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Review Article

Association of TSHR gene polymorphisms with thyroid eye disease: an updated systematic review and meta-analysis

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Abstract

Background: The contribution of thyroid-stimulating hormone receptor (TSHR) gene polymorphisms to thyroid eye disease (TED) remains uncertain despite their established association with Graves' disease (GD). We systematically evaluated whether TSHR variants confer susceptibility to orbital involvement.

Methodology: PubMed/MEDLINE, Embase, Scopus, Web of Science, and supplementary sources were searched for studies published through 31 July 2026. The review followed PRISMA 2020 guidance and used a prespecified registered PROSPERO protocol (CRD420261532037). Eligible genetic association studies examining TSHR variants in TED were reviewed, prioritizing comparisons between GD patients with and without ophthalmopathy. Variant-specific associations were assessed using odds ratios (ORs) and 95% confidence intervals (CIs), with random-effects meta-analysis where comparable data permitted.

Results: Fifteen studies published between 1995 and 2026 were included, of which ten reported clearly defined TED-specific outcomes. The pooled allelic analysis of rs179247 showed no significant association with TED (A versus G: OR 1.02, 95% CI 0.97–1.07; I^2=36%). In contrast, the rs12885526 GG genotype was associated with ophthalmopathy in a single Brazilian study (OR 2.94, 95% CI 1.32–6.55). Neither the investigated coding-region polymorphism (OR 0.98, 95% CI 0.60–1.59) nor TSHR copy-number variation (OR 1.28, 95% CI 0.92–1.78) demonstrated significant associations in available individual-study comparisons. Differences in ancestry, phenotype definition, and comparator selection limited cross-study comparability.

Conclusions: TSHR-associated genetic susceptibility to TED appears variant-specific and distinct from general GD predisposition. Current evidence does not support routine single-variant genetic testing for TED risk prediction. Larger, ethnically diverse prospective studies with standardized phenotyping and functional validation are needed to establish reproducible genetic markers.

Keywords: Genetic susceptibility, Graves' orbitopathy, rs12885526, rs179247, Systematic review and meta-analysis, Thyroid eye disease, Thyroid-stimulating hormone receptor (TSHR), TSHR gene polymorphisms

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1. Introduction

Thyroid eye disease (TED), also known as Graves' orbitopathy or thyroid-associated ophthalmopathy, is an autoimmune inflammatory disorder of the orbit that occurs most commonly in association with Graves' disease. The disease is characterized by inflammation and remodelling of orbital soft tissues, including enlargement of the extraocular muscles and expansion of orbital adipose tissue. Clinically, TED may manifest with eyelid retraction, proptosis, periocular swelling, exposure keratopathy, restrictive strabismus and diplopia, while severe disease can result in compressive optic neuropathy and irreversible visual loss.[1,2] Beyond its potential threat to vision, TED can substantially impair appearance, daily functioning and quality of life, making it an important disorder at the interface of ophthalmology, oculoplastic surgery and endocrinology.[3]

The pathogenesis of TED is complex and reflects interactions among autoimmune susceptibility, environmental exposures and orbital tissue-specific immune responses. Cigarette smoking, thyroid dysfunction, elevated thyrotropin receptor antibody levels and radioiodine exposure in susceptible individuals are established or proposed modifiers of disease development and severity.[3,4] At the cellular level, orbital fibroblasts are considered central effector cells.

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These cells express thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R), and activation of these interconnected signalling pathways promotes cytokine production, hyaluronan accumulation, adipogenesis and tissue expansion within the confined orbital space.[5,6] The expression of TSHR in orbital fibroblasts provides an important mechanistic link between thyroid autoimmunity and orbital manifestations and has made the receptor a major focus of genetic and immunological investigation in TED.[7]

The TSHR gene, located on chromosome 14q31, encodes the G-protein-coupled receptor responsible for mediating the effects of thyroid-stimulating hormone. In Graves' disease, TSHR additionally functions as a principal autoantigen targeted by stimulating autoantibodies.[8] Genetic studies have demonstrated that several single-nucleotide polymorphisms within the TSHR locus are associated with susceptibility to autoimmune thyroid disease, particularly variants situated within intron 1. Among these, rs179247 and rs12101255 have emerged as the most consistently investigated susceptibility polymorphisms. These variants are thought to influence TSHR transcription, alternative splicing or intrathymic receptor expression, potentially modifying immune tolerance to TSHR and thereby facilitating the development of pathogenic autoimmunity.[9]

Although the association between TSHR polymorphisms and Graves' disease is well established, their specific contribution to the development of TED remains less certain. Case-control studies evaluating rs179247, rs12101255, rs12885526, rs2268458 and other TSHR variants have reported inconsistent findings across populations.[10,11] For example, studies in European and South American populations have suggested associations between selected TSHR polymorphisms and Graves' orbitopathy, whereas other investigations have failed to demonstrate statistically significant differences between Graves' disease patients with and without orbital involvement.[12,13] Such discrepancies may reflect differences in ethnicity, allele frequencies, linkage disequilibrium patterns, sample size, disease classification, smoking exposure, duration of Graves' disease and the definition of TED severity or activity.

A previous meta-analysis by Xiong et al. evaluated TSHR polymorphisms in relation to both Graves' disease and Graves' ophthalmopathy and identified significant susceptibility signals for several intronic variants, particularly rs179247 and rs12101255.[14] However, the evidence available at that time was limited by the relatively small number of ophthalmopathy-specific studies, heterogeneous phenotypic definitions and restricted representation of different ancestral populations. Since that analysis, additional genetic association studies and broader assessments of autoimmune thyroid disease susceptibility have been published, including newer population-specific investigations and updated systematic evidence regarding rs179247.[15,16] These developments provide a rationale for reassessing the magnitude, consistency and population specificity of the association between TSHR polymorphisms and TED.

An updated systematic review and meta-analysis may therefore help resolve conflicting individual-study findings by increasing statistical power and providing pooled estimates of genetic effects. Importantly, separate analyses according to individual single-nucleotide polymorphisms, ethnicity, genotype model and diagnostic criteria may clarify whether apparent inconsistencies arise from true biological variation or methodological heterogeneity. Such an analysis may also help determine whether TSHR polymorphisms are associated specifically with orbital disease susceptibility rather than merely reflecting the underlying genetic predisposition to Graves' disease.

Accordingly, the present systematic review and meta-analysis aims to evaluate the association between TSHR gene polymorphisms and susceptibility to thyroid eye disease, with particular emphasis on commonly investigated variants such as rs179247 and rs12101255. The study further seeks to quantify the strength of these associations, assess between-study heterogeneity and explore potential sources of variation according to ethnicity, genetic model and study characteristics. A clearer understanding of the genetic contribution of TSHR to TED may enhance insight into disease pathogenesis and could ultimately contribute to improved genetic risk stratification and individualized approaches to patients with Graves' disease.

