

Influence of Interleukin-18 and Interleukin-17 Receptor A gene polymorphisms on the risk of thyroid cancer among Chinese Han population

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Abstract

Background Thyroid cancer (TC) is a common endocrine pathology with an increasing incidence worldwide. It has been reported that high genetic impact is involved in the pathogenesis of TC, as well as cytokines, especially the interleukins play a crucial role in it. This study was designed to detect the association of IL-18 and IL-17RA polymorphisms with TC risk.

Methods This case-control study conducted 365 TC patients and 503 healthy controls from Chinese Han population. Three selected SNPs (IL-18 rs360718, IL-18 rs1946519, and IL-17RA rs4819554) were genotyped to investigate the possible association of the polymorphisms with the risk of TC. Multifactor dimensionality reduction (MDR) was used to analyze the interactions of SNP-SNP.

Results IL-17RA rs4819554 was associated with the decreased risk of TC under dominant model (OR = 0.76, 95% CI = 0.56-0.99, $p = 0.04$). IL-18 rs360718 significantly decreased the risk at age ≤ 44 years (C vs. A, OR = 0.63, 95% CI = 0.41-0.97, $p = 0.033$; CC vs. AA, OR = 0.12, 95% CI = 0.01-0.91, $p = 0.040$). On the contrast, among people older than 44 years, IL-18 rs1946519 (C vs. A, OR = 1.77, 95% CI = 1.03-3.06, $p = 0.040$) shown an increased risk with TC. MDR analysis revealed a positive interaction between the SNPs.

Conclusion The present study firstly demonstrated that IL-18 rs360718, rs1946519 and IL-17RA rs4819554 polymorphisms might be related to thyroid cancer. The results were significantly worthy of further validation by larger studies.

1 Introduction

Thyroid cancer (TC), a common endocrine malignancy, accounting for more than 90% of endocrine cancers, had constantly increased worldwide recent years[1]. TC led the fifth most common cancer in women in the United States[2], while the estimates of cancer incident cases and deaths were 143.9 thousand and 6500 respectively in China[3]. Although the exact pathophysiologic mechanisms of TC remained elusive, accumulating evidence indicated that the inter-individual genetic factors, especially the single nucleotide polymorphisms (SNPs) in tumor-associated genes took essential part in the genetic susceptibility to TC[4-7].

Cytokines were molecules that contribute to regulate activation, growth, and differentiation of some target cells[8]. Importantly, they were pro-and anti-inflammatory mediators that played a crucial role in the induction and effector phases of the inflammatory and immune responses, and functioned as a regulator in development and growth of both normal and neoplastic thyroid cells[9]. Interleukin-18 (IL-18), a pleiotropic pro-inflammatory cytokine that induced interferon-gamma (IFN- γ) production and was involved in T helper type 1 development, was cloned for the first time in 1995[10]. Previous studies and clinical trials were indicated not only the antitumoral activity of *IL-18* but also the possibility and efficacy of using it for therapeutic purposes. Additionally, evaluating the relevance between SNPs of *IL-18* and different neoplastic conditions had attracted much attention[11]. Besides, interleukin-17 receptor A (*IL-*

17RA) was identified as the receptor of IL-17A and IL-17F[12]. It was expressed on a wide range of tissues and cell types, including several types of cancer cells[13]. Therefore, *IL-17RA* had become a point of interest for its mediation of some important signaling pathway.

Although, polymorphisms of *IL-18* and *IL-17RA* obtained much attention with the risk of TC, there were none of relevant research in Han Chinese population. The present study was aim to detect the possible association among the polymorphisms of three SNPs (*IL-18* rs360718, *IL-18* rs194651, and *IL-17RA* rs4819554) in Han Chinese population. This might reveal a new perspective of the prevention and treatment of thyroid cancer in the future.

2 Methods

2.1 Ethical approval of the current hospital-based study

The current case-control study was obtained the permission by the Review Board of the Hainan General Hospital. All subjects provided written inform consent to be included in the study.

2.2 Study participants

A total of 365 TC patients (mean age: 43.98 ± 15.17) and 503 healthy control subjects (mean age: 44.16 ± 12.37) were enrolled in this case-control study. All patients were Chinese Han adults and recruited from the Hainan General Hospital. The inclusion criteria for the patients were: patients who were recently diagnosed and identified as TC, according to diagnostic imaging and histopathological examination. The healthy controls without medical history of any type of cancer were randomly recruited from the health checkup at the same time.

