

Genetic Insight into Hypothyroidism and Dyslipidemia: Pilot Analysis of Thyroid Hormone Receptor Gene Polymorphisms in Mysuru, India

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Abstract: The present study focused on the demographic, biochemical, and genetic characteristics that might be associated with hypothyroidism by investigating two SNPs of the THRA gene, rs12939700 (A/G) and rs939348 (C/T), in 25 cases and 25 controls. The demographic profile showed that patients had a higher mean age and BMI as compared to controls, with men showing higher values of BMI. At the biochemical level, patients presented with highly elevated TSH and drastically diminished T4, whereas T3 remained within the normal range; further, total cholesterol, LDL, and triglycerides were also significantly increased with reduced HDL, indicating thyroid-related dyslipidemia. Characterization of SNPs using agarose gel electrophoresis, Sanger sequencing, and capillary electrophoresis showed a characteristic genotype distribution, as genetic diversity was observed only within the patient cohort. ANOVA testing showed a significant difference for rs939348 ($F = 4.61$, $p = 0.037$), while for rs12939700, no significant change was observed. Chi-square analysis did not observe any significant association between either of the SNPs and diseased status. Regression analysis reported that rs12939700 AG genotype significantly increased the chances of hypothyroidism ($OR = 6.69$, $p = 0.019$), while other genotypes did not reveal any significant findings, and highly large or undefined odds ratios for rs939348 suggested model instability rather than actual effects. The results confirm biochemical markers of primary hypothyroidism with dyslipidemia; however, genetic investigation based on the present sample suggests that only rs12939700 (A/G) has a minor association with disease susceptibility. Results emphasize the potential role of THRA polymorphisms in hypothyroidism risk; however, larger studies will be required for confirmation of genetic susceptibility.

Keywords: Hypothyroidism; Dyslipidemia; TSHR gene polymorphism; Thyroid hormones; metabolic profile.

INTRODUCTION

Metabolism is regulated by the thyroid gland by the secretion of hormones. Thyroid conditions range between benign goiters and malignancies and are the second most common endocrine disease in the world with over 200 million people in the world and 42 million in India with nearly 60 percent of them not known of their condition. Hyperthyroidism is the overproduction of hormones by the thyroid, which causes the levels of the TSH to reduce; hypothyroidism is the under-production of hormones by the thyroid, making the levels of TSH high. Women are more commonly affected as opposed to men and the risk of hypothyroidism increases with age. Iodine deficiency, autoimmune diseases and some drugs are the most common causes of thyroid abnormalities though age, gender, obesity, ethnicity and geographical location also influence prevalence of these disorders [1-5]. Recent genetic investigations of the TSH receptor (TSHR) gene have yielded inconclusive findings. Initial case-control studies on protein-coding mutations (D36H, D727E, P52T) yielded conflicting result [6-8]. Subsequent research identified correlations with mutations in noncoding areas, such as intron-1 and intron-7, including a C/G alteration in intron-1 associated with

Graves's disease in Singapore, as well as additional intronic relationships documented in Japanese and Caucasian populations. Recent studies concentrated on intron-1 SNPs (rs179247, rs2268458, rs12101255) among Asian, European, and Iranian populations, but produced inconsistent results [9-18].

AIM: To assess the demographic, physiological, metabolic, and genetic determinants linked to hypothyroidism, particularly emphasizing dyslipidemia and the TSHR gene polymorphism.

OBJECTIVE:

- 1) To compare demographic variables (age, sex, BMI) between hypothyroid patients and healthy controls.
- 2) To determine the occurrence of comorbid clinical risk factors, including dyslipidemia, tobacco use, and alcohol consumption.
- 3) To compare the levels of thyroid hormones (TSH, T3, T4) and lipid profiles indicators (total cholesterol, LDL, HDL, triglycerides) in the two groups.
- 4) To ascertain the genotype distribution of the TSHR polymorphism in patients and controls.
- 5) To assess the statistical association between TSHR polymorphism using chi-square test between control and patient groups.

- 6) To analyze the model regression between different TSHR population receptor hormone polymorphism in control and healthy patients.

MATERIAL AND METHODS

Study Design: This was a pilot case - control study was performed in Biochemistry laboratory of JSS Hospital, Mysuru. after clearance from the institutional ethical committee (JSSMC/IEC/17112021/41 NCT/2021-22) and obtaining informed consent from participants.

