Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **44** Issue **S-1 Year 2023** Page **1016:1032***

TSH Receptor Gene and Autoimmune Thyroid Diseases

Manjusha K[1], Desigamani K[2], Sumanth Kumar B[3], A Gnanavel[4], Jeyapal V[5], Jineesh VC[1], Sureka V[6], Dinesh Roy D[7*]

[1]Research Scholar, Meenakshi Academy of Higher Education and Research (MAHER-Deemed to be University), West K.K Nagar, Chennai, Tamil Nadu, India.
[2]Professor, Dept. of Biochemistry, Meenakshi Medical College and Research Institute (MMCHRI), Enathur, Kanchipuram, Tamilnadu
[3]Associate Professor, Dept. of Biochemistry, Meenakshi Medical College & Research Institute (MMCHRI), Enathur, Kanchipuram, Tamilnadu
[4]Professor, Dept. of Anatomy, Meenakshi Medical College and Research Institute (MMCHRI), Enathur, Kanchipuram, Tamilnadu
[5]Senior Cardiologist, Hridalaya Heart Foundation, Thiruvananthapuram-695024
[6]Dean- Research, Meenakshi Academy of Higher Education and Research (MAHER-Deemed to be University), West K.K Nagar, Chennai, Tamil Nadu, India.
[7]Cytogeneticist, Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, Kerala, India
ORCID ID: 0009-0005-7124-148X[7]

**Corresponding author's E-mail: drdineshroyd@gmail.com*

Article History

Received: 06 June 2023
Revised: 05 Sept 2023
Accepted: 17 Oct 2023

Abstract

The primary regulators of thyroid activity are the thyroid-stimulating hormone (TSH) and its receptor (TSH-R). Studies have shown that genetic variants in the TSHR gene can increase susceptibility to autoimmune thyroid diseases (AITD). The TSHR gene is located on chromosome 14q31 and encodes a membrane-bound receptor that interacts with TSH to regulate thyroid hormone synthesis and secretion. AITD including Graves' disease (GD) and Hashimoto's thyroiditis (HT), are the most common thyroid disorders, affecting millions of people worldwide. In AITD, autoantibodies can bind to and activate the TSHR, leading to increased thyroid hormone production and secretion in GD, or thyroid destruction and hypothyroidism in HT. In addition to its role in thyroid hormone synthesis and secretion, some studies also revealed that the TSHR has also been implicated in a variety of other physiological processes, including bone metabolism, reproduction, and immune regulation. Genetic variation in the TSHR region may affect the expression, post-translational processing, and/or protein structure, which in turn may cause or worsen the autoimmune response. The TSHR gene and its products are widely used in diagnostic testing for AITD. Understanding the molecular mechanisms underlying the interaction between the TSHR and autoantibodies is critical for developing new diagnostic and therapeutic strategies for AITD.

Keywords: *Thyroid-Stimulating Hormone; Autoimmune Thyroid Diseases; Hyperthyroidism; Thyroid-Stimulating Hormone Receptor Gene; Gene Mutation; Congenital Hypothyroidism; Thyroid Cancer*

1. Introduction

The thyroid-stimulating hormone receptor (TSHR) gene, is a gene that codes for a receptor protein found on the surface of thyroid cells. This receptor is specific to thyroid-stimulating hormone (TSH), produced by the pituitary gland and stimulates the thyroid gland to produce and release thyroid hormones, which have an impact on almost all body cells and organs. Jeziorowska et al. (2006) explained that, "the human TSHR gene has been mapped to chromosome 14q31 and cDNA of TSHR

codes for the protein of 764 amino acids, including a signal peptide of 20 amino acids" [1]. Davies et al. [2] defined that, "TSHR is a G protein–linked, 7–transmembrane domain (7-TMD) receptor that undergoes complex posttranslational processing unique to this glycoprotein receptor family". Citterio et al. [3] stated that, "thyroid hormone synthesis is stimulated by TSH activating its receptor (TSHR), which upregulates the activity of many thyroid gene products which are involved in hormonogenesis".

TSHR and its ligand, TSH, are key regulators of thyroid activity. According to Pang et al. [4] "TSHR, as a kind of thyroid specific gene, plays a key role in the regulation of thyroid's physiological functions and the occurrence and development of thyroid diseases". Among the glycoprotein hormone receptors, the TSH receptor on the thyrocyte surface is distinctive in that it consists of two subunits: an extracellular A-subunit along with B-subunit which is transmembrane and cytosolic [5]. Kleinau et al. [6] defined that, "the extracellular A-subunit possesses the TSH binding sites, composed of the leucine rich repeat domain (LRRD) and conformational change upon binding with TSH or stimulatory auto-antibodies leads to activation of TSHR, thereby switches on the intracellular B-subunit-coupled downstream signalling pathways". Chen et al. [7] noted that, "the gene encodes a full-length protein residue, harbouring a molecular weight of 87 kDa. In thyroid cells or extra-thyroidal cells, it may also exist as a single polypeptide chain in some circumstances".

According to National Library of Medicine [8], "the TSHR gene provides instructions for making a protein known as a receptor, that attaches (binds) to the TSH hormone and this receptor spans the membrane of certain cells (called follicular cells) in the thyroid gland, which is a butterfly-shaped tissue in the lower neck". It is a 7-TDM G protein-coupled receptor anchored to the plasma membrane surface of thyrocytes and several other cell types [9]. Recently, National Center for Biotechnology Information (NCBI) [10] reported that, "an important regulator of thyroid cell metabolism is the membrane protein produced by this gene and the activity of encoded protein, which is a receptor for thyrothropin and thyrostimulin is adenylate cyclase mediated. The defect in this gene causes different forms of hyperthyroidism".

Chu & Yeh [11] pointed out that, "the relationships have been established between genetic variations in TSHR gene and thyroid diseases, such as autoantibody-mediated and genetic variant-induced hyperactivation or repression of TSHR, causing hyper- or hypo-thyroidism". Kopp [12] explained that, "TSHRs are directly involved in the pathogenesis of Graves' disease, autoimmune hypothyroidism, toxic adenomas, familial and sporadic non-autoimmune hyperthyroidism, and certain forms of resistance to TSH". Pujol-Borrell et al. [13] denoted that, "TSHR is of special interest as it codes for the target of TSHR stimulating antibodies (TSAbs), which are unequivocally pathogenic and an exception in autoimmunity by being stimulating rather than neutral, blocking, or cytotoxic".

Kleinau & Krause [14] pointed out that, "TSHR is a family member of cell surface glycoprotein hormone receptors that includes those for luteinizing hormone (LH) and follicle stimulating hormone (FSH)". Citterio et al. [15] mentioned that, "TSHR stimulation influences several important thyroglobulin post-translational modifications that could increase de novo T3 formation". Rapoport et al. [16] stated that, "the multimeric structure of TSHR drives affinity maturation of the pathogenic autoantibodies in Graves' disease (GD). Variations in TSHR gene is a predominant candidate for GD, which is the most common autoimmune thyroid diseases (AITD). Shih et al. [17] reported that, "the expression and functional role of TSHR in a variety of non-thyroid cancerous tissues, including melanoma, glioma, lung cancer, breast cancer, ovarian cancer and liver cancer, have been reported".

2. Materials And Methods

In this research endeavor, we embarked on an extensive examination of the thyroid-stimulating hormone receptor (TSHR) gene and its significance in the context of autoimmune thyroid diseases (AITD). Our research methodology involved a thorough and all-encompassing literature review, drawing from a multitude of reputable sources. In June 2023, we executed a systematic search that harnessed the resources of esteemed databases, such as PubMed, Web of Science, as well as pertinent medical and scientific journals. Our overarching objective was to encompass articles published up to a predetermined date, thereby constructing a current and comprehensive foundation upon which our investigation could be firmly built.

Literature search

The literature search was conducted with meticulous attention to detail, forming an essential component of our research strategy. This process played a pivotal role in acquiring a diverse range of scholarly articles and scientific insights that are foundational to our study's objectives. To ensure precision, we strategically selected specific keywords for the search, including "thyroid-stimulating hormone," "autoimmune thyroid diseases," "hyperthyroidism," "thyroid disease," "gene mutation," "Congenital Hypothyroidism," and "thyroid cancer." These keywords were chosen with precision to guarantee that the articles retrieved were directly pertinent to the TSHR gene and its associations with thyroid health. This strategic inclusion of keywords was instrumental in enabling us to access highly relevant research findings.

Review Method and Selection Criteria

The review methodology was meticulous in maintaining the quality and relevance of the included studies. We adhered to a stringent set of criteria during the selection process. This included evaluating studies for their alignment with our research objectives based on the specified keywords, ensuring they were published in peer-reviewed journals to guarantee credibility, considering the availability of full-text articles for comprehensive analysis, and prioritizing studies involving human adult subjects to maintain relevance to autoimmune thyroid diseases and the TSHR gene. Exclusions were made for studies that did not meet these criteria or were unrelated, resulting in a rigorous selection process to uphold the quality and relevance of the synthesized research in our review.

Data Extraction

In our study, data extraction played a critical role as it systematically organized essential findings and insights from the chosen research. This process involved identifying and collecting key data points related to the TSHR gene, encompassing genetic variations, its function in thyroid processes, its connection to autoimmune thyroid diseases, and the underlying molecular mechanisms. Our comprehensive approach covered various aspects, including statistics, experimental outcomes, and clinical results. Overall, our research methodology, selection criteria, and data extraction procedures were thoughtfully devised to provide a strong foundation for exploring the TSHR gene's significance in autoimmune thyroid diseases and its potential implications for diagnostics and therapeutics.

