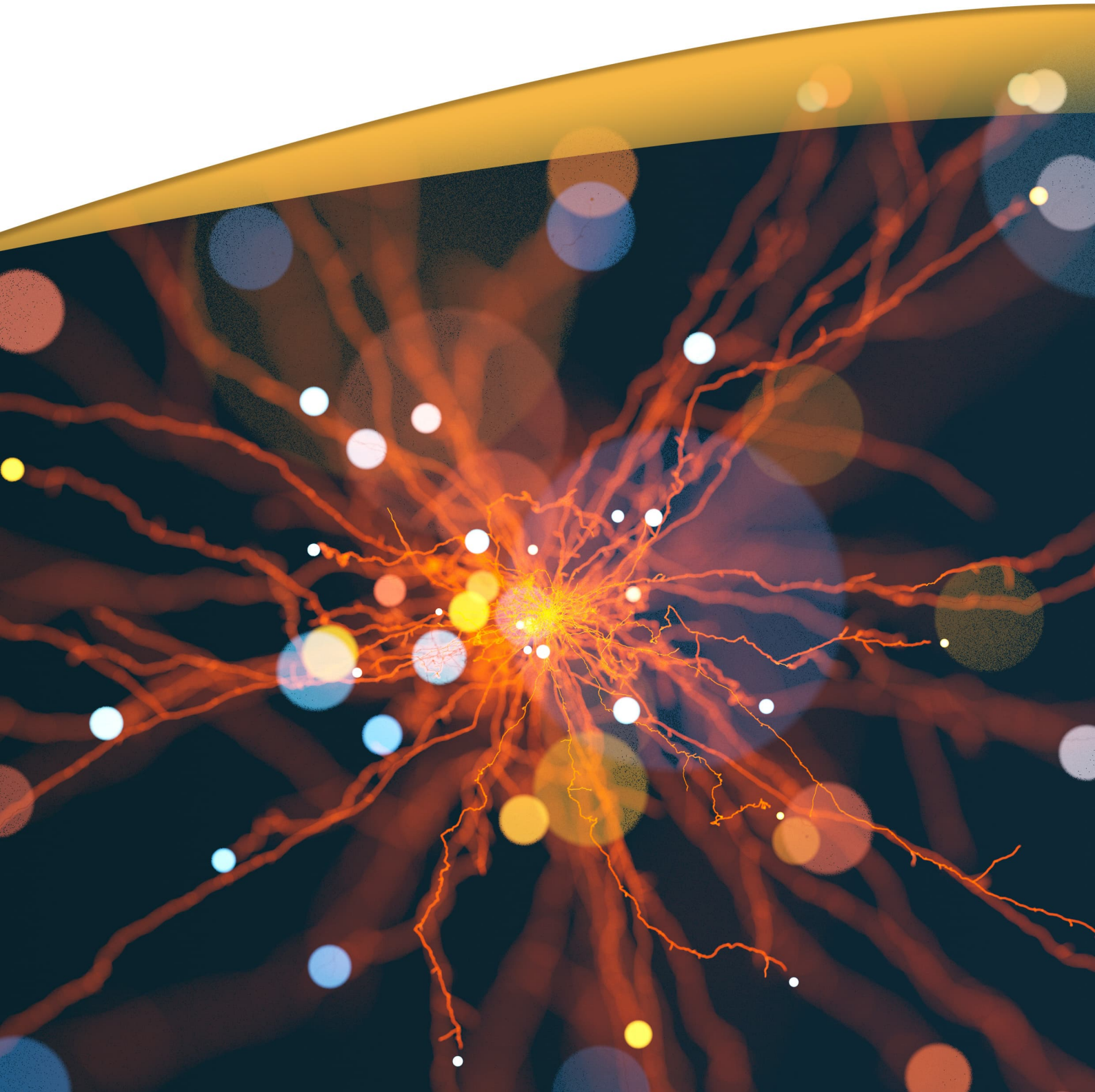


Thyroid Balance Report



Thyroid Balance

The thyroid is an endocrine gland in the neck that produces two thyroid hormones - triiodothyronine (T3) and thyroxine (T4), and calcitonin. Thyroid hormones control the metabolism of almost every cell in the body, with wide-ranging metabolic, developmental and cardiovascular effects.

Thyroid activity is altered by genetics and environmental factors: nutrients (tyrosine, selenium and iodine), toxins (fluoride, chlorine or moulds), psychosocial or physical stressors, bacteria and viruses. Insufficiency or excess can result in HPT axis (Hypothalamus-Pituitary-Thyroid) dysfunction, autoimmune thyroid diseases (AITDs) such as Graves' and Hashimoto's, thyroid sensitive cancers (although rare), and impact transport, activation and response to thyroid hormones.

Thyroid dysfunction can result in many different symptoms. Hypothyroidism (under activity) can cause weight gain, fatigue, low libido, cold intolerance, dry skin, constipation and depression. Symptoms of hyperthyroidism (over activity) include anxiety, heat intolerance, heart palpitations, insomnia and weight loss.

The Thyroid Balance report analyses the genes involved in the thyroid hormone lifecycle: synthesis - centrally in the thyroid, activation in peripheral tissues, transport and metabolism, processing of cofactors (vitamins D and A) and inhibitors (stress and toxins). It also examines genes that confer susceptibility to inflammation and autoimmunity. The report is organised accordingly including personalised summary diagrams and detailed results followed by a generic thyroid system guide.

