StrateGene

Genetic Pathway Analysis

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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: bengreenfield

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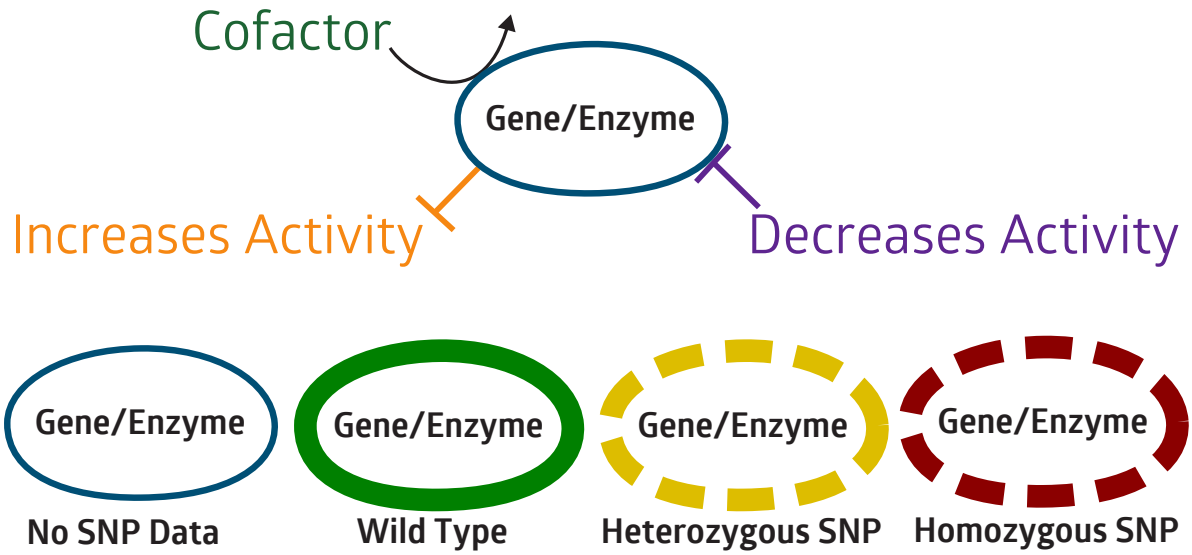
Symbols and Colors



Section 1: Overview

Core SNPs

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

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

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

Bonus SNPs

RS#	Call	Risk Allele	Gene	Variation	Result
rs12934922	TT	T	**BCO1**	R267S	+/+
rs7501331	CC	T	**BCO1**	A379V	-/-
rs6420424	AG	A	**BCO1 (PKD1L2)**	C754T	+/-
rs11645428	AG	G	**BCO1**		+/-
rs6564851	TT	G	**BCO1**		-/-
rs601338	AG	A	**FUT2**		+/-
rs1800566	GG	A	**NQO1**		-/-
rs1800562	GG	A	**HFE**	C282Y	-/-
rs1799945	CC	G	**HFE**	H63D	-/-
i3002468	AA	T	**HFE**	Ser65Cys	-/-
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	TT	C	**APOE**		-/-

