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Original Article

Association between SMAD3 and SMAD7 gene polymorphisms and susceptibility to stress urinary incontinence in Chinese women

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Abstract: Objective: This study aimed to investigate the correlation between single nucleotide polymorphisms (SNPs) in SMAD3 and SMAD7 genes and the genetic risk of stress urinary incontinence (SUI) in Chinese women. Methods: A case-control study was conducted with 117 women diagnosed with SUI and 103 healthy controls. SNPs in SMAD3 (rs28683050, rs12901499) and SMAD7 (rs12953717, rs4939827) were analyzed using polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP). Allele and genotype frequencies were assessed using the SHEsis online platform. Epidemiological, clinical, and laboratory data were collected retrospectively. SUI patients underwent pelvic floor muscle training (PFMT), and treatment outcomes were evaluated after 3 months. Results: The G allele and GG genotype of rs12901499 in SMAD3 were significantly more common in the SUI case group (p_allele < 0.001, p_genotype = 0.002). Similarly, the T allele and TT genotype at rs12953717 in SMAD7 were more frequent in the SUI case group (p_allele = 0.002, p_genotype = 0.007). Multivariate logistic regression revealed that body mass index (BMI), family history, and the rs12901499 and rs12953717 polymorphisms were significant risk factors for SUI ($P < 0.05$). Furthermore, the TT genotype at rs12953717 was associated with poorer PFMT treatment outcomes. Conclusion: Our findings suggest that the rs12901499 and rs12953717 polymorphisms are potential risk factors for SUI in women. Additionally, the rs12953717 polymorphism may influence the effectiveness of PFMT in SUI treatment.

Keywords: Stress urinary incontinence, single nucleotide polymorphisms, SMAD3, SMAD7, pelvic floor muscle training

Introduction

Urinary incontinence (UI), defined as any involuntary loss of urine, is a common condition among women [1]. Based on clinical manifestations, UI is categorized into stress UI (SUI), urgency UI (UUI), and mixed UI (MUI) [2]. SUI is the most prevalent type of UI. The International Continence Society defines SUI as an insufficient contraction of the detrusor muscle and an increase in intra-abdominal pressure, leading to a rise in bladder pressure that exceeds the maximum urethral pressure, resulting in involuntary urine loss during activities such as coughing, sneezing, or physical exercise [3, 4]. Epidemiological studies indicate that up to 25% of women aged 45-64 years and 30% of women aged 65 years experience UI symptoms. The prevalence of SUI ranges from 10% to 58.4% and increases with age [5, 6]. SUI significantly impacts women's quality of life, both physically and mentally [7]. Pathogenic factors associated with SUI include parity (especially vaginal delivery), age, and obesity [8, 9]. Some studies suggest a hereditary predisposition to SUI, as daughters and sisters of women with UI have an increased risk of developing the condition [10]. Additionally, research has identified a genetic link between SUI and single nucleotide polymorphisms (SNPs) [11]. However, evidence regarding SNPs in SUI remains limited. Therefore, exploring the relationship between SNPs and SUI holds high clinical value for early diagnosis and treatment outcomes.

The transforming growth factor-β (TGF-β) pathway, involved in collagen synthesis and degradation, plays a crucial role in the pathogenesis

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of SUI [12]. Among the key intracellular signaling components of the TGF-β family are mothers against decapentaplegic homologs (SMADs), which are important in SUI pathogenesis. Abnormal expression of SMADs has been associated with disease progression [13]. Wang et al. found that the expression of T-box brain protein 2 (TbR-2) and SMAD7 in the anterior vaginal wall of SUI rats was significantly increased, while SMAD3 expression was significantly decreased [13]. Other studies reported reduced expression of SMAD3 and TGF-β1 in patients with pelvic organ prolapse (POP) and UUI [14]. In addition, the expression levels of TGF-β/SMAD pathway-related proteins were closely correlated with fibromuscular system impairment in SUI rats [15]. These findings suggest that SMAD3 and SMAD7 play a multifaceted role in SUI. However, the genetic association of these genes with SUI remains unclear.

