

StrateGene

Genetic Pathway Analysis

Although this report may provide useful diagnostic information, by providing this report, Seeking Health Educational Institute, Inc. (SHEI) does not make or suggest any specific diagnosis or therapeutic course of treatment or action. Any such diagnosis and/or treatment/ therapeutic plan is strictly a matter between the patient and his or her health care professional.

In order to receive advice with regard to how to use the information in this document, please see the [Directory](#), which is a directory of healthcare practitioners who have taken Dr. Ben Lynch's courses. There is also a [Facebook group](#), which purchasers of StrateGene are welcome to join.

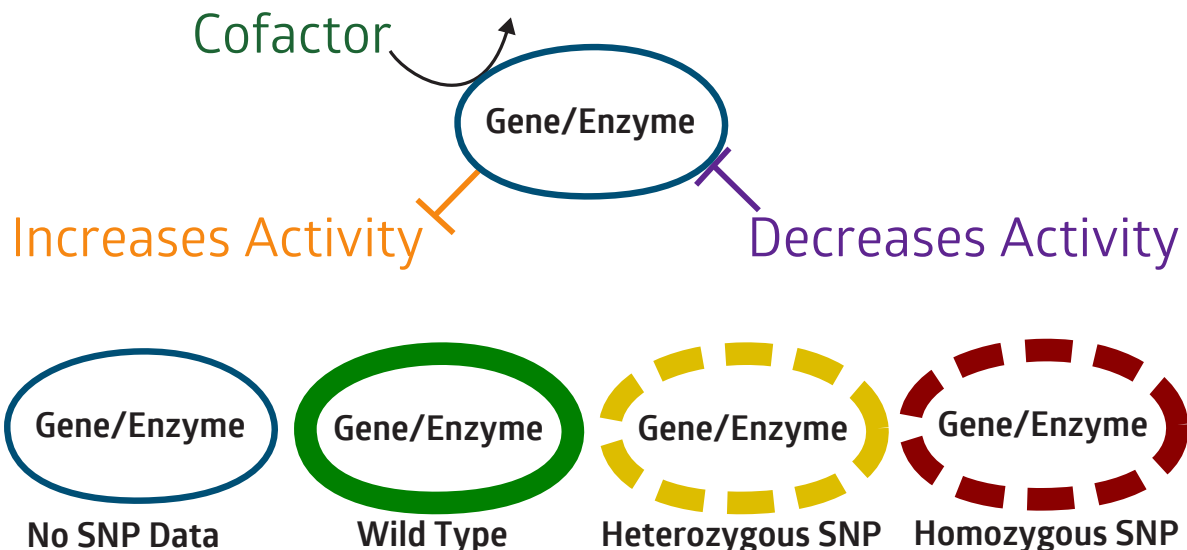
Prepared For: ZackA

Report Time: 10/16/17 UTC
Raw Data Extraction Date: 10/6/17
StrateGene: v1.18 ([Version History](#))
Current Bibliography: <http://strategene.org/bibliography/>

Go To:

[Overview](#) | [Folate](#) | [Methionine](#) | [Transsulfuration](#) | [Biopterin](#) | [Histamine](#) | [Bonus](#) | [FAQ](#) | [Glossary](#)

Symbols and Colors



Section 1: Overview

Core SNPs

RS#	Call	Risk Allele	Gene	Variation	Result
rs1051266	CC	T	SLC19a1	G80A	-/-
rs2236225	AG	A	MTHFD1	G1958A	+/-
rs1801131	GT	G	MTHFR	A1298C	+/-
rs1801133	GG	A	MTHFR	C677T	-/-
rs1801394	AG	G	MTRR	A66G	+/-
rs1532268	CT	T	MTRR	C524T	+/-
rs72558181	NA	T	MAT1A	R264H	NA
rs28934891	CC	T	CBS	D444N	-/-
rs4920037	GG	A	CBS	C19150T	-/-
rs234706	AG	A	CBS	C699T	+/-
rs4880	AG	A	SOD2	A16V	+/-
rs1799895	NA	G	SOD3	Ex3-631C>G	NA
rs1695	AA	G	GSTP1	Ile105Val	-/-
rs1138272	CC	T	GSTP1	A114V	-/-
rs1050828	C	T	G6PD	G202A	-/-
rs1050829	T	C	G6PD	A376G	-/-
rs5030868	G	A	G6PD	C563T (Medit.)	-/-
rs1050450	NA	A	GPX1	Pro199Leu	NA
rs1800783	NA	A	NOS3/eNOS	-1495A>T	NA
rs1800779	AG	G	NOS3/eNOS	A(-922)G	+/-
i6018900	NA	T	SULT1A1	638G>A	NA
rs6323	NA	G	MAOA	T941G	NA
rs1137070	NA	T	MAOA	1410T>C	NA
rs1799836	NA	C	MAOB		NA
rs4680	AG	A	COMT	V158M	+/-
rs4633	CT	T	COMT	H62H	+/-
rs10156191	NA	T	AOC1 (DAO)	Thr16Met	NA

-/- = not present; +/- = one mutation; +/+ = double mutation; +/-* = mutation on the X chromosome in a male.

