Original Article

The Association of Telomerase Reverse Transcriptase (TERT) Promoter Single Nucleotide Polymorphism (SNP) rs2853669 with Aggressive Features in Papillary Thyroid Cancer

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ABSTRACT

Objective: To detect the single nucleotide polymorphism rs2853669 in the telomerase reverse transcriptase promoter among patients' samples of papillary thyroid carcinoma and control samples, and then explore its correlation with specific clinicopathological parameters related to aggressive characteristics of papillary thyroid carcinoma.

Study Design: A retrospective study

Place and Duration of Study: This study was conducted at the Department of Pathology & Forensic Medicine, Faculty of Medicine, AL Anbar University, Ramadi Iraq and University of Baghdad, Baghdad, Iraq. from 1st June 2022 to 30th June 2023.

Methods: The samples collected were formalin-fixed paraffin-embedded tissue blocks from registered and stored cases of histologically proven papillary type thyroid carcinoma collected from the National Center for Education Laboratories, Medical City Campus - Baghdad and AL-Kimma private hospital. These tissue samples include 60 cases of papillary thyroid cancer and 15 cases of multinodular goiter. The telomerase reverse transcriptase promoter single nucleotide polymorphism rs2853669 was examined in 75 samples of papillary thyroid carcinoma and multinodular goiter, by real-time polymerase chain reaction subsequently correlating the findings with the clinicopathological features of papillary thyroid carcinoma, like age, sex, papillary thyroid carcinoma variants, size of the tumors, presence of capsules, multifocality, extrathyroid extension and lymph node metastasis.

Results: The rs2853669 A>G polymorphism was detected as AG genotype 40 (67%) the odd ratio was 1.111, p=0.0852 and confidence interval was (0.3658 to 3.3748), while GG genotype was evident in 14 of patients group (23%), the odd ratio was 0.687, P=0.567 and confidence interval was (0.1901 to 2.4864). The AA genotype was evident in 6/60 (10%), the odd ratio was 0.22, p=0.022, and the confidence interval was (0.0503 to 0.7956.), Allele study, the most frequent allele in the patients' group was G allele 68 (57%), with a p-value of 0.0852. Regarding the correlation with clinicopathological parameters, multifocality is present in 52% of cases, with a p-value =0.05

Conclusion: The rs2853669 polymorphism is present in high rate(67% of AG genotype, and 23% in GG genotype) in patients with papillary thyroid carcinoma , and correlates significantly with multifocality.

Key Words: Papillary thyroid carcinoma, Single nucleotide polymorphism, rs2853669, TERT promoter

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INTRODUCTION

Papillary thyroid carcinoma is the predominant form of thyroid carcinoma, constituting about 80% of instances.[1,2]

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The prevalence of papillary thyroid carcinoma (PTC), especially microcarcinoma, has risen due to the extensive use of ultrasonic examination.[3-5] The reported incidence of papillary carcinoma has more than quadrupled in several nations during the past fifty years.[6-8] Thyroid carcinoma in Iraq constitutes 1.7% Among recently identified neoplasms and 2.75% of female cancers, ranking second among the ten most prevalent tumors in females in the last Iraqi Cancer Registry.[9,10] Subtyping depends upon a mix of architectural characteristics, the existence or nonexistence of cytological features, and the magnitude

of the growth.[11] PTC typically exhibits an indolent nature and a favourable prognosis post-surgery, with 10-year survival rates for adults ranging from 92% to 98%.[12] However, a subset of PTC patients (5–10%) may progress to extremely severe metastatic malignancy.[13] Several risk factors indicate a poor prognosis, including male gender, advanced age, increased tumor size (≥4 cm), and gross extrathyroidal extension (ETE)[14], the existence of lymph node metastases measuring ≥3 cm and distant metastases.[15]

The TERT SNP, rs2853669 A>G, is situated in the promoter region of TERT. It impedes an ETS2 binding point situated adjacent to an Ebox. Research on rs2853669 indicated a significant association with decreased survival and elevated cancer risk in patients with hepatocellular carcinoma.[16]Numerous studies suggest that rs2853669 may influence cancer development in conjunction with certain TERT mutations.[17] It was reported that it could influence telomere length and telomerase activity.[18] A research by Rachakonda et al[19] indicated that, in patients with urothelial bladder cancer, TERT rs2853669 may be associated with survival, prognosis, and tumor recurrence. There is controversy about the role of TERT SNP role in different malignancies, our aim is to detect the frequency of TERT polymorphism among PTC samples and detect the correlation with aggressive features of PTC.

