



methylationIQ

Welcome to the future of health and human potential

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SAMPLE REPORT



Recommendations in this report apply to all ages, however for any patient under 18 years, a guardian must purchase the test and be present for the report recommendations. The information in this report is not intended to treat, diagnose or cure any medical condition or disease.

This test is used for clinical purposes. It should not be regarded as investigational or for research. Only the genomic regions listed below were tested; there is a possibility that the tested individual is a carrier for additional, undetected mutations. Although molecular tests are highly accurate, rare diagnostic errors may occur that interfere with analysis. Sources of these errors include sample mix-up, trace contamination, and other technical errors. The presence of additional variants nearby may interfere with mutation detection. Genetic counseling is recommended to properly review and explain these results to the tested individual.

SAMPLE REPORT



METHYLATION

SAMPLE REPORT

Methylation

MTHFR 677

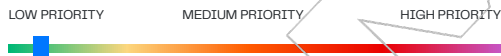


The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase, which converts folate into the active form, methylfolate. Variants in this gene affect enzymatic function.

- You have the heterozygous MTHFR 677 genotype that is associated with a reduced enzymatic function of approximately 30%
- You have an increased need for riboflavin and methylfolate for normal homocysteine levels
- Tetrahydrobiopterin (BH4) structurally resembles folate and has been described to be reduced in endothelial cells when increased levels of homocysteine are present
- Low levels of BH4 are associated with low levels of serotonin, dopamine, melatonin, norepinephrine, epinephrine and a reduced detoxification of ammonia
- Coenzyme Q10 production requires B1, B2, B3, B5, B6, B12, folate and BH4 in the Krebs Cycle
- Folate is depleted by excess sun exposure – especially in light-skinned individuals – making certain times of the year more important for higher levels of folate
- Proton pump inhibitors, oral contraceptives, NSAIDs, anticonvulsants, antivirals, antibiotics, acid blockers/antacids, and hypothyroidism may negatively affect MTHFR gene function

Methylation

MTHFR 1298



MTHFR 1298 converts 5-methylfolate (5-MTHF) to tetrahydrofolate (THF). Unlike MTHFR 677, the 1298 variant does not lead to elevated homocysteine levels unless paired with a heterozygous MTHFR 677.

- You have the wild-type MTHFR 1298 genotype
- Your genotype is not associated with elevated homocysteine levels

Methylation

MTHFD1

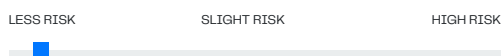


Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1) encodes a protein that possesses three distinct enzymatic activities in the interconversion of 1-carbon derivatives of tetrahydrofolate. Variants are associated with reduced enzymatic function.

- You have the heterozygous MTHFD1 genotype associated with reduced enzymatic function
- The heterozygous genotype is associated with an increased need for folic acid, especially in pregnant women

Methylation

Synthetic Folic Acid



Variants in MTHFR and DHFR can affect the metabolism of synthetic folic acid, leading to high circulating levels.

- Your genotype combinations may improve the metabolism of synthetic folic acid
- Research has found that those with the highest folic acid intake display a significantly greater incidence of lymphocyte genomic damage, a decrease in global DNA methylation, and reduced gene expression of select DNA repair and one carbon cycle genes

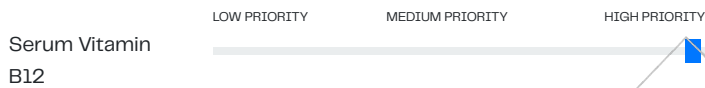
Methylation



Methyl donors include methionine, betaine, folate, B12, and choline. Approximately 60% of dietary methyl groups are from choline. These all contribute to the primary methyl donor for DNA methylation, S-adenosylmethionine (SAME). Choline and betaine play a crucial role in homocysteine metabolism, especially for those with variants in MTHFR.