Predicted **NAT2 acetylator phenotype with probability estimate: INTERMEDIATE (0.996965)**

Note: Since 23andMe didn't test for GSTT1 SNPs in your sample, the possibility of a GSTT1 deletion polymorphism could not be determined.


Bonus SNPs

RS#	Call	Risk Allele	Gene	Variation	Result
rs12934922	AT	T	BCO1	R267S	+/-
rs7501331	CC	T	BCO1	A379V	-/-
rs6420424	AG	A	BCO1 (PKD1L2)	C754T	+/-
rs11645428	AG	G	BCO1		+/-
rs6564851	GT	G	BCO1		+/-
rs601338	AG	A	FUT2		+/-
rs1800566	GG	A	NQO1		-/-
rs1800562	GG	A	HFE	C282Y	-/-
rs1799945	CC	G	HFE	H63D	-/-
i3002468	--	T	HFE	Ser65Cys	NC
rs7946	TT	T	PEMT	5465G>A	+/+
rs174537	GG	G	FADS1 (MYRF)		+/+
rs174548	CC	G	FADS1		-/-
rs1535	AA	G	FADS2		-/-
rs1800629	GG	A	TNF-alpha		-/-
rs34637584	GG	A	LRRK2	2109S	-/-
rs2228570	NA	G	VDR	Fok1	NA
rs731236	AG	G	VDR	Taq1	+/-
rs1544410	CT	T	VDR	Bsm1	+/-
rs7412	CC	C	APOE	Arg176Cys	+/+
rs429358	CT	C	APOE		+/-

-/- = not present; +/- = one mutation; +/+ = double mutation; +/-* = mutation on the X chromosome in a male.

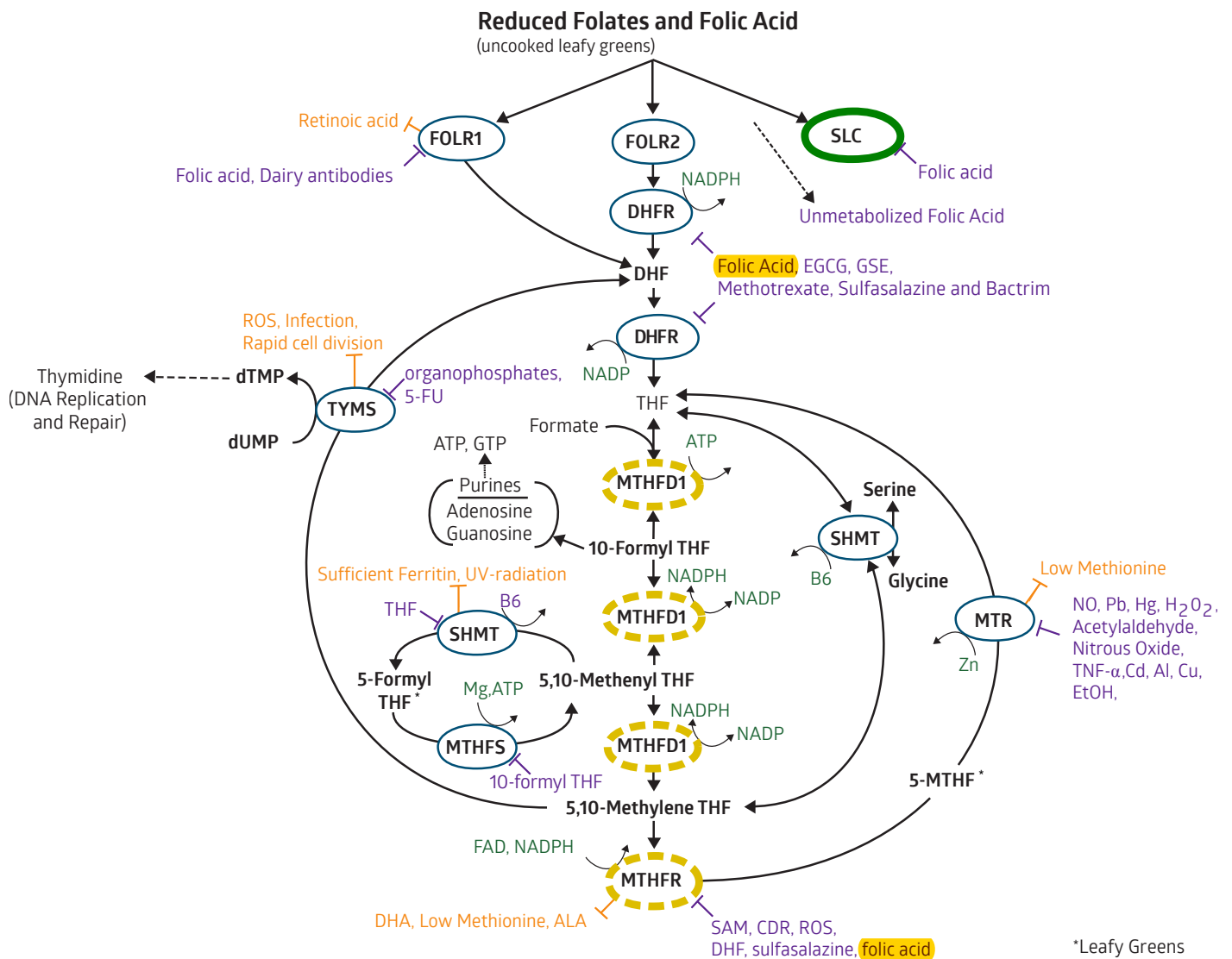
APOE genotype: APOE 3/4

Bonus SNPs are not represented in the Pathway Planner graphics, but may provide useful additional information to assist patient care decisions. (See the [Bonus Section](#) for further information.)

