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IL1A & IL1B genetic polymorphisms are risk factors for thyroid cancer in a Chinese Han population

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ABSTRACT

Introduction: Thyroid carcinoma accounts for a large proportion of endocrine neoplasia, and the relationship between inflammation and thyroid cancer has been previously validated. IL-1α (Interleukin 1 alpha) and IL-1β (Interleukin 1 beta), encoded by *IL1A* and *IL1B*, respectively, are implicated in numerous inflammatory responses and in tumor progression. The objective of this research was to assess the association of genetic polymorphisms of *IL1A* and *IL1B* with the risk of thyroid cancer in a Chinese Han population.

Materials and methods: Genotypes of the 12 candidate SNPs in *IL1A* and *IL1B* were identified among 208 thyroid cancer patients and 279 healthy controls using an Agena MassARRY method. Genetic model analysis was carried out to evaluate the significant links between the variants and thyroid cancer risk. HaploReg v4.1 and the GTEx database were used for SNP functional annotation and expression quantitative trait loci (eQTL) analysis, respectively.

Results: Significant associations were detected between *IL1A* rs3783521 and an increased thyroid cancer risk in our study population ($p < 0.05$). *IL1A* rs3783546 and rs3783521 were associated with an increased cancer risk in men, and *IL1B* rs3136558 and rs1143623 were associated with an decreased cancer risk in women. Meanwhile, rs3783550, rs3783546, rs1609682, and rs3783521 in *IL1A* were identified as biomarkers of risk among individuals aged ≤48 years. Rs3136558 and rs1143623 in the *IL1B* gene showed strong correlations with a susceptibility to thyroid cancer among individuals aged > 48 years. Additionally, bioinformatics and eQTLs analysis also provided supporting evidence for the effects of the SNPs on gene regulation.

Conclusions: Our study is the first to report that *IL1A* and *IL1B* polymorphisms are risk factors for thyroid carcinoma in a Chinese Han population.

1. Introduction

Thyroid carcinoma is the most commonly diagnosed endocrine malignancy with a rising incidence worldwide [1]. A global cancer investigation found that the occurrence of thyroid cancer is three-fold more frequent among women than men [2]. In China, a rapid increase in thyroid cancer cases was reported in a previous work [3]. However, the etiology of thyroid neoplasia remains incompletely elucidated. To our knowledge, radiation exposure and iodine deficiency or excess are two major contributing factors underlying thyroid oncogenesis, followed by eating habits and residential environments [4].

In addition to the external triggers mentioned above, an increasing number of researchers have gradually directed their attention to genetic factors in order to further reveal the endogenetic causes of thyroid cancer development and to provide new therapeutic strategies. Genome-wide association studies (GWAS) of thyroid cancer have identified numerous single nucleotide polymorphisms (SNPs) related to cancer risk and overall survival (OS) in different cohorts [5,6]. Currently, exploring the relationships between these single polymorphic markers within important genes and carcinogenesis is a vital step in delivering personalized risk estimations and treatment programs for thyroid cancer.

Inflammation, commonly known to be involved in carcinogenesis of various malignant tumors, has been proven to be implicated in the development of thyroid cancer [7]. Moreover, a distinct relationship between chronic thyroiditis and thyroid cancer has been established in

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previous research [8]. An interesting array of inflammatory cytokines and chemokines, which have been detected in inflammatory and immune microenvironments, exert pro-tumorigenic effects, including genomic instability induction, metastasis dysregulation and tumor-associated proliferation or apoptosis [9].

