



# Is There a Relationship Between Pelvic Organ Prolapse and Tissue Fibrillin-1 Levels?

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**Purpose:** Pelvic organ prolapse is a multifactorial disorder in which extracellular matrix defects are implicated. Fibrillin-1 level is reduced in stress urinary incontinence. In Marfan syndrome, which is associated with mutations in Fibrillin-1, pelvic floor disorders are commonly observed. We hypothesize that Fibrillin-1 gene expression is altered in pelvic organ prolapse.

**Methods:** Thirty women undergoing colporrhaphy or hysterectomy because of cystocele, rectocele, cystoectocele, or uterine prolapse were assigned to a pelvic prolapse study group, and thirty women undergone hysterectomy for nonpelvic prolapse conditions were assigned to a control group. Real-time polymerase chain reaction was conducted on vaginal tissue samples to measure the expression of Fibrillin-1. Expression levels were compared between study and control groups by Mann-Whitney U test with Bonferroni revision.

**Results:** Fibrillin-1 gene expression was not significantly lower in the study group than in the control group. Similarly, no significant correlation between Fibrillin-1 levels and grade of pelvic prolapse was found. Age over 40 years ( $P = 0.018$ ) and menopause ( $P = 0.027$ ) were both associated with reduced Fibrillin-1 levels in the pelvic prolapse group, whereas the delivery of babies weighing over 3,500 g at birth was associated with increased Fibrillin-1 expression ( $P = 0.006$ ).

**Conclusions:** The results did not indicate a significant reduction in Fibrillin-1 gene expression in pelvic prolapse disorders; however, reduced Fibrillin-1 may contribute to increased pelvic organ prolapse risk with age and menopause. Increased Fibrillin-1 gene expression may be a compensatory mechanism in cases of delivery of babies with high birth weight. Further studies are needed for a better understanding of these observations.


**Keywords:** Extracellular Matrix; Fibrillin; Pelvic Organ Prolapse

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## INTRODUCTION

Pelvic organ prolapse (POP) is a common pelvic floor disorder

[1]. The lifetime cumulative risk of POP has been estimated at 12.6% for adult women, with the risk increasing with age [2]. The etiology of POP is complex and multifactorial, and epide-

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miological studies suggest that multiple pathologies contribute to full anatomical loss. The mechanisms underlying pelvic floor support failure remain poorly understood; however, studies in both humans and animals implicate defects in the extracellular matrix (ECM) or fibrous connective tissue causing reduced tissue strength and defective repair [3]. The ECM of the pelvic floor, which is termed the endopelvic fascia, is responsible for maintaining the position of organs adjacent to the vagina.

The largest structures in the ECM are elastic fibers, which consist of a core of elastin, which is a cross-linked polymer of tropoelastin, supported on a lattice of microfibrils [4]. The elastic fibers enable tissue stretching. Microfibril proteins such as fibrillins and fibulins play an essential role in the assembly of elastic fibers. Fibrillins, which have three known forms Fibrillin-1, Fibrillin-2, and Fibrillin-3, are major structural elements of microfibrils [5-7]. Mutation of the Fibrillin-1 gene is the cause of Marfan syndrome, and POP is more prevalent in women with this disease [8]. Fibrillin-1 gene expression is reduced in women with stress urinary incontinence (SUI) [9], a pelvic floor dysfunction that is frequent feature of POP [1]. Reduction in other ECM proteins levels that interact with Fibrillin-1, such as fibulin-5 and the small leucine-rich repeat proteoglycan (SLPR) decorin, has been observed in POP [10].

However, none of the studies to date have evaluated the relationship between Fibrillin-1 gene expression and POP. The present study is aimed at investigating the altered expression of the Fibrillin-1 gene in POP, by examining the differences in Fibrillin-1 expression between women with POP and those with no history of POP.

## MATERIALS AND METHODS

The study was carried out at the Obstetrics and Gynecology Departments of 3 different hospitals: Turgut Ozal University Hospital in Ankara, Etlik Zubeyde Hanim Education and Research Hospital in Ankara, and Nenehatun Maternity Hospital in Erzurum, Turkey, between January and October 2013.

The study was approved by Etlik Zubeyde Hanim Education and Research Hospital Ethical Committee and complied with the Helsinki Declaration, 2011. Informed consent was obtained from all participants before the start of the study.

