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Original Research

Relationship between *MUC17* Gene Polymorphisms and Endometriosis in Central Plains Chinese Women

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Abstract

Background: Endometriosis is one of the common benign gynecological diseases among reproductive aged women, which almost lead to pelvic pain, infertility and menstrual disorders. There is no blood test available for the diagnosis of endometriosis. *MUC17* has been revealed to play a role in a variety of cancers, but the role of *MUC17* single nucleotide polymorphisms (SNPs) in endometriosis susceptibility remains unclear. **Methods**: In the present study, genotyping for four *MUC17* polymorphisms in 117 endometriosis patients and 118 female control participants was undertaken using the Agena Mass ARRAY. An unconditional logistic regression model was used to estimate the role of *MUC17* gene polymorphisms in endometriosis. **Results**: Bioinformatics analysis showed that rs6966570 could be relevant to the transcription factor binding sites of proteins bound and was related to expression quantitative trait Loci (eQTL) and Motifs. Rs10246021 affected eQTL and Motifs. Nevertheless, there was no significant difference in the frequency of mutation of *MUC17* gene between the case group and the control group ($p > 0.05$), the C allele of rs11979706 (OR: 0.37; 95% CI: 0.18–0.74; p: 0.03), the T allele of rs10246021 (OR: 0.43; 95% CI: 0.21–0.88; p: 0.018), the T allele of rs6966570 (OR: 0.45; 95% CI: 0.22–0.92; p: 0.026), and the T allele of rs4729655 (OR: 0.48; 95% CI: 0.26–0.88; p: 0.017) may be protective factors for the occurrence of dysmenorrhea in endometriosis. Logistic regression analysis indicated genotypes *MUC17* rs11979706 CC and rs4729655 TT contribute a lower risk to dysmenorrhea ($p = 0.024$, $p = 0.034$), respectively. Haplotype analysis showed that individuals with CTTT haplotypes had a lower risk of developing dysmenorrhea ($p = 0.008$). In the log-additive model, the rs4729655 was associated with endometriosis-induced infertility. **Conclusions**: On the whole, these findings demonstrate that *MUC17* gene polymorphisms was not correlated with endometriosis susceptibility but was associated with secondary dysmenorrheal and infertility in Central Plains Chinese women.

Keywords: endometriosis; *MUC17*; single nucleotide polymorphisms; dysmenorrhea

1. Introduction

Endometriosis is defined as the presence of functional endometrial glands and stroma outside the uterine cavity with features of an array of symptoms including dysmenorrhea, infertility, excessive menstrual pain, pelvic pain with defecation and chronic pelvic pain, affecting 5–10% of women of reproductive age [1,2]. The most common locations for the ectopic endometrial implants are the ovaries, the uterosacral ligaments and the posterior cul-de-sac [3]. Diagnosis for endometriosis is solely made through surgery as no consistent biomarkers for disease diagnosis exist. The global average time of delayed diagnosis of endometriosis is 10 years [4], while it is 13 years in Chinese women [5]. Surgery combined with hormone drugs are commonly used to treat endometriosis. But the current treatments are mainly aimed at target symptoms but not the underlying mechanisms of disease. Furthermore, the overall rate of recurrence 5 years after the operation is up to 50%. The theory of transplantation for the etiology of this disease is widespread. However, the exact pathogenesis of endometriosis is still obscure [6]. With the advent of genome-wide association studies (GWAS), some loci related to endometriosis have been revealed [7,8], which implies that gene mutations may serve a crucial purpose in the occurrence of endometriosis. Mucins are a group of high-molecular-weight glycoprotein, which can be divided into transmembrane and secretory categories. They affect the occurrence of cancer by regulating inflammation, cell adhesion or apoptosis, and can even supervise the damage and repair of epithelial cells [9–11], which is being recognized by clinical research institutes as a target for the treatment of inflammation and cancer [12,13].

