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Association Of Tshr Gene Polymorphism (Rs74067403, Rs1054708 and Rs2268458) In Patients with Graves' Disease in Coastal Andhra Pradesh

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ABSTRACT

Graves' disease (GD) is an autoimmune thyroid disorder marked by hyperthyroidism and the presence of thyroid-stimulating hormone receptor (TSHR) autoantibodies. Genetic susceptibility is a key factor in GD pathogenesis, with TSHR gene polymorphisms playing a significant role. This study evaluated the association of three TSHR single nucleotide polymorphisms (SNPs)—rs74067403, rs1054708, and rs2268458—with GD in a population from Coastal Andhra Pradesh, India. A case-control design included 170 confirmed GD patients and 170 age- and sex-matched healthy controls. Genomic DNA was isolated and genotyped using allele-specific PCR. Chi-square tests and odds ratios (OR) with 95% confidence intervals (CI) assessed genotype-disease associations. The rs74067403 AG genotype was significantly associated with increased GD risk (OR = 2.38; 95% CI: 1.18–4.78; p = 0.0145), while the AA genotype appeared protective. The rs2268458 TC genotype showed a strong association with GD (OR = 11.13; p < 0.0001), and the C allele was more frequent among cases. In contrast, rs1054708 was monomorphic (TT) in all participants and showed no disease association. Additionally, both rs74067403 and rs2268458 were significantly associated with remission after radioiodine therapy and orbitopathy in GD patients. Overall, rs74067403 and rs2268458 may serve as potential genetic markers for GD risk in this region, while rs1054708 appears non-contributory. These findings underscore the importance of region-specific genetic studies in understanding autoimmune thyroid disease.

Keywords: *Graves' disease, TSHR gene, SNP, rs74067403, rs1054708, rs2268458, autoimmune thyroid disease, genetic susceptibility*.

1. INTRODUCTION

Graves' disease (GD) is a common autoimmune thyroid disorder and a leading cause of hyperthyroidism worldwide, with a particularly significant burden in iodine-sufficient regions (Burch & Cooper, 2015; Taylor et al., 2018; Wu *et al.,* 2023). It is characterized by the production of autoantibodies that stimulate the thyroid-stimulating hormone receptor (TSHR), resulting in excessive thyroid hormone production and diffuse goiter (Kahaly & Bartalena, 2017; Davies *et al.,* 2020). The clinical spectrum of GD also includes extrathyroidal manifestations such as Graves' orbitopathy (GO) and, less commonly, pretibial myxedema and acropachy (Menconi *et al.,* 2014; Kraus *et al.,* 2018). While environmental factors such as stress, smoking, iodine intake, and infections are known to trigger or exacerbate the condition, the etiology of Graves' disease is strongly influenced by genetic predisposition (Tomer & Huber, 2009; Grixti et al., 2023).

Among the genes implicated in GD, the TSHR gene has emerged as a primary susceptibility locus. The TSHR gene, located on chromosome 14q31, encodes a G-protein–coupled receptor that mediates the action of thyroid-stimulating hormone (TSH) (Kleinau & Krause, 2009; Brand *et al.,* 2009). Variations in this gene can alter receptor expression, splicing, or immunogenicity, thereby modulating the autoimmune response. Numerous genome-wide association studies (GWAS) and population-specific genetic investigations have consistently reported associations between intronic SNPs in the TSHR gene and the risk of developing GD (Panicker *et al.,* 2008; Taylor *et al.,* 2015). However, the strength and pattern of these associations can vary across ethnicities and geographical regions, necessitating localized studies to better understand the region-specific genetic determinants (Kuś *et al.,* 2020; Williams *et al.,* 2023).

As a genetically diverse nation, India presents a unique opportunity to study such associations in various sub-populations (Ramgopal *et al.,* 2018; Unnikrishnan *et al.,* 2013; Lombardi *et al.,* 2017). The coastal region of Andhra Pradesh in South India has witnessed a growing prevalence of autoimmune thyroid diseases, yet limited data exist on the genetic underpinnings

of GD in this population. To address this gap, the present study investigates the association of three (intronic 1) TSHR single-nucleotide polymorphisms—rs74067403, rs1054708, and rs2268458 with Graves' disease in individuals from Coastal Andhra Pradesh. These polymorphisms were selected based on prior evidence of involvement in thyroid autoimmunity and their potential functional relevance.

