

## Review Article

# Association of COL1A1 Sp1-binding site polymorphism with susceptibility to pelvic organ prolapse: a meta-analysis

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**Abstract:** *Introduction:* Growing studies explored the association of polymorphism in COL1A1 Sp1-binding site with susceptibility to pelvic organ prolapse (POP), but the results have remained controversial and conflicting. To investigate the effect of COL1A1 Sp1-binding site polymorphism on POP, we performed a meta-analysis. *Methods:* We searched PubMed and HuGE for case-control studies concerning the association between COL1A1 Sp1-binding site polymorphism and POP from 1980 to July 1, 2015. Pooled analysis of the data in qualified reports has been performed by Stata 12.0. *Result:* In all, four published case-control studies including 698 participants were contained in quantitative syntheses. In the overall meta-analysis, an increased POP risk was detected in the heterozygous model of COL1A1 Sp1-binding site polymorphisms (GT vs. GG: OR=1.43, 95% CI, 1.02-2.00, P=0.040). *Conclusion:* The overall results suggest that COL1A1 Sp1-binding site polymorphisms may be associated with an increased POP risk.

**Keywords:** Pelvic organ prolapse (POP), polymorphism, COL1A1, susceptibility, meta-analysis

## Introduction

Pelvic organ prolapse (POP) is downward descent of female pelvic organs, including the bladder, uterus, and the small and large bowel, resulting in protrusion of the vagina, uterus, or both. Although it is not considered a life-threatening condition, POP does affect a woman's daily activities and quality of life. Pelvic organ prolapse also results in considerable economic cost. More than 225000 inpatient surgical procedures for POP were undertaken and over US\$1 billion were cost per year in the USA alone [1]. Pregnancy and vaginal childbirth have been recognized as the major causes for POP development, however, these factors do not totally explain the pathophysiology of POP in all women [2, 3]. In fact, pelvic floor dysfunctions have been observed in nulliparous women and the absence of condition has been identified in many multiparous women [3, 4]. It seems that genetics contribute significantly to the development of POP.

Type 1 collagen is the main component of connective tissue throughout the body. Its molecular structure is heterotrimeric and it is formed by two  $\alpha$ -1 chains and one  $\alpha$ -2 chain which are the products of COL1A1(17q21.33) and COL1A2(7q22.1) genes, respectively [5, 6]. The transcription of  $\alpha$ -1 chain is regulated by the promoter and the first intron of COL1A1 gene. Sp1 transcription factor binds to the first intron which is required for enhanced transcriptional activity, and modulates gene transcription. In the case of a nucleotide substitution (guanine (G) to thymidine (T)) within the first intron, the binding affinity of Sp1 transcription factor to this variated site increases. Thus, the expression of the COL1A1 gene is changed, resulting in an abnormal  $\alpha$ -1 chain product [6].

Several studies and meta-analyses have been conducted to demonstrate the association between the COL1A1 Sp1-binding site polymorphism and osteoporosis within the last decade [7, 8]. Skorupski et al. [9] investigated the association between COL1A1 Sp1-binding site and

stress urinary incontinence (SUI) in women and found that the GT genotype (OR=4.98) and TT genotype (OR=2.23) in subjects was associated with SUI. Sioutis et al. [10] found that the polymorphic T allele of Sp1 COL1A1 was over-represented in the SUI patients and the odds ratio for developing SUI was 2.19 (95% CI 1.149-4.176). Several studies researched the association between the COL1A1 Sp1-binding site and POP, however, due to the limitations of subjects, the results were inconsistent and controversial. Cartwright et al. [11] performed a systematic review and meta-analysis of genetic association studies of urinary symptoms and prolapse in women. However, the previous meta-analysis did not cover all eligible studies related to POP and COL1A1 Sp1 polymorphism. To clarify the authentic effect of COL1A1 Sp1 polymorphism on susceptibility to pelvic organ prolapse, we performed a meta-analysis concerning this subject. All potential genetic models were used in our meta-analysis to make the results more robust and reliable.

