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RESEARCH ARTICLE

Biochemical Test of Thyroid Gland and Allelic Frequency rs12917707 in Iraqi Patients with Thyroid Cancer

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ABSTRACT

Thyroid cancer, one of the most common kinds of endocrine cancer, affects both sexes equally but is more prevalent in women. Several variables led to the development of this kind of cancer, such as genes and their polymorphism. This article evaluates the rs12917707 polymorphism associated with the UMOD gene that regulates several biochemical factors. The change in the blood concentration of these factors is associated with thyroid cancer. Blood samples were taken from 75 patients with thyroid cancer and 50 healthy controls. Then, genomic DNA was extracted, and the allelic and genotypic frequency of the rs12917707 polymorphism was determined using the TaqMan technique. In addition, the blood concentrations of biochemical components (T3, T4, TSH, vitamin D, RBC, WBC, PLT, and HGB) were evaluated using the ELISA technique. According to the data, the rs12917707 polymorphism is significantly associated with thyroid cancer susceptibility. The hormones T3, T4, TSH, and vitamin D are significantly associated with an elevated risk of thyroid cancer. In contrast, RBC, WBC, PLT, and HGB variables were not significantly associated with thyroid cancer. In general, genetic and biochemical components investigated in this work interact with the beginning of thyroid cancer.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, making up around 3-4% of all human malignancies (1). It can manifest in four distinct ways: follicular, papillary, medullary, or anaplastic. Parafollicular cells (C cells) are the origin of cancer in the medullary thyroid, while the follicles are the origin of cancer in the other three types of thyroid cancer (2). Papillary thyroid carcinoma is one of the most common types, with an 80% incidence rate (1). Epidemiological studies show that the prevalence of thyroid cancer, especially the papillary variant, has increased globally (3). Thyroid cancer is more common in women than men, especially between 30 and 50 (4) (5).

The thyroid gland secretes essential hormones in cell proliferation, apoptosis, differentiation, and metabolism. Thyroid cancer is triggered by a disruption in these hormones (6). Significant physiological effects are caused when triiodothyronine (T3) binds to alpha (TRA) and beta (TR) nuclear receptors functions (6, 7). Studies have shown that T3 develops various tumors (8). Hormone T4 increases the proliferation of tumor cells and also leads to increased angiogenesis (9). Thus, T4 is involved in cancer cell metastasis (10), and TSH is also an essential contributor “to the development

of papillary and follicular thyroid cancers" (11). In addition, various studies have shown that cancerous cells and platelets have mutual effects. Paraneoplastic thrombocytosis is the platelet increase caused by malignant cells' stimulation of platelet production. Conversely, platelets sustain tumor development, invasion of surrounding tissues, and dissemination (12). Therefore, inflammatory indicators in cancer patients may be determined by measuring neutrophil count, lymphocyte count, PLTs, and platelet markers (13).

Due to environmental factors and genetic variability, thyroid cancer rates differ from country to country (14). Thyroid tumor risk factors include radiation exposure, becoming older, being a man, having a goitre, or having another benign thyroid illness (15-17). SNPs, or variations in a single nucleotide, are a source of genetic variation in the human genome: genetic susceptibility or resistance to cancer (17). Under the same environmental conditions, the risk of cancer and its clinical incidence differs in people with different genetic backgrounds. Genetic factors are crucial in increasing cancer risk and its clinical impact. In similar circumstances, the risk of cancer in people with a genetically sensitive background is higher than in people with a resistant genotype. Polymorphisms can weaken the protective mechanisms or increase the damage caused by environmental carcinogens. Genome comprehensive association studies on different cancers indicate the role of different polymorphisms in human cancers (18).

One essential gene that thyroid hormones affect is the uromodulin gene (*UMOD*) (19, 20), which encodes a protein of 639 amino acids (21). "It has an N-terminal region, followed by 3-replicate regions similar to EGF, a domain with 8 conserved cysteines (D8C), and a domain at the end". There are 130 amino acids in the second D8C, and four disulfide bridges are formed between cysteines (22). The human kidney has this protein mostly in its thick apical membrane found in the ascending ring and the complicated distal tube. Moreover, it is a glycoprotein associated with the GPI anchor. Its possible role is in cell adhesion, signal transduction, inhibition of calcium oxalate crystal accumulation, protection against UTIs and adjusting one's defensive mechanisms to concentrate urine. It may also act as a potential nephrogenic antigen (23). It also has the potential for immune regulation (24). Multiple scientific studies have linked UMOD gene mutations to Familial Juvenile Hyperuricemia Nephropathy (FJHN), also associated with the thyroid and parathyroid disorders (25). *UMOD* gene expression decreases under the influence of thyroid hormones, especially the T4 hormone (19, 20). *UMOD* has several polymorphisms, one of which is rs12917707-G> T polymorphism, which is in the first part of the genome called is involved in regulating the expression of the *UMOD* gene (26).

