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Exploring The Link Between TSHR Gene Polymorphism and Thyroid Function Parameters in Thyroid Disorder Patients

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ABSTRACT

Background and Objectives: Most common autoimmune thyroid diseases are Hashimoto's thyroiditis and Graves' disease which are caused by immune system and genetic factors. In this study the association between the thyroid function test (TFT) values and the TSHR gene polymorphism c.1349G>T will be investigated, which leads to a p.Arg450Leu amino acid change, in patients with thyroid disorders.

Methods: A cross-sectional study investigating, 50 thyroid dysfunction patients and 50 samples of healthy controls participated. The immunoassay was used to measure the serum levels of TSH, FT3, and FT4. Allele-specific ARMS-PCR was used to genotype the TSHR c.1349G>T (p.Arg450Leu) polymorphism.

Results: Hyperthyroid patients displayed suppressed TSH and raised FT3/FT4 levels, and hypothyroid patients displayed considerably elevated TSH and decreased FT3/FT4 levels. The hyperthyroid group had a higher frequency of the c.1349G>T variation of the TSHR gene (p.Arg450Leu) than the hypothyroid and control groups. The T allele was found to be statistically significantly associated with a higher incidence of hyperthyroidism ($P<0.01$). Serum TSH levels did not significantly differ between homozygous and heterozygous carriers of the mutation.

Conclusion: The research suggests a possible relationship between thyroid dysfunction, specifically hyperthyroidism, and the TSHR c.1349G>T (p.Arg450Leu) polymorphism. Thyroid disease risk prediction and diagnosis accuracy may be improved by performing genetic screening.

Keywords: ARMS-PCR with TFTs, Hormone levels, hyperthyroidism, polymorphism, TSHR gene

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INTRODUCTION

The prevalence of thyroid diseases is higher in women and older people, and they impact 5% to 10% of the population globally, making them a serious public health concern.[1] Amongst the most common endocrine disorders are autoimmune thyroid diseases (AITDs), of which Hashimoto's thyroiditis (HT) and Graves' disease (GD) are the most prevalent.[2] Graves' disease is an autoimmune disease and one of the most frequent causes of hyperthyroidism, which is caused by the presence of thyroid-stimulating immunoglobulins (TSIs) that bind to thyroid- stimulating hormone receptor (TSHR) on the thyroid follicular cells and stimulate the uncontrolled production of thyroid hormones.[3] While in Hashimoto's thyroiditis (HT) the immune-system cells lead to death of thyroid tissues and results in hypothyroidism. Both disorders may have similar clinical symptoms, but they have different causes, which frequently makes diagnosis more difficult.[4] Thyroid function tests (TFTs) are the cornerstone to distinguish between GD and HT, specifically when the findings are vague. TSH, FT3, and FT4 serum levels, and presence of thyroid-specific autoantibodies, assist proper diagnose and guide the treatment plan. Many genetic variations have been linked to autoimmune thyroid illnesses, genetic predispositions have an important role in these conditions.[5] TSHR gene has an important role in regulating thyroid hormones. The G protein-coupled receptor encoded by this gene, which is found on chromosome 14q31, and triggers intracellular signaling cascades when it binds to TSH, produce and release T3 and T4.[6] There is a relation between many thyroid conditions, like autoimmune conditions, familial non-autoimmune hyperthyroidism, and toxic thyroid nodules, to variations in the TSHR gene.[7, 8]

The arginine-to-leucine substitution at codon 450 (p.Arg450Leu) is caused by the single-nucleotide polymorphism (SNP) c.1349G>T. This change, which takes place in the extracellular region of the receptor, influences both ligand binding and signal transduction.[9] The variation is a associated with enhanced receptor sensitivity and modified immunological responses in some areas, which may impact the manifestation of the disease.[10,11] These correlations are not always seen, most likely due to environmental and ethnic factors.[12] Despite continuing studies on this topic, knowledge between the relationship of this polymorphism and thyroid hormone levels, especially within particular ethnic or regional groupings, is still deficient. Studying the TSHR gene's variations may help in the diagnosis of the illness, understanding the causes, and assessing individual's risks for developing thyroid disorders.

