



Association of TAB2 gene polymorphism with endometrial cancer susceptibility and clinical analysis

TAB2 gen polimorfizminin endometriyal kanser duyarlılığı ve klinik analizle ilişkisi

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Abstract

Objective: Transforming growth factor- β -activated kinase 1 binding protein 2 (TAB2) plays a vital role in inflammatory pathways. It has also been considered a potential target for the enhancement of the antiestrogen effects. Previous evidence has indicated that TAB2 gene variants are associated with several diseases, whereas their potential correlation with endometrial cancer (EC) is unclear. This study aims to initially explore the association between TAB2 gene polymorphisms (rs237028 /AG, rs521845 T/G, and rs652921 T/C) and EC.

Materials and Methods: Polymerase chain reaction-restriction fragment length polymorphism was applied to determine the genotype composition and the allele frequencies of TAB2 gene variant polymorphisms in 270 EC patients and 294 healthy controls.

Results: The G allele of rs521845 was related to the increase of EC risk [p=0.08, odds ratio (OR): 0.72, 95% confidence interval (CI): 0.56-0.91]. Moreover, EC risk was associated with rs521845 in different genetic models (p=0.017, OR: 0.63, 95% CI: 0.44-0.91 in the codominant model; p=0.0051, OR: 0.61, 95% CI: 0.43-0.87 in the dominant model). For rs237028, the percentage of AG genotype in patients with highly differentiated tumours (G1) was significantly higher than that in moderately, poorly differentiated patients (G2/G3) (p=0.031, OR: 0.77, 95% CI: 0.45-1.30).

Conclusion: Our results showed that the rs521845 polymorphism of TAB2, was associated with EC risk, suggesting that TAB2 may play a crucial role in EC prognosis.

Keywords: Endometrial cancer, TAB2, polymorphisms, risk

Öz

Amaç: Dönüştürücü büyüme faktörü- β ile aktive olan kinaz 1 bağlayıcı protein 2 (TAB2), enflamatuvar yollarda hayati bir rol oynar. Ayrıca anti-östrojen etkilerinin artırılması için potansiyel bir hedef olarak da kabul edilmiştir. Önceki kanıtlar, TAB2 gen varyantlarının çeşitli hastalıklarla ilişkili olduğunu gösterirken, endometriyal kanser (EK) ile potansiyel ilişkisi belirsizdir. Bu çalışma, TAB2 gen polimorfizmleri (rs237028 /AG, rs521845 T/G ve rs652921 T/C) ile EK arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Polimeraz zincir reaksiyonu-restriksiyon parça uzunluk polimorfizmi, 270 EK'li hastada ve 294 sağlıklı kontrolde TAB2 gen varyantı polimorfizmlerinin genotip kompozisyonunu ve alel frekanslarını belirlemek için uygulandı.

Bulgular: Rs521845'in G aleli, EK riskinde artışla ilişkilidi [p=0,08, olasılık oranı (OR): 0,72, %95 güven aralığı (GA): 0,56-0,91]. Dahası, EK riski farklı genetik modellerde rs521845 ile ilişkilidi [kodominant modelde (p=0,017, OR: 0,63, %95 GA: 0,44-0,91); dominant modelde (p=0,0051, OR: 0,61, %95

PRECIS: This study investigates the association between TAB2 gene polymorphisms and endometrial cancer (EC). The rs521845 G allele was linked to increased EC risk, while the rs237028 AG genotype correlated with tumor differentiation. Findings suggest TAB2 may play a key role in EC prognosis.

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GA: 0,43-0,87). Rs237028 için, iyi farklılaşmış tümörleri olan hastalarda (G1) AG genotipinin yüzdesi, orta derecede farklılaşmış tümörleri olan hastalardan (G2/G3) önemli ölçüde daha yüksekti ($p=0,031$, OR: 0,77, %95 GA: 0,45-1,30).

Sonuç: Sonuçlarımız *TAB2*'nin rs521845 polimorfizminin EK riskiyle ilişkili olduğunu gösterdi ve bu da *TAB2*'nin EK prognozunda önemli bir rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: Endometrial kanser, *TAB2*, polimorfizmler, risk

Introduction

Endometrial cancer (EC) is ranked as one of the significant gynecologic malignancies, with an estimated 420,242 new cases diagnosed and 97,704 deaths worldwide in 2022^(1,2). Among malignant tumours of the female reproductive system in China, the incidence of EC is only lower than that of cervical cancer, and it mainly occurs in postmenopausal women⁽³⁾. However, in the past decade, the onset age of this disease has tended to become younger, and the incidence rate in young women has increased steadily year by year⁽⁴⁾. EC risk factors include persistent estrogen stimulation without progesterone antagonism⁽⁵⁾, obesity, diabetes, and hypertension, and infertility⁽⁶⁾. However, the molecular pathogenesis of EC remains unclear.

