

The Impact of *BCL11A* Polymorphisms on Endometrial Cancer Risk Among Chinese Han Females

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Background: Endometrial carcinoma (EC) is one of the most common malignant gynecological malignancies. *BCL11A* gene may have a tumor-suppressor role in EC. Until now, no studies have reported the effect of *BCL11A* variants on EC predisposition in Chinese population.

Methods: Six *BCL11A* polymorphisms were genotyped using Agena MassARRAY system among 509 EC patients and 506 matched healthy women. Risk assessment of the *BCL11A* polymorphisms for EC risk was performed by calculating odds ratios (OR) with 95% confidence intervals (CI) through logistic regression models.

Results: We found that rs7581162 (OR = 1.29, $p = 0.012$), rs10189857 (OR = 1.26, $p = 0.028$), rs1427407 (OR = 1.30, $p = 0.015$), rs766432 (OR = 1.27, $p = 0.025$), and rs6729815 (OR = 1.32, $p = 0.008$) in *BCL11A* were associated with higher susceptibility to EC in Chinese Han women. Age and BMI stratified analysis displayed that the risk association between *BCL11A* variants and EC predisposition might be age- and BMI-dependent. Haplotype analysis revealed that $A_{rs10189857}T_{rs1427407}$ and $G_{rs10189857}G_{rs1427407}$ haplotypes were related to an increased risk of EC. MDR analysis indicated that rs1427407 was the most influential attributor on EC risk in the single-locus model, and the best combination was the two-locus model containing rs7581162 and rs766432.

Conclusion: Our study provided the first evidence that rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 in *BCL11A* were risk factors for EC in Chinese Han women. These findings add our understanding of the role of *BCL11A* gene in EC pathogenesis.

Keywords: endometrial carcinoma, *BCL11A* variants, susceptibility, haplotype analysis, MDR analysis

Introduction

Endometrial carcinoma (EC) occurs in the endometrium characterized by a thickening or mass of the endometrium.¹ EC is one of the most common malignant gynecological tumors with an estimated age-standardized incidence risk of 13.1.² In China, EC ranks fourth among female cancers in both incidence and mortality, and the incidence increases steadily with decreasing age at diagnosis.^{3,4} Risk factors for EC are unopposed estrogen, family history of EC, age, excess body weight, diabetes, hypertension, and Lynch syndrome.⁵ Although several risk factors have been identified, endometrial carcinogenesis remains poorly understood. Genetic variants such as single nucleotide polymorphisms (SNPs) are known to play important roles in cancer predisposition.^{6–8} Many SNPs related to EC susceptibility have been identified in previous genome-wide association studies (GWAS), but many polymorphic loci have not been reported.

The B-cell lymphoma/leukemia 11A (*BCL11A*) gene encodes a C2H2 type zinc finger protein transcription factor, and the role of *BCL11A* in tumors appears to be contextual. In some cancers, it has oncogenic effects,⁹ while in some cancers, it may act as a tumor suppressor.¹⁰ For example, *BCL11A*, as an oncogene, promoted tumor formation, cancer cell mobility and epithelial-mesenchymal transition by activating the Wnt/ β -catenin signaling pathway in breast cancer carcinogenesis.¹¹ Downregulation of *BCL11A* protein in colorectal cancer cells was related to enhanced radioresistance, supporting *BCL11A* as a tumor-suppressor role.¹² The expression of *BCL11A* in ER-/PR-EC was higher than that in

normal endometrium, atypical hyperplasia endometrium, and ER+/PR+EC.¹³ Moreover, the expression of *BCL11A* in EC was associated with age, menopause, EC classification, para-aortic lymph node metastasis, tumor differentiation, histological type, ER/PR expression and p53 expression.¹³ A targeted next-generation sequencing study displayed that *BCL11A* mutations were associated with endometriosis and tumor lesions.¹⁴ In EC, consistent with an anti-cancer function, credible variants in *BCL11A* were associated with reduced *BCL11A* expression in endometrial tumors.¹⁵ A GWAS study in an Australian population found that *BCL11A* polymorphism was associated with EC risk.¹⁶ Until now, there were no studies reported the effect of *BCL11A* genetic variants on EC predisposition in Chinese population.

Here, six SNPs (rs7581162, rs10189857, rs1427407, rs766432, rs6729815, and rs2556378) in *BCL11A* with a minor allele frequency (MAF) > 0.05 in dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>) and the call rate >95% in our study population were randomly selected and genotyped to evaluate the potential association between *BCL11A* variants and EC risk among the Chinese Han women at single-SNP or combined SNPs interface.

Materials and Methods

Subjects

A total of 509 patients with EC and 506 matched healthy women were recruited from Hainan General Hospital (Table 1). All participants were genetically unrelated Han Chinese women. Patients were diagnosed with EC based on histopathologic biopsies using the guidelines of the International Federation of Obstetrics and Gynecology (FIGO) criteria. Patients who received preoperative chemotherapy, radiotherapy, or hormone therapy were excluded. Patients with immunological diseases or other cancers were also excluded. Age-matched healthy control underwent routine gynecologic examination at the same hospital. Selection criteria included no malignancy, no history of cancer and no chronic or acute disease. Demographical and clinical characteristics were collected from medical records. This study was approved by the ethics committee of Hainan General Hospital (Ethical approval No.: Med-Eth-Re [2018] 14), in compliance with the Declaration of Helsinki. Informed consent was obtained from all recruited participants.

SNP Selection and Genotyping

Six SNPs (rs7581162, rs10189857, rs1427407, rs766432, rs6729815, and rs2556378) in the *BCL11A* gene with minor allele frequency (MAF) > 0.05 in the dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>) and call rate > 95% were selected. The potential functions of these polymorphisms were evaluated through the HaploReg v4.1 (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>), RegulomeDB (<https://regulome.stanford.edu/regulome-search/>) and GTEx Portal databases (<https://gtexportal.org/home/>).

