# StrateGene®

## Strategic Genetic Analysis

Presented by SeekingHealth®

## Prepared For: Ben

What you're about to uncover in these upcoming pages is extremely powerful!

You finally have the opportunity to 'peek under the hood' and see You.

By discovering your unique genetic makeup using StrateGene®, you'll learn how you can truly optimize your life.

There is no such thing as a "bad" report, or a "good" report—just unique. You won't find any 'red' or 'yellow' colors here that symbolize 'bad' or 'warning'. Instead, you'll learn that some of your genes naturally work slower and some naturally work faster. It's important that you know this information so you can adapt. If you don't know how your genes are built, you've no idea how your choices impact you.

You can change the way your genes function by changing your environment, mindset, food, and lifestyle. Your StrateGene® Report helps you make targeted choice after targeted choice which creates the optimal environment for your genes—one choice at a time. The result? You'll ultimately function at your best—and you'll know why.

Your journey to the best version of You is about to begin!

Here is where you start: 👉 "How to Understand Your StrateGene® Report" 👈

To get the most out of your report, we encourage you to have a health professional help you analyze your StrateGene® Report. They will help you implement specific recommendations. It will be more efficient, cost-saving, and rewarding.

**Important Disclaimer:**

Although this report may provide useful diagnostic information, StrateGene.Me, Dirty Genes LLC, and Seeking Health LLC do not make or suggest any specific diagnosis or therapeutic course of treatment or action. Any such diagnosis and/or treatment plan is strictly a matter between the patient and his or her qualified healthcare professional.

The StrateGeneV1 array is a single-nucleotide polymorphism (SNP)-based assay, used to detect variants for the generation of the StrateGene report. It demonstrates a 99.98% concordance internally and 99.67% concordance with previously validated SNP-based assay.

To best navigate this report, we highly recommend saving and reading it on Acrobat Reader (For PC users) or Preview (For Mac users).

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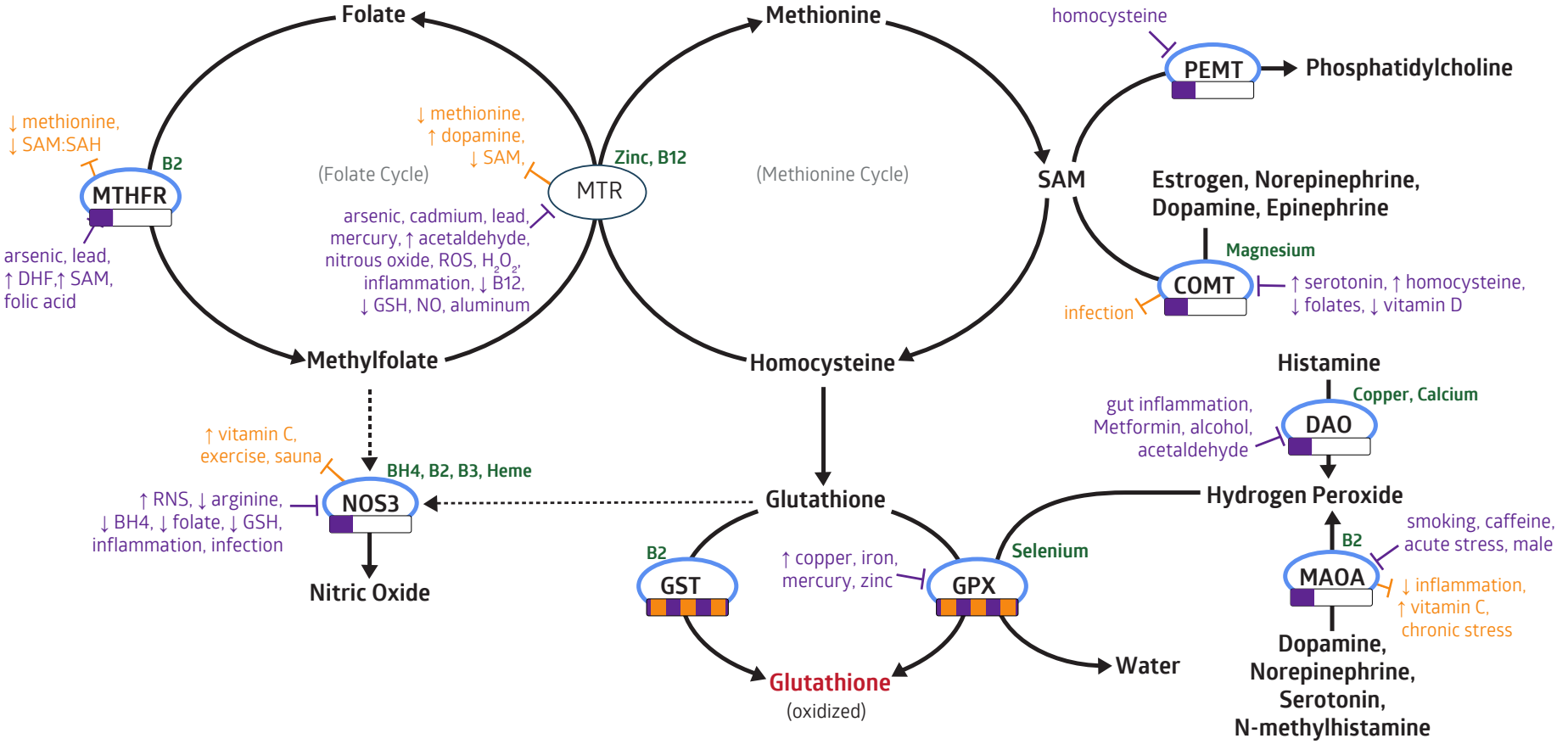
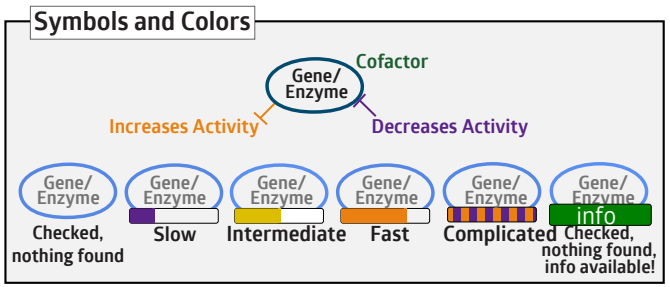
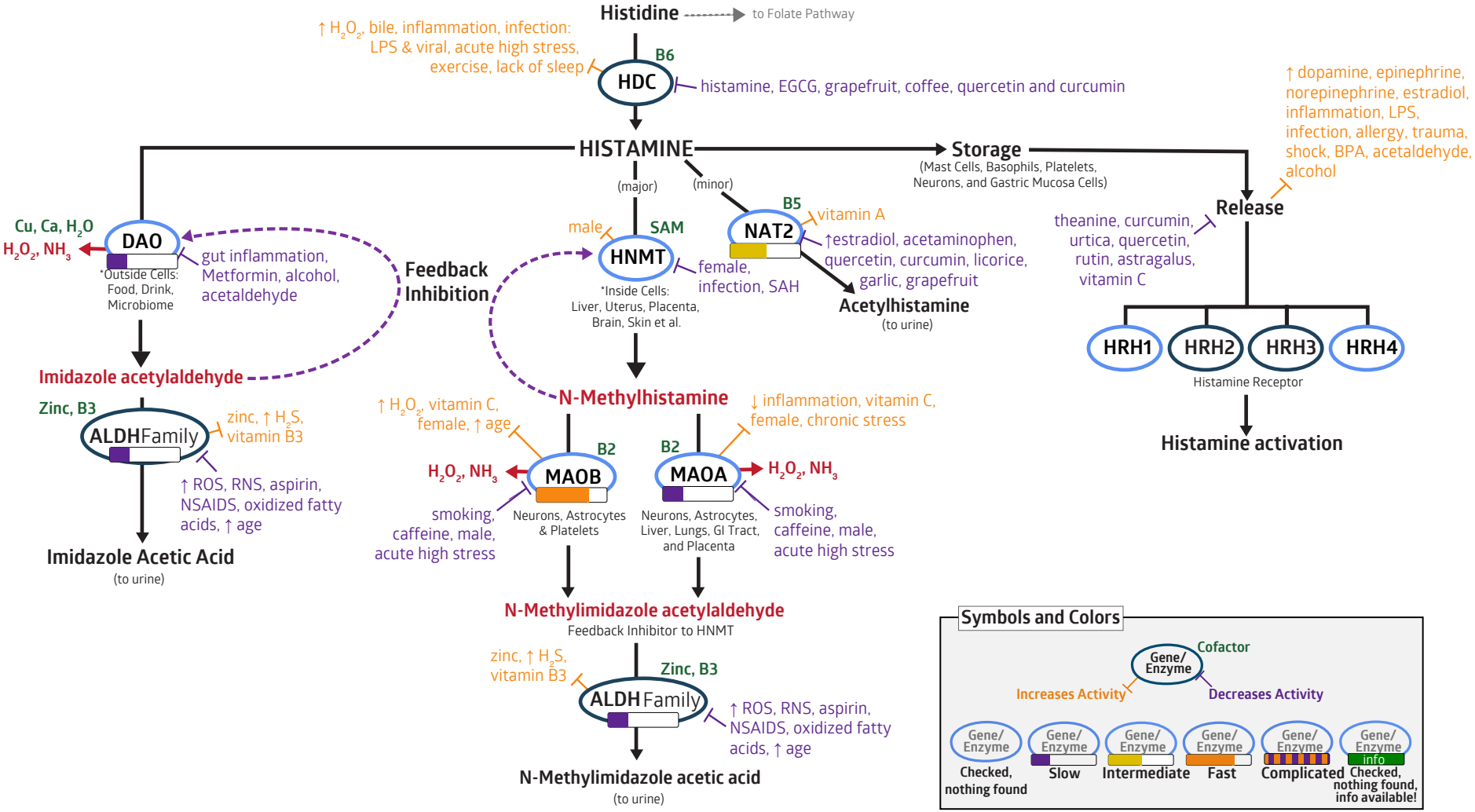
# The Super Seven (from Dirty Genes)





# Histamine


Histidine
to Folate Pathway
↑ $H_2O_2$, bile, inflammation, infection: LPS & viral, acute high stress, exercise, lack of sleep
B6
HDC
histamine, EGCG, grapefruit, coffee, quercetin and curcumin
HISTAMINE
Storage
(Mast Cells, Basophils, Platelets, Neurons, and Gastric Mucosa Cells)
↑ dopamine, epinephrine, norepinephrine, estradiol, inflammation, LPS, infection, allergy, trauma, shock, BPA, acetaldehyde, alcohol
Release
theanine, curcumin, urtica, quercetin, rutin, astragalus, vitamin C
(major)
(minor)
Cu, Ca, $H_2O$
$H_2O_2$, $NH_3$
DAO
*Outside Cells: Food, Drink, Microbiome
gut inflammation, Metformin, alcohol, acetaldehyde
Feedback Inhibition
male
SAM
HNMT
*Inside Cells: Liver, Uterus, Placenta, Brain, Skin et al.
female, infection, SAH
B5
NAT2
vitamin A
↑estradiol, acetaminophen, quercetin, curcumin, licorice, garlic, grapefruit
Acetylhistamine
(to urine)
HRH1
HRH2
HRH3
HRH4
Histamine Receptor
Histamine activation
Imidazole acetylaldehyde
Zinc, B3
ALDHFamily
zinc, ↑ $H_2S$, vitamin B3
↑ ROS, RNS, aspirin, NSAIDS, oxidized fatty acids, ↑ age
Imidazole Acetic Acid
(to urine)
N-Methylhistamine
↑ $H_2O_2$, vitamin C, female, ↑ age
↓ inflammation, vitamin C, female, chronic stress
B2
MAOB
MAOA
$H_2O_2$, $NH_3$
smoking, caffeine, male, acute high stress
Neurons, Astrocytes & Platelets
Neurons, Astrocytes, Liver, Lungs, GI Tract, and Placenta
N-Methylimidazole acetylaldehyde
Feedback Inhibitor to HNMT
zinc, ↑ $H_2S$, vitamin B3
Zinc, B3
ALDH Family
↑ ROS, RNS, aspirin, NSAIDS, oxidized fatty acids, ↑ age
N-Methylimidazole acetic acid
(to urine)
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
info
Checked, nothing found, info available!

# THE DAO/AOC1 GENE

The DAO (diamine oxidase or amine oxidase aka AOC1) gene expresses an enzyme which catalyzes the degradation of compounds such as histamine and polyamines (putrescine, spermine, and spermidine) to form hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$). Copper (Cu) and calcium (Ca) are cofactors for this reaction.

Histamine metabolized by DAO comes from foods, drinks and bacteria found in the digestive tract.

Polyamines are involved in allergic and immune responses as well as cell proliferation, tissue differentiation, tumor formation, and possibly pre-programmed cell death (apoptosis).

Placental DAO is thought to play a role in healthy pregnancy as high histamine during pregnancy leads to many pregnancy complications. Thus, DAO is a very important gene to keep clean during pregnancy. DAO is feedback inhibited by its end product so be sure the ALDH family of genes is functioning well.

**Important Notes:**

- The more the DAO enzyme reduces histamine, the more hydrogen peroxide and ammonia are produced. These compounds are quite reactive and may damage the intestinal lining and contribute to numerous problems.
- As with many genes, DAO is heavily influenced by the environment, food and lifestyle. Even if one does not have variants, the DAO gene may be significantly underperforming leading to histamine intolerance.
- Histamine intolerance is extremely common and really impacts one's quality of life. Be sure to read the DAO chapter in *Dirty Genes* and take the quiz to see how your DAO is acting in real time.

## 💩 Dirties your DAO/AOC1 gene

**Environment:** Avoid aldehydes from the environment such as smog, vehicle emissions, smoking (especially secondhand exposures), cooking fumes, formaldehyde from building materials; xenoestrogens. The harder the DAO enzyme needs to work in order to detoxify these environmental chemicals, the more ammonia ($NH_3$) and hydrogen peroxide ($H_2O_2$) are produced as by-products.

## Notable variation:

SNP: **DAO/AOC1 -691G>T rs2052129 (+/-, GT)**
This GT variant may exhibit slightly less activity compared to wild type.

SNP: **DAO/AOC1 47C>T rs10156191 (+/-, CT)**
This CT variant exhibited slightly less activity in one vitro experiment.

## Dirties your DAO/AOC1 gene, continued...

**Lifestyle:** Avoid alcohol, especially red wine and champagne. Alcohol is especially problematic if individuals have inherited either a fast ADH1B (not present) or fast ADH1C (not present) and/or slow ALDH2 (present). Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections. Some gastrointestinal tract bacteria are big producers and/or stimulators of histamine as well as the common parasite: *Blastocystis hominis*.

**Food:** Avoid known food allergies and intolerances, leftovers, histamine liberating foods, non-fresh foods especially fish and meat.

**Supplements and Medications:**

- Be very mindful of what probiotics you are taking. *Lactobacillus fermentum* and *L. bulgaricus* are known to increase histamine.
- If side effects from the DAO enzyme supplement occur, it may be due to the increased ammonia and hydrogen peroxide produced as reactive metabolites. Consult your healthcare provider or pharmacist.
- Many medications interact with this enzyme. Metformin, Tagamet, Verapamil and Amiloride are known to slow DAO.

## Cleans your DAO/AOC1 gene

**Environment:** When traveling in high risk countries, use a quality water filter which removes bacteria and parasites such as *Blastocystis hominis*.

**Lifestyle:** Healthy digestion with good levels of pancreatic enzymes, bile and stomach hydrochloric acid. Pregnancy increases DAO enzyme as the placenta produces DAO. This is a big reason why some women feel better during pregnancy.

**Food:**

- Focus on B6, calcium and copper rich foods, and identify lower histamine containing foods and choose them as staples. Typically, the more aged a food or drink is, the more histamine it contains.
- Rinsing meat and meat prior to cooking is not recommended by food safety guidelines and may spread bacteria in the kitchen. However, carefully doing so may wash off histamine produced by bacteria.
- Rinsing lunch deli meats and patting dry prior to assembling sandwich or eating may support reduction in histamine.
- Frying and grilling increases histamine level in meat while stewing/braising/boiling has little influence or even decreases it. These methods may help those histamine-sensitive as compared with frying and grilling.

## Cleans your DAO/AOC1 gene, continued...

**Supplements and Medications:**

- Consider vitamin B6, calcium, copper, additionally consider *Saccharomyces boulardii* especially after a course of antibiotics. Use probiotics which are known to reduce or balance histamine.
- For additional real-time support while drinking or consuming high-histamine foods, use a DAO enzyme supplement. Support elimination of hydrogen peroxide and ammonia by using pyrroloquinoline quinone (PQQ), acetyl-L-carnitine, ornithine, S-acetyl glutathione or liposomal glutathione.
- Also support the ALDH2 enzyme with zinc, vitamin B1 and B3 to break down the acetaldehyde generated by the DAO enzyme.
- If presence of small intestinal bacterial overgrowth (SIBO), consider gallbladder support and/or ox bile. SIBO may increase histamine levels and overtax DAO.
- If DAO is overwhelmed, histamine may be absorbed into the blood and start impacting intracellular histamine levels thereby putting a burden on HNMT. Thus, supporting the HNMT enzyme may be needed in addition to DAO, MAOA, NAT2 and ALDH2. If the HNMT gene is experiencing a heavy workload, then other methyltransferase genes such as COMT, GAMT and PEMT may become slowed.

# THE MAOA GENE

The MAOA (monoamine oxidase A) gene produces an enzyme that processes both internally-produced and externally-derived dietary and environmental amines. Riboflavin (B2) is the cofactor and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

The amount of hydrogen peroxide generated by MAOA is so significant that it consumes large amounts of glutathione.

In the histamine pathway, MAO enzymes detoxify histamine. Histamine is a vasoactive amine that acts on blood vessels to alter their permeability and causes vasodilation. Therefore, in addition to their role in maintaining normal mood and brain function, MAO enzymes also play a major role in regulating blood pressure. A side effect of MAO inhibiting medications is orthostatic hypotension (a lightheaded feeling when standing quickly). But combining a MAO inhibiting medication with high tyramine foods can cause high blood pressure.

If MAO enzymes are not functioning well, N-methylhistamine may accumulate. N-methylhistamine causes feed-back inhibition of HNMT, resulting in a build-up of histamine.

This perspective on the Histamine pathway debunks the popular idea of 'Over and Undermethylation'.

'Undermethylation' is the idea that histamine levels are high due to poor methylation status and low SAM, whereas 'overmethylation' is the idea that histamine levels are too low due to excessive methylation and high SAM.

Indeed, HNMT requires SAM as a methyl donor in order to process histamine. However, you can have a situation where methylation status is absolutely fine, but histamine levels are still high.

In this case, the cause of high histamine could well be sluggish MAO enzymes and/or sluggish ALDH enzymes and have nothing to do with methylation status.

Interestingly, excessive serotonin and high histamine in the brain are associated with migraines. Riboflavin (B2), the cofactor of MAOA, is known to be effective in reducing incidence of migraines and headaches.

MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of having two X chromosomes. MAOA activity tends to naturally increase throughout adolescence into adulthood.

## Notable variation:

SNP: **MAOA T941G rs6323 (-/-, T)**

This wild type (TT in women, T in men) appears to possess lower MAOA activity compared to the GG variant. This may slow the clearing out of N-methylhistamine and potentially lead to higher histamine levels.

## Slows down your MAOA gene

**Environment:**

- Research shows a noisy sleep environment (near highway, train tracks, airports, city life, college dorms) increases catecholamine levels and workload on the MAOA enzyme.
- Early childhood mistreatment and maternal stress in utero have been shown to downregulate MAOA.
- Passive exposure to smoke (even in utero) slows the MAO genes. Smoking while pregnant is associated with aggressive traits in offspring.

**Lifestyle:**

- Short-term, high stress situations reduce the activity of MAO enzymes presumably in order to respond to the "fight or flight" situation by reducing the break down of stress hormones.
- Smoking (strongly) and caffeine (weakly) reduce MAO activity and raise catecholamine levels. Hence people suffering from depression often self-medicate with these substances. Using food and herbs to slow MAO (see below) may help when trying to quit smoking.
- Alcohol actually increases MAO activity initially, but large amounts (more than one glass) can overwhelm MAO capacity, resulting in a build-up of histamine.
- Alcohols, such as champagne and wine which contain high levels of amines such as tyramine and histamine increase MAO workload to the greatest extent and may exacerbate histamine symptoms. MAOA activity may be regulated naturally with healthy foods and supplements (see below).
- Iron deficiency anemia can cause a decrease in MAO activity and research indicates that insufficient levels of dietary iron in the womb can lead to poorer cognitive functioning and maladaptive social behaviors, including aggressive temperament in offspring.

**Food:**

- Riboflavin (B2)-deficient or iron-deficient diet causes cofactor-related enzyme limitations. Avoid simple, processed carbohydrates.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to detoxify histamine (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Limit excessive consumption of tryptophan rich foods for the same reason.

## Slows down your MAOA gene, continued...

**Supplements and Medications:**

- Excessive tryptophan will dirty MAOA by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement but use the pulse method instead.
- For those with a fast MAOA genotype that is expressing itself (or your MAOA is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOA: 5-hydroxytryptophan (5-HTP), garlic extract, berberine, curcumin, quercetin, green tea, *Rhodiola rosea*. Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine.
- Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Speeds up your MAOA gene

**Lifestyle:**

- Chronic, low-level stress causes MAO enzymes to upregulate presumably as a result of the need to break down the increased amount of stress hormones being produced.
- Low estrogen tends to raise MAOA activity. Therefore, the postpartum estrogen drop, as well as perimenopausal estrogen decline, seem to relate to upregulated MAOA levels in the brain. Fluctuations in estrogen during the menstrual cycle may contribute to mood swings through a similar relationship.
- Alcohol increases MAO activity, which may cause a build-up of toxic acetaldehydes if you have fast ADH1B (not present) or slow ALDH1B1 (not present) or slow ALDH2 (present). While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then low-histamine beverages such as gin, vodka, rum or bourbon are better choices, especially if you take a MAO inhibitor.

**Food:** Iron, riboflavin (B2), vitamin C and E rich foods along with cruciferous vegetables, eggs or broccoli sprouts support glutathione production and thus support MAOA indirectly.

**Supplements and Medications:** Optimize riboflavin (B2) and iron. Vitamin C and vitamin E are free radical scavengers and reduce the hydrogen peroxide produced by MAO. PQQ (pyrroloquinoline quinone), liposomal glutathione or S-acetyl glutathione also support elimination of hydrogen peroxide.

# THE MAOB GENE

The MAOB (monoamine oxidase B) gene produces an enzyme that catalyzes the removal of an amine group from both internally-produced and externally-derived dietary and environmental amines. Riboflavin (B2) is the cofactor and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

In the histamine pathway, MAO enzymes detoxify histamine. Histamine is a vasoactive amine that acts on blood vessels to alter their permeability and causes vasodilation. Therefore, in addition to their role in maintaining normal mood and brain function, MAO enzymes also play a major role in regulating blood pressure. A side effect of MAO inhibiting medications is orthostatic hypotension (a lightheaded feeling when standing quickly). But combining a MAO inhibiting medication with high tyramine foods can cause high blood pressure.

MAOB is the predominate form of MAO in the brain. The amount of hydrogen peroxide generated by MAOA is so significant that it consumes large amounts of glutathione.

If MAO enzymes are not functioning well, N-methylhistamine may accumulate which causes a build-up of histamine due to feed-back inhibition of HNMT. Interestingly, excessive serotonin and high histamine in the brain are associated with migraines. Riboflavin (B2), the cofactor of MAOB, is known to be effective in reducing incidence of migraines and headaches. It is also important for the down-stream ALDH enzymes to be working well for the whole pathway to run smoothly.

MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of having two X chromosomes.

## Slows down your MAOB gene

**Lifestyle:**

- Limit alcohol (more than one glass), caffeine (weakly inhibits), iron deficiency anemia, smoking (both active and passive exposures) which all inhibit MAO activity.
- Short-term, acute, high stress situations reduce the activity of MAOB enzymes, presumably as response to the "fight or flight" situation by reducing the break down of stress hormones.
- Males have only one copy, so inherently possess less activity. Stress sensitive females (higher basal heart rate, lower peak estrogen and progesterone) appear to have less activity.

### Notable variation:

SNP: **MAOB -36A>G rs1799836 (+/+*, C)**

Research indicates contradictory findings for this CC variant, but metabolomic research indicates this variant appears to upregulate MAOB in vivo; however epigenetic influence is likely as powerful in overall activity in addition to haplotype inheritance.

## Slows down your MAOB gene, continued...

**Food:**

- Avoid simple, processed carbohydrates; riboflavin (B2)-deficient diet, iron-deficient diet.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to degrade serotonin (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Avoid excessive consumption of tryptophan rich foods for the same reason.

**Supplements and Medications:**

- Excessive tryptophan will slow MAOB by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement but use the pulse method instead.
- For those with a fast MAOB genotype that is expressing itself (or your MAOB is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOB: Garlic extract, berberine, curcumin, quercetin, green tea, EGCG from green tea, silymarin, *Glycyrrhiza spp.* (licorice), *Lamiaceae* (mint family: lavender, oregano, rosemary, sage, thyme, etc); *Rhodiola rosea*, *Scutellaria spp.* (skullcap), *Piper methysticum* (kava-kava), *Baptisia officinalis* (wild indigo), gentian, *Symphytum spp.* (comfrey), *Phellodendron amurense* (Amur corktree), *Cyamopsis psoralioides* (bakuchi seed), *Psoralea corylifolia* (babchi seed).
- A comprehensive list of herbs with MAOB inhibition effects can be found in Table 1 here.
- Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine. Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bio-identical estrogen (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, or if there are other indications for its use.

## Speeds up your MAOB gene

**Lifestyle:**

- Long-term, low-level ongoing stress causes MAOB upregulation. MAOB activity also naturally increases with age, especially after 60 years of age.
- Estrogen tends to inhibit MAOB, therefore an age-related decline in estrogen is likely to further increase MAOB activity.
- Increased MAOB activity will cause an increased throughput of N-Methylimidazole acetylaldehyde. It is therefore important that your aldehyde dehydrogenase enzymes (ALDH family) are working well to safely process this out of the body. Those with a slow ALDH1B1 (not present) or ALDH2 (present) may be at a disadvantage.
- Not only may high levels of acetaldehydes cause flushing, irritation to the respiratory tract and neuro-inflammation, but N-Methylimidazole Acetaldehyde itself causes feedback inhibition of the HNMT gene (which is the first step in the detoxification of histamine). Therefore, histamine symptoms are likely to increase if MAOB is upregulated and ALDH enzymes are not supported.
- Alcohol also increases MAOB activity. While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then avoiding high-histamine ones such as wine and champagne would be advisable. Low-histamine alcohols such as gin, vodka, rum or bourbon are better choices, especially if you take a MAO inhibitor.

**Food:** Consider riboflavin (B2), vitamin C and E rich along with cruciferous vegetables, eggs or broccoli sprouts to support glutathione.

**Supplements and Medications:** Optimize riboflavin (B2). Vitamin C and vitamin E, liposomal glutathione, S-acetyl glutathione, PQQ (pyrroloquinoline quinone) and carnosine are free radical scavengers and reduce the hydrogen peroxide produced by MAO.

# THE ALDH2 GENE

The ALDH2 (aldehyde dehydrogenase family member 2) gene expresses an enzyme which converts aldehydes to carboxylic acids, usually for use in the muscle and heart.

In the histamine pathway, ALDH2 helps detoxify acetaldehyde intermediates of histamine using the cofactor niacin (B3).

ALDH2 is best known for its role as the second enzyme in the major pathway for processing acetaldehyde from alcohol. In most people, ALDH2 transforms this acetaldehyde rapidly into to less harmful acetate and water. However, if acetaldehyde isn't broken down quickly, it accumulates in the liver and body and contributes to a hungover feeling and results in what is known as the "Asian flush".

If the toxic acetaldehydes are not processed quickly enough by the ALDH2 enzyme, then the HNMT and DAO enzymes are instructed to slow down via the mechanism of feedback inhibition. Thus, the high histamine symptoms one is experiencing may not be due to a slow HNMT (not present) and/or slow AOC1 (present). Rather, the histamine symptoms are actually triggered by the dirty downstream effect of the slowed ALDH genes.

Clean up the ALDH genes so the acetaldehydes clear out thereby removing the feedback inhibition on DAO and HNMT. Adequate thiamine (B1) is particularly important in this process. Another possible scenario is fast HNMT and/or DAO that produce excessive acetaldehydes that feedback inhibit these same enzymes. This goes to show that the entire pathway must be supported versus just one gene.

## 💩 Dirties your ALDH2 gene

**Environment:** Minimize exposure to aldehydes from the environment such as vehicle emissions, smoking (especially secondhand exposures), cooking fumes, formaldehyde from building materials, disinfectants, drugs, perfumes, fungicides and pesticides, carbon tetrachloride (dry cleaning), hydrogen sulfide and many other environmental chemicals. Minimize oxidative stress to decrease aldehydes created internally by reactive oxygen species.

**Lifestyle:** Avoid alcohol, smoking, insulin resistance, oxidized LDL, high kynurenine. Work with your healthcare provider to identify *Candida* dysbiosis which generates endogenous acetaldehyde.

## Notable variation:

SNP: **ALDH2 699T>C rs737280 (+/-, TC)**

This TC variant may decrease enzyme activity and makes exposures to pesticides more risky. Due to lack of research in other ethnicities, these results may be applicable only to those of European descent.