This study that included 50 adults (25 clinically confirmed hypothyroid patients and 25 age and sex matched healthy controls) in Mysuru, India. All the participants were recorded in terms of demographics, including age, sex, and BMI. Data on clinical information, such as dyslipidemia status, smoking, and alcohol consumption, were recorded by using structured questionnaires. Venous blood samples were taken in the fasting condition to examine the level of thyroid hormone (TSH, T₃, T₄) and the lipid parameters (total cholesterol, LDL, HDL, triglycerides) through the routine biochemical analysis. Peripheral blood leukocytes were used to isolate genomic DNA and PCR-based methods used to genotype the TSHR polymorphism. Genotype and allele frequencies were calculated and chi-square tests applied to analyze the correlation between the genotypes. To compare biochemical parameters in different groups, independent t-tests were used, with the significance of 0.05 set. All data were analyzed with the help of traditional statistical numbers in order to determine the demographic differences, the metabolic processes changes, and genetic correlations of hypothyroidism and dyslipidemia.

Criteria for Inclusion:

Patients aged 20 to 69 years of Mysuru, India. Hypothyroid patients identified by clinical examination and biochemical test (increased TSH and low or normal T₄ level). Normal levels of TSH, T₃, and T₄ levels in healthy individuals. Patients willing to provide informed permission and who provided a blood specimen for analysis.

Criteria for Exclusion:

Individuals with known autoimmune diseases other than thyroidism. Individuals who were currently taking lipid-lowering medication, corticosteroids, anticonvulsants, or hormones Pregnant or lactating women Individuals who suffered from chronic diseases such as diabetes, kidney disease, liver disease, cardiovascular disease, or any type of acute inflammatory illness Individuals who had previously undergone thyroid surgery or radioactive iodine treatment Ethical Approval Statement: Ethical approval was obtained from the Institutional Ethics Committee, and all participants signed an informed written consent form prior to enrollment. Participant confidentiality was strictly maintained, and all

procedures performed on human participants conformed to approved institutional review board guidelines.

Work protocol:

Participants were recruited in the research upon the provision of written informed consent, and demographic and clinical information was collected at the time of recruitment.

Approximately 5 mL of peripheral blood was obtained from each participant by venipuncture using sterile EDTA (2ml) and Plain (3ml) vacutainer tubes. Samples were delivered on ice to the laboratory for prompt processing. EDTA sample stored at -4°C for Molecular analysis, Plain vacutainer was fractionated into plasma/serum and cellular components using centrifugation at 3,000 rpm for 10 minutes. The plasma or serum component was used for biochemical assessments, including thyroid function tests (TFTs) and lipid profile evaluations, conducted using automated analyzers such the Roche Cobas e601/e411 platform in accordance with the manufacturer's guidelines.

The Genomic DNA was extracted from EDTA-anticoagulated blood samples using the Qiagen QIAamp Blood Mini Kit (*cat. nos. 51104 and 51106*) followed the manufacturer's protocol.

The concentration and purity of the extracted DNA were measured on a Nano-Drop spectrophotometer, ensuring that samples had A₂₆₀/A₂₈₀ ratios ranging between 1.8 and 2.0. The integrity of DNA was also verified by electrophoresis on a 1% agarose gel stained with an appropriate DNA dye. Further studies were done only with high-quality DNA. Target DNA fragments harboring the single nucleotide polymorphisms rs939348 and rs12939700 within the THRA gene were delimited based on NCBI reference sequences. Primers flanking these positions were designed using Primer3/Primer-BLAST with optimized melting temperature, GC content, and amplification specificity. The genomic DNA was used as a template for locus-specific PCR amplifications. PCR amplification was performed with Taq DNA polymerase, buffer, MgCl₂, dNTPs, and the specific forward and reverse primers. Amplification conditions were optimized by running a temperature gradient to determine the optimal annealing temperature. The optimized general PCR cycling profile usually included an initial denaturation at 95 °C for 3 min, followed by 30-35 cycles of denaturation at 95 °C for 30 s, annealing at the assay-specific optimized temperature for 30 s, extension at 72 °C for 30 s, and a final extension at 72 °C for 5 min. The products obtained after PCR were analyzed on 1.5-2% agarose gel to check the expected size and specificity of amplicons. The successful PCR products were cleaned by enzymatic cleaning or spin-column purification and then sequenced. According to the study design, SNP

genotyping was performed by Sanger sequencing. A PCR product, having been purified, was mixed with sequencing primers and reaction mixture and treated with cycle sequencing, followed by capillary electrophoresis in an automated DNA sequencer. Chromatograms were reviewed manually for nucleotide changes at target loci. All the genotypic data collected were subjected to statistical analysis along with the biochemical tests, which included but were not limited

to TFTs and lipid profiles. Regarding the associations between genotypes of THRA SNPs and clinical parameters, respective statistical analyses have been performed, including allele/genotype frequency comparison, association analysis, and multivariate regression modeling where appropriate. Results were analyzed to determine whether variation at rs939348 and rs12939700 contributes to phenotypic differences or disease-related outcomes in the research population.