3. Results and Discussion

TSHR Autoantibodies (TRAb)

Weetman [18] pointed out that, “antibodies to the TSHR play a unique role in the development of autoimmune hyper- and hypothyroidism but antibodies to thyroid peroxidase (TPO) and thyroglobulin (TG) neither play a major nor casual role in the pathophysiology of AITD”. TSH receptor autoantibodies (TRAb) remains the sole cause of the hyperthyroidism in GD. Giannone et al. [19] showed that, “the reported prevalence of TRAb in patients with chronic thyroiditis (CT) range from 0 to 48%”. Smith et al. [20] stated that, “auto antibodies for TSHR result in GD with over-activity of the thyroid gland”. The amount of TSHR expressed is determined by TSHR gene polymorphisms, and this could have an impact on TRAb synthesis.

Menconi et al. [21] denoted that, “organs other than the thyroid can also be affected by the TRAb, leading to the extrathyroidal manifestations of GD, namely Graves' ophthalmopathy, which is observed in ~50% of patients, and Graves' dermopathy and acropachy, which are quite rare”. A study done by Kahaly & PD [22] stated that, “autoantibodies to the TSHR (anti-TSHR-Ab) are directly involved in the pathophysiology of GD and HT, where GD is caused by TSAb, which act as agonists by stimulating thyroid growth and synthesis of thyroid hormone in an unregulated manner”. TRAb binds to the TSHR in specific binding sites, while Sanders et al. [23] stated that, “in rare cases, TRAb act as antagonists and prevent the TSH-R binding and stimulating activities of TSH and can cause hypothyroidism”.

According to Brent [24], “autoantibodies to various thyroid antigens are the most important biomarkers that are used to differentiate AITD from other thyroid conditions”. Zöphel et al. [25] added that, “Anti-TSHR-Ab can be detected with immunoassays, which measure TSHR-binding inhibitory immunoglobulins (TBII) and with cell-based bioassays, which measure either TSAb or TBAb”. Diana et al. [26] differentiated that, “cell-based bioassays is more sensitive in detecting low concentrations of

anti-TSHR-Ab compared to TBII binding assays and it can exclusively differentiate between the anti-TSHR-Ab functionality". Thus, they can be utilised as a reliable biomarker for the detection of AITD.

TSHR blocking autoantibodies (TBAb)

Zöphel et al. [25] defined that, "blocking anti-TSHRAb (TBAb) acts as TSHR antagonists, which block the action of the TSH and can cause the hypothyroidism". Brent [24] denoted that, "anti-TSHR-Ab are directly involved in the pathophysiology of GD and HT". Furmaniak et al. [27] added that, "anti-TSHR-Ab that bind to the TSHR and neither activate the cAMP pathway nor stimulate thyroid hormone synthesis, but rather act as TSHR antagonists inhibiting the activation of signal transduction pathways, are defined as blocking anti-TSHR-Ab or TBAb". Takasu & Matsushita [28] found that, "in 9% of individuals with goitrous and 25% of atrophic thyroiditis individuals, TBAbs were found".

According to Diana et al. [26], "TBAb were prevalent in both subjects with HT (11 %) as well as in those with GD (8 %)". In 1987, Chiovato et al. [29] stated that, "on Italian population two studies were performed and in the first were evaluated 38 patients with chronic thyroiditis (CT) and hypothyroidism and TRAb were found in 15%". Recently, Giannone et al. [19] reported that, "the prevalence of TRAb reported between 1978 and 2021 in a total of 2,308 patients with CT varied between 0 and 48% with a similar prevalence for TBAb". The study also showed a "prevalence of TBAb-positive patients with HT and GD was 67 of 722 (9·3%) and 15 of 357 (4·2%)". Kahaly et al. [30] added that, "it is becoming clear that in addition to the well-known T-cell-mediated cytotoxicity and the involvement of CDC in HT, thyroid dysfunction and hypothyroidism can be induced by the occurrence and presence of TBAb".

Allelein et al. [31] reported that, "in GD patients with a duration of less than six months, 27/29 (93%) and 28 (97%) were TSHR-Ab positive with the bridge and TSAb bioassay". Diana et al. [32] also stated that, "cell-based bioassays are more sensitive in detecting low anti-TSHR-Ab concentrations and exclusively differentiate between the anti-TSHR-Ab functionality". Li et al. [33] showed that "bioassays that measure TSHR-blocking activity are based on the cell-based systems, but they detect the ability of patient antisera to block TSH or TSAb-stimulated cAMP levels or luciferase expression".

TSHR gene polymorphism

Jeziorowska et al. [1] mentioned that, "a study of some familial cases has allowed identification of mutations in several known genes, including that encode the TSHR". Sancak et al. [34] observed that patients with thyroid nodules showed TSHR gene polymorphism. Fuhrer [35] reported that, "22 different causative loss-of function mutations in TSHR gene have been reported as occurring in families from different ethnic and geographical origins". Mon et al. [36] stated that, "TSHR mutation rate is higher in patients with hyperfunctioning thyroid nodules with a prevalence ranging from 20% to 82%". Mai & Burch [37] reported that, "TSHR hyperactivation can also occur as a consequence of activating mutations in the TSHR, a rare condition that has been described primarily in patients of European ancestry".

In 2009, Weetman [38] defined that, "it is possible that altered splicing of the exons coding the extracellular domain of the receptor, produced by the polymorphism, could lead to a more immunogenic TSH-R protein being produced". Citterio et al. [39] observed that, "thyroglobulin secreted from thyrocytes with genetic deletion of TSHRs consistently exhibited decreased de novo T3 formation compared with T3 synthesized in the thyroglobulin secreted from thyrocytes with stimulated TSHRs". Kumorowicz-Czoch et al. [40] found that, "TSHR gene copy number variations (CNVs) are involved in the occurrence of congenital hypothyroidism". Pang et al. [41] stated that, "aberrant TSH levels were associated with the CNV of the TSHR gene". He also added that, "TSHR CNVs were higher in a population of patients with TSH abnormalities when compared to healthy controls, indicating that TSH abnormalities are at risk due to TSHR".

Chu et al. [42] found that, "TSHR gene polymorphisms associated with GD/ Graves ophthalmopathy (GO) susceptibility were found to be located in intron 1". However, Dechairo et al. [43] revealed that, "by the identification of linkage disequilibrium blocks using 40 SNPs, it has been possible to hone down and delineate a particular intronic TSHR SNP (rs2268458), which is consistently associated with GD". In 2005, Hiratani et al. [44] reported that, "the strong association within TSHR intron-7 and -8 (especially rs2268475, rs1990595 and rs3783938), and the study also investigated three variants within

intron-1 and identified some evidence of association with TSHR intron-1 SNP, rs2268474 (P=0.026) in the Japanese, and TSHR gene became the first GD's specific locus". This review focus on the autoimmune disease that impacts the thyroid gland as a result of a TSHR gene mutation.

Autoimmune thyroid disease (AITD)

The thyroid gland is the most common organ that is affected by autoimmune disease. In the words of Antonelli et al. [45] autoimmune thyroid disorder (AITD) are brought on by immune system instability that leads to an immune attack on the thyroid. It is an organ specific and T cell-mediated autoimmune disorders [46]. Most prevalent autoimmune condition which affects women is thyroid autoimmunity (TAI), 5-20% women of reproductive age is affected by this condition [47]. Ragusa et al. [48] reported that, "AIT occurs in about 0.3-1.5/1000 subjects/year, with a major frequency in women than in men (4-10 times)". Moreover, Artini et al. [49] stated that, "the thyroid autoimmunity can cause subclinical or overt hypothyroidism or it may be associated to them; it can also be present without thyroid disfunction and therefore remain latent, asymptomatic or undiagnosed for a long time".

AITDs, which frequently affect specific organs and range in severity and treatability from mild to severe, include Hashimoto's disease (HD) and GD [50]. These are two complex disorders that are influenced by both genetic as well as environmental factors. Lymphocytic infiltration of thyroid and autoantibody production against thyroid-specific antigens, such as TSHR, TG, and TPO, are characteristics of AITDs [51]. Werner et al. [52] observed that, "HD and postpartum thyroiditis/painless thyroiditis share a predominately T cell-mediated autoimmunity, while Graves' disease is characterized by a primarily humoral response and the presence of anti- thyroid stimulating hormone receptor antibodies".

Wiersinga [53] explained that, "polymorphisms in thyroid genes (TG, TSHR) and immunoregulatory genes (HLA, CTLA4, PTPN22, CD40, FCRL3, IL2RA, FOXP3) would contribute for about 70% to AITD, and environmental exposures (like iodine, smoking, infections, parity) for the remaining 30%". According to Brand & Gough [51], "three gene regions consistently associated with AITD include the Human Leucocyte Antigen (HLA) region, cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and tyrosine-protein phosphatase nonreceptor type 22 (PTPN22), which represent general autoimmune risk loci and encode molecules vital for correct immune system function". Ragusa et al. [48] added that, "other AITD genes [FCRL3, TSH receptor (TSH-R), and HLA class I were identified through further case-control studies, and confirmed by genome-wide association studies (GWAS)".

