Methylation Report

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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 (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 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 synsthesis, 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

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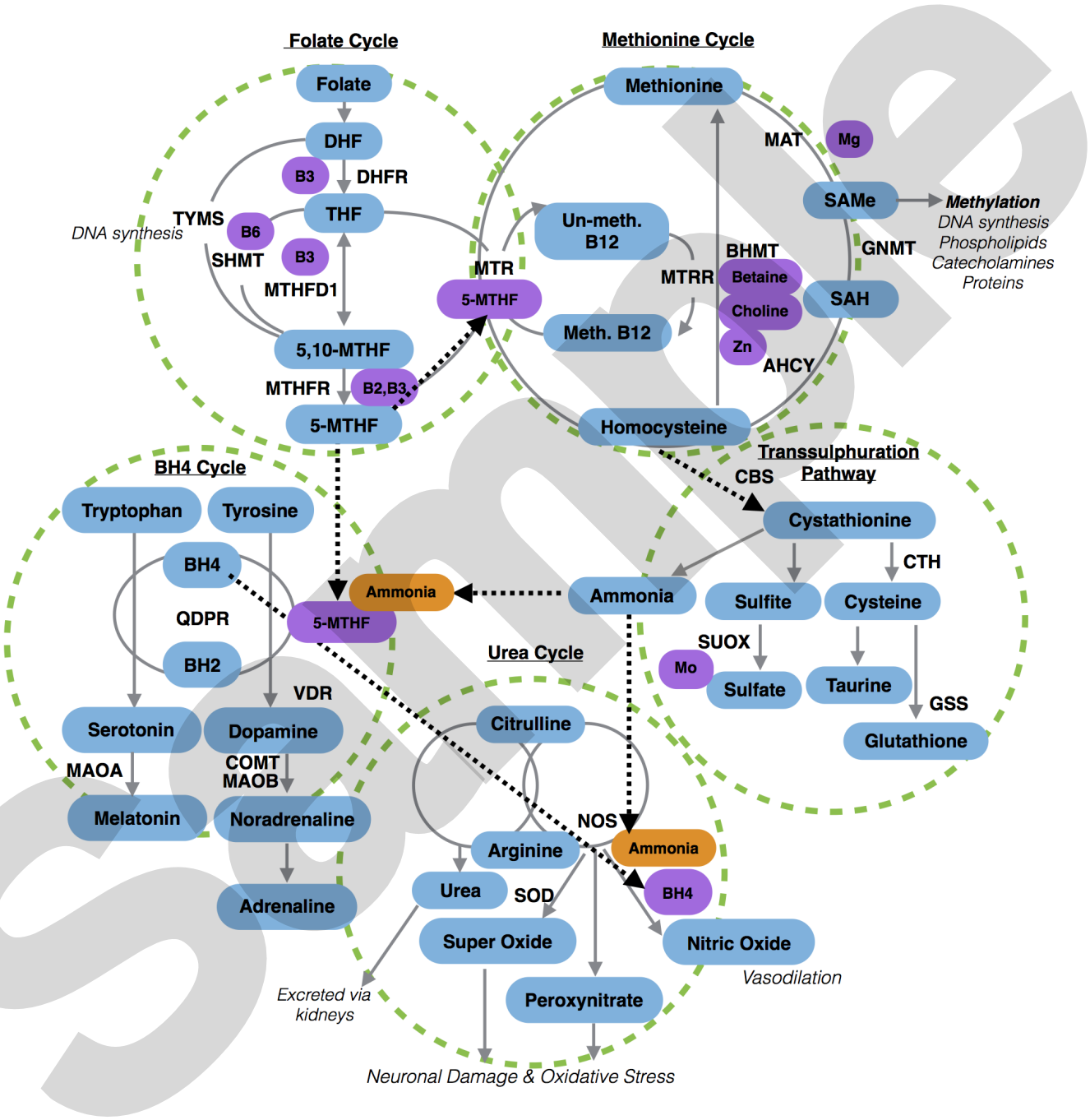
Overview



