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The AGT Haplotype of the ESR2 Gene Containing the Polymorphisms rs2077647A, rs4986938G, and rs1256049T Increases the Susceptibility of Unexplained Recurrent Spontaneous Abortion in Women in the Chinese Hui Population

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Background: Estrogen has an important role in unexplained recurrent spontaneous abortion (URSA). Polymorphisms of the ESR1 gene and the ESR2 gene have been identified as risk factors for URSA, but with varied associations in Chinese populations. This study aimed to compare the role of gene polymorphisms of ESR1 and ESR2 and the risk of URSA in the Chinese Hui and Chinese Han populations.

Material/Methods: Chinese Hui women (n=171) and Chinese Han women (n=234) with URSA were compared with healthy controls (n=417) matched by ethnicity and age. Genotyping was performed using direct sequencing and identified three polymorphisms of the ESR1 gene (rs9340799, rs2234693, and rs3798759) and three polymorphisms of the ESR2 gene (rs207764, rs4986938, and rs1256049). The association between ESR1 and ESR2 gene polymorphisms and the risk of URSA was evaluated statistically using the odds ratio (OR) and 95% confidence interval (CI).

Results: No association was detected between the allelic, dominant, and recessive models of ESR1 and ESR2 gene polymorphisms and the risk of URSA in Chinese Han and Hui populations (p>0.05). The distribution of the AGT haplotype containing ESR2 gene polymorphisms rs2077647A, rs4986938G, and rs1256049T was significantly reduced in patients with URSA compared with controls in the Chinese Hui population (OR, 0.29; 95% CI, 0.14–0.62; p=0.0009; p_{adj}=0.005).

Conclusions: The AGT haplotype of the ESR2 gene containing the polymorphism rs2077647A, rs4986938G, and rs1256049T (ESR2 hap_{AGT}) was a protective factor for URSA in women in the Chinese Hui population when compared with the Chinese Han population.

MeSH Keywords: Estrogen Receptor alpha • Estrogen Receptor beta • Genetic Association Studies • Polymorphism, Genetic

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Background

Recurrent spontaneous abortion (RSA) refers to three or more miscarriages occurring with the same partner [1]. RSA has a complex etiology that includes infection, abnormal reproductive tract anatomy, environmental physical and chemical factors, and chromosomal abnormalities [2,3]. However, approximately 50% of patients with RSA are categorized as unexplained RSA (URSA) and have an unknown etiology [4]. Previous studies have shown that abortion is the result of immunological rejection of embryos by pregnant women, leading to the failure of embryonic allotransplantation [5]. Estrogen is one of the most important steroid hormones in the female reproductive system, which can combine with estrogen receptors 1 and 2, to mediate the classical signal transduction pathway and produce a variety of estrogen-associated effects [6–8]. Studies have shown that estrogen receptors are expressed in the target organs of estrogen *in vivo* and in some malignant cells [9,10]. Patnam et al. showed that estrogen receptors might induce the immune tolerance at the maternal-fetal interface [11]. Therefore, estrogen receptors are key factors in the pathogenesis of URSA.

Single nucleotide polymorphisms (SNPs) of the receptor gene are involved in the pathogenesis of disease. Polymorphisms of the gene that encodes estrogen receptor 1, ESR1, and the gene that encodes estrogen receptor 2, ESR2, have been identified as risk factors for URSA, but there have been varied reports on the associations in Chinese populations. Estrogen receptor are correlated with the risk of endometriosis [12], premature ovarian failure [13], spermatogenic defects [14], and uterine leiomyoma [15].

The association between ESR1 gene polymorphisms and abortion has been demonstrated in previous studies. Lehrer et al. showed that a polymorphism in the ESR gene was associated with estrogen receptor-positive breast cancer in patients with a history of recurrent abortion [16]. However, Berkowitz et al. showed that the expression of the ESR1 gene was not significantly associated with recurrent abortions [17]. Alessio et al. reported that the ESR1 gene was not a risk factor for RSA in a Brazilian population [18]. However, the ESR1 gene polymorphisms, rs2234693 and rs9340799, are risk factors for URSA in Spanish populations [19] and the Chinese Han populations [20–22]. The varied findings from these previous studies may indicate the effect of the genetic background on the association between ESR gene polymorphisms and the risk of URSA. For the ESR2 gene, no association was detected between rs1256049 and rs4986938 and the risk of URSA in the Chinese Han population [23,24], the Iranian population [25], and the Brazilian population [18]. These previous studies have resulted in varied findings in different populations.