• 1ST SET

Primer ID	Sequence (5' → 3') (rs12939700)	Size (bp)	GC (%)	T _m (°C)	Product length (bp)
OF	CACCGAACTCTTCCCCCACTCTT	24	58.33	66.55	308bp
OR	AACTGCAGGACACAGCTCCCC	22	63.64	67.30	
IF (C)	AGAGCTGGGGGCTGAGGGAGGCC	23	69.57	69.96	194bp
IR (A)	GAAGGAGAGAAGGGGTGTGGGAGT	24	58.33	65.81	160bp
Allele Frequency	Global	102768	C=0.947688	A=0.052312	(D=46)

• 2ND SET

Primer ID	Sequence (5' → 3') (rs12939700)	Size (bp)	GC (%)	T _m (°C)	Product length (bp)
OF	ATCCACGCAGAGCCTAGCACA	22	59.09	66.54	306bp
OR	CATTCCCGCACAGTGGCTGAG	21	61.90	64.40	
IF (T)	TCCCCTGAACTCAGGTGCAGCAT	23	56.52	66.55	209bp
IR (C)	GACCTGGGCCTTGTGAACGCG	21	66.67	66.89	140bp
Allele Frequency	Global	187064	T=0.739736	C=0.260264	D=43

THRA	Amplicon Length: 350	Start	Stop	Length	Tm
rs939348 40075600	Forward	43	65	23	62
	CTGGAGGGTAGAGGAAGTAGATG (Sense)				
	Reverse	375	393	19	62
	CAGTTGAGCTAGCGGCTTC (AntiSense)				

Primers Synthesised by Juniper Diagnostics, Bangalore, karnataka, India

RESULTS

Table 1: Control group: Females (34%) had a mean age of 39.41 ± 10.93 years and a BMI of 24.99 ± 3.22 ; men (16%) had a mean age of 36.25 ± 5.5 years and a BMI of 22.89 ± 1.45 . Patient demographics: Females (24%) had a mean age of 42.5 ± 9.3 years and a BMI of 25.97 ± 4.4 ; men (26%) had a mean age of 46.46 ± 13.07 years and a BMI of 27.32 ± 4.9 .

Table 1: Demography analysis (n=25 control, n=25 patient group):

			Frequency	%	Mean	Std. Deviation	Minimum	Maximum	95% Confidence interval of Mean	Mean \pm Std.
Age_yrs	Control	F	17	34%	39.41	10.93	21	56	33.79 - 45.03	39.41 \pm 10.93
		M	8	16%	36.25	5.5	26	43	31.65 - 40.85	36.25 \pm 5.5
	Patient	F	12	24%	42.5	9.3	28	57	36.59 - 48.41	42.5 \pm 9.3
		M	13	26%	46.46	13.07	23	71	38.56 - 54.36	46.46 \pm 13.07
BMI_kg/m2	Control	F	17	34%	24.99	3.22	17.6	30.6	23.33 - 26.64	24.99 \pm 3.22
		M	8	16%	22.89	1.45	21.5	25	21.68 - 24.1	22.89 \pm 1.45
	Patient	F	12	24%	25.97	4.4	17.8	33.6	23.17 - 28.76	25.97 \pm 4.4
		M	13	26%	27.32	4.9	20.9	39.3	24.35 - 30.28	27.32 \pm 4.9

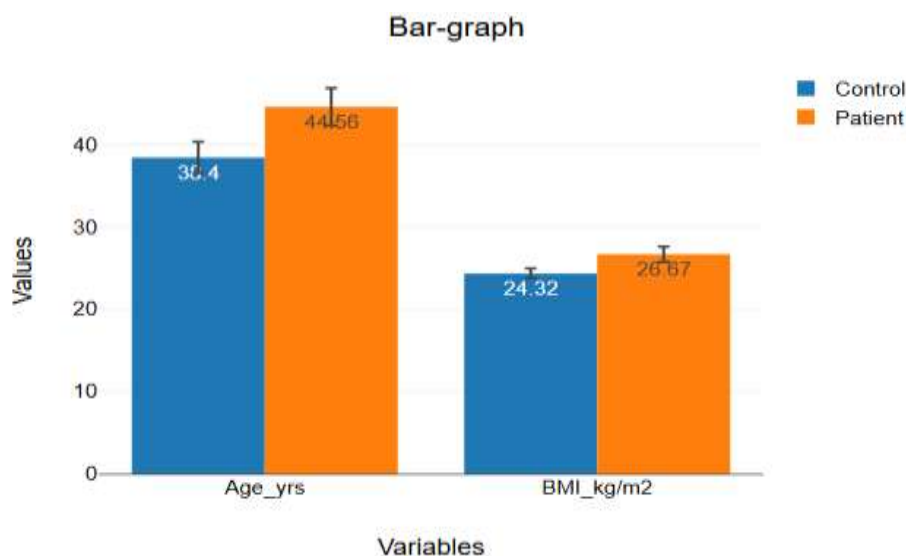


Fig 1: shows the bar-graph of variables age and BMI with mean values and standard error.