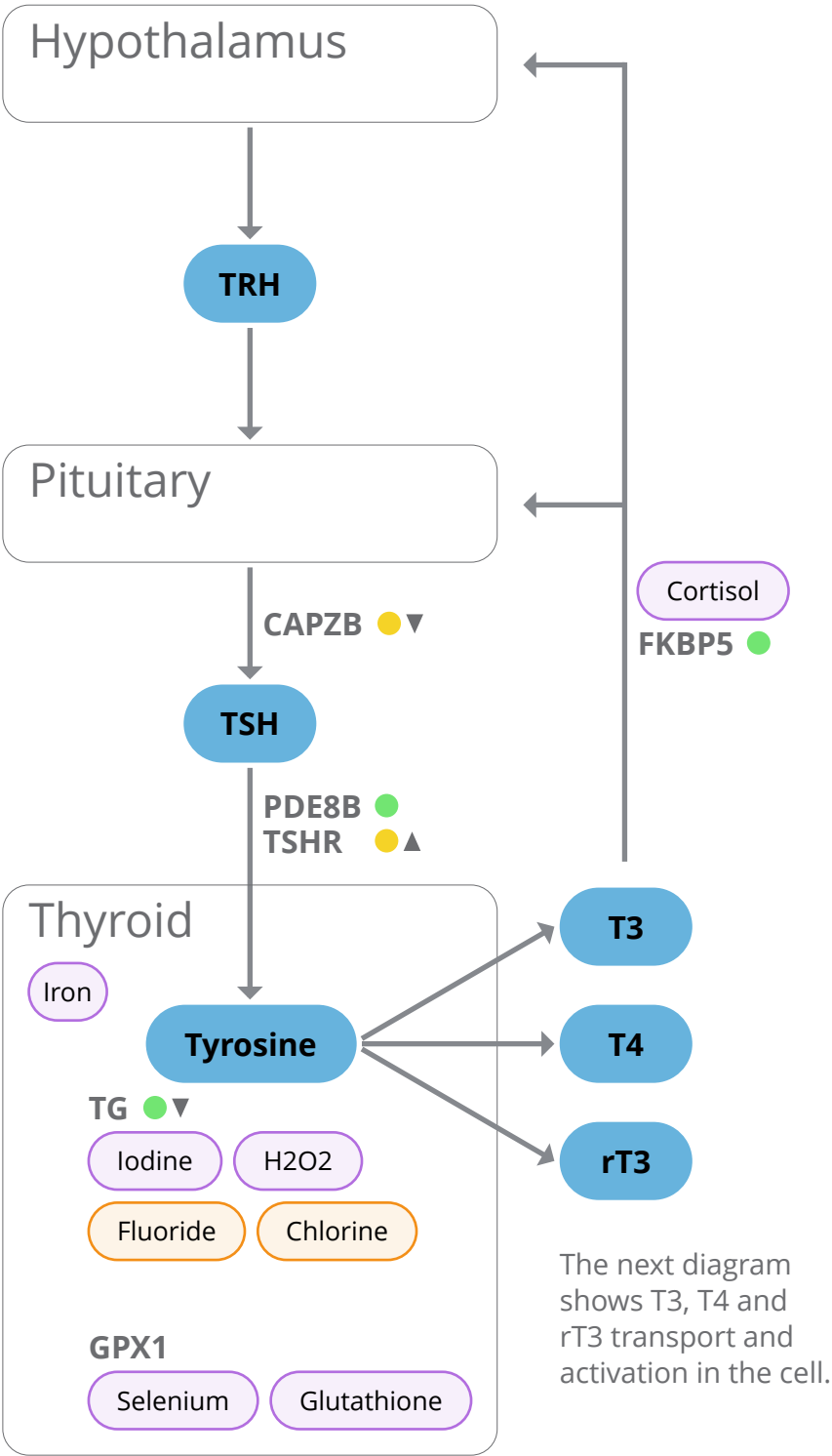
HPT Axis Diagram

Autoimmune

CTLA4 ●●
FOXE1 ●▲▲
PTPN22 ●
HLA-DQA1 ●▼
HLA-DQB1 ●

Inflammation

IL6 ●▲▲
TNF ●
GC ●▼
VDR ●●▼▼
CD40 ●▲▲
FCRL3 ●▲

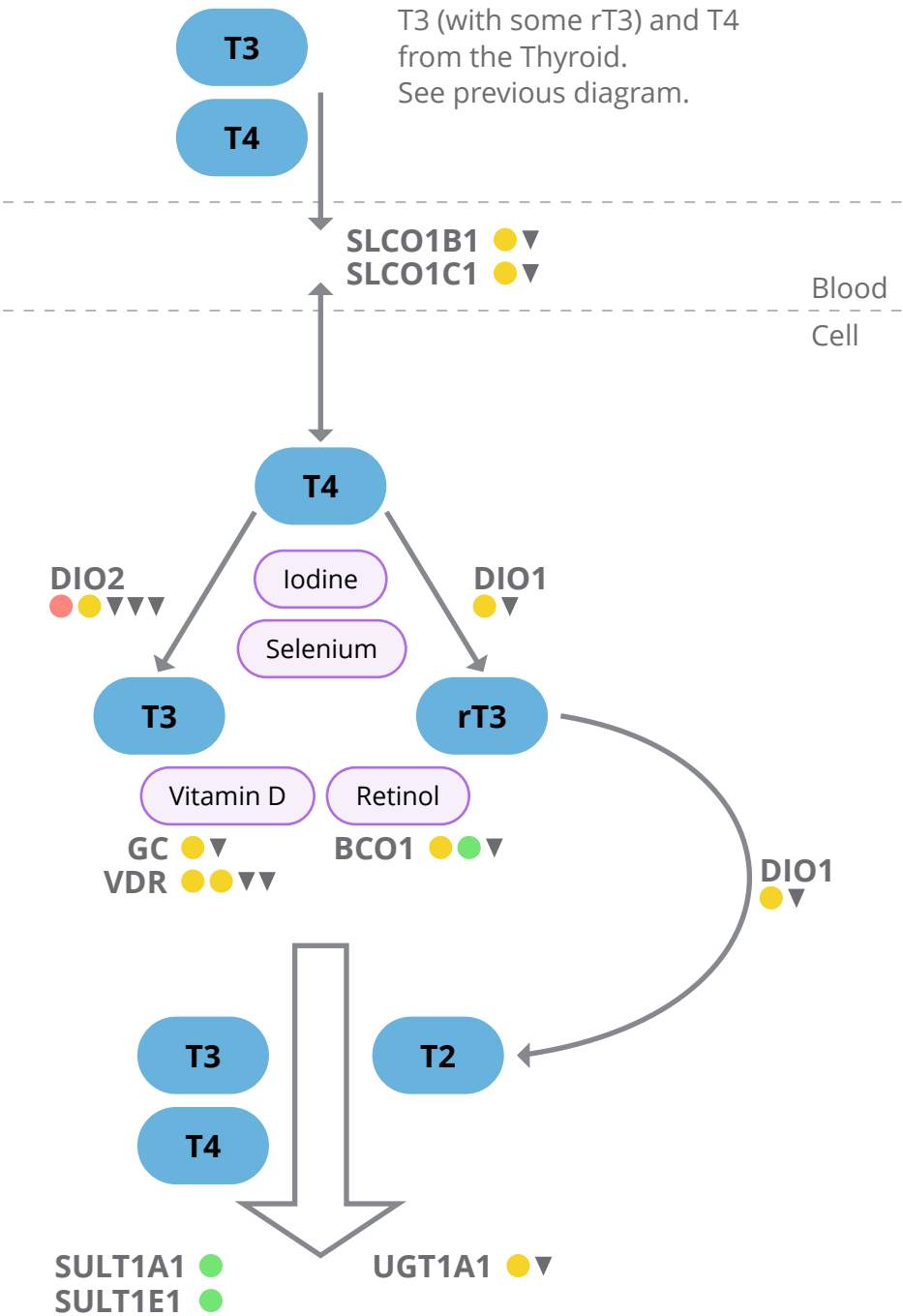


Transport and Activation Diagram

Transport

Activation

Metabolism



Detailed Results for HPT Axis

CAPZB rs10917469	GA ▼	 This SNP is located near to the CAPZB gene. Each G allele is associated with lower serum TSH levels, subsequent down-regulation of thyroid hormone synthesis and risk of hypothyroidism. Consider this result alongside PDE8B which may also influence TSH levels.
FKBP5 rs1360780	CC	 Normal regulation of cortisol in response to stress. No disruption to the HPT axis negative feedback loop. Regardless of FKBP5 genotype, chronic psychological or physical stress can increase cortisol and negative feedback on the HPT axis, and reduce TSH and thyroid hormone synthesis.
GPX1 rs1050450	--	No result. It was not possible to read the genetic code at this location.
PDE8B rs4704397	GG	 Normal cAMP degradation and thyroid gland sensitivity to TSH. Not associated with risk of hypothyroidism or miscarriage. Consider this result alongside CAPZB which may also influence TSH levels.
TG rs2076740	TC ▼	 Normal activity. No increased risk of developing autoimmune thyroid disease. Tg provides tyrosine for thyroid hormone (TH) synthesis and enables storage of inactive TH and iodine. Tg is a major AITD susceptibility gene. As the C allele is recessive a homozygous genotype (CC) is required to have a negative impact.
TSHR rs179247	GA ▲	 Some increased risk of developing TSI antibodies which overstimulate TSHR and increase TSH levels. This can result in Graves' disease (hyperthyroidism) or, less frequently, Hashimoto's. TSI antibodies are further stimulated by inflammatory substances such as TNF. Anti-inflammatory nutrients such as vitamin D may help reduce risk.

