Systematic review and meta-analysis of genetic association studies of pelvic organ prolapse

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Received: 6 January 2021 / Accepted: 24 March 2021 / Published online: 24 April 2021 © The Author(s) 2021

Abstract

Introduction and hypothesis Family and twin studies demonstrate that pelvic organ prolapse (POP) is heritable, but the genetic etiology is poorly understood. This review aimed to identify genetic loci and specific polymorphisms associated with POP, while assessing the strength, consistency, and risk of bias among reported associations.

Methods Updating an earlier systematic review, PubMed and HuGE Navigator as well as relevant conference abstracts were searched using genetic and phenotype keywords from 2015 to 2020. Screening and data extraction were performed in duplicate. Fixed and random effects meta-analyses were conducted using co-dominant models of inheritance. We assessed credibility of pooled associations using interim Venice criteria.

Results We screened 504 new abstracts and included 46 published and 7 unpublished studies. In pooled analyses we found significant associations for four polymorphisms: rs2228480 at the ESR1 gene (OR 0.67 95% CI 0.46–0.98, I² = 0.0%, Venice rating BAB), rs12589592 at the FBLN5 gene (OR 1.46 95% CI 1.11–1.82, I² = 36.3%, Venice rating BBB), rs484389 in the PGR gene (OR 0.61 95% CI 0.39–0.96, I² = 32.4%, Venice rating CBB), and rs1800012 at the COL1A1 gene (OR 0.80 95% CI 0.66–0.96, I² = 0.0%, Venice rating BAB). Further credible novel variants have also been recently identified in genome-wide association studies.

Conclusion The genetic contributions to POP remain poorly understood. Several biologically plausible variants have been identified, but much work is required to establish the role of these genes in the pathogenesis of POP or to establish a role for genetic testing in clinical practice.

Keywords Genetics · Prolapse · Meta-analysis

Presentation Information Presented at the International Urogynecological Association Virtual 45th Annual Scientific Meeting, August 30–September 4, 2020.

Introduction

The existence of inherited risk factors for pelvic floor disorders has been recognized for > 150 years [1], and multiple studies have confirmed familial aggregation of pelvic organ prolapse (POP). Three large meta-analyses demonstrated a significant impact of family history on the development of or recurrence of POP with odds ratios ranging between 1.84 to 2.64 [2–4] with an affected first-degree relative (mother or sister). Large population database studies have shown similar results. In a Swedish registry including data for 61,323 women with a history of POP surgery, the relative risk of prolapse surgery was found to be 6.58 (95% CI 6.32–6.86) for their sisters and 2.56 (2.41–2.73) for their mothers [5]. These results were further clarified in a population-based study in the USA involving 453,522 total women and 4628 women with a history of POP surgery that found that risk increased with increasing numbers of affected relatives, from RR of 2.36 (95% CI 2.15–2.58) for ≥ 1 affected first-degree relative to RR 6.26 with ≥ 3 first-degree
Eligibility criteria and including all prolapse studies from that work [6]. Having ≥ 3 affected third-degree relatives (first cousins) carried a similar risk to having one affected first-degree relative. A relevant family history is also associated with earlier onset disease [7]. Maternal inheritance of POP has been found to be a more significant contributor to the development of POP, but paternal inheritance also contributes to risk [6, 7].

Family studies, particularly those involving nuclear family members, provide limited information on heritability, as they do not control for shared exposure to environmental risk factors. Twin studies have been used to formally quantify the heritability of prolapse. In a sample of 16,886 Swedish twins aged > 50 years, heritability was estimated as 43% for prolapse surgery [8], suggesting prolapse is of similar heritability to other pelvic floor disorders including urinary incontinence.

Given the strong heritability findings, genetic studies are justified to find POP predisposition variants. Early linkage studies identified target regions that have prompted multiple follow-up candidate gene studies. The first linkage analysis investigated a single three-generation Filipino pedigree with six affected women with early-onset POP, and they identified the candidate gene \textit{LAMC1} under their 1q31 linkage peak [9]. Two additional linkage studies involving women of European descent identified the chromosome 9q21, 10q24–26 (includes candidate gene \textit{LOXL4}), and the 17q25 (includes candidate gene \textit{TIMP2}) regions as showing significant evidence of linkage [10, 11]. A follow-up study involving Russian women with POP identified a significant haplotype association in the 9q21 region with results driven primarily by SNP rs12237333 [12]. These linkage analyses have been followed by multiple candidate gene studies and recently genome-wide association studies (GWAS) that are the main focus for this systematic review.

**Objective**

Identification of the genetic variants underlying the heritability of POP would provide useful markers for clinical risk, prognosis, and treatment response. In addition, these insights should help explain the pathogenesis of POP, potentially offering new drug targets and preventative strategies. The aim of this systematic review was therefore to assess which polymorphisms and/or genetic loci have been tested for an association with pelvic organ prolapse in women, while assessing the strength, consistency, and potential for bias, among published associations.

