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Assessment of Thyroid Peroxidase TPO Gene *(rs732609)* Polymorphism in Papillary Thyroid Cancer in Al -Diwaniyah province.

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Abstract

Background Approximately 80% of all instances of thyroid cancer are papillary, also known as PTC, thyroid carcinomas. It is influenced by both genetic and environmental factors and makes up the great majority of thyroid cancer cases.

Objectives explore the potential link between papillary thyroid cancer (PTC) and rs732609, a polymorphism in the thyroid peroxidase gene, as a potential risk factor .

Methods: There were 52 patients with PTC and 48 healthy controls in the research. Using T-ARMS-PCR, researchers in Al-Diwaniyah Governorate identified and genotyped TPO (rs732609) A/C in both healthy control samples and patients to investigate the potential link between TPO and PTC susceptibility.

Results Product Finish Based on the research, TPO (*rs732609*) as a risk factor enhanced PTC. According to multiple genetic models, that the homozygous CC genotype increased the risk of The risk of disease development is almost three times higher for PTC in the testes compared to other genotypes.was associated with an insignificant risk (OR=2.84), while the presence of both the A and C genotypes was associated with a substantial risk (OR= 1.83).A complex interplay of genes influenced the likelihood of PTCs.

Conclusion. There was clear evidence that the TPO (*rs732609*) polymorphism, influenced by age, gender, was linked to an increased risk of PTC in the Al-Diwaniyah Governorate.

Keywords: papillary thyroid carcinoma (PTC), TPO *(rs732609)*, risk factor.

Introduction

Thyroid cancer is outpacing all other malignancies in terms of annual growth rate, surpassing even leukemia, pancreatic cancer, stomach cancer, and liver cancer combined. These papillary event cases are often small and localized. Those who are diagnosed with these small, locally localized papillary thyroid tumours have a 99% chance of being alive after 20 years (Liao et al., 2023). Several of these tumours can be treated with thyrotropin suppression medication or radioactive iodine ablation. Research has shown that these

treatments are beneficial for more advanced thyroid tumours (Fridman et al., 2012), however here are some general conclusions. Cancers affecting women between the ages of 33 and 70 are quite common, and the prevalence of thyroid cancer in women is around three times faster than in males. Differentiated thyroid cancer (DTC) was found to be substantially more common among those older than 55 years (HR 1.78). Additionally, with great survival rates and a very young average age at diagnosis, PTC is a secondary cancer in women with thyroid cancer. The development of a PTC is a common complication for women with thyroid cancer (Sonnefeld et al., 2020). The rate of thyroid cancer in females is approximately three times greater than in males (Figge et al., 2016). Recent years have seen a gradual accumulation of evidence suggesting genetic factors had a significant impact in the development of PTC. Using genome-wide association studies (GWAS), Jin et al. (2021) discovered several SNPs in the PTC locus and other variable genes that enhance vulnerability. Thyroid follicular cells all have the TPO gene on their surface. This gene specifies a protein-containing heme that is connected to the cell membrane. It plays a crucial role in the synthesis of thyroid hormones by facilitating the following reactions: the process whereby iodide is oxidized in thyroid cells by means of hydrogen peroxide, attached to tyrosine residues in thyroglobulin (TG) to create iodothyronine (iodide ramification), and finally coupled with certain of these hormonally inert iodotryrosine residues, specifically mono iodotryrosine and di iodotyrosine, to generate the active iodothyronine, thyroxine (T4), and tri iodothyronine (T3) (van der Vliet ,2023). The TPO gene contains the instructions for making enzymes that the body needs to make thyroid hormones. Metabolism, development, and growth are all regulated by thyroid hormones (Liu et al., 2020). Some thyroid disorders, including autoimmune thyroiditis, congenital hypothyroidism, and papillary thyroid cancer, can be caused by mutations in the TPO gene. (Naqvi et al., 2023). Researchers have focused a lot of attention on the ratios of different SNPs in the (TPO). A favorable association has also been demonstrated by numerous studies. The results indicate that the most frequent type of thyroid cancer is papillary thyroid carcinoma (PTC).. Thinking about the co-dominant mode changed the frequency distribution dramatically. Differences in genotype between the experimental and control groups ($p = 0.044$). The following genotypes are present: homozygous TT (OR=4.03) and heterozygous C/T. were identified as significant risk factors in the risk investigation (OR= 2.09). Because of this, those who possess the homozygous TT genotype are approximately four times more likely to acquire a disease compared to those who do not. Using studies in dominant and recessive modes, we discovered a statistically significant difference between the control and patient groups ($p > 0.05$). The Kazakh population study linked the risk of papillary thyroid cancer susceptibility candidate gene 2 (PTCSC2) at locus rs965513 to an increased risk of papillary thyroid cancer (PTC). (Mussazhanova et al., 2020). It was in research of Chinese population that Shen discovered the TPO rs2048722, PTCSC2 rs925489, and SEMA4G rs4919510 polymorphisms were linked to THCA risk. Gender, age, smoking status, and alcohol consumption were among other factors.