The *MUC17* gene is located in the q22.1 region of the chromosome, whose full-length open reading frame transcribes 13 exons [14]. This protein has two EGF-like domains, promoting cell proliferation, migration and restraining cell apoptosis by ErbB2 mechanism [15,16]. Previous studies have demonstrated that *MUC17* is critical for the progression of breast cancer, colon cancer, cholangiocarcinoma, and pancreatic ductal adenocarcinoma [17,18]. Particularly, evidence showed that *MUC17* expression is elevated in epithelial ovarian cancer patients [19], patients with endometriosis have a higher risk of developing ovarian cancer [20]. Hence, we hypothesized that *MUC17*

Table 1. Functional annotation of *MUC17* SNPs using RegulomeDB and HaploReg.

SNP	Gene	chromosome	Position	RegulomeDB	HaploReg
rs4729655	*MUC17*	7q22.1	101058170	4	Selected eQTL
rs6966570	*MUC17*	7q22.1	101051777	4	Proteinsbound, Motifs changed, Selected eQTL hits
rs10246021	*MUC17*	7q22.1	101049399	5	Motifs changed, Selected eQTL hits
rs11979706	*MUC17*	7q22.1	101038078	5	DNase, missense

SNP, single nucleotide polymorphism; eQTL, expression quantitative trait loci; 4, TF binging + DNase peak; 5, TF binging or DNase peakHWE.

may be the same risk factor in endometriosis as in ovarian cancer. Moreover, a study of small sample size in Taiwan province found that the *MUC17* mutation was associated with the development of endometriosis. There was only one case reported so far. Therefore, we carried out a study on women in central China to ascertain the correlation between genetic variations of *MUC17* and endometriosis among population in this area.

2. Methods

2.1 Study Participants

In the present case-control study, 117 endometriosis patients were enrolled at The Third Affiliated Hospital of Zhengzhou University between October 2018 and December 2019, and they were all diagnosed with histopathological examination. Participants in the controlled group were selected from unrelated patients who underwent laparoscopy or laparoscopic surgery and excluded endometriosis and adenomyosis due to hydrosalpinx, simple ovarian cyst or teratoma over the same period. All participants were native populations of Henan and surrounding provinces and not related. Those with genetic disorders in the family history, gynecological benign or malignant neoplasm, and who have taken any hormone drugs within three months were excluded. There were no statistical differences in the mean ($\pm$ SD) age (32.50 $\pm$ 6.67, 32.85 $\pm$ 6.73 years) and the mean body mass index (BMI) (23.3 $\pm$ 4.2, 23.9 $\pm$ 2.9 kg/m^2) between the case group and the control group respectively ($p > 0.05$). We also recorded some clinical information on patients, including dysmenorrhea, cancer antigen 125 (CA125) levels and fertility. This study was approved by The Third Affiliated Hospital of Zhengzhou University, and all participants have signed informed consent.

2.2 Polymorphism Selection and Genotyping

Combining with previously published reports, and a minor allele frequency of greater than 5% in the East Asian population, we selected rs11979706, rs10246021, rs6966570, and rs4729655 from gnomAD databases (https://macarthurlab.org/2018/10/17/gnomad-v2-1/). Genomic DNA was isolated by Genomic DNA Purification Kit (BioTeke, Biotechnology, Beijing, China) in accordance with the manufacturer's instructions. The DNA concentration and purity were determine dusing a Nanodrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA). We performed primers designing with Mass ARRAY Assay Design 3.1 Software (Agena, San Diego, California, USA). Agena Mass ARRAY RS1000 was utilized for SNP genotyping [21], and the data were analyzed using Mass ARRAY Typer 4.0 software (Agena Bioscience Inc, San Diego, California, USA). In this study, the rate of success in genotyping was above 95%. In order to confirm the robustness of the technology, we randomly chose 10% of samples for genotyping in duplicate.

2.3 Bioinformatics Analyses

To confirm the effect of *MUC17* SNPs on allele-specific transcriptional regulation and chromatin structure, we used RegulomeDB [22] and HaploReg V4 [23].