IL1A (Interleukin 1 alpha) and *IL1B* (Interleukin 1 beta) are two distinct genes encoding IL-1α and IL-1β, respectively, which belong to the IL-1 protein cluster and serve as pro-inflammatory factors [10]. The complicated and pleiotropic impacts of IL-1α and IL-1β have been validated in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions [11]. IL-1α is widely acknowledged to be one of the "alarm cytokines" that exhibits multiple biological characteristics in malignant transformation of tumor cells as well as immune and inflammatory reactions [12,13]. However, the pleiotropic effects of IL-1α in cancer progression that have been confirmed depend on different forms. Studies focusing on functional analysis have demonstrated that overexpression of membrane-associated IL-1α can promote anti-tumor immunity, whereas the N-terminal precursor of IL-1α can not only stimulate the activation of the pro-inflammatory genes but also alter the expression of various oncogenes and tumor suppressor genes [11,12,14]. IL-1β, identified as a crucial modulator, mainly mediates its final target IL-6 and both of them are implicated in the development of the abnormal behavior of tumor cells [15–17]. IL-1β secreted in a microenvironment impacts malignant proliferation and invasion by activating tumor-mediated genes [11]. Therefore, it is reasonable to conclude that IL-1α and IL-1β are multifunctional cytokines during tumorigenesis.

Recently, researchers have uncovered genetic polymorphisms in genes associated with several diseases and variants in interleukin genes have been identified as risk determinants in diverse types of cancers [18–22]. However, relationships between the variations occurring in *IL1A* and *IL1B* and thyroid cancer are seldom reported. Owing to the crucial roles of *IL1A* and *IL1B* in tumor malignant progression, we speculated that the polymorphic variants located in these two genes possess the potential to influence individual susceptibility to thyroid cancer. In this work, we conducted a case-control study in order to elucidate the potential roles of single nucleotide polymorphisms (SNPs) in *IL1A* and *IL1B* in thyroid cancer predisposition among Chinese Han individuals. The current study evaluated the individual effects of 12 variants, which are likely to serve as new targets for thyroid cancer early assessment and prevention.

2. Materials and methods

2.1. Participants statement

In the current research, 208 cases (154 women and 54 men, mean aged 46.32 ± 13.44 years) who had been pathologically confirmed to have thyroid cancer were recruited from the First Affiliated Hospital of Xi'an Jiaotong University from 2015 to 2017. The control group was comprised of 206 women and 73 men, for a total of 279 individuals with a mean age of 48.33 ± 12.42. These healthy subjects were volunteer blood donors from an outpatient health clinic in the same region as the cases. A structured questionnaire, including demographic characteristics (age, sex, place of residence, etc.) and a negative family history of autoimmune and thyroid-related diseases or other types of tumors, was completed for selection of eligible controls. The selected subjects involved in this research were all adults (aged over 18 years old) when diagnosed or volunteering. All participants in our study were of Chinese Han ancestry from northwestern China.

2.2. Ethnical statement

Our study was conducted with the appropriate approval of the ethics committee from the First Affiliated Hospital of Xi'an Jiaotong University. All procedures performed in this study were in accordance with the ethical standards of the ethics committee from the First Affiliated Hospital of Xi'an Jiaotong University and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from each participant at recruitment after fully describing our research to them.

2.3. SNP selection

Searching the 1000 Genomes database (http://www.internationalgenome.org/) and dbSNP database (http://www.bioinfo.org.cn/relative/dbSNP%20Home%20Page.htm), we screened SNPs in *IL1A* and *IL1B* for minor allele frequencies beyond 5% in a global population to ensure a valid statistical analysis. Finally, five SNPs (rs3783550, rs3783546, rs2856838, rs1609682, and rs3783521) in *IL1A* and seven SNPs (rs2853550, rs1143643, rs3136558, rs1143630, rs1143627, rs16944, and rs1143623) in *IL1B* were selected for use.