2. Materials and Methods

2.1. Study design and reporting framework

This systematic review and meta-analysis was designed to evaluate the association between genetic polymorphisms of the thyroid-stimulating hormone receptor (TSHR) gene and susceptibility to thyroid eye disease (TED), also referred to as Graves' orbitopathy (GO), Graves' ophthalmopathy, or thyroid-associated ophthalmopathy. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and its accompanying explanation and elaboration guidance. The methodological framework, including the eligibility criteria, literature-search strategy, data-extraction procedures, risk-of-bias assessment, and statistical-analysis plan, was predefined to minimize selective inclusion, reporting bias, and analytical bias. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the title *"Association of TSHR Gene Polymorphisms with Thyroid Eye Disease: An Updated Systematic Review and Meta-analysis"* and published under registration number CRD420261532037. The study identification, screening, eligibility assessment, and final inclusion process are summarized in the PRISMA 2020 flow diagram. **(Figure 1)**

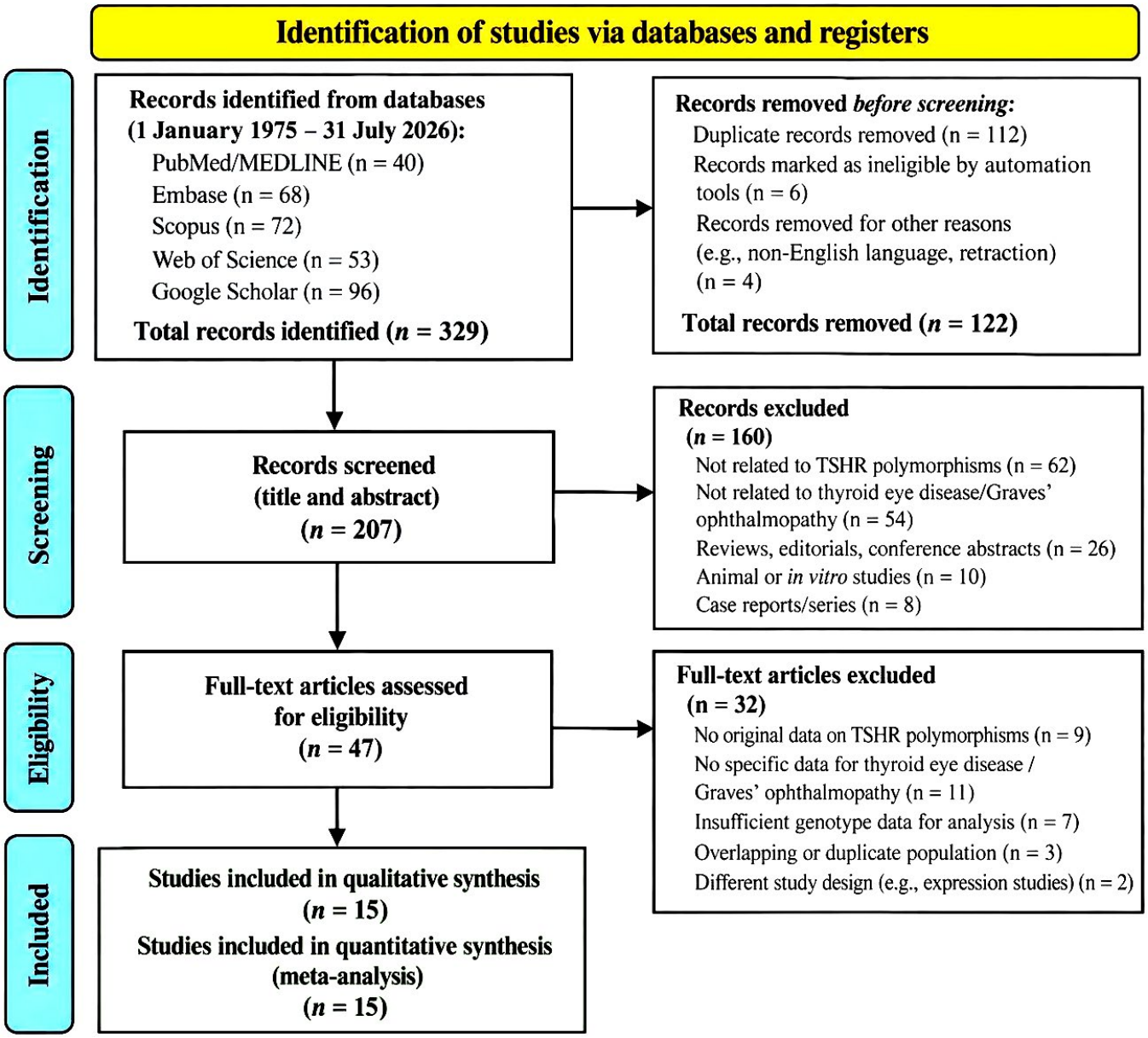

Figure 1: PRISMA 2020 flow diagram of the study identification, screening, eligibility assessment, and inclusion process**.** A total of 329 records were identified through database searching. After removal of 122 records before screening, 207 records underwent title and abstract screening, of which 160 were excluded. Forty-seven full-text articles were assessed for eligibility, and 32 were excluded for predefined reasons. Ultimately, 15 studies were included in the qualitative synthesis and 15 were included in the quantitative synthesis (meta-analysis). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TSHR, thyroid-stimulating hormone receptor.

2.2. Literature search strategy

A comprehensive literature search was conducted to identify potentially eligible studies published between 1 January 1975 and 31 July 2026. The electronic databases searched were PubMed/MEDLINE, Embase, Scopus, and Web of Science. Google Scholar was additionally searched as a supplementary source to identify potentially relevant studies not retrieved through the principal bibliographic databases. Reference lists of eligible primary studies, previous systematic reviews and meta-analyses, and relevant narrative reviews were also screened manually to identify additional publications. The search strategy combined controlled vocabulary and free-text terms related to the thyroid-stimulating hormone receptor (TSHR), genetic variation, and the thyroid eye disease phenotype. The core search concept was:

("thyroid stimulating hormone receptor" OR "thyrotropin receptor" OR "TSHR") AND ("polymorphism" OR "single nucleotide polymorphism" OR "SNP" OR "variant" OR "genotype" OR "allele" OR "genetic association" OR "copy number variation") AND ("thyroid eye disease" OR "Graves' ophthalmopathy" OR "Graves' orbitopathy" OR "thyroid-associated ophthalmopathy" OR "thyroid ophthalmopathy" OR "endocrine ophthalmopathy" OR "Graves' eye disease").

Database-specific strategies were adapted according to the indexing system and syntax of each platform.

MeSH terms were incorporated for PubMed/MEDLINE and Emtree terms for Embase, while appropriate title, abstract, keyword, and topic-field searches were used for Scopus and Web of Science. Additional targeted searches were conducted using frequently investigated TSHR variants, including rs179247, rs12101255, rs12885526, rs2268458, P52T, D36H, and D727E, to minimize the possibility of missing studies indexed primarily by variant identifier rather than by gene name. No restrictions were imposed on geographic location, ethnicity, genetic ancestry, or clinical setting. No language restriction was applied at the search stage. Non-English reports were considered for inclusion where sufficient information could be obtained for eligibility assessment and data extraction. Google Scholar was used as a supplementary search source through focused combinations of TSHR-related, polymorphism-related, and TED/GO-related terms. Search results were screened in a predefined sequence to improve reproducibility. Backward and forward citation searching was also performed for key eligible studies and relevant reviews. All retrieved records were imported into a reference-management database, and duplicate citations were removed before title and abstract screening. The complete database-specific search strategies, search dates, and numbers of records retrieved from each source were documented and will be reported in the supplementary material.