2.4 Statistical Analysis

The χ^2-test was adopted to evaluate Hardy–Weinberg equilibrium (HWE). Allele heterogeneity of patients and controls was determined by applying the Fisher's exact test and the χ^2-test. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using a logistic regression adjusted for age through the PLINK software [24]. Four Genetic models were applied to estimate the relationship between SNPs and EMs. The linkage disequilibrium (LD) coefficient r^2 among SNPs were assessed with Haploview software [25]. The genetic effects of haplotypes were also analyzed with PLINK software. All statistical tests were with a two-sided *p*-value, and the threshold of *p* was set as 0.05.

3. Results

3.1 Bioinformatics Analyses

Although RegulomeDB lacks sufficient evidence to prove that four loci affect transcription factor binding (Table 1), HaploReg predicted that rs6966570 was likely to affect Proteins bound and was related to eQTL and Motifs. Additionally, rs10246021 may influence eQTL and Motifs. The evidence of rs4729655 affecting EQTL is also available. Additionally, rs11979706 mutation can give rise to mistranslation.

3.2 MUC17 Gene Polymorphisms and Endometriosis

The duplicate genotyping results were of 100% concordance. Firstly, as shown in Table 2, the distribution

Table 2. The basic information and allele frequencies of the SNPs.

	Allele	allele frequencies		HWE	MAF	OR	(95% CI)	*p*
		Case, N (%)	Control, N (%)					
rs11979706	G	184 (78.6)	194 (82.2)	0.42	0.19	0.83	(0.53–1.30)	0.427
	C	50 (21.4)	42 (17.8)					
rs10246021	G	186 (79.5)	196 (83.0)	0.83	0.19	0.82	(0.51–1.32)	0.410
	T	48 (20.5)	40 (17.0)					
rs6966570	C	184 (78.7)	195 (82.6)	0.68	0.20	0.80	(0.51–1.27)	0.355
	T	50 (21.3)	41 (17.4)					
rs4729655	C	153 (65.9)	152 (64.7)	0.19	0.35	1.04	(0.99–1.09)	0.848
	T	79 (34.1)	82 (35.3)					

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequencies.

$p < 0.05$ indicates statistical significance.

of all the genotypes was in the HWE ($p > 0.05$). Therefore, study subjects are regionally representative. Secondly, Table 2 summarizes the alleles frequencies of the *MUC17* gene among the endometriosis and the control group. The result did not show any statistically significant difference between the two groups ($p > 0.05$), nor the genotypes analysis under each logistic regression model (codominant, dominant, recessive and additive) ($p > 0.05$) (Table 3). Lastly, link age analysis indicated that rs11979706, rs10246021, rs6966570, and rs4729655 exhibit extremely significant linkage disequilibrium (Fig. 1). We further examined the effect of the haplotype "GGCC", "CTTT" and "GGCT" frequencies in the development of endometriosis. Similarly, no association with EMs risk was found ($p > 0.05$) (Table 4).

3.3 MUC17 SNP Polymorphism and Clinical Parameters of Endometriosis Patients

Taking account into dysmenorrhea, infertility, as well as CA125 levels associated with endometriosis [26], we further investigated the role of the four SNPs of the *MUC17* gene with regard to dysmenorrhea, infertility and serum CA125 levels in patients. However, as shown in Table 5, none of the gene polymorphisms associations with infertility and CA125 levels was discovered ($p > 0.05$), whereas when patients were analyzed according to the occurrence of dysmenorrhea, some significant association was detected.

Of note, in the allele model, the C allele of rs11979706 (OR: 0.37; 95% CI: 0.18–0.74; $p = 0.03$), the T allele of rs10246021 (OR: 0.43; 95% CI: 0.21–0.88; *p*: 0.018), the T allele of rs6966570 (OR: 0.45; 95% CI: 0.22–0.92; *p*: 0.026), and the T allele of rs4729655 (OR: 0.48; 95% CI: 0.26–0.88; *p*: 0.017) reduced the risk of the occurrence of dysmenorrhea in endometriosis (Table 5). Further logistic regression analysis was carried out. After adjustment for age and BMI, we observed that the frequency of the heterozygous variant of rs11979706 was a protective factor in patients with endometriosis (Table 5). The Recessive model after adjustment for age showed that the individuals with *MUC17* rs11979706 CC genotype have a 93% lower risk of dysmenorrheal than GC + GG genotype (OR: 0.07; 95% CI: 0.01–0.72; *p*: 0.024). Meanwhile, individuals with rs4729655 TT genotype have a 72% lower risk of dysmenorrheal than CT + CC genotype (OR: 0.28; 95% CI: 0.09–0.91; *p*: 0.034). It is also worth noting that the "log-additive" could be an extremely sensitive model in our case. In this model, all four genetic loci were significantly