Recent studies have increasingly linked SMAD3 and SMAD7 to the genetic risk of several diseases. For instance, the rs28683050 polymorphism in SMAD3 has been associated with chronic obstructive pulmonary disease [16]. Sharma et al. found a significant correlation between the G allele of SMAD3 rs12901499 and knee osteoarthritis risk, in combination with the BMP5 rs921126 polymorphism [17]. Yao et al. identified that the rs4939827 and rs4464148 polymorphisms in SMAD7 are risk factors for colorectal cancer in Caucasians, while the rs12953717 polymorphism is associated with susceptibility to colorectal cancer in both Caucasians and Asians [18]. Based on these findings, we hypothesize that SNPs in SMAD3 and SMAD7 may be significantly associated with the susceptibility to and development of SUI. The aim of this study is to investigate the relationship between SUI risk and SMAD3/SMAD7 polymorphisms in Chinese women.

Materials and methods

Study population

The sample size was calculated based on previous studies using the Power and Sample Size online tool (http://powerandsamplesize.com/). Epidemiological, clinical, and laboratory data were retrospectively collected. A total of 117 women with SUI who were admitted to the Jinshan Branch of Shanghai Sixth People's Hospital were included in the study, all of whom had SUI as their primary complaint. All patients underwent gynecological examination, urine pad tests, and cotton swab tests. The diagnostic criteria for SUI were based on the European Association of Urology Guidelines on the Diagnosis and Treatment Management of SUI [19]. Additionally, 103 women without UI who underwent physical examination during the same period were included as the control group. Exclusion criteria for both the SUI and control groups included a history of hormone use, gynecologic inflammation, pathological obstetric history (e.g., macrosomia, dystocia, perineal laceration), gynecologic malignancies, internal or surgical diseases (e.g., diabetes, connective tissue disorders), and pelvic or vaginal surgery within the past three months. The study protocol was designed in accordance with the ethical guidelines of the Declaration of Helsinki [20] and was approved by the Ethics Committee of the Jinshan Branch of Shanghai Sixth People's Hospital (Approval No. jszxyy20-2119).

SNP selection

SNP selection was based on a PubMed search (https://pubmed.ncbi.nlm.nih.gov/) using the keywords "SMAD" and "single nucleotide polymorphism". Through literature review, candidate SNP loci associated with SUI or potentially related to SUI were identified [16-18, 21, 22]. Four SNP loci from the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP) with minor allele frequencies (MAF) greater than 0.05 in the Chinese population were selected. The chosen SNPs were rs28683050 and rs12901499 for SMAD3, and rs12953717 and rs4939827 for SMAD7.

Genotyping

Fasting venous blood (4 mL) was collected in an ethylenediaminetetraacetic acid (EDTA) tube, centrifuged at 1500 g for 20 minutes at 4°C, and plasma was separated and stored at -80°C. Genomic DNA was extracted using a whole blood DNA extraction kit (Qiagen, Germany). The absorbance values of the DNA samples were measured to determine their purity and concentration. Qualified samples were stored at -20°C. The genotypes of SMAD3 and SMAD7 were analyzed using polymerase

Table 1. Comparison of clinical data between control and SUI group

Characteristics	Control group (n = 103)	SUI group (n = 117)	t/χ^2	*p*-value
Age (years), mean ± SD	52.14±8.68	52.91±9.48	0.623	0.534
BMI (kg/m^2), mean ± SD	24.69±4.03	26.82±3.51	4.166	< 0.001
Family history for SUI, n (%)	5 (4.85)	64 (54.70)	63.220	< 0.001
ICIQ-FLUTS, median (IQR)	1.0 (0.0-1.0)	11.0 (8.0-14.0)	/	< 0.001
Bladder Filling (score)	1.0 (0.0-1.0)	1.0 (1.0-3.0)	/	< 0.001
Voiding symptoms (score)	0.0 (0.0-0.0)	1.0 (1.0-2.0)	/	< 0.001
Incontinence symptoms (score)	0.0 (0.0-0.0)	8.0 (6.0-10.0)	/	< 0.001

SUI, stress urinary incontinence; SD, standard deviation; BMI, body mass index; ICIQ-FLUTS, International Consultation on Incontinence Modular Questionnaire for Female Lower Urinary Tract Symptoms, IQR: interquartile range.

chain reaction-restriction fragment length polymorphism (PCR-RFLP).

ICIQ-FLUTS questionnaire

The International Urinary Incontinence Advisory Committee Questionnaire Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) includes 12 questions, divided into three categories: bladder filling (4 questions, scored 0-16), voiding symptoms (3 questions, scored 0-12), and incontinence symptoms (5 questions, scored 0-20) [23]. The ICIQ-FLUTS is a widely used international questionnaire with a moderate number of items, and it covers nearly all lower urinary tract symptoms, making it suitable for screening lower urinary tract symptoms in relevant populations.

