Original Article

SAGE Open Medicine

SAGE Open Medicine
Volume 12: 1–7
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DOI: 10.1177/20503121241303075
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The LncRNA PRNCR1 rs13252298 GG genotype is correlated with reducing susceptibility to recurrent spontaneous miscarriage in a southern Chinese population

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Abstract

Background: LncRNAs play diverse roles and participate in various biological processes within the human body. It has been frequently reported that they are involved in the occurrence and development of recurrent spontaneous miscarriage. *PRNCR1*, a crucial player in several types of cancers, may also have implications for recurrent spontaneous miscarriage risk. However, the correlation between *PRNCR1* rs13252298 A > G polymorphism and this risk remains unclear. In summary, we conducted the following experiments to investigate the association between the *PRNCR1* polymorphic site rs13252298 and susceptibility to recurrent spontaneous miscarriage.

Method: Our research included 695 healthy controls and 413 patients with recurrent spontaneous miscarriage from southern China. Genotyping was performed using the TaqMan method.

Result: Our findings revealed that there is a relationship between *PRNCR1* rs13252298 A > G polymorphism and lower susceptibility to recurrent spontaneous miscarriage (AG and AA: adjusted OR = 0.794, 95% CI = 0.527–1.196, $p = 0.2696$; GG and AA: adjusted OR = 0.705, 95% CI = 0.542–0.917, $p = 0.0092$; dominant model: adjusted OR = 0.722, 95% CI = 0.563–0.926, $p = 0.0104$; recessive model: adjusted OR = 0.949, 95% CI = 0.644–1.398, $p = 0.7912$).

Conclusion: The results of our study demonstrate that the *PRNCR1* rs13252298 A > G allele may contribute to a decreased risk of recurrent spontaneous miscarriage. The rs13252298 polymorphism could potentially serve as a biomarker for detecting recurrent spontaneous miscarriage risk and aiding prevention efforts.

Keywords

Recurrent spontaneous miscarriage, *PRNCR1*, single nucleotide polymorphism, LncRNA, reproduction

Date received: 1 August 2024; accepted: 11 November 2024

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Introduction

The recurrent spontaneous miscarriage (RSM) is defined as two or more consecutive losses of clinical pregnancies before the 20th week of gestation with one sexual partner.[1] The risk of RSM is about 2.5%, which is approximately 4 million miscarriages worldwide per year.[2,3] The incidence of RSM in China is comparable to that in foreign countries. However, due to the vast population base in China, the absolute number of patients experiencing RSM is relatively high. Therefore, it is imperative to investigate the etiology of this condition.[4] RSM not only causes trauma to women's bodies but also has certain adverse effects on their psychology and family relations, and even leads to the occurrence of diseases such as depression.[5] But the cause of more than half of RSMs remains unknown.[6] Therefore, to reduce the harm caused by RSM to women, it is necessary to deepen our understanding of its risk factors and help reduce its incidence.

Susceptibility to RSM may be associated with multiple factors such as hormone or metabolic disorders, autoimmunity, and genetics.[7] Genetic polymorphisms, such as single nucleotide polymorphisms (SNPs), have been reported by us to be associated with susceptibility to RSMs.[8–10] The findings of a case–control study indicate that *HOTAIR* gene polymorphisms are significantly associated with RSM, suggesting their potential utility as genetic markers for the clinical diagnosis of RSM.[11] In addition, a Korean team found that the *VEGFR-2* (Vascular endothelial growth factor receptor-2) −604 T > C polymorphism may increase susceptibility to RSMs, and *VEGFR-2* was also reported to be involved in the development of different diseases.[12] The vascular endothelial growth factor family of proteins are important for angiogenesis. Its 3′-untranslated region SNP was also indicated to be related to the susceptibility to RSMs.[13] A later study showed that another circulatory system SNP-related gene was associated with RSM.[14] Specifically, these authors noted that the *SERPINA4* (Serpina family A member 4) rs2070777 AA genotype may increase the risk of RSMs in a southern Chinese population. The endocrine system may also be involved in RSMs. One study found that the rs2234693 polymorphism of oestrogen receptor 1 was associated with RSMs in Tunisian women.[15]