2.4. DNA isolation and SNP genotyping

Genomic DNA extraction from the collected whole blood sample was performed by using a GoldMag DNA Purification Kit (GoldMag Co. Ltd., Xi'an City, China) in accordance with the protocol recommended by the manufacturer. Concentration and purity of the obtained DNA was evaluated with an ultraviolet spectrophotometer (Nanodrop 2000, Thermo Scientific, Waltham, Massachusetts, USA) prior to SNP genotyping. A multiplexed SNP MassEXTEND assay was designed using Agena Bioscience Assay Design Suite software, version 2.0 (https://agenacx.com/online-tools/). Primers for SNP identification during the experiment are presented in Supplementary Table S1. SNP genotyping was conducted by utilizing the MassARRAY Nanodispenser and MassARRAY iPLEX platform (Agena Bioscience, San Diego, CA, USA), following the standard instructions of the protocol. The call rate for the selected SNPs was > 99%. Data processing and output were carried out with Agena Bioscience TYPER software, version 4.0.

2.5. Statistical analysis

SPSS 19.0 (SPSS, Chicago, IL, USA) and Microsoft Excel were used for data estimation and association analysis. Distribution differences of sex and age between the thyroid cancer patients and healthy subjects were detected with Pearson's χ^2 test and an independent sample *t*-test. All SNPs were assessed for deviation from Hardy-Weinberg equilibrium (HWE) in the control group by comparing the experimental data with the expected heterozygosity with Fisher's exact test. Pearson's χ^2 test was applied for detection of the differences for both allele and genotype frequencies between cases and controls. The observed p values were two-sided and $p < 0.05$ was considered statistically significant for all tests. Moreover, SNPstats software (https://www.snpstats.net/start.htm) was implemented in the genetic model analysis (including codominant, dominant, recessive, overdominant and log-additive model) in order to determine the associations of these polymorphisms with the risk of thyroid cancer in Chinese Han people. Odds ratio (OR) values and 95% confidence intervals (CIs) were provided for evaluation of the minor allele effect with or without adjustments for sex and age using logistic regression analysis [23].

2.6. SNP functional annotation

The HaploReg v4.1 database (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) was employed for exploring functional annotations of the candidate SNPs. With searching in this online tool, the genetic variants can be visualized along with protein binding information, the effect of SNPs on DNAses, regulatory motifs, and expression from eQTL (expression Quantitative Trait Loci) studies.

Table 1
Distributions of age and sex in thyroid cancer cases and healthy controls.

Variable	Cases	Controls	*p*-value
Sex			0.960[a]
Male	54 (26.0%)	73 (26.2%)	
Female	154 (74.0%)	206 (73.8%)	
Total	208	279	
Age (years)	46.32	48.33	0.090[b]
Standard deviation	13.44	12.42	

p^a-value: *p*-value obtained from Pearson's χ^2 test.
p^b-value: *p*-value obtained from an independent sample *t*-test.

2.7. Expression quantitative trait loci (eQTL) analysis for SNPs

The impacts of *IL1A* and *IL1B* SNPs on gene expression were assessed by the public GTEx (the Genotype-Tissue Expression) database (https://gtexportal.org/home/). GTEx researchers have explored the differences of gene expression levels under different genotypes in various tissues and have indicated them with statistically significant *p*-values ($p < 0.05$).

3. Results

3.1. Demographic characteristics of the study population

In this present study, a convenience sample of 208 thyroid cancer patients (54 men and 154 women) was studied as well as a confirmed cohort comprising 279 controls (73 men and 206 women) in healthy physical conditions, with average ages of 46.32 ± 0.93 and 48.33 ± 0.74, respectively (Table 1). There were no differences of sex or age distributions between the cases and controls because of the *p* value > 0.05 from Pearson's χ^2 and independent sample *t*-test. The case and control groups consisted of unrelated individuals matched for ethnicity, age, and sex.