SUI treatment

Pelvic floor muscle training (PFMT) was performed under the guidance of a therapist for at least 3 months as the first-line treatment for patients with SUI, based on previous studies [24, 25]. Specifically, patients performed continuous pelvic floor muscle contractions (anal contraction) for at least 3 seconds, followed by relaxation for 2-6 seconds, for a total duration of 15-30 minutes per session, repeated three times daily for a minimum of 3 months. After 3 months of training, patients were followed up in the outpatient clinic to assess both subjective and objective treatment outcomes. Effective treatment was defined by one of the following criteria: (a) complete resolution of UI symptoms, no urine leakage, an ICIQ-FLUTS score of 0, and normal pelvic floor indicators; (b) a significant reduction in the frequency of UI and urine leakage, with a more than 50% decrease in ICIQ-FLUTS score compared to baseline, and improvement in pelvic floor indicators; or (c) a slight decrease in UI and urine leakage frequency, with less than a 50% reduction in ICIQ-FLUTS score compared to baseline, and improvement in pelvic floor indicators [7, 26]. Patients who did not meet any of these criteria were considered to have an ineffective treatment outcome.

Statistical analyses

Statistical analysis was performed using SPSS version 22.0. Continuous data are expressed as mean ± standard deviation (SD), and group comparisons were made using the t-test. For data with non-normal distribution, the Mann-Whitney U test was used. Categorical data are presented as numbers and percentages, with comparisons made using the χ^2 test. Multivariate logistic regression was employed to identify risk factors for SUI in women. The SHEsis online platform (http://analysis.bio-x.cn/myAnalysis.php) was used to assess Hardy-Weinberg equilibrium (HWE) and verify the representativeness of the sample. A *p*-value of < 0.05 was considered statistically significant, unless otherwise specified.

Results

Clinical pathological data of the control and SUI group

The basic demographic information of the control and SUI groups is shown in **Table 1**. All participants were female. There was no significant age difference between the two groups, and the mean age of the study population was similar (P = 0.534). Body mass index (BMI) and family history of SUI were significantly different between the SUI and control groups (both P <

Table 2. HWE analysis of SNP genotypes in control and SUI group

SNPs	Genotype	Control (n = 103)	χ^2	*p*-value	SUI (n = 117)	χ^2	*p*-value
rs28683050	CC	55 (53.40)	2.425	0.119	55 (47.01)	2.295	0.130
	CT	36 (34.95)			45 (38.46)		
	TT	12 (11.65)			17 (14.53)		
rs12901499	AA	37 (35.92)	0.013	0.909	21 (17.95)	< 0.001	0.983
	AG	49 (47.57)			57 (48.72)		
	GG	17 (16.50)			39 (33.33)		
rs12953717	CC	52 (50.49)	0.047	0.829	38 (32.48)	0.006	0.939
	CT	43 (41.75)			57 (48.72)		
	TT	8 (7.77)			22 (18.80)		
rs4939827	CC	45 (43.69)	1.356	0.244	61 (52.14)	< 0.001	0.990
	CT	50 (48.54)			47 (40.17)		
	TT	8 (7.77)			9 (7.69)		

HWE, Hardy-Weinberg equilibrium; SNP, Single nucleotide polymorphisms; SUI, stress urinary incontinence.