- Your genotype combination is associated with a higher than average requirement for choline and betaine to maintain healthy methylation and homocysteine levels
- Low choline intake can manifest as memory issues, NAFLD, anxiety, neurological disorders, breast cancer, histamine issues, gallbladder issues, and SIBO
- Nighttime pain relievers, antihistamines, sleep aids, antidepressants, incontinence drugs, and narcotic pain relievers may deplete choline
- Intense endurance exercise depletes choline levels, and increasing phosphatidylcholine has been found to improve exercise capacity during high-intensity cycling and running, as well as reduce muscle soreness

Methylation



The FUT2 gene rs601338 has been shown to be a potential functional variant associated with vitamin B12 status and a major FUT2 secretor-defining SNP in European, African, and Indian populations.

- You have the wild-type FUT2 genotype, associated with lower serum B12 levels
- Low vitamin B12 can be the result of low vitamin B12 intake from a vegan or vegetarian diet, medications that deplete B12, low stomach acid and intrinsic factor, or bowel surgery that affects B12 absorption
- High levels of folate without sufficient B12 exacerbate the effects of vitamin B12 deficiency
- Low B12 levels and an increased risk of H. pylori have been associated with the FUT2 wild-type genotype
- Testing B12 is recommended

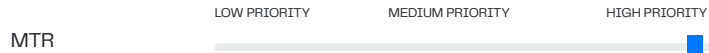
Methylation



Transcobalamin II (TCN2, or holotranscobalamin when bound) transports B12 to peripheral tissues. Approximately 20–25% of circulating cobalamin binds to TCN2, which is active vitamin B-12. Variants in the TCN2 gene are associated with reduced vitamin B12 transport into cells.

- You have the homozygous TCN2 genotype
- In those of European descent, this genotype is associated with significantly lower concentrations of holotranscobalamin and higher concentrations of homocysteine than subjects with the wild-type genotype
- In those of Chinese descent, the CG and GG genotypes were higher in patients with mild, moderate, and severe ulcerative colitis compared with those with remission ulcerative colitis
- You may be more sensitive to low levels of dietary lithium to assist B12 transport
- High B12 supplementation depletes lithium levels, and dosing lithium supplementation should be done with caution due to its suppressing effect on the thyroid hormones

Methylation



Methionine synthase (MTR) codes for the enzyme that converts homocysteine to methionine. Methionine is an essential amino acid necessary for protein synthesis and the production of S-adenosylmethionine (SAMe). Vitamin B12 deficiency inhibits methionine synthase. The result is reduced methionine synthesis, with subsequent lowering of the SAMe concentration.

- You have the wild-type MTR genotype that is associated with a slight increase in homocysteine levels and is more pronounced with low B12 and zinc status
- Studies suggest that alcohol, mercury, and nitrous oxide may reduce or inhibit methionine synthase, consequently impacting methylation reactions
- Vitamin B12 in the form of methylcobalamin and zinc are required for optimal MTR activity and methionine production
- When MTR and MTR are inhibited, the compensation pathway is BHMT (betaine-homocysteine methyltransferase), increasing betaine and choline requirements

Methylation



The MTRR gene is required for converting the inactive form of methionine synthase (MTR) to its active form. MTRR helps recycle B12. If MTR is optimally functioning, MTRR variants may be less pronounced. The combination of the wild-type MTR genotype and homozygous MTRR genotype may lead to issues with B12.

- Your MTRR genotype is associated with improved gene function, assisting B12 and homocysteine metabolism

Methylation

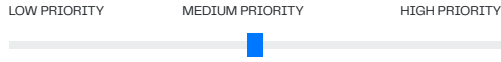


Vitamin B6 plays a vital role in homocysteine metabolism and CBS gene function. The NBPF3 gene is associated with serum vitamin B6 levels.

- You have the homozygous genotype for NBPF3 that is associated with a higher than average requirement for B6 to maintain healthy methylation and homocysteine levels
- Many medications deplete B6, including antibiotics, oral contraceptives, ACE inhibitors, antacids, and proton pump inhibitors

Methylation

CBS and Homocysteine

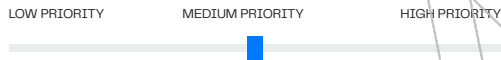


The Cystathionine Beta-Synthase (CBS) enzyme pulls homocysteine to hydrogen sulfide (H₂S) and glutathione, requiring B6 and SAMe as a modulator. Research has hypothesized that rs2851391 variants might reduce the activity of CBS, increase homocysteine levels, and marginally decrease plasma B12 levels.