In addition to coding genes related to RSM, SNPs in noncoding genes may affect the occurrence of RSM. Long noncoding RNAs (lncRNAs) are noncoding RNAs longer than 200 nucleotides. Several studies have shown that lncRNAs play an important role in many life activities.[16,17] Importantly, regulatory changes in lncRNAs may be associated with the incidence of RSM. Previously, we conducted research on the relationship between *MALAT1* (Metastasis Associated Lung Adenocarcinoma Transcript 1) rs619586 and RSM and found that the rs619586 G variant conferred a decrease in susceptibility to RSM.[18] Later, we explored other possible RSM-related lncRNA SNPs and found that two more were associated with RSM.[8,9] Prostate cancer-associated noncoding RNA 1 (*PRNCR1*) is one lncRNA that we were highly concerned about. Expression changes in *PRNCR1* are thought to mediate damage to vascular endothelial cells.[19] In addition, *PRNCR1* has been reported to modulate the invasion and migration of lung cancer cells, and the invasion of trophoblast cells that are important to placenta formation.[20]

Although multiple *PRNCR1* SNPs can affect the functions of this lncRNA to some extent, the relationship between the rs13252298 polymorphism and RSM is not yet studied.[21,22] Thus, we hypothesized that the *PRNCR1* rs13252298 polymorphism might be associated with susceptibility to RSM. In this study, we determined the relationship between the *PRNCR1* rs13252298 polymorphism and susceptibility to RSM in a southern China population.

Methods

Study subjects

According to the calculation, the appropriate sample composition is 317 people per group. On this basis, we tried to increase the sample size of this study. In the end, a total of 695 healthy controls and 413 patients diagnosed with RSMs at Women and Children's Medical Center between June 2022 and July 2023 were included in this prospective cohort study. The diagnosis of RSM patients was defined as two or more continuous pregnancy losses before 20 weeks of gestation.[23] The healthy controls in this study were age-matched with the patients, all of whom had at least two normal pregnancies and had no history of miscarriage. Written informed consent was obtained from all of the participants.

The exclusion criteria: patients with history of abnormal uterine anatomy; arterial or venous thrombosis; uterine abnormalities; metabolic disorders; liver or kidney dysfunction; and autoimmune conditions.

Genotyping and DNA extraction

Total genomic DNA was extracted from the blood using a TIANamp Blood DNA Kit (TianGen Biotech, Beijing, China). We performed the TaqMan real-time polymerase chain reaction on an ABI Q6 (QuantStudio™ 6 Flex Real-Time PCR System, Applied Biosystems, Foster City, CA, USA) to determine the genotype of SNP rs13252298. Approximately 10% of the samples were selected randomly for sequencing for quality control purposes and validation of the genotyping results. These results were 100% consistent. The Clinical Biological Resource Bank of the Women and Children's Medical Center Affiliated to Guangzhou Medical University supplied all blood samples needed for the research.

Statistical analyses

We calculated the Hardy–Weinberg equilibrium (HWE) of the control subjects using the goodness-of-fit Chi-square test. Chi-square test was conducted to compare demographic

Table 1. Frequency distribution of selected characteristics in recurrent miscarriage and controls.

Variables	Cases ($n=413$)		Controls ($n=695$)		p-Value[a]	Statistical power[b]
	No.	%	No.	%		
Age range, year	22–47		21–44		0.0628	0.0707
Mean ± SD	33.30 ± 4.75		32.06 ± 3.88			
<35	255	61.74	517	74.39		
35–40	109	26.39	157	22.59		
>40	49	11.86	21	3.02		
No. of miscarriage/%						
2–3	359	86.92				
⩾4	54	13.08				

[a]Two-sided χ^2 test for distributions between recurrent miscarriage patients and controls.
[b]Statistical power was calculated using the number of observations in each subgroup and the corresponding ORs and p-values in this table.