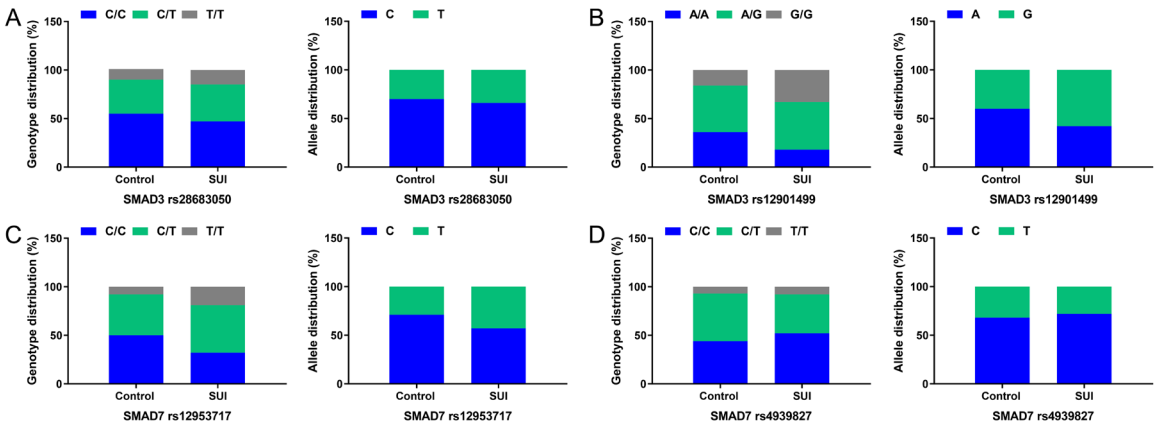

Figure 1. Distribution of genotypes and alleles in control and SUI groups. A. Genotype (P = 0.614) and allele (P = 0.297) distribution of rs28683050. B. Genotype (P = 0.002) and allele (P < 0.001) distribution of rs12901499. C. Genotype (P = 0.007) and allele (P = 0.002) distribution of rs12953717. D. Genotype (P = 0.431) and allele (P = 0.329) distribution of rs4939827. After Bonferroni's correction, P < 0.0125 was considered statistically significant. SUI, stress urinary incontinence; SMAD, mothers against decapentaplegic homolog.

0.001), and the ICIQ-FLUTS scores were significantly higher in the SUI group compared to the control group (P < 0.001).

SNPs of SMAD3 and SMAD7 are associated with the risk of SUI patients

Before analyzing the association between SNPs and SUI risk, the genotype distribution of four SNPs in SMAD3 and SMAD7 was tested for Hardy-Weinberg equilibrium (HWE). The results are shown in **Table 2**. The *p*-values from the HWE test for the genotype distribution of all four loci in both the control and SUI groups were greater than 0.05. The relationship between polymorphisms at these loci and SUI susceptibility was further explored (**Figure 1**; **Table 3**). Both the G allele and GG genotype at rs12901499 showed significantly higher frequencies in the SUI group (**Figure 1B**, p allele < 0.001, p genotype = 0.002). SUI patients were more likely to carry the T allele and TT genotype at rs12953717 (**Figure 1C**, p allele = 0.002, p genotype = 0.007). No significant differences were observed in the allele or genotype frequencies of the other two SNP loci (rs28683050 and rs4939827) between the control and SUI groups (**Figure 1A**, **1D**, P > 0.05).

Key polymorphic loci of SMAD3 and SMAD7 as potential risk factors for SUI

To evaluate whether these SNPs could serve as risk factors for SUI, multivariate regression

Table 3. Allele frequencies and genotype distribution of SNPs in SMAD3 and SMAD7

SNPs	Genotype			χ^2	*p*-value	Allele		χ^2	*p*-value
rs28683050	CC	CT	TT	0.975	0.614	C	T	1.089	0.297
Control (n = 103)	55 (53.40)	36 (34.95)	12 (11.65)			146 (70.87)	60 (29.13)		
SUI (n = 117)	55 (47.01)	45 (38.46)	17 (14.53)			155 (66.24)	79 (33.76)		
rs12901499	AA	AG	GG	12.820	0.002	A	G	13.270	< 0.001
Control (n = 103)	37 (35.92)	49 (47.57)	17 (16.50)			123 (59.71)	83 (40.29)		
SUI (n = 117)	21 (17.95)	57 (48.72)	39 (33.33)			99 (42.31)	135 (57.69)		
rs12953717	CC	CT	TT	9.820	0.007	C	T	9.984	0.002
Control (n = 103)	52 (50.49)	43 (41.75)	8 (7.77)			147 (71.36)	59 (28.64)		
SUI (n = 117)	38 (32.48)	57 (48.72)	22 (18.80)			133 (56.84)	101 (43.16)		
rs4939827	CC	CT	TT	1.683	0.431	C	T	0.951	0.329
Control (n = 103)	45 (43.69)	50 (48.54)	8 (7.77)			140 (67.96)	66 (32.04)		
SUI (n = 117)	61 (52.14)	47 (40.17)	9 (7.69)			169 (72.22)	65 (27.78)		

After multiple Bonferroni corrections, $P < 0.0125$ indicated statistical significance. SNPs, Single nucleotide polymorphisms; SUI, stress urinary incontinence.

Table 4. Key polymorphic loci of SMAD3 and SMAD7 were potential risk factors for SUI

Characteristics	OR-value	95% CI	*p*-value
BMI	1.200	1.083-1.328	< 0.001
Family history	29.053	10.011-84.317	< 0.001
rs12901499	2.498	1.522-4.101	< 0.001
rs12953717	2.056	1.212-3.487	0.008

BMI, body mass index; OR, odd ratio; CI, confidence interval.

analysis was conducted. The independent variables included BMI, family history, and genotypes of rs12901499 and rs12953717, which were significantly different between the SUI and control groups, with the presence or absence of SUI as the dependent variable (**Table 4**). The results indicated that all variables included in the analysis were potential risk factors for SUI.