**Materials and methods**

**Eligibility criteria**

This review updates an earlier review using the same eligibility criteria and including all prolapse studies from that work [13]. The protocol for the earlier work was prospectively registered (PROSPERO 2011:CRD42012001983), and we made no changes to the methods [14]. We pre-specified inclusion of both case-control and cross-sectional designs, with both population-based samples and other sampling methods. We included association studies testing for any genetic polymorphism at the nucleotide level, including SNPs, deletions, duplications, and copy-number variants, but excluded larger microscopic variants at the karyotype level.

There are no gold standard diagnostic methods. For pelvic organ prolapse, validated staging systems, including POP-Q, have been widely used, but again there is no universally accepted criterion for diagnosis. We therefore expected to accept diagnostic criteria for prolapse as specified within each study. In view of heterogeneity in definitions across studies, we tested for heterogeneity between studies with different criteria in different settings. We accepted definitions based on symptom questionnaires, clinical examination, or other validated assessments. We considered the population of interest as women aged ≥ 18 years.

**Search strategy**

We updated the earlier systematic review, using an identical search strategy [13]. We combined searches from PubMed, HuGE Navigator, and an extensive selection of genetic, urological, and urogynaecological conference reports. In this update we searched PubMed from January 1, 2015, to November 1, 2020, using a combination of genetic and phenotype keywords and MeSH terms:

(polymorphism OR SNP OR CNV OR "copy number variation" OR mutation OR genetic OR chromosome OR VNTR OR InDel OR microsatellite) AND (prolapse OR "Pelvic Organ Prolapse"[MeSH]) NOT mitral NOT carcinoma [Title] NOT cancer [Title] NOT (animals[mh] NOT humans[mh])

In this update we searched HuGE Navigator, also from January 1, 2015, to November 1, 2020, using the phenotype indexing term “pelvic organ prolapse.”

In addition, we searched conference abstracts for annual meetings of the American Society of Human Genetics, American Urological Association, American Urogynecologic Society, European Association of Urology, European Society of Human Genetics, International Continence Society, International Urogynecological Association, and Society of Gynecologic Surgeons 2005–2020.

**Screening and data extraction**

We developed standardized data forms for this study and conducted pilot screening and data extraction training exercises to
achieve a high level of consensus between reviewers. All screening and data extraction were then performed independently and in duplicate by methodologically trained reviewers. Reviewers screened study reports by first screening titles and abstracts to select papers for full-text assessment and then screening full-text papers to confirm eligibility of the articles. Screening discrepancies were resolved by adjudication. We hand searched reference lists of all included articles, applying the same standardized screening process. When more than one report was identified for the same association in the same study population, we included the publication with the largest sample size.

We contacted study authors by email, with a reminder after 1 month, for clarifications, additional information about methodology, and additional subgroup analyses where necessary. Data extracted included information on the setting for each study, details of the sampling strategy and sampled populations (age, parity, ethnic/racial composition, and BMI), the overall sample size and proportion genotyped, the outcome assessments used and phenotypic definitions, the genotyping method employed, and the genotyping quality control applied. Where possible we extracted or requested from authors full genotype frequencies among both cases and controls.

**Statistical analysis and risk of bias assessments**

For polymorphisms assessed in ≥ 2 studies for the same phenotype and evaluated with similar case definitions, we conducted fixed or random effects meta-analyses as appropriate using the Metan package (Stata 12.1). In situations where a proxy SNP had been selected for genotyping in one or more studies, high linkage disequilibrium (defined as $D' \geq 0.8$) with another SNP of interest, these SNPs were considered as being equivalent for meta-analysis purposes; results are reported based on the original significant SNP identifier. Linkage disequilibrium was assessed between pairs of SNPs using the LDpair tool [15, 16] and an appropriate racially and ethnically matched population (e.g., Utah residents from North and West Europe [CEU] for Caucasian European populations). In all cases we worked from genotype or allele frequencies rather than using precalculated effect sizes. In the absence of a clear rationale supporting any specific model of inheritance, we used the allelic association test and co-dominant models of inheritance for all polymorphisms. We assessed the credibility of pooled associations using the interim Venice criteria [17] (see Table 1). We used the $I^2$ statistic as a measure of between study heterogeneity. We recalculated the power of each study and retested for departure from Hardy-Weinberg equilibrium. We made assessments of risk of bias in phenotype definitions, genotyping, and population stratification. We used the Hartord test of funnel plot asymmetry and the significance chasing bias test [18] to investigate possible reporting biases. Throughout these assessments we used $p < 0.05$ as the criterion for significance, except in relation to GWAS, where $p < 5 \times 10^{-8}$ is accepted as the criterion for significance. Reporting of this review complies with recommendations of both the HuGE Handbook and the PRISMA statement.