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

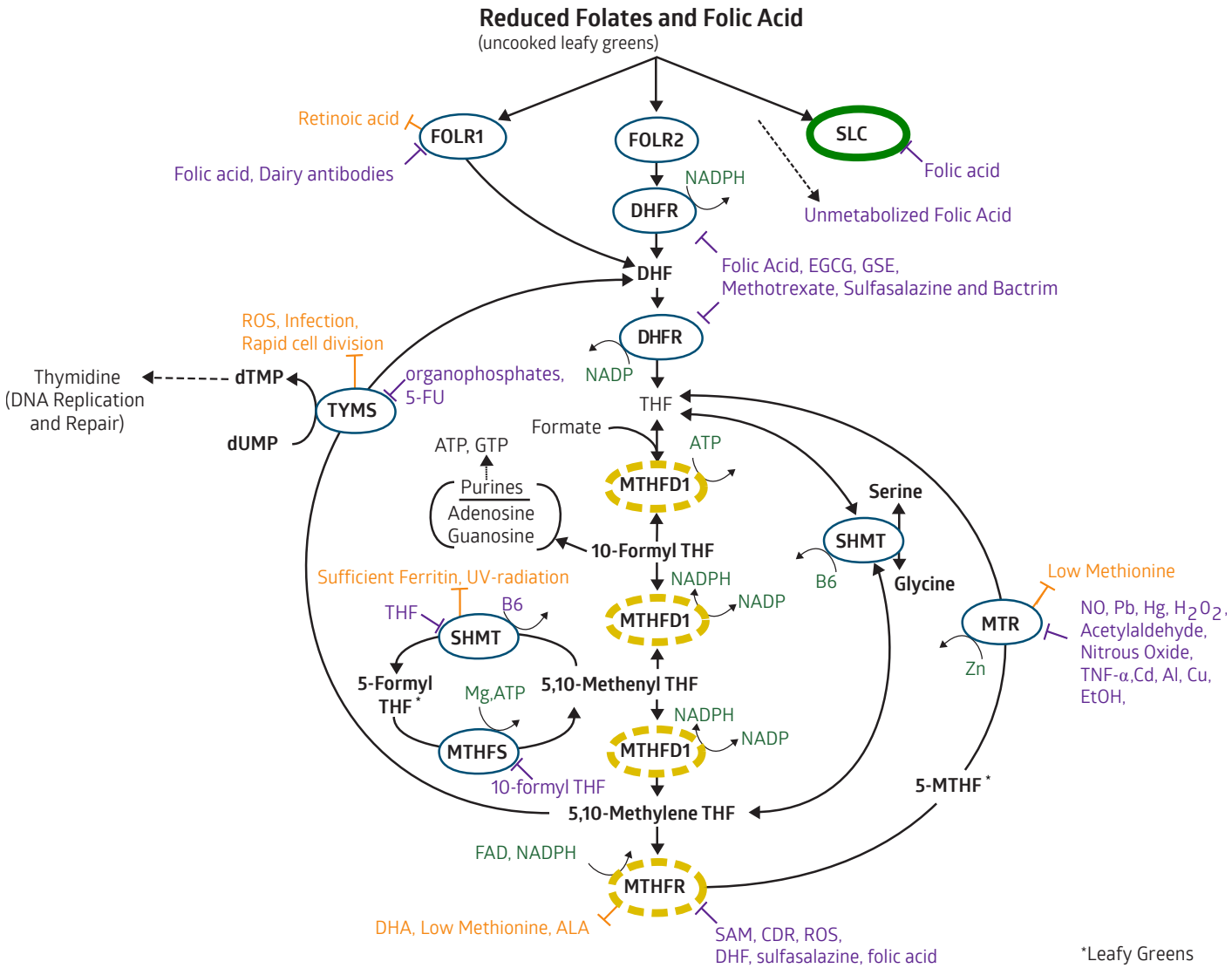
APOE genotype: APOE 3/3

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), sulfasalzine, folic acid, phenytoin (Dilantin)