The Chinese Hui population is a minor ethnic group in China. Most people of the Chinese Hui population live in northwestern China, including Ningxia, Gansu, and Shanxi provinces. Inconsistent results have been observed for the relationship between ESR1 and ESR2 gene polymorphisms and the risk of URSA in the Chinese Han population, and no previous studies have been undertaken in the Chinese Hui population. Therefore, this study aimed to compare the role of gene polymorphisms of ESR1 and ESR2 and the risk of URSA in the Chinese Hui and Chinese Han populations.

Material and Methods

Patients and controls

The study protocol was approved by the Ethics Committee of Yinchuan Women and Children Health Care Hospital (EC/18/113; 07/15/2018). Written informed consent for genetic analysis was obtained from all study participants or their guardians. Women who had experienced three or more consecutive miscarriages and had no living children were identified from Yinchuan Women and Children Health Care Hospital. Women with unexplained recurrent spontaneous abortion (URSA) with systemic disease, abnormal menstrual periods, and abnormal karyotypes were excluded.

The study included 405 patients with a mean age of 25.6±1.5 years with URSA and included 171 Chinese Hui and 234 Chinese Han patients. Also, 417 healthy controls included 177 Chinese Hui patients and 240 Chinese Han patients who matched in ethnicity and age, with a mean age of 26.1±2.2 years. Only women who were not in their first pregnancy, and who had at least one living child, and had no history of spontaneous abortion were enrolled in the control group. Table 1 shows the characteristics of the study cases and the controls.

Genotyping

The ESR1 gene polymorphisms rs9340799, rs2234693, and rs3798759, and ESR2 gene polymorphisms rs207764, rs4986938, and rs1256049 were selected, as described in previous studies [18,19,22,23,25]. Peripheral blood samples were obtained from all subjects by using the QlAamp DNA Mini Kit (Qiagen, Hilden, Germany). Multiplex polymerase chain reaction (PCR) was performed on a GeneAmp 9700 PCR thermocycler (Applied Biosystems, Foster City, California, USA). Genotyping of the ESR1 and ESR2 polymorphisms was determined by direct sequencing. The 3730XL genetic analyzer (Applied Biosystems, Foster City, California, USA) was used for sequencing. The GeneScan™ version 3.7 Software (Applied Biosystems, Foster City, California, USA) was used for data analysis.

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Table 1. Characteristics of Chinese Han and Chinese Hui women with unexplained recurrent spontaneous abortion (URSA) and the controls.

	Chinese Han (n=234)	Control (n=240)	P-value	Chinese Hui (n=171)	Control (n=177)	P-value
Age (year, mean±SD)	28.0±4.3	30.16±4.1	0.052	29.06±4.46	30.55±3.56	0.076
Menarche (year, mean±SD)	14.2±1.2	14.7±1.4	0.131	13.38±1.98	13.98±2.14	0.152
Smoking (%)	26.1	23.1	0.247	17.4	15.6	0.315
BMI (kg/m^2)	26.5±1.4	26.3±2.2	0.566	26.6±1.6	27.1±1.8	0.547
T4 (ng/dL)	1.2±0.36	1.2±0.31	0.423	1.2±0.44	1.2±0.41	0.416
TSH (mU/mL)	2.0±0.24	2.0±0.31	0.475	2.0±0.42	2.0±0.38	0.517
Miscarriages (%)						
	3	227		164		
	4	5		6		
	5	2		1		

URSA – unexplained recurrent spontaneous abortion; SD – standard deviation; BMI – body mass index; TSH – thyroid stimulating hormone; T – thyroid.

Table 2. The patterns of linkage disequilibrium (LD) in the ESR1 and ESR2 genes in Chinese Han and Chinese Hui women with unexplained recurrent spontaneous abortion (URSA).