2.3 SNPs selection and genotyping

We identified two single nucleotide polymorphisms (SNPs) in *IL-18* and one in *IL-17RA* with a minor allele frequency (MAF) > 0.05 in Chinese Han population from the NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>) and the 1000 Genomes Projects (<http://www.internationalgenome.org/>). The 5mL blood samples from all participants were collected in vacutainers which contained Ethylenediaminetetraacetic acid (EDTA). To extract gDNA, the GoldMag whole blood genomic DNA purification kit (GoldMag Co. Ltd., Xi'an, China) was used and then, the extracted gDNA was stored at -80°C until analysis. The MassARRAY iPLEX platform (Agena, San Diego, CA, U.S.A) was used for evaluating *IL-18* and *IL-17RA* gene polymorphisms. The primers for amplification and single base extension were designed using the Agena Bioscience Assay Design Suite V2.0 software. Subsequently, Data management was conducted by Agena Bioscience 4.0 software.[14]. Genotyping was completed by two laboratory technicians in a double-blinded method. Importantly, we randomly selected about 10% of the samples to repeat genotyping for the quality control, the reproducibility was > 99%.

2.4 Bioinformatics analysis

Online softwares, HaploReg v4.1 (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>) and SNP info Web Server (<https://snpinformation.nih.gov/snpinfo/index.html>), took essential part in predicting the possible functional effects on these candidate SNPs. GEPIA datasets (<http://gepia.cancer-pku.cn/>) was used to predict the expression of *IL-18* and *IL-17RA*.

2.5 Data analysis

SPSS 20.0 (SPSS Inc., IBM, USA) statistical software and PLINK software were used for this study. The categorical variables were evaluated using Pearson's χ^2 test, and student's t-test was performed to analyze the differences in the age distribution between the cases and controls. Hardy-Weinberg equilibrium (HWE) was tested by χ^2 test for each SNP which was selected in this study. χ^2 test or Fisher's exact test were used to compare the genotype and allele frequencies between cases and controls. For respective genotype, we used logistic regression analysis to assess the relevance of selected SNPs with TC risk by odds ratios (ORs) and 95% confidence intervals (CIs) based on previous methods[15]. Haploview software (version 4.2) and PLINK software were used for analyzing the Linkage disequilibrium (LD) and haplotype[16]. Multifactor dimensionality reduction (MDR) (version 3.0.2) was performed to evaluate the interactions between SNP and SNP in the TC risk[17]. A two-tailed p -value <0.05 was statistically significant for all the analyses.

3 Results

3.1 Characteristic of the study participants

IL-17RA and *IL-18* polymorphisms were analyzed in 365 patients (97 men and 268 women) and 503 unrelated disease controls (137 men and 366 women). The characteristic of participants included in this study were listed in **Table 1**. The cases and controls appeared to be adequately matched on age and sex as suggested by the student-t and χ^2 tests respectively ($p = 0.857$, $p = 0.877$).

3.2 Genotyping of the SNPs in *IL-18* and *IL-17RA*

SNPs in *IL-18* (rs360718 and rs1946519) and *IL-17RA* (rs4819554) were successfully genotyped. The details of these SNPs and potential function predicted by HaploReg database about them were presented in **Table 2**. The Hardy-Weinberg equilibrium (HWE) tests for the *IL-18* and *IL-17RA* polymorphisms were shown in **Table 2**, and the results indicated that the frequencies of genetic polymorphisms were all in the HWE (p value > 0.05). Additionally, mRNA levels of *IL-18* was up-regulated in TC ($p < 0.01$, **Fig 1**), while there was no statistically significant in mRNA level of *IL-17RA* gene based on GEPIA database (**supplementary figure 1**). And then, the association between the expression of *IL-18* and the prognosis of TC which predicted by GEPIA database was shown in **supplementary figure 2**. It indicated that the expression of *IL-18* had a modest relationship with the prognosis of TC (hazard ratio = 0.32, Log-rank $p = 0.04$).

