TSH Receptor Gene Polymorphisms in Graves' Disease and Graves' Ophthalmopathy: Current Evidence, Molecular Mechanisms, and Clinical Implications

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Abstract

Background: Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism and results from a complex interplay between genetic susceptibility, immune dysregulation, and environmental triggers. Among the numerous genetic loci implicated in disease pathogenesis, the thyroid-stimulating hormone receptor (TSHR) gene represents the most disease-specific susceptibility gene because it encodes the primary autoantigen targeted by thyroid-stimulating antibodies. Genetic polymorphisms within the TSHR gene have been associated with susceptibility to GD across diverse populations and are increasingly recognized for their potential role in determining disease phenotype, severity, recurrence, and the development of Graves' ophthalmopathy (GO), the most common extrathyroidal manifestation of the disease. Despite considerable advances in genetic research, the clinical significance of TSHR polymorphisms remains incompletely understood, particularly regarding their contribution to personalized risk assessment and precision medicine.

Aim: This review aims to provide a comprehensive and updated overview of the molecular biology of the TSHR gene, the functional significance of major TSHR polymorphisms, and their association with Graves' disease and Graves' ophthalmopathy. In addition, it critically evaluates current evidence from genetic association studies, genome-wide association studies, and meta-analyses, while discussing the underlying molecular mechanisms linking genetic variation to immune dysregulation and disease expression. The review also explores the translational implications of TSHR polymorphisms in disease prediction, prognosis, therapeutic decision-making, and future precision medicine approaches.

Conclusion: Accumulating evidence demonstrates that TSHR gene polymorphisms are key contributors to genetic susceptibility in Graves' disease and may influence both disease onset and the clinical spectrum of autoimmune thyroid disorders. Functional variants appear to alter immune tolerance, receptor expression, and autoantigen presentation, thereby facilitating the generation of pathogenic thyroid-stimulating antibodies and perpetuating autoimmune responses. Although the strength of genetic associations varies among different ethnic populations, consistent findings support the pivotal role of TSHR as a central genetic determinant of GD. Future integration of TSHR genotyping with other susceptibility genes, epigenetic biomarkers, and immunological profiling may improve individualized risk stratification, early identification of patients at risk for Graves' ophthalmopathy, and the development of targeted therapeutic strategies, advancing precision medicine in autoimmune thyroid disease.

Keywords: TSH Receptor Gene, Polymorphisms, Graves' Disease, Graves' Ophthalmopathy

Introduction

Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism and represents one of the most extensively investigated organ-specific autoimmune disorders. The disease develops through a complex interaction between inherited genetic susceptibility and environmental factors that disrupt immune tolerance to thyroid-specific antigens. The hallmark of GD is the production of thyroid-stimulating hormone receptor antibodies (TRAbs), which activate the thyroid-stimulating hormone receptor (TSHR), resulting in persistent thyroid hormone overproduction, diffuse thyroid enlargement, and systemic manifestations of thyrotoxicosis. Beyond thyroid dysfunction, approximately 25–50% of patients develop Graves' ophthalmopathy (GO), an inflammatory orbital disease that substantially contributes to morbidity, impaired quality of life, and long-term disability. **[1]**

Although environmental factors including cigarette smoking, excessive iodine exposure, infections, psychological stress, and female sex hormones contribute to disease initiation, genetic susceptibility accounts for nearly 70–80% of the overall risk of developing Graves' disease. Genome-wide association studies and candidate gene analyses have identified numerous susceptibility loci involving immune regulatory pathways, including the human leukocyte antigen (HLA) region, cytotoxic T-lymphocyte-associated protein 4 (CTLA4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), CD40, and Fc receptor-like 3 (FCRL3). Among these, the TSHR gene is unique because it encodes not only the principal autoantigen responsible for disease development but also the functional receptor through which pathogenic autoantibodies exert their biological effects. **[2]**