3.2. Basic information and preliminary statistics of the selected SNPs

To conduct the statistical analyses, we genotyped five SNPs in *IL1A* and seven SNPs in *IL1B* among our study individuals. Basic information and preliminary statistical results of the selected 12 SNPs are listed in Table 2. All of the SNPs are on chromosome 2 and were located in different regions of the genes *IL1A* and *IL1B*. The selected *IL1A* variants are distributed in the introns, except rs3783521, which resides in the *IL1A* promoter. The *IL1B* SNPs were found in the promoter (rs1143627, rs16944 and rs1143623), intron (rs1143643, rs3136558 and rs1143630) and downstream region (rs2853550). Deviation from Hardy-Weinberg equilibrium ($p < 0.05$) was evaluated in the control group and all of the selected SNPs showed the expected *p* values ($p > 0.05$), which suggested that none of the selected variants should be excluded from further study. Moreover, significant differences in allele distribution of each SNP was detected between thyroid cancer patients and eligible controls. According to the allele risk model, there were no variants exhibiting obvious correlations with thyroid cancer ($p > 0.05$).

3.3. Genetic model analysis of the selected SNPs

Genetic model analysis of the general population is shown in Table 3. Our analysis revealed a moderate relationship between *IL1A* rs3783521 and an increased risk of thyroid carcinoma based on the dominant model with adjustments for sex and age (after adjustment: OR = 1.45, 95% CI: 1.00–2.10, $p = 0.047$). However, risk associations did not exist for the other selected SNPs (Supplementary Table S2). Furthermore, we performed a stratified analysis by both sex and age in order to explore the effects of these polymorphisms among specific populations.

When stratified by sex, our results uncovered an undesirable association of the heterozygous genotype in *IL1A* rs3783546 and rs3783521 with thyroid cancer susceptibility in accordance with the overdominant genetic model analysis in men (rs3783546: OR = 2.36, 95% CI: 1.13–4.93, $p = 0.021$; rs3783521: OR = 2.26, 95% CI: 1.09–4.69, $p = 0.028$) (Table 4). In women, *IL1B* rs3136558 and rs1143623 exerted protective roles against the development of thyroid cancer under both the overdominant and dominant models (rs3136558 overdominant model: OR = 0.64, 95% CI: 0.42–0.98, $p = 0.039$; rs1143623 dominant model: OR = 0.62, 95% CI: 0.40–0.96, $p = 0.033$) (Table 4).

Stratified analysis by age demonstrated remarkable relationships between an enhanced thyroid cancer risk and *IL1A* rs3783546 (dominant model: OR = 1.86, 95% CI: 1.10–3.14, $p = 0.020$; overdominant model: OR = 1.79, 95% CI: 1.07–2.99, $p = 0.025$) and rs3783521 (dominant model: OR = 1.83, 95% CI: 1.08–3.08, $p = 0.023$; overdominant model: OR = 1.75, 95% CI: 1.05–2.92, $p = 0.030$) in both dominant and overdominant models among individuals with an age under 48. *IL1A* rs3783550 (dominant model: OR = 1.75, 95% CI: 1.04–2.95, $p = 0.034$) and rs1609682 (dominant model: OR = 1.75, 95% CI: 1.04–2.95, $p = 0.034$) only showed significant effects in the dominant model (Table 4). Because of their similar genotype frequency distribution among the cases and controls, the statistical results of rs3783550 and rs1609682 did not display any differences. Additionally, the *IL1B* rs3136558 G/G genotype was identified as a genetic risk factor

Table 2
Basic information and allele frequency of the selected SNPs in *IL1A* and *IL1B*.