The aim of this study was to compare a cohort of patients with thyroid dysfunction to a group of healthy people from the same population to examine the association between thyroid function tests and the TSHR c.1349G>T (p.Arg450Leu) polymorphism. It is hypothesized that the TSHR c.1349G>T (p.Arg450Leu) polymorphism is significantly associated with thyroid dysfunction and altered thyroid function test parameters. Individuals carrying the T allele are expected to show lower TSH and higher FT3 and FT4 levels compared to those with the wild-type genotype.

METHODS

Study Design and Ethical Approval

This cross-sectional study investigated the relationship between thyroid function tests and the TSHR gene polymorphism c.1349G>T (p.Arg450Leu). Data and samples were collected from the Central Laboratory in Erbil, Iraq, between June and September 2024, with verbal consent obtained from each participant.

Study Participants

One hundred participants were included in the study, fifty of whom had thyroid dysfunction and the other fifty were healthy controls who were matched for age and sex. Twenty-five of the patients were diagnosed with hypothyroidism, while the remaining twenty-five were diagnosed with hyperthyroidism. The patients were diagnosed based on medical history, physical examination findings, and thyroid function test results.

Inclusion Criteria

- Adult participation ranged in age from 18 to 65.
- Individuals who were not receiving treatment at the time of recruitment but had verified thyroid dysfunction.
- Those with no personal or family history for autoimmune or thyroid conditions.

Exclusion Criteria

- Those diagnosed with systemic autoimmune disorders.
- Those who had taken medications for thyroid condition within 3 months.

Blood Sample Collection

Each participant provided 7ml of venous blood, collected aseptically. The sample was divided: 3ml into an EDTA tube for genomic DNA extraction and 4ml into a gel tube for serum separation. The serum samples were centrifuged at 3000rpm for 10 minutes and stored at -20°C for biochemical analysis. EDTA samples were stored at 4°C for DNA isolation.

Thyroid Hormone Analysis

The COBAS e411 (Roche Diagnostics, Germany) was used to measure the serum concentrations of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH). Those are the normal ranges of the thyroid hormone tests:

TSH: 0.27–4.2 µIU/mL, FT3: 3.1–6.8 nmol/L, and FT4: 12–22 nmol/L

DNA Extraction and Genotyping

The genomic DNA was extracted from the blood, by using the ADD BIO DNA Extraction Kit (ADD BIO Inc., South Korea).. Using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA), DNA yield and purity were measured; acceptable A260/A280 ratios between 1.8 and 2.0. Utilizing the allele- specific amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) technique that is used at the Medical Research Center/Hawler Medical University in Erbil City/ IRAQ, the TSHR gene c.1349G>T polymorphism (which results in the p.Arg450Leu amino acid substitution;) was genotyped. The following ingredients were included in the 20 µL PCR reaction volume:

3 µl of genomic DNA, 1 µl primer (Forward), 1 µl primer (reverse), 10 µl master mix, and 5 µl DdH2O

Thermal Cycling Conditions Included

Initial denaturation at 95°C for 5 minutes, 35 cycles of denaturation at 95°C for 30 seconds. Annealing at 65°C for 30 seconds, at 62°C for 30 seconds and at 50°C for 30 seconds. Extension at 72°C for 30 seconds, and final extension at 72°C for 5 minutes.

The PCR product will be visualized on 1% (agarose gel electrophoresis) for 60 minutes at 75 V., and the gel will be stained with ethidium bromide. A 100 bp DNA ladder was used as a molecular size marker. Electrophoresis results were visualized using a UV transilluminator, and genotypes were determined based on banding patterns.

Statistical Analysis

Statistical Package for Social Sciences (SPSS version 23) used for statistical analysis. Independent samples T test and Chi-squared test were used and p value of ≤ 0.05 was considered as statistically significant.

RESULTS

The study comprised 100 participants, consisting of 50 individuals with thyroid dysfunction and 50 age- and sex-matched healthy controls. 25 patients had Hyperthyroidism and the other 25 had Hypothyroidism. They were diagnosed using clinical presentation and thyroid function tests (TFTs). Statistically there was no significant difference in the mean age of both groups, which were 39.98 ± 12.45 years and 39.32 ± 11.40 years, respectively (p= 0.78). Female-to-male ratio was approximately 5:1 in both groups.