The TSHR gene, located on chromosome 14q31, has therefore emerged as the most disease-specific genetic determinant of Graves' disease. Multiple single nucleotide polymorphisms (SNPs), particularly those located within intron 1 of the TSHR gene, have consistently demonstrated significant associations with disease susceptibility across different ethnic populations. Functional studies indicate that these variants may influence central and peripheral immune tolerance by modifying thymic TSHR expression, alternative mRNA splicing, and receptor transcription, thereby facilitating the escape of autoreactive T lymphocytes and promoting autoimmune responses directed against thyroid tissue. These discoveries have substantially improved the understanding of the molecular mechanisms underlying GD and have positioned TSHR as a central link between genetic predisposition and autoimmune activation. **[3]**

Graves' ophthalmopathy represents the most clinically significant extrathyroidal manifestation of GD and is characterized by immune-mediated inflammation of orbital fibroblasts, adipogenesis, glycosaminoglycan accumulation, and extraocular muscle enlargement. Emerging evidence suggests that genetic variations within the TSHR gene may not only increase susceptibility to GD but may also influence the risk, severity, and clinical phenotype of ophthalmopathy through altered receptor expression in orbital tissues and interaction with the insulin-like growth factor-1 receptor (IGF-1R) signaling pathway. Nevertheless, published studies remain heterogeneous, with variable findings across different ethnic groups and study populations, highlighting the need for critical synthesis of the available evidence. **[4]**

Despite remarkable advances in molecular genetics, several important knowledge gaps remain. Many published studies have focused on individual polymorphisms without adequately integrating functional mechanisms, ethnic variability, genotype–phenotype correlations, or the translational value of genetic testing in routine clinical practice. Furthermore, the rapid expansion of genome-wide association studies, epigenetic research, transcriptomics, and precision medicine has generated new insights that have not been comprehensively consolidated into a contemporary review focusing specifically on TSHR polymorphisms and their relationship with both Graves' disease and Graves' ophthalmopathy.

Accordingly, this review aims to provide an updated and comprehensive overview of the molecular biology of the TSHR gene, the functional significance of major TSHR polymorphisms, and their contribution to the pathogenesis of Graves' disease and Graves' ophthalmopathy. Furthermore, it critically examines evidence from genetic association studies and meta-analyses, discusses the underlying molecular mechanisms linking genetic variation to disease susceptibility and clinical phenotype, and explores the potential role of TSHR polymorphisms in risk prediction, prognostic

stratification, and the future implementation of precision medicine in autoimmune thyroid disease. **[5]**

Epidemiology and Disease Burden of Graves' Disease and Graves' Ophthalmopathy

Graves' disease (GD) is the leading cause of endogenous hyperthyroidism worldwide and accounts for approximately 60–80% of all cases of thyrotoxicosis in iodine-sufficient regions. The disease affects nearly 1–2% of women and approximately 0.1–0.2% of men during their lifetime, with an annual incidence ranging from 20 to 50 cases per 100,000 individuals. Although GD may occur at any age, it is most frequently diagnosed between 30 and 60 years of age and demonstrates a marked female predominance, with female-to-male ratios ranging from 5:1 to 10:1. This striking sex disparity reflects the influence of sex hormones, X chromosome-related immune regulation, and the higher prevalence of autoimmune diseases among women. **[6]**

The global epidemiology of Graves' disease exhibits substantial geographic and ethnic variation, reflecting differences in genetic background, environmental exposures, iodine nutrition, and healthcare accessibility. Large genome-wide association studies have demonstrated that susceptibility alleles within the TSHR locus, HLA region, CTLA4, and other immune regulatory genes vary considerably among European, Asian, and Middle Eastern populations, contributing to differences in disease prevalence and clinical phenotype. These observations emphasize that both inherited genetic architecture and environmental modifiers shape disease susceptibility, making population-specific genetic investigations essential for understanding regional differences in GD occurrence. **[7]**

Graves' ophthalmopathy (GO), also referred to as thyroid eye disease, represents the most common extrathyroidal manifestation of GD and develops in approximately one-quarter to one-half of affected individuals. While most patients experience mild ocular symptoms, approximately 3–5% develop moderate-to-severe or sight-threatening disease characterized by marked proptosis, restrictive ophthalmopathy, exposure keratopathy, or compressive optic neuropathy. The risk of GO is substantially increased by cigarette smoking, persistent thyrotoxicosis, elevated thyroid-stimulating hormone receptor antibody (TRAb) concentrations, and radioiodine therapy in susceptible individuals, highlighting the multifactorial nature of orbital disease development. **[8]**

