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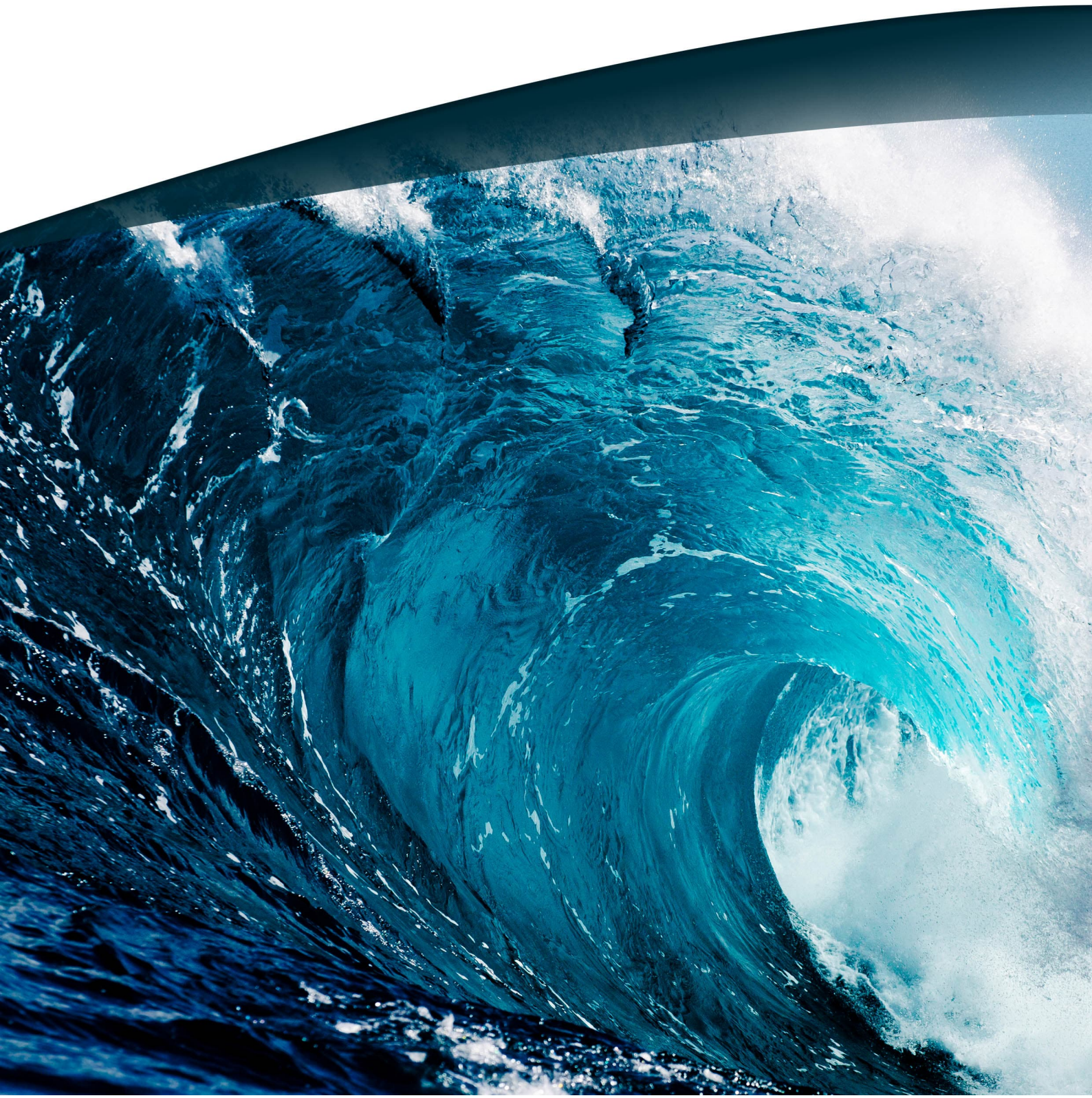
Hormones Report



Report for Vaness Kimbell (CP00096235)

A hormone is a signalling molecule that is made by specialist cells, usually within an endocrine gland.

The body produces more than 50 hormones to control and coordinate metabolism, energy level, reproduction, growth & development, and response to injury, stress, and environmental factors. Hormones are produced in different organs and tissues, and have broad functions. There are three classes of hormones - steroid hormones (corticosteroids and sex steroids), amines (present in the Nervous System Report), and proteins and peptides.

The focus of this report is mainly steroid hormones, plus adrenaline, insulin and melatonin. Steroid hormone imbalances can have serious physical and mental health effects. Symptoms and consequences of steroid hormone imbalances include fertility issues, PCOS (polycystic ovary syndrome), endometriosis, menstrual irregularities, excess facial hair (for women) or breast tissue (for men), osteoporosis, heart disease, blood clots, acne, sexual dysfunction, low libido, mood swings, poor memory, weight gain and hormone sensitive cancers.

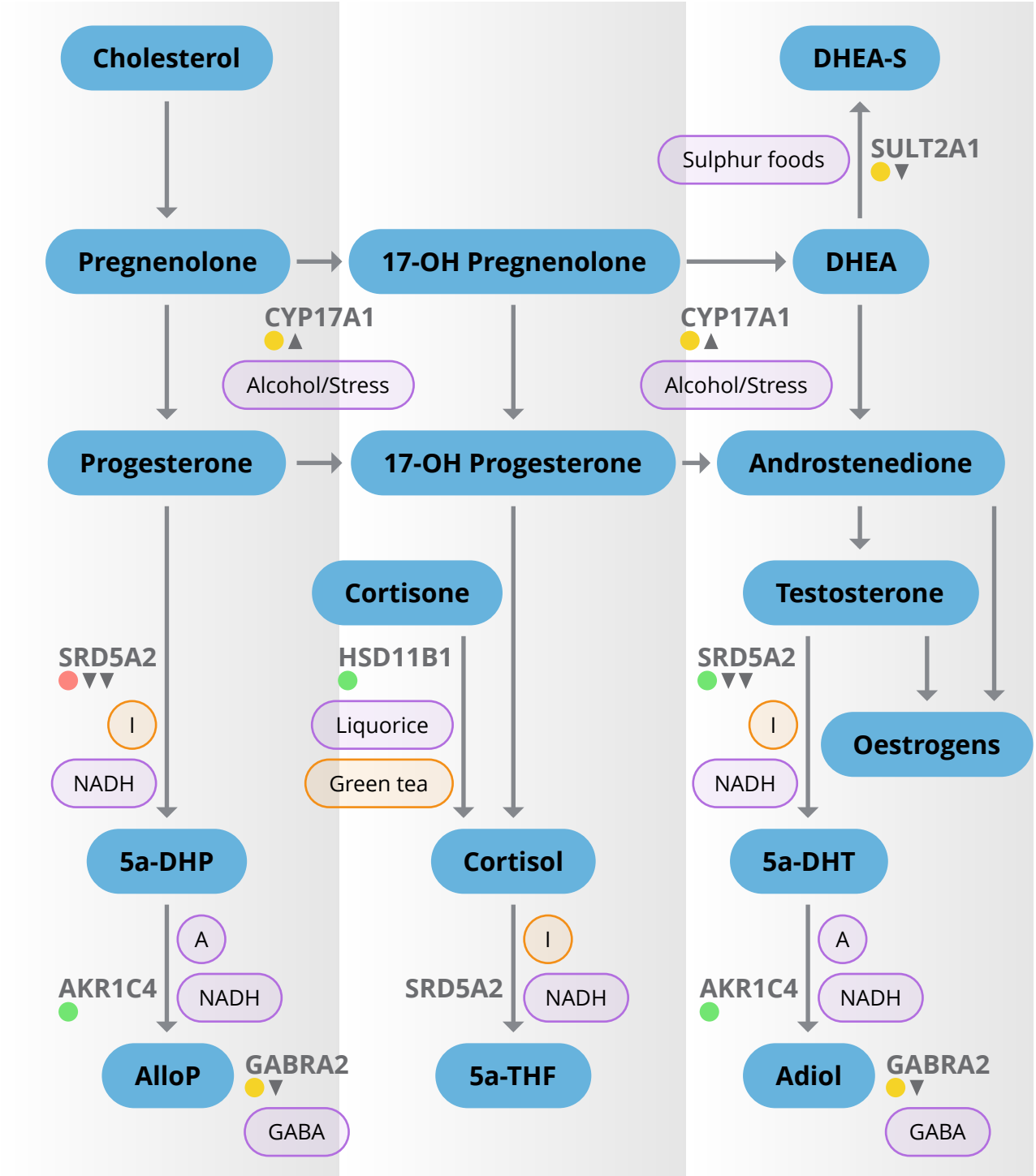
Steroid hormone activity is altered by genetics and environmental factors. Insufficiency or excess can result in HP-GA axis (Hypothalamus-Pituitary-Gonads/Adrenal) dysfunction, which, in turn, can impact synthesis, activation, response and metabolism of these hormones.

