ORIGINAL RESEARCH ARTICLE

Association between genetic polymorphisms in chromosome region 9q21 and pelvic organ prolapse in Northwestern Chinese women

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Abstract

This study aimed to explore the association between genetic polymorphisms in the chromosome region 9q21 and the risk of pelvic organ prolapse (POP) in Northwestern Chinese women. A case-control study was conducted with 241 POP patients and 268 healthy controls, analyzing ten single nucleotide polymorphisms (SNPs) across five genes using PCR amplification and Sequenom MassArray. The results revealed significant associations between three SNPs—rs2297002 in GOLM1, rs7450 in MAK10, and rs3814535 in TLE1—and POP. Specifically, the TC genotype of rs2297002, the GA genotype of rs7450, and the AA genotype of rs3814535 were linked to an increased or decreased risk of POP. The study suggests that these genetic variants might contribute to the pathogenesis of POP in this population, offering potential markers for early diagnosis and further investigation into the molecular mechanisms underlying POP. *(Afr J Reprod Health 2024; 28 [9]: 180-190).*

Keywords: MAK10,GOLM1,Pelvic organ prolapse,Genome wide linkage studies

Résumé

Cette étude visait à explorer l'association entre les polymorphismes génétiques dans la région chromosomique 9q21 et le risque de prolapsus des organes pelviens (POP) chez les femmes chinoises du nord-ouest. Une étude cas-témoins a été menée auprès de 241 patientes atteintes de POP et de 268 témoins sains, analysant dix polymorphismes nucléotidiques simples (SNP) sur cinq gènes à l'aide de l'amplification par PCR et du Sequenom MassArray. Les résultats ont révélé des associations significatives entre trois SNP (rs2297002 dans GOLM1, rs7450 dans MAK10 et rs3814535 dans TLE1) et le POP. Plus précisément, le génotype TC de rs2297002, le génotype GA de rs7450 et le génotype AA de rs3814535 étaient liés à un risque accru ou réduit de POP. L'étude suggère que ces variantes génétiques pourraient contribuer à la pathogenèse du POP dans cette population, offrant des marqueurs potentiels pour un diagnostic précoce et une étude plus approfondie des mécanismes moléculaires sous-jacents au POP. *(Afr J Reprod Health 2024; 28 [9]: 180-190).*

Mots-clés: MAK10, GOLM1, prolapsus des organes pelviens, études de liaison à l'échelle du génome

Introduction

Pelvic organ prolapse (POP) is a gynaecological condition caused by loss of supporting tissues strength of the pelvic floor, which results in abnormal locations and dysfunction of pelvic organs[1-2]. Several epidemiological studies report that POP is a major global public health problem that significantly affect the physical and mental health of millions of women[3-4]. As the pathogenesis of POP remains unclear, it is crucial to explore the risk factors in order to prevent and diagnose POP at an early stage and to improve the quality of life of women. large number of previous investigations have documented that POP is the result of a combination of risk factors, which can be divided into four main categories: predisposing factors[5], aggravating factors,[6] decompensating factors[7], and genetic factors. Predisposing factors include parity, vaginal delivery, fetal macrosomia (> 4000 g), prolonged second stage of labour, forceps delivery, previous hysterectomy, etc. Aggravating factors include obesity, constipation, heavy physical labour, chronic obstructive pulmonary disease and other factors that cause chronic increased abdominal pressure.

Decompensation factors include age and hormone levels. In addition, patients with family histories of POP have an earlier onset and rapid progress of the disease. The prevalence of relatives of high-grade POP patients is 2.4-5 times higher than that of the general population[8-10]. This suggests that genetic factors may be involved in the pathogenesis of POP. However, susceptibility genes associated with the development of POP are not fully understood.

