Supplemental information

A multi-level investigation of the genetic

relationship between endometriosis

and ovarian cancer histotypes

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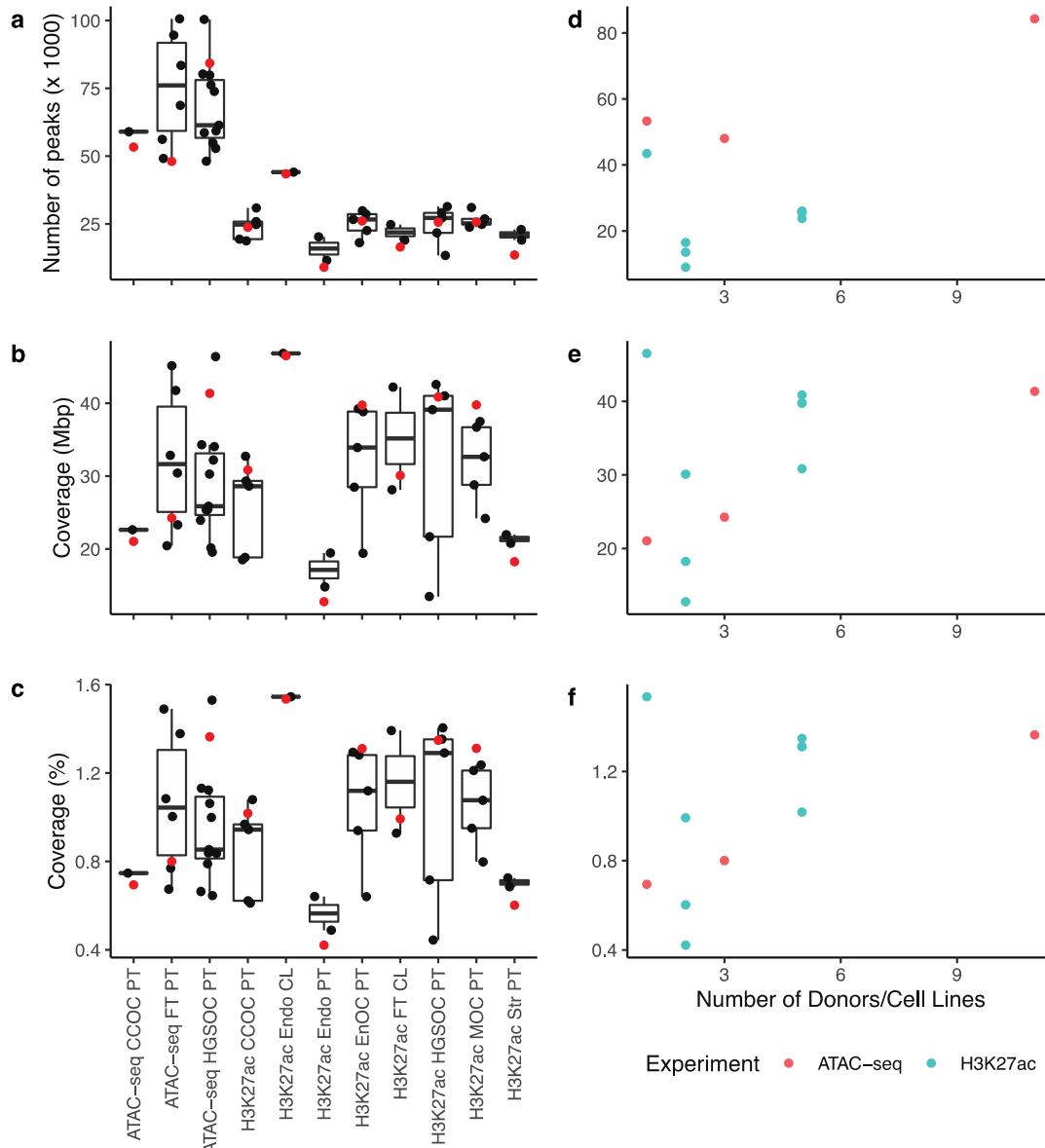
Figure S1. ATAC-seq and H3K27ac ChIP-seq coverage and peaks. (a) Number of peaks and (b) genome coverage in Mbp and (c) genome coverage in percentage for sample peak sets (black dots) and consensus peak sets (red dots). (d) Number of peaks (e) and genome coverage in Mbp and (g) genome coverage in percentage for consensus peak sets as a function of the number of donors. Endo, endometriosis; FT, fallopian tube; Str, endometriosis-associated stroma; CCOC, clear cell ovarian cancer; EnOC, endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; MOC, mucinous ovarian cancer. Data for both primary tissues (PT) and cell lines (CL) is shown. Related to STAR Methods and Table S5.