Method

Study design and sample

The case control study comprises 100 blood samples obtained between September 2023 and January 2024. Of these, 52 were drawn from patients with thyroid cancer, and 48 were drawn from healthy individuals who did not have any chronic diseases, thyroid nodules, or thyroid hormone disorders. This brings the total number of blood samples collected to 100. Blood samples were taken from individuals diagnosed with papillary thyroid carcinoma following their diagnosis by specialist oncologists at AlDiwaniyah Teaching

Hospital (Oncology Consultation) / Al-Diwaniyah Governorate. Demographic information was collected on each participant after obtaining the initial approvals from the Al-Diwaniyah Health Directorate and the patients' assent. The current study is Molecular part. Genetic polymorphism was performed for the TPO gene (rs732609) A/C variation using Tetra- ARMS- PCR Method, which carried out a particular set of primers.5 ml of venous blood was drawn from a control group and patients with cancer and papillary cancer from Al-Diwaniyah Teaching Hospital from October 2023 until February 2023 in 2024 AD. Their ages were (33-75) years. 2 ml was placed in tubes containing the anti-seizure substance EDTA to conduct the genetic aspect of the study; it was stored at a temperature of (-20) until a decision was made.

Genomic DNA Extraction

Following the extraction of genomic DNA from blood samples by the manufacturer's instructions, the Gene aid's gSYAN extraction of DNA kit for frozen blood, USA, was used for genomic DNA estimate DNA purity test was used to quantify the DNA concentration in the blood. The test was evaluated by reading the readout at 260 and 280 nanometers by means of a Nanodrop spectrophotometer (THERMO. USA). The T-ARMS-PCR method detected and genotype the TPO (rs2048722) C/T gene polymorphism in both patient and healthy control samples. The production of the ARMS-PCR master mix Using the GoTaq® G2 Together with the Green Master Mix kit, we created a T-ARMS-PCR master mix. As per the instructions provided by the Manufacturer, we ran two reactions on each sample using this mix. PCR reaction mix using T-ARMS: The mentioned PCR master mix components were placed in an Exispin vortex centrifuge and spun at 3000 rpm for 3 minutes. Afterward, it was put into a PCR thermocycler (USA: BioRad). Examining T-ARMS-PCR End-Results The analysis of the T-ARMS-PCR products was carried out using agarose gel electrophoresis.

Statistical analysis

Data were statistically analyzed using version 26 of the Software for Social Science Statistics (SPSS), and the findings were presented afterward. Will, the qualitative The numbers and percentages were used to represent the variables, and the mean ± standard deviation (SD) was used for all variables that were normally distributed. The following paragraphs illustrate the statistical test that was used: 1- To estimate the relationship between any two variables in which they were categorical, use the Two-part chi-square test for estimating the dissimilarity in means between any two customarily distributed variables use the independent samples t-test, While the ANOVA test was used for comparing differences in mean between three or more groups. At a P-value of equal or less than 0.05, the level of significance was determined Furthermore, after accounting for age and sex, the odds ratio (OR) and 95% confidence interval (95% CI) were used to estimate the risk of PTC linked to the candidate SNP polymorphism and the serum hormones (TSH, T4.T3), once both significant and non-significant covariates had been eliminated.