Beyond its endocrine manifestations, Graves' disease imposes a substantial clinical and socioeconomic burden. Persistent hyperthyroidism increases the risk of atrial fibrillation, heart failure, osteoporosis, skeletal muscle dysfunction, neuropsychiatric disorders, infertility, and adverse pregnancy outcomes, while Graves' ophthalmopathy may lead to chronic visual impairment, facial disfigurement, psychological distress, reduced work productivity, and impaired health-related quality of life. Despite advances in therapeutic options, disease relapse remains common after antithyroid drug withdrawal, underscoring the importance of identifying genetic and molecular biomarkers capable of predicting disease susceptibility, severity, and long-term outcomes. **[9]**

Molecular Biology and Structure of the Thyroid-Stimulating Hormone Receptor

The thyroid-stimulating hormone receptor (TSHR) is the central molecular regulator of thyroid growth, differentiation, and hormone synthesis, and it occupies a unique position in the pathogenesis of Graves' disease because it serves as both the physiological receptor for thyroid-stimulating hormone (TSH) and the principal autoantigen targeted by thyroid-stimulating autoantibodies. The human **TSHR** gene is located on chromosome **14q31** and spans approximately 190 kb, comprising 10 exons. Exons 1–9 encode the large extracellular domain responsible for ligand recognition, whereas exon 10 encodes part of the extracellular region together with the seven transmembrane helices and intracellular cytoplasmic tail that mediate signal transduction. This distinctive gene organization enables precise regulation of receptor synthesis and function while providing several regions susceptible to genetic variation associated with autoimmune thyroid disease. **[10]**

TSHR belongs to the class A G protein-coupled receptor (GPCR) superfamily and is predominantly expressed on the basolateral membrane of thyroid follicular epithelial cells. Structurally, the mature receptor consists of a large leucine-rich repeat extracellular domain responsible for high-affinity TSH binding, a hinge region that participates in receptor activation, seven transmembrane α-helices, and an intracellular C-terminal domain that interacts with heterotrimeric G proteins. Following post-

translational cleavage, the receptor is divided into α- and β-subunits that remain linked by disulfide bonds, a characteristic feature believed to influence receptor stability, ligand binding, and autoimmune recognition. Importantly, TSHR is also expressed at lower levels in orbital fibroblasts, adipocytes, bone cells, and several extrathyroidal tissues, providing a biological explanation for the systemic manifestations of Graves' disease, particularly Graves' ophthalmopathy. **[11]**

Binding of TSH to the extracellular domain induces conformational changes that activate intracellular G-protein signaling pathways, predominantly the Gsα–adenylyl cyclase–cyclic adenosine monophosphate (cAMP) cascade. Elevated intracellular cAMP activates protein kinase A (PKA), leading to transcription of genes involved in iodide uptake through the sodium-iodide symporter, thyroglobulin synthesis, thyroid peroxidase activity, follicular cell proliferation, and secretion of thyroxine (T4) and triiodothyronine (T3). Under certain physiological conditions, TSHR can additionally signal through Gq/11 proteins, activating phospholipase C, intracellular calcium mobilization, protein kinase C, and mitogen-activated protein kinase (MAPK) pathways, thereby regulating thyroid cell growth and differentiation beyond hormone synthesis alone. **[12]**

In Graves' disease, receptor physiology is fundamentally altered by thyroid-stimulating hormone receptor antibodies (TRAbs), particularly stimulating antibodies (TSAbs), which bind to TSHR and mimic the biological action of TSH. Unlike pituitary-derived TSH, whose secretion is tightly controlled by negative feedback, TSAbs continuously activate TSHR independently of hypothalamic-pituitary regulation, resulting in persistent stimulation of thyroid hormone synthesis, diffuse thyroid hyperplasia, and sustained hyperthyroidism. Furthermore, activation of TSHR expressed on orbital fibroblasts promotes cytokine production, adipocyte differentiation, hyaluronan accumulation, and tissue remodeling, processes that contribute directly to the pathogenesis of Graves' ophthalmopathy. These observations establish TSHR as the pivotal molecular link connecting thyroid autoimmunity with both endocrine and extrathyroidal manifestations of the disease. **[13]**