2.3. Eligibility criteria

Studies were considered eligible according to prespecified population, exposure, comparator, outcome, and study-design criteria. Eligible studies included original human genetic association investigations evaluating one or more polymorphisms or germline genetic variants in the thyroid-stimulating hormone receptor (TSHR) gene in patients with Graves' disease and/or thyroid eye disease/Graves' orbitopathy (TED/GO). Studies were included if they met all of the following criteria:

1. Employed a case-control, cohort, cross-sectional genetic association, or other comparable observational design.
2. Investigated one or more TSHR polymorphisms, single-nucleotide variants, coding or regulatory variants, or copy-number variants.
3. Included patients with clinically diagnosed TED/GO or provided a clearly defined subgroup of Graves' disease patients with ophthalmic involvement.
4. Included an appropriate comparator group, preferentially Graves' disease patients without TED/GO, or alternatively healthy or population-based controls when TED-specific comparisons were available.
5. Reported genotype frequencies, allele frequencies, odds ratios, or sufficient numerical data to derive an effect estimate with a corresponding 95% confidence interval.
6. Represented an independent study population.

The preferred comparison for assessment of TED-specific genetic susceptibility was Graves' disease with TED/GO versus Graves' disease without TED/GO. This comparison was prioritized because it more directly evaluates whether a TSHR variant is associated specifically with orbital involvement rather than merely reflecting genetic susceptibility to Graves' disease. Studies comparing TED/GO cases with healthy controls were also eligible but were analyzed separately because such comparisons may reflect both Graves' disease susceptibility and ophthalmic disease susceptibility. Studies were excluded if they were narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, letters without original genetic data, case reports, uncontrolled case series, conference abstracts without sufficient extractable information, animal studies, in-vitro investigations, gene-expression studies without germline genetic data, or studies evaluating genes other than TSHR without separately extractable TSHR-specific results. Studies in which the TED/GO phenotype was not adequately defined or could not be distinguished from Graves' disease without ophthalmic involvement were not included in the primary quantitative analysis. Where multiple publications originated from the same or overlapping study population, only the report providing the largest relevant sample size, most complete genotype information, or most appropriate TED/GO comparison was included in a given pooled analysis to avoid double counting. Companion publications were used only to supplement methodological or clinical information where necessary. Studies that otherwise met the eligibility criteria but did not provide sufficient genotype or allele data for quantitative pooling were retained in the qualitative synthesis when they contributed relevant information to the review question. Only studies providing adequate and comparable genetic data were included in the SNP-specific meta-analyses.

2.4. Study selection

All records identified through the literature search were imported into a reference-management database, and duplicate citations were removed before screening. Two reviewers independently screened the titles and abstracts of all unique records against the predefined eligibility criteria. Articles considered potentially relevant by either reviewer underwent full-text assessment. The same reviewers independently evaluated the full-text articles for final eligibility, and any disagreement regarding study inclusion was resolved through discussion and consensus; where necessary, a third reviewer adjudicated unresolved discrepancies. The study-selection process was documented using a PRISMA 2020 flow diagram, including the numbers of records identified, duplicates removed, records screened, full-text articles assessed, reasons for exclusion at the full-text stage, and studies included in the qualitative and quantitative syntheses. The characteristics of the studies meeting the final eligibility criteria are summarized in **Table 1**.

Table 1: Characteristics of the studies included in the systematic review evaluating the association between TSHR genetic variants and thyroid eye disease/Graves' orbitopathy

Study	Design	Sample/ comparator	TSHR marker(s)	Genotyping/ genetic measure	TED/GO-specific outcome	Key result/ relevance
Cuddihy et al.,[17]	Case-control genetic association	125 AITD patients (91 GD, 34 HT) and 121 controls	TSHR codon 52 polymorphism	PCR with AciI restriction digestion; sequencing confirmation	Ophthalmopathy not the primary stratified endpoint in the accessible record	Early coding-region TSHR association study; useful background for historical susceptibility variants.
Watson et al.,[18]	Case-control genetic association	88 GD without eye disease; 53 GD with ophthalmopathy; 39 autoimmune hypothyroidism; 156 controls	Coding-region TSHR polymorphism	PCR, oligonucleotide mismatch hybridization, direct sequencing	Yes: GD with ophthalmopathy vs GD without clinically apparent eye disease	No significant difference in polymorphism distribution between GD subgroups.
Ho et al.,[19]	Case-control / clinical-genetic association	GD cohort with multi-ethnic controls; exact subgroup counts require full text	D36H, P52T, D727E	Genotyping of three germline TSHR polymorphisms	Yes: associations with Graves' ophthalmopathy assessed	Evaluated disease state and GO associations across multiple TSHR coding variants.
Syed et al.,[20]	Case-control / gene-gene interaction study	NR in accessible record	TSHR genotype plus PTPN12 polymorphism	SNP genotyping; interaction analysis	Yes: association with Graves' ophthalmopathy	Reported preliminary evidence of interaction between PTPN12 and TSHR genotype in GO.
Yin et al.,[21]	Case-control genetic association	GD/GO patients and controls; exact subgroup counts require full text	TSHR susceptibility variants including intronic markers	SNP genotyping	Yes: susceptibility to GD and GO evaluated	Directly examined whether TSHR genetic variation contributes to GO susceptibility.
Liu et al.,[22]	Case-control genetic association	404 GD patients plus other AITD groups/controls; GO subgroup reported	Intronic TSHR SNPs including rs179247 and related variants	SNP genotyping	Yes: rs179247 association with ophthalmopathy reported	Reported association of rs179247 with ophthalmopathy among GD patients.
Yin et al.,[23]	Genetic profiling study	GD patients stratified by GO phenotype; detailed counts require full text	Multiple GD susceptibility loci including TSHR	Multilocus genetic profiling	Yes: tested for a distinct genetic contribution to GO	Found further evidence against a distinct GO-specific genetic contribution beyond GD susceptibility.