### Dirties your ALDH2 gene, continued...

**Food:**

- Limit oxidized omega-6 fatty acids (from old or processed oils, microwaved fatty foods).
- Avoid known allergens.
- Avoid foods high in acetaldehyde such as fish products, canned vegetables, fermented foods: yogurt, vinegar, kombucha, fermented mushrooms, tempeh, miso, pickled vegetables and kimchi. Other foods containing acetaldehyde include very ripe fruit, artificial flavors like lemon flavoring, ground and instant coffee. Many aldehydes are found in drinking water so use a filter.

**Supplements and Medications:** Acetaminophen (Tylenol), aspirin and *Pueraria lobata* (kudzu) have been shown to inhibit ALDH2 and worsen symptoms after drinking alcohol.

## Cleans your ALDH2 gene

**Environment:** Employ strategies to reduce exposure to sources of acetaldehyde and other environmental chemicals.

**Lifestyle:** Filter drinking water

**Food:** Vitamins C, B1 & B3, zinc, magnesium and resveratrol rich (especially when consuming alcohol), diet rich in vegetables from the brassica family, broccoli sprouts

**Supplements and Medications:**

- Zinc, niacin (B3), glutathione, sulforaphane, resveratrol with vitamin C (especially when consuming alcohol).
- Thiamine (B1) is especially important as acetaldehyde damages enzymes which are B1 dependent.
- Some herbs have been shown in mice to speed up the biotransformation of acetaldehyde into less toxic end products. These herbs include *Lycium chinense* (goji berry), *Acanthopanax sessiliflorus, Ixeris dentata, Polypori umbellati* (zhu ling).

# THE NAT2 GENE

The NAT2 (N-acetyltransferase 2) gene expresses an enzyme which conducts phase II acetylation reactions in the liver which combine the starting product with acetyl-CoA to make the end product less toxic. Pantothenic acid (B5) is a cofactor for this reaction.

NAT2 participates in the acetylation and detoxification of histamine as well as a plethora of hydrazine and arylamine drugs and also carcinogens such as heterocyclic amines.

NAT2 is also the minor route of histamine elimination while the HNMT gene processes the bulk of intracellular histamine.

Polymorphisms in the NAT2 gene result in individuals being categorized as rapid, intermediate, or slow acetylators.

## Dirties your NAT2 gene

**Environment:**

- Avoid exposure to environmental arylamine chemicals such as found in the leather, rubber, printing, and textiles industries or to large quantities of paint.
- Avoid diisocyanate, which is in chemicals used in the production of polyurethane products, such as rigid and flexible foams, coatings, adhesives, sealants and elastomers. Workers exposed to these were more susceptible to asthma, especially those with slow NAT2 activity.

**Food:** Grapefruit is an known inhibitor so best to avoid for slow types especially during times of environmental exposures.

**Supplements and Medications:** Sadly, there is no research looking at fast/slow acetylators and how they respond to known in vitro NAT2 inhibitors or promoters in real life. Many of these compounds (curcumin, quercetin, garlic) are healthy foods with constituents known to promote health (flavonoids, polyphenols). Therefore do not avoid these, but consider pulsing them, as in not using as daily staples. Acetaminophen may also be problematic for slow types.

## Cleans your NAT2 gene

**Food:** Vitamin A, B5 rich

**Supplements and Medications:** Consider Vitamin A, B5.

## Notable variation:

### A NAT2 Intermediate Haplotype

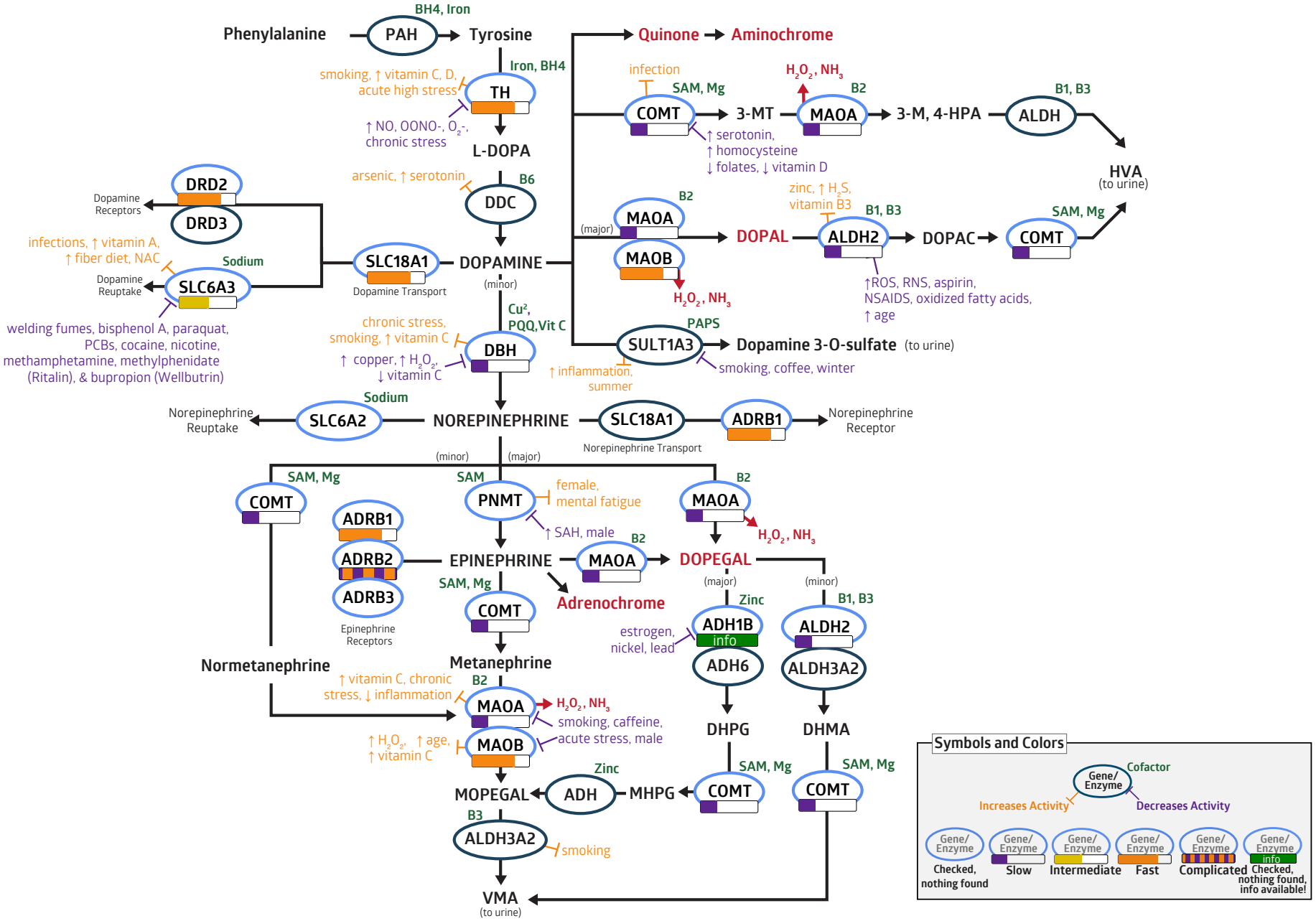
This genotype implies an intermediate rate of clearance of various drugs, environmental chemicals and histamine relative to the slow and fast genotypes.

Recent research into NAT2 fast versus slow resulted in the opposite speed predicted in persons of same ethnicity and genotype living in vastly different geographic areas. It is presumed that local environmental, dietary and microbiome population differences underlie this observation.

In other words, your genotype (as shown, for example, in this report) may predict one type, but your local environment and lifestyle may influence its expression in the opposite direction.

| Gene | rsID | Alias | Variant Allele | Call |
|---|---|---|---|---|
| NAT2 | rs1041983 | C282T | T | CC |
| NAT2 | rs1801280 | T341C (I114T) | C | TC |
| NAT2 | rs1799929 | C481T | T | CT |
| NAT2 | rs1799930 | G590A (R197Q) | A | GG |
| NAT2 | rs1208 | A803G (K268R) | G | GA |
| NAT2 | rs1799931 | G857A (G286E) | A | GG |

# Dopamine


Phenylalanine
BH4, Iron
PAH
Tyrosine
Iron, BH4
smoking, ↑ vitamin C, D, acute high stress
TH
↑ NO, OONO-, O2-, chronic stress
L-DOPA
arsenic, ↑ serotonin
B6
DDC
DOPAMINE
(minor)
Quinone
Aminochrome
infection
SAM, Mg
COMT
3-MT
H2O2, NH3
B2
MAOA
3-M, 4-HPA
B1, B3
ALDH
HVA
(to urine)
↑ serotonin, ↑ homocysteine ↓ folates, ↓ vitamin D
B2
(major)
MAOA
MAOB
H2O2, NH3
DOPAL
zinc, ↑ H2S, vitamin B3
B1, B3
ALDH2
DOPAC
SAM, Mg
COMT
↑ROS, RNS, aspirin, NSAIDS, oxidized fatty acids, ↑ age
DRD2
DRD3
Dopamine Receptors
infections, ↑ vitamin A, ↑ fiber diet, NAC
Sodium
SLC6A3
Dopamine Reuptake
welding fumes, bisphenol A, paraquat, PCBs, cocaine, nicotine, methamphetamine, methylphenidate (Ritalin), & bupropion (Wellbutrin)
SLC18A1
Dopamine Transport
Cu², PQQ,Vit C
chronic stress, smoking, ↑ vitamin C
↑ copper, ↑ H2O2, ↓ vitamin C
DBH
PAPS
SULT1A3
Dopamine 3-O-sulfate (to urine)
↑ inflammation, summer
smoking, coffee, winter
Sodium
Norepinephrine Reuptake
SLC6A2
NOREPINEPHRINE
SLC18A1
Norepinephrine Transport
ADRB1
Norepinephrine Receptor
(minor)
(major)
SAM, Mg
COMT
Normetanephrine
SAM
PNMT
female, mental fatigue
↑ SAH, male
B2
MAOA
H2O2, NH3
ADRB1
ADRB2
ADRB3
Epinephrine Receptors
EPINEPHRINE
B2
MAOA
DOPEGAL
SAM, Mg
COMT
Metanephrine
Adrenochrome
(major)
(minor)
Zinc
B1, B3
estrogen, nickel, lead
ADH1B
info
ADH6
ALDH2
ALDH3A2
↑ vitamin C, chronic stress, ↓ inflammation
B2
MAOA
H2O2, NH3
smoking, caffeine, acute stress, male
↑ H2O2, ↑ age, ↑ vitamin C
MAOB
DHPG
DHMA
Zinc
SAM, Mg
SAM, Mg
MOPEGAL
ADH
MHPG
COMT
COMT
B3
ALDH3A2
smoking
VMA
(to urine)
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
info
Checked, nothing found, info available!

# THE TH GENE

The TH (tyrosine hydroxylase) gene expresses an enzyme which catalyzes the conversion of L-tyrosine to dihydroxyphenylalanine (L-DOPA).

TH is mainly expressed in brain and adrenal glands, and is the rate limiting step in the synthesis of the catecholamines (dopamine, norepinephrine and epinephrine).

TH requires oxygen ($O_2$), iron ($Fe^{2+}$) and tetrahydrobiopterin ($BH_4$) as cofactors.

TH is dependent on the effective recycling of biopterin Biopterin pathway.

## Dirties your TH gene

**Environment:** Organophosphate pesticides, nickel exposure

**Lifestyle:** Acute and chronic stress. Limit excessive exercise which is an overlooked factor in increased oxidative stress. Avoid cigarette smoke, including secondhand smoke.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your TH gene

**Lifestyle:** Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Iron, vitamins C and D rich, high fiber diet

**Supplements and Medications:** Consider iron, vitamin C, vitamin D, butyrate, EGCG from green tea, melatonin, *Bacopa monneri* (brahmi), *Ginkgo biloba, Panax ginseng*. Tyrosine may be useful in a low dopamine state.

## Notable variation:

SNP: **TH A-581G rs10770140 (+/-, CT)**
This CT variant may have an intermediate effect with increased transcriptional binding and increased sympathetic activity and catecholamine secretion compared to wild type.

SNP: **TH C-824T rs10770141 (+/-, AG)**
This AG variant may have 60% higher transcriptional binding compared to wild type with increased sympathetic activity and catecholamine secretion compared to wild type.

# THE MAOA GENE

The MAOA (monoamine oxidase A) gene produces an enzyme that catalyzes the removal of an amine group from both internally-produced and externally-derived dietary and environmental amines.

Riboflavin (B2) is the required cofactor and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

The amount of hydrogen peroxide generated by MAOA is so significant that it consumes large amounts of glutathione.

In the dopamine pathway, MAOA enzymes process the stress hormones dopamine, norepinephrine and epinephrine.

When MAOA performs this job, toxic levels of some substances may be created as unwelcome free riders:

- Reactive DOPAL (dihydroxyphenylacetaldehyde) when dopamine is processed.
- DOPEGAL (3,4-dihydroxyphenylglycolaldehyde), toxic to the brain, when norepinephrine is processed.
- Reactive and neurotoxic adrenochrome, when epinephrine is processed inefficiently.

If MAOA is slow (present) or COMT is slow (present) there is also potential for neurotoxic dopamine quinone to form.

Other genes also play a role:

A slow ALDH2 (present) increases the risk of formation of toxic DOPAL and DOPEGAL. A slow ADH1B (not present) may also lead to increased DOPEGAL.

As you can see, the function of several genes influence the result of what your MAOA is doing.

Note: MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of two X chromosomes. Males have XY chromosomes and females are XX.

MAOA activity tends to naturally increase throughout adolescence into adulthood.

## Notable variation:

SNP: **MAOA T941G rs6323 (-/-, T)**
This genotype (TT in women, T in men) lowers MAOA activity.

## Slows down your MAOA gene

**Environment:** Research shows a noisy sleep environment (near highway, train tracks, airports, city life, college dorms) increases catecholamine levels and workload on the MAOA enzyme. Early childhood mistreatment and maternal stress in utero have been shown to downregulate MAOA. In addition, passive exposure to smoke (even in utero) slows the MAO genes. Smoking while pregnant is associated with aggressive traits in offspring.

**Lifestyle:**

- Short-term, high stress situations reduce the activity of MAO enzymes presumably in order to respond to the "fight or flight" situation by reducing the break down of stress hormones.
- Iron deficiency anemia can cause a decrease in MAO activity and research indicates that insufficient levels of dietary iron in the womb can lead to poorer cognitive functioning and maladaptive social behaviors including aggressive temperament in offspring.
- Smoking (strongly) and caffeine (weakly) reduce MAO activity and raise catecholamine levels. Hence people suffering from depression often self-medicate with these substances. Using food and herbs to slow MAO (see below) may help when quitting smoking.
- Alcohol actually increases MAO activity, which is one reason why some people may use alcohol to help them relax. However, although alcohol may give an initial “relaxing” effect due to the faster processing of stress hormones, excessive or “binge” drinking can quickly overwhelm the capacity of the MAO enzymes, resulting in a build-up of damaging compounds such as dopamine quinones as well as an increased production of hydrogen peroxide which can cause neurological damage. Alcoholic beverages containing high levels of amines such as champagne and wine increase MAO workload to the greatest extent. In order to relax, MAOA activity may be regulated naturally with healthy foods and supplements (see below).

**Food:**

- Avoid simple, processed carbohydrates; riboflavin (B2)-deficient diet, iron-deficient diet.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to degrade serotonin (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Avoid excessive consumption of tryptophan rich foods for the same reason.

### Slows down your MAOA gene, continued...

**Supplements and Medications:**

- Excessive tryptophan will dirty MAOA by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement but use the pulse method instead.
- For those with a fast MAOA genotype that is expressing itself (or if your MAOA is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOA: 5-hydroxytryptophan (5-HTP), garlic extract, berberine, curcumin, quercetin, green tea, *Rhodiola rosea*.
- Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine. Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Speeds up your MAOA gene

**Lifestyle:**

- Chronic, low-level stress causes MAO enzymes to upregulate presumably as a result of the need to break down the increased amount of stress hormones being produced.
- Low estrogen tends to raise MAOA activity. Therefore, the postpartum estrogen drop, as well as perimenopausal estrogen decline, seem to relate to upregulated MAOA levels in the brain. Fluctuations in estrogen during the menstrual cycle may contribute to mood swings through a similar relationship.
- Alcohol increases MAO activity, which reduces important neurotransmitters, and may result in both neurological and immunological deregulation. While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then non-tyramine containing alcohols such as gin, vodka, rum, bourbon are better choices, especially if you take a MAO inhibitor.

**Food:** Choose iron, riboflavin (B2), vitamin C and E rich. Opt for lower amine containing foods which are low in histamine and tyramine.

**Supplements and Medications:** Optimize riboflavin (B2) and iron. Vitamin C, vitamin E, liposomal glutathione, S-acetyl glutathione, carnosine and PQQ (pyrroloquinoline quinone) are free radical scavengers and reduce the hydrogen peroxide produced by MAOA. It's very important to support ALDH2 and ADH1B enzymatic function as the reactive metabolites (DOPAL and DOPEGAL) generated by MAOA must be eliminated or damage may occur.

# THE MAOB GENE

The MAOB (monoamine oxidase B) gene produces an enzyme that catalyzes the removal of an amine group from both internally-produced and externally-derived dietary and environmental amines and is the predominate form of MAO in the brain.

Riboflavin (B2) is the cofactor required for MAOB enzyme and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

Significant amounts of glutathione are required to neutralize this hydrogen peroxide.

In the dopamine pathway, MAOB processes dopamine in the brain and central nervous system and typically this function increases as one ages, depleting dopamine and exacerbating disorders such as Parkinson's. Thus, many natural and pharmaceutical MAOB inhibitors exist to help slow MAOB and preserve dopamine.

MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of two X chromosomes. Males have XY chromosomes and females have XX chromosomes.

## Slows down your MAOB gene

**Lifestyle:**

- Avoid alcohol (more than one glass), caffeine (weakly inhibits), iron deficiency anemia, smoking (both active and passive exposures).
- Short-term, acute, high stress situations reduce the activity of MAOB enzymes (as response to the "fight or flight" situation by reducing the break down of stress hormones).
- Males have only one copy, so inherently possess less activity. Stress sensitive females (higher basal heart rate, lower peak estrogen and progesterone) appear to have less activity.

**Food:**

- Avoid simple, processed carbohydrates; riboflavin (B2)-deficient diet, iron-deficient diet.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to degrade serotonin (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Avoid excessive consumption of tryptophan rich foods for the same reason.

## Notable variation:

SNP: **MAOB -36A>G rs1799836 (+/+*, C)**

Research indicates contradictory findings for this variant (CC in women, C in men), but metabolomic research indicates this variant appears to upregulate MAOB in vivo. A careful examination of symptoms related to MAO activity (mood, appetite, etc.) may offer signs of this increased activity.

## Slows down your MAOB gene, continued...

**Supplements and Medications:**

- Excessive tryptophan will dirty MAOB by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement, but rather use the pulse method.
- For those with a fast MAOB genotype that is expressing itself (or your MAOB is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOB: Garlic extract, berberine, curcumin, quercetin, EGCG from green tea, silymarin, *Glycyrrhiza spp.* (licorice), *Lamiaceae* (mint family: lavender, oregano, rosemary, sage, thyme, etc); *Rhodiola rosea*, *Scutellaria spp.* (skullcap), *Piper methysticum* (kava-kava), *Baptisia officinalis* (wild indigo), gentian, *Symphytum spp.* (comfrey), *Phellodendron amurense* (Amur corktree), *Cyamopsis psoralioides* (bakuchi seed), *Psoralea corylifolia* (babchi seed).
- A comprehensive list of herbs with MAOB inhibition effects can be found in Table 1 here.
- Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine. Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Speeds up your MAOB gene

**Lifestyle:**

- Long-term, low-level ongoing stress causes MAOB upregulation. MAOB activity also naturally increases with age, especially after 60 years of age.
- Estrogen tends to inhibit MAOB, therefore an age-related decline in estrogen is likely to further increase MAOB activity.
- Since MAOB processes dopamine in the brain and central nervous system, increased MAOB activity may cause a depletion of dopamine and exacerbate disorders such as Parkinson's.
- Alcohol increases MAOB activity, further increasing the risk of both neurological and immunological deregulation. While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then non-tyramine containing alcohols such as gin, vodka, rum, bourbon are better choices, especially if you take a MAO inhibitor.

**Food:** Iron, riboflavin (B2), vitamin C and E rich

## Speeds up your MAOB gene, continued...

**Supplements and Medications:** Optimize riboflavin (B2) and iron. Vitamin C, vitamin E, liposomal glutathione, S-acetyl glutathione, carnosine and PQQ (pyrroloquinoline quinone) are free radical scavengers and reduce the hydrogen peroxide produced by MAOA. It's very important to support ALDH2 and ADH1B enzymatic function as the reactive metabolites (DOPAL and DOPEGAL) generated by MAOA must be eliminated or damage may occur.

# THE ALDH2 GENE

The ALDH2 (aldehyde dehydrogenase 2 family member) gene expresses an enzyme which converts aldehydes using the cofactor niacin (B3) for use as energy, usually in the muscle and heart.

ALDH2 also performs the role of neutralizing internally-produced lipid peroxidation products formed due to oxidative stress as well as aldehydes from the environment (see below), which put additional strain on this enzyme.

If ALDH2 enzyme is not expressing well, there is increased potential for damage in the brain caused by the reactive neurotoxic compounds, dihydroxyphenylacetaldehyde (DOPAL) and 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL).

It's incredibly important to support the function of ALDH2 especially if MAOA is functioning at a faster rate (not present).

Adequate thiamine (B1) is also important.

## 💩 Dirties your ALDH2 gene

**Environment:**

- Minimize exposure to aldehydes from the environment such as vehicle emissions, smoking (especially secondhand exposures), cooking fumes, formaldehyde from building materials, disinfectants, drugs, perfumes, fungicides and pesticides, carbon tetrachloride (dry cleaning), hydrogen sulfide and many other environmental chemicals.
- Minimize oxidative stress to decrease aldehydes created internally by reactive oxygen species.

**Lifestyle:**

- Limit alcohol, smoking, insulin resistance, oxidized LDL, high kynurenine which can all inhibit ALDH2.
- Work with your healthcare provider to identify *Candida* dysbiosis which generates endogenous acetaldehyde.

### Notable variation:

SNP: **ALDH2 699T>C rs737280 (+/-, TC)**
This TC variant may decrease enzyme activity and makes exposures to pesticides more risky. Due to lack of research in other ethnicities, these results may be applicable only to those of European descent.

## Dirties your ALDH2 gene, continued...

**Food:**

- Limit oxidized omega-6 fatty acids (from old or processed oils).
- Minimize known allergens.
- Limit foods high in acetaldehyde such as fish products, canned vegetables, fermented foods: yogurt, vinegar, kombucha, fermented mushrooms, tempeh, miso, pickled vegetables and kimchi.
- Limit other foods containing acetaldehyde include very ripe fruit, artificial flavors like lemon flavoring, ground and instant coffee.
- Many aldehydes are found in drinking water so use a filter.

**Supplements and Medications:** Acetaminophen (Tylenol), aspirin

## Cleans your ALDH2 gene

**Environment:** Employ strategies to reduce exposure to sources of acetaldehyde and other environmental chemicals.

**Food:** Choose vitamin B1, B3, C zinc, magnesium rich sources; especially when consuming alcohol. Opt for a diet rich in vegetables from the brassica family, broccoli sprouts.

**Supplements and Medications:** Thiamine (B1) is especially important as acetaldehyde damages enzymes which are B1 dependent. Consider zinc, niacin (B3), sulforaphane, resveratrol with vitamin C (especially when consuming alcohol). Some herbs have been shown in mice to speed up the biotransformation of acetaldehyde into less toxic end products. These herbs include *Lycium chinense* (goji berry), *Acanthopanax sessiliflorus*, *Ixeris dentata*, *Polypori umbellati* (zhu ling).

# THE SLC18A1 GENE

The SLC18A1 (solute carrier family 18 member A1 aka VMAT1) gene expresses a cell membrane transporter for dopamine, serotonin, epinephrine and norepinephrine in the presynaptic neurons.

Within the presynaptic neuron, SLC18A1 transports the neurotransmitters into vesicles for storage and later release.

## 💩 Dirties your SLC18A1 gene

**Environment:** Environmental chemicals including polychlorinated biphenyls (PCBs) and organochlorine pesticides have been shown to inhibit SLC18A1 activity and deplete dopamine stores in experimental animals. Exposure to organochlorines may be associated with an increased incidence of Parkinson's disease.

**Food:** Avoid organochlorine pesticides in food; see the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your SLC18A1 gene

**Lifestyle:** Acute and chronic stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https::://www.ewg.org/foodnews/clean-fifteen.php/).

**Supplements and Medications:** *Ginkgo biloba* has been found to regulate various dopamine genes (in mice) including SLC18A1 and reduce neurotoxicity caused by environmental chemicals. Consider physiological dose of lithium orotate 5 mg per day.

### Notable variation:

SNP: **SLC18A1 C407T rs1390938 (+/+, AA)**
This AA variant increased transport of dopamine 240% more than wild type to the presynaptic cleft as shown by in vitro research model. It increased transport of norepinephrine by 1300% (and likely epinephrine as well, not studied).

# THE DRD2 GENE

The DRD2 (dopamine receptor D2) gene expresses an enzyme which functions as a receptor for dopamine. At presynaptic terminals DRD2 receptors regulate the release, uptake and synthesis of dopamine.

Dopamine is a key neurotransmitter that regulates a variety of physiological functions, including reward behavior, regulation of movement, attention, learning and memory.

## Dirties your DRD2 gene

**Environment:** Bisphenol A (BPA), welding fumes and formaldehyde

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your DRD2 gene

**Lifestyle:** Exercise, cognitive behavior therapy or psychotherapy

**Supplements and Medications:** Optimize riboflavin (B2) and iron. Vitamin C, vitamin E, liposomal glutathione, S-acetyl glutathione, carnosine and PQQ (pyrroloquinoline quinone) are free radical scavengers and reduce the hydrogen peroxide produced by MAO.

## Notable variation:

SNP: **DRD2 -83G>T rs1076560 (-/-, CC)**
CC carriers exhibit the most common, wild type receptor expression. They may feel a boost in mood from enjoyable music and may especially benefit from dopamine boosting strategies. CC carriers may benefit from better fine motor skill (writing) retention if they perform aerobic exercise directly after learning the skill.

# THE SLC6A3 GENE

The SLC6A3 (solute carrier family 6 member 3 aka DAT) gene expresses a reuptake transporter for dopamine.

SLC6A3 transports dopamine out of the synaptic cleft and back into the presynaptic neuron thus reducing dopamine activity. Within the presynaptic neuron, other transporters then sequester the dopamine into vesicles for storage and later release.

Dopamine plays a role in reward-motivated behavior and the rate at which SLC6A3 removes dopamine from the synapse can have a profound effect on the amount of dopamine in the cell.

SLC6A3 works by coupling the transport of dopamine into the cell with the flow of sodium and chloride ions into the cell, from high to low concentration. Two sodium and one chloride ions are transported by SLC6A3 along with the dopamine substrate.

## Dirties your SLC6A3 gene

**Environment:** Welding fumes, bisphenol A (BPA), pesticides (especially paraquat), polychlorinated biphenyls (PCBs), gram negative infections (especially Lyme)

**Lifestyle:** Nicotine, cocaine; hostile, aggressive situations; absence of maternal affection, low positive social connection

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your SLC6A3 gene

**Lifestyle:** Create warm and reinforcing interactions that would promote or reward prosocial behavior, strong social ties with friendly peers, positive measures to negotiate conflicts or disagreements.

**Food:** Vitamin A, high levels of butyrate (short chain fatty acids), high fiber diet

**Supplements and Medications:** *Ginkgo biloba*, N-acetylcysteine (NAC) increases dopamine binding to the transporter.

## Notable variation:

SNP: **SLC6A3 1215A>G rs6347 (+/-, TC)**

This TC variant appears to be a tag SNP for the true functional variant which appears to increase expression relative to TT but less than CC. Thus, TC individuals may have intermediate synaptic dopamine levels as a consequence of more average numbers of re-uptake transporters.

# THE DBH GENE

The DBH (dopamine-β-hydroxylase) gene expresses an enzyme which catalyzes the conversion of dopamine to norepinephrine using cofactors: vitamin C, PQQ (pyrroloquinoline quinone) and copper ($Cu^{2+}$).

Both dopamine and norepinephrine are important neurotransmitters that play a key role in the autonomic nervous system. Research indicates that a higher dopamine to norepinephrine ratio may be related to impulsiveness and this could be a result of lower DBH activity.

## Dirties your DBH gene

**Lifestyle:** Nicotine increases DBH activity: there is some evidence that those with a down-regulated DBH gene are more likely to use smoking as self-medication to balance stress hormones. Consider using herbs (below) as an alternative to smoking. A metabolite of *Clostridia spp.*, 4-cresol, inhibits DBH.

**Food:** Prolonged fasting reduces DBH activity

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your DBH gene

**Lifestyle:** Engage in moderate exercise and cold exposure. Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy. Work with your healthcare provider to identify and treat a *Clostridium difficile* infection.

**Food:** Vitamin C, zinc and copper rich

**Supplements and Medications:**

- Consider zinc and vitamin C. Optimise copper (copper is a required cofactor of DBH but excessive levels have been found to inhibit DBH).
- In vitro evidence shows that *Rauwolfia spp.* (Indian snakeroot) and physiological doses of lithium orotate 5 mg per day can upregulate DBH function, so these may be helpful for people with a slow variant but contraindicated for people with an upregulating variant. On the other hand, there is also in vitro evidence that *Hypericum perforatum* (St. John's wort) and *Panax ginseng* inhibits the DBH function, so these herbs may be helpful for people with a fast variant but may be contraindicated for people with an downregulating variant. Keep in mind what these substances may have unpredicted metabolic effects at other points in the biochemical flow.