Result

Characteristics of the study population

In this research, 52 individuals diagnosed with papillary thyroid carcinoma and 48 healthy individuals served as controls. (Table 1) shows the demographics of both the patients and the participants in the control group. According to age, the mean age of patients with papillary thyroid cancer was 49.40 ± 8.80 years old and that of control subjects was 47.20 ± 12.62 years old and there was no significant difference between both

groups (P = 0.313). Regarding to gender, in overall, 19 (17.0%) male and 81 (81.0%) female were included. Patients with papillary thyroid cancer included 7 (13.5 %) cases were male gender and 45 (86.5%) cases were female, while control subjects included 12 (25.0 %) cases were male gender The gender distribution of patients and control subjects did not differ significantly (P = 0.142), with 36 (75.0%) cases being female.

Detection of Genes Polymorphisms

The distribution data of TPO (rs732609) A/C Genotypes AC, CC, and AA may each be located here. examination of the TPO (rs732609) A/C gene polymorphism using T-ARMS-PCR products. M stands for marker, which ranges from 2000 to 100 base pairs. At the 181-bp T-ARMS-PCR product, the AA wild type homozygote displayed just the A allele. The 205bp T- ARMS-PCR result demonstrated that the lane (CC) mutant type homozygote had just the C allele, but the lane (AC) heterozygote had both the A and C alleles, as seen at 181bp and 205bp, respectively. The 330 bp mark indicated the outer internal control. The product of T-ARMS-PCR.

Table (1): *TPO (rs732609) A/C* POLY genotype frequency in patients and control.

Mode	*TPO (rs732609)*	Patients *n* = 52	control *n* = 48	*P*	OR	95% CI
Codominant	CC	11 (21.2%)	5 (10.4 %)	0.146 ¥ NS	2.84	0.86-9.28
	A/C	17 (32.7%)	12 (25.0 %)		1.83	0.73- 4.55
	AA	24 (46.2 %)	31 (64.6 %)		Re ference	
Dominant	CC+ A/C	28 (53.8 %)	17 (35.4 %)	0.064 ¥ NS	Re ference	
	AA	24 (46.2 %)	31 (64.6 %)		0.47	0.21-1.05
Recessive	CC	11 (21.2%)	5 (10.4 %)	0.143 ¥ NS	2.31	0.73-7.21
	A/C +AA	41 (78.8%)	43 (89.6%)		Re ference	
Alleles	C	39 (37.5%)	22 (22.9%)	0.025 ¥ S	2.01	1.08-3.75
	A	65 (62.5%)	74 (77.8%)		Reference	

¥: Chi-square test; S: significant at $P > 0.05$; NS: not significant at P > 0.05

Table 1 shows the results of applying the Hardy-Weinberg equation to the TPO (rs732609) A/C genotypes, as well as the distributions of AA, AC, and CC within the control group. In the control group, 31 out of 48 individuals had the wild AA genotype, 12 had the AC genotype, and 1 had the mutant CC genotype (table 3.19). (P = 0.129) There was no statistically significant difference between the predicted and observed distributions of control subjects' TPO (rs732609) A/C genotypes. Table 2 displays the results of a genotype/allele frequency comparison between patients and healthy controls with respect to

the TPO (rs732609) A/C SNP (2). With respect to the co-dominant mode,

The frequency distribution of genotypes differed significantly (p = 0.146) between the control group and the patients. Based on the results of the risk study, it was shown that the homozygous CC genotype did not pose a substantial risk (OR=2.84), but the heterozygous A/C genotype did (OR= 1.83). This indicates that compared to patients with other genotypes, those with a homozygous CC genotype have a roughly threefold increased risk of developing illness. There was no significant difference ($p<0.05$) between the control and sick groups when it came to the dominant and recessive mode analyses. However, when looking at the allele analysis, the control group and the patients were significantly different (P= 0.025). Therefore, the same SNPs may be linked to lower risks in one nation and higher ones in another. There may be moderate-penetrant alleles for PTC, since the risk of PTC is five times higher in first-degree relatives of PTC patients compared to the general population, which is in line with this theory.