### Patients

In total, 60 women, 30 women in the POP group and 30 women in the control group, matched for age, parity, and body mass index (BMI) were included in the study. Demographic characteristics of the patients are shown in Table 1. Women in the POP group had undergone colporrhaphy and/or vaginal hysterectomy for POP. The women in the control group had undergone total abdominal hysterectomy for other benign conditions. The median age of the POP patients was 45.5 years (range, 27–71 years); 12 patients were pre- and 18 were postmenopausal and the median parity was 3 (range, 1–5). The median age of the control patients was 47 years (range, 26–53 years); 3 patients were pre- and 27 were postmenopausal and the median parity was 2 (range, 1–5). Women with a history of endometriosis, gynecologic malignancies, pelvic inflammatory conditions, connective tissue disorders, emphysema, prior pelvic surgery, SUI, or diseases requiring systemic glucocorticoid treatment were excluded from

**Table 1.** Demographic characteristics of women in study and control groups

Characteristic	Study group (n = 30)	Control group (n = 30)	P-value
Age (yr)	45.5 (27–71)	47 (26–53)	0.899
Parity (n)	3 (1–5)	2 (1–5)	0.324
Body mass index (kg/m <sup>2</sup> )	28.5 (23–39)	29.3 (23–45)	0.221
Vaginal deliveries (n)	1 (1–3)	1 (1–3)	0.352
Delivery weight (g)	3,525 (3,200–3,800)	3,400 (2,700–4,750)	0.339
Menopause, n (%)			0.008*
Yes	18 (60)	27 (90)	
No	12 (40)	3 (10)	
Postmenopausal period (yr)	0 (0–26)	0 (0–6)	0.009*
Fibrillin-1 level	0.066 (0.005–0.429)	0.085 (0.010–0.439)	0.114

Values are presented as median (range) unless otherwise indicated.

\*P < 0.05 was considered statistically significant.

the study. All participants underwent a gynecological examination. Pelvic support was assessed by means of a physical exam to confirm support loss with motion and/or prolapse. The degree of descent was graded according to the POP quantification (POP-Q) system [11] in both POP and control subjects. Neither premenopausal nor postmenopausal women had received hormonal therapy for at least 12 months prior to the study.