Table 1 Basic Information of Endometrial Cancer and Health Controls

Characteristics	Cases (n = 509)	Control (n = 506)	p-value
Age (years, mean ± SD)	54.94 ± 8.85	54.61 ± 9.07	0.553
BMI (kg/m ²)			
≥ 24	199 (39.1%)	191 (37.7%)	0.699
< 24	310 (60.9%)	315 (62.3%)	
CEA (ng/mL, mean ± SD)	11.20 ± 2.09	2.08 ± 2.22	< 0.001
AFP (ng/mL, mean ± SD)	8.96 ± 5.32	2.86 ± 1.17	< 0.001
CA199 (U/mL, mean ± SD)	17.87 ± 20.99	12.79 ± 10.45	< 0.001
CA125 (U/mL, mean ± SD)	24.22 ± 39.00	12.97 ± 9.51	< 0.001
Stage			
I–II	261 (51.3%)		
III–IV	93 (18.3%)		
Missing	155 (30.5%)		

Notes: p values were calculated using χ^2 tests or Student's t-test. Bold indicated that $p < 0.05$ meant the data was statistically significant.

Abbreviations: SD, standard deviation; BMI, body mass index; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA, carbohydrate antigen.

Venous blood (5 mL) was collected from each subject in an EDTA vacutainer tube. Genomic DNA was isolated using a commercially available GoldMag DNA Purification Kit (GoldMag Co. Ltd, Xi'an, China). Genotyping was performed by the Agena MassARRAY system (Agena, San Diego, CA, USA) as previously described. Primers design (Suppl Table 1) and data interpretation were performed by the corresponding supporting software following the manufacturer's instructions. The MassARRAY platform is based on MALDI-TOF (matrix-assisted laser desorption/ionization—time of flight) mass spectrometry. The analytical accuracy of MALDI-TOF MS is quite high, 0.1–0.01% of the determined mass.^{17,18} Furthermore, 5% of the samples were used for re-genotyping to quality control, and the consistency rate was 100%.

Statistical Analysis

Age and clinical characteristics were expressed as mean \pm standard deviation (SD), and differences between EC patients and health controls were evaluated by Student's *t*-test. The difference of body mass index (BMI) between cases and controls were analyzed by χ^2 -test Hardy–Weinberg equilibrium (HWE) was assessed to compare the genotype frequencies in controls using the goodness-of-fit chi-square test. Comparison of genotype and allele frequencies in cases and controls were performed by χ^2 -test. The major-type allele was used as a reference, and minor-type allele was used as a risk factor. Risk assessment of *BCL11A* polymorphisms for EC risk was performed by calculating odds ratios (OR) with 95% confidence intervals (CI) using logistic regression models. *D'* values for pairwise linkage disequilibrium (LD) plots were generated by Haploview software (version 4.2). The relationship of *BCL11A* haplotypes with EC susceptibility was evaluated by χ^2 -test and logistic regression model. Multifactor dimensionality reduction (MDR) analysis was performed using MDR_3.0.2 software to identify high-order interaction models for EC predisposition. False-positive report probability (FPRP) analysis was used to evaluate the noteworthy associations and statistical power of the significant findings.^{19,20} We set 0.2 as a FPRP threshold and assigned a prior probability of 0.1 for an association with genotypes under investigation. Analysis of Variance (ANOVA) was performed for the correlation of *BCL11A* variants with CEA, AFP, CA199, CA125 of EC patients and healthy controls. Data analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and PLINK version 1.0.7 software. *p*-value was two-tailed and *p* < 0.05 was defined statistical significance, whereas adjusted *p* < 0.05/5 was considered significant after Bonferroni correction.

Results

Subject Characteristics

In the study, we enrolled 509 EC patients (54.94 \pm 8.85 years) and 506 healthy controls (54.61 \pm 9.07 years), as shown in Table 1. Age and BMI distributions were not significantly different between cases and controls (*p* = 0.553, and *p* = 0.669, respectively). There were significant difference in the levels of CEA, AFP, CA199, and CA125 between two groups (*p* < 0.001). There were 261 cases of I–II stage and 93 cases of III–IV stage.

Relationships of *BCL11A* Polymorphisms with EC Predisposition

Six SNPs in *BCL11A* were genotyped for subsequent studies, and the call rates were > 99.5%, as summarized in Table 2. The genotype distribution of rs2556378 polymorphism was not inconsistent with HWE (*p* = 0.001), therefore, this variant was excluded from subsequent studies. The MAFs of rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 in EC patients were higher than those in healthy controls. *BCL11A* rs7581162-T (OR = 1.29, 95% CI: 1.06–1.57, *p* = 0.012), rs10189857-A (OR = 1.26, 95% CI: 1.03–1.54, *p* = 0.028), rs1427407-T (OR = 1.30, 95% CI: 1.05–1.60, *p* = 0.015), rs766432-C (OR = 1.27, 95% CI: 1.03–1.56, *p* = 0.025), and rs6729815-T (OR = 1.32, 95% CI: 1.07–1.62, *p* = 0.008) was associated with the increased risk of EC. The significance of rs6729815 still existed after Bonferroni correction. The potential function of these polymorphisms by HaploReg v4.1 database and RegulomeDB database was displayed in Table 2. Based on GTEx Portal database, the genotypes of rs1427407 (*p* = 0.00026) was related to the mRNA expression of *BCL11A* in cell (Suppl Figure 1).

Multiple genetic models were used to evaluate the relationship of *BCL11A* polymorphisms to EC predisposition. After adjusting for age, rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 were associated with higher EC susceptibility (Table 3). Specifically, the TT genotype of rs7581162 (genotype: TT vs AA, OR = 2.16, 95% CI: 1.27–3.69, *p* = 0.005;

Table 2 Basic Characteristics and Allele Model About Candidate SNPs in the *BCL11A* Gene