**Narrative summaries**

For completeness of this review, we additionally provide summaries of the four genome-wide association studies (GWAS) reported to date. Where possible, significant GWAS findings have been included in meta-analyses. However suggestive and non-significant GWAS findings are typically not reported; hence, we are unable to include most null findings from GWAS in the meta-analyses.

**Results**

**Included studies**

We screened 504 new abstracts for this review (Fig. 1), eventually including 46 published and 7 unpublished studies, of which 20 had been previously included in the review we updated [13]. A large majority of studies had enrolled either women of European or East Asian descent, with limited representation of other ethnicities.

**Meta-analyses**

We conducted 24 separate meta-analyses for variants in or near 16 different genes or genetic loci. Four of these 12 genes had significant findings in pooled analyses: rs2228480 in the $ESR1$ gene, rs12589592 in the $FBLN5$ gene, rs484389 in the $PGR$ gene, and rs1800012 in the $COL1A1$ gene (Figs. 2, 3, 4, and 5).

**ESR1 gene**

$ESR1$ is an estrogen receptor gene, which was identified as relevant in candidate gene studies because of the epidemiological association between estrogen status and prolapse. Two studies from Taiwan and China assessed the same three variants (rs17847075, rs2228480, and rs2234693) and could be included in meta-analyses [19, 20]. In pooled analyses, rs2228480 showed a large protective effect with low heterogeneity (OR = 0.67, 95% CI: 0.46–0.98, $I^2 = 0.0\%$, Venice rating BAB). The risk variant is common in the populations assessed, and so despite the low total sample size ($n = 339$), this confers moderate epidemiological credibility.
FBLN5 gene

FBLN5 has been investigated as a candidate gene for prolapse as fibulins play a critical role in the assembly of elastic fibers, believed to provide strength and flexibility in the pelvic floor. Three studies from Brazil, Russia, and China assessed the same two variants (rs2018736 and rs12589592) of which two studies could be included in meta-analyses [19, 21, 22]. No significant

Table 1 Summary of interim Venice guideline ratings of credibility of genetic associations

| Criteria                       | Categories                                                                 |
|--------------------------------|---------------------------------------------------------------------------|
| Amount of evidence             | A: Large-scale evidence ($n>1000$ with risk allele)                        |
|                                | B: Moderate amount of evidence ($n = 100–1000$)                           |
|                                | C: Little evidence ($n<100$)                                              |
| Replication                    | A: Extensive replication including at least one well-conducted meta-analysis with little between-study inconsistency ($I^2 <25\%$) |
|                                | B: Well-conducted meta-analysis with some methodological limitations or moderate between-study inconsistency ($I^2 25\%–50\%$) |
|                                | C: No association; no independent replication; failed replication; scattered studies; flawed meta-analysis or large inconsistency ($I^2 >50\%$) |
| Protection from bias           | A: Bias, if at all present, could affect the magnitude but probably not the presence of the association |
|                                | B: No obvious bias that may affect the presence of the association but there is considerable missing information on the generation of evidence |
|                                | C: Considerable potential for or demonstrable bias that can affect even the presence or absence of the association |

Strong credibility for an association requires an AAA rating. Any B rating confers maximum moderate credibility, while any C rating confers weak credibility. Abridged from Table 4 in Ioannidis et al. [18]

Figs. 1 Flowchart outlining the literature search and article evaluation process. a ASHG, ESHG, ICS, IUGA, AUA, SGS, AUGS, and EAU abstracts 2005–2020 using search interfaces at http://www.ics.org/publications/abstracts, http://www.sciencedirect.com/science/journal/15699056, http://www.jurology.com/supplements, http://www.asgh.org/meetings/meetings_abstract_search.shtml, and/or full text search of abstract book PDFs. b Includes reviews ($n = 2$), inapplicable phenotypes ($n = 3$), and other study designs including pharmacogenetic studies, gene expression studies, or methylation studies ($n = 33$)
**Fig. 2** Forest plot of meta-analysis of studies of the rs2228480 SNP in the gene *ESR1*

**Fig. 3** Forest plot of meta-analysis of studies of the rs12589592 SNP in the gene *FBLN5*
**Fig. 4** Forest plot of meta-analysis of studies of the rs484389 SNP in the gene *PGR*