METHODS

This study represents a retrospective study, all samples collected were formalin-fixed paraffin-embedded tissue blocks that represent registered and stored cases of histologically proven papillary type thyroid carcinoma that were collected from the National Center for Education Laboratories, Medical City Campus - Baghdad and AL-Kimma private hospital-Baghdad/Iraq, from 1stJune2022 to 30thJune 2023.These tissue samples consist of 60 samples with a final diagnosis of papillary thyroid carcinoma (12males and 48 females), and 15 control tissue samples(1 male and 14 females) that represent samples with the final diagnosis of multinodular goiter. Inclusion criteria encompassed all cases with a final diagnosis of PTC, regardless of patient age or sex. Exclusion criteria involved papillary microcarcinoma variants, due to their typically low-risk clinical behaviour, as well as any samples that were damaged, inadequately preserved, or lacking complete clinical or pathological data were excluded. Several clinicopathological parameters that including sex, age (all ages included in the study), histopathologic types, size of tumor (maximum diameter), multifocal lesions, capsulation, lymph nodes metastasis and existence of extrathyroidal extension. Paraffin blocks were prepared for all cases, and slices were stained with haematoxylin and eosin (H and E). Subsequently, all slides were re-evaluated, and findings were recorded.

DNA extraction: By using Quick-DNA™ FFPE Kit [Catalog No. D3067-E (50 Preps.), Zymo Research Corporation D3067/ USA]. Deparaffinization was done by removing a trim (≤20µm thick) of a tissue sample of paraffin block that was transferred toa 1.5 ml microcentrifuge tube, then added400µl of deparaffinization solution to the sample. incubated at55ºc for 1minute, vortexed then the deparaffinization solution. Then tissue digestion through adding a mixture of (H2O45µl, 2X digestion Buffer45µl and Proteinase K10µL) then incubated at 55ºC overnight.DNA purification by adding 350µl of Genomic lysis buffer and mixed then added 135µl of isopropanol then mixed and centrifuged, transferred the supernatant to a zymo-spin II column in collection tube and centrifuged. added 400 µl of genomic DNA wash 1,700µl of genomic DNA wash 2 and 200µl of genomic DNA wash 2 subsequently and centrifuged after each step then transferred the content to a clean microcentrifuge tub and added ≥50µl of DNA elution buffer and incubation then centrifuged to elute the DNA

Molecular detection of TERT SNP rs2853669 A/G by real-time PCR: For TERT SNP rs2853669 A/G (ID:C-8773290-20,20X Assay Working, Thermo-Fisher Scientific / USA), Diluted the 40X Custom SNP Genotyping Assay to a 20X working stock solution. Vortexed and centrifuged the 20X Assay Working Stock. Completely homogenize TaqMan® Genotyping Master Mix by spinning the container. Resuspended the thawed frozen samples by vertexing, and then centrifuged the tubes briefly and calculatedthe overall number of reactions to be conducted for each assay. Calculated the total volume of each component required for each assay. We added (2X TaqMan® Master,20X Assay Working, DNA Sample Volume, and nuclease-free water) to a sterile, tube then transferred the mixture to the thermal cycler (Table 1).

The data was entered and analyzed through SPSS-29. The significance of the disparity between various means (quantitative data) was assessed utilizing the Student's t-test for the difference between two independent means or the ANOVA test for differences among more than two independent means. The importance of the variance across various percentages (qualitative data) was assessed using the Pearson Chi-square test(χ^2-test), using Yate's adjustment or the Fisher Exact test where appropriate. Statistical significance was deemed present when the P value was less than or equal to 0.05.