Therefore, this research aimed to determine the correlation between thyroid hormones (T3, T4, TSH), vitamin D, WBC, HGB, RBC, PLT, age and rs12917707 polymorphism with thyroid cancer and also to investigate the relationship between this polymorphism and other case factors.

MATERIAL AND METHOD

Sample collection

For this reason, case-control research was conducted on 75 patients with thyroid cancer (43 males and 32 female) and 50 healthy individuals (30 males and 20 female) who did not have thyroid dysfunction and each species of cancer, systemic disease, infectious and inflammatory diseases were performed with written consent. Those with high blood pressure, diabetes, autoimmune disease, chronic inflammatory diseases, impaired liver functions, impaired kidney functions, or haematological laboratory findings were excluded from the study. The subjects' demographic characteristics and laboratory data were obtained from the hospital's computer database. Thyroid

cancer patients and healthy people had around 4 milliliters of blood taken from their left antecubital vein. Two milliliters of blood were left to coagulate in a laboratory incubator for five minutes.

"The samples were centrifuged for 10 minutes at 3000 rpm to separate the serum sample. The obtained serums were divided into three 0.5 ml microtubes. Isolated serum samples were stored in 1 ml Eppendorf microtubules at -80 ° C. The remaining 2 ml of blood was stored in EDTA tubes for DNA extraction at -20 ° C".

Ethical approvals

After getting clearance from the ethical committees of the Biology Department/College of Science/University of Baghdad, the Iraqi Ministry of Health and Environment gave the go-ahead to collect blood from participants.

Measurement of homogram

Beckman Coulter (Beckman Coulter In.; Bre CA) LH 780 automatic analyzer was used to perform hemogram tests, including hemoglobin (Hgb); blood counts consist of three "different types of cells: white blood cells (WBC), red blood cells (RBC), and platelets (PLT)". Checks for biochemical and pathological abnormalities, in addition to hemograms, were performed in the hospital laboratory.

Evaluation of T3, T4, TSH hormones and vitamin D

The levels of T3, Vitamin D, thyrotropin-releasing hormone, thyrotropin-stimulating hormone, and T4. A Canadian firm produces the kits (DBC Company, Ontario, Canada). The Austrian business Tecan and the fashion model Sunrise provided the ELISA vocalist.

DNA extraction

DNA extraction from blood with Quick-gDNA TM Blood MiniPrep Cat. Nos (Catalog No: D3072). The production of Zymo, USA, complied with the guidelines set out by the producer protocol.

Real-Time PCR

A real-time PCR test was performed using an SNP assay supplied by Thermofisher Company for rs12917707 polymorphism (Cat # C__31122302_20). The reaction was prepared using 10µl of TaqMan® Genotyping Master Mix Sacace Italy (Catalog No: 25025), 0.25µl of Taqman assay, 3 µl of DNA and then the completed to 20 µl by adding 6.75 µl. This reaction was performed in the Sa-cycler-96, programmed at temperatures of "95 degrees Celsius for ten minutes, followed by forty cycles of 95 degrees Celsius for fifteen minutes and 60 degrees Celsius for one minute". Next, the statistics and curves drawn by the device were examined (Figure 1). Each curve within the plot represents a single sample amplification. Results have appeared in two channels as logarithmic increment curves, representing one sample. The FAM channel shows the T allele, and the Hex channel shows the G allele.

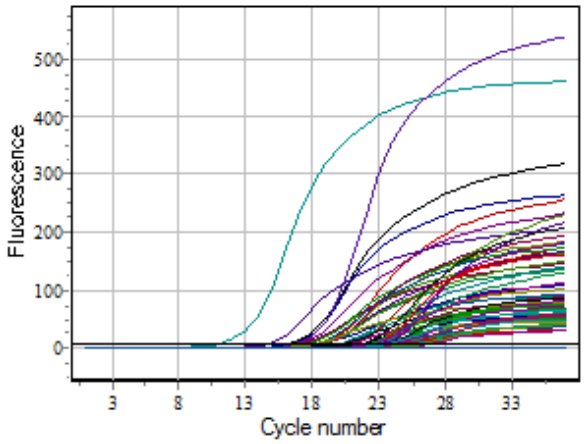

Figure 1: Curve for rs12917707 polymorphism study using Taqman method

Statistical analysis

IBM SPSS version 26.0 was used to determine the means and standard errors (27). "Student T-test and analysis of variance table were also used to investigate the probabilities (Duncan test). Pearson's chi-square test determines statistical significance when working with non-parametric data". It was determined that there was a correlation between the two parameters of interest using Pearson's method. WinPepi 11.65 can compute the odd ratio, 95% confidence interval, and Fisher's exact probability for a set of genotype and allele frequencies (28).