Previous research have shown that in the process of tumour formation and progression, in addition to the activation of related proto-oncogenes and inactivation of tumour suppressor genes, inflammatory stimulation and avoidance of immune surveillance are also important pathogenic factors⁽⁷⁾. Therefore, the tumour microenvironment⁽⁸⁾ has become a research hotspot, as it is composed of tumour-related cells, inflammatory cells, immune cells, various cytokines secreted by related cells, and extracellular matrix⁽⁹⁾. Evidence from multiple sources has suggested that a critical factor in the occurrence and development of EC is the inflammatory microenvironment, and various inflammatory immune responses jointly promote the angiogenesis, proliferation, and invasion of EC⁽¹⁰⁾.

Transforming growth factor- β -activated-activated kinase 1 (TAK1) binding protein 2 (*TAB2*) is crucial to tumour necrosis factor (TNF) receptor-associated factor 6 (TRAF6) as a K63-polyubiquitin-binding TAK1 adaptor protein⁽¹¹⁾, which is critical to TAK1 activation and downstream interleukin (IL)-1 β induced nuclear factor- κ B and mitogen-activated protein kinase pathway activation^(12,13). TNF and IL-1-induced signal pathway activation is vital to inflammation, immunity, and cancer development⁽¹⁴⁾; *TAB2* has been suggested to be meaningful in several diseases. Moreover, the *TAB2* gene, which encodes *TAB2* protein, is identified to be significantly correlated with diseases such as coronary heart disease⁽¹⁵⁾, dilated cardiomyopathy (DCM)⁽¹⁶⁾, congenital heart disease⁽¹⁷⁾, breast cancer⁽¹⁸⁾, and epithelial ovarian cancer⁽¹⁹⁾. Endometrial, breast, and ovarian cancers share some hormonal and epidemiologic risk factors⁽²⁰⁾. Currently, no studies have been conducted on EC and *TAB2* gene variation.

With the implementation of the Human Genome Project, single nucleotide polymorphism (SNP) research has become an essential approach in studying disease-related genes⁽²¹⁾. Single nucleotide polymorphisms are the most common

genetic variations in the human genome, and they can affect the expression of a gene, leading to certain changes in cells. To date, genome-wide association studies have confirmed multiple SNPs associated with EC^(22,23). Based on the above, we hypothesized that *TAB2* gene polymorphism was associated with EC risk. To test our hypothesis, we conducted the following studies to assess the role of rs237028 (A/G), rs521845 (T/G), and rs652921 (T/C). To our knowledge, this study would be the first to evaluate the correlation between *TAB2* gene polymorphism and EC susceptibility.

Materials and Methods

Study Subjects

In this retrospective study, 270 EC women (mean age: 51.63 $\pm$ 9.79 years) were recruited from the West China Second Hospital of Sichuan University from July 2010 to July 2016. All patients were diagnosed with EC by pathologists after histologic examination of biopsy tissue. Patients with autoimmune diseases or other malignancies were excluded to avoid multifactorial effects. The tumour stage is defined by the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system for EC. The control group consisted of 294 healthy women (mean age: 51.86 $\pm$ 12.70 years) who had no abnormal EC clinical symptoms and other underlying diseases and were randomly selected from routine physical examinations.

The present study was approved by the Medical Ethical Review Committee of West China Second Hospital of Sichuan University (approval number: 038, date: 03.03.2022), and all participants gave informed consent.

DNA Extraction and Genotyping

The DNA isolation kit (BioTeke, Peking, China) was used to extract subjects' genomic DNA from blood samples per the manufacturer's instructions and stored the DNA at -20 °C. The rs237028 (A/G), rs521845 (T/G), and rs652921 (T/C) SNPs in the *TAB2* gene were genotyped using polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis. Primer3.0 software was used to design primer sequences, which are shown in Table 1. The total volume of the PCR reaction was 10 mL, including 100 ng of the genomic DNA, 5 mL 2 $\times$ Power Taq PCR MasterMix (BioTeke, Peking, China), 0.15 mL each primer, 3.7 mL ddH₂O. The PCR cycle conditions of all SNPs were 95 °C for 4 minutes, followed by 30 cycles at 94 °C for 30 seconds, 60 °C for 30 seconds, 72 °C for 30 seconds and a final extension at 72 °C for 10 minutes. Then, PCR products were digested by restriction enzymes (shown in Table 1).

