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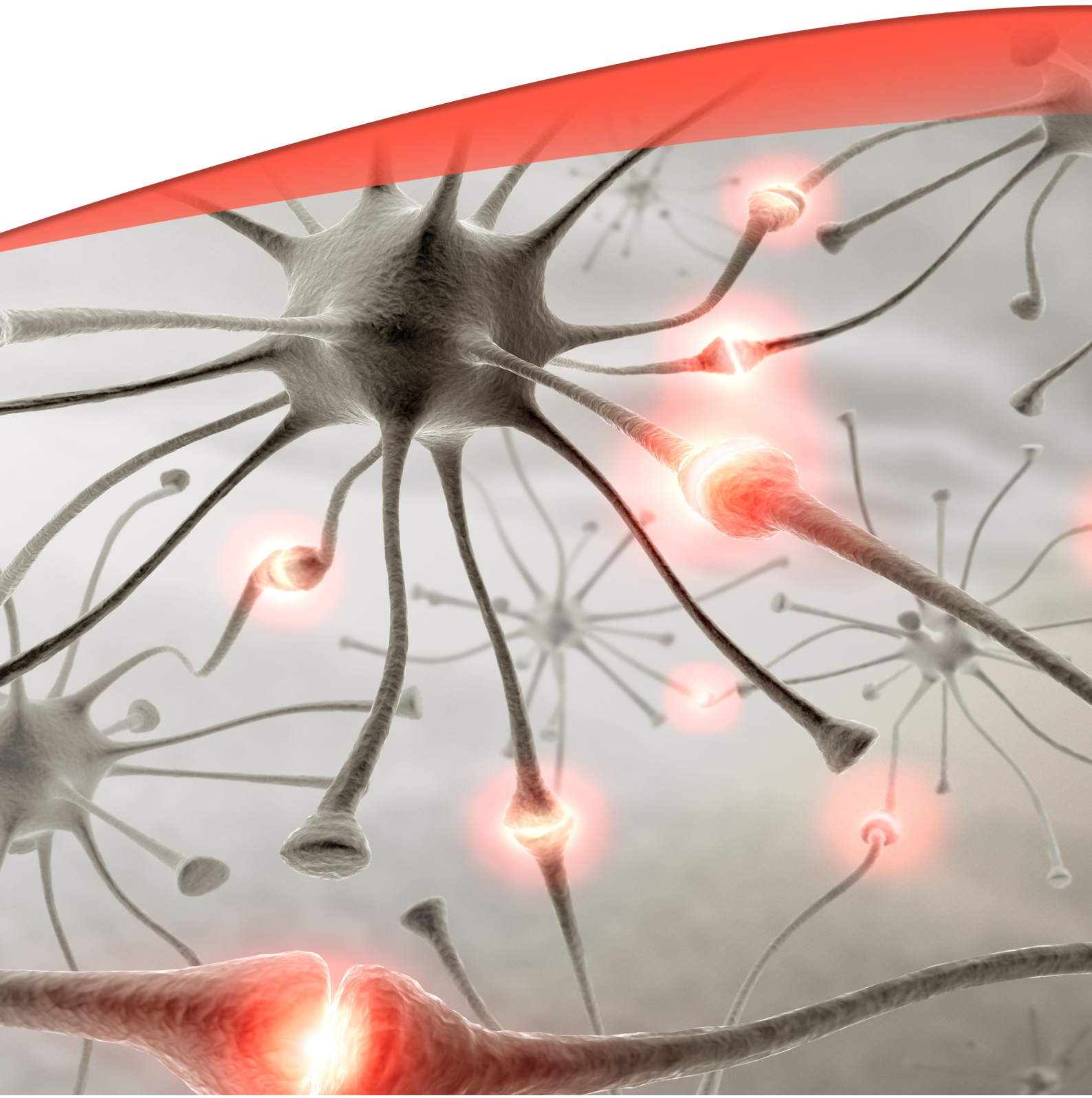
Nervous System Report



Report for Emma Beswick 2021 (CP00057322)

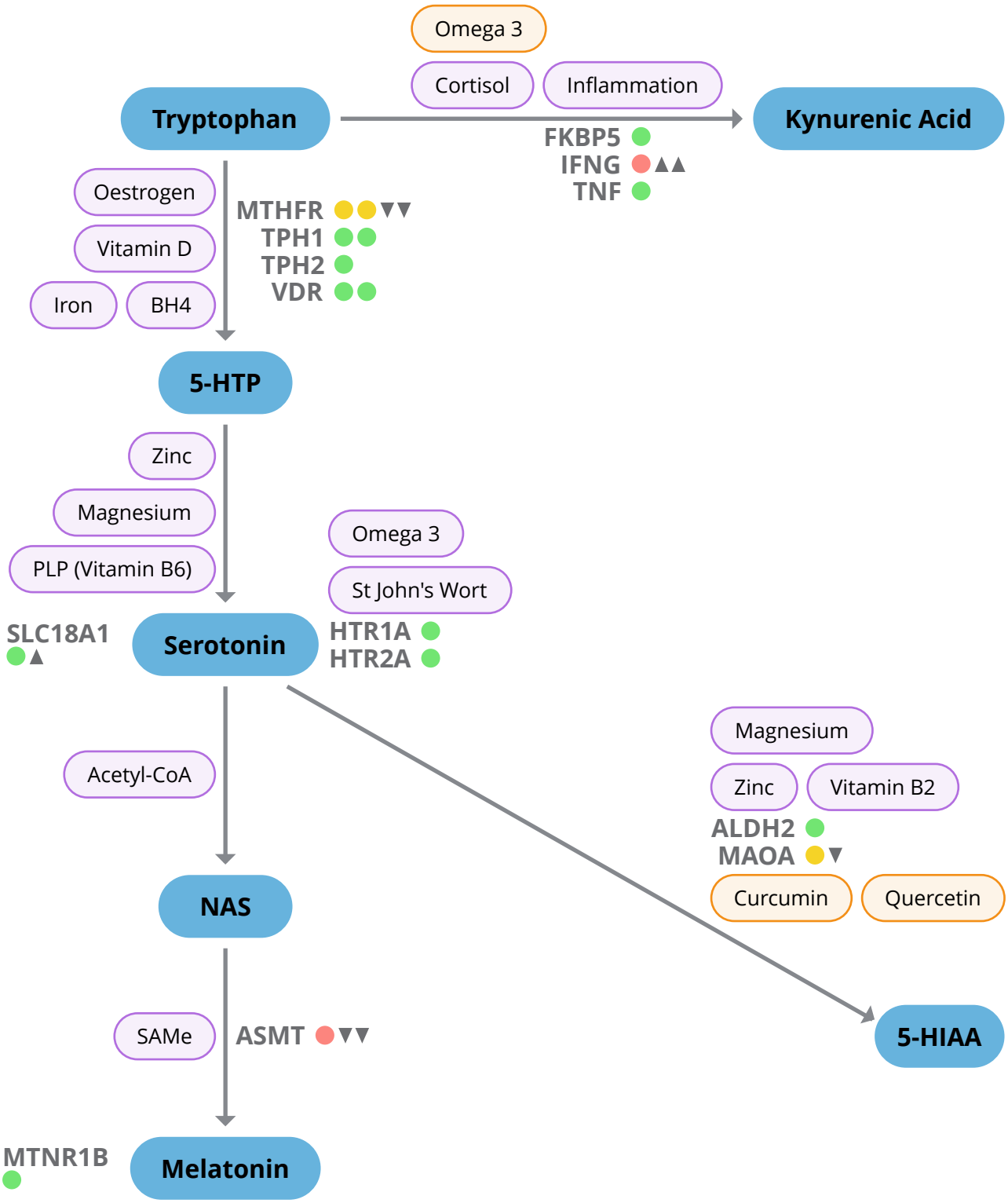
The nervous system is a complex system which enables the transmission of messages around the mind and body, enabling an individual to respond to their environment. The messages are communicated via neurons which are supported and nourished by glial cells. A neurotransmitter is a molecule that carries signals between neurons and across nerve junctions (synapses). In order for us to interact effectively with our environment, the excitatory and inhibitory neurotransmitters must remain in balance.