Chemokines and cytokines have a significant part in the immune-pathogenesis of AITDs. Brand & Gough [51] also stated that, "it is possible that inheritance of susceptibility alleles at more than one of these genes may have an additive effect on AITD risk". Kivity et al. [54] showed that "the prevalence of vitamin D deficiency was 2.5-fold higher in females with thyroid autoimmunity as compared with healthy individuals and that vitamin D deficiency also correlated to the presence of thyroid antibodies". We will be delving into the specifics of AITD further down the line.

Graves' Disease

According to Menconi et al. [21], "Graves' disease (GD) is an autoimmune disorder involving the thyroid gland, typically characterized by the presence of circulating autoantibodies that bind to and stimulate the TSHR, resulting in hyperthyroidism and goiter". Eliana et al. [55] described GD as "the most common condition found in thyrotoxicosis, caused by a complex relationship between genetic factors and environmental influences". Tomer & Huber [56] reported that, "the majority of investigators share the concept that GD is a multifactorial disease caused by a complex interaction between genetic and environmental factors that lead to the loss of immune tolerance to thyroid antigens, and therefore to the initiation of an immune reaction against the thyroid". In 2008, Brent [57] explained that, "the prevalence of GD in America and Europe is about 0.5- 1%, while in Indonesia is estimated at about 0.05%".

TSHR gene is one of the most closely linked gene to GD. Liao et al. [58] defined that, "the development of GD is correlated with TSHR, which is crucial for stimulating the development and differentiation of the thyroid gland". Xiong et al. [59] denoted that, "though the genetic associations of the TSHR gene have been studied in different ethnic groups for a long time, there is still controversy about the genetic

associations for GD". Fujii et al. [60] stated that, "polymorphisms in TSHR gene determine the amount of TSHR expressed, which may in turn influence TRAb production". Płoski et al. [61] suggested that, "TSHR gene polymorphisms may influence the protein structure, which alter the autoimmune response against the TSHR in GD and GO". Ho et al. [62] pointed out that, "GD was linked to an SNP in the intron 1 of TSHR gene". A study conducted by Dechairo et al. [43] confirmed that the events involving GD were influenced by the TSHR gene rs2268458 in intron-1. Stefan et al. [63] also found that, "development of GD is strongly associated with the SNPs of TSHR gene within the enhancer regions".

Fujii et al. [60] revealed that, "among the evaluated TSHR gene SNPs, the rs4411444 GG genotype and the rs4903961 C allele in the enhancer regions of the TSHR gene were most strongly associated with the development of GD, especially intractable disease". Eliana et al. [55] found that, "GD subjects with CC genotype TSHR gene SNP rs2268458 of intron 1 were at risk for relapse of 13.3 times higher than those with TT genotype". Maia et al. [64] reported that, "the diagnosis of GD was based on standard clinical criteria, including increased serum levels of free thyroxine (FT4) and triiodothyronine (T3), undetectable TSH, positive TRAb values, presence of diffuse goiter by ultrasonography, and increased thyroidal uptake of pertechnetate".

Table 1- Polymorphism of TSHR gene associated with GD

Polymorphism	Population	Cases	Control	Polymorphism identified (%)	Disease Risk	Reference
(intron 1) rs2268458	Caucasian (USA)	346	402	51.1	YES	Yin et al. [65]
(intron 1) rs179247	Japanese	112	56	39.3	YES	Inoue et al. [66]
(chr.14q GD1 locus) rs2284720	Caucasian (USA)	225	183	29.1	YES	Tomer et al. [56]
(intron 1) rs179247	Caucasian (Poland)	226	–	58.2	n.d*	Jurecka-Lubieniecka et al. [67]
rs12101261 rs179243	Chinese Han	5 368	4942	–	YES	Liu et al. [68]
(intron 1) rs179247	Brazilian	279	296	41.9	YES	Bufalo et al. [69]

Graves Ophthalmopathy

Graves' ophthalmopathy or Graves' orbitopathy was defined by Menconi et al. [21] as, "enlargement and inflammation of orbital tissues, especially retroorbital fat". Xiong et al. [59] explained the characters of GO as, "retraction of the upper eyelids, chemosis, palpebral oedema, exophthalmus and extra ocular muscle hypertrophy". It is also known as thyroid eye disease (TED). Bartalena & Fatourechi [70] reported that, "about 25–50% of GD patients have clinical signs of GO, most having only mild disease". Bahn [71] explained that, "it is the most common extrathyroidal feature of GD, is clinically present in about 50% of patients, and, although its pathogenesis remains to be completely elucidated, it is believed to be due to an autoimmune reaction against antigens shared by the thyroid and orbital tissues, among which the TSHR is the most reasonable candidate".

Wiersinga et al. [72] stated that, "a prerequisite for the involvement of TSHR as an autoantigen in GO is the expression of the receptor on target cells of affected orbital tissues". Several investigations have shown that TSHR mRNA and protein are present in GO patients' orbital tissue. In an experimental *in vivo* study with mouse models, Schlüter & colleagues [73] found that, "100% of GO mice of both sexes equally developed TRAbs with an inhibition activity range of 80% inhibition of TSH binding and 90% of both sexes exhibited TSHR antibodies with stimulating activity (TSAbs) to the mouse TSHR when compared to the respective ß-Gal immunized control mice".

In 2000, Khoo et al. [74] reported that, "using adequately sensitive assays, autoantibodies directed against the thyrotropin receptor can be detected in essentially every patient with GO". High TRAb levels in the early stages of GO indicate a poor prognosis since they are correlated with the severity and

clinical activity of the disease [75]. A study done by Bufalo et al. [69] he found that, "individuals with GO also presented lower mean TRAb levels (96.3 ± 143.9 U/L) than individuals without GO (98.3 ± 201.9 U/L)".

Hashimoto's Thyroiditis

Hashimoto's disease (HD), also known as chronic lymphocytic thyroiditis, is an autoimmune disorder in which the immune system attacks the thyroid gland, leading to inflammation and damage to the thyroid tissue. Ragusa et al. [48] defined that, "Hashimoto's thyroiditis (HT), the most frequent AITD, is the leading cause of hypothyroidism in the iodine-sufficient areas of the world". Diana et al. [76] specified that, "HT is the major cause of autoimmune hypothyroidism". Combining genetic predisposition and environmental variables, HT is caused by a lack of immunological tolerance, which results in an autoimmune attack on thyroid tissue and the development of the disease [48]. The disease is characterized by specific histopathological abnormalities, which include a high degree of infiltration by lymphocytes, the presence of lymphoid germinal centers, and damage to the thyroid follicles.

Iddah & Macharia [77] stated that, "about 20% of postpartum thyroiditis patients develop the classical HT in later years". Studies have identified variations in the TSHR gene that are associated with an increased risk of developing HT. In particular, mutations that affect the expression or function of the TSHR protein can contribute to the development of the disease. Zaaber et al. [76] reported that, "determining role of thyroid-specific gene in AITD pathogenesis, the TSHR gene could conceivably be a candidate gene for HT". The minor genotypes and alleles of TSHR gene SNPs were thought to be more common in HD since the pathological condition of HD is typically characterised by an absence of a break in immunological tolerance to the TSHR antigen [60]. His team also observed that, "SNP E1-5 in the TSHR gene enhancer region, the frequencies of both minor genotypes and alleles were higher in HD patients than in controls". In the study done by Zaaber et al. [76] suggested that, "the TSHR rs1054708 polymorphism can be a protective factor against HT and AITD".

Diana et al. [76] mentioned that, "decreased thyroid hormone production in HT may be caused by TBAb which rather than causing thyroid cell death, bind to the TSHR and interfere with the ability of thyrocytes to respond to TSH". Patients with GD may also be TBAb-positive, especially during or after anti-thyroid medications, however most of the TBAb-positive individuals have HT. Levine [79] explained that, "HD is diagnosed by the absence of TRAb and the presence of other thyroid autoantibodies, including anti-Tg antibodies (TgAb) and/or anti-TPO antibodies (TPOAb)". Giannone et al. [19] identified that, "the prevalence of TBAb-positive patients with HT in the study was found to be 67 of 722 (9.3%)".

TSHR Gene In Other Thyroid Associated Diseases

One of the most prevalent endocrine disorders in the world is probably thyroid related disease. Thyroid gland has a significant impact on many physiological processes and cellular metabolism regulation. The execution of bodily processes may be disrupted by thyroid gland disorders. The regulation of our body's metabolism is greatly influenced by thyroid hormones. Gessl et al. [80] stated that, "women experience thyroid disorders in all of their forms significantly more frequently than males". Garber et al. [81] reported that the thyroid disorders will affect 1 in 8 American women at some point in their lives. In addition, some genetic conditions such as Down syndrome and Turner syndrome are known to increase the likelihood of thyroid disorders. Environmental factors such as iodine intake, radiation exposure, and viral infections can interact with genetic factors and contribute to the development of thyroid disorders. Moreover, Klein & Danzi [82] stated that, "thyroid hormones have an intimate relationship with cardiac function and some of the most significant clinical signs and symptoms of thyroid disease are the cardiac manifestations".