Table 1. Information on PCR-RFLP in enrolled subjects

SNPs	Primer sequence	Major/minor gene	Annealing temperature (°C)	Restriction enzyme	Product size (Bp)
rs237028	F: 5'-GCAGACTTGGAAAAGCAAACA-3'	A/G	58.0	Hpy188I	A: 138
	R: 5'-CCAGCCTGAGCAACAAGAG-3'				G: 32 + 106
rs521845	F: 5'-TAGGGCGGTTGAGAAGTGAA-3'	T/G	60.0	AclI	T: 120
	R: 5'-CCTGGGTGACTGAGCTCTTA-3'				G: 20 + 120
rs652921	F: 5'-GGCCATTGGCTCAGAAAT-3'	T/C	62.0	BsaJI	T: 104
	R: 5'-GAGGGAGCTCAGTGAATTG-3'				C: 21 + 83

PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphisms, SNP: Single nucleotide polymorphism, Bp: Base pair

Finally, the genotype of the sites was determined through the Fragment Analyzer 96 Automated CE system (AATI, America); about 10% of the samples were randomly selected for repeated determination, and the results were 100% consistent.

Statistical Analysis

Version 20.0 of the SPSS software package for Windows (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The genotype associations between the *TAB2* gene and EC were calculated by SNPstats online analysis software (<https://www.snpsstats.net/start.htm>), which assessed the frequency distributions of four genetic models (codominant, dominant, recessive, and overdominant) in EC women and healthy controls. Chi-square tests were conducted to compare allele frequencies, genotype distributions, and the Hardy-Weinberg equilibrium between the two groups. Odds ratios (ORs) and respective 95% confidence intervals (CIs) were used to assess the influences of different alleles and genotypes. The primary parameters compared included allele frequency, genotype distribution, OR, and 95% CI between EC patients and controls. $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics and Hardy-Weinberg Equilibrium Test

Between the EC patients and control subjects, there was no statistically significant difference ($p > 0.05$) in general characteristics, such as mean age, body mass index (BMI), menopausal ratio, pregnancy history, etc. (shown in Table 2). Among the 270 EC patients, 247 patients had abnormal uterine bleeding, and 268 had received surgical treatment. The primary histopathological type of these patients was endometrioid adenocarcinoma. The genotypes of the three SNPs (rs237028, rs521845, rs652921) in the two groups all conformed to Hardy-Weinberg equilibrium.

TAB2 Gene Polymorphisms and EC Susceptibility

The differences in the allele frequencies and genotypes of the three SNPs between patients with EC and controls are

presented in Table 3. The genotype distributions of T/T, T/G, and G/G for rs521845 were 32.1%, 52.2%, and 15.7% in the case group and 43.5%, 44.9%, and 11.6% in the control group, respectively. Significance had been observed in the codominant model ($p = 0.017$). In the dominant model, compared with the T/T genotype, T/G or G/G genotypes were associated with a significantly decreased risk of EC ($p = 0.0051$, OR: 0.61, 95% CI: 0.43-0.87). Similarly, the frequency of G allele of rs521845 was higher in patients (42%) than in controls (34%) ($p = 0.08$, OR: 0.72, 95% CI: 0.56-0.91). Meanwhile, similar results were observed between patients with endometrioid adenocarcinoma and controls. No significant correlation was found between EC and rs237028 or rs652921.

Association Between *TAB2* Gene Polymorphisms and Clinical Features

To learn more about the association between the three SNPs and EC, we stratified these EC patients according to age, BMI, family history of cancer, menopausal status, histological types, FIGO grades, myometrium invasion, parametrial invasion, cervical invasion, and lymph nodes status (Tables 4, 5, and 6). It was observed that for rs237028, the percentage of AG genotype in patients with highly differentiated tumours (G1) was significantly higher than that in moderately differentiated patients (G2/G3) ($p = 0.031$, OR: 0.77, 95% CI: 0.45-1.30). In addition, there were no statistically significant differences among subgroups of other SNPs.

Discussion

The *TAB2* gene maps on chromosome 6q25.1 and encodes a scaffold protein that forms a kinase complex that links TRAF6 and TAK1, thus determining TAK1 activation⁽²⁴⁾. TAK1 has been implicated in regulating various cellular processes, including embryonic development, differentiation, autophagy, apoptosis, and cell survival has been thought to be related to the occurrence and development of cancer⁽²⁵⁾. *TAB2*, as an essential protein for TAK1 activation, has been studied in many diseases. Initially, Sanjo et al.⁽²⁶⁾ found that *TAB2* was necessary for embryonic development by preventing

Table 2. Baseline characteristics of endometrial cancer patients and health controls