↑ DHA and ALA (PUFAs), low methionine

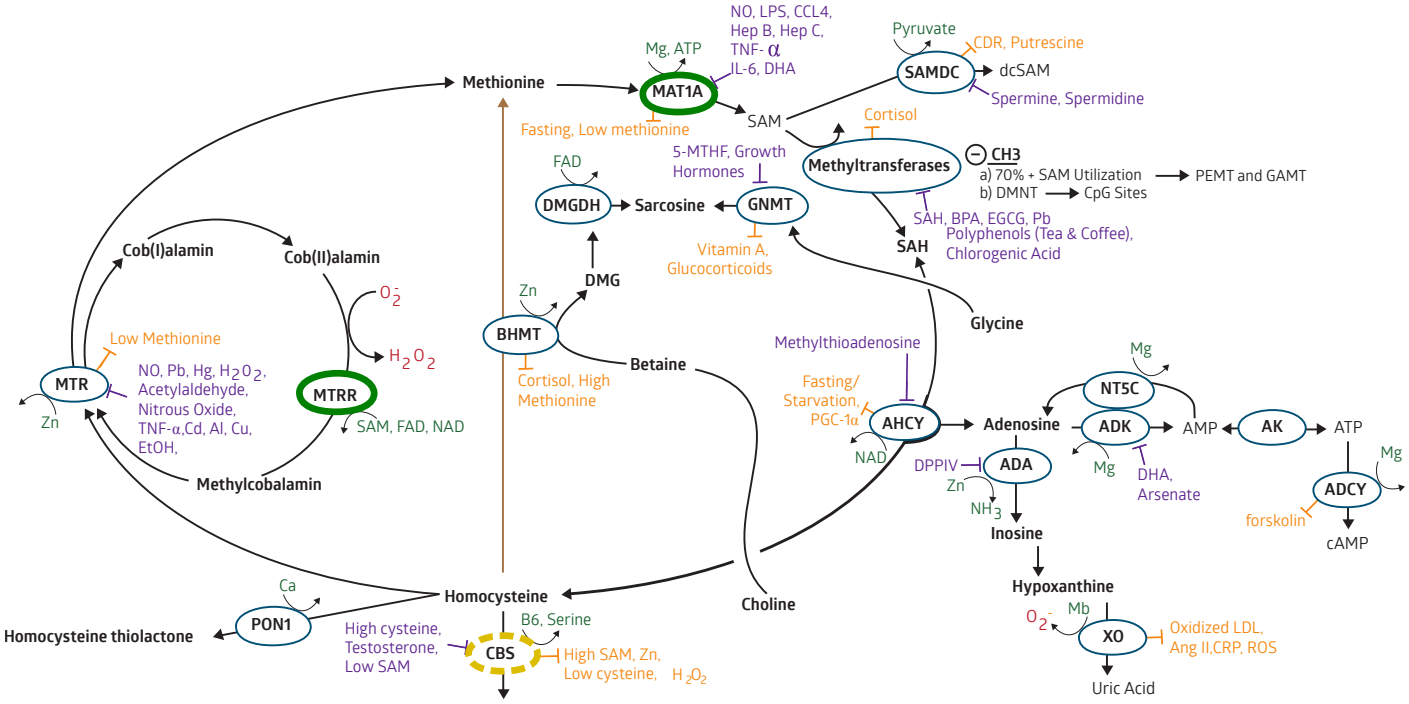
SNP(s) Found:

MTHFR C677T (+/-, AG) ~30% ↓

- This variant reduces the activity of MTHFR by ~30%.
- Associated symptoms and conditions may be premature coronary artery disease, male infertility (especially in Asians), hypertension, congenital heart disease (in Asians/ Caucasians where both mother and child have at least one T allele), and possibly oral clefts, Down syndrome, and fetal anticonvulsant syndrome.

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.