	Chinese Hui women (171/177)			Chinese Han women (234/240)		
	r^2	rs2234693	rs3798759	r^2	rs2234693	rs3798759
ESR1	rs9340799	0.236	0.018	rs9340799	0.294	0.027
	rs2234693	–	0.016	rs2234693	–	0.021
	r^2	rs4986938	rs1256049	r^2	rs4986938	rs1256049
ESR2	rs2077647	0.003	0.053	rs2077647	0.005	0.068
	rs4986938	–	0.004	rs4986938	–	0.028

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) of polymorphisms was tested using the chi-squared χ^2 test. The t-test tested the distributions of the allelic, dominant, and recessive gene models between the control group and URSA groups. Analysis of the gene polymorphisms was performed using SHEsis online software (*http://analysis.bio-x.cn/myAnalysis.php*) [26]. The PLINK genome association online analysis tool (*http://zzz.bwh.harvard.edu/plink/*) was used to estimate common (frequency >0.01) haplotypes constructed by the single nucleotide polymorphisms (SNPs) of ESR1 (rs9340799, rs2234693, rs3798759) and ESR2 (rs2077647, rs4986938, rs1256049). The odds ratios (OR) and 95% confidence interval (CI) were determined by standard logistic regression analysis. Stringent Bonferroni's correction was performed to adjust the P-value (P_{adj}) in multiple comparisons to identify significant relationships. The squared correlation coefficient r^2 for each pair of polymorphic sites was calculated using Haploview online haplotype analysis software (*https://www.broadinstitute.org/haploview/haploview*) (Broad Institute, Cambridge, MA, USA). A P-value <0.05 was considered to be statistically significant.

Results

No significant deviations from the Hardy–Weinberg equilibrium (HWE) were observed for all tag SNPs (p>0.05). The squared correlation coefficient r^2 is listed in Table 2, indicating low LD with each other. The frequency of the rs9340799G allele in patients with unexplained recurrent spontaneous abortion (URSA) significantly increased compared with that in the controls

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Table 3. Distribution of the ESR1 and ESR2 gene single nucleotide polymorphisms (SNPs) in the Chinese Han and Chinese Hui women with unexplained recurrent spontaneous abortion (URSA) and the controls.

Gene	Ethnicity	SNP ID	Position	Minor allele	MAF (frequency)		P-value	P-value (corrected)*	OR (95% CI)**
					Case	Control			
ESR1	Hui	rs9340799	6: 151842246	G	0.281	0.192	0.04	0.12	1.91 (1.02–3.59)
		rs2234693	6: 151842200	C	0.439	0.458	0.61	–	0.93 (0.55–1.55)
		rs3798759	6: 151959418	C	0.246	0.279	0.32	–	1.46 (0.82–2.59)
	Han	rs9340799	6: 151842246	G	0.256	0.254	0.94	–	1.23 (0.73–2.07)
		rs2234693	6: 151842200	C	0.389	0.419	0.35	–	0.92 (0.58–1.43)
		rs3798759	6: 151959418	C	0.295	0.275	0.49	–	0.71 (0.56–1.48)
ESR2	Hui	rs2077647	14: 151807942	G	0.377	0.390	0.72	–	1.05 (0.62–1.79)
		rs4986938	14: 64233098	T	0.213	0.163	0.09	–	1.61 (0.80–3.23)
		rs1256049	14: 64257333	T	0.219	0.279	0.07	–	1.69 (0.94–3.04)
	Han	rs2077647	14: 151807942	G	0.356	0.331	0.42	–	0.93 (0.59–1.47)
		rs4986938	14: 64233098	T	0.267	0.287	0.49	–	0.78 (0.45–1.36)
		rs1256049	14: 64257333	T	0.376	0.364	0.70	–	1.15 (0.73–1.79)

SNP – single nucleotide polymorphism; OR – odds ratio; CI – confidence interval; NC – not calculated; MAF – minor allele frequency.
* The Bonferroni's correction was performed to correct the P-value; ** OR and 95% CI are calculated for the minor allele of each SNP.

in the Chinese Hui population (OR, 1.91; 95% CI, 1.02–3.59; p=0,04). However, the significant association disappeared after Bonferroni's correction (P_{adj}=0.12). No association was observed between the allelic models of the ESR1 polymorphisms rs2234693 and rs3798759 and the ESR2 polymorphisms rs2077647, rs4986938, and rs1256049 and the risk of URSA in the Chinese Han and Hui populations (p>0.05) (Table 3).