Immunopathogenesis of Graves' Disease

Graves' disease develops through the loss of immune tolerance to thyroid-specific antigens in genetically susceptible individuals following exposure to environmental triggers. Central and peripheral immune tolerance normally eliminate or suppress autoreactive lymphocytes; however, defects in these regulatory mechanisms permit activation of autoreactive $CD4^+$ T lymphocytes that recognize thyroid antigens, particularly the thyroid-stimulating hormone receptor (TSHR). Activated T helper cells subsequently stimulate B lymphocytes to differentiate into plasma cells that produce thyroid-stimulating hormone receptor antibodies (TRAbs), the pathogenic hallmark of Graves' disease. The interaction between genetic susceptibility genes, including **TSHR**, **HLA**, **CTLA4**, and **PTPN22**, together with environmental factors such as smoking, infections, stress, iodine excess, and female sex hormones, initiates and perpetuates the autoimmune cascade leading to sustained thyroid stimulation. **[14]**

Thyroid-stimulating hormone receptor antibodies constitute a heterogeneous group of immunoglobulins with distinct biological activities. Stimulating antibodies (TSAbs) bind to the extracellular domain of TSHR and mimic the physiological action of TSH, resulting in persistent receptor activation and uncontrolled thyroid hormone synthesis. In contrast, blocking antibodies inhibit receptor activation and are more frequently associated with autoimmune hypothyroidism, whereas neutral antibodies may contribute to inflammation through alternative signaling pathways without directly affecting thyroid function. In Graves' disease, stimulating antibodies predominate and continuously activate intracellular signaling independent of hypothalamic-pituitary feedback, producing diffuse thyroid hyperplasia and excessive secretion of triiodothyronine (T3) and thyroxine (T4). Serum TRAb concentrations also correlate with disease activity, therapeutic response, relapse risk, and the likelihood of developing Graves' ophthalmopathy. **[15]**

Cell-mediated immunity plays an equally important role in disease pathogenesis. During the active phase of Graves' disease, T helper 1 (Th1) cells predominate and secrete pro-inflammatory cytokines, including interferon-γ (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-α (TNF-α), which promote antigen presentation and amplify autoimmune inflammation. As the disease progresses, T

helper 2 (Th2) responses facilitate B-cell activation and antibody production, while Th17 lymphocytes contribute to chronic inflammation through secretion of IL-17 and related cytokines. Concurrently, quantitative and functional impairment of regulatory T cells (Tregs) diminishes peripheral immune tolerance, allowing persistent activation of autoreactive lymphocytes and chronic autoimmune thyroid injury. This dynamic interaction among adaptive immune cell subsets underlies both thyroid dysfunction and systemic autoimmune manifestations. **[16]**

The immunopathogenesis of Graves' ophthalmopathy extends beyond the thyroid gland and involves autoimmune activation within orbital connective tissues. Orbital fibroblasts express both TSHR and insulin-like growth factor-1 receptor (IGF-1R), making them direct targets of circulating autoantibodies. Activation of these receptors stimulates fibroblast proliferation, adipocyte differentiation, hyaluronan synthesis, and secretion of multiple inflammatory cytokines and chemokines, resulting in glycosaminoglycan accumulation, edema, enlargement of extraocular muscles, and expansion of orbital fat. These pathological changes produce the characteristic clinical manifestations of Graves' ophthalmopathy, including proptosis, diplopia, eyelid retraction, and, in severe cases, compressive optic neuropathy. Increasing evidence also indicates functional crosstalk between TSHR and IGF-1R signaling pathways, providing the biological rationale for recently developed targeted therapies directed against IGF-1R in patients with active moderate-to-severe thyroid eye disease. **[17]**

The Thyroid-Stimulating Hormone Receptor (TSHR) Gene

The **TSHR** gene is one of the most extensively investigated susceptibility genes in autoimmune thyroid disease and remains the only gene that is both disease-specific and directly involved in the pathogenesis of Graves' disease. Located on chromosome **14q31**, the gene spans approximately 190 kb and consists of 10 exons separated by large intronic regions. Exons 1–9 encode most of the extracellular ligand-binding domain, whereas exon 10 encodes the remaining extracellular segment together with the transmembrane and intracellular domains responsible for signal transduction. This genomic organization provides multiple regulatory regions where genetic variants may influence transcription, alternative splicing, and receptor expression, thereby contributing to disease susceptibility. **[18]**