Association of key polymorphic loci of SMAD3 and SMAD7 with SUI treatment effect

After identifying the association between the four SNPs and the risk of SUI in women, we evaluated the association between the genotype distribution of these SNPs and SUI treatment outcomes. After 3 months of PFMT, patients were divided into effective and ineffective groups based on subjective and objective indicators of SUI. The results showed that patients carrying the TT genotype at rs12953717 were less responsive to treatment (**Figure 2C**, $P < 0.001$), whereas no significant relationship was found between the other three loci and treatment effectiveness (**Figure 2A**, **2B**, **2D**, $P > 0.05$, **Table 5**).

Discussion

SMAD family members, key intracellular effectors of TGF-β signaling, play critical roles in both physiological and pathological processes [27]. These family members are involved in various conditions, including myocardial disease, organ fibrosis, and carcinogenesis [27-29]. Numerous studies have also shown that SMAD family genes interact with other signaling pathways to contribute to the development of human diseases [30]. In particular, the abnormal expression of SMAD family genes has been implicated in the development of UI, including SUI [13, 31]. However, research examining the relationship between SMAD family genes and SUI risk is limited.

In this study, we enrolled 117 women with SUI and 103 healthy controls. We explored the differences in the genotype and allele distribution of four SNPs in SMAD3 and SMAD7 between SUI patients and healthy individuals. Our findings suggest that the allele frequencies and genotype distributions of the rs12901499 loci of SMAD3 and rs12953717 loci of SMAD7 are associated with SUI susceptibility, indicating that these SNPs may be potential genetic risk factors for SUI.

While studies on the genetic factors underlying SUI are still scarce compared to other genetic diseases, recent research has begun to shed light on genetic susceptibility to UI. For exam-

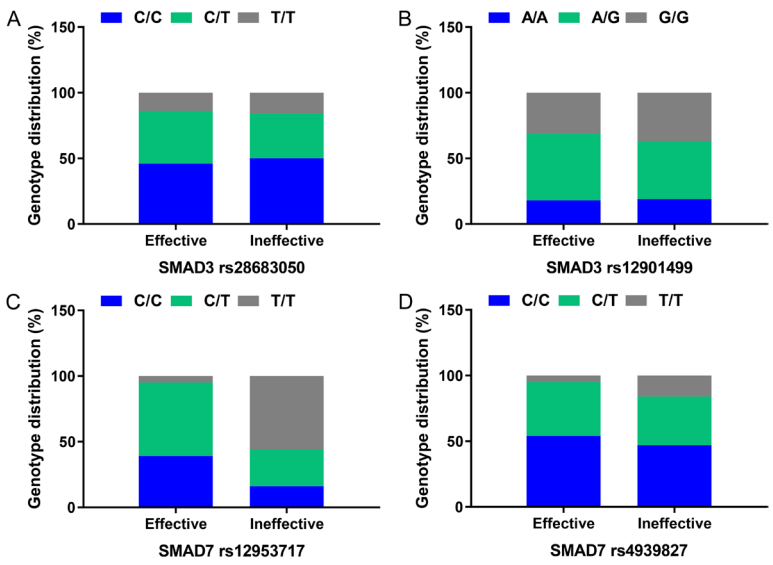

Figure 2. Distribution of genotypes in the effective and ineffective group. A. Genotype (P = 0.856) distribution of rs28683050. B. Genotype (P = 0.791) distribution of rs12901499. C. Genotype (P < 0.001) distribution of rs12953717. D. Genotype (P = 0.141) distribution of rs4939827. SMAD, mothers against decapentaplegic homolog.

ple, the 5-HT2A gene has been linked to UI onset, with the T102C gene variation showing a significant association with UI development [11]. Moreover, UI has been associated with functional dependency and systolic hypertension, suggesting a genetic influence involving serotonergic pathways [32]. Additionally, polymorphisms in COLIA1, particularly the Sp1 variant, have been shown to increase the prevalence of SUI in postmenopausal women [33]. Collagen II, a key component of the extracellular matrix (ECM), plays an important role in urethral tissue integrity, and its regulation may be critical in the pathogenesis of SUI [34].