The main excitatory (stimulating) neurotransmitters are acetylcholine, adrenaline, dopamine, glutamate, histamine, noradrenaline, and phenethylamine (PEA), while the key inhibitory (calming) neurotransmitters are gamma amino butyric acid (GABA), serotonin and melatonin. Their lifecycle involves the synthesis, signalling, transport and metabolism.

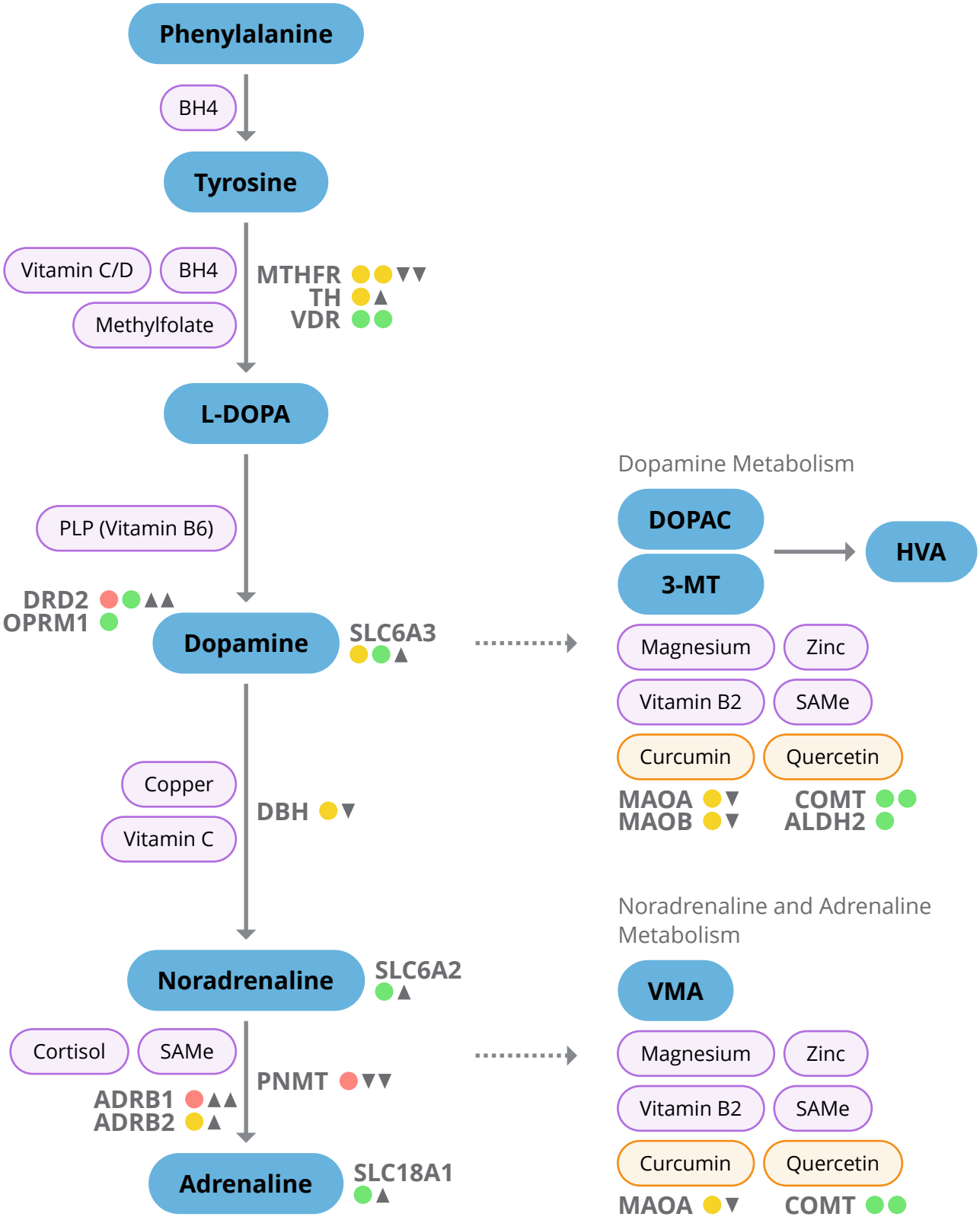
Neurotransmitter imbalances can have serious physical and mental health effects. Symptoms of neurotransmitter imbalance include: mood disorders and depression, attention deficit and obsessive compulsive disorders, addictive behaviours, motor control disruption, anger, aggression and restlessness.

This report examines the genes, nutrients, and lifestyle and environmental factors that can impact the nervous system. It provides personalised summary diagrams and detailed results followed by a generic nervous system guide.