By evaluating the genotypic and allelic distributions of these SNPs in GD patients and healthy controls, and correlating them with clinical, demographic, and treatment response variables, this study aims to elucidate the genetic contribution of TSHR variants to GD susceptibility in this region. The findings are expected to enhance our understanding of the molecular basis of GD in South Indian populations and may aid in developing genotype-based predictive and therapeutic strategies for managing the disease..

2. MATERIALS AND METHODS

Study Design and Participants: This hospital-based case-control study was conducted in the coastal districts of Andhra Pradesh, India, to investigate the association of thyroid-stimulating hormone receptor (TSHR) gene polymorphisms (rs74067403, rs1054708 and rs2268458) with Graves' disease. A total of 170 unrelated patients with clinically and biochemically confirmed Graves' disease were recruited, along with 170 age- and sex-matched healthy controls from the same geographical region. The sample size was determined based on allele frequencies reported in previous studies and calculated using standard statistical formulae (Lwanga & Lemeshow, 1991) to achieve 80% power at a 5% level of significance.

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of Andhra University (IEC Approval No: 52, dated 01-04-2022). Written informed consent was obtained from all participants before sample collection and study procedures.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients: Males and females diagnosed with Graves' disease.
- Controls: Individuals without a family history or symptoms of autoimmune diseases and not on any medication.

Exclusion Criteria:

- Individuals unwilling to participate or provide samples.
- Patients under 20 years of age.
- Pregnant women.
- Individuals with psychiatric conditions.

Genomic DNA Extraction: Genomic DNA was extracted from whole blood using the HiPurA® Blood Genomic DNA Miniprep Purification Kit following the manufacturer's instructions. The protocol involved lysis of blood samples, protein digestion with Proteinase K, ethanol-mediated DNA precipitation, and binding to spin columns, followed by washing and elution. DNA quality and quantity were assessed via UV spectrophotometry and 0.8% agarose gel electrophoresis. The purity of DNA was confirmed using the A260/A280 absorbance ratio.

PCR-RFLP Genotyping: Three TSHR SNPs (rs74067403, rs1054708, and rs2268458) were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

For rs74067403:

- Forward Primer: 5'-CAGTTGAATGCCATGTCTGG-3'
- Reverse Primer: 5'-GCATGGTGGGAAGTGAAAAC-3'
- PCR Conditions: Initial denaturation at 94°C for 5 min; 35 cycles of 94°C for 1 min, 58°C for 1 min, 72°C for 1 min; final extension at 72°C for 10 min
- Amplicon Size: 300 bp
- Restriction Enzyme: PsiI; digestion overnight at 37°C
- Expected Bands: AA = 173+127 bp, AG = 300+173+127 bp, GG = 300 bp

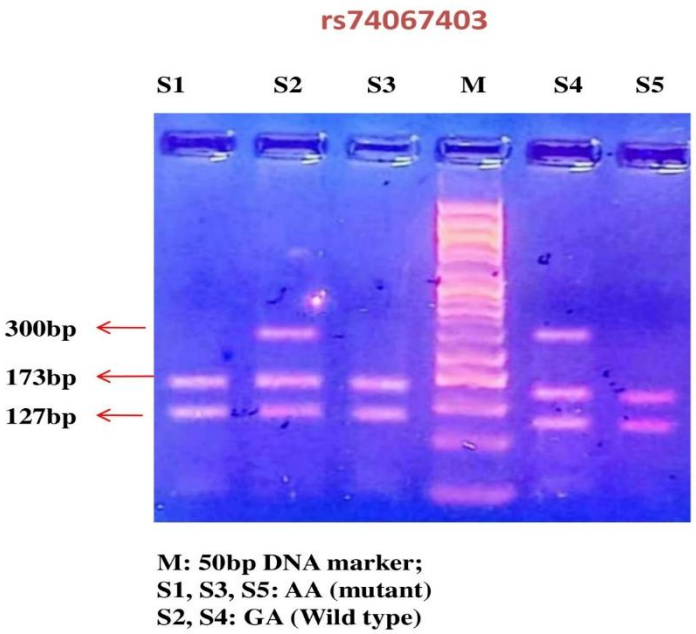

Figure 1: PCR-RFLP Genotyping of TSHR SNP rs74067403

For rs1054708:

- Forward Primer: 5'-TGCTTCCTTTGGTGGGAATA-3'
- Reverse Primer: 5'-ACCAGCAGATTTTGGAGTTG-3'
- PCR Conditions: 94°C for 5 min; 35 cycles of 95°C for 1 min, 57°C for 1 min, 72°C for 1 min; final extension at 72°C for 10 min
- Amplicon Size: 331 bp
- Restriction Enzyme: NlaIII; digestion overnight at 37°C
- Expected Bands: TT = 195+80+56 bp, TC = all five bands, CC = 107+88+80+56 bp

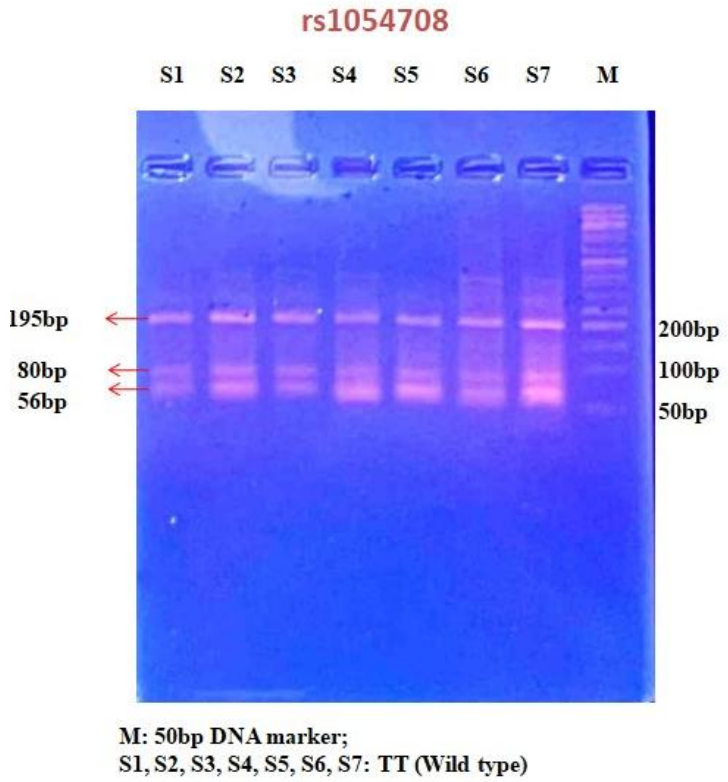

Figure 2: PCR-RFLP Analysis of TSHR SNP rs1054708

For rs2268458:

- Forward Primer: 5'-CTAACCAGCAGAGGGAGCAC-3'
- Reverse Primer: 5'-CCACTGCTTAAAGCCCAGAT-3'
- PCR Conditions: 94°C for 5 min; 30 cycles of 94°C for 30 sec, 69°C for 30 sec, 72°C for 40 sec; final extension at 72°C for 7 min
- Amplicon Size: 162 bp
- Restriction Enzyme: Alu I; digestion overnight at 37°C
- Expected Bands: TT = 162 bp, TC = 162+100+62 bp, CC = 100+62 bp

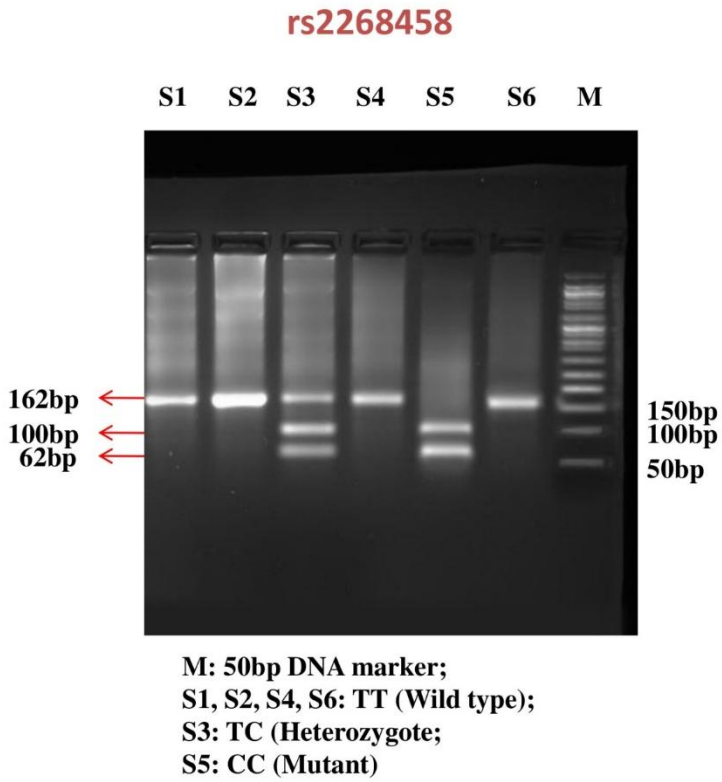

Figure 3: PCR-RFLP Analysis of TSHR SNP rs2268458

All PCR products were analysed by 3% agarose gel electrophoresis, stained with ethidium bromide.