**Fig. 5** Forest plot of meta-analysis of studies of the rs1800012 SNP in the gene *COL1A1*
| First author | Journal & year | Country | Descent/ethnicity/racea | Gene symbols(s) | Polymorphism(s) dbSNP ID | Case definition | Control definition | n Cases genotyped | n Controls genotyped |
|--------------|----------------|---------|-------------------------|-----------------|--------------------------|----------------|-------------------|-------------------|---------------------|
| Abulaizi [19] | Int Urogynecol J 2020 | China | Mixed Chinese | ESR1, ESRB, ZFAT, FBLN5, PGR, COL3A1, MMP9, LAMC1 | rs17847075, rs2234693, rs2228480, rs1271572, rs2987983, rs1256049, rs484389, rs500760, rs1800255, rs391253, rs17576, rs1036819, rs10911193, rs20563, rs2018736, rs12589592, rs1455311, rs1036819, rs430794, rs8027714, rs1810636, rs2236479, rs1800255 | POP ≥ stage 3 | POP stage 0 or 1 | 88 | 108 |
| Allen-Brady [29] | Obstet Gynecol 2011 | USA, Netherlands | White and Northern European descent | LINC0108, ZFAT, Intergenic, Intergenic, Intergenic, COL18A1, COL3A1 | rs1455311, rs1036819, rs430794, rs8027714, rs1810636, rs2236479, rs1800255 | Surgically treated/recurrent POP with family history | Illumina iControlDB and HapMap Utah population controls | 191 | 3036 |
| Ashikari [37] | Neurourology 2019 (ICS abstract) | Japan | Japanese | COL3A1 | rs1800255 | POP ≥ stage 3 | POP stage 0 or 1 | 40 | 17 |
| Campeau [38] | Neurourology 2011 (ICS Abstract) | USA | Not stated | MMP1 | rs1144393, rs498186, rs473509 | Surgically treated POP | Hospital controls “without POP” | 63 | 93 |
| Batista [39] | Eur J Obstet Gynecol 2020 | Brazil | Brazilian | COL1A1, COL3A1, LINC0108, ZFAT, Intergenic, Intergenic, Intergenic, COL18A1, COL3A1 | rs1800012, rs1800025, rs6852257, rs1036819, rs4436246, rs77662161, rs6051098, rs72794445 | POP ≥ stage 3 | POP stage 0 or 1 | 348 | 286 |
| Bizjak [31] | Int Urogynecol J 2008 | Taiwan | Taiwanese | ESRI | rs10911193, rs20563, rs20558, rs17847075, rs2207647, rs2234693, rs3798577, rs2228480 | POPQ ≥ 2 | POPQ < 2 | 88 | 153 |
| First author | Journal & year | Country | Descent/ethnicity/racea | Gene symbols(s) | Polymorphism(s) dbSNP ID | Case definition | Control definition | n Cases genotyped | n Controls genotyped |
|--------------|----------------|---------|-------------------------|----------------|--------------------------|----------------|-------------------|-------------------|-------------------|
| Chen [41]    | Int J Clin Exp Pathol 2015 | China  | Han Chinese            | RAGE           | rs184003 rs55640627       | POP ≥ stage 3 | POP stage 0 or 1  | 24                | 25                |
| Chen [23]    | Acta Obs Gyn 2009 | Taiwan | Taiwanese               | PGR            | rs500760 rs484389         | POPQ≥2         | POPQ<2            | 87                | 150               |
| Chen [42]    | Int Urogynecol J 2008 | Taiwan | Taiwanese               | COL3a1         | rs1800255 rs1801184      | POPQ≥2         | POPQ<2            | 84                | 147               |
| Chen [43]    | Eur J Obs Gyn 2010 | Taiwan | Taiwanese               | MMP9           | rs3918242 rs17576 rs2250889 | POPQ≥2         | POPQ<2            | 92                | 152               |
| Chen [44]    | Eur J Obs Gyn 2008 | Taiwan | Taiwanese               | ESR2           | rs2987983 rs1271572 rs944459 rs1256049 rs1255998 | POPQ≥2         | POPQ<2            | 69                | 141               |
| Chen [45]    | Hereditas 2020 | China  | Chinese                | LAMC1          | rs20558 rs20563 rs10911193 rs64244889 rs10911241 rs3768617 rs12073936 rs729819 rs10911214 rs669133 | POP stage III or IV | POP stage 0 or 1 | 161               | 235               |
| Cho [24]     | Yonsei Med J 2009 | Korea  | Korean                  | COL1A1         | rs1800012                | Surgically treated POPQ=0 | POPQ<3         | 15                | 15                |
| Choy [46]    | Neurol Urodyn 2007 (ICS Abstract) | Hong Kong | Chinese                | EDN1           | rs5370 rs10478694        | Hospital “normal” controls and HapMap Han Chinese controls | 60 (rs5370) and 67 (rs10478694) | 210               |
| de Paula [22] | Rev Assoc Med Bras 2020 | Brazil | Brazilian               | FBLN5          | rs12586948               | POP stage III or IV | POP stage 0 or 1 | 112               | 180               |
