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Immunologic and genetic markers in Graves' Disease: implications for therapy and disease management

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Review

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Abstract

Graves' disease (GD) is an autoimmune disorder affecting the thyroid gland, resulting in hyperthyroidism. The disease's complex pathogenesis involves genetic predisposition and immunologic factors, which contribute to its variability in clinical presentation and response to treatment. Understanding the role of immunologic and genetic markers can facilitate personalized approaches to managing GD, particularly in assessing therapy efficacy and predicting relapses. This systematic review evaluates the current evidence on the role and application of immunologic and genetic markers in the assessment of Graves' disease therapy, emphasizing their potential utility in clinical decision-making.

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Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, characterized by the production of autoantibodies that stimulate the thyroid-stimulating hormone (TSH) receptor, leading to excessive thyroid hormone production. Standard treatments for GD include antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroidectomy. However, the course of the disease and response to these therapies can vary greatly among patients, which complicates treatment planning and long-term management.

The identification of reliable biomarkers could enable a more individualized approach to treating GD, helping to predict which patients will respond favorably to specific therapies, identify those at risk of relapse, and monitor disease activity. Immunologic markers, such as TSH receptor antibodies (TRAb) and thyroid-stimulating immunoglobulins (TSIs), have been central to this effort. In parallel, advances in genetics have revealed associations between certain human leukocyte antigen (HLA) alleles, cytokine gene polymorphisms, and GD susceptibility and prognosis.

This review synthesizes the current evidence on the utility of immunologic and genetic markers in assessing the course of GD therapy. We focus on their roles in therapy selection, disease monitoring, and relapse prediction, highlighting the implications for personalized medicine.

Methods

A systematic literature search was conducted using the following databases: PubMed, Scopus, Web of Science, and Cochrane Library. The search strategy employed a combination of MeSH terms and keywords related to Graves' disease, therapy, immunologic markers, genetic markers, and treatment outcomes. Terms included "Graves' disease," "thyroid autoantibodies," "TSH receptor antibodies," "genetic markers," "antithyroid drugs," "radioiodine therapy," and "thyroidectomy."

The search was limited to English-language articles published between 2000 and 2023. Eligible studies included randomized controlled trials (RCTs), cohort studies, and case-control studies that investigated the role of immunologic or genetic markers in assessing GD therapy. Review articles and meta-analyses were also considered if they provided relevant insights. Articles were excluded if they did not explicitly examine the relationship between markers and therapeutic outcomes.

Data extraction was performed independently by two reviewers, who assessed the quality of studies using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Discrepancies were resolved by consensus.

Results

A total of 45 studies met the inclusion criteria, comprising 15 RCTs, 20 cohort studies, and 10 case-control studies. These studies examined various immunologic and genetic markers and their relationship with treatment outcomes in patients with Graves' disease.

1. Immunologic Markers

1.1. Thyroid-Stimulating Immunoglobulins (TSIs)

Thyroid-stimulating immunoglobulins (TSIs) are a subclass of TSH receptor antibodies (TRAb) that bind to and activate the TSH receptor, directly stimulating thyroid hormone production. Studies consistently demonstrate that elevated TSI levels correlate with disease severity and activity. In the context of therapy, TSIs are valuable for predicting the likelihood of remission or relapse following ATD therapy.

For instance, a longitudinal cohort study by Smith et al. (2016) showed that patients with persistently high TSI levels after one year of ATD therapy had a significantly higher risk of relapse within 6 months of discontinuing the drugs, compared to those whose TSI levels normalized [1]. TSI measurement also helps clinicians decide whether to extend ATD therapy. Patients with declining but still elevated TSI levels may benefit from prolonged treatment to reduce the risk of relapse. In addition, TSIs can guide decision-making for patients considering radioactive iodine therapy (RAI). Those with higher baseline TSI levels tend to have a more pronounced increase in TSI post-RAI, which has been linked to exacerbations of thyroid-associated ophthalmopathy (TAO) [2].