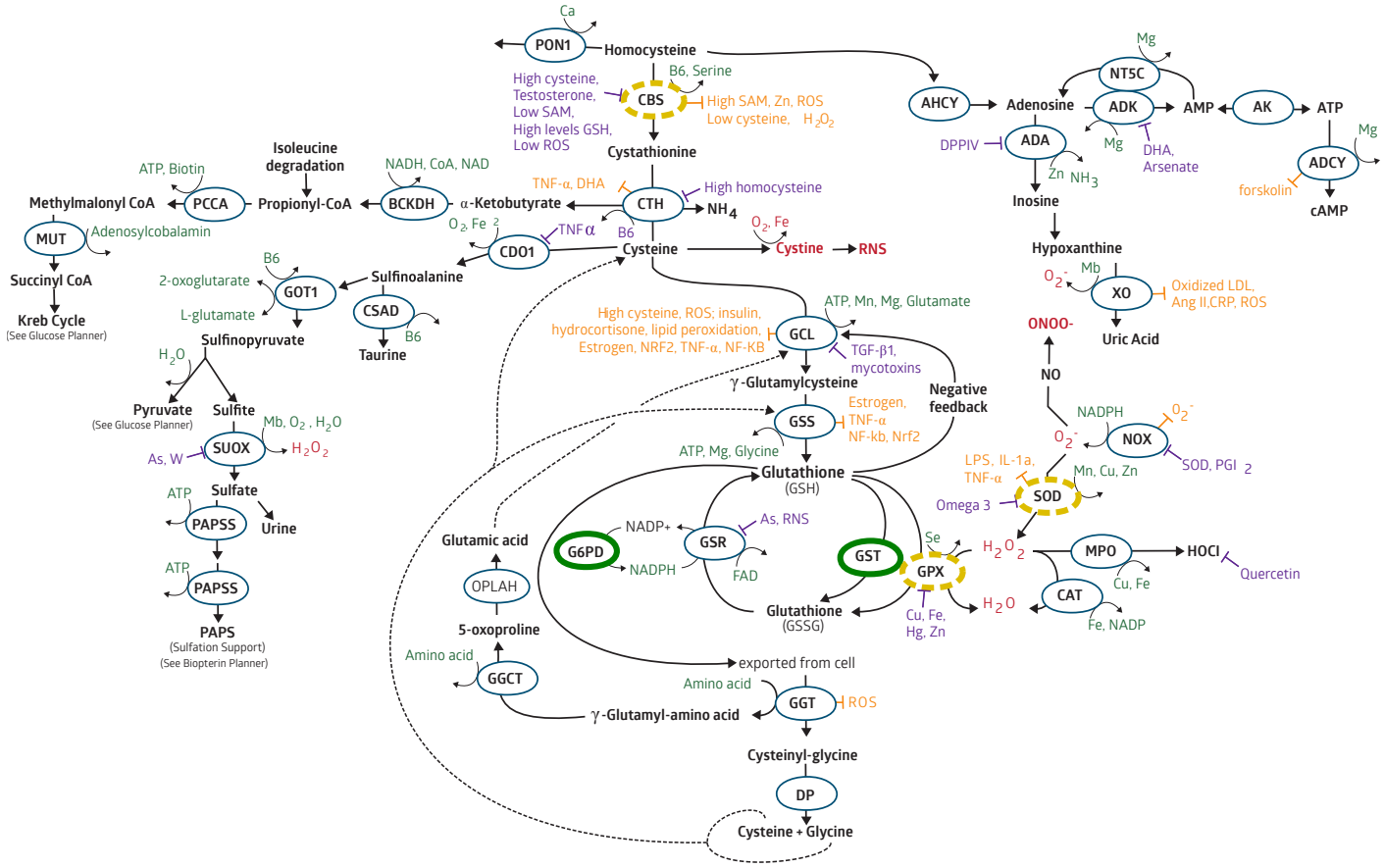
2.2.1 METHIONINE CYCLE SNPS

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 C19150T (+/-, AG) ↓

- This variant likely results in decreased CBS activity.
- Associated symptoms are increased levels of urinary monomethylarsonic acid (an arsenic metabolite that is more acutely toxic than inorganic arsenic), and increased homocysteine.

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), accoustic neuroma, more toxic effects from high levels of iron, and earlier onset of symptoms in Wilsons Disease due to potentiated toxicity of copper.

GPX

The GPX (Glutathione peroxidase 1) gene encodes a protein responsible for the detoxification of peroxides. There are 8 known isoforms of glutathione peroxidase (GPx 1-8). This family of enzymes primarily protects from harmful levels of hydrogen peroxide within the cell.

Factors influencing GPX:

Cofactors: Selenium, in the form of a selenoprotein

↓ Cu, Fe, Hg, Zn

↑ High H2O2, high ROS, spirulina, vitamin C, and, indirectly, via increased glutathione production: alpha-lipoic acid and sulforaphane.