Thyroid Function Test Parameters

COBAS e411 immunoassay analyzer used to measure serum levels of TSH, free triiodothyronine (FT3), and free thyroxine (FT4). In the control group (n = 50), the mean FT3 and FT4 values were 2.11 ± 0.45 pmol/L and 123.03 ± 30.91 pmol/L, respectively, while the mean TSH level was 2.28 ± 1.14 µIU/mL. In the patient group (n = 50), the mean FT3 and FT4 levels were significantly higher (6.98 ± 5.63 pmol/L and 20.60 ± 13.27 pmol/L, respectively), and the TSH level was elevated (3.87 ± 5.44 µIU/mL). Statistically significant differences were observed between the two groups for all the three hormonal parameters: FT3 ($P < 0.001$), FT4 ($P < 0.001$), and TSH ($P = 0.046$). Thyroid function test results across study groups are shown in Table 1.

Genotype Distribution of TSHR c.1349G>T (p.Arg450Leu)

ARMS-PCR used to analyze all 100 subjects' genotypes for the TSHR c.1349G>T polymorphism. Genotyping was confirmed through agarose gel electrophoresis, which distinguished between wild-type

and mutant (T) alleles based on specific banding patterns. The genotypes were categorized as homozygous wild-type (GG), heterozygous (GT), and homozygous mutant (TT).

In the patient group (n = 50),

- 18 patients (36%) had the GT genotype,
- 14 patients (28%) had the TT genotype, and

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- 18 patients (36%) had the GG genotype.

In the control group (n = 50),

- 35 individuals (70%) had the GG genotype,
- 15 individuals (30%) had the GT genotype, and
- none (0%) had the TT genotype.

The TT genotype was observed only among patients, with 10 out of 14 TT cases presenting with hyperthyroidism. A statistically significant difference in genotype frequency was found between patients and controls ($p= 0.00005$, χ^2 test).

Table 1. Thyroid function test results across study groups

Group	TSH (µIU/mL)	FT3 (pmol/L)	FT4 (pmol/L)
Hyperthyroid (n=25)	0.18 ± 0.11	5.93 ± 0.44	20.10 ± 2.80
Hypothyroid (n=25)	6.47 ± 2.10	2.79 ± 0.52	10.90 ± 1.80
Control (n=50)	2.28 ± 1.14	2.11 ± 0.45	123.03 ± 30.92

Association Between Genotype and Hormone Levels

The association between TSHR c.1349G>T genotypes and thyroid hormone levels was evaluated among all study participants. In individuals with the TT genotype (n = 14), serum TSH levels were significantly suppressed, with a mean value of 0.19 ± 0.08 µIU/mL. Correspondingly, FT3 and FT4 levels were elevated, averaging 5.97 ± 0.51 pmol/L and 19.8 ± 2.7 pmol/L, respectively, indicating a strong association with hyperthyroid features. Participants carrying the GT genotype (n = 33) exhibited intermediate hormone levels, with mean TSH of 2.74 ± 1.92 µIU/mL, FT3 of 4.12 ± 0.68 pmol/L, and FT4 of 16.7 ± 2.3 pmol/L. In contrast, individuals with the GG genotype (n = 53) had hormone values within normal limits, including TSH at 2.96 ± 1.34 µIU/mL, FT3 at 3.45 ± 0.56 pmol/L, and FT4 at 14.8 ± 1.9 pmol/L, consistent with euthyroid status. Statistical analysis using one-way ANOVA demonstrated a significant association between genotype and all three hormonal parameters ($P < 0.001$), suggesting that the presence of the T allele, particularly in homozygous form, is correlated with altered thyroid function and predisposes to hyperthyroidism.

Correlation Analysis

A correlation analysis was conducted to evaluate the relationship between TSHR c.1349G>T genotypes and thyroid hormone levels (TSH, FT3, and FT4). The analysis revealed a strong negative correlation between the number of T alleles and serum TSH levels, indicating that as the number of T alleles increases (from GG to GT to TT), TSH concentrations decrease markedly. This inverse relationship was particularly evident in TT individuals, who consistently exhibited suppressed TSH values. Additionally, there was a positive correlation between T allele presence and both FT3 and FT4 levels, suggesting that the T allele is associated with elevated levels of circulating thyroid hormones. These trends support the hypothesis that the mutant T allele of the TSHR gene is functionally linked to altered thyroid regulation, especially in promoting hyperthyroid activity. The findings are consistent with the genotype- hormone associations described earlier and further emphasize the functional impact of this polymorphism on thyroid homeostasis. Mentioned in Table 1 and Table 2.