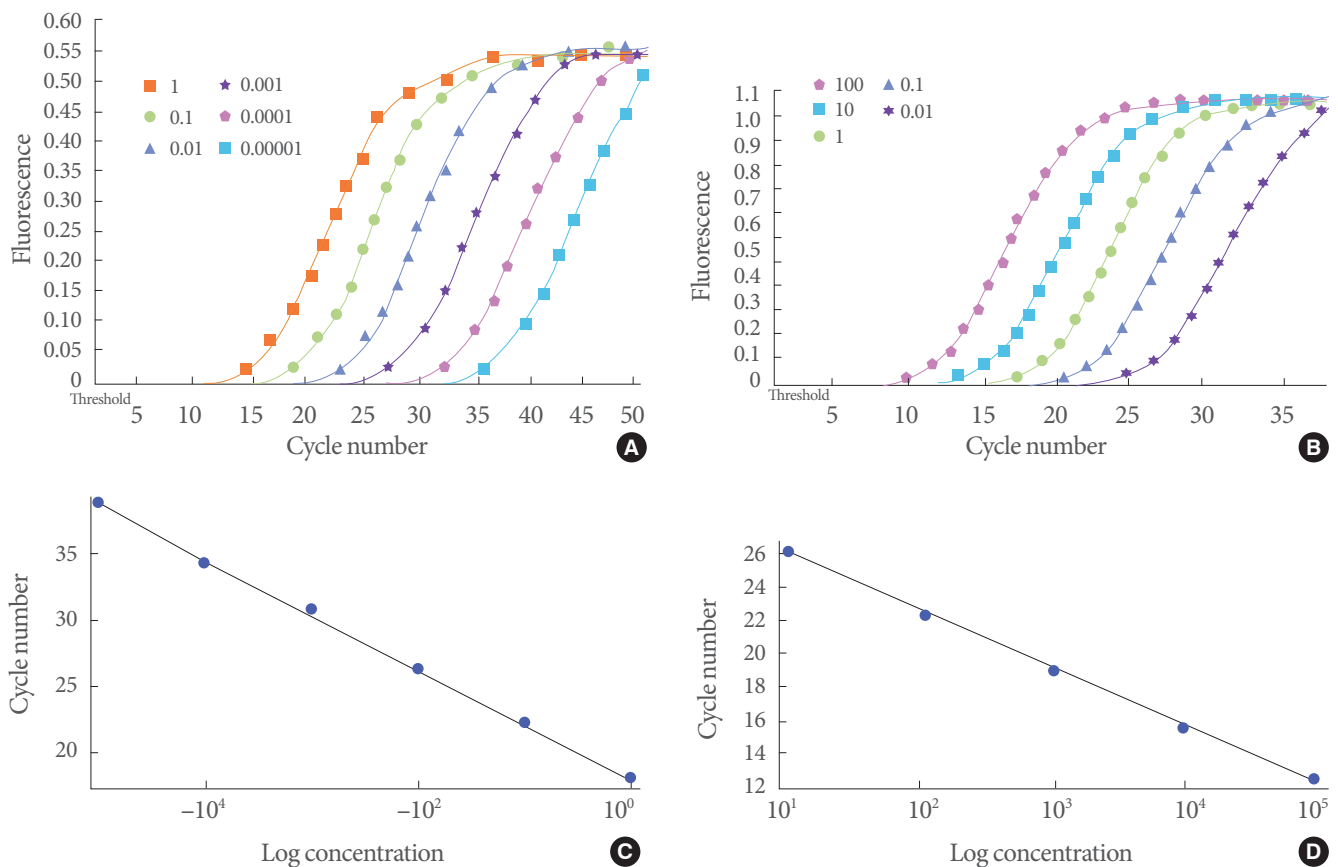
**Biopsies**

During surgery, periurethral (5 mm from the urethral orifice) and full-thickness biopsies of the vaginal wall were obtained, including mucosal and submucosal tissues (6 mm in diameter and 10 mm in depth). This biopsy site has been demonstrated to be representative of the endopelvic fascia [12]. Biopsies were immediately transferred to liquid nitrogen and stored at -70°C until further analysis.

**RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction**

Total RNA was extracted from tissues by using TRIzol reagent (Life Technologies, Carlsbad, CA, USA) according to the manufacturer’s instructions. RNA concentration was measured and purity was assessed by a NanoDrop spectrophotometer (Thermo Fisher Scientific Inc., Wilmington, DE, USA). One microgram of the RNA sample was then transcribed into cDNA by using the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Vilnius, Lithuania) and oligo(dT) primers.

For quantitative real-time polymerase chain reaction (qRT-PCR), cDNA samples were amplified by Rotor-Gene Q Real-Time PCR (QIAGEN, Heidelberg, Germany) by using the QuantiTect SYBR Green PCR kit (QIAGEN). PCR primer sequences for Fibrillin-1 mRNA were as follows: Fibrillin-1 RAS2 5'-TGACTGGCCCACACGTGCATAG-3' (sense) and Fibril-



**Fig. 1.** Amplification plots of Fibrillin-1 mRNA (A) and housekeeping β-actin mRNA (B). Serial dilutions of Fibrillin-1 and β-actin cDNA plasmids were prepared and amplification was performed by quantitative real-time polymerase chain reaction. For each dilution, fluorescence is plotted against the cycle number. Log concentration and cycle numbers of each dilution are shown. Serial dilutions of Fibrillin-1 and β-actin cDNA plasmids were prepared and amplification was performed. Log concentrations of Fibrillin-1 mRNA (C) and β-actin mRNA (D) were plotted against the cycle number.