RESULTS

According to Hardy Weinberg equilibrium, the patient's group was 10.15, P-value=0.005. Genotyping study: the majority were AG genotyping 40 out of 60 of the patient's group (67%) and in 6 samples out of 15 (33%)

in the control group, the odd ratio was 1.111, p-value =0.0852 and confidence interval was (0.3658 to 3.3748), while GG genotype was evident in 14 samples out of 60 of patient group, (23%), the odd ratio was 0.687, P value = 0.567 and confidence interval was (0.1901 to 2.4864). The AA genotype was evident in 6 samples out of 60 (10%), the odd ratio was 0.22, p-value = 0.022, and confidence interval was (0.0503 to 0.7956). The major allele in the patients' group was G allele 68 (57%) and in the control group 14 (47%), the minor allele in the study was A 52 (43%), and in the control group16 (53%). Odd ratio 0.6691 p-value = 0.326 and confidence interval 0.2997 to 1.4937 (Table2, Fig. 1).

Regarding clinicopathological parameters the mean age for the patient group was 46.6±14.0(23-85) years, regarding gender there were 47(78.3%) females and 13(21.7%) males (Table 3), classical variant was evident in 43/60 (71.7%) while follicular variant was evident in 16(26.7%)(PTC histological variant in Figure 2), infiltrative tumors was evident in 42(70%), regarding the size of tumors, the medium and large size in which the tumors more than 2cm were 35(58.3%) while tumors ≥4cm is only 6(10%), multifocal tumors were present in 30(50%), extra thyroid extension was established in only 3(5%), while LN metastasis was evident in 17(28.3%) [Table 4].

Among the correlation of TERT polymorphism with the clinicopathological parameter classical variant was more evident in AG and GG genotypes than the follicular variant 72%, and 64% respectively, regarding gender female gender was more evident in all genotypes, the infiltrative tumors was more evident in AG and GG genotype 67% and 86% respectively, multifocal tumors evident in AG and GG genotype in 52% and 50% while LN metastasis was evident in AG and GG in 27% and 36% (Table 5). Tumor size more than 2cm was in AG and GG 26/40(65%),7/14(50%) respectively (Tables 6-7).

The correlation between age and the presence of SNPis more evident with age groups 30-39 14/40 and 50-59 years 10/40 in AG genotype, 40-49 4/14 and 50-59-years 6/14, in GG genotype (Table 8, Fig. 3).

Table No.1: cycles of real-time PCR for detection of TERT polymorphism

Predesigned SNP		
Temperature	**Duration**	**Cycles**
95°C	10 minutes	HOLD
95°C	15 seconds	40
60°C	1 minute (scanning)	

Table 2: Detection of TERT polymorphism in patient and control groups

Genotype	Control	Patient	ODD	P-Value	C.I.
AA	5 (33%)	6 (10%)	0.22	0.022	0.0503 to 0.7956
AG	6 (40%)	40 (67%)	1.111	0.0852	0.3658 to 3.3748
GG	4 (27%)	14 (23%)	0.687	0.567	0.1901 to 2.4864
A	16 (53)	52 (43)	0.6691	0.326	0.2997 to 1.4937
G	14 (47)	68 (57)			

Table No.3: Age and genderparameters rates inPTC and control group

Parameter		Patients (n=60)		Controls (MNG) [n=15]		P value
		No.	%	No.	%	
Age (years)	<30	3	5.0	-	-	0.273
	30-39	19	31.7	4	26.7	
	40-49	12	20.0	7	46.7	
	50-59	18	30.0	3	20.0	
	60-69	3	5.0	1	6.7	
	≥70	5	8.3	-	-	
Gender	Male	13	21.7	2	13.3	0.535
	Female	47	78.3	13	86.7	