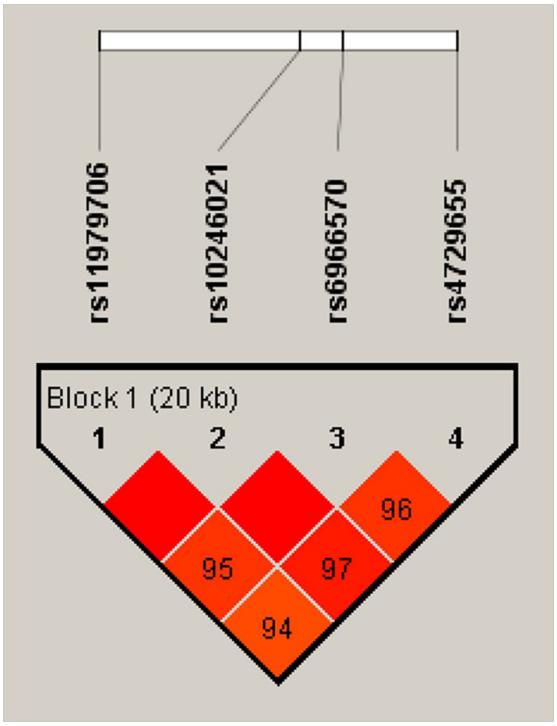

Fig. 1. The LD (linkage disequilibrium) among 4 SNPs of the *MUC17* gene. Haplotype blocks for the 117 control subjects and 118 endometriosis patients were constructed according to the confidence interval approach using Haploview software. The values within each red square indicate the score of the related r2 measure for allelic association between SNPs. The greater the score correspond to higher degrees of LD, up to a maximum of 1.

Table 3. *MUC17* genotype distributions based on logistic regression model analysis in endometriosis patients and controls.

SNP	Model	Genotype	Case, N (%)	Control, N (%)	OR (95% CI)	p^a
rs11979706	Codominant	GG	72 (61.5)	82 (69.5)	1	0.348
		GC	40 (34.2)	30 (25.4)	0.61 (0.28–1.34)	
		CC	5 (4.3)	6 (5.1)	1.09 (0.58–2.02)	
	Dominant	GG	72 (61.5)	82 (69.5)	1	0.242
		GC + CC	45 (38.5)	36 (30.5)	0.72 (0.42–1.24)	
	Recessive	GG + GC	112 (95.7)	112 (94.9)	1	0.639
		CC	5 (4.3)	6 (5.1)	1.34 (0.39–4.60)	
	Log-additive	—	—	—	0.83 (0.53–1.29)	0.421
rs10246021	Codominant	GG	74 (63.2)	82 (69.5)	1	0.672
		GT	38 (32.5)	32 (27.1)	0.85 (0.37–1.96)	
		TT	5 (4.3)	4 (3.4)	0.90 (0.45–1.78)	
	Dominant	GG	74 (63.2)	82 (69.5)	1	0.368
		GT + TT	43 (36.8)	36 (30.5)	0.77 (0.45–1.34)	
	Recessive	GG + GT	112 (95.7)	114 (96.6)	1	0.858
		TT	5 (4.3)	4 (3.4)	0.88 (0.22–3.41)	
	Log-additive	—	—	—	0.82 (0.52–1.29)	0.392
rs6966570	Codominant	CC	73 (62.4)	81 (68.7)	1	0.654
		CT	38 (32.5)	33 (27.9)	0.81 (0.42–1.57)	
		TT	6 (5.1)	4 (3.4)	0.98 (0.43–2.119)	
	Dominant	CC	73 (62.4)	80 (67.8)	1	0.374
		CT + TT	44 (37.6)	38 (32.2)	0.78 (0.45–1.34)	
	Recessive	CC + CT	111 (94.9)	114 (96.6)	1	0.609
		TT	6 (5.1)	4 (3.4)	0.71 (0.19–2.61)	
	Log-additive	—	—	—	0.80 (0.51–1.26)	0.341
rs4729655	Codominant	CC	55 (47.4)	50 (42.7)	1	0.542
		TC	43 (37.1)	52 (44.5)	1.37 (0.78–2.41)	
		TT	18 (15.5)	15 (12.8)	0.95 (0.64–1.42)	
	Dominant	CC	55 (47.4)	50 (42.7)	1	0.502
		TC + TT	61 (52.6)	67 (57.3)	1.19 (0.71–2.01)	
	Recessive	CC + TC	98 (84.5)	102 (87.2)	1	0.570
		TT	18 (15.5)	15 (12.8)	0.80 (0.38–1.69)	
	Log-additive	—	—	—	1.06 (0.74–1.53)	0.760