and genotypic differences between controls and RSM cases. Unconditional univariate and multivariate logistic regression analyses were performed. Age-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the correlation between *PRNCR1* polymorphisms and the susceptibility to RSMs. Stratified analysis was also performed based on the number of miscarriages and age. Statistical significance was set at $p<0.05$; Sample size was calculated by PASS software,version 11.0 (NCSS, USA). All statistical tests were bilateral and calculated using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Population characteristics

Table 1 shows the demographic characteristics of the healthy control and RSM groups. According to the PASS software sample size calculation, the appropriate sample composition is 317 people per group. On this basis, we tried to increase the sample size of this study.We enrolled 413 patients with RSMs (22–47 years of age) and 695 healthy controls (21–44 years of age). There were no significant differences between RSM patients and healthy controls (33.3 ± 4.75 vs 32.1 ± 3.88 years of age, respectively, $p=0.0628$). Furthermore, approximately 86.9% of patients with RSMs experienced two or three miscarriages, and approximately 13.1% of RSM patients experienced four or more miscarriages in this study.

Association between the PRNCR1 *rs13252298 polymorphism and RSM susceptibility*

Table 2 shows the genotype distribution of the *PRNCR1* rs13252298 A>G polymorphism in the miscarriage and control groups. The *PRNCR1* rs13252298 A>G genotype was determined using the HWE in the control group ($p=0.505$). We observed that *PRNCR1* rs13252298 was significantly associated with a lower risk of RSMs (adjusted OR = 0.801, 95% CI = 0.534–1.201, $p=0.2828$; GG and AA: adjusted OR = 0.705, 95% CI = 0.542–0.917, $p=0.009$; dominant model: adjusted OR = 0.722, 95% CI = 0.563–0.926, $p=0.010$; recessive model: adjusted OR = 0.937, 95% CI = 0.644–1.398, $p=0.7912$; over-dominant inheritance model: OR = 0.770, 95% CI = 0.602–0.985, $p=0.6406$).

Stratification analysis of the selected polymorphism and RSMs

Both age and number of miscarriages may be associated with susceptibility to RSM.[2,24] As shown in Table 3, to further explore the relationship between the *PRNCR1* rs13252298 polymorphism and susceptibility to RSM, we stratified the patients and controls subjects by age and number of miscarriages. Our stratification analysis results suggested that the *PRNCR1* rs13252298 A>G polymorphism was significantly associated with RSM susceptibility in the younger age group (OR = 0.613, 95% CI = 0.453–0.829, $p=0.001$), and the fewer number of miscarriages group (adjusted OR = 0.740, 95% CI = 0.571–0.959, $p=0.023$).

Discussion

RSM is a relatively common obstetric disease that causes serious harm to women and their families, but the cause of some RSMs is still unclear.[25] A large number of studies have suggested that lncRNAs may affect the stability of embryos through various functions, and thus participate in mediating the occurrence of RSM.[26–28] The effects of LncRNA on the placenta can be summarized into four parts: regulation of cell migration and invasion,[29] impact on placental angiogenesis,[30] regulation of cell cycle and proliferation, and involvement in inflammation and immune response.[31,32] These four parts play an important role in the stability and development of the placenta. Therefore, the presence of lncRNAs may have an important impact on the occurrence and development of RSMs. In this study, we investigated the association between a lncRNA *PRNCR1*

Table 2. Genotype and allele frequencies of PRNCR1 in RM patients and controls.

Genotype/allele	RM ($N=413$)	Controls ($N=695$)	p-Value[a]	Statistical power[b]	OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value[c]
PRNCR1/rs13252298 A > G (HWE = 0.5051)								
AA	194 (46.97)	277 (39.86)			1	/	1	/
AG	173 (41.89)	336 (48.35)	/		0.801 (0.534–1.201)	0.2828	0.794 (0.527–1.196)	0.2696
GG	46 (11.14)	82 (11.80)	/		**0.735 (0.567–0.953)**	**0.0201**	**0.705 (0.542–0.917)**	**0.0092**
Dominant	194 (46.97)	277 (39.86)	**0.0205**	**0.0696**	**0.748 (0.585–0.956)**	**0.0206**	**0.722 (0.563–0.926)**	**0.0104**
Recessive	367 (88.86)	613 (88.20)	0.7394	0.0100	0.937 (0.639–1.376)	0.7411	0.949 (0.644–1.398)	0.7912
	Homozygote	Heterozygote	p-value	Statistical power[b]	OR (95% CI)	p-Value		
Over-dominant inheritance model	599	509	0.4370	0.0630	0.770 (0.602–0.985)	0.6406		