This report describes the genes, nutrients, and lifestyle and environmental factors that can impact steroid hormones.

It provides three personalised summary pathways and detailed results, followed by a generic steroid hormones guide. The hormones and pathways covered are:

- Steroid Hormones
- Oestrogen Lifecycle
- HPA and HPG Axis

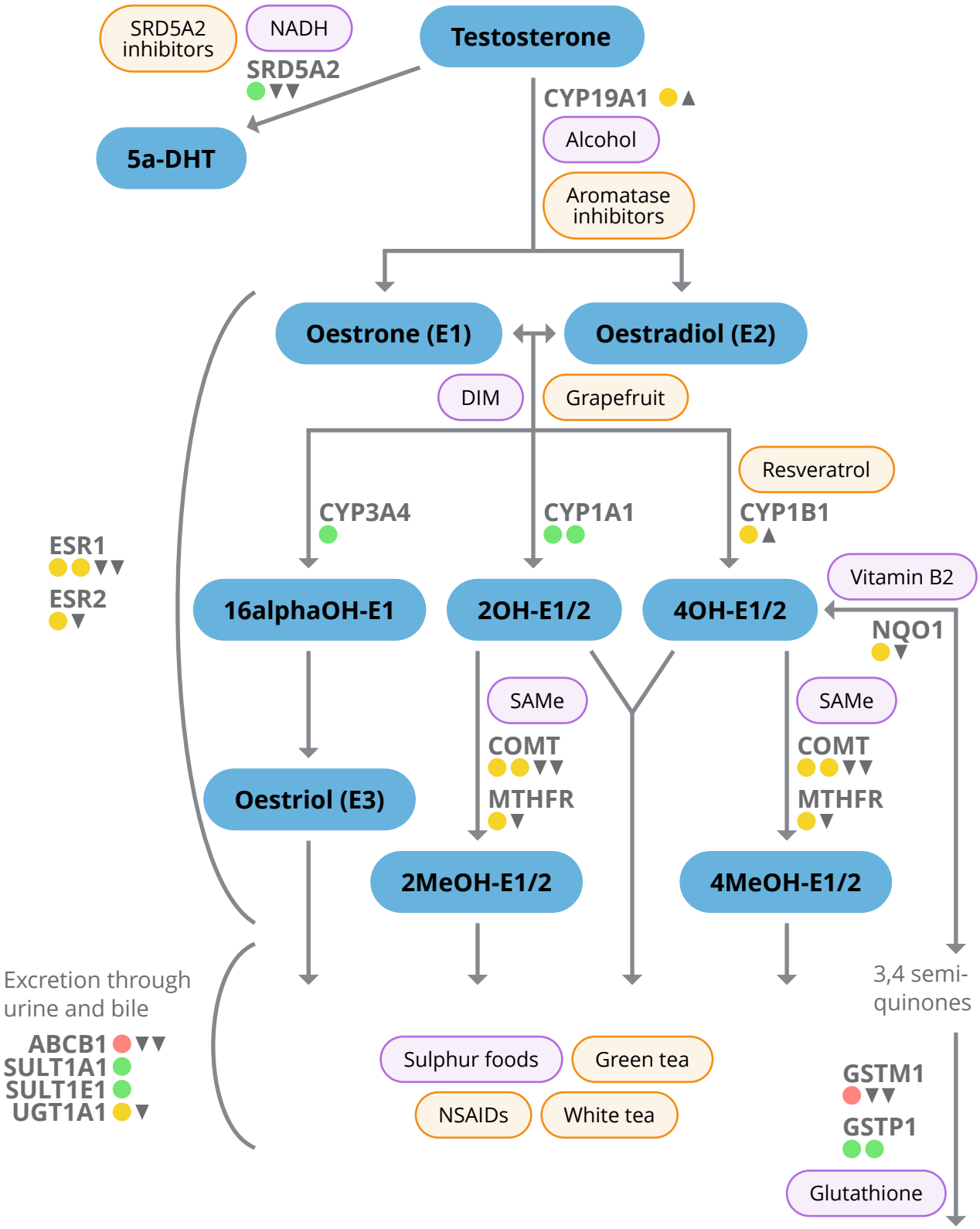
Steroid Hormones



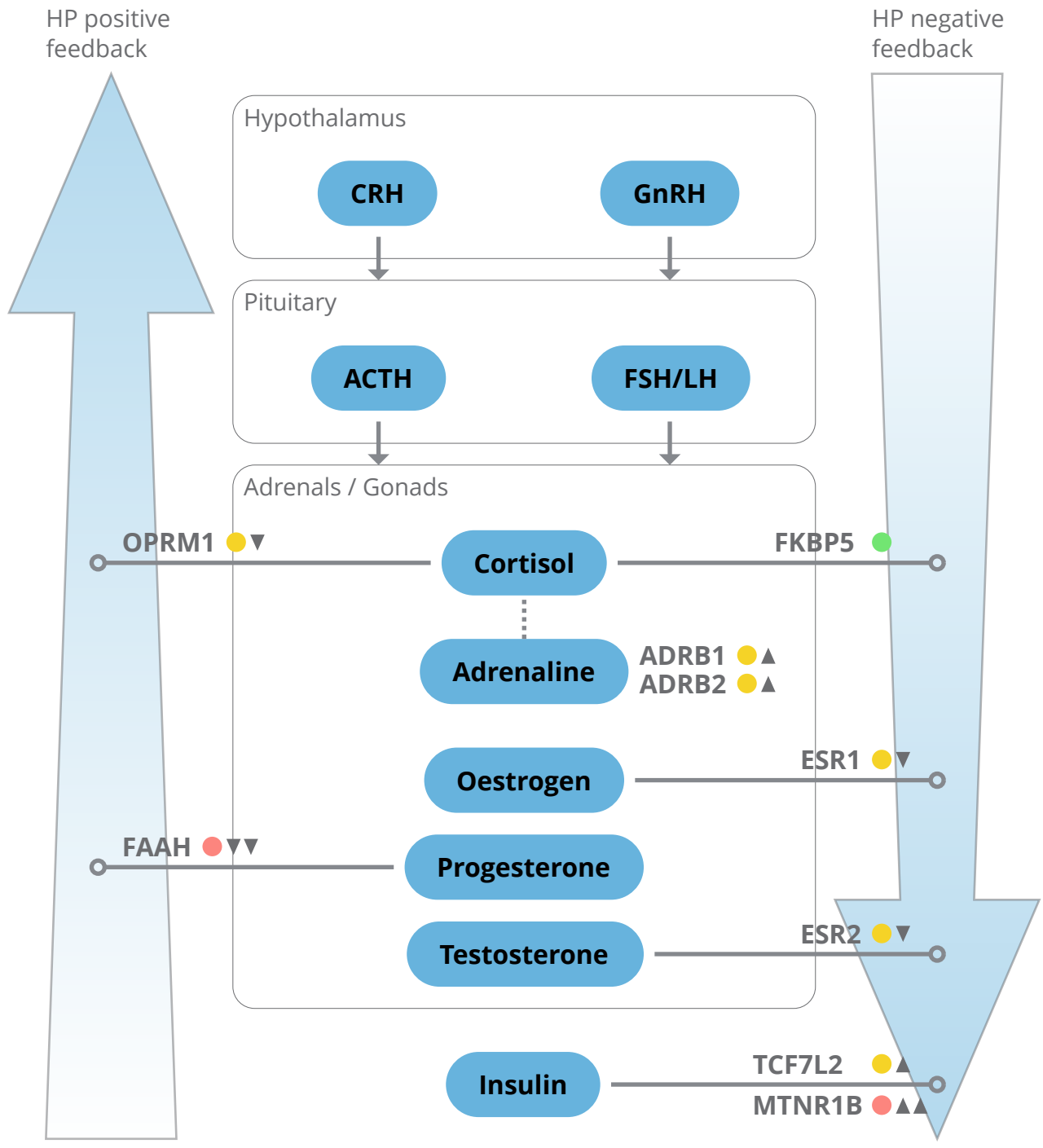
A **3a-HSD activators** include calcium, omega 3-fatty acids in particular palmitoylethanolamide (PEA), evening primrose oil, gingko biloba, crocus sativus and SSRIs.