Iodine intake is a major risk factor for thyroid disease. Other factors of thyroid diseases include age, smoking status, genetic susceptibility, ethnicity, exposure to endocrine disruptors, and the development of innovative therapies such immune checkpoint inhibitors [83]. Worldwide populations are at risk for the prevalent disorders of hypothyroidism and hyperthyroidism, which have the potential to have severe health effects. TSH and its receptor TSHR are the primary regulators of thyroid activity. TSH levels

that are higher or lower are signs of hypothyroidism or hyperthyroidism, respectively. A few thyroid diseases other than AITDs that are associated with TSHR gene were briefly discussed below.

Subclinical Hypothyroidism

Subclinical hypothyroidism refers to a mild form of hypothyroidism that is not accompanied by any noticeable symptoms. It can occur in individuals of any age and is often a precursor to overt hypothyroidism. Biondi & Cooper [84] reported that, "the prevalence of subclinical hypothyroidism increases with aging and ranges from 3 to 16 % in individuals aged 60 years and older". Metwalley & Farghaly [85] explained subclinical hypothyroidism as, "the condition associated with an increased serum TSH concentration but a normal serum free thyroxine (FT4) level" The most frequent cause of subclinical hypothyroidism is autoimmunity.

Redford & Vaidya [86] described that, "subclinical hypothyroidism in younger patients (<65 years) is associated with an increased risk of coronary heart disease, heart failure and cerebrovascular disease. The risk increases with increasing levels of thyroid stimulating hormone, and is particularly high in patients with TSH levels ≥10.0 mu/L". Shin et al. [87] reported that, "patient with subclinical hypothyroidism, harbored (dual oxidase 2) DUOX2 (p.H189=, p.G488R) and TSHR (p.A204V) mutations". Atzmon et al. [88] showed that, "the high prevalence of the TSHR SNPs is associated with higher serum TSH levels and two SNPs were found in TSHR gene (namely rs10149689 and rs12050077) which are associated with increased TSH level". Research on the TSHR gene has led to the development of drugs that target this receptor, such as thyrotropin alfa, which is used to treat hypothyroidism.

Congenital Hypothyroidism

Subclinical congenital hypothyroidism (SCH) is a condition that is present at birth and is caused by an underactive thyroid gland. In a study by Rastogi & LaFranchi [89] explained that, "congenital hypothyroidism (CH) is a common endocrine disorder with prevalence ranging from 1:2000 to 1:4000 newborns". Based on genetic alterations, Fu & colleagues in 2016 [90] classified CH into two groups: (i) caused by disorders in the development of thyroid gland (thyroid dysgenesis) and (ii) abnormalities in the synthesis of thyroid hormone (dyshormonogenesis). Thyroid dysgenesis contributes the majority (80–85%) of the cases of CH [91]. According to Hermanns et al. [92], CH has been linked with TSHR mutations. Liu et al. [93] & Jain et al. [94] reported that, "dyshormonogenesis which comprises the final 15-20% of instances, is associated with mutations in DUOX2, TG, TPO, Pendrine (SLC26A4), dehalogenase 1 (DEHAL1) and sodium iodide symporter (NIS) genes".

One of the reported causes of CH is the thyroid dysgenesis which is associated with the TSHR gene mutation. More than 60 mutations have been found so far in TSHR gene. Schoenmakers & Chatterjee [95] added that, "both biallelic or monoallelic TSHR mutations lead to a wide spectrum of phenotypes, ranging from mild SCH with elevated TSH levels but normal thyroid hormone levels, to overt CH with thyroid hypoplasia". Fu et al. [90] found that, "monoallelic TSHR pathogenic variants were associated with SCH, while CH was linked to TSHR pathogenic variants in combination with other monoallelic pathogenic variants in DUOX2 or TG gene". Cassio et al. [96] observed that, "most of the patients with TSHR mutated variants have a normal size thyroid gland, while several patients show decreased (hypoplastic) thyroid glands". Shin et al. [87] identified that in 80% of the patients studied, the most common genetic causes of CH was TSHR and DUOX2 mutations.

Table 2- Genes associated with most common thyroid diseases.

Disease	Gene associated	Gene location	Encoding Protein function	Reference

Graves' Disease	*TSHR*	14q31.1	Regulates thyroid hormone expression and production.	Simmonds [97]
	HLA	6p21	Presenting endogenous antigens, such a virally derived antigens, for recognition by CD8+ T cells.	
	CTLA4	2q33.2	CTLA4 plays a role in inhibiting T-cell signalling.	
	PTPN22	1p13	T-cell signal transduction through interaction with molecules essential for T-cell receptor signalling.	
	CD40	20q12.2	Expressed on the surface of immune and non-immune cells.	Wang et al. [98]
Graves' Ophthalmopathy	*TSHR*	14q31.1	Activation of signaling pathways, contributes to the inflammatory response and cytokines, chemokines production.	Gillespie et al. [99]
	IL1B	2q14	Stimulating retroorbital fibroblast proliferation, glycosaminoglycan synthesis, and expression of immunomodulatory molecules.	Liu et al. [100]
Hashimoto's Disease	*CTLA-4*	2q33	Expressed on the surface of activated T lymphocytes, is a negative regulator of T-cell activation.	Ji et al. [101]
	MAGI3	6q15	Modulates activity of AKT/PKB which is expressed in the thyroid and regulates apoptosis.	Ajjan & Weetman [102]
	IL17F	6p12	Regulation of immune responses and inflammation.	Walsh et al. [103]
Hyperthyroidism	*TSHR*	14q31.1	Regulation of thyroid hormone production by the thyroid gland.	Cho et al. [104]
	GNAS	20q13.3	Mediates intracellular signaling pathways that are activated by various hormones and neurotransmitter.	Palos-Paz et al. [105]
Subclinical Hypothyroidism	*TSHR*	14q31.1	Regulates thyroid function through TSHR signalling pathways.	Shin et al. (2021) [87]
	DUOX2	15q15.3	Expressed as an important component of the thyroid hormone synthesis pathway.	
Congenital Hypothyroidism	*TSHR*	14q31.1	Mediates the effects of TSH and is important for the development and function of the thyroid gland.	Fu et al. [90]
	DUOX2	15q15.3	Production of hydrogen peroxide (H2O2) in the thyroid follicular cells for production of thyroid hormones.	

Hyperthyroidism

Kravets [106] stated that, "Hyperthyroidism is an excessive concentration of thyroid hormones in tissues caused by increased synthesis of thyroid hormones, excessive release of preformed thyroid hormones, or an endogenous or exogenous extrathyroidal source". Ross et al. [107] defined that, "overt hyperthyroidism is a subnormal serum TSH with elevated serum levels of free T3 and/or FT4". Graves' disease, toxic multinodular goitre, and toxic adenoma are the three most frequent causes of an excessive

production of thyroid hormones. Guerri et al. [108] added that, "too much production of the hormone thyroxine, which can accelerate body metabolism, causing unintentional weight loss and a rapid or irregular heartbeat".

According to De Leo et al. [109], "the nonautoimmune hyperthyroidism (NAH) has autosomal dominant inheritance and is caused by mutations in TSHR". These mutations result in the production of an overactive thyroid gland, which produces excess thyroid hormone. Paschke et al. [110] explained that, "constitutively activating germline mutations in the TSHR gene leading to NAH may be inherited in an autosomal dominant manner (familial or hereditary, FNAH), or may occur sporadically as a de novo condition, called: persistent sporadic congenital non-autoimmune hyperthyroidism (PSNAH)". Cho et al. [104] noted that, "nonautoimmune congenital hyperthyroidism by activating germline mutations in the TSHR gene shows a persistent and severe hyperthyroidism". Lüblinghoff et al. [111] described that, "the mutation affecting all thyroid cells, thus, associated with a diffuse enlargement of the thyroid gland or nodular transformation especially at later stages".

Subclinical Hyperthyroidism

Subclinical hyperthyroidism (SHyper) is used to define only by laboratory results rather than clinical criteria (Bahn et al., 2011) [71]. The level of thyroid hormone in these patients were usually found to be in between middle to upper normal range with suppressed thyrotropin and normal free T3 and T4 level [112]. According to Lueblinghoff et al. [113], "SHyper affects 0.5% of children and 15% of the elder people". Older patients with subclinical hyperthyroidism are usually asymptomatic [114] whereas, Mild adrenergic symptoms could occur in younger people [84]. Biondi & Cooper [115] identified that, "individuals with SHyper are more susceptible to bone and cardiovascular problems".

The causes of overt hyperthyroidism and SHyper are the same. Toxic adenoma or toxic multinodular goiter and Graves' disease are the common endogenous causes of SH [107] and the exogenous causes include "excessive levothyroxine, liothyronine usage or desiccated thyroid may reflect inadvertent overtreatment or intentional thyrotropin suppression" [116]. Genetic hyperthyroidism is brought on by activating mutations of the TSHR gene [117]. A plausible aetiology could not be found despite clinical and biochemical evidence that point to a TSH-R mutation. Nishihara et al. [118] added that, "mutations in TSHR can cause not only familial nonautoimmune hyperthyroidism and toxic adenoma, but also severe hyperthyroidism requiring surgery in neonatal period".