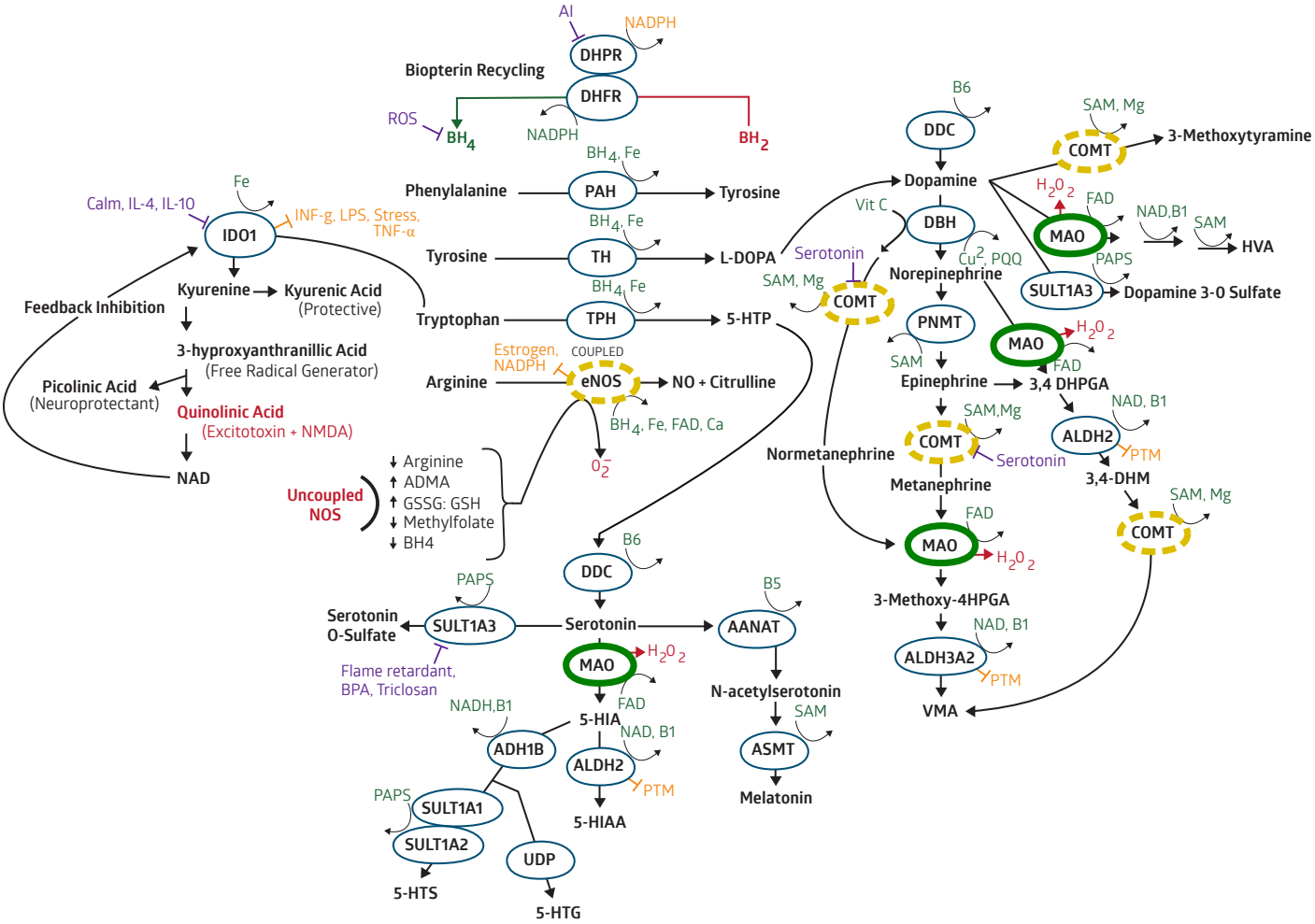
SNP(s) Found:

GPX1 Pro199Leu (+/-, AG) ~9-13% ↓

- This variant downregulates the enzyme's activity in RBC by between 9% (AG/AA) to 13% (AA in males).
- Associated symptoms and conditions may be osteoporosis, cardiovascular diseases, drug-induced liver damage, peripheral neuropathy in diabetes, and cancer (lung and breast). In AA Japanese men an increased risk for metabolic syndrome was found. Carriers may also be at increased risk for mortality in septic shock. However, in a Danish population, an association with longevity was found, which may be due to advantageous effects of oxidative stress in certain amounts and contexts.