I **5aR inhibitors** include saw palmetto, stinging nettle, quercetin, zinc, flaxseed, EGCG (epigallocatechin gallate), soy isoflavones, and medications.

Oestrogen Lifecycle



HPA and HPG Axis



If HPA response is blunted, support with Vitamin C, B vitamins and liquorice. Beware of dependency on alcohol and caffeine.

If HPA is overactive, support with anti-inflammatory foods and stress management techniques. Beware of disrupted sleep patterns and limit consumption of simple carbohydrates.

Detailed Results for Progesterone

AKR1C4
rs17134592

CC

Normal function of the 3-HSD enzyme, no lower AlloP production. AlloP has neuroprotective, antidepressant, and anxiolytic effects by increasing sensitivity of GABA receptors. Hence, normal 3-HSD activity is not associated to increased risk of anxiety, depression and emotional lability.

Omega 3 fatty acids, in particular, palmitoylethanolamide (PEA) and evening primrose oil, as well as gingko biloba, and crocus sativus can help to support 3-HSD. NADH (the reduced form of NAD, vitamin B3) is a cofactor, which supports 3-HSD activity. Avoid or reduce nicotine (smoking), chronic stress and insulin (resistance) which may inhibit 3-HSD.

GABRA2
rs279858

CT ▼

Decreased GABRA2 receptor activity, reduced sensitivity to GABA and AlloP. This may increase risk of anxiety. As alcohol has GABAergic effects, withdrawal may exacerbate symptoms.

The medicinal herb valerian activates GABA receptors and L-theanine and rosemarinic acid (found in rosemary, lemon balm, sage, thyme and peppermint) can help maintain GABA levels by inhibiting its breakdown.

SRD5A2
rs523349

CC ▼▼

Slower 5a-reductase (5aR) activity and conversion from progesterone to 5a-DHP, which could lead to lower AlloP levels. Low AlloP has been associated with increased risk of anxiety, depression, and emotional lability - symptoms of PMS and PMDD.

NADH (the reduced form of NAD, vitamin B3) is a cofactor, which supports 5aR activity. If 5aR is suspected to be slow, reduce consumption of 5aR inhibitors such as ECGC a major constituent in green tea, zinc, quercetin, stinging nettle, soy isoflavones and saw palmetto.

Detailed Results for Cortisol

CYP17A1
rs743572

GA▲

Up-regulated CYP17A1 activity and more rapid conversion away from progesterone to cortisol, androgens and oestrogens. This activity can be further upregulated by stress, blood sugar dysregulation, excess insulin, and alcohol.

CYP17A1 activity can be reduced by polyphenols found in berries, cocoa, nuts, flaxseeds and many herbs & spices such as cloves, peppermint, sage, oregano and thyme.

HSD11B1
rs12086634

TT

Normal HSD11B1 activity. No increased conversion of cortisone to cortisol. Inflammation, metabolic syndrome, weight gain, insulin resistance and type 2 diabetes can increase HSB11B1 activity.

If cortisol is high, reduce stressors which increase cortisol production, and support detoxification via glucuronidation (gut) and liver support.

Detailed Results for Testosterone

AKR1C4
rs17134592

CC

Normal function of the 3-HSD enzyme, normal metabolism of 5a-DHT to Adiol.

Normal 3-HSD activity can also support the anti-inflammatory, neuroprotective and antidepressant effects of the 5a-DHT metabolite, and neurosteroid, Adiol.

Omega 3 fatty acids, in particular, palmitoylethanolamide (PEA) and evening primrose oil, as well as gingko biloba, and crocus sativus can help to support 3-HSD. NADH (the reduced form of NAD, vitamin B3) is a cofactor, which supports 3-HSD activity. Avoid or reduce nicotine (smoking), chronic stress and insulin (resistance) which may inhibit 3-HSD.

SRD5A2
rs523349

CC ▼▼

Slower 5a-reductase (5aR) activity and conversion from testosterone to 5a-DHT, which could lead to lower DHT levels. Lower 5a-DHT may be protective from prostate cancer, hair loss and PCOS symptoms.
However, lower 5a-DHT may also be detrimental and contribute to low androgen symptoms (low libido, fatigue, depression), and low Adiol.

If symptoms of low androgen are present, consider NADH (the reduced form of NAD, vitamin B3) cofactor. If 5aR is suspected to be slow, reduce consumption of 5aR inhibitors such as ECGC a major constituent in green tea, zinc, quercetin, stinging nettle, soy isoflavones and saw palmetto.

SULT2A1
rs182420

TC ▼

Relatively slower SULT2A1 activity. Associated with lower sulphoconjugation of DHEA to DHEAS, which may worsen symptoms in women with PCOS due to higher active androgens.

Ensure adequate sulphur-containing nutrients in the diet to support this pathway. Fish oil, and vitamin E may help reduce androgen levels.

Detailed Results for Oestrogen Lifecycle

ABCB1 rs1045642	AA ▼▼	Low ABCB1 enzyme activity, also known as MDRP1 (multidrug resistance protein 1 or P-glycoprotein) due to differential transport of drugs into/ out of cells thereby impacting their efficacy or toxicity. Less effective transport of substrates across cellular membranes - slower detoxification of steroids. Increased risk of toxicity and worse prognosis in some cancers. Ensure detoxification via other pathways.
COMT rs4633	TC ▼	Reduced COMT activity leading to less efficient inactivation of oestrogen via methylation. Poor methylation will further impede COMT activity due to low availability of cofactor SAMe. Review your MTHFR result to assess methyl need. A diet rich in B vitamins will help to improve methylation in general.
COMT rs4680	AG ▼	Reduced COMT activity leading to less efficient inactivation of oestrogen via methylation. Poor methylation will further impede COMT activity due to low availability of cofactor SAMe. Review your MTHFR result to assess methyl need. A diet rich in B vitamins will help to improve methylation in general.
CYP19A1 rs10046	AG ▲	Possible increased conversion of androgens to oestrogens. Diet and lifestyle factors such as inflammation, excess adipose tissue, high insulin levels and stress will further increase CYP19A1 activity. Maintaining a healthy weight, balancing blood sugar, reducing inflammation and stress will help balance CYP19A1 activity. DIM, green tea and zinc have been shown to reduce CYP19A1 activity. Also, vitamin D is required for its proper functioning.
CYP1A1 rs1048943	TT	Normal CYP1A1 enzyme activity and normal hydroxylation of oestrogens to 2OH oestrogens. Ensure phase II detoxification pathways are working optimally since increasing phase I enzymes can increase the production of free radicals. Consider antioxidants to neutralise free radicals.
CYP1A1 rs4646903	AA	Normal CYP1A1 enzyme activity. Not associated with increased susceptibility to PCOS. Care should be taken to improve phase II detoxification.