OR: odds ratio; HWE: Hardy–Weinberg equation.
[a]χ^2 tests were used to determine differences in genotype distributions between the RM patients and the controls.
[b]Statistical power was calculated using the number of observations in each subgroup and the corresponding ORs and p-values in this table.
[c]Adjusted for age. Statistically significant values are shown in bold ($p < 0.05$).

Table 3. Stratification analysis for associations between, PRNCR1 polymorphism and recurrent miscarriage risk in a south Chinese population.

Variable	rs13252298 (cases/controls)		p-Value	Statistical power[b]	OR (95% CI)	p-Value	Adjust OR (95% CI)	p-value[a]
	AG + GG	AA						
Age								
<35	122/133	310/207	**0.0014**	**0.1148**	**0.613 (0.453–0.829)**	**0.0015**	/	/
35–40	65/44	96/61	0.8039	0.0152	0.939 (0.570–1.547)	0.8037	/	/
>40	32/17	12/9	0.5171	0.0774	1.412 (0.496–4.016)	0.518	/	/
No. of miscarriage/%								
2–3	167/277	192/418	**0.0379**	**0.0639**	**0.762 (0.589–0.985)**	**0.0381**	**0.740 (0.571–0.959)**	**0.0229**
4⩾	27/277	27/418	0.1437	0.0534	0.663 (0.381–1.154)	0.1437	0.656 (0.371–1.160)	0.1471

[a]Adjusted for age. Statistically significant values are shown in bold ($p < 0.05$).
[b]Statistical power was calculated using the number of observations in each subgroup and the corresponding ORs and p-values in this table.

polymorphism (rs13252298 A > G) and susceptibility to RSMs.

Located on chromosome 8q24, *PRNCR1* participates in the regulation of many biological activities. It was first identified as being involved in prostate carcinogenesis.[33] Some studies suggest that *PRNCR1* can regulate angiogenesis,[19] and the proliferation and apoptosis of trophoblast cells, with increased expression potentially being associated with preeclampsia.[34] During normal placental development, maternal arteries undergo remodeling, but in preeclamptic placentas, trophoblast cells are unable to complete the remodeling of spiral arteries, leading to placental ischemia. The proper function of blood vessels and trophoblast cells is crucial for placental development and the maintenance of pregnancy. Therefore, if the role of *PRNCR1* in these processes is disrupted, it may lead to placental insufficiency, thereby increasing the risk of miscarriage. *PRNCR1* is also involved in the development of ovarian cancer, and expression of *PRNCR1* has been reported to improve the ability of cancer cells to proliferate, migrate, and invade.[35] Furthermore, one of the *PRNCR1* SNPs is reported to be associated with lung cancer susceptibility.[36] In all, *PRNCR1* can regulate cell proliferation, migration, and invasion abilities. Its SNPs have also been reported to affect the function of *PRNCR1*, making it play different roles in the human body.

In our study, we found that the *PRNCR1* rs13252298 polymorphism was associated with susceptibility to RSMs. However, our results also showed that only women in the GG homozygous population had a significantly reduced susceptibility to RSMs, while the heterozygous results were not significant (AG and AA: adjusted OR = 0.794, 95% CI = 0.527–1.196, $p = 0.2696$; GG and AA: adjusted OR = 0.705, 95% CI = 0.542–0.917, $p = 0.0092$; dominant model: adjusted OR = 0.722, 95% CI = 0.563–0.926, $p = 0.0104$). As it is widely believed

that previous miscarriages are related to the risk of additional miscarriages, our results came to the same conclusion: patients with fewer miscarriages had a lower susceptibility to RSM (adjusted OR = 0.740, 95% CI = 0.571–0.959, $p = 0.023$).[37]

Maternal age is another important factor affecting susceptibility to RSMs, and rs13252298 was only associated with a reduced susceptibility to RSMs in women younger than 35 years of age (OR = 0.613, 95% CI = 0.453–0.829, $p = 0.001$). To the best of our knowledge, this is the first study to discuss the association between the rs13252298 GG allele and RSMs in a population from southern China; we conclude that the rs13252298 GG allele plays a significant role in RSM pathogenesis.

