

**POLYMORPHISMS OF COL1A1 AND MMP-9 AND RISK OF PELVIC ORGAN PROLAPSE**Hypothesis / aims of study

Pelvic prolapse is a major health problem for women in the menopausal years. The etiology of genital prolapse is probably multifactorial. The mechanical stability of the genitourinary tract depends on intact, functional collagen fibers to support the bladder's neck, urethra and pelvic organs. Moreover, continuous tissue remodelling makes the relationship between the production of collagen and its degradation critical to the maintenance of tensile strength. There is evidence that qualitative and quantitative changes in connective tissue in the pelvic floor can result in pelvic prolapse. Furthermore, there is evidence that polymorphisms of the genes involved in the collagen remodelling COL1A1 gene could affect the pelvic floor function.

We tested the hypothesis that the G/T type of transcription factor Sp1-binding site polymorphism of the COL1A1 gene and the polymorphic site -1562 in the promoter region of the *MMP-9* gene predisposes for the development of pelvic organ prolapse.

Study design, materials and methods

Between may 2004 and may 2007, one hundred-twenty four women with  $\geq$  stage II pelvic organ prolapse (POP group) were considered for the study. Ninety age-matched women without pelvic pathologies were recruited at the menopause outpatient clinic to serve as controls. Inclusion criteria were age  $\leq$  80 years and caucasian race. Exclusion criteria were: previous hysterectomy or previous pelvic surgery for pelvic organ prolapse or stress urinary incontinence, and malignant conditions. The mean age of the patients was  $61.8 \pm 11$  years. The mean parity was  $2.8 \pm 1.1$  and  $2.2 \pm 1.0$ , respectively. The BMI was  $20.6 \pm 1.6$  in POP group and  $22.7 \pm 1.2$  in controls group.

At enrollment blood samples were collected in sodium citrate from a peripheral vein and stored at  $-20^{\circ}\text{C}$ . Genomic DNA was extracted with standard techniques. The polymorphism in the Sp1 binding site in the first intron of one of the type I collagen genes *COL1A1* and polymorphic site -1562 in the promoter region of the *MMP-9* gene were evaluated by polymerase chain reaction and restriction analysis.

Results

The GG polymorphism in COL1A1 gene was identified in 67 (54%), GT sequence in 48 (39%) and TT in 9 (7%) patient with pelvic prolapse. The distribution of the COL1A1 gene polymorphisms in the control group were: 57 (64%), 27 (30%) and 5 (6%), respectively.

Genotype CC in MMP-9 gene was found in 91 (73%), CT in 28 (23%) and TT in 5 (4%) women with POP group. The distribution of genotype of MMP-9 gene in controls was CC =77%, CT= 21% and TT =2%

Moreover, we found a higher familiarity for pelvic organ prolapse in POP group than controls patients (POP: 43/124 (35%); Controls: 14/90 (16%);  $p < 0.002$ ; OR 2.9 (95%CI 1.5-5-7)).

Interpretation of results

No association was found between investigated polymorphic variants and pelvic organ prolapse. Moreover the high familiarity suggests that genetic effects contribute to the occurrence of pelvic prolapse.

Concluding message

The polymorphism at the Sp1 binding site of the gene encoding alpha-1 chain of type 1 collagen and polymorphic site -1562 in the promoter region of the *MMP-9* gene are not associated with an increased risk of pelvic organ prolapse in women. However, new innovative studies, aimed at evaluating all genes involved in the connective tissue remodelling are necessary.

<b>Specify source of funding or grant</b>	/
<b>Is this a clinical trial?</b>	No
<b>What were the subjects in the study?</b>	HUMAN
<b>Was this study approved by an ethics committee?</b>	Yes
<b>Specify Name of Ethics Committee</b>	FONDAZIONE I.R.C.C.S POLICLINICO OSPEDALE MAGGIORE MANGIAGALLI E REGINA ELENA
<b>Was the Declaration of Helsinki followed?</b>	Yes
<b>Was informed consent obtained from the patients?</b>	Yes