Thyroid Cancer

According to Cabanillas et al. [119], around 95% of thyroid malignancies are differentiated thyroid tumours (DTC), which include follicular thyroid cancer (FTC), papillary thyroid cancer (PTC), poorly differentiated thyroid cancer (PDTC) and Hürthle cell carcinoma. The most common subtype of thyroid cancer is differentiated, and for the majority of patients, the usual treatment is successful. Sung et al. [120] revealed that, "the incidence of thyroid cancer has increased rapidly and 586,202 new cases of thyroid cancer occurred globally in 2021". Being one of the most prevalent endocrine malignancy, DTC has consistently been seen with an incredibly long-term prognosis [121].

According to the findings from thyroid cancer DNA sequencing research, the majority of thyroid malignancies have a hereditary foundation. Franco et al. [122] "TSHR is the endogenous receptor for TSH and acts as the shared growth signalling receptor for benign thyrocytes and DTC". Shih et al. [123] found that "expression of TSHR was observed in both non-cancerous and cancerous hepatocellular carcinoma (HCC) tissues". In 2011, Fiore et al. [124] analyzed the attendance of PTC, elevated levels of antithyroid antibodies (ATA) and TSH in 13,738 patients with AITD". Gérard et al. [125] suggested that, "previous studies assessing thyroid differentiation markers of resected DTC specimens suggest that TSHR remains stalely expressed in the context of losing other markers, such as NIS and thyroglobulin". According to D'Agostino et al. [126] "the TSHR and NIS are key players in radioiodine-based treatment of differentiated thyroid cancers". Medici et al. [127] found that, "However, low titers of anti-TPO are also often detected in patients with thyroid carcinoma and sub-acute thyroiditis". Shih et al. [123] also reported that, "TSHR has been found in a number of extra-thyroid malignancies, such as ovarian, breast, and lung cancer".

4. Conclusion

Certain variations in genes such as TSHR, TPO, and DUOX2 have been associated with an increased risk of developing thyroid disorders such as hypothyroidism, hyperthyroidism, AITD and thyroid cancer. These genes are essential for controlling thyroid hormone synthesis and metabolism. In conclusion, the TSHR gene plays a critical role in the pathogenesis of autoimmune thyroid diseases and genetic variants in the TSHR gene can increase susceptibility to AITD, while autoantibodies that bind to and activate the TSHR are the hallmark of Graves' disease. Dysregulation of TSHR signalling, whether through genetic mutations or autoantibodies, can lead to altered thyroid hormone production and secretion, resulting in hyperthyroidism or hypothyroidism. Diagnostic testing for AITD often involves measurement of TSHR autoantibodies, which are highly specific for Graves' disease and can also be present in some cases of Hashimoto's thyroiditis. Ongoing research into the TSHR gene and its products, including autoantibodies, is likely to yield further insights into the complex mechanisms underlying AITD. These insights will help improve patient outcomes and lead to more targeted therapeutic interventions for these common and debilitating thyroid disorders.

Conflict of Interest

The Authors declare that there is no conflict of interest.

Author's Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References:

1. Jeziorowska, A., Pniewska-Siark, B., Brzeziańska, E., Pastuszak-Lewandoska, D., & Lewiński, A. (2006). A novel mutation in the thyrotropin (thyroid-stimulating hormone) receptor gene in a case of congenital hypothyroidism. Thyroid, 16(12), 1303-1309.
2. Davies, T. F., Ando, T., Lin, R. Y., Tomer, Y., & Latif, R. (2005). Thyrotropin receptor–associated diseases: from adenomata to Graves disease. The Journal of clinical investigation, 115(8), 1972-1983.
3. Citterio, C. E., Targovnik, H. M., & Arvan, P. (2019). The role of thyroglobulin in thyroid hormonogenesis. Nature Reviews Endocrinology, 15(6), 323-338.
4. Pang, Y., Guan, Y., Jin, X., Shen, H., Liu, L., Jia, Q., ... & Zhang, X. (2018). Association of TSHR gene copy number variation with TSH abnormalities. Biological Trace Element Research, 186, 85-90.
5. Rapoport, B., Aliesky, H. A., Chen, C. R., & McLachlan, S. M. (2015). Evidence that TSH receptor A-subunit multimers, not monomers, drive antibody affinity maturation in Graves' disease. The Journal of Clinical Endocrinology & Metabolism, 100(6), E871-E875.
6. Kleinau, G., Worth, C. L., Kreuchwig, A., Biebermann, H., Marcinkowski, P., Scheerer, P., & Krause, G. (2017). Structural–functional features of the thyrotropin receptor: a class A G-protein-coupled receptor at work. Frontiers in endocrinology, 8, 86.
7. Chen, C. R., Chazenbalk, G. D., Wawrowsky, K. A., McLachlan, S. M., & Rapoport, B. (2006). Evidence that human thyroid cells express uncleaved, single-chain thyrotropin receptors on their surface. Endocrinology, 147(6), 3107-3113.
8. National Library of Medicine, Medline Plus., 2015. https://medlineplus.gov/genetics/gene/tshr/#function
9. Davies, T., Marians, R., & Latif, R. (2002). The TSH receptor reveals itself. The Journal of clinical investigation, 110(2), 161-164.
10. National Center for Biotechnology Information (NCBI)., 2023. https://www.ncbi.nlm.nih.gov/gene/7253
11. Chu, Y. D., & Yeh, C. T. (2020). The molecular function and clinical role of thyroid stimulating hormone receptor in cancer cells. Cells, 9(7), 1730.
12. Kopp, P. (2001). Human Genome and Diseases: Review¶ The TSH receptor and its role in thyroid disease. Cellular and molecular life sciences CMLS, 58, 1301-1322.
13. Pujol-Borrell R, Giménez-Barcons M, Marín-Sánchez A, Colobran R. Genetics of Graves' disease: special focus on the role of TSHR gene. Hormone and Metabolic Research. 2015 Sep;47(10):753-66.
14. Kleinau G, Krause G. Thyrotropin and homologous glycoprotein hormone receptors: structural and functional aspects of extracellular signaling mechanisms. Endocrine reviews. 2009 Apr 1;30(2):133-51.
15. Citterio, C. E., Veluswamy, B., Morgan, S. J., Galton, V. A., Banga, J. P., Atkins, S., ... & Arvan, P. (2017). De novo triiodothyronine formation from thyrocytes activated by thyroid-stimulating hormone. Journal of Biological Chemistry, 292(37), 15434-15444.
16. Rapoport, B., Aliesky, H. A., Chen, C. R., & McLachlan, S. M. (2015). Evidence that TSH Receptor A-Subunit Multimers, Not Monomers, Drive Antibody Affinity Maturation in Graves' Disease. The Journal of clinical endocrinology and metabolism, 100(6), E871–E875.