RESULTS

Sample size

There were a total of 75 persons with thyroid cancer and 50 healthy controls in the research. The investigations found no statistically significant difference in average age between the control and patient groups (P> 0.05), with the ages of both groups averaging 59.26 1.74 and 59.41 1.2, respectively (Table 1). The average age of the participants is listed in Table 1.

(Table 1). The average age of the participants

Gender	**Age mean ± SE**		**Probability**
	Control group	**Patients group**	
Males	58.58 ± 2.27	60.07 ± 1.57	0.951 NS
Females	60.0 ± 2.72	58.53 ± 1.88	0.963 NS
Total	59.26 ± 1.74	59.41 ± 1.20	0.940 NS
Probability	0.970 NS	0.936 NS	
NS: Non-significant (P> 0.05)			

Serum levels of biochemical and cellular factors in the studied groups

After evaluation, Table 2 summarizes the findings from measuring biochemical and cellular variables in plasma "from the patient and control groups, including a statistically significant difference in the amount of T3 hormone between the sexes". A highly significant increment in patients than in control (81.02 ± 1.34 vs 2.36 ± 0.15, P= 4.86 x 10^{-13}). The female group also showed an increment in patients than in control (81.25 ± 2.93 vs 2.15 ± 0.15, p= 4.85 x 10^{-13}). The levels of T4 showed a highly

significant level in patients than in control of both males (183.26 ± 1.56 vs 84.08 ± 1.79) and females (183.28 ± 1.50 vs 85.58 ± 2.76). The TSH levels in males showed higher levels in patients than in control (75.19 ± 2.95 vs 2.46 ± 0.13); in females, the TSH showed slightly higher levels than males, and patients showed significantly higher levels than control (81.25 ± 2.93 vs 2.15 ± 0.15, p= 4.85 x 10^{-13}).

Table 2: Comparison of serum thyroid function tests levels in the studied groups

Parameter	Gender	Control group	Patients group	Probability
T3	Males	2.36 ± 0.15	81.02 ± 1.34	4.86 x 10^{-13} **
	Females	2.15 ± 0.15	81.25 ± 2.93	4.85 x 10^{-13} **
	Total	2.26 ± 0.11	81.12 ± 1.46	2.75 x 10^{-77} **
	Probability	1.0 NS	1.0 NS	
T4	Males	84.08 ± 1.79	183.26 ± 1.56	4.86 x 10^{-13} **
	Females	85.58 ± 2.76	183.28 ± 1.50	4.85 x 10^{-13} **
	Total	84.80 ± 1.61	183.27 ± 1.09	3.49 x 10^{-86} **
	Probability	0.955 NS		
TSH	Males	2.46 ± 0.13	75.19 ± 2.95	4.85 x 10^{-13} **
	Females	2.53 ± 0.15	79.75 ± 1.77	4.86 x 10^{-13} **
	Total	2.49 ± 0.10	77.13 ± 1.86	1.49 x 10^{-62} **
	Probability	1.0 NS	0.401 NS	

Vitamin D results showed a statistically significant difference when comparing the control group to the sick group (P 0.001). (Table 3), the patients showed a significantly lower level than the control in males (11.67 ± 0.69 vs 22.42 ± 1.13, p= 5.98 x 10^{-13}). And also females (11.56 ± 0.79 vs 21.29 ± 1.12, p= 2.55 x 10^{-10}).

Table 3: Comparison of serum Vitamin D3 levels in the studied groups

Gender	Vitamin D level mean ± SE		Probability
	Control group	Patients group	
Males	22.42 ± 1.13	11.67 ± 0.69	5.98 x 10^{-13} **
Females	21.29 ± 1.12	11.56 ± 0.79	2.55 x 10^{-10} **
Total	21.88 ± 0.79	11.63 ± 0.52	6.62 x 10^{-21} **
Probability	0.852 NS	1.0 NS	
NS: Non-significant (P > 0.05), **: Significant (P < 0.001)			

Hematological test results are tabulated below (Table 4). No statistically significant differences were found in the male or female test findings compared to the control group.

Table 4: Comparison of hematological parameters levels in the studied groups

Parameter	Gender	WBCs count mean ± SE (x10^3)		Probability
		Control group	Patients group	
WBC	Males	7.24 ± 0.24	7.09 ± 0.23	0.978 NS
	Females	7.13 ± 0.33	7.78 ± 0.22	0.330 NS
	Total	7.19 ± 0.20	7.39 ± 0.17	0.442 NS
	Probability	0.994 NS	0.164 NS	
HGB	Males	12.79 ± 0.38	12.20 ± 0.32	0.729 NS
	Females	12.06 ± 0.43	12.04 ± 0.51	1.0 NS
	Total	12.44 ± 0.29	12.13 ± 0.28	0.463 NS
	Probability	0.671 NS	0.990 NS	
RBC	Males	4.07 ± 0.11	4.02 ± 0.08	0.990 NS