### Notable variation:

SNP: **DBH -1021C>T rs1611115 (+/-, TC)**
This TC variant displayed 10% less activity in several ethnicities compared to wild type, thus reducing the conversion of dopamine to norepinephrine.

# THE COMT GENE

The COMT (catechol-O-methyltransferase) gene expresses a phase II enzyme which degrades and inactivates catechol-containing compounds such as the catecholamines (dopamine, epinephrine, and norepinephrine), catechol estrogens, and various drugs and substances that have a catechol structure. Magnesium is a cofactor for the reaction.

COMT acts by catalyzing the transfer of a methyl group from S-adenosylmethionine (SAM), resulting in the generation of S-adenosylhomocysteine (SAH). A build-up of SAH inhibits SAM binding and reduces COMT activity.

Genetic variants that decrease the activity of COMT can lead to elevations in 4-hydroxy-estrogens, which have been shown to damage DNA and have carcinogenic potential.

If COMT enzyme is functioning slowly, there is also more potential for the neurotoxic compound dopamine quinone to form, especially in the presence of other reactive oxygen species.

If both COMT and MAOA are functioning slowly, there is more potential for neurotoxic adrenochrome to form.

A faster COMT enzyme may be more protective against the reactive neurotoxic compounds of dopamine quinone and adrenochrome, however higher levels of COMT activity result in the depletion of levels of dopamine and norepinephrine.

## Dirties your slow COMT gene

**Environment:**

- Research shows a noisy sleep environment (near highway, train tracks, airports, city life, college dorms) increases catecholamine levels and workload on the COMT enzyme thereby making this slow COMT even slower.
- Avoid clutter and disorganization (e.g., desk, closet, kitchen, garage).
- Avoid stressful environments (e.g., city life, emergency rooms); early-life adversity (e.g., victim of abuse, robbery, mugging, rape, assault, not living with biological parents); WiFi, bluetooth, dirty electricity especially by work place and bed.
- Hyperestrogenism, xenoestrogens increase COMT's workload.

## Notable variation:

### A Slow COMT Haplotype

Your COMT haplotype pattern is calculated as SLOW. This is based on a combination of 4 SNPs, which is the best way to determine COMT SNP effects. This combination confers low COMT activity and high pain sensitivity.

In vivo analysis of this combination indicates that this haplotype shows a dramatic reduction in gene expression and enzymatic activity in vitro compared to the high activity haplotype. The slower expression and activity of this haplotype may increase a tendency to higher levels of dopamine and estrogen catechols. Higher dopamine and estrogen catechols may increase symptoms of anxiety, irritability, difficulty falling asleep, significant PMS, migraines, headaches and increased cardiovascular risk. When this slow haplotype is optimized, it may lead to increased executive function meaning increased focus, drive and enhanced learning (e.g., Type A personality).

Although you were born with this genotypic slow speed for COMT, it does not mean that it functions at a slow speed all the time. In fact, it fluctuates many times a day. Your lifestyle, foods, environment, supplements and medications easily influence COMT to function faster or slower. The key is knowing how your daily choices influence your COMT. Then you can learn to keep it balanced. Read *Dirty Genes* and take the quizzes to see how your COMT and MAOA are expressing. This haplotype may be further amplified by a slow MAOA and lessened by a fast MAOA.

| Gene | rsID | Alias | Variant Allele | Call |
|---|---|---|---|---|
| COMT | rs6269 | -98A>G | G | AG |
| COMT | rs4633 | C186T | T | CT |
| COMT | rs4818 | C408G | G | CG |
| COMT | rs4680 | V158M | A | GA |

### Dirties your slow COMT gene, continued...

**Lifestyle:** A fast-paced, high stress lifestyle may be unsuited for this haplotype.

**Food:**

- GAPS, Paleo, Carnivore or otherwise high protein diet may exacerbate the effects of this haplotype especially in the evening.
- Any catechol-containing foods (e.g., curries, golden milk or chai with turmeric, curcumin) and caffeine drinks (e.g., energy drinks, coffee, green tea) may also exacerbate.
- Caffeine may increase cardiovascular risk susceptibility especially when combined with caffeine-sensitivity variations in ADORA/2A (adenosine receptors), ADA (breaks down adenosine), DRD2 (dopamine receptor) and CYP1A2 (breaks down caffeine).

**Supplements and Medications:** These may exacerbate: tyrosine, EGCG from green tea, inositol, 5-HTP, adrenal cortex, nootropics (e.g., huperzine A, choline, methylfolate, methylcobalamin), stimulants (e.g., *Panax ginseng*, caffeine), *Mucuna pruriens*, stimulating ADHD medications (e.g., methamphetamines), birth control and steroids (e.g., cortisol). Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your slow COMT gene

**Environment:**

- Create low stress, safe, nurturing environments and sources of joy. Nature settings may be best.
- Implement KonMari method (Marie Kondo) to organize and create a healing space.
- Feng shui to assist in creating harmony and ease of flow.
- Sleep with airplane mode enabled on phone. Turn off bluetooth and WiFi. Aim to use wired ethernet versus WiFi.
- Test electrical outlets for dirty electricity and clean up using Greenwave devices.
- Supportive and nurturing parenting techniques are especially important for slow COMT children.

**Lifestyle:** Use acute and chronic stress management techniques (e.g., breathing meditations, mindfulness); exercise which nourishes (e.g., yoga, hiking in nature, non-competitive team sports, cross country skiing, paddleboarding, walking your dog, gardening).

**Food:** Start your day with a balanced meal (protein, carbs and fat). Dinner should be lighter protein, higher fat and some carbs as excess protein may disturb sleep. Consider ketogenic diet, intermittent fasting or time-restricted eating.

## Cleans your slow COMT gene, continued...

**Supplements and Medications:**

- Optimize magnesium and vitamin D.
- Optimize methylation: Be mindful with L-5-MTHF as it is most stimulating for neurotransmission. Folinic acid is a gentler support and often tolerated better for those with a slow COMT. Natural folates from food help to optimize, but not over-stimulate neurotransmitters.
- Lithium orotate 5 mg per day may be supportive along with herbal adaptogens like *Passiflora, Eleuthrococcus, Withania somnifera* (ashwagandha).
- *Silybum marianum* (milk thistle), Curcumin, DIM (diindolylmethane), calcium-D-glucarate, indole-3-carbinol can indirectly reinforce COMT activity by lowering estrogens, supporting liver or slowing conversion of testosterone to estrogen.
- Consider creatine and phosphatidylcholine as two supplements that support methylation by sparing the utilization of S-adenosylmethionine (SAMe). Choose non-GMO soy or sunflower derived phosphatidylcholine.
- Supporting a slow MAOA may be supportive as well so consider using riboflavin (B2).
- If combined with other genetic variants which enhance neurotransmission, one must really focus on balancing stress reduction techniques and not just use supplements. It won't work.
- Be mindful that these supplement recommendations are for those truly experiencing a Slow COMT (as determined by quiz scores in *Dirty Genes*, your health professional and/or lab testing), not just having a Slow COMT haplotype.

# THE ADRB1 GENE

ADRB1 (adrenoceptor beta 1) gene expresses receptors for epinephrine and norepinephrine.

The three subtypes of ADRB, β1, β2, β3, are located primarily in the central nervous system (CNS), heart, coronary artery, kidney and muscle.

ADRB receptors are involved in development, behavior, smooth muscle tone, heart function, and energy metabolism.

All three β-subtypes also coexist in both white and brown adipose tissue. In white adipose tissue, attachment of epinephrine and norepinephrine to the ADRB receptors is thought to stimulate lipolysis (the release of fat stores for fuel) in response to fasting, whereas in brown adipose tissue, they stimulate heat production in response to cold exposure or overfeeding.

ADRB1 binds epinephrine and norepinephrine with approximately equal affinity.

## 💩 Dirties your ADRB1 gene

**Environment:** Coercive, hostile or aggressive situations; low positive social connection

**Lifestyle:** Thyroid dysregulation (both hypo and hyperthyroidism)

## Cleans your ADRB1 gene

**Lifestyle:** Create warm and reinforcing interactions that would promote or reward prosocial behavior, strong social ties with friendly peers, positive measures to negotiate conflicts or disagreements.

### Notable variation:

SNP: **ADRB1 1165G>C rs1801253 (-/-, CC)**
This CC variant has greater downstream stimulation from its agonists: epinephrine and norepinephrine.

# THE ADRB2 GENE

ADRB2 (adrenoceptor beta 2) gene expresses receptors for epinephrine and norepinephrine.

The three subtypes of ADRB: β1, β2, β3, are located primarily in the central nervous system (CNS), heart, coronary artery, kidney and muscle.

ADRB receptors are involved in development, behavior, smooth muscle tone, heart function, and energy metabolism.

All three β-subtypes also coexist in both white and brown adipose tissue. In white adipose tissue, attachment of epinephrine and norepinephrine to the ADRB receptors is thought to stimulate lipolysis (the release of fat stores for fuel) in response to fasting, whereas in brown adipose tissue, they stimulate heat production in response to cold exposure or overfeeding.

ADRB2 binds epinephrine with an approximately 30-fold greater affinity than norepinephrine.

## Dirties your ADRB2 gene

**Environment:** Coercive, hostile or aggressive situations; low positive social connection

**Lifestyle:** Thyroid dysregulation (both hypo and hyperthyroidism)

## Cleans your ADRB2 gene

**Lifestyle:** Create warm and reinforcing interactions that would promote or reward prosocial behavior, strong social ties with friendly peers, take positive measures to negotiate conflicts or disagreements.

# THE ADH1B/1C GENE

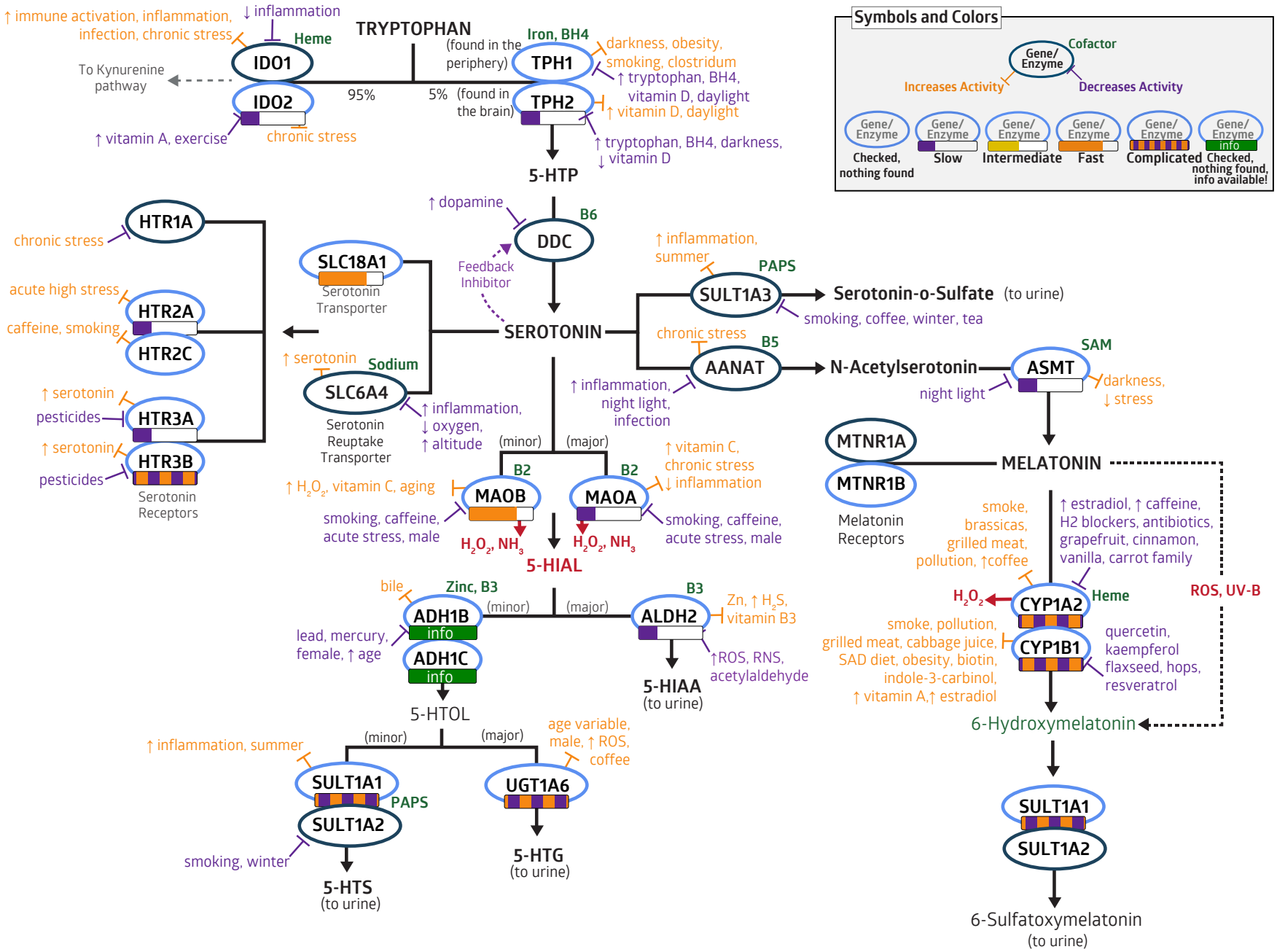
The complete discussion of this gene is under Serotonin.

### Notable variation:

SNP: **ADRB2 5285A>G rs1042713 (-/-, GG)**
This GG wild type showed enhanced agonist-promoted downregulation relative to AA. GG have enhanced receptor function compared with the receptor function of AA. Thus, the GG genotype shows more vasodilation in response to endogenous b-agonists epinephrine and norepinephrine. GG carriers saw improved lipid markers (serum cholesterol and LDL-cholesterol) by following a lower calorie, low fat diet as compared to a moderately high protein diet.

SNP: **ADRB2 79C>G rs1042714 (+/-, GC)**
Presumably this GC variant exhibits intermediate response to receptor downregulation of endogenous agonist binding of epinephrine and norepinephrine between CC and GG. GC has blunted receptor function and less vasodilation compared with the receptor function of wild type, but more than GG. In vivo studies indicate perhaps haplotype analysis is a better predictor of function, where the alleles of rs1042713 override the contribution of rs1042714.

# Serotonin


↑ immune activation, inflammation, infection, chronic stress
↓ inflammation
Heme
IDO1
To Kynurenine pathway
IDO2
↑ vitamin A, exercise
chronic stress
TRYPTOPHAN
95%
5%
(found in the periphery)
(found in the brain)
Iron, BH4
TPH1
TPH2
darkness, obesity, smoking, clostridum
↑ tryptophan, BH4, vitamin D, daylight
↑ vitamin D, daylight
↑ tryptophan, BH4, darkness, ↓ vitamin D
5-HTP
↑ dopamine
B6
DDC
Feedback Inhibitor
SEROTONIN
HTR1A
chronic stress
HTR2A
acute high stress
caffeine, smoking
HTR2C
HTR3A
↑ serotonin
pesticides
HTR3B
↑ serotonin
pesticides
Serotonin Receptors
SLC18A1
Serotonin Transporter
↑ serotonin
Sodium
SLC6A4
Serotonin Reuptake Transporter
↑ inflammation, ↓ oxygen, ↑ altitude
↑ inflammation, summer
PAPS
SULT1A3
Serotonin-o-Sulfate (to urine)
smoking, coffee, winter, tea
chronic stress
B5
AANAT
N-Acetylserotonin
SAM
ASMT
darkness, ↓ stress
night light
↑ inflammation, night light, infection
(minor)
(major)
B2
MAOB
↑ H2O2, vitamin C, aging
smoking, caffeine, acute stress, male
H2O2, NH3
B2
MAOA
↑ vitamin C, chronic stress ↓ inflammation
smoking, caffeine, acute stress, male
H2O2, NH3
5-HIAL
MTNR1A
MTNR1B
Melatonin Receptors
MELATONIN
smoke, brassicas, grilled meat, pollution, ↑coffee
↑ estradiol, ↑ caffeine, H2 blockers, antibiotics, grapefruit, cinnamon, vanilla, carrot family
H2O2
CYP1A2
Heme
ROS, UV-B
smoke, pollution, grilled meat, cabbage juice, SAD diet, obesity, biotin, indole-3-carbinol, ↑ vitamin A,↑ estradiol
CYP1B1
quercetin, kaempferol flaxseed, hops, resveratrol
6-Hydroxymelatonin
SULT1A1
SULT1A2
6-Sulfatoxymelatonin
(to urine)
bile
Zinc, B3
ADH1B
info
lead, mercury, female, ↑ age
ADH1C
info
5-HTOL
(minor)
(major)
B3
ALDH2
Zn, ↑ H2S, vitamin B3
↑ROS, RNS, acetylaldehyde
5-HIAA
(to urine)
↑ inflammation, summer
SULT1A1
PAPS
SULT1A2
smoking, winter
5-HTS
(to urine)
age variable, male, ↑ ROS, coffee
UGT1A6
5-HTG
(to urine)
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
Checked, nothing found, info available!
info

# THE IDO2 GENE

The IDO2 (Indoleamine 2,3-dioxygenase 2) gene expresses an enzyme which catalyzes the first and rate-limiting step in the conversion of tryptophan to kynurenine using heme as a cofactor. (The affinity of IDO2 for tryptophan is much lower than that of IDO1.)

Tryptophan is required by T lymphocytes for cell division and proliferation. Therefore, IDO plays an important role in modulating T-cell behavior by controlling the amount of tryptophan available.

Depletion of tryptophan, via IDO activity, promotes immune tolerance, helps to prevent autoimmunity and is important in pregnancy for preventing rejection of the fetus. However, excessive depletion of tryptophan, due to upregulation of IDO can result in the suppression of T cells and natural killer (NK) cells.

A suppressed immune system increases the risk of opportunistic bacterial, fungal, parasitic, viral infections and cancer, especially in the immunocompromised. This is known as 'Immune Escape.'

Additionally, upregulated IDO2 may enhance pain sensitivity because tryptophan metabolites produced by IDO are irritants to the nervous system.

## 💩 Dirties your IDO2 gene

**Environment:** Work with your healthcare provider to identify and treat any infections, as evidenced by increased susceptibility to opportunistic infections such as *Candida spp., Aspergillus spp.,* Lyme, Herpes or Epstein-Barr virus. Also avoid mold exposures: Pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and mycotoxins. Avoid industrial pollution, dioxins.

**Lifestyle:**

- Excessive exercise, and/or chronic low level stress.
- Evaluate heme deficiency. Many parasites and gram negative bacteria need the iron-containing heme, to reproduce and cause infection. Parasites and bacterial pathogens must either synthesize their own heme or acquire heme from the host. Thus, untreated chronic parasites and bacterial infections may create a heme deficiency.
- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.
- People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.

### Notable variation:

SNP: **IDO2 R248W rs10109853 (+/+, TT)**
This TT variant produces an inactive enzyme with over 95% reduction in activity in vitro.

### Dirties your IDO2 gene, continued...

**Food:**

- Avoid diet high in fat (>60% of calories), fatty meats and animal fats such as butter or lard which concentrate dioxins.
- Avoid the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein.

**Supplements and Medications:** Consider *Saccharomyces bouldardii* while taking antibiotics and pay attention to probiotics after an antibiotic course as more susceptible to *Candida* dysbiosis. Avoid proton pump inhibitor drugs (Prilosec, Prevacid, Nexium). Many other medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your IDO2 gene

**Environment:** Use an extractor hood while cooking and high-smoke point oils like ghee or avocado oil.

**Lifestyle:** Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Focus on vitamin A, beta carotene and heme-iron rich sources. Studies show that appropriate levels of vitamin A help to balance IDO activity and support production of T cells and natural killer (NK) cells. Opt for a diet rich in cruciferous vegetables.

**Supplements and Medications:** Optimizing levels of iron and vitamin A is important but high levels taken long term may have negative consequences. Always strive to obtain these nutrients from food sources first and follow the pulse method when supplementing, as described in the *Dirty Genes* book. Seek guidance from a qualified health professional. Optimize niacin (B3).

# THE TPH2 GENE

The TPH2 (tryptophan hydroxylase 2) gene expresses an enzyme which catalyzes the initial, rate-limiting step in the production of the neurotransmitter serotonin. This process requires oxygen ($O_2$), iron ($Fe^{2+}$) and tetrahydrobiopterin ($BH_4$) as cofactors. TPH2 is dependent on the recycling of biopterin (see biopterin recycling pathway).

Whereas TPH1 is mainly expressed in peripheral tissues such as the skin and gut, TPH2 is exclusively expressed in neuronal cells in the brain and central nervous system. Although 90% of the body's serotonin production is generated by TPH1 in the gut, this serotonin cannot pass the blood-brain barrier into the brain. Therefore, TPH2 is responsible for the majority of brain-generated serotonin.

Serotonin generated in peripheral tissues by THP1 is involved in the regulation of gut motility and vascular tone, while serotonin generated in the brain by TPH2 is involved more in the regulation of mood, confidence and wakefulness. The exception to this is that TPH1 is found in the pineal gland in the brain and is actually there at levels some 150 times higher than TPH2. This may be due to the need to generate melatonin in the pineal gland brain at night, while serotonin in other parts of the brain is low.

Vitamin D has been found to have an opposite effect on the two enzymes. Vitamin D activates the transcription of TPH2 in the brain and represses the transcription of TPH1 in tissues outside the blood-brain barrier.

Vitamin D naturally follows a diurnal rhythm, with lower levels at night, rising to a maximum at around midday. This provides the body with a mechanism to control the level of serotonin generated in the brain: with higher levels of vitamin D during daylight hours activating TPH2 to increase serotonin in the brain and increase wakefulness, while lower levels of vitamin D at night reduces serotonin in the brain and reduces stimulation. Vitamin D also fluctuates seasonally, with generally lower levels observed during the winter months. This may be one explanation for the Seasonal Affective Disorder (SAD) suffered by people who are not exposed to sufficient daylight.

## 💩 Dirties your TPH2 gene

**Environment:** Avoid mold exposure: pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and mycotoxins.

**Lifestyle:** Minimize coercive, hostile or aggressive situations, low positive social connection, early life stresses. Living in northern latitudes and/or shiftwork will reduce exposure to natural daylight and reduce TPH2 activation in the brain.

## Notable variation:

SNP: **TPH2 G-703T rs4570625 (-/-, GG)**
This GG variant may have reduced serotonergic transmission and reduced amygdala activation compared to GT and TT.

## Dirties your TPH2 gene, continued...

**Food:** Low tryptophan containing meals may reduce the amount of available tryptophan for TPH2 to function. Conversely, high protein meals such as GAPS and Paleo may reduce tryptophan from entering the brain.

**Supplements and Medications:** Pay attention to probiotics after an antibiotic course as dysbiosis decreases intestinal serotonin levels.

## Cleans your TPH2 gene

**Environment:**

- Use an extractor hood while cooking and high-smoke point oils such as ghee or avocado oil.
- Utilize air filtration systems to remove molds, bacteria and viruses and water filtration to remove potential pathogenic bacteria.

**Lifestyle:**

- Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.
- Create warm and reinforcing interactions that would promote or reward prosocial behavior, strong social ties with friendly peers.

**Food:** Choose iron, vitamin D, folate rich foods. A balanced meal with protein and carbohydrate may increase tryptophan delivery in the brain. Ketogenic diet (high fat with some protein) also appears to deliver tryptophan quite effectively to the brain which may be one of the mechanisms of how the ketogenic diet helps those with seizures.

**Supplements and Medications:**

- Consider 5-HTP, vitamin D, iron, niacin (B3).
- Optimize $BH_4$ levels with sufficient folinic acid, antioxidants like liposomal glutathione, PQQ and vitamin C.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

# THE SLC18A1 GENE

The SLC18A1 (solute carrier family 18 member A1 aka VMAT1) gene expresses a cell membrane transporter for dopamine, serotonin, epinephrine and norepinephrine in the presynaptic neurons.

Within the presynaptic neuron, SLC18A1 transports the neurotransmitters into vesicles for storage and later release.

## 💩 Dirties your SLC18A1 gene

**Environment:** Environmental chemicals including polychlorinated biphenyls (PCBs) and organochlorine pesticides have been shown to inhibit SLC18A1 activity and deplete dopamine stores in experimental animals.

**Food:** Avoid organochlorine pesticides in food; see the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

**Supplements and Medications:**

- Methamphetamine, MDMA (also known as Ecstasy).
- Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your SLC18A1 gene

**Lifestyle:** Acute and chronic stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https::://www.ewg.org/foodnews/clean-fifteen.php/).

**Supplements and Medications:** *Ginkgo biloba* has been found (in mice) to positively regulate SLC18A1 and reduce neurotoxicity caused by environmental chemicals. Consider physiological dosage of lithium orotate 5 mg per day.

### Notable variation:

SNP: **SLC18A1 C407T rs1390938 (+/+, AA)**
This AA variant increased transport of serotonin by 370% more than wild type to the presynaptic cleft as shown by in vitro research model.

# THE HTR2A GENE

The HTR2A (5-hydroxytryptamine receptor 2A ) gene expresses a receptor for serotonin found in various parts of the brain, central and peripheral nervous system as well as platelets, cardiovascular and gastrointestinal tissue.

In addition to serotonin, HTR2A receptors also function as receptors for various drugs and psychoactive substances.

HTR2A receptors also play a role in behavior, memory, learning, intestinal smooth muscle contraction and platelet aggregation.

## Dirties your HTR2A gene

**Lifestyle:** Acute stress, secondhand smoke, dehydration

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your HTR2A gene

**Lifestyle:**

- Optimize hydration by drinking water with appropriate electrolyte balance. Hydration is not just drinking water but the process of causing something to absorb water. Electrolytes enhance water absorption inside cells.
- Acute stress management techniques are recommended such as breathing exercises, cognitive reframing (choosing a different way to perceive the situation), progressive muscle relaxation.

**Food:** Foods rich in calcium and omega-3 fatty acids alpha-linolenic acid (ALA) and docosahexaenoic acid (DHA).

**Supplements and Medications:** Consider myo-inositol, N-acetylcysteine (NAC), alpha lipoic acid, calcium, omega-3 fish oils.

## Notable variation:

SNP: **HTR2A G-1438A rs6311 (-/-, CC)**
The CC variant appears to have lower expression of HTR2A serotonin receptors, resulting in lower serotonin binding and reduced serotonergic activity compared to T allele carriers. C allele can offer protection against some psychiatric diseases but increases risk for other diseases.

# THE HTR3A GENE

The HTR3A (5-hydroxytryptamine receptor 3A) gene expresses a receptor for 5-hydroxytryptamine (serotonin) that differs structurally and functionally from all other serotonin receptors.

The 5-HT3 receptors are found throughout the central and peripheral nervous system and are activated by many compounds beyond serotonin, such as local and general anesthetics.

5-HT3 receptors in the CNS may play roles in a variety of functions including vomiting, cognition, anxiety and regulation of the reward system.

## Dirties your HTR3A gene

**Environment:** Avoid organochlorine pesticides; see the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

**Lifestyle:** Adverse life events (abuse, neglect, poverty, discrimination); nicotine, alcohol.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your HTR3A gene

**Environment:** Create warm and reinforcing interactions that would promote or reward prosocial behavior. Create strong social ties with friendly peers.

**Lifestyle:** Create safe, nurturing home and school environment. Take measures to negotiate and resolve conflicts or disagreements, seek conflict resolution, practice reframing techniques (how one chooses to respond to a situation) and mindfulness. Consider psychotherapy, acupuncture, homeopathy for past trauma. Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Choose serotonin-rich foods. Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https::://www.ewg.org/foodnews/clean-fifteen.php/).

**Supplements and Medications:** 5-hydroxytryptophan (5-HTP)

## Notable variation:

SNP: **HTR3A C178T rs1062613 (-/-, CC)**

This CC variant contains an intact repression site, and therefore has lower expression and fewer receptors on the cell surface. In addition, CC carriers have approximately 30% lower 5-hydroxyindoleacetic acid (5-HIAA) levels in the cerebrospinal fluid. 5-HIAA is the main metabolite of serotonin, suggesting that 5-HT3A-containing receptors regulate the serotonin turnover rates in the central nervous system.

# THE HTR3B GENE

The HTR3B (5-hydroxytryptamine receptor 3B) gene expresses a receptor for 5-hydroxytryptamine (serotonin) that differs structurally and functionally from all other serotonin receptors.

The 5-HT3 receptors are found throughout the central and peripheral nervous system and are activated by many compounds beyond serotonin, such as local and general anesthetics.

5-HT3 receptors in the CNS may play roles in a variety of functions including vomiting, cognition, anxiety and regulation of the reward system.

## Dirties your HTR3B gene

**Environment:** Avoid organochlorine pesticides; see the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

**Lifestyle:** Adverse life events (abuse, neglect, poverty, discrimination), nicotine, alcohol.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your HTR3B gene

**Environment:** Create warm and reinforcing interactions that would promote or reward prosocial behavior. Create strong social ties with friendly peers.

**Lifestyle:** Create safe, nurturing home and school environment. Take measures to negotiate and resolve conflicts or disagreements, seek conflict resolution, practice reframing techniques (how one chooses to respond to a situation) and mindfulness. Consider psychotherapy, acupuncture, homeopathy for past trauma. Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** Choose serotonin-rich foods. Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https::://www.ewg.org/foodnews/clean-fifteen.php/).