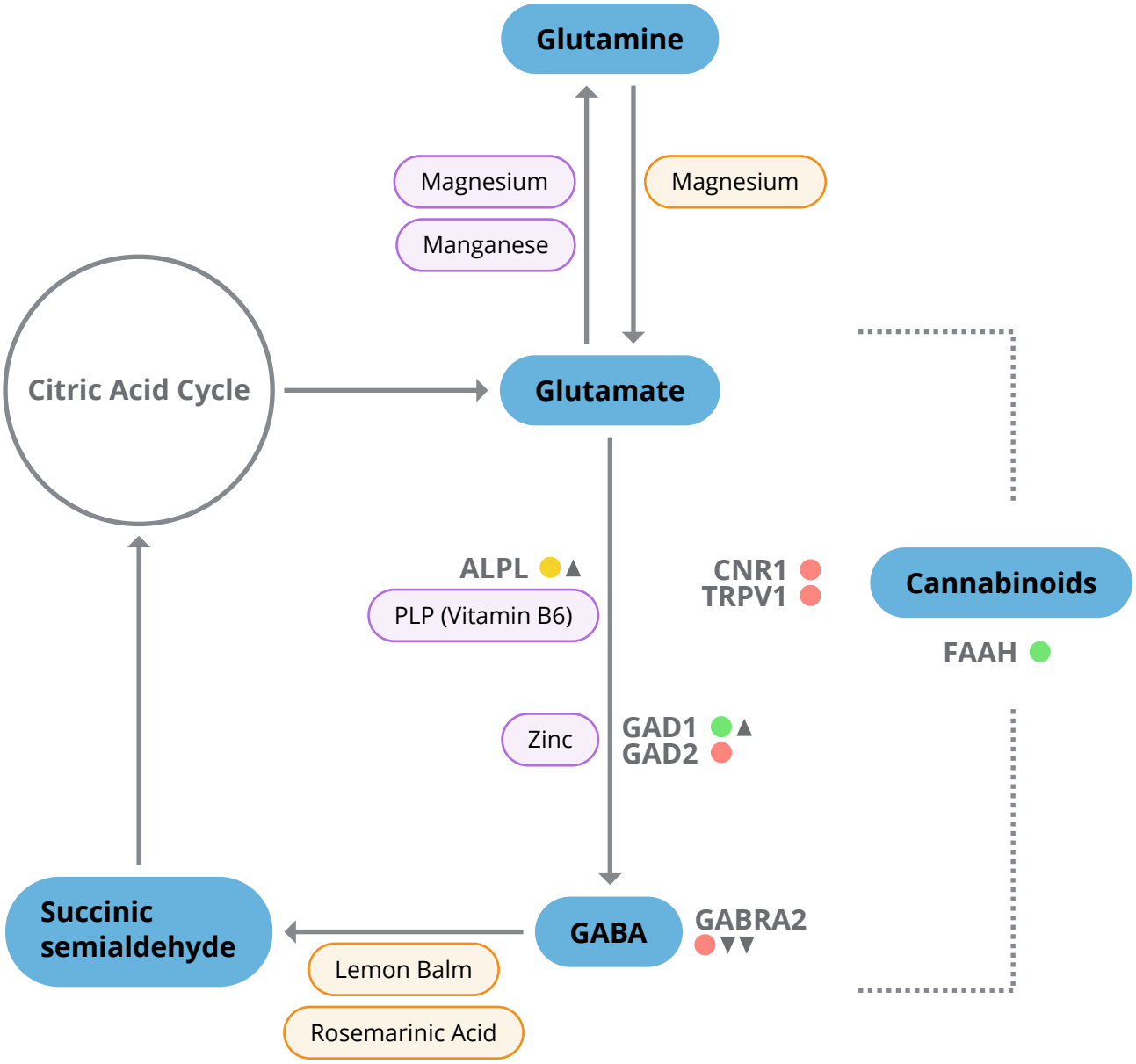
Serotonin and Melatonin Diagram



Dopamine and Adrenergic Diagram



GABA and Cannabinoids Diagram



Detailed Results for Kynurenic Acid

FKBP5 rs1360780	CC	No variance. Normal FKBP5 expression and cortisol regulation in response to stress. No negative impact on serotonin synthesis. Moderate exercise can help lower stress levels.
IFN-gamma rs2430561	TT ▲▲	The T allele is associated with increased IFNG expression which helps the host's defence against viral infection. However, over-expression of IFNG and stimulation of the kynurenine pathway can 'steal' the tryptophan needed for serotonin synthesis and result in lower serotonin levels. Follow an anti-inflammatory diet including omega 3 (found in oily fish) and brassica foods to inhibit the kynurenic pathway.
TNF rs1800629	GG	Normal TNF activity, and immune response. Not associated with excessive inflammation or kynurenine pathway disruption to serotonin synthesis.

Detailed Results for Serotonin

ALDH2 rs671	GG	Good ability to breakdown the metabolites of catecholamine neurotransmitters, including serotonin. Serotonin metabolism may also be affected by other genetic variants, particularly on the MAOA gene. Support this pathway by limiting alcohol consumption and increasing co-factors - vitamins B2 and B3, magnesium, molybdenum and zinc.
HTR1A rs6295	CC	No impact on HTR1A expression or release of serotonin. Normal sensitivity to serotonin, facilitating prosocial, antidepressant, anxiolytic and analgesic affects.
HTR2A rs6311	CC	No impact on the receptor expression. Normal sensitivity to serotonin. The C allele is associated with leadership and popularity.
MAOA rs6323	TG ▼	Lower MAOA activity and slower breakdown of monoamine neurotransmitters, which can contribute to higher levels. Curcumin and quercetin may reduce MAOA activity, whilst vitamin B2, magnesium and zinc may increase it.
MTHFR rs1801131	GT ▼	Reduced gene function which may result in lower methyl-folate and slower conversion of BH2 to BH4 - needed for neurotransmitter synthesis. Methylation can be supported by adequate consumption of folate containing foods (such as green leafy vegetables, citrus fruits, beans and liver) and cofactors - vitamins B2 and B3.
MTHFR rs1801133	AG ▼	Up to 40% reduction in gene function, enhanced by rs1801131, which may impact supply of methyl-folate needed for BH4, which is needed for serotonin synthesis. Associated with higher risk of depression. Methylation can be supported through a diet rich in folate and other B vitamins (B2, B3, B12) and co-factors including magnesium and zinc.
SLC18A1 rs1390938	GA ▲	The A allele is protective. It is associated with increased SLC18A1 transporter activity and therefore more serotonin release and effect. It has been associated with resilience to disorders such as affective anxiety, depressiveness, bipolar disorder and alcohol use.
TPH1 rs1799913	GG	Normal (good) serotonin synthesis. Ensure sufficient intake of tryptophan, found in turkey, chicken, bananas, avocados and many other foods, and cofactors - BH4 and iron.

Detailed Results for Serotonin (continued)

TPH1 rs1800532	GG	Normal (good) serotonin synthesis. Ensure sufficient intake of tryptophan, found in turkey, chicken, bananas, avocados and many other foods, and cofactors - BH4 and iron.
TPH2 rs4570625	GG	No impact on serotonin synthesis. Ensure sufficient intake of tryptophan (in turkey, chicken, bananas, avocados and many other foods), carbohydrate - to support transport across the blood brain barrier, and cofactors - BH4 and iron.
VDR rs1544410	CC	Good response to Vitamin D which will support serotonin synthesis. Support vitamin D status with regular exposure to sunlight and consumption of oily fish and other vitamin D sources.
VDR rs731236	AA	Good response to Vitamin D which will support serotonin synthesis. Support vitamin D status with regular exposure to sunlight and consumption of oily fish and other vitamin D sources.