- You have the heterozygous genotype for the CBS rs2851391 gene
- Deficiencies in CBS activity are the most frequent cause of familial high homocysteine and the underlying cause of the CBS genetic disorder homocystinuria, which is characterized by severe high homocysteine levels
- High homocysteine leads to high SAH and low SAMe, which inhibits AHCY and results in the diminished secretion of a selenium transporter
- Elimination of selenium requires SAMe, which is a cofactor for CBS like B6
- Depleted levels of SAMe have been implicated in many of the disorders that can be beneficially affected by intakes of boron greater than or equal to 3 mg/d, including arthritis, osteoporosis, cancer, diabetes, and impaired brain function
- Ensuring healthy homocysteine, SAMe, and B6 levels mitigate the risk of selenium building up while assisting arsenic detoxification

Methylation

CBS and Arsenic Metabolism



The Cystathionine Beta-Synthase (CBS) enzyme pulls homocysteine to hydrogen sulfide (H₂S) and glutathione, requiring B6 and SAMe as a modulator. CBS rs234709 and rs4920037 assists in arsenic detoxification.

- Your CBS genotype combination is associated with a reduced detoxification of arsenic
- The highest dietary sources of inorganic arsenic include contaminated groundwater and rice
- High arsenic levels may deplete SAMe
- A consistent and growing body of evidence has shown that people who metabolize arsenic poorly may be at two to four times the risk of developing certain cancers and other arsenic-related diseases than people who are better metabolizers
- Selenium can also be problematic in higher doses for those with elevated homocysteine due to a reduced conversion of selenomethionine to selenohomocysteine, selenocystathionine and selenocysteine
- Chlorogenic acid – a polyphenol highest in light roast coffee – has been found to inhibit arsenic-induced neurotoxicity in mice
- Chlorogenic acid is also found in moringa tea, strawberries, cherries, bilberries, and wild blueberries

Methylation

COMT



Catechol-O-methyltransferase (COMT) is a magnesium and SAMe-dependent, catecholamine-metabolizing enzyme, including dopamine, epinephrine, estrogen, and dietary catecholamines. Approximately 95% of SAMe is used in methylation reactions that influence the activity of DNA, RNA, proteins, phospholipids, hormones, and neurotransmitters.

- You have the wild-type COMT genotype that is associated with faster enzymatic activity and requires an average magnesium intake

Methylation

AHGY



The AHGY gene provides instructions for producing the enzyme S-adenosylhomocysteine hydrolase. S-adenosylhomocysteine hydrolase converts S-adenosylhomocysteine to adenosine and homocysteine. There is limited evidence showing variants in AHGY reduce enzymatic function, but the effects on the methylation cycle and overall health are currently unknown.

- You have the wild-type genotype for AHGY
- High homocysteine leads to high SAH and low SAME, which inhibits AHGY
- Normalizing homocysteine levels ensures optimal AHGY gene function

SAMPLE REPORT

The Methylation panel is designed with genetic variants associated with determining optimal requirements of micronutrients such as folate, choline, betaine, B2, B6, B12, and magnesium, which contribute to DNA methylation as methyl donors, co-factors, and regulators of homocysteine.

Dietary nutrient intake and bioactive food components are essential environmental factors that may influence DNA methylation by directly inhibiting enzymes that catalyze DNA methylation or by changing the availability of substrates required for those enzymatic reactions, such as the availability and utilization of methyl groups.

Nutrigenomic research has discovered that humans have higher and lower micronutrient requirements based on environmental adaptations. The most common example is the MTHFR 677 gene and folate requirements. Variants in MTHFR are more common closer to the equator, while the wild-type genotype is more common in northern latitudes. Evidence suggests that genetic variants do not show dysfunction but changes in enzymatic activity based on latitude, environmental pressures, and dietary intake over thousands of years.