SNP	Chromosome	Position	Alleles A/B	Gene	Role	Minor allele frequency		HWE p^a-value	OR (95% CI)	p^b-value
						Case	Control			
rs3783550	chr2	113532885	T/G	IL1A	Intron(boundary)	0.363	0.317	0.890	1.23 (0.94–1.60)	0.135
rs3783546	chr2	113534830	C/G	IL1A	Intron	0.363	0.317	0.890	1.23 (0.94–1.61)	0.128
rs2856838	chr2	113539972	A/G	IL1A	Intron	0.257	0.231	1.000	1.15 (0.86–1.55)	0.348
rs1609682	chr2	113540205	T/G	IL1A	Intron(boundary)	0.363	0.317	0.890	1.23 (0.94–1.60)	0.135
rs3783521	chr2	113543577	G/A	IL1A	Promoter	0.365	0.317	0.890	1.24 (0.95–1.62)	0.121
rs2853550	chr2	113587121	A/G	IL1B	Downstream	0.103	0.102	1.000	1.01 (0.67–1.54)	0.951
rs1143643	chr2	113588302	C/T	IL1B	Intron	0.464	0.507	1.000	0.84 (0.65–1.09)	0.182
rs3136558	chr2	113591275	G/A	IL1B	Intron	0.367	0.378	0.373	0.95 (0.73–1.24)	0.726
rs1143630	chr2	113591655	T/G	IL1B	Intron	0.155	0.170	1.000	0.89 (0.63–1.26)	0.514
rs1143627	chr2	113594387	A/G	IL1B	Promoter	0.519	0.482	0.905	1.16 (0.90–1.50)	0.251
rs16944	chr2	113594867	A/G	IL1B	Promoter	0.476	0.509	1.000	0.88 (0.68–1.13)	0.306
rs1143623	chr2	113595829	G/C	IL1B	Promoter	0.388	0.419	0.389	0.88 (0.68–1.14)	0.323

SNP: Single nucleotide polymorphism; HWE: Hardy-Weinberg equilibrium; OR: Odds ratio; 95% CI: 95% confidence interval.
HWE p^a-value: *p*-value obtained from Fisher's exact test.
p^b-value: *p*-value obtained from Pearson's χ^2 test.

Table 3
Significant genetic variants in *IL1A* associated with susceptibility to thyroid cancer in a Chinese Han population.

Gene	SNP	Model	Genotype	Control	Case	Adjustment by sex and age	
						OR (95% CI)	*p*-value
IL1A (N = 487)	rs3783521 (call rate 99.79%)	Codominant	A/A	129 (46.2%)	77 (37.2%)	1.00	0.120
			G/A	123 (44.1%)	109 (52.7%)	1.49 (1.01–2.19)	
			G/G	27 (9.7%)	21 (10.1%)	1.27 (0.67–2.41)	
		Dominant	A/A	129 (46.2%)	77 (37.2%)	1.00	***0.047***
			G/A-G/G	150 (53.8%)	130 (62.8%)	***1.45 (1.00–2.10)***	
		Recessive	A/A-G/A	252 (90.3%)	186 (89.9%)	1.00	0.930
			G/G	27 (9.7%)	21 (10.1%)	1.03 (0.56–1.88)	
		Overdominant	A/A-G/G	156 (55.9%)	98 (47.3%)	1.00	0.057
			G/A	123 (44.1%)	109 (52.7%)	1.42 (0.99–2.04)	
		Log-additive	–	–	–	1.25 (0.94–1.65)	0.120

SNP: Single nucleotide polymorphism; OR: Odds ratio; 95% CI: 95% confidence interval.
p-value: *p*-value calculated by logistic regression analysis with adjustments for sex and age.
Bold italics indicate the SNP with statistical significance ($p < 0.05$).

in the predisposition to tumorigenesis under codominant and recessive models in the cohort aged over 48 (codominant model: OR = 2.19, 95% CI: 1.01–4.79, $p = 0.013$; recessive model: OR = 2.66, 95% CI: 1.30–5.45, $p = 0.007$), whereas the G/A genotype was a relative protective factor against thyroid cancer according to the analysis of the overdominant model (OR = 0.56, 95% CI: 0.33–0.95, $p = 0.029$) (Table 4). We detected evidence for *IL1B* rs1143623 being associated with a decreased risk of thyroid cancer in the overdominant model as well (OR = 0.54, 95% CI: 0.32–0.91, $p = 0.021$) (Table 4).