Section 2: Results

2.1 The Folate Cycle

For life to occur, the folate cycle must be functioning. There are three major aspects of this biochemical cycle. First, components of energy via ATP and GTP are needed. Folate provides the building blocks for ATP synthesis. Secondly, folate provides the building blocks for DNA bases. Thirdly, folate feeds into the methylation cycle, thereby supporting methylation. If the folate cycle is not functioning optimally, dysfunction in the areas of energy generation, DNA synthesis/repair and methylation occurs.



2.1.1 FOLATE CYCLE SNPS

MTHFD1

The MTHFD1 (Methylenetetrahydrofolate dehydrogenase 1) gene expresses a trifunctional enzyme that interconverts tetrahydrofolate (THF) derivatives for nucleotide synthesis in the cytoplasm. THF is **important** in the de novo synthesis of purines and thymidylate and in the **regeneration of methionine from homocysteine**.

Factors influencing MTHFD1:

Cofactor: Mg-ATP

SNP(s) Found:

MTHFD1 G1958A (+/-, AG) ↓

- The heterozygous variant's impact on enzyme activity is unclear, however the homozygous variant has been found to reduce the activity of MTHFD within murine cells by up to 34%.
- Associated symptoms and conditions may be choline deficiency with related dysfunction (e.g., fatty liver), neural tube defects, and placental abruption. AA and AG women should consider supplementing with choline before and during pregnancy, and after menopause.

MTHFR

The MTHFR (Methylenetetrahydrofolate reductase) gene expresses an enzyme that catalyzes the reduction of inactive 5,10-methylenetetrahydrofolate to active 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is critical for the remethylation of homocysteine to methionine, which **supports DNA methylation and S-adenosylmethionine (SAME), neurotransmitter, and phospholipid production**.

Factors influencing MTHFR:

Cofactor: FAD

↓ SAM, CDR (cell danger response), ROS, DHF (dihydrofolate), sulfasalazine, folic acid, phenytoin (Dilantin)

↑ DHA and ALA (PUFAs), low methionine

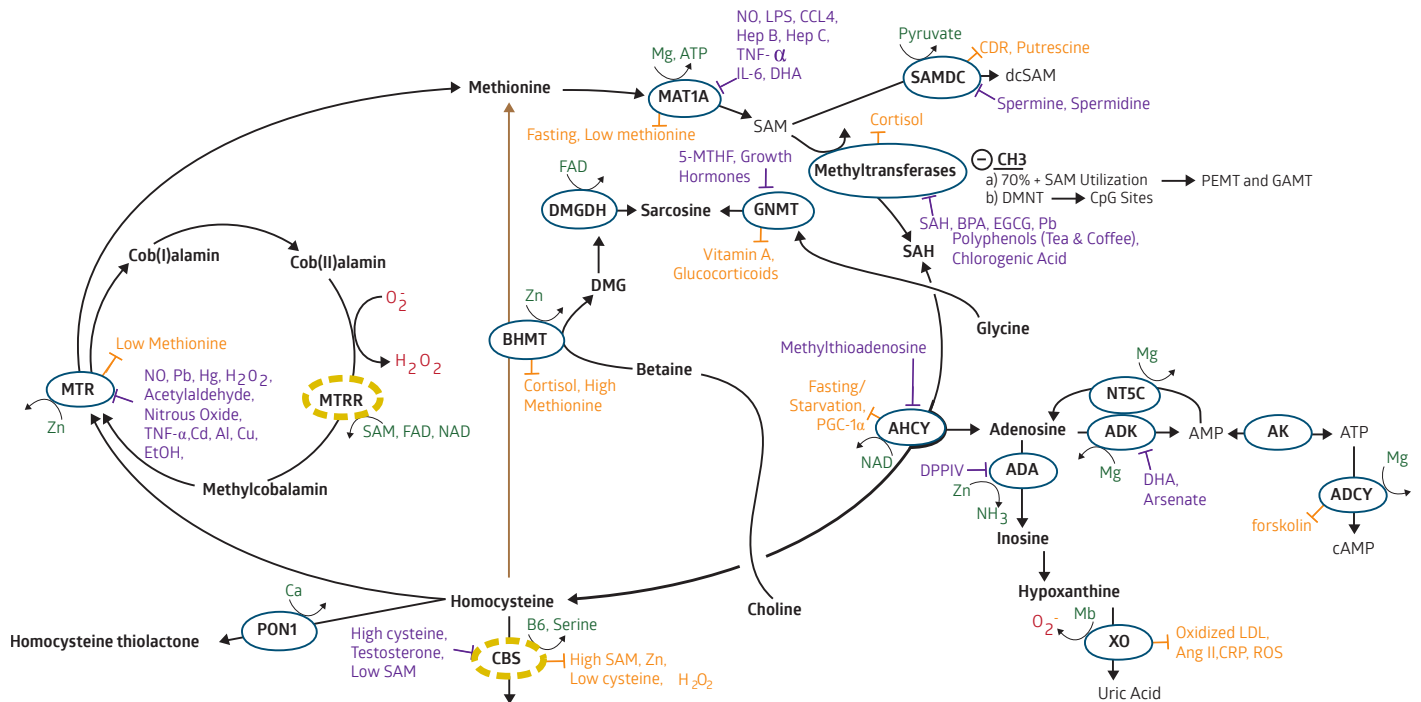
SNP(s) Found:

MTHFR A1298C (+/-, GT) ~20% ↓

- This variant reduces the activity of the MTHFR enzyme by ~20%.
- Associated symptoms and conditions may be neural tube defects (MTHFR 677CT plus MTHFR 1298AC has equal risk for NTD as MTHFR 677TT alone), Alzheimer's disease, schizophrenia.

2.2 The Methionine Cycle

The methionine cycle's main feature is the recycling of homocysteine back into SAMe. Since SAMe is the primary methyl donor in numerous biochemical processes in the body, it is critically important that the methionine cycle functions properly. **If the methionine cycle is dysfunctional, methylation becomes inhibited and homocysteine levels may increase.** The inhibition of SAMe production and/or utilization leads to significant biochemical disturbances. Evaluating methionine cycle function provides a foundation towards identifying the individual's ability to not only produce SAMe but also to utilize it.



2.2.1 METHIONINE CYCLE SNPS

MTRR

The MTRR (Methionine synthase reductase) gene expresses the enzyme needed to restore oxidized cobalamin(II) to CH₃-cobalamin(III) in order to maintain the enzymatic activity of MTR (methionine synthase). MTR, in turn, is responsible for maintaining ample tetrahydrofolate and methionine pools in the cell, which is vital for cellular methylation.

Factors influencing MTRR:

Cofactors: FAD, FMN

↓ Oxidative stress

↑ IGF-1, dopamine

SNP(s) Found:

MTRR A66G (+/-, AG) ↓

- This variant causes a lower affinity of MTRR for the substrate methionine synthase (MTR).
- Associated symptoms and conditions may be altered blood or plasma levels of homocysteine, folate, or vitamin B12 in some but not all studies. (Coexistence with MTHFR C677TT genotype may raise homocysteine more than MTHFR C677TT alone.) Birth defects: Neural tube defects when cobalamin status is low or when MTHFR C677TT is present, Down syndrome, Ventricular Septal Defect (VSD/CHD). Higher risk for meningioma.

MTRR C524T (+/-, CT) ↓

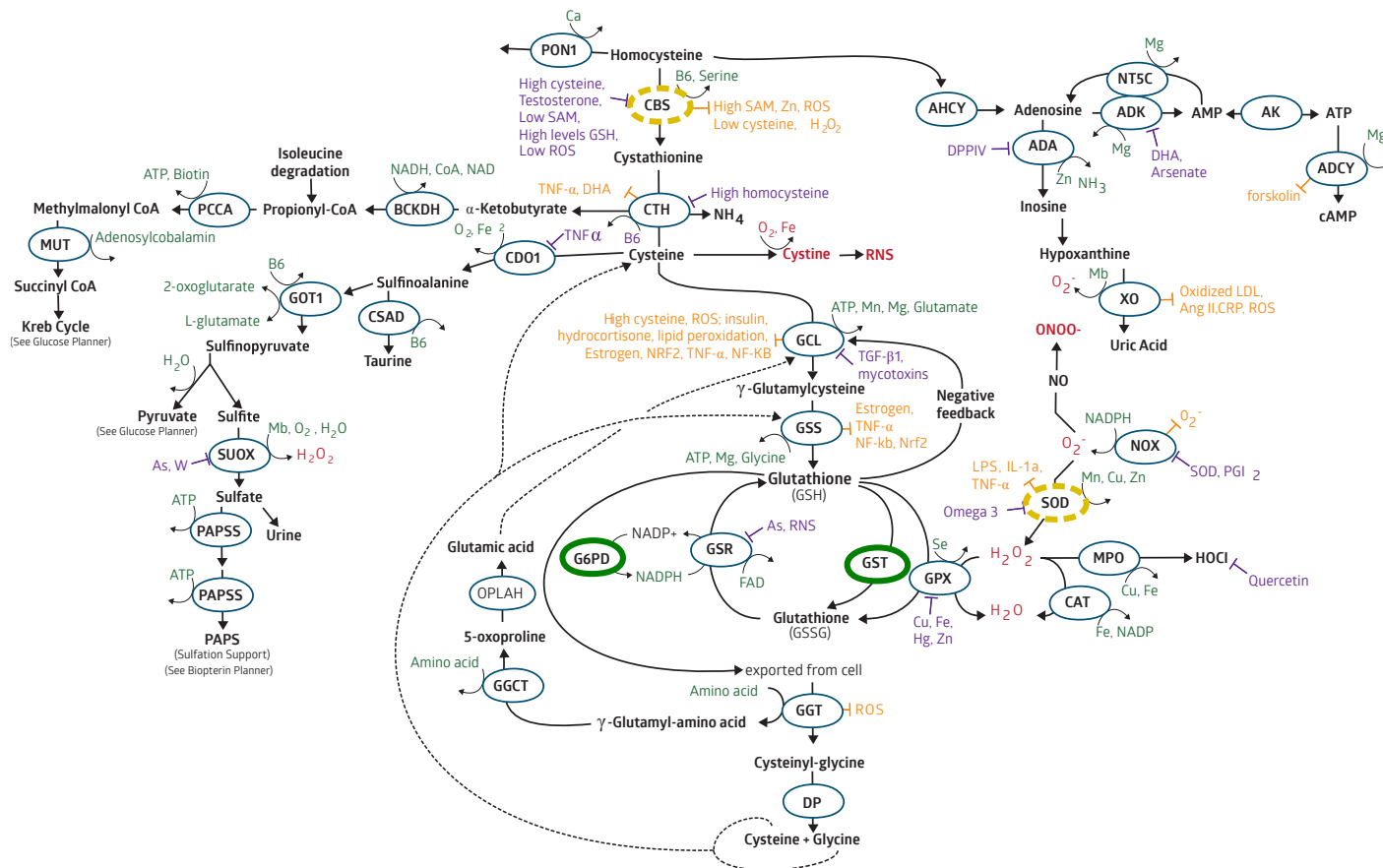
- This variant causes a lower affinity of MTRR for the substrate methionine synthase (MTR).
- Associated symptoms and conditions may be Ventricular Septal Defect (VSD/CHD) and schizophrenia (for the heterozygous variant).