Detailed Results for Autoimmune

CTLA4 rs231775	AA	 CTLA4 is involved in the regulation of self-tolerance by the immune system. SNPs affect the inhibitory function of the molecule with reduced control of T-cell proliferation. All 3 CTLA4 SNPs are closely linked and the risk of AITD is increased with the number of risk alleles. Normal (not increase) risk of developing Graves' disease or Hashimoto's thyroiditis.
CTLA4 rs231779	CC	 No increased risk of Graves' disease. All 3 CTLA4 SNPs are closely linked and the risk of AITD is increased with the number of risk alleles.
CTLA4 rs3087243	--	No result. It was not possible to read the genetic code at this location.
FOXE1 rs7850258	GG▲▲	 Also called TTF2 (Thyroid Transcription Factor 2) the FOXE1 gene is involved in thyroid gland development and Tg and TPO expression. The G allele is associated with higher activity and greater risk of developing autoantibodies and hypothyroidism, and of cleft lip and cleft palate.
HLA-DQA1 rs2187668	TC ▼	 The T allele, a proxy for the HLA-DR3 genotype, enables the presentation of Tg peptides to T-cells which increases the risk of autoimmune thyroid disease. Risk of Graves' disease, and to a lesser extent Hashimoto's, is further increased in combination with TG risk variants.
HLA-DQB1 rs7454108	TT	 No variance. Not associated with risk of celiac disease, autoimmune thyroid disease or other autoimmune conditions.
PTPN22 rs2476601	GG	 No variance. No increased risk of developing autoimmune diseases. PTPN22 is a negative regulator of T-cell activation. Consider this result alongside the HLA gene results.