Characteristics	Number of case (%)	Number of controls (%)	p
Sample size	270	294	
Age mean ± SD (range) (year)	51.63±9.79 (25-81)	51.86±12.70 (28-75)	0.81
BMI mean ± SD (kg/m²)	24.14±3.42	24.32±3.26	0.59
History of pregnancy			
Yes	254 (94.1%)	277 (94.2%)	0.54
No	16 (5.9%)	17 (5.8%)	
Menopausal status			
Premenopausal	131 (48.5%)	128 (43.5%)	0.14
Postmenopausal	139 (51.5%)	166 (56.5%)	
Family history of cancer			
Yes	21 (7.8%)	19 (6.5%)	0.33
No	249 (92.2%)	275 (93.5%)	
Abnormal uterine bleeding			
Yes	254 (94.1%)		
No	13 (4.8%)		
FIGO grade			
G1	97 (35.9%)		
G2	98 (36.3%)		
G3	75 (27.8%)		
FIGO stage			
I	205 (75.9%)		
II	22 (8.1%)		
III	29 (10.7%)		
IV	12 (4.4%)		
Unknown	2 (0.7%)		
Histology			
Endometrioid adenocarcinoma	228 (84.4%)		
Non-endometrioid adenocarcinoma	42 (15.6%)		
Myometrial invasion			
<1/2	167 (61.9%)		
≥1/2	60 (22.2%)		
No	43 (15.9%)		
Parametrial invasion			
Yes	23 (8.5%)		
No	245 (90.7%)		
Cervical invasion			
Yes	43 (15.9%)		
No	225 (83.3%)		

Table 2. Continued

Characteristics	Number of case (%)	Number of controls (%)	p
Vascular invasion			
Yes	23 (8.5%)		
No	216 (80.0%)		
Lymph node status			
Yes	23 (8.5%)		
No	216 (80.0%)		
IHC			
ER (+)	198/222		
PR (+)	188/221		
P53 (+)	132/212		
SD: Standard deviation, BMI: Body mass index, FIGO: International Federation of Gynecology and Obstetrics, IHC: Immunohistochemistry, ER: Estrogen, PR: Progesterone			

hepatocyte apoptosis. Owerbach et al.⁽²⁷⁾ thatfirst identified that the *TAB2* gene was associated with susceptibility to type 1 diabetes mellitus. It’s worth noting that in Thienpont et al.’s⁽²⁸⁾ study, the *TAB2* gene was expressed in the developing heart and was mutated, deleted, or disrupted by a translocation among congenital heart defect patients. This suggested that the gene plays a vital role in the development of embryos and the formation of heart valves, a finding that has been linked to much subsequent research on the gene. Weiss et al.’s⁽²⁹⁾ report supported the association of *TAB2* haploinsufficiency with various congenital heart defects. Cheng et al.^(30,31) found that *TAB2* microdeletion is a risk factor for hypoplastic left heart syndrome (HLHS) and proposed the necessity of SNP microarray analysis and molecular testing for a *TAB2* loss of function variant in HLHS patients.

TAB2 is not just part of the inflammatory pathway, but also considered a potential target to potentiate antiestrogen action⁽³²⁾. Evidence provided by Reineri et al.⁽¹⁸⁾ suggested that *TAB2*, in conjunction with the nuclear receptor corepressor complex and its novel functional domain, interacts with estrogen receptors in breast cancer cells. EC’s leading risk factor is exposure to endogenous and exogenous oestrogens, and estrogen requires estrogen to function physiologically through estrogen receptor α (ERS1). The *ESR1* gene, encoding the estrogen receptor 1, is an identified oncogene for EC⁽³³⁾. It is worth noting that the *TAB2* gene is close to the *ESR1* gene on the chromosome. This suggests that the *TAB2* gene may be interlinked with the *ESR1* gene, jointly affecting the occurrence and development of EC.

In the latest study, Shen et al.⁽¹⁶⁾ confirmed that the *TAB2* gene polymorphism is associated with susceptibility to DCM in a Chinese population. Furthermore, their results showed that the risk of DCM was higher among G (A/G-G/G) carriers of rs237028, C carriers (C/T-C/C) of rs652921,

and G carriers (T/G-G/G) of rs521845. Interestingly, Huang et al.⁽¹⁹⁾ showed that only rs237028 polymorphism in the *TAB2* gene was significantly associated with ovarian cancer susceptibility.

Although *TAB2* gene variants are significantly associated with various diseases, the association with EC remains unclear. Accordingly, we decided to investigate whether the *TAB2* gene polymorphism has an impact on EC. We selected the three SNPs located on the intron of the *TAB2* gene, may influence the regulation of gene expression. In the present study, we first confirmed that the rs521845 polymorphism in *TAB2* is significantly associated with EC susceptibility. Our data showed that the decrease in EC risk was related to the T allele of rs521845. Moreover, in both codominant and dominant models, the TT genotype of rs521845 was correlated with a lower EC risk. Therefore, *TAB2* might be a potential protective factor for EC. However, the other two SNPs (rs237028, rs652921) had no significant link with EC.