17. Shih, Y. L., Huang, Y. H., Lin, K. H., Chu, Y. D., & Yeh, C. T. (2018). Identification of functional thyroid stimulating hormone receptor and TSHR gene mutations in hepatocellular carcinoma. Anticancer Research, 38(5), 2793-2802.
18. Weetman A. P. (2000). Graves' disease. The New England journal of medicine, 343(17), 1236–1248.
19. Giannone, M., Dalla Costa, M., Sabbadin, C., Garelli, S., Salvà, M., Masiero, S., ... & Betterle, C. (2022). TSH-receptor autoantibodies in patients with chronic thyroiditis and hypothyroidism. Clinical Chemistry and Laboratory Medicine (CCLM), 60(7), 1020-1030.
20. Smith, B. R., Sanders, J., & Furmaniak, J. (2007). TSH receptor antibodies. Thyroid, 17(10), 923-938.
21. Menconi, F., Marcocci, C., & Marinò, M. (2014). Diagnosis and classification of Graves' disease. Autoimmunity reviews, 13(4-5), 398-402.
22. Kahaly, G. J., & PD, O. (2017). Graves' disease. N Engl J Med, 376(2), 184.
23. Sanders, P., Young, S., Sanders, J., Kabelis, K., Baker, S., Sullivan, A., ... & Rees Smith, B. (2011). Crystal structure of the TSH receptor (TSHR) bound to a blocking-type TSHR autoantibody. Journal of molecular endocrinology, 46(2), 81.
24. Brent, G. A. (2008). Graves' disease. New England Journal of Medicine, 358(24), 2594-2605.
25. Zöphel, K., Roggenbuck, D., & Schott, M. (2010). Clinical review about TRAb assay's history. Autoimmunity reviews, 9(10), 695-700.
26. Diana, T., Wüster, C., Kanitz, M., & Kahaly, G. J. (2016). Highly variable sensitivity of five binding and two bio-assays for TSH-receptor antibodies. Journal of endocrinological investigation, 39, 1159-1165.
27. Furmaniak, J., Sanders, J., & Rees Smith, B. (2013). Blocking type TSH receptor antibodies. Autoimmunity highlights, 4(1), 11-26.
28. Takasu, N., & Matsushita, M. (2012). Changes of TSH-stimulation blocking antibody (TSBAb) and thyroid stimulating antibody (TSAb) over 10 years in 34 TSBAb-positive patients with hypothyroidism and in 98 TSAb-positive Graves' patients with hyperthyroidism: reevaluation of TSBAb and TSAb in TSH-receptor-antibody (TRAb)-positive patients. Journal of thyroid research, 2012.
29. Chiovato, L., Vitti, P., Lombardi, A., Lopez, G., Santini, F., Macchia, E., ... & Pinchera, A. (1987). Detection and characterization of autoantibodies blocking the TSH-dependent cAMP production using FRTL-5 cells. Journal of endocrinological investigation, 10, 383-388.
30. Kahaly, G. J., Kanitz, M., Kolbe, E., Matheis, N., & Diana, T. (2014). Thyroid stimulating autoantibodies are clinically useful and predictive in graves' disease–A prospective trial. Eur Thyroid J, 3(suppl 1), 24.
31. Allelein, S., Diana, T., Ehlers, M., Kanitz, M., Hermsen, D., Schott, M., & Kahaly, G. J. (2019). Comparison of a bridge immunoassay with two bioassays for thyrotropin receptor antibody detection and differentiation. Hormone and Metabolic Research, 51(06), 341-346.
32. Diana, T., Krause, J., Olivo, P. D., König, J., Kanitz, M., Decallonne, B., & Kahaly, G. J. (2017). Prevalence and clinical relevance of thyroid stimulating hormone receptor-blocking antibodies in autoimmune thyroid disease. Clinical & Experimental Immunology, 189(3), 304-309.
33. Li, Y., Kim, J., Diana, T., Klasen, R., Olivo, P. D., & Kahaly, G. J. (2013). A novel bioassay for anti-thyrotrophin receptor autoantibodies detects both thyroid-blocking and stimulating activity. Clinical & Experimental Immunology, 173(3), 390-397.
34. Sancak, S., Jaeschke, H., Eren, F., Tarcin, O., Guellueoglu, B., Sen, L. S., ... & Eszlinger, M. (2011). High prevalence of TSHR/Gsα mutation-negative clonal hot thyroid nodules (HNs) in a Turkish cohort. Hormone and metabolic research, 43(08), 562-568.
35. Führer, D., Lachmund, P., Nebel, I. T., & Paschke, R. (2003). The thyrotropin receptor mutation database: update 2003. Thyroid, 13(12), 1123-1126.
36. Mon, S. Y., Riedlinger, G., Abbott, C. E., Seethala, R., Ohori, N. P., Nikiforova, M. N., ... & Hodak, S. P. (2018). Cancer risk and clinicopathological characteristics of thyroid nodules harboring thyroid-stimulating hormone receptor gene mutations. Diagnostic cytopathology, 46(5), 369-377.
37. Mai, V. Q., & Burch, H. B. (2012). A Stepwise Approach to the Evaluation and Treatment of Subclinicalhyperthyroidism. Endocrine Practice, 18(5), 772-780.
38. Weetman A. P. (2009). The genetics of autoimmune thyroid disease. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme, 41(6), 421–425.
39. Citterio, C. E., Veluswamy, B., Morgan, S. J., Galton, V. A., Banga, J. P., Atkins, S., ... & Arvan, P. (2017). De novo triiodothyronine formation from thyrocytes activated by thyroid-stimulating hormone. Journal of Biological Chemistry, 292(37), 15434-15444.
40. Kumorowicz-Czoch, M., Madetko-Talowska, A., Tylek-Lemanska, D., Pietrzyk, J. J., & Starzyk, J. (2015). Identification of deletions in children with congenital hypothyroidism and thyroid dysgenesis with the use of multiplex ligation-dependent probe amplification. Journal of Pediatric Endocrinology and Metabolism, 28(1-2), 171-176.

41. Pang, Y., Guan, Y., Jin, X., Shen, H., Liu, L., Jia, Q., ... & Zhang, X. (2018). Association of TSHR gene copy number variation with TSH abnormalities. Biological Trace Element Research, 186, 85-90.
42. Chu, X., Pan, C. M., Zhao, S. X., Liang, J., Gao, G. Q., Zhang, X. M., Yuan, G. Y., Li, C. G., Xue, L. Q., Shen, M., Liu, W., Xie, F., Yang, S. Y., Wang, H. F., Shi, J. Y., Sun, W. W., Du, W. H., Zuo, C. L., Shi, J. X., Liu, B. L., … China Consortium for Genetics of Autoimmune Thyroid Disease (2011). A genome-wide association study identifies two new risk loci for Graves' disease. Nature genetics, 43(9), 897–901.
43. Dechairo, B. M., Zabaneh, D., Collins, J., Brand, O., Dawson, G. J., Green, A. P., Mackay, I., Franklyn, J. A., Connell, J. M., Wass, J. A., Wiersinga, W. M., Hegedus, L., Brix, T., Robinson, B. G., Hunt, P. J., Weetman, A. P., Carey, A. H., & Gough, S. C. (2005). Association of the TSHR gene with Graves' disease: the first disease specific locus. European journal of human genetics : EJHG, 13(11), 1223–1230.
44. Hiratani, H., Bowden, D. W., Ikegami, S., Shirasawa, S., Shimizu, A., Iwatani, Y., & Akamizu, T. (2005). Multiple SNPs in intron 7 of thyrotropin receptor are associated with Graves' disease. The Journal of clinical endocrinology and metabolism, 90(5), 2898–2903.
45. Antonelli, A., Ferrari, S. M., Corrado, A., Di Domenicantonio, A., & Fallahi, P. (2015). Autoimmune thyroid disorders. Autoimmunity reviews, 14(2), 174–180.
46. Orgiazzi J. (2012). Thyroid autoimmunity. Presse medicale (Paris, France : 1983), 41(12 P 2), e611–e625.
47. Poppe, K., Glinoer, D., Tournaye, H., Devroey, P., Schiettecatte, J., Haentjens, P., & Velkeniers, B. (2006). Thyroid autoimmunity and female infertility. Verhandelingen - Koninklijke Academie voor Geneeskunde van Belgie, 68(5-6), 357–377.
48. Ragusa, F., Fallahi, P., Elia, G., Gonnella, D., Paparo, S. R., Giusti, C., Churilov, L. P., Ferrari, S. M., & Antonelli, A. (2019). Hashimotos' thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best practice & research. Clinical endocrinology & metabolism, 33(6), 101367.
49. Artini, P. G., Uccelli, A., Papini, F., Simi, G., Di Berardino, O. M., Ruggiero, M., & Cela, V. (2013). Infertility and pregnancy loss in euthyroid women with thyroid autoimmunity. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology, 29(1), 36–41.
50. Menconi, F., Oppenheim, Y. L., & Tomer, Y. (2008). Graves disease. Diagnostic criteria in autoimmune diseases, 231-235.
51. Brand, O. J., & Gough, S. C. L. (2010). Genetics of thyroid autoimmunity and the role of the TSHR. Molecular and cellular endocrinology, 322(1-2), 135-143.
52. Werner, S. C., Ingbar, S. H., Braverman, L. E., & Utiger, R. D. (Eds.). (2005). Werner & Ingbar's the thyroid: a fundamental and clinical text (Vol. 549). Lippincott Williams & Wilkins.
53. Wiersinga W. M. (2014). Thyroid autoimmunity. Endocrine development, 26, 139–157.
54. Kivity, S., Agmon-Levin, N., Zisappl, M., Shapira, Y., Nagy, E. V., Dankó, K., Szekanecz, Z., Langevitz, P., & Shoenfeld, Y. (2011). Vitamin D and autoimmune thyroid diseases. Cellular & molecular immunology, 8(3), 243–247.
55. Eliana, F., Suwondo, P., Asmarinah, A., Harahap, A., Djauzi, S., Prihartono, J., & Pemayun, T. G. D. (2017). The Role of Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) Gene, Thyroid Stimulating Hormone Receptor (TSHR) Gene and Regulatory T-cells as Risk Factors for Relapse in Patients with Graves Disease. Acta medica Indonesiana, 49(3), 195–204.
56. Tomer, Y., Hasham, A., Davies, T. F., Stefan, M., Concepcion, E., Keddache, M., & Greenberg, D. A. (2013). Fine mapping of loci linked to autoimmune thyroid disease identifies novel susceptibility genes. The Journal of clinical endocrinology and metabolism, 98(1), E144–E152.
57. Brent G. A., 2008. Clinical practice. Graves' disease. The New England journal of medicine, 358(24), pp.2594–2605.
58. Liao, W. L., Wan, L., Wang, T. Y., Chen, C. C., Tse, S. S., Lu, C. H., & Tsai, F. J. (2014). Association of TLR7 and TSHR copy number variation with Graves' disease and Graves' ophthalmopathy in Chinese population in Taiwan. BMC ophthalmology, 14, 15.
59. Xiong, H., Wu, M., Yi, H., Wang, X., Wang, Q., Nadirshina, S., Zhou, X., & Liu, X. (2016). Genetic associations of the thyroid stimulating hormone receptor gene with Graves diseases and Graves ophthalmopathy: A meta-analysis. Scientific reports, 6, 30356.
60. Fujii, A., Inoue, N., Watanabe, M., Kawakami, C., Hidaka, Y., Hayashizaki, Y., & Iwatani, Y. (2017). TSHR Gene Polymorphisms in the Enhancer Regions Are Most Strongly Associated with the Development of Graves' Disease, Especially Intractable Disease, and of Hashimoto's Disease. Thyroid : official journal of the American Thyroid Association, 27(1), 111–119.
61. Płoski, R., Brand, O. J., Jurecka-Lubieniecka, B., Franaszczyk, M., Kula, D., Krajewski, P., Karamat, M. A., Simmonds, M. J., Franklyn, J. A., Gough, S. C., Jarząb, B., & Bednarczuk, T. (2010). Thyroid

