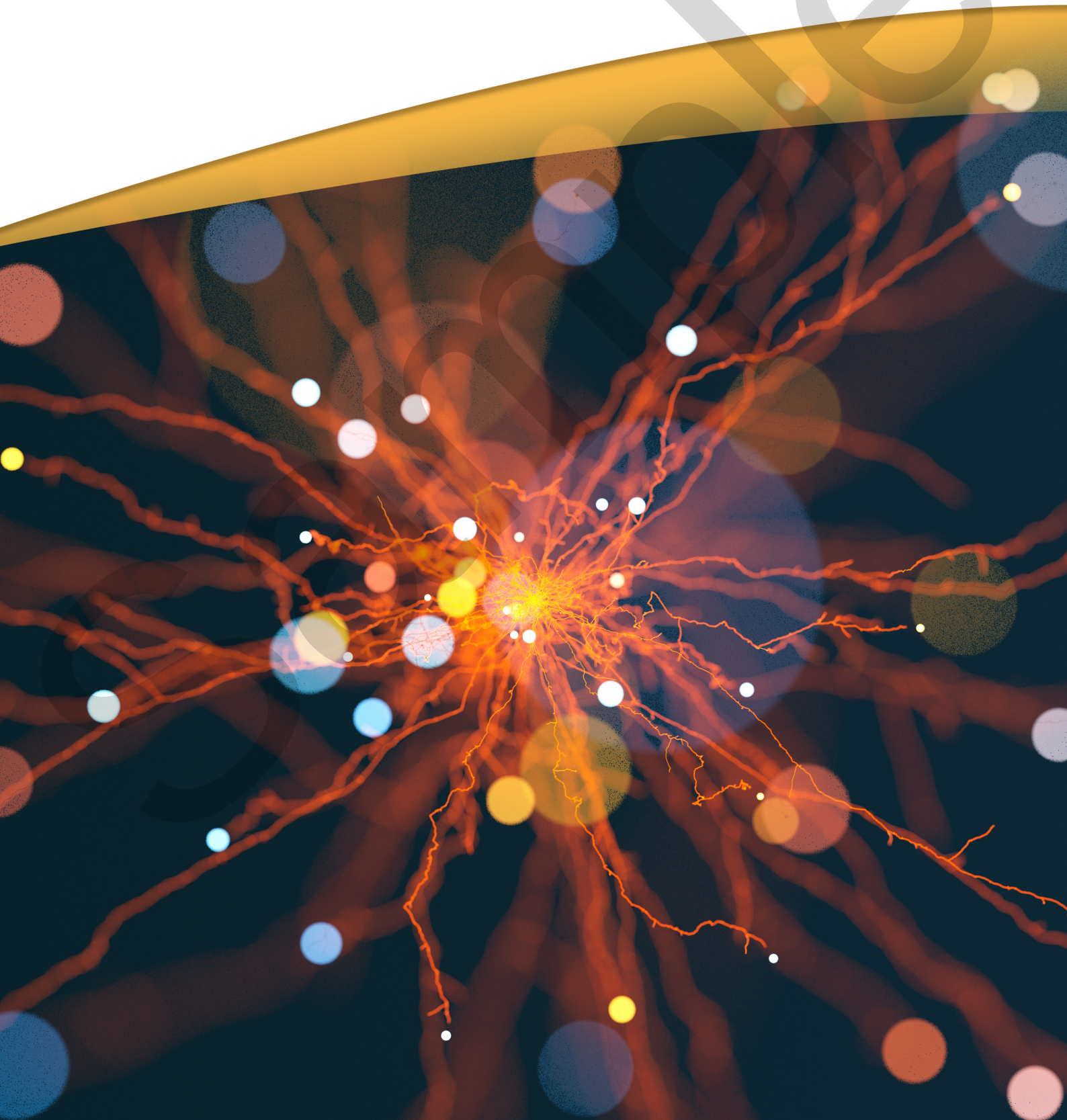
Lifecode GX ®
— Professional Genotype Analysis —

Thyroid Balance Report



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.