lin-1 RAS2 5'- TGACATTGACCCCTTGTGACAGGA-3' (antisense). Fibrillin-1 gene expression was normalized to that of the housekeeping gene  $\beta$ -actin, by using primers 5'- GGC-CAACCGCGAGAAGATGAC-3' (sense) and 5'-GCTCG-TAGCTCTTCTCCAGGG-3' (antisense). Total reaction volume of qRT-PCR was 50  $\mu$ L, containing 25  $\mu$ L of SYBR Green mix, 1  $\mu$ L of each 20 pmol/ $\mu$ L primer, 5  $\mu$ L of cDNA, and nuclease-free water up to a total volume of 50  $\mu$ L. Samples were denatured at 95°C for 15 minutes followed by 40 cycles of denaturing, annealing, and extension at 95°C for 15 seconds, 60°C for 30 seconds, and 72°C for 30 seconds, respectively. Characteristic melting curves were obtained at the end of the amplification by cooling to 65°C for 15 seconds and then to 40°C for a further 30 seconds. Serial 10-fold dilutions were prepared from known quantities of  $\beta$ -actin and Fibrillin-1 PCR products to be used as standards to measure expression level of the unknown samples.

Data were analyzed using the Rotor-Gene Q Series Software 2.1.0 (Qiagen, Heidelberg, Germany) and expression levels were calculated by the standard curve method. Values were normalized to the level of  $\beta$ -actin for each sample (Fig. 1).

### Statistical Analysis

SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The compatibility of the data with normal distribution was assessed graphically and by the Shapiro-Wilk test. In order to represent continuous data, median (range) was used for nonnormally distributed parameters, and number and percentage for categorical data. In order to compare data from three independent groups, the Kruskal-Wallis test was used for nonnormally distributed data. The Mann-Whitney test with Bonferroni correction was used for comparison between two sets of data established as significant by the Kruskal-Wallis test. Correlation between parameters was assessed using Spearman rank correlation coefficient.  $P < 0.05$  was considered statistically significant.

Statistical power analysis showed that at least 59 patients were needed to achieve 85% power when alpha error was set to 0.05, beta error to 0.20, and effect size to 0.35.

## RESULTS

In total, 60 women were included in the study: 30 women in the POP group and 30 women in the control group. The median age of the subjects was 45.5 years (range, 27–71 years). Demographic features of patients are shown in Table 1. There was no statistical difference in age, parity, BMI, or delivery weight between the study and control groups. Menopause ratio and median time after menopause were significantly higher in the pelvic prolapse group ( $P < 0.05$ ) (Table 1). Surgery indications are shown in Table 2.

There was no statistically significant difference in median Fibrillin-1 levels between the study and control groups (Table 1). Correlation analysis revealed a moderate negative correlation between Fibrillin-1 expression and age, and a moderate positive correlation between Fibrillin-1 expression and delivery weight in the POP group (Rho = -0.520,  $P = 0.006$  and Rho = 0.413,  $P = 0.036$ , respectively) (Table 3). No significant correlations

**Table 2.** Surgery indications

Group	No. (%)
Study (n = 30)	
Uterine prolapse	6 (20.0)
Rectocele	3 (10.0)
Cystocele	18 (60.0)
Cystocele	3 (10.0)
Control (n = 30)	
DUB	10 (33.3)
Endometrial hyperplasia	1 (3.3)
Myoma uteri	19 (63.3)

DUB, dysfunctional uterine bleeding.

**Table 3.** Correlation between Fibrillin-1 expression and pelvic relaxation stages/demographic characteristics

Fibrillin-1	Postmenopausal period	Age	Body mass index	Gravidity	Parity	Vaginal delivery	Delivery weight	Cystocele stage	Rectocele stage	Cystocele stage
Case										
Rho	-0.420	-0.520 <sup>a)</sup>	-0.140	-0.188	-0.332	0.243	0.413 <sup>a)</sup>	-0.037	0.101	0.038
P-value	0.032*	0.006*	0.496	0.358	0.097	0.232	0.036*	0.858	0.625	0.852
Control										
Rho	0.051	0.015	0.023	-0.057	-0.009	-0.110	-0.241	-	-	-
P-value	0.794	0.939	0.905	0.770	0.965	0.569	0.207	-	-	-

\* $P < 0.05$  was considered statistically significant. <sup>a)</sup>Rho was considered as significant correlation.

were observed with respect to these parameters in the control group (Table 3).