Statistical Analysis: Data were analysed using SPSS version 24.0. The genotypic and allelic frequencies were compared between cases and controls using the Chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the strength of associations. A p-value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

This study evaluated the association of three single nucleotide polymorphisms (SNPs) in the thyroid-stimulating hormone receptor (TSHR) gene—rs74067403, rs1054708, and rs2268458—with Graves' disease (GD) in individuals from Coastal Andhra Pradesh. A total of 170 patients with clinically and biochemically confirmed GD and 170 age- and sex-matched healthy controls were genotyped using the PCR-RFLP method. The genotypic and allelic frequencies of each SNP were statistically analysed, along with associations with demographic, clinical, and treatment-related variables.

ASSOCIATION OF TSHR RS74067403 WITH GRAVES 'DISEASE

Table 1: Genotype and Allele Distribution for rs74067403 among Cases and Controls

Marker	Genotype	Cases	%	Controls	%	Test for Heterogeneity
rs74067403	AA	142	84%	157	92%	χ 2= 6.240 P= 0.012
	AG	28	16%	13	8%	
	GG	0	0%	0	0%	
	A allele	312	92%	327	96%	χ 2= 5.8399; P= 0.015667
	G allele	28	8%	13	4%	

Table 2: Genotype and Allele Distribution of TSHR rs74067403 Polymorphism among Graves' Hyperthyroidism Cases and Controls with Odds Ratios and p-values

System	Genotype	Cases	%	Controls	%	Odds ratio	(95% CI)	p Value
rs74067403	AA	142	84%	157	92%	0.4199	0.2094 to 0.8421	0.0145
	AG	28	16%	13	8%	2.3814	1.1874 to 4.7757	0.0145
	GG	0	0%	0	0%	1.0000	0.0197 to 50.6908	1
	A allele	312	92%	327	96%	0.4430	0.2254 to 0.8708	0.0182
	G allele	28	8%	13	4%			

Table 3: Association of TSHR rs74067403 Genotypes with Demographic and Biochemical Parameters among Graves' Hyperthyroidism Cases

Variables	Cases (n=170)			X^2	P-Value
Genotypes	GG	AG	AA		
Age ≤40	0	12	66	0.1244	0.724
Age >40	0	16	76		
TSH (µ IU/mL) n=161	0	26	135	0.2305	0.631
FT3 (pg / mL) n=20	0	4	16	0.207	0.649
FT4 (ng / dL) n=122	0	19	103	0.251	0.616
T3 (ng /mL) n=89	0	15	74	0.021	0.885
T4 (µ g/ dL) n=108	0	22	86	3.268	0.071
TRAb<1.75IU/L-Negative (n=1)	0	0	1	0.191	0.662
>1.75 IU/L-Positive	0	168	0		

The rs74067403 SNP exhibited a significant difference in genotype and allele frequencies between GD cases and controls. The AG genotype was significantly more frequent among cases (16%) compared to controls (8%) with an odds ratio (OR) of 2.38 (95% CI: 1.18–4.78, p = 0.0145), suggesting a possible risk association. Conversely, the AA genotype was more common in controls (92%) than in cases (84%), indicating a protective effect (OR = 0.42, p = 0.0145). Allelic analysis showed a higher frequency of the G allele in cases (8%) than in controls (4%) (p = 0.0157), reinforcing its potential contribution to disease susceptibility.

However, when correlating rs74067403 genotypes with biochemical markers (TSH, FT3, FT4, T3, and T4) and TRAb levels, no statistically significant associations were observed. Similarly, no strong demographic associations were identified, except for female gender and iodized salt intake, which showed statistically significant differences ($p < 0.05$). Notably, the AG genotype and G allele were significantly more frequent among GD patients with Graves' orbitopathy (GO), indicating a potential role in extrathyroidal manifestations.