Genome wide linkage studies (GWLS) and genome wide association studies (GWAS) have suggested that chromosome region 9q21 may be associated with high grade POP[11]. Furthermore, the association of gene polymorphisms in the region 9q21 with POP has been validated in the Russian population[12]. These studies suggested that gene polymorphisms in the region 9q21 may play an important role in POP. However, as susceptibility SNP loci may differ between countries, regions and race, the risk of triggering POP may also probably be different. The association of gene polymorphisms in the chromosome 9q21 region with the POP in women in northwest China is currently unclear. Therefore, in this study, we aimed to investigate whether Genetic polymorphisms in Chromosome Region 9q21 are associated with POP development in Northwestern Chinese Women.

Methods

Study population

This study was supported by Medical and Health Sciences and Technology Innovation Project of the Ministry of Science and Technology olif China. The study was a case-control study. All patients and controls were recruited between February 2014 and October 2015 from six regions of Gansu Province (Jinchang, Lanzhou, Tianshui, Baiyin, Jinchang and Pingliang). The POP group consisted of 241 patients with POP in stages II-IV. The control group consisted of 268 health women. The general demographic and clinical data were collected including age, body mass index (BMI), race, heaviest birth weight, and POP-Q stage/ Other data collected include mode of delivery, parity, previous history of pelvic surgery, spinal surgery, chronic constipation, chronic cough, gynaecological disease, physical illness, previous lifestyle and behavioural habits such as smoking and alcohol consumption.

Inclusion criteria for this study were: 1) local residence for ≥ 5 years and age ≥ 20 years; 2) a symptomatologic diagnosis of POP by a specialist obstetrician and gynaecologist; and 3) signed informed consent. The exclusion criteria were: 1) patients with indefinite diagnosis; 2) patients with known connective tissue disorders (e.g. Marfan syndrome or Ehlers-Danlos syndrome), female malignancies and neurological disorders (e.g. sclerosis or stroke); 3) women with neuropsychiatric disorders; 4) patients with related specific disorders such as genital tract malformations; 5) patients had used any form of estrogen and progesterone in the last 3 months 6) subjects with incomplete information or unwilling to participate in the study.

Blood sample collection

After approval by the hospital ethics committee and informed consent from the study participants, 5ml of venous blood was taken by a dedicated nursing staff during the face-to-face collection of clinical information. Blood sample were placed in an EDTA anticoagulation tube, mixed thoroughly and stored in an ultra-low temperature refrigerator at -80°C.

SNP selection

In this study, according to the NCBI (http://www.ncbi.nlm.nih.gov/ncbisearch), Ensembl (http://asia.ensembl.org/index.html/), and HapMap databases (http://hapmap.ncbi.nlm.nih.gov) databases as well as published articles[13-22], a total of 10 SNPs from 5 candidate genes were selected.

PCR amplification and Identification of SNPs by Sequenom MassArray

Genomic DNA was extracted and purified from whole blood samples using the Thermo Scientific GeneJET Whole Blood Genomic DNA Purification Kit. Quality control was performed using agarose gel

Table 1: The specific sequence information for the primers

SNP_ID	Forword 5'->3'	Reverse 5'->3'
rs2807303	ACGTTGGATGCCCCTTCAATTTGGGGTTAA	ACGTTGGATGAGCTTCTTTTACCACATCTC
rs2378383	ACGTTGGATGGATTTTCTCTCCAGACGCTC	ACGTTGGATGAGAGAGCTAGACTCCAATAC
rs3814534	ACGTTGGATGGTCAATCAAAGTAACGTGGG	ACGTTGGATGTAACTCGAGCCCTCAGCTTC
rs3814535	ACGTTGGATGAAGTAACGTGGGGCTGGCTA	ACGTTGGATGTTTTGCTAACTCGAGCCCTC
rs7866234	ACGTTGGATGAACCACTGAACCTGGACATC	ACGTTGGATGACCTGAGGATTTACTCCAGC
rs7450	ACGTTGGATGATGTGCCCTCTAAGAGTTGG	ACGTTGGATGGTGAAACTTGTTTGAGAGAG
rs2225237	ACGTTGGATGAAGGGTCACAGACCAAACAC	ACGTTGGATGTTTTCTCCCACGAGGCATTC
rs3750390	ACGTTGGATGAAATCCAGTCCAGCCACAAC	ACGTTGGATGCTGAGAGGAAACAAAGCAGG
rs2297002	ACGTTGGATGACGTTTCCCTTCCCTTGTGG	ACGTTGGATGTTCTGTTTCAGCTCCAAGCC
rs3750389	ACGTTGGATGTGAAGCCCAAGACGATGATG	ACGTTGGATGAGATGATGGGCTTGGGAAAC

