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Genetic Architecture of Graves' Disease and Graves' Ophthalmopathy: From Susceptibility Genes to Precision Medicine

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ABSTRACT

Background: Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism and results from a multifactorial interaction between genetic susceptibility, immune dysregulation, epigenetic modifications, and environmental factors. Over the past two decades, advances in molecular genetics have substantially improved understanding of the complex genetic architecture underlying GD and its major extrathyroidal manifestation, Graves' ophthalmopathy (GO). Numerous susceptibility genes involved in immune regulation, antigen presentation, T-cell activation, and thyroid-specific autoimmunity have been identified, including the human leukocyte antigen (HLA) region, thyroid-stimulating hormone receptor (TSHR), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), protein tyrosine phosphatase non-receptor type 22 (PTPN22), CD40, and Fc receptor-like 3 (FCRL3). In addition, emerging evidence highlights the important contribution of epigenetic mechanisms, non-coding RNAs, and gene–environment interactions in disease initiation, progression, and clinical heterogeneity. Despite these advances, the translation of genetic discoveries into routine clinical practice remains limited, emphasizing the need for an integrated understanding of molecular pathways and their potential applications in precision medicine.

Aim: This review aims to comprehensively summarize the current knowledge regarding the genetic and epigenetic architecture of Graves' disease and Graves' ophthalmopathy. It discusses the biological functions and clinical significance of major susceptibility genes, the role of genome-wide association studies, epigenetic regulation, non-coding RNAs, and environmental modifiers in disease pathogenesis. Furthermore, the review critically evaluates emerging evidence supporting the implementation of polygenic risk assessment, molecular biomarkers, and targeted therapeutic strategies that may facilitate personalized management of autoimmune thyroid disease.

Conclusion: Graves' disease is a complex polygenic autoimmune disorder in which multiple susceptibility genes interact with epigenetic alterations and environmental exposures to disrupt immune tolerance and promote thyroid autoimmunity. While individual genetic variants confer only modest effects, their combined influence contributes substantially to disease susceptibility, phenotypic diversity, therapeutic response, and the risk of developing Graves' ophthalmopathy. Recent advances in genomics, transcriptomics, and systems biology have expanded the understanding of disease mechanisms and opened new opportunities for precision endocrinology. Future integration of genetic, epigenetic, immunological, and clinical data through multi-omics approaches and artificial intelligence-based predictive models may improve early disease prediction, individualized risk stratification, prognostic assessment, and targeted therapeutic interventions, ultimately advancing personalized care for patients with Graves' disease and Graves' ophthalmopathy.

Keywords: Graves' Disease, Graves' Ophthalmopathy, Precision Medicine

1. Introduction

Graves' disease (GD) is the most common cause of autoimmune hyperthyroidism and represents one of the most prevalent organ-specific autoimmune disorders encountered in clinical endocrinology. The disease results from the loss of immune tolerance to thyroid antigens, leading to the production of thyroid-stimulating hormone receptor antibodies (TRAbs) that continuously activate the thyroid-stimulating hormone receptor (TSHR). Persistent receptor stimulation promotes diffuse thyroid hyperplasia and excessive secretion of thyroid hormones, producing the characteristic manifestations of thyrotoxicosis, including weight loss, palpitations, heat intolerance, tremor, neuropsychiatric symptoms, and cardiovascular complications. In addition to thyroid dysfunction, GD is a systemic autoimmune disorder that may involve the orbit, skin, and, rarely, the extremities, making it a disease with substantial multisystem clinical consequences. **[1]**

Although Graves' disease has long been recognized as an autoimmune disorder, accumulating evidence demonstrates that its development is largely determined by inherited genetic susceptibility interacting with environmental and hormonal factors. Family clustering, twin studies, and genome-wide association studies have shown that genetic factors account for approximately 70–80% of disease susceptibility, while environmental exposures such as cigarette smoking, excess iodine intake, psychological stress, infections, pregnancy, and female sex hormones influence disease initiation and progression. Rather than resulting from a single pathogenic mutation, GD is now recognized as a complex polygenic disorder in which multiple susceptibility genes collectively disrupt immune tolerance and promote autoimmunity against thyroid tissue. **[2]**