	Females	3.77 ± 0.11	3.98 ± 0.09	0.467 NS
	Total	3.92 ± 0.08	4.01 ± 0.06	0.408 NS
	Probability	0.220 NS	0.988 NS	
PLT	Males	330.89 ± 11.54	308.51 ± 8.15	0.391 NS
	Females	284.71 ± 12.82	316.88 ± 9.72	0.160 NS
	Total	308.72 ± 9.12	312.08 ± 6.22	0.753 NS
	Probability	0.025 *	0.922 NS	

Genotypic and allelic frequency of rs12917707 polymorphism in the studied groups

The GG, TG and TT genotypes showed higher frequencies 40%, 30.67 and 29.33% in the patient group than in the control group 6%, 26% and 68%, respectively. This genotypic difference was determined using a chi-square test at the p0.05 significance level Significantly different TT and GG genotypes were observed between sick and healthy populations (p 0.001), but in the TG genotype, there was a difference between healthy and sick individuals. No significance was observed (P> 0.05) (Table 3). Allelic frequencies "in both the patient and control groups" were analyzed as well. Among those with the disease, 55% had the G allele, and 45% had the T allele, whereas those without it had 19% and 81%, respectively. Allelic distribution significantly differed between sick and healthy groups (p 0.001). (Table 5).

Table (5): Comparison of genotypic and allelic frequency of rs12917707 polymorphism in the study population

SNP: rs **Genotype**	**Patients No. (%)**	**Control No. (%)**	**P-value**	**Chi-Square (χ^2)**
TT	30 (40.0)	3 (6.0)	2.4×10^{-5} **	17.848
TG	23 (30.67)	13 (26.0)	0.572 NS	0.319
GG	22 (29.33)	34 (68.0)	2.1×10^{-5} **	18.138
Allele Frequency				
T	83 (55)	19 (19)	1.0×10^{-8} **	32.793
G	67 (45)	81 (81)	1.0×10^{-8} **	32.793
NS: Non-significant (P > 0.05), **: Significant (P < 0.001)				

Evaluation of the relationship between rs12917707 polymorphism and serum levels of biochemical and cellular factors

Different rs12917707 polymorphism genotypes and blood levels of biochemical and cellular components in healthy controls and patients were compared. Specifically, this research found a statistically significant link between T3, T4, and TSH, as shown in Table (7). The genotype TT showed a higher level of T3 in both patients and control (84.60 ± 1.49 and 2.50 ± 0.30, respectively). Moreover, T4 also showed a higher level within the TT genotype in both the patient and control group (184.67 ± 1.31 and 90.00 ± 11.37, respectively). The TSH also showed a higher level within the TT genotype (81.20 ± 1.68) in patients and control (2.37 ± 0.26). The results are summarized in Table (6).

Table (6): Comparison of T3 with the genotypic frequency of rs12917707 polymorphism

parameter	Genotypes	Control group	Patients group	Probability
T3	TT	2.50 ± 0.30^{A}	84.60 ± 1.49^{A}	6.31 x 10^{-13} **
	TG	2.19 ± 0.25^{A}	81.78 ± 1.75^{AB}	6.30 x 10^{-13} **
	GG	2.27 ± 0.12^{A}	75.68 ± 3.96^{B}	6.31 x 10^{-13} **
T4	TT	90.00 ± 11.37^{A}	184.67 ± 1.31^{A}	6.31 x 10^{-13} **
	TG	84.31 ± 3.85^{A}	183.52 ± 2.08^{A}	6.31 x 10^{-13} **
	GG	84.53 ± 1.67^{A}	181.09 ± 2.48^{A}	6.31 x 10^{-13} **
TSH	TT	2.37 ± 0.26^{A}	81.20 ± 1.68^{A}	6.31 x 10^{-13} **
	TG	2.29 ± 0.22^{A}	78.17 ± 3.92^{AB}	6.31 x 10^{-13} **
	GG	2.58 ± 0.12^{A}	70.50 ± 4.02^{B}	6.31 x 10^{-13} **

The comparison among the different genotypes of rs12917707 in male and female control and patients' groups in response to vitamin D are summarized in Table (7). Patients were found to have a statistically significant difference from control in male (12.47 ± 0.82 vs 26.67 ± 4.49, respectively) and female (10.65 ± 0.90 vs 22.39 ± 1.44, respectively). The results failed to show a significant difference in response to genotypes.

Table (7): Comparison of Vitamin D with a genotypic frequency of rs12917707 polymorphism

Genotypes	Vitamin D level mean ± SE		Probability
	Control group	Patients group	
TT	26.67 ± 4.49^{A}	12.47 ± 0.82^{A}	0.00008 **
TG	22.39 ± 1.44^{A}	10.65 ± 0.90^{A}	4.47 x 10^{-9} **
GG	21.27 ± 0.95^{A}	11.50 ± 0.97^{A}	6.46 x 10^{-10}**
Duncan test: The similar letters referred to non-significant differences between the genotypes of the same group, **: Significant (P < 0.001)			

The comparison among the different genotypes of rs12917707 in male and female control and patient groups in response to WBC, HGB, RBC, and PLT are summarized in Table (8). The results none-significant differences among the different genotypes and the different hematological parameters.