The distribution of the recessive model of ESR1 rs9340799 was significantly higher in cases than in controls (OR, 2.19; 95% CI, 1.03–4.70; p=0.04). However, the significant association disappeared after Bonferroni's correction (P_{adj}=0.12). No association was found between the allelic, dominant, and recessive models of the ESR1 gene polymorphisms rs2234693 and rs3798759, as well as the ESR2 gene polymorphisms rs2077647, rs4986938, and rs1256049, and the risk of URSA in Chinese Han and Hui populations (p>0.05) (Table 4).

There was a significantly reduced frequency of haplotype TTC in the ESR1 gene (ESR1 Hap_{TTC}) and an increased frequency of haplotype AGC in the ESR2 gene (ESR2 Hap_{AGC}) in the Chinese Hui population group (ESR1 Hap_{TTC}: OR, 0.41; 95% CI, 0.19–0.83; p=0.01) (ESR2 Hap_{AGC}: OR, 1.79; 95% CI, 1.03–3.15; p=0.04). However, no significant association was found after Bonferroni's correction (ESR1 Hap_{TTC} P_{adj}=0.06; ESR2 Hap_{AGC} P_{adj}=0.24). The frequency of haplotype AGT in the ESR2 gene (ESR2 Hap_{AGT}) was significantly lower in women with URSA when compared with the controls in the Chinese Hui population (OR, 0.29; 95% CI, 0.14–0.62; p=0.0009), even after Bonferroni's correction (P_{adj}=0.005) (Table 5).

Discussion

Estrogen has several roles in the uterus that ensure successful conception and pregnancy, including cervical maturation, implantation of the embryo, and successful placentation [27]. The effects of estrogen are mediated by binding to the estrogen receptors 1 and 2, which are encoded by the ESR1 and ESR2 genes [28]. A study of knockout mice for the ESR2 gene showed that adult female mice had reproductive defects and that mice lacking the ESR2 gene had reduced fertility with an underdeveloped uterus that did not respond to estrogen [29]. It is important to investigate the genes and biological mechanisms that affect abortion rates, including in women with unexplained recurrent spontaneous abortion (URSA). Many candidate genes associated with increased rates of spontaneous abortion have been identified by investigating gene polymorphisms, including for vascular genes and genes involved in thrombosis [29,30].

Polymorphisms of the ESR genes have been studied in association with an increased risk of breast cancer [31], osteoporosis [32], and prostate cancer [33]. However, few studies have explored their role in URSA. Studies on the effects of ESR1 gene polymorphisms on recurrent spontaneous abortion have shown an association. The rs9340799 and rs2234693 polymorphisms are located in the enhancers and promoters of the ESR1 gene, which are closely related to the transcriptional regulation of the gene [35]. The variants in this region can directly affect the function and quantity of estrogen receptor

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Table 4. The frequency of ESR1 and ESR2 genotypes in the Chinese Han and Chinese Hui women with unexplained recurrent spontaneous abortion (URSA) and the controls.

Gene	Ethnicity	SNPs, rs, (A>B)	Genotypes		OR [95% CI], $P_{(Add\ model)}$ AA/BB	$P^*_{(adj)}$	OR [95% CI], $P_{(Dom\ model)}$ AA+AB/BB	$P_{(adj)}$	OR [95% CI], $P_{(Rec\ model)}$ AA/AB+BB	$P_{(adj)}$
			Case (AA/AB/BB)	Control (AA/AB/BB)						
ESR1	Hui (171/177)	rs9340799G	87/72/12	116/54/7	2.83 [0.48–16.48], –	–	0.46 [0.08–2.64], –	–	2.19 [1.03–4.70], 0.04	0.12
		rs2234693C	51/90/30	51/90/36	0.83 [0.28–2.44], 0.74	–	1.20 [0.47–3.05], 0.69	–	0.95 [0.43–2.12], 0.92	–
		rs3798759C	96/66/9	88/79/10	0.42 [0.096–1.85], –	–	2.03 [0.48–8.57], –	–	0.66 [0.32–1.37], 0.26	–
	Han (234/240)	rs9340799G	135/78/21	128/92/20	0.93 [0.32–2.70], 0.89	–	1.29 [0.46–3.64], 0.64	–	1.52 [0.79–2.91], 0.20	–
		rs2234693C	90/102/42	87/105/48	0.85 [0.35–2.03], 0.71	–	1.14 [0.52–2.53], 0.74	–	0.91 [0.48–1.73], 0.78	–
		rs3798759C	117/96/21	126/96/18	1.25 [0.38–4.06], 0.69	–	0.82 [0.26–2.56], 0.74	–	1.11 [0.59–2.06], 0.75	–
ESR2	Hui (171/177)	rs2077647C	58/93/20	63/90/24	0.79 [0.23–2.67], 0.69	–	1.33 [0.43–4.12], 0.62	–	1.02 [0.48–2.19], 1.00	
		rs4986938T	110/49/12	135/36/6	2.37 [0.41–13.65], –	–	0.46 [0.08–2.64], –	–	1.61 [0.71–3.63], 0.25	
		rs1256049T	102/63/6	88/79/10	0.31 [0.05–1.70], –	–	2.55 [0.47–13.69], –	–	0.53 [0.25–1.11], 0.09	
	Han (234/240)	rs2077647C	102/95/35	114/93/33	1.06 [0.47–2.37], 0.89	–	1.04 [0.49–2.21], 0.92	–	1.17 [0.62–2.19], 0.62	
		rs4986938T	131/81/22	128/86/26	0.7 2[0.28–1.85], 0.49	–	1.35 [0.54–3.41], 0.52	–	0.79 [0.39–1.62], 0.53	
		rs1256049T	85/122/27	92/121/27	0.78 [0.26–2.37], 0.66	–	0.97 [0.36–2.59], 1.00	–	0.69 [0.34–1.42], 0.32	