Table 2: Associated patient risk factor variables percentage analysis:

	Frequency	%
Dyslipidemia	88	41.51%
Smoker	62	29.25%
Alcohol	62	29.25%
Total	212	100%

Table 2 indicates that dyslipidemia, smoker and alcohol percentage and frequency.

Table 3: Analytical variables with independent t-test (two-tailed, assuming unequal variances where appropriate):

Statistic	TSH (mIU/L)	Total T4 (µg/dL)	Total T3 (nmol/L)	Total Chol. (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Trig. (mg/dL)
Mean	7.25	4.73	2.37	204.74	132.48	46.49	145.03
Std. Deviation	5.77	1.48	0.69	45.45	36.39	11.49	55.92
Minimum	0.01	2.12	1.06	132.67	3.62	1.33	0
Maximum	17.87	8.33	3.64	334.42	222.86	88.82	92.99
95% CI Lower	5.61	4.30	2.17	191.82	122.13	43.22	129.14
95% CI Upper	8.88	5.15	2.56	217.66	142.82	49.76	160.93
Mean ± Std. Dev.	7.25 ± 5.77	4.73 ± 1.48	2.37 ± 0.69	204.74 ± 45.45	132.48 ± 36.39	46.49 ± 11.49	145.03 ± 55.92
p-value (vs. normal)	<0.001	<0.001	0.094	0.010	0.002	0.040	0.003

Table 3: TSH and T4 exhibited considerable deviations from normal ($p < 0.001$), T3 shown no notable alterations, and all lipid markers, except HDL, were raised with significant p-values, suggesting pronounced thyroid-related dyslipidemia.

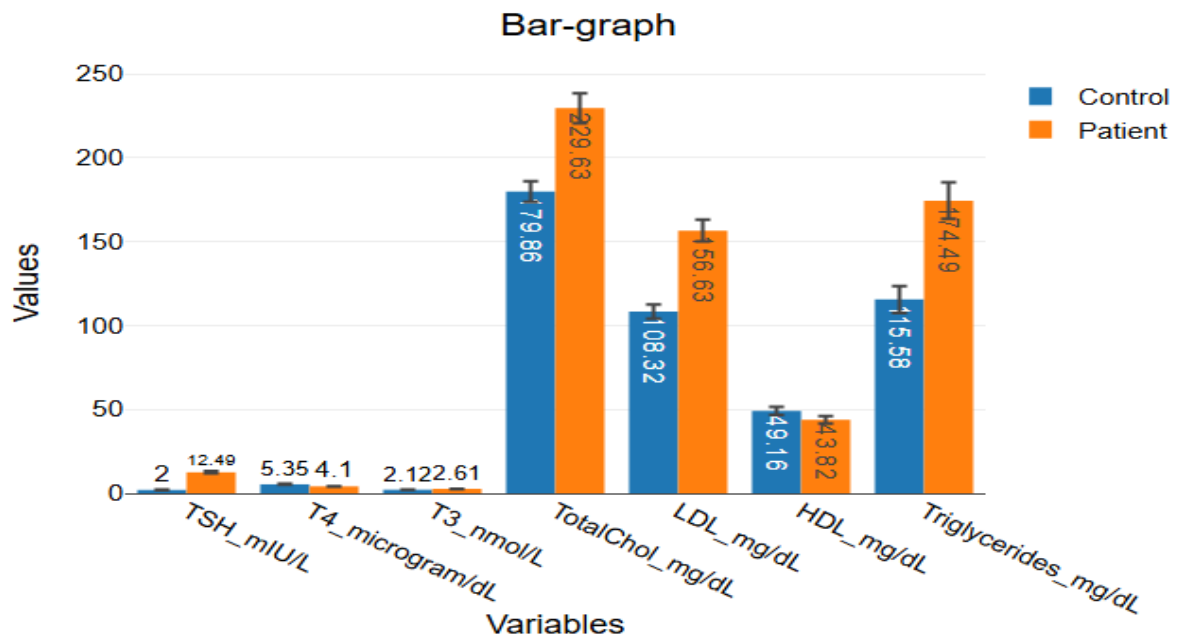


Fig 2: shows the analytical variables being tested with the mean and standard deviation.