stimulating hormone receptor (TSHR) intron 1 variants are major risk factors for Graves' disease in three European Caucasian cohorts. PloS one, 5(11), e15512.
62. Ho, S. C., Goh, S. S., & Khoo, D. H. (2003). Association of Graves' disease with intragenic polymorphism of the thyrotropin receptor gene in a cohort of Singapore patients of multi-ethnic origins. Thyroid : official journal of the American Thyroid Association, 13(6), 523–528.
63. Stefan, M., Wei, C., Lombardi, A., Li, C. W., Concepcion, E. S., Inabnet, W. B., 3rd, Owen, R., Zhang, W., & Tomer, Y. (2014). Genetic-epigenetic dysregulation of thymic TSH receptor gene expression triggers thyroid autoimmunity. Proceedings of the National Academy of Sciences of the United States of America, 111(34), 12562–12567.
64. Maia, A. L., Scheffel, R. S., Meyer, E. L., Mazeto, G. M., Carvalho, G. A., Graf, H., Vaisman, M., Maciel, L. M., Ramos, H. E., Tincani, A. J., Andrada, N. C., Ward, L. S., & Brazilian Society of Endocrinology and Metabolism (2013). The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: recommendations by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism. Arquivos brasileiros de endocrinologia e metabologia, 57(3), 205–232.
65. Yin, X., Latif, R., Bahn, R., & Davies, T. F. (2012). Genetic profiling in Graves' disease: further evidence for lack of a distinct genetic contribution to Graves' ophthalmopathy. Thyroid : official journal of the American Thyroid Association, 22(7), 730–736.
66. Inoue, N., Watanabe, M., Katsumata, Y., Hidaka, Y., & Iwatani, Y. (2013). Different genotypes of a functional polymorphism of the TSHR gene are associated with the development and severity of Graves' and Hashimoto's diseases. Tissue antigens, 82(4), 288–290.
67. Jurecka-Lubieniecka, B., Ploski, R., Kula, D., Szymanski, K., Bednarczuk, T., Ambroziak, U., Hasse-Lazar, K., Hyla-Klekot, L., Tukiendorf, A., Kolosza, Z., & Jarzab, B. (2014). Association between polymorphisms in the TSHR gene and Graves' orbitopathy. PloS one, 9(7), e102653.
68. Liu, B. L., Yang, S. Y., Liu, W., Xue, L. Q., Chen, X., Pan, C. M., Gu, Z. H., Zhan, M., Zhang, X. M., Liang, J., Gao, G. Q., Du, W. H., Yuan, G. Y., Ying, R., Zhao, S. X., & Song, H. D. (2014). Refined association of TSH receptor susceptibility locus to Graves' disease in the Chinese Han population. European journal of endocrinology, 170(1), 109–119.
69. Bufalo, N. E., Dos Santos, R. B., Marcello, M. A., Piai, R. P., Secolin, R., Romaldini, J. H., & Ward, L. S. (2015). TSHR intronic polymorphisms (rs179247 and rs12885526) and their role in the susceptibility of the Brazilian population to Graves' disease and Graves' ophthalmopathy. Journal of endocrinological investigation, 38, 555-561.
70. Bartalena, L., & Fatourechi, V. (2014). Extrathyroidal manifestations of Graves' disease: a 2014 update. Journal of endocrinological investigation, 37(8), 691–700.
71. Bahn R. S. (2010). Graves' ophthalmopathy. The New England journal of medicine, 362(8), 726–738.
72. Wiersinga, W. M., & Kahaly, G. J. (Eds.). (2017). Graves' orbitopathy: a multidisciplinary approach-questions and answers. Karger Medical and Scientific Publishers.
73. Schlüter, A., Flögel, U., Diaz-Cano, S., Görtz, G. E., Stähr, K., Oeverhaus, M., ... & Berchner-Pfannschmidt, U. (2018). Graves' orbitopathy occurs sex-independently in an autoimmune hyperthyroid mouse model. Scientific reports, 8(1), 13096.
74. Khoo, D. H., Eng, P. H., Ho, S. C., Tai, E. S., Morgenthaler, N. G., Seah, L. L., ... & Aw, S. E. (2000). Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: prevalence, natural history, and thyrotropin receptor antibody levels. Thyroid, 10(12), 1093-1100.
75. Lytton, S. D., Ponto, K. A., Kanitz, M., Matheis, N., Kohn, L. D., & Kahaly, G. J. (2010). A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves' orbitopathy. The Journal of Clinical Endocrinology & Metabolism, 95(5), 2123-2131.
76. Diana, T., Olivo, P. D., & Kahaly, G. J. (2018). Thyrotropin receptor blocking antibodies. Hormone and metabolic research, 50(12), 853-862.
77. Iddah, M. A., & Macharia, B. N. (2013). Autoimmune thyroid disorders. International Scholarly Research Notices, 2013.
78. Zaaber, I., Mestiri, S., Marmouch, H., & Tensaout, B. B. H. J. (2020). Polymorphisms in TSHR gene and the risk and prognosis of autoimmune thyroid disease in Tunisian population. Acta Endocrinologica (Bucharest), 16(1), 1.
79. Levine, S. N. (1983). Current concepts of thyroiditis. Archives of internal medicine, 143(10), 1952-1956.
80. Gessl, A., Lemmens-Gruber, R., & Kautzky-Willer, A. (2012). Thyroid disorders. Sex and Gender Differences in Pharmacology, 361-386.
81. Garber, J. R., Cobin, R. H., Gharib, H., Hennessey, J. V., Klein, I., Mechanick, J. I., ... & Woeber for the American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults, K. A. (2012). Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid, 22(12), 1200-1235.

82. Klein, I., & Danzi, S. (2016). Thyroid disease and the heart. Current problems in cardiology, 41(2), 65-92.
83. Taylor, P. N., Albrecht, D., Scholz, A., Gutierrez-Buey, G., Lazarus, J. H., Dayan, C. M., & Okosieme, O. E. (2018). Global epidemiology of hyperthyroidism and hypothyroidism. Nature Reviews Endocrinology, 14(5), 301-316.
84. Biondi, B., Palmieri, E. A., Fazio, S., Cosco, C., Nocera, M., Saccà, L., ... & Perticone, F. (2000). Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. The Journal of Clinical Endocrinology & Metabolism, 85(12), 4701-4705.
85. Metwalley, K. A., & Farghaly, H. S. (2021). Subclinical hypothyroidism in children: updates for pediatricians. Annals of Pediatric Endocrinology & Metabolism, 26(2), 80.
86. Redford, C., & Vaidya, B. (2017). Subclinical hypothyroidism: Should we treat?. Post reproductive health, 23(2), 55-62.
87. Shin, J. H., Kim, H. Y., Kim, Y. M., Lee, H., Bae, M. H., Park, K. H., ... & Kwak, M. J. (2021). Genetic evaluation of congenital hypothyroidism with gland in situ using targeted exome sequencing. Annals of Clinical & Laboratory Science, 51(1), 73-81.
88. Atzmon, G., Barzilai, N., Surks, M. I., & Gabriely, I. (2009). Genetic predisposition to elevated serum thyrotropin is associated with exceptional longevity. The Journal of Clinical Endocrinology & Metabolism, 94(12), 4768-4775.
89. Rastogi, M. V., & LaFranchi, S. H. (2010). Congenital hypothyroidism. Orphanet journal of rare diseases, 5(1), 1-22.
90. Fu, C., Wang, J., Luo, S., Yang, Q., Li, Q., Zheng, H., Hu, X., Su, J., Zhang, S., Chen, R., Luo, J., Zhang, Y., Shen, Y., Wei, H., Meng, D., Gui, B., Zeng, Z., Fan, X., & Chen, S. (2016). Next-generation sequencing analysis of TSHR in 384 Chinese subclinical congenital hypothyroidism (CH) and CH patients. Clinica chimica acta; international journal of clinical chemistry, 462, 127–132.
91. Szinnai, G. (2014). Clinical genetics of congenital hypothyroidism. Paediatric Thyroidology, 26, 60-78.
92. Hermanns, P., Grasberger, H., Cohen, R., Freiberg, C., Dörr, H. G., Refetoff, S., & Pohlenz, J. (2013). Two cases of thyroid dysgenesis caused by different novel PAX8 mutations in the DNA-binding region: in vitro studies reveal different pathogenic mechanisms. Thyroid, 23(7), 791-796.
93. Liu, S. G., Zhang, S. S., Zhang, L. Q., Li, W. J., Zhang, A. Q., Lu, K. N., ... & Ma, X. (2012). Screening of PAX8 mutations in Chinese patients with congenital hypothyroidism. Journal of endocrinological investigation, 35, 889-892.
94. Jain, V., Agarwal, R., Deorari, A. K., & Paul, V. K. (2008). Congenital hypothyroidism. Indian journal of pediatrics, 75(4), 363–367.
95. Schoenmakers, N., & Chatterjee, V. K. (2015). Thyroid gland: TSHR mutations and subclinical congenital hypothyroidism. Nature reviews. Endocrinology, 11(5), 258–259.
96. Cassio, A., Nicoletti, A., Rizzello, A., Zazzetta, E., Bal, M., & Baldazzi, L. (2013). Current loss-of-function mutations in the thyrotropin receptor gene: when to investigate, clinical effects, and treatment. Journal of clinical research in pediatric endocrinology, 5 Suppl 1(Suppl 1), 29–39.
97. Simmonds M. J. (2013). GWAS in autoimmune thyroid disease: redefining our understanding of pathogenesis. Nature reviews. Endocrinology, 9(5), 277–287.
98. Wang, D., Chen, J., Zhang, H., Zhang, F., Yang, L., & Mou, Y. (2017). Role of Different CD40 Polymorphisms in Graves' Disease and Hashimoto's Thyroiditis. Immunological investigations, 46(6), 544–551.
99. Gillespie, E. F., Papageorgiou, K. I., Fernando, R., Raychaudhuri, N., Cockerham, K. P., Charara, L. K., Goncalves, A. C., Zhao, S. X., Ginter, A., Lu, Y., Smith, T. J., & Douglas, R. S. (2012). Increased expression of TSH receptor by fibrocytes in thyroid-associated ophthalmopathy leads to chemokine production. The Journal of clinical endocrinology and metabolism, 97(5), E740–E746.
100. Liu, N., Li, X., Liu, C., Zhao, Y., Cui, B., & Ning, G. (2010). The association of interleukin-1alpha and interleukin-1beta polymorphisms with the risk of Graves' disease in a case-control study and meta-analysis. Human immunology, 71(4), 397–401.
101. Ji, R., Feng, Y., & Zhan, W. W. (2013). Updated analysis of studies on the cytotoxic T-lymphocyte-associated antigen-4 gene A49G polymorphism and Hashimoto's thyroiditis risk. Genetics and molecular research : GMR, 12(2), 1421–1430.
102. Ajjan, R. A., & Weetman, A. P. (2015). The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme, 47(10), 702–710.
103. Walsh, J. P., Berry, J., Liu, S., Panicker, V., Dayan, C. M., Brix, T. H., Hegedüs, L., Hou, P., Shi, B., & Morahan, G. (2011). The clinical presentation of autoimmune thyroid disease in men is associated with IL12B genotype. Clinical endocrinology, 74(4), 508–512.