To evaluate the associations between *IL-18*, *IL-17RA* variants and the TC risk, five inheritance models (Allele, Genotype, Dominant, Recessive and Log-additive) adjusted for potential confounding variables (age, and gender) were applied. The results shown in **Table 3** indicated that *IL-17RA* rs4819554 polymorphism was associated with the decreased risk of thyroid cancer under dominant model (GG-GA vs. AA, OR = 0.76, 95% CI = 0.56-0.99, $p = 0.040$). However, *IL-18* rs360718 and rs1946519 polymorphisms presented no statistically difference in genotype frequencies between the TC patients and the healthy controls ($p \geq 0.05$). Logistic regression analyses indicated that none of these two SNPs in *IL-18* were associated with any change of susceptibility to TC (**Table 3**).

Stratification analysis by age and gender was performed. The results of subgroup test of age indicated that *IL-18* rs360718 (C vs. A, OR = 0.63, 95%CI = 0.41-0.97, $p = 0.033$; CC vs. AA, OR = 0.12, 95% CI = 0.01-0.91, $p = 0.040$) showed a decreasing-risk effect at age ≤ 44 years (**Table 4**). On the contrast, among people older than 44 years, *IL-17RA* rs4819554 (G vs A, OR = 0.76, 95%CI = 0.58-1.00, $p = 0.047$) was associated with the modestly decreased risk of TC which need to be further investigated (**Table 4**). *IL-18* rs1946519 (C vs. A, OR = 1.77, 95% CI = 1.03-3.06, $p = 0.040$) shown an increased risk. Also, the results of stratification analysis by gender were listed in **Table 4**. There was no statistically significant difference between man and woman.

Furthermore, we researched the linkage disequilibrium (LD) and haplotype analyses of the SNPs in *IL-18*. The reconstructed LD plot was presented in **Figure 2**, and the LD block was comprised of two SNPs including *IL-18* rs360718 and *IL-18* rs1946519. The frequencies distribution of haplotypes in the cases and controls were showed in **Table 5**. The results indicated an association of CA haplotype with a modestly increased risk of TC which needed to be further detected in the future (OR = 1.34, 95% CI = 1.00-1.78, $p = 0.047$).

3.4 SNP-SNP interactions.

SNP-SNP interactions were analyzed by MDR method. Obviously, there were interactions between locus and locus presented in a dendrogram and the Fruchterman-Reingold in **Figure 3**. Subsequently, analysis for 3 SNPs in *IL-17RA* and *IL-18* were presented in **Table 6**. The results indicated that *IL-17RA* rs4819554 was the best single-locus model to predict TC (testing accuracy = 0.526, CVC = 9/10, $p = 0.626$). The best two-locus model was the combined of *IL-18* rs1946519 and *IL-17RA* rs4819554 (testing accuracy = 0.514, CVC = 8/10, $p = 0.008$). The three-locus model included *IL-17RA* rs4819554, *IL-18* rs1946519 and *IL-18* rs360718 (testing accuracy = 0.527, CVC = 10/10, $p = 0.001$).

4 Discussion

This case-control study aimed to investigated the potential effects of *IL-18* and *IL-17RA* gene polymorphisms on TC in Chinese Han population. Our findings suggested that *IL-17RA* rs4819554 was associated with the decreased risk of TC. Especially in patients who were older than 44 years old, a modestly statistical relevance between *IL-17RA* rs4819554 and decreasing risk effect of TC deserved further research. Additionally, *IL-18* rs360718 was detected to shown a significantly decreased risk with

TC in patients under 44 years of age, whereas rs1946519 had an effect of increased risk with TC in patients 44 years and older. To our knowledge, this is the first study to report the effect of these SNPs in TC individuals.

IL-18 gene was located on chromosome 11 in humans and functionally, *IL-18* was first identified as “IFN γ -including factor” isolated in the serum of mice [18], [19]. In the previous studies, the expression of *IL-18* were significantly associated with multiple kinds of tumors, such as breast cancer, hepatocellular carcinoma, renal-cell carcinoma, and lung cancer.[19]. It also has been reported that *IL-18* polymorphisms (rs1946519, rs360718) were associated with TC risk in Iran and Korean population [11, 23], however, there was none of reports about these correlations with Chinese Han population. At present, we firstly examined the role of *IL-18* genetic polymorphisms (rs360718 and rs1946519) and the susceptibility to TC in Han Chinese population, and found that *IL-18* SNP rs1946519 conferred increased risk to TC in the patients older than 44 years, while *IL-18* rs360718 shown a significantly decreasing-risk effect with TC in patients under 44 years of age. Haplotype analysis revealed that the CA haplotype in *IL-18* rs360718 was modestly correlated with an increased risk of TC which needed to be further detected. Therefore, it was highly speculated that *IL-18* rs1946519 and rs360718 polymorphisms may affect the progression of thyroid cancer related to the age of patients. Further large-scale studies are needed to verify the results of our findings.