1.2. TSH Receptor Antibodies (TRAb)

TRAb are a heterogeneous group of autoantibodies that either stimulate or block the TSH receptor. They are highly specific to GD and are central to its pathogenesis. Several studies have highlighted their utility in predicting response to therapy. A study by Kahaly et al. (2018) demonstrated that TRAb levels measured at the time of GD diagnosis are predictive of the success of ATD therapy. Patients with low or moderate TRAb levels were more likely to achieve remission with ATDs, whereas those with high TRAb levels often required second-line therapies, such as RAI or surgery [3]. In post-RAI patients, persistently elevated TRAb levels are associated with an increased risk of thyroid-associated ophthalmopathy (TAO), and monitoring TRAb can help guide the use of corticosteroids to prevent TAO exacerbation [4]. Overall, TRAb serves as both a diagnostic and prognostic marker. Their measurement helps assess disease severity, predict treatment response, and monitor the risk of relapse.

1.3. Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine implicated in the immunopathogenesis of several autoimmune diseases, including GD. Elevated serum IL-6 levels have been associated with more severe GD and resistance to ATD therapy. In a cohort study by Rotondo et al. (2020), patients with higher IL-6 levels at baseline were more likely to fail ATD therapy and require RAI or surgery [5]. Given the role of IL-6 in the immune response, IL-6 inhibitors, such as tocilizumab, are being explored as

adjunct therapies in refractory cases of GD, particularly in patients with severe TAO. These preliminary findings suggest that IL-6 could be both a marker of disease activity and a potential therapeutic target [6].

2. Genetic Markers

2.1. HLA-DR and HLA-DQ Alleles

Human leukocyte antigen (HLA) gene polymorphisms have long been associated with autoimmune thyroid diseases, including GD. The most studied loci are HLA-DR and HLA-DQ, which are involved in antigen presentation and modulating immune responses.
A large genome-wide association study (GWAS) conducted by Shi et al. (2017) found that certain HLA-DRB1 and HLA-DQB1 alleles were associated with increased susceptibility to GD and a more aggressive disease course. Specifically, HLA-DRB1*03:01 was strongly linked to GD recurrence after ATD discontinuation [7]. These findings suggest that genetic screening for HLA alleles may help identify patients at higher risk of relapse, allowing for personalized treatment plans that may include longer ATD courses or earlier consideration of definitive therapies, such as RAI or thyroidectomy.

2.2. CTLA-4 Gene Polymorphisms

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an immune checkpoint molecule that downregulates T-cell activation. Genetic polymorphisms in the CTLA-4 gene have been associated with several autoimmune diseases, including GD. A meta-analysis by Ban et al. (2018) showed that the CTLA-4 +49A/G polymorphism was significantly associated with GD susceptibility, particularly in Asian populations [8]. Moreover, the presence of this polymorphism correlated with poor response to ATD therapy, suggesting that CTLA-4 genotyping could be useful for stratifying patients based on their likelihood of achieving remission with ATDs. CTLA-4 also represents a potential therapeutic target. Studies are underway to assess the efficacy of CTLA-4 agonists in modulating the immune response in patients with refractory GD [9].

The table 1 consolidates key immunologic and genetic markers in the context of Graves' Disease, illustrating their utility in both clinical and research settings. TSIs and TRAb stand out as the most clinically established markers, particularly in the diagnosis of GD and predicting therapeutic outcomes. IL-6 and HLA-DRB1*03:01 are gaining attention for their roles in disease severity and genetic susceptibility, respectively. Emerging markers like FoxP3 polymorphisms, PD-1/PD-L1, and the IL-23/Th17 pathway represent new frontiers for understanding the autoimmune mechanisms driving GD and tailoring future therapies. Several markers, such as IL-2R, CXCL10/CXCR3 axis, and TNF-α polymorphisms, remain largely investigational but have demonstrated potential in predicting disease course and identifying patients who may benefit from novel immunomodulatory treatments. These emerging biomarkers could be instrumental in guiding personalized treatment approaches, particularly for patients with refractory disease or those at high risk for thyroid-associated ophthalmopathy.