electrophoresis, and DNA concentration and purity were assessed by spectrophotometry. Only DNA samples with an A260/A280 ratio between 1.8 and 2.0 were considered qualified and subsequently adjusted to a concentration of 150 ng/mL. For each SNP of interest, we downloaded the 100 bp reference sequences flanking the SNP site from the NCBI database (http://www.ncbi.nlm.nih.gov/). PCR and single base extension primers were then designed using Sequenom's Assay Design 3.1 software. The specific primer sequences are provided in Table 1. This approach ensured high-quality DNA samples and appropriately designed primers for our genotyping analysis.

Multiplex PCR was carried out in 384-well plates in a total volume of 5 mL per reaction system. The PCR reaction conditions were: pre-denaturation at 95°C for 2 min; 45 cycles of 95 °C for 20 s, 56 °C for 30 s and 72 °C for 60 s. The resin was precipitated and transferred to a 384-well SpectroCHIP (Sequenom) chip using a MassARRAY Nanodispenser RS1000 spotter for natural crystallisation. MALDI-TOF mass spectrometry was performed and data collected for genotype analysis using TYPER4.0 software (Sequenom).

Statistical analysis

Statistical software SPSS24.0 was used to perform statistical analysis. All data conformed to normal distribution and were expressed as $\bar{x} \pm s$. Count data were compared by χ^2 tests, and measurement data were compared by the independent sample t-test between two groups. The statistically significant genotype between POP group and Control group were screened for multivariate logistic regression analysis. Results tested are presented as odds ratio (OR) with 95% CI. Haploview software was used to plot the linkage disequilibrium (LD) between SNPs at r^2.

Ethical issues

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Maternal and Child Health Care Hospital of Gansu Province (approval number: MCHCG-2014-023). All participants provided written informed consent before enrollment in the study.

Patient confidentiality was maintained throughout the study, with all personal identifiers removed from the data before analysis. The genetic samples were coded and stored securely, with access restricted to authorized research personnel only. Participants were informed of their right to withdraw from the study at any time without consequence.

The potential risks and benefits of the study were clearly explained to all participants. While there were no direct benefits to the participants, they were informed that their participation could contribute to a better understanding of the genetic factors associated with pelvic organ prolapse, potentially benefiting future patients.

All genetic testing was conducted in accordance with relevant guidelines and regulations. The results of the genetic tests were not disclosed to participants unless they specifically requested this information and genetic counseling was provided.

The study was registered in the Chinese Clinical Trial Registry (ChiCTR-ROC-14005253) prior to participant recruitment.

Results

Comparison of general clinical data

A total of 241 POP patients and 268 healthy controls were included in this study. The mean age of patients of POP was 56.72±13.00 years (range: 31–88 years) and the mean age of controls was 53.81±17.34 (range: 26-91 years). Apart from age, there were no statistically significant differences between the two groups in terms of BMI, number of deliveries, mode of delivery and fetal weight (P>0.05) as in Table 2.

Genetic frequency distributions of two groups and Hardy-Weinberg equilibrium test

In the control group, the genotype distributions for rs2297002, rs2378383, s375039, rs381453, rs3814535, rs2807303, rs3750389, rs7450, rs7866234 were consistent with the Hardy-Weinberg genetic equilibrium law, indicating that the subjects were all randomized populations and were representative of the population .In contrast, the genotype frequencies of trs3750389 and rs2225237 were not consistent with the Hardy-Weinberg genetic equilibrium law and were therefore discarded in the subsequent study.