**Supplements and Medications:** 5-hydroxytryptophan (5-HTP)

## Notable variation:

SNP: **HTR3B A386C rs1176744 (+/-, AC)**
This AC variant may cause a increased in single channel mean open time compared with wild type in vitro. This represents a significant increase in receptor signaling.

# THE MAOA GENE

The MAOA (monoamine oxidase A) gene produces an enzyme that catalyzes the removal of an amine group from both internally-produced and externally-derived dietary and environmental amines. Riboflavin (B2) is the required cofactor and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

The amount of hydrogen peroxide generated by MAOA is so significant that it consumes significant amounts of glutathione.

In the serotonin pathway, MAO enzymes process and detoxify the neurotransmitter serotonin. In all of these reactions, MAOA represents the major route, and MAOB the minor route. Serotonin is a neurotransmitter that helps us feel at peace, optimistic, and self-confident. However, serotonin can easily become dysregulated. Low levels of serotonin can cause anxiety, depression, cravings and insomnia. High levels of serotonin can also cause anxiety (this time associated with irritability rather than depression), as well as rapid heart rate, high blood pressure and a host of other symptoms.

MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of two X chromosomes.

## Slows down your MAOA gene

**Environment:**

- Research shows that a noisy sleep environment (near highway, train tracks, airports, city life, college dorms) increases catecholamine levels and workload on the MAOA enzyme.
- Early childhood mistreatment and maternal stress in utero have been shown to downregulate MAOA.
- Passive exposure to smoke (even in utero) slows the MAO genes. Smoking while pregnant is associated with aggressive traits in offspring.

## Notable variation:

SNP: **MAOA T941G rs6323 (-/-, T)**
This genotype (TT in women, T in men) lowers MAOA activity and may exhibit higher levels of serotonin.

## Slows down your MAOA gene, continued...

**Lifestyle:**

- Short-term, high stress situations reduce the activity of MAO enzymes presumably in order to respond to the "fight or flight" situation by reducing the break down of stress hormones.
- Iron deficiency anemia can cause a decrease in MAO activity as research indicates that insufficient levels of dietary iron in the womb can lead to poorer cognitive functioning and maladaptive social behaviors including aggressive temperament in offspring.
- Smoking (strongly) and caffeine (weakly) reduce MAO activity and raise catecholamine levels. Hence people suffering from depression often self-medicate with these substances. Using food and herbs to slow MAO (see below) may help when quitting smoking.
- Alcohol actually increases MAO activity, but some alcoholic beverages at the time of consumption can overwhelm MAO capacity. This is why alcohol can cause an initial “antidepressant/euphoric” effect as it temporarily reduces the degradation of serotonin and dopamine. However, excessive or “binge” drinking causes a rapid build-up of chemicals, which can result in both immediate mood changes and also long-term neurological damage. Alcoholic beverages containing high levels of amines such as champagne and wine increase MAO workload to the greatest extent. To improve mood, MAOA activity may be regulated naturally with healthy foods and supplements (see below).

**Food:**

- Avoid simple, processed carbohydrates; riboflavin (B2)-deficient diet, iron-deficient diet.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to degrade serotonin (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Avoid excessive consumption of tryptophan rich foods for the same reason.

**Supplements and Medications:**

- Excessive tryptophan will dirty MAOA by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement but use the pulse method instead. However, for those with a fast MAOA genotype that is expressing itself (or your MAOA is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOA: 5-hydroxytryptophan (5-HTP), garlic extract, berberine, curcumin, quercetin, green tea, *Rhodiola rosea*.
- Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine. Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Speeds up your MAOA gene

**Lifestyle:**

- Chronic, low-level stress causes MAO enzymes to upregulate presumably as a result of the need to break down the increased amount of stress hormones being produced.
- Alcohol increases MAO activity, which reduces important neurotransmitters, and may result in both neurological and immunological deregulation. While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then non-tyramine containing alcohols such as gin, vodka, rum, bourbon are better choices, especially if you take a MAO inhibitor.
- Low estrogen tends to raise MAOA activity. Therefore, the postpartum estrogen drop, as well as perimenopausal estrogen decline, seem to relate to upregulated MAOA levels in the brain. Fluctuations in estrogen during the menstrual cycle may contribute to mood swings through a similar relationship.
- MAOA activity tends to naturally increase throughout adolescence into adulthood.

**Food:** Iron rich, riboflavin (B2), vitamin C and E rich

**Supplements and Medications:**

- Optimize riboflavin (B2) and iron.
- Vitamin C and vitamin E are free radical scavengers and reduce the hydrogen peroxide produced by MAO. PQQ (pyrroloquinoline quinone) and liposomal glutathione also assist with hydrogen peroxide removal.
- While 5-hydroxytryptophan (5-HTP) or inositol may be useful to calm a fast MAO when serotonin is low, lithium at low dose, together with adequate B2, is very useful to support a slow MAOA when serotonin is high.
- Lithium activates the serotonin transporter SLC18A1 and helps to clear excess serotonin, thus reducing the workload on MAOA. Consider low dose lithium orotate 5 mg per day as required.

# THE MAOB GENE

The MAOB (monoamine oxidase B) gene produces an enzyme that catalyzes the removal of an amine group from both internally-produced and externally-derived dietary and environmental amines. It is the predominate form of MAO in the brain. Riboflavin (B2) is the cofactor required for MAOB enzyme and the by-products of this reaction are hydrogen peroxide ($H_2O_2$) and ammonia ($NH_3$).

Significant amounts of glutathione are required to neutralize this hydrogen peroxide.

In the serotonin pathway, MAO enzymes process and detoxify the neurotransmitter serotonin. In all of these reactions, MAOA represents the major route, and MAOB the minor route. Serotonin is a neurotransmitter that helps us feel at peace, optimistic, and self-confident. However, serotonin can easily become dysregulated. Low levels of serotonin can cause anxiety, depression, cravings and insomnia. High levels of serotonin can also cause anxiety (this time associated with irritability rather than depression), as well as rapid heart rate, high blood pressure and a host of other symptoms.

MAO enzymes are located on the X chromosome. Therefore, males only inherit one allele and females have inherently higher activity as a result of two X chromosomes.

## Slows down your MAOB gene

**Lifestyle:**

- Avoid alcohol (more than one glass), caffeine (weakly inhibits), iron deficiency anemia, smoking (both active and passive exposures).
- Short-term, acute, high stress situations reduce the activity of MAOB enzymes (as response to the "fight or flight" situation by reducing the break down of stress hormones).
- Stress sensitive females (higher basal heart rate, lower peak estrogen and progesterone) appear to have less activity.
- Males have only one copy, so inherently possess less activity.

## Notable variation:

SNP: **MAOB -36A>G rs1799836 (+/+*, C)**

Research indicates contradictory findings for this variant (CC in women, C in men), but metabolomic research indicates this variant appears to upregulate MAOB in vivo. A careful examination of symptoms related to MAO activity (mood, appetite, etc.) may offer signs of this increased activity.

## Slows down your MAOB gene, continued...

**Food:**

- Avoid simple, processed carbohydrates; riboflavin (B2)-deficient diet, iron-deficient diet.
- Foods containing naturally-occurring amines may reduce the capacity of MAO enzymes to degrade serotonin (an internally-produced amine). These include tyramine containing foods: aged cheeses; cured, smoked or processed meat or fish; fermented foods and sauces: yeast spreads (marmite), tempeh, miso, tamari; beer, wine and champagne; tofu and soy milk, fava beans and snow peas.
- Avoid excessive consumption of tryptophan rich foods for the same reason.

**Supplements and Medications:**

- Excessive tryptophan will dirty MAOB by increasing its workload and this may result in hyperactivity and sweating. Therefore, do not over supplement but use the pulse method instead. However, if your fast MAOB genotype is expressing itself (or your MAOB is acting fast due to other factors such as chronic stress or low estrogen), then these supplements may be useful to calm a fast MAOB: Garlic extract, berberine, curcumin, quercetin, EGCG from green tea, silymarin, *Glycyrrhiza spp.* (licorice), *Lamiaceae* (mint family: lavender, oregano, rosemary, sage, thyme, etc); *Rhodiola rosea*, *Scutellaria spp.* (skullcap), *Piper methysticum* (kava-kava), *Baptisia officinalis* (wild indigo), gentian, *Symphytum spp.* (comfrey), *Phellodendron amurense* (Amur corktree), *Cyamopsis psoralioides* (bakuchi seed), *Psoralea corylifolia* (babchi seed).
- A comprehensive list of herbs with MAOB inhibition effects can be found in Table 1 here.
- Many medications interact with this enzyme especially reversible MAO inhibitors such as pseudoephedrine, ephedrine, norephedrine. Beware concurrent use of multiple medications as MAO inhibition effects are often additive. Consult your healthcare provider or pharmacist.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Speeds up your MAOB gene

**Lifestyle:**

- Long-term, low-level ongoing stress causes MAOB upregulation. MAOB activity also naturally increases with age, especially after the age of 60.
- Estrogen tends to inhibit MAOB, therefore an age-related decline in estrogen is likely to further increase MAOB activity. Since MAOB processes serotonin in the brain and central nervous system, increased MAOB activity causes a depletion of serotonin and may exacerbate issues such as post-menopausal depression.
- Alcohol increases MAOB activity, further increasing the risk of mood swings and depression. While drinking alcohol is not encouraged, if occasional alcoholic beverages are consumed then non-tyramine containing alcohols such as gin, vodka, rum, bourbon are better choices, especially if you take a MAO inhibitor.

**Food:** Iron, riboflavin (B2), vitamin C and E rich

**Supplements and Medications:** Optimize riboflavin (B2) and iron. Vitamin C and vitamin E are free radical scavengers and reduce the hydrogen peroxide produced by MAO. PQQ (pyrroloquinoline quinone), liposomal glutathione or s-acetyl glutathione also support elimination of hydrogen peroxide.

# THE ADH1B/1C GENE

The ADH1B and ADH1C (alcohol dehydrogenase 1B/1C) genes express enzymes which detoxify a wide variety of alcohol substrates: ethanol, retinol, other aliphatic alcohols, hydroxysteroids and lipid peroxidation products.

In the serotonin pathway, ADH1B converts 5-hydroxyindole- acetaldehyde (5-HIAL) to 5-hydroxytryptophol (5-HTOL), using the cofactors zinc and NAD+, the active form of niacin (B3).

## 💩 Dirties your ADH1B/1C gene

**Environment:** Avoid acetaldehyde from the environment such as smog, vehicle emissions, smoking (especially secondhand exposures), cooking fumes, formaldehyde from building materials, industrial air pollution and disinfectants, drugs and perfumes; lead, mercury, dioxin compounds.

**Lifestyle:**

- Smoking and alcohol reduces ADH capacity to detoxify alcohol itself.
- Minimize oxidative stress to decrease endogenous aldehydes created by reactive oxygen species.
- High T4/hyperthyroidism may reduce production of ADH in the liver.
- Treat any *Candida* dysbiosis which generates endogenous acetaldehyde.
- Females tend to have lower ADH activity and ADH activity in males reduces with age.

**Food:** Limit fermented foods high in acetaldehyde such as yogurt, vinegar, kombucha, fish products, fermented mushrooms, miso, tempeh, pickled vegetables and kimchi. Other foods containing acetaldehyde include very ripe fruit, artificial flavors like lemon flavoring, ground and instant coffee. Many aldehydes are found in drinking water so use a filter.

**Supplements and Medications:** Avoid H2 blockers (Tagamet, Fluxid, Pepcid, Axid, Zantac). Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your ADH1B/1C gene

**Environment:** Employ strategies to reduce exposure to sources of acetaldehyde in the environment.

**Lifestyle:** Ensure sufficient bile acid production as bile acid helps to activate ADH activity.

**Food:** Zinc and niacin (B3) rich

### Notable variation:

While no notable variation was found, we are presenting this gene's information to you because it's so important. Remember, lifestyle, food, environment and nutrients play a significant role in genetic expression — often significantly more than a genetic variation.

## Cleans your ADH1B/1C gene, continued...

**Supplements and Medications:**

- Choose zinc, niacin (B3) rich sources. Thiamine (B1) is also especially important as acetaldehyde damages enzymes which are B1 dependent.
- Consider resveratrol with vitamin C (especially when consuming alcohol).
- Some herbs have been shown in mice to slow down the biotransformation of alcohol into the more toxic acetaldehyde. These herbs include *Acanthopanax sessiliflorus, Ixeris dentata, Glycyrrhiza uralensis* (Chinese licorice), *Hovenia dulcis* (Japanese raisin tree), *Liriope platyphylla* (lilyturf), *Lycium chinense* (goji berry), *Pueraria thunbergiana* (kudzu).

# THE ALDH2 GENE

The ALDH2 (aldehyde dehydrogenase 2 family member) gene expresses an enzyme which converts aldehydes to carboxylic acids.

In the serotonin pathway, ALDH2 converts 5-hydroxyindole- acetaldehyde (5-HIAL) to the final product 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. This reaction uses niacin (B3) as a cofactor.

ALDH2 also performs the vital role of neutralizing internally-produced lipid peroxidation products formed due to oxidative stress.

Many commonly found environmental chemicals put additional strain on this enzyme.

## Dirties your ALDH2 gene

**Environment:** Avoid aldehydes from the environment such as vehicle emissions, smoking (especially secondhand exposures), cooking fumes, formaldehyde from building materials, disinfectants, drugs, perfumes, fungicides and pesticides, carbon tetrachloride (dry cleaning), hydrogen sulfide and many other environmental chemicals. Also minimize oxidative stress to decrease aldehydes created internally by reactive oxygen species.

**Lifestyle:** Limit alcohol, smoking, insulin resistance, oxidized LDL, high kynurenine which can all inhibit ALDH2. Work with your healthcare provider to identify *Candida* dysbiosis which generates endogenous acetaldehyde.

**Food:** Limit oxidized omega-6 fatty acids (from old or processed oils), known allergens, foods high in acetaldehyde such as fish products, canned vegetables, fermented foods: yogurt, vinegar, kombucha, fermented mushrooms, tempeh, miso, pickled vegetables and kimchi. Other foods containing acetaldehyde include very ripe fruit, artificial flavors like lemon flavoring, ground and instant coffee. Many aldehydes are found in drinking water so use a filter.

**Supplements and Medications:** Acetaminophen (Tylenol), aspirin

## Cleans your ALDH2 gene

**Environment:** Employ strategies to reduce exposure to sources of acetaldehyde and other environmental chemicals.

**Food:** Choose vitamin B1, B3, C zinc, magnesium rich sources; especially when consuming alcohol. Opt for a diet rich in vegetables from the brassica family, broccoli sprouts.

## Notable variation:

SNP: **ALDH2 699T>C rs737280 (+/-, TC)**

This TC variant may decrease enzyme activity and makes exposures to pesticides more risky. Due to lack of research in other ethnicities, these results may be applicable only to those of European descent.

## Cleans your ALDH2 gene, continued...

**Supplements and Medications:**

- Thiamine (B1) is especially important as acetaldehyde damages enzymes which are B1 dependent. Consider zinc, niacin (B3), sulforaphane, resveratrol with vitamin C (especially when consuming alcohol).
- Some herbs have been shown in mice to speed up the biotransformation of acetaldehyde into less toxic end products. These herbs include *Lycium chinense* (goji berry), *Acanthopanax sessiliflorus*, *Ixeris dentata*, *Polypori umbellati* (zhu ling).

# THE ASMT GENE

The ASMT (acetylserotonin O-methyltransferase) gene expresses an enzyme which catalyzes the final step in the synthesis of melatonin using S-adenosylmethionine (SAM) as a cofactor.

## Dirties your ASMT gene

**Environment:** Exposure to artificial light in the evening

**Lifestyle:** Emotional stressors

**Food:** Aspartame consumption

**Supplements and Medications:** Avoid tyrosine in the evening as tyrosine increases catecholamines (dopamine and epinephrine). These can disrupt melatonin production.

## Cleans your ASMT gene

**Environment:** Support your circadian rhythm through exposure to morning sunlight without sunglasses. In the winter, exposure to bright uniform light on first waking is advised. Practice good sleep hygiene: bedtime rituals, warm bathing, a cool and dark bedroom with no distractions or screen devices. In the evening avoid bright or blue light sources. Use screen programs that filter blue spectrum from electronic devices, as well as limiting screen time in evening. Use pools of light rather than uniform, overhead lighting in the home environment after sunset. Spend as much time outdoors, year-round, as possible.

**Lifestyle:** Increase your serotonin levels by daily exercise: walking, dancing, sports or gardening (anything enjoyable and preferably outdoors). Engage in mindfulness, especially in the evening: meditation, prayer or gratitude practice. Participate in mood elevating activities: games, humor, hobbies and socializing with friends and family. Encourage pleasant, healthy touch as experienced by the individual: massage, acupressure, cat on the lap, hugs, weighted blanket. Utilize aromatherapy: especially lavender and ylang-ylang oils.

**Food:** Choose tryptophan rich foods especially at dinner. Include some complex carbohydrate foods high in fiber balanced with healthy fat and proteins.

**Supplements and Medications:** Consider S-adenosylmethionine (SAMe), 5-hydroxytryptophan (5-HTP), melatonin or extended-release melatonin.

## Notable variation:

SNP: **ASMT -310G>A rs4446909 (-/-, GG)**

This GG wild type variant exhibits approximately 20% less ASMT activity and lower melatonin levels compared to AA in human blood cells.

# THE CYP1A2 GENE

The CYP1A2 (cytochrome P450 monooxygenase 1A2) gene expresses an enzyme which is involved in degrading various compounds made in the body such as fatty acids, steroid hormones, vitamins, melatonin and cholesterol. It also detoxifies ingested compounds such as caffeine, aflatoxin B1 and many medications.

CYP1A2 requires oxygen and heme as necessary cofactors.

The issue of speed/rate of degradation of compounds by CYP1A2 is somewhat moot, as some end products are less toxic while others are more toxic.

The overall transformation rate of any compound by this enzyme also varies on any given day depending on the exposures encountered that impact the enzyme: dietary choices, environmental contaminants, medications.

## Slows down your CYP1A2 gene

**Lifestyle:**

- Alcohol; coumarins found in perfumes, shampoos, lotions, body care products which are significantly absorbed through the skin all slow this enzyme.
- Evaluate heme deficiency. Heme is a cofactor for CYP1A2. However, many parasites and gram negative bacteria need the iron-containing cofactor, heme, to reproduce and cause infection. Parasites and bacterial pathogens must synthesize their own heme or acquire heme from the host. Thus, untreated chronic parasites and bacterial infections may create a heme deficiency.
- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.
- People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.

## Notable variation:

SNP: **CYP1A2 -163C>A rs762551 (-/-, AA)**
Caffeine metabolism in wild type AA smokers appeared 50-60% faster compared to non-smokers of any genotype. This shows that AA individuals are more susceptible to smoke and high coffee consumption in speeding up action of CYP1A2. Some research has specifically analyzed melatonin metabolism in regards to genotype and smoking and surprisingly saw no correlation between smoking, genotype and melatonin metabolism although the study was small in size.

### Slows down your CYP1A2 gene, continued...

**Food:**

- A diet rich in vegetables from the umbel (carrot) family: carrots, celery, celeriac, cilantro, fennel, parsley, parsnips; as well as seeds from this family commonly used as spices: asafoetida, caraway, coriander, cumin, dill, fennel, curry powder all slow this enzyme.
- Other inhibitors include grapefruit and its juice; naturally occurring coumarin rich spices; foods such as Cassia cinnamon, Mexican vanilla, tonka beans, strawberries, bilberries, cherries, apricots, green tea, honey.
- Meat cooked using methods that employ lower, indirect heat such as braising or stewing can decrease polyaromatic hydrocarbon (PAH) formation. Polyaromatic hydrocarbons from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar. Use the extractor hood while cooking along with high smoke point oils such as avocado or ghee.

**Supplements and Medications:** Caffeine alone (not coffee); herbs high in coumarins such as *Artemisia spp.* (wormwood), *Verbascum thapsus* (mullein), *Melilotis spp.* (sweet clover), *Angelica spp.* (dong quai), *Ferula communis, Glycyrrhiza spp.* (licorice), *Mentha spp.* (peppermint and spearmint) all have potential to inhibit. H2 blockers (Tagamet, Fluxid, Pepcid, Axid, Zantac); antibiotics, estrogens and oral contraceptives containing estrogens can slow CYP1A2. Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Speeds up your CYP1A2 gene

**Environment:** Smoke from any source: cigarettes, marijuana, incense, woodsmoke, diesel exhaust, smog, cooking fumes.

**Food:**

- Opt for a diet rich in vegetables from the brassica family.
- Avoid foods high in polyaromatic hydrocarbons: meat, fish, shellfish and poultry especially if smoked; food products of any type originating from polluted environments (e.g., produce grown near highways or downwind from air pollution sources) or cooked over woodfire; deep-fried foods, coffee, baked goods: especially bread and pizza from wood-fired ovens. All these food products can speed up and overtax CYP1A2.
- Heavy coffee use (3 or more cups/day) will increase activity of CYP1A2 due to the polyaromatic hydrocarbon content of roasted coffee beans.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

# THE CYP1B1 GENE

The CYP1B1 (cytochrome P450 monooxygenase 1B1) gene expresses an enzyme which, using oxygen and heme as cofactors, degrades melatonin in tissues other than the liver such as the retina and the colon.

CYP1B1 also plays an important role throughout the body in the first phase of detoxifying compounds such as polycyclic aromatic hydrocarbons (PAH), dietary plant flavonoids, genotoxic catechol estrogens, and converting retinol (a vitamin A compound) to retinal.

The rate of degradation by CYP1B1 is a somewhat moot issue, as some end products are less toxic while others are more toxic.

The overall transformation rate of any compound by this enzyme also varies on any given day depending on the exposures encountered that impact the enzyme: dietary choices, environmental contaminants, medications, etc.

## Slows down your CYP1B1 gene

**Environment:** Use an extractor hood while cooking and high-smoke point oils such as ghee or avocado oil.

**Lifestyle:**

- Evaluate heme deficiency. Many parasites and gram negative bacteria need the iron-containing cofactor, heme, to reproduce and cause infection. Parasites and bacterial pathogens must either synthesize their own heme or acquire heme from the host. Thus, untreated chronic parasites and bacterial infections may create a heme deficiency.
- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.
- People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.

**Food:** Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon (PAH) formation. Polyaromatic hydrocarbons (PAH) from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar. Use high smoke point oils such as ghee or avocado oil.

## Notable variation:

SNP: **CYP1B1 CYP1B1*4 rs1800440 (+/-, TC)**

This TC variant exhibits similar kinetics to wild type CYP1B1 but 60% lower expression levels. The resulting protein also exhibited reduced half-life which implies a downregulated enzyme compared to wild type. All of the research into function of CYP1B1 concerns its other substrates: estrogens, pollutants like smoke and polyaromatic hydrocarbons (PAH) found in food as these are activated into carcinogens via this enzyme. Little is known about how CYP1B1 mutations effect melatonin metabolism. In general, a downregulated CYP1B1 appears to be more beneficial as it is slower in the bio-activation of carcinogens, giving time for downstream enzymes to neutralize the toxic intermediates.

**Indeterminate CYP1B1 Haplotype**

**Note**: The presence of one or more SNPs in this haplotype couldn't be determined from your saliva sample. This prevents us from using this haplotype in the assessment of this gene.

| Gene | rsID | Alias | Variant Allele | Call |
|---|---|---|---|---|
| CYP1B1 | rs1056827 | | A | CA |
| CYP1B1 | rs10012 | | G | - |

### Slows down your CYP1B1 gene, continued...

**Supplements and Medications:**

- Diindolylmethane (DIM), quercetin, kaempferol, flaxseed, resveratrol, *Humulus lupulus* (hops), *Trifolium praetense* (red clover) all have potential to slow CYP1B1.
- In the end, it is impossible to predict with pinpoint accuracy how an individual will react to a given dose of substrate metabolized by CYP1B1, as its activity is dynamic and reflects changing diet and environmental conditions. If melatonin for sleep at bedtime results in daytime grogginess, consider decreasing the amount taken as there may be slower metabolism of melatonin due to this genetic variant as well as interaction with other metabolizing genes or diet. Conversely, melatonin for sleep at bedtime may not result in improved sleepiness. If this describes you, consider increasing the amount taken or use a time release form as there may be faster metabolism of melatonin due to this genetic variant as well as interaction with other metabolizing genes or diet.
- Special notes for melatonin dosing: One study looked at a very small number of autistic children who stopped responding to bedtime dosing (ranging from 2.5 to 10 mg) of melatonin after initial improvement in sleep. The children were determined to be slow melatonin metabolizers as evidenced by high plasma melatonin levels during midday when levels should have been low. Reducing dose to 0.1 mg restored efficacy of bedtime melatonin for sleep. This study did not examine CYP1B1 genotype but did look at CYP1A2 status and most were what is considered the "fast" metabolizer of caffeine genotype. In short: genotype is not always predictive of response in an individual.

## Speeds up your CYP1B1 gene

**Environment:** Smoke from any source such as incense, woodsmoke, air pollution, vehicle exhaust, cooking especially with low smoke point oils

**Lifestyle:** Smoke from any source: cigarettes, marijuana, secondhand exposures will induce this enzyme.

**Food:**

- Avoid high-temperature cooking methods that generate polyaromatic hydrocarbons (PAH). These include grilling, charring, barbecuing and deep-frying. Avoid cured/smoked deli foods, burnt toast and high-temperature roasted items such as coffee. Avoid food products of any type originating from polluted environments (e.g., produce grown near highways or downwind from air pollution sources).
- Normal function requires biotin, vitamin A, beta carotene and iron-rich foods. Avoid the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein.

**Supplements and Medications:** Consider biotin, vitamin A or beta carotene and iron.

# THE SULT1A1 GENE

The SULT1A1 and SULT1A2 (sulfotransferase 1A1 and 1A2) genes express enzymes in the phase II liver sulfation pathway, which are important for catalyzing the addition of a sulfate group to many hormones, neurotransmitters, drugs, and environmental compounds. 3'-phospho-5'-adenylyl sulfate (PAPS) is required as the sulfate donor for these reactions.

In the serotonin pathway, sulfation by SULT1A1 and SULT1A2 represents the minor pathway for excretion of serotonin (via 5-hydroxytryptophol) and the major pathway for the excretion of melatonin (via 6-Hydroxymelatonin).

## 💩 Dirties your SULT1A1 gene

**Environment:** Avoid smoke from incense, woodsmoke, air pollution, vehicle exhaust, cooking oils; halogenated organochlorides, xenoestrogens (bodycare and home cleaning products, plastics).

**Lifestyle:** Coffee and caffeine; smoke from any source: cigarettes, marijuana, secondhand exposures can all inhibit SULT enzymes.

**Food:** Minimize xenoestrogen compounds: animal products (especially dairy). Avoid high-temperature cooking methods that generate polyaromatic hydrocarbons (PAH) in foods through burning and smoke. These include grilling, charring, barbecuing and deep-frying. Avoid cured/smoked deli foods, bread and pizza from wood-fired ovens, burnt toast, high-temperature roasted items such as coffee and any type of food products originating from polluted environments (e.g., produce grown near highways or downwind from air pollution sources) which can all slow SULT. Be especially careful if family history of colon or breast cancer.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your SULT1A1 gene

**Environment:** Choose bodycare and home cleaning products low in xenoestrogens.

**Food:** Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon formation. Polyaromatic hydrocarbons (PAH) from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar.

**Supplements and Medications:** Non-hormonal, barrier contraceptive methods; non-hormonal management of menopausal symptoms: herbs, nutrition, acupuncture, homeopathy

### Notable variation:

SNP: **SULT1A1 SULT1A1*2 rs1042028 (NA)**
**Note**: Unfortunately, the presence of this SNP could not be determined from your sample. This prevents its use in the assessment of this gene.

# THE UGT1A GENE

The UGT1A6 (UDP-glucuronosyltransferase family 1 member A6) gene expresses an enzyme in the phase II liver glucuronidation pathway which is important in the elimination of potentially harmful xenobiotics and endogenous compounds such as steroids, bilirubin, hormones, and drugs (especially aspirin and acetaminophen).

In the serotonin pathway, UGT is the major route for the excretion of 5-hydroxytryptophol (5-HTOL), which is a metabolite of serotonin.

## Dirties your UGT1A gene

**Environment:** Persistent organochloride pollutants (PCB, DDT), bisphenol A (BPA), plastics, compounds in some antibacterial soaps and dioxin-like compounds can all have long-term inhibitory effects on the glucuronidation capacity of the liver.

**Lifestyle:** UGT1A6 activity naturally declines with advancing age and females naturally have lower expression than males.

**Food:** Limit synthetic food dyes (such as halogenated xanthene food dyes, phloxine, erythrosine, and rose bengal). Avoid high-temperature cooking methods that generate polyaromatic hydrocarbons (PAH) in foods through burning and smoke such as grilling, charring, barbecuing and deep-frying. Avoid cured/smoked deli foods, bread and pizza from wood-fired ovens, burnt toast, high-temperature roasted items such as coffee and any type of food products originating from polluted environments (e.g., produce grown near highways or downwind from air pollution sources).

**Supplements and Medications:** Avoid non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen (Tylenol). Herbs with potential for drug interactions due to inhibition are *Silybum marianum* (milk thistle) or silymarin, *Astragulus spp.*, curcumin (conflicting data), *Hypericum perforatum* (St. John's wort), *Glycyrrhiza spp.*, esp. isoliquiritigen (licorice), piperine, *Serenoa repens* (saw palmetto). Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your UGT1A gene

**Food:**

- Choose ellagic acid, quercetin, coumarin or flavone rich sources as well as Taraxacum (dandelion), rooibos, honeybush, rosemary and green teas.
- Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon formation (PAH). PAH from chargrilling meat may be reduced by marinating meats for 4 hours prior to grilling.