IL-17 family, included six polypeptides, *IL-17A-F*, and five receptors, *IL-17RA-E*[24]. The chemokine *IL-17*, a proinflammatory cytokine, was mainly produced by T-helper cells (Th17), macrophages and CD8+ T cells. Importantly, the function of *IL-17* was mediated by *IL-17RA*, also named CD217, which was located in 22q11.1 and had been recognized as a valuable biomarker for diverse diseases[25, 26]. Upon the stimulation with *IL-17*, *IL-17RA* initiated the activation of downstream signaling pathways to induce the production of pro-inflammatory molecules[13, 27]. Further evaluation revealed that *IL-17RA* could function as an inhibitor of signaling through the way called receptor-mediated internalization of the ligand[12, 28]. Several research had indicated the *IL-17* played important role in the development and prevention of TC[29, 30]. Moreover, it had reported that *IL-17* and *IL-17RA* polymorphisms were correlation with TC risk in Korean population[31]. In the present study, we firstly found that *IL-17RA* (rs4819554) polymorphism was associated with the decreased risk of thyroid cancer under dominant model (GG-GA vs AA, OR = 0.76 95% CI = 0.56-0.99, $p = 0.04$). Furthermore, among people older than 44 years, *IL-17RA* rs4819554 was associated with the modestly decreased risk (G vs A, OR = 0.76, 95% CI = 0.58-1.00, $p = 0.047$) of TC. These decreasing-risk effects deserve further discussion by in-depth functional and large sample size studies to elucidate the impact of *IL-17RA* rs4819554 polymorphism on TC. Finally, the potential SNP-SNP interactions among *IL-18* rs1946519, rs360718 and *IL-17RA* rs4819554 were determined by MDR. The analysis of the SNP-SNP interactions presented strong interaction between these SNPs regarding susceptibility to TC.

With the exceptions of the findings about the interaction between *IL-18*, *IL-17RA* polymorphism and TC risk, several limitations of this study should be pointed out. Firstly, we only genotyped three SNPs in the *IL-18* and *IL-17RA* in this study. More other SNPs should be examined in future studies. Second, our study

enrolled only a moderate number of subjects, and we needed to conduct a larger survey to confirm our study.

5 Conclusions

In conclusion, our findings indicated relevance between *IL-18*, *IL-17RA* and thyroid cancer in Han Chinese population. The large population-based prospective and further functional studies are being planned to provide evidences which were more accurate about the influence of genetic polymorphisms on TC.

Declarations

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This research received no external funding.

Conflict of Interest

The authors have no actual or potential conflicts of interest related to this manuscript.

Author contributions

Bo Yuan, Yanhai Yin, Fen Li: Conceptualization. Yanhai Yin and Fen Li: Methodology. Liangqian Tong and Chaoqun Wang: Software. Kun Liang, Chunru Chen and Rufen Dai: Validation. Yanhai Yin, Fen Li and Liangqian Tong: Data curation. Yanhai Yin: Writing-original draft preparation. Yanhai Yin and Fen Li: Writing-review and editing. Yanhai Yin and Fen Li: Visualization

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Tables

Characteristics	Cases n=365	Controls n=503	<i>p</i>
Age (years) mean ± SD	43.98±15.17	44.16±12.37	0.852
Age (years)			
≤ 44	172 (47.1%)	239 (47.5%)	
> 44	193 (52.9%)	264 (52.5%)	
Gender			
Male	97 (26.6%)	137 (27.2%)	0.877
Female	268 (73.4%)	366 (72.8%)	

Table 1 Characteristics of patients with thyroid cancer and controls

Table 2 The information and HWE about the SNPs

SNP ID	Genes	Chr: Position	Role	Alleles(A/B)	MAF		p- value for HWE	Haploreg	SNPinfo web server
					Cases	Controls			
rs360718	IL-18	11: 112164016	5'UTR	C/A	0.118	0.146	0.150	Promoter histone marks, Enhancer histone marks, DNase, Proteins bound, GRASP QTL hits, Selected eQTL hits	TFBS
rs1946519	IL-18	11: 112164784	Upstream	C/A	0.527	0.481	0.653	Promoter histone marks, Enhancer histone marks, DNase, Motifs changed, Selected eQTL hits	TFBS
rs4819554	IL- 17RA	22:17084145	Upstream	G/A	0.375	0.421	0.854	Promoter histone marks, Enhancer histone marks, DNase, Motifs changed, Selected eQTL hits,	TFBS