Within the pelvic prolapse group, Fibrillin-1 expression was significantly lower in patients over 40 years old and in those

**Table 4.** Association between demographic characteristics and Fibrillin-1 ratio in the pelvic prolapse group

Demographic attribute	No.	Fibrillin-1	P-value
Age (yr)			0.018*
< 40	15	0.075 (0.005–0.429)	
≥ 40	15	0.035 (0.015–0.103)	
Parity			0.083
2	12	0.081 (0.0345–0.429)	
3	10	0.036 (0.021–0.092)	0.043 <sup>*.a)</sup>
4	4	0.072 (0.064–0.075)	
≥ 5	4	0.015 (0.005–0.056)	0.049 <sup>*.b)</sup>
Vaginal deliveries			0.403
1	24	0.047 (0.005–0.429)	
2	4	0.080 (0.067–0.084)	
3	2	0.064 (0.049–0.079)	
Body mass index (kg/m <sup>2</sup> )			0.782
< 25	6	0.077 (0.021–0.103)	
25–30	14	0.058 (0.015–0.429)	
≥ 30	10	0.056 (0.005–0.092)	
Delivery weight (g)			0.006*
< 3,500	10	0.029 (0.005–0.075)	
≥ 3,500	20	0.078 (0.021–0.429)	
Menopause (n)			0.027*
Yes	18	0.032 (0.015–0.103)	
No	12	0.076 (0.005–0.429)	
Postmenopausal period (yr)			0.889
< 5	2	0.034 (0.021–0.047)	
≥ 5	12	0.032 (0.015–0.103)	

Values are presented as median (range).

\*P < 0.05 was considered statistically significant. <sup>a)</sup> Comparing parity 2 and 3. <sup>b)</sup> Comparing parity 2 and 5.

with menopause, and significantly higher in patients who had delivered infants with birth weight of over 3,500 g (Table 4). Fibrillin-1 levels were significantly decreased after the third parity, although the significance levels were marginal (P = 0.049) (Table 4). Other demographic attributes were not associated with significantly altered Fibrillin-1 expression (Table 4). With respect to the type and POP-Q stage of pelvic prolapse, no statistically significant difference was observed in Fibrillin-1 expression between patients with 4th stage cystocele and those with other stages of cystocele and without prolapse (Table 5). There was no significant difference in Fibrillin-1 levels with respect to other types and prolapse stages (Table 5). With respect to age over 40 years and menopause, Fibrillin-1 levels were significantly lower

**Table 5.** Distribution of Fibrillin-1 values according to pelvic prolapse type

POP surgery	No.	Fibrillin-1	P-value
Only cystocele	3	0.054 (0.021–0.080)	0.718
Only rectocele	3	0.077 (0.015–0.098)	
Cystocele	18	0.049 (0.005–0.429)	
Cystocele, POP-Q stage			0.294
1	1	0.005 (-)	
2	8	0.049 (0.021–0.080)	
3	10	0.064 (0.015–0.429)	
4	5	0.041 (0.028–0.092)	
Rectocele, POP-Q stage			0.304
1	1	0.049 (-)	
2	19	0.041 (0.015–0.080)	
3	3	0.072 (0.021–0.429)	
Uterine prolapse			0.231
Yes	6	0.047 (0.021–0.072)	
No	22	0.075 (0.005–0.429)	

Values are presented as median (range).

POP, pelvic organ prolapse; POP-Q, POP quantification.

**Table 6.** Decrease in Fibrillin-1 levels with age and menopause in POP group but not in control group subjects

Demographic attribute	Study group	Control group	P-value
Age (yr)			
< 40	0.075 (0.005–0.429)	0.041 (-)	0.400
≥ 40	0.035 (0.015–0.103)	0.085 (0.010–0.439)	0.026*
P-value	0.018*	0.552	
Menopause (n)			
Yes	0.032 (0.015–0.103)	0.092 (0.021–0.383)	0.469
No	0.076 (0.005–0.429)	0.080 (0.010–0.439)	0.501
P-value	0.027*	0.866	

Values are presented as median (range).

POP, pelvic organ prolapse.

\*P < 0.05 was considered statistically significant.



in the POP group compared to the control group (Table 6).

## DISCUSSION

This case-control study was undertaken to investigate the differences in Fibrillin-1 gene expression between women with and without POP. The results indicated no statistical difference between the study and control groups.