## Methods

### *Literature search*

Searches from databases PubMed and HuGE Navigator were combined. We searched PubMed up to July 1, 2015, without language restrictions, using a combination of gene and disorders key words and Medical Subject Headings (MeSH) terms: Search ("Pelvic Organ Prolapse" [Mesh]) OR ("Urinary Incontinence" [Mesh]) OR prolapse OR pelvic floor OR uterus OR uterine OR vaginal OR bladder OR small bowel OR rectum OR cystocele OR rectocele OR enterocele) AND ("Collagen Type I" [Mesh]) OR collagen, type I, alpha 1 OR COL1A1) AND ("Polymorphism, Genetic" [Mesh]) OR polymorphism OR genetic polymorphism OR SNPs OR mutation OR genetic OR variation).

We searched HuGE Navigator with the phenotype indexing term: (pelvic organ prolapse), up to July 1, 2015, without language restrictions.

In order to identify the extra eligible studies, we searched the reference list of all relevant studies, including original articles, reviews, and meta-analyses.

### *Inclusion and exclusion criteria*

Studies met the following criteria are included in our meta-analysis: (1) studies investigating the association of COL1A1 Sp1-binding site

polymorphism with POP risk; (2) case-control studies and studies included available genotype frequencies; (3) inclusion of comprehensive data to calculate odds ratio (OR) and 95% confidence interval (CI). All animal studies, case reports, reviews, abstracts, conference proceedings, editorials and reports with incomplete data were excluded.

### *Literature review and data extraction*

All study screening and data extraction have been performed by 2 reviewers independently. After title and abstract screening, reviewers selected papers for full-text assessment, then full-text studies were reviewed to confirm eligibility of the articles. Any disagreement was discussed and resolved in a consensus meeting. For each study, the following variables were extracted: the name of first author, year of publication, ethnicity, number of cases and controls, genotype and allele frequencies for cases and controls, and result of Hardy-Weinberg equilibrium (HWE).