Table 4: Association of TSHR rs74067403 Genotypes and Alleles with Graves' Orbitopathy in Graves' Hyperthyroidism Patients

	Genotypes			X^2	P-Value	Alleles		X^2	P-Value
TSHR rs74067403	GG	AG	AA			G	A		
GD with GO	0	9	16	10.46	0.0012	9	41	7.39	0.0066

(n=25)									
GD without GO (n=145)	0	19	126			19	271		

Furthermore, genotype distribution influenced treatment outcomes. A significant association was found between genotype and remission following radioactive iodine (RAI) therapy ($p < 0.001$), suggesting genotype-dependent treatment responsiveness. No significant association was observed between genotype and hypothyroidism post-treatment.

Table 5: Association of TSHR rs74067403 Genotypes with Treatment Modalities and Clinical Outcomes among Graves' disease Cases

Modality of Treatment	**Remission**			**Chi square (P-Value)**	**Hypothyroidism(n=30)**			**Chi square (P-Value)**
	Genotypes				**Genotypes**			
	GG	**AG**	**AA**		**GG**	**AG**	**AA**	
Anti-thyroid drugs (n=72)	0	12	60	0.45 (0.50)	0	0	0	
RAI therapy (n=56)	0	20	36	22.49 (<0.001)	0	6	24	0.33 (0.57)
Thyroidectomy (n= 2)	0	1	1	1.64 (0.20)	0	1	1	1.64 (0.20)

ASSOCIATION OF TSHR RS1054708 WITH GRAVES 'DISEASE

Table 6: Genotype and Allele Distribution of TSHR rs1054708 Among Graves' Hyperthyroidism Cases and Controls

Markers	**Genotype**	**Cases**	**%**	**Controls**	**%**	**Test for Heterogeneity**
rs1054708	TT	170	100%	170	100%	NC
	TC	0	0%	0	0%	
	CC	0	0%	0	0%	
	T allele	340	100%	340	100%	NC
	C allele	0	0%	0	0%	

In contrast, rs1054708 was found to be monomorphic in the study population. All cases and controls carried the homozygous TT genotype, and no C allele carriers (TC or CC genotypes) were detected. Thus, no analysis of heterogeneity or association with GD could be performed. This result suggests that rs1054708 does not contribute to GD susceptibility in this South Indian cohort. Zaaber *et al.* had reported that the rs1054708 C-bearing genotypes were more common in male AITD patients and in those with younger onset (Zaaber, 2020). The lack of polymorphism in this region contrasts with other reports from different populations and highlights the importance of regional genetic variability in association studies.

ASSOCIATION OF TSHR RS2268458 WITH GRAVES 'DISEASE

The rs2268458 SNP demonstrated the most robust association with GD among the three polymorphisms studied. The heterozygous TC genotype was significantly more prevalent in GD cases (64%) than controls (14%), yielding an OR of 11.13 (95% CI: 6.49–19.09, $p < 0.0001$). The TT genotype was more frequent in controls (86%) and appeared protective (OR = 0.0853, $p < 0.0001$). Allele analysis confirmed the increased presence of the C allele in GD cases (33%) versus controls (7%) ($p < 0.0001$).

Table 7: Genotype and Allele Distribution of TSHR rs2268458 Among Graves' Hyperthyroidism Cases and Controls

Markers	Genotype	Cases	%	Controls	%	Test for Heterogeneity
rs2268458	TT	60	35%	147	86%	$\chi 2$=93.718; P= <0.0001
	TC	108	64%	23	14%	
	CC	2	1%	0	0%	
	T allele	228	67%	317	93%	$\chi 2$ = 73.208; P= <0.0001
	C allele	112	33%	23	7%	

Table 8: Genotype and Allele Distribution of TSHR rs2268458 Among Graves' Disease Cases and Controls with Odds Ratios and p-values

System	**Genotype**	**Cases**	**%**	**Controls**	**%**	**Odds ratio**	(95% CI)	**p Value**
rs2268458	TT	60	35%	147	86%	0.0853	0.0497 to 0.1465	< 0.0001
	TC	108	64%	23	14%	11.1332	6.4933 to 19.0886	< 0.0001
	CC	2	1%	0	0%	0.1977	0.0094 to 4.1480	0.2965
	T allele	228	67%	317	93%	5.0593	0.2411 to 106.1774	0.2965
	C allele	112	33%	23	7%			

Although the rs2268458 genotypes did not show strong correlations with biochemical markers or demographic factors, a borderline association with FT4 levels was noted (p = 0.078). Importantly, genotype-level association with GO was statistically significant (p = 0.0189), suggesting its role in orbital involvement.