Over the past two decades, advances in molecular genetics have identified numerous susceptibility loci associated with Graves' disease and Graves' ophthalmopathy. These genes participate in diverse biological pathways including antigen presentation, T-cell activation, immune checkpoint regulation, B-cell differentiation, cytokine signaling, and thyroid-specific immune tolerance. Among the most consistently replicated susceptibility genes are the human leukocyte antigen (HLA) region, thyroid-stimulating hormone receptor (**TSHR**), cytotoxic T-lymphocyte-associated protein 4 (**CTLA4**), protein tyrosine phosphatase non-receptor type 22 (**PTPN22**), **CD40**, and **FCRL3**. More recently, epigenetic mechanisms, non-coding RNAs, and genome-wide association studies have further expanded understanding of disease pathogenesis, demonstrating that genetic predisposition alone is insufficient without complex interactions among multiple molecular pathways. **[3]**

From a clinical perspective, understanding the genetic architecture of Graves' disease extends beyond explaining disease pathogenesis. Genetic discoveries are increasingly contributing to improved disease classification, identification of high-risk individuals, prediction of treatment response and relapse, assessment of Graves' ophthalmopathy risk, and development of targeted biological therapies. Furthermore, the emergence of polygenic risk scores, next-generation sequencing, and precision medicine approaches offers the possibility of individualized disease prediction and management, moving beyond conventional "one-size-fits-all" treatment strategies. These advances have significant implications for future endocrine practice and may ultimately improve long-term clinical outcomes in patients with autoimmune thyroid disease. **[4]**

Despite remarkable progress in identifying susceptibility genes, several important challenges remain. Many reported genetic associations exhibit ethnic variability, modest effect sizes, and limited clinical applicability when considered individually. Moreover, the interaction between genetic variants, epigenetic modifications, environmental triggers, and immune dysregulation remains incompletely understood. Therefore, this review aims to provide a comprehensive and clinically oriented overview of the genetic architecture of Graves' disease and Graves' ophthalmopathy by critically examining the major susceptibility genes, emerging epigenetic mechanisms, and recent advances in precision medicine that may influence future diagnostic, prognostic, and therapeutic strategies. **[5]**

2. Genetic Basis of Graves' Disease

Graves' disease (GD) is a classic example of a complex polygenic autoimmune disorder in which multiple susceptibility genes interact with environmental and immunological factors to initiate disease. Unlike monogenic disorders caused by mutations in a single gene, the genetic architecture of GD consists of numerous common genetic variants, each conferring a relatively modest increase in disease risk. Collectively, however, these variants substantially influence individual susceptibility by regulating immune tolerance, antigen presentation, lymphocyte activation, cytokine production, and thyroid-specific immune responses. The recognition of GD as a polygenic disease has fundamentally changed current concepts of disease pathogenesis and has provided the basis for modern genetic and translational research. **[6]**

Evidence supporting a strong genetic contribution to Graves' disease originates from family aggregation studies demonstrating that first-degree relatives of affected individuals have a markedly increased risk of developing autoimmune thyroid disease compared with the general population. Familial clustering extends beyond Graves' disease itself, as relatives frequently develop other autoimmune thyroid disorders, including Hashimoto's thyroiditis, suggesting the presence of shared genetic susceptibility pathways. These observations indicate that inherited immune dysregulation, rather than thyroid-specific abnormalities alone, underlies the development of autoimmune thyroid disease. **[7]**

Twin studies provide some of the strongest evidence for the heritable nature of Graves' disease. Concordance rates are consistently higher among monozygotic twins than dizygotic twins, with heritability estimates approaching 70–80%. Nevertheless, incomplete concordance among genetically identical twins indicates that genetic susceptibility alone is insufficient for disease development. Environmental exposures, epigenetic modifications, hormonal influences, and stochastic immune events are also required to trigger the loss of self-tolerance and initiate autoimmune thyroid inflammation. These findings support the widely accepted multifactorial threshold model for Graves' disease pathogenesis. **[8]**

Genome-wide association studies (GWAS) have considerably expanded the understanding of the genetic architecture of Graves' disease by identifying numerous susceptibility loci across different ethnic populations. These investigations consistently demonstrate that genetic variants may be broadly classified into two major categories: immune regulatory genes, including **HLA**, **CTLA4**, **PTPN22**, **CD40**, and **FCRL3**, which influence immune function, and thyroid-specific genes, particularly **TSHR** and **thyroglobulin (TG)**, which regulate thyroid autoimmunity directly. The interaction between these two groups of genes ultimately determines disease susceptibility, clinical phenotype, and, potentially, therapeutic response. **[9]**

From a clinical perspective, understanding the genetic basis of Graves' disease has important implications beyond disease pathogenesis. Although individual susceptibility genes currently have limited diagnostic utility because of their modest effect sizes, combining multiple genetic variants into polygenic risk models may improve prediction of disease development, recurrence following antithyroid drug therapy, and the likelihood of Graves' ophthalmopathy. Such approaches represent an important step toward precision endocrinology, where genetic information may eventually complement conventional clinical and biochemical markers to support individualized patient management. **[10]**