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

[a]Calculated by logistic regression model after adjusting for age and BMI.

$p < 0.05$ indicates statis.

Table 4. *MUC17* haplotype frequencies in endometriosis patients and controls.

SNP	Freq	Haplotype	endometriosis %	control %	p
rs11979706/rs10246021/ rs6966570/rs4729655	0.645	GGCC	65.7	65.4	0.816
	0.185	CTTT	17.1	20.5	0.383
	0.153	GGCT	17.0	14.1	0.370

SNP, single nucleotide polymorphism.

$p < 0.05$ indicates statistical significance.

associated with dysmenorrhea ($p > 0.05$), even rs11979706 and rs4729655 seem to influence infertility risk. However, similar conclusions were not discovered in other models.

As shown in Table 6, the four protective alleles haplotypes were available for analysis. Unsurprisingly, haplotype "CTTT" showed a lower frequency of dysmenorrhea in the endometriosis group ($p = 0.008$). On the contrary, patients with haplotype "GGCC" showed a significantly increased frequency of dysmenorrhea ($p = 0.045$) (Table 6, Fig. 2). Therefore, *MUC17* haplotypes could be an indicator of dysmenorrhea in patients.

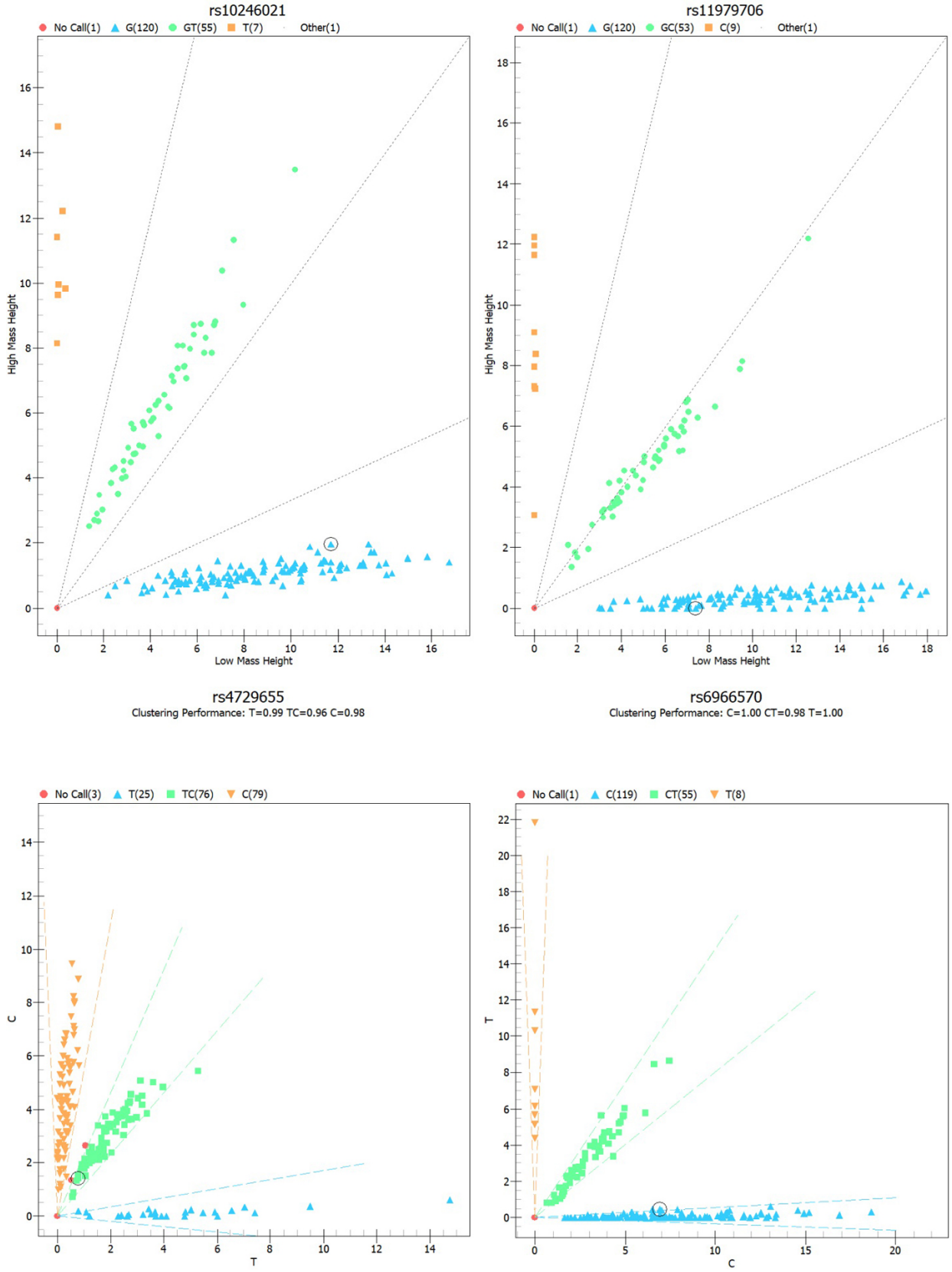

Fig. 2. The LD (linkage disequilibrium) among 4 SNPs of the *MUC17* gene that associated with dysmenorrhea in endometriosis patients. Haplotype blocks for the 26 patients without infertility and 88 patients with infertility were constructed according to the confidence interval approach using Haploview software. The values within each red square indicate the score of the related r2 measure for allelic association between SNPs. The greater the score correspond to higher degrees of LD, up to a maximum of 1.

Table 5. Associations of *MUC17* SNP polymorphism and clinical characteristics of endometriosis patients.