| dos Santos [32] | Int Urogynecol J 2018 | Brazil | Brazilian               | COL18A1        | rs2236479 rs2862296      | POP ≥ stage 3 | POP stage 0 or 1  | 285               | 247               |
| Feiner [25]  | Int Urogynecol J 2009 | Israel  | Caucasian or Ashkenazi-Jewish | LOXL4 COL1a | rs2862296 rs1800012      | POPQ≥2         | POPQ<2            | 36                | 36                |
| Ferrari [27] | Arch Gynecol Obstet 2012 | Italy  | Italian                 | COL1a MMP9 MMP1 MMP3 | rs1800012 rs3918242 rs1799750 rs3025058 | POPQ≥2         | POPQ<2            | 137               | 96                |
| First author | Journal & year | Country | Descent/ethnicity/racea | Gene symbols(s) | Polymorphism(s) dbSNP ID | Case definition | Control definition | n Cases genotyped | n Controls genotyped |
|--------------|----------------|---------|-------------------------|-----------------|--------------------------|----------------|--------------------|-----------------|-------------------|
| Ferrell [47] | Reprod Sci 2009 | USA     | African American or Caucasian | LLOXL1          | rs16958477                | POP ≥ stage II | POP < stage II     | 137             | 130               |
| Fu [48]      | J Urol 2009 (AUA Abstract) | USA | Not stated | LAMC1/LLOXL1 | rs10911193              | POP ≥ stage III | No POP or UI      | 61              | 33                |
| Giri [36]    | PLOS ONE 2015 | USA     | African American and Hispanic | ABCA1/FHAD1/ANKS4B/MAML2/MMP9 | rs7035589 | POP ≥ stage I | POP stage 0 | 1399 | 1253 |
| Gnersel [49] | Rev Bras Ginecol Obstet 2019 | Brazil | Brazilian | Brazilian |                          | POP ≥ stage III | POP stage 0 or 1 | 1399 | 1253 |
| Jeon [50]    | J Urol 2009 | Korea   | Korean | COL3a1 | rs111929073              | POPQ≥2 | POPQ<2 and no USI | 36              | 36                |
| Karachalios [51] | Biomed Rep 2016 | Greece | White | MMP3 | rs3025058 | POPQ≥2 | POPQ<2 | 80 | 80 |
| Kasyan [52]  | Urologia 2017 | Russia  | White | COL3A1 | rs1800255 | POP and UI | No PFD | 52 | 21 |
| Khadzhieva [21] | Maturitas 2014 | Russia | White | FBLN5 | rs2430339 | POP ≥ stage III | POP stage 0 | 210 | 292 |
| Khadzhieva [53] | Genetika 2015 | Russia | White | FBLN3/LLOXL1 | rs2165241 | POP ≥ stage III | POP stage 0 | 210 | 292 |
| Khadzhieva [12] | Biomed Res Int 2015 | Russia | White | LINC01088/ZFAT/COL18A1/TLE4/TLE1/LNC10723989/FRMD3/COL18A1 | rs1455311 | POP ≥ stage III | POP stage 0 | 210 | 292 |
| First author          | Journal & year            | Country     | Descent/ethnicity/race | Gene symbols(s) | Polymorphism(s) dbSNP ID | Case definition | Control definition | n Cases genotyped | n Controls genotyped |
|----------------------|---------------------------|-------------|------------------------|-----------------|--------------------------|----------------|-------------------|-------------------|--------------------|
| Kieserman-Shmokler   | Int Urogynaec J 2019      | USA         | European               | NPAP1, GDF7, SALL1, GSTM1, GSTT1, GSTP1 | rs1810636, rs2236479, rs8027714, rs1325192, rs93086894 | POPQ ≥ 3      | POPQ < 2         | 189               | 156                |
| Kim [54]             | Euro J Obstet Gynecol Repro Biol 2014 | Korea      | Korean                  | Null            | Null                     | rs1136410       | POPQ ≥ 3         | 185               | 155                |
| Kim [55]             | Menopause 2014            | Korea       | Korean                  | PARP1           | rs4870723, rs2305600, rs2305598, rs2305603, rs3827852, rs45348, rs764225569, rs388222, rs2231068, rs7491798, rs2586488 | POP ≥ stage 3 | POP stage 0     | 48                | 48                 |
| Li [33]              | Menopause 2020            | China       | Chinese                | COL14A1, COL5A1, COL4A2, COL3A1, COL1A1, COL18A1 | rs4870723, rs2305600, rs2305598, rs2305603, rs3827852, rs45348, rs764225569, rs388222, rs2231068, rs7491798, rs2586488 | POPQ ≥ 2      | POPQ < 2         | 272               | 82                 |
| Lince [56]           | Int Urogynaecol J 2014    | The Netherlands | ≈ 99% Dutch            | COL3a1          | rs111929073               | POPQ ≥ 3      | POPQ < 2         | 112               | 180                |