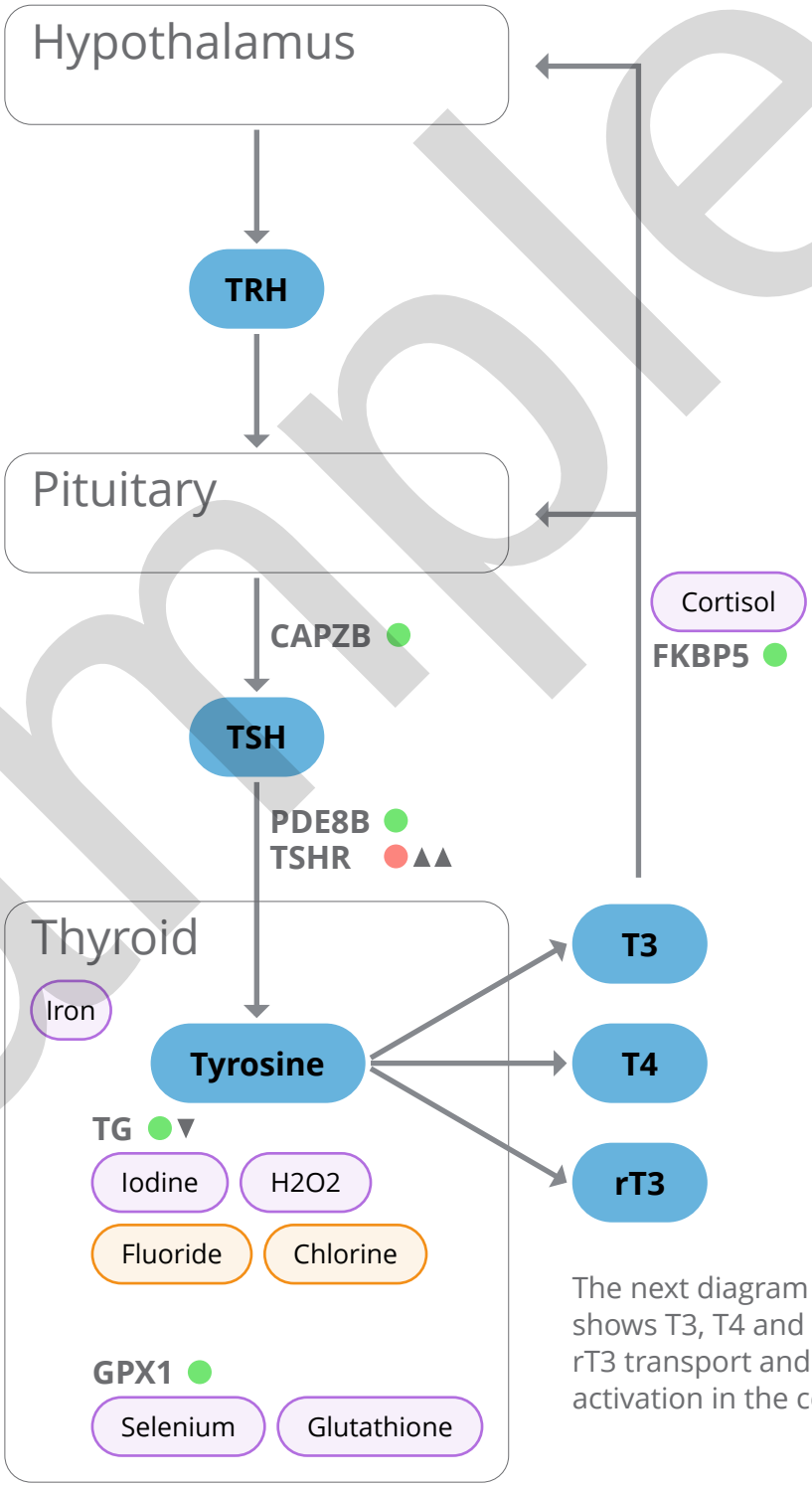
HPT Axis Diagram

Autoimmune

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

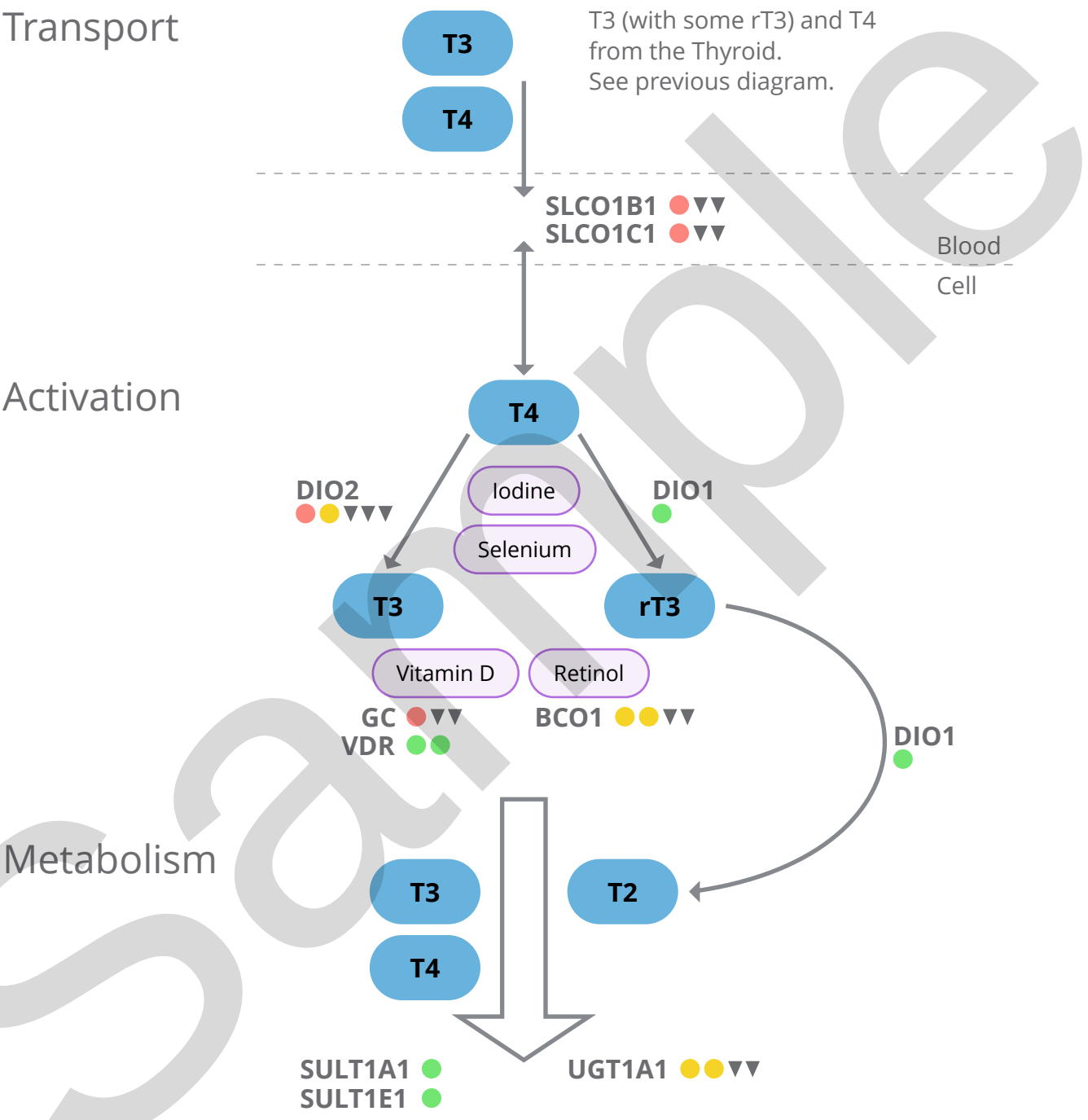
Inflammation

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



The next diagram shows T3, T4 and rT3 transport and activation in the cell.

Transport and Activation Diagram



Detailed Results for HPT Axis

CAPZB [redacted]	AA	No variance. No impact on TSH levels or thyroid hormone levels. This SNP is located near to the CAPZB gene. Consider this result alongside PDE8B which may also influence TSH levels.
FKBP5 [redacted]	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	GG	Normal GPX activity. GPX supports the removal of hydrogen peroxide (H2O2) by glutathione, which protect cells from oxidative damage. Normal (not increased) risk of developing TPO antibodies and Hashimoto's thyroiditis. GPX is selenium dependent.