SNPs ID	Chr: Position	Allele (Minor/ Major)	Call Rate	O(HET)	E(HET)	p^a - value for HWE	MAF		Allele Model		Haploreg	Regulome DB
							Case	Control	OR (95% CI)	p^b		
rs7581162	2:60,477,349	T/A	99.9%	0.384	0.362	0.219	0.287	0.238	1.29 (1.06–1.57)	0.012	Promoter histone marks, Enhancer histone marks, Motifs changed, GRASP QTLhits	TF binding or DNase peak
rs10189857	2:60,486,100	A/G	99.8%	0.345	0.346	1.000	0.264	0.222	1.26 (1.03–1.54)	0.028	DNase, Motifs changed, NHGRI/EBI GWAS hits	TF binding or DNase peak
rs1427407	2:60,490,908	T/G	99.8%	0.310	0.321	0.486	0.246	0.200	1.30 (1.05–1.60)	0.015	Enhancer histone marks, Proteins bound, Motifs changed, NHGRI/EBI GWAS hits, GRASP QTL hits	TF binding or DNase peak
rs766432	2:60,492,835	C/A	100%	0.338	0.335	0.895	0.254	0.212	1.27 (1.03–1.56)	0.025	Enhancer histone marks, DNase, Motifs changed, NHGRI/EBI GWAS hits, GRASP QTL hits	TF binding + any motif + DNase Footprint + DNase peak
rs6729815	2:60,496,537	T/C	100%	0.330	0.335	0.790	0.262	0.212	1.32 (1.07–1.62)	0.008*	Enhancer histone marks, Motifs Changed, NHGRI/EBI GWAS hits	TF binding + DNase peak
rs2556378	2:60,535,367	T/G	100%	0.405	0.352	0.001	/	/	/	/	Promoter histone marks, Enhancer histone marks, DNase, NHGRI/EBI GWAS hits, GRASP QTL hits	eQTL + TF binding/ DNase peak

Notes: p^a -values for the HWE test were calculated using goodness of fit χ^2 test. p^b were calculated using by Fisher's exact test. Bold indicated that $p < 0.05$ meant the data was statistically significant. * p indicate that after Bonferroni correction ($p < 0.05/5$) means the data is statistically significant.

Abbreviations: SNP, single-nucleotide polymorphism; MAF, minor allele frequency; O(HET), observed heterozygosity; E(HET), expected heterozygosity; HWE, Hardy–Weinberg equilibrium.

recessive: TT vs AA-AT, OR = 2.03, 95% CI: 1.20–3.42, $p = 0.008$; and additive: AA+AT+TT, OR = 1.30, 95% CI: 1.07–1.59, $p = 0.010$) and AA genotype of rs10189857 (genotype: AA vs GG, OR = 1.78, 95% CI: 1.05–3.01, $p = 0.033$; and additive: GG+GA+AA, OR = 1.26, 95% CI: 1.03–1.54, $p = 0.027$) contributed to increased EC risk. Rs1427407 had a risk-effect for EC under the genotype (GT vs GG: OR = 1.33, 95% CI: 1.02–1.74, $p = 0.033$), dominant (GT-TT vs GG: OR = 1.37, 95% CI: 1.06–1.76, $p = 0.016$) and additive (GG+GT+TT: OR = 1.30, 95% CI: 1.05–1.60, $p = 0.014$) models. Rs766432 was associated with increased EC predisposition (dominant: AC-CC vs AA, OR = 1.32, 95% CI: 1.03–1.70, $p = 0.029$; and additive: AA+AC+CC, OR = 1.28, 95% CI: 1.04–1.57, $p = 0.022$). Moreover, rs6729815 might have higher risk for the occurrence EC in the genotype (TT vs CC: OR = 1.94, 95% CI: 1.14–3.29, $p = 0.015$), dominant (CT-TT vs CC: OR = 1.32, 95% CI: 1.03–1.70, $p = 0.030$), recessive (TT vs CC-CT: OR = 1.79, 95% CI: 1.06–3.02, $p = 0.028$) and additive (TT+CC+CT: OR = 1.31, 95% CI: 1.07–1.61, $p = 0.009$) models. The significance of rs7581162 in the genotype and recessive models and rs6729815 in the additive model still existed after Bonferroni correction.

Stratified Analysis for the Contribution of BCL11A Variant to EC Risk

We further explored the stratified analysis by age and BMI for the relationships of *BCL11A* variants with EC risk (Table 4). In the subjects with age > 55 years/BMI ≥ 24 kg/m², no significant association between *BCL11A* polymorphism with the susceptibility to EC occurrence was observed. Among those aged 55 or younger and those had BMI < 24 kg/m², we found that rs7581162-T, rs10189857-A, rs1427407-T, rs766432-C, and rs6729815-T were risk factors for the development of EC.

The results of age stratification (age ≤ 55 years) were as follows: in the allele (rs7581162, OR = 1.40, $p = 0.010$; rs10189857, OR = 1.38, $p = 0.016$; rs1427407, OR = 1.44, $p = 0.008$; rs766432, OR = 1.42, $p = 0.010$; and rs6729815, OR = 1.48, $p = 0.004$, respectively), genotype (rs7581162, OR = 2.84, $p = 0.001$; rs10189857, OR = 2.53, $p = 0.005$; rs1427407, OR = 2.37, $p = 0.012$; rs766432, OR = 2.55, $p = 0.008$; and rs6729815, OR = 2.70, $p = 0.003$, respectively), dominant (rs1427407, OR = 1.41, $p = 0.043$), recessive (rs7581162, OR = 2.78, $p = 0.001$; rs10189857, OR = 2.44, $p = 0.006$; rs1427407, OR = 2.18, $p = 0.022$; rs766432, OR = 2.35, $p = 0.014$; rs6729815, OR = 2.52, $p = 0.004$, respectively) and additive (rs7581162, OR = 1.38, $p = 0.012$; rs10189857, OR = 1.36, $p = 0.020$; rs1427407, OR = 1.41, $p = 0.011$; rs766432, OR = 1.40, $p = 0.012$; rs6729815, OR = 1.43, $p = 0.006$, respectively) models. The significance of rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 among those aged 55 or younger still existed after Bonferroni correction.

