Evaluation of common genetic risk factors for differentiated thyroid cancer in the Thai population

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Abstract. Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy. This disease includes papillary and follicular thyroid tumors, and accounts for the majority of thyroid cancer cases. Although both genetic and environmental variables contribute to the genesis of DTC, specific genetic variants in the Thai population remain to be fully understood. The present case-control study aimed to investigate six single nucleotide polymorphisms (SNPs) associated with DTC susceptibility that had previously been described in genome-wide association studies; namely, rs944289, rs2439302, rs966423, rs116909374, rs1799782 and rs861539, and assess these within a Thai population. A total of 233 patients with histologically confirmed DTC (84.1% papillary, 12.9% follicular, 2.6% mixed and 0.4% Hürthle cell) and 176 control subjects with no history of thyroid disease were enrolled in the present study. Polymerase chain reaction-restriction fragment length polymorphism was used for genotyping. The results of the present study revealed that the six SNPs were not statistically significant (P<0.05) in the Thai population. Moreover, results of the sex-stratified analysis demonstrated that statistically significant associations were apparent between three SNPs in males; namely, SNPs rs2439302 (CC vs. CG genotype: OR, 3.325; P=0.024), rs966423 (CC vs. CT genotype: OR, 0.263; P=0.024; C vs. T allele: OR, 3.780; P=0.015) and rs1799782 (CC vs. CT genotype: OR, 0.194; P=0.046). Collectively, results of the present study may provide useful insights into the genetic diversity associated with cancer risk within the Thai population and highlight the requirement for sex stratification in genetic investigations of thyroid cancer.

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine malignancy worldwide, accounting for 6.59% of all cancers reported by the Siriraj Cancer Registry 2023 in Thailand (1-3). Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are the two most common subtypes, comprising 80-85 and 10-15% of cases, respectively. Notably, these diseases are generally associated with a positive prognosis (4). Poorly differentiated subtypes, though less common (5%), are associated with poor outcomes. Although the specific etiology of DTC is yet to be fully understood, genetic and environmental factors may play a key role in disease development (5,6), with childhood radiation exposure being a major environmental risk factor for PTC (7).

Recent advancements in genome-wide association studies (GWAS) have identified several genetic markers that may be associated with an increased risk of thyroid cancer, particularly DTC and PTC. Notably, single nucleotide polymorphisms (SNPs), such as rs944289, rs2439302, rs966423, rs116909374, rs1799782 and rs861539, have been implicated in these associations (8,9). The six aforementioned SNPs; namely, rs944289, rs2439302, rs966423, rs116909374, rs1799782 and rs861539, were selected based on their significant associations with an increased risk of DTC, particularly PTC, as previously demonstrated in multiple GWAS. These genetic variants are implicated in thyroid cancer predisposition across diverse populations, and are associated with disease susceptibility, tumor initiation and progression, and patient prognosis. Moreover, the aforementioned genetic variants may interact with key signaling pathways, including MAPK and PI3K signaling pathways, in addition to environmental factors, such as radiation exposure.

The SNP rs944289 is located near the *PTCSC3* gene region, and results of a previous study highlighted significant associations between this polymorphism and the pathogenesis of PTC. Its role in disease susceptibility was confirmed through various studies, highlighting the potential impact on PTC

risk across different populations (10,11). Moreover, the SNP rs2439302 is located in the *NRG1* gene region and demonstrates a clear association with thyroid cancer in Icelandic individuals. The results of previous studies revealed that this SNP may be associated with reduced *NRG1* expression (12,13). The SNP rs966423 has been identified as a potential risk factor for thyroid cancer; however, the specific mechanism remains poorly understood. This SNP may interact with other genetic markers to influence overall cancer susceptibility (11,14). The results of a previous study revealed that SNP rs116909374 exhibited potential as a risk factor for thyroid cancer in both Icelandic and non-Icelandic populations (15). In addition, polymorphisms in DNA repair genes; namely, *XRCC1* (rs1799782) and *XRCC3* (rs861539), may be associated with an increased risk of DTC development (11,16).

The present study aimed to assess the potential association of rs944289, rs2439302, rs966423, rs116909374, rs1799782 and rs861539 with the occurrence of DTC. Notably, the aforementioned SNPs are involved in pathways that impact tumor development and progression, highlighting their potential as targets for genetic testing. In addition, they may exhibit potential in the development of personalized treatment strategies for the management of thyroid cancer.