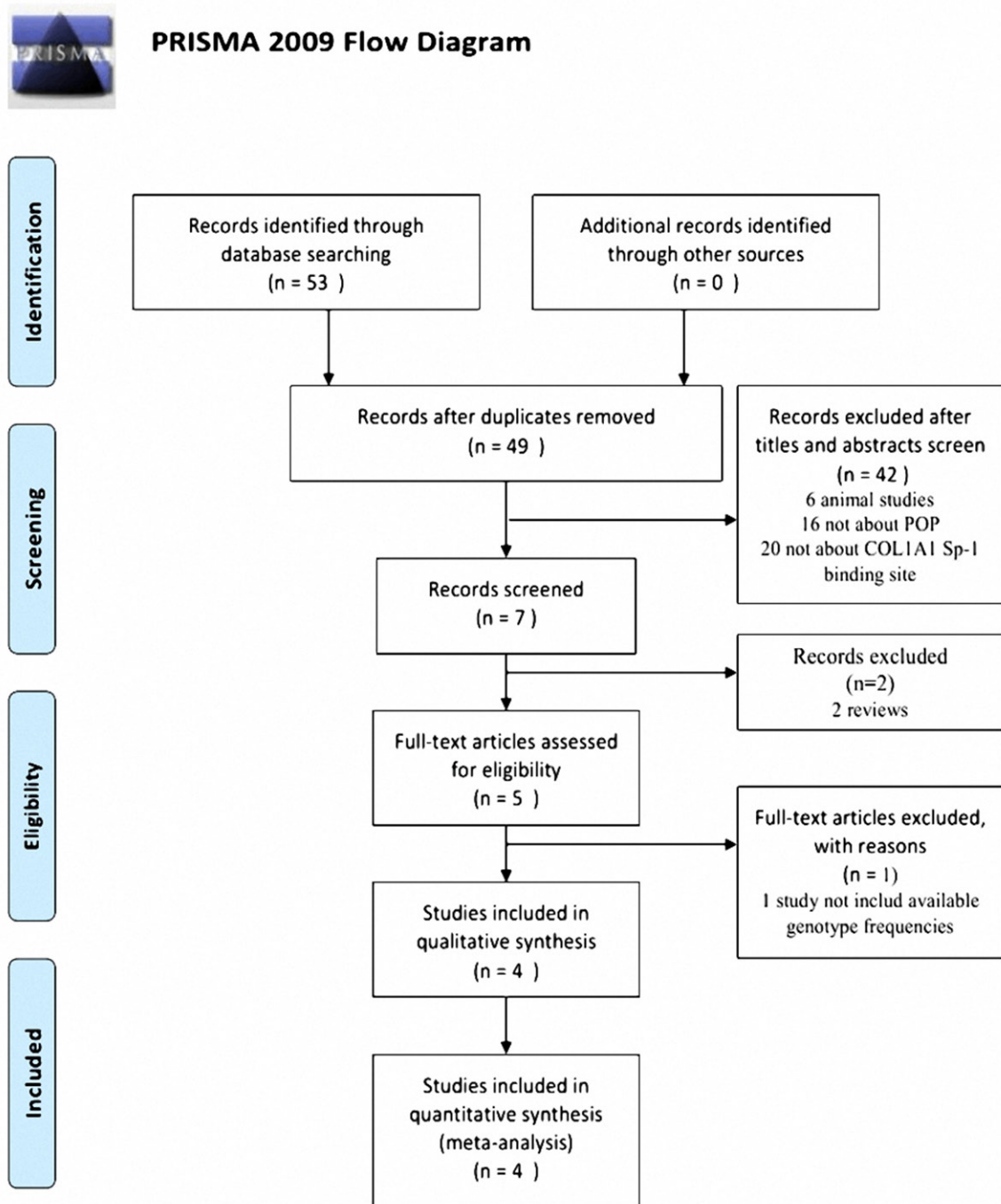
### *Meta-analysis*

We assessed the deviation from HWE for the genotype distribution in controls, according to the HWE principle and formula [12]. Meta-analysis for COL1A1 Sp1-binding site polymorphism was performed with STATA/SE 12.0 (StataCorp LP, College Station, TX). The association of COL1A1 Sp1-binding site polymorphism with risk of POP was measured by odds ratios (ORs) and 95% confidence intervals (CI). The significance of pooled OR was evaluated with the Z-test, and statistical significance was considered as a  $P$ -value of  $<0.05$ . We measured associations of all the potential genetic models (additive model: T vs. G, dominant model: GT+TT vs. GG, recessive model: TT vs. GT+GG, heterozygous model: GT vs. GG, homozygous: TT vs. GG) with POP risk. Heterogeneity test was conducted with the  $I^2$  test. If  $I^2 \leq 50\%$ , fixed effect model was adopted to pool studies, or the random effect model was used when  $I^2 > 50\%$  [13]. Furthermore, potential publication was diagnosed and measured by using the Harbord's and Peters' weighted linear regression test and Funnel plots.

## Results

### *Characteristics of eligible studies*

According to our search criterion, 53 studies were retrieved. Among them, the majority were



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

**Figure 1.** The Flow chart of literature search and assessment progress.

excluded after the first screening based on abstracts or titles, mainly because they were duplicate records, not relevant to the COL1A1

Sp1-binding site polymorphism and POP risk, or not case-control studies. Afterwards, a total of 5 full-text studies were preliminarily identi-

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**Table 1.** Information of included studies

References	Journal and year	Country	Descent, ethnicity, race	Gene symbols	Polymorphism (s) db SNP ID	Case definition	Control definition	Cases genotyped, n	Controls genotyped, n
Ferrari et al [16]	<i>Arch Gynecol Obstet</i> 2012	Italy	Italian	COL1A1 MMP9 MMP1 MMP3	rs1800012 rs3018242 rs1799750 rs3025058	POP-Q $\geq$ 2	POP-Q<2	137	96
Skorupski et al [18]	<i>Ginekol Pol</i> 2007	Poland	Polish	COL1A1	rs1800012	POP-Q $\geq$ 2	Patients treated for benign gynecological conditions other than SUI or POP	37	40
Feiner et al [15]	<i>Int Urogynecol J</i> 2009	Israel	Caucasian or Ashkenazi-Jewish	COL1A1	rs1800012	POP-Q $\geq$ 3	POP-Q $\leq$ 1	36	36
Rodrigues et al [17]	<i>Int Urogynecol J</i> 2008	Brazil	White or nonwhite	COL1A1	rs1800012	POP-Q $\geq$ 3	POP-Q<2 and no SUI	107	209

POP-Q: pelvic organ prolapse quantification; SUI: stress urinary incontinence.