## Notable variation:

### A UGT1A6 UGT1A6*1 Haplotype

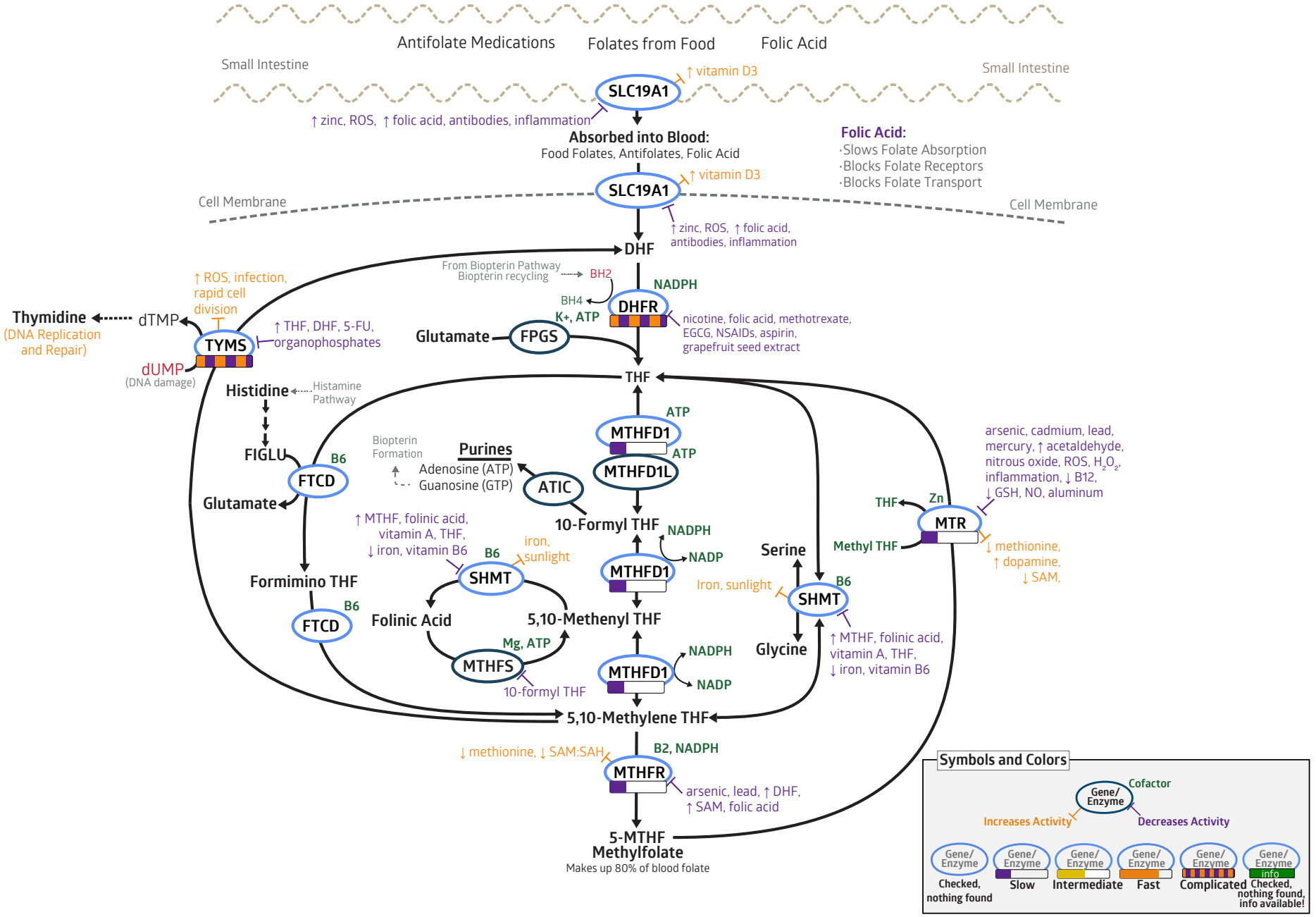
The functional effect of this wild type/UGT1A6*1 variant depends on the substrate. Initial studies using different substrates (serotonin, 5-hydroxytryptophol, 4-nitrophenol, acetaminophen) showed similar results with 50% lower glucuronidation compared with UGT1A6*2. However, this same UGT1A6*1/wild type variant was faster in glucuronidation of some common medications, like aspirin and beta blockers. In general, males have higher activity than females. Overall, these variants were predicted to account for only 15-20% of the observed 1300% variability in glucuronidation of UGT1A6 substrates by human liver microsomes suggesting that environmental influence is huge.

| Gene | rsID | Alias | Variant Allele | Call |
|---|---|---|---|---|
| UGT1A6 | rs6759892 | Ser7Ala | G | TT |
| UGT1A6 | rs2070959 | Thr181Ala | G | AA |
| UGT1A6 | rs1105879 | Arg184Ser | C | AA |

## Cleans your UGT1A gene, continued...

**Supplements and Medications:** Consider calcium-D-glucarate, rosmarinic acid, quercetin, astaxanthin. Herbs high in coumarins such as *Artemisia spp.* (wormwood), *Verbascum thapsus* (mullein), *Melilotis spp.* (sweet clover), *Angelica spp.* (dong quai), *Ferula communis, Glycyrrhiza spp.* (licorice), *Mentha spp.* (peppermint and spearmint) can be useful.

# Folate


Antifolate Medications
Folates from Food
Folic Acid
Small Intestine
Small Intestine
SLC19A1
↑ vitamin D3
↑ zinc, ROS, ↑ folic acid, antibodies, inflammation
Absorbed into Blood:
Food Folates, Antifolates, Folic Acid
Folic Acid:
·Slows Folate Absorption
·Blocks Folate Receptors
·Blocks Folate Transport
SLC19A1
↑ vitamin D3
Cell Membrane
Cell Membrane
↑ zinc, ROS, ↑ folic acid, antibodies, inflammation
DHF
From Biopterin Pathway
Biopterin recycling
BH2
BH4
NADPH
DHFR
K+, ATP
nicotine, folic acid, methotrexate, EGCG, NSAIDs, aspirin, grapefruit seed extract
Glutamate
FPGS
THF
↑ ROS, infection, rapid cell division
Thymidine
(DNA Replication and Repair)
dTMP
TYMS
↑ THF, DHF, 5-FU, organophosphates
dUMP
(DNA damage)
Histidine
Histamine Pathway
ATP
MTHFD1
ATP
MTHFD1L
FIGLU
B6
FTCD
Glutamate
Biopterin Formation
Purines
Adenosine (ATP)
Guanosine (GTP)
ATIC
10-Formyl THF
NADPH
NADP
MTHFD1
↑ MTHF, folinic acid, vitamin A, THF, ↓ iron, vitamin B6
B6
iron, sunlight
SHMT
Formimino THF
B6
FTCD
Folinic Acid
5,10-Methenyl THF
Mg, ATP
MTHFS
10-formyl THF
NADPH
NADP
MTHFD1
5,10-Methylene THF
Serine
Iron, sunlight
B6
SHMT
Glycine
↑ MTHF, folinic acid, vitamin A, THF, ↓ iron, vitamin B6
THF
Zn
MTR
Methyl THF
arsenic, cadmium, lead, mercury, ↑ acetaldehyde, nitrous oxide, ROS, $H_2O_2$, inflammation, ↓ B12, ↓ GSH, NO, aluminum
↓ methionine, ↑ dopamine, ↓ SAM,
↓ methionine, ↓ SAM:SAH
B2, NADPH
MTHFR
arsenic, lead, ↑ DHF, ↑ SAM, folic acid
5-MTHF
Methylfolate
Makes up 80% of blood folate
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
Checked, nothing found, info available!
info

# THE DHFR GENE

The DHFR (dihydrofolate reductase) gene expresses an enzyme which converts dihydrofolate (DHF) into tetrahydrofolate (THF), using NADPH (a form of niacin) as a cofactor.

DHFR plays a critical role in the folate cycle by regulating the amount of THF in the cell.

The DHFR enzyme is also involved in the regeneration of dihydrobiopterin ($BH_2$) back to the active tetrahydrobiopterin ($BH_4$) form. $BH_4$ is required for neurotransmitter synthesis and nitric oxide production. If DHFR is processing synthetic folic acid, $BH_4$ levels may drop and oxidized $BH_2$ may increase thereby decreasing neurotransmitter and nitric oxide production (see Biopterin pathway).

It has been demonstrated that DHFR works slowly in humans.

Synthetic folic acid isn't active in the human body until it has been transformed by the DHFR enzyme, but supplemental doses of synthetic folic acid (as little as 200 mcg) saturate the capacity of this enzyme. This causes blood levels of unmetabolized folic acid to rise. Rising synthetic folic acid levels block folate receptors and reduce the ability of natural food folates to bind to them.

## Dirties your DHFR gene

**Environment:** Minimize smoke from any source: cigarettes, marijuana, incense, woodsmoke, diesel exhaust, smog, cooking fumes.

**Lifestyle:** Smoking and abnormal blood sugars are especially serious for this gene and should be addressed as a first priority.

**Food:** Minimize foods or beverages enriched with synthetic folic acid.

**Supplements and Medications:** Limit synthetic folic acid, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin. Many medications interact with this enzyme. Consult your healthcare provider or pharmacist. EGCG from green tea, grapefruit seed extract and *Salvia miltiorrhiza* are known inhibitors as well, so pulsing these may be prudent if using them.

## Cleans your DHFR gene

**Environment:** Use an extractor hood while cooking and high-smoke point oils like ghee or avocado oil. Use air filters.

**Food:** Focus on unprocessed, whole foods high in natural folate (B9) and niacin (B3).

## Notable variation:

SNP: **DHFR 19bp Del/Ins rs70991108 (-/-, II)**

The effect of this II variant on enzyme function from in-vitro experiments is conflicting. All DHFR genes are slow at processing synthetic folic acid in amounts > 250 mcg in humans regardless of variants. It is included here for investigational purposes in anticipation of future research that can better characterize its impact.

## Cleans your DHFR gene, continued...

**Supplements and Medications:**

- Optimize niacin (B3), methylfolate or folinic acid (B9), vitamin C.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

# THE MTHFD1 GENE

The MTHFD1 (methylenetetrahydrofolate dehydrogenase) gene expresses an enzyme which conducts three separate enzyme activities along the path of converting tetrahydrofolate (THF) to methylfolate (5-MTHF) using NADPH and ATP as cofactors. NADPH is niacin (B3) dependent.

MTHFD1 regulates the formation of many types of folate, and all of the enzyme activities of MTHFD1 are reversible and flow in the direction-dependent upon the body's various folate requirements at any given time.

If the MTHFD1 enzyme is functioning more slowly, potentially less folinic acid and less methylfolate will be produced. Serum folates may then appear to be fine yet the reduced, more active forms of folate may be deficient. When less folate is available for the methylation cycle, choline deficiency may result. This occurs because during folate deficiency, choline steps in to help produce phosphatidylcholine and betaine.

## Dirties your MTHFD1 gene

**Environment:** Living in sunny areas leads to increased folate demand to repair sun-damaged skin. Naturally darker skin can help, but does not reduce folate demand entirely.

**Lifestyle:** Pregnant or breastfeeding women use more folate and choline. 90% of women are choline deficient and if they are low in folate as well, there are going to be complications.

**Food:**

- Folate deficient diets, high fat diets, high simple carbohydrate diets and high calorie density diets may increase this gene's workload as these diets are strongly associated with fatty liver and gallstones.
- A choline deficient diet is also detrimental as choline is an important nutrient required for the production of phosphatidylcholine (important for healthy cell membranes) and betaine (important for homocysteine recycling). People with MTHFD1 variants are more likely than non-variant carriers to develop signs of choline deficiency on a low-choline diet. Vegans and vegetarians are more susceptible to choline deficiency as well.

## Cleans your MTHFD1 gene

**Environment:** Protect skin from strongest sun rays of the day (10 a.m. to 4 p.m.) by using zinc oxide, hats and sun-protective clothing.

**Food:** Folate (B9), choline, betaine, glycine and niacin (B3) rich

## Notable variation:

SNP: **MTHFD1 G1958A rs2236225 (+/-, GA)**
This GA variant decreases the metabolic activity of MTHFD1 within mice cells by 25% on average. The enzyme loses stability as body temperature rises so its function becomes more compromised during fevers. The activity and stability of the enzyme can be improved by sufficient folate (B9). This variant is especially worrisome for pregnant or lactating women as choline demand increases.

SNP: **MTHFD1 T105C rs1076991 (+/-, TC)**
This TC variant may decrease MTHFD1 activity up to 30% in vitro.

## Cleans your MTHFD1 gene, continued...

**Supplements and Medications:** Folinic acid (note: not folic acid) is shown to support those with MTHFD1 insufficiency. Consider also betaine, choline bitartrate and phosphatidylcholine as choline and folate have an inverse relationship. This especially if low functioning PEMT (present) or CHDH (unknown).

If one is deficient in choline, more folate is used. If one is deficient in folate, more choline is used. Thus, supporting with folinic acid, betaine, choline bitartrate and/or phosphatidylcholine are excellent considerations.

Choose non-GMO soy or sunflower derived phosphatidylcholine. Consider glycine and serine as well. Additionally, more THF substrate may be provided by supporting the MTR gene with L-5-MTHF, methylcobalamin or hydroxocobalamin. Consider more folinic acid during exposure to summer sun, especially while pregnant or breastfeeding.

# THE MTHFR GENE

The MTHFR (methylenetetrahydrofolate reductase) gene expresses an enzyme which produces the body's primary form of folate called 5-MTHF (aka 5-methyl THF, L-5-MTHF, methylfolate), which represents over 80% of the body's folate. In the process, the MTHFR enzyme uses FAD, a form of riboflavin (B2), as a cofactor.

5-MTHF is utilized in the production of S-adenosylmethionine (SAM), which subsequently regulates around 200 processes including DNA methylation, neurotransmitter and phospholipids production. Since the MTHFR gene is the rate-limiting step in the generation of 5-MTHF, it is subsequently also the rate-limiting enzyme in the whole process of SAM production.

The MTHFR gene connects the folate pathway, via 5-MTHF, with the SAM cycle via the MTR gene. This is why a slow MTHFR may increase homocysteine levels.

## Dirties your MTHFR gene

**Environment:** Avoid lead and arsenic. Living in sunny areas leads to increased folate demand to repair sun-damaged skin. Naturally dark skin can reduce demand, but not entirely.

**Lifestyle:** Hyper and hypothyroidism, insulin resistance

**Food:** Foods or beverages enriched with synthetic folic acid

**Supplements and Medications:** Avoid synthetic folic acid, aspirin, other salicylates (NSAIDs). Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your MTHFR gene

**Environment:** Protect skin from strongest sun rays of the day (10 a.m. to 4 p.m.) by using zinc oxide, hats and sun protective clothing.

**Food:** Choose riboflavin (B2) rich, choline and betaine rich, natural folate rich, polyphenol rich, low sugar. See "Your Clean Genes Recipes" in the *Dirty Genes* book.

## Notable variation:

SNP: **MTHFR C677T rs1801133 (+/-, GA)**

This GA variant decreases binding of the cofactor, riboflavin (B2), which decreases MTHFR enzyme activity by about 30% less than wild type. The enzyme loses stability as body temperature rises, so its function becomes compromised during fevers. The activity and stability of the enzyme improves by consuming sufficient folate (B9) and riboflavin (B2).

## Cleans your MTHFR gene, continued...

**Supplements and Medications:** The MTHFR enzyme produces methylfolate (5-MTHF). Thus, supplementing with L-5-MTHF may be useful. Be careful, however, as this is a very powerful type of folate. Often it is over-prescribed and leads to many side effects. If using it, consider lower amounts such as 400 mcg to 1,000 mcg of L-5-MTHF.

A way to support MTHFR with fewer side effects is to optimize the cofactor riboflavin (B2), although sufficient B2 cannot help if one is folate deficient.

Another way to support this gene is by indirectly supporting methylation by using supplements which conserve SAM. The body's production of both creatine and phosphatidylcholine use up nearly 80% of SAM; so by supplementing with them, one conserves SAM and generates less homocysteine. Choose non-GMO soy or sunflower derived phosphatidylcholine. Consider choline, betaine, omega-3: alpha-linolenic acid (ALA) and docosahexaenoic acid (DHA) fatty acids. Vitamin C showed ability to decrease hypermethylation of MTHFR in a positive way. Consider more folinic acid, L-5-MTHF or choline, whichever is well tolerated, during exposure to summer sun especially while pregnant or breastfeeding.

# THE TYMS GENE

The TYMS (thymidylate synthase) gene expresses an enzyme which methylates uracil (an RNA base) to become thymine (a DNA base). Thymine (from dTMP) is incorporated into DNA. Uracil (from dUMP) is incorporated into RNA.

If folate is deficient, or if TYMS isn't functioning well, uracil, instead of thymine, gets incorporated into DNA. This causes DNA strands to break more easily which causes problems with DNA replication. Eventually, this leads to an increased risk of certain cancers.

## 💩 Dirties your TYMS gene

**Environment:** Living in sunny areas leads to increased folate demand to repair sun-damaged skin. Naturally darker skin can help, but does not reduce folate demand entirely.

**Food:** The organophosphate pesticides malathion and chlorpyrifos are commonly used on all fruits, vegetables, and many grains like wheat, oats and rye. Avoid the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your TYMS gene

**Environment:** Protect skin from strongest sun rays of the day (10 a.m. to 4 p.m.) by using zinc oxide, hats and sun protective clothing.

**Food:** Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean Fifteen as explained by Environmental Working Group (https://www.ewg.org/foodnews/clean-fifteen.php/).

**Supplements and Medications:** Consider more folinic acid, methylfolate (L-5-MTHF) or choline, whichever is well tolerated, during exposure to summer sun especially while pregnant or breastfeeding.

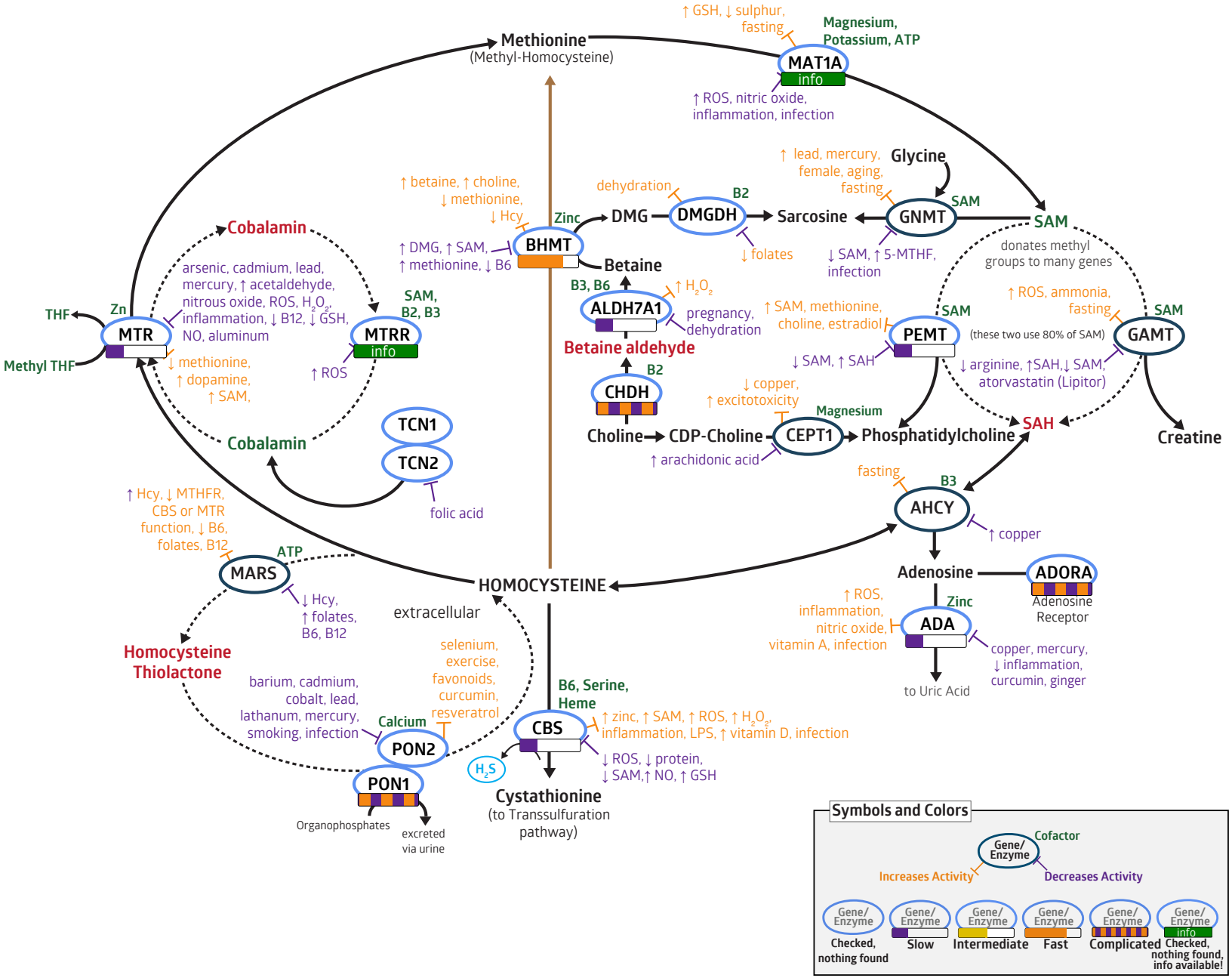
# THE MTR GENE

The complete discussion of this gene is under SAM.

### Notable variation:

SNP: **TYMS Ins/Del rs779037237 (NA)**
**Note**: Unfortunately, the presence of this SNP could not be determined from your sample. This prevents its use in the assessment of this gene.

# SAM


↑ GSH, ↓ sulphur, fasting
Magnesium, Potassium, ATP
Methionine
(Methyl-Homocysteine)
MAT1A
info
↑ ROS, nitric oxide, inflammation, infection
↑ lead, mercury, female, aging, fasting
Glycine
SAM
GNMT
donates methyl groups to many genes
↑ betaine, ↑ choline, ↓ methionine, ↓ Hcy
dehydration
B2
Zinc
DMG
DMGDH
Sarcosine
↓ folates
↓ SAM, ↑ 5-MTHF, infection
↑ DMG, ↑ SAM, ↑ methionine, ↓ B6
BHMT
Betaine
B3, B6
↑ $H_2O_2$
ALDH7A1
pregnancy, dehydration
Betaine aldehyde
B2
CHDH
Cobalamin
arsenic, cadmium, lead, mercury, ↑ acetaldehyde, nitrous oxide, ROS, $H_2O_2$, inflammation, ↓ B12, ↓ GSH, NO, aluminum
THF
Zn
MTR
Methyl THF
↓ methionine, ↑ dopamine, ↑ SAM,
SAM, B2, B3
MTRR
info
↑ ROS
Cobalamin
TCN1
TCN2
folic acid
↑ SAM, methionine, choline, estradiol
SAM
PEMT
(these two use 80% of SAM)
↓ SAM, ↑ SAH
↑ ROS, ammonia, fasting
SAM
GAMT
↓ arginine, ↑SAH,↓ SAM, atorvastatin (Lipitor)
Creatine
↓ copper, ↑ excitotoxicity
Magnesium
Choline
CDP-Choline
CEPT1
Phosphatidylcholine
↑ arachidonic acid
SAH
fasting
B3
AHCY
↑ copper
↑ Hcy, ↓ MTHFR, CBS or MTR function, ↓ B6, folates, B12
ATP
MARS
↓ Hcy, ↑ folates, B6, B12
HOMOCYSTEINE
Adenosine
ADORA
Adenosine Receptor
↑ ROS, inflammation, nitric oxide, vitamin A, infection
Zinc
ADA
copper, mercury, ↓ inflammation, curcumin, ginger
to Uric Acid
Homocysteine Thiolactone
extracellular
selenium, exercise, favonoids, curcumin, resveratrol
barium, cadmium, cobalt, lead, lathanum, mercury, smoking, infection
Calcium
PON2
PON1
Organophosphates
excreted via urine
B6, Serine, Heme
CBS
↑ zinc, ↑ SAM, ↑ ROS, ↑ $H_2O_2$, inflammation, LPS, ↑ vitamin D, infection
↓ ROS, ↓ protein, ↓ SAM,↑ NO, ↑ GSH
$H_2S$
Cystathionine
(to Transsulfuration pathway)
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
Checked, nothing found, info available!

# THE MTR GENE

The MTR (methionine synthase) gene expresses a four-domain enzyme which regenerates homocysteine back to methionine, a process that ultimately generates the body's master methyl donor: S-adenosylmethionine (SAM).

MTR is a very complex and sensitive enzyme. It requires vitamin B12 and zinc as cofactors, and has to coordinate a complex interaction with the MTHFR gene (using L-5-MTHF to remethylate homocysteine back to methionine) and the MTRR gene complex (using SAM to remethylate cobalamin back to methylcobalamin). It's no wonder that high homocysteine is common!

MTR is a redox sensing gene meaning it slows down in the presence of oxidative stress. Thus, MTR is a decision-making point:

If oxidative stress is low, MTR functions well and the methylation cycle recycles homocysteine back into SAM. If, on the other hand, oxidative stress is high, MTR does not function well and CBS is stimulated. The CBS enzyme then uses homocysteine to start the process of making glutathione.

Once glutathione levels are restored, oxidative stress goes down and the MTR gene can function again, recycling homocysteine back into SAM.

If the MTR substrate levels of homocysteine are too low (<5 umol/L adult), then the methylation cycle may not work sufficiently.

## 💩 Dirties your MTR gene

**Environment:** Identify heavy metal exposures including mercury, copper, lanthanum, lead, cadmium, barium; avoid inhaled nitrous oxide aka laughing gas (dental procedures, pre-op and maternity wards); acetaldehyde (rule out *Candida* dysbiosis), oxidative stress, inflammation, chlorine, formaldehyde. It is also important to avoid factors which slow MTHFR and MTRR.

**Lifestyle:** Identify and treat hyper or hypothyroidism, insulin resistance. Limit alcohol, bathing in chlorinated water or frequent use of swimming pools or hot tubs. Overtraining causes significant inflammation. It is also important to avoid factors which slow MTHFR and MTRR.

## Notable variation:

SNP: **MTR 1710G>T rs3768142 (+/-, GT)**
This GT variant has 10-15% lower activity in an in vitro study.

Note: The functional variant rs1131450 is being replaced by rs3768142 due to an inability to confidently determine alleles for rs1131450. See the FAQ for more information.

SNP: **MTR -186G>T rs28372871 (+/-, GT)**
This GT variant lowers promoter activity and reduces binding affinity resulting in 25% lower activity.

SNP: **MTR A2756G rs1805087 (-/-, AA)**
The functional effect of this AA wild type is controversial. Older studies indicate in vitro upregulation compared to GG while newer studies appear to show downregulation in humans.

This variant is a good example of a "trade-off" SNP where the minor allele, as well as wild type or ancestral allele, can be found to be epidemiologically risky or beneficial depending on environmental/epigenetic factors, degree of DNA methylation and baseline metabolic conditions in an individual.

## Dirties your MTR gene, continued...

**Food:**

- Insufficient protein in the diet, especially if homocysteine levels are < 5 umol/L in children and adults, can slow MTR.
- Rancid cooking oils, cooking on high heat or chargrilled foods may hinder MTR due to increased demand for glutathione and thus less glutathione available for neutralizing hydrogen peroxide.
- Farmed fish can be high in heavy metals, therefore avoid Atlantic salmon or other fish or shellfish not labeled as wild-caught. Large ocean fish such as tuna, swordfish, king mackerel or bluefish may be high in mercury too.
- It is also important to avoid foods which slow MTHFR and MTRR.

**Supplements and Medications:**

- Inhaled nitrous oxide aka 'laughing gas' (dental procedures, pre-op and maternity wards) damages vitamin B12.
- Cyanocobalamin may slow MTR as MTR needs methylated cobalamin.
- Although cyanocobalamin does not contain much cyanide, it uses up glutathione which could be used for better purposes, especially in those already deficient.

## Cleans your MTR gene

**Environment:**

- Utilize chlorine filters for bath, shower and drinking as chlorine uses up glutathione.
- Create a low formaldehyde environment: instead of synthetic carpet, laminate flooring or furniture consider solid wood, concrete, cork, tile or real linoleum.
- One should also support environmental recommendations for MTHFR and MTRR.

**Lifestyle:** Exercise but do not overtrain.

## Cleans your MTR gene, continued...

**Food:**

- Focus on vitamin B12, zinc and sulfur rich (for glutathione production) foods.
- Aim for balanced protein intake which is also called 'Nitrogen balanced'.
- If protein intake is too low, especially in pregnancy, breastfeeding or growing children, homocysteine levels may be too low (< 5 umol/L).
- Alaskan salmon is lower in heavy metals as are smaller fish like herring or sardines.
- One should also eat for a clean MTHFR and MTRR.

**Supplements and Medications:** Vegans, vegetarians and those with malabsorption issues (gastritis, etc.) may need methylcobalamin or hydroxocobalamin (B12) supplementation. Hydroxocobalamin neutralizes the toxicity of cyanide, therefore discontinue cyanocobalamin and switch to hydroxocobalamin. Consider zinc, methylfolate (L-5-MTHF) and betaine. Antioxidants such as liposomal glutathione, S-acetyl glutathione or PQQ (pyrroloquinoline quinone). One must also evaluate supplements which support MTHFR and MTRR.