Unlike many autoimmune susceptibility genes that primarily regulate immune cell function, the TSHR gene encodes the principal autoantigen recognized by pathogenic thyroid-stimulating hormone receptor antibodies (TRAbs). During normal immune development, expression of TSHR within the thymus contributes to central immune tolerance by facilitating deletion of autoreactive T lymphocytes. Experimental studies have demonstrated that reduced thymic expression of TSHR impairs negative selection of autoreactive T cells, allowing these lymphocytes to escape into the peripheral circulation where they may initiate autoimmune responses against thyroid tissue. Consequently, alterations in TSHR gene regulation represent one of the earliest molecular events linking genetic susceptibility to the development of Graves' disease. **[19]**

The TSHR gene is subject to complex transcriptional regulation and generates multiple messenger RNA splice variants through alternative splicing mechanisms. These isoforms differ in their structural composition and biological activity, with some producing truncated soluble receptor fragments that may enhance autoantigen presentation or modify immune recognition. Functional polymorphisms, particularly those located within intron 1, have been shown to influence TSHR transcription by altering transcription factor binding sites, chromatin accessibility, and epigenetic regulation. These molecular alterations ultimately affect receptor abundance and immune tolerance rather than receptor function itself, explaining why most susceptibility-associated variants are located within non-coding regulatory regions instead of protein-coding exons. **[20]**

Accumulating evidence from genome-wide association studies (GWAS), fine-mapping analyses, and functional genomic investigations has consistently identified the TSHR locus as one of the strongest non-HLA genetic determinants of Graves' disease. The most robust associations involve intron 1 polymorphisms, particularly **rs179247** and **rs12101255**, which have been replicated across European and Asian populations. These variants are believed to reduce thymic TSHR expression, facilitating defective central immune tolerance and increasing susceptibility to thyroid autoimmunity. Because these

polymorphisms influence disease initiation rather than thyroid hormone synthesis directly, they represent attractive candidates for genetic risk prediction and may contribute to future precision medicine strategies aimed at identifying individuals at increased risk before clinical disease develops. **[21]**

Major TSHR Gene Polymorphisms Associated with Graves' Disease

Advances in candidate gene studies and genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) within the **TSHR** gene that contribute to susceptibility to Graves' disease. Unlike pathogenic mutations that alter receptor structure or signaling, the majority of GD-associated polymorphisms are located within non-coding intronic regions, particularly intron 1, indicating that disease susceptibility is primarily mediated through alterations in gene regulation rather than changes in receptor protein sequence. These regulatory variants influence transcriptional activity, mRNA processing, chromatin accessibility, and immune tolerance, thereby increasing the likelihood of autoimmune recognition of the TSH receptor. **[22]**

Among the identified variants, **rs179247** and **rs12101255** are the most consistently replicated susceptibility polymorphisms across different ethnic populations. Both SNPs are located within intron 1 and exhibit strong linkage disequilibrium, forming a susceptibility haplotype that has demonstrated significant associations with Graves' disease in European, Asian, and several Middle Eastern populations. Functional studies suggest that the disease-associated alleles reduce thymic expression of the TSHR gene, impairing central immune tolerance by limiting the negative selection of autoreactive T lymphocytes. Consequently, self-reactive T cells escape thymic deletion and subsequently stimulate autoreactive B cells to produce pathogenic thyroid-stimulating hormone receptor antibodies (TRAbs). **[23]**

Additional polymorphisms, including **rs2268458**, **rs2284722**, **rs4903964**, **rs179243**, and several neighboring intronic variants, have also been investigated for their contribution to disease susceptibility. Although individual studies have reported variable effect sizes, these variants appear to modify transcription factor binding, enhancer activity, or epigenetic regulation of the TSHR locus rather than directly affecting receptor structure or ligand binding. Differences in allele frequencies, linkage disequilibrium patterns, environmental exposures, and study design contribute to the heterogeneity observed among different populations, emphasizing that the cumulative effect of multiple variants rather than a single polymorphism is likely responsible for disease predisposition. **[24]**