Detailed Results for Melatonin

ASMT rs4446909	GG▼▼	The G allele reduces the expression of ASMT which negatively impacts the conversion of N-acetyl-serotonin (NAS) to melatonin. Low levels of melatonin are linked to sleep disruption and mood disorders. Support ASMT activity by ensuring sufficient SAMe, the master methyl donor. Low methylation status will further impact melatonin synthesis.
MTNR1B rs10830963	CC	Normal melatonin receptor activity. No impact on sleep patterns or blood sugar metabolism.

Detailed Results for Dopamine

ALDH2 rs671	GG	Good ability to breakdown the metabolites of catecholamine neurotransmitters - serotonin, dopamine, noradrenaline, adrenaline and histamine. Support this pathway by limiting alcohol consumption and increasing cofactors - vitamins B2 and B3, magnesium, molybdenum and zinc.
COMT rs4633	CC	Normal COMT activity (high) and efficient breakdown of dopamine. Whilst this is generally positive, it may contribute to low dopamine. To support dopamine levels, ensure good intake of dopamine substrates and cofactors, such as meats, fish, eggs, spinach, nuts and seeds.
COMT rs4680	GG	Normal COMT activity (high) and efficient breakdown of dopamine. Whilst this is generally positive, it may contribute to low dopamine. To support dopamine levels, ensure good intake of dopamine substrates and cofactors, such as meats, fish, eggs, spinach, nuts and seeds.
DRD2 rs1076560	CC	Normal DRD2 dopamine receptor activity. This genotype is associated with balanced dopamine levels and lower risk of opioid, cocaine and alcohol dependence. Ensure good intake of dietary protein and vitamins - PLP (B6), methyl-folate (B9) and methyl-cobalamin (B12) - sleep and regular exercise to support dopamine levels naturally.
DRD2 rs6277	GG▲▲	Higher DRD2 expression which inhibits dopamine when it is already low. Low dopamine is associated with reduced executive functioning, abnormal reward seeking and addictive behaviours. However, high levels of dopamine can also increase DRD2 activation. The GG genotype has been linked to schizophrenia due to its potential for phasic activity (high and low dopamine).
MAOA rs6323	TG ▼	Lower MAOA activity and slower breakdown of dopamine, which can contribute to higher levels. Curcumin and quercetin may reduce MAOA activity, whilst vitamin B2, magnesium and zinc may increase it.
MAOB rs1799836	CT ▼	Lower MAOB activity and slower metabolism of neurotransmitters, which can contribute to higher dopamine levels. If symptoms of high dopamine are present, vitamin B2, magnesium and zinc can help support MAOB activity.

Detailed Results for Dopamine (continued)

MTHFR rs1801131	GT ▼	Reduced gene function which may result in lower methyl-folate and slower conversion of BH2 to BH4 - needed for neurotransmitter synthesis. Methylation can be supported by adequate consumption of folate containing foods (such as green leafy vegetables, citrus fruits, beans and liver) and cofactors - vitamins B2 and B3.
MTHFR rs1801133	AG ▼	Up to 40% reduction in gene function, enhanced by rs1801131, which may impact supply of methyl-folate needed for BH4, which is needed for dopamine synthesis. Associated with higher risk of depression. Methylation can be supported through a diet rich in folate and other B vitamins (B2, B3, B12) and co-factors including magnesium and zinc.
OPRM1 rs1799971	AA	The A allele is associated with normal OPRM1 activity (high) and increased sensitivity to opioids, including morphine.
SLC6A3 rs27072	CC	Normal transporter activity (not decreased) and normal dopamine levels.
SLC6A3 rs6347	CT ▲	The C allele increases the SLC6A3 dopamine transporter expression, hence dopamine levels are lower since it is removed more quickly. This variant has been associated with increased risk of alcohol dependence. Regular exercise and a good sleep routine will help support dopamine levels naturally.
TH rs10770141	GA ▲	The A allele is associated with higher activity, faster synthesis and higher levels of dopamine and noradrenaline. This may be positive or negative depending on the context. Increased risk of hypertension (high blood pressure) in response to stress; however dopamine and noradrenaline support cognitive functioning so can reduce the risk of developing neurodegenerative conditions such as Alzheimer's and Parkinson's disease. Vitamin C is a cofactor of this reaction.
VDR rs1544410	CC	Good response to Vitamin D which will support normal (to high) dopamine levels. Support vitamin D status with regular exposure to sunlight and consumption of oily fish and other vitamin D sources.
VDR rs731236	AA	Good response to Vitamin D which will support normal (to high) dopamine levels. Support vitamin D status with regular exposure to sunlight and consumption of oily fish and other vitamin D sources.

Detailed Results for Noradrenaline

COMT rs4633	CC	Normal COMT activity (high) and efficient breakdown of adrenaline and noradrenaline. Ensure sufficient intake of B vitamins, zinc and magnesium to provide methyl groups to support COMT activity.
COMT rs4680	GG	Normal COMT activity (high) and efficient breakdown of adrenaline and noradrenaline. Ensure sufficient intake of B vitamins, zinc and magnesium to provide methyl groups to support COMT activity.
DBH rs1611115	CT ▼	Decreased noradrenaline levels. The variant T allele reduces DBH gene expression, leading to reduced noradrenaline levels. To support this pathway, ensure adequate levels of the co-factors copper and vitamin C.
MAOA rs6323	TG ▼	Lower MAOA activity and slower breakdown of adrenaline and noradrenaline, which can contribute to higher levels. Curcumin and quercetin may reduce MAOA activity, whilst vitamin B2, magnesium and zinc may increase it.
SLC6A2 rs5569	AG ▲	No impact on the transport or removal of noradrenaline (not up-regulated) or negative impact on noradrenaline levels. Although the G allele is linked to increased transporter activity, it is overridden by the dominant A allele.