Detailed Results for Inflammation

CD40 rs1883832	CC ▲▲	 Increased risk of CD40 over-expression and promotion of thyroid inflammation, which may initiate or potentiate Graves' disease.
FCRL3 rs7528684	AG ▲	 Normal FCRL3 expression. Normal (not increased or decreased) risk of developing autoimmune thyroid disease.
GC rs2282679	GT ▼	 Poor Transporter. Decreased circulation of vitamin D which may reduce its availability to counteract inflammation.
IL6 rs1800795	GG ▲▲	 Interleukin 6 stimulates inflammatory and autoimmune processes. An increased activity is associated with increased risk of autoimmune diseases, particularly Grave's disease. Ensure intake of anti-inflammatory nutrients such as omega 3 fatty acids in oily fish, like sardines, salmon and mackerel.
TNF rs1800629	GG	 Normal activity. This genotype is not associated with increased activity, inflammation or risk of Graves' disease. TNF is an inflammatory cytokine that plays a pivotal role in regulating immunological reactions and the development of autoimmune diseases.
VDR rs1544410	TC ▼	 Lower sensitivity. Reduced vitamin D receptor activity and response to vitamin D, which may result in symptoms of insufficiency. Higher levels of vitamin D may be needed to achieve the same anti-inflammatory effects.
VDR rs731236	GA ▼	 Lower sensitivity. Reduced vitamin D receptor activity and response to vitamin D, which may result in symptoms of insufficiency. Higher levels of vitamin D may be needed to achieve the same anti-inflammatory effects.

Detailed Results for Transport

SLCO1B1 rs4149056	CT ▼	Less efficient transport of thyroid hormone (T4), bilirubin, oestrogen and some medications (including statins) into cells, which can result in higher serum levels, but lower cellular levels. Hence T4/ T3 serum levels may not reflect cellular activity.
SLCO1C1 rs10770704	CT ▼	Less efficient transport of thyroid hormone (T4) into cells, hence serum T4 levels may not reflect cellular T4/ T3 activity. Reduced transport of T4 into the brain may increase the risk of fatigue and depression.

Detailed Results for Activation

BCO1 rs12934922	AA	 Normal converter of beta-carotene to retinol (preformed vitamin A). As retinol is a co-activator of thyroid hormone, insufficiency may impact thyroid hormone function. The two BCO1 SNPs should be examined together, the effect of negative genotypes is additive.
BCO1 rs7501331	TC ▼	 Reduced ability to convert beta-carotene to retinol (preformed vitamin A). As retinol is a co-activator of thyroid hormone, insufficiency may impact thyroid hormone function. The two BCO1 SNPs should be examined together, the effect of negative genotypes is additive.
DIO1 rs2235544	AC ▼	 Less efficient conversion of T4 to T3 in peripheral tissues, which may impact bone density and central nervous system activity (leading to depression), and reduced clearance of rT3. The DIO genes are selenium dependent. DIO1 is the main DIO in the thyroid gland. It activates T4 to T3 (and rT3) and deactivates rT3 to T2.
DIO2 rs12885300	CC ▼▼	 The wild C allele is associated with increased risk of bipolar disorder, particularly in combination with the higher risk DIO2 rs225014 C allele. Both DIO2 SNPs should be examined together, rs225014 having a stronger impact.
DIO2 rs225014	CT ▼	 The variant C allele is associated with lower DIO2 expression and T3 levels. Increased risk of hypothyroidism, depression, type 2 diabetes and osteoarthritis. This genotype may respond better to combined T4/T3 therapy or higher dose T4 than standard T4 therapy.
GC rs2282679	GT ▼	 Poor Transporter. Decreased circulation of vitamin D which may cause symptoms of vitamin D insufficiency.
VDR rs1544410	TC ▼	 Lower sensitivity. Reduced vitamin D receptor activity in response to vitamin D. Vitamin D and T3 interact in tissues where both VDR and thyroid hormone receptors are present, with genomic and non-genomic effects. Higher levels of vitamin D may be needed to achieve the same benefit.
VDR rs731236	GA ▼	 Lower sensitivity. Reduced vitamin D receptor activity in response to vitamin D. Vitamin D and T3 interact in tissues where both VDR and thyroid hormone receptors are present. Higher levels of vitamin D may be needed to achieve the same benefit.

Detailed Results for Metabolism

SULT1A1 rs9282861	CC	 Normal SULT1A1 activity. Sulphonation is a key pathway for metabolism of thyroid hormones and is an important source of iodides for re-use, for thyroid hormone synthesis. It is inhibited by oestrogens, thyroid hormone and many xenobiotic substances. Sulphur, found in garlic, onions and leeks, is needed to support this pathway.
SULT1E1 rs3736599	CC	 Normal sulphonation of thyroid hormones, and sex steroid hormones - oestrogen, DHEA and pregnenolone. The SULT1E1 gene is inhibited by oestrogen, and by many xenobiotic substances. Sulphur, found in garlic, onions and leeks, is needed to support this pathway.
UGT1A1 rs4148324	TG ▼	 Less efficient glucuronidation of thyroid hormones and oestrogens. Assess gut health since glucuronidation is impeded by dysbiosis.

A Guide to the Thyroid System

This guide contains detailed explanations of the metabolism and genes involved for each of these sections: HPT Axis, Autoimmune and Inflammation, Transport, Activation, and Metabolism. In addition, a Thyroid Functional Testing section explains the different tests possible to check the thyroid condition.

The HPT Axis

The Hypothalamus-Pituitary-Thyroid Axis is the core pathway for thyroid hormone synthesis.

The hypothalamus produces TRH (Thyrotropin Releasing Hormone) that binds to its receptor TRHR in the pituitary gland. This stimulates the pituitary gland to produce TSH (Thyroid Stimulating Hormone), as well as prolactin. TSH interacts with the TSHR (Thyroid Stimulating Hormone Receptor) stimulating the thyroid gland to synthesise and release thyroid hormone.