SNP	Allele /Genotype	CA125 value				Reproduction ability				Dysmenorrhea			
		CA125 <35[a], N	CA125 ≥35[a], N	OR (95% CI)	p^b	non-infertility, N	Infertility, N	OR (95% CI)	p[b]	non-dysmenorrhea, N	dysmenorrhea, N	OR (95% CI)	p[b]
rs11979706	C/G	50/184	42/194	0.93 (0.41–2.12)	0.869	37/137	5/49	0.39 (0.14–1.04)	0.051	21/53	19/137	0.37 (0.18–0.74)	0.030*
	CC /GC/GG	5/40/72	6/30/82	1.92 (0.45–8.22)	0.661	6/26/56	0/5/22	0.51 (0.17–1.51)	0.095	5/11/21	1/17/60	2.10 (0.54–8.14)	0.035*
				0.70 (0.26–1.89)				0.00 (0.00–NA[b])				0.26 (0.08–0.79)	
	Dominant			1.09 (0.37–3.18)	0.863			0.41 (0.14–1.19)	0.103			0.39 (0.17–0.91)	0.031
	Recessive			0.46 (0.06–3.31)	0.447			0.46 (0.06–3.31)	0.074			0.07 (0.01–0.72)	0.024*
	Log-additive			0.94 (0.44–2.02)	0.882			0.37 (0.14–1.06)	0.046*			0.40 (0.20–0.80)	0.008*
rs10246021	T/G	48/186	40/196	0.91 (0.39–2.10)	0.832	35/139	5/49	0.91 (0.39–2.10)	0.072	19/55	19/137	0.43 (0.21–0.88)	0.018*
	TT/GT/GG	5/38/74	4/32/82	2.15 (0.49–9.46)	0.576	4/27/56	0/5/22	0.55 (0.12–2.9)	0.133	3/13/21	1/17/60	1.36 (0.34–5.33)	0.060
				0.64 (0.22–1.82)				0.90 (0.27–2.9)				0.34 (0.10–1.08)	
	Dominant			1.09 (0.37–3.18)	0.863			0.41 (0.14–1.19)	0.103			0.39 (0.17–0.91)	0.031
	Recessive			0.38 (0.04–3.05)	0.367			0.38 (0.04–3.05)	0.153			0.14 (0.01–1.45)	0.102
	Log-additive			0.89 (0.40–1.96)	0.781			0.40 (0.15–1.09)	0.066			0.43 (0.21–0.90)	0.024*
rs6966570	T/C	50/184	41/195	0.95 (0.41–2.21)	0.916	36/138	5/49	0.38 (0.13–1.12)	0.081	19/55	20/136	0.45 (0.22–0.92)	0.026*
	TT/CT/CC	6/38/73	4/33/81	2.29 (0.52–10.02)	0.535	4/28/55	0/5/22	0.45 (0.15–1.32)	0.112	3/13/21	1/18/59	1.44 (0.37–5.65)	0.592
				0.65 (0.23–1.84)				0.00 (0.00–NA)				0.34 (0.11–1.09)	
	Dominant			1.17 (0.41–3.39)	0.763			0.38 (0.13–1.12)	0.080			0.42 (0.18–0.97)	0.043*
	Recessive			0.38 (0.04–3.04)	0.367			0.00 (0.00–NA)	0.155			0.14 (0.01–1.45)	0.103
	Log-additive			0.94 (0.42–2.07)	0.876			0.39(0.14–1.05)	0.056			0.45 (0.22–0.93)	0.032*
rs4729655	TC	6/111	4/114	1.43 (0.66–3.07)	0.359	67/105	13/41	0.52 (0.26–1.04)	0.062	32/40	46/110	0.48 (0.26–0.88)	0.017*
	TT/TC/CC	18/43/55	15/52/50	1.24 (0.39–3.95)	0.609	14/39/33	1/11/15	0.39 (0.13–1.14)	0.204	8/16/12	6/34/38	1.42 (0.59–3.42)	0.079
				1.30 (0.53–3.16)				0.53 (0.22–1.28)				0.48 (0.26–0.91)	
	Dominant			1.63 (0.62–4.27)	0.320			0.53 (0.22–1.28)	0.158			0.53 (0.23–1.24)	0.142
	Recessive			1.34 (0.24–7.52)	0.736			0.18(0.02–1.51)	0.126			0.28 (0.09– 0.91)	0.034*
	Log-additive			1.45 (0.70–3.00)	0.314			0.49 (0.24–0.99)	0.046*			0.47 (0.25–0.88)	0.017*

*Indicates statistical significance.

[a]CA125 level: KU/L.

[b]Calculated by logistic regression model after adjusting for age and BMI.

$p < 0.05$ indicates statistical significance.

Table 6. *MUC17* haplotype frequencies and the association with dysmenorrhea characteristic of endometriosis patients.

SNP	Haplotype	Freq	Non-dysmenorrhea, %	Dysmenorrhea, %	*p*
rs11979706/rs10246021/rs6966570/rs4729655	GGCC	0.651	69.8	57.6	0.045*
	CTTT	0.169	12.6	27.0	0.008*
	GGCT	0.167	17.6	15.4	0.631

*Indicates statistical significance; SNP, single nucleotide polymorphism.

$p < 0.05$ indicates statistical significance.