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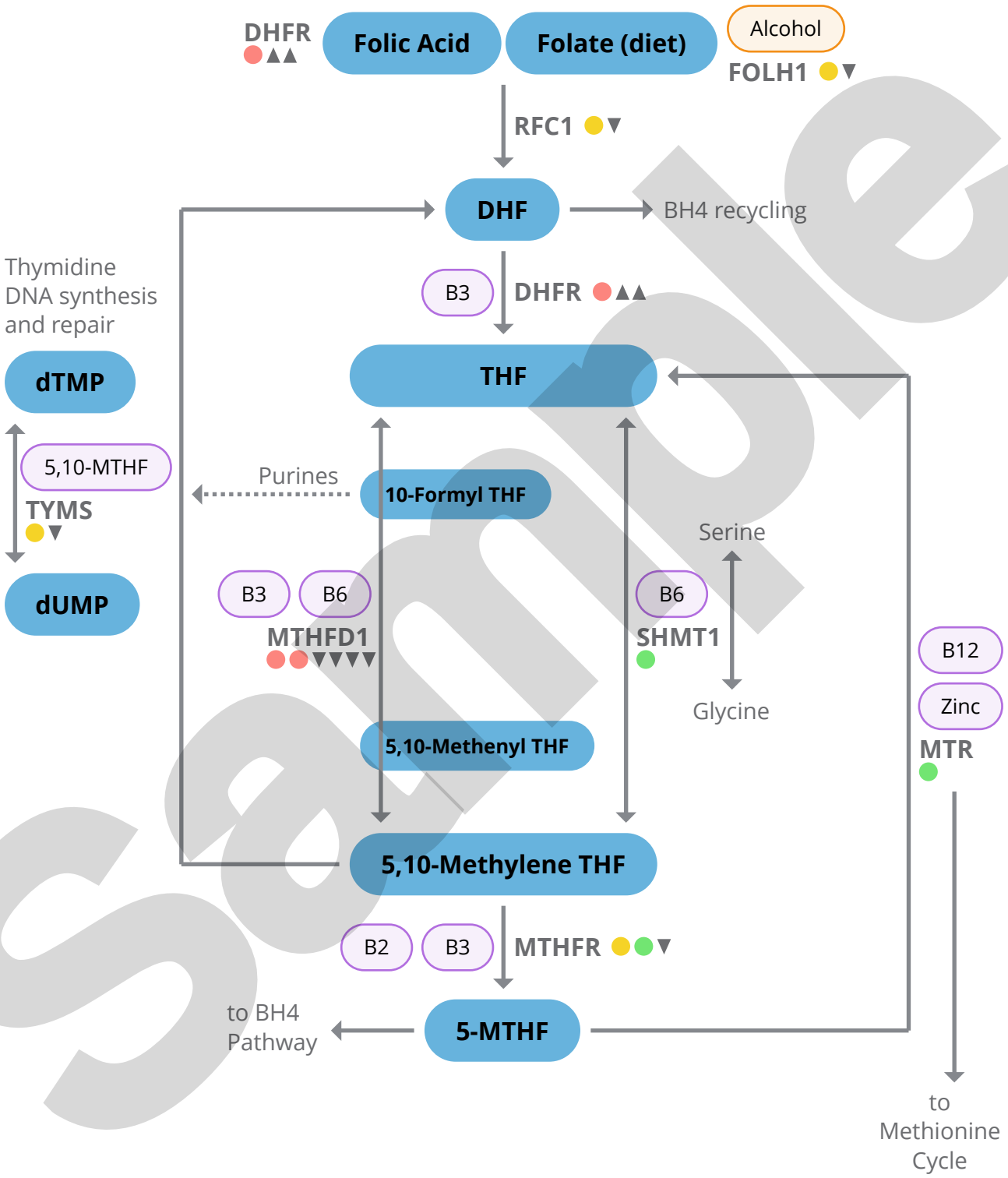
Folate Cycle