Conclusion

According to the degree of differentiation of EC tissue, EC tissue differentiation can be classified as the grade 1 (highly differentiated, G1), the grade 2 (moderately differentiated, G2), and the grade 3 (poorly differentiated, G3). The lower the degree of differentiation, the more malignancy is exhibited. For rs237028, patients with A/G genotype had lower-grade tumours (G1), compared to patients with genotype A/A or G/G. Stratified analysis of the three SNP genotypes of the *TAB2* gene showed no significant differences in age, BMI, family history, and menopause history. Although rs521845 variation in *TAB2* was associated with EC susceptibility, there were no significant differences in the clinicopathological features of EC such as pathological stage, histological grade, and histological type among patients with different genotypes.

Table 3. Distribution of SNPs in TAB2 between patients and controls as well as their association with endometrial cancer risk

	Genotype	Cases		Controls n=294 (%)	Logistic regression				
					Cases vs. controls		EA vs. control		
					OR (95% CI)	p	OR (95% CI)	p	
rs237028									
Genetic model	Codominant	A/A	142 (55.9%)	116 (54%)	177 (60.2%)	1.00	0.36	1.00	0.15
		A/G	99 (39%)	89 (41.4%)	98 (33.3%)	0.79 (0.56-1.13)		0.72 (0.50-1.05)	
		G/G	13 (5.1%)	10 (4.7%)	19 (6.5%)	1.17 (0.56-2.46)		1.25 (0.56-2.77)	
	Dominant	A/A	142 (55.9%)	116 (54%)	177 (60.2%)	1.00	0.31	1.00	0.16
		A/G-G/G	112 (44.1%)	99 (46%)	117 (39.8%)	0.84 (0.60-1.18)		0.77 (0.54-1.11)	
	Recessive	A/A-A/G	241 (94.9%)	205 (95.3%)	275 (93.5%)	1.00	0.50	1.00	0.38
		G/G	13 (5.1%)	10 (4.7%)	19 (6.5%)	1.28 (0.62-2.65)		1.42 (0.64-3.11)	
	Overdominant	A/A-G/G	155 (61%)	126 (58.6%)	196 (66.7%)	1.00	0.17	1.00	0.06
A/G		99 (39%)	89 (41.4%)	98 (33.3%)	0.78 (0.55-1.11)		0.71 (0.49-1.02)		
Allele	A	383 (75%)	321 (75%)	452 (77%)	1.00	0.57	1.00	0.41	
	G	125 (25%)	109 (25%)	136 (23%)	0.92 (0.70-1.22)		0.89 (0.66-1.18)		
rs521845									
Genetic model	Codominant	T/T	86 (32.1%)	72 (31.7%)	128 (43.5%)	1.00	0.017	1.00	0.017
		T/G	140 (52.2%)	118 (52%)	132 (44.9%)	0.63 (0.44-0.91)		0.63 (0.43-0.92)	
		G/G	42 (15.7%)	37 (16.3%)	34 (11.6%)	0.54 (0.32-0.92)		0.52 (0.30-0.89)	
	Dominant	T/T	86 (32.1%)	72 (31.7%)	128 (43.5%)	1.00	0.0051	1.00	0.0057
		T/G-G/G	182 (67.9%)	155 (68.3%)	166 (56.5%)	0.61 (0.43-0.87)		0.60 (0.42-0.87)	
	Recessive	T/T-T/G	226 (84.3%)	190 (83.7%)	260 (88.4%)	1.00	0.16	1.00	0.12
		G/G	42 (15.7%)	37 (16.3%)	34 (11.6%)	0.70 (0.43-1.14)		0.67 (0.41-1.11)	
	Overdominant	T/T-G/G	128 (47.8%)	109 (48%)	162 (55.1%)	1.00	0.17	1.00	0.11
T/G		140 (52.2%)	118 (52%)	132 (44.9%)	0.78 (0.55-1.11)		0.75 (0.53-1.07)		
Allele	T	312 (58%)	262 (58%)	388 (66%)	1.00	0.008	1.00	0.007	
	G	224 (42%)	192 (42%)	200 (34%)	0.72 (0.56-0.91)		0.70 (0.55-0.91)		