PDE8B [redacted]	GG	No impact on thyroid gland sensitivity to TSH or levels of TSH. Not associated with risk of hypothyroidism or miscarriage. Consider this result alongside CAPZB which may also influence TSH levels.
TG [redacted]	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 [redacted]	AA ▲▲	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.

Some pages have been omitted in the sample

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 (H202), 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 H202, 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 dessicated 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-glucurodinase 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

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

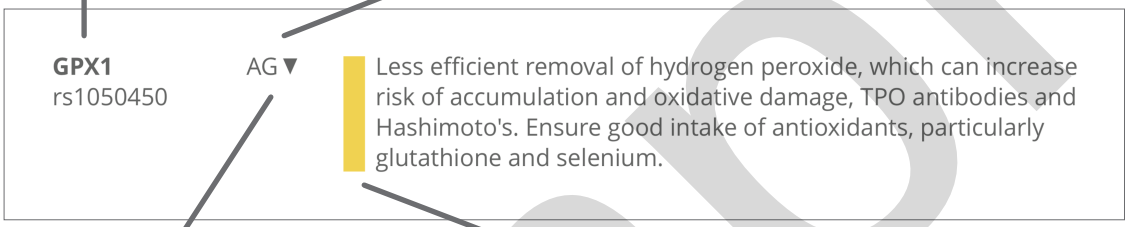
How to Read the Report

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.