Table (8); Comparison of hematological parameters with the genotypic frequency of rs12917707 polymorphism

Parameter	Genotypes	Control group	Patients group	Probability
WBC	TT	7.0 ± 1.53^{A}	7.34 ± 0.30^{A}	0.999 NS
	TG	7.12 ± 0.39^{A}	7.45 ± 0.26^{A}	0.986 NS
	GG	7.23 ± 0.23^{A}	7.39 ± 0.31^{A}	0.999 NS
HGB	TT	12.77 ± 1.09^{A}	11.89 ± 0.53^{A}	0.988 NS
	TG	12.41 ± 0.61^{A}	12.47 ± 0.46^{A}	1.00 NS
	GG	12.42 ± 0.35^{A}	12.11 ± 0.40^{A}	0.996 NS
RBC	TT	4.10 ± 0.21^{A}	3.96 ± 0.10^{A}	0.998 NS
	TG	3.79 ± 0.14^{A}	4.0 ± 0.10^{A}	0.898 NS
	GG	3.96 ± 0.10^{A}	4.01 ± 0.12^{A}	0.967 NS
PLT	TT	357.68 ± 4.33^{A}	309.67 ± 10.20^{A}	0.749 NS
	TG	285.31 ± 23.15^{A}	317.91 ± 11.29^{A}	0.590 NS
	GG	313.35 ± 9.68^{A}	309.27 ± 11.26^{A}	1.0 NS

DISCUSSION

Among endocrine tumors, thyroid carcinoma has the highest incidence rate, in which many factors, including oncogenes, tumor suppressor genes, biochemical factors, and growth factors, affect thyroid growth (29). Thyroid cancer rates are rising slowly but steadily everywhere in the globe. Researchers have zeroed in on potential causes of this malignancy because of its growing incidence rate. Thyroid cancer has several risk factors, such as being older, being female, having a family history of the disease, or having a genetic mutation (30). The amount of thyroid hormones in the body is regulated, in part, by the polymorphism rs12917707 in the promoter region of the UMOD gene. This research aimed to examine rs12917707 polymorphism and biochemical variables in thyroid cancer patients with thyroid cancer.

Our present data show that men and women "in both the patient and control groups" saw a significant rise in their T3 hormone levels compared to their respective norms. According to several studies, the thyroid hormone T3 is linked to increased cancer cell proliferation (31). According to research published by Perri et al., this homerone boosts the expression of Cyclin D1, a key cell cycle regulator. T3 stimulates cyclin D1 expression through the TRb1 / Oct-1 complex, which resides in the cyclin D1 promoter region near the Octamer-1 transcription factor (31). In addition, Wang et al. found that T3 induced PDZK1 gene expression in TPC-1 cells, which resulted in increased cell proliferation of papillary thyroid cancer cells, which was subsequently suppressed by silencing PDZK1 (8). When comparing the patient group to the control group, T4 levels were considerably higher in the former. This was also true when comparing the female and male patient and control groups. Multiple cancer cell lines respond favorably to T4, a thyroid hormone, by multiplying. Receptors in the extracellular domain of v3 integrin are required for T4 action at the cell surface (32). Cancer cells with elevated integrin expression promote increased endothelial cell and platelet proliferation, making t4 a driving force in both tumor development and progression and in the coagulation and blood clotting processes that characterize cancer metastasis (11). Serum TSH levels were significantly higher in the sick group than in the control group. There was a significant difference in serum TSH levels between the sexes within each group. Different types of thyroid cancer, including papillary and follicular tumors, respond to pituitary TSH and proliferate as a result. It is usual practice to suppress this hormone using exogenous thyroxine to manage these malignancies. Different types of thyroid cancer respond to TSH because it activates a protein-coupled receptor (GPCR) found only in G cells (11). T4 and TSH hormones were shown to be independently linked with disease-specific survival in another investigation of a similar cohort of patients with differentiated thyroid cancer (33). It may be concluded from the current research that an increase in T3, T4, and TSH hormones plays a role in the formation of thyroid cancer and that the pace of cancer advancement and the total quantity of this disease can be slowed or stopped by suppressing these hormones. Thyroid cancer screening factors may be useful biomarkers. The blood vitamin D levels of both the control and patient groups were found to be substantially lower than those of the control group. The amounts of this vitamin were also shown to be significantly lower between the sexes in this investigation. This means that the treatment was different for the sick group than the control group. Clone, breast, prostate, and pancreatic cancer are some malignancies linked to low vitamin D levels (30). Cell differentiation and proliferation benefit from vitamin D. (30). Davis states that vitamin D, receptors, and metabolites play a significant role in tumor initiation, progression, and prognosis. Studies have shown that high blood vitamin D levels may protect against thyroid cancer (30). The research conducted by Zhao et al. Thyroid cancer risk was also elevated in those with low blood vitamin D levels, according to a meta-analysis (30). "In contrast, no statistically significant differences were found between the patient and control groups in the WBC, HGB, RBC, or PLT analysis". No such differences were found when comparing the sexes within each group. These findings suggest that thyroid cancer does not alter white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), or platelet (PLT) counts.