CBS

For information and SNPs related to CBS, please see the transsulfuration pathway section below.

2.3 The Transsulfuration Pathway

The utilization and regulation of cysteine levels are the primary objectives for the transsulfuration pathway. Homocysteine provides the highly needed cysteine substrate for glutathione, taurine, sulfate, hydrogen sulfide and some Krebs Cycle intermediates. If sufficient cofactors are available and if epigenetic factors are favorable, cysteine can participate in this process. On the other hand, when the amount of cysteine exceeds the level needed to synthesize substrate, it must be eliminated as it is harmful in high amounts. Dysfunction in the transsulfuration pathway contributes to a myriad of symptoms and conditions.



2.3.1 TRANSSULFURATION PATHWAY SNPS

CBS

The CBS (Cystathionine beta-synthase) gene encodes the first **rate-limiting enzyme in the transsulfuration pathway**, used for the conversion of homocysteine to cystathionine. A byproduct of this reaction is hydrogen sulfide, which provides important cytoprotective and signaling effects.

Factors influencing CBS:

Cofactors: **P5P and heme**

↓ High cysteine, Testosterone, Low SAM, High levels of GSH (reduced glutathione), low ROS, insulin.

↑ High SAM, Zn, high ROS, low cysteine, H₂O₂, Endotoxemia/LPS, TNF-alpha

SNP(s) Found:

CBS C699T (+/-, AG) ↓↑

- The kinetic effect of this SNP is controversial. Most studies indicate upregulation, but the science is mixed. (See the [FAQ](#) for more information.)
- Associated symptoms and conditions may be pre-eclampsia and increased total cholesterol, LDL, triglycerides.

SOD2

The SOD2 (superoxide dismutase 2) gene encodes a mitochondrial protein that serves as an **important defense against superoxide radicals** by converting them to hydrogen peroxide.

Factors influencing SOD2:

Cofactors: Mn²⁺ (Note: Mn³⁺ can increase ROS and is toxic, as do supraphysiological levels of Mn²⁺)

↓ Selenium, IGF-1

↑ LPS, IL-1a, TNF-alpha, exercise, high MUFA/Mediterranean diet, EtOH, high ROS, vitamin C, sulforaphane, melatonin.

NOTE: SOD2 A16V (rs4880) below is a good example of a "trade-off" SNP where the "risk" allele, as well as wild or ancestral allele, can be found to be epidemiologically risky or beneficial depending on environmental/epigenetic factors. (See the [FAQ](#) for more information.)