Materials and methods

Subjects. The present study was approved (approval no. Si 222/2018) by the Institutional Review Board at Faculty of Medicine Siriraj Hospital (Bangkok, Thailand). In total, 233 patients with DTC and 176 healthy subjects provided written informed consent prior to participation or the use of their specimens was approved by the ethics committee. Clinicopathological characteristics of patients (including sex and age distribution) are provided in Table II. Control participants were selected following screening of medical history questionnaires to exclude individuals with a personal history of thyroid disorders, thyroid-related symptoms, current use of thyroid medications, or family history of thyroid disorders in first-degree relatives. A retrospective chart review was carried out to obtain each patient's medical history, including pathological reports and all available radiological examinations. In total, 233 patients with DTC were treated at the Thyroid Clinic, Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Siriraj Hospital (Bangkok, Thailand) from May 2018 to April 2020. All patients with DTC were histologically confirmed as having the DTC subtype. All patients underwent total or near-total thyroidectomy, and at least one series of radioactive iodine ablation (30-200 mCi). Genomic DNA was extracted from peripheral blood using the 5 PRIME ArchivePure DNA Blood kit (5 PRIME, Inc.). DNA samples were used as templates in genotyping analysis.

Genotyping analysis. In total, six polymorphisms; namely, rs944289, rs2439302, rs966423, rs116909374, rs1799782 and rs861539, were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with a set of primers and restriction enzymes displayed in Table I. The primers used in the present study were designed in-house using Primer3 based on the target sequences obtained from UCSC Genome Browser. PCR was carried out in a 20 μl reaction containing 50 ng of genomic DNA, 0.2 mM of each primer, 0.2 mM dNTP mixture, 1.5 mM $MgCl_2$, 1X Taq buffer with $(NH_4)_2SO_4$, and 0.5 U Taq DNA polymerase (Thermo Fisher Scientific, Inc.). PCR conditions were as follows: Initial denaturation at 94˚C for 5 min; 35 cycles of 94˚C for 30 sec, 56˚C for 30 sec and 72˚C for 45 sec; followed by a final extension at 72˚C for 10 min. At least three samples per SNP were selected to confirm the accuracy of genotyping using direct sequencing of PCR products.

Statistical analysis. All statistical analyses were performed using SPSS Statistics (version, 29.0; IBM Corp.). Normal distribution was tested using a Kolmogorov-Smirnov test. Values with normal distribution were expressed as mean (SD) and non-normal distribution were expressed as median (25-75th percentiles). Genotypic distributions were examined for a significant departure from the Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit Chi-squared test. The potential association between genotype/allele and risk of DTC was assessed using Chi-squared or Fisher's exact tests according to the size of the study, and the results were expressed as odds ratios (OR) with a 95% confidence interval (CI). Adjusted ORs were calculated using binary logistic regression analysis with the primary outcome as the dependent variable. Age was included as a covariate to statistically control for its potential confounding effect on the outcome. $P<0.05$ was considered to indicate a statistically significant difference. Post-hoc power calculations using G*Power 3.1 software (17) were conducted to evaluate the adequacy of the sample size.

Results

Clinical findings. In total, 233 patients with DTC who were treated at the Thyroid Clinic were enrolled in the present study. Of these patients, 196 patients (84.1%) exhibited PTC, 30 patients (12.8%) exhibited FTC, six patients (2.6%) exhibited mixed papillary and FTC, and one patient (0.4%) exhibited Hürthle cell carcinoma, according to the World Health Organization criteria. There were 187 women and 46 men (female to male ratio, 4.1) included in the present study, with a mean age of 51.1±14.9 years (range, 18-88 years). In total, 176 control subjects without a history of thyroid disease were included in the present study (female to male ratio, 3.8) with a median age of 27 years (22-34), ranging from 19 to 87 years of age.

Genotyping analysis. Genotyping analysis was used to examine the potential association between six SNPs and DTCs. Notably, the data included genotype and allele frequencies in cases and controls, HWE, P-values, OR with 95% CI, and corresponding P-values for association analyses (Table III). The results of the present study revealed that the ORs were indicative of specific directions for each SNP; however, the results did not reach statistical significance ($P<0.05$). The adjusted OR remained non-significant following comprehensive age adjustment, suggesting that these findings are not artifacts of the age imbalance between groups (data not shown). All SNPs included in the control group exhibited HWE ($P>0.05$), confirming appropriate genotype distribution patterns. Notably, the rs116909374 SNP lacked variation in

Table I. List of primers and restriction enzymes for SNPs detection in the present study.