4. Discussion

Endometriosis is a common gynecological disease, and secondary dysmenorrhea is a typical manifestation of endometriosis. In our study, 67.8% of the patients with endometriosis had dysmenorrhea symptoms. Previous reports showed that dysmenorrhea is caused by the local inflammatory response due to the ectopic implantation of endometrial cells. This response leads to the release of inflammatory factors, promoting uterine contraction, afterwards, triggering dysmenorrhea. Yang B *et al.* [27] found *MUC17* maintained the MYH9-p53-RhoA regulatory feedback loop through the EGF-like domain and downstream sequence, and then activated p38 signal to transduce NF-κB pathway inhibiting the expression of IL1 and IL8 etc. Other studies have shown that the NF-κB pathway can influence dysmenorrhea severity by modulating the expression of prostaglandin synthesis enzyme COX-2 [28]. IL1β was related to a pain effect of dysmenorrhea [29]. IL-8 is also associated with the severity of dysmenorrhea and the proliferation of endometrium stromal cells [30,31]. Furthermore, our results suggest that the variants (rs11979706, rs10246021, rs6966570, rs4729655) of *MUC17* were linked to the incidence of dysmenorrhea. In addition, bioinformatics analysis found that the rs4729655 SNP site is positioned in the 3′-UTR of *MUC17*, and genetic variation in the 3'UTR of the target gene may affect miRNA binding and miRNA stability. Hence, we suspect that mutations at rs4729655 affect P53 or P38 pathway by regulating specifically targeted miRNA to regulate inflammatory response. Furthermore, the mutation of rs11979706 can produce missense mutation, and previous study has revealed that missense mutations in the mucin gene may affect the immune response and cell survival by creating new antigen determinants [32]. On the other hand, our study found rs11979706, rs10246021, rs6966570, and rs4729655 show strong linkage disequilibrium, and the variations of rs10246021 and rs6966570 may affect the entire haplotype to work. The above observations provide clues for us to infer that genetic element may lead to altered endometriosis-associated dysmenorrhea by affecting the expression of *MUC17* protein and the release of inflammatory cytokines.

However, unfortunately, we did not discover that *MUC17* (rs11979706, rs10246021, rs6966570, rs4729655) gene polymorphisms were associated with endometriosis in Central Plains Chinese women. Similar to our results, Yang C *et al.* [33] failed to show a correlation between rs4729655 polymorphism and the risk of endometriosis in Taiwan population either. However, they revealed the genetic variation of rs4729655 was associated with a lower risk of infertility, which was also reflected in the data we obtained, not obvious, though. As they research suggests, the rs4729655 could link to endometriosis-related infertility through regulate miR-4508 and miR-3158-3p expression. Moreover, rs11979706 also played a protector role in our study, which may work through the missense mutations and haplotype mechanisms above mentioned.

However, several limitations need consideration in our study. Endometriosis may be a disease caused by multiple factors and genes. Whether the interaction with other genes can affect the occurrence and development of endometriosis requires a lot of cellular and molecular biological evidence. Moreover, the sample size of our research is small, and whether this result can be necessarily generalizable to the whole Chinese population has yet to be confirmed by a larger cohort, multi-regional, and multi-ethnic joint research.

5. Conclusions

In conclusion, this study showed that the *MUC17* gene polymorphism could not be a significant relevant factor to endometriosis in Central Plains Chinese women. Nonetheless, *MUC17* SNP locis and haplotype could be potential targets of endometriosis dysmenorrhea and treatment in this population, and reference index for patients with endometriosis-induced infertility to choose in vitro fertilization (IVF). Future study should be in larger populations, in an attempt to clarify the relationship between *MUC17* gene polymorphism and endometriosis, and establish the system of endometriosis cell lines research to perform functional tests to further understand the association between *MUC17* locus mutation and endometriosis.

Author Contributions

MQ—Conceptualization, Formal Analysis, Investigation, Methodology, Software, Resources, Writing - original draft; HZ—Conceptualization, Formal Analysis, Data Curation, Methodology, Resources, Writing - original draft; YX—Data Curation, Methodology, Resources, Software, Writing - review & editing. LY—Conceptualization, Formal Analysis, Investigation, Project administration, Writing - review & editing. All authors read and approved the

final manuscript.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of The Third Affiliated Hospital of Zhengzhou University (Approval number: (2019) Medical ethics review NO.20).

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Conflict of Interest

The authors declare no conflict of interest.

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