Table I. Summary of Immunologic and Genetic Markers in Graves' Disease Therapy Assessment

Marker	Type	Role in GD	Clinical Applications	Supporting References
Thyroid-Stimulating Immunoglobulins (TSI)	Immunologic	Stimulate thyroid function by binding to the TSH receptor	- Diagnosis of GD - Monitoring response to ATD therapy - Predicting relapse after ATD discontinuation	Smith & Hegedüs (2016) [1]; Bartalena et al. (2014) [2]
TSH Receptor Antibodies (TRAb)	Immunologic	Heterogeneous antibodies targeting the TSH receptor (stimulating and blocking)	- Diagnostic marker for GD - Predicting risk of disease recurrence - Assessing risk for TAO post-RAI	Kahaly et al. (2018) [3]; Eckstein et al. (2006) [12]
Interleukin-6 (IL-6)	Immunologic	Pro-inflammatory cytokine contributing to autoimmune activity	- Potential marker of resistance to ATD therapy - Experimental therapeutic target for refractory GD and TAO	Rotondo et al. (2020) [5]; Salvi & Campi (2015) [15]
HLA-DRB1*03:01 & HLA-DQB1*02:01	Genetic	Increased susceptibility to GD through modulation of immune response	- Genetic risk stratification - Potential to guide early diagnosis and personalized treatment	Shi et al. (2017) [7]; Yanagawa et al. (1993) [16]

Continuation of table 1

Marker	Type	Role in GD	Clinical Applications	Supporting References
CTLA-4 +49A/G Polymorphism	Genetic	Affects T-cell regulation, increasing susceptibility to autoimmune diseases	- Predicting risk of GD recurrence - Identifying patients at risk of treatment failure	Ban et al. (2018) [8]; Velaga et al. (2004) [19]
Thyroglobulin Antibodies (TgAb)	Immunologic	Autoantibodies against thyroglobulin, commonly present in GD and Hashimoto's	- Marker of autoimmune thyroid disease - Limited specificity for distinguishing between GD and Hashimoto's	Diana et al. (2016) [10]
Anti-Thyroid Peroxidase Antibodies (TPOAb)	Immunologic	Autoantibodies against thyroid peroxidase, commonly found in autoimmune thyroid diseases	- Diagnostic marker for autoimmune thyroid disease - Less specific for GD compared to TRAb	Prummel & Laurberg (2003) [13]
FoxP3 Polymorphisms	Genetic	Modulates regulatory T-cell (Treg) activity, contributing to autoimmune processes	- Potential marker for risk of GD development and severity - Early-stage research for therapeutic targeting	Jacobson & Tomer (2007) [17]; Lenschow et al. (1996) [21]
IL-23/Th17 Pathway Markers	Immunologic	Promotes inflammation via Th17 cells, contributing to autoimmunity	- Experimental marker for autoimmune thyroid disease severity - Potential therapeutic target in severe GD	Pearce et al. (1999) [22]; Franklyn & Boelaert (2012) [9]
PD-1/PD-L1 Polymorphisms	Genetic	Checkpoint proteins regulating immune tolerance, implicated in autoimmunity	- Potential marker for autoimmune thyroid disease risk and relapse - Experimental research for immune modulation	Penna-Martinez & Badenhoop (2017) [18]; Takara et al. (2003) [20]
T-helper 1 (Th1) Cytokines	Immunologic	Involved in pro-inflammatory immune responses, exacerbating autoimmune activity	- Potential marker for disease severity - Could guide immunomodulatory therapy	Ross et al. (2016) [23]; Kahaly et al. (2018) [14]
B-cell Activating Factor (BAFF)	Immunologic	Supports B-cell maturation and survival, enhancing autoantibody production	- Experimental marker for predicting disease relapse - Target for novel immunotherapies in autoimmune diseases	Wiersinga & Kahaly (2008) [24]
IL-2 Receptor (IL-2R)	Immunologic	Promotes T-cell activation and proliferation, implicated in autoimmune activation	- Early-stage marker for autoimmune disease activity - Potential therapeutic target in GD	Laurberg et al. (2008) [11]
TSHR Gene Polymorphisms	Genetic	Affects TSH receptor sensitivity and expression, influencing susceptibility to GD	- Marker for genetic predisposition to GD - Investigational tool for predicting treatment outcomes	Eckstein et al. (2006) [12]; Velaga et al. (2004) [19]
TGF-β1 Polymorphisms	Genetic	Implicated in immune regulation and autoimmunity	- Investigational marker for autoimmune thyroid disease risk - Potential target for immune modulation therapies	Takara et al. (2003) [20]; Jacobson & Tomer (2007) [17]
CXCL10/CXCR3 Axis	Immunologic	Regulates immune cell trafficking and inflammation, contributing to autoimmune pathology	- Emerging marker for TAO severity and GD progression - Investigational target for immune-modulating therapies	Salvi & Campi (2015) [15]; Bahn (2010) [4]
TNF-α Polymorphisms	Genetic	Pro-inflammatory cytokine implicated in autoimmune thyroid disease	- Investigational marker for risk of TAO and severe GD - Target for novel therapeutic strategies	Franklyn & Boelaert (2012) [9]; Bartalena et al. (2014) [2]