Similarly, members of the SMAD family, such as SMAD3 and SMAD7, are known to regulate collagen synthesis and degradation in tissues, making them integral in extracellular matrix remodeling [35]. Recent studies have demonstrated that abnormal SMAD signaling can contribute to collagen dysregulation and tissue fibrosis, further implicating SMADs in the pathogenesis of SUI [35]. Indeed, SNPs in SMAD3 and SMAD7 have been associated with other diseases, such as chronic obstructive pulmonary disease and [16], colorectal cancer as well as knee osteoarthritis [16, 17, 21]. However, to our knowledge, the association between SMAD3 and SMAD7 SNPs and SUI risk had not been previously reported.

In our study, we found that the distribution frequencies of the G allele and GG genotype at the rs12901499 loci of SMAD3, as well as the T allele and TT genotype at the rs12953717 loci of SMAD7, were significantly higher in women with SUI compared to the control group. These results indicate that the polymorphisms at these loci are associated with SUI susceptibility. The findings also suggest that dysregulated collagen production, potentially mediated by SMAD family signaling, may play a key role in the development of SUI.

To exclude the influence of confounding factors on the occurrence of SUI, a multivariate regression analysis was performed. The results showed that BMI, family history, and the genotypes of rs12901499 and rs12953717 were potential risk factors for SUI. The factors influencing SUI occurrence are complex, and thus, only a limited number of indicators were identified as independent risk factors. A previous study by Xie et al. found that teenage childbearing was an independent risk factor for SUI in American women [36]. Another study identified age, vaginal delivery, parity, bladder neck descent, and the angle of the internal urethral orifice funnel as independent risk factors for postpartum SUI [37]. These results suggest that genetic factors, such as SNPs, may also play a role in the risk of SUI.

The outcomes of conservative treatment for SUI are limited, including lifestyle interventions, PFMT, laser therapy, and drug therapy [38]. The effectiveness of treatment largely depends on patient adherence and compliance. Surgical treatment, while effective, often leads to surgery-related complications and higher costs [39]. PFMT is the most commonly used physical therapy for SUI patients, but its effectiveness varies among individuals. Additionally, genetic variants of SNPs have been strongly associated with treatment outcomes in various

Table 5. Association of SMAD3 and SMAD7 gene polymorphisms with treatment efficacy of SUI patients

SNPs	Genotype	Effective group (n = 85)	Ineffective group (n = 32)	χ^2	*p*-value
rs28683050	CC	39 (45.88)	16 (50.00)	0.312	0.856
	CT	34 (40.00)	11 (34.38)		
	TT	12 (14.12)	5 (15.63)		
rs12901499	AA	15 (17.65)	6 (18.75)	0.468	0.791
	AG	43 (50.59)	14 (43.75)		
	GG	27 (31.76)	12 (37.50)		
rs12953717	CC	33 (38.82)	5 (15.63)	40.530	< 0.001
	CT	48 (56.47)	9 (28.13)		
	TT	4 (4.71)	18 (56.25)		
rs4939827	CC	46 (54.12)	15 (46.88)	3.915	0.141
	CT	35 (41.18)	12 (37.50)		
	TT	4 (4.71)	5 (15.63)		

SNP, Single nucleotide polymorphisms.

diseases [40]. In this study, we examined the association between SMAD3 and SMAD7 SNPs and treatment outcomes in SUI patients. The results showed that patients with the TT genotype at the rs12953717 locus of SMAD7 were less responsive to PFMT, whereas the other three loci were not associated with treatment outcomes. These findings suggest that genetic polymorphisms may influence PFMT efficacy.

This study has several limitations. First, the sample size was limited, and larger samples are needed to verify whether SNPs of SMAD3 and SMAD7 can serve as diagnostic criteria for SUI. Second, the study population consisted only of Chinese patients, and the findings may vary across different ethnic groups. Moreover, the results need to be validated using diverse analytical methods, including bioinformatics and genomic analyses. Finally, we focused on only four key loci; future studies should explore other loci within the SMAD3 and SMAD7 genes associated with SUI.

In conclusion, this study suggests that the rs12901499 polymorphism in SMAD3 and the rs12953717 polymorphism in SMAD7 are associated with the risk of SUI. Furthermore, the rs12953717 polymorphism in SMAD7 was also linked to treatment outcomes. These findings indicate that SNPs in the SMAD genes could serve as susceptibility markers for SUI in the Chinese population.

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Disclosure of conflict of interest

None.

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