Table 2: Comparison of general clinical data

	POP group（n=241）	**Control group（n=268）**	**χ2/T value**	***P* value**
Age (years)	56.72±13.00	53.81±17.34	-2.146	0.032*
BMI (kg/m2)	25.8±4.2	25.3±3.9	1.357	0.4403
Mode of delivery			2.483	0.289
vaginal delivery	224	248		
Midwifery	2	0		
C-section	7	10		
Parity (times)			2.286	0.515
1	32	47		
2	89	90		
3 or more times	118	131		
Heaviest birth weight (g)			0.256	0.88
<2500g	6	5		
2500-3999g	210	223		
>=4000g	21	20		
POP-Q stage			509	<0.001
≤ I	0	268		
II	140	0		
III-IV	101	0		

As determined by chi-square test, the genotype distribution frequencies of rs2807303, rs2378383, rs3814534, rs7866234, rs3750390 and rs3750389 were not statistically significant (***P***>0.05) between the POP and control groups, indicating that polymorphisms at these loci were not significantly associated with the POP. Rs3814535, rs2297002 and rs7450 genotype frequency distribution were significantly different between the 2 groups (***P***=0.02, ***P***=0.01, ***P***=0.00) ,as shown in Table 3.

Table 3: Genetic frequency distributions of two groups and Hardy-Weinberg equilibrium test

SNP	**Gene name**	**Allele**	**POP group Genotype**			**HW*P* val**	**Control group Genotype**			**HW*P*val**	**χ2**	***P***
			AA	**AB**	**BB**		**AA**	**AB**	**BB**			
rs2807303	TLE4	G>A	50.00%	42.17%	7.83%	0.694	50.39%	42.64%	6.98%	0.415	0.13	0.94
rs2378383	TLE4	A>G	76.19%	22.38%	1.43%	0.83	77.86%	21.37%	0.76%	0.382	0.58	0.75
rs3814534	TLE1	G>A	31.03%	47.41%	21.55%	0.511	35.66%	44.96%	19.38%	0.22	1.22	0.54
rs3814535	TLE1	G>A	70.95%	27.39%	1.66%	0.405	62.69%	31.34%	5.97%	0.214	7.98	0.02*
rs7866234	UBQLN1	A>C	52.84%	40.61%	6.55%	0.61	51.52%	43.18%	5.30%	0.111	0.77	0.68
rs7450	MAK10	A>C	30.25%	55.88%	13.87%	0.022*	41.35%	39.85%	18.80%	0.09	12.95	0.00*
rs2225237	GOLM1	G>A	28.21%	51.28%	20.51%	0.023*	26.52%	57.58%	15.91%	0.007*	2.48	0.29
rs3750390	GOLM1	C>T	30.87%	52.17%	16.96%	0.331	27.48%	51.91%	20.61%	0.485	1.01	0.6
rs2297002	GOLM1	G>T	28.21%	50.00%	21.79%	0.95	22.56%	56.39%	21.05%	0.037*	2.92	0.23
rs3750389	ADRB3	T>C	32.49%	54.85%	12.66%	0.029*	44.78%	40.30%	14.93%	0.059	9.78	0.01*

Table 4: Analysis of the association between polymorphisms of rs3814535, rs2297002, rs7450 and POP

SNP	Model	Genotype	POP group	Control group	OR (95% CI)	*P*
rs2297002	Heterozygous model	TT	78	119	1(reference)	
		TC	129	109	1.806(1.231-2.648)	0.002*
	Homozygous model	CC	30	40	1.169(0.658-1.989)	0.58
	Dominant model	TC+CC	159	149	1.631(1.131-2.341)	0.01*
	Recessive model	TT+TC	207	228	1(reference)	
		CC	30	40	0.826(0.496-1.375)	0.462
rs3814535						
	Heterozygous model	GG	170	169	1(reference)	
		GA	67	83	0.772(0.525-1.136)	0.189
	Homozygous model	AA	4	16	0.249(0.081-0.759)	0.014
	Dominant model	GA+AA	237	252	0.713(0.492-1.034)	0.078
	Recessive model	GG+GA	71	99	1(reference)	
		AA	4	16	0.266(0.088-0.807)	0.012
rs7450						
	Heterozygous model	GG	72	110	1(reference)	
		GA	133	106	1.917(1.296-2.836)	0.001
	Homozygous model	AA	33	50	1.008(0.593-1.714)	0.293
	Dominant model	GA+AA	166	156	1.626(1.124-2.351)	0.01*
	Recessive model	GG+GA	205	216	1(reference)	
		AA	33	50	0.695(0.431-1.123)	0.136