Study	Design	Sample/ comparator	TSHR marker(s)	Genotyping/ genetic measure	TED/GO-specific outcome	Key result/ relevance
Liao et al.,[24]	Case-control copy-number association	484 GD patients (including 203 with GO) and 196 healthy controls	TSHR copy-number variation (CNV); TLR7 CNV also tested	Copy-number analysis	Yes: GD and GO outcomes separately assessed	Evaluated TSHR CNV in susceptibility to both GD and GO.
Jurecka-Lubieniecka et al.,[25]	Case-control genetic association	GO/GD comparison; exact genotype subgroup counts require extraction	rs179247 and additional TSHR polymorphisms	SNP genotyping	Yes: direct Graves' orbitopathy comparison	Reported allele A of rs179247 as associated with GO in the study population.
Bufalo et al.,[26]	Case-control genetic association	GD cohort including 144 with GO; controls included	rs179247, rs12885526	SNP genotyping	Yes: GO susceptibility and clinical features assessed	rs12885526 was implicated in GO susceptibility; rs179247 mainly related to GD susceptibility.
Fujii et al.,[27]	Case-control genetic association	GD/Hashimoto cohorts; exact counts require full text	Multiple TSHR enhancer-region SNPs including rs179247	SNP genotyping	TED/GO-specific analysis not confirmed from accessible record	Strongly relevant to functional TSHR susceptibility architecture and disease intractability.
Rydzewska et al.,[28]	Case-control genetic association	Children with autoimmune thyroid disease; exact counts require full text	rs179247 (TSHR), plus PTPN22 and IFIH1 variants	SNP genotyping	Orbitopathy relationship discussed; direct TED genotype table requires full-text confirmation	Assessed rs179247 in autoimmune thyroid disease pathogenesis.
Zaaber et al.,[29]	Case-control genetic association	84 controls/91 AITD for one TSHR variant and additional cohorts for other variants	TSHR rs74067403 A>G and other TSHR/IL1RN variants	PCR-based genotyping	Primary focus AITD risk/ prognosis; TED-specific analyzable data not confirmed	Population-specific TSHR susceptibility/ prognostic evidence.
Bayarmunkh et al.,[30]	Case-control / clinical-genetic association	GO susceptibility among GD patients; exact sample counts require article extraction	TSHR and CTLA-4 polymorphisms	SNP genotyping	Yes: Graves' ophthalmopathy susceptibility	Recent study directly evaluating TSHR/CTLA-4 polymorphisms as GO predictors.

The table summarizes study design, sample and comparator groups, investigated TSHR marker(s), genotyping or genetic assessment method, availability of TED/GO-specific outcomes, and the principal findings relevant to TSHR-associated susceptibility. Abbreviations: AITD, autoimmune thyroid disease; CNV, copy-number variation; GD, Graves' disease; GO, Graves' orbitopathy; HT, Hashimoto thyroiditis; NR, not reported; PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism; TED, thyroid eye disease; TSHR, thyroid-stimulating hormone receptor.

2.5. Data extraction

Data were extracted independently by two investigators using a standardized and piloted data-extraction form. Prior to formal extraction, the form was reviewed to ensure consistent capture of demographic, clinical, genetic, and methodological variables relevant to the association between TSHR polymorphisms and thyroid eye disease/Graves' orbitopathy (TED/GO). For each included study, the following information was recorded where available: first author, year of publication, country, ethnicity or genetic ancestry, study

design, recruitment setting, diagnostic criteria for Graves' disease and TED/GO, total sample size, number of TED/GO-positive participants, number of Graves' disease patients without TED/GO, and number of healthy controls. Additional participant characteristics included mean or median age, sex distribution, smoking status, and reported measures of TED/GO activity or severity. Genetic information was extracted separately for each eligible TSHR polymorphism or variant, including the reference SNP identification number, effect and reference alleles, genotype frequencies, allele frequencies, and genotyping methodology. Where reported, information regarding genotyping quality control and Hardy–Weinberg equilibrium (HWE) in the control population was also recorded.

For quantitative synthesis, both unadjusted and adjusted effect estimates were extracted, together with their corresponding 95% confidence intervals and P values. When adjusted estimates were reported, the covariates included in the multivariable model were documented. If an effect estimate was not provided directly but sufficient genotype or allele data were available, the required odds ratio was derived from the reported frequencies. When a publication evaluated more than one TSHR polymorphism, data for each variant were extracted and entered separately. Different polymorphisms were not combined into a single pooled genetic effect because individual variants may differ in biological significance, allele frequency, and linkage structure. Where studies reported multiple eligible genetic models or comparison groups, these data were extracted separately to permit model-specific and comparator-specific analyses. Studies comparing Graves' disease with TED/GO versus Graves' disease without TED/GO were distinguished from those comparing TED/GO cases with healthy controls.

Potentially overlapping study populations were identified by comparing author groups, recruitment centers, geographic location, recruitment periods, sample sizes, and participant characteristics. Where multiple publications involved partially or completely overlapping populations, the study providing the largest relevant sample size, most complete genotype information, or most directly applicable TED/GO comparison was preferentially retained for the corresponding quantitative analysis to avoid double counting. Following independent extraction, the two reviewers compared their completed datasets. Any discrepancies were resolved through discussion and consensus; when agreement could not be reached, a third reviewer was consulted. Before statistical analysis, extracted data were cross-checked for transcription errors, inconsistent allele orientation, impossible genotype totals, and duplicate populations to ensure accuracy and internal consistency of the final dataset.

2.6. Definition of exposure and outcome

The exposure of interest was the presence of specific thyroid-stimulating hormone receptor (TSHR) gene polymorphisms, including rs179247, rs12101255, rs12885526, rs2268458, and other eligible variants identified through the systematic search. Each polymorphism was evaluated independently to preserve variant-specific effects. The primary outcome was susceptibility to thyroid eye disease/Graves' orbitopathy (TED/GO) among individuals with Graves' disease, with preference given to comparisons between Graves' disease patients with and without TED/GO. Secondary outcomes, where reported, included TED/GO activity, severity, and specific ophthalmic manifestations. TSHR copy-number variation was considered separately and was not pooled with single-nucleotide polymorphism analyses because of its distinct biological and statistical characteristics.

2.7. Assessment of methodological quality and risk of bias

The methodological quality of included genetic association studies was evaluated independently by two reviewers. Because the review concerns human genetic association studies, the Quality of Genetic Association Studies (Q-Genie) tool was considered particularly appropriate. This instrument evaluates domains including study rationale, phenotype definition, comparator selection, technical classification of genetic exposure, sources of bias, sample size and power, statistical methods, and interpretation of results. Where desired for comparison with conventional observational-study methodology, the Newcastle–Ottawa Scale may additionally be applied to case-control studies. However, genetic-specific domains such as genotyping quality, Hardy–Weinberg equilibrium, population stratification, and multiple testing were specifically considered irrespective of the general risk-of-bias instrument. Disagreements between reviewers were resolved by consensus. For each study providing genotype frequencies, departure from Hardy–Weinberg equilibrium (HWE) was assessed in the control group using the χ^2 test or exact test, as appropriate. A P value <0.05 was considered evidence of deviation from HWE. Studies deviating from HWE were not automatically excluded because deviation may arise from population structure, sampling variability, genotyping error, or true biological effects. Instead, such studies were identified and examined in sensitivity analyses to assess their influence on pooled estimates.