104. Cho, W. K., Ahn, M. B., Jang, W., Chae, H., Kim, M., & Suh, B. K. (2018). Nonautoimmune congenital hyperthyroidism due to p.Asp633Glu mutation in the TSHR gene. Annals of pediatric endocrinology & metabolism, 23(4), 235–239.
105. Palos-Paz, F., Perez-Guerra, O., Cameselle-Teijeiro, J., Rueda-Chimeno, C., Barreiro-Morandeira, F., Lado-Abeal, J., Galician Group for the Study of Toxic Multinodular Goitre, Araujo Vilar, D., Argueso, R., Barca, O., Botana, M., Cabezas-Agrícola, J. M., Catalina, P., Dominguez Gerpe, L., Fernandez, T., Mato, A., Nuño, A., Penin, M., & Victoria, B. (2008). Prevalence of mutations in TSHR, GNAS, PRKAR1A and RAS genes in a large series of toxic thyroid adenomas from Galicia, an iodine-deficient area in NW Spain. European journal of endocrinology, 159(5), 623–631.
106. Kravets I. (2016). Hyperthyroidism: Diagnosis and Treatment. American family physician, 93(5), 363–370.
107. Ross, D. S., Burch, H. B., Cooper, D. S., Greenlee, M. C., Laurberg, P., Maia, A. L., Rivkees, S. A., Samuels, M., Sosa, J. A., Stan, M. N., & Walter, M. A. (2016). 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid : official journal of the American Thyroid Association, 26(10), 1343–1421.
108. Guerri, G., Bressan, S., Sartori, M., Costantini, A., Benedetti, S., Agostini, F., Tezzele, S., Cecchin, S., Scaramuzza, A., & Bertelli, M. (2019). Hypothyroidism and hyperthyroidism. Acta bio-medica : Atenei Parmensis, 90(10-S), 83–86.
109. De Leo, S., Lee, S. Y., & Braverman, L. E. (2016). Hyperthyroidism. Lancet (London, England), 388(10047), 906–918.
110. Paschke, R., Niedziela, M., Vaidya, B., Persani, L., Rapoport, B., & Leclere, J. (2012). 2012 European thyroid association guidelines for the management of familial and persistent sporadic non-autoimmune hyperthyroidism caused by thyroid-stimulating hormone receptor germline mutations. European thyroid journal, 1(3), 142–147.
111. Lüblinghoff, J., Nebel, I. T., Huth, S., Jäschke, H., Schaarschmidt, J., Eszlinger, M., & Paschke, R. (2012). The leipzig thyrotropin receptor mutation database: update 2012. European thyroid journal, 1(3), 209–210.
112. Carlé, A., Andersen, S. L., Boelaert, K., & Laurberg, P. (2017). MANAGEMENT OF ENDOCRINE DISEASE: Subclinical thyrotoxicosis: prevalence, causes and choice of therapy. European journal of endocrinology, 176(6), R325–R337.
113. Lueblinghoff, J., Mueller, S., Sontheimer, J., & Paschke, R. (2010). Lack of consistent association of thyrotropin receptor mutations in vitro activity with the clinical course of patients with sporadic non-autoimmune hyperthyroidism. Journal of endocrinological investigation, 33(4), 228–233.
114. Rosario, P. W., Carvalho, M., & Calsolari, M. R. (2016). Symptoms of thyrotoxicosis, bone metabolism and occult atrial fibrillation in older women with mild endogenous subclinical hyperthyroidism. Clinical endocrinology, 85(1), 132–136.
115. Biondi, B., & Cooper, D. S. (2010). Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid : official journal of the American Thyroid Association, 20(2), 135–146.
116. Biondi, B., & Cooper, D. S. (2010). Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid, 20(2), 135-146.
117. Özsu, E., Yeşiltepe Mutlu, G., Çizmecioğlu, F. M., Bircan, R., & Hatun, Ş. (2017). Two siblings with familial subclinical hyperthyroidism with unknown etiology. Medicine Science.
118. Nishihara, E., Chen, C. R., Higashiyama, T., Mizutori-Sasai, Y., Ito, M., Kubota, S., ... & Rapoport, B. (2010). Subclinical nonautoimmune hyperthyroidism in a family segregates with a thyrotropin receptor mutation with weakly increased constitutive activity. Thyroid, 20(11), 1307-1314.
119. Cabanillas, M. E., McFadden, D. G., & Durante, C. (2016). Thyroid cancer. The Lancet, 388(10061), 2783-2795.
120. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.
121. Viola, D., Valerio, L., Molinaro, E., Agate, L., Bottici, V., Biagini, A., Lorusso, L., Cappagli, V., Pieruzzi, L., Giani, C., Sabini, E., Passannati, P., Puleo, L., Matrone, A., Pontillo-Contillo, B., Battaglia, V., Mazzeo, S., Vitti, P., & Elisei, R. (2016). Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. Endocrine-related cancer, 23(4), R185–R205.
122. Franco, A. T., Malaguarnera, R., Refetoff, S., Liao, X. H., Lundsmith, E., Kimura, S., Pritchard, C., Marais, R., Davies, T. F., Weinstein, L. S., Chen, M., Rosen, N., Ghossein, R., Knauf, J. A., & Fagin, J. A. (2011). Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. Proceedings of the National Academy of Sciences of the United States of America, 108(4), 1615–1620.

123. Shih, Y. L., Huang, Y. H., Lin, K. H., Chu, Y. D., & Yeh, C. T. (2018). Identification of Functional Thyroid Stimulating Hormone Receptor and TSHR Gene Mutations in Hepatocellular Carcinoma. Anticancer research, 38(5), 2793–2802.
124. Fiore, E., Rago, T., Latrofa, F., Provenzale, M. A., Piaggi, P., Delitala, A., ... & Vitti, P. (2011). Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocrine Related Cancer, 18(4), 429.
125. Gérard, A. C., Daumerie, C., Mestdagh, C., Gohy, S., De Burbure, C., Costagliola, S., ... & Many, M. C. (2003). Correlation between the loss of thyroglobulin iodination and the expression of thyroid-specific proteins involved in iodine metabolism in thyroid carcinomas. The Journal of Clinical Endocrinology & Metabolism, 88(10), 4977-4983.
126. D'Agostino, M., Sponziello, M., Puppin, C., Celano, M., Maggisano, V., Baldan, F., Biffoni, M., Bulotta, S., Durante, C., Filetti, S., Damante, G., & Russo, D. (2014). Different expression of TSH receptor and NIS genes in thyroid cancer: role of epigenetics. Journal of molecular endocrinology, 52(2), 121–131.
127. Medici, M., Porcu, E., Pistis, G., Teumer, A., Brown, S. J., Jensen, R. A., Rawal, R., Roef, G. L., Plantinga, T. S., Vermeulen, S. H., Lahti, J., Simmonds, M. J., Husemoen, L. L., Freathy, R. M., Shields, B. M., Pietzner, D., Nagy, R., Broer, L., Chaker, L., Korevaar, T. I., … Peeters, R. P. (2014). Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. PLoS genetics, 10(2), e1004123.
128. Shih, Y. L., Huang, Y. H., Lin, K. H., Chu, Y. D., & Yeh, C. T. (2018). Identification of Functional Thyroid Stimulating Hormone Receptor and TSHR Gene Mutations in Hepatocellular Carcinoma. Anticancer research, 38(5), 2793–2802.