Supplementary Table S1. Forty one candidate genes/molecules and two microRNAs (miRNAs) that are implicated in POP etiology through other evidence than our exome chip study, i.e., genetic association and/or mutation studies, miRNA/mRNA/protein expression studies and/or genetic animal model studies.

Gene/miRNA/molecule	Evidence for involvement in POP etiology	Level of evidence *
BMP1	BMP1 expression was significantly upregulated in the vaginal wall of patients with POP compared to healthy controls, and this difference was seen regardless of menopausal status[1].	+
CASP3	CASP3 expression was found to be significantly increased in the uterosacral ligaments (USLs) of women with POP compared to healthy controls[2].	+
CDH1	CDH1 expression was found to be significantly increased in vaginal cells of premenopausal women with POP compared to healthy controls[3].	+
COL1A1	A meta-analysis of genetic studies indicated that rs1800012 in *COL1A1* is associated with POP[4]; the expression of COL1A1 was found to be different in USLs and in the anterior vaginal wall of women with POP compared to healthy controls[5].	+++
COL3A1	While several individual studies reported associations of SNPs within this gene with POP[6,7], a meta-analysis could not replicate this[4]; the expression of COL3A1 was found to be different in the anterior vaginal wall of women with POP compared to healthy controls[5].	+++
COL18A1	A GWAS showed that rs2236479 in *COL18A1* was significantly associated with POP[8]	+
ECM1	In a case-control study, ECM1 gene expression was found to be upregulated in women with POP[9].	+
ELN	A decreased expression of ELN fibers in the anterior vaginal wall and USLs[5] of POP patients was reported; conversely, an increased ELN expression in the anterior vaginal wall of POP patients was also reported[10,11].	+++
ESR1	In a case-control study, rs2228480 in *ESR1* was found to be significantly associated with POP[12].	+
ESR2	A haplotype of five SNPs in *ESR2* is associated with POP[13]; ESR2 expression was found to be significantly decreased in women with POP compared to healthy controls[5,14].	+++

Supplementary Table 1 - continued.		
Gene/miRNA/molecule	**Evidence for involvement in POP etiology**	**Level of evidence ***
FBLN3	A GWAS showed that two SNPS in *FBLN3* (rs1430191, located 287 kb downstream and rs3791675, intronic) are associated at genome-wide significant level (P < 5,00E-08) with POP[15]. Female *Fbln3* knockout mice also show failure of pelvic organ support[16].	++
FBLN5 [a]	Two SNPS in *FBLN5* (rs2018736 and rs12589592) are significantly associated with POP[17]; a decreased expression of FBLN5 protein in the USLs, cardinal ligaments and in the pubocervical fascia[9] of patients with POP was reported, whereas an increased expression of FBLN5 mRNA in the USLs[5] and in the uterine cervix[11] of POP patients was found; female *Fbln5* knockout mice develop POP, which increases progressively with age and after delivery[18]. FBLN5 gene expression in USLs from women with POP increased with severity of POP[11].	+++
GSTP1	Ile105Val, a missense mutation in *GSTP1*, is a *protective* factor against advanced POP[19].	+
GPX1	GPX1 expression was found to be significantly decreased in the pelvic support structures of women with POP compared to healthy controls[5]. In a case-control study, GPX1 protein content and enzymatic activity was found to be downregulated in the cardinal ligaments of women with POP[20].	++
HIF1A	In a case-control study, fibroblasts from anterior vaginal wall tissues from postmenopausal women with POP had more HIF-1α expressed in the nucleus when compared to healthy controls[21].	+
HLA-DQA1	HLA-DQA1 expression was found to be significantly increased in the uterosacral and round ligaments of women with POP compared to healthy controls[5].	+
HLA-DQB1	HLA-DQB1 expression was found to be significantly increased in the uterosacral and round ligaments of women with POP compared to healthy controls[5].	+
ITGB1	ITGB1 expression in uterosacral ligaments from women with POP increased with disease severity[11].	+

Supplementary Table 1 - continued.		
Gene/miRNA/molecule	**Evidence for involvement in POP etiology**	**Level of evidence ***
LAMC1	A variant in the promoter region of *LAMC1* gene (rs10911193) has been associated with familial POP[22], but this is not the case for women with POP in the general population[23].	+
LOX	The promoter region of *LOX* was found to contain 66 methylated CG sites in women with POP versus only one methylated CG site in healthy controls, which indicates that methylation in the promoter region may specifically suppress LOX gene expression in women with POP[24]; the expression of LOX mRNA in the anterior vaginal wall and USLs[5] of POP patients was found to be significantly decreased; LOX expression was also found to be significantly decreased in vaginal cells of premenopausal women with POP compared to healthy controls[3].	+++
LOXL1	The expression of LOXL1 protein was found to be significantly decreased in the USLs, cardinal ligaments and anterior vaginal wall[5] of women with POP compared to healthy controls; a significantly decreased expression of LOXL1 mRNA in the anterior vaginal wall and USLs[5] of women with POP was reported; LOXL1 expression was also found to be significantly decreased in vaginal cells of premenopausal women with POP compared to healthy controls[3]; LOXL1 gene expression in USLs from women with POP increased with disease severity[11]; female *Loxl1*-deficient mice develop POP[25].	+++
miR-221	The expression of miR-221 was found to be significantly increased in the USLs of women with POP compared to healthy controls[5].	+
miR-222	The expression of miR-222 was found to be significantly increased in the USLs of women with POP compared to healthy controls[5].	+
MMP1	A SNP in *MMP1* was reported to be significantly associated with POP[26]. In addition, the combination of SNPS in *MMP1* and *MMP3* was found to be associated with POP, indicating genetic interaction - or epistasis - between *MMP1* and *MMP3*[27]; MMP1 expression was found to be significantly increased in the vaginal mucosa and USLs[5] of women with POP compared to healthy controls.	+++