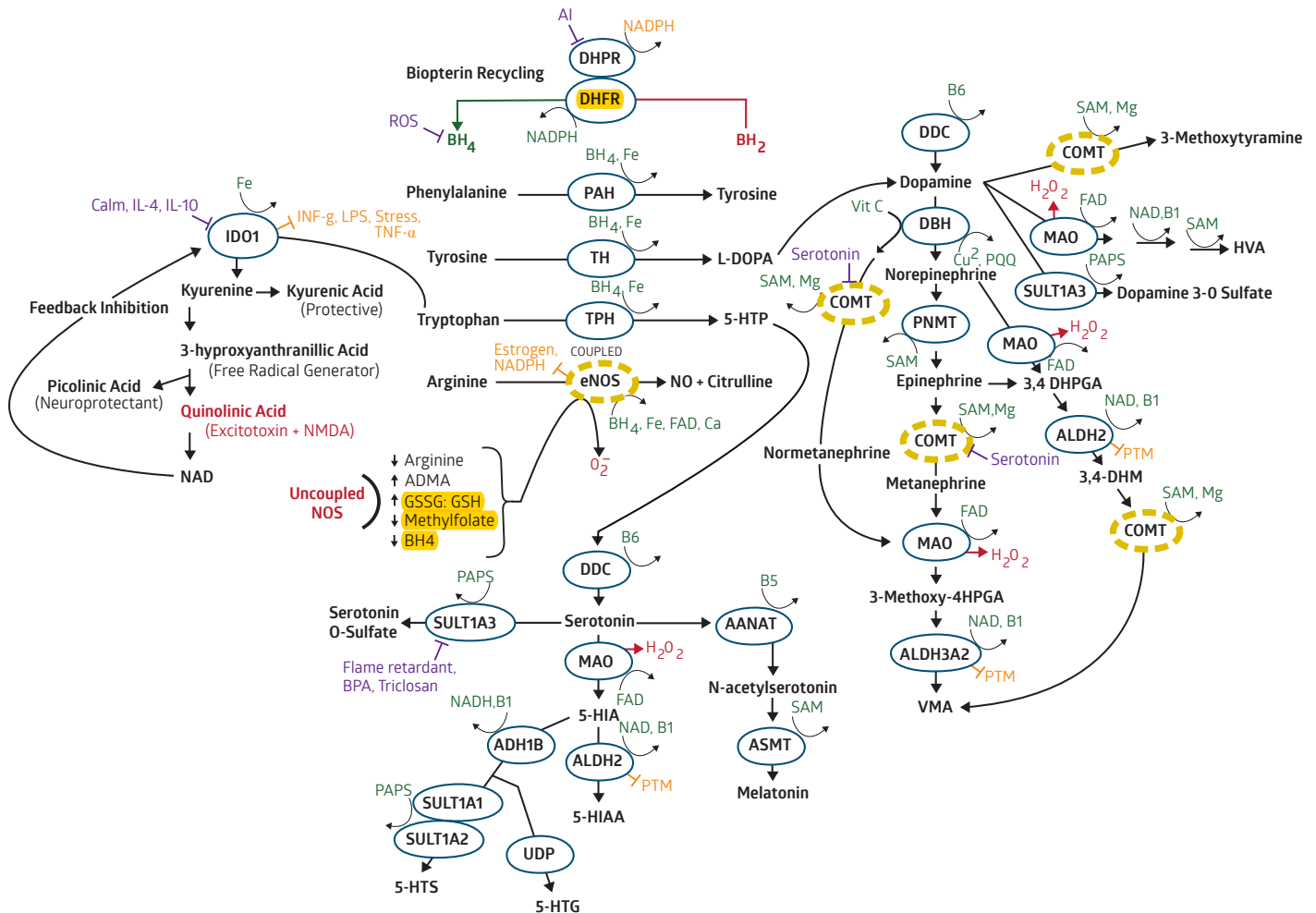
SNP(s) Found:

SOD2 A16V (+/-, AG) ↓↑ ?

- This variant may imply **intermediate activity** relative to AA and GG.
- Associated symptoms and conditions may be osteoporosis, higher total oxidant stress (found in East Asians), acoustic neuroma, more toxic effects from high levels of iron, and earlier onset of symptoms in Wilsons Disease due to potentiated toxicity of copper.

2.4 The Biopterin Pathway

Biopterin is an essential cofactor for neurotransmission and nitric oxide production. The synthesis of dopamine, serotonin, melatonin, norepinephrine, epinephrine and nitric oxide are dependent upon healthy biopterin levels. Neurotransmission and nitric oxide synthesis is negatively affected when oxidized biopterin is not reduced, or substrates and other cofactors are deficient. Evaluating the biopterin pathway allows for an understanding of how the common neurotransmitters and nitric oxide are formed and metabolized.



2.4.1 BIOPTERIN PATHWAY SNPS

NOS3 (eNOS)

The NOS3/eNOS (Nitric oxide synthase 3, endothelial) gene product, eNOS, regulates production of nitric oxide (NO) in endothelial blood vessel cells. The gasotransmitter NO, produced by eNOS, inhibits platelet aggregation, results in relaxation and inhibition of cell proliferation of endothelial smooth muscle, stimulates angiogenesis, **acts as an anti-inflammatory, and prevents oxidative damage.**

Factors influencing NOS3 (eNOS):

Cofactors: Heme, FAD, FMN, tetrahydrobiopterin (BH4)

↓ TNF-alpha, low arginine, low BH4, low methylfolate, high ADMA, high GSSG (oxidized glutathione), high peroxynitrate, and a "SAD"-diet (a diet high in fat and refined carbohydrates)

↑ Estrogen, NADPH, acetylcholine, serotonin, insulin, vinegar

SNP(s) Found:

NOS3/eNOS A(-922)G (+/-, AG) ↓

- This variant is theorized to decrease NOS3 activity.
- Associated symptoms and conditions may be ischemic stroke and limb defects in children born to smoking mothers who do not supplement with vitamins during pregnancy.