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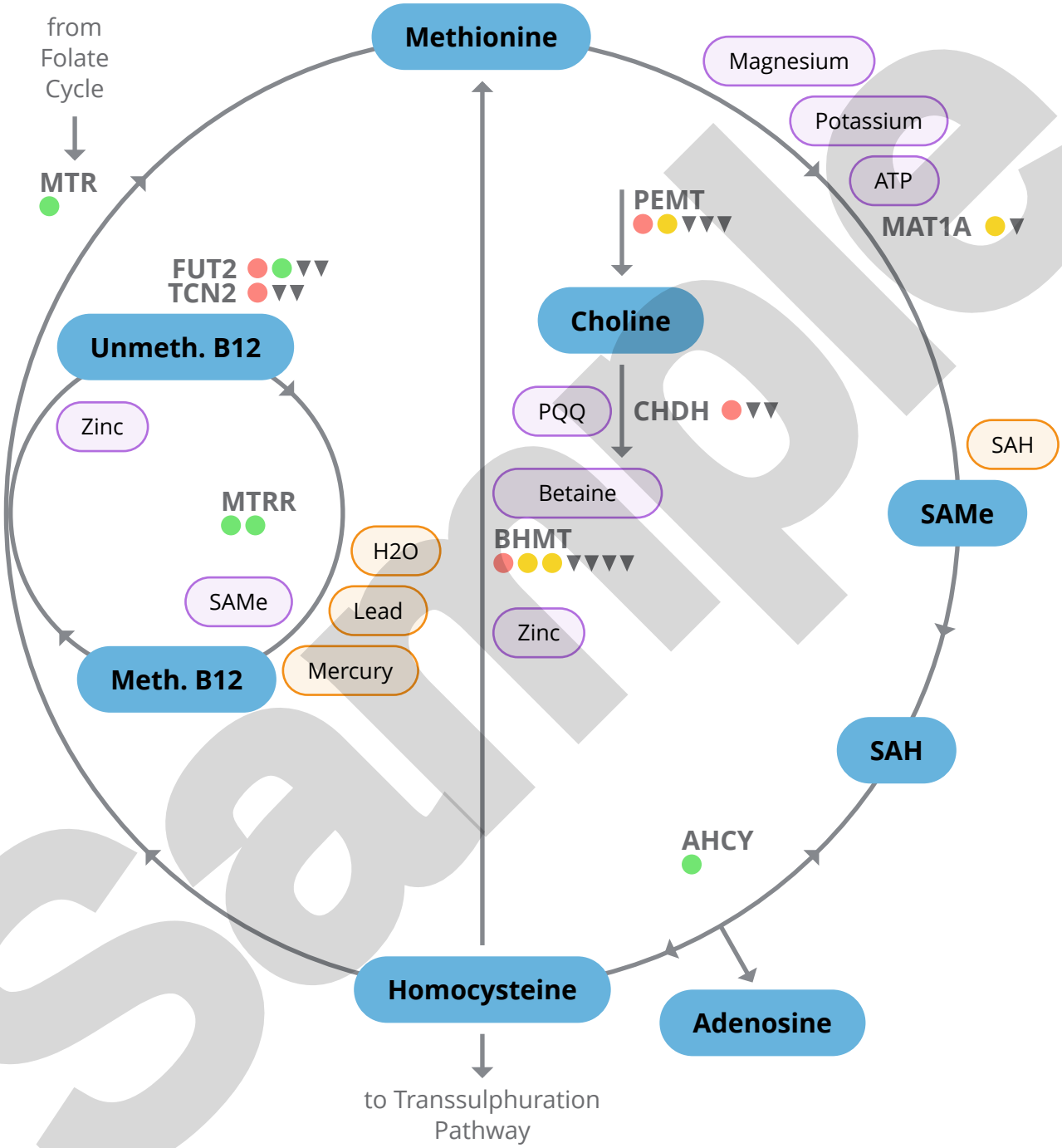
Methionine Cycle