Recent fine-mapping studies have further demonstrated that TSHR polymorphisms interact with other susceptibility loci, including **HLA**, **CTLA4**, **PTPN22**, and **FCRL3**, to generate a polygenic risk profile for Graves' disease. Rather than acting independently, these genetic variants collectively influence antigen presentation, immune checkpoint regulation, T-cell activation, and maintenance of immune tolerance. This polygenic model explains why individual TSHR polymorphisms confer only modest increases in disease risk, whereas combining multiple susceptibility alleles substantially improves genetic risk prediction. Consequently, future polygenic risk scores incorporating TSHR variants may facilitate earlier identification of high-risk individuals and support personalized preventive and therapeutic strategies in autoimmune thyroid disease. **[25]**

Association of TSHR Gene Polymorphisms with Graves' Disease

Genetic association studies performed over the past two decades have firmly established the **TSHR** locus as one of the strongest disease-specific susceptibility regions for Graves' disease (GD). Unlike immune regulatory genes that predispose to multiple autoimmune disorders, TSHR polymorphisms demonstrate a unique and highly specific association with autoimmune thyroid disease because the encoded receptor serves as the primary target of pathogenic thyroid-stimulating hormone receptor antibodies (TRAbs). Initial candidate gene studies were subsequently confirmed by large genome-wide association studies (GWAS), which consistently identified variants within intron 1 of the TSHR gene as independent risk factors for GD. These findings provided compelling evidence that genetic alterations affecting TSHR expression and immune tolerance play a fundamental role in disease initiation rather

than representing secondary consequences of thyroid autoimmunity. **[26]**

Among the numerous polymorphisms investigated, **rs179247** and **rs12101255** have shown the strongest and most reproducible associations with Graves' disease. Both variants are located within intron 1 and are inherited in strong linkage disequilibrium, forming a susceptibility haplotype that has been replicated across multiple European cohorts. Functional investigations demonstrated that the disease-associated alleles reduce thymic TSHR messenger RNA expression, thereby impairing central immune tolerance and allowing autoreactive T lymphocytes to escape thymic deletion. This mechanism provides one of the clearest functional explanations linking a common genetic polymorphism to the development of organ-specific autoimmunity and represents a landmark discovery in Graves' disease genetics. **[27]**

Similar associations have been confirmed in several Asian populations, including Chinese, Japanese, and Korean cohorts, although differences in allele frequencies and effect sizes have been reported. Meta-analyses combining data from diverse ethnic groups consistently demonstrate that intron 1 polymorphisms significantly increase susceptibility to Graves' disease regardless of ancestry, while also highlighting population-specific genetic heterogeneity. These differences likely reflect variations in linkage disequilibrium patterns, environmental exposures such as iodine intake, and interactions with other susceptibility loci including **HLA**, **CTLA4**, and **PTPN22**. Consequently, TSHR polymorphisms should be interpreted within the broader context of polygenic inheritance rather than as isolated genetic determinants. **[28]**

Studies from Middle Eastern and North African populations remain comparatively limited despite the high prevalence of autoimmune thyroid disease in these regions. Available evidence suggests that TSHR polymorphisms contribute to disease susceptibility in Arab populations; however, the magnitude of association varies among studies, probably because of differences in sample size, genetic background, and study methodology. In Egypt, investigations evaluating TSHR polymorphisms have been relatively scarce and have generally included modest patient cohorts. Nevertheless, preliminary findings indicate that variants within the TSHR locus may contribute to genetic susceptibility among Egyptian patients with Graves' disease, supporting the need for larger multicenter studies incorporating comprehensive SNP analysis and functional validation. Such studies are particularly important because population-specific genetic data are essential for developing clinically relevant risk prediction models. **[29]**