SNP ID	Primer sequence (5'-3')	Annealing temperature (˚C)	Length of fragment (bp)	Restriction enzyme
rs944289	F: GCAGCTGCAGATTTATTGCTT R: GCCATGCACTACCCAGTTCT	56	811	*Bsr*DI
rs2439302	F: TGCAAGAATGGCCTAACACAATGTGTAATCTT TGTTTCCT R: ACTTCTGTTCCTGAGTCATC	56	211	*Bfa*I
rs966423	F: CCCACGTGGAGAGGTGAGAAAAGTAGGGTGG AAGAGGACA R: TCTGTCTGTGCTCCAAGGTG	56	218	*Nla*III
rs116909374	F: GAACAGCATTCACTTTGAGCA R: TGTGCTCTAATCCTAGCACCAT	56	700	*Nsi*I
rs1799782	F: CCCTCCTTTCCCAGGACTC R: GAGAAAGTGGATCCAGGATGA	56	597	*Pvu*II
rs861539	F: TTTCAGACGGTCGAGTGACAG R: CAGAGGTGCACACACCACAT	56	567	*Nla*III

SNP, single nucleotide polymorphism; F, forward; R, reverse.

Table II. Characteristics of patients and controls.

Characteristics	Case (n=233)	Control (n=176)
Age, years	51.02±14.90	27 (22-34)
Sex		
Female	187 (80.26%)	139 (78.98%)
Male	46 (19.74%)	37 (21.02%)
Tumor type		
PTC	196 (84.12%)	
FTC	30 (12.88%)	
Mix	6 (2.58%)	
Hürthle	1 (0.43%)	

this population, limiting its utility in the present association study. Post-hoc power calculation analysis yielded a power (1-β) of 0.82, exceeding the conventional threshold of 0.80. This confirmed that the sample size of the present study was sufficient to detect ORs of ≥1.8 with appropriate statistical power, while maintaining a 5% Type I error rate and considering sex-specific genetic effects for these SNPs. The results of the present study also revealed significant genetic associations for three SNPs; namely, rs2439302, rs966423 and rs1799782. Notably, the results were categorized by sex, and presented with OR, 95% CI and corresponding p-values (Table IV). rs2439302 demonstrated a significant association in men when comparing the CC and CG genotypes (OR, 3.325; 95% CI, 1.171-9.442; P=0.024), whereas no significant associations were observed in women. Similarly, for rs966423 in males, two significant associations were identified; namely, the CC vs. CT genotype comparison (OR, 0.263; 95% CI, 0.082-0.841; P=0.024) and the C vs. T allele comparison (OR, 3.780; 95% CI, 1.291-11.068; P=0.015). Notably, no significant associations were found in women for this SNP. The results of the present study also revealed a signification association for the CC vs. CT genotype for rs1799782 in men (OR, 0.194; 95% CI, 0.039-0.968; P=0.046); however, there was no statistically significant association in women. Collectively, the results of the present study revealed that all statistically significant associations (P<0.05) were exclusively observed in men, indicating potential sex-specific genetic effects of these SNPs. Although significant associations were observed exclusively in men, these findings should be interpreted with caution due to the limited male sample size (n=46), as this may reduce statistical power and lead to effect size overestimation. The observed OR suggested both increased and decreased risks depending on the specific comparison, with no statistically significant findings in women for any of the tested SNPs or comparisons.

Discussion

The distribution of DTC subtypes in the present study is consistent with global trends, where PTC is consistently reported as the most prevalent form of DTC. On the other hand, mixed papillary and FTCs and Hürthle cell carcinomas are rare with low prevalence rates (4,18). The female to male ratio of patients with DTC observed in the present study was 4.1, and this was consistent with previous findings (19). A total of six SNPs with susceptibility to DTC were observed in a previous study and were therefore used in the present case-control association study. A total of two SNPs; namely, rs966423 and rs1799782, demonstrated consistent trends; however, these did not demonstrate statistical significance (P<0.05).

Table III. Genotype and allele frequencies of SNPs in cases and controls with corresponding odds ratios and P-values for association.