The associated results of BMI stratification (BMI < 24 kg/m²) were as follows: rs7581162 in the allele (OR = 1.42, $p = 0.006$), genotype (OR = 2.41, $p = 0.009$), dominant (OR = 1.45, $p = 0.022$), recessive (OR = 2.14, $p = 0.022$), and additive (OR = 1.44, $p = 0.005$) models; rs10189857 in the allele (OR = 1.37, $p = 0.017$), genotype (OR = 1.43, $p = 0.037$), dominant (OR = 1.47, $p = 0.018$), and additive (OR = 1.38, $p = 0.016$) models; rs1427407 in the allele (OR = 1.41, $p = 0.012$), genotype (OR = 1.57, $p = 0.009$), dominant (OR = 1.57, $p = 0.007$), and additive (OR = 1.41, $p = 0.012$) models; rs766432 in the allele (OR = 1.37, $p = 0.019$), genotype (OR = 1.52, $p = 0.014$), dominant (OR = 1.53, $p = 0.010$), and additive (OR = 1.39, $p = 0.015$) models; rs6729815 in the allele (OR = 1.50, $p = 0.003$), genotype (OR = 1.57, $p = 0.009$, and OR = 1.99, $p = 0.042$), dominant (OR = 1.63, $p = 0.003$), and additive (OR = 1.49, $p = 0.003$) models. The significance of rs7581162, rs1427407, and rs6729815 among those with BMI < 24 kg/m² still existed after Bonferroni correction.

The association of these SNPs with the stage of EC patients was assessed (Suppl Table 3). However, no significant association was detected between *BCL11A* SNPs and at age in EC patients.

The Association Between BCL11A Haplotypes and EC Susceptibility

Moreover, haplotype analysis was performed to estimate the association between *BCL11A* haplotypes and EC susceptibility. As shown in Figure 1, rs10189857 and rs1427407 are in linkage disequilibrium. Haplotype analysis revealed that A_{rs10189857}T_{rs1427407} (adjusted OR = 1.30, 95% CI: 1.05–1.60, $p = 0.016$) and G_{rs10189857}G_{rs1427407} (adjusted OR = 1.26, 95% CI: 1.03–1.54, $p = 0.023$) haplotypes were related to the increased EC risk (Suppl Table 2). Furthermore, AT (adjusted OR = 1.42, 95% CI: 1.09–1.85, $p = 0.010$) and GG (adjusted OR = 1.36, 95% CI: 1.05–1.75, $p = 0.019$) haplotypes also conferred higher EC predisposition among subjects with age ≤ 55 years.

Table 3 The Effect of BCL11A SNPs on the Susceptibility to Endometrial Cancer

SNPs ID	Model	Genotype	Case	Control	Crude Analysis		Adjusted by Age	
					OR (95% CI)	p	OR (95% CI)	p
rs7581162	Genotype	AA	261	288	1		1	
		AT	204	194	1.16 (0.90–1.50)	0.259	1.16 (0.90–1.50)	0.257
		TT	44	23	2.11 (1.24–3.59)	0.006*	2.16 (1.27–3.69)	0.005*
	Dominant	AA	261	288	1		1	
		AT-TT	248	217	1.26 (0.98–1.62)	0.066	1.27 (0.99–1.62)	0.063
	Recessive	AA-AT	465	482	1		1	
		TT	44	23	1.98 (1.18–3.34)	0.010	2.03 (1.20–3.42)	0.008*
Log-additive	—	—	—	1.30 (1.06–1.59)	0.011	1.30 (1.07–1.59)	0.010	
rs10189857	Genotype	GG	280	305	1		1	
		GA	189	174	1.18 (0.91–1.54)	0.209	1.18 (0.91–1.54)	0.206
		AA	40	25	1.74 (1.03–2.95)	0.038	1.78 (1.05–3.01)	0.033
	Dominant	GG	280	305	1		1	
		GA-AA	229	199	1.25 (0.98–1.61)	0.076	1.26 (0.98–1.62)	0.072
	Recessive	GG-GA	469	479	1		1	
		AA	40	25	1.63 (0.98–2.74)	0.062	1.66 (0.99–2.79)	0.054
Log-additive	—	—	—	1.25 (1.02–1.53)	0.030	1.26 (1.03–1.54)	0.027	
rs1427407	Genotype	GG	291	325	1		1	
		GT	186	156	1.33 (1.02–1.74)	0.034	1.33 (1.02–1.74)	0.033
		TT	32	23	1.55 (0.89–2.72)	0.122	1.59 (0.91–2.78)	0.107
	Dominant	GG	291	325	1		1	
		GT-TT	218	179	1.36 (1.06–1.75)	0.017	1.37 (1.06–1.76)	0.016
	Recessive	GG-GT	477	481	1		1	
		TT	32	23	1.40 (0.81–2.43)	0.228	1.43 (0.82–2.49)	0.204
Log-additive	—	—	—	1.29 (1.05–1.59)	0.016	1.30 (1.05–1.60)	0.014	
rs766432	Genotype	AA	281	313	1		1	
		AC	197	171	1.28 (0.99–1.67)	0.061	1.29 (0.99–1.67)	0.058
		CC	31	22	1.57 (0.89–2.77)	0.121	1.60 (0.90–2.84)	0.107
	Dominant	AA	281	313	1		1	
		AC-CC	228	193	1.32 (1.02–1.69)	0.032	1.32 (1.03–1.70)	0.029
	Recessive	AA-AC	478	484	1		1	
		CC	31	22	1.43 (0.81–2.50)	0.214	1.45 (0.83–2.55)	0.194
Log-additive	—	—	—	1.27 (1.03–1.56)	0.025	1.28 (1.04–1.57)	0.022	
rs6729815	Genotype	CC	283	315	1		1	
		CT	185	167	1.23 (0.95–1.61)	0.120	1.23 (0.95–1.61)	0.119
		TT	41	24	1.90 (1.12–3.23)	0.017	1.94 (1.14–3.29)	0.015
	Dominant	CC	283	315	1		1	
		CT-TT	226	191	1.32 (1.03–1.69)	0.031	1.32 (1.03–1.70)	0.030
	Recessive	CC-CT	468	482	1		1	
		TT	41	24	1.76 (1.05–2.96)	0.033	1.79 (1.06–3.02)	0.028
Log-additive	—	—	—	1.30 (1.07–1.60)	0.010	1.31 (1.07–1.61)	0.009*	

Notes: p values were calculated by logistic regression analysis without or with adjustments for age. Bold indicated that $p < 0.05$ meant the data was statistically significant.