Detailed Results for Adrenaline

ADRB1 rs1801253	CC ▲▲	Relatively high sensitivity to adrenaline and noradrenaline. Greater stimulation of noradrenaline release has been associated with heart failure. Carriers of the C allele are reported to respond well to beta blocker drugs to lower blood pressure. Adrenaline and noradrenaline levels can be reduced by limiting consumption of stimulants such as caffeine.
ADRB2 rs1042713	AG ▲	The G allele is associated with a greater sensitivity enhanced fight or flight response to adrenaline, including increases in heart rate, vasodilation of airways, and energy release (glycolysis and lipolysis). This genotype may be more vulnerable to physiological effects, such as hypertension and metabolic dysfunction, in response to chronic stress.
COMT rs4633	CC	Normal COMT activity (high) and efficient breakdown of adrenaline and noradrenaline. Ensure sufficient intake of B vitamins, zinc and magnesium to provide methyl groups to support COMT activity.
COMT rs4680	GG	Normal COMT activity (high) and efficient breakdown of adrenaline and noradrenaline. Ensure sufficient intake of B vitamins, zinc and magnesium to provide methyl groups to support COMT activity.
MAOA rs6323	TG ▼	Lower MAOA activity and slower breakdown of adrenaline and noradrenaline, which can contribute to higher levels. Curcumin and quercetin may reduce MAOA activity, whilst vitamin B2, magnesium and zinc may increase it.
PNMT rs876493	AA ▼▼	Reduced PNMT activity and slower conversion of noradrenaline to adrenaline, which has been linked to hypertension. As SAMe is a cofactor for PNMT, ensure sufficient B vitamins, zinc and magnesium to support SAMe synthesis.
SLC18A1 rs1390938	GA ▲	The A allele is protective. It is associated with increased SLC18A1 transporter activity and therefore more adrenaline release and effect. It has been associated with resilience to disorders such as affective anxiety, depressiveness, bipolar disorder and alcohol use.

Detailed Results for GABA

ALPL rs4654748	TC ▲	The C allele is associated with faster clearance of Vitamin B6 by ALPL, and hence lower B6 status. As the GAD enzymes require B6 as a cofactor, this could negatively impact the synthesis of GABA. Good sources of B6 include organ meats, pork, chicken, tuna, salmon, chickpeas, sweet potatoes, hazelnuts and bananas.
CNR1 rs1049353	CC	Normal activation of CNR1. Less regulation of Glutamate and GABA - more potential for excess in response to stress. Associated with lower adiponectin levels. However, likely better response to antidepressants if male. To reduce stress, exercise and maintain a healthy diet. Omega fatty acids, chocolate and exercise can support eCB levels and improve regulation.
FAAH rs324420	CC	The wild C allele confers normal (fast) FAAH activity and breakdown of endocannabinoids (eCBs). As eCBs help regulate glutamate and GABA, this genotype may be interpreted as positive.
GABRA2 rs279858	CC ▼▼	Decreased GABRA2 receptor activity, reduced sensitivity to GABA. This genotype has been associated with increased risk of alcohol dependence as alcohol activates GABA receptors, promoting relaxation and reducing anxiety. By binding to GABRA2, the medicinal herb valerian activates GABA receptors and has similar sedative effects as alcohol, and can reduce the risk of dependence. L-theanine and rosemarinic acid (found in rosemary, lemon balm, sage, thyme and peppermint) can help support GABA levels by inhibiting its breakdown.
GAD1 (GAD67) rs3749034	AG ▲	The A allele is the variant and less common allele, and is associated with increased GAD1 expression compared to the G allele. This may confer higher levels of GABA (and relatively low glutamate) and protection against schizophrenia and panic disorders. Ensure sufficient availability of B6 (PLP) to support GAD activity.
GAD2 (GAD65) rs2236418	AA	A is the wild and most common allele, and is associated with normal GAD2 activity (relatively low compared to the G allele) which may result in lower levels of GABA. In females, this has been linked to harm avoidance and anxiety-like traits. Ensure sufficient availability of B6 (PLP) to support GAD activity.

Detailed Results for GABA (continued)

TRPV1 rs8065080	TT	Normal (relatively slower) TRPV1 activity. Lower pain tolerance (heat, cold and pinprick) and less sensitivity to endocannabinoids (eCB). More sensitive to capsaicin (in chilli peppers) and other spicy foods (pepper, garlic, mustard and wasabi) and to salt. More inflammation. Possible risk of episodic migraine evolution to chronic form. Relatively lower inhibition of Glutamate and GABA. This genotype is present in 62% of the population in Europe, 85% in Africa and only 26% in South Asia. Omega fatty acids, chocolate and exercise can support eCB levels and improve regulation.

A Guide to the Nervous System

This guide contains detailed explanations of the neurotransmitters and genes involved in the Nervous System.

Serotonin and Melatonin

Serotonin, or 5-HT, is associated with wellbeing and is popularly referred to as the 'happiness neurotransmitter'. The majority of serotonin is made in the gut where it regulates gastrointestinal movements. The remainder is synthesised in the central nervous system (CNS) where, with melatonin, it affects mood, appetite and sleep. Serotonin also affects cognitive functions including memory and learning.

Melatonin is a sleep hormone naturally produced in the pineal gland of the brain. It regulates sleep and plays a role in maintaining the circadian rhythm, the body's natural time clock. It is also an antioxidant. It suppresses insulin which is not needed during sleep.

Lifecycle

Serotonin synthesis is a two step process starting with the essential amino acid tryptophan. However, reduced availability of tryptophan to make serotonin can be a major factor in depression. Conversely, too much tryptophan can have an inhibitory effect on serotonin production as it inhibits TPH activity. Raised cortisol levels due to stress (exacerbated by an FKBP5 SNP), or inflammation resulting from infection or injury, may cause tryptophan to be redirected to the kynurenic pathway. This 'tryptophan steal' can slow the rate of serotonin synthesis. The extent of inflammation can be modulated by genetics, in particular variants that up-regulate pro-inflammatory molecules. These include IFN-gamma, TNF, and the TDO and IDO enzymes that catalyse kynurenine synthesis.

When tryptophan is not redirected to the kynurenic acid pathway it is converted to 5-HTP by the enzyme tryptophan-5-hydroxylase which exists in two different forms - TPH2 in the brain and TPH1 in the digestive system.

This step can be slowed due to insufficiency of the methyl-folate dependent cofactor BH4, which can be impacted by SNPs on the MTHFR gene. Vitamin D is also a cofactor of this step, which is why we test for VDR SNPs. The subsequent conversion of 5-HTP to serotonin is dependent on vitamin B6 (PLP form).

The serotonin receptors HTR1A and HTR2A are activated by serotonin and control the release of a number of excitatory and inhibitory neurotransmitters, including acetylcholine, adrenaline, dopamine, glutamate, noradrenaline and as well as the hormones corticotropin, cortisol, prolactin and vasopressin. They are the target of many drugs including antidepressants, antipsychotics and anti-migraine agents.

The vesicular monoamine transporter VMAT1 (coded by the SLC18A1 gene), moves serotonin and other neurotransmitters into the vesicles, ready to be released into the synapse. Thus, an increase in VMAT1 (SLC18A1) activity can result in higher levels of neurotransmitters.

Serotonin is broken down to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase A (MAOA) and aldehyde dehydrogenase 2 (ALDH2).