Platelet count studies in several human malignancies show that the amount of PLT considerably decreases in epithelial ovarian and lung tumors but shows no change in breast and colon cancers (34). Platelets' ability to produce and secrete vascular endothelial growth factor (VEGF) boosts tumour angiogenesis and metastasis. Some malignancies have a significantly increased risk of recurrence and metastasis when a patient has an abnormally high platelet count (34). These findings are consistent with those of previous research by Dincel and colleagues (34), which found no statistically significant difference in PLT levels between papillary thyroid cancer patients. Contrary to the findings of the current study, it was reported in another study that the ratio of neutrophils to lymphocytes is positively correlated with the ratio of platelets to lymphocytes and the number of white blood cells, all of which serve as prognostic markers of thyroid cancer and thyroiditis. Reports also show that the quantity of thyroglobulin is connected to the number of white blood cells and that a higher thyroglobulin level is associated with a worse chance of survival for those with thyroid cancer (35). According to the research done on RBC and HGB, no studies were conducted. The frequency of the TT mutant genotype in the sick group (40%) was substantially higher than in the control group (6%), and the rate of the wild GG genotype in the control group (68%), according to studies of the rs12917707 polymorphism in humans' genes. exceeds the percentage found in the patient group by a wide margin (29%). The frequency of the mutant T allele was found to be 55% higher in the patient group compared to the control group's 19%, while the frequency of the wild G allele “was found to be 45% higher in the patient group compared to the control group's 12%. A larger percentage of people (81%) are in the control group than the ill group (45%). Current findings support a causal relationship between rs12917707 polymorphism and thyroid cancer”. In light of the lack of previous research linking this polymorphism to cancer, ours is the first study of its kind. Diabetes, CKD, and eGFR have been the primary foci of research into this polymorphism (eGFR). In particular, the rs12917707 variation in the UMOD promoter region has been demonstrated to influence the production of this gene, resulting in a lower basal GFR, according to studies of this polymorphism. This polymorphism has been linked to renal disease and failure (36,40). Dinic et al. analyzed the rans12917707 variation in severe, stable, and control groups of Caucasian patients with IgA nephropathy (IgAN). As far as they could tell, there was no discernible difference between the three groups regarding the allele/genotype ratio. Studies comparing the rs12917707 genotypes of healthy people and patients with severe IgAN found no significant difference, indicating that this gene is unlikely to have a role in the etiology of IgAN. Consequently, no significant findings were reported in their data (37). According to GWAS results, the influence of the UMOD polymorphism on SCr increased with both age and the presence of comorbidities (such as hypertension, diabetes, atherosclerosis, and heart failure) (37,43). Furthermore, rs12917707 polymorphism was substantially linked with CKD and eGFR in an analysis of 2388 CKD patients and 17489 non-CKD controls and a secondary analysis of 1932 CKD patients and 19534 controls of European ancestry (38,41). “Serum levels of T3, T4, and TSH were shown to be considerably elevated in the patient group compared to the control group and more in patients with the mutant TT genotype compared to patients with a greater frequency of the wild GG genotype”. Since this research demonstrated a correlation between the TT genotype's prevalence and illness incidence, the TT genotype carries a greater risk than the other genotypes. TSH levels were shown to be unrelated to uromodulin excretion in this investigation, which contradicted a prior study (39,42).

In a study examining the link between this polymorphism and low vitamin D levels, researchers found no statistically significant association between the two, leading researchers to conclude that patients with the mutant TT genotype were more likely to experience a decrease in vitamin D levels than those with the Wild GG genotype. “No significant difference was seen between the patient and control groups when this polymorphism was compared to the other parameters investigated” (WBC, HGB, RBC, PLT). These findings support the hypothesis that the TT genotype is a risk factor for the illness via altering blood levels of the hormones T3, T4, and TSH and the quantity of vitamins.

CONCLUSION

TT genotype and T allele rs12917707 polymorphism are essential genetic factors in regulating serum levels of thyroid hormones and vitamin D, and all of these factors interact with each other to increase the susceptibility to thyroid cancer. Therefore, studying these biochemical and genetic factors can be essential biomarkers for early Thyroid cancer testing and therapy.

