;85(3):442-8. (<http://www.ncbi.nlm.nih.gov/pubmed/24997136>)

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

Cui X1, Pelekanos M, Liu PY, Burne TH, McGrath JJ, Eyles DW. (2013). The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. *J. Neuroscience* (16), 236:77-87 (<http://www.ncbi.nlm.nih.gov/pubmed/23352937>)

Wang L, Ma J, Manson JE, Buring JE, Gaziano JM, Sesso HD. (2013). A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms, and risk of hypertension in men. *Eur J Nutr*, 52, (7):1771-9 (<http://www.ncbi.nlm.nih.gov/pubmed/23262750>)



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