3.4. Potential regulatory role of promising SNPs

We performed a functional prediction of the statistically significant variants in the HaploReg v4.1 database in order to further explore their regulatory roles. All six SNPs distributed in *IL1A* and *IL1B* exhibited potential biological functions in gene modulation (Supplementary Table S3). The results also suggested functional importance of the SNP rs1143623 in the *IL1B* gene in regard to gene expression.

3.5. eQTL analysis of gene expression

Using the GTEx database, SNPs rs3783521, rs3783546, rs3783550 and rs1609682 of *IL1A* and rs1143623 of *IL1B* were associated with gene expression. These variants were identified as eQTLs in skin, pituitary and testis with significant *p*-values (Supplementary Table S4).

4. Discussion

A chronic inflammatory response is related to the occurrence and progression of thyroid cancer. Notably, several studies have revealed that multiple factors can sustain and enhance the progression of thyroid tumors [24–26]. In this process, two identified cytokines IL-1α and IL-1β, acting as pro-inflammatory proteins with distinct functions, are not only involved in the processes of inflammation but also in the development of malignancy, whereas less is known with respect to their genetic variations and their relationship to thyroid cancer in a Chinese Han population. In this study, we examined 12 SNPs of *IL1A* and *IL1B* genes to determine if there was any correlation with the susceptibility to thyroid cancer in a Chinese Han cohort. Statistical and bioinformatics results revealed correlations between rs3783521, rs3783546, rs3783550, rs1609682, rs3136558 and rs1143623 and the development of thyroid cancer in both total and stratified populations, which will help to improve our understanding of *IL1A* and *IL1B* in this disease.

Researchers focused on thyroiditis and thyroid cancer have observed aberrant expression of *IL1A* and *IL1B* in patients, which implies possible associations of them with tumor occurrence [27–29]. Our study showed new evidence for the involvement of *IL1A* and *IL1B* in thyroid cancer. Genetic determinants within *IL1A* and *IL1B* were related to the thyroid carcinoma risk among Chinese Han individuals. For variations in *IL1A*, relationships between rs3783521, rs3783546, rs3783550, rs1609682 and disease risk have been reported in published

Table 4
Significant variants in *IL1A* and *IL1B* and their correlations with thyroid cancer susceptibility with stratification by sex or age.

	SNP	Gene	Dominant[a]		Recessive[b]		Overdominant[c]		Log-additive[d]	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Male	rs3783546	IL1A	1.86 (0.90–3.87)	0.094	0.55 (0.16–1.88)	0.330	***2.36 (1.13–4.93)***	***0.021***	1.24 (0.73–2.11)	0.430
	rs3783521	IL1A	1.80 (0.87–3.72)	0.110	0.56 (0.16–1.91)	0.340	***2.26 (1.09–4.69)***	***0.028***	1.22 (0.73–2.08)	0.460
Female	rs3136558	IL1B	0.77 (0.50–1.18)	0.230	1.51 (0.81–2.80)	0.190	***0.64 (0.42–0.98)***	***0.039***	0.97 (0.71–1.32)	0.820
	rs1143623	IL1B	***0.62 (0.40–0.96)***	***0.033***	0.91 (0.51–1.64)	0.760	0.67 (0.44–1.03)	0.066	0.77 (0.57–1.05)	0.098
≤48	rs3783546	IL1A	***1.86 (1.10–3.14)***	***0.020***	1.03 (0.45–2.33)	0.950	***1.79 (1.07–2.99)***	***0.025***	1.43 (0.96–2.12)	0.074
	rs3783521	IL1A	***1.83 (1.08–3.08)***	***0.023***	1.03 (0.46–2.34)	0.940	***1.75 (1.05–2.92)***	***0.030***	1.42 (0.96–2.10)	0.080
	rs3783550	IL1A	***1.75 (1.04–2.95)***	***0.034***	1.12 (0.50–2.50)	0.780	1.64 (0.98–2.72)	0.057	1.40 (0.95–2.07)	0.086
	rs1609682	IL1A	***1.75 (1.04–2.95)***	***0.034***	1.12 (0.50–2.50)	0.780	1.64 (0.98–2.72)	0.057	1.40 (0.95–2.07)	0.086
> 48	rs3136558	IL1B	0.94 (0.55–1.61)	0.830	***2.66 (1.30–5.45)***	***0.007***	***0.56 (0.33–0.95)***	***0.029***	1.27 (0.88–1.85)	0.210
	rs1143623	IL1B	0.62 (0.36–1.06)	0.078	1.40 (0.66–2.94)	0.380	***0.54 (0.32–0.91)***	***0.021***	0.85 (0.57–1.25)	0.410