3. Human Leukocyte Antigen (HLA): The Major Genetic Determinant of Graves' Disease

Among all genetic susceptibility loci identified in Graves' disease (GD), the **human leukocyte antigen (HLA)** region remains the strongest and most consistently replicated genetic determinant across different ethnic populations. Located on chromosome 6p21, the HLA complex encodes major histocompatibility complex (MHC) molecules that play a fundamental role in adaptive immunity by presenting antigenic peptides to T lymphocytes. Variations within HLA genes can alter antigen presentation, modify T-cell selection, and influence immune tolerance, thereby increasing susceptibility to autoimmune diseases. Numerous genome-wide association studies have confirmed that HLA polymorphisms contribute more substantially to the genetic risk of GD than any other immune-regulatory locus, emphasizing their central role in disease initiation. **[11]**

The strongest associations have been reported for **HLA class II** alleles, particularly **HLA-DRB1**, **HLA-DQA1**, and **HLA-DQB1**, which regulate antigen presentation to $CD4^+$ helper T lymphocytes. These molecules determine the efficiency with which thyroid-derived peptides, including fragments of the thyroid-stimulating hormone receptor (TSHR) and thyroglobulin (TG), are presented to autoreactive T cells. Enhanced presentation of self-antigens promotes activation of autoreactive lymphocytes, stimulation of B cells, and subsequent production of thyroid-stimulating hormone receptor antibodies (TRAbs). Consequently,

HLA polymorphisms represent one of the earliest immunological events in the development of Graves' disease and provide the molecular basis for the loss of immune tolerance. **[12]**

The clinical significance of HLA polymorphisms extends beyond disease susceptibility. Several studies have demonstrated associations between specific HLA alleles and disease phenotype, age at onset, severity of hyperthyroidism, persistence of thyroid-stimulating antibodies, and the development of Graves' ophthalmopathy. However, these associations vary considerably among different ethnic groups because allele frequencies differ across populations. For example, **HLA-DR3** has been consistently associated with Graves' disease in Caucasian populations, whereas different HLA alleles predominate in East Asian populations. These ethnic differences highlight the importance of conducting population-specific genetic studies and caution against directly extrapolating findings from one population to another. **[13]**

Although HLA polymorphisms remain unsuitable as stand-alone diagnostic biomarkers because of their relatively low specificity, they contribute significantly to modern polygenic risk models. Combining HLA variants with other susceptibility genes, including **TSHR**, **CTLA4**, and **PTPN22**, improves genetic risk prediction compared with analysis of individual loci alone. Future integration of HLA genotyping with clinical characteristics, thyroid autoantibody profiles, and molecular biomarkers may facilitate earlier identification of high-risk individuals, individualized follow-up strategies, and more accurate prediction of disease recurrence and Graves' ophthalmopathy, representing an important step toward precision medicine in autoimmune thyroid disease. **[14]**

4. Thyroid-Stimulating Hormone Receptor (TSHR)

The **thyroid-stimulating hormone receptor (TSHR)** is the only thyroid-specific susceptibility gene consistently associated with Graves' disease (GD), distinguishing it from other genetic loci that broadly regulate immune function. Located on chromosome **14q31**, the TSHR gene encodes a G protein-coupled receptor expressed predominantly on thyroid follicular cells, where it regulates thyroid hormone synthesis, iodine uptake, and thyroid growth in response to pituitary thyroid-stimulating hormone (TSH). In Graves' disease, however, the receptor also serves as the principal autoantigen recognized by thyroid-stimulating hormone receptor antibodies (TRAbs), placing TSHR at the center of disease pathogenesis. This unique dual role explains why TSHR polymorphisms have consistently emerged as major susceptibility loci in genetic studies of autoimmune thyroid disease. **[15]**

Genome-wide association studies and candidate gene analyses have identified several polymorphisms within the **TSHR** gene, particularly intron 1 variants such as **rs179247** and **rs12101255**, as important contributors to Graves' disease susceptibility. Unlike mutations that alter receptor structure or function, these polymorphisms are located within regulatory regions and primarily influence gene expression. Functional studies have demonstrated that disease-associated alleles reduce thymic TSHR expression, impairing central immune tolerance and allowing autoreactive T lymphocytes to escape negative selection. These autoreactive cells subsequently activate B lymphocytes, resulting in persistent production of pathogenic TRAbs and chronic thyroid autoimmunity. **[16]**