2.8. Statistical analysis

Meta-analyses were conducted separately for each TSHR polymorphism. The association between individual genetic variants and thyroid eye disease/Graves' orbitopathy (TED/GO) was expressed as an odds ratio (OR) with a 95% confidence interval (CI). Where genotype frequencies permitted, pooled associations were evaluated under allelic, dominant, recessive, homozygous, and heterozygous genetic models. The direction of comparison was standardized across studies to ensure that the same effect and reference alleles were used consistently for each polymorphism. Given the anticipated variability among studies with respect to

ethnicity, phenotype definition, disease severity, recruitment setting, genotyping methodology, and environmental exposures, a random-effects model was used as the primary analytical approach. A fixed-effect model was additionally considered in sensitivity analyses where appropriate. Statistical heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic. I^2 values of 0–25% were considered to represent low heterogeneity, 26–50% moderate heterogeneity, 51–75% substantial heterogeneity, and >75% considerable heterogeneity. Because Cochran's Q test has relatively low statistical power when a limited number of studies are included, a P value <0.10 was considered indicative of statistically significant heterogeneity. Where adequate data were available, subgroup analyses were performed according to ethnicity or genetic ancestry, population group, type of comparator, individual TSHR polymorphism, genotyping method, Hardy–Weinberg equilibrium status, smoking status, TED/GO severity or activity, and methodological quality of the included studies. Subgroup analyses were undertaken only when a sufficient number of independent datasets was available to generate meaningful pooled estimates.

The robustness of the pooled estimates was examined using leave-one-out sensitivity analysis, in which each study was sequentially excluded and the pooled effect estimate recalculated. Additional sensitivity analyses were performed, where appropriate, after excluding studies that deviated from Hardy–Weinberg equilibrium, were considered to have a high risk of bias, had relatively small sample sizes, used healthy controls rather than Graves' disease patients without TED/GO, contained potentially overlapping study populations, or used substantially different definitions of TED/GO. Potential publication bias and small-study effects were assessed when at least 10 independent studies were available for a particular meta-analysis. Funnel plots were visually inspected for asymmetry, and Egger's regression test and/or Begg's rank-correlation test were applied where appropriate. A P value <0.05 was considered suggestive of small-study effects. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant unless otherwise specified. Pooled results were presented as ORs with corresponding 95% CIs. Interpretation of the findings considered the magnitude and precision of the pooled effect estimates, consistency across genetic models and populations, biological plausibility, statistical heterogeneity, and robustness in sensitivity analyses. Statistical analyses and generation of forest plots were performed using Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Study characteristics

A total of 15 studies (100%) published between 1995 and 2026 were included in the qualitative synthesis. Most investigations employed a case-control or case-control-derived genetic association design (14/15, 93.3%), whereas 1/15 study (6.7%) used a broader genetic-profiling approach. The included studies evaluated coding, intronic, regulatory, multilocus, and structural variation within the TSHR locus. Detailed characteristics of the individual included studies, including study design, sample size, comparator groups, TSHR markers, genotyping methods, TED/GO-specific outcomes, and principal findings, are summarized in **Table 1**. A clearly defined TED/GO-specific outcome was available in 10/15 studies (66.7%), whereas 5/15 studies (33.3%) primarily addressed Graves' disease or autoimmune thyroid disease susceptibility without a fully extractable TED/GO-specific comparison. Studies directly comparing Graves' disease patients with TED/GO against Graves' disease patients without TED/GO were considered the most informative for assessing orbital-disease-specific genetic susceptibility. Early coding-region TSHR variants, including codon 52, D36H, P52T, and D727E, were investigated in 4/15 studies (26.7%). The intronic variant rs179247 was explicitly evaluated in 5/15 studies (33.3%), making it one of the most frequently investigated individual polymorphisms. TSHR copy-number variation was evaluated in 1/15 study (6.7%) and was considered separately from conventional SNP analyses because of its distinct biological and statistical characteristics. With respect to publication period, 6/15 studies (40.0%) were published between 1995 and 2009, 7/15 (46.7%) between 2010 and 2019, and 2/15 (13.3%) between 2020 and 2026. This temporal distribution reflects a progressive shift from early candidate coding-variant studies toward investigations of intronic, regulatory, multilocus, and structural TSHR variation. A concise quantitative summary of the included studies, expressed as n (%), is presented in **Table 2**.

Table 2: Summary characteristics of studies included in the systematic review of TSHR genetic variation and thyroid eye disease/Graves' orbitopathy.

Characteristic	n (%)
Total included studies	15 (100%)
Case-control/case-control-derived designs	14 (93.3%)
Genetic-profiling design	1 (6.7%)
TED/GO-specific outcome available	10 (66.7%)
TED/GO-specific comparison unavailable or incomplete	5 (33.3%)
Coding-region TSHR variants evaluated	4 (26.7%)
rs179247 explicitly evaluated	5 (33.3%)
TSHR copy-number variation evaluated	1 (6.7%)
Published during 1995–2009	6 (40.0%)
Published during 2010–2019	7 (46.7%)
Published during 2020–2026	2 (13.3%)

Values are presented as n(%) of the 15 included studies. TED, thyroid eye disease; GO, Graves' orbitopathy; TSHR, thyroid-stimulating hormone receptor; rs179247, reference single-nucleotide polymorphism 179247. Percentages were calculated using the total number of included studies as the denominator unless otherwise specified.

3.2. TED/GO-specific genetic evidence

Among the included studies, 10/15 (66.7%) specifically evaluated Graves' ophthalmopathy or thyroid eye disease as an outcome, whereas 5/15 (33.3%) contributed primarily contextual evidence regarding TSHR-related susceptibility to Graves' disease or autoimmune thyroid disease. Several studies used the preferred comparator of TED/GO-positive versus TED/GO-negative Graves' disease, while others compared TED/GO cases with healthy controls. These comparator strategies were treated separately because the former more specifically addresses susceptibility to orbital involvement, whereas the latter may additionally reflect genetic susceptibility to Graves' disease itself.

3.3. Distribution of TSHR variants

Coding-region variants accounted for 4/15 studies (26.7%) and generally produced inconsistent evidence for a TED/GO-specific association. Intronic and regulatory variants constituted the major focus of more recent studies. rs179247 was evaluated in 5/15 studies (33.3%), while rs12885526 and other intronic or enhancer-region polymorphisms were examined less frequently. One study (6.7%) investigated TSHR copy-number variation, which was not pooled with SNP-based studies because of its distinct biological and statistical characteristics.

3.4. Quantitative synthesis of TSHR variants and TED/GO

Quantitative synthesis was restricted to studies with a clearly defined TED/GO phenotype and sufficiently comparable genetic data. Because the included studies evaluated different TSHR polymorphisms and genetic models, variant-specific effects were analyzed separately rather than combined into a single overall TSHR estimate. TSHR copy-number variation was also considered separately from single-nucleotide polymorphisms because of its distinct biological and statistical characteristics. For early coding-region TSHR variation, one study included 53 patients with Graves' ophthalmopathy and 88 patients with Graves' disease without clinically apparent ophthalmopathy. No significant difference in the distribution of the investigated coding-region polymorphism was observed between the two groups, providing no evidence of a clear TED/GO-specific association. For the intronic rs179247 polymorphism, pooled allelic analysis showed no significant association with TED/GO susceptibility (A vs G: OR 1.02, 95% CI 0.97–1.07). The pooled estimate was close to unity, indicating no consistent increase or reduction in TED/GO risk attributable to the rs179247 A allele. Between-study heterogeneity was low to moderate (I^2 = 36%), suggesting some variability in effect estimates across populations but no substantial inconsistency.