Detailed Results for Oestrogen Lifecycle (continued)

CYP1B1
rs1056836
CG ▲

Associated with potential up-regulated CYP1B1 enzyme activity and increased hydroxylation of oestrogen to 4OH oestrogen. This is unfavourable since 4OH has been shown to promote the synthesis of the harmful free radical molecules - 3,4 semi-quinones, which damage DNA and potentially initiate cancer. Diet and lifestyle factors such as smoking, stress and eating charred foods can increase CYP1B1 activity regardless of genotype and should be avoided. Flavonoids and resveratrol can slow it down.

CYP3A4
rs2740574
TT

Normal (slow) CYP3A4 enzyme activity and hydroxylation of oestrogens to 16aOH-E1. This is favourable since 16aOH-E1 is a strong form of oestrogen that some studies have associated with oestrogen excess conditions. 16aOH-E1 levels can increase due to diet and lifestyle factors such as obesity, excess alcohol consumption, stress, certain medications and toxic chemical exposure.
Care should be taken to minimise risk by exercising regularly and minimising alcohol consumption and chemical exposure.

ESR1
rs2234693
CT ▼

This (PvuII) TC genotype is associated with reduced negative feedback (hence down regulation) and prolonged positive feedback, particularly in response to stress, resulting in higher GnRH and oestrogen production. Increased risk of oestrogen-linked conditions.

Care should be taken to reduce circulating oestrogen by improving phase II elimination via methylation (COMT), sulphonation (SULT) and glucuronidation (UGT) pathways.

ESR1
rs9340799
GA ▼

The (XbaI) G allele is associated with reduced ESR1 sensitivity to oestrogen and loss of protective effects with increased risk of dyslipidemia, hypertension, central obesity, type 2 diabetes, and cognitive impairment and Alzheimer's Disease.

Encouraging CYP1A1 activity over CYP1B1 and CYP3A4 will also ensure that 'beneficial' 2OH oestrogens are dominant in circulation over the 'harmful' 4OH and 16aOH-E1. Detoxification pathways should be supported.

ESR2
rs4986938
TC ▼

ESR2 is activated by oestrogen, with generally anti-proliferative (anti-cancer) effects.
This genotype has more risk of cardiovascular, metabolic and neurodegenerative conditions, particularly after menopause.

Detailed Results for Oestrogen Lifecycle (continued)

GSTM1 GSTM1	DD▼▼	The GSTM1 gene is absent (null). Loss of function of the GSTM1 gene, poor glutathione transferase activity and inability to neutralise 3,4 semi-quinones. Increase antioxidants including glutathione, and address inflammation and oxidative stress which deplete glutathione levels further.
GSTP1 rs1138272	CC	Associated with normal glutathione transferase activity. High levels of oxidative stress and low glutathione levels will slow GST activity regardless of genotype. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended.
GSTP1 rs1695	AA	Normal glutathione transferase activity and ability to neutralise 3,4 semi-quinones. High levels of oxidative stress and low glutathione levels will slow GSTM1 activity regardless of genotype. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended.
MTHFR rs1801133	AG▼	Decreased MTHFR enzyme activity which may lead to impaired methylation and less effective inactivation of oestrogens via the COMT enzyme. A diet rich in green leafy vegetables and low in alcohol is recommended to ensure adequate amounts of folate. Also ensure that glucuronidation and sulphonation pathways are supported to encourage oestrogen elimination.
NQO1 rs1800566	AG▼	Less effective conversion (reduction) from E2 3,4 quinones to E2 hydroquinones. This can result in more toxicity and an increased risk of oxidative stress and cancer. As NQO1 is a flavoprotein, supporting flavin levels with vitamin B2 can be helpful. THF (folate) can also act as a reducing agent. Glucosinolate derived compounds, such as sulforaphane, found in cruciferous vegetables (and mustard, cabbage and horseradish) are known to effectively induce NQO1.
SRD5A2 rs523349	CC ▼▼	Slower 5aR activity. Slower conversion from testosterone to 5a-DHT. A slower SRD5A2 activity can be beneficial to prevent prostate cancer and aggressiveness. It's also beneficial for women with PCOS, and protective against hair loss for both men and women.

Detailed Results for Oestrogen Lifecycle (continued)

SULT1A1 rs9282861	CC	Normal sulphate-conjugation of oestrogen and steroid hormones (and their metabolites). A diet low in sulphur will impede this pathway regardless of genotype - ensure adequate sulphur-containing nutrients in the diet to support this pathway.
SULT1E1 rs3736599	CC	Normal sulphoconjugation (detoxification) of substrates including oestrogen, DHEA and pregnenolone. Associated with decreased risk of endometrial cancer. A diet low in sulphur will impede this pathway regardless of genotype - ensure adequate sulphur-containing nutrients in the diet to support this pathway.
UGT1A1 rs4148324	TG ▼	Possible slower UGT1A1 enzyme activity and glucuronidation of oestrogen (and steroid hormones). Avoid carbohydrate-free diets since glucose is needed for this pathway to function optimally. Apples, alfalfa and broccoli can support UGT / glucuronic acid. Ensure healthy gut protocols are in place since dysbiosis impedes this pathway. Calcium d-glucarate has been shown to improve glucuronidation by inhibiting beta-glucuronidase produced by unhealthy gut bacteria.

Detailed Results for HPA Axis

ADRB1 rs1801253	CG▲	Higher sensitivity to adrenaline (due to the C allele). Greater stimulation of noradrenaline release can increase the risk of heart problems. Carriers of the C allele are reported to respond well to beta blocker drugs to lower blood pressure. Reduce adrenaline and noradrenaline levels by limiting consumption of stimulants such as caffeine, and managing sugar and stress levels.
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.
FKBP5 rs1360780	CC	Normal regulation of cortisol in response to stress. No disruption to the HPA axis negative feedback loop. Regardless of FKBP5 genotype, chronic psychological or physical stress can increase cortisol and negative feedback on the HPA axis, and reduce hormone synthesis.
MTNR1B rs10830963	GG▲▲	Increased sensitivity to melatonin and suppression of insulin release, and consequently increased risk of blood sugar dysregulation (hyperglycaemia). Avoid consumption of simple carbohydrates (sugar) near to sleep and wake times when melatonin levels are higher, as this can increase the risk of type 2 diabetes.
OPRM1 rs1799971	GA▼	Decreased OPRM1 activity. Reduced HPA axis response to stress, which leads to reduced cortisol levels. A blunted HPA response to stress can result in depressive symptoms and/or aggressiveness. Individuals who experience an attenuated HPA response to stress may also experience a blunted HPA response to alcohol and may therefore consume excessive amounts of alcohol to increase cortisol secretion and achieve the desired biological response.

Detailed Results for HPA Axis (continued)

TCF7L2
rs7903146

TC ▲

Over-expression of TCF7L2 so impaired (reduced) insulin release. Greater risk of experiencing hyperglycaemia which can lead to insulin resistance and type 2 diabetes, especially when cortisol levels are high due to stress or simple carbohydrate consumption.
Avoid or minimise sugary, processed foods. Choose foods with a low GI (glycemic index).

Detailed Results for HPG Axis

ESR1
rs2234693
CT ▼

Oestrogen receptor alpha (ESR1) controls oestrogen levels via negative and positive feedback to the HP axis. This (PvuII) TC genotype is associated with reduced negative feedback and prolonged positive feedback, particularly in response to stress, resulting in higher GnRH and oestrogen production.