SNP, single nucleotide polymorphism;

MAF, minor allele frequency;

eQTL, expression quantitative trait loci;

TFBS, transcription factor binding sites

Table 3 Relationships between the *IL-18*, *IL-17RA* SNPs and thyroid cancer risk

SNP ID	Model	Genotype	Case	Control	Adjusted by age and gender	
					OR (95% CI)	<i>p</i>
IL-18 rs360718	Allele	A	640	857	1.00	
		C	86	147	1.20 (0.99-1.46)	0.098
	Genotype	AA	281	370	1.00	
		CC	4	15	0.35 (0.11-1.06)	0.064
		CA	78	117	0.87 (0.63-1.22)	0.439
	Dominant	AA	281	370	1.00	
		CC-CA	82	132	0.82 (0.60-1.12)	0.214
	Recessive	CA-AA	359	487	1.00	
		CC	4	15	0.36 (0.12-1.09)	0.071
	Log-additive	-	-	-	0.79 (0.60-1.05)	0.099
IL-18 rs1946519	Allele	A	336	514	1.00	
		C	374	476	1.20 (0.99-1.46)	0.063
	Genotype	AA	78	136	1.00	
		CC	97	117	1.44 (0.98-2.13)	0.063
		CA	180	242	1.30 (0.92-1.18)	0.133
	Dominant	AA	78	136	1.00	
		CC-CA	277	359	1.34 (0.98-1.85)	0.070
	Recessive	CA-AA	258	378	1.00	
		CC	97	117	1.21 (0.89-1.66)	0.225
	Log-additive	-	-	-	1.20 (0.99-1.46)	0.064
IL-17RA rs4819554	Allele	A	456	579	1.00	
		G	274	421	0.83 (0.68-1.01)	0.057
	Genotype	AA	146	166	1.00	
		GG	55	87	0.72 (0.48-1.08)	0.109
		GA	164	247	0.76 (0.56-1.02)	0.064
	Dominant	AA	146	166	1.00	
		GG-GA	219	334	0.76 (0.56-0.99)	0.040
	Recessive	GA-AA	310	413	1.00	
		GG	55	87	0.84 (0.58-1.22)	0.360
	Log-additive	-	-	-	0.83 (0.68-1.01)	0.057

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age and gender.

$p < 0.05$ means the data is statistically significant.

Table 4 Relationships between the candidate SNPs and thyroid cancer risk according to the stratification by age and gender

SNP ID	Allele/genotype	Control	Case	OR (95% CI)	<i>p</i>	Control	Case	OR (95% CI)	<i>p</i>
Age		> 44				≤ 44			
IL-18 rs360718	A	454	334	1.00		75	36	1.00	
	C	72	50	0.94 (0.64-1.39)	0.770	403	306	0.63 (0.41-0.97)	0.033
	AA	195	145	1.00		175	136	1.00	
	CC	4	3	1.01 (0.22-4.58)	0.995	11	1	0.12 (0.01-0.91)	0.040
	CA	64	44	0.94 (0.60-1.46)	0.768	53	34	0.84 (0.51-1.37)	0.477
IL-18 rs1946519	A	269	172	1.00		229	168	1.00	
	C	247	206	1.30 (1.00-1.70)	0.050	245	164	1.10 (0.83-1.45)	0.522
	AA	70	38	1.00		58	42	1.00	
	CC	59	55	1.77 (1.03-3.06)	0.040	113	84	1.21 (0.69-2.12)	0.514
	CA	129	96	1.37 (0.85-2.21)	0.200	66	40	1.22 (0.75-1.98)	0.431
IL-17RA rs4819554	A	297	244	1.00		282	212	1.00	
	G	227	142	0.76 (0.58-1.00)	0.047	194	132	0.91 (0.68-1.20)	0.905
	AA	83	79	1.00		83	67	1.00	
	GG	48	28	10.63 (0.36-1.10)	0.103	39	27	0.83 (0.46-1.50)	0.529
	GA	131	86	0.70 (0.46-1.05)	0.086	116	78	0.84 (0.54-1.29)	0.420
Gender		Male				Female			
IL-18 rs360718	A	234	169	1.00		623	471	1.00	
	C	40	23	0.80 (0.46-1.38)	0.416	107	63	0.78 (0.56-1.09)	0.141
	AA	101	73	1.00		269	208	1.00	
	CC	4	0	-	-	11	4	0.47	0.202