Table 5: Association between haplotypes of rs7450 and rs2297002 and POP

Haplotype*	Frequency *n* (%) POP group	Control	*P*	*Chi Square*
CG	92.7(0.473)	133.7(0.503)	＞0.05	0.533
TT	89.8(0.458)	106.2(0.458)	＞0.05	0.9853
CT	10.3（0.052）	8.5（0.032）	＞0.05	0.2676
TG	3.2（0.016）	2.2（0.008）	＞0.05	0.4323

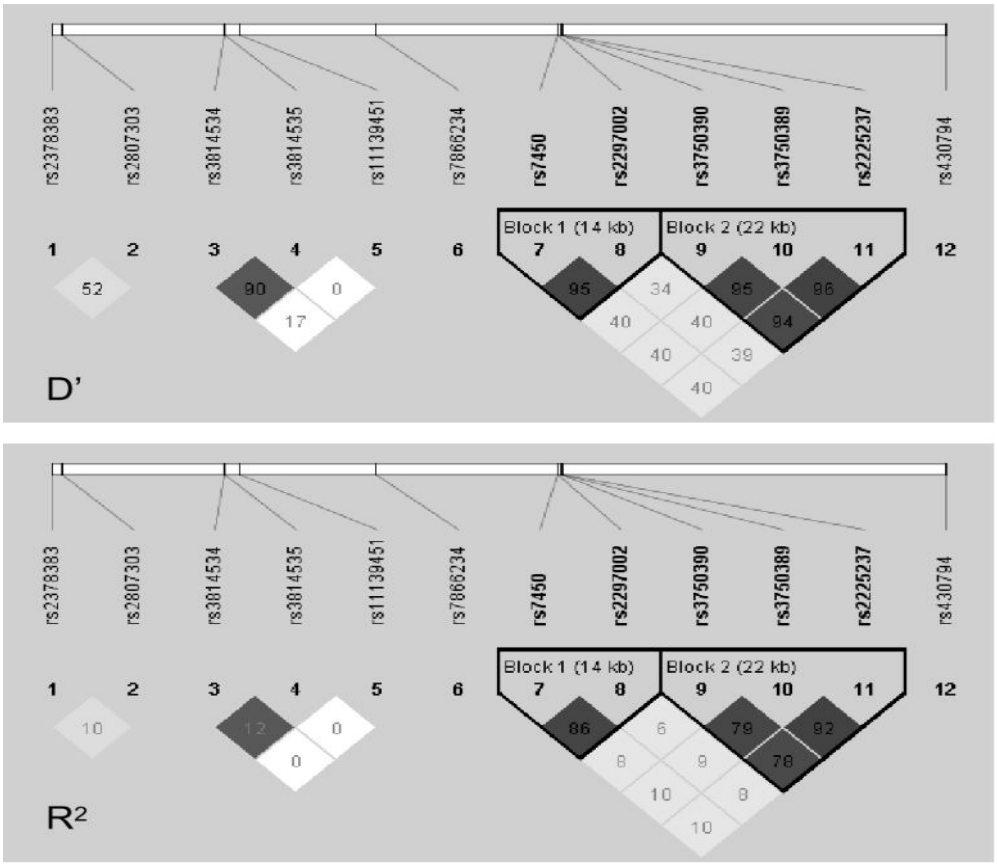

Figure 1: Linkage disequilibrium test for 10 SNPs in chromosome region 9q21

Analysis of the association between polymorp hisms of rs3814535, rs2297002, rs7450 and POP