This is considered detrimental in high oestrogen conditions (pre-menopause), and a risk factor for PCOS, anxiety and depressive disorders. Consider the whole lifecycle of oestrogen, and stress load.

ESR2
rs4986938
TC ▼

ESR2 is activated by oestrogen and testosterone. It generally opposes ESR1 activity, and is anti proliferative in the context of prostate and ovarian cancer, although it may be proliferative in breast cells. It also interacts with androgens (testosterone and DHT) to block CRH and lower cortisol (modulate HPA activity) and modulates cholesterol and insulin degradation.

The T allele is less active, and confers less protection against prostate and ovarian cancer, and more risk of cardiovascular, metabolic and neurodegenerative conditions (particularly after menopause). Less effective regulation of HPA which may result in higher cortisol, and symptoms of depression.

FAAH
rs324420
AA ▼▼

Slower (up to 50%) breakdown of endocannabinoids (eCBs) by FAAH, resulting in higher levels of eCBs - AEA (anandamide) and 2-AG. Excess AEA may disrupt (prevent) ovulation and fertility (low sperm count in men). Progesterone and oestrogen support FAAH activity, which allows ovulation to happen.

AEA levels must drop to trigger the stress response so a slow FAAH may lead to a blunted HPA response, which may be beneficial or not depending on the context, such as emotional suppression.

In the case of a blunted HPA response, consider therapies to support adrenal health such as vitamin C, B vitamins and liquorice.

A Guide to the Steroid Hormones

This guide contains detailed explanations of the hormones and genes involved in steroid hormones lifecycle and regulation.

Steroid hormones are a group of hormones derived from cholesterol that act as chemical messengers in the body. They are involved in the regulation of many physiological processes, such as the development and function of the reproductive system, metabolism, inflammation and immune system.

Steroid hormones exert their action through their receptors. They have been classified into two classes: corticosteroids (produced in the adrenal cortex), and sex steroids (produced in the gonads or placenta). Within those two classes are five types defined according to the receptors they bind: glucocorticoids and mineralocorticoids (both corticosteroids), and androgens, oestrogens, and progestogens (sex steroids). Vitamin D has the chemical structure of a steroid hormone, is derived from cholesterol, and has similar effects to the corticosteroids and sex steroids, but is not part of one class.

Steroid hormones are generally carried in the blood, bound to specific carrier proteins. Further metabolism and catabolism occurs in the liver, in other peripheral tissues, and in target tissues. This guide will describe the regulation, synthesis, signalling, transport and metabolism of corticosteroids and sex steroids hormones.

Cholesterol is the precursor of steroid hormones. It travels through the blood on lipoproteins. Two types of lipoproteins carry cholesterol throughout the body: LDL (low-density lipoprotein) - called bad cholesterol as high levels raise the risk for heart disease and stroke - and HDL (high-density lipoprotein) - called good cholesterol as it absorbs cholesterol and carries it back to the liver.

Note: The term ‘steroid’ describes both hormones produced by the body and artificially produced medications that have a similar action.

Steroid Hormones

Progesterone

Progesterone is the only naturally produced progestogen in our body. It is made from pregnenolone, the ‘mother’ hormone. In women, progesterone prepares the lining of the uterus for implantation of the ovum (female reproductive cell). It is essential for the maintenance of pregnancy and for normal cycle regulation. Men also need progesterone (lower levels than women) to produce testosterone, and progesterone is involved in sperm development.

AlloP (Allopregnanolone) is made from progesterone and plays an important role in neurological functions. It exerts neuroprotective, antidepressant and anxiolytic effects via GABA receptors. Indeed, progesterone is typically regarded as the calming, anxiety-relieving hormone, and is important both in women and in men.

Symptoms of low progesterone in women include mood swings, migraines, PMS (premenstrual syndrome), fibroids, irregular/short cycle, painful/heavy periods, depression/anxiety, disrupted sleep, infertility/recurrent misacarriage, and accumulation of fat in the hips and thighs (along with oestrogen dominance). Symptoms of low progesterone in men include depression, irritability, low libido, erectile dysfunction, muscle loss, fatigue, and memory loss or trouble concentrating.

The CYP17A1 gene hydroxylates pregnenolone to androstenedione and progesterone to testosterone. Single Nucleotide Polymorphisms (SNPs) may upregulate this enzymatic activity, which can result in low progesterone, and higher cortisol and androgen levels. Additionally, stress and alcohol promote this pathway.

Whilst 5aR (5alpha-Reductase) is best known for converting testosterone into 5a-DHT and cortisol into 5a-THF, it also reduces progesterone to 5a-DHP using NADH as a cofactor. 5aR is coded by the SDR5A2 gene. A SNP on this gene slows its activity which may contribute to lower AlloP levels. It can also lead to higher cortisol levels, and adverse metabolic effects such as weight gain or insulin resistance. Lower 5aR activity is detrimental in the context of low levels of AlloP which have been associated with increased risk of anxiety and depression.

AKR1C4 is the gene that codes for 3alpha-hydroxysteroid dehydrogenase (3a-HSD), which converts 5a-DHP to AlloP with NADH as a cofactor. A SNP on AKR1C4 has been associated with a 66 to 80% decrease in the catalytic activity of the enzyme which may confer lower AlloP production and depression and anxiety.

In the context of PMDD (premenstrual dysphoric disorder), a cyclic mood disorder with paradoxical sensitivity to changes in AlloP levels, it has been hypothesised that stabilising AlloP levels could reduce symptoms of irritability, low mood, anxiety, food cravings and bloating.

SSRIs can directly enhance the conversion from 5a-DHP to AlloP, and have been shown to have a short onset of action (and at relatively low doses) which may help resolve irritability, affectivity lability and mood swings. Calcium, omega 3-fatty acids and evening primrose oil can also increase 3a-HSD's activity.

3a-HSD also plays an important role in deactivating other endogenous steroids (including 5a-DHT), as well as progestogens and prostaglandins. Thus, a SNP on AKR1C4 has been associated with increased mammographic density, and breast cancer risk with oestrogen and progestin therapy. 3a-HSD also helps to detoxify exogenous compounds containing a keto-group, including xenobiotics, environment pollutants and drugs.

GABA is the major inhibitory neurotransmitter in the brain where it acts on GABA-A receptors such as GABRA2. A SNP on GABRA2 is associated with a decreased GABRA2 receptor activity, and a reduced sensitivity to GABA and AlloP. This may increase the risk of anxiety. The medicinal herb valerian activates GABA receptors and L-theanine and rosemarinic acid (found in rosemary, lemon balm, sage, thyme and peppermint) can help maintain GABA levels by inhibiting its breakdown.

Cortisol

Cortisol is a glucocorticoid hormone which is mainly produced in the adrenal glands and is released with a diurnal cycle and in response to stress and low blood sugar. It raises blood sugar by gluconeogenesis (synthesis of new sugar) and by reducing insulin sensitivity. Cortisol also regulates and modulates inflammation (and inhibits the immune system), regulates hunger cravings, digestion, blood pressure, sleep/wake patterns and capacity to cope with stress.

5aR (5alpha-Reductase) converts cortisol into 5a-THF, which is inactive. If 5aR is slower, this can result in higher cortisol levels and less lipogenesis (fat synthesis). However, if 5aR is faster, this can lead to lower cortisol but more lipogenesis. An increased hepatic 5aR activity in insulin resistant patients may represent a compensatory response to clear hepatic cortisol in an attempt to preserve insulin sensitivity.

As the body perceives stress, adrenal glands make and release cortisol into the bloodstream. This causes an increase in heart rate and blood pressure while digestion and immunity are shut down. While having an efficient stress response is necessary, chronic production of cortisol can lead to complications such as insulin resistance and obesity.