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

References

BCO1 Beta-Carotene Oxygenase 1

Lietz G et al. "Single nucleotide polymorphisms upstream from the beta-carotene 15,15 -monoxygenase gene influence provitamin A conversion efficiency in female volunteers." J. Nutr (2012): 142 :161S–165S; doi: 10.3945/jn.111.140756. (https://www.ncbi.nlm.nih.gov/pubmed/22113863)

CAPZB Capping Actin Protein of muscle Z-line subunit Beta

Vijay Panicker et al. "A Locus on Chromosome 1p36 Is Associated with Thyrotropin and Thyroid Function as Identified by Genome-wide Association Study." Am J Hum Genet (2010): 87(3): 430–435. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933351/)

CD40 CD40 molecule

Xiao-Xiong Wang et al. "Association between the CD40 rs1883832 polymorphism and Graves' disease risk: a meta-analysis." EXCLI J (2019): 18: 10–20. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6449683/)

Xiaoming Chen et al. "Correlation between CTLA-4 and CD40 gene polymorphisms and their interaction in Graves' disease in a Chinese Han population." BMC Med Genet (2018): 19: 171. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142355/)

CTLA4 Cytotoxic T-lymphocyte Associated protein 4

Gu LQ et al. "Clinical associations of the genetic variants of CTLA-4, Tg, TSHR, PTPN22, PTPN12 and FCRL3 in patients with Graves' disease." Clin Endocrinol (2010): 72(2): 248-55. (https://www.ncbi.nlm.nih.gov/pubmed/19438904?dopt=Abstract)

Xiaoming Chen et al. "Correlation between CTLA-4 and CD40 gene polymorphisms and their interaction in Graves' disease in a Chinese Han population." BMC Med Genet (2018): 19: 171. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6142355/)

DIO1 Iodothyronine Deiodinase 1

Marco Medici et al. "Genetic Determination of the Hypothalamic-Pituitary-Thyroid Axis: Where Do We Stand?" Endocrine Reviews (2015): Vol 36, Issue 2, 214–244; https://doi.org/10.1210/er.2014-1081. (https://academic.oup.com/edrv/article/36/2/214/2354676)

Panicker V et al. "A Common Variation in Deiodinase 1 Gene DIO1 Is Associated with the Relative Levels of Free Thyroxine and Triiodothyronine." The Journal of Clinical Endocrinology and Metabolism (2008): 93(8): 3075-3081; doi:10.1210/jc.2008-0397. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2515080/)

Philibert RA et al. "The Relationship of Deiodinase 1 Genotype and Thyroid Function to Lifetime History of Major Depression in Three Independent Populations." American journal of medical genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics (2011): 156(5): 593-599; doi:10.1002/ajmg.b.31200. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3236034/)

DIO2 Iodothyronine Deiodinase 2

Gałecka et al. "Association of the DIO2 gene single nucleotide polymorphisms with recurrent depressive disorder." Acta Biochim Pol (2015): 62(2): 297-302. (https://www.ncbi.nlm.nih.gov/pubmed/26098717)

He B et al. "Association of genetic polymorphisms in the type II deiodinase gene with bipolar disorder in a subset of Chinese population." Prog Neuropsychopharmacol Biol Psychiatry (2009): 33: 986–90. (https://www.ncbi.nlm.nih.gov/pubmed/19427350)

Vijay Panicker, Ponnusamy Saravanan, Bijay Vaidya, Jonathan Evans, Andrew T. Hattersley, Timothy M. Frayling, Colin M. Dayan; Common Variation in the DIO2 Gene Predicts Baseline Psychological Well-Being and Response to Combination Thyroxine Plus Triiodothyronine Therapy in Hypothyroid Patients, The Journal of Clinical Endocrinology & Metabolism, Volume 94, Issue 5, 1 May 2009, Pages 1623–1629, https://doi.org/10.1210/jc.2008-1301 (https://www.ncbi.nlm.nih.gov/pubmed/19190113)

Yalakanti et al. "Association of Type II 5 Monodeiodinase Thr92Ala Single Nucleotide Gene Polymorphism and Circulating Thyroid Hormones Among Type 2 Diabetes Mellitus Patients." Indian J Clin Biochem (2016): 31(2): 152–161. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4820430/)

FCRL3 Fc receptor like 3

Thabet MM, Wesoly J, Slagboom PE, Toes RE, Huizinga TW. FCRL3 promoter 169 CC homozygosity is associated with susceptibility to rheumatoid arthritis in Dutch Caucasians. Ann Rheum Dis. 2007;66(6):803–806. doi:10.1136/ard.2006.064949 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1362949/)

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