In the evening, stimulated by darkness, N-acetyl-serotonin (NAS) is created and then converted to melatonin by the acetylserotonin O-methyltransferase (ASMT) enzyme with SAMe as cofactor. Reduced melatonin synthesis can cause circadian dysrhythmia and insomnia. The MTNR1B gene is found mainly in the eyes and brain and is involved in the neurobiological effects of melatonin in response to darkness and light. Variants in MTNR1B are associated with disturbed sleeping patterns (particularly early waking) and increased risk of impaired blood glucose metabolism linked to type 2 diabetes.

Serotonin and melatonin levels can be impacted by nutrition and lifestyle factors such as protein intake and exercise. There are many different triggers and mediators of imbalance, the most common being stress, inflammation, light exposure and genetics.

Imbalance

An imbalance in serotonin levels can lead to an array of problems. Whilst most people are aware of the connection between low serotonin and depression, high levels of serotonin can also be problematic.

Low Serotonin:
- Anxiety or worry
- Depression or low mood
- Appetite, hunger or cravings
- Increased pain sensitivity
- Migraines
- Obsessive compulsive disorder (OCD)
- Insomnia
- Constipation

High Serotonin:
- Anxiety, irritability or restlessness
- Bone loss
- High blood pressure
- Gut sensitivity or diarrhoea
- Carcinoid syndrome
- Headache
- Fatigue
- Weight gain

An imbalance in melatonin levels can also lead to various problems.

Low Melatonin:
- Mood disorders (seasonal affective disorder, bipolar disorder and major depressive disorder)
- Sleep disturbances

High Melatonin:
- Nausea
- Dizziness
- Headaches
- Irritability or anxiety
- Diarrhea
- Joint pain

Follow-up testing

Speak to a health professional about clinical testing such as:

Organic acids
- 5-hydroxyindoleacetate (5-HIAA) (serotonin)

Inflammatory markers
- Kynurenate (KYN)
- Quinolinate (QUIN)
- Picolinate

Methylation markers
- Methylmalonate (B12)
- Formiminoglutamate (FIGLU)
- Xanthurenate (B6)
- SAH: SAMe
- Homocysteine

Genetics
- Methylation
- Oestrogen

Dopamine and Adrenergic

Dopamine is a powerful neurotransmitter sometimes called the 'feel good' neurotransmitter. It is not only involved in pleasure but also in reward (motivation) and in motion. Dopamine is produced in different areas of the brain including in the substantia nigra and the ventral tegmental area.

Noradrenaline is responsible for mobilising the brain and body in response to stressful situations. An increase in noradrenaline raises blood pressure and heart rate, triggers glucose release, stimulates wakefulness, and provokes sweating.

Adrenaline is the hormone and neurotransmitter responsible for increasing blood flow. This plays a particularly important role in the 'fight or flight' response. It is often used as medication in extreme situations such as cardiac arrest, superficial bleeding and anaphylaxis. An excess of adrenaline can cause tachycardia, cardiac arrhythmia, hypertension, anxiety and panic attacks.

Lifecycle

Dopamine synthesis is composed of three steps: First, phenylalanine is converted into another amino acid, tyrosine. This reaction is catalysed by the phenylalanine hydroxylase enzyme with tetrahydrobiopterin (BH4) as a cofactor. Then, tyrosine hydroxylase (TH) catalyses the conversion of tyrosine to L-DOPA, with BH4 and vitamin D as cofactors. Finally, L-DOPA is converted into dopamine via the DDC enzyme with vitamin B6 as cofactor. Dopamine receptors (DRDs) are a class of G protein-coupled receptors that are activated by dopamine.

The OPRM1 gene encodes the mu opioid receptor (MOR), to which opioids bind causing dopamine to be released. When OPRM1 activity is decreased (for example, due to SNPs), the effect of the opioids is lower which is associated with more pain. Individuals with lower OPRM1 sensitivity may have higher propensity for social alcohol drinking and impulsivity. The mu opioid receptor plays an important role in dependence on alcohol and other drugs of abuse via its modulation of the dopamine system.

The dopamine transporter DAT (encoded by the SLC6A3 gene), is a membrane-spanning protein that pumps the neurotransmitter dopamine out of the synaptic cleft back into the cytosol. This system permits the active reuptake of dopamine from the synapse and therefore regulates dopaminergic neurotransmission. Dopamine is broken down into inactive metabolites by several enzymes: the monoamine oxidases - MAOA, MAOB, COMT (catechol-o-methyltransferase) and ALDH2. The main metabolite homovanillic acid (HVA) is filtered out by the kidneys and then excreted in the urine.

The metabolism, synthesis, and reuptake pathways of serotonin and dopamine are intertwined. This means that imbalances in one often affect the other. Both serotonin and dopamine are synthesised using the (Vitamin B6 dependent) enzyme DDC and metabolised (broken down) by MAO enzymes.

When the minor tyramine pathway is activated, tyrosine is converted into tyramine instead of L-DOPA. Tyramine can then directly form dopamine, and increase noradrenaline, leading to blood vessel constriction and increased blood pressure.

Noradrenaline is formed from dopamine using the dopamine beta-hydroxylase (DBH) enzyme and copper, oxygen and vitamin C as cofactors. However, copper overload can up-regulate the pathway, depleting dopamine and creating excess noradrenaline. The noradrenaline transporter NET (encoded by the SLC6A2 gene), is a monoamine transporter and is responsible for the re-uptake (removal) of extracellular noradrenaline.

Noradrenaline is converted to adrenaline via the phenylethanolamine N-methyltransferase (PNMT) enzyme, stimulated by cortisol and with SAMe as cofactor. The adrenergic receptors (ADRB1 & ADRB2) are a class of G protein-coupled receptors that are activated by noradrenaline and adrenaline.

Also known as VMAT1 (Vesicular monoamine transporter 1), SLC18A1 is an integral membrane protein, which transfers monoamines, such as noradrenaline, adrenaline, dopamine, and serotonin, into vesicles, ready to release the neurotransmitters into synapses. Noradrenaline and adrenaline are also broken down into inactive metabolites by MAOA and COMT.

Dopamine, noradrenaline and adrenaline levels can all be impacted by nutrition and lifestyle aspects such as exercise and sleep. Both too high and too low levels can be problematic.

Imbalance

An imbalance in dopamine levels can lead to a multitude of issues.

Low Dopamine:
- Lack of motivation
- Fatigue or insomnia
- Addictions and cravings
- Mood issues
- Depression
- Parkinson's disease (resting tremor)
- Decreased libido
- Anxiety
- Pain

High Dopamine:
- Possible ADHD
- Addiction
- Psychosis
- Nausea
- Anxiety

An imbalance in adrenaline and noradrenaline levels can also lead to an array of problems.