Supplementary Table 1 - continued.		
Gene/miRNA/molecule	**Evidence for involvement in POP etiology**	**Level of evidence ***
MMP2	MMP2 expression was found to be significantly increased in the USLs and anterior vaginal wall[5] of women with POP compared to healthy controls; MMP2 was found to be differentially expressed in fibroblasts from the prolapsed site of women with POP[28]; MMP2 expression was also found to be significantly decreased in vaginal cells of premenopausal women with POP compared to healthy controls[3].	+++
MMP3	The combination of SNPS in *MMP1* and *MMP3* was found to be associated with POP, indicating genetic interaction - or epistasis - between *MMP1* and *MMP3*[27]; MMP3 expression was found to be significantly increased in the anterior vaginal wall of women with POP compared to healthy controls[5,12]; MMP3 expression was also found to be significantly increased in vaginal cells of premenopausal women with POP compared to healthy controls[3].	+++
MMP8	In a case-control study, MMP8 gene and protein expression were upregulated in vaginal tissue from women with severe POP (POP-Q ≥III) compared to women with mild POP (POP-Q=2)[5].	+
MMP9	In a case-control study, rs3918253 and rs3918256 in *MMP9* were found to be significantly associated with POP[29]; MMP9 expression was found to be significantly increased in the anterior vaginal wall of women with POP compared to healthy controls [5].	+++
NOP56	A GWAS showed that rs1810636, a SNP 16 kb downstream of NOP56, was significantly associated with POP[8].	+
PARP1	Val762Ala, a missense mutation in *PARP1*, is associated with a *decreased* risk of advanced POP[30].	+
PLAUR [b]	PLAUR expression was found to be significantly increased in the uterosacral and round ligaments of women with POP compared to healthy controls[5].	+
PR	In a case-control study, rs484389 in *PR* was found to be significantly associated with POP[31]; PR expression was found to be significantly decreased in the USLs of *post*menopausal women with POP while PR expression in the cardinal ligaments was reported to be significantly increased in *pre*menopausal women with POP[5].	+++

Supplementary Table 1 - continued.		
Gene/miRNA/molecule	**Evidence for involvement in POP etiology**	**Level of evidence ***
RAGE/AGE complex	Advanced Glycation End (AGE) products have been found to be increased in the vaginal-epithelial and muscularis tissues from pre-menopausal women with POP[32,33]. In vitro studies have shown that AGEs inhibit the proliferation of and decreases collagen I expression in human vaginal fibroblasts from women with POP through signaling involving the receptor of AGEs (RAGE)[34].	+++
SERPINA1	SERPINA1 mRNA was found to be significantly downregulated in vaginal tissue[5,35] and USLs[5] of women with POP compared to healthy controls.	+++
SMAD3	In a case control study, Smad-3 and phosphorylated Smad-3 were higher in the muscularis layer of vaginal tissues from premenopausal women with POP[33].	+
TBX5	A GWAS showed that rs1247943, a SNP that is located 118 kb downstream from *TBX5*, was associated with POP at genome-wide significant level [15].	+
TGFB1	In a case-control study, a significant negative correlation between POP-Q stage and the expression of TGFB1 in the pubocervical fascia was found[5]. In a second case-control study, a similar negative correlation between POP-Q stage and expression of TGFB1 in vaginal fibroblasts was reported[36].	++
TIMP1	In a case-control study, TIMP1 gene and protein expression were downregulated in vaginal tissue from women with severe POP (POP-Q ≥III) compared to women with mild POP (POP-Q=2) and to controls[5].	+
TIMP2	TIMP2 expression was found to be significantly decreased in the USLs of women with POP compared to healthy controls[5]; the expression of TIMP2 was also found to be different in vaginal cells of premenopausal women with POP compared to healthy controls[3].	+++
TNFSF10	The expression of TNFSF10 (other name: TRAIL) was found to be significantly increased in the uterosacral and round ligaments of women with POP compared to healthy controls[5].	+

Supplementary Table 1 - continued.		
Gene/miRNA/molecule	**Evidence for involvement in POP etiology**	**Level of evidence ***
VIM [c]	A case-control study found incresaed vimentin (VIM) in the cytoskeleton of cells from the vaginal wall and the USLs in women with POP[37].	+
WNK1	A whole exome sequencing study identified multiple mutations in *WNK1* in women with POP[38].	+
WNT4	A GWAS showed that rs3820282, an intronic SNP in *WNT4*, was associated at genome-wide significant level with POP[15].	+

Abbreviations: GWAS, genome-wide association study; POP, pelvic organ prolapse; POP-Q, Pelvic Organ Prolapse Quantification system; SNP(s), single nucleotide polymorphism(s); USLs, uterosacral ligaments.

***** The level of evidence for the involvement of each gene and/or its encoded protein in POP etiology is indicated as follows: '+', implicated in POP through a single genetic association/mutation study, miRNA/mRNA/protein expression study or genetic animal model study ; **'++'** implicated in POP through 2 independent genetic association/mutation studies, miRNA/mRNA/protein expression studies and/or genetic animal model studies ; '+++', implicated in POP through at least 3 independent genetic association/mutation studies, miRNA/mRNA/protein expression studies and/or genetic animal model studies.

Within our set of differentially expressed genes in an independent POP cohort (see Methods), the expression of three of the 40 additional genes from the landscape was different: the expression of *FBLN5* was downregulated (FC= -1,41 ; corrected P=8.56E-03) [a], the expression of *PLAUR* was upregulated (FC= 1,61 ; corrected P=2.25E-02) [b], and the expression of *VIM* was upregulated (FC= 1,20 ; corrected P=3.59E-02) [c].

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