An upregulated CYP17A1 gene (due to SNPs or stress) also sets the scene for a higher cortisol synthesis. This can potentially lead to a "pregnenolone steal", which is when high stress perception leads to an elevated use of pregnenolone for cortisol production, reducing the total amount of pregnenolone available for the production of other steroid hormones, such as progesterone.

Stress/cortisol increases testosterone levels in women but reduces them in men. In men, high levels of stress can lead to metabolic syndrome as cortisol inhibits testosterone production. In women, high levels of stress can lead to higher levels of testosterone, especially women with higher BMI.

High cortisol symptoms include hypertension, diabetes, cancer, stroke, anxiety, sugar cravings, insulin dysregulation, weight gain (belly fat), metabolic syndrome, high blood pressure, suppressed immune system, digestive issues, poorer memory, anxiety, and depression. After continuous (chronic) high cortisol, low cortisol will eventually follow. Symptoms include irritability, burnout, depression, low blood pressure, orthostatic hypotension, uncharacteristic pessimism, chronic fatigue, low energy, food and sugar cravings, poor exercise tolerance or recovery, and low immune reserves.

11-beta-hydroxysteroid dehydrogenase (HSD11B1) is responsible for the interconversion of biologically active cortisol and inactive cortisone. The type I isoform, encoded by the HSD11B1 gene has two separate enzymatic activities: dehydrogenase (cortisol to cortisone) with NAD as cofactor and oxidoreductase (cortisone to cortisol) with NADPH. A SNP on HSD11B1 confers higher activity and conversion of cortisone to cortisol, and more risk of central (visceral) obesity, Type 2 Diabetes (T2D) and metabolic syndrome. It also participates in acne vulgarisms (AV) and skin tags (STs) pathogenesis, particularly in the context of stress. HSD11B1 can be further upregulated with liquorice, grapefruit, inflammation, obesity and insulin, whereas salicylate (aspirin), green tea (ECGC), sleep, citrus peel extract and oestrogen have an downregulating effect. Reducing stress and supporting detoxification of cortisol can be helpful too.

Testosterone

Androgens are considered as the male sex hormones because of their masculinising effects. They include androstenediol, androstenedione, dehydroepiandrosterone, dihydrotestosterone and testosterone. Testosterone is the key male sex hormone. It regulates fertility, muscle mass, fat distribution and red blood cell production. Symptoms of low testosterone in men may include low sex drive, erectile dysfunction, depressed mood, decreased sense of well-being, difficulties with focus and memory, fatigue and loss of muscular strength.

Testosterone is converted into, more potent, 5a-DHT by 5aR (5alpha-Reductase) coded for by the SRD5A2 gene. 5aR activity is higher in men. High testosterone levels in women can contribute to PCOS (polycystic ovary syndrome), increased acne, body and facial hair (called hirsutism), balding at the front of the hairline, increased muscle bulk and a deepening voice. There has also been some associations with diabetes and insulin resistance, and symptoms worsen with weight gain.

The use of 5aR inhibitor drugs (such as finasteride) can inhibit conversion to 5a-DHT, a more potent form of testosterone, which can be desirable in some conditions (PCOS). As these drugs can cause undesirable side effects, another consideration could be to consume natural 5aR inhibitors such as polyunsaturated fatty acids, green tea and riboflavin (B2). 5aR inhibitors include saw palmetto, stinging nettle, quercetin, zinc flaxseed, EGCG (Epigallocatechin gallate), soy isoflavones, and medications.

AKR1C4 also converts 5a-DHT to neurosteroid Adiol with NADH as a cofactor. A normal 3-HSD activity can support the anti-inflammatory, neuroprotective and antidepressant effects of the DHT metabolite, and neurosteroid, Adiol. Omega 3 fatty acids, in particular, palmitoylethanolamide (PEA) and evening primrose oil, as well as ginkgo biloba, and crocus sativus can help to support 3-HSD. A SNP on AKR1C4 has been associated with up 66 to 80% lower 3-HSD activity in metabolising 5a-DHT. Higher 5a-DHT can be associated with increased risk of prostate cancer, particularly in the context of exposure to certain pesticides. Nicotine (smoking), chronic stress and insulin (resistance) may further inhibit 3-HSD.

Dehydroepiandrosterone (DHEA) is a hormone that is produced in the adrenal glands. DHEA is a precursor to other hormones, including testosterone and oestrogen. DHEA levels naturally peak in early adulthood and then slowly fall with age. Low levels of DHEA may be associated with decreases in bone or muscle mass, energy, strength, stamina, exercise tolerance and libido. Dehydroepiandrosterone sulfate (DHEAS) is an endogenous androstane steroid produced by the adrenal cortex and a metabolite of DHEA. SULT2A1 catalyses the sulfo conjugation of DHEA to DHEAS. Sulphur-containing foods and vitamin D can support SULT2A1 activity. High DHEAS is a strong indicator of adrenal dysfunction and is associated with conditions of androgen excess in women with PCOS. Fish oil and vitamin E can help reduce androgen levels.

Oestrogen Lifecycle

Testosterone is a precursor of oestrogen via the CYP19A1 gene. A SNP on this gene can increase the conversion of androgens to oestrogens. Inflammation, high insulin levels, obesity, androgens and alcohol will further increase its activity. DIM, green tea, zinc, vitamin E, resveratrol, flavonoids, and aromatase inhibitors can reduce CYP19A1 activity. However, vitamin D is required for its proper functioning, which is why maintaining normal levels of vitamin D is needed.

Oestrogen

Oestrogens and progesterone are considered the two major female sex hormones because of their feminising effects. The main role of oestrogen in the body is to increase the growth and production of cells. It is responsible for the development and regulation of the female reproductive system and secondary sex characteristics (breasts and pubic hair). It is also involved in maintaining bone density, blood clotting and it affects skin, hair, mucous membranes and pelvic muscles. Oestrogen moves through the blood and is active in the cells where oestrogen receptors (ERs) are present. ERs mediate the action of oestrogens.

There are two types of oestrogen receptors:

- ER alpha - coded by the ESR1 gene, which increases the action of the attached oestrogen and;
- ER beta - coded by the ESR2 gene, which decreases the action of the attached oestrogen

The ESR2 gene controls the action of the oestrogen receptor beta, one of two main oestrogen receptors which mediate the action of oestrogen in the body. ESR2 is thought to be anti-proliferative due to its opposition to the action of oestrogen receptor alpha (ESR1) in reproductive tissue. Variants in ESR2 are linked to cardiovascular risk in menopausal women due to increased blood coagulation.

Oestrogen levels fluctuate throughout life, naturally increasing during puberty and pregnancy, and falling after menopause. During the menstrual cycle, oestrogen levels peak during ovulation, dropping off if pregnancy does not occur.

Men also produce and require oestrogen for the maturation of sperm and to support libido but at significantly lower levels.

There are three different types of oestrogen in the body:

- Oestrone (E1): the predominant oestrogen produced after menopause
- Oestradiol (E2): the predominant and most potent oestrogen produced by women of childbearing age
- Oestriol (E3): the predominant oestrogen produced during pregnancy and also the weakest form

Abnormal oestrogen levels (too high or too low) can have a number of negative effects on health and wellbeing.

In women low oestrogen can result in less frequent or no periods, dry skin, mood swings, low sexual drive, dryness and thinning of the vagina, difficulty sleeping, hot flashes and/or

night sweats; and high oestrogen is associated with female gynaecological issues: fibroids, cysts, endometriosis, PMS, fibrocystic breasts, heavy menstrual bleeding, painful periods, clotting, breast swelling and tenderness, skin-related issues: acne, rashes, weight gain (mainly waist, hips and thighs), feeling depressed or anxious, thyroid dysfunction, increased blood clotting, low progesterone, and ER positive cancers of breast, ovaries, uterus and kidneys.

In men, low oestrogen can lead to excess belly fat and low sex drive, whereas high oestrogen can result in infertility and appearance of breasts.