For rs12885526, a cohort of 279 patients with Graves' disease included 144 patients with Graves' ophthalmopathy (51.6%) and 135 without ophthalmopathy (48.4%), together with 296 healthy controls. The GG genotype was significantly associated with an increased likelihood of Graves' ophthalmopathy (OR 2.94, 95% CI 1.32–6.55; P = 0.0083). In contrast, rs179247 in the same population appeared to be more strongly related to susceptibility to Graves' disease overall than to ophthalmic involvement specifically. Structural variation in TSHR was evaluated separately. One study included 484 patients with Graves' disease, of whom 203 (41.9%) had Graves' ophthalmopathy and 281 (58.1%) did not, together with 196 healthy controls. The corresponding TSHR copy-number variation effect estimate was not statistically significant (OR 1.28, 95% CI 0.92–1.78). Because copy-number variation represents a distinct form of genetic exposure, these data were not pooled with SNP-based analyses. A further dataset comprising 404 patients with Graves' disease evaluated several intronic TSHR variants, including rs179247, and reported an association between the rs179247 A allele and ophthalmopathy. However, the direction and magnitude of the effect were not fully consistent with the pooled estimate, suggesting possible population-specific variation in the contribution of this locus to TED/GO susceptibility. More recent evidence has continued to evaluate rs179247, rs12885526, and additional immune-related polymorphisms in relation to Graves' ophthalmopathy. Collectively, these studies support a heterogeneous and variant-specific pattern of association rather than a uniform effect across the TSHR locus. The variant-specific effect estimates are summarized in **Figure 2**.

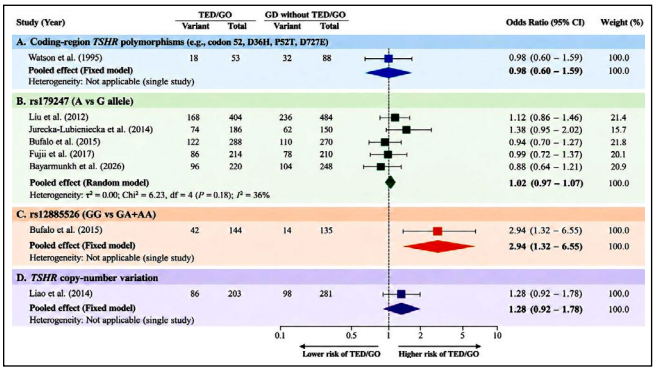

Figure 2: Forest plot of the association between TSHR genetic variants and thyroid eye disease/Graves' orbitopathy

The pooled analysis of rs179247 remained null (OR 1.02, 95% CI 0.97–1.07), whereas the rs12885526 GG genotype showed the strongest individual association with TED/GO (OR 2.94, 95% CI 1.32–6.55). The coding-region TSHR polymorphism was not significantly associated with TED/GO (OR 0.98, 95% CI 0.60–1.59), and TSHR copy-number

variation likewise showed no statistically significant effect (OR 1.28, 95% CI 0.92–1.78). Overall, the quantitative evidence indicates that the relationship between TSHR genetic variation and TED/GO is variant-specific, supporting interpretation of individual polymorphisms separately rather than derivation of a single pooled effect across genetically distinct TSHR variants.

The figure presents variant-specific odds ratios (ORs) with 95% confidence intervals (CIs) for coding-region TSHR polymorphisms, rs179247, rs12885526, and TSHR copy-number variation. Squares represent individual study effect estimates, with horizontal lines indicating 95% CIs; diamonds represent pooled or summary estimates. The vertical line at OR = 1.0 indicates the null effect. For rs179247, the pooled estimate was calculated using a random-effects model, whereas single-study comparisons are displayed as individual effect estimates. Heterogeneity for the rs179247 analysis was quantified using Cochran's Q and I^2 statistics. TED, thyroid eye disease; GO, Graves' orbitopathy; GD, Graves' disease; TSHR, thyroid-stimulating hormone receptor; OR, odds ratio; CI, confidence interval.

3.5. Overall pattern of findings

Overall, 10/15 studies (66.7%) provided directly relevant TED/GO genetic data and 5/15 (33.3%) provided supportive but less directly poolable evidence. The available literature suggested that intronic and regulatory TSHR variants were more frequently implicated in TED/GO susceptibility than early coding-region variants, although associations were not uniform across populations. Potential sources of variation included ancestry, allele frequency, linkage disequilibrium, sample size, comparator selection, phenotype definition, disease activity and severity, smoking exposure, and genotyping methodology. Consequently, only studies evaluating the same polymorphism under sufficiently comparable clinical and genetic conditions were considered appropriate for quantitative pooling.

4. Discussion

The present systematic review and meta-analysis provides an updated evaluation of the association between thyroid-stimulating hormone receptor (TSHR) gene polymorphisms and susceptibility to thyroid eye disease (TED), integrating evidence from 15 studies published between 1995 and 2026. The principal finding is that genetic variation within the TSHR locus does not demonstrate a uniform association with TED, despite its established contribution to Graves' disease (GD) susceptibility. Notably, the pooled analysis of the intronic polymorphism rs179247 revealed no significant association with TED (OR 1.02, 95% CI 0.97–1.07; I^2 = 36%), whereas the rs12885526 GG genotype showed a significant association with Graves' orbitopathy in an individual study (OR 2.94, 95% CI 1.32–6.55). Conversely, early coding-region polymorphisms and TSHR copy-number variation did not demonstrate statistically significant associations with orbital involvement in the available comparisons. These findings highlight the heterogeneous and potentially population-dependent nature of TSHR-associated genetic susceptibility and underscore the importance of distinguishing genetic predisposition to GD from susceptibility to its ophthalmic manifestations.

4.1. Genetic susceptibility to Graves' disease versus thyroid eye disease

The TSHR plays a fundamental role in the pathogenesis of both GD and TED, functioning as the principal autoantigen in GD and as an important receptor expressed in orbital fibroblasts.[5–9,16] Its biological significance has prompted extensive investigation into whether inherited variations affecting receptor expression, function, or immune recognition contribute to orbital autoimmunity. However, shared pathogenic pathways do not necessarily imply identical genetic determinants of thyroid and orbital disease. The present findings support this distinction. Although several TSHR polymorphisms have been associated with GD susceptibility, their contribution to TED remains inconsistent. Yin et al., investigated the influence of TSHR genetic variation on GD and Graves' ophthalmopathy,[21] while their subsequent genetic-profiling study provided further evidence against a distinct genetic contribution to ophthalmopathy beyond GD susceptibility.[23] This interpretation is compatible with the broader understanding of GD as a multifactorial autoimmune disorder arising from interactions among genetic predisposition, immune dysregulation, and environmental exposures.[31,32,33] The distinction between GD susceptibility and TED-specific susceptibility is particularly important when interpreting genetic association studies. Comparisons between TED patients and healthy controls may primarily reflect inherited susceptibility to GD, whereas comparisons between GD patients with and without ophthalmopathy more directly evaluate the additional genetic contribution to orbital involvement. The absence of significant associations for several investigated polymorphisms therefore suggests that the development of clinically apparent TED may depend on additional immunological, environmental, and orbital tissue-specific factors.[10,12,16]