Table 9: Association of TSHR rs2268458 Genotypes with Demographic and Biochemical Parameters among Graves' disease Cases

Variables	**Cases**			**X^2**	**P-Value**
Genotypes	**TT**	**TC**	**CC**		
Age ≤40 (n=78)	28	50	0	0.023	0.879
Age >40 (n=92)	32	58	2		
TSH (µ IU/mL) n=163	57	104	2	0.184	0.668
FT3 (pg / mL) n=20	9	11	0	0.932	0.334
FT4 (ng / dL) n=122	48	73	1	3.105	0.078
T3 (ng /mL) n=89	31	58	0	0.017	0.896
T4 (µ g/ dL) n=108	39	67	2	0.085	0.771
TRAb<1.75IU/L-Negative (n=1)	0	1	0	0.543	0.461

>1.75 IU/L-Positive	60	107	2		

Table 10: Association of TSHR rs2268458 Genotypes and Alleles with Graves' Orbitopathy among Graves' Disease Cases

	Genotypes			X^2	P-Value	Alleles		X^2	P-Value
TSHR rs2268458	**TT**	**TC**	**CC**			**T**	**C**		
GD with GO (n=25)	14	9	2	5.51	0.0189	37	13	1.28	0.2578
GD without GO(n=145)	46	99	0			191	99		

Treatment outcome analysis revealed a significant association between genotype and remission following RAI therapy ($p < 0.001$). However, genotype did not significantly predict the development of hypothyroidism post-treatment.

Table 11: Association of TSHR rs2268458 Genotypes with Treatment Outcomes (Remission and Hypothyroidism) in Graves' disease Cases

Modality of Treatment	Remission			Chi square (P-Value)	Hypothyroidism(n=30)			Chi square (P-Value)
	Genotypes				Genotypes			
	TT	TC	CC		TT	TC	CC	
Anti-thyroid drugs (n=72)	30	41	1	2.29 (0.13)	0	0	0	
RAI therapy (n=56)	43	12	1	64.27 (<0.001)	10	20	0	0.1 (0.75)
Thyroidectomy (n= 2)	1	1	0	0.19 (0.66)	1	1	0	0.19 (0.66)

Significant genotype associations were also observed with demographic variables, including gender, residence (urban vs. rural), smoking, and iodized salt intake. The TC genotype was more frequent among both male and female GD patients compared to controls, and among rural residents and iodized salt users.

COMPARISON WITH PREVIOUS STUDIES: Our findings align with several published studies emphasizing the relevance of TSHR intron 1 polymorphisms (particularly rs2268458) in GD susceptibility (Wei *et al.,* 2016; Tyagi *et al.,* 2024; Naghibi *et al.,* 2022). The lack of association for rs1054708 and the modest effect of rs74067403 also correspond with findings from previous research, including Zaaber et al. (2020) and Wang *et al.* (2021). The evidence reinforces the notion that certain TSHR variants, especially rs2268458, may influence disease susceptibility and therapeutic outcomes across genetically diverse populations.

4. CONCLUSION

This study investigated three TSHR gene polymorphisms (rs74067403, rs1054708, and rs2268458) concerning Graves' disease in Coastal Andhra Pradesh. Among the variants studied, rs2268458 exhibited the most significant association with GD susceptibility. The C allele and TC genotype of rs2268458 were significantly more prevalent in GD patients compared to controls, suggesting this variant may serve as a strong genetic marker for increased risk. Additionally, rs2268458 genotypes showed a significant association with clinical outcomes such as treatment remission following radioactive iodine therapy and the presence of orbitopathy. In contrast, rs74067403 showed a moderate association with GD and orbitopathy, though no significant correlations were observed with most biochemical or demographic parameters. Meanwhile, rs1054708 appeared monomorphic in this cohort, limiting its utility as a predictive or diagnostic marker in this population. Overall, the findings of this study highlight the role of TSHR genetic polymorphisms—particularly rs2268458—in modulating individual

susceptibility to Graves' disease in this region. These results support the need for further population-specific genomic studies and may eventually contribute to personalized approaches in predicting disease risk, tailoring therapy, and managing autoimmune thyroid disorders

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