The CAPZB and PDE8B genes regulate levels of TSH. Having a SNP on either of these genes can increase the risk of developing hypothyroidism. SNPs on the TSHR gene can increase the sensitivity of TSHR to TSI (Thyroid Stimulating Immunoglobulin), increasing TSH production and the risk of hyperthyroidism and Graves' disease.

The main thyroid hormones: T3, T4 and rT3 are synthesised by the thyroid gland, in a ratio of about 90% of T4, around 9% of T3 and less than 1% of rT3. Tg (Thyroglobulin) provides the tyrosine needed for thyroid hormone synthesis, and also enables storage of inactive thyroid hormones and iodine. Variants on the TG gene are associated with susceptibility to autoimmune thyroid diseases (AITDs) - Graves' disease and Hashimoto's thyroiditis.

The TPO gene oxidises iodide to iodine, with the cofactor hydrogen peroxide (H₂O₂), and catalyses the conjugation of tyrosine residues and iodine to make T4, T3 and rT3. The GPX1 (Glutathione Peroxidase 1) gene is critical to removal of excess H₂O₂, which can otherwise damage the thyroid. Selenium is needed to make glutathione peroxidase, and glutathione is needed as a cofactor. Fluoride and chlorine have been associated with higher TSH and hypothyroidism.

Thyroid hormone levels are kept in balance via a negative feedback loop. If too much T3 or T4 is present, the negative feedback loop signals to the hypothalamus and the pituitary gland to reduce thyroid hormone production. Cortisol can upregulate the feedback loop. Having a SNP on the FKBP5 gene can impede the removal of cortisol and increase the negative feedback effect.

What can go wrong?

A hypothalamus injury or tumour can result in insufficient TRH and hypothyroidism. A tumour or a problem with the pituitary gland can cause an excess of TSH to overstimulate the thyroid and result in hyperthyroidism. Environmental factors including poor nutrient status, high toxic load and stress can also result in imbalance. Iodine is an essential component of thyroid hormones, and iodine deficiency is the top cause of hypothyroidism worldwide. However, excess iodine can increase the risk of AITD, particularly Hashimoto's. Other nutrients that are necessary for HPT support are tyrosine, iron, selenium and glutathione. Conversely, chlorine and fluoride, even at low levels, can inhibit thyroid hormone synthesis. Genetic variances (SNPs) on the genes involved in the HPT Axis mean that the risk of developing thyroid imbalances varies significantly between individuals.

Autoimmune and Inflammation

Autoimmune thyroid diseases (AITDs) result from dysregulation of the immune system leading to an immune attack on the thyroid. Thyroid autoantibodies develop when a person's immune system mistakenly targets components of the thyroid gland or thyroid proteins, leading to chronic inflammation of the thyroid (thyroiditis), tissue damage, and/or disruption of thyroid function.

The prevalence of AITDs is estimated to be 5% however, the prevalence of antithyroid antibodies without clinical disease may be even higher, and women have far greater risk than men.

The two main AITDs are Graves' disease (GD) and Hashimoto's thyroiditis (HT). While clinically different, Graves' disease and Hashimoto's thyroiditis share immune-genetic mechanisms. AITDs are T cell-mediated organ-specific autoimmune disorders and are the most frequent autoimmune disorders and the most common pathological conditions of the thyroid gland.

Genetic variants provide the primary risk for AITDs. Several genes have been identified as significantly associated with AITDs and the presence of thyroid antibodies. Indeed, AITDs arise due to complex interactions between numerous environmental and genetic factors.

Genes that confer susceptibility to AITDs have been identified and grouped as:

- Thyroid-specific genes: TSHR, GPX1 and TG
- Immune-modulating genes: the HLA family, CTLA4, PTPN22 and FOXE1
- Inflammation-modulating genes, including IL6, TNF, CD40, FCRL3, and VDR and GC genes which impact Vitamin D (an anti-inflammatory agent)

Several environmental factors have been identified as triggers for AITDs: imbalance between stimuli and inhibitors, intolerance to specific foods, 'leaky gut', high toxic load, radiation, iodine (high or low), inflammation, smoking, alcohol, infection and stress. Autoimmune diseases often occur together so having one increases the risk of developing others.

Transport

Thyroid hormone transporters are key to thyroid hormone action and function. Circulating T4 and T3 do not passively cross cell membranes and need to be actively transported including to and

from liver, thyroid follicular cells and astrocytes and neurons in the brain. There are three main transporters types: MCTs (monocarboxylate transporters), Solute Carrier Organic Anions (SLCOs) (also called Organic Anion Transporting Peptides OATPs) and LATs (L-type amino acid transporters).

Solute Carrier Organic Anions (SLCOs) transport thyroid hormones, including their sulphate conjugates. SLCO1C1 has a high specificity and affinity to T4 and rT3 and facilitates transport of T4 into astrocytes (in the brain) for conversion to T3 by DIO2. SNPs on SLCO1C1 are linked to reduced transport, and fatigue and depression. SLCO1B1 is expressed in the liver. The SNP on this gene is linked to reduced transport and clearance of statins, bilirubin, E1S (oestrogen sulphate) and T4S (T4 sulphate).

Monocarboxylate transporter MCT8 (also called SLC16A2) transports thyroid hormones (T4, T3, rT3 and T2) out of the thyroid and into peripheral cells. As these SNPs are very rare we do not test for them. L-type amino acid transporters (LATs) transport both T4 and T3 but with lower affinity than the other transporters.