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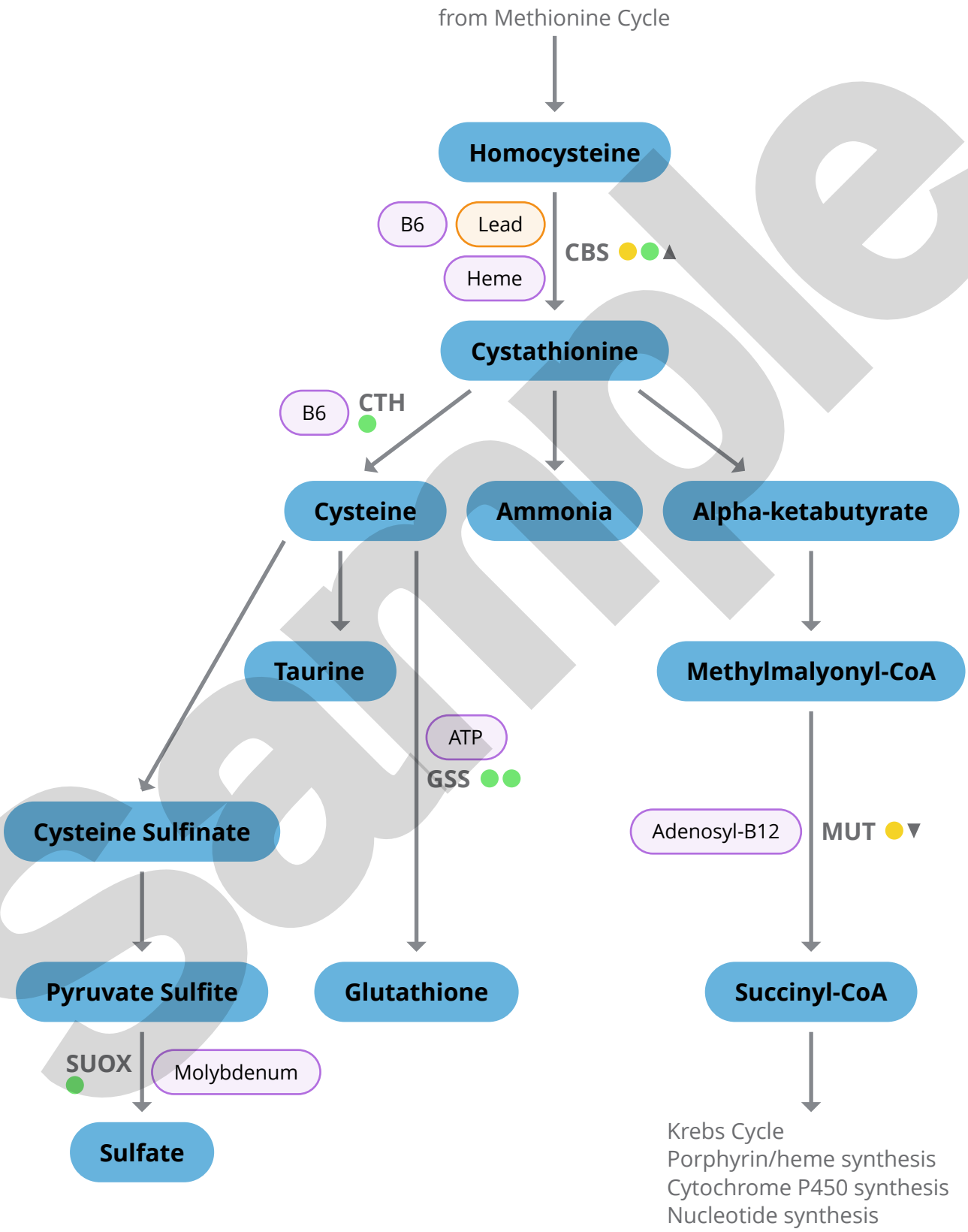
Transsulphuration Pathway