# THE MTRR GENE

The MTRR (methionine synthase reductase) gene expresses an enzyme which supports the MTR enzyme by restoring its B12 cofactor.

If MTRR is unable to restore the damaged vitamin B12, then the MTR enzyme cannot function and the methylation cycle is compromised.

In order for MTRR to repair oxidized vitamin B12, it needs three cofactors: FAD, a form of riboflavin (B2); NAD, a form of niacin (B3) and S-adenosylmethionine (SAM). (Repair of the oxidized vitamin B12 cofactor occurs approximately once every 200 enzyme turnovers so not much SAM is used.)

The interaction between MTRR, MTR and MTHFR is significant and all three must be functioning well.

## 💩 Dirties your MTRR gene

**Lifestyle:** High oxidative stress which may be caused by overtraining, low antioxidants, infections and the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein.

**Supplements and Medications:** Inhaled nitrous oxide aka laughing gas (dental procedures, pre-op and maternity wards) damages vitamin B12.

## Cleans your MTRR gene

**Food:** Riboflavin (B2), niacin (B3) and B12 rich

**Supplements and Medications:** Optimize riboflavin (B2) levels and B12 levels using methylcobalamin or hydroxocobalamin. Very little SAM is used by MTRR so supplementing with SAMe is likely not needed. Consider SAM conserving nutrients such as creatine and phosphatidylcholine. Choose non-GMO soy or sunflower derived phosphatidylcholine. Consider antioxidants such as PQQ (pyrroloquinoline quinone), S-acetyl glutathione, liposomal glutathione and SOD (superoxide dismutase).

### Notable variation:

While no notable variation was found, we are presenting this gene's information to you because it's so important. Remember, lifestyle, food, environment and nutrients play a significant role in genetic expression — often significantly more than a genetic variation.

# THE MAT1A GENE

The MAT1A (methionine adenosyl transferase 1A) gene expresses an enzyme which transfers adenosine (from ATP) to methionine to form S-adenosylmethionine (SAM).

MAT1A requires magnesium and potassium as cofactors and the substrate methionine, which is a sulfur-containing amino acid supplied from ingested and absorbed protein.

SAM is your body's primary methyl donor, and supports over 200 methylation reactions, so if MAT1A's formation of SAM is not functioning well, then neither are 200 other enzymatic reactions.

Some key enzymes requiring SAM are COMT (estrogen and dopamine metabolism), GAMT (creatine formation), ASMT (melatonin formation), PEMT (phosphatidylcholine formation), PNMT (norepinephrine metabolism), HNMT (histamine metabolism) and elimination of arsenic, to name a few.

As you can see, a lack of SAM is a very significant problem.

## 💩 Dirties your MAT1A gene

**Environment:** Carbon tetrachloride

**Lifestyle:** Limit alcohol and caffeine. Work with your healthcare provider to identify and treat intestinal dysbiosis; infections including hepatitis B and hepatitis C; or hypoxia.

**Food:** Excessive protein intake (more than 1 or 2 grams of protein per kg [2.2 lbs] of body weight). Excessive caffeine intake causes loss of magnesium and potassium which are both needed as cofactors.

**Supplements and Medications:** Avoid acetaminophen (Tylenol), inhaled nitrous oxide aka laughing gas (dental procedures, pre-op and maternity wards); antacids (as they suppress stomach acid and thereby reduce protein absorption and lower methionine which is needed to make SAM).

## Cleans your MAT1A gene

**Lifestyle:** Consider intermittent fasting or short term fasting especially during times of high homocysteine as it lowers methionine, the substrate of homocysteine. Long term fasting (many days) may be problematic due to protein deficiency.

**Food:** Focus on magnesium and potassium rich sources. Consume, digest and absorb appropriate amounts of protein (approximately 0.8 grams of protein per kg [2.2 lbs] of body weight).

### Notable variation:

While no notable variation was found, we are presenting this gene's information to you because it's so important. Remember, lifestyle, food, environment and nutrients play a significant role in genetic expression — often significantly more than a genetic variation.

## Cleans your MAT1A gene, continued...

**Supplements and Medications:**

- Optimize magnesium and potassium. Studies indicate that 99% of women and 90% of men are potassium deficient. Electrolytes may be a great source of potassium.
- Use appropriate probiotics and antimicrobials as needed.
- Liposomal glutathione, PQQ (pyrroloquinoline quinone) or S-acetyl glutathione as needed.
- Digestive enzymes and protein powders may be needed if protein absorption is an issue.

# THE PEMT GENE

The PEMT (phosphatidylethanolamine N-methyltransferase) gene expresses an enzyme that generates phosphatidylcholine (PC) from phosphatidyl ethanolamine (PE).

PC is crucial for maintaining a healthy cell membrane and permeability as well as bile flow, liver health, muscle health and brain development.

PEMT is stimulated by estradiol so men as well as women with low estradiol may have lower PC synthesis.

Bile should consist of 10 parts PC to 1 part cholesterol. If this ratio is off, gallstones may occur.

PC is also high in breastmilk. If low, it may lead to mastitis.

PEMT needs a lot of S-adenosylmethionine (SAM) to function. Thus, PEMT may be greatly impacted by other genes that require SAM: GAMT, COMT and HNMT or generate SAM: MTHFR, MAT1A, MTR, MTRR and CBS.

## 💩 Dirties your PEMT gene

**Lifestyle:**

- Pregnancy and breastfeeding utilizes large amounts of phosphatidylcholine (PC).
- Type 1 diabetes tends to depress PC production.
- Estrogen promotes expression of this gene, therefore post-menopausal women are at higher risk due to potentially lower estrogen levels.

**Food:** High fat diets or ketogenic diets utilize significant amounts of bile. Bile flow requires 10 parts PC and 1 part cholesterol. Gallstones form if this ratio is imbalanced.

**Supplements and Medications:**

- Watch for symptoms of depression from phosphatidylcholine supplementation which may result from an imbalanced ratio of acetylcholine to serotonin. Choose non-GMO soy or sunflower derived phosphatidylcholine.
- Some medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Notable variation:

🧬 SNP: **PEMT G5465A rs7946 (+/+, TT)** 🎯
This TT variant has approximately 30% lower PEMT activity.

## Cleans your PEMT gene

**Lifestyle:** Healthy estrogen levels in women of reproductive age help promote optimal expression of PEMT. Pregnancy increases estrogen levels which may further enhance expression.

**Food:** Adequate protein intake; foods rich in betaine, choline, vitamin E

**Supplements and Medications:** Consider choline or phosphatidylcholine (PC) supplementation especially for pregnant or breastfeeding women, growing children, non-egg eating vegetarians, and vegans. 800 mg of choline or PC daily is recommended during pregnancy or breastfeeding.

However, be aware that excessive choline intake may exacerbate underlying insulin resistance. Consider betaine, vitamin E, SAMe (S-adenosylmethionine).

If depression results from PC or choline supplementation: consider uridine, 5-hydroxytryptophan (5-HTP) or inositol along with PQQ (pyrroloquinoline quinone) and liposomal curcumin.

For postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus) if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use. This strategy for PEMT may not be useful if you possess the T variant of rs3760188 (not present).

# THE CHDH GENE

The CHDH (choline dehydrogenase) gene expresses an enzyme which catalyzes the conversion of choline to betaine aldehyde, using riboflavin (B2) as a cofactor.

CHDH plays an important role in regulating the concentrations of choline and betaine in blood, cells and especially sperm and egg.

Choline is important for regulation of gene expression, the biosynthesis of lipoproteins and membrane phospholipids and for the biosynthesis of the neurotransmitter acetylcholine.

Betaine plays important roles as a primary intracellular osmoprotectant (raises osmotic pressure inside the cell, stabilizes proteins and membranes when salt levels or temperatures are unfavorable). Betaine also acts as a methyl donor for the conversion of homocysteine to methionine.

## Dirties your CHDH gene

**Lifestyle:** Vegans and vegetarians or those consuming low choline diets will likely have a slow CHDH due to lack of substrate. Limit alcohol, especially in A allele carriers of rs12676 (unknown). Pregnancy and breastfeeding may increase demand on this gene as well.

**Food:** Avoid choline deficiency. Low folate consumption increases the utilization of choline thereby increasing risk of choline deficiency.

## Cleans your CHDH gene

**Food:** Riboflavin (B2), betaine and choline rich. Indirect support is via folate rich foods.

**Supplements and Medications:** Consider choline bitartrate and phosphatidylcholine as two useful supplements to support choline deficiency, especially if low functioning PEMT (present) or MTHFD1 (present).

Be mindful to avoid GMO soy derived phosphatidylcholine.

Optimize riboflavin (B2) and betaine especially in vegans, women who are pregnant or breastfeeding, and couples trying to conceive.

Choline and folate have an inverse relationship. If one is choline deficient, more folate is used. If one is folate deficient, more choline is used. If one is deficient in both, problems are likely to develop especially during pregnancy.

### Notable variation:

SNP: **CHDH G233T rs12676 (NC)**
**Note**: Unfortunately, the presence of this SNP could not be determined from your sample. This prevents its use in the assessment of this gene.

SNP: **CHDH A119C rs9001 (-/-, TT)**
This TT wild type has slower choline metabolism which may result in less betaine synthesis.

# THE ALDH7A1 GENE

The ALDH7A1 (aldehyde dehydrogenase family member A1) gene expresses an enzyme which metabolizes betaine aldehyde to betaine. It requires niacin (B3) as a cofactor.

The ALDH7A1 enzyme also protects cells from oxidative stress by degrading aldehydes generated via alcohol metabolism, lipid peroxidation and other causes of oxidative stress.

Aldehydes can be very damaging compounds so it is vital to clear them from the body. To underscore this point, ALDH7A1 doubles in activity during late pregnancy, a time of increased oxidative stress, and returns to normal levels postpartum.

## Dirties your ALDH7A1 gene

**Environment:** Minimize air pollutants (formaldehyde, acetaldehyde, acrolein) which are mainly from fuel combustion (natural gas, gas, diesel).

**Lifestyle:** Dehydration, hydrogen peroxide

## Cleans your ALDH7A1 gene

**Environment:** Utilize air filters, especially choosing the 'Recirculation of Air' option for in your car versus the "Outside Air" option that allows in vehicle exhaust while driving. Be sure to use high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood.

**Lifestyle:** Optimize hydration by drinking water with appropriate electrolyte balance. Hydration is not just drinking water but the process of causing something to absorb water. Electrolytes enhance water absorption inside cells.

**Food:** Niacin (B3), pyridoxine (B6), thiamine (B1), betaine rich

**Supplements and Medications:** Optimize niacin (B3), thiamine (B1) and pyridoxine (B6). Aldehydes damage B1, so additional B1 will be needed if aldehydes are high.

## Notable variation:

SNP: **ALDH7A1 395T>C rs13182402 (+/-, AG)**

No functional studies exist for this AG variant. It appears to decrease expression thus causing acetaldehyde buildup from alcohol and decreased betaine formation. Note: Due to lack of research in other ethnicities, this observation may be applicable only to Asians.

# THE BHMT GENE

The BHMT (betaine-homocysteine S-methyltransferase) gene expresses an enzyme, primarily located in the liver and kidney, which is important for homocysteine metabolism.

Requiring zinc as a cofactor, it catalyzes the transfer of a methyl group (-CH3) from trimethylglycine (TMG aka betaine) to homocysteine to produce dimethylglycine (DMG) and methionine.

If the MTR/MTRR gene complex is slowed for any reason, BHMT steps up as an important alternative route for homocysteine recycling.

This is a perfect example of how the body has back-up systems in place in case one fails.

## 💩 Dirties your BHMT gene

**Lifestyle:** Vegan or vegetarian diet can hamper this gene as choline is found mainly in meat, poultry, fish and dairy. Hypo or hypertonic dehydration (water deprivation, excessive sweating, high blood sugar, heat stroke, heat exhaustion, vomiting, diarrhea, burns, muscle damage, low sodium diet); blood sugar dysregulation, hyperthyroidism can all impede BHMT.

**Food:** Low choline/taurine diet (low protein with low animal meat or organ content), low betaine intake

**Supplements and Medications:** Dimethylglycine (DMG) is known to potentially increase homocysteine due to feedback inhibition. Low pyridoxine (B6), acetaminophen (Tylenol), some diuretics can also interfere. Consult your healthcare provider or pharmacist.

## 🧹 Cleans your BHMT gene

**Lifestyle:** Optimize hydration by drinking water with appropriate electrolyte balance. Hydration is not just drinking water but the process of causing something to absorb water. Electrolytes enhance water absorption inside cells.

**Food:** Choline, taurine, betaine, zinc and pyridoxine (B6) rich

**Supplements and Medications:** Optimize zinc and pyridoxine (B6). Consider TMG (betaine; trimethylglycine), choline bitartrate. TMG in gram doses may be very effective in lowering stubbornly elevated levels of homocysteine. TMG may also help support weakened kidneys as kidneys are naturally high in betaine when healthy.

If TMG supplementation does not result in lower homocysteine or improved mental symptoms, DMG (dimethylglycine) supplementation may be useful instead. DMG is not recommended for pregnant or nursing mothers due to lack of research.

### Notable variation:

SNP: **BHMT 716G>A rs3733890 (+/+, AA)**

This AA variant has a lower Km value, greater stability and high substrate affinity which means it can work faster compared to wild type.

# THE ADA GENE

The ADA (adenosine deaminase) gene expresses an enzyme which breaks down adenosine to inosine and ammonia requiring zinc as a cofactor.

ADA is involved in immune system maintenance and development, neurotransmission, gestation maintenance and stimulates release of excitatory amino acids.

Adenosine is a calming neurotransmitter which builds up throughout the day increasing sleep pressure. Caffeine is a known inhibitor of adenosine receptors, which, when blocked, prevent adenosine binding thereby increasing wakefulness.

Serum ADA is a marker of T-cell activation, and studies show that serum ADA activity is significantly increased in women with recurrent spontaneous abortions, preeclampsia, and hyperemesis gravidarum where enhanced cell-mediated immunity is thought to be an important disease trigger. There have also been reports showing low levels of both maternal serum and placental ADA activity in anembryonic pregnancies and missed abortions.

## Dirties your ADA gene

**Environment:** Work with your healthcare provider to identify and treat heavy metal exposures especially cadmium and mercury, inflammation due to IgE, IgG food sensitivities and seasonal allergies, parasitic or helminth infection.

**Lifestyle:** Prolonged periods of demanding cognitive activity

**Supplements and Medications:** Since progesterone can inhibit ADA, the use of oral prescription progesterone as a sleep aid for women may exacerbate morning grogginess in those with the rs73598374-T variant (present). Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your ADA gene

**Lifestyle:** Blue blocking glasses in the evening with a dark sleeping environment and bright light therapy in the morning may be beneficial to counteract morning sleepiness due to this variant.

**Food:** Magnesium, zinc, vitamin A rich, turmeric, ginger

**Supplements and Medications:** *Urtica urens* (stinging nettle), naringin (from grapefruit), berberine, curcumin

## Notable variation:

SNP: **ADA G22A rs73598374 (+/-, CT)**

This CT variant exhibits approximately 35% less ADA activity and higher level of both circulating and intracellular adenosine compared to wild type. Increased sleepiness may occur due to higher adenosine levels. Caffeine is known to block adenosine binding to the adenosine receptor thereby increasing wakefulness.

# THE ADORA2A GENE

The ADORA2A (adenosine receptor A2A) gene express receptors that bind adenosine. Adenosine receptor A2A is one of four types of adenosine receptors, each with a different binding capacity and tissue distribution.

Adenosine is involved in immune system maintenance and development, neurotransmission and gestation maintenance. Adenosine is a calming neurotransmitter. As the day progresses, adenosine levels build up creating a natural sleepiness. The higher the adenosine level, the better one is prepared for sleep.

ADORA2A may interact with various other genes influencing how one responds to caffeine. These include: ADA (which breaks down adenosine), COMT (slowed by caffeine), DRD2 (dopamine receptor) and CYP1A2 (breaks down caffeine).

## Dirties your ADORA2A gene

**Lifestyle:**

- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections.
- Be mindful your adenosine receptor may have altered sensitivity to adenosine and this can affect sensitivity to caffeine.
- Limit excessive alcohol or caffeine containing beverages or supplements.

## Cleans your ADORA2A gene

**Supplements and Medications:** Appropriate probiotics

## Notable variation:

SNP: **ADORA2A C1976T rs5751876 (+/-, TC)**
The TC variant appears to decrease the affinity of ADORA2A receptor for adenosine which may be associated with greater anxiety and insomnia after caffeine.

SNP: **ADORA2A rs2236624 (+/-, TC)**
This TC variant may not vary considerably from wild type, as the research finds only homozygous TT shows a significant functional change. PET scans of human brains that carry the T allele do show increased availability of A1A receptors, presumably as a result of fewer A2A receptors from downregulated ADORA2A, however it does not appear to have a large effect on disease expression.

SNP: **ADORA2A Del/Ins rs35060421 (NA)**
**Note**: Unfortunately, the presence of this SNP could not be determined from your sample. This prevents its use in the assessment of this gene.

# THE PON1 GENE

The PON1 (serum paraoxonase 1) gene expresses an enzyme which acts as a potent antioxidant requiring calcium as a cofactor.

In the SAM cycle, PON1 converts harmful homocysteine thiolactone back to homocysteine.

PON1 also helps to neutralize hydrogen peroxide ($H_2O_2$), and plays a major role in preventing the formation of oxidized LDL which could contribute to atherosclerosis.

In addition, PON1 has the ability to degrade the toxic metabolites of a variety of organophosphate insecticides. PON1 also metabolizes substrates such as glucuronide drugs, cyclic carbonates, estrogen esters, and other lactones such as statin medications.

## 💩 Dirties your PON1 gene

**Environment:** Minimize ionizing radiation and environmental chemicals such as organophosphate pesticides (known to contribute to ADHD in children), polyaromatic hydrocarbons (PAH), carbon tetrachloride, non-dioxin-like PCBs and dichloroacetic acid (a major by-product of water disinfection by chlorination).

Avoid the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).

Avoid smoke from any source such as incense, woodsmoke, air pollution, vehicle exhaust, cooking without an extractor hood especially with low smoke point oils.

Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections; heavy metal exposures including mercury, copper, lanthanum, lead, cadmium, barium.

**Lifestyle:** In general, males have less PON1 activity and are therefore more susceptible to environmental factors that inhibit PON1 activity. A high LDL:HDL ratio, thyroid, liver or kidney disease can also all stress PON1.

**Food:** PON1 is especially sensitive to damage from the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein.

**Supplements and Medications:** Some medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Notable variation:

SNP: **PON1 575A>G rs662 (+/-, TC)**

This CT allele is likely to exhibit intermediate activity between the two extremes. The CC (wild type) has more paraoxanase activity for organophosphates (and thus less cancer and neurodegenerative disease risk) but less activity of peroxidase towards cholesterol resulting in more lipid oxidation and cardiovascular disease. On the other hand, the homozygous TT allele has less paraoxanase activity for organophosphates, but more activity of peroxidase resulting in less lipid oxidation. The CT allele may have intermediate activity of both reactions. CT allele carriers, especially males, may be more sensitive to cadmium inhibition. Carriers of a C allele may also be more susceptible to lipid free radical damage. Therefore SAD diet, trans fats, ω-6 fatty acids (especially if heated), smoking, alcohol, occupational or hobby exposures to heavy metals pose a higher risk. Moderate evidence suggests mercury from fish may influence C carriers adversely. Adequate selenium status may mitigate the adverse effects of heavy metals.

SNP: **PON1 L55M rs854560 (+/-, AT)**

The AT variant may have a slight reduction in enzyme arylesterase and paraoxonase activity.

### Cleans your PON1 gene

**Environment:** Utilize air filters, especially choosing the 'Recirculation of Air' option for in your car versus the "Outside Air" option that allows in vehicle exhaust while driving. Be sure to use high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood.

**Lifestyle:** High intensity interval training (HIIT) as well as moderate, regular exercise like walking increases PON1 activity, especially when undertaken regularly.

**Food:**

- Focus on calcium, selenium, lycopene rich sources. Opt for a Mediterranean diet rich in extra virgin olive oil, cold water fish, legumes, nuts, seeds, fruits and vegetables.
- Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon (PAH) formation.
- Polyaromatic hydrocarbons from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. (Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar.)
- Use an extractor hood while cooking and high-smoke point oils like ghee or avocado oil.

**Supplements and Medications:**

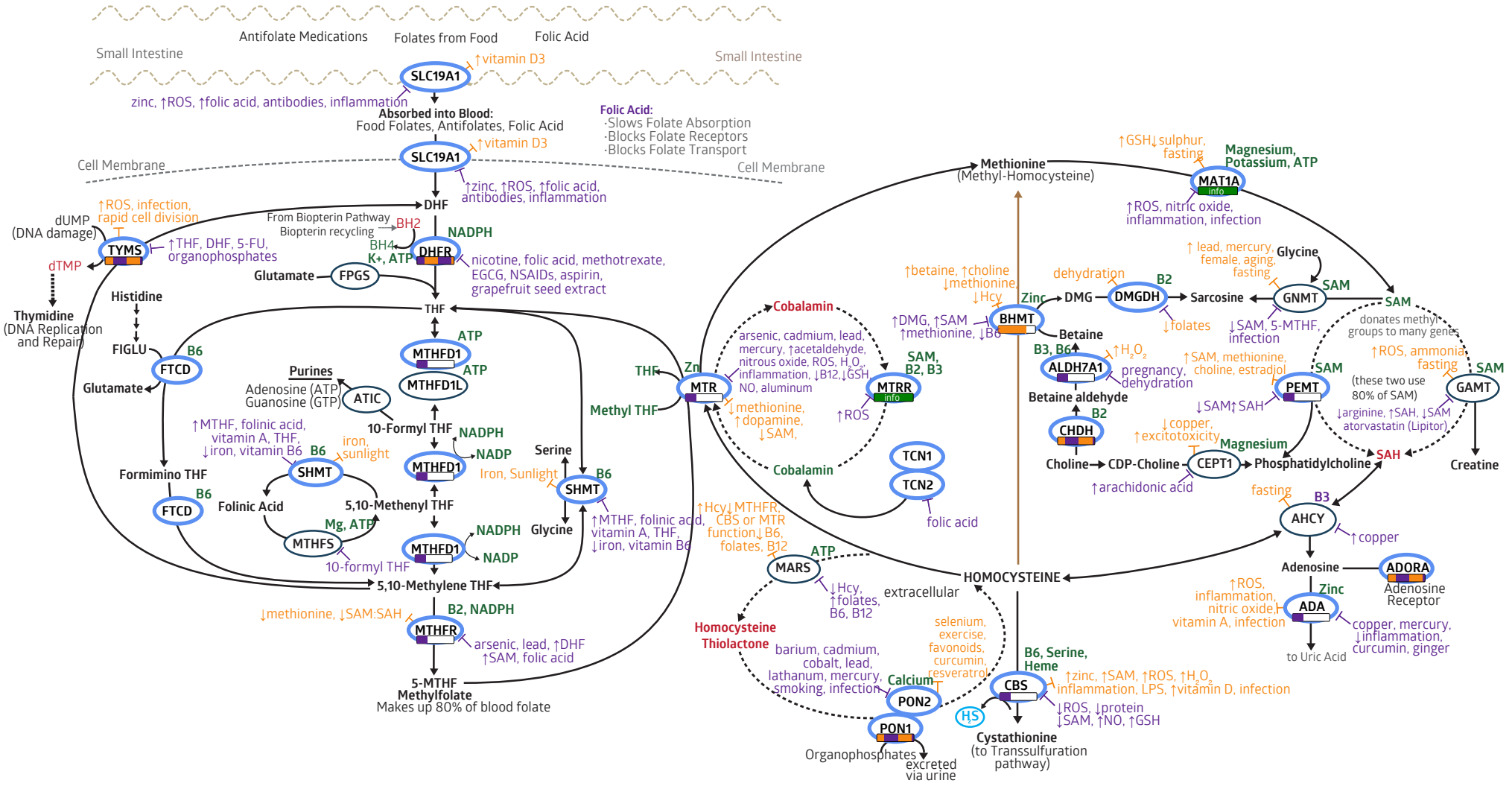
- Consider omega-3 fish oils, N-acetylcysteine (NAC), quercetin, L-carnitine, low dose aspirin, *Lactobacillus spp.*, artichoke, berberine, curcumin, licorice, resveratrol, *Ilex paraguariensis* (yerba mate) and pomegranate, vitamin E (alpha-tocopherol). Use methylation support supplements as needed to optimize homocysteine levels.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause and other indications for its use. Estrogen indirectly supports increased PON1 activity by raising HDL levels, as well as increasing PON1 activity.

## THE CBS GENE

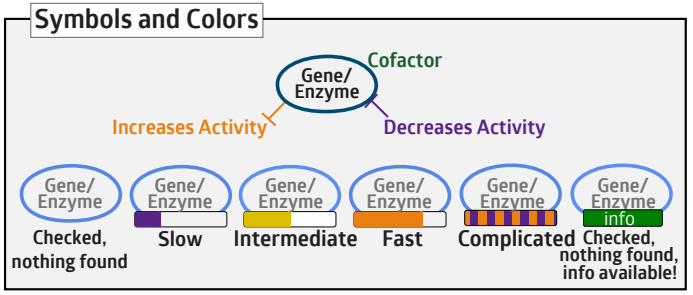
The complete discussion of this gene is under Glutathione.

# Methylation

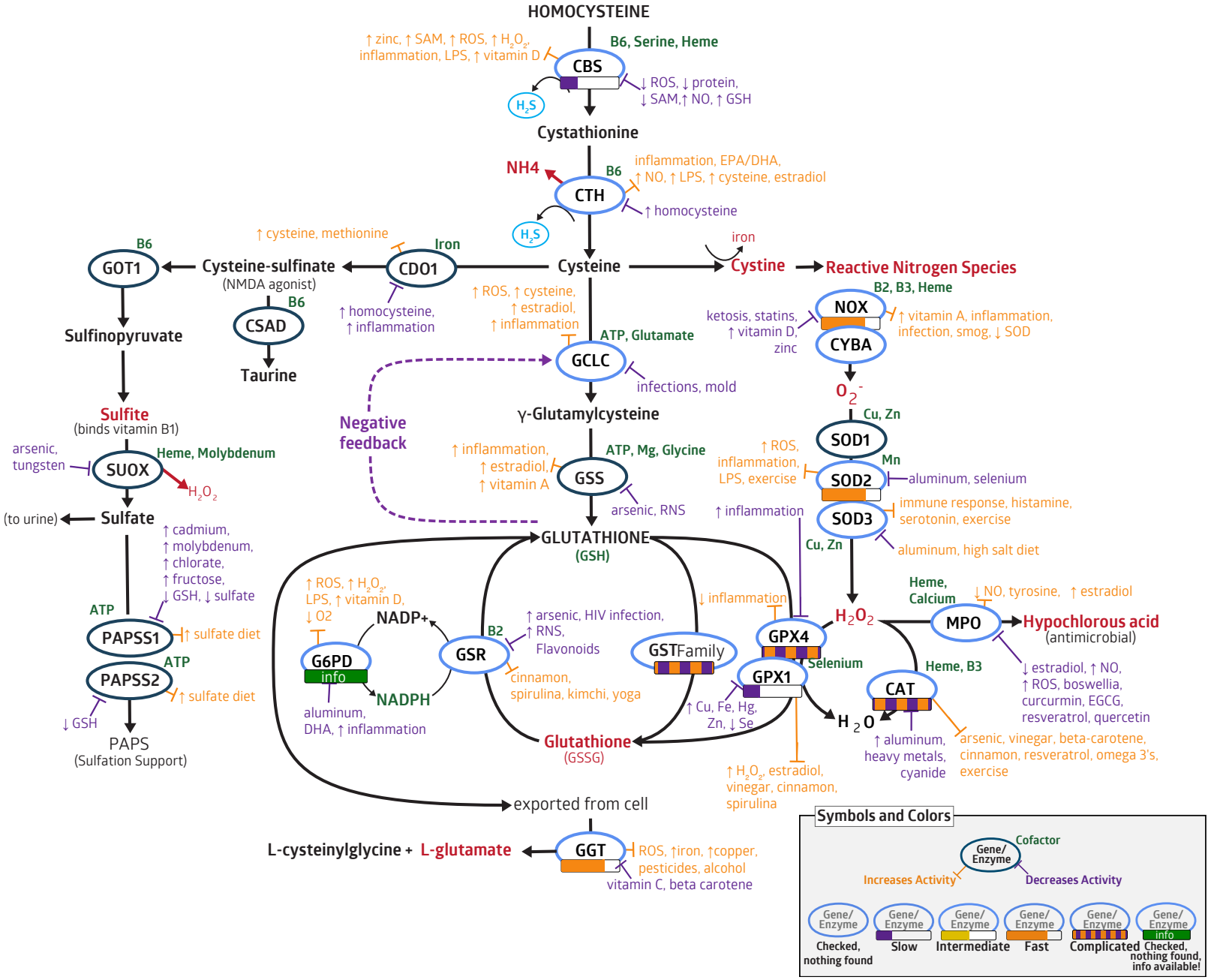





## Symbols and Colors



# Glutathione



# THE CBS GENE

The CBS (cystathionine beta-synthase) gene expresses an enzyme which catalyzes the conversion of homocysteine to cystathionine by the addition of serine requiring pyridoxine (B6) and heme as cofactors. CBS is the first rate-limiting step in the glutathione pathway.

CBS controls whether homocysteine is conserved for the SAM cycle, by recycling homocysteine back to S-adenosylmethionine (SAM) or whether homocysteine is removed from the cycle by being shunted into the glutathione pathway.