Table 4: Summary analysis:

Variable	Finding	Clinical Implication
TSH	↑↑↑ in Patients	Primary hypothyroidism
T4	↓↓↓ in Patients	Confirms low thyroid hormone
T3	No significant difference	T3 often preserved early in hypothyroidism
Total Cholesterol, LDL, Triglycerides	↑↑↑ in Patients	Dyslipidemia secondary to hypothyroidism
HDL	↓ in Patients	Reduced protective HDL

Table 4: Patients exhibited high TSH, diminished T4, stable T3, increased total cholesterol/LDL/triglycerides, and decreased HDL, indicative of primary hypothyroidism and concomitant dyslipidemia

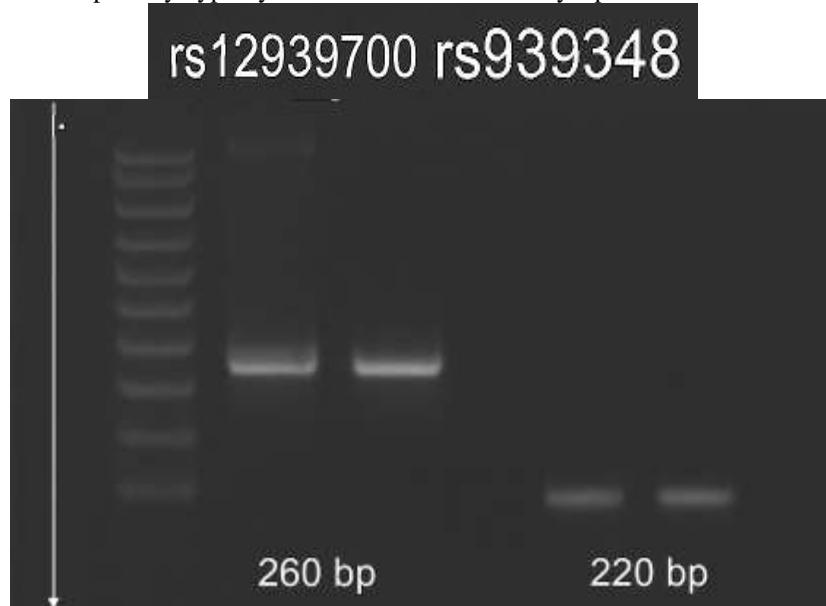
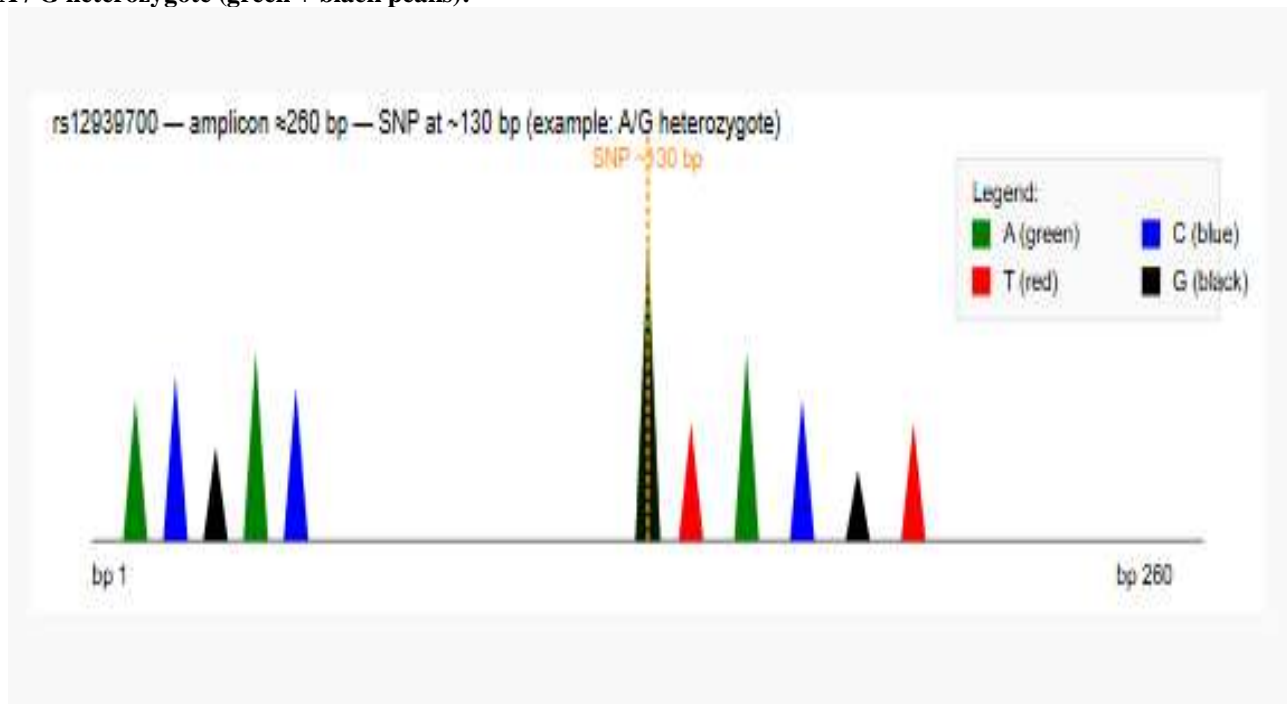


Fig 3: Agarose gel electrophoresis bands for the two loci studied in the laboratory

A / G heterozygote (green + black peaks):



C / T heterozygote (blue + red peaks):