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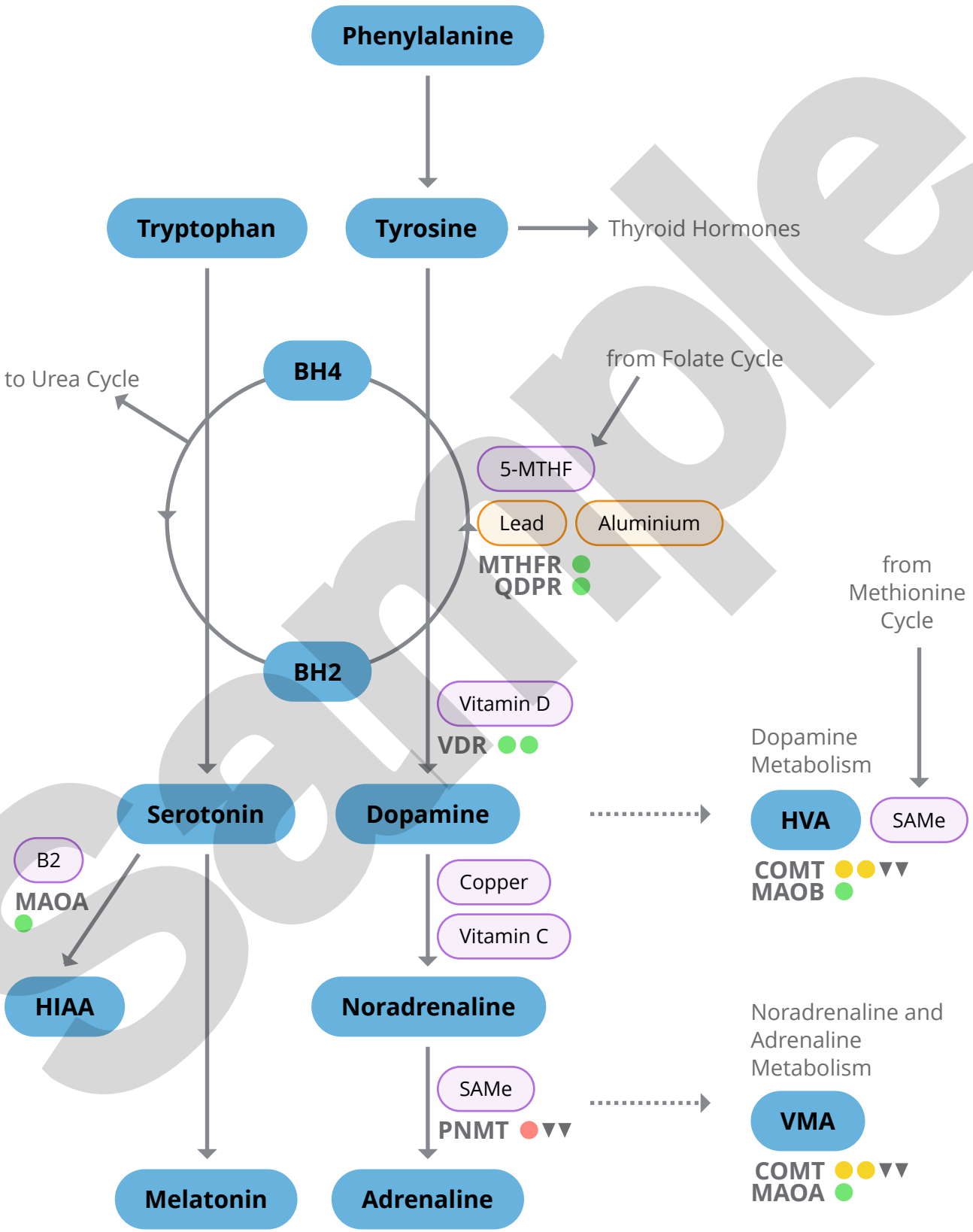
BH4 Cycle / Neurotransmitter Metabolism