A byproduct of CBS' conversion of homocysteine to cystathionine is hydrogen sulfide ($H_2S$), which is an important synaptic modulator and neuroprotectant in the brain. $H_2S$ is also involved in blood pressure regulation and healthy respiratory function.

Hydrogen sulfide levels must be optimized. Too low and one may experience hypertension or difficulty breathing (asthma). Too high and one may experience fatigue, headaches, irritability.

## Dirties your CBS gene

**Environment:** High levels of hydrogen sulfide are toxic to humans. Since the CBS enzyme produces hydrogen sulfide, an excessive amount of hydrogen sulfide may be produced especially if the environment is also contributing to the levels. Tropical areas may have higher amounts of hydrogen sulfide in the air and water. Sewers can also vent fumes high in hydrogen sulfide.

**Lifestyle:** Peroxynitrite from an uncoupled NOS3 enzyme increases CBS expression. In fact, any reactive oxygen species increases CBS expression in order to stimulate production of glutathione. However, a prolonged increased CBS expression may lower vitamin B6 levels, lower homocysteine too much (< 5 umol/L), increase hydrogen sulfide levels excessively, and burden other downstream enzymes such as SUOX and GSR.

Increased burden on SUOX may then in turn increase sulfites and deplete molybdenum. Increased burden on GSR may deplete riboflavin thereby increasing oxidized glutathione.

People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may have impaired CBS function as heme is the required cofactor for this enzyme.

Also, many parasites and gram negative bacteria need heme to reproduce and cause infection. These pathogens must synthesize their own heme or steal heme from the host. Thus, untreated chronic parasite or bacterial infections may create a heme deficiency. (Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.)

Hydrogen sulfide producing bacteria may increase/elevate hydrogen sulfide levels to unhealthy levels. Discuss with your healthcare provider if you exhibit "rotten egg" smelling gas, diarrhea, or other digestive issues.

Intensive exercise and overtraining increase inflammation which may push the CBS enzyme to work excessively.

## Notable variation:

SNP: **CBS rs4920037 (+/-, GA)**
This GA variant may result in decreased CBS activity.

SNP: **CBS C699T rs234706 (+/-, GA)**
The kinetic effect of this GA variant is controversial. Most studies indicate upregulation, but the science is mixed.

### Dirties your CBS gene, continued...

**Food:** Low protein diets may impair CBS enzyme from functioning from lack of substrate, homocysteine. Conversely, high protein, GAPS and Paleo diets may instead overwhelm the CBS enzyme with homocysteine due to increased methionine, cysteine and sulfur levels.

While these nutrients are necessary and supportive in the right amounts, they may be harmful when in excess or in short supply. The issue is quantity: a kale smoothie with two eggs and broccoli for breakfast is a perfect example of excessive cysteine and sulfur. Not everyone can tolerate a green smoothie or a high protein diet.

**Supplements and Medications:** Consider using *Saccharomyces boulardii* while using antibiotics and probiotics after a course of antibiotics. Limit acetaminophen (Tylenol). If the CBS gene is overtaxed, intake of sulfur-containing supplements such as N-acetylcysteine (NAC), methylsulfonylmethane (MSM) may be problematic. Maternal folic acid supplementation decreased expression of CBS.

## Cleans your CBS gene

**Environment:** Avoid areas with higher levels of hydrogen sulfide.

**Lifestyle:** Exercise at a sustainable level with ability to fully recover within 24-48 hours.

**Food:**

- Focus on heme, iron, zinc, pyridoxine (B6) and vitamin D rich sources, and strive for protein intake at about 0.8 grams per kg (2.2 lbs) of body weight.
- Protein intake drives up homocysteine, so if homocysteine levels are elevated above > 8 umol/L in adults, reduce protein intake by the amount recommended by your healthcare provider.
- Find a level of sulfur-containing food consumption that agrees with your unique constitution. If consuming too much sulfur or protein, you may begin to smell like sulfur - skin, breath, stool, urine, flatulence. This is a sign to reduce intake slightly and discuss with your healthcare provider other potential causes.
- If the CBS enzyme is unresponsive to vitamin B6, consider betaine rich foods.

**Supplements and Medications:** Optimize pyridoxine (B6), glutathione, iron, zinc, vitamin D, probiotics. If the CBS enzyme is unresponsive to vitamin B6, consider betaine (TMG) or choline (but not in excessive amounts). If excessive hydrogen sulfide levels are present, use hydroxocobalamin (B12) to help reduce it. The element molybdenum and calcium-D-glucarate are very important for reducing sensitivity to sulfites and sulfur. Liposomal glutathione may also slow down a fast CBS enzyme especially if hydrogen peroxide levels are stimulating it. PQQ (pyrroloquinoline quinone) may also help reduce oxidative stress and thereby slow an overexpressed CBS gene. Using anti-inflammatories, such as curcumin, may assist in balancing an overreactive CBS.

# THE G6PD GENE

The G6PD (glucose-6-phosphate dehydrogenase) gene expresses an enzyme which recycles NADP+ back to NADPH.

NADPH is, in turn, a vital cofactor for the GSR (glutathione reductase) enzyme to recycle damaged or oxidized glutathione back to its healthy, active form.

Glutathione is an important antioxidant but when it's oxidized, it can damage other proteins via a process called glutathionylation. Therefore, G6PD plays an integral role in supporting the body's antioxidant defense system.

G6PD deficiency impairs intracellular calcium transport and impacts all the major enzymes dependent on NADPH: antioxidant enzymes such as GSR and catalase; nitric oxide synthase, dihydrofolate reductase, NADPH oxidase, cytochrome p450 enzymes, oxidoreductases, and lipid synthesis enzymes such as HMG CoA reductase.

The G6PD protein is located on the X chromosome, therefore males only inherit one allele and females have inherently higher activity as a result of two X chromosomes.

Over 400 variants are known to cause mild to severe G6PD deficiency and this test does not investigate all possible variants for the condition.

## 💩 Dirties your G6PD gene

**Environment:** Aluminum, polycyclic aromatic hydrocarbons (PAH), oxidative stress

**Lifestyle:** Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections. Starvation, fasting, blood sugar dysregulation can all stress G6PD.

**Food:** Fava beans, omega-6 fats

**Supplements and Medications:** Acetaminophen (Tylenol), aspirin, high dose vitamin C

## Cleans your G6PD gene

**Lifestyle:** Engage in moderate exercise, especially if supported concurrently with below supplements.

**Food:** Choose a high complex carbohydrate, low fat diet with mono-unsaturated fats, vitamin D and E rich foods.

**Supplements and Medications:** Optimize Vitamin D, vitamin E, omega-3: alpha-linolenic acid (ALA) and docosahexaenoic acid (DHA).

### Notable variation:

While no notable variation was found, we are presenting this gene's information to you because it's so important. Remember, lifestyle, food, environment and nutrients play a significant role in genetic expression — often significantly more than a genetic variation.

# THE GSTA1 GENE

The GSTA1 (glutathione S-transferase alpha 1) gene expresses an enzyme of the alpha class glutathione S-transferase (GST) which functions to add glutathione to target electrophilic compounds, including carcinogens, therapeutic drugs, environmental chemicals and products of oxidative stress.

The alpha class of the GST enzymes (GSTA1 being one of them) exhibit glutathione peroxidase activity neutralizing reactive oxygen species and the products of peroxidation.

Found mainly in liver and kidney, the GSTA1 enzyme also metabolizes bilirubin and certain anti-cancer drugs in the liver.

## 💩 Dirties your GSTA1 gene

**Environment:**

- Avoid exposure to mold: pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and mycotoxins.
- Avoid xenobiotics of all types such as plasticizers, polyaromatic hydrocarbons (PAH), pesticides and smoke.
- Cooking itself, especially without proper ventilation or with low smoke point oils like walnut, flaxseed, wheatgerm can dramatically reduce indoor air quality.

**Lifestyle:** Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections. Limit use of synthetic chemicals in everyday life.

**Food:** Limit fatty meats and animal fats such as butter or lard which concentrate dioxins; nitrosamines found in cured meats, cooked bacon, beer, some cheeses, non-fat dry milk.

**Supplements and Medications:** Avoid acetaminophen (Tylenol), NSAIDs. Consider *Saccharomyces boulardii* while taking antibiotics and probiotics afterwards.

### Notable variation:

While no notable variation was found, we are presenting this gene's information to you because it's so important. Remember, lifestyle, food, environment and nutrients play a significant role in genetic expression — often significantly more than a genetic variation.

## Cleans your GSTA1 gene

**Environment:**

- Use water filters especially for drinking/cooking and showering.
- Utilize air filtration/dehumidifiers to remove allergic triggers and lower humidity to reduce mold growth.
- Choose high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood.
- Choose the 'Recirculation of Air' option for in your car versus the "Outside Air" option to reduce in-vehicle exhaust while driving.

**Lifestyle:** Choose non-toxic products for household and bodycare use.

**Food:**

- Follow a whole foods plant-based diet rich in fiber, cruciferous vegetables, garlic, onions, soy, lycopene, selenium, vitamin C, coumarins.
- Consider whey protein powder for gluathione support.
- If you do choose to eat meat, purchase organic, free range meat and utilize cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon (PAH) formation.
- Polyaromatic hydrocarbons (PAH) from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased in a study by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar.

**Supplements and Medications:** Spirulina, selenium, liposomal glutathione, S-acetyl glutathione, N-acetylcysteine (NAC), vitamin C, probiotics, EGCG from green tea, *Cinnamomi cassiae* and *Rhodiola rosea*

# THE GSTO GENE

The GSTO1 and 2 (glutathione S-transferase omega 1 and 2) genes express enzymes of the omega class glutathione S-transferase (GST) which catalyzes thioltransferase, ascorbate, and S-phenacyl glutathione reductase reactions.

The two genes are also involved in the detoxification steps of arsenic biotransformation and are thought to activate interleukin-1b.

GSTO2 possesses twice the antioxidant activity of GSTO1.

## 💩 Dirties your GSTO gene

**Environment:**

- Avoid mold exposure: pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and specifically ochratoxins.
- Avoid xenobiotics of all types such as plasticizers, polyaromatic hydrocarbons (PAH), pesticides and smoke.
- Couples considering conception should avoid any and all sources of arsenic or cadmium and detox any arsenic and other detected heavy metal burden well in advance of conception.

**Lifestyle:**

- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections, hypoxia.
- Limit use of synthetic chemicals in everyday life, especially halogenated organochlorides, xenoestrogens (bodycare and home cleaning products, plastics).
- Avoid smoke from incense, woodsmoke, air pollution, vehicle exhaust, cooking oils.

**Food:** Limit fatty meats and animal fats such as butter or lard which concentrate dioxins; nitrosamines found in cured meats, cooked bacon, beer, some cheeses, non-fat dry milk.

## Notable variation:

🧬 SNP: **GSTO1 -2200G>A rs11509438 (-/-, GG)** 🎯
The GG wild type has 120% higher activity when compared with the minor variant enzyme in vitro. This translates to potentially lower levels of compounds that contribute to neuro and cardiovascular inflammation. The efficiency of biotransformation of arsenic into less toxic metabolites is still unknown.

🧬 SNP: **GSTO1 C419A rs4925 (-/-, CC)** 🎯
The CC wild type exhibits 80% higher activity when compared with the minor variant enzyme in vitro. This translates to lower levels of compounds that contribute to neuro and cardiovascular inflammation. However, the efficiency of biotransformation of arsenic into less toxic metabolites may be lower. Although limited evidence is available, this may equate to increased levels of compounds that may initiate some cancers.

🧬 SNP: **GSTO2 A424G rs156697 (+/+, AA)** 🎯
This AA variant is thought to have higher enzyme expression and appears more beneficial. It is included here for investigational purposes in anticipation of future research that can better characterize its impact.

## Cleans your GSTO gene

**Environment:**

- Use water filters especially for drinking/cooking and showering.
- Utilize air filtration/dehumidifiers to remove allergic triggers and lower humidity to reduce mold growth. Choose high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood. -Choose the 'Recirculation of Air' option for in your car versus the "Outside Air" option to reduce in-vehicle exhaust while driving.

**Lifestyle:** Choose non-toxic products for household and bodycare use.

**Food:**

- Follow a whole foods plant-based diet rich in fiber, cruciferous vegetables, garlic, onions, soy, lycopene; selenium, vitamin C and coumarin rich foods, whey protein powder.
- Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon (PAH) formation.
- Polyaromatic hydrocarbons from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar.
- Be sure to use high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood.

**Supplements and Medications:** Spirulina, sulforaphane, selenium, liposomal glutathione, S-acetyl glutathione, N-acetylcysteine, vitamin C, probiotics, EGCG, *Cinnamomi cassiae* and *Rhodiola rosea*

# THE GSTP1 GENE

The GSTP1 (glutathione S-transferase pi 1) gene expresses an enzyme of the pi class glutathione S-transferase (GST) which detoxifies polyaromatic hydrocarbons (PAH) using glutathione.

The GSTP1 gene is also a tumor suppressor gene and is implicated in a large variety of detoxification and metabolism reactions which prevents cells from genome damage and cancer initiation.

## 💩 Dirties your GSTP1 gene

**Environment:**

- Identify and treat heavy metal burden especially aluminum, mercury.
- Avoid mold exposure: pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and mycotoxins.
- Minimize exposure to xenobiotics of all types such as plasticizers, polyaromatic hydrocarbons (PAH), pesticides and smoke.

**Lifestyle:**

- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections including viral hepatitis.
- Infrequent or minimal sweating may lead to increased chemical burden as many compounds sweat out via the skin: our largest detoxification organ.
- Limit use of synthetic chemicals in everyday life.

**Food:**

- Limit fatty meats and animal fats such as butter or lard which concentrate dioxins.
- Avoid the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/).
- Consider *Saccharomyces boulardii* while taking antibiotics and probiotics afterwards.

**Supplements and Medications:** Acetaminophen (Tylenol), non-steroidal anti-inflammatory drugs (NSAIDs)

## Notable variation:

⧖ SNP: **GSTP1 GSTP1*B rs1695 (-/-, AA)** ☯

The AA wild type functional effect varies depending on the substrate. The AA active site may better accommodate more bulky compounds but has a smaller range of substrates it can conjugate. Relative to GG individuals, AA individuals have decreased ability to conjugate polyaromatic hydrocarbons (PAH), similar ability to conjugate the pesticide atrazine but more ability to conjugate the cancer drug busulfan or some benzene derivatives. A allele carriers may be at increased risk for inflammation from passive tobacco smoke, asbestos; conflicting evidence for polyaromatic hydrocarbons (PAH), ozone

⧖ SNP: **GSTP1 A114V rs1138272 (-/-, CC)** ☯

This CC wild type shows increased activity relative to TT via higher expression and improved substrate access to the catalytic site. The C major allele seems more efficient at overall detoxification of most, but not all compounds.

## Cleans your GSTP1 gene

**Environment:**

- Use water filters especially for drinking/cooking and showering.
- Utilize air filtration/dehumidifiers to remove allergic triggers and lower humidity to reduce mold growth.
- Choose high smoke point oils such as avocado oil or ghee, cook in a well-ventilated area and use the extractor hood.
- Choose the 'Recirculation of Air' option for in your car versus the "Outside Air" option to reduce in-vehicle exhaust while driving.

**Lifestyle:** Choose non-toxic products for household and bodycare use.

**Food:**

- Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https://https://www.ewg.org/foodnews/clean-fifteen.php/).
- Whole foods plant-based diet rich in fiber, cruciferous vegetables, garlic, onions, soy, lycopene; selenium, vitamin C and coumarin rich foods, whey protein powder are all good choices.
- Choose meat cooking methods that employ lower, indirect heat such as braising or stewing which decrease polyaromatic hydrocarbon (PAH) formation. Polyaromatic hydrocarbons from chargrilling meat may also be reduced by marinating meats for 4 hours prior to grilling in beer, vinegar or tea (both green or black) based sauces including lemon, onions, garlic, or alternatively: spraying meat with culinary vinegar prior to grilling. Polyaromatic hydrocarbon formation was decreased by almost 80% using white wine vinegar, 66% by red wine and cider vinegar, and 55% by raspberry vinegar.

**Supplements and Medications:** Spirulina, selenium, liposomal glutathione, S-acetyl glutathione, N-acetylcysteine (NAC), vitamin C, probiotics, EGCG from green tea, sulforaphane, *Cinnamomi cassiae* and *Rhodiola rosea*

# THE NOX GENE

The NOX (NADPH oxidase) genes express enzymes which catalyze the production of a superoxide free radical ($O_2^-$). NOX2 is composed of 2 cytochrome subunits coded by the genes CYBA and CYBB and uses riboflavin (B2), niacin (B3) and heme as cofactors.

NOX is found in two places: one in white blood cells (neutrophilic) and the other in vascular cells. Neutrophilic NOX produces superoxide almost instantaneously, whereas the vascular version produces superoxide in minutes to hours.

The enzymes become rapidly activated in the presence of bacteria and other pathogens and generates superoxide in an attempt to kill and eliminate them. However, persistent stimulation of NOX2 may lead to excessive production of superoxide in vascular cells, increasing susceptibility to cardiovascular disease.

This is yet another reason why it's so important to identify infections of any type (bacterial, viral, mold, parasites) in every part of the body (nose, mouth, ears, sinuses, bones, blood, digestive system to name a few).

## 💩 Dirties your NOX gene

**Environment:**

- Evaluate heme deficiency. Heme is an essential cofactor for NOX. However, many parasites and gram negative bacteria need heme to reproduce and cause infection. These pathogens must synthesize their own heme or steal heme from the host. Thus, untreated chronic parasite or bacterial infections may create a heme deficiency. Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.
- Be mindful of tick infested areas as they increase the risk of Lyme disease.
- People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.
- Avoid mold exposure: pay attention to indoor air quality of home, school or workplace, especially if history of water damage and potential for mold and mycotoxins.
- Cooking itself, especially without proper ventilation or with low smoke point oils like walnut, flaxseed, wheatgerm can dramatically reduce indoor air quality.

## Notable variation:

SNP: **NOX -930G>A rs9932581 (-/-, CC)**

This CC variant exhibits higher enzyme expression in vitro with more generation of reactive oxygen species, especially in response to smoking or obesity. This can increase risk for cardiovascular and other inflammatory diseases, but is protective against pathogenic bacteria and fungi as it results in more oxidative stress needed to fight infection.

## Dirties your NOX gene, continued...

**Lifestyle:**

- Obesity typically causes inflammation and taxes NOX.
- Avoid smoke from incense, woodsmoke, air pollution, vehicle exhaust, cooking with low smoke point oils.
- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections.

**Food:** NOX is especially sensitive to damage from the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium and low in fiber and good quality protein. Especially avoid oxidized omega-6 fatty acids (from rancid, processed or low smoke point cooking oils), saturated fats, microwaved foods containing cholesterol or animal products.

**Supplements and Medications:** Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your NOX gene

**Environment:** Use an extractor hood while cooking. Utilize air filtration systems to remove molds, bacteria and viruses and water filtration to remove potential pathogenic bacteria.

**Lifestyle:** Maintain optimal weight and blood sugars. Nutritional ketosis may be helpful, as can cardiovascular exercise. Stress management techniques are recommended such as meditation, breathing exercises, mindfulness, outdoor time, massage, pet therapy, moderate physical exercise.

**Food:** When cooking, use high smoke point oils such as ghee or avocado oil. Opt for a whole foods plant based or Mediterranean diet rich in extra virgin olive oil, cold water fish, legumes, nuts, seeds, fruits and vegetables. Choose vitamin A, riboflavin (B2), heme and non-heme iron rich foods. Foods naturally rich in SOD include cabbage, Brussels sprouts, wheat grass, barley grass and broccoli.

**Supplements and Medications:**

- Optimize riboflavin (B2), niacin (B3), iron, vitamin A and D levels.
- While you need NOX to express during acute infections in order to produce sufficient oxidants to target and kill pathogens, chronically activated NOX will lead to persistent and unwanted oxidative stress. In those in this situation of upregulated NOX unrelated to infection, a SOD supplement may be helpful in neutralization of high oxidant levels, as well as supporting the genes downstream of NOX: CAT and GPX.
- Spirulina, berberine, green tea, resveratrol, curcumin, olive leaf extract, hesperidin and quercetin all have been shown to lower oxidative stress from overactive NOX genes.
- In the scenario of acute infections, antimicrobials and other pro-oxidant therapies such as IV vitamin C, can assist in the elimination of the infection thereby reducing the need for NOX to over-express.

# THE SOD2 GENE

The SOD2 gene (mitochondrial superoxide dismutase 2 – also known as MnSOD) expresses an enzyme in the mitochondria that reduces levels of superoxide radicals by converting them into hydrogen peroxide, using manganese (Mn) as a cofactor.

Superoxide radicals are important and useful in the body when present in the right amount. Superoxide radicals participate in a beneficial purging process known as “programmed cell death” where a burst of superoxide radicals causes death to damaged and worn-out cells. However, an excess of superoxide may cause inflammation resulting in uncontrolled death of healthy cells.

SOD2 enzymes take the very reactive superoxide radicals made by NOX and convert them into slightly less reactive, but still damaging, hydrogen peroxide.

Like superoxide, hydrogen peroxide is also important and useful in the right amount. In the body it is used to kill bacteria, fungi and other pathogens. However, again, in excess, hydrogen peroxide can also cause inflammation and cell damage/death.

The hydrogen peroxide generated by SOD2 is converted to water and oxygen by either GPX or CAT enzymes. Therefore, the balance between these enzymes is crucial in controlling the levels of these highly reactive, yet important compounds.

If SOD2 is working slowly, superoxide levels may build up. This increases the risk of superoxide combining with nitric oxide to generate peroxynitrite, which is an other damaging and reactive pro-oxidant.

On the other hand, if SOD2 is working quickly, and doing a good job of reducing superoxide, this may then cause a build-up of hydrogen peroxide. This is especially the case for those with slow GPX1 (present) or slow CAT(unknown) genes who cannot convert the damaging hydrogen peroxide to harmless water fast enough.

An ideal situation is when SOD2 works quickly along with GPX and CAT also functioning well. This demonstrates the importance, again, of how many genes are required to function well, and interact with each other, in order to provide optimal health.

The activity of SOD2 is naturally higher in females by approximately 15%.

## Notable variation:

SNP: **SOD2 A16V rs4880 (+/-, AG)**
This AG variant may result in 15-20% higher activity in vivo relative to wild type GG.

## 💩 Dirties your SOD2 gene

**Environment:** Work with your healthcare provider to identify and treat any infections: viral, bacterial or fungal; heavy metals or bisphenol A (BPA) burden.

**Lifestyle:**

- Work with your healthcare provider to identify and treat sleep apnea.
- Extensive exercise or overtraining causes significant inflammation and oxidative stress.
- Limit alcohol.

**Food:** Avoid the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber.

**Supplements and Medications:** While pro-oxidant therapies such as ozone, IV vitamin C, hyperbaric oxygen therapy (HBOT) are very beneficial for many people, they may exacerbate those with a weakened anti-oxidant response. If experiencing pain or significant worsening of symptoms with these pro-oxidant therapies, it may be good to evaluate the anti-oxidant genes such as SOD, CAT, GPX. Be mindful of manganese supplementation. While it is the cofactor, high manganese is proinflammatory and may lead to an exacerbation of symptoms. Do not oversupplement with manganese.

## Cleans your SOD2 gene

**Lifestyle:** Physical exercise in moderation. Exercise increases oxidative stress. If post-workout soreness extends beyond 48 hours, then consider reducing intensity, frequency and duration.

**Food:**

- Choose a low sodium diet of 1,200-1,500 mg sodium/day.
- Focus on sources rich in manganese, vitamin C and sulforaphane such as cruciferous vegetables like broccoli, cabbage, cauliflower, Brussels sprouts and kale
- Opt for a Mediterranean diet rich in extra virgin olive oil, cold water fish, legumes, nuts, seeds, fruits and vegetables or whole food plant-based diet.
- A moderate protein diet of 0.8 grams of protein per kg (2.2 lbs) of body weight per day is recommended. However after age 65, moderate protein is associated with reduced mortality suggesting an increased protein intake and the resulting increase in IGF-1 and SOD2 may prove beneficial in older adults.

## Cleans your SOD2 gene, continued...

**Supplements and Medications:**

- Optimize manganese and selenium.
- Consider *Lactobacillus spp.*, melatonin, lutein, pygnogenol, curcumin, resveratrol, carnitine, PQQ (pyrroloquinoline quinone), SOD, carnosine, CoQ10, *Rhodiola rosea*.
- When supporting SOD, it is important to also support downstream enzymes, GPX and CAT, with their cofactors. If you don not, an increase in SOD activity may burden these enzymes leading to excessive hydrogen peroxide ($H_2O_2$) levels.
- Additional support of GSR is needed to recycle oxidized glutathione back to its active, reduced form.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

# THE GPX1 GENE

The GPX1 (glutathione peroxidase 1) gene expresses an enzyme which is responsible for the detoxification of peroxides such as hydrogen peroxide, organic hydroperoxides and lipid hydroperoxides. Selenium is required for the active catalytic site.

There are 8 known isoforms of glutathione peroxidase (GPX 1-8). GPX1 primarily protects against harmful levels of hydrogen peroxide within the cell by transforming it to water.

## Dirties your GPX1 gene

**Environment:** Identify and treat heavy metal burden especially mercury (Hg). Avoid excess iron (Fe) which, in the presence of hydrogen peroxide, increases oxidative stress and causes cell damage. Therefore, individuals with familial hemochromatosis (HFE), postmenopausal women and men should identify any unwanted sources of iron in diet such as well water, cookware, supplements. Avoid chlorine found in shower, drinking water, swimming pools, hot tubs; formaldehyde found in carpets, new furniture, cabinets, gas appliances.

**Lifestyle:** Alcohol

**Supplements and Medications:** Avoid iron (Fe) if elevated.

## Cleans your GPX1 gene

**Food:** Drink vinegar: one tbsp apple cider vinegar in glass of water before meals. Choose selenium vitamin C rich sources; sulforaphane rich found in cruciferous vegetables such as broccoli, cabbage, cauliflower, Brussels sprouts and kale.

**Supplements and Medications:** Consider vitamin E, liposomal glutathione, S-acetyl glutathione, cinnamon, curcumin, genistein, melatonin, resveratrol, spirulina, *Hippophae rhamnoides* (sea buckthorn), *Rhodiola rosea, Cinnamomi cassiae* and *Withania somnifera* (ashwagandha) which help to reduce inflammation.

Optimize selenium, copper and zinc. Copper and especially zinc are shown to inhibit GPX1 activity. This is useful and necessary under conditions of bacterial infection, when adequate levels of copper and especially zinc allow for the immune system to generate sufficient hydrogen peroxide to fight infections. However, avoid over-supplementation. Use the 'pulse method' described in the *Dirty Genes* book.

Estrogen increases GPX activity. If you are a postmenopausal woman: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Notable variation:

SNP: **GPX1 P198L rs1050450 (+/-, GA)**
This GA variant downregulates the enzyme's activity in red blood cells between 5% to 10% by impacting how selenium binds to the active enzyme. A allele carriers are less responsive to selenium regardless of whether from food or supplements.

SNP: **GPX1 -46C>T rs1800668 (+/-, GA)**
This GA variant has 20% less activity than wild type in vivo.

# THE GPX4 GENE

The GPX4 (glutathione peroxidase 4) gene expresses and enzyme which is responsible for the detoxification of phospholipid hydroperoxide, fatty acid hydroperoxide and cholesterol hydroperoxide found in cell membranes and lipoproteins. Selenium is required for the active catalytic site.

There are 8 known isoforms of glutathione peroxidase (GPX 1-8). GPX4 protects against cell death resulting from an iron-triggered accumulation of lipid reactive oxygen species.

## 💩 Dirties your GPX4 gene

**Environment:** Avoid smoke from any source: cigarettes, marijuana, incense, woodsmoke, diesel exhaust, smog, cooking fumes. Individuals with familial hemochromatosis (HFE), men and postmenopausal women should identify any unwanted sources of iron in diet such as well water, cookware, supplements. Use air filtration systems that remove combustion products from natural gas fireplaces, cooktops or ranges; formaldehyde sources such as carpets, new furniture, cabinets, gas appliances. Use water filters to remove chlorine sources such from shower, drinking water, swimming pools, hot tubs, baths.

**Food:** Limit arachidonic acid, avoid rancid omega-6 fats; heating low smoke point oils like walnut, flaxseed, wheatgerm can make them unfit for consumption.

**Supplements and Medications:** Iron, especially if elevated

## Cleans your GPX4 gene

**Environment:** Use an extractor hood while cooking and high-smoke point oils like ghee or avocado oil.

**Food:** Opt for whole food plant-based diet, choose selenium rich sources.

**Supplements and Medications:** Consider selenium. The optimal benefits of supplementation on DNA stability are observed when the serum selenium level reaches between 160> x >120 ng/ml.

### Notable variation:

SNP: **GPX4 C718T rs713041 (NC)**
**Note**: Unfortunately, the presence of this SNP could not be determined from your sample. This prevents its use in the assessment of this gene.

# THE CAT GENE

The CAT (catalase) gene expresses an enzyme which catalyzes the decomposition of hydrogen peroxide into oxygen and water using niacin (B3) and heme as cofactors.

Hydrogen peroxide is a by-product of many normal metabolic processes but can cause harmful oxidative damage to cells and tissues if not neutralized.

The catalase enzyme is therefore important for protecting cells from oxidative damage, and it has one of the highest activities of the antioxidant enzymes. One catalase molecule converts millions of hydrogen peroxide molecules to water and oxygen each second.

Catalase can also use hydrogen peroxide to catalyze the break down of various metabolites and chemicals including formaldehyde, formic acid, phenols, acetaldehyde and alcohols.