Table (2): Hardy Weinberg equation

Genotypes	Observed	Expected	χ^2	*P*
Homozygote reference AA	31	28.5	5.498	0.129 ¥ NS
Heterozygote AC	12	17.0		
Homozygote variant CC	5	2.5		

¥: Chi-square test; NS: Non-significant at $P < 0.05$

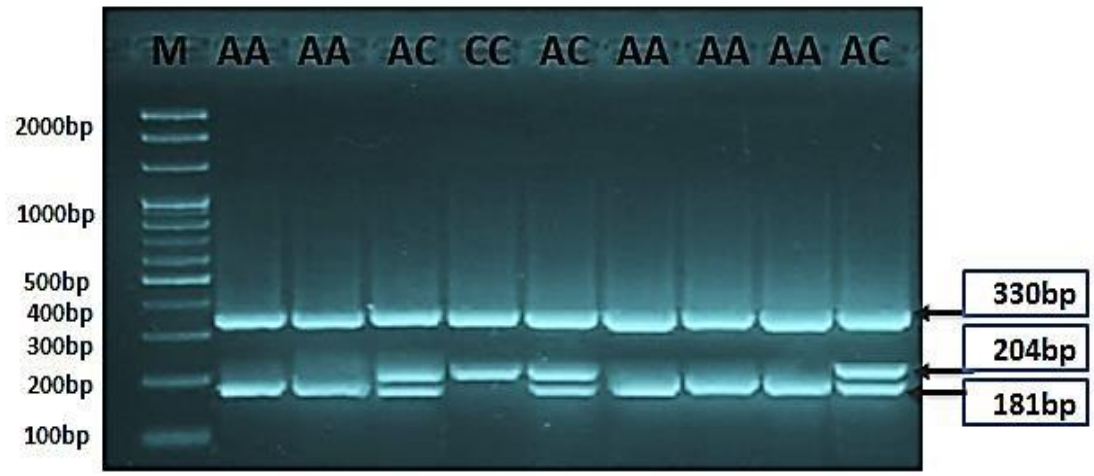

Figure (1): The image displayed an agarose gel electrophoresis of the T-ARMS-PCR product, which was used to analyses the TPO (rs732609) A/C gene polymorphism. M stands for marker, which ranges from 2000 to 100 base pairs. At the 181-bp T-ARMS-PCR product, the AA wild type homozygote displayed just the A allele. The 205bp T-ARMS-PCR result demonstrated that the lane (CC) mutant type homozygote had just the C allele, but the lane (AC) heterozygote had both the A and C alleles, as seen at 181bp and 205bp, respectively. The 330 bp mark indicated the outer internal control. The product of T-ARMS-PCR

Discussion

Papillary thyroid carcinoma (THCA) is one of the most common forms of thyroid cancer and affects individuals globally. as shown in the table, the age group of adults over 50 years old comprises the biggest percentage (46.2%) of the patients, according to the present findings regarding the demographic features of the study group shown in table (1) This corresponds to the findings of Chereau et al. (2016), which demonstrated that papillary thyroid cancer (PTC) is more common in older patients, particularly those over the age of 50. It also agrees with the findings of Dies et al. (2022) regarding patients diagnosed with papillary carcinoma of the thyroid with advanced-stage disease (III/IV) who are 55 years of age or older. Stage III/IV indicates that the cancer has spread to other sensitive areas of the body, like the lungs and bones, or that there is spasm in the external tissues, including the large blood vessels. Worldwide, the incidence rates of thyroid cancer have been steadily rising for decades, with a greater increase in papillary carcinomas compared to other forms and a higher increase in females than males. The causes of the rising incidence and gender disparities in thyroid cancer are unclear, and the only known risk factor is female gender (Briseis et al., 2009).

There were 45 females (86.5% of the total) and 7 males (13.5%) among the patients with papillary thyroid carcinoma in the present study's demographic analysis. The results of this investigation agreed with Kilfoy's It has been suggested that the gender difference in papillary thyroid cancer may be attributed to the fact that a woman's sex Her hormone levels change when she is pregnant and during her menstrual cycle. The majority of women reach or enter menopause between the ages of 40 and 49, which also happens to be the peak incidence of papillary thyroid cancer in this age group (Kilfoy et al., 2009). It is well-established that sex hormones are significant carcinogens for breast and prostate cancers. By regulating the actions of sex hormones, especially estrogen, hormone-specific nuclear receptors regulate gene expression and the biology of tumor cells Higa et al., (2013).