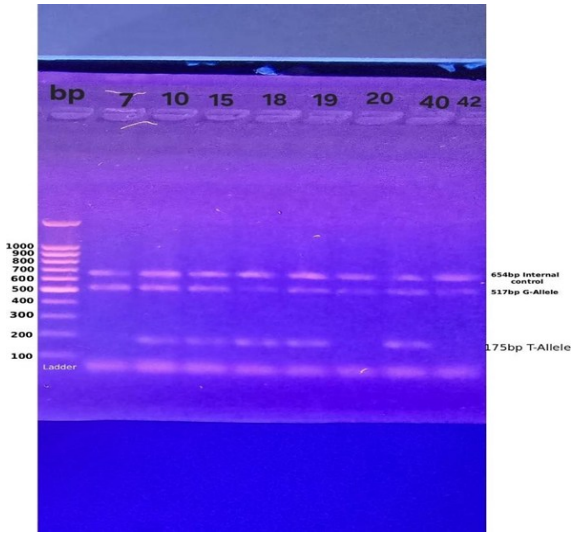

Figure 1. ARMS-PCR genotyping for patient group

The DNA ladder in Lane 1, ranging from 100 bp to 1000 bp, displays molecular size reference. Lanes 2 to 8 display patient samples with clear amplification bands. Distinct bands displayed at 175 bp, 517 bp, and 654 bp confirms successful allele- specific amplification of the TSHR gene polymorphism (c.1349G>T). The banding patterns suggest different genotypic profiles among the patients, indicating a mix of homozygous and heterozygous variants.

Lane 1 contains the DNA ladder (100–1000 bp), is a molecular weight marker for band size estimation. Lanes 2 to 9 display control samples, each of them showing clear and specific amplification band. The bands at 517 bp, and 654 bp correspond to allele-specific regions of the TSHR gene (c.1349G>T). The banding pattern across control lanes indicates the predominance of the homozygous wild-type (GG) genotype in the healthy population.

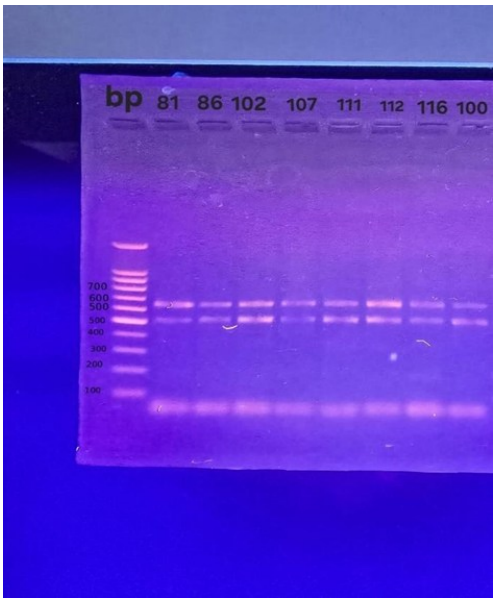

Figure 2. ARMS-PCR genotyping for control samples

Table 2. Genotype distribution of TSHR c.1349G>T polymorphism

	Table 2			
Groups		GG	GT	TT
Patients (n=30)	Hyperthyroid n=16 Hypothyroid n=14	11 (36.7%)	11 (36.7%)	8 (26.7%)
Controls (n=30)		21 (70%)	9 (30%)	0 (0%)

DISCUSSION

This study examined the relationship between thyroid function test parameters and the TSHR gene polymorphism c.1349G>T (p.Arg450Leu;) in a Kurdish cohort that included 50 thyroid dysfunction patients and 50 healthy controls. The important results showed that hyperthyroid individuals were more likely to have the T allele, especially the TT genotype, which was linked to different hormonal patterns, specifically decreased TSH levels and increased FT3 and FT4. These findings highlight the significance of TSHR gene variations in illness susceptibility and phenotypic expression, and they confirm the increasing amount of evidence pointing to a genetic foundation for autoimmune thyroid diseases.

The G protein-coupled receptor encoded by the thyroid-stimulating hormone receptor (TSHR) gene, which is found on chromosome 14q31, mediates TSH activity in thyroid follicular cells, controlling the production and secretion of thyroid hormones.[15] Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two conditions that can be exacerbated by genetic changes in this gene that interfere with normal TSH signaling.[16] The c.1349G>T single nucleotide polymorphism (SNP), which causes an amino acid change at codon 450 replacing arginine with leucine was found to be statistically significantly associated with hyperthyroidism. Interestingly, the TT genotype was only detected in patients and was more common in those with Graves' disease, indicating that this variant may have a pathogenic role in the onset of the illness.