## 💩 Dirties your CAT gene

**Environment:** Pesticides, pollutants, metals, smoking. Iron overload, individuals with familial hemochromatosis (HFE) or thalassemia. Men and postmenopausal women should identify any unwanted sources of iron in diet such as well water, cookware, supplements.

**Lifestyle:**

- Evaluate heme deficiency. Many parasites and gram negative bacteria need heme to reproduce and cause infection. These pathogens must synthesize their own heme or steal heme from the host. Thus, untreated chronic parasite or bacterial infections may create a heme deficiency. Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency.
- People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.
- Individuals with beta-thalassemia may be at increased risk for serious complications due to increased oxidative stress. Therefore, avoid vigorous exercise or overtraining which causes significant inflammation and oxidative stress.

**Food:** Avoid the standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein. Individuals with a dirty CAT should seriously consider eating nutritious whole foods.

**Supplements and Medications:** Iron, especially if elevated

## Notable variation:

SNP: **CAT 1167C>T rs769217 (-/-, CC)**
Wild type CC carriers exhibit faster transcription compared to variant carriers and thus have slightly higher catalase levels compared to TT. This may increase susceptibility to pulmonary oxidative damage from ozone and air pollution.

SNP: **CAT -262C>T rs1001179 (+/-, CT)**
The CT variant results in a mild downregulation. Carriers of a T allele may therefore be slightly more prone to systemic oxidative stress damage from pesticides, pollutants, metals, smoking.

## Cleans your CAT gene

**Lifestyle:** Engage in enjoyable exercise, especially moderate-intensity continuous training.

**Food:** Choose beta-carotene, niacin (B3), heme and non-heme iron, omega-3 fatty acid rich sources. Following a diet rich in fruit and vegetables with additions of vinegar, garlic, cinnamon, black tea can support catalase.

**Supplements and Medications:** Consider niacin (B3), iron, appropriate probiotics, beta-carotene, omega-3 fatty acids, inositol, melatonin, resveratrol, carnitine, catalase, liposomal glutathione, s-acetyl-glutathione, PQQ (pyrroloquinoline quinone), carnosine, *Rhodiola rosea*, *Cinnamomi cassiae*, *Hippophae rhamnoides* (sea buckthorn).

# THE GGT1 GENE

The GGT1 (gamma-glutamyl transferase 1) gene expresses an enzyme that catalyzes the first step in the degradation of extracellular glutathione (GSH). GGT1 is part of the cell antioxidant defense mechanism. It is involved in leukotriene metabolism and plays a role in regulating the balance of oxidative stress.

Glutathione is an important antioxidant consisting of three amino acids: glutamate-cysteine-glycine. The action of GGT1 cleaves the amino acid bond to release glutamate. The remaining cysteinyl-glycine molecule is a reactive thiol compound that can play a pro-oxidant role in certain health conditions. In particular it causes the reduction of metals such as ferric iron Fe(III) and copper ($Cu^{2+}$), resulting in the production of reactive oxygen species (ROS).

The prooxidant role of GGT1 is suggested as an explanation for the observed relationship between high levels of serum GGT1 and vascular damage due to oxidized LDL.

## Dirties your GGT1 gene

**Environment:** Avoid the Dirty Dozen as explained by Environmental Working Group (https://www.ewg.org/foodnews/). Avoid smoke from any source such as incense, woodsmoke, air pollution, vehicle exhaust, cooking without an extractor hood especially with low smoke point oils.

**Lifestyle:**

- Extensive exercise or overtraining causes significant inflammation and oxidative stress, as does smoking, excessive alcohol consumption, obesity, diabetes and hypertension.
- Work with your healthcare provider to identify and treat high copper and high iron.

**Food:** High iron and heme from red meat and organ meats

**Supplements and Medications:** Iron, especially if elevated, can cause oxidative damage. Many medications interact with this enzyme. Consult your healthcare provider or pharmacist.

## Cleans your GGT1 gene

**Food:** Consumption of fruits and vegetables high in vitamin C and beta-carotene can help to reduce damage due to oxidative stress. Foods that support glutathione production include radish, broccoli sprouts, onions and garlic. Consume organic fruits, organic vegetables, organic grain and organic dairy products whenever possible. Prioritize your food dollars by knowing the Clean 15 as explained by Environmental Working Group (https:://www.ewg.org/foodnews/clean-fifteen.php/).

## Notable variation:

SNP: **GGT1 -1207T>C rs4820599 (+/-, AG)**

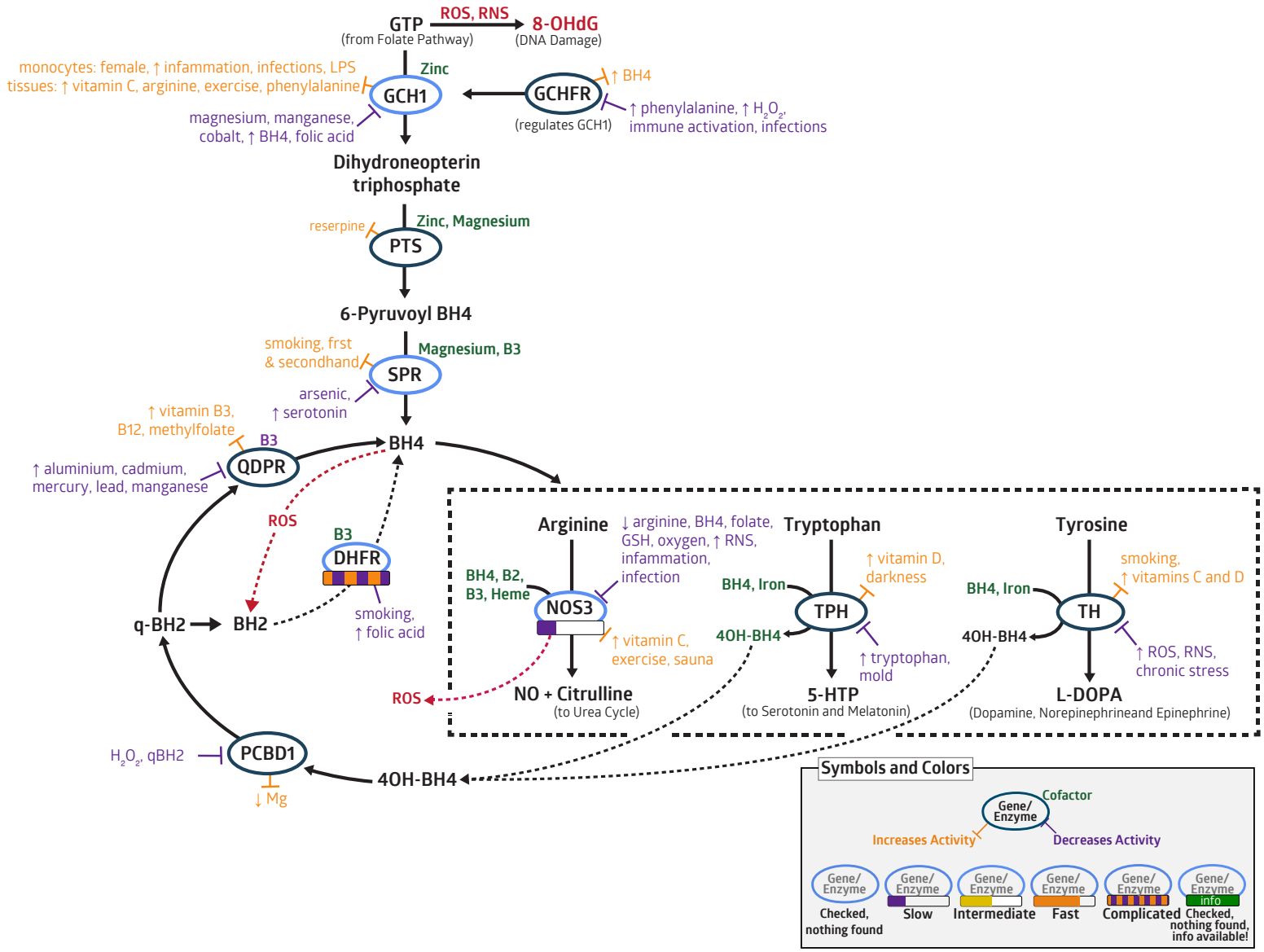
This AG variant appears to upregulate GGT activity adversely compared to wild type AA, which reduces the availability of active glutathione and reduces the antioxidant capacity to neutralize oxidative stress. Serum GGT has been found to increase significantly in some women after menopause.

## Cleans your GGT1 gene, continued...

**Supplements and Medications:** Consider niacin (B3), iron, appropriate probiotics, beta-carotene, omega-3 fatty acids, inositol, melatonin, resveratrol, carnitine, catalase, liposomal glutathione, s-acetyl-glutathione, PQQ (pyrroloquinoline quinone), carnosine, *Rhodiola rosea*, *Cinnamomi cassiae*, *Hippophae rhamnoides* (sea buckthorn).

# Biopterin




GTP
(from Folate Pathway)
ROS, RNS
8-OHdG
(DNA Damage)
monocytes: female, ↑ infammation, infections, LPS
tissues: ↑ vitamin C, arginine, exercise, phenylalanine
Zinc
GCH1
magnesium, manganese, cobalt, ↑ BH4, folic acid
GCHFR
(regulates GCH1)
↑ BH4
↑ phenylalanine, ↑ H2O2, immune activation, infections
Dihydroneopterin triphosphate
reserpine
Zinc, Magnesium
PTS
6-Pyruvoyl BH4
smoking, frst & secondhand
arsenic, ↑ serotonin
Magnesium, B3
SPR
↑ vitamin B3, B12, methylfolate
B3
QDPR
↑ aluminium, cadmium, mercury, lead, manganese
BH4
ROS
B3
DHFR
smoking, ↑ folic acid
q-BH2
BH2
Arginine
↓ arginine, BH4, folate, GSH, oxygen, ↑ RNS, infammation, infection
BH4, B2, B3, Heme
NOS3
↑ vitamin C, exercise, sauna
ROS
NO + Citrulline
(to Urea Cycle)
Tryptophan
↑ vitamin D, darkness
BH4, Iron
TPH
4OH-BH4
↑ tryptophan, mold
5-HTP
(to Serotonin and Melatonin)
Tyrosine
smoking, ↑ vitamins C and D
BH4, Iron
TH
4OH-BH4
↑ ROS, RNS, chronic stress
L-DOPA
(Dopamine, Norepinephrineand Epinephrine)
H2O2, qBH2
PCBD1
↓ Mg
4OH-BH4
Symbols and Colors
Gene/ Enzyme
Cofactor
Increases Activity
Decreases Activity
Checked, nothing found
Slow
Intermediate
Fast
Complicated
info
Checked, nothing found, info available!

# THE NOS3 GENE

The NOS3 (nitric oxide synthase 3, endothelial aka eNOS) gene expresses an enzyme that regulates production of nitric oxide (NO) in endothelial blood vessel cells using cofactors tetrahydrobiopterin ($BH_4$), heme, riboflavin (B2) and niacin (B3).

Nitric oxide, a vital gasotransmitter molecule, inhibits platelet aggregation, results in relaxation and inhibition of cell proliferation of endothelial smooth muscle, stimulates angiogenesis, acts as an anti-inflammatory molecule, and prevents oxidative damage.

NOS3 is very important for pregnancy, cardiovascular health and general blood flow. NOS3 can generate a significant amount of superoxide, a reactive oxygen species which is very damaging to $BH_4$ recycling.

If NOS3 lacks any of its cofactors or is inhibited in any way (low glutathione, high homocysteine, low arginine), it may utilize arginine to synthesize harmful superoxide instead useful nitric oxide. This is called NOS uncoupling. This explains why there can be resistance to nitroglycerin and supplemental arginine. Read the NOS3 chapter in *Dirty Genes* to learn more about this important gene.

## 💩 Dirties your NOS3 gene

**Environment:** Avoid carbon monoxide, due to less oxygen availability; and smoking, due to depletion of glutathione.

**Lifestyle:**

- Mouth breathing is damaging to nasal nitric oxide uptake in the lungs. Snoring is a sign of impaired breathing while sleeping. Check for sleep apnea or other causes.
- Elevated blood sugars and inflammation are especially serious for this gene and should be addressed as a first priority.
- Evaluate heme deficiency. Heme is an essential cofactor for NOS, but many parasites and gram negative bacteria may steal the iron-containing heme, to reproduce and cause infection. Thus, untreated chronic parasite or bacterial infections may create a heme deficiency.
- Work with your healthcare provider to identify and treat intestinal dysbiosis or other infections rather than just correcting a heme deficiency. People with heme synthesis issues such as sideroblastic anemia or one of the many porphyria disorders may be at disadvantage due to low heme.

## Notable variation:

SNP: **NOS3 A-922G rs1800779 (+/-, GA)**
This GA variant may decrease NOS3 activity via altered transcription rate and thus reduce NO production.

SNP: **NOS3 G894T rs1799983 (+/-, TG)**
This TG variant results in lower gene expression and thus lower NO levels. T allele carriers may improve lipid and other cardiovascular profiles by consuming higher omega-3 fatty acids, compared to those with GG genotype.

SNP: **NOS3 T-1495A rs1800783 (+/-, AT)**
This AT variant may decrease NOS3 activity.

SNP: **NOS3 T786C rs2070744 (+/-, CT)**
This CT variant results in slightly lower gene expression and thus lower NO levels. Daily exercise such as walking increases nitric oxide levels with improved blood flow and blood pressure in C allele carriers. Excessive exercise or overtraining can result in suboptimal expression of NOS3 due to increased oxidative stress as a result of compounds such as hydrogen peroxide. Do not overtrain.

### Dirties your NOS3 gene, continued...

**Food:** Avoid saturated animal fats and standard American diet (SAD) which is of poor nutritional value: high in processed carbohydrates, sodium, oxidized inflammatory fats, and low in fiber and good quality protein. While this may seem obvious, it's incredibly important to consume nutritious foods if one has a dirty NOS3. Foods which slow MTHFR (folate pathway) and GST/GPX (glutathione pathway) will also slow NOS3.

**Supplements and Medications:** Consider *Saccharomyces boulardii* while taking antibiotics and probiotics afterwards. High amounts of arginine or nitroglycerin may deplete other cofactors thereby contributing to NOS uncoupling.

## Cleans your NOS3 gene

**Environment:** Limit exposure to synthetic chemicals as NOS3 is sensitive to environmental contaminants. Indoor and outdoor air quality is a big issue. Use an extractor hood while cooking and high-smoke point oils like ghee or avocado oil. Use air filters in your home and especially in your car, choosing the 'Recirculation of Air' option versus the "Outside Air" option that allows in vehicle exhaust while driving.

**Lifestyle:** Engage in regular thermal therapy such as: hot yoga, steam rooms, hot baths, far-infrared sauna. Breathe through the nose. Exercise in an environment with minimal pollution. Do not exercise during heavy traffic hours or near busy streets. Ideally, exercise out in nature or indoors with filtered air. Track sleep quality with a device such as an Oura Ring or have your health professional evaluate you for sleep apnea.

**Food:**

- Choose arginine, riboflavin (B2), folate (B9), vitamin C, nitrate and iron/heme-iron rich sources.
- Opt for a Mediterranean diet rich in extra virgin olive oil, cold water fish, legumes, nuts, seeds, fruits and vegetables.
- Drink strong *Hibiscus sabdariffa* tea. Take apple cider vinegar: one tablespoon in glass of water before meals 2x/day.
- Keep nitrogen balance in order as excessive protein intake may drive up homocysteine. High homocysteine will dirty NOS3 significantly.
- Cruciferous vegetables are important to support production of glutathione which is needed to keep NOS3 cofactor, $BH_4$, undamaged. If $BH_4$ is damaged, the NOS3 enzyme falters and symptoms may occur.

## Cleans your NOS3 gene, continued...

**Supplements and Medications:**

- Consider appropriate amounts of B2, B3, probiotics, melatonin, vitamin C, flavonoids, artichoke leaf extracts and artichoke flavonoids, resveratrol, PQQ (pyrroloquinoline quinone), liposomal glutathione, S-acetyl glutathione, arginine, citrulline, aspirin.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and iif there are other indications for its use.

# THE DHFR GENE

The DHFR (dihydrofolate reductase) is involved in the salvage route regenerating dihydrobiopterin ($BH_2$) back to the active tetrahydrobiopterin ($BH_4$) form.

$BH_4$ is required for neurotransmitter synthesis and nitric oxide production. If DHFR is busy processing synthetic folic acid, $BH_4$ levels may drop and oxidized $BH_2$ may increase thereby decreasing neurotransmitter and nitric oxide production.

It is very important to keep synthetic folic acid out of one's diet so that the DHFR enzyme can effectively regenerate the very important $BH_4$ cofactor.

## Dirties your DHFR gene

**Environment:** Avoid smoke from any source such as incense, woodsmoke, air pollution, vehicle exhaust, cooking without an extractor hood especially with low smoke point oils.

**Lifestyle:** Smoking and abnormal blood sugars are especially serious for this gene and should be addressed as a first priority.

**Food:** Foods or beverages enriched with synthetic folic acid

**Supplements and Medications:** Avoid synthetic folic acid, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin. Many medications interact with this enzyme. Consult your healthcare provider or pharmacist. EGCG from green tea, grapefruit seed extract and *Salvia multirrhiza* are known inhibitors as well so pulsing these may be prudent if using them.

## Cleans your DHFR gene

**Food:** Folate (B9), niacin (B3) rich, whole foods

**Supplements and Medications:**

- Optimize niacin (B3), methylfolate or folinic acid (B9), vitamin C.
- Postmenopausal women only: Discuss with your healthcare provider the prescription use of bioidentical estrogens (and progesterone if intact uterus), if you are under 55 and within 4 years of the onset of menopause, and if there are other indications for its use.

## Notable variation:

SNP: **DHFR 19bp Del/Ins rs70991108 (-/-, II)**

The effect of this II variant (aka insertion/insertion) on enzyme function from in-vitro experiments is conflicting. All DHFR genes are slow at processing synthetic folic acid in amounts > 250 mcg in humans regardless of variants. It is included here for investigational purposes in anticipation of future research that can better characterize its impact.

# Advanced Tables

## Histamine

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| HRH1 | rs901865 | CC | | T | -17T>C | -/- |
| HRH4 | rs11665084 | CC | | T | 413C>T | -/- |
| HRH4 | rs11662595 | AA | | G | 249A>G | -/- |
| DAO/ AOC1 | rs2052129 | GT | | T | -691G>T | +/- |
| DAO/ AOC1 | rs10156191 | CT | | T | 47C>T | +/- |
| HNMT | rs11558538 | CC | | T | C314T | -/- |
| MAOA | rs6323 | T | | G | T941G | -/- |
| MAOA | rs1137070 | C | | T | 1410T>C | -/- |
| MAOB | rs1799836 | C | | C | -36A>G | +/+* |
| MAOB | rs2311013 | T | | A | 1155T>A | -/- |
| MAOB | rs5905512 | G | | A | 15106T>C | -/- |
| ALDH1B1 | rs2228093 | CC | | T | ALDH1B1*2 | -/- |
| ALDH2 | rs671 | GG | | A | ALDH2*2 | -/- |
| ALDH2 | rs737280 | TC | | C | 699T>C | +/- |

• **A NAT2 Intermediate Haplotype Found**

-/- variant allele not present; +/- heterozygous genotype; +/+ homozygous genotype; +/+* hemizygous genotype (male X); = much slower; = slower; = intermediate speed; = faster; = much faster; = ambiguous; = unknown

## Dopamine

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| TH | rs2070762 | AA | | G | 127T>C | -/- |
| TH | rs10770140 | CT | | C | A-581G | +/- |
| TH | rs10770141 | AG | | A | C-824T | +/- |
| TH | rs10840491 | GG | | A | -1374C>T | -/- |
| MAOA | rs6323 | T | | G | T941G | -/- |
| MAOA | rs1137070 | C | | T | 1410T>C | -/- |
| MAOB | rs1799836 | C | | C | -36A>G | +/+* |
| MAOB | rs2311013 | T | | A | 1155T>A | -/- |
| MAOB | rs5905512 | G | | A | 15106T>C | -/- |
| ALDH2 | rs671 | GG | | A | ALDH2*2 | -/- |
| ALDH2 | rs737280 | TC | | C | 699T>C | +/- |
| SLC18A1 | rs1390938 | AA | | A | C407T | +/+ |
| DRD2 | rs1800497 | GG | | A | Taq1A | -/- |
| DRD2 | rs2283265 | CC | | A | g.113414814C>A | -/- |
| DRD2 | rs12364283 | AA | | G | -1189T>C | -/- |
| DRD2 | rs1076560 | CC | | A | -83G>T | -/- |
| SLC6A3 | rs6347 | TC | | T | 1215A>G | +/- |
| DBH | rs1611115 | TC | | T | -1021C>T | +/- |
| SLC6A2 | rs28386840 | AA | | T | A-3081T | -/- |
| SLC6A2 | rs2242446 | TT | | C | -182T>C | -/- |
| SLC6A2 | rs5569 | GG | | A | G1287A | -/- |
| ADRB1 | rs1801253 | CC | | G | 1165G>C | -/- |
| ADRB2 | rs1042713 | GG | | A | 5285A>G | -/- |
| ADRB2 | rs1800888 | CC | | T | 491C>T | -/- |
| ADRB2 | rs1042714 | GC | | G | 79C>G | +/- |
| ADRB3 | rs4994 | AA | | G | 190T>C | -/- |

• **A Slow COMT Haplotype Found**

# Advanced Tables

## Serotonin

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| IDO2 | rs10109853 | TT | much slower | T | R248W | +/+ |
| IDO2 | rs4503083 | TT | | A | T1077A | -/- |
| TPH1 | rs1799913 | GG | | T | A779C | -/- |
| TPH1 | rs1800532 | GG | | T | A218C | -/- |
| TPH2 | rs11178997 | TT | | A | T-473A | -/- |
| TPH2 | rs4570625 | GG | slower | T | G-703T | -/- |
| SLC18A1 | rs1390938 | AA | much faster | A | C407T | +/+ |
| HTR2A | rs6311 | CC | slower | T | G-1438A | -/- |
| HTR2C | rs6318 | G | | C | G68C | -/- |
| HTR2C | rs3813929 | C | | T | C759T | -/- |
| HTR3A | rs1062613 | CC | slower | T | C178T | -/- |
| HTR3B | rs1176744 | AC | unknown | C | A386C | +/- |
| MAOA | rs6323 | T | slower | G | T941G | -/- |
| MAOA | rs1137070 | C | | T | 1410T>C | -/- |
| MAOB | rs1799836 | C | faster | C | -36A>G | +/+* |
| MAOB | rs2311013 | T | | A | 1155T>A | -/- |
| MAOB | rs5905512 | G | | A | 15106T>C | -/- |
| ADH1B | rs1229984 | CC | | T | ADH1B*2 | -/- |
| ADH1B | rs2066702 | GG | | A | ADH1B*3 | -/- |
| ALDH2 | rs671 | GG | | A | ALDH2*2 | -/- |
| ALDH2 | rs737280 | TC | slower | C | 699T>C | +/- |
| ASMT | rs4446909 | GG | slower | A | -310G>A | -/- |
| ASMT | rs5989681 | GG | | C | -201G>C | -/- |
| MTNR1B | rs10830963 | CC | | G | 10922C>G | -/- |
| CYP1A2 | rs762551 | AA | ambiguous | C | -163C>A | -/- |
| CYP1B1 | rs1800440 | TC | slower | C | CYP1B1*4 | +/- |
| SULT1A1 | rs1042028 | NA | | T | SULT1A1*2 | NA |

- **Indeterminate CYP1B1 Haplotype**
- **A UGT1A6 UGT1A6*1 Haplotype Found**

## Folate

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| SLC19A1 | rs1051266 | CC | | T | G80A | -/- |
| DHFR | rs70991108 | II | unknown | D | 19bp Del/Ins | -/- |
| MTHFD1 | rs2236225 | GA | slower | A | G1958A | +/- |
| MTHFD1 | rs1076991 | TC | slower | T | T105C | +/- |
| MTHFR | rs1801133 | GA | slower | A | C677T | +/- |
| MTHFR | rs1801131 | TT | | G | A1298C | -/- |
| FTCD | rs61735836 | CC | | T | C301T | -/- |
| SHMT1 | rs1979277 | GG | | A | C1420T | -/- |
| TYMS | rs779037237 | NA | | D | Ins/Del | NA |

-/- variant allele not present; +/- heterozygous genotype; +/+ homozygous genotype; +/+* hemizygous genotype (male X); much slower; slower; intermediate speed; faster; much faster; ambiguous; unknown

# Advanced Tables

## SAM

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| MTR | rs3768142 | GT | | G | 1710G>T | +/- |
| MTR | rs28372871 | GT | | G | -186G>T | +/- |
| MTR | rs1805087 | AA | | G | A2756G | -/- |
| MTRR | rs1532268 | CC | | T | C524T | -/- |
| MTRR | rs1801394 | AA | | G | G66A | -/- |
| TCN1 | rs34324219 | CC | | A | 901G>T | -/- |
| TCN2 | rs526934 | AA | | G | | -/- |
| TCN2 | rs9606756 | AA | | G | 67A>G | -/- |
| MAT1A | rs72558181 | CC | | T | 791G>A | -/- |
| PEMT | rs7946 | TT | | T | G5465A | +/+ |
| PEMT | rs3760188 | CC | | T | 29420C>T | -/- |
| CHDH | rs12676 | - | | A | G233T | NC |
| CHDH | rs9001 | TT | | G | A119C | -/- |
| ALDH7A1 | rs13182402 | AG | | G | 395T>C | +/- |
| BHMT | rs3733890 | AA | | A | 716G>A | +/+ |
| DMGDH | rs121908331 | TT | | C | 326A>G | -/- |
| ADA | rs73598374 | CT | | T | G22A | +/- |
| ADORA2A | rs5751876 | TC | | T | C1976T | +/- |
| ADORA2A | rs2236624 | TC | | T | | +/- |
| ADORA2A | rs35060421 | NA | | I | Del/Ins | NA |
| PON1 | rs662 | TC | | T | 575A>G | +/- |
| PON1 | rs854560 | AT | | T | L55M | +/- |
| PON2 | rs7493 | GG | | C | 896C>G | -/- |

-/- variant allele not present; +/- heterozygous genotype; +/+ homozygous genotype; +/+* hemizygous genotype (male X); = much slower; = slower; = intermediate speed; = faster; = much faster; = ambiguous; = unknown

## Glutathione

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| CBS | rs121964962 | CC | | T | 919G>A | -/- |
| CBS | rs121964970 | CC | | T | V168M | -/- |
| CBS | rs121964972 | GG | | A | T353M | -/- |
| CBS | rs121964973 | GG | | A | T191M | -/- |
| CBS | rs398123151 | GG | | A | R336C | -/- |
| CBS | rs28934891 | CC | | T | D444N | -/- |
| CBS | rs4920037 | GA | | A | | +/- |
| CBS | rs5742905 | AA | | G | T833C | -/- |
| CBS | rs234706 | GA | | A | C699T | +/- |
| CTH | rs28941785 | CC | | T | 200C>T | -/- |
| CTH | rs28941786 | CC | | G | 718C>G | -/- |
| GCLC | rs17883901 | GG | | A | C-129T | -/- |
| GCLM | rs41303970 | GG | | A | -588C>T | -/- |
| GSR | rs1002149 | GG | | T | -386C>A | -/- |
| G6PD | rs1050829 | T | | C | A376G | -/- |
| G6PD | rs5030868 | G | | A | C563T | -/- |
| GSTA1 | rs3957357 | GG | | A | C-69T | -/- |
| GSTO1 | rs11509438 | GG | | A | -2200G>A | -/- |
| GSTO1 | rs4925 | CC | | A | C419A | -/- |
| GSTO2 | rs156697 | AA | | A | A424G | +/+ |
| GSTP1 | rs1695 | AA | | G | GSTP1*B | -/- |
| GSTP1 | rs1138272 | CC | | T | A114V | -/- |
| NOX | rs9932581 | CC | | T | -930G>A | -/- |
| SOD2 | rs4880 | AG | | A | A16V | +/- |
| SOD3 | rs1799895 | CC | | G | R213G | -/- |
| GPX1 | rs1050450 | GA | | A | P198L | +/- |
| GPX1 | rs1800668 | GA | | A | -46C>T | +/- |
| GPX4 | rs713041 | - | | T | C718T | NC |
| CAT | rs769217 | CC | | T | 1167C>T | -/- |
| CAT | rs1001179 | CT | | T | -262C>T | +/- |
| MPO | rs2243828 | AA | | G | 2036A>G | -/- |
| GGT1 | rs4820599 | AG | | G | -1207T>C | +/- |

## Biopterin

| Gene | SNP rsID | Call | Impact | Variant Allele | Alias | Result |
|---|---|---|---|---|---|---|
| GCH1 | rs841 | GG | | A | C243T | -/- |
| NOS3 | rs1800779 | GA | | G | A-922G | +/- |
| NOS3 | rs3918226 | CC | | T | C-716T | -/- |
| NOS3 | rs1799983 | TG | | T | G894T | +/- |
| NOS3 | rs1800783 | AT | | A | T-1495A | +/- |
| NOS3 | rs2070744 | CT | | C | T786C | +/- |
| DHFR | rs70991108 | II | | D | 19bp Del/Ins | -/- |

-/- variant allele not present; +/- heterozygous genotype; +/+ homozygous genotype; +/+* hemizygous genotype (male X);
= much slower; = slower; = intermediate speed;
= faster; = much faster; = ambiguous; = unknown