From a clinical perspective, TSHR polymorphisms appear to influence disease susceptibility rather than determining the severity of hyperthyroidism itself. Several studies have reported associations between specific TSHR variants and earlier disease onset, increased risk of recurrence following antithyroid drug withdrawal, and susceptibility to Graves' ophthalmopathy, although these findings have not been entirely consistent across different ethnic populations. The relatively modest effect size of individual polymorphisms suggests that TSHR variants should be considered within the broader context of polygenic inheritance, where interactions with immune-regulatory genes and environmental exposures collectively determine disease phenotype. **[17]**

The clinical importance of TSHR extends beyond genetics because it has become a major therapeutic target in Graves' disease and thyroid eye disease. The receptor interacts closely with the insulin-like growth factor-1 receptor (IGF-1R), particularly within orbital fibroblasts, amplifying inflammatory signaling responsible for Graves' ophthalmopathy. Improved understanding of TSHR biology has therefore contributed not only to clarification of disease mechanisms but also to the development of targeted therapeutic strategies and personalized approaches to disease management. As precision medicine continues to evolve, integrating TSHR genetic profiling with clinical and immunological biomarkers may enhance risk prediction and optimize treatment selection for patients with autoimmune thyroid disease. **[18]**

5. Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4)

The **cytotoxic T-lymphocyte-associated protein 4 (CTLA4)** gene is one of the earliest and most extensively investigated non-HLA susceptibility genes in Graves' disease (GD). Located on chromosome **2q33**, CTLA4 encodes an inhibitory immune checkpoint receptor expressed primarily on activated T lymphocytes and regulatory T cells (Tregs). Physiologically, CTLA4 functions as a negative regulator of T-cell activation by competing with CD28 for binding to CD80/CD86 molecules on antigen-presenting cells, thereby limiting excessive immune responses and maintaining peripheral immune tolerance. Genetic variants that impair CTLA4 expression or function reduce this inhibitory signaling, allowing persistent activation of autoreactive T cells and increasing susceptibility to autoimmune diseases, including Graves' disease. **[19]**

Several polymorphisms within the **CTLA4** gene have been associated with Graves' disease, among which the **A49G (rs231775)** polymorphism in exon 1 and the **CT60 (rs3087243)** polymorphism in the 3′ untranslated region have received the greatest attention. Meta-analyses involving diverse ethnic populations have consistently demonstrated significant associations between these variants and increased susceptibility to GD, although the strength of association varies according to ancestry. Functional studies suggest that these polymorphisms may alter CTLA4 surface expression, receptor trafficking, or production of soluble CTLA4, resulting in impaired immune checkpoint function and enhanced activation of autoreactive T lymphocytes. Consequently, CTLA4 variants are considered important contributors to the breakdown of peripheral immune tolerance in autoimmune thyroid disease. **[20]**

Unlike the thyroid-specific **TSHR** gene, CTLA4 is a generalized autoimmune susceptibility gene and has been implicated in numerous autoimmune disorders, including type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, and autoimmune thyroid diseases. This broad disease association reflects its central role in immune regulation rather than organ-specific autoimmunity. In patients with Graves' disease, CTLA4 polymorphisms may influence disease susceptibility more strongly than disease severity, although several studies have reported associations with persistent thyroid-stimulating hormone receptor antibody (TRAb) positivity, recurrence after antithyroid drug therapy, and coexistence of multiple autoimmune disorders. These observations further support the concept that immune checkpoint dysfunction contributes to chronic autoimmune activation. **[21]**

From a clinical perspective, the discovery of CTLA4 as a susceptibility gene has important implications for precision medicine and immunotherapy. Although CTLA4 genotyping is not currently recommended for routine clinical practice, its inclusion in polygenic risk models may improve prediction of autoimmune thyroid disease in genetically predisposed individuals. Moreover, the success of immune checkpoint-targeted therapies in oncology has stimulated growing interest in understanding CTLA4-mediated immune regulation in autoimmune diseases. Continued investigation of CTLA4 signaling pathways may identify novel therapeutic strategies capable of restoring immune tolerance while minimizing systemic immunosuppression, thereby improving long-term outcomes in Graves' disease. **[22]**

6. Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22)