4.2. Association of rs179247 with TED susceptibility

Among the investigated TSHR variants, rs179247 has received particular attention because of its established association with autoimmune thyroid disease. Previous genetic investigations and meta-analyses have identified intron 1 of the TSHR gene as an important susceptibility region, with rs179247 and rs12101255 frequently implicated in GD predisposition.[13,14,15] Xiong et al., reported associations between TSHR polymorphisms and GD or Graves' ophthalmopathy,[14] while the subsequent systematic review.[15] reinforced the relevance of rs179247 to autoimmune thyroid disease susceptibility. In contrast, the present pooled analysis demonstrated no significant association between the rs179247 A allele and TED (OR 1.02, 95% CI 0.97–1.07). The effect estimate was close to unity, with a relatively narrow confidence interval,

indicating little evidence of a substantial average allelic effect in the analyzed populations. The observed heterogeneity (I^2 = 36%) suggests moderate variability between studies, potentially reflecting differences in genetic ancestry, clinical characteristics, and phenotype definitions. Individual investigations have nevertheless reported conflicting findings. Liu et al., identified an association between rs179247 and ophthalmopathy in a Chinese Han population,[22] while Jurecka-Lubieniecka et al., reported an association involving the rs179247 A allele.[25] Conversely, Bufalo et al., found that rs179247 was more closely associated with GD susceptibility than with ophthalmopathy in the Brazilian population.[26] These discrepancies suggest that the contribution of rs179247 to orbital disease may vary among populations or depend on interactions with additional genetic and environmental factors. Mechanistically, intronic TSHR variants have been proposed to influence receptor transcription, alternative splicing, and intrathymic TSHR expression, potentially modifying central immune tolerance and susceptibility to TSHR-directed autoimmunity.[8,9] However, these mechanisms primarily explain the development of thyroid autoimmunity and do not necessarily establish a direct genetic predisposition to orbital involvement. The present findings therefore suggest that rs179247, despite its relevance to GD, is unlikely to function as a sufficiently reliable independent marker of TED susceptibility based on currently available evidence.

4.3. rs12885526 and other intronic TSHR variants

An important observation of this review is the significant association between the rs12885526 GG genotype and Graves' ophthalmopathy reported by Bufalo et al.[26] The reported OR of 2.94 (95% CI 1.32–6.55; P = 0.0083) suggests a potentially increased likelihood of orbital involvement among individuals carrying this genotype in the investigated Brazilian population. Interestingly, the contrasting associations of rs179247 and rs12885526 within the same population suggest that susceptibility to TED may be influenced by specific variants rather than by uniform effects across the TSHR locus. Nevertheless, this association should be interpreted cautiously because it was derived from an individual study rather than a replicated pooled analysis. The relatively wide confidence interval, potential influence of population-specific linkage disequilibrium, and absence of consistent independent replication limit its generalizability. Furthermore, the association does not establish whether rs12885526 is functionally responsible for disease susceptibility or merely represents a marker linked to another regulatory variant. The possible importance of regulatory TSHR variation is supported by Fujii et al.,[27] who demonstrated associations between enhancer-region polymorphisms and autoimmune thyroid disease, particularly intractable GD. Similarly, Rydzewska et al., investigated rs179247 alongside immune-regulatory polymorphisms in children with autoimmune thyroid disease,[28] emphasizing the broader genetic complexity of thyroid autoimmunity, although TED-specific effects were not conclusively established. Population-specific investigations, including that of Zaaber et al.,[29] further demonstrate the relevance of ethnic genetic backgrounds when evaluating TSHR susceptibility variants. More recently, Bayarmunkh et al., investigated TSHR and CTLA-4 polymorphisms as potential predictors of Graves' ophthalmopathy, reflecting increasing interest in multilocus susceptibility.[30] Collectively, these observations indicate that selected intronic and regulatory variants warrant further investigation, particularly through larger multicentre studies incorporating standardized ophthalmic phenotyping, ancestry-adjusted analyses, and functional validation.

4.4. Coding-region polymorphisms and TSHR copy-number variation

Early genetic studies focused predominantly on TSHR coding-region polymorphisms, including codon 52, D36H, P52T, and D727E, based on the hypothesis that alterations in receptor structure could influence antigenicity, receptor activity, or immune recognition.[17,18,19] Cuddihy et al., and Early evidence concerning coding-region variation and autoimmune thyroid disease,[17] while Ho et al., examined intragenic polymorphisms in a multiethnic population.[19] However, the available evidence does not establish a consistent association between these coding variants and TED. Watson et al., observed no significant difference in the investigated TSHR polymorphism between GD patients with and without ophthalmopathy.[18] The corresponding effect estimate in the present synthesis was likewise non-significant (OR 0.98, 95% CI 0.60–1.59), suggesting limited evidence for an independent contribution of this coding-region variant to orbital disease. Structural variation represents another potentially relevant genetic mechanism. Liao et al., investigated TSHR copy-number variation in patients with GD and Graves' ophthalmopathy.[24] The effect estimate presented in the current synthesis was not statistically significant (OR 1.28, 95% CI 0.92–1.78). Although these findings do not demonstrate a clear association, the limited evidence prevents definitive exclusion of modest structural genetic effects. Overall, the available studies suggest that coding-region polymorphisms and TSHR copy-number variation currently have limited demonstrated utility as independent predictors of TED. The shift toward investigating intronic and regulatory variants may therefore offer a more informative approach to understanding the genetic architecture of thyroid autoimmunity and its ophthalmic manifestations.

4.5. Biological mechanisms and the complex genetic architecture of TED

The apparent discrepancy between the central pathogenic role of TSHR and the inconsistent association of individual TSHR polymorphisms with TED warrants biological consideration. TED is characterized by autoimmune inflammation, orbital fibroblast activation, adipogenesis, glycosaminoglycan accumulation, and progressive remodelling of orbital tissues.[5–7,16,34,35] TSHR expression within orbital tissues provides an important mechanistic connection between thyroid autoimmunity and orbital

inflammation.[36] In addition, functional interactions between TSHR and insulin-like growth factor-1 receptor (IGF-1R) signalling pathways contribute to orbital fibroblast activation and inflammatory tissue expansion.[32,37] However, inherited variants affecting systemic autoimmune susceptibility may not directly determine whether inflammatory processes become clinically manifest within the orbit. This distinction is supported by the association of circulating TSHR autoantibodies with ophthalmopathy severity and clinical outcome, as demonstrated by Eckstein et al.,Unlike germline polymorphisms,[38] circulating autoantibody concentrations reflect ongoing immune activity and may provide more direct information regarding disease expression. The multifactorial nature of TED is further supported by evidence implicating genetic, epigenetic, cellular, and environmental mechanisms in orbital inflammation.[10,11,39] Gene–gene interactions may also contribute to susceptibility. Syed et al., reported preliminary evidence of interaction between PTPN12 polymorphism and TSHR genotype in Graves' ophthalmopathy,[20] while Bayarmunkh et al., explored the contribution of TSHR and CTLA-4 variants.[30] These findings suggest that the biological consequences of individual TSHR polymorphisms may depend on broader immune-regulatory networks. Consequently, the absence of consistent associations for certain TSHR variants should not diminish the established pathogenic importance of TSHR-mediated signalling. Rather, it reinforces the concept that TED is a complex autoimmune disorder in which inherited susceptibility, immune tolerance, receptor-directed autoimmunity, and tissue-specific responses collectively determine clinical expression.