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Our findings that the TSHR c.1349G>T polymorphism particularly the TT genotype is strongly associated with hyperthyroidism agree with the pathophysiological mechanisms described by Smith and Hegedüs,[4] who emphasized the role of inappropriate TSH receptor activation by stimulating autoantibodies in the development of Graves' disease. Similarly, our results suggest that enhanced TSHR activity, potentially driven by genetic alterations such as the T allele, may contribute to the thyrotoxic phenotype. Furthermore, these results are in line with those reported by Morshed and Davies,[19] who proposed that structural variations in the TSH receptor, including genetic polymorphisms, can influence both immune reactivity and receptor functionality, ultimately promoting disease susceptibility. The observed parallels imply that the T allele may exert dual effects enhancing receptor sensitivity and increasing immunogenic potential thereby predisposing individuals to hyperthyroid states. Minor discrepancies in the magnitude of association compared to previous studies[17] may be attributed to inter-population genetic variability, differences in sample sizes, or methodological approaches. These results are in line with earlier research showing that mutations in the TSHR gene can change ligand binding, interfere with downstream signaling, and reduce immunological tolerance. These changes could result in constitutive receptor activation or elevated receptor sensitivity, which are pathways that are involved in the development of autoimmune thyroid disorders.[18,19] In individuals with familial non- autoimmune hyperthyroidism, for instance,[2] found constitutively activating TSHR mutations, suggesting that gain-of-function changes in this gene can cause thyrotoxicosis on its own.[20] Similarly, via increasing receptor immunogenicity,[2] suggested that changed TSHR activity may disrupt self- tolerance and promote autoimmune reactions, especially in GD.[21]

According to our findings, the TT genotype was linked to higher FT3 and FT4 and significantly reduced TSH levels (mean: 0.19 ± 0.08 µIU/mL), which is consistent with the hyperthyroid biochemical profile. The c.1349G>T polymorphism's functional consequence is supported by this genotype-specific hormonal tendency. A potential dose-dependent or semi-dominant inheritance pattern was suggested by the intermediate levels displayed by the GT heterozygous genotype (TSH: 2.74 ± 1.92 µIU/mL; FT3: 4.12 ± 0.68 pmol/L; FT4: 16.7 ± 2.3 pmol/L). Yoshihara et al.'s research, which found comparable associations between TSHR genotypes and thyroid function indicators in Japanese populations, supports these findings.[22]

Furthermore, there was a significant difference in the genotype distribution between the patients and the controls (Table 2)While both the GT and TT genotypes were more common in the disease group (36.0% and 28.0%, respectively), the GG genotype was far less common in the healthy population (70%). The presence of the T allele increases the likelihood of having thyroid dysfunction, according to this skewed distribution.

Interestingly, our analysis did not find a significant correlation between this polymorphism and hypothyroidism, even though the T allele is clearly linked to hyperthyroidism. Because GD and HT are caused by different pathophysiological pathways, this uniqueness may be explained. HT usually involves cytotoxic T-cell-mediated follicular destruction and TSHR-blocking antibodies, whereas GD involves TSHR-stimulating antibodies.[23] Because HT is more frequently associated with other genetic loci like HLA-DR3 and CTLA -4, a gain-of-function polymorphism in TSHR may contribute to GD susceptibility but not necessarily to HT.[24]

Along with genotypic effects, TSH levels and FT3/FT4 were significantly inversely correlated in both patients and controls. The hypothalamic-pituitary-thyroid system's feedback regulatory axis, in which elevated thyroid hormones inhibit TSH synthesis through negative feedback, is highlighted by this physiological relationship.[25] More significantly, the idea that this polymorphism improves thyroid hormone synthesis is supported by the positive association found between the presence of the T allele and increased FT3/FT4 concentrations.

Additionally, our study adds to the expanding body of research on thyroid disease's population-specific genetics. Few studies have examined Middle Eastern ethnic groups; most prior research has concentrated on East Asian or European populations. Because of its low outbreeding and relative genetic homogeneity, the Kurdish population is a unique genetic reservoir that can be used to identify founder mutations or risk alleles particu-

lar to the population.[26] The T allele's potential as a screening or diagnostic marker in this population is demonstrated by the observed frequency of 0.45 in patients compared to 0.15 in controls.