The **protein tyrosine phosphatase non-receptor type 22 (PTPN22)** gene is one of the most important non-HLA immune regulatory genes implicated in autoimmune diseases, including Graves' disease (GD). Located on chromosome **1p13**, PTPN22 encodes the lymphoid tyrosine phosphatase (LYP), a critical intracellular regulator of T-cell receptor (TCR) signaling. Under physiological conditions, LYP functions as a negative regulator of T-cell activation by limiting antigen receptor signaling and maintaining immune homeostasis. Genetic alterations affecting PTPN22 may disrupt this tightly controlled process, allowing autoreactive T lymphocytes to escape immune regulation and promoting the development of autoimmune thyroid disease. **[23]**

The most extensively investigated polymorphism within the **PTPN22** gene is the **1858C>T (rs2476601)** variant, which results in an arginine-to-tryptophan substitution at codon 620 (R620W). This functional polymorphism has been associated with an increased risk of several autoimmune disorders, including Graves' disease, type 1 diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus. Functional studies suggest that the R620W variant alters the interaction between lymphoid tyrosine phosphatase and C-terminal Src kinase (CSK), leading to abnormal regulation of T-cell activation and impaired immune tolerance. Consequently, carriers of the risk allele exhibit an increased likelihood of developing autoimmune thyroid disease, particularly in European populations. **[24]**

The association between **PTPN22** polymorphisms and Graves' disease demonstrates considerable ethnic variability. While the rs2476601 variant is consistently associated with increased susceptibility in Caucasian populations, it is rare or virtually absent in many Asian populations, indicating that its contribution to disease risk differs substantially according to ancestry. These

findings illustrate the complex genetic heterogeneity of Graves' disease and emphasize the importance of considering population-specific genetic backgrounds when interpreting association studies or developing genetic risk prediction models. The absence of this polymorphism in certain populations also suggests that alternative susceptibility genes may play a more prominent role in disease pathogenesis. **[25]**

From a clinical perspective, PTPN22 represents an important component of the polygenic architecture of Graves' disease rather than an independent diagnostic biomarker. Although routine genetic testing is not currently recommended, incorporation of PTPN22 into polygenic risk scores alongside **HLA**, **TSHR**, **CTLA4**, and other susceptibility loci may improve prediction of disease susceptibility and facilitate earlier identification of individuals at increased genetic risk. Furthermore, a better understanding of intracellular T-cell signaling pathways regulated by PTPN22 may contribute to the future development of targeted immunomodulatory therapies aimed at restoring immune tolerance in autoimmune thyroid disease. **[26]**

7. Cluster of Differentiation 40 (CD40)

The **cluster of differentiation 40 (CD40)** gene is an important immune-regulatory susceptibility gene that contributes to the development of Graves' disease (GD) through its role in adaptive immune activation. Located on chromosome **20q13**, CD40 encodes a transmembrane costimulatory receptor expressed on B lymphocytes, dendritic cells, macrophages, thyroid follicular cells, and orbital fibroblasts. Interaction between CD40 and its ligand (CD40L, CD154), expressed on activated $CD4^+$ T lymphocytes, provides an essential signal for B-cell proliferation, immunoglobulin class switching, cytokine secretion, and the generation of high-affinity antibodies. Dysregulation of this pathway enhances autoimmune responses and promotes the production of pathogenic thyroid-stimulating hormone receptor antibodies (TRAbs), thereby contributing to the initiation and persistence of Graves' disease. **[27]**

Among the identified genetic variants, the **CD40 C/T polymorphism (rs1883832)** located within the Kozak sequence has been the most extensively investigated in autoimmune thyroid disease. Functional studies have demonstrated that the susceptibility allele increases translational efficiency and results in higher CD40 protein expression on antigen-presenting cells and B lymphocytes. Enhanced CD40 expression amplifies T-cell–B-cell interactions, facilitating autoantibody production and perpetuating chronic autoimmune inflammation. Multiple association studies and meta-analyses have confirmed that rs1883832 is associated with an increased risk of Graves' disease, particularly in European and Asian populations, although the magnitude of association varies among ethnic groups. **[28]**

Beyond disease susceptibility, activation of the CD40-CD40L signaling pathway has important clinical implications because it contributes to both thyroidal and extrathyroidal autoimmune inflammation. Increased CD40 expression has been demonstrated in thyroid tissue from patients with Graves' disease, where it promotes local cytokine production and sustained lymphocytic infiltration. Furthermore, orbital fibroblasts express functional CD40 receptors, and their activation stimulates the release of pro-inflammatory mediators, extracellular matrix remodeling, and tissue expansion that characterize Graves' ophthalmopathy. These findings suggest that CD40 participates not only in the initiation of autoimmune thyroid disease but also in disease progression and tissue-specific injury. **[29]**