Results of the mutivariable logistic regression indicated that the mutant heterozygous genotype (TC) of rs2297002 significantly increased the risk of POP compared to the wild-type TT genotype (OR=1.806 (1.231-2.648); P=0.002). Furthermore, the dominant model (TT vs TC+CC) analysis indicated that mutations in the C allele of rs2297002 may increase the risk of POP (OR=1.631 (1.131-2.341); P=0.01). For rs3814535，compared with the homozygous wildtype genotype (GG) , the homozygous variant genotype (AA) was associated with a significantly decreased incidence of POP (OR=0.249 (0.081-0.759)); P=0.014). Furthermore, the recessive model indicated that AA vs GG+GA in the rs3814535 would reduce the risk of POP (OR=0.266 (0.088-0.807)); P=0.012). Finally, our

result demonstrated that compared with the homozygous wildtype genotype (AA) , heterozygous variant genotype (GA) was associated with a significantly increased incidence of POP (OR=0.249 (0.081-0.759)); P=0.014) for rs3814535. Furthermore, the dominant model (GA+AA vs AA) analysis indicated that mutations in the A allele of rs3814535 would increase the risk of POP (OR=1.631 (1.131-2.341); P=0.01), as shown in Table 4.

Linkage disequilibrium test for SNP and haplotype analysis

In the current study, we applied SHEsis software[23] to perform a linkage disequilibrium test and our results pointed to a linkage disequilibrium between the rs7450 and rs2297002 (D' = 0.95, r 2 = 0.86), as shown in Figure 1. Finally, haplotype analysis indicated that all haplotypes were not associated with the POP. Table 5.

Discussion

The pathogenesis of pelvic organ prolapse (POP) is complex, with current studies suggesting that its occurrence and development result from combined environmental and genetic factors. Differences in POP susceptibility under similar exposure factors may be attributed to variations in individual genetic backgrounds. Genetic analysis has indicated that POP might be an autosomal genetic disease, with 30% attributable to genetic factors. The close relationship between POP occurrence and genetic polymorphisms underscores the clinical significance of further exploring POP-related genetic factors for understanding its pathogenesis mechanisms and prevention[24].

Allen-Brady et al. analyzed 70 pelvic floor dysfunction patients from 32 families using genome-wide linkage studies (GWLS). Their results indicated that susceptibility genes affecting pelvic floor structure stability are present in the 9q21 region[25]. Further investigation suggested that rs12237222, rs12551710, and rs2236479, located in the 9q21 region, may be related to POP occurrence[26]. However, the impact of genetic polymorphisms in the chromosome 9q21 region on POP risk requires further exploration, particularly in females from northwest China, where such studies are lacking.

In this case-control study, we investigated the association between 10 SNP loci on five genes (TLE4, TLE1, UBQLN1, MAK10, ADRB3) in the chromosome 9q21 region and POP risk in a female population from northwest China. Our study confirmed that GOLM1-rs297002C/T, MAK10-rs7450A/G, and TLE1-rs3814535A/G genotype polymorphisms correlated with genetic susceptibility to POP in this population. For rs297002, TC genotype individuals showed a 1.806-fold increased risk of POP compared to TT genotype individuals. For rs7450, individuals with the GA genotype had a 1.917-fold increased risk of POP compared to those with the GG genotype. For rs3814535, the risk of POP was reduced to 0.249 for the AA genotype compared to the GG genotype.

This study has several notable strengths. Firstly, it addresses a gap in the literature by focusing on POP genetic factors in females from northwest China, an underrepresented population in previous research, enhancing the generalizability of the findings. Secondly, the case-control design is robust for evaluating genetic associations with disease risk. Finally, the examination of multiple SNP loci across different genes provides a comprehensive genetic analysis, offering insights into the genetic basis of POP.