*p indicate that after Bonferroni correction ($p < 0.05/5$) means the data is statistically significant.

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

MDR Analysis for the Effect of BCL11A SNP-SNP Interaction on EC Risk

MDR analysis was applied to explore the effect of *BCL11A* SNP-SNP interaction on EC risk. The dendrogram (Figure 2A) and Fruchterman Reingold (Figure 2B) showed that the *BCL11A* SNP-SNP interaction had a strong redundant effect. The best single-locus and multi-locus models of *BCL11A* SNPs for EC susceptibility were summarized

Table 4 Stratification Analysis by Age and BMI for the Effect of *BCL11A* SNPs on the Susceptibility to Endometrial Cancer

SNPs ID	Model	Genotype	Case	Control	OR (95% CI)	p	Case	Control	OR (95% CI)	p
Age			> 55 years				≤ 55 years			
rs7581162	Allele	A	333	326	1		393	444	1	
		T	113	96	1.15 (0.84–1.57)	0.373	179	144	1.40 (1.09–1.82)	0.010
	Genotype	AA	117	123	1		144	165	1	
		AT	99	80	1.30 (0.88–1.92)	0.185	105	114	1.06 (0.75–1.50)	0.746
		TT	7	8	0.92 (0.32–2.61)	0.872	37	15	2.84 (1.50–5.40)	0.001*
	Dominant	AA	117	123	1		144	165	1	
		AT-TT	106	88	1.27 (0.87–1.85)	0.224	142	129	1.27 (0.91–1.76)	0.158
	Recessive	AA-AT	216	203	1		249	279	1	
	TT	7	8	0.82 (0.29–2.30)	0.707	37	15	2.78 (1.49–5.18)	0.001*	
Log-additive	—	—	—	—	1.18 (0.84–1.64)	0.343	—	—	1.38 (1.08–1.78)	0.012
rs10189857	Allele	G	344	331	1		405	453	1	
		A	102	89	1.10 (0.80–1.52)	0.551	167	135	1.38 (1.06–1.80)	0.016
	Genotype	GG	128	131	1		152	174	1	
		GA	88	69	1.31 (0.88–1.94)	0.190	101	105	1.10 (0.78–1.56)	0.588
		AA	7	10	0.72 (0.26–1.94)	0.512	33	15	2.53 (1.33–4.85)	0.005*
	Dominant	GG	128	131	1		152	174	1	
		GA-AA	95	79	1.23 (0.84–1.81)	0.291	134	120	1.28 (0.92–1.78)	0.142
	Recessive	GG-GA	216	200	1		253	279	1	
	AA	7	10	0.65 (0.24–1.74)	0.389	33	15	2.44 (1.29–4.60)	0.006*	
Log-additive	—	—	—	—	1.11 (0.80–1.55)	0.540	—	—	1.36 (1.05–1.75)	0.020
rs1427407	Allele	G	353	342	1		415	464	1	
		T	93	80	1.13 (0.81–1.57)	0.485	157	122	1.44 (1.10–1.89)	0.008*
	Genotype	GG	134	140	1		157	185	1	
		GT	85	62	1.43 (0.96–2.15)	0.081	101	94	1.27 (0.89–1.80)	0.187
		TT	4	9	0.46 (0.14–1.54)	0.209	28	14	2.37 (1.21–4.67)	0.012
	Dominant	GG	134	140	1		157	185	1	
		GT-TT	89	71	1.31 (0.89–1.94)	0.177	129	108	1.41 (1.01–1.97)	0.043
	Recessive	GG-GT	219	202	1		258	279	1	
	TT	4	9	0.41 (0.12–1.35)	0.142	28	14	2.18 (1.12–4.23)	0.022	
Log-additive	—	—	—	—	1.14 (0.80–1.60)	0.472	—	—	1.41 (1.08–1.83)	0.011

(Continued)

Table 4 (Continued).

SNPs ID	Model	Genotype	Case	Control	OR (95% CI)	p	Case	Control	OR (95% CI)	p
rs766432	Allele	A	350	338	1		409	459	1	
		C	96	86	1.08 (0.78–1.50)	0.653	163	129	1.42 (1.09–1.85)	0.010
	Genotype	AA	130	135	1		151	178	1	
		AC	90	68	1.37 (0.92–2.04)	0.118	107	103	1.23 (0.87–1.74)	0.248
		CC	3	9	0.34 (0.09–1.30)	0.114	28	13	2.55 (1.27–5.09)	0.008*
	Dominant	AA	130	135	1		151	178	1	
		AC-CC	93	77	1.25 (0.85–1.84)	0.254	135	116	1.37 (0.99–1.91)	0.059
	Recessive	AA-AC	220	203	1		258	281	1	
		CC	3	9	0.30 (0.08–1.14)	0.078	28	13	2.35 (1.19–4.64)	0.014
	Log-additive	—	—	—	1.09 (0.77–1.53)	0.644	—	—	1.40 (1.08–1.83)	0.012
rs6729815	Allele	C	347	338	1		404	459	1	
		T	99	86	1.12 (0.81–1.55)	0.490	168	129	1.48 (1.14–1.93)	0.004*
	Genotype	CC	131	135	1		152	180	1	
		CT	85	68	1.29 (0.87–1.92)	0.212	100	99	1.20 (0.84–1.70)	0.316
		TT	7	9	0.80 (0.29–2.21)	0.668	34	15	2.70 (1.42–5.14)	0.003*
	Dominant	CC	131	135	1		152	180	1	
		CT-TT	92	77	1.23 (0.84–1.81)	0.289	134	114	1.39 (1.00–1.94)	0.050
	Recessive	CC-CT	216	203	1		252	279	1	
		TT	7	9	0.73 (0.27–2.00)	0.540	34	15	2.52 (1.34–4.74)	0.004*
	Log-additive	—	—	—	1.13 (0.81–1.58)	0.477	—	—	1.43 (1.11–1.85)	0.006*
BMI			≥ 24 kg/m ²				< 24 kg/m ²			
rs7581162	Allele	A	293	287	1		433	483	1	
		T	105	93	1.11 (0.80–1.53)	0.541	187	147	1.42 (1.10–1.83)	0.006*
	Genotype	AA	109	105	1		152	183	1	
		AT	75	77	0.94 (0.62–1.42)	0.756	129	117	1.33 (0.95–1.85)	0.092
		TT	15	8	1.77 (0.71–4.37)	0.218	29	15	2.41 (1.24–4.68)	0.009*
	Dominant	AA	109	105	1		152	183	1	
		AT-TT	90	85	1.01 (0.68–1.51)	0.948	158	132	1.45 (1.06–1.99)	0.022
	Recessive	AA-AT	184	182	1		281	300	1	
		TT	15	8	1.82 (0.75–4.41)	0.188	29	15	2.14 (1.12–4.08)	0.022
	Log-additive	—	—	—	1.10 (0.79–1.53)	0.569	—	—	1.44 (1.11–1.86)	0.005*