| Maeda [57]           | Euro J Obstet Gynecol Repro Biol 2019 | Brazil      | White or non-white     | MMP3            | rs3025058                 | POP ≥ stage 3 | POP stage 0 or 1 | 33                | 33                 |
| Martins [58]         | Neurourol Urodyn 2011     | Brazil      | White or non-white     | COL3a1          | rs10911193, rs2228480    | POP ≥ stage 3 | POP stage 0 or 1 | 33                | 33                 |
| Nakad [59]           | Taiwan J Obstet Gynecol 2017 | Taiwan     | Taiwanese              | ESRA, LAMC1     | rs1048661, rs3825942, rs78803776, rs41429348, rs41435250, rs369758147 | POP ≥ stage 3 | POP stage 0 or 1 | 48                | 18                 |
| Neupane [60]         | Female Pelvic Med Reconstr Surg 2014 | USA         | White                  | WNT4, GDF7, EFEMP1 | rs3820282, rs9306894, rs3791675 | POP ≥ stage 3 | POP stage 0 or 1 | 15,010            | 340,734            |
| Olafsdottir [34]     | Commun Biol 2020          | Iceland/UK | White                  | NPAP1, GDF7, SALL1, GSTM1, GSTT1, GSTP1 | rs1810636, rs2236479, rs8027714, rs1325192, rs93086894 | ICD 9/10 codes indicating POP | Unselected female population controls | 15,010            | 340,734            |
| First author | Journal & year | Country        | Descent/ethnicity/race | Gene symbols(s) | Polymorphism(s) dbSNP ID | Case definition | Control definition | n Cases genotyped | n Controls genotyped |
|--------------|----------------|----------------|------------------------|-----------------|--------------------------|----------------|-------------------|-----------------|-------------------|
| Palos [61]   | Int Urogynecol J 2020 | Brazil          | White or non-white     | **COL1a1**      | rs1107946                | POP ≥ stage 3  | POP stage 0 or 1  | 112             | 180               |
| Rao [62]     | PLOS ONE 2015    | China           | Han Chinese            | WNK1            |                          | POP ≥ stage III| Healthy post-menopausal POP < stage II and no SUI | 161             | 231               |
| Rodrigues [26]| Int Urogynecol J 2008 | Brazil          | White or non-white     | **COL1a1**      | rs1800012                | POP ≥ stage III|                  | 107             | 209               |
| Romero [63]  | J Pelv Med Surg 2008 | USA            | White                  | **MMP1**        | rs1801230                | POPQ ≥ 3       | POPQ<2 and no UI | 45              | 38                |
| Rosa [64]    | Rev Bras Ginecol Obstet 2019 | Brazil        | White or non-white     | **COLIA2**      | rs42524                  | POP ≥ stage 3  | POP stage 0 or 1  | 112             | 180               |
| Rusina [65]  | Neurol Urodyn 2014 (ICS Abstract) | Russia       | White                  | NAT2,GSTT1,GSTM1| rs1799929,rs1799931NullNull | POP ≥ stage I  | POP stage 0 and no UI | 63              | 89                |
| Skorupski [28]| Int Urogynecol J 2009 (IUGA abstract) | Poland        | Polish                 | **COL1a1**      | rs1800012                | POPQ ≥ 2       | POPQ<2 and no UI | 120             | 97                |
| Skorupski [66, 67]| Ginekol Polska 2010/Int Urogynecol J 2013 | Poland        | Polish                 | **MMP1, MMP3**  | rs1799750,rs3025058      | POPQ ≥ 2       | POPQ<2            | 132             | 133               |
| Teixeira [68] | Int Urogynecol J 2020 | Brazil          | White or non-white     | **COL3A1**      | rs1800255                | POP ≥ stage 3  | POP stage 0 or 1  | 112             | 180               |
| Vishwajit [69]| Neurol Urodyn     | USA            | Not stated              | **MMP1**        | rs1799750                | Unclear        | Unclear          | 40              | 15                |
| Wang [70]    | J Obstet Gynaecol Res. 2015 | China        | Chinese                | **MMP10**       | rs17435959,rs17293607    | Unclear        | Unclear          | 91              | 172               |
| Wu [71]      | USA             | Non-Hispanic white | LAMC1                  | rs10911193,rs1413390 | POPQ ≥ 3       | POPQ<2            | 239             | 197               |
pooled effect was observed for rs2018736, but a large effect was seen at rs12589592 with moderate heterogeneity (OR 1.43 95% CI 1.11–1.82, $I^2 = 36.3\%$, Venice rating BBB). The risk variant is common in the populations assessed, and so despite the low total sample size ($n = 568$), this confers moderate epidemiological credibility.