Our findings are beneficial for clinicians assessing the risk of RSM in different individuals. Although the impact of the *PRNCR1* rs13252298 A > G polymorphism on miscarriage risk varies among different genotypes, overall, the GG genotype significantly reduces the risk. Implementing personalized medicine based on genotype information can help in risk assessment and management for each patient. For instance, patients with the GG genotype might need to focus on other potential miscarriage risk factors, while those with AG or AA genotypes might require more comprehensive intervention measures. Additionally, genotype information can inform clinical decision-making. For patients with AG or AA genotypes, clinicians might consider more proactive preventive measures or treatment plans to lower miscarriage risk, which could include medication, lifestyle changes, or early monitoring. Conversely, for patients with the GG genotype, concerns about miscarriage risk may be alleviated, allowing a focus on other aspects of health management.

There are several limitations to our current findings. First, the patients studied were limited to a southern Chinese population, and no cases or controls from other ethnic groups were assessed. Larger populations and ethnic groups should be included to verify our results. Second, because of the absence of data, we did not consider other potentially important factors such as smoking, drinking, and lifestyle habits in the stratified analysis, which may have affected our results.

In conclusion, the results of this study suggest that the rs13252298 GG allele of *PRNCR1* is associated with decreased susceptibility to RSMs and protection against miscarriage. In addition, the protective effect is most pronounced in women younger than 35 years of age and in patients who have had less than four miscarriages. However, future research should include a larger sample size and more parameters to further explore the role of *PRNCR1* in defining the susceptibility to RSMs.

Conclusion

These results suggested that a polymorphic site of *PRNCR1* gene (rs13252298) may be associated with decreased susceptibility to recurrent miscarriage in a southern Chinese population.

Acknowledgements

We would like to thank the Clinical Biological Resource Bank of Women and Children's Medical Center Affiliated to Guangzhou Medical University for providing all the clinical samples.

Author contribution

Conceptualization: Liandong Zuo and Hanran Mai. Data curation: Yufen Xu, Lanyan Fu, Lei Pi, and Huazhong Zhou. Formal analysis: Junyi Ke, Xilian Luo, and Chenlu Wang. Funding acquisition: Liandong Zuo, Di Che, and Xiaoqiong Gu. Investigation: Liandong Zuo and Hanran Mai. Methodology: Zilin Zheng. Project administration: Liandong Zuo and Hanran Mai. Resources: Yufen Xu, Lanyan Fu, Lei Pi, Huazhong Zhou, and Jieyi Luo. Software: Junyi Ke and Yueling Lin. Supervision: Liandong Zuo and Xiaoqiong Gu. Validation: Hanran Mai. Visualization: Menghua He. Writing – original draft: Hanran Mai. Writing – review & editing: Yanxia Qu and Hanran Mai. All authors reviewed the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Guangzhou Medical and Health Technology Projects (China, 20191A011021 and 20231A011037), the Guangdong Natural Science Foundation (China, 2019A1515012061), Guangzhou Science and Technology Program Key Projects (China, 201904010486, 202201020613, 202201020611), Guangzhou Health Commission (China, 20211A011034), Guangdong Basic and Applied Basic Research Foundation (China, 2022A1515011237), and the Guangzhou Science and technology project (China, 202201020632, 202201020638, 202201020611 and 202206010100).

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Ethics Review Committee of the Women and Children's Medical Center, Guangzhou Medical University (2016102416). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all patients for being included in the study. This article does not contain identifiable data.

Informed consent

Written informed consent was obtained from all subjects before the study.

Trial registration

Not applicable.

Patient consent for publication

Not applicable.

Consent for publication

All authors have read and approved the final manuscript.

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