From a therapeutic perspective, the CD40-CD40L pathway represents a promising target for future immunomodulatory interventions. Although no CD40-directed therapies have yet become standard treatment for Graves' disease, experimental studies indicate that selective inhibition of this signaling pathway may reduce autoreactive B-cell activation while preserving overall immune competence. When integrated with other susceptibility genes such as **HLA**, **TSHR**, **CTLA4**, and **PTPN22**, CD40 polymorphisms may also improve polygenic risk prediction models and contribute to personalized approaches for identifying individuals at increased risk of developing Graves' disease or severe Graves' ophthalmopathy. **[30]**

8. Fc Receptor-Like 3 (FCRL3)

The **Fc receptor-like 3 (FCRL3)** gene has emerged as an important non-HLA susceptibility gene in several autoimmune diseases, including Graves' disease (GD). Located on chromosome **1q23**, FCRL3 belongs to the Fc receptor-like family of immunoregulatory proteins and is predominantly expressed on mature B lymphocytes, plasma cells, and subsets of regulatory T cells. Although its precise physiological function has not been fully elucidated, FCRL3 is believed to regulate B-cell activation, differentiation, antibody production, and immune tolerance. Given the central role of B cells in producing thyroid-stimulating hormone receptor antibodies (TRAbs), genetic alterations affecting FCRL3 expression may contribute directly to the development and persistence of thyroid autoimmunity. **[31]**

The most extensively investigated polymorphism within the **FCRL3** gene is the promoter variant **−169C>T (rs7528684)**, which influences transcriptional activity by modifying nuclear factor-κB (NF-κB) binding. Functional studies have demonstrated that the susceptibility allele increases FCRL3 gene expression, thereby enhancing B-cell activation and promoting autoantibody production. Several case-control studies have reported significant associations between this polymorphism and Graves' disease, particularly in East Asian populations, although the magnitude of association has varied among different ethnic groups. These findings suggest that FCRL3 contributes to disease susceptibility by augmenting humoral immune responses rather than directly affecting thyroid-specific pathways. **[32]**

From a clinical perspective, FCRL3 polymorphisms appear to influence the risk of developing autoimmune thyroid disease rather than determining disease severity or therapeutic response. Unlike thyroid-specific susceptibility genes such as **TSHR**, FCRL3 represents a generalized immune regulatory gene that has also been implicated in rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune conditions. Consequently, its presence reflects an underlying predisposition to immune dysregulation rather than organ-specific autoimmunity. Nevertheless, incorporation of FCRL3 into polygenic risk models may improve the identification of individuals genetically predisposed to Graves' disease, particularly when combined with major susceptibility genes including **HLA**, **TSHR**, **CTLA4**, **PTPN22**, and **CD40**. **[33]**

Although current evidence supports an association between FCRL3 polymorphisms and Graves' disease susceptibility, several limitations remain. Many published studies involve relatively small sample sizes, and inconsistent findings across different populations indicate that the contribution of FCRL3 may depend on ethnic background, linkage disequilibrium patterns, and interactions with other susceptibility genes. Future multicenter studies integrating genomic, transcriptomic, and functional immunological analyses are needed to clarify the biological role of FCRL3 and determine whether this pathway may serve as a biomarker for disease prediction or a potential target for immunomodulatory therapy in autoimmune thyroid disease. **[34]**

9. Additional Genetic Susceptibility Genes

Although **HLA**, **TSHR**, **CTLA4**, **PTPN22**, **CD40**, and **FCRL3** account for a substantial proportion of the inherited risk for Graves' disease (GD), numerous additional susceptibility genes contribute to disease development through their effects on immune regulation and thyroid-specific autoimmunity. Genome-wide association studies have identified variants within genes involved in antigen presentation, cytokine signaling, T-cell differentiation, and immune tolerance, supporting the concept that Graves' disease is a highly polygenic disorder. Individually, these genes exert relatively modest effects; however, their cumulative interaction significantly influences disease susceptibility, clinical phenotype, and therapeutic response. **[35]**

One of the most important thyroid-specific susceptibility genes is the **thyroglobulin (TG)** gene. Thyroglobulin serves as the precursor protein for thyroid hormone synthesis and represents one of the principal thyroid autoantigens targeted during autoimmune thyroid disease. Several polymorphisms within the TG gene have been associated with increased susceptibility to Graves' disease, particularly when inherited together with high-risk HLA alleles. Experimental studies suggest that these variants may alter antigen processing or peptide presentation, thereby facilitating activation of autoreactive T lymphocytes and enhancing thyroid-specific immune responses. The combined contribution of TG and TSHR polymorphisms highlights the importance of thyroid-specific autoantigens in disease initiation. **[36]**