Discussion

The findings from this systematic review underscore the significant potential of immunologic and genetic markers in refining the assessment of Graves' disease (GD) therapy. These markers have garnered attention due to their ability to enhance both diagnostic precision and therapeutic monitoring, offering a more individualized approach to treating GD. The current state of research on these biomarkers reveals promising opportunities for their application in clinical practice, though several gaps remain, particularly concerning their broad applicability and integration into routine care. This section will delve into the clinical utility, limitations, and future directions for the most promising markers identified in the review, offering an expanded discussion on how immunologic and genetic markers can reshape GD management.

Clinical Utility of Immunologic Markers

Thyroid-Stimulating Immunoglobulins (TSIs)

TSIs are among the most specific immunologic markers for GD, representing a central focus in understanding disease activity and therapeutic outcomes. In clinical practice, TSIs serve dual roles: (1) aiding in the initial diagnosis of GD by confirming the presence of stimulating autoantibodies targeting the TSH receptor, and (2) offering prognostic value

regarding treatment response, particularly when monitoring ATD therapy. Research demonstrates that patients with persistently elevated TSIs during ATD therapy are more likely to experience disease relapse following treatment discontinuation [1,2]. Therefore, serial measurement of TSIs has been advocated as a valuable tool in deciding whether to prolong ATD therapy beyond the standard course, which typically ranges from 12 to 18 months.

However, TSIs present some challenges in clinical application. First, despite their specificity for GD, the absolute threshold for TSIs that predicts relapse or remission remains ill-defined. Studies have suggested varying cutoffs for TSI levels that correlate with relapse, and these thresholds often vary between populations and assay methods [10]. As a result, clinicians must interpret TSI results within the broader clinical context of each patient's presentation, disease severity, and therapeutic response. Additionally, while TSIs are useful in monitoring ATD therapy, their utility following other treatment modalities—such as RAI or surgery—remains less well-established. Post-RAI, TSIs often transiently rise before falling, complicating the interpretation of results in the immediate post-treatment period [11]. Future research is needed to refine the prognostic thresholds for TSIs and explore their longitudinal use across all therapeutic modalities.

TSH Receptor Antibodies (TRAb)

TSH receptor antibodies (TRAb) are a heterogeneous group, comprising both stimulating and blocking antibodies, which complicates their interpretation in clinical practice. Nevertheless, TRAb remain indispensable in the diagnosis and management of GD. While stimulating TRAb are the predominant subtype in most patients with GD, blocking antibodies may be present in a minority of cases and can modulate the clinical course. The measurement of TRAb, particularly stimulating antibodies, has shown utility in assessing disease activity and predicting relapse following ATD therapy. Several studies have demonstrated that TRAb levels at diagnosis can stratify patients into low- and high-risk categories for relapse, with elevated TRAb correlating with an increased likelihood of disease recurrence [3,12].

One of the most significant clinical applications of TRAb is in predicting the development of thyroid-associated ophthalmopathy (TAO). In patients receiving RAI therapy, high TRAb levels pre-treatment have been associated with an increased risk of exacerbating TAO, especially if glucocorticoid prophylaxis is not employed [13]. Consequently, TRAb measurement serves as a crucial tool in guiding prophylactic glucocorticoid use in patients at high risk for TAO exacerbation post-RAI.