There are substantial indications in the literature to suggest that alterations in microfibril components, particularly in Fibrillin-1, are relevant in pelvic prolapse and POP. Fibrillin-1 gene expression is reduced in SUI, a pelvic floor disorder often associated with POP [9]. Furthermore, POP is prevalent in Marfan syndrome [8]. Additionally, Fibrillin-1 mutation and/or reduced synthesis or deposition is a marker for other connective tissue disorders including stiff skin syndrome, Weill-Marchesani syndrome, aortic aneurysm and dissection, and lens luxation [13-15]. With respect to other microfibril components in POP, studies have suggested that the expression of fibulin-5 is reduced in women with POP [10]. Additionally, POP has been demonstrated to occur in fibulin-5 knockout mice [16]. Fibulin-5 plays a role in the organization of elastic fiber assembly on the microfibril lattice by acting as an adapter protein linking components such as Fibrillin-1 [17]. Fiber assembly involves cross-linking of collagen and elastic fibers, for which SLPRs such as decorin, lumican, and fibromodulin are important [10]. In particular, decorin-Fibrillin-1 interactions are crucial for the assembly of elastic fibers [10,18]. Additionally, decorin mediates Fibrillin-1 protein expression [19]. Reduced expression of decorin and other SLPRs has been observed in women with POP [10].

The data described above strongly suggest that patients with POP may show altered Fibrillin-1 levels; however, our results showed that there was no statistically significant reduction in Fibrillin-1 gene expression in women with pelvic prolapse disorders, which is consistent with findings of other studies [10]. Established risk factors for prolapse include increasing age and higher parity, the number of vaginal deliveries, giving birth to infants of high birth weight, presence of menopause, and time after menopause [1,20,21]. Analysis of the pelvic prolapse group in our study with respect to these parameters confirmed that Fibrillin-1 levels were significantly reduced in women over 40 years of age and in women who had experienced menopause. This was not observed in the control group, suggesting that the reduction in Fibrillin-1 was not necessarily a result of aging or menopause per se. Fibrillin is the major constituent of microfibrils,

which support elastic fibers of the ECM that enable tissue stretching [4-7]. Therefore, it is not entirely unreasonable to suggest that a reduction in Fibrillin-1 levels after menopause may make women more vulnerable to POP because of potential negative effects on pelvic floor integrity. Alternatively, the presence of POP in addition to age over 40 years or presence of menopause may cause a reduction in Fibrillin-1. Thus, these findings may have clinical significance in the context of the increased risk of POP with advancing age and menopause. Further studies in larger groups of subjects would be helpful in clarifying whether there is a difference in Fibrillin-1 levels, which becomes more pronounced with age and/or menopause, between women with and without POP. We found that, strictly, there was no significant difference between the groups; however, our data were at the borderline of significance ( $P=0.066$ ). Studies in larger cohorts would be helpful for clarification.

In contrast, women who had delivered babies with birth weight of over 3,500 g showed an unexpected higher expression of Fibrillin-1. High birth weight is a risk factor for the development of POP, and it has been suggested that elastic fibers are critical in maintaining vaginal wall support. Pelvic floor disorders, such as POP, are associated with increased expression of ECM proteases in both humans and in mouse models of POP, including matrix metalloprotease-9 (MMP-9), which may cause reduced fibrillin protein levels [22,23]. The observed increase in Fibrillin-1 gene expression may represent a mechanism to compensate for effects of MMP-9 and other proteases on elastic fibers in POP. However, this is speculative, and a definitive explanation of the increase in Fibrillin-1 gene expression would require further studies on larger samples of patients.

Although we carried out a power analysis to determine appropriate sample size, our study was limited by the relatively small number of subjects. This may have contributed to the lack of statistically meaningful differences in Fibrillin-1 expression between the control and pelvic prolapse groups. Therefore, larger studies with more patients are necessary. Our study did yield results with potential clinical relevance in terms of indicating a possible role for fibrillin in women aged over 40 years, particularly in those who have experienced menopause, as the presence of menopause was itself significantly associated with POP. Furthermore, Fibrillin-1 levels may be of significance in women with POP who have delivered babies with birth weight over 3,500 g. Currently, fibrillin is not a marker for predicting pelvic prolapse development. However, fibrillin levels may be indicative of the risk of pelvic prolapse development when con-

sidered together with factors such as age and menopause stage. Larger studies with more patients would be needed to confirm the potential role of Fibrillin-1 in POP development.

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