Table 3. Continued

		Genotype	Cases		Controls n=294 (%)	Logistic regression			
						Cases vs. controls		EA vs. control	
			Total n=270 (%)	EA n=228 (%)		OR (95% CI)	p	OR (95% CI)	p
rs652921									
Genetic model	Codominant	T/T	74 (29.5%)	59 (28.1%)	98 (33.3%)	1.00		1.00	0.45
		C/T	126 (50.2%)	104 (49.5%)	137 (46.6%)	0.82 (0.56-1.21)		0.79 (0.53-1.20)	
		C/C	51 (20.3%)	47 (22.4%)	59 (20.1%)	0.87 (0.54-1.41)		0.76 (0.46-1.25)	
	Dominant	T/T	74 (29.5%)	59 (28.1%)	98 (33.3%)	1.00	0.33	1.00	0.21
		C/T-C/C	177 (70.5%)	151 (71.9%)	196 (66.7%)	0.84 (0.58-1.20)		0.78 (0.53-1.15)	
	Recessive	T/T-C/T	200 (79.7%)	163 (77.6%)	235 (79.9%)	1.00	0.94	1.00	0.53
		C/C	51 (20.3%)	47 (22.4%)	59 (20.1%)	0.98 (0.65-1.50)		0.87 (0.57-1.34)	
	Overdominant	T/T-C/C	125 (49.8%)	106 (50.5%)	157 (53.4%)	1.00	0.40	1.00	0.52
	C/T	126 (50.2%)	104 (49.5%)	137 (46.6%)	0.87 (0.62-1.21)		0.89 (0.62-1.27)		
Allele	T	274 (55.0%)	222 (53.0%)	333 (57.0%)	1.00	0.50	1.00	0.25	
	C	228 (45.0%)	198 (47.0%)	255 (43.0%)	0.92 (0.72-1.17)		0.86 (0.67-1.10)		
SNP: Single nucleotide polymorphism, TAB2: Transforming growth factor-β-activated kinase 1 binding protein 2, EA: Endometrioid adenocarcinoma, OR: Odds ratio, CI: Confidence interval									

Table 4. Association between the genotype distribution of rs237028 polymorphism of TAB2 gene and clinical features

Clinical characteristics		Genotype			Genetic model							
		AA	AG	GG	Codominant (AA vs. AG vs. GG)		Dominant (AA vs. AG/GG)		Recessive (AA/AG vs. GG)		Overdominant (AA/GG vs. AG)	
					OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	<50	57			AG: 0.95 (0.56-1.60)	0.76	1.00 (0.60-1.65)	1.00	1.54 (0.46-5.15)	0.47	0.92 (0.55-1.53)	0.74
	≥50	85	58	9	GG: 1.51 (0.44-5.13)							
BMI	<27	112	81	11	AG: 0.83 (0.43-1.59)	0.78	0.81 (0.43-1.52)	0.51	0.73 (0.16-3.41)	0.68	0.85 (0.45-1.62)	0.63
	≥27	30	18	2	GG: 0.68 (0.14-3.23)							
Family history of cancer	Negative	135	92	10	AG: 1.47 (0.50-4.32)	0.11	1.89 (0.70-5.14)	0.21	4.86 (1.20-19.70)	0.049	1.10 (0.41-3.00)	0.85
	Positive	7	7	3	GG: 5.79 (1.29-25.86)							
Menopausal status	Premenopausal	68	49	5	AG: 0.94 (0.56-1.57)	0.75	0.99 (0.60-1.62)	0.96	1.51 (0.48-4.75)	0.48	0.91 (0.55-1.50)	0.71
	Postmenopausal	74	50	8	GG: 1.47 (0.46-4.71)							
Pathological type	EA	116	89	10	AG: 0.50 (0.23-1.09)	0.15	0.59 (0.29-1.20)	0.14	1.71 (0.45-6.51)	0.45	0.49 (0.23-1.05)	0.05
	Non-EA	26	10	3	GG: 1.34 (0.34-5.21)							
FIGO grade	G1	50	41	1	AG: 0.77 (0.45-1.30)	0.031	0.91 (0.54-1.52)	0.71	7.28 (0.93-56.84)	0.014	0.69 (0.41-1.17)	0.17
	G2-G3	92	58	12	GG: 6.52 (0.83-51.55)							
FIGO stage	I	105	78	10	AG: 0.81 (0.44-1.49)	0.79	0.82 (0.45-1.48)	0.50	0.98 (0.26-3.69)	0.98	0.81 (0.44-1.49)	0.51
	II-IV	35	21	3	GG: 0.90 (0.23-3.46)							
Myometrial invasion	<1/2	117	84	12	AG: 0.80 (0.42-1.51)	0.58	0.76 (0.41-1.41)	0.38	0.56 (0.12-2.63)	0.44	0.84 (0.44-1.58)	0.59
	≥1/2	84	64	10	GG: 0.51 (0.11-2.45)							
Parametrial invasion	Negative	125	92	12	AG: 0.63 (0.25-1.62)	0.61	0.64 (0.26-1.57)	0.32	0.82 (0.10-6.62)	0.85	0.65 (0.26-1.65)	0.35
	Positive	15	7	1	GG: 0.69 (0.08-5.72)							
Cervical invasion	Negative	119	82	11	AG: 1.17 (0.58-2.36)	0.90	1.16 (0.59-2.28)	0.67	0.96 (0.20-4.51)	0.96	1.17 (0.59-2.32)	0.65
	Positive	21	17	2	GG: 1.03 (0.21-4.98)							
Vascular invasion	Negative	117	84	12	AG: 0.91 (0.45-1.84)	0.66	0.85 (0.42-1.70)	0.64	0.44 (0.06-3.49)	0.39	0.96 (0.48-1.94)	0.91
	Positive	23	15	1	GG: 0.42 (0.05-3.42)							
Lymph node status	Negative	112	80	10	AG: 0.60 (0.22-1.63)	0.44	0.71 (0.29-1.77)	0.46	1.92 (0.39-9.38)	0.45	0.57(0.21-1.52)	0.25
	Positive	14	6	2	GG: 1.60 (0.32-8.06)							