**PGR gene**

*PGR* has been investigated as a candidate gene for prolapse, as it codes for the progesterone receptor, and changes in serum progesterone cyclically, during pregnancy, and after menopause are all observed to have an influence on prolapse. Two studies from China each assessed the same two common polymorphisms and could be included in meta-analyses [19, 23]. No significant pooled effect was observed for rs500760, but a large effect was seen at rs484389 with moderate heterogeneity (OR = 0.61, 95% CI: 0.39–0.96, $I^2 = 32.4\%$, Venice rating CBB). The risk variant is common in the populations assessed, but the low total sample size ($n = 336$) confers weak epidemiological credibility.

**COL1A1 gene**

*COL1A1* has been investigated as a candidate gene for prolapse as it forms type 1 collagen, the most abundant human collagen. The rs1800012 was identified as a replicated locus in our earlier review, but we could now include six studies with a moderate protective effect with no heterogeneity (OR = 0.80, 95% CI: 0.66–0.96, $I^2 = 0.0\%$, Venice rating BAB) [24–28]. The risk variant is common in the populations assessed, and with a moderate sample size ($n = 1264$), this confers moderate epidemiological credibility.

**Other genes**

We conducted further meta-analyses for variants in *COL3A1* type 3 collagen (8 studies), *COL18A1* collagen type 18 (3 studies), *LAMC1* Laminin, gamma 1 (6 studies), *ZFAT* (3 studies), *MMP1* matrix metalloproteinase 1 (3 studies), *MMP3* matrix metalloproteinase 3 (4 studies), *MMP9* matrix metalloproteinase 9 (4 studies), *MMP10* matrix metalloproteinase 10 (2 studies), and four other variants identified from GWAS (rs1455311, rs430794, rs8027714, and rs1810636). None of these meta-analyses showed significant pooled effects. Results are summarized in Table 3. Many genes had been assessed in a single study only and as such require replication for credibility (Table 2).

**Narrative summary of GWASes**

The first GWAS for POP involved 115 surgically treated, related POP cases who were part of high-risk POP
pedigrees and 2976 population-based controls [29]. They identified six variants at chromosomal regions 4q21 (rs1455311), 8q24 (rs1036819), 9q22 (rs430794), 15q11 (rs8027714), 20p13 (rs1810636), and 21q22 (rs2236479). Five of these six SNPs have subsequently been identified as at risk of genotyping error on one or more Illumina arrays, which may have led to spurious association signals [30]. The original study observed nominally or trending towards significance for some variants in a Dutch validation cohort of 76 POP cases. Subsequent independent replication studies [31–33, 12, 34, 19, 35] have tested for association at some or all of these six SNPs, with rs1036819 close to ZFAT replicating in one study [19], rs8027714 on chromosome 15q11 replicating in another study [35], and rs1810636 on chromosome 20p13, demonstrating replication in another study [31], but with no overall significant replication for any SNP observed in our meta-analyses (see Table 3).

A further GWAS using African American and Hispanic women from the Women’s Health Initiative Hormone Therapy study [36] included 1427 cases with any diagnosis of POP (grades 1–3) and 317 cases diagnosed with moderate/severe POP (grades 2–3) and 1274 controls without POP (grade 0). Although they did not identify any variants meeting

Table 3 Summary of meta-analyses

| Gene symbols(s) | Polymorphism dbSNP ID | n studies | n participants | Pooled OR | 95% CI | p | I² |
|-----------------|----------------------|-----------|---------------|-----------|-------|---|----|
| ESR1            | rs17847075           | 2         | 340           | 0.90      | 0.55–1.47 | 0.68 | 51.6% |
| ESR1            | rs2228480            | 2         | 339           | 0.67      | 0.46–0.98 | 0.04 | 0.0%  |
| ESR1            | rs2234693            | 2         | 339           | 0.93      | 0.67–1.27 | 0.63 | 0.0%  |
| ZFAT            | rs1036819            | 3         | 804           | 0.78      | 0.42–1.12 | 0.15 | 45.7% |
| FBLN5           | rs2018736            | 2         | 543           | 0.97      | 0.46–2.06 | 0.94 | 82.4% |
| FBLN5           | rs12589592           | 2         | 568           | 1.46      | 1.11–1.82 | 0.005 | 36.3% |
| LINC01088       | rs1455311            | 2         | 699           | 1.01      | 0.77–1.34 | 0.93 | 75.2% |
| LOC100507103    | rs430794             | 2         | 704           | 1.21      | 0.95–1.54 | 0.12 | 0.0%  |
| NPAP1           | rs8027714            | 2         | 705           | 0.93      | 0.50–1.73 | 0.82 | 44.8% |
| LOC105372507    | rs1810636            | 2         | 698           | 1.03      | 0.82–1.29 | 0.82 | 75.8% |
| PGR             | rs2228480            | 2         | 336           | 0.61      | 0.39–0.96 | 0.003 | 32.4% |
| PGR             | rs500760             | 2         | 337           | 1.04      | 0.70–1.53 | 0.86 | 0.0%  |
| COL3A1          | rs18000255           | 7         | 1795          | 1.01      | 0.87–1.18 | 0.86 | 0.0%  |
| COL3A1          | rs111929073          | 2         | 385           | 0.99      | 0.81–1.21 | 0.93 | 0.0%  |
| MMP9            | rs3918278            | 4         | 1159          | 1.24      | 0.70–2.19 | 0.46 | 65.4% |
| MMP9            | rs175756             | 4         | 809           | 0.98      | 0.67–1.41 | 0.89 | 58.2% |
| LAMC1           | rs10911193           | 6         | 1830          | 1.08      | 0.89–1.33 | 0.43 | 0.0%  |
| LAMC1           | rs20563              | 2         | 1272          | 1.08      | 0.92–1.27 | 0.69 | 0.0%  |
| LAMC1           | rs20558              | 4         | 1179          | 1.15      | 0.97–1.35 | 0.11 | 0.0%  |
| COL18A1         | rs2236479            | 4         | 1112          | 1.01      | 0.81–1.90 | 0.93 | 32.2% |
| MMP1            | rs1799750            | 3         | 601           | 0.82      | 0.64–1.04 | 0.10 | 25.1% |
| COL1A1          | rs1800012            | 6         | 1264          | 0.80      | 0.66–0.96 | 0.02 | 0.0%  |
| MMP3            | rs3025058            | 4         | 925           | 0.96      | 0.79–1.15 | 0.67 | 0.0%  |
| MMP10           | rs17435959           | 2         | 305           | 2.42      | 0.55–10.8 | 0.25 | 37.1% |