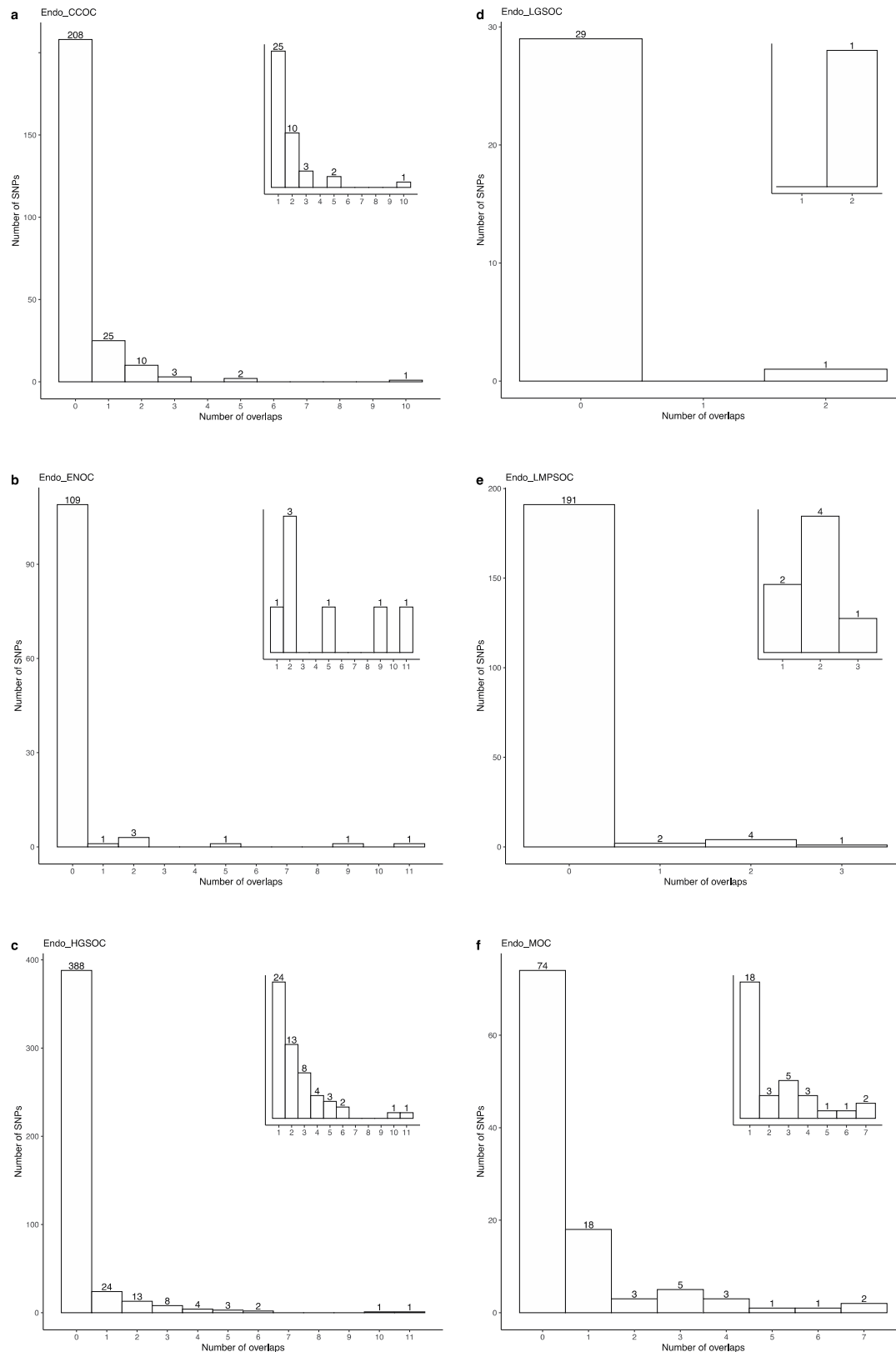
Figure S2. Associated SNPs overlap biofeatures. Histogram of number of SNPs associated with endometriosis and (a) clear cell ovarian cancer (CCOC), (b) endometrioid ovarian cancer (ENOC), (c) high-grade serous ovarian cancer (HGSOC), (d) Low-grade serous ovarian cancer (LGSOC), (e) low malignant potential serous ovarian cancer (LMPSOC) and (f) mucinous ovarian cancer (MOC), that overlap *n* biofeatures. Inset histograms show the number of overlaps ≥ 1. Related to Figure 1 and Table S7.