Approximately 95% of SAME is used in methylation reactions that influence the activity of DNA, RNA, proteins, phospholipids, hormones, and neurotransmitters. ATP is highly dependent on magnesium, and SAME is made from ATP and methionine. Choline accounts for 60% of methyl donors and DNA methylation patterns change as we age. It has been proposed that folate, choline, betaine, B6, B12, and methionine are critical factors in delaying the progressive deterioration of DNA methylation patterns and diseases associated with aging.

Methylation Panel Modules and SNPs

Modules

- MTHFR 677
- MTHFR 1298
- MTHFD1
- Synthetic Folic Acid
- PEMT
- Serum Vitamin B12
- TCN2
- MTR
- MTRR
- Serum Vitamin B6
- CBS and Homocysteine
- CBS and Arsenic Metabolism

- COMT
- AHCY

SNP List

- MTHFR 677
- MTHFR 1298
- COMT
- MTRR
- MTR
- PEMT
- DHFR
- MTHFD1
- FUT2
- NBPF3
- CBS
- TCN2
- AHCY

Gene Highlight: MTHFR 677

The MTHFR gene stands for methylenetetrahydrofolate reductase. The MTHFR 677 gene produces the MTHFR enzyme, which converts methyl folate to 5-MTHF and helps regulate homocysteine levels.

The reduced enzymatic function of the heterozygous MTHFR 677 is estimated at 30%, and the homozygous MTHFR 677 genotype at 50–70%.

We are discovering that personalized medicine is becoming dependent on understanding how certain genotypes respond or do not respond to specific therapies.

Many interpretations of the MTHFR gene center around the fearful consequences of variants. Yet, less is said about how common variants are in this gene and why they were selected.

The highest cluster of the homozygous MTHFR 677 genotype is found in Mexico and Hispanics in the US, Italy, Northern China, Spain, and France. The lowest frequency is found in black people (within and outside Africa), Inuit, Finland, Canada, the Netherlands, Germany, and Russia.¹

One hypothesis is that the homozygous MTHFR genotype was selected based on higher folate intake and UV exposure, both common in Mediterranean climates. What happens in the body when MTHFR enzymatic function is reduced is that thymidine production increases. Thymidine enhances the repair of UV-induced DNA damage to help quickly repair sun damage.²

The sun also depletes folate due to UV radiation. However, darker skin—common in the Mediterranean—contains higher melanin levels, which helps protect against folate loss. Increased thymidine and darker skin protect against the hot sun of the Mediterranean. At the same time, the environment

provides more folate-rich fruits and vegetables year-round to supply more dietary folate for other biochemical functions.

In colder climates of northern Europe, we start to see fewer MTHFR variants. The wild-type becomes the dominant selection due to less UV radiation and lower plant-based folate availability. Along with lighter skin adaptation to northern latitudes for more efficient vitamin D synthesis, the wild-type MTHFR genotype would have been selected to require less folate intake and thymidine production for UV-induced DNA repair.

Another hypothesis is that malaria exposure – caused by a parasite through mosquito bites and prevalent in the Eastern Mediterranean and Southeast Asia – altered the MTHFR genotype selection.³

A study of mice infected with malaria was performed with three groups: wild-type MTHFR genotype, heterozygous genotype, and homozygous genotype. The MTHFR homozygous mice had higher T-lymphocytes and natural killer cells, showed protection against malaria, and lived longer than the wild-type.⁴

How is MTHFR connected to this? The malaria parasite needs higher amounts of folate to survive and replicate. Reduced MTHFR function lowered folate levels and boosted levels of thymidine, which may increase lymphocyte replication and immune function in response to malaria. Evolution naturally remedied a situation that antifolate drugs try to mimic. Therefore, in malaria-endemic regions, a homozygous MTHFR 677 genotype becomes advantageous.

Gene Highlight: PEMT

PEMT stands for phosphatidylethanolamine N-methyltransferase. This gene encodes an enzyme that converts phosphatidylethanolamine to phosphatidylcholine by methylation in the liver. Methyltransferases control the methylating capacity of the cell. Variants increase the need for dietary choline intake.

Choline is a water-soluble micronutrient that is similar to the B-vitamin family. It is unique because the body can produce varying amounts of choline depending on your genes.