rs10189857	Allele	G	296	289	1		453	495	1	
		A	102	91	1.09 (0.79–1.52)	0.587	167	133	1.37 (1.06–1.78)	0.017
	Genotype	GG	114	108	1		166	197	1	
		GA	68	73	0.88 (0.58–1.35)	0.564	121	101	1.43 (1.02–2.00)	0.037
	Dominant	AA	17	9	1.76 (0.75–4.14)	0.196	23	16	1.75 (0.89–3.42)	0.104
		GG	114	108	1		166	197	1	
	Recessive	GA-AA	85	82	0.98 (0.65–1.46)	0.917	144	117	1.47 (1.07–2.03)	0.018
		GG-GA	182	181	1		287	298	1	
Log-additive	AA	17	9	1.85 (0.80–4.28)	0.153	23	16	1.52 (0.79–2.95)	0.212	
	—	—	—	1.09 (0.79–1.50)	0.620	—	—	1.38 (1.06–1.78)	0.016	
rs1427407	Allele	G	304	299	1		464	507	1	
		T	94	81	1.14 (0.81–1.60)	0.442	156	121	1.41 (1.08–1.84)	0.012
	Genotype	GG	118	117	1		173	208	1	
		GT	68	65	1.04 (0.68–1.59)	0.867	118	91	1.57 (1.12–2.21)	0.009*
	Dominant	TT	13	8	1.56 (0.62–3.95)	0.344	19	15	1.57 (0.77–3.18)	0.214
		GG	118	117	1		173	208	1	
	Recessive	GT-TT	81	73	1.09 (0.73–1.64)	0.664	137	106	1.57 (1.13–2.17)	0.007*
		GG-GT	186	182	1		291	299	1	
Log-additive	TT	13	8	1.54 (0.62–3.85)	0.352	19	15	1.33 (0.66–2.68)	0.419	
	—	—	—	1.13 (0.81–1.58)	0.478	—	—	1.41 (1.08–1.84)	0.012	
rs766432	Allele	A	303	298	1		156	499	1	
		C	95	84	1.11 (0.80–1.55)	0.533	164	131	1.37 (1.05–1.78)	0.019
	Genotype	AA	71	70	1		165	199	1	
		AC	12	7	1.00 (0.65–1.52)	0.985	126	101	1.52 (1.09–2.12)	0.014
	Dominant	CC	116	114	1.64 (0.62–4.34)	0.321	19	15	1.58 (0.78–3.21)	0.208
		AA	83	77	1		165	199	1	
	Recessive	AC-CC	187	184	1.05 (0.70–1.58)	0.799	145	116	1.53 (1.11–2.10)	0.010
		AA-AC	12	7	1		291	300	1	
Log-additive	CC	—	—	1.64 (0.63–4.29)	0.313	19	15	1.34 (0.67–2.69)	0.411	
	—	71	70	1.11 (0.79–1.55)	0.559	—	—	1.39 (1.07–1.82)	0.015	

(Continued)

Table 4 (Continued).

SNPs ID	Model	Genotype	Case	Control	OR (95% CI)	p	Case	Control	OR (95% CI)	p
rs6729815	Allele	C	300	193	1		451	504	1	
		T	98	89	1.08 (0.77–1.49)	0.665	169	126	1.50 (1.15–1.95)	0.003*
	Genotype	CC	117	110	1		166	205	1	
		CT	66	73	0.85 (0.56–1.30)	0.456	119	94	1.57 (1.12–2.21)	0.009*
		TT	16	8	1.84 (0.76–4.50)	0.179	25	16	1.99 (1.03–3.87)	0.042
		Dominant	CC	117	110	1		166	205	1
	Recessive	CT-TT	82	81	0.95 (0.63–1.42)	0.802	144	110	1.63 (1.18–2.26)	0.003*
		CC-CT	183	183	1		285	299	1	
	Log-additive	TT	16	8	1.96 (0.81–4.72)	0.134	25	16	1.68 (0.88–3.23)	0.116
		—	—	—	—		—	—	1.49 (1.15–1.93)	0.003*

Notes: p values were calculated by Fisher's exact test or logistic regression analysis with adjustments for age. Bold indicated that $p < 0.05$ meant the data was statistically significant. *p indicate that after Bonferroni correction ($p < 0.05/5$) means the data is statistically significant.

Abbreviations: SNP, single nucleotide polymorphism; BMI, body mass index; OR, odds ratio; 95% CI, 95% confidence interval.