Nonetheless, it is necessary to recognize some restrictions. First, the sample size may restrict the ability to identify subtle effects or interactions with other loci, even though it is adequate to identify significant genotype-phenotype relationships. Larger, multi-center cohorts should be included in future studies to support the current findings and investigate possible gene-environment interactions. A dependable technique for identifying known single nucleotide polymorphisms (SNPs), ARMS-PCR is not sensitive enough to discover new or extra variations in linkage disequilibrium with c.1349G>T. Whole-exome or targeted sequencing are examples of broader genomic studies that might offer a more thorough comprehension of TSHR gene variations. The part epigenetic processes play in controlling TSHR expression is another crucial factor to consider. According to earlier research, autoimmune thyroid illnesses affect the methylation patterns of the TSHR gene, which may have an impact on immunological reactivity and receptor function.[27] Further research using transcriptome and methylation profiling techniques might provide more detailed understanding of how these SNPs affect gene activity in addition to their coding impacts. This study's results, despite these drawbacks, offer strong proof that the TSHR c.1349G>T polymorphism plays a role in the pathophysiology of thyroid dysfunction, especially hyperthyroidism. The correlation between elevated hormone activity and the TT genotype underscores its possible significance as a genetic risk factor and a potential target for targeted therapies. Personalized
management techniques, genetic counseling, or closer clinical surveillance may be beneficial for people with this genotype to lower their risk of thyrotoxicosis.

The findings emphasize the importance of including molecular screening in routine diagnostic procedures and the part that genetic predisposition plays in autoimmune thyroid illness. Confirming these results and clarifying the molecular pathways connecting TSHR variation to thyroid dysfunction would require more studies in a variety of groups.

CONCLUSION

This study demonstrates a significant association between the TSHR gene polymorphism c.1349G>T (p.Arg450Leu) and thyroid hormone levels among Kurdish patients with thyroid dysfunction. The T allele, particularly in the TT genotype, was linked to decreased TSH and increased FT3 and FT4 levels, indicating its potential role as a genetic susceptibility marker for Graves' disease. These findings highlight the value of incorporating molecular genotyping alongside thyroid function tests to enhance diagnostic accuracy and support personalized management of autoimmune thyroid disorders. Further large-scale and multi-ethnic studies are recommended to confirm these results and explore the underlying molecular mechanisms.

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REFERENCES

1. Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull. 2011;99(1):39–51. https://doi.org/10.1093/bmb/ldr030
2. Brent GA. Mechanisms of thyroid hormone action. J Clin Invest. 2012;122(9):3035–43. https://doi.org/10.1172/jci60047
3. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14(2):174–80. https://doi.org/10.1016/j.autrev.2014.10.016
4. Smith TJ, Hegedüs L. Graves' disease. N Engl J Med. 2016;375(16):1552–65. https://doi.org/10.1056/nejmra1510030
5. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26(10):1343–421. https://doi.org/10.1089/thy.2016.0229
6. Rapoport B, McLachlan SM. The thyrotropin receptor in Graves' disease. Thyroid. 2014;24(3):401–10 https://doi.org/10.1089/thy.2007.0170
7. Davies, T. F., Yin, X. & Latif, R. Te genetics of the thyroid stimulating hormone receptor: History and relevance. Tyroid 20 (7), 727–736 (2010). https://doi.org/10.1089/thy.2010.1638