Betaine is a methyl donor that can be obtained from the diet or formed inside the body through irreversible oxidation of choline. Betaine donates a methyl group to homocysteine, resulting in its conversion to methionine. Several studies reported inverse correlations between dietary choline or betaine intake, plasma levels, and homocysteine bioavailability in humans. The role of betaine in the methylation process becomes more crucial under conditions of folate deficiency, such as excessive alcohol consumption that impairs folate metabolism.⁵

Choline is a precursor to acetylcholine, a neurotransmitter of the vagus nerve that innervates multiple organs, including the lungs, heart, liver, stomach, and temporal lobe of the brain (memory). Lactobacillus probiotics in fermented foods and drinks also produce acetylcholine in the gut.

Choline is responsible for shuttling fat out of the liver, aiding the gallbladder and healthy cell membranes to protect against inflammation, lowering anxiety, and preventing damage from glutamate spikes and healthy DNA. Choline deficiency also increases sensitivity to carcinogenic chemicals.

Research shows that people in northern countries have the highest dietary intake of choline, whereas Mediterranean countries have the lowest intake.⁶ One hypothesis is that variants in PEMT reduced enzymatic function in northern climates in response to a higher choline intake.

Those having variants in the PEMT gene (rs7946) are associated with having lower phosphatidylcholine production in the liver, and 80% of the women who were homozygous and 43% of subjects who were heterozygous for the (rs12325817) PEMT gene manifested signs of choline depletion.

More than 40% of women have a genetic polymorphism in PEMT (rs12325817) that makes this gene unresponsive to estrogen (estrogen stimulates PEMT), and these women have the same high choline requirement as men.⁷

In a study looking at Europeans, African, Asian, and Mexican Americans, it was those with European ancestry that had a higher prevalence of four SNPs that increased the risk of organ dysfunction when consuming a low-choline diet.⁸

Homocysteine

Homocysteine is an amino acid found in the blood. Elevated homocysteine has been correlated with inflammation, high blood pressure (in certain populations), heart disease, blood clots, depression, macular degeneration, dementia, and cancer.

Homocysteine regulation depends on the enzymatic function of genes and the required cofactors of all the methylation SNPs in this panel. To achieve optimal results, the dietary and supplement protocol can be customized to understand each individual's varying requirements.

Fertility

Numerous studies have found a potential link between MTHFR and infertility based on ethnicity. Due to variants in MTHFR increasing folate requirements, this is a foundational requirement for fertility.

In folate deficiency, both betaine and choline supplementation prevented DNA hypomethylation. In women, a higher folate intake was associated with higher ovarian reserve, higher rates of implantation, clinical pregnancy, and live births in those undergoing IVF treatment.⁹

SNPs in the choline metabolism pathway have been associated with infertility and reduced sperm motility.¹⁰

People with the homozygous NBPF3 gene have approximately a 2.90 ng/mL lower vitamin B6 blood concentration than people with the wild-type genotype. Vitamin B6 supports progesterone

production and sperm quality and helps produce cervical mucus, which helps move sperm to the egg and protects both the egg and sperm.

Women of reproductive age, especially current and former users of oral contraceptives, are most at risk of B6 deficiency. Data suggests that oral contraceptive users have extremely low plasma B6 levels. Three-quarters of the women who reported using oral contraceptives but not vitamin B6 supplements were vitamin B6 deficient.¹¹

Pregnancy

Folate is one of the most well-known nutrients during pregnancy for preventing spina bifida and a deficiency has widespread consequences in fetal development. The MTHFR 677 gene plays a prominent role in folate requirements during pregnancy.

Choline plays an important role in the liver, and gallbladder, vulnerability to toxins, preventing spinal cord and brain defects, and the future mental health of the child. Genetic polymorphisms in PEMT may alter the dietary requirement for choline and increase the likelihood of developing signs of deficiency (fatty liver, gallbladder issues during pregnancy) when choline intake is inadequate.