The α- and β-estrogen receptors, which regulate the effects of estrogen, are expressed in papillary thyroid cancer (Lorenz., 2020). Polymorphisms in estrogen receptors may be a risk factor for thyroid cancer, as stated by Jamshidi et al. (2021). According to Yao et al. (2011), oestrogen has the ability to significantly speed up the proliferation of thyroid cancer cell lines, in contrast to male sex hormones. It changes the expression of oestrogen receptor subtypes in thyroid cancer cell lines. According to Denaro et al. (2023) and Li et al. (2024), oestrogen has type-specific effects on thyroid cancer cell lines. In papillary thyroid cancer, the levels of oestrogen receptor-α are significantly elevated. Krashin et al. (2019) states that TPO is crucial for the manufacture of thyroid hormone. Catalysing iodide oxidation, TG iodination, and iodothyronine coupling, TPO is located in the apical membrane of thyroid follicular cells. Deficiency in thyroid hormone synthesis due to a permanent iodine organification defect is most commonly caused by mutations within TPO, according to numerous reports Shah et al., (2023).

This study found that many Iraqi individuals have similar genetic variations within the TPO that put them at risk for PTC. Prior research indicated that the TPO rs2048722 and rs732609 polymorphisms had a role in PTC, and this was corroborated by functional evidence demonstrating that the TPO enzyme was dysfunctional (Shen et al., 2023). The results of this study provide new evidence linking TPO and PTC, which has been supported by previous research that has focused on the significance of TPO polymorphisms

and found a strong correlation with disease development (Yu et al., 2023). Several SNPs in TPO are well-known. This is demonstrated by the findings. Here we examine the link between TC and variations in thyroid-specific genes. SNPs in the genes for thyroid hormone receptors, TC, and TG were linked to TC. In 2023, Tasnim et al. Congenital hypothyroidism is associated with TPO gene mutations, and there is some evidence that TPO may play a role in thyroid cancer Naqvi et al., (2023).

As a result, we used Tetra-ARMS-PCR to look for genetic variants in TPO (rs732609) that could be a marker for PTC susceptibility, and we chose TPO (rs732609) for our evaluation of genetic connections with PTC risk. Figure 3–20 shows the results of the study's analysis of the gene and allele frequencies of the TPO (rs732609) polymorphism in 52 patients with PTC and 48 healthy controls. There are statistically significant differences in the distribution of the genotype frequencies of TPO (rs732609) between the two groups (P= 0.044). These findings point to a link between the TPO (rs732609) polymorphism and a higher risk of PTC. This finding is in agreement with what Cipollini et al. (2023) demonstrated, namely, that the We observed relationships between the risk of DTC and the rs2048722 and rs732609 TPO polymorphisms in both the Italian and Spanish populations, when it comes to genotype frequencies. Additionally, the (rs732609) variant allele was present in both groups. For the Spanish population, we discovered a favorable one (dominant model; p-trend 5 0.026).

In a separate study, Cipollini et al. (2013) discovered that the case group had a greater frequency of the CC genotype and C allele of TPO (rs732609) compared to the control group. However, the difference in frequency was not statistically significant. Table 3-20 shows the genotype and allele frequencies of the TPO) SNP (rs732609) in comparison to the control group and the patients. Patients and controls differed significantly ($p > 0.05$) with respect to the co-dominant, dominant, and recessive modes. But the current findings demonstrated a very substantial correlation between a greater risk of PTC and the TPO (rs732609) variation C allele (OR= 2.67; 95% CI 1.38-5.17). A study conducted by Cipollini1 et al.
(2023) found a high risk of PTC with an odds ratio (OR) of 1.19, which is similar to the present data.

Ethical Approval

Ensuring compliance with all official regulations set by the University of AL-Qadisiyah and the Iraqi Ministry of Health, this work was also completed with the full informed consent and agreement of all patients.

Conclusions

In conclusion, our work showed a strong correlation between polymorphisms in the TPO gene and papillary thyroid cancer (PTC), namely in patients with the homozygous CC genotype of the TPO *(rs732609)* gene This suggests that the risk of disease development is around three times higher for patients with the homozygous cc genotype compared to people with other.

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