Low Noradrenaline or Adrenaline:
- Depression or low mood
- Poor attention and lack of focus
- Addictions and cravings
- Alzheimer's disease
- Anorexia nervosa
- Fatigue
- Obsessive behaviour (adrenaline)
- Hypotension

High Noradrenaline or Adrenaline:
- ADHD
- Anxiety and depression
- Bipolar disorder
- Hyperglycemia and hyperinsulinemia
- Obstructive sleep apnea
- PTSD
- Anger or violent behaviour
- Migraine
- Orthostatic intolerance

Follow-up testing

Speak to a health professional about clinical testing such as:

Organic acids
- Homovanillate (HVA) (dopamine)
- Vanilmandelate (VMA) (adrenaline and noradrenaline)

Cofactors
- Vitamin D

Methylation markers
- Methylmalonate (B12)
- Formiminoglutamate (FIGLU)
- Xanthurenate (B6)
- SAH: SAMe
- Homocysteine

Genetics
- Methylation
- Detoxification

GABA and Cannabinoids

GABA, gamma-aminobutyric acid, is an amino acid and neurotransmitter. It is sometimes known as the 'off' switch. Indeed, it is the major inhibitory neurotransmitter in the brain: at a synapse level, GABA decreases a neuron's action potential, or excitability. It is critical for relaxation, improves memory and mood, relieves anxiety, promotes sleep, moderates blood pressure, and influences catecholamine release and cytokine and hormone production. Disruption of GABA neurotransmission leads to many neurological diseases including epilepsy and general anxiety disorder.

Glutamate is the major excitatory neurotransmitter, sometimes known as the 'on' switch. At a synapse level, glutamate increases a neuron's action potential. It optimises memory and learning, inhibits sleep, improves libido, regulates appetite and increases gut motility.

The most significant impacts on the effect of GABA and glutamate are due to variations in the amount of neurotransmitter and number of receptors.

Lifecycle

Glutamate is synthesised from glutamine. Glutamate's main receptors are NMDA receptors. These are ion channel proteins found in neurons. When activated by the binding of glutamate and glycine, positively charged ions flow through the cell membrane and start the metabolic cascade. This can be blocked by magnesium. There is no clinically significant SNP to report on these receptors.

Glutamate is broken down into glutamine by the glutamine synthetase (GS) enzyme in the astrocytes. This is essential and protective since the enzyme catalyses the condensation of glutamate and ammonia, which is toxic to the brain, (back) into glutamine. Magnesium and manganese are cofactors. Otherwise, glutamate would build up and kill cells by excitotoxicity, due to overactivation of glutamate receptors.

GABA is synthesised from glutamate by the glutamate decarboxylase (GAD) enzyme. GAD uses PLP (vitamin B6) and zinc as cofactors. The GAD1 and GAD2 genes encode glutamate decarboxylase-67 (GAD67) and glutamate decarboxylase-65 (GAD65) respectively which catalyse the conversion to GABA. The GABA synthesised by GAD65 is used for neurotransmission, whereas GABA synthesised by GAD67 is used for synaptogenesis and protection against neuronal injury. The enzymatic activity of GAD65 has been shown to be more responsive to PLP (vitamin B6) than that of GAD67. The ALPL gene encodes a tissue-nonspecific and membrane bound alkaline phosphatase enzyme, which catalyses hydrolysis reactions including of PLP (pyridoxal-5-prime-phosphate, vitamin B6) to PL. The slower the clearance of vitamin B6 by ALPL, the better support of GAD enzymes.

There are two types of GABA receptors: GABA-A and GABA-B. GABA-A receptors are ligand-gated chloride channels (also known as ionotropic receptors). When activated, Cl- ions pass through the neuron's membrane, which causes hyper-polarisation, leading to inhibitory actions. GABRA2 is a member of the GABA-A receptor gene family of ligand-gated ion channels through which GABA acts.

GABA is broken down by the GABA transaminase (GABA-T) enzyme. It catalyses the conversion of GABA and 2-oxoglutarate into succinic semialdehyde and glutamate.

Cannabinoids interact to regulate glutamate and GABA. The cannabinoid receptor 1 (CNR1) gene encodes one of two cannabinoid receptors (the other being CNR2).

TRPV1's (transient receptor potential vanilloid 1) main function is the detection and regulation of body temperature. Although it is not strictly a cannabinoid receptor, it is activated by the endocannabinoids anandamide (AEA) and 2-Arachidonoylglycerol (2-AG) and by cannabidiol (as well as capsaicin, responsible for the burning sensation of chilli peppers). TRPV1 regulates glutamate release in the brain and has been proposed as a target for pain, anxiety and impairment of memory formation. Higher TRPV1 activity is associated with higher pain tolerance.

The FAAH (fatty acid amide hydrolase) gene regulates the metabolism (breakdown) of endocannabinoids (eCBs), anandamide (AEA) and 2-arachidonoylglycerol (2-AG), after reuptake which is why a slower deactivation may be considered unfavourable.

Imbalance

An imbalance in GABA levels can lead to an array of problems. Both low and high levels can be a problem due to their effect on action potential firing.

Low GABA:
- Anxiety
- Inability to focus or ADHD
- Low energy
- Panic attacks or disorders
- General or social anxiety disorders or phobias
- Seizures or convulsions
- Muscle tremors or spasms

High GABA:
- Anxiety
- Excessive need for sleep
- Lethargy
- Decreased drive and motivation
- Migraines

An imbalance in glutamate levels can also lead to an array of problems. Both low and high levels can be a problem due to their effect on action potential firing.

Low Glutamate:
- Agitation
- Insomnia
- Chronic fatigue
- Depression
- Lethargy
- Migraines

High Glutamate:
- Anxiety
- Insomnia
- Panic
- Bipolar disorder
- OCD
- Depression
- Hyperthyroidism
- Migraines
- Chronic pain

Follow-up testing

Speak to a health professional about clinical testing such as:

Organic acids
- GABA levels
- Glutamate levels

Infammatory Markers
- See Serotonin section

Genetics
- Nutrient Core

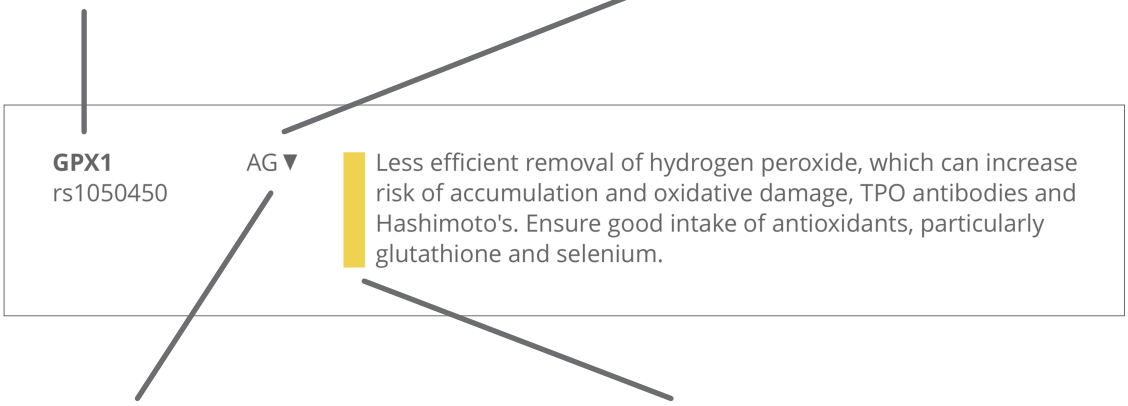
How to Read the Report

Genes

Results are listed in order of the gene short name. The 'rs' number is the reference sequence number that identifies a specific location on the genome. It is also known as a SNP (Single Nucleotide Polymorphism) pronounced 'snip', polymorphism or mutation.