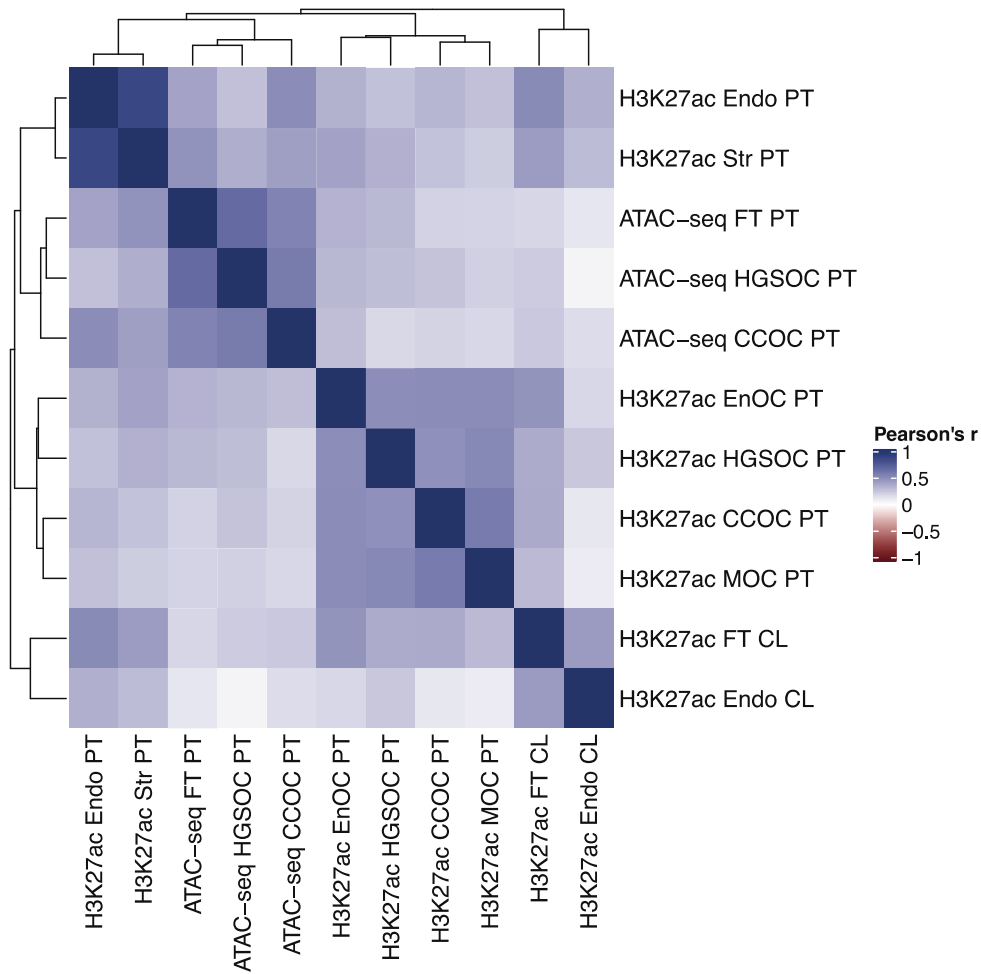
Figure S3. Correlation between biofeature overlap. Pearson's correlation coefficient between ATAC-seq and H3K27ac ChiP-seq biofeatures based on the overlap with SNPs associated with both endometriosis and ovarian cancer risk. Endo, endometriosis; FT, fallopian tube; Str, endometriosis-associated stroma; CCOC, clear cell ovarian cancer; EnOC, endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; MOC, mucinous ovarian cancer. Data for both primary tissues (PT) and cell lines (CL) is shown. Related to Figure 1 and Table S5.