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 -1495A>T (+/-, AT) ↓

- This variant is theorized to decrease NOS3 activity.
- Associated symptoms and conditions may be unexplained stillbirth and diabetic nephropathy.

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.

MAO A

The MAO A (monoamine oxidase type A) gene codes for the mitochondrial membrane enzyme that catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. MAO A preferentially oxidizes biogenic amines such as 5-hydroxytryptamine (5-HT), norepinephrine and epinephrine. MAO A oxidizes dopamine, noradrenaline, adrenaline, tryptamine and tyramine. MAO A is located on the x chromosome and females have inherently higher activity as a result of two x chromosomes.

Factors influencing MAO A:

Cofactor: FAD

↓ Smoking, caffeine, berberine, curcumin, quercetin; androgens (including testosterone), estrogen (in kidney, uterus and brain). Tyramine containing foods: aged cheeses, cured, smoked or processed meats, fermented foods and sauces, soy products, fava beans and snow peas, yeast spreads (marmite), beer and some alcohols. Reversible MAO inhibitors (e.g. pseudoephedrine, ephedrine, norephedrine) heteroaryl-based chalcones are potent MAO-A inhibitors, moclobemide. Beware of polypharmacy and drug-food interactions as MAO inhibition effects are often additive.

↑ Reserpine, progesterone, EtOH, valproic acid, diabetes, T2 cytokines, and ascorbic acid in doses >4 grams (which can also reverse inhibition caused by caffeine).

> NOTE: The MAO A variant most studied consists of a 30 base-pair variable number tandem repeat (VNTR) located in the promoter region of the gene popularly known as the "warrior gene". This VNTR variant, unfortunately, cannot be ascertained reliably from 23andMe raw data.
>
> MAO A and B SNPs discussed below are good examples of "trade-off" SNPs 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:

MAOA T941G (-/-, T) ↓

- This variant is associated with normal / wild type MAO A (slower activity compared to GG and GT).

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 norephinephrine.

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 catecholestrogen 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)