REFERENCES

1. Romei C, Ciampi R, Elisei R. A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nature Reviews Endocrinology. 2016;12(4):192.
2. Figlioli G, Landi S, Romei C, Elisei R, Gemignani F. Medullary thyroid carcinoma (MTC) and RET proto-oncogene: mutation spectrum in the familial cases and a meta-analysis of studies on the sporadic form. Mutation Research/Reviews in Mutation Research. 2013;752(1):36-44.
3. Sipos J, Mazzaferri EL. Thyroid cancer epidemiology and prognostic variables. Clinical oncology. 2010;22(6):395-404.
4. Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. A systematic review of trends in the incidence rates of thyroid cancer. Thyroid. 2016;26(11):1541-52.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin. 2018;68(6):394-424.
6. Liu F, Zhu Y, Qian Y, Zhao Y, Zhao X, Zhang J, et al. Effects of gold nanorods modified with anti-epidermal growth factor receptor monoclonal antibody on laryngeal cancer cells. Turkish Journal of Biology. 2018;42(2):144-51.
7. Foster JR, Tinwell H, Melching-Kollmuss S. A review of species differences in the control of, and response to, chemical-induced thyroid hormone perturbations leading to thyroid cancer. Archives of Toxicology. 2021;95(3):807-36.
8. Wang Y, Cheng Y, Sun R, Lang J, Yang L, Zhao D. T3 Up-Regulates PDZK1 to Promote the Proliferation of Papillary Thyroid Cancer Cells. 2021.
9. Davis PJ, Goglia F, Leonard JL. Nongenomic actions of thyroid hormone. Nature Reviews Endocrinology. 2016;12(2):111-21.
10. Mousa SA, Glinsky GV, Lin H-Y, Ashur-Fabian O, Hercbergs A, Keating KA, et al. Contributions of thyroid hormone to cancer metastasis. Biomedicines. 2018;6(3):89.
11. Mousa SA, Hercbergs A, Lin H-Y, Keating KA, Davis PJ. Actions of Thyroid Hormones on Thyroid Cancers. Frontiers in Endocrinology. 2021;12.
12. Akpinar I, Sayin MR, Gursoy YC, Aktop Z, Karabag T, Kucuk E, et al. Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon. Journal of cardiology. 2014;63(2):112-8.
13. Oncel M, Kiyici A, Oncel M, Sunam GS, Sahin E, Adam B. Evaluation of platelet indices in lung cancer patients. Asian Pacific Journal of Cancer Prevention. 2015;16(17):7599-602.
14. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence, 1973–2002. Cancer causes & control. 2009;20(5):525-31.
15. Navarro Silvera SA, Miller AB, Rohan TE. Risk factors for thyroid cancer: a prospective cohort study. International journal of cancer. 2005;116(3):433-8.
16. Liu Y, Su L, Xiao H. Review of factors related to the thyroid cancer epidemic. International journal of endocrinology. 2017;2017.
17. Gonzalez FJ. Genetic polymorphism and cancer susceptibility: fourteenth Sapporo Cancer Seminar. AACR; 1995.