Activation

In the thyroid and peripheral tissue cells, the deiodinases (DIOs) 'de-iodinate' (remove iodine) from thyroid hormones to activate or deactivate them, and release iodine for reuse. DIOs are selenocysteine-dependent membrane proteins which means they need selenium to function. Selenium deficiency can therefore contribute to lower T3 levels. There are three major deiodinases: DIO1, DIO2 and DIO3.

DIO1 is the main DIO in the thyroid gland. It activates T4 to T3 (and rT3) and de-activates rT3 to T2. DIO1 activity is impacted by iodine deficiency. SNPs can also result in lower DIO1 activity and consequently (lower) T3, higher T4 and rT3, and may increase the risk of depression.

DIO2 is the major converter of T4 to T3 in the thyroid and in peripheral tissue cells. It is widely expressed, including in the thyroid and the brain. DIO2 is upregulated in the thyroid in Graves' disease and follicular adenomas. The DIO2 rs225014 SNP is associated with lower DIO2 expression which can lead to hypothyroidism, depression and fatigue. Another DIO2 SNP rs12885300 has been linked to increased risk of bipolar disorder.

DIO3 is the major deactivator of T4 to rT3. It is active in pregnancy and newborns and reactivated in critical illness and starvation (or fasting). There are no meaningful DIO3 SNPs to report.

The majority of hypothyroid patients are treated with L-thyroxine which requires deiodination to T3 for physiological activity. However, changes in DIO function could impair L-thyroxine therapy. Indeed, the rs225014 SNP on the DIO2 gene is implicated in decreased clinical effect of T4 therapy. Therapeutic considerations in the context of DIO2 SNPs and hypothyroidism may include: increasing T4 dosage, T3 therapy or combination T4 and T3 therapy (including NDT - natural desiccated thyroid).

Once inside the cell, thyroid hormones can have genomic or non-genomic effects via thyroid hormone receptors (THR). Non-genomic effects include: regulation of mitochondrial metabolism, stimulation of glucose uptake, intracellular and membrane effects (including transport into and out of the cell), and regulation of bone maintenance. THRB is a thyroid hormone receptor with SNPs linked to thyroid hormone resistance but they are very rare (1 in 40,000) and the impact is not well understood. Hence we do not report them.

Genomic effects of THRs involve interaction (binding) with other receptors including Retinoid X Receptor Alpha (RXRA) and Vitamin D Receptor (VDR). RXRA is activated by retinoic acid and subsequently forms heterodimers with THRs (and Vitamin D Receptors) stimulating genomic transcription and translation which are necessary for growth and development.

Hence we report SNPs on the BCO1, GC and VDR genes which impact availability and sensitivity to retinol and vitamin D.

Metabolism

Thyroid hormones are metabolised through the Phase 2, sulphonation and glucuronidation, detoxification pathways in the liver.

SULT genes (SULTA1 and SULT1E1) are involved in sulphonation and transform thyroid hormones to sulphated forms such as T3S (T3-sulphate). T-sulphates are rapidly degraded by DIO1, for elimination (hence this is considered irreversible). However, when DIO1 is inhibited, due to (non-thyroid) critical illness, hypothyroidism, fasting or selenium deficiency, T-sulphates may be reactivated. The oestrogen sulpho-transferase (SULT1E1) is also an important enzyme for sulphation of thyroid hormones. A diet low in sulphur will impede this pathway regardless of genotype.

UGT genes (UGT1A1) are involved in glucuronidation and elimination of bilirubin, steroid and thyroid hormones, bile acids, and retinoids, as well as xenobiotics such as environmental chemicals, pollutants and medication. UGT1A1 is the main contributor to thyroid hormone glucuronidation in the liver with rT3 being the main substrate, and some metabolism of T4. UGT1A1 transforms these thyroid hormones to iodothyronine glucuronides, using UDP-glucuronic acid as cofactor. When thyroid hormones are elevated, glucuronidation becomes more important as a mechanism to return levels to normal. However beta-glucuronidase bacteria, which can be elevated in dysbiosis, can liberate the glucuronides which are then reabsorbed.

Functional Testing

Thyroid functional tests are used to check the function of the thyroid. They may be requested if a patient is thought to suffer from a thyroid condition or to monitor thyroid hormone levels or response to medication.

The first test a health practitioner will usually order to detect thyroid dysfunction is a test for thyroid stimulating hormone (TSH). If the TSH level is abnormal, a test for free thyroxine (free T4) can confirm the diagnosis. Optimal reference ranges depend on the method of analysis and will vary according to the laboratory.

TSH – to test for hypothyroidism, hyperthyroidism, screen newborns for hypothyroidism, and monitor treatment for thyroid disorders

Free T4 – to test for hypothyroidism, hyperthyroidism, screen newborns for hypothyroidism, and to monitor treatment of thyroid disease

Free T3 – primarily to test for hyperthyroidism, especially when the free T4 is not elevated; when people are iodine-deficient, the thyroid makes much more T3 than T4

Total T3 – in general, high total or free T3 results may indicate an overactive thyroid gland (hyperthyroidism) and low total or free T3 results may indicate an underactive thyroid gland (hypothyroidism)

Reverse rT3 – less frequently tested, rT3 may be high during fasting, starvation, illness such as liver disease and during times of increased stress, and in patients with fibromyalgia and chronic fatigue syndrome (CFS)

Testing for thyroid antibodies, such as thyroid peroxidase antibody (TPO), is usually ordered to help diagnose an autoimmune thyroid disease and to distinguish it from other forms of thyroid dysfunction. There are many different methodologies for thyroid antibody testing and each has different reference ranges. If someone is undergoing regular testing to monitor changes over time it is best to use the same lab test. The main antibodies are:

TPOAb – Thyroid Peroxidase antibody - the most common test for AITDs (Hashimoto's or Graves' disease)

TgAb – Thyroglobulin antibody - targets thyroglobulin (stored in the thyroid). Present in Hashimoto's or Graves' or thyroid cancer.