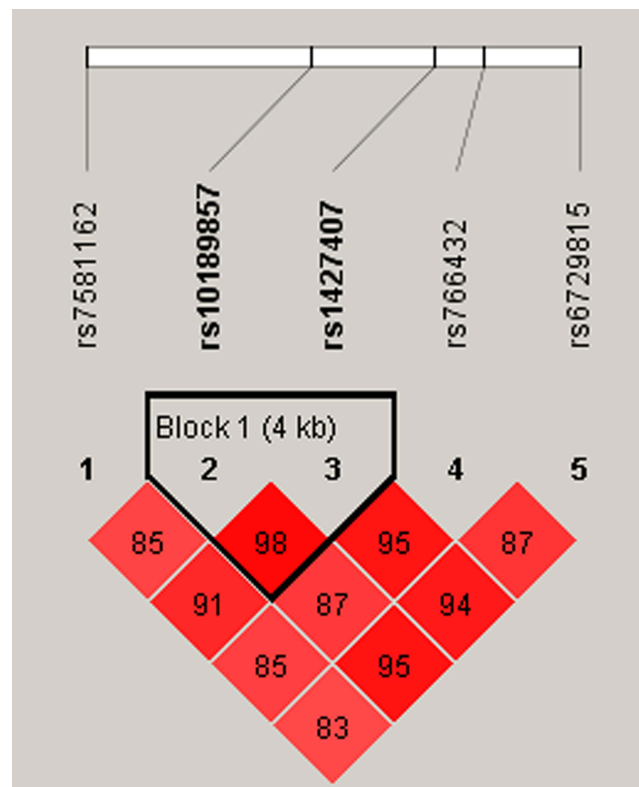


Figure 1 LD plots of six SNPs in the *BCL11A* gene. The number in the diamond indicates the D' value of pairwise LD between SNPs.

in Table 5. In the single-locus model, rs1427407 was the most influential attributor for EC risk (testing accuracy = 0.5356, cross-validation consistency (CVC) = 10/10). In the multi-locus model, the best combination was a two-locus model containing rs7581162 and rs766432 (testing accuracy= 0.5336, CVC= 5/10).

FPRP Analysis for the Significant Findings

FPRP analysis was carried out to interrogate whether the significant findings were deserving attention (Suppl Table 4). At the prior probability level of 0.1, the significant association for rs7581162, rs10189857, rs1427407, rs766432 and rs6729815 remained noteworthy in the overall analysis (FPRP < 0.2) and statistical power > 85% under the allele model. In the subgroup at age < 55 years, significant findings remained noteworthy for these variants.

The Relationship of *BCL11A* SNPs with Characteristics Among EC Patients/Healthy Controls

The relationship of *BCL11A* SNPs with CEA, AFP, CA199, and CA125 among EC patients/healthy controls were assessed, as displayed in Suppl Table 5. However, no statistically association was observed.

Discussion

In this study, we found that rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 in *BCL11A* were associated with EC susceptibility in Chinese Han women, especially in subjects aged ≤ 55 years and BMI <24 kg/m². Haplotype analysis showed that rs10189857 and rs1427407 were in linkage disequilibrium, and the $A_{rs10189857}T_{rs1427407}$ and $G_{rs10189857}G_{rs1427407}$ haplotypes were related to the increased EC risk. MDR analysis indicated that rs1427407 was the most influential attributor on EC risk in the single-locus model, and the best combination was a two-locus model containing rs7581162 and rs766432. Our study is the first to report that *BCL11A* variants were risk factors for EC in Chinese Han females.

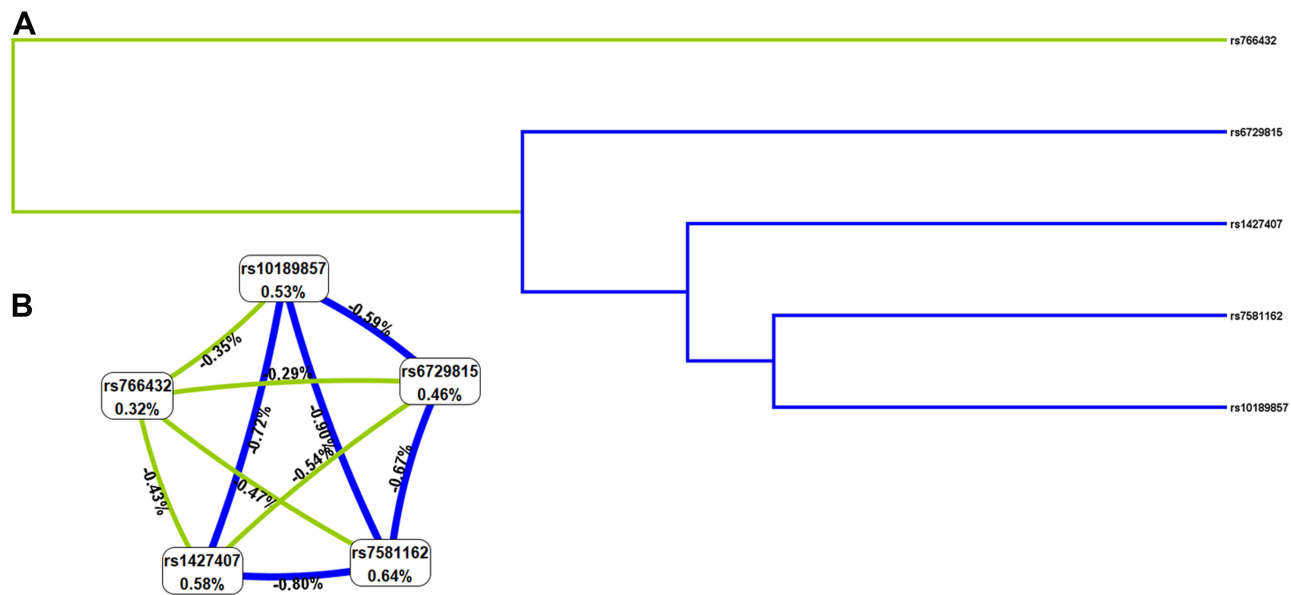


Figure 2 The dendrogram (A) and Fruchterman Reingold (B) of *BCL11A* SNP-SNP interaction for EC risk. (A) Short connections among nodes represent stronger redundant interactions. Green and blue color indicated weak interactions. (B) This graphical model describes the percent entropy explained by each SNP. Values in nodes represent the information gains of individual attribute (main effects). Values between nodes are information gains of each pair of attributes (interaction effects). Positive percent entropy indicates synergy whereas the negative percent entropy indicates redundancy.