Biosynthesis and Activation

E1 and E2 are derived from the androgenic sex hormones testosterone and androstenedione via CYP19A1, which produces the enzyme aromatase. Variants on CYP19A1 can cause upregulated (undesirable) conversion of androgens to oestrogens.
Once produced, oestrogens are activated via hydroxylation - the addition of an OH group (oxygen and hydrogen). Hydroxylated oestrogens (also called catechol oestrogens) are released into circulation where they exert their influence by binding to ERs and can be protective, or reactive and potentially harmful.

CYP3A4 converts E1 to 16alpha OH-E1, a strong form of oestrogen that binds to alpha ERs. It is also involved in the conversion of E2 to E3. Variants on CYP3A4 can result in upregulation and care should be taken to support downstream phase II detoxification pathways. Grapefruit has been shown to inhibit CYP3A4 enzyme activity.

CYP1B1 converts oestrogens to 4OH oestrogens, which can promote synthesis of the harmful molecules, 3,4 semi-quinones, which release free radicals, damage DNA and potentially initiate cancer. Variants on CYP1B1 are associated with increased production of 4OH oestrogens and may also result in other circulating pro-carcinogens. It is particularly important for individuals with variants to ensure that the downstream phase II pathways are working optimally. Smoking and inflammation can promote this pathway but flavonoids and resveratrol can slow it down.

CYP1A1 is the most favourable of the hydroxylation pathways as it converts oestrogens into 2OH oestrogens which are neutral or even beneficial in the body. Variants on CYP1A1 cause upregulated enzyme activity which is desirable for oestrogen metabolism but can lead to high amounts of circulating pro-carcinogens if phase II detoxification pathways (methylation, sulphation, glucuronidation and glutathione conjugation) are not working optimally. Diindolylmethane (DIM), a compound derived from cruciferous vegetables and indole-3-carbinol (I3C) has been found to potently stimulate CYP1A1.

Semiquinone Free Radicals

3,4 semiquinones, the potent free radicals produced by 4OH oestrogens, are neutralised by the antioxidant glutathione via the glutathione transferase enzymes GSTP1 and GSTM1. N-acetylcysteine (NAC), as the precursor to glutathione, also helps GST enzymes to detoxify the semiquinones. These genes are highly polymorphic and one or both copies are often entirely absent. Variants lead to decreased ability to deactivate toxins and carcinogens, including 3,4 semiquinones. Increasing antioxidants including glutathione may help as well addressing inflammation and oxidative stress which deplete glutathione levels. Furthermore, NQO1 is a member of the NAD(P)H dehydrogenase (quinone) family. A SNP decreases NQO1 activity, which means there is less conversion from 3,4 semiquinones to 4OH-E1/2. This can result in more toxicity and an increased risk of oxidative stress and cancer. As NQO1 is a flavoprotein, supporting flavin levels with vitamin B2 can be helpful.

Deactivation and Elimination

At the end of its life oestrogen is converted in the liver via a series of phase II enzymes which prepare it for excretion through the bowel and kidneys.

Methylation is a major mechanism for preventing the potentially harmful effects of oestrogen in the body. It is a vital phase II process which renders catechol oestrogens

inactive and prepares them for elimination via the addition of a methyl group. Oestrogen is methylated via the COMT enzyme, a reaction which requires SAMe as a methyl donor. Variants on COMT cause decreased methylation of oestrogen. 'Poor methylators', particularly those who also have variants on the MTHFR gene, may also have difficulty inactivating oestrogen due to low cofactor SAMe. Methylation support can improve oestrogen deactivation via COMT.

E1, E2 and their metabolites are also deactivated via conjugation by the sulphotransferase enzymes SULT1A1 and SULT1E1. Variants on SULT genes cause impaired conjugation of oestrogen. Sulphated oestrogens can also be deconjugated back into active oestrogen by sulphatases (STs), adding them back to the circulating pool of oestrogen. Sulphur-containing nutrients (found in garlic, onion, Brussels sprouts and kale) can support sulphation.

Glucuronidation is another major phase II pathway involved in the metabolism of oestrogen rendering it water-soluble and ready for excretion. Once glucuronidated via UDP-glucuronosyltransferase (UGT1A1), oestrogen is excreted through the bile to the small intestine. UGT variants cause reduced oestrogen glucuronidation. Dysbiosis leading to excess beta-glucuronidase production causes oestrogen metabolites to become de-conjugated and re-absorbed into the entero-hepatic circulation. Calcium d-glucarate has been shown to improve glucuronidation by inhibiting beta-glucuronidase. Green and white teas (EGCG - Epigallocatechin gallate) and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen inhibit glucuronidation.

At the end of their life, all steroid hormones are converted in the liver via a series of phase II enzymes which prepare them for excretion through the bowel and kidneys. The detoxification of steroid hormones is the same as that for oestrogens.

Furthermore, ABCB1, also known as Multi Drug Resistance 1 (MDR1) or P-Glycoprotein (P-GP), also plays a role in the detoxification of steroid hormones. It codes a vital ATP-dependent Phase III antiporter protein responsible for actively transporting various xenobiotics, drugs, lipids, steroids and Phase II conjugates across cellular membranes for excretion. This protein is also an integral part of the blood-brain barrier and functions as a drug-transport pump transporting a variety of drugs from the brain back into the blood. A SNP on ABCB1 can lower its function, consequently lowering detoxification of steroid hormones, which can be detrimental.

The sex hormone binding globulin (SHBG) regulates steroid responses by transporting androgens and oestrogens in the blood. A variance (SNP) on this gene is associated with higher SHBG, which may decrease the concentration of active, unbound androgens and oestrogens and reduce the risk of PCOS and T2D. Additionally, higher levels of SHBG have been linked to lower post-menopausal endometrial cancer risk. Tea and soy foods consumption could have a protective effect on endometrial cancer among premenopausal women that carry the less beneficial genotype (lower SHBG).

HPA Axis

The hypothalamic–pituitary–adrenal axis (HPA axis) is a major neuroendocrine system that controls responses to stress.

The HPA axis relies on a series of hormonal signals to keep the sympathetic nervous system, the ‘gas pedal’, pressed down. If the brain perceives something as dangerous, the hypothalamus releases CRH, which travels to the pituitary gland, triggering the release of ACTH. ACTH stimulates the adrenal glands to release cortisol. The body thus stays revved up and on high alert. When the threat passes, cortisol levels fall. The parasympathetic nervous system, ‘the brake’, then dampens the stress response. The three hormones CRH, ACTH and cortisol form a regulatory system with negative feedback in order to adjust the plasma cortisol levels to align with requirements. The activation of the HPA axis during stress affects multiple systems in the body.

Adrenaline

Adrenaline is the hormone and neurotransmitter that plays an important role in the fight or flight (short term) stress response - by increasing heart rate, blood pressure, expanding air passages of the lungs, enlarging the pupil in the eye, redistributing blood to the muscles and altering the body's metabolism to maximise blood glucose levels. ADRB1 and ADRB2 are the adrenergic receptors that are activated by adrenaline.

Adrenaline can be used as a medication in extreme situations such as cardiac arrest, superficial bleeding and anaphylaxis. However, excess levels of adrenaline cause tachycardia, cardiac arrhythmia, hypertension, anxiety and panic attacks. Exogenous stimulants such as caffeine and sugar can be detrimental as they trigger adrenaline release.

Cortisol

FKBP5 is an important stress regulating gene responsible for controlling the body's response to cortisol by signalling to the brain to lower the levels after they have been raised in response to stress (negative feedback loop). FKBP5 forms a complex with the glucocorticoid receptor (GR) and regulates its activity. When it is attached to inactive GR, it reduces GR affinity for glucocorticoids and also decreases overall GR signaling.

SNPs on the FKBP5 gene are associated with prolonged stress response and increased reactivity due to impaired lowering of cortisol levels after a stressful event. This FKBP5 genotype is also linked to stress-related disorders such as depression, anxiety and post traumatic stress disorder (PTSD) in adulthood particularly as a result of childhood trauma.