TAB2: Transforming growth factor-β-activated kinase 1 binding protein 2, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, EA: Endometrioid adenocarcinoma, FIGO: International Federation of Gynecology and Obstetrics

Table 5. Association between the genotype distribution of rs652921 polymorphism of TAB2 gene and clinical features

Clinical characteristics		Genotype			Genetic model							
		TG		GG	Codominant (TT vs. TG vs. GG)		Dominant (TT vs. TG/GG)		Recessive (TT/TG vs. GG)		Overdominant (TT/GG vs. TG)	
		TT	TG	GG	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	<50	36	56	16	TG: 1.08 (0.63-1.86)	0.92	1.10 (0.65-1.85)	0.72	1.12 (0.57-2.20)	0.75	1.03 (0.63-1.67)	0.92
	≥50	50	84	26	GG: 1.17 (0.55-2.49)							
BMI	<27	67	117	32	TG: 0.69 (0.35-1.37)	0.43	0.78 (0.41-1.47)	0.45	1.37 (0.62-3.00)	0.44	0.67 (0.36-1.23)	0.2
	≥27	19	23	10	GG: 1.10 (0.46-2.64)							
Family history of cancer	Negative	80	129	38	TG: 1.14 (0.40-3.19)	0.88	1.20 (0.45-3.20)	0.72	1.29 (0.41-4.06)	0.67	1.01 (0.41-2.46)	0.99
	Positive	6	11	4	GG: 1.40 (0.37-5.27)							
Menopausal status	Premenopausal	42	67	21	TG: 1.04 (0.61-1.78)	0.97	1.02 (0.61-1.70)	0.94	0.93 (0.48-1.80)	0.83	1.06 (0.65-1.71)	0.82
	Postmenopausal	44	73	21	GG: 0.95 (0.46-2.00)							
Pathological type	EA	72	118	37	TG: 0.96 (0.46-1.99)	0.79	0.90 (0.44-1.81)	0.76	0.71 (0.26-1.94)	0.49	1.07 (0.55-2.08)	0.84
	Non-EA	14	22	5	GG: 0.69 (0.23-2.08)							
FIGO grade	G1	25	56	15	TG: 0.61 (0.35-1.09)	0.25	0.64 (0.37-1.11)	0.11	1.01 (0.51-2.00)	0.99	0.68 (0.41-1.13)	0.13
	G2-G3	61	84	27	GG: 0.74 (0.34-1.62)							
FIGO stage	I	60	108	36	TG: 0.69 (0.37-1.27)	0.14	0.62 (0.34-1.11)	0.11	0.50 (0.20-1.25)	0.11	0.89 (0.50-1.57)	0.68
	II-IV	25	31	6	GG: 0.40 (0.15-1.07)							
Myometrial invasion	<1/2	53	83	30	TG: 0.77 (0.41-1.47)	0.24	0.68 (0.37-1.26)	0.23	0.51 (0.20-1.30)	0.14	0.97 (0.53-1.75)	0.91
	≥1/2	24	29	6	GG: 0.44 (0.16-1.20)							
Parametrial invasion	Negative	74	129	40	TG: 0.52 (0.21-1.29)	0.21	0.48 (0.20-1.13)	0.09	0.48 (0.11-2.14)	0.3	0.68 (0.29-1.61)	0.38
	Positive	11	10	2	GG: 0.34 (0.07-1.59)							
Cervical invasion	Negative	70	115	38	TG: 0.97 (0.48-1.98)	0.40	0.85 (0.43-1.70)	0.65	0.50 (0.17-1.48)	0.18	1.19 (0.62-2.29)	0.61
	Positive	15	24	4	GG: 0.49 (0.15-1.58)							
Vascular invasion	Negative	71	121	35	TG: 0.75 (0.35-1.61)	0.71	0.81 (0.40-1.66)	0.57	1.20 (0.49-2.93)	0.69	0.75 (0.38-1.48)	0.41
	Positive	14	18	7	GG: 1.01 (0.38-2.74)							
Lymph node status	Negative	62	118	35	TG: 0.43 (0.17-1.09)	0.13	0.41 (0.17-0.98)	0.048	0.51 (0.11-2.30)	0.35	0.57 (0.23-1.39)	0.21
	Positive	11	9	2	GG: 0.32 (0.07-1.54)							