Table 4 Interim Venice ratings of the credibility of replicated associations

| Gene symbols(s) | Polymorphism dbSNP ID | Pooled OR | 95% CI | I² | Venice rating | Overall credibility |
|-----------------|----------------------|-----------|-------|----|---------------|---------------------|
| ESR1            | rs2228480            | 0.67      | 0.46–0.98 | 0.0% | BAB           | Moderate            |
| FBLN5           | rs12589592           | 1.46      | 1.11–1.82 | 36.3% | BBB           | Moderate            |
| PGR             | rs484389             | 0.61      | 0.39–0.96 | 32.4% | CBB           | Weak                |
| COL1A1          | rs1800012            | 0.80      | 0.66–0.96 | 0.0% | BAB           | Moderate            |
genome-wide significance, they did identify a number of variants that met \( p < 10^{-6} \).

The largest POP meta-analysis of two GWA studies involved 3409 cases from Iceland and 131,444 controls and 11,601 cases and 209,288 controls from UK Biobank, all of which were of European ancestry [34]. POP cases were identified based on ICD 9/10 coding therefore representing women who had presented for care. They identified eight variants at seven loci meeting the genome-wide significance criterion in the meta-analysis with results driven mainly by UK Biobank data. The significant SNPs include rs3820282, rs9306894, rs7682992, rs127943, rs12325192, rs72624976, and rs1430191. None of the lead POP variants were coding or in high linkage disequilibrium (LD) with coding variants. We can consider them each as having moderate credibility (Venice rating ABB). This study did not replicate any variants identified by earlier GWASes [29, 36] Table 4.

Finally, a recently reported GWAS utilizing 1329 women with diagnosed and/or surgically treated prolapse and 16,383 hospital controls did not identify any variants meeting genome-wide significance [35]. However, testing associations from previous GWASes showed nominal replication for rs8027714 [29] and for rs9306894 [34].

Conclusions

Given current evidence supporting a genetic predisposition for pelvic organ prolapse, we have identified four variants through meta-analysis of candidate gene studies significantly associated with POP (rs2228480 in the ESR1 gene, rs12589592 in the FBLN5 gene, rs484389 in the PGR gene, and rs1800012 in the COL1A1 gene). In each meta-analysis we have at most moderate evidence in support of an association with POP. A much larger, recent prospective meta-analysis of two genome-wide association studies has identified eight variants significantly associated with POP [34], with recent evidence of replication for two of these variants in an independent population [35]. As the sizes of GWAS meta-analyses grow, further novel variants are likely to be identified providing novel insights into pathogenesis. Given the impact of pelvic floor disorders on women’s health, additional work needs to be done to provide further validation of POP predisposition variants in a variety of different populations to establish the role of these genes in the pathogenesis of prolapse and to establish a possible role for genetic testing in clinical practice that could improve patients’ outcomes and address the best treatment options.

Acknowledgements  The authors gratefully acknowledge the support of Prof. Jan Deprest, Prof. Maria Bortolini, and the members of the International Urogynaecology Consultation Pathophysiology Group for their help in bringing this project to fruition.

Declaration

Conflict of interest  None.

Ethical approval  Not required as systematic review.

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