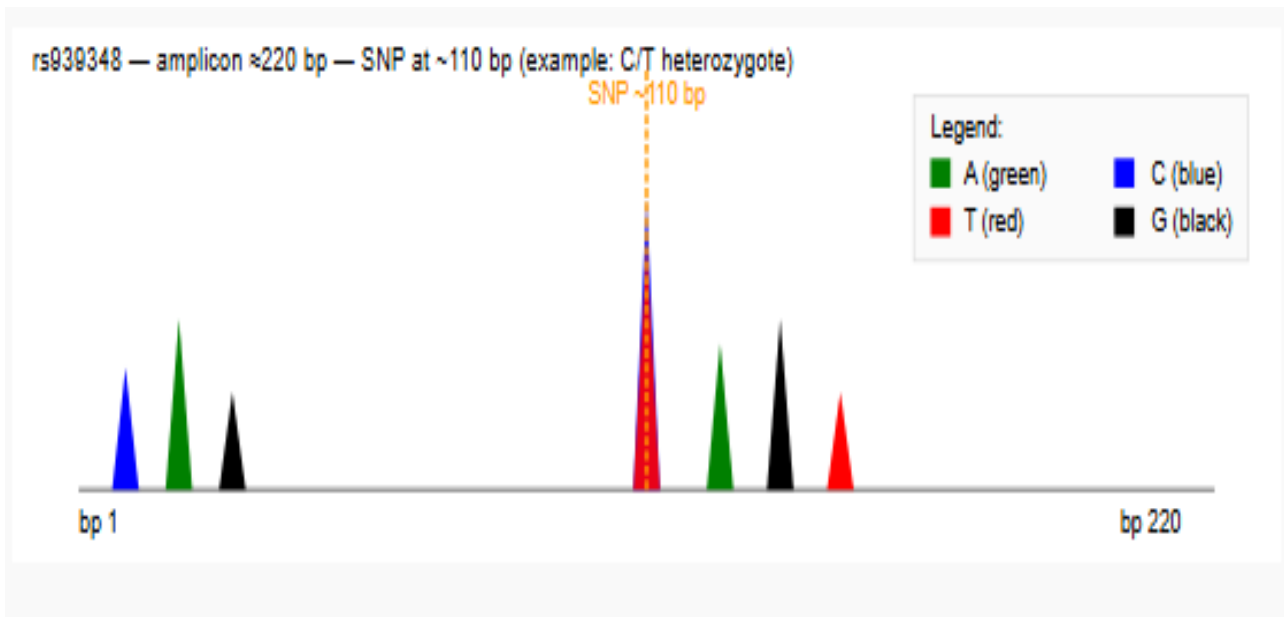
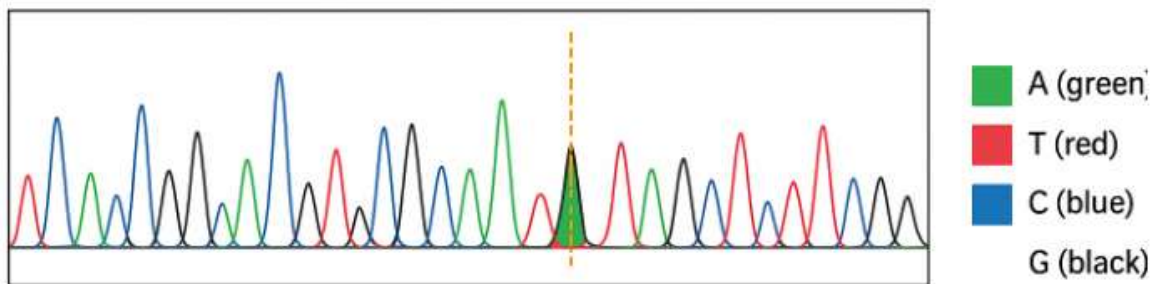


Fig 4: shows the SNP peaks for the 2 loci being studied in the Sanger sequencing method.

rs12939700 — amplicon ≈260 bp — SNP at ≈130 bp (example: A/G heterozygote)



rs9393488 — amplicon ≈220 bp — SNP at ≈110 bp (example: C/T heterozygote)

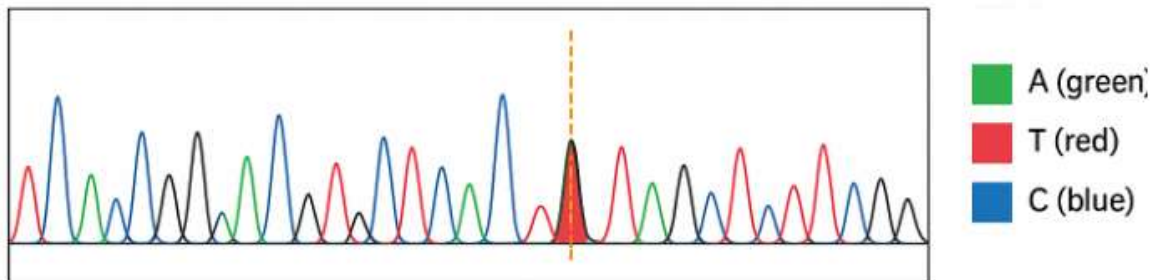


Fig 5: shows the capillary electrophoresis peaks for the SNP for the two loci studied.