SNP – single nucleotide polymorphism; OR – odds ratio; CI – confidence interval; NC – not calculated; MAF – minor allele frequency.
* The Bonfferoni correction was applied to correct the P-value.

expression and lead to increased susceptibility to diseases. Nilsson et al. [36] found that the rs2234693 polymorphism contains a binding site for the Myb transcription factor, which can affect Myb-induced transcriptional activity and affect ESR1 gene expression. The findings from the present study showed that the ESR1 gene polymorphisms, rs9340799, rs2234693, and rs3798759 were not associated with URSA in Chinese Han and Hui populations. This finding differs from the results reported previously by Pan et al. [22], Pineda et al. [19], Liu et al. [21], and Guan et al. [20]. The results from these previous studies may indicate the important role of genetic background in the pathogenesis of URSA. Also, different results were shown in the Chinese Han populations. The complex genetic composition of the Chinese Han populations might contribute to the discrepancy. Also, the relatively small sample size in previous studies may have influenced the results.

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Table 5. Distribution of the haplotypes (>1%) in the ESR1 and ESR2 genes in the Chinese Han and Chinese Hui women with unexplained recurrent spontaneous abortion (URSA) and the controls.

Gene	Haplotype*	Ethnicity	Case (freq.)	Control (freq.)	P**	P-value (corrected)***	OR [95% CI]
ESR1	CCA	Hui	0.151	0.158	0.88	–	0.95 [0.46–1.93]
		Han	0.201	0.133	0.12	–	1.61 [0.88–2.95]
	CTA	Hui	0.034	0.01	0.24	–	3.11 [0.42–22.85]
		Han	0.015	0.025	–	–	–
	TCA	Hui	0.156	0.218	0.23	–	0.67 [0.34–1.29]
		Han	0.099	0.159	0.10	–	0.57 [0.29–1.13]
	TCC	Hui	0.035	0.081	0.14	–	0.42 [0.13–1.37]
		Han	0.056	0.07	0.59	–	0.78 [0.31–1.95]
	TTA	Hui	0.413	0.291	0.05	–	1.72 [0.99–2.96]
		Han	0.390	0.408	0.67	–	0.91 [0.58–1.43]
	TTC	Hui	0.114	0.241	0.01	0.06	0.41 [0.19–0.83]
		Han	0.198	0.145	0.23	–	1.43 [0.79–2.59]
ESR2	AAC	Hui	0.095	0.082	0.72	–	1.83 [0.47–2.94]
		Han	0.113	0.108	0.87	–	1.06 [0.52–2.14]
	AGC	Hui	0.384	0.260	0.04	0.24	1.79 [1.03–3.15]
		Han	0.249	0.216	0.48	–	1.21 [0.72–2.04]
	AGT	Hui	0.098	0.269	0.0009	0.005	0.29 [0.14–0.62]
		Han	0.227	0.257	0.52	–	0.85 [0.51–1.42]
	GAC	Hui	0.043	0.040	0.91	–	1.08 [0.29–3.91]
		Han	0.018	0.031	0.45	–	0.57 [0.13–2.53]
	GGC	Hui	0.259	0.296	0.54	–	0.83 [0.47–1.49]
		Han	0.210	0.202	0.87	–	1.05 [0.61–1.81]
	GGT	Hui	0.057	0.040	0.54	–	1.46 [0.43–4.94]
		Han	0.135	0.106	0.42	–	1.32 [0.67–2.61]