COMT

The COMT (catechol-O-methyltransferase) gene encodes the COMT enzyme, which is an important catabolic enzyme, especially in the prefrontal cortex, where it **degrades catecholamines**. Since the COMT enzyme is involved in the degradation of catechol estrogens, genetic mutations that decrease enzymatic activity can lead to elevations in catechol estrogens, which have been shown to damage DNA and have carcinogenic potential. Higher levels of COMT enzymatic activity also result in decreased levels of dopamine and norepinephrine.

Factors influencing COMT:

Cofactor: Mg²⁺

↓ Serotonin, anti-psychotic Rx, low folate or Vit D, estrogen, quercetin, EGCG, soy isoflavones, TNF-alpha.

↑ Hypoxia, traumatic brain injury, LPS, L-dopa, testosterone. Progesterone may increase or decrease activity depending on progesterone receptor distribution.

NOTE: COMT regulation has complex, tissue-specific, reciprocal relations with many pathways in the body such as folate-homocysteine metabolism and catecholesterogen metabolism. COMT V158M (rs4680) below is a good example of a "trade-off" SNP where the "risk" allele, as well as wild or ancestral allele, can be found to be epidemiologically risky or beneficial given environmental/epigenetic factors.

SNP(s) Found:

COMT V158M (+/-, AG)

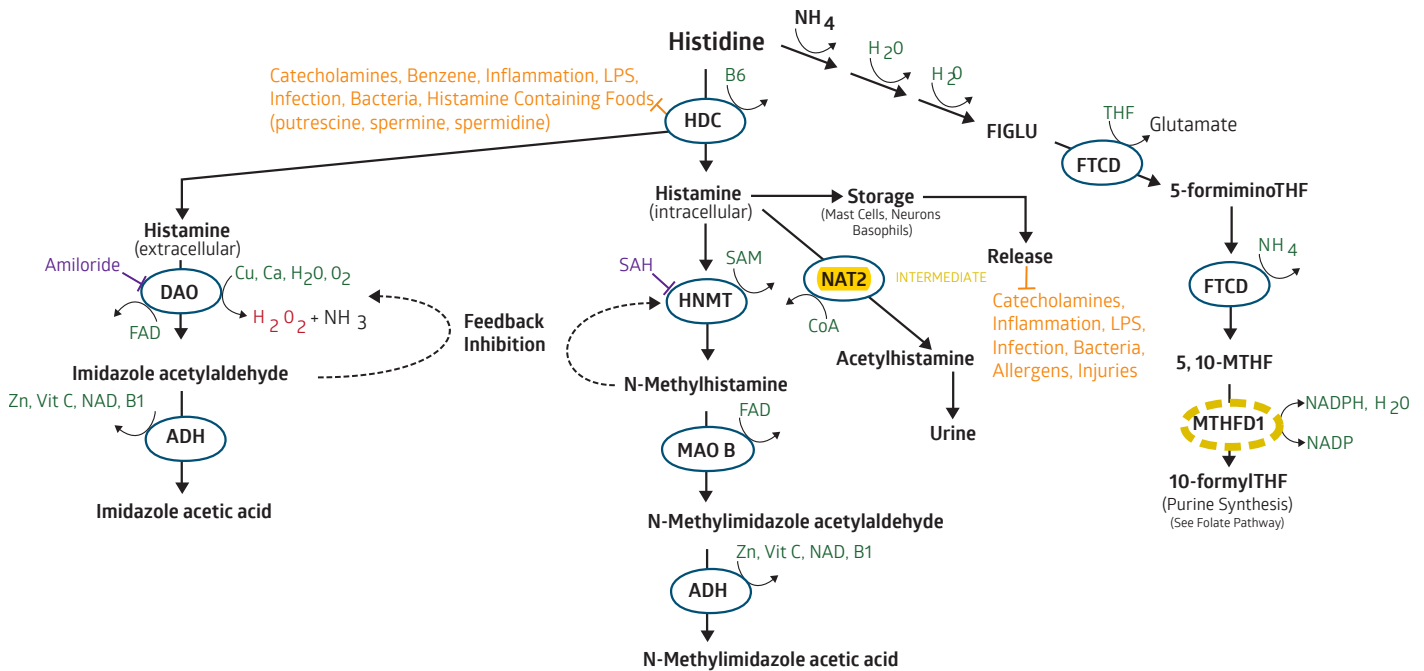
- This variant is associated with **intermediate levels of COMT activity** (vs. AA and GG). There is mounting evidence this variant contributes to the most balanced metabolism of neurotransmitters.
- May be protective against schizophrenia, and is associated with better outcomes in low back pain compared to AA or GG types.