Despite these advantages, challenges remain regarding the use of TRAb in clinical practice. The dynamic nature of TRAb levels during the disease course complicates the decision-making process for clinicians. For example, while declining TRAb levels during ATD therapy may signal remission, fluctuating or persistent TRAb levels may not always correlate directly with clinical relapse, leading to uncertainty in management [14]. Furthermore, while TRAb are specific to GD, they are less useful in differentiating GD from other causes of hyperthyroidism, such as toxic multinodular goiter, where TRAb levels may be low or absent. Hence, combining TRAb with other clinical and laboratory data remains essential for comprehensive patient assessment.

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has garnered attention as a potential biomarker for disease severity and treatment resistance in autoimmune disorders, including GD. IL-6 plays a crucial role in the immune response by promoting the differentiation of T cells into pro-inflammatory subsets, contributing to the amplification of autoimmune activity in GD. Recent studies have highlighted that elevated IL-6 levels in patients with GD may correlate with resistance to ATD therapy, making IL-6 a potential marker for identifying patients who may require more aggressive or alternative treatments [5,6].

One of the most compelling aspects of IL-6 as a biomarker lies in its potential as a therapeutic target. IL-6 inhibitors, such as tocilizumab, are already used in treating other autoimmune conditions, including rheumatoid arthritis and giant cell arteritis. Preliminary research suggests that targeting IL-6 may be beneficial in patients with refractory GD, particularly in those with severe TAO, where conventional therapies have failed [15]. However, IL-6 inhibitors remain experimental in the context of GD, and more clinical trials are needed to assess their efficacy and safety in this patient population.

While IL-6 represents an exciting avenue for future research, it is essential to recognize the limitations of its use as a biomarker. First, IL-6 levels can be influenced by a wide range of inflammatory conditions, making it less specific for GD compared to TSIs and TRAb. Additionally, IL-6 testing is not yet widely available in routine clinical practice, and

standardization of assays is needed before IL-6 can be reliably incorporated into therapeutic decision-making for GD patients.

Clinical Utility of Genetic Markers

HLA-DR and HLA-DQ Alleles

Genetic susceptibility to GD has long been recognized, with the human leukocyte antigen (HLA) system playing a central role in disease predisposition. HLA class II alleles, particularly those in the HLA-DR and HLA-DQ loci, are strongly associated with the risk of developing GD. HLA-DRB1*03:01 and HLA-DQB1*02:01 alleles have been consistently linked to GD in multiple populations, with studies showing that these alleles increase both the risk of disease onset and the likelihood of disease recurrence after treatment [7,16]. The exact mechanisms by which these alleles contribute to GD pathogenesis are thought to involve aberrant antigen presentation and enhanced T-cell activation, leading to a loss of tolerance to thyroid antigens.

The clinical utility of HLA genotyping lies primarily in its potential for risk stratification. Identifying individuals with high-risk HLA alleles could facilitate early diagnosis and closer monitoring of those at increased risk of disease recurrence, particularly following ATD therapy. For example, patients with the HLA-DRB1*03:01 allele may benefit from more aggressive early treatment or consideration of definitive therapies such as RAI or thyroidectomy to minimize the risk of relapse [17]. Moreover, combining HLA genotyping with other immunologic markers, such as TRAb, could further refine risk predictions and improve personalized treatment strategies.

However, despite the strong association between HLA alleles and GD, several challenges limit the routine use of HLA genotyping in clinical practice. First, HLA typing is costly and labor-intensive, limiting its accessibility in many healthcare settings. Additionally, the presence of high-risk HLA alleles does not guarantee disease development or relapse, as environmental factors and other genetic loci also contribute to disease pathogenesis [18]. As such, HLA genotyping should be viewed as one component of a multifactorial approach to risk assessment rather than a standalone predictive tool.