SNP ID	Nearest gene	Genotype/ Allele	Frequency in case	Frequency in control	HWE P-value	Odds ratio (95% CI)	P-value
rs944289	*PTCSC3*	CC	39	28	0.521	1.00	-
		CT	89	72		0.887 (0.499-1.579)	0.685
		TT	51	31		1.181 (0.611-2.284)	0.621
		Missing	55	45		-	-
		C	167	128		1.00	-
		T	191	134		0.915 (0.665-1.259)	0.587
rs2439302	*NRG1*	CC	102	86	0.864	1.00	-
		CG	67	48		1.177 (0.736-1.881)	0.496
		GG	9	5		1.518 (0.490-4.699)	0.469
		Missing	56	37		-	-
		C	271	220		1.00	-
		G	85	58		0.841 (0.576-1.227)	0.368
rs966423	*DIRC3*	CC	176	127	0.936	1.00	-
		CT	42	44		0.689 (0.426-1.114)	0.128
		TT	1	3		0.241 (0.025-2.339)	0.220
		Missing	14	2		-	-
		C	394	298		1.00	-
		T	44	50		1.502 (0.975-2.315)	0.065
rs116909374	*MBIP*	CC	202	175	NA	1.00	-
		CT	1	0		NA	NA
		TT	0	0		NA	NA
		Missing	31	1		-	-
		C	405	350		1.00	-
		T	1	0		NA	NA
rs1799782	*XRCC1*	CC	65	57	1.000	1.00	-
		CT	33	48		0.603 (0.342-1.064)	0.081
		TT	8	10		0.702 (0.259-1.898)	0.485
		Missing	128	61		-	-
		C	163	162		1.00	-
		T	49	68		1.3963 (0.911-2.140)	0.125
rs861539	*XRCC3*	CC	142	139	0.925	1.00	-
		CT	23	19		1.185 (0.618-2.272)	0.609
		TT	1	1		0.979 (0.061-15.805)	0.988
		Missing	68	17		-	-
		C	307	297		1.00	-
		T	25	21		0.868 (0.476-1.585)	0.646

The results of previous GWAS highlighted rs966423 as a variant associated with an increased risk of thyroid cancer, including PTC. Previous studies using various populations, including Chinese and Slovak cohorts, demonstrated that rs966423 was associated with the development of PTC (13,20). Research on the Icelandic population revealed a strong association between rs966423 and thyroid cancer, with an OR of 1.34, indicating a higher risk for carriers of this variant (15). The TT genotype of rs966423 was associated with increased overall mortality in patients with DTC, suggesting that this variant may affect the clinical course of the disease (21). However, the limited predictive power of rs966423 for thyroid cancer was observed in some populations (22). The results of a previous study demonstrated no statistically significant correlation between the rs966423 polymorphism in the *DIRC3* gene or any histopathological or clinical features, including initial response to therapy, response at follow-up, or overall mortality in patients with DTC (23). The results of the present study revealed that the T allele of rs966423 exhibited no significant association with disease development. Collectively, these results suggested that rs966423 may not act as a useful indicator for the clinical course or prognosis of thyroid cancer. This highlights a discrepancy in findings and suggests that the

Table IV. Sex-stratified analysis of three SNPs with corresponding odds ratios.

		Female		Male	
SNP ID	Genotype/ Allele	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P-value
rs2439302	CC vs. CG	0.912 (0.536-1.553)	0.735	3.325 (1.171-9.442)	0.024
	CC vs. GG	1.444 (0.417-5.001)	0.562	1.750 (0.100-30.592)	0.701
	C vs. G	0.975 (0.636-1.497)	0.909	0.462 (0.204-1.045)	0.064
rs966423	CC vs. CT	0.857 (0.501-1.466)	0.573	0.263 (0.082-0.841)	0.024
	CC vs. TT	0.371 (0.033-4.141)	0.420	NA	NA
	C vs. T	1.222 (0.754-1.981)	0.417	3.780 (1.291-11.068)	0.015
rs1799782	CC vs. CT	0.726 (0.393-1.340)	0.305	0.194 (0.039-0.968)	0.046
	CC vs. TT	0.524 (0.164-1.671)	0.275	1.750 (0.151-20.231)	0.654
	C vs. T	1.404 (0.879-2.244)	0.156	1.434 (0.506-4.067)	0.497

observed association may be influenced by other genetic or environmental factors.