**Table 2.** The distribution of COL1A1 Sp1-binding site polymorphisms in POP

Study name	Case (n)					Control (n)					P of HWE
	GG	GT	TT	G	T	GG	GT	TT	G	T	
Ferrari et al	75	53	9	203	71	61	30	5	152	40	P=0.606
Skorupski et al	26	10	1	62	12	27	9	4	63	17	P=0.038
Feiner et al	24	12	-	60	12	28	7	1	63	9	P=0.505
Rodrigues et al	71	33	3	175	39	154	52	3	360	58	P=0.553

HWE: Hardy-Weinberg Equilibrium.

fied for further detailed evaluation (**Figure 1**). One of the 5 articles was excluded [14] because the study found only the wild type GG allele among all 30 participants. Eventually, four case-control studies [15-18] were included in quantitative synthesis. Detailed information, such as author name, journal and year, country, ethnicity, gene symbols, SNP ID, case and control definition, numbers about cases and controls were summarized in **Table 1**. The results of HWE test in the control population and genotype frequencies of COL1A1 Sp1-binding site polymorphism were retested and extracted from all eligible publications (**Table 2**). There was significant deviation from Hardy-Weinberg equilibrium in one report [18], suggesting significant potential for bias. Considering the sample size in this study in relatively small which may contribute the deviation from Hardy-Weinberg equilibrium, we do not exclude this report from our meta-analysis.

#### Quantitative data synthesis

Our results revealed that individuals carrying the variant GT genotype had an increased POP risk compared with the GG genotype (GT vs. GG: OR=1.43, 95% CI=1.02-2.00, P=0.040) (**Figure 2A**). However, there was no significant difference in other genetic models (TT vs. GG: OR=1.09, 95% CI=0.49-2.39, P=0.840; GT+TT vs. GG: OR=1.38, 95% CI=1.00-1.91, P=0.053; TT vs. GT+GG: OR=0.97, 95% CI=0.44-2.13 P=0.947; T vs. G: OR=1.26, 95% CI=0.95-1.66, P=0.104) (**Figure 2B-E; Table 3**). In all genetic comparisons, fixed effect model (Mantel-Haenzel method) was used since there was no obvious heterogeneity across included studies.

#### Publication bias

We performed improved Galbraith's funnel plots by using Harbord's linear regression test