Table No.4: Clinicopathological parameters in 60 PTC samples

Parameter		No.	%
Type of PTC	Classical	43	71.7
	Follicular	16	26.7
	Sclerosing + Hobnail	1	1.7
Presence of capsule	Infiltrative	42	70.0
	Encapsulated	18	30.0
Size (cm)	Small	25	41.7
	Medium	18	30.0
	Large	17	28.3
Size (cm)	1.0---	11	18.3
	1.5	14	23.3
	2.0	13	21.7
	2.5	5	8.3
	3.0	6	10.0
	3.5	5	8.3
	4.0	6	10.0
Multiplicity	Unifocal	30	50.0
	Multifocal	30	50.0
Extra thyroid extension	Positive	3	5.0
	Negative	52	86.7
	Not identified	5	8.3
LN metastasis	Positive	17	28.3
	Negative	34	56.7
	Not identified	9	15.0

Table No.5: The correlation between clinicopathological parameters and TERT polymorphism

Clinicopathological Parameter	AA	AG	GG	P-value
Type of PTC				
Classical	3 (50%)	29(72.5%)	9(64.3%)	0.724
Follicular	3 (50%)	9(22.5%)	4(28.6%)	
Classical with poorly differentiated	-	2 (5%)	-	
Sclerosing + Hobnail PTC	-	-	1 (7.1%)	
Gender				

Female	5(83.3%)	30 (75%)	12(85.7%)	0.673
Male	1(16.7%)	10 (25%)	2 (14.3%)	
Presence of capsule				
Encapsulated	3 (50%)	13(32.5%)	2 (14.3%)	0.376
Infiltrative	3 (50%)	27(67.5%)	12 (85.7)	
Extra thyroid extension				
Positive	-	3 (7.5%)	-	0.454
Negative	6 (100%)	37(92.5%)	14 (100%)	
Multiplicity				
Multifocal	2(33.3%)	21(52.5%)	7 (50%)	0.05
Unifocal	4(66.7%)	19(47.5%)	7 (50%)	

Lymph Node metastasis				
Positive	1(16.6%)	11(27.5%)	5 (35.7%)	0.945
Negative	5(83.4%)	29(72.5%)	9 (64.3%)	

Table No.6: Correlation between the size of tumors (2 cm) and SNP presence

SNP	Size <2	Size ≥2	Total	P-value
AA	4 (66.7 %)	2(33.3 %)	6 (100%)	0.263
AG	14 (35%)	26 (65%)	40(100 %)	
GG	7 (50%)	7 (50.%)	14(100 %)	
Total	25(41.7 %)	35(58.3 %)	60100 %	

Table No.7: Correlation of size of tumor groups and TERTSNP

SNP	Size in cm							Total
	1-<1.5	1.5-<2	2-<2.5	2.5-<3	3-<3.5	3.5-<4	≥4	
AA	1 (16.7%)	3 (49.9%)	1 (16.7%)	-	-	-	1 (16.7%)	6 (100%)
AG	7 (17.5%)	7 (17.5%)	9 (22.5%)	4 (10%)	5 (12.5%)	4 (10%)	4 (10%)	40 (100%)
GG	3 (21.5%)	4 (28.6%)	3 (21.5%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	1 (7.1%)	14 (100%)
Total	11 (18.3%)	14 (23.3%)	13 (21.7%)	5 (8.3%)	6 (10%)	5 (8.3%)	6 (10%)	60 (100%)

P value = 0.46

Table No. 8: Correlation between the size of tumors and genotypes ofTERT SNP in PTC and control samples

Age (years)	AA		AG		GG	
	Patients	Controls	Patients	Controls	Patients	Controls
30-39	3 (13%)	2 (8.7%)	14 (60.87%)	2 (8.7%)	2 (8.7%)	-
40-49	1 (5.26%)	2 (10.53%)	7 (36.84%)	4 (21.05%)	4 (21.05%)	1 (5.26)
50-59	2 (9.52%)	1 (4.76%)	10 (47.62%)	-	6 (28.57%)	2 (9.25)
60-69	-	-	2 (50%)	-	1 (25%)	1 (25)
<30	-	-	2 (66.67%)	-	1(33.33%)	-
>70	-	-	5 (100%)	-	-	-