Additional immune regulatory genes implicated in Graves' disease include **FOXP3**, **IL2RA (CD25)**, **CD226**, **ICAM1**, **TNF**, **IL6**, and **IFNG**. These genes participate in multiple immunological pathways, including regulatory T-cell development, cytokine production, leukocyte adhesion, and inflammatory signaling. Variants affecting these pathways may impair immune tolerance, amplify inflammatory responses, and promote sustained activation of autoreactive lymphocytes. Although the effect size of each individual polymorphism is generally small, simultaneous inheritance of multiple susceptibility alleles substantially increases the probability of autoimmune thyroid disease, illustrating the cumulative nature of genetic risk in GD. **[37]**

From a clinical perspective, these additional susceptibility genes currently have limited value as independent diagnostic or prognostic biomarkers because of their relatively modest individual contributions to disease risk. However, their importance becomes more evident when incorporated into comprehensive polygenic risk scores alongside major susceptibility loci such as **HLA**, **TSHR**, **CTLA4**, **PTPN22**, **CD40**, and **FCRL3**. As genomic technologies continue to evolve, integrating multiple genetic variants with clinical characteristics, thyroid autoantibody profiles, and environmental exposures may improve individualized risk prediction, facilitate earlier diagnosis, and support precision medicine strategies for patients with Graves' disease and Graves' ophthalmopathy. **[38]**

10. Epigenetic Regulation in Graves' Disease

Although genetic susceptibility plays a fundamental role in the development of Graves' disease (GD), inherited genetic variants alone cannot fully explain disease onset, incomplete concordance among monozygotic twins, or the marked variability in clinical presentation. Increasing evidence indicates that **epigenetic mechanisms** provide the molecular link between genetic predisposition and environmental exposures by regulating gene expression without altering the underlying DNA sequence. These mechanisms are dynamic and reversible, allowing environmental factors such as smoking, iodine intake, infections, psychological stress, medications, and hormonal changes to modify immune responses and contribute to the initiation or progression of autoimmune thyroid disease. Consequently, epigenetic dysregulation has become an important area of investigation in understanding the heterogeneous clinical behavior of Graves' disease. **[39]**

The principal epigenetic mechanisms implicated in Graves' disease include **DNA methylation, histone modification, and chromatin remodeling**. DNA methylation generally suppresses gene transcription through the addition of methyl groups to cytosine residues within CpG islands, whereas histone acetylation and methylation regulate chromatin accessibility and transcriptional activity. Several studies have demonstrated abnormal methylation patterns in peripheral blood mononuclear cells and thyroid tissue obtained from patients with Graves' disease, affecting genes involved in immune regulation, cytokine signaling, and T-cell activation. These alterations may enhance autoreactive lymphocyte survival, impair immune tolerance, and promote persistent autoimmune inflammation. **[40]**

Furthermore, accumulating evidence suggests that epigenetic modifications may influence disease activity, response to therapy, and the development of Graves' ophthalmopathy. Unlike inherited genetic polymorphisms, epigenetic alterations are potentially reversible, making them attractive targets for future therapeutic intervention. Advances in high-throughput sequencing and multi-omics technologies are expected to improve understanding of epigenetic signatures associated with disease susceptibility, relapse, and treatment outcomes. Integration of epigenetic biomarkers with genetic and clinical data may ultimately facilitate more accurate risk stratification and individualized management strategies for patients with Graves' disease, representing an important step toward precision endocrinology.

11. Genetics of Graves' Ophthalmopathy

Graves' ophthalmopathy (GO), also known as thyroid eye disease (TED), is the most common extrathyroidal manifestation of Graves' disease, affecting approximately 25–50% of patients during the course of their illness. However, only a subset of individuals with Graves' disease develops clinically significant orbital involvement, suggesting that genetic susceptibility contributes to disease expression in addition to thyroid autoimmunity. Current evidence indicates that GO shares many genetic risk factors with Graves' disease, including **HLA**, **TSHR**, **CTLA4**, **PTPN22**, and **CD40**, but additional genetic, immunological, and environmental factors determine orbital inflammation, tissue remodeling, and disease severity. This complex genetic background partly explains the marked heterogeneity in clinical presentation, ranging from mild ocular discomfort to severe proptosis, diplopia, compressive optic neuropathy, and vision loss. **[35]**