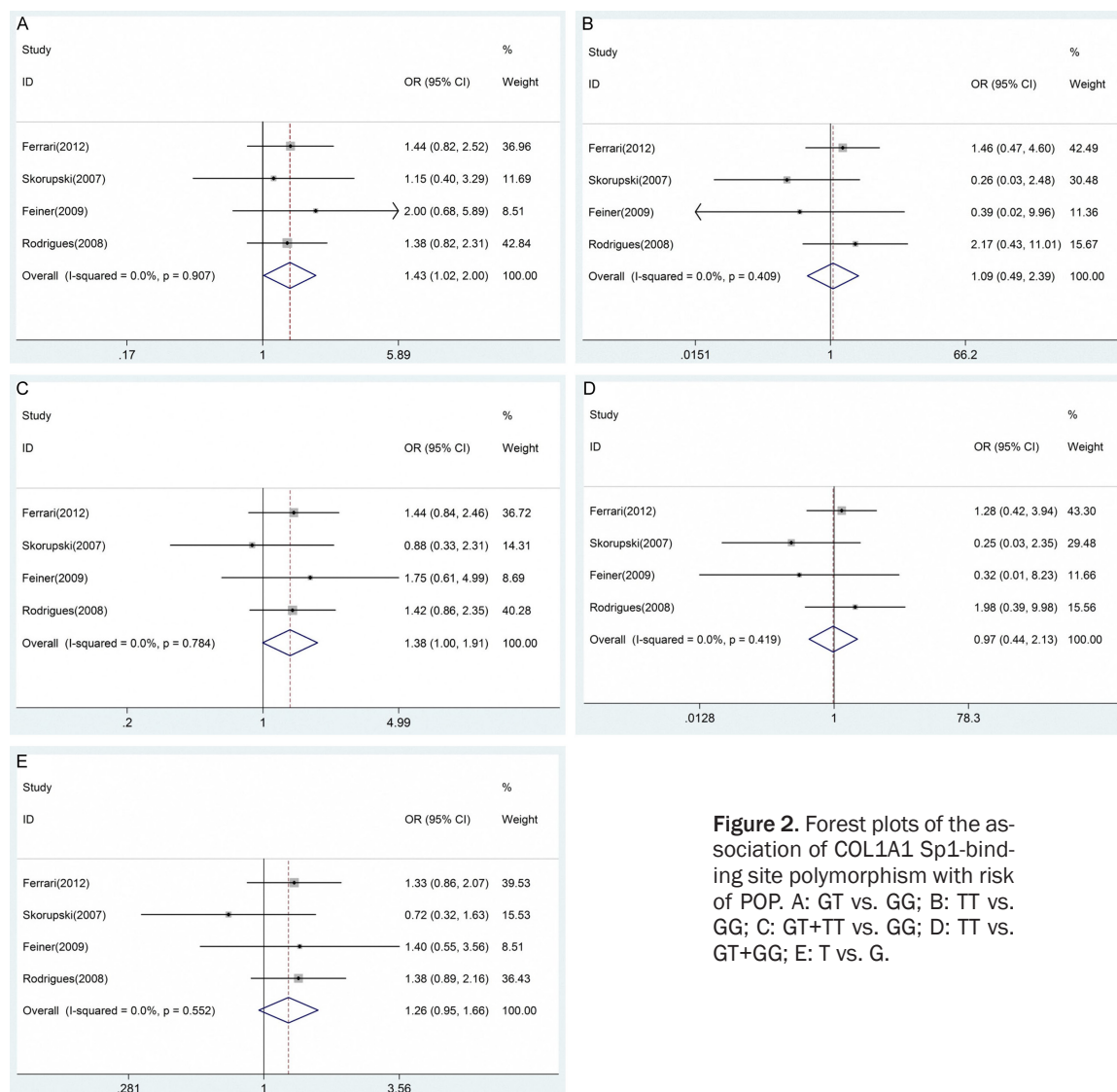
and Peters' linear regression test to assess the publication bias of all included studies. As demonstrated in **Figure 3**, the funnel plots did not display any evidence of obvious asymmetry under the heterozygous models (GT vs. GG P=0.780). Peters' test also suggested that there was no obvious statistical publication bias under the heterozygous models (GT vs. GG P=0.726).

#### Discussion

Several studies focused on the different quantity and type of collagen fibers in pelvic tissue. Gabriel et al. [19] found that major expression of type III collagen in specimens from the uterosacral ligaments had a significant association with POP, and it might be a typical characteristic of the connective tissue of patients with such a disease. Yucel et al. [20] showed a decreased expression of collagen type I and increased expression of collagen type III in uterosacral ligaments of women with POP compared with non-POP subjects, suggesting that alterations in these subtypes of collagen is associated with POP. COL1A1 Sp1 polymorphism has been studied in association with osteoporosis and it contributes modestly to the reduction of bone mineral density (BMD) and an increased risk of fracture [21]. Collagen I is thought to be the main structural component of endopelvic supporting ligaments and vaginal tissue. [22]. The available data on gene and protein expression in pelvic tissue from women with POP suggested that increasing COL1A1 expression contributes to reduced collagen I content, while the decreased type 1 collagen contributes to tissue laxity and prolapse [22, 23]. Recently, several studies have been performed to research the associations between the COL1A1 Sp1-binding site polymorphism and the susceptibility on POP [14-18]. Despite all of the five studies didn't demonstrated statistically significant associations between the



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**Figure 2.** Forest plots of the association of COL1A1 Sp1-binding site polymorphism with risk of POP. A: GT vs. GG; B: TT vs. GG; C: GT+TT vs. GG; D: TT vs. GT+GG; E: T vs. G.