Personalised Result

Your genotype result is shown as two letters (A,G,T or C) which represent the DNA bases present at that location.



Arrow Direction

The direction of the arrow indicates the potential effect of the SNP on gene expression, where applicable - it can increase or decrease activity, or neither.

▲ up-regulates or increases the activity and effect on the gene

▼ down-regulates or decreases the activity and effect on the gene

No arrow - no effect on the activity of the gene

Highlight Colour

The genotype result highlight indicates the potential effect of the SNP on gene function in a particular context.

RED the effect of the variant is negative

AMBER the effect of the variant is somewhat negative

GREEN no variation, or the effect of the variant is positive

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ADRB1 Adrenoceptor Beta 1

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ADRB2 Beta-2-Adrenergic Receptor

Adrenergic-beta(2) receptor polymorphism and athletic performance. Vishnu Sarpeshkar and David J Bentley. J Hum Genet. 2010 Aug;55(8):479-85. doi: 10.1038/jhg.2010.42. Epub 2010 Apr 30. (https://pdfs.semanticscholar.org/735d/bd52384920347e78f9e188593b957887e2f6.pdf)

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ALDH2 Aldehyde Dehydrogenase 2 Family (mitochondrial)

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ALPL Alkaline Phosphatase

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ASMT Acetylserotonin O-Methyltransferase

Gałecki P, Szemraj J, Bartosz G, Bieńkiewicz M, Gałecka E, Florkowski A, Lewiński A, Karbownik-Lewińska M. Single-nucleotide polymorphisms and mRNA expression for melatonin synthesis rate-limiting enzyme in recurrent depressive disorder. J Pineal Res. 2010 May;48(4):311-7. doi: 10.1111/j.1600-079X.2010.00754.x. PMID: 20433639. (https://www.ncbi.nlm.nih.gov/pubmed/20433639)

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CNR1 cannabinoid receptor 1

Hill MN, Patel S. Translational evidence for the involvement of the endocannabinoid system in stress-related psychiatric illnesses. Biol Mood Anxiety Disord. 2013 Oct 22;3(1):19. doi: 10.1186/2045-5380-3-19. PMID: 24286185; PMCID: PMC3817535. (https://pubmed.ncbi.nlm.nih.gov/24286185/)

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COMT Catechol-O-Methyltransferase

Stein DJ, Newman TK, Savitz J, Ramesar R. (2006). Warriors versus worriers: the role of COMT gene variants. CNS Spectr;11(10): pp. 745-8. (http://www.ncbi.nlm.nih.gov/pubmed/17008817?dopt=Abstract)

Xu K1, Ernst M, Goldman D. (2006). Imaging genomics applied to anxiety, stress response, and resiliency. Neuroinformatics; 4(1):51-64. (http://www.ncbi.nlm.nih.gov/pubmed/16595858)

DBH Dopamine Beta-Hydroxylase

Barrie et al. (2014). Regulatory Polymorphisms in Human DBH Affect Peripheral Gene Expression and Sympathetic Activity. Circulation Research, 2014 Dec 5; 115(12): 1017–1025. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4258174/)

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DRD2 Dopamine Receptor D2

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FAAH Fatty Acid Amide Hydrolase

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FKBP5 FK506 Binding Protein 5

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GABRA2 Gamma-Aminobutyric Acid Type A Receptor Alpha 2 Subunit

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GAD1 (GAD67) Glutamate Decarboxylase 1 (brain, 67kDa)

Article Source: Gender Differences in Associations of Glutamate Decarboxylase 1 Gene (GAD1) Variants with Panic Disorder Weber H, Scholz CJ, Domschke K, Baumann C, Klauke B, et al. (2012) Gender Differences in Associations of Glutamate Decarboxylase 1 Gene (GAD1) Variants with Panic Disorder. PLOS ONE 7(5): e37651. https://doi.org/10.1371/journal.pone.0037651 (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0037651)

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HTR1A 5-Hydroxytryptamine Receptor 1A

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HTR2A 5-Hydroxytryptamine Receptor 2A

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IFN-gamma Interferon Gamma

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MAOB Monoamine Oxidase B

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MTHFR Methylenetetrahydrofolate Reductase (NAD(P)H)

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MTNR1B Melatonin Receptor 1B

Comai S, Gobbi G. Unveiling the role of melatonin MT2 receptors in sleep, anxiety and other neuropsychiatric diseases: a novel target in psychopharmacology. Journal of Psychiatry & Neuroscience : JPN. 2014 Jan;39(1):6-21. DOI: 10.1503/jpn.130009. PMID: 23971978; PMCID: PMC3868666. (http://europepmc.org/articles/PMC3868666)

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OPRM1 Opioid Receptor Mu 1

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PNMT Phenylethanolamine N-Methyltransferase

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SLC18A1 Solute Carrier Family 18 Member A1

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SLC6A2 Solute Carrier Family 6 Member 2

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SLC6A3 Solute Carrier Family 6 Member 3

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TH Tyrosine Hydroxylase

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TNF Tumor Necrosis Factor

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TPH1 Tryptophan Hydroxylase 1

Chen et al. (2012). Association between the TPH1 A218C polymorphism and risk of mood disorders and alcohol dependence: evidence from the current studies. Journal of Affective Disorders, 138(1-2):27-33. (https://www.ncbi.nlm.nih.gov/pubmed/21601290?dopt=Abstract)

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TPH2 Tryptophan Hydroxylase 2

Latsko et al. (2016). A Novel Interaction between Tryptophan Hydroxylase 2 (TPH2) Gene Polymorphism (rs4570625) and BDNF Val66Met Predicts a High-Risk Emotional Phenotype in Healthy Subjects. PLoS One, 2016; 11(10). (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5047464/)

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TRPV1 Transient receptor potential cation channel subfamily V member 1

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