IL-18 rs1946519	CA	32	23	0.99 (0.54-1.84)	0.982	85	55	(0.15-1.50) 0.84 (0.57-1.23)	0.364
	A	144	88	1.00		348	248	1.00	
	C	128	96	1.23 (0.84-1.79)	0.284	107	278	1.19 (0.95-1.49)	0.127
	AA	39	20	1.00		97	58	1.00	
	CC	31	24	1.52 (0.71-3.24)	0.282	86	73	1.42 (0.91-2.23)	0.123
IL-17RA rs4819554	CA	66	48	1.43 (0.74-2.77)	0.285	176	132	1.25 (0.84-1.87)	0.263
	A	152	123	1.00		427	333	1.00	
	G	118	71	0.74 (0.51-1.09)	0.124	303	203	0.86 (0.68-1.08)	0.192
	AA	44	39	1.00		122	107	1.00	
	GG	27	13	0.54 (0.25-1.20)	0.131	60	42	0.80 (0.50-1.28)	0.347
	GA	64	45	0.79 (0.45-1.41)	0.433	183	119	0.74 (0.52-1.05)	0.091

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated by logistic regression analysis with adjustments for age.

p < 0.05 indicates statistical significance.

Table 5 Haplotype frequencies in *IL-18* rs360718 and their association with thyroid cancer

Haplotype	Frequency		Crude analysis		Adjusted by age and gender	
	Case	Control	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
AC	0.53	0.48	1.21 (1.00-1.47)	0.050	1.21 (1.00-1.47)	0.051
CA	0.89	0.85	1.34 (1.00-1.78)	0.048	1.34 (1.00-1.78)	0.048
AA	0.36	0.37	0.94 (0.77-1.15)	0.541	0.94 (0.77-1.15)	0.548

OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated using Pearson’s χ^2 tests with and without adjustment by gender and age.

p < 0.05 indicates statistical significance.

Table 6 MDR analysis of SNP-SNP interactions in relation to TC risk.

Model	Training Bal. Acc	Testing Bal. Acc	OR (95% CI)	Testing χ^2 value	<i>p</i> value	CVC
rs4819554 (IL-17RA)	0.535	0.526	1.34 (1.00,1.80)	0.238	0.626	9/10
rs1946519(IL-18), rs4819554 (IL-17RA)	0.549	0.514	1.48 (1.11,1.98)	7.008	*0.008	8/10
rs1946519 (IL-18), rs360718 (IL-18), rs4819554 (IL-17RA)	0.559	0.527	1.64 (1.22,2.21)	10.762	*0.001	10/10

MDR, multifactor dimensionality reduction;

Bal. Acc., balanced accuracy;

CVC, cross-validation consistency;

OR, odds ratio; 95% CI, 95% confidence interval.

p values were calculated using χ^2 tests. **p* < 0.05 indicates statistical significance.