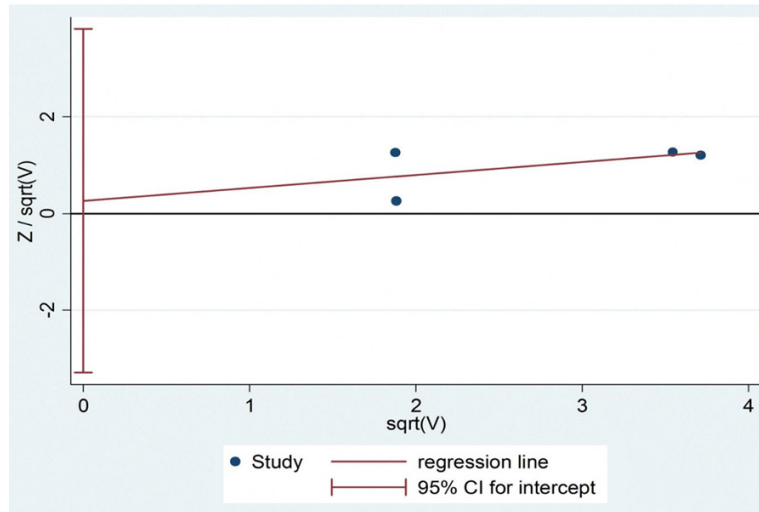
**Table 3.** The results of heterogeneity test and meta-analysis in all genetic models for COL1A1 Sp1-binding site polymorphism in POP

Genotype	OR (95% CI)	Pooled P-value	I-squared (%)	P-value
T vs. G	1.26 (0.95-1.66)	0.104	0.0	0.552
GT+TT vs. GG	1.38 (1.00-1.91)	0.053	0.0	0.784
TT vs. GT+GG	0.97 (0.44-2.13)	0.947	0.0	0.419
TT vs. GG	1.09 (0.49-2.39)	0.840	0.0	0.409
GT vs. GG	1.43 (1.02-2.00)	0.040	0.0	0.907

COL1A1Sp1-binding site and a risk of development of POP, our study revealed inconsistency result. Considering that the studies involving in our meta-analysis completely met all the screening criteria, the results from these pooled studies were more credible than those from single study. After searching the PubMed

and HuGE Navigator and excluded the irrelevant studies according to our criteria, a total of 4 case-control studies were available up to July 1, 2015. Our results demonstrate that the heterozygous model (GT vs. TT) is associated with an increased POP risk while no significant difference are found in other genetic models, suggesting that the genotype GT may play a vital role in the susceptibility on POP.

However, there are several limitations of the current meta-analysis, which must be taken into consideration. Because the sample size of each individual study is relatively small and



**Figure 3.** Improved Galbraith funnel plot for publication bias test Heterozygous model: GT vs. GG.

there is no uniform standard staging system for POP. In spite of all of the four studies included in this article used POP Quantification (POP-Q) for anatomic staging, the criterion in each study for identifying the control groups are not totally consistent. Therefore, we performed publication bias test to avoid such potential discrepancy in our meta-analysis, which indicates no obvious selection bias and confirms the reliability and stability of our results.

In conclusion, this meta-analysis demonstrates that COL1A1 Sp1-binding polymorphism (G→T) probably increase the susceptibility to pelvic organ prolapse. Since pelvic organ prolapse is a common disease caused by multiple factors, it is important to perform well-design and large scale studies, including comprehensive individual data, homogenous patients and underlying source population based controls, standardized genotyping methods to thoroughly reveal the association of COL1A1 Sp1-binding site polymorphism with pelvic organ prolapse risk. Even though our knowledge about the pathogeny and genetic risk of prolapse is still limited, it should be aware that the mutation of COL1A1 Sp1-binding site may play a role in a selected subgroup of women with POP.

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#### Disclosure of conflict of interest

None.

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