P value = 0.228

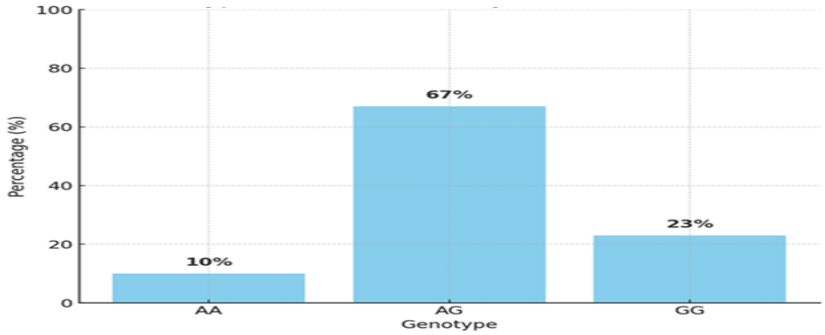

Figure No. 1: Percentage and distribution of SNP genotypes in PTC samples

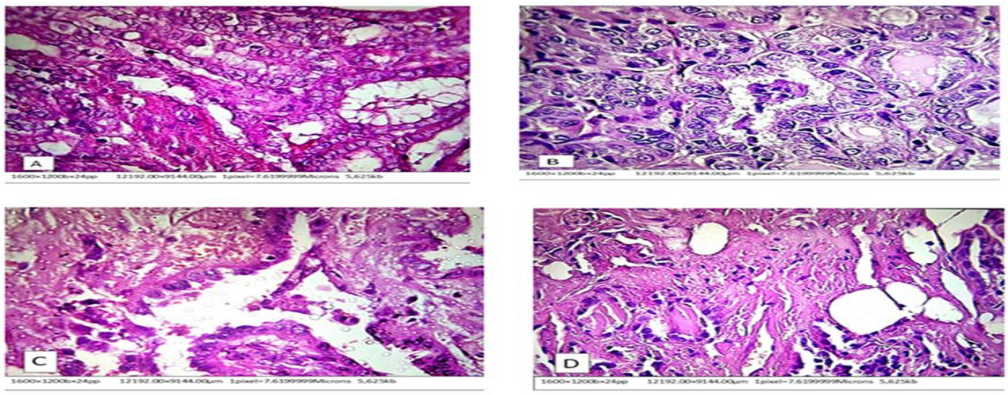

Figure No. 2: Variants of PTC. A: classical variant X400 B: follicular variant X400 C: hobnail variant X400, and D: sclerosing variant X100.(H &E stain)