Previous studies have investigated the association between the rs1799782 polymorphism in the *XRCC1* gene and thyroid carcinoma; however, contradictory results were observed. A previous study including a Chinese cohort demonstrated that the homozygous TT genotype of rs1799782 was associated with a markedly elevated risk of DTC, with an OR of 2.09, indicating a two-fold increase in risk (16). The results of a further previous study revealed that the T allele of rs1799782 was associated with an increased risk of PTC in a Han Chinese population, with an adjusted OR of 1.61 (24). The results of a meta-analysis also confirmed the aforementioned association between the rs1799782 polymorphism and an increased risk of thyroid cancer in specific genetic models (25). The results of the present study revealed that the T allele of rs1799782 was associated with DTC development, with an OR of 1.3963. However, these results were not statistically significant. Moreover, several previous studies indicated that the rs1799782 polymorphism may be associated with a reduced risk of thyroid cancer. In a Pakistani population, the homozygous mutant TT of rs1799782 significantly decreased the risk of thyroid cancer, with an OR of 0.71 (26).

The results of the present study also revealed a significant genetic association for three SNPs; namely, rs2439302, rs966423 and rs1799782. Although numerous previous studies do not provide male-specific data for these three SNPs, the overall findings suggested that these SNPs may contribute to thyroid cancer risk and progression in men in a similar manner to women. The results of the present study also revealed that the CG genotype of rs2439302 and T allele of rs966423 in male patients was significantly associated with an increased risk of DTC, while the CT genotypes of rs966423 and rs1799782 were associated with a decreased risk of DTC. However, the present study included a limited number of male patients. Thus, further investigations focused on male populations are required to verify the observed sex-specific associations.

Although rs944289 and rs2439302 polymorphisms have been consistently associated with an increased risk of thyroid cancer in Chinese, Japanese and Korean populations (12,27-29), the results of the present study revealed no association between the four SNPs; namely, rs944289, rs2439302, rs116909374 and rs861539, and this result was further verified in additional investigations. For example, the results of a previous study revealed that the potential effect of rs944289 and the strength of its association may vary among populations (30). Moreover, rs2439302 may influence susceptibility to thyroid cancer; however, the specific impact is not definitive across all ethnicities. In a Turkish population, the observed association between rs2439302 and thyroid cancer risk was not statistically significant, highlighting that this association may differ among populations (31). The limited clinical potential for predicting thyroid cancer was further demonstrated through assessing the association of key SNPs, such as rs2439302 with cancer risk, suggesting that although there may be an association, its predictive power may remain low (22). In addition, the results of a previous study revealed that the rs116909374 SNP may be associated with thyroid cancer risk, particularly in European populations. However, its role in the Chinese population is yet to be clearly established (13). In addition, research involving the Han Chinese population revealed no polymorphism for rs116909374, further supporting the lack of association with thyroid cancer in this demographic (22). This result was consistent with those of the present study. Although previous results in Chinese and Pakistani populations suggested that the rs861539 variant T allele was associated with an elevated risk of thyroid cancer (16,32), results of a meta-analyses focused on the rs861539 polymorphism did not demonstrate a significant association, or the association was not consistent across ethnic subgroups (33). Notably, large amounts of data for certain SNPs may be missing, which may affect the power of the analysis. Moreover, an age discrepancy among participants is acknowledged as a limitation due to its potential influence on the study outcomes. Additional studies with larger sample sizes are therefore required to confirm these findings.

The present study may provide novel insights into specific genetic factors that are associated with DTC susceptibility, and the results demonstrated that these may differ between sexes in

the Thai population. Specifically, significant associations with rs2439302, rs966423 and rs1799782 were only observed in males. Results of the present study highlighted the importance of sex stratification in genetic association studies of DTC, and may provide useful insights into genetic heterogeneity in thyroid cancer risk among the Thai population. Further investigations with larger cohorts are required to confirm these associations, and determine the clinical impact on risk assessment and the development of treatment strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PY was responsible for study design, carrying out the experiments, analysis, supervision, conceptualization, manuscript writing and editing of the final version of the manuscript. AL was responsible for carrying out the experiments and editing of the final version of the manuscript. JS was responsible for carrying out the experiments and editing of the final version of the manuscript. SA was responsible for study design, carrying out the experiments, analysis, supervision, conceptualization, manuscript writing and editing of the final version of the manuscript. PY and SA confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. Si 222/2018) by the Institutional Review Board at Faculty of Medicine Siriraj Hospital (Bangkok, Thailand). All participants provided written informed consent prior to participating in the study or the use of their specimens was approved by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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