18. Stracquadanio G, Wang X, Wallace MD, Grawenda AM, Zhang P, Hewitt J, et al. The importance of p53 pathway genetics in inherited and somatic cancer genomes. Nature reviews cancer. 2016;16(4):251-65.
19. Sanchez E, Küpfer E, Goedbloed DJ, Nolte AW, Lüddecke T, Schulz S, et al. Morphological and transcriptomic analyses reveal three discrete primary stages of postembryonic development in the common fire salamander, Salamandra salamandra. Journal of Experimental Zoology Part B: Molecular and Developmental Evolution. 2018;330(2):96-108.
20. Page RB, Monaghan JR, Walker JA, Voss SR. A model of transcriptional and morphological changes during thyroid hormone-induced metamorphosis of the axolotl. General and comparative endocrinology. 2009;162(2):219-32.
21. Pennica D, Kohr WJ, Kuang W-J, Glaister D, Aggarwal BB, Chen EY, et al. Identification of human uromodulin as the Tamm-Horsfall urinary glycoprotein. Science. 1987;236(4797):83-8.
22. Yang H, Wu C, Zhao S, Guo J. Identification and characterization of D8C, a novel domain in liver-specific LZP, uromodulin and glycoprotein 2, mutated in familial juvenile hyperuricaemic nephropathy. FEBS letters. 2004;578(3):236-8.
23. Dahan K, Devuyst O, Smaers M, Vertommen D, Loute G, Poux J-M, et al. A cluster of *UMOD* gene mutations cause familial juvenile hyperuricemic nephropathy with abnormal expression of uromodulin. Journal of the American Society of Nephrology. 2003;14(11):2883-93.
24. DENG Z, JOHNSON K, ENGELWARD B, LANE S, CALLEN D, SAMSON L, et al., editors. NEW REGIONS OF CONSERVED SYNTENY AND LINKAGE BETWEEN HUMAN-CHROMOSOME 16P12-] P13 AND MOUSE CHROMOSOME-16 AND CHROMOSOME-11. CYTOGENETICS AND CELL GENETICS; 1995: KARGER ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
25. Lee Y-K, Lee DH, Noh J-W. Familial Juvenile Hyperuricemic Nephropathy and Uromodulin Gene Mutation. Journal of Genetic Medicine. 2013;10(1):7-12.
26. Abdel-Hady Algharably E, Beige J, Kreutz R, Bolbrinker J. Effect of *UMOD* genotype on long-term graft survival after kidney transplantation in patients treated with cyclosporine-based therapy. The pharmacogenomics journal. 2018;18(2):227-31.
27. Released IC. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. 2016.
28. Abramson JH. WINPEPI updated: computer programs for epidemiologists and their teaching potential. Epidemiologic Perspectives & Innovations. 2011;8(1):1-9.
29. Jameson JL. Disorders of the thyroid gland. Harrison's principles of internal medicine. 2005:2104-13.
30. Zhao J, Wang H, Zhang Z, Zhou X, Yao J, Zhang R, et al. Vitamin D deficiency as a risk factor for thyroid cancer: A meta-analysis of case-control studies. Nutrition. 2019;57:5-11.
31. Perri A, Catalano S, Bonofiglio D, Vizza D, Rovito D, Qi H, et al. T3 enhances thyroid cancer cell proliferation through TRβ1/Oct-1-mediated cyclin D1 activation. Molecular and Cellular Endocrinology. 2014;382(1):205-17.
32. Davis PJ, Lin H-Y, Hercbergs A, Mousa SA. Actions of l-thyroxine (T4) and tetraiodothyroacetic acid (tetrac) on gene expression in thyroid cancer cells. Genes. 2020;11(7):755.
33. Diessl S, Holzberger B, Mäder U, Grelle I, Smit JW, Buck AK, et al. Impact of moderate vs stringent TSH suppression on advanced differentiated thyroid carcinoma survival. Clinical endocrinology. 2012;76(4):586-92.
34. Dincel O, Bayraktar C. Evaluation of platelet indices as a useful marker in papillary thyroid carcinoma. Bratislavske lekarske listy. 2017;118(3):153-5.
35. Song SS, Huang S, Park S. Association of polygenetic risk scores related to cell differentiation and inflammation with thyroid cancer risk and genetic interaction with dietary intake. Cancers. 2021;13(7):1510.

36. Prudente S, Di Paola R, Copetti M, Lucchesi D, Lamacchia O, Pezzilli S, et al. The rs12917707 polymorphism at the *UMOD* locus and glomerular filtration rate in individuals with type 2 diabetes: evidence of heterogeneity across two different European populations. Nephrology Dialysis Transplantation. 2017;32(10):1718-22.
37. Dinic M, Ghisdal L, Racapé J, Thibaudin L, Gatault P, Essig M, et al. *UMOD* polymorphism rs12917707 is not associated with severe or stable IgA nephropathy in a large Caucasian cohort. BMC nephrology. 2014;15(1):1-6.
38. Cañadas-Garre M, Anderson K, McGoldrick J, Maxwell A, McKnight A. Genomic approaches in the search for molecular biomarkers in chronic kidney disease. Journal of translational medicine. 2018;16(1):1-44.
39. Troyanov S, Delmas-Frenette C, Bollée G, Youhanna S, Bruat V, Awadalla P, Devuyst O, Madore F. Clinical, Genetic, and Urinary Factors Associated with Uromodulin Excretion. Clin J Am Soc Nephrol. 2016 Jan 7;11(1):62-9. doi: 10.2215/CJN.04770415. Epub 2015 Dec 18. PMID: 26683887; PMCID: PMC4702232
40. Kanval, N., Ihsan, H., Irum, S., & Ambreen, I. (2024). Human Capital Formation, Foreign Direct Investment Inflows, and Economic Growth: A Way Forward to Achieve Sustainable Development. Journal of Management Practices, Humanities and Social Sciences, 8(3), 48-61.
41. Rashid, A., Jehan, Z., & Kanval, N. (2023). External Shocks, Stock Market Volatility, and Macroeconomic Performance: An Empirical Evidence from Pakistan. Journal of Economic Cooperation & Development, 44(2), 1-26.
42. Jam, F. A., Mehmood, S., & Ahmad, Z. (2013). Time series model to forecast area of mangoes from Pakistan: An application of univariate ARIMA model. *Acad. Contemp. Res*, *2*, 10-15.
43. Jam, F. A., Rauf, A. S., Husnain, I., Bilal, H. Z., Yasir, A., & Mashood, M. (2014). Identify factors affecting the management of political behavior among bank staff. *African Journal of Business Management*, *5*(23), 9896-9904.