Results published in *The American Journal of Psychiatry* by Freedman's group show that 76 percent of newborns whose mothers received choline supplements had normal inhibition to the sound stimuli, while 43 percent of the newborns did not. Those who do not have a normal inhibition to the sound stimuli have been found to have an increased risk for attention problems, social withdrawal, and, later in life, schizophrenia.¹²

Low B6 is associated with gestational diabetes and "prenatal depression"—described as pessimism, crying, irritability, changes in sleep habits, nausea, or appetite disorders. Vitamin B6 plays a very important role in mental health, needed in the formation of histamine, serotonin, and dopamine.

All forms of vitamin B6, especially PLP, cross the placenta into the fetal blood where its concentrations are two to five times higher than those in maternal blood. The most substantial decrease in plasma PLP levels is found between the fourth and eighth months of pregnancy, paralleling the period of most intensive growth of the fetus.

Anxiety and Depression

MTHFR 677 may participate in the development of anxiety or depression through epigenetic DNA methylation modifications, metabolic disorders, and neurotransmitter disturbances, together with other genetic variants and environmental stressors. PEMT variants are also associated with mood, with one study finding that women with higher choline intake have the lowest anxiety.¹³

Studies have found that variants in MTHFR 677 are associated with an increased risk of anxiety and depression, including postmenopausal depression and depression related to childhood trauma.¹⁴ However, these associations may depend on race, with Asians having a higher risk of depression.¹⁵

Studies have found that MTHFR 677 polymorphism with high homocysteine levels was associated with decreased cortical thickness, subcortical gray matter, and white matter volume and density in patients with mental illness.¹⁶

A meta-analysis concluded that individuals with depression have lower serum levels of folate and dietary folate intake than individuals without depression. Supportive research has shown that folate supplementation improved the efficacy of traditional antidepressant medications and may prove beneficial for patients with depression.¹⁷

Cancer

B-vitamins may protect from developing cancer but play a detrimental role in patients diagnosed with cancer.¹⁸ Folate deficiency causes massive incorporation of uracil into human DNA and chromosome breaks leading to cancer and cognitive defects. However, many types of cancer have shown increased folate receptor expression levels compared with healthy tissues, where folate acts as a double-edged sword for cancer growth.

One of the main concerns is related to synthetic folic acid and cancer risk. Folic acid may interfere with the metabolism, cellular transport, and regulatory functions of the natural folates in the body by competing with the reduced forms for binding with enzymes, carrier proteins, and binding proteins.¹⁹

The folate receptor has a higher affinity for folic acid than methyl-THF—the primary form of folate in the blood. A meta-analysis found cancer incidences were higher in the folic acid-supplemented groups than in the non-folic acid-supplemented groups.²⁰ One study found that food folate intake was not significantly related to breast cancer risk, but total folate intake, mainly from folic acid supplementation, significantly increased breast cancer risk by 32%.²¹

folate cycle. Dihydrofolate reductase (DHFR), catalyzes both these reactions. Enzyme activity varies markedly between individuals with genetic mutations, and therefore, the plasma concentration of unmetabolized folic acid may differ according to their DHFR and MTHFR activity. High folic acid will also cause dihydrofolate to inhibit MTHFR, which may be even more impactful for those with variants in these SNPs.

The increased intake of vitamins B2, B6, and B12 has been shown in human studies to inversely correlate with the reduced risk of cancers such as esophageal cancer, cervical intraepithelial neoplasia, colorectal cancer, and prostate cancer.²²

In case-control studies, dietary choline intake is associated with a decreased risk of breast cancer, colorectal cancer, and liver cancer.²³

A meta-analysis of 11 epidemiological studies supported the protective role of dietary betaine and choline against several types of cancer, with the most considerable effect reported for breast cancer, followed by nasopharyngeal and lung cancers. In this meta-analysis, an increment in dietary betaine and choline of 100 mg/day reduced cancer incidence by 11%.²⁴

Discussion

The Methylation Panel has a foundational targeted application for inflammation, high blood pressure, fertility, heart disease, blood clots, depression, macular degeneration, dementia, and cancer.

Discovering genetic variants can help influence the course of prevention and synergistic treatment for numerous health disorders.

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