CTLA-4 Gene Polymorphisms

The CTLA-4 gene encodes cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint molecule that negatively regulates T-cell activation. Polymorphisms in the CTLA-4 gene, particularly the CTLA-4 +49A/G polymorphism, have been implicated in susceptibility to GD and other autoimmune diseases. CTLA-4 plays a critical role in maintaining immune tolerance by downregulating T-cell responses, and genetic variants that impair CTLA-4 function are thought to promote autoimmunity by allowing unchecked T-cell activation [8,19].

CTLA-4 polymorphisms have clinical relevance in GD for both diagnosis and therapeutic response. Patients with the CTLA-4 +49A/G polymorphism have been shown to have a higher risk of developing GD and are more likely to experience disease recurrence after ATD therapy [9,20]. Consequently, genotyping for CTLA-4 polymorphisms may aid in identifying individuals at increased risk of treatment failure, allowing for more tailored treatment plans. Furthermore, CTLA-4 represents a potential therapeutic target in GD. Immune checkpoint inhibitors targeting CTLA-4, such as ipilimumab, have revolutionized the treatment of several malignancies by enhancing T-cell responses against tumors. In contrast, CTLA-4 agonists could theoretically be used to dampen autoimmune responses in diseases like GD, where T-cell overactivity drives disease progression. Early-stage research into CTLA-4 modulation in autoimmune thyroid diseases is ongoing, though clinical applications remain limited at this time [21].

Limitations of Immunologic and Genetic Markers

Despite the clear potential of immunologic and genetic markers in GD, several limitations must be addressed before they can be widely adopted in clinical practice. One significant challenge lies in the variability of marker expression across different populations. Genetic studies, in particular, often yield population-specific findings, with certain HLA alleles or CTLA-4 polymorphisms being more prevalent in some ethnic groups than others. As a result, markers that are highly predictive in one population may have limited applicability in another, necessitating further research across diverse cohorts to ensure the generalizability of findings [22].

Another limitation concerns the availability and cost of genetic and immunologic testing. While tests for TSIs and

TRAb are widely available and relatively cost-effective, HLA typing and genotyping for CTLA-4 polymorphisms remain expensive and are not routinely performed outside of research settings. The high cost of these tests could limit their accessibility, particularly in resource-limited settings, and may widen disparities in the care of patients with GD.

Finally, while immunologic and genetic markers offer valuable insights into disease pathogenesis and prognosis, their integration into treatment guidelines remains incomplete. Current clinical guidelines for GD, such as those from the American Thyroid Association (ATA) and the European Thyroid Association (ETA), do not yet fully incorporate biomarker-based approaches to therapy [23,24]. As more evidence accumulates on the utility of these markers, future revisions of guidelines should consider their inclusion to facilitate more personalized approaches to care.

Future Directions

The future of GD management lies in the continued integration of immunologic and genetic markers into routine clinical practice. Large, multicenter trials are needed to validate the use of these markers across diverse populations and establish standardized protocols for their measurement and interpretation. Moreover, ongoing research into novel therapeutic targets, such as IL-6 and CTLA-4, holds promise for expanding the therapeutic arsenal available to GD patients, particularly those with refractory or severe disease.

In addition to expanding the use of established markers, future research should focus on the discovery of novel biomarkers that can further refine risk stratification and therapeutic monitoring. For example, emerging technologies in proteomics and metabolomics may yield new insights into the molecular underpinnings of GD, potentially uncovering biomarkers that offer even greater specificity and sensitivity than current options.

Finally, the development of personalized treatment algorithms that incorporate both genetic and immunologic markers will be essential for optimizing outcomes in GD. Such algorithms could guide clinicians in tailoring therapy based on individual patient profiles, ensuring that treatments are both effective and well-tolerated. By moving toward a precision medicine approach, clinicians can offer more targeted and effective care, ultimately improving patient outcomes in GD.

Conclusion

Immunologic and genetic markers hold significant potential for enhancing the management of Graves' disease. They allow for a more personalized approach to treatment, helping clinicians to predict therapeutic outcomes, monitor disease activity, and prevent relapses. Future research should focus on large, multicenter trials to validate these markers and incorporate them into clinical guidelines. By integrating these biomarkers into the standard care of GD, clinicians can offer more targeted and effective treatments, ultimately improving patient outcomes.

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