Among the shared susceptibility genes, **TSHR** plays a particularly important role because the receptor is expressed not only in thyroid follicular cells but also in orbital fibroblasts and fibrocytes. Autoantibody-mediated activation of TSHR stimulates intracellular signaling pathways that promote fibroblast proliferation, adipocyte differentiation, hyaluronic acid synthesis, and extracellular matrix expansion within orbital tissues. These pathological processes result in enlargement of extraocular muscles, orbital fat expansion, tissue edema, and progressive proptosis that characterize Graves' ophthalmopathy. Functional studies have demonstrated that TSHR signaling is further amplified through interaction with the insulin-like growth factor-1 receptor (IGF-1R), creating a pathogenic receptor complex that enhances inflammatory cytokine production and orbital tissue remodeling. This molecular interaction has become the basis for targeted biological therapy in thyroid eye disease. **[36]**

Although genetic predisposition is essential, environmental and clinical factors substantially modify the risk of developing Graves' ophthalmopathy. Cigarette smoking remains the strongest modifiable risk factor, significantly increasing both disease incidence and severity while reducing responsiveness to immunosuppressive therapy. Additional contributors include persistent hyperthyroidism, elevated thyroid-stimulating hormone receptor antibody (TRAb) levels, radioactive iodine therapy in susceptible individuals, and delayed restoration of euthyroidism. These observations illustrate the importance of gene–environment interactions in determining disease phenotype and emphasize that genetic susceptibility alone is insufficient for orbital disease development. Consequently, comprehensive management of Graves' disease requires early identification and

modification of these clinical risk factors in genetically predisposed patients. **[37]**

Recent advances in molecular genetics and targeted therapeutics have transformed the management of Graves' ophthalmopathy. Improved understanding of TSHR and IGF-1R signaling has led to the development of biologic therapies that specifically interrupt disease-driving pathways rather than providing nonspecific immunosuppression. Furthermore, ongoing genomic and transcriptomic studies are identifying additional molecular biomarkers that may facilitate early prediction of orbital disease, assessment of disease activity, and individualized therapeutic selection. Integration of genetic profiling with clinical risk factors, imaging findings, and circulating biomarkers may ultimately enable precision medicine approaches capable of identifying patients at greatest risk for severe ophthalmopathy and optimizing personalized treatment strategies before irreversible orbital fibrosis develops. **[38]**

Conclusion

Graves' disease is a complex autoimmune disorder that arises from the interaction of multiple genetic susceptibility loci, epigenetic modifications, immune dysregulation, and environmental triggers. Advances in molecular genetics have transformed the understanding of disease pathogenesis, demonstrating that no single gene is solely responsible for disease development. Instead, susceptibility results from the cumulative effects of numerous immune-regulatory and thyroid-specific genes, including **HLA**, **TSHR**, **CTLA4**, **PTPN22**, **CD40**, **FCRL3**, and several additional loci that collectively influence immune tolerance, antigen presentation, lymphocyte activation, and autoantibody production.

Among these susceptibility genes, the HLA region remains the strongest genetic determinant of disease risk, whereas the TSHR gene occupies a unique position as the principal thyroid-specific autoantigen directly involved in disease pathogenesis. Other immune-regulatory genes further modify disease susceptibility by altering T-cell activation, B-cell differentiation, cytokine signaling, and maintenance of immune homeostasis. Increasing evidence also highlights the important contribution of epigenetic regulation and gene–environment interactions in explaining the clinical heterogeneity observed among patients with Graves' disease and Graves' ophthalmopathy.

Although remarkable progress has been achieved in identifying genetic susceptibility factors, translation of these discoveries into routine clinical practice remains limited. Most individual genetic variants exert only modest effects and therefore cannot currently be used as independent diagnostic or prognostic biomarkers. However, integrating multiple susceptibility genes with epigenetic markers, thyroid autoantibody profiles, and conventional clinical parameters offers a promising strategy for improving disease prediction, identifying individuals at increased risk of relapse or Graves' ophthalmopathy, and optimizing individualized patient management.

The emergence of genome-wide association studies, next-generation sequencing, transcriptomics, artificial intelligence, and multi-omics technologies is rapidly expanding the field of precision endocrinology. These advances are expected to facilitate the development of validated polygenic risk scores, identify novel therapeutic targets, and improve understanding of disease mechanisms across diverse populations. Future large-scale multicenter studies incorporating functional genomics and longitudinal clinical data will be essential to validate these approaches and establish their clinical utility. Ultimately, integrating genetic, epigenetic, immunological, and clinical information has the potential to transform the management of Graves' disease from a reactive treatment paradigm toward predictive, preventive, and personalized medicine, thereby improving long-term outcomes and quality of life for affected patients.

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