COMT H62H (+/-, CT) ↓

- This variant is likely associated with **intermediate COMT activity** due to reduced expression relative to wild type (CC).
- The CT genotype was found to be protective for schizophrenia and had significantly better outcomes in low back pain than CC or TT types.

2.5 The Histamine Pathway

Histamine is a significant player in human health. The histamine pathway controls the regulation of intracellular and extracellular histamine. Understanding how histamine is formed and metabolized both intracellularly and extracellularly may provide significant findings in resolving health complaints.



2.5.1 HISTAMINE PATHWAY SNPS

NAT2

The NAT2 (N-Acetyltransferase 2) gene encodes for an enzyme which is **responsible for phase II activation or detoxification of xenobiotics** such as arylamines. NAT2 is also involved in the acetylation of the neurotransmitter serotonin and compounds such as histamine. Polymorphisms in this gene affect enzymatic activity and result in a categorization of rapid, intermediate, or slow acetylators.

Factors influencing NAT2:

Cofactor: Acetyl CoA

- ↓ Acetaminophen, Cisplatin, Triazole, glycyrrhizic acid (licorice root), diallyl sulfide (garlic)
- ↑ Ezogabine, Chlorzoxazone

Predicted NAT2 Acetylator Phenotype:

INTERMEDIATE (0.996965)

- This phenotype implies an **intermediate rate of clearance of various drugs, environmental chemicals, and histamine** relative to the slow and fast phenotypes.

Section 3: Bonus SNPs

Bonus SNPs are not represented in the Pathway Planner graphics, but may provide useful additional information to assist patient care decisions. Note: Discussed below are SNPs for which a notable genotype was found (usually +/+ and +/-).

BCO1 (PKD1L2) C754T (+/-, AG) ↓

AA females are 60% less efficient than GG at beta carotene conversion. AG females rate of conversion is 25% less efficient. Note: The intrinsic variability in the BCO1 activity is found in men as well, presumably due to the same SNPs, but currently there is no published research that examines a male population to investigate the impact. **Consider Vitamin A supplementation** especially in vegan individuals.

BCO1 rs11645428 (+/-, AG) ↓

GG females are 50% less efficient at conversion than AA, with AG women in between. GG females are 50% less efficient at conversion than AA, with AG women in between. Note: The intrinsic variability in the BCO1 activity is found in men as well, presumably due to the same SNPs, but currently there is no published research that examines a male population to investigate the impact. **Consider Vitamin A supplementation especially in vegan** individuals.

BCO1 rs6564851 (+/-, GT) ↓

GG females are 50% less efficient at conversion than TT, with GT women in between. Note: The intrinsic variability in the BCO1 activity is found in men as well, presumably due to the same SNPs, but currently there is no published research that examines a male population to investigate the impact. **Consider Vitamin A supplementation especially in vegan individuals.**

FUT2 rs601338 (+/-, AG)

Carriers of at least one G allele are secretors and are more likely to be B12 deficient. For more information about secretor status see the work of [Peter D'Adamo, ND](#)

PEMT 5465G>A (+/+, TT) ↓

TT **decreases PEMT activity by approximately 30%**. CT also decreases PEMT activity but not as much as TT. A meta-analysis of all studies on NAFLD showed a significant association with TT individuals, especially in Asian populations. In a large case-controlled study, CT and TT Caucasian women with low betaine intake had 2x the risk for breast CA. A case controlled study showed increased risk for Alzheimers in CT and TT Chinese women. It is theorized in humans with enough choline from dietary sources, rs7946-TT is **helpful as it spares methyl groups for other biological activities**. It is also theorized this SNP is selected for because it protects against disease, most notably, malaria, via diminished choline in the human host which impairs the replication of the malaria parasite. **Consider supplementing with choline** before and during pregnancy, and after menopause.

FADS1 (MYRF) rs174537 (+/+, GG) ↑

GG and GT individuals have higher than average arachidonic acid (AA), LDL and total cholesterol levels due to upregulated elongation of omega 6 PUFAs to pro-inflammatory compounds. **Consider limiting dietary sources of omega-6 PUFAs, esp. AA.**

VDR Taq1 (+/-, AG)

Ancestral allele (A) is reported here as minus (-) and mutated/derivative allele (G) as plus (+). Regardless of allele inheritance (AA, AG, or GG), **maintenance of optimal serum 25-hydroxy Vitamin D levels is recommended.** Evaluation of 1,25-hydroxy D status may also be warranted. (Also see the [FAQ](#) for more information.)

VDR Bsm1 (+/-, CT)

Ancestral allele (C) is reported here as minus (-) and mutated/derivative allele (T) as plus (+). Regardless of allele inheritance (CC, CT, or TT), **maintenance of optimal serum 25-hydroxy Vitamin D levels is recommended.** Evaluation of 1,25-hydroxy D status may also be warranted. (Also see the [FAQ](#) for more information.)

APOE genotype: APOE 3/4

More information on ApoE status can be found [here](http://www.ncbi.nlm.nih.gov/pubmed/19414656) (http://www.ncbi.nlm.nih.gov/pubmed/19414656). Go to the free full text link, and scroll through the article to the section: "ApoE Genotype".