Although individual TSHR polymorphisms generally confer only modest increases in disease risk, their cumulative contribution becomes clinically meaningful when integrated with other susceptibility genes and immunological biomarkers. Recent advances in polygenic risk modeling indicate that combining TSHR variants with established immune-related loci and clinical parameters may substantially improve prediction of disease susceptibility, recurrence after antithyroid therapy, and progression to Graves' ophthalmopathy. Future research integrating genomic, transcriptomic, epigenetic, and functional immunological data is expected to refine these predictive models and facilitate the implementation of precision medicine strategies for patients with autoimmune thyroid disease. **[30]**

TSHR Gene Polymorphisms and Graves' Ophthalmopathy

Graves' ophthalmopathy (GO), also known as thyroid eye disease (TED), is the most frequent extrathyroidal manifestation of Graves' disease and develops in approximately 25–50% of affected patients. Although thyroid-stimulating hormone receptor antibodies (TRAbs) are considered the principal drivers of orbital autoimmunity, only a subset of patients with Graves' disease develop clinically significant ophthalmopathy, suggesting that additional genetic and environmental factors influence disease susceptibility and severity. Among the genetic determinants investigated, polymorphisms within the **TSHR** gene have attracted considerable attention because of the receptor's expression in orbital fibroblasts and its central role in autoimmune activation. Current evidence suggests that TSHR variants may contribute not only to the development of Graves' disease but also to the heterogeneous clinical manifestations of orbital involvement. **[31]**

The biological basis for this association lies in the expression of TSHR on orbital fibroblasts, preadipocytes, and fibrocytes that infiltrate orbital tissues during active disease. Binding of thyroid-stimulating antibodies to these receptors activates intracellular signaling pathways, leading to increased

production of cyclic adenosine monophosphate (cAMP), secretion of pro-inflammatory cytokines, adipocyte differentiation, and excessive synthesis of hyaluronan and other glycosaminoglycans. These pathological processes promote orbital tissue expansion, extraocular muscle enlargement, edema, and fibrosis, ultimately resulting in proptosis, diplopia, eyelid retraction, and, in severe cases, compressive optic neuropathy. Consequently, genetic variants capable of modifying TSHR expression or receptor availability may influence the magnitude of orbital autoimmune responses. **[32]**

Several candidate gene studies have investigated whether common TSHR polymorphisms, particularly **rs179247** and **rs12101255**, are associated with the occurrence or severity of Graves' ophthalmopathy. Although some studies reported significant associations between specific alleles and increased risk of ophthalmopathy, others failed to demonstrate independent effects after adjustment for established clinical risk factors such as smoking, TRAb concentration, age, sex, and duration of hyperthyroidism. These inconsistent findings likely reflect differences in ethnic background, sample size, disease classification, and study methodology. Current evidence therefore suggests that TSHR polymorphisms alone are insufficient to predict ophthalmopathy but may contribute modestly as part of a broader polygenic susceptibility profile. **[33]**

An important advance in understanding Graves' ophthalmopathy has been the recognition of functional crosstalk between the TSHR and insulin-like growth factor-1 receptor (IGF-1R). Experimental studies have demonstrated that these receptors form functional signaling complexes on orbital fibroblasts, amplifying inflammatory signaling following receptor activation. This interaction enhances cytokine production, extracellular matrix remodeling, adipogenesis, and fibroblast proliferation, thereby contributing to disease progression. The clinical relevance of this pathway is supported by the successful use of IGF-1R-targeted therapy in patients with active moderate-to-severe thyroid eye disease, highlighting the importance of receptor biology beyond genetic susceptibility alone. Future investigations integrating TSHR polymorphisms with transcriptomic, epigenetic, and proteomic analyses may improve identification of patients at increased risk for severe ophthalmopathy and facilitate individualized therapeutic strategies. **[34]**

Clinical Implications of TSHR Gene Polymorphisms

The growing understanding of **TSHR** gene polymorphisms has important implications for the clinical management of Graves' disease (GD). Although routine genetic testing is not currently recommended in clinical practice, identification of disease-associated TSHR variants has substantially improved understanding of disease susceptibility and pathogenesis. When combined with established clinical factors, including family history, smoking status, thyroid-stimulating hormone receptor antibody (TRAb) levels, age, and sex, TSHR polymorphisms may contribute to more accurate risk stratification for individuals with increased genetic susceptibility to autoimmune thyroid disease. As genetic technologies become more accessible and cost-effective, incorporation of TSHR genotyping into comprehensive risk prediction models may facilitate earlier identification of susceptible individuals before the onset of overt clinical disease. **[35]**