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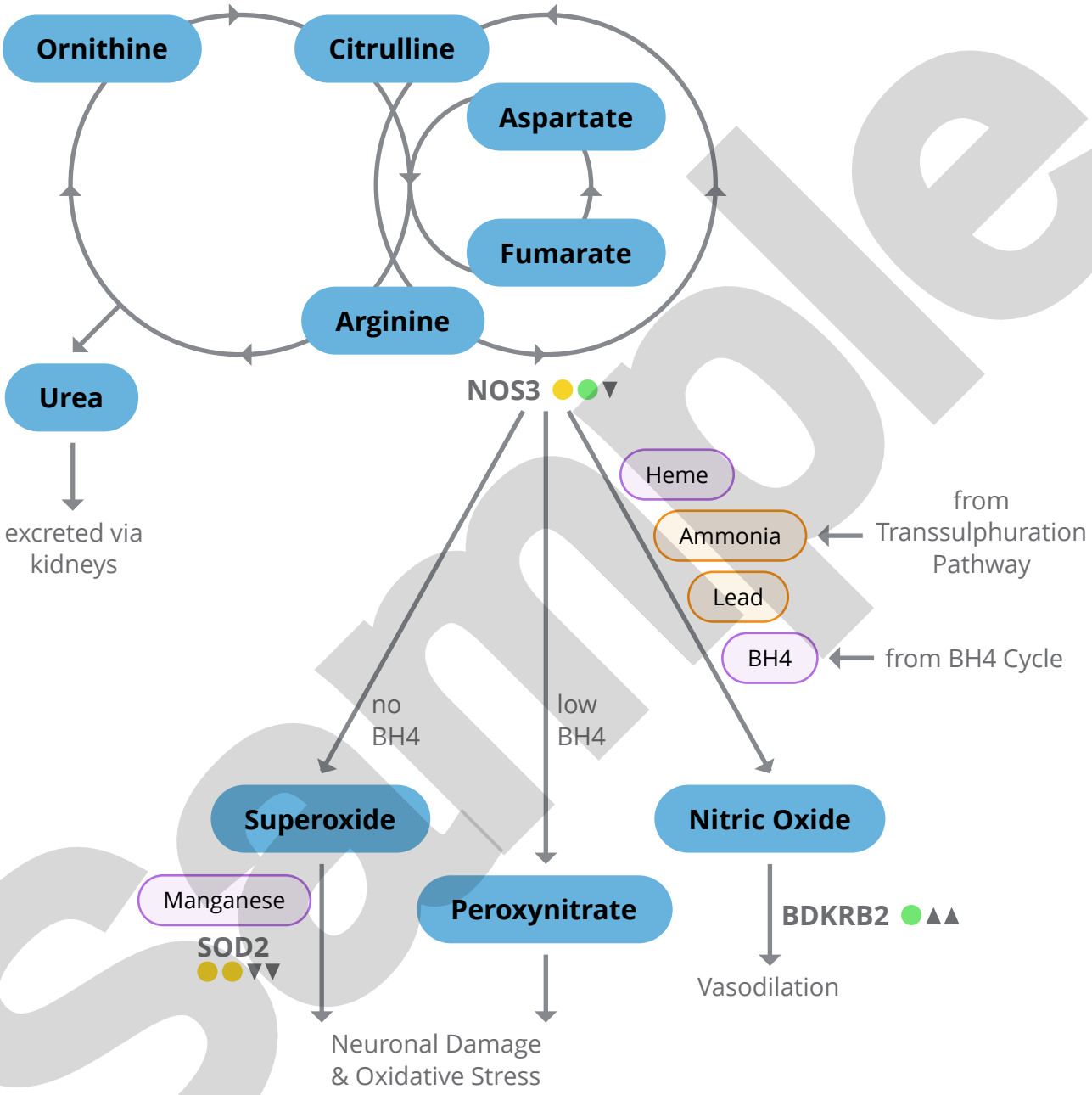
Urea Cycle



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Detailed Results for Folate Cycle

DHFR
rs70991108

DD▲▲

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.

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).

FOLH1

TC ▼

Impaired intestinal absorption of dietary folate and lower red blood cell folate levels, which can increase the risk of neural tube defects and elevated homocysteine.

Mono glutamate forms of folate may improve folate status, particularly if gut health is suboptimal.

MTHFD1

TT ▼▼

Reduced 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 and other developmental disorder.

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.

MTHFD1

AA ▼▼

Reduced 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.

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.

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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). Folates 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 (CH3) to the methionine cycle for the conversion of homocysteine to methionine and to drive the conversion of BH2 to BH4 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 in19-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

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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.

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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.

GPX1 rs1050450	AG ▼	Less efficient removal of hydrogen peroxide, which can increase risk of accumulation and oxidative damage, TPO antibodies and Hashimoto's. Ensure good intake of antioxidants, particularly glutathione and selenium.

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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AHCY S-Adenosylhomocysteine Hydrolase

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BDKRB2 Bradykinin Receptor Beta 2

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BHMT Betaine-homocysteine S-methyltransferase

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CBS Cystathionine Beta-Synthase

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CHDH choline dehydrogenase

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COMT Catechol-O-Methyltransferase

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CTH Cystathionine Gamma-Lyase

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