TSHRab – Thyroid Stimulating Hormone Receptor antibodies - present in Graves' disease.

Other tests that can be performed include:

Nutrient tests – of Vitamin D, Vitamin A (retinol), Folate, B12, Selenium, Iodine and Ferritin status

CRP – C Reactive Protein - a marker for inflammation

Calcitonin – to help detect the presence of excessive calcitonin production (can occur in some thyroid cancers)

Thyroglobulin – to monitor the treatment of thyroid cancer and to detect recurrence

Fine-needle biopsy – inserting a needle into the thyroid and removing a small amount of tissue and/or fluid from a nodule or other area for examination

Thyroid scans – that use radioactive iodine to look for thyroid gland abnormalities and to evaluate thyroid function (for iodine uptake) in different areas of the thyroid

Thyreflex – a non-invasive test which measures the speed of the brachioradialis reflex in your forearm

How to Read the Report

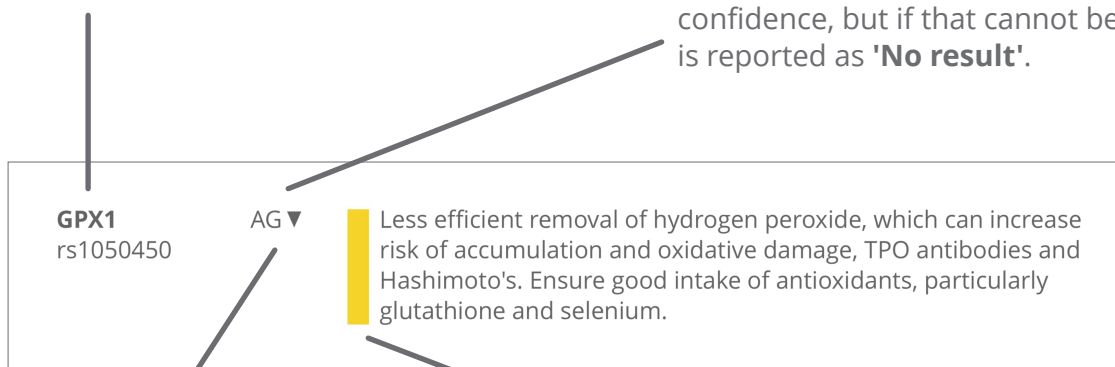
Genes

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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BCO1 Beta-Carotene Oxygenase 1

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CAPZB Capping Actin Protein of muscle Z-line subunit Beta

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CD40 CD40 molecule

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CTLA4 Cytotoxic T-lymphocyte Associated protein 4

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DIO1 Iodothyronine Deiodinase 1

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DIO2 Iodothyronine Deiodinase 2

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FCRL3 Fc receptor like 3

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FKBP5 FK506 Binding Protein 5

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FOXE1 Forkhead Box E1

Andrew C Lidral et al. "A single nucleotide polymorphism associated with isolated cleft lip and palate, thyroid cancer and hypothyroidism alters the activity of an oral epithelium and thyroid enhancer near FOXE1." *Hum Mol Genet* (2015): 24(14): 3895–3907. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4476440/>)

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GC Group-specific component (vitamin D binding protein)

Ahn et al. "Genome-wide association study of circulating vitamin D levels." *Human Molecular Genetics* (2010): 19(13): 2739–2745. (<http://europepmc.org/abstract/MED/20418485>)

Thomas J Wang et al. "Common genetic determinants of vitamin D insufficiency: a genome-wide association study." In *The Lancet* (2010), Vol 376, Issue 9736, 180–188, ISSN 0140-6736; [https://doi.org/10.1016/S0140-6736\(10\)60588-0](https://doi.org/10.1016/S0140-6736(10)60588-0). (<http://www.sciencedirect.com/science/article/pii/S0140673610605880>)

GPX1 Glutathione Peroxidase 1

Gholinejad, Zafar et al. "Association of glutathione peroxidase 1 gene polymorphism (rs1050450) with Hashimoto's thyroiditis in Northwest Iran." *Meta Gene* 17 (2018): 216–222. (<https://www.sciencedirect.com/science/article/pii/S2214540018301440>)

HLA-DQA1 Major Histocompatibility Complex Class II, DQ Alpha 1

Tomer Y. Genetic susceptibility to autoimmune thyroid disease: past, present, and future. *Thyroid*. 2010;20(7):715–725. doi:10.1089/thy.2010.1644 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2949235/>)

HLA-DQB1 Major Histocompatibility Complex Class II, DQ Beta 1

Minelli R, Gaiani F, Kayali S, et al. Thyroid and celiac disease in pediatric age: a literature review. *Acta Biomed*. 2018;89(9-S):11–16. Published 2018 Dec 17. doi:10.23750/abm.v89i9-S.7872 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502193/>)

IL6 Interleukin 6

Imani D, Rezaei R, Razi B, Alizadeh S, Mahmoudi M. Association Between IL6-174 G/C Polymorphism and Graves' Disease: A Systematic Review and Meta-Analysis. *Acta Med Iran*. 2017 Nov;55(11):665–671. PMID: 29307154. (<https://pubmed.ncbi.nlm.nih.gov/29307154/>)

PDE8B Phosphodiesterase 8B

Farah Y Alul et al. "Genetic associations with neonatal thyroid stimulating hormone levels." *Pediatr Res* (2013): 73(4 0 1): 484–491. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775497/>)