Table 5: shows the SNP on the two loci:

SNP ID	Nucleotide Change	Location / Region	Possible Genotypes
rs12939700	C → A	3'-UTR / splicing region of THRA	CC, CA, AA
rs939348	T → C	Intron 2 of THRA	TT, TC, CC

Table 6: ANOVA test result:

Locus (SNP ID)	Alleles	Statistic	Value	p-value	Interpretation
rs12939700	A / G	F	3.09	0.085	No significant difference ($p > 0.05$)
rs939348	C / T	F	4.61	0.037	Significant difference ($p < 0.05$)

Table 6: rs939348 (C/T), $F = 4.61$, $p = 0.037$, indicating a significant difference ($p < 0.05$).

Table 7: Chi-square test result:

Locus (SNP ID)	Alleles	Statistic	Value	p-value	df	Interpretation
rs12939700	A / G	χ^2	3.04	0.218	2	No significant association ($p > 0.05$)
rs939348	C / T	χ^2	4.47	0.107	2	No significant association ($p > 0.05$)

Table 7: The chi-square analysis for the locus rs12939700 (A/G) yielded a χ^2 value of 3.04 with 2 degrees of freedom and a p-value of 0.218, indicating no statistically significant relationship between this SNP and the examined condition, since the p-value exceeds 0.05. The locus rs939348 (C/T) had a chi-square value of 4.47 with 2 degrees of freedom and a p-value of 0.107, above the 0.05 criterion. Consequently, no substantial correlation was seen between this SNP and the disease under consideration.

Table 8: Distribution analysis (n=25 control and n=25 patient):

	Control	CC	AA	Patient	CT	AG	TT	GG
Group	25	0	0	25	0	0	0	0
rs939348 (C/T, 220bp)	0	22	0	0	19	0	9	0
rs12939700 (A/G, 260bp)	0	0	15	0	0	23	0	12

Table 8: Distribution analysis for different loci.

Table 9: Regression model analysis:

Locus / Variable	Coefficient (B)	Standard Error	z	p-value	Odds Ratio	95% CI
rs12939700 (A/G, 260bp)						
Constant	-1.17	0.72	1.62	.105	0.31	0.08 – 1.28
Group Control	0.20	0.76	0.27	.791	1.22	0.27 – 5.45
AA	-20.53	7539.85	0.00	.998	0	0 – ∞
AG	1.90	0.81	2.34	.019	6.69	1.37 – 32.76
rs939348 (C/T, 220bp)						
Constant	-21.99	7445.60	0.00	.998	0	0 – ∞
Group Control	0.41	0.94	0.43	.666	1.50	0.24 – 9.46
CC	22.50	7445.60	0.00	.998	5,902,157,705.76	0 – ∞
TT	0.11	13,135.24	0.00	1.000	1.11	0 – ∞

Table 9: The regression model for rs12939700 (A/G) indicated that the AG genotype substantially elevated the chances of the condition (OR = 6.69, $p = 0.019$), whereas the AA genotype had no substantial impact owing to model instability, and group status was not a significant predictor. For rs939348 (C/T), none of the predictors, including the CC or TT genotypes, exhibited statistically significant impacts, since all p-values were non-significant and the very high or undefined odds ratios suggest model non-convergence rather than a genuine biological effect.

CONCLUSION

Ureteric obstruction is a common urological condition that can lead to significant renal impairment if not promptly recognized and managed. Hydronephrosis, the dilation of the renal collecting system, serves as a key marker of the severity of obstruction and reflects the degree of renal functional compromise. The findings of this study demonstrate that increasing severity of hydronephrosis is associated with progressive deterioration of renal function, as evidenced by rising serum creatinine, declining eGFR, and reduced split renal function in the affected kidney. These results underscore the clinical importance of early detection and assessment of hydronephrosis severity in patients with ureteric obstruction to guide timely intervention and preserve renal function.

In the present study, the majority of patients with ureteric obstruction were within the 40–59-year age group (43.8%), with a mean age of 48.2 ± 13.7 years, indicating that the condition predominantly affects individuals in the middle decades of life. This finding

closely aligns with the observations of Jeevaraman *et al.*[14], who reported the highest incidence between 21–49 years (~60%), and Jagannath *et al.*[15], who found a similar concentration between 31–50 years (~52%). A male predominance (65%) was noted in our study, consistent with the findings of both Jeevaraman *et al.*[14] (57.8%) and Jagannath *et al.*[15] (57.8%), reflecting the higher predisposition of males to stone formation, possibly due to dietary, metabolic, and occupational factors. The right side was slightly more affected (52.5%) than the left (47.5%), which also corresponds with the trends reported by both reference studies, where right-sided involvement was marginally higher (~50.37%). The most common cause of obstruction in our cohort was ureteric calculus (72.5%), followed by stricture (17.5%) and external compression (10%), reinforcing the established understanding that calculi remain the predominant etiology of ureteric obstruction in most adult populations.