Figures

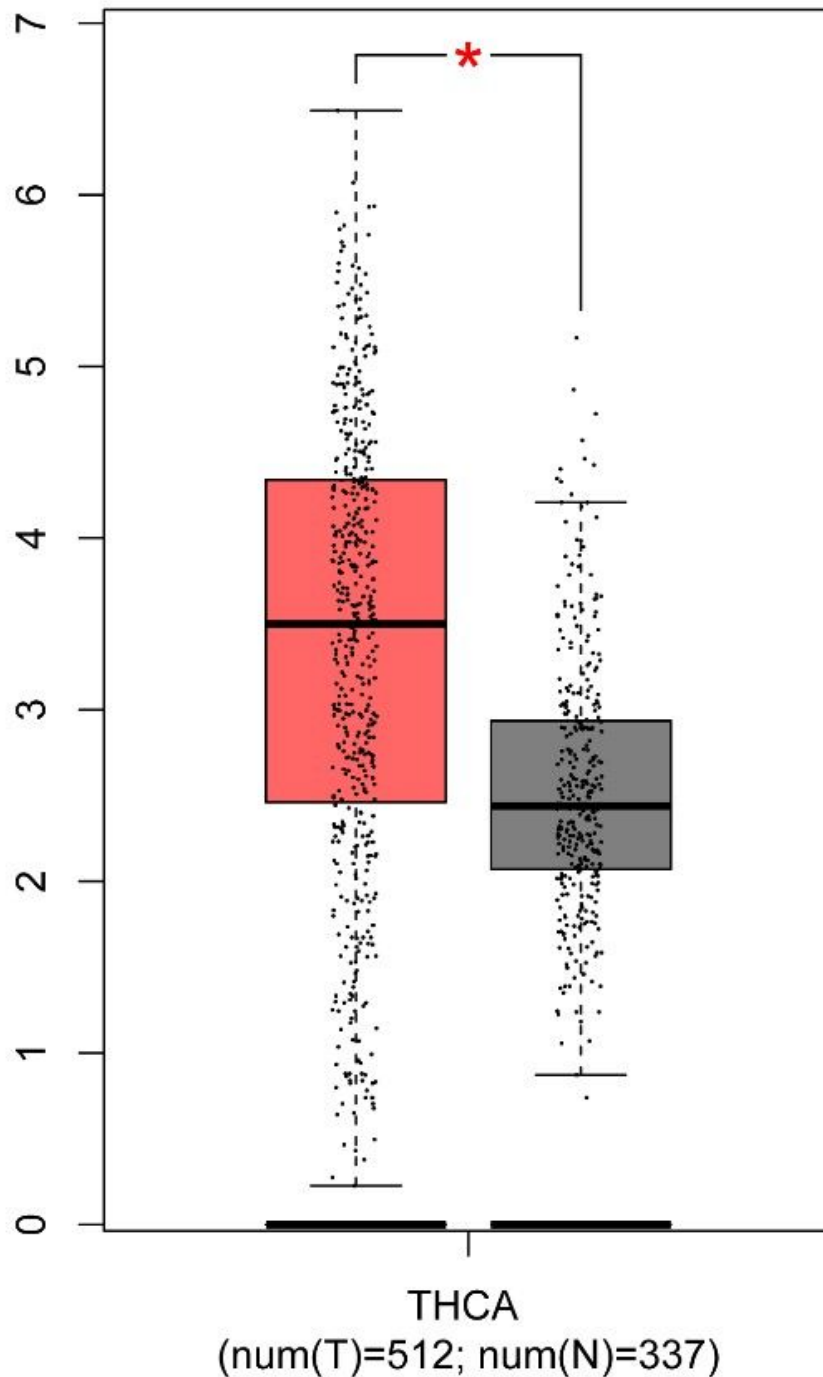


Figure 1

IL-18 gene expression is up-regulated in TC compared with that in normal thyroid tissues. Each bar represents the average level of IL-18 expression. Error bars represent the standard deviation of the mean value. Data was extracted from the GEPIA database (<http://gepia.cancer-pku.cn/>). Asterisk indicates statistical significance ($p < 0.01$).