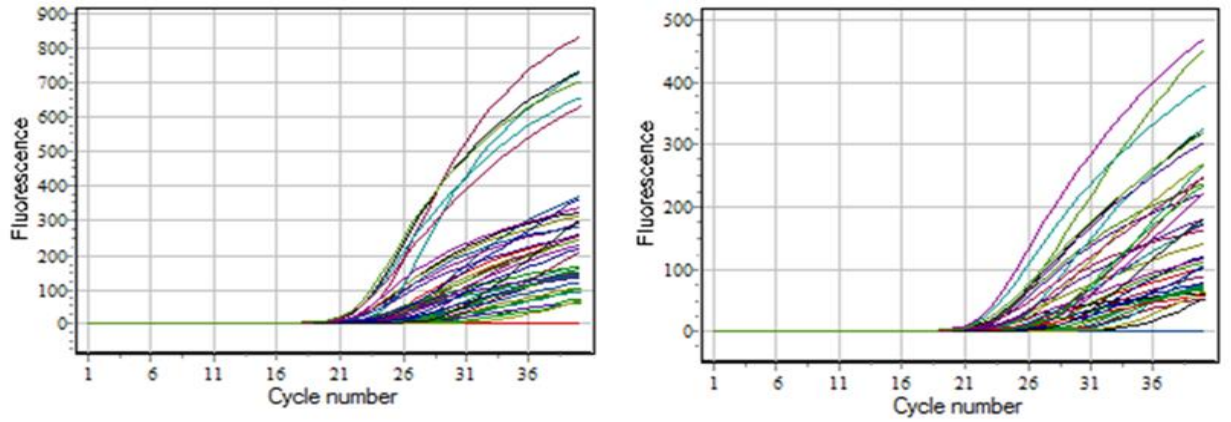

Figure No. 3: RT-PCR curves of the First allele (FAM channel), RT-PCR curves of the second allele (HEX channel)

DISCUSSION

Papillary thyroid carcinoma represents the most prevalent form of thyroid cancer. While most cases exhibit a favourable prognosis, some may be associated with aggressive behaviour. Numerous studies have identified a correlation between aggressive behaviour and various genetic alterations, particularly involving the TERT and BRAF genes. TERT polymorphism refers to variations in the TERT gene, while single nucleotide polymorphisms (SNPs) are variations occurring at single nucleotide locations within the genome. SNPs are categorized into two forms: coding SNPs and noncoding SNPs. Noncoding SNPs encompass regulatory, untranslated, intron, silent, and genomic SNPs. Regulatory SNPs (rSNPs) are located in noncoding regions, including promoters, enhancers, and the 3′ ends of genes(20).Some rSNPs may influence the expression of adjacent genes and the tumorigenesis or proliferation of certain carcinomas.[21]rs2853669 has been identified in some malignant neoplasms, including hepatocellular carcinomas[22], other neoplasms such as lung carcinomas and glioblastoma. A study revealed the conjunction of rs2853669 and C228T is substantially associated with increased tumor development in patients with PTC.[23]

Investigated in TERT rs2853669 SNP in Iraqi patients with Papillary thyroid carcinoma was 40 (67%)for heterozygous genotype AG and homozygous GG genotype 14(23%). The result showed that AG genotype may be a risk factor since odd ratio 1.111 but it is statistically not significant (CI=0.3658 to 3.3748, p-value=0.0852) While AA genotype odd ratio=0.22 that is mean it maybe protective factor that is confirmed by (CI=0.0503 to 0.7956, p vale=0.022) that mean is statistically significant. The G allele was found in 68 (57%) while the A allele was 52 (43%). A comparable result was observed in K. Vidinov et.al[24]in Bulgarian population they found that G allele frequency was 52.49%, homozygous GG genotype 5/18(27.7%)and heterozygousgenotype 13/18(72.3%), although the study done by Sanger sequencing, while in Tatsuya et al[23]the rate of genetic frequencies of rs3853669 was 58.6%. High variation in the percentage of genotypeslike AA in Tatsuya etal[25] 87.5%, thesevariations may related to differences in samples size, exclusion criteria, method of DNAextraction, detection method of polymorphism, and possible geographical difference in the pattern TERT promotor polymorphism. Regarding the clinicopathological parameters including gender, variant of PTC, size of tumors, presence of capsule, extra thyroid extension and LN metastasis, although some parameters shown an increasing rate with the TERT SNP presence but failed to establish statistically significant correlation except for multifocal tumors. While the finding that reported by Vidinov etal[24], all clinical parameters were statistically not significant.

CONCLUSION

The rs2853669 polymorphism is present at an increasing rate in PTC samples, in 67% in AG genotype, 23% in GG genotype, and correlates significantly with multifocality with P-value=0.05 while other parameters of tumor aggressiveness like large tumor size, lymph node metastasis and extra-thyroid extension shown no significant correlation with TERT SNP.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Wafaa Khalel Ibrahim, Khitam Razzak AL-Khafaji
Drafting or Revising Critically:	Wafaa Khalel Ibrahim, Khitam Razzak AL-Khafaji
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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