In this study, hydronephrosis severity among patients with ureteric obstruction was distributed as 26 patients (32.5%) with mild, 28 patients (35.0%) with moderate,

and 26 patients (32.5%) with severe hydronephrosis. These findings align with previous reports demonstrating that hydronephrosis commonly presents across a spectrum of severity in adults with urinary tract obstruction. Alshoabi *et al.*[16], in an ultrasonographic assessment of 233 patients, reported that hydronephrosis occurred in varying grades, with the majority exhibiting moderate obstruction (Grade 2: 58.8%). Similarly, Mahmud *et al.*[17] observed a comparable range of hydronephrosis severity among 248 patients with urinary stones, indicating that obstruction may manifest from mild to severe forms. Collectively, these studies highlight that hydronephrosis in ureteric obstruction typically spans a wide severity spectrum, consistent with the distribution seen in our cohort.

Renal function in our study declined progressively with increasing hydronephrosis severity. Patients with mild hydronephrosis had a mean serum creatinine of 1.0 ± 0.2 mg/dL, eGFR of 85.1 ± 9.5 mL/min/1.73 m², and split renal function of $44.8 \pm 3.5\%$, whereas those with moderate and severe hydronephrosis exhibited progressively higher serum creatinine, lower eGFR, and reduced split renal function, with all differences being statistically significant ($p < 0.001$). These findings are in line with previous studies demonstrating a clear relationship between hydronephrosis severity and renal impairment. Mohammadi-Sichani *et al.*[18] reported that higher grades of hydronephrosis were significantly associated with lower GFR ($p = 0.000$), while Singla *et al.*[19] observed that adults with ureteropelvic junction obstruction exhibited lower split renal function in more severe cases. Collectively, these findings reinforce that increasing hydronephrosis severity in ureteric obstruction correlates strongly with deterioration in renal function.

A strong positive correlation was observed between hydronephrosis grade and serum creatinine ($r = 0.79$, $p < 0.001$), and strong negative correlations with eGFR ($r = -0.82$, $p < 0.001$) and split renal function ($r = -0.85$, $p < 0.001$). These results indicate that as hydronephrosis severity increases, renal function worsens proportionally. Similar trends were noted by Kumar *et al.*[20], who demonstrated a linear relationship between the severity of histological changes and preoperative split renal function in patients with ureteropelvic junction obstruction, showing that greater obstruction corresponded to lower renal function. Likewise, Wang *et al.*[21] reported that higher grades of obstructive hydronephrosis were associated with greater functional impairment, including significant reductions in GFR. Together, these findings affirm that hydronephrosis grade serves as a reliable indicator of renal function decline in ureteric obstruction.

Finally, a clear relationship was observed between the duration of symptoms, severity of hydronephrosis, and renal function. Patients presenting within ≤ 48 hours

predominantly exhibited mild hydronephrosis (69.2%), whereas those with symptom duration > 48 hours had a higher frequency of moderate (64.3%) and severe (84.6%) hydronephrosis. Correspondingly, the mean eGFR progressively declined with increasing hydronephrosis grade, from 85.1 ± 9.5 mL/min/1.73 m² in mild cases to 36.8 ± 11.2 mL/min/1.73 m² in severe cases ($p < 0.001$). These findings are consistent with Li *et al.*[22], who reported significantly lower pre-treatment eGFR among patients with longer symptom duration and more advanced hydronephrosis grades, suggesting that both duration of obstruction and hydronephrosis severity are strong predictors of renal functional impairment. This emphasizes the importance of early diagnosis and prompt intervention to prevent irreversible renal damage in ureteric obstruction.

Limitations of the study

The study had a few limitations:

- The study was conducted with a relatively small sample size, which may limit the generalizability of the findings to the broader population.
- As a single-center study based in one hospital, the results may not fully represent the national population or reflect variations in other regions.

CONCLUSION

This study demonstrated that increasing severity of hydronephrosis was closely associated with progressive deterioration of renal function in patients with ureteric obstruction. Patients with more advanced hydronephrosis showed higher serum creatinine and lower eGFR and split renal function values, indicating significant impairment of renal performance. A clear correlation was also observed between longer duration of symptoms and greater hydronephrosis severity, emphasizing the impact of delayed presentation on renal outcome. These findings highlight that both the degree and duration of obstruction are critical determinants of renal function, underscoring the importance of early diagnosis and timely intervention to prevent permanent renal damage.

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