Beyond disease susceptibility, TSHR polymorphisms may have prognostic value by influencing disease phenotype, treatment response, and recurrence following antithyroid drug therapy. Several studies have suggested that patients carrying susceptibility alleles within the TSHR locus exhibit higher TRAb concentrations, prolonged autoimmune activity, and an increased likelihood of relapse after discontinuation of antithyroid medications. Although current evidence remains insufficient to support genotype-guided therapeutic decisions, integrating genetic information with biochemical markers and clinical characteristics may improve individualized treatment planning and assist clinicians in selecting patients who may benefit from earlier definitive therapy with radioiodine or thyroidectomy. **[36]**

The expanding field of precision medicine offers additional opportunities for the clinical application of TSHR genetics. Advances in genome-wide association studies, next-generation sequencing, transcriptomics, and artificial intelligence-based predictive modeling have enabled the development of polygenic risk scores that combine multiple susceptibility loci rather than relying on individual genetic variants. Because Graves' disease is a complex polygenic disorder, integrating TSHR polymorphisms

with other established susceptibility genes, epigenetic biomarkers, and immunological profiles is likely to provide more accurate prediction of disease onset, recurrence, and Graves' ophthalmopathy than single-gene analysis alone. Continued validation of these approaches in large prospective multicenter cohorts will be essential before their implementation in routine endocrine practice. **[37]**

Future Perspectives

Rapid advances in genomics and systems biology are reshaping the understanding of Graves' disease and creating new opportunities for personalized medicine. Future research is expected to move beyond the investigation of individual susceptibility genes toward integrated multi-omics approaches that combine genomic, epigenomic, transcriptomic, proteomic, and metabolomic data. Such comprehensive analyses may identify novel molecular pathways involved in immune dysregulation, clarify the functional consequences of TSHR polymorphisms, and improve prediction of disease susceptibility and progression. Furthermore, advances in single-cell RNA sequencing and spatial transcriptomics are providing unprecedented insights into the cellular interactions within thyroid and orbital tissues, allowing more precise characterization of the immune microenvironment underlying Graves' disease and Graves' ophthalmopathy. **[38]**

Another promising direction involves the development of precision medicine strategies based on integrated genetic and immunological profiling. Polygenic risk scores incorporating TSHR together with other susceptibility loci, including **HLA**, **CTLA4**, **PTPN22**, **CD40**, and **FCRL3**, may improve early identification of individuals at high risk of developing Graves' disease or severe Graves' ophthalmopathy. In parallel, continued development of targeted immunotherapies directed against TSHR- and IGF-1R-mediated signaling pathways is expected to transform disease management by providing more selective treatment with fewer adverse effects than conventional immunosuppressive approaches. Large multicenter studies involving ethnically diverse populations, including underrepresented Middle Eastern and African cohorts, will be essential to validate genetic biomarkers and establish their clinical utility in routine endocrine practice. **[39,4-]**

Conclusion

Graves' disease is a complex autoimmune disorder resulting from intricate interactions between genetic susceptibility, immune dysregulation, and environmental influences. Among the numerous susceptibility genes identified to date, the **TSHR** gene occupies a unique position because it encodes the primary autoantigen responsible for disease initiation and progression. Accumulating evidence demonstrates that polymorphisms within the TSHR locus, particularly intron 1 variants such as **rs179247** and **rs12101255**, contribute to defective immune tolerance and increase susceptibility to Graves' disease across multiple ethnic populations. Although their association with Graves' ophthalmopathy remains less consistent, these variants appear to participate in the broader genetic architecture underlying orbital disease. Continued integration of TSHR genetics with functional genomics, epigenetics, immunophenotyping, and artificial intelligence-based risk prediction models is expected to facilitate earlier diagnosis, improved prognostic stratification, and individualized therapeutic approaches. Ultimately, a more comprehensive understanding of TSHR biology will support the transition from conventional disease management toward precision medicine for patients with Graves' disease and Graves' ophthalmopathy.

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