DOI: doi.org/10.15218/edj.2025.13

8. Peeters, R. P. & Toor, H. V. Polymorphism in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in health subjects. J. Clin. Endocrinol. Metab. 88(6), 2880– 2888 (2003). https://doi.org/10.1210/jc.2002-021592
9. Chaker, L., Bianco, A. C., Jonklaas, J. & Peeters, R. P. Hypothyroidism. Lancet 390(10101), 1550–1562 (2017). https://doi.org/10.1016/s0140-6736(17)30703-1
10. Fang Y, Sun F, Zhang RJ, Zhang CR, Yan CY, Zhou Z, Zhang QY, Li L, Ying YX, Zhao SX, Liang J. Mutation screening of the TSHR gene in 220 Chinese patients with congenital hypothyroidism. Clinica Chimica Acta. 2019 Oct 1;497:147-52. https://doi.org/10.1016/j.cca.2019.07.031
11. Alzahrani, A. S. et al. Diagnosis and management of hypothyroidism in Gulf Cooperation Council (GCC) countries. Adv. Ter. 37(7), 3097–3111 (2020). https://doi.org/10.1007/s12325-020-01382-2
12. Grixti L, Lane LC, Pearce SH. The genetics of Graves' disease. Reviews in endocrine and metabolic disorders. 2024 Feb;25 (1):203-14. https://doi.org/10.1007/s11154-023-09848-8
13. Duprez L, Parma J, Van Sande J, Rodien P, Dumont JE, Vassart G, Abramowicz M. TSH receptor mutations and thyroid disease. Trends in Endocrinology & Metabolism. 1998 May 1;9(4):133-40. https://doi.org/10.1016/s1043-2760(98)00036-8
14. 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. https://doi.org/10.1055/s-0035-1559646
15. Latif R, Morshed SA, Davies TF. Thyroid-stimulating hormone receptor: An example of a multi- functional G protein-coupled receptor. Endocr Pract. 2009;15(1):40–6. https://doi.org/10.1371/journal.pone.0075100
16. Szkudlinski MW, Fremont V, Ronin C, Weintraub BD. Thyroid -stimulating hormone and thyroid- stimulating hormone receptor structure-function relationships. Physiological reviews. 2002 Apr 1;82(2):473-502. https://doi.org/10.1152/physrev.00031.2001
17. Bhanothu, Venkanna, Simeone Fernandes, Sudha Chandrashekhar Rao, Rachna Keshwani, Shagun W. Shagun, Suchitra Surve, Shailesh Pande, Sudhakar DVS, Neha Minde, and Shivamkumar Sriwas. "Use of Allele-Specific-Amplification Refractory Mutation System– Polymerase Chain Reaction for the Detection of Thyroid-Stimulating Hormone Receptor Gene Mutation in an Indian Family with Thyroid Dyshormonogenesis." Annals of Neonatology 6, no. 1 (2024): 7-36. Here is the direct link to the article: https://anj.journals.ekb.eg/article_317051.html
18. Davies TF, Yin X, Latif R. The genetics of the thyroid stimulating hormone receptor: history and relevance. Thyroid. 2010 Jul 1;20(7):727-36. https://doi.org/10.1089/thy.2010.1638
19. Morshed SA, Davies TF. Graves' disease mechanisms: The role of stimulating, blocking, and cleavage region TSH receptor antibodies. Horm Metab Res. 2015;47(10):727–34. https://doi.org/10.1055/s-0035-1559633
20. Brand OJ, Gough SC. Genetics of thyroid autoimmunity and the role of TSHR. Mol Cell Endocrinol. 2010;322(1–2):135–43. https://doi.org/10.1016/j.mce.2010.01.013
21. Bahn RS. Current insights into the pathogenesis of Graves' ophthalmopathy. Horm Metab Res. 2015;47(10):773–8. https://doi.org/10.1055/s-0035-1555762
22. Fujii A, Inoue N, Watanabe M, Kawakami C, Hidaka Y, Hayashizaki Y, Iwatani Y. 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. 2017 Jan 1;27 (1):111-9. https://doi.org/10.1089/thy.2016.0345
23. Tomer Y, Huber A. The etiology of autoimmune thyroid disease: a story of genes and environment. J Autoimmun. 2009;32(3–4):231–9.https://doi.org/10.1016/j.jaut.2009.02.007
24. Ban Y, Tomer Y. The contribution of immune regulatory and thyroid specific genes to the etiology of Graves' and Hashimoto's diseases. Autoimmunity. 2003 Sep 1;36(6-7):367-79. https://doi.org/10.1080/08916930310001603037
25. Costa-e-Sousa RH, Hollenberg AN. Minireview: the neural regulation of the hypothalamic- pituitary-thyroid axis. Endocrinology. 2012 Sep 1;153(9):4128-35. https://doi.org/10.1210/en.2012-1467
26. Davies TF, Yin X, Latif R. The genetics of the thyroid stimulating hormone receptor: history and relevance. Thyroid. 2010 Jul 1;20(7):727-36. https://doi.org/10.1089/thy.2010.1638
27. Razmara E, Salehi M, Aslani S, Bitaraf A, Yousefi H, Colón JR, Mahmoudi M. Graves' disease: introducing new genetic and epigenetic contributors. Journal of molecular endocrinology. 2021 Feb 1;66(2):R33-55. https://doi.org/10.1530/JME-20-0078.