

# Genetics of pelvic organ prolapse; identification of specific gene defects in patients and their family members.

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Genetic analysis of the familial inheritance pattern of the COL3A1 2209G>A polymorphism.

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruiting
<b>Health condition type</b>	Reproductive tract and breast disorders congenital
<b>Study type</b>	Observational invasive

## Summary

### ID

NL-OMON33518

### Source

ToetsingOnline

### Brief title

Genetics of pelvic organ prolapse

### Condition

- Reproductive tract and breast disorders congenital
- Uterine, pelvic and broad ligament disorders

### Synonym

Pelvic organ prolapse, Urogenital prolapse

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Sint Radboud

**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** collagen, genetic polymorphism, Pelvic floor, pelvic organ prolapse

## Outcome measures

### Primary outcome

Presence of the COL3A1 2209G>A polymorphism in family members of patients with the homozygous form of this polymorphism.

### Secondary outcome

Presence of pelvic organ prolapse and related conditions such as inguinal hernia in family members of patients with the homozygous form of the COL3A1 2209G>A polymorphism.

## Study description

### Background summary

Pelvic organ prolapse (POP) is a common health problem in women, with prevalence numbers varying from 8.3% to 30.8% (Eva 2003, MacLennan 2000, Samuelsson 1999, Slieker-ten Hove 2009, Tegerstedt 2005) . The condition brings along a substantial impact on quality of life, as is indicated by Digesu and colleagues (Digesu 2005). Women complaining of prolapse not only experience more urinary and bowel symptoms, but also encounter greater impairment regarding for instance general health and personal relationships. The life-time risk of a woman to undergo at least one operation for prolapse or urine incontinence is 11.1%. When considering all interventions, 29.2% are repeat procedures (Olsen 1997). This is not only very inconvenient for the patient, it also carries a large burden for society. In 1997 the direct annual costs of prolapse operations in the United States were \$1012 million (Subak 2001), a number that probably only has increased in recent years. Moreover this sum is presumably an underestimation, because the analysis did not include costs of evaluation, diagnostic tests, preoperative therapies, complications requiring readmission to the hospital or outpatient treatment, and indirect costs such as lost wages. Concluding it can be said that pelvic organ prolapse gives a high medical and social burden.

In order to take better preventative measurements and provide better treatment

options, it is of critical importance to know the underlying cause of prolapse. So far, a lot of risk factors are identified. For instance the number of vaginal births (Chiaffarino 1999, Rortveit 2007) maximal birth weight (Rortveit 2007), heavy physical work (Slieker-ten Hove 2009, constipation (Rortveit 2007) and race (Dietz 2003, Rortveit 2007) all seem to increase the risk of developing a pelvic organ prolapse later in life. However, different studies show conflicting results regarding these factors. Moreover, not all women with substantial risk factors develop POP, whereas other women with few to no risk factors develop POP at an early age. This makes an underlying susceptibility caused by a genetic component likely.

In recent years several studies have suggested a strong genetic component in the development of pelvic organ prolapse. The risk of a women to develop POP is significantly increased when her mother or sister has a history of prolapse, with OR varying from 1.7 to 3.2 (Slieker-ten Hove 2009, Chiaffarino 1999). However, a potential hereditary risk factor implies that male family members may also play a role in passing on the genetic factor. For this reason McLennan et al. (MacLennan 2008) involved both male and female relatives in their survey. As hernia is considered to have the same pathophysiology as female prolapse, they considered family history to be positive if at least one of the family members reported hernia or prolapse in their past medical history. They demonstrated that, even after adjustment for confounders such as vaginal delivery, the risk of developing POP was significantly higher in women with a positive family history (OR 1.4, CI 95% 1.2-1.8).

Jack et al. (Jack 2006) were the first to look at the inheritance pattern of prolapse within a family. They selected 10 families of patients with a grade III or IV prolapsed under the age of 55. Within these families they observed a dominant inheritance pattern with incomplete penetrance, through both maternal and paternal relatives. For sisters of these prolapse patients the relative risk to develop POP was five times that of the general population. The study suggested that inheritable, genetic variation can make women susceptible to prolapse. However no attempt was made to identify the underlying genetic mutation.

It is known that type III collagen is of special importance in tissue repair following mechanical stretch such as in delivery or POP. Several studies have indeed reported an increase in type III collagen in samples from vaginal and supportive tissue in women with POP . Type III collagen polymorphisms may result in a decrease in tissue repair and may lead to impaired tensile strength of ligaments and supportive tissues. These polymorphisms have been reported in various diseases in which an impaired tensile strength may be part of the molecular pathophysiology, including mitral valve prolapse and vascular aneurisms . Chen and co-workers have suggested that a COL3A1 polymorphism in exon 30 (rs1800255) was related to POP in Taiwanese women. Our research group recently confirmed this finding in a larger population of 202 Dutch POP patients and 102 parous controls. The homozygous nucleotide substitution in

exon 30 of gene encoding type III collagen (COL3A1 2209G>A) can be detected in 13.4% of patients with POP compared to 2.9% in woman without POP. The odds ratio for the presence of POP in a woman with this homozygous COL3A1 2209G>A polymorphism is 5.0 (95% confidence interval 1.4; 17.1). Hemizygous polymorphism does not correlate with the presence of POP.

We hypothesize that the COL3A1 2209G>A polymorphism is a inheritable genetic defect, responsible for the increased susceptibility to pelvic organ prolapse in women. To verify this hypothesis, we will have to investigate the family members of patients with the above mentioned homozygous polymorphsim.

### **Study objective**

Genetic analysis of the familial inheritance pattern of the COL3A1 2209G>A polymorphism.

### **Study design**

Cohort study

### **Study burden and risks**

Vena puncture

POP-Q (= gynecologic investigation to determine the degree of pelvic organ prolapse) in female subjects.

Questionnaire regarding general and (in female subjects) obstetric history as well as prolapse symptoms.

The whole investigation can take place in one out patient department visit en will take approximately 45 minutes.

Burden: some patients might experience the gynecologic investigation as a burden. The investigation however, will be done by an experienced doctor en will take only one or two minutes. Since there is only one (international acknowledged) standardised method to evaluate pelvic organ prolapse, there is no alternative for this investigation.

Risks: none.

## **Contacts**

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

First and second degree relatives of patients with COL3A1 2209G>A polymorphism

### Exclusion criteria

-Genetic diseases with a known increased risk of POP (such as Ehlers Danlos, Marfan and Steinert\*s disease)

-Problems with regards to the patient\*s understanding of the study

## Study design

### Design

Study type: Observational invasive

Intervention model: Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

## Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	22-06-2009
Enrollment:	50
Type:	Actual

## Medical products/devices used

Registration:	No
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## Ethics review

Approved WMO	
Date:	16-06-2009
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

### Register

CCMO

### ID

NL26578.091.09