SNP: Single nucleotide polymorphism; OR: Odds ratio; 95% CI: 95% confidence interval.
p-value: *p*-value calculated by logistic regression analysis with adjustment.
Bold italics indicate the SNP with statistical significance ($p < 0.05$).
[a] Dominant model: BB vs. AB + AA.
[b] Recessive model: BB + AB vs. AA.
[c] Overdominant: BB + AA vs. AB.
[d] Additive model: For each A allele increase (A: minor allele, B: wild allele).

research [30,31]; moreover, these variants were proven to be associated with thyroid cancer risk in our work. Rs3783521 was confirmed to be associated with an increased risk of thyroid cancer in both the total population and in men. Stratified analysis by age or sex also yielded significant correlations for the other SNPs with thyroid cancer development in subgroups. These single polymorphic markers could serve as predictors to facilitate the evaluation of thyroid cancer risk in Chinese Han people. Rs3136558 and rs1143623 are the only two SNPs located in *IL1B* that exhibited remarkable correlations with individual thyroid cancer susceptibility. A significant association of rs3136558 with the development of papillary thyroid carcinoma (PTC) has been previously reported in a Korean group, which emphasizes the significance of rs3136558 in both populations [32]. Additionally, rs1143627, rs1143643 and rs1143630 in *IL1B* have been considered to be genetic risk factors for PTC in a Korean population, and a correlation between rs1143627 and autoimmune thyroid disease was demonstrated in a Japanese cohort [32,33]. Nevertheless, there were no relationships detected between them and thyroid cancer risk in our Chinese Han population. This discrepancy might be explained by the clinical heterogeneity of the populations.

In accordance with the functional annotation of the SNPs, all promising SNPs with statistical significance harbored potential roles in gene regulation. Meanwhile, eQTL analysis underlined the association of SNPs with gene expression in different tissues. We thus speculated that the genetic alterations occurring in the SNPs could affect gene expression, which eventually resulted in the differences of individual cancer predisposition.

Several limitations should be considered in this study. First, our research was conducted only based on a Chinese Han population. However, various frequencies of genetic polymorphisms among different ethnic populations may lead to different significant results. Therefore, the generalizability of our significant SNPs needs to be further confirmed in groups with different genetic backgrounds. Second, potential selection bias cannot be completely avoided in this research. Third, the underlying mechanism by which the significant variants affect thyroid cancer development remains unclear. Further functional experiments are required to better elucidate the influences of these polymorphisms at the molecular level.

In conclusion, our data suggest that rs3783521, rs3783546, rs3786550 and rs1609682 in *IL1A*, rs3136558 and rs1143623 in *IL1B* are significant risk factors associated with thyroid cancer. These variants may be considered to be markers during the assessment of thyroid cancer susceptibility in Chinese Han populations.

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Author contributions statement

Yuan Shao, Qing Zhang, Huajing Li and Na Duan conceived, designed and performed all of the experiments; Huajing Li and Na Duan analyzed the data. Yuan Shao, Qing Zhang, Huajing Li and Na Duan discussed the results and wrote the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

None.

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Data availability statement

All data generated or analyzed during this study are included in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105869.

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