Numerous studies suggest that collagen and elastin biosynthesis, as well as extracellular matrix (ECM) metabolism, play key roles in POP pathology[27-28]. The pelvic floor connective tissue is composed of ECM, consisting of collagen, elastin, and proteoglycan, with collagen as the main component. It has been suggested that decreased collagen content or increased collagen degradation may contribute to POP occurrence by reducing pelvic floor connective tissue strength. GOLM1 has been reported to play an important role in ECM metabolism. Several studies have shown that GOLM1 positively regulates various metal matrix proteinases. For example, Li et al. demonstrated that GOLM1 promoted MMP-13 expression in gastric and breast cancers, facilitating tumor cell migration[29-30]. Additionally, GOLM1 was shown to

promote MMP-1 and MMP-9 protein expression through the GSK3β pathway[31]. Liu et al. found that GOLM1 knockdown inhibited MMP-2 expression and suppressed cell invasion in hepatocellular carcinoma cells[32]. Collectively, these findings suggest that GOLM1's function is closely related to metallo-matrix proteases and ECM degradation, potentially involving it in the pathological process of POP.

The TLE1 gene, a member of the Groucho/TLE family of transcriptional co-repressors, primarily regulates the transcriptional activity of various genes[33]. The estrogen receptor (ER) binds to chromatin with the assistance of other proteins. Current findings indicate that TLE1 assists ER-chromatin interactions and promotes ER transcription effects as one of the ER pathway's transcriptional regulators[34]. Furthermore, specific TLE1 silencing inhibits ER binding to genomic ER binding sites and disrupts phosphorylated RNA Pol II recruitment. ER, a nuclear transcription factor, is widely expressed in various tissues, including ligaments, muscles, and fascia[35]. Clinical studies have noted a significant reduction in ER-alpha protein expression in POP patients' tissues compared to controls, significantly associated with POP[36]. Numerous studies have pointed out that decreased estrogen levels in postmenopausal women may be closely related to reduced female pelvic floor supporting tissue tone[37-38]. Hsieh et al. observed estrogen's effect on isolated human fibroblasts using different concentrations and found that estrogen regulates collagen content[39]. These studies suggest that TLE1 may play a key role in POP pathology by mediating ER's regulatory effects, thus indirectly regulating collagen content. MAK10, also known as Naa35, has been studied mostly in brewer's yeast, and its biological function remains unclear. It is hypothesized that MAK10 may affect corresponding functional abnormalities by influencing mitochondria, potentially causing muscle relaxation.

However, the study has several limitations. The relatively small sample size may limit the statistical power to detect smaller effects or generalize findings to broader populations. Additionally, the study's focus on a specific geographic and ethnic population may restrict the applicability of the findings to other groups. The cross-sectional design also limits the ability to establish causality. Furthermore, the potential impact of environmental or lifestyle factors, which were not controlled for, may confound the observed genetic associations.

In conclusion, this study evaluated 10 SNP loci in the chromosome 9q21 region and identified rs297002, rs7450, and rs3814535 as being associated with POP susceptibility in females from northwest China. This finding helps explain the functional pathogenic loci in this region and provides clues for early POP diagnosis and pathogenesis. Further experiments are needed to verify the effect of these loci in larger sample sizes and different regional populations to improve the identification of molecular biology and genetic mechanisms in this region related to POP development.

These findings have important implications for both clinical practice and public health policy. The identification of specific genetic polymorphisms associated with POP suggests potential for developing genetic screening tools to identify at-risk individuals, particularly in similar populations. This could inform targeted prevention strategies and personalized treatment plans based on genetic risk profiles. From a policy perspective, incorporating genetic counseling and testing into routine healthcare services for high-risk populations could be beneficial. Additionally, integrating genetic insights with traditional epidemiological data could enhance POP management and prevention strategies.

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Authors' contributions

JW and QL conceptualised this study. YW,BHM, WJX, XYL, CBT, and YL worked on the literature review.JW, QL, and YS worked on the data analysis and interpretation of results. All authors worked on the discussion of the findings. All the authors read and approved the final manuscript.

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Conflict of interests

The authors declare no competing interests.

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