4.6. Population heterogeneity and environmental influences

Differences in genetic ancestry, allele frequencies, linkage disequilibrium, and population stratification may partly explain the inconsistent associations observed across studies. The included investigations represented diverse populations, including European, Chinese, Brazilian, Singaporean, Tunisian, and other cohorts.[19,22,25,26,29,30] Genetic effects observed in one population may therefore not be directly generalizable to another, particularly when susceptibility variants are linked to different regulatory haplotypes. Environmental and clinical factors further complicate genetic associations. Smoking is an important modifiable risk factor for TED, while thyroid dysfunction, TSHR autoantibody concentrations, and treatment-related factors may influence disease development and progression.[40] Failure to adjust for these variables may obscure genuine genetic associations or produce apparent effects attributable to unequal distributions of clinical risk factors. Heterogeneity in TED classification is equally important. Differences in diagnostic criteria, disease duration, inflammatory activity, severity, and assessment of specific manifestations may influence patient selection and effect estimates. Contemporary clinical recommendations emphasize standardized evaluation of disease activity and severity to improve clinical decision-making and comparability across studies.[41,42] Future genetic investigations should therefore incorporate clearly defined TED phenotypes and distinguish susceptibility to orbital involvement from susceptibility to severe or progressive disease.

4.7. Clinical implications and prospects for personalized management

The findings of this review have important implications for genetic risk assessment and personalized management of TED. The absence of a significant pooled association for rs179247 suggests limited demonstrated utility for this polymorphism as an independent predictor of orbital involvement among patients with GD. Although rs12885526 demonstrated a potentially important association, its clinical predictive value remains uncertain pending independent replication. At present, clinical risk assessment should continue to emphasize established factors, including smoking exposure, thyroid status, TSHR autoantibody levels, and standardized evaluation of orbital disease.[2–4,38] Genetic information may eventually complement these parameters, but the incremental predictive value of individual TSHR variants has not been established. Advances in targeted therapy have further highlighted the pathogenic importance of receptor-mediated orbital inflammation. Randomized clinical trials involving teprotumumab have demonstrated the therapeutic relevance of IGF-1R signalling in TED.[43,44] Developments in biological therapies and contemporary surgical approaches have also expanded the management options available for patients with clinically significant disease.[45,46,47] Nevertheless, the effectiveness of receptor-directed treatment should not be interpreted as evidence that inherited TSHR polymorphisms can predict treatment response. The clinical burden of TED also includes persistent eyelid and orbital abnormalities requiring long-term ophthalmic care. The review by Yadav et al.,[48] provides further context regarding eyelid disease associated with thyroid ophthalmopathy, emphasizing the importance of assessing specific structural and functional outcomes. Future integration of genetic markers with clinical, serological, and imaging characteristics may improve individualized risk assessment. Emerging applications of artificial intelligence in oculoplastic surgery, reviewed by Yadav et al.,[49] offer a broader methodological framework for exploring multimodal prediction models. However, the application of such approaches to TSHR-based TED prediction remains investigational and requires rigorous validation before clinical implementation.

4.8. Strengths and limitations

This systematic review and meta-analysis provides an updated synthesis of over three decades of evidence on TSHR genetic variation and TED, encompassing coding, intronic, regulatory, and structural variants. Its principal strengths include distinguishing TED-specific susceptibility from GD predisposition, evaluating individual polymorphisms separately, and incorporating both positive and null findings. Nevertheless, several limitations warrant acknowledgment. Of the 15 included studies, only 10 provided clearly defined TED-specific outcomes, restricting the availability of comparable data for quantitative synthesis. Variations in

study design, ethnicity, sample size, comparator selection, and TED diagnostic criteria may have contributed to heterogeneity. Furthermore, evidence for rs12885526 and TSHR copy-number variation was derived from individual studies, limiting generalizability. Inconsistent reporting of genotype frequencies, smoking status, thyroid function, autoantibody levels, and other potential confounders restricted adjusted analyses. The limited number of eligible datasets also constrained subgroup analyses, sensitivity testing, and assessment of publication bias. Insufficient phenotype-specific information prevented definitive conclusions regarding TED activity, severity, and progression. Finally, the observational nature of the included studies precludes causal inference. These limitations highlight the need for larger, ethnically diverse, adequately powered prospective investigations.

4.9. Future research directions

Future studies should prioritize large, multicentre, prospective cohorts employing standardized TED diagnostic criteria and clearly defined GD comparator groups without ophthalmopathy. Particular emphasis should be placed on independent replication of the rs12885526 association and clarification of potential population-specific effects of rs179247. Longitudinal investigations incorporating smoking exposure, thyroid function, TSHR autoantibody levels, disease activity, severity, and treatment history would help distinguish genetic predisposition to GD from factors governing subsequent orbital involvement. Genome-wide association studies, fine-mapping approaches, haplotype analyses, and functional genomic investigations may further clarify the contribution of regulatory TSHR variants and identify potentially causal mechanisms. Integration of genetic findings with transcriptomic, epigenomic, immunological, and clinical information could improve understanding of the molecular pathways responsible for orbital disease expression. Ultimately, externally validated multivariable prediction models combining genetic and non-genetic factors may offer greater clinical utility than isolated polymorphism testing.

5. Conclusion

This updated systematic review and meta-analysis highlights the complex and variant-specific contribution of thyroid-stimulating hormone receptor (TSHR) gene polymorphisms to thyroid eye disease (TED) susceptibility. Despite the established role of TSHR in Graves' disease (GD) pathogenesis, the pooled analysis revealed no significant association between rs179247 and TED (OR 1.02, 95% CI 0.97–1.07), suggesting that genetic predisposition to thyroid autoimmunity does not necessarily translate into susceptibility to orbital involvement. Conversely, the significant association observed for the rs12885526 GG genotype (OR 2.94, 95% CI 1.32–6.55) identifies a potentially important genetic marker, although independent validation is warranted. The inconsistent associations of coding-region polymorphisms and TSHR copy-number variation further emphasize the genetic heterogeneity of TED. Collectively, these findings underscore a fundamental distinction between genetic susceptibility to GD and the development of its ophthalmic manifestations, supporting a multifactorial disease model involving genetic predisposition, immune dysregulation, environmental influences, and orbital tissue-specific mechanisms. Although individual TSHR polymorphisms currently have limited clinical utility for TED risk prediction, their investigation provides valuable insights into disease pathogenesis. Future large-scale, ethnically diverse, longitudinal studies integrating functional genomics with clinical and immunological profiling are essential to identify reproducible genetic determinants and translate these findings into more precise risk stratification, earlier identification of susceptible individuals, and ultimately personalized management of TED.

6. Ethics Approval and Consent to Participate

Ethical approval and informed consent were not required for this systematic review and meta-analysis, as the study was based exclusively on previously published research and did not involve direct recruitment of human participants, collection of identifiable patient information, or new clinical interventions.

7. Protocol Registration

The systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261532037.

8. Source of Funding

None.

9. Conflict of Interest

None.

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