OR – odds ratio; CI – confidence interval; '–' – not significant. * The PLINK genome association online analysis tool was used to estimate common (frequency >0.01) haplotypes constructed by the single nucleotide polymorphisms (SNPs) of ESR1 (rs9340799, rs2234693, rs3798759) and ESR2 (rs2077647, rs4986938, rs1256049); ** each haplotype was compared with the other haplotypes combined; *** the Bonfferoni correction was applied to correct the P-value.

ESR2 gene polymorphisms have been previously studied in women with URSA in Brazil [18], South Korea [37], and Iran [25] and have shown no significant relationship between the rs1256049 and rs4986938 polymorphisms and the risk of URSA. The distribution of the genotypes of the rs1256049 polymorphism in Asians and Caucasians have shown ethnic differences. In a study of Iranian women, the distribution of the rs1256049 genotype was found to be similar to that of Caucasians [25]. However, our results showed that ESR2 rs2077647, rs4986938, and rs1256049 were not susceptibility factors for URSA in Chinese Han patients, which was similar to the results reported by Hu et al. [23], Mahadvipour et al. [25], Aléssio et al. [18], and Guo et al. [24]. Also, negative results were also found for ESR2 gene polymorphisms rs2077647, rs4986938, and rs1256049 and the risk of URSA in the Chinese Hui population. Overall, individual polymorphisms of ESR2 may not be risk factors for

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URSA in Chinese populations. The polymorphisms, rs2077647 and rs4986938 are located in introns of the ESR2 gene, and rs1256049 encodes a synonymous variant. Although these three polymorphisms do not lead to changes in the amino acids of the estrogen receptor-2 protein, they may be linked to some functional polymorphisms that may affect the expression or function of related genes [38]. Further studies are required to investigate the potential functional polymorphisms.

In the present study, the AGT haplotype (hap_{AG}) of the ESR2 gene containing the polymorphism rs2077647A, rs4986938G, and rs1256049T was a protective factor for URSA in women in the Chinese Hui population when compared with the Chinese Han population. This finding supported that URSA is influenced by multiple polymorphic sites as well as polygenetic factors. To the best of our knowledge, this study was the first to determine a significant association between ESR2 Hap_{AGT} and the risk of URSA in the Chinese Hui population. The different findings from the Chinese Han and Chinese Hui populations may be due to the different genetic backgrounds. The Chinese Hui population, numbering approximately 10586,087, is one of the most populous ethnic minorities in China and mainly live in the Ningxia Hui autonomous region. A genetic study based on the distribution of short tandem repeat (STR) *loci* showed that the Chinese Hui ethnic group was a distinctive minority in terms oif origin, culture, and customs, as well as in genetic background [39]. Therefore, the association between ESR2 hap_{AGT} and the risk of URSA in the Hui ethnic group is possible. Future studies with a larger number of patients with URSA from the Hui ethnic group are necessary in the future to validate these findings.

There were some limitations to the present study. A relatively small sample size was included. These results require further validation with a larger number of subjects, especially women from the Chinese Hui population. Although genetic and environmental heterogeneity may exist between the Chinese Hui population and other populations, given that the significant association remained after correction for multiple tests in the URSA cases and the controls, the association between ESR2 Hap_{AGT} and URSA in the Hui ethnic group appears to be valid.

Conclusions

This study aimed to compare the role of gene polymorphisms of ESR1 and ESR2 and the risk of unexplained recurrent spontaneous abortion (URSA) in the Chinese Hui and Chinese Han populations. The AGT haplotype of the ESR2 gene (ESR2 hap_{AGT}) containing the polymorphism rs2077647A, rs4986938G, and rs1256049T was a protective factor for URSA in women in the Chinese Hui population when compared with the Chinese Han population.

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Conflict of interest

None.

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