Michaela Granfors et al. "Phosphodiesterase 8B gene polymorphism in women with recurrent miscarriage: A retrospective case control study." *BMC Medical Genetics* (2012): 13: 121. (<https://bmcmmedgenet.biomedcentral.com/articles/10.1186/1471-2350-13-121>)

PTPN22 protein tyrosine phosphatase non-receptor type 22

Kalthoum Tizaoui et al. "Association of PTPN22 1858C/T Polymorphism with Autoimmune Diseases: A Systematic Review and Bayesian Approach." *J Clin Med* (2019): 8(3): 347. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6462981/>)

SLCO1B1 Solute Carrier Organic Anion Transporter Family Member 1B1

Van der Deure WM et al. "Organic anion transporter 1B1: an important factor in hepatic thyroid hormone and estrogen transport and metabolism." *Endocrinology* (2008): 149(9): 4695–701; doi: 10.1210/en.2008-0169. (<https://www.ncbi.nlm.nih.gov/pubmed/18499754>)

SLCO1C1 Solute Carrier Family 21, Member 1C1

Panicker V. "Genetics of Thyroid Function and Disease." *The Clinical Biochemist Reviews* (2011): 32(4): 165–175. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3219766/>)

Visser TJ et al. "Cellular uptake of thyroid hormones." *Endotext* [Internet] (2000): South Dartmouth, MDText.com, Inc., (last update: June 15, 2016). (<https://www.ncbi.nlm.nih.gov/books/NBK285565/>)

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

Christopher C Ebmeier et al. "Human Thyroid Phenol Sulfotransferase Enzymes 1A1 and 1A3: Activities in Normal and Diseased Thyroid Glands, and Inhibition by Thyroid Hormones and Phytoestrogens." *The Journal of Clinical Endocrinology & Metabolism* (2004): Vol 89, Issue 11, 5597–5605; <https://doi.org/10.1210/jc.2003-031939>.
(<https://academic.oup.com/jcem/article/89/11/5597/2844552>)

SULT1E1 Sulfotransferase Family, 1E, Member 1

Kester MH et al. "Sulfation of thyroid hormone by estrogen sulfotransferase." *J Clin Endocrinol Metab* (1999): 84(7): 2577-80.
(<https://www.ncbi.nlm.nih.gov/pubmed/10404840>)

Monique H A Kester et al. "Potent Inhibition of Estrogen Sulfotransferase by Hydroxylated Metabolites of Polyhalogenated Aromatic Hydrocarbons Reveals Alternative Mechanism for Estrogenic Activity of Endocrine Disruptors." *The Journal of Clinical Endocrinology & Metabolism* (2002): Vol 87, Issue 3, 1142–1150; <https://doi.org/10.1210/jcem.87.3.8311>.
(<https://academic.oup.com/jcem/article/87/3/1142/2846988>)

TG Thyroglobulin

Eschler DC, Hasham A, Tomer Y. Cutting edge: the etiology of autoimmune thyroid diseases. *Clin Rev Allergy Immunol*. 2011;41(2):190–197. doi:10.1007/s12016-010-8245-8 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129418/>)

Yoshiyuki Ban et al. "Amino acid substitutions in the thyroglobulin gene are associated with susceptibility to human and murine autoimmune thyroid disease." *Proc Natl Acad Sci U S A* (2003): 100(25): 15119–15124.
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC299918/>)

TNF Tumor Necrosis Factor

Catherine M. Phillips. "Nutrigenetics and Metabolic Disease: Current Status and Implications for Personalised Nutrition." *Nutrients* (2013): 5(1), 32-57; doi:10.3390/nu5010032. (<http://www.mdpi.com/2072-6643/5/1/32/htm>)

Tu Y, Fan G, Zeng T, Cai X, Kong W. Association of TNF- promoter polymorphism and Graves' disease: an updated systematic review and meta-analysis. *Biosci Rep*. 2018;38(2):BSR20180143. Published 2018 Mar 21. doi:10.1042/BSR20180143
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5861325/>)

TSHR Thyroid Stimulating Hormone Receptor

Mihaela Stefan, Larissa C Faustino. "Genetics of Thyroid-Stimulating Hormone Receptor—Relevance for Autoimmune Thyroid Disease." *Front. Endocrinol* (2017): 8: 57. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5376554/>)

Xiong H, Wu M, Yi H, Wang X, Wang Q, Nadirshina S, et al. Genetic associations of the thyroid stimulating hormone receptor gene with Graves diseases and Graves ophthalmopathy: a meta-analysis. *Sci Rep* (2016) 6:30356. doi:10.1038/srep30356
(<https://www.nature.com/articles/srep30356>)

UGT1A1 UDP Glucuronosyltransferase Family 1, Member A1

Robin P Peeters, Theo J Visser. "Metabolism of Thyroid Hormone." Feingold KR, Anawalt B, Boyce A, et al. editors, *Endotext*, Internet, South Dartmouth (MA): MDText.com; <https://www.ncbi.nlm.nih.gov/books/NBK285545/>.
(<https://www.ncbi.nlm.nih.gov/books/NBK285545/>)

VDR Vitamin D (1,25- dihydroxyvitamin D3) Receptor

Bikle DD. "Vitamin D Metabolism, Mechanism of Action, and Clinical Applications." *Chemistry & biology* (2014): 21(3): 319-329; doi:10.1016/j.chembiol.2013.12.016. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3968073/#!po=54.5000>)

Dohee Kim. "The Role of Vitamin D in Thyroid Diseases." *Int J Mol Sci*. (2017): 18(9): 1949.
(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5618598/>)

Wang J, Lv S, Chen G, et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015; 7: 2485-98. (<https://www.ncbi.nlm.nih.gov/pubmed/25854833>)



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