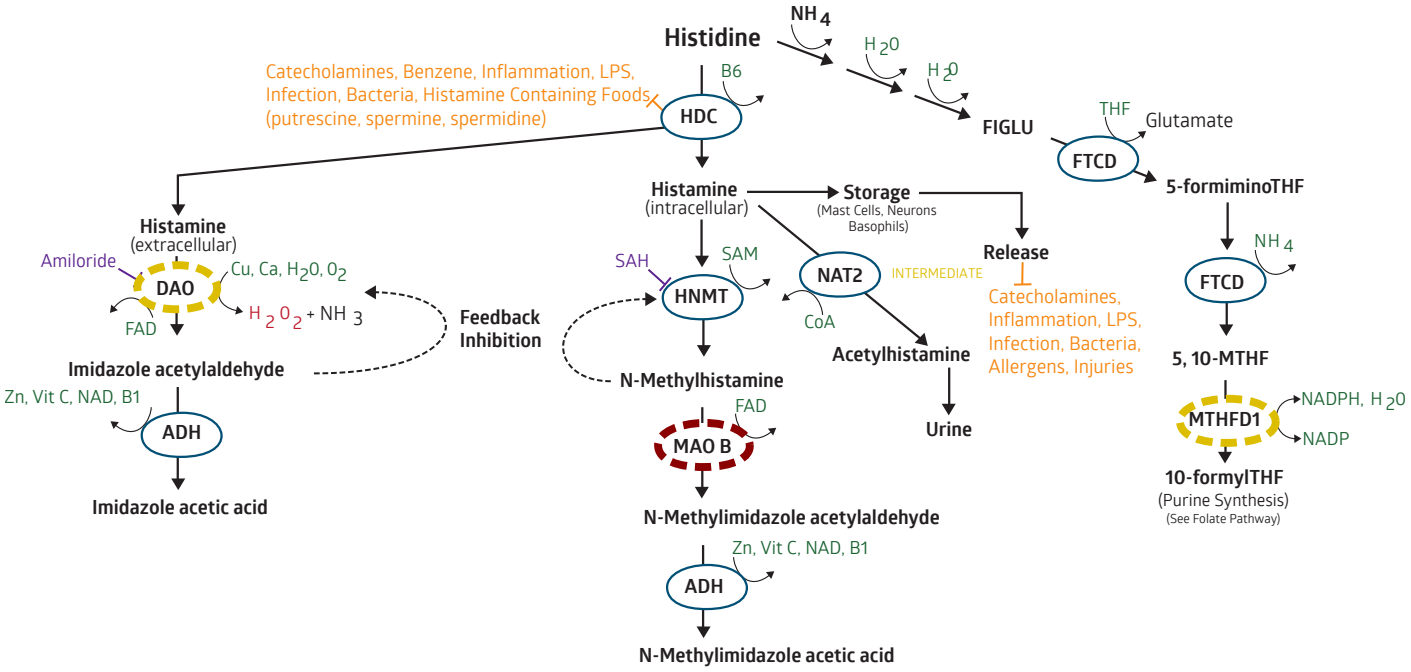
- This variant is associated with intermediate levels of COMT activity (vs. AA and GG). There is mounting evidence this variant contributes to the most balanced metabolism of neurotransmitters.
- May be protective against schizophrenia, and is associated with better outcomes in low back pain compared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

AOC1

The AOC1 (Diamine Oxidase; Amine Oxidase, Copper Containing 1) gene encodes a metal-binding membrane glycoprotein (**DAO** , Diamine Oxidase) that oxidatively deaminates putrescine and histamine, thereby forming hydrogen peroxide.

Factors influencing AOC1:

Cofactors: Cu, Ca

↓ Amiloride

SNP(s) Found:

AOC1 (DAO) Thr16Met (+/-, CT) ↓

- The heterozygous variant's impact on DAO activity is unclear, however the homozygous variant is associated with reduced DAO activity and increased circulating histamine levels.
- Associated symptoms and conditions may be migraines and hypersensitivity to NSAIDs.

MAO B

The MAO B (monoamine oxidase type B) gene codes for the mitochondrial membrane enzyme that catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. MAO B preferentially degrades benzylamine and phenylethylamine. MAO B is most abundant in serotonergic and histaminergic neurons and glial cells. MAO B oxidizes dopamine, noradrenaline, adrenaline, tryptamine and tyramine. MAO B is located on the X chromosome.

Factors influencing MAO B:

Cofactor: FAD

↓ Acetylenic compounds such as chlorgyline, 1-deprenyl, and pargyline; Rasagiline (a Parkinson's drug), smoking, caffeine, berberine, curcumin, quercetin, EGCG, androgens (including testosterone), estrogen (in liver, kidney and uterus). Tyramine containing foods: aged cheeses, cured, smoked or processed meats, fermented foods and sauces, soy products, fava beans and snow peas, yeast spreads (marmite), beer and some alcohols. Phellodendron amurense, Cyamopsis psoralioides, Glycyrrhiza glabra and G. uralensis root, and many more herbs that can be found here . Beware of polypharmacy and drug-food interactions as MAO inhibition effects are often additive.

↑ Reserpine, progesterone, alcohol, increasing age, H2O2, and ascorbic acid in doses >4 grams (which can also reverse inhibition caused by caffeine).

SNP(s) Found:

MAOB rs1799836 (+/+*, C) ↓

- This variant is associated with lower MAO B activity in the brain.
- Associated symptoms and conditions are schizophrenia (in a Han Chinese population and in a Spanish population).

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 converson 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.

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 3/3
More information on ApoE status can be found here (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".