

O-116 Genetic association analyses identify links between pelvic prolapse (PP) and connective tissue biology, cardiovascular and reproductive health.

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Study question: Can genome-wide association analysis unravel the biological underpinnings of PP and facilitate personalized risk assessment via genetic risk scores construction?

Summary answer: We unravel novel links with urogenital development and vascular health in PP and present polygenic risk score as a tool to stratify PP risk.

What is known already: Prolapse is characterized by a descent of the pelvic organs into the vaginal cavity. PP affects around 40% of women after menopause and is the main indication for major gynecological surgery, having an important health, social and economic burden. Although the etiology and biological mechanisms underlying PP remain poorly understood, prior studies suggest genetic factors might play a role. Recently, a genome-wide association study (GWAS) identified seven genome-wide significant loci, located in or near genes involved in connective tissue metabolism and estrogen exposure in the etiology of PP.

Study design, size, duration: We conducted a three-stage case-control genome-wide association study. Firstly, in the discovery phase, we meta-analyzed Icelandic, UK Biobank and the FinnGen R3 datasets, comprising a total of 20118 cases and 427426 controls of European ancestry. For replication we used an independent dataset from Estonian Biobank (7968 cases and 118895 controls). Finally, we conducted a joint meta-analysis, containing 28086 cases and 546321 controls, which is the largest GWAS of PP to date.

Participants/materials, setting, methods: We performed functional annotation on genetic variants unraveled by GWAS and integrated these with expression quantitative trait loci and chromatin interaction data. In addition, we looked at enrichment of association signal on gene-set, tissue and cell type level and analyzed associations with other phenotypes both on genetic and phenotypic level. Colocalisation analyses were conducted to help pinpoint causal genes. We further constructed polygenic risk scores to explore options for personalized risk assessment and prevention.

Main results and the role of chance: In the discovery phase, we identified 18 genetic loci and 20 genetic variants significantly associated with POP ($p < 5 \times 10^{-8}$) and 75% of the variants show nominal significance association ($p < 0.05$) in the replication. Notably, the joint meta-analyses detected 20 genetic loci significantly associated with POP, from which 13 loci were novel. Novel genetic variants are located in or near genes involved in gestational duration and preterm birth (rs2687728 $p = 2.19 \times 10^{-9}$, *EEFSEC*), cardiovascular health and pregnancy success (rs1247943 $p = 5.83 \times 10^{-18}$, *KLF13*), endometriosis (rs12325192 $p = 3.72 \times 10^{-18}$, *CRISPLD2*), urogenital tract development (rs7126322, $p = 4.35 \times 10^{-15}$, *WT1* and rs42400, $p = 4.8 \times 10^{-10}$, *ADAMTS16*) and regulation of the oxytocin receptor (rs2267372, $p = 4.49 \times 10^{-13}$, *MAFF*). Further analyses demonstrated that POP GWAS signals colocalise with several eQTLs (including *EEFSEC*, *MAFF*, *KLF13*, etc.), providing further evidence for mapping associated genes. Tissue and cell enrichment analyses underlined the role of the urogenital system, muscle cells, myocytes and adipocytes ($p < 0.00001$, $FDR < 0.05$). Furthermore, genetic correlation analyses supported a shared genetic background with gastrointestinal disorders, joint and musculoskeletal disorders and cardiovascular disease. Polygenic risk scores analyses included a total of 125551 people in the target dataset, with 5379 prevalent patients and 2517 incident patients. Analyzing the best GRS as a quintile showed association with incident disease (Harrell c-statistic = 0.603, $SD = 0.006$).

Limitations, reasons for caution: This GWAS meta-analyses focused on European ancestry populations, which challenges the generalizability of GWAS findings to non-European populations. Moreover, this study included women with PP from population-based biobanks identified using the ICD-10 code N81, which limits analyses considering different disease stages and severity.

Wider implications of the findings: Our study provides genetic evidence to improve the current understanding of PP pathogenesis and serves as basis for further functional studies. Moreover, we provide a genetic tool for

personalized risk stratification, which could help prevent PP development and improve the quality of a vast quantity of women.

Trial registration number: not applicable