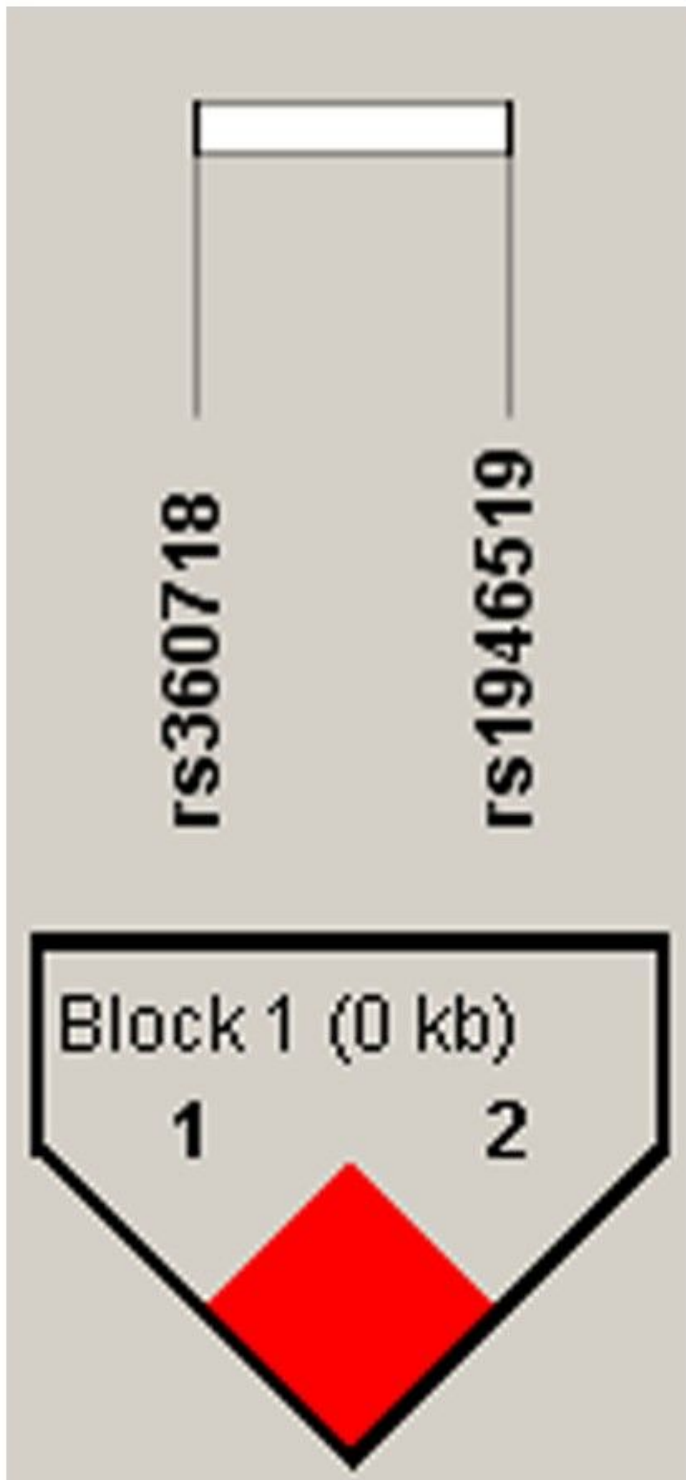


Figure 2

Haplotype block map for two SNPs in IL-18 gene.

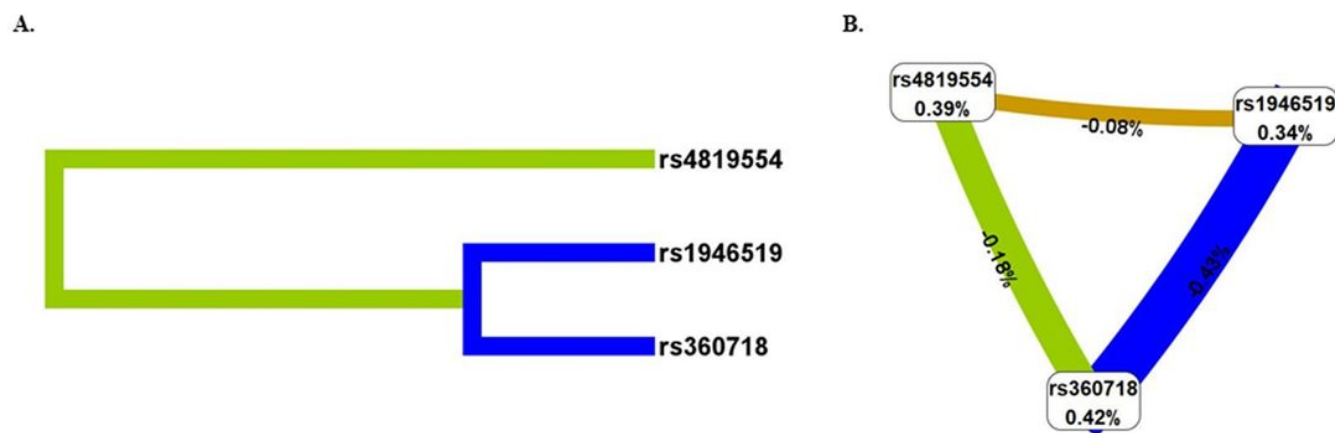


Figure 3

SNP-SNP interaction dendrogram (A) and Fruchterman-Reingold (B). The dendrogram and Fruchterman-Reingold comprises a spectrum of colors that represent a continuum from synergy to redundancy, orange represents a relatively high degree of synergy (positive information gain) and blue represents redundancy (negative information gain).

Supplementary Files

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- [supplymentaryfigure1.tif](#)
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