TAB2: Transforming growth factor-β-activated kinase 1 binding protein 2, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, EA: Endometrioid adenocarcinoma, FIGO: International Federation of Gynecology and Obstetrics

Table 6. Association between the genotype distribution of rs5652921 polymorphism of TAB2 gene and clinical features

Clinical characteristics		Genotype		Genetic model						Recessive (TT/TC vs. CC)		Dominant (TT vs. TC/CC)		Overdominant (TT/CC vs. TC)	
		TT	TC	CC	Codominant (TT vs. TC vs. CC)		P	OR (95% CI)	P		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)
					OR (95% CI)	TC: 1.08 (0.60-1.95) CC: 0.78 (0.38-1.62)									
Age	<50														
	≥50	45	79	28			0.63		0.96		0.75 (0.40-1.39)	0.36		1.20 (0.72-1.99)	0.49
BMI	<27	58	105	39											
	≥27	16	21	12			0.50		0.59		1.36 (0.65-2.84)	0.43		0.69 (0.37-1.30)	0.25
Family history of cancer	Negative	69	118	46											
	Positive	5	8	5			0.73		0.87		1.56 (0.53-4.61)	0.43		0.78 (0.30-2.05)	0.61
Menopausal status	Premenopausal	35	57	28											
	Postmenopausal	39	69	23			0.5		0.92		0.70 (0.38-1.30)	0.26		1.23 (0.75-2.02)	0.41
Pathological type	EA	59	104	47											
	Non-EA	15	22	4			0.13		0.28		0.37 (0.13-1.11)	0.049		1.18 (0.60-2.31)	0.63
FIGO grade	G1	25	47	18											
	G2-G3	49	79	33			0.88		0.66		1.03 (0.54-1.96)	0.93		0.88 (0.53-1.48)	0.63
FIGO stage	I	54	92	42											
	II-IV	19	33	9			0.42		0.72		0.60 (0.27-1.32)	0.19		1.23 (0.69-2.19)	0.48
Myometrial invasion	<1/2	49	69	35											
	≥1/2	16	32	10			0.41		0.53		0.70 (0.32-1.53)	0.36		1.50 (0.82-2.75)	0.19
Parametrial invasion	Negative	65	114	47											
	Positive	8	11	4			0.82		0.55		0.80 (0.26-2.47)	0.69		0.90 (0.38-2.13)	0.81
Cervical invasion	Negative	62	101	44											
	Positive	11	24	7			0.6		0.62		0.74 (0.31-1.78)	0.49		1.40 (0.72-2.73)	0.32
Vascular invasion	Negative	62	107	44											
	Positive	11	18	7			0.98		0.86		0.93 (0.38-2.26)	0.87		0.99 (0.49-2.01)	0.98
Lymph node status	Negative	56	100	43											
	Positive	8	11	4			0.78		0.51		0.76 (0.25-2.36)	0.63		0.91 (0.38-2.15)	0.83

TAB2: Transforming growth factor-β-activated kinase 1 binding protein 2, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, EA: Endometrioid adenocarcinoma, FIGO: International Federation of Gynecology and Obstetrics

In summary, polymorphisms found in the rs521845 site of the *TAB2* gene may serve as a novel genetic marker of susceptibility to EC in Chinese women. The findings of other independent research groups suggest that the *TAB2* gene may play an essential role in EC's molecular pathogenesis. However, the function and the underlying signal transduction mechanisms of *TAB2* in EC development need to be clarified. This study has certain limitations. Although these deficiencies were random, due to incomplete clinical information of some patients, they may affect the accuracy and objectivity of stratified analysis results. Therefore, these findings need to be further confirmed in a larger cohort. Secondly, the functions of the three SNPs studied in this research and the potential mechanism of rs521845 SNP in the development of EC are still unclear. Further investigations are warranted.

Ethics

Ethics Committee Approval: The present study was approved by the Medical Ethical Review Committee of West China Second Hospital of Sichuan University (approval number: 038, date: 03.03.2022).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: Y.W., Design: Y.W., Data Collection or Processing: S.L., Analysis or Interpretation: S.L., Literature Search: S.L., Writing: S.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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