The OPRM1 gene encodes the mu opioid receptor (MOR). Opioids such as morphine, heroin, fentanyl and methadone bind to this receptor. It has an important role in developing dependence on drugs of abuse such as nicotine, cocaine and alcohol via its modulation of the dopamine system. When OPRM1 activity is decreased (for example, due to SNPs), there is a reduced HPA axis response to stress. This may increase risk for alcohol misuse.

Insulin

Insulin is a hormone that helps to keep blood sugar in balance. Insulin release triggers cells to take in glucose when levels of blood sugar rise due to carbohydrate consumption or stress. It also inhibits the liver from breaking down glycogen for energy, and unused glucose is stored as fat. The TCF7L2 gene is involved in regulating blood sugar by stimulating insulin release. A SNP on TCF7L2 is associated with up to 5x lower insulin response to ingested glucose, and is strongly associated with Type 2 Diabetes (T2D) and with gestational diabetes (in pregnancy). This risk can be reduced by limiting simple carbohydrates (sugar) consumption. Regular exercise can also help increase insulin sensitivity.

Melatonin

Melatonin is a sleep hormone that is naturally produced in the pineal gland of the brain. It regulates sleep and plays an important role in maintaining the circadian rhythm, the body's natural time clock. It is also an antioxidant and it suppresses insulin during sleep as it is not needed. Melatonin also has a regulating effect on the HPA axis having an opposite pattern to cortisol. Disruption of cortisol - melatonin cycles, for example due to excessive stressors, or irregular sleep patterns, can also affect HPA axis regulation. A SNP on the MTNR1B (melatonin receptor 1B) gene results in increased expression and greater inhibitory effect of melatonin on insulin release, leading to reduced insulin secretion, increased fasting glucose, and risk of type 2 diabetes.
Low melatonin symptoms include mood disorders and sleep disturbances while high levels of melatonin can lead to nausea and dizziness, headaches, irritability or anxiety, diarrhea and joint pain.

HPG Axis

The hypothalamus regulates the production of oestrogen, testosterone and progesterone via gonadotropin-releasing hormone (GnRH) which stimulates the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As levels of oestrogen, testosterone and progesterone rise, a negative feedback loop signals the hypothalamus to slow GnRH secretion.
Trauma or damage to the hypothalamus, including having excess cortisol, can reduce GnRH, LH and FSH production, causing loss of menstrual cycles in women and loss of sperm production in men.

Production of oestrogens varies widely over the course of the menstrual cycle: oestrogen levels rise as the follicle develops followed by an increase in progesterone as well. Oestrogens have a negative feedback on GnRH.

Around the 14th day of the cycle, the pituitary abruptly changes its response to the persistently high oestrogen levels and switches to positive feedback mode. The consequent increase in LH and FSH, provokes ovulation - when the follicle ruptures and the egg is released. The corpus luteum cells produce progesterone which is (usually) higher than oestrogen during this luteal phase.
If pregnancy does not occur both oestrogen and progesterone levels decrease. The declining levels of oestrogen release the negative feedback on GnRH and FSH production, allowing the cycle to begin over again.

The ESR1 gene plays an important role in regulation of the negative and positive feedback to the hypothalamus and pituitary. A SNP on the ESR1 gene has been associated with greater vulnerability to dysregulation, particularly in response to stress, and prolonged positive feedback resulting in higher GnRH and more oestrogen release.

When fight or flight reflexes are triggered the body prioritises production of cortisol, the primary stress hormone, sometimes at the expense of progesterone. Low progesterone can disrupt menstrual cycles and contribute to oestrogen dominance.

Oestrogens also have a direct effect on insulin, as E2 improves insulin sensitivity and is protective against diabetes. Indeed, E2 regulates insulin action via effects on insulin-sensitive tissues or by regulating factors that contribute to insulin resistance (such as oxidative stress). It is also involved in the reduction of inflammation and appetite. Overall, E2 exerts a positive (helpful) regulation on insulin action, so this benefit may be reduced in menopause. However, high E2 levels have also been linked to insulin resistance in conditions like PCOS, obesity and pregnancy.

FAAH is responsible for the inactivation and clearance of fatty acid amides (FAAs) including the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) after reuptake. FAAH is regulated by progesterone, which stimulates its activity.

The wild allele confers fast FAAH activity and breakdown of endocannabinoids (eCBs). As during the stress response, FAAH lowers AEA levels, a normal (fast) function of FAAH is favourable. Indeed, AEA and 2-AG act bidirectionally to regulate the stress response. AEA levels rapidly decline resulting in the initiation and generation of the stress response (HPA axis activation and anxiety), whereas 2-AG rises later, resulting in the tempering, habituation, and termination of the HPA axis response.

How to Read the Report

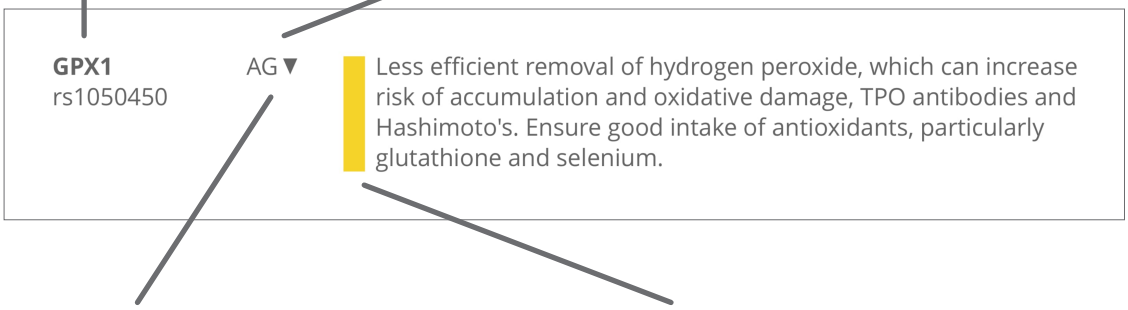
Genes

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.

Multiple attempts are made to achieve the required level of statistical confidence, but if that cannot be met it is reported as **'No result'**.



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

Pathway Diagram Key

Cofactor Inhibitor

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HSD11B1 hydroxysteroid 11-beta dehydrogenase 1

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MTHFR Methylenetetrahydrofolate Reductase (NAD(P)H)

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MTNR1B Melatonin Receptor 1B

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NQO1 NAD(P)H Quinone Dehydrogenase 1

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OPRM1 Opioid Receptor Mu 1

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SRD5A2 steroid 5 alpha-reductase 2

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SULT1A1 Sulfotransferase Family, Cytosolic, 1A, Phenol-Preferring, Member 1

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SULT1E1 Sulfotransferase Family, 1E, Member 1

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SULT2A1 Sulfotransferase Family, Cytosolic, 2A, Dehydroepiandrosterone (DHEA)-preferring, Member 1

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TCF7L2 Transcription Factor 7-Like 2

Ding W, Xu L, Zhang L, et al. Meta-analysis of association between TCF7L2 polymorphism rs7903146 and type 2 diabetes mellitus. BMC Medical Genetics. 2018;19:38. doi:10.1186/s12881-018-0553-5. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5842570/)

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UGT1A1 UDP Glucuronosyltransferase Family 1, Member A1

Juulia Jylhävä, Leo-Pekka Lyytikäinen, Mika Kähönen, Nina Hutri-Kähönen, Johannes Kettunen, Jorma Viikari, Olli T. Raitakari, Terho Lehtimäki and Mikko Hurme, (2012), A Genome-Wide Association Study Identifies UGT1A1 as a Regulator of Serum Cell-Free DNA in Young Adults: The Cardiovascular Risk in Young Finns Study, PLoS One; 7(4): e35426. (http://europepmc.org/articles/PMC3325226)

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