The *BCL11A* gene, located on 2p16, spans 102 kb, which is considered to be an oncogene in malignant haematological diseases, and is first detected in B-cell chronic lymphocytic leukaemia.²¹ *BCL11A* can cause transcriptional repression of mammalian target genes by binding to DNA motifs and promoting the deacetylation of H3/H4 histone.²² *BCL11A* may participate in cell cycle and cell growth by inhibiting of P21 induction.²³ In addition, *BCL11A* is involved in cell apoptosis by upregulating the expression of *BCL2*, *BCL2-xL*, and *MDM2* and inhibiting the activity of *P53*.²⁴ These studies support the possible involvement of *BCL11A* in tumorigenesis. Studies have found that *BCL11A* is abnormally expressed in EC tissues, which is related to EC classification, lymph node metastasis, tumor differentiation, histological type, ER/PR expression.¹³ Targeted next-generation sequencing evaluated *BCL11A* mutations in patients with endometriosis.¹⁴ These lines of evidence have led us to formulate the hypothesis that *BCL11A* could be of pathogenic importance in EC.

Genetic variations of *BCL11A* gene may be associated with gene expression, thereby affecting the occurrence and development of disease. To date, *BCL11A* polymorphisms have been reported to be associated with various cancer, such as pancreatic cancers, laryngeal squamous cell carcinoma, and chronic lymphocytic leukemia.^{25–27} Previous study have revealed that *BCL11A* rs7579014 is a risk locus for EC occurrence and is related to the expression of *BCL11A* in endometrial tumors.¹⁵ *BCL11A* rs148261157 has been reported to increase the risk of EC.¹⁶ However, the association between rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 in *BCL11A* and EC susceptibility has not been

Table 5. SNP-SNP Interaction Models of the *BCL11A* Gene the Predisposition of Endometrial Cancer

Model	Training Bal. Acc.	Testing Bal. Acc.	CVC	OR (95% CI)	p
rs1427407	0.5356	0.5356	10/10	1.35 (1.05–1.74)	0.0277
rs7581162, rs766432	0.5412	0.5336	5/10	1.42 (1.08–1.86)	0.0106
rs7581162, rs10189857, rs766432	0.5447	0.5287	4/10	1.44 (1.12–1.86)	0.0047
rs7581162, rs10189857, rs1427407, rs766432	0.5470	0.5208	4/10	1.47 (1.14–1.90)	0.0029
rs7581162, rs10189857, rs1427407, rs766432, rs6729815	0.5479	0.5178	10/10	1.46 (1.14–1.88)	0.0029

Notes: p values were calculated using χ^2 tests. Bold indicated that $p < 0.05$ meant the data was statistically significant.

Abbreviations: MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross-validation consistency; OR, odds ratio; CI, confidence interval.

reported. Our study displayed that the MAFs of these five SNPs in *BCL11A* were higher in EC patients than in healthy controls, and had the increased risk effect on EC predisposition. To date, the functions of these SNPs have not been reported. In bioinformatics analysis, results from HaploReg v4.1 database displayed that these SNPs may be associated with promoter/Enhancer histone marks, DNase, proteins bound, motifs changed, NHGRI/EBI GWAS hits, and/or GRASP QTL hits.²⁸ Previously, rs766432 in the intronic regions of *BCL11A* gene may affect the binding of protein to this region.²⁹ Rs1427407 in the second intron of the trans-acting element *BCL11A* is associated with the expression of *BCL11A*.³⁰ Based on GTEx Portal database, the genotypes of rs1427407 was related to the mRNA expression of *BCL11A* in cell. These results suggest that these loci may be involved in EC carcinogenic by affecting the expression or function of *BCL11A*, which requires further experimental confirmation.

Age is a risk factor for the development of EC.³¹ A study reported that median age at diagnosis of endometrial cancer was 55 years.³² Besides, the mean ages of EC patients and the controls were respectively 54.94 ± 8.85 years and 54.61 ± 9.07 years in the study. In order to explore the contribution of age, we have divided the cases and controls into two groups as ≤ 55 years and > 55 years. The results of age-stratified analysis displayed that rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 were associated with EC susceptibility in subjects aged ≤ 55 years, but not in subjects aged > 55 years, suggesting that the risk association between *BCL11A* variants and EC predisposition might be age-dependent. Obesity is a risk factor for endometrial cancer risk and mortality.³³ Using body mass index (BMI) as a measure of obesity, we assessed the association of *BCL11A* variants with BMI. Among those aged 55 or younger and those had BMI < 24 kg/m², we found that rs7581162-T, rs10189857-A, rs1427407-T, rs766432-C, and rs6729815-T were risk factors for the development of EC. The underlying mechanism of this correlation awaits further study. Haplotype-based analysis may be more effective than single-locus analysis when there is linkage disequilibrium among SNPs.³⁴ Haplotype analysis revealed that rs10189857 and rs1427407 were in linkage disequilibrium, and the $A_{rs10189857}T_{rs1427407}$ and $G_{rs10189857}G_{rs1427407}$ haplotypes were related to an increased risk of EC. MDR analysis was used to identify specific combination effects of genetic variants with high-order interactions.³⁵ In this study, we found that rs1427407 was the most influential attributor for EC risk in the single-locus model, and the best combination was the two-locus model incorporating rs7581162 and rs766432 in *BCL11A*.

Although our results provided evidence on the relationship between *BCL11A* polymorphisms and EC predisposition, several limitations should not be neglected. First, our subjects were recruited from a hospital that may contribute to selection bias. Second, due to the lack of adequate personal information, this study failed to assess the impact of gene-environment interactions on EC susceptibility and the association of genetic variants with clinicopathological data of EC patients. In the future, we would like to enlarge sample size and complete the clinicopathological data to evaluate the relationship. Third, although our findings suggested that *BCL11A* variants were associated with increased the risk of EC, the potential mechanisms and functions of these SNPs underlying the association have not been revealed. Fourth, the expression data of *BCL11A* is missing. In subsequent research, we would design detailed experiments to further explore the expression data of *BCL11A* and the potential mechanisms and functions of these SNPs in EC.

In conclusion, our study first provides evidence that rs7581162, rs10189857, rs1427407, rs766432, and rs6729815 in *BCL11A* are risk factors for EC occurrence in Chinese Han women. These findings increased our understanding of the role of *BCL11A* gene in EC pathogenesis. However, the expression data of *BCL11A* and the association between SNPs and *BCL11A* expression need further explore in the more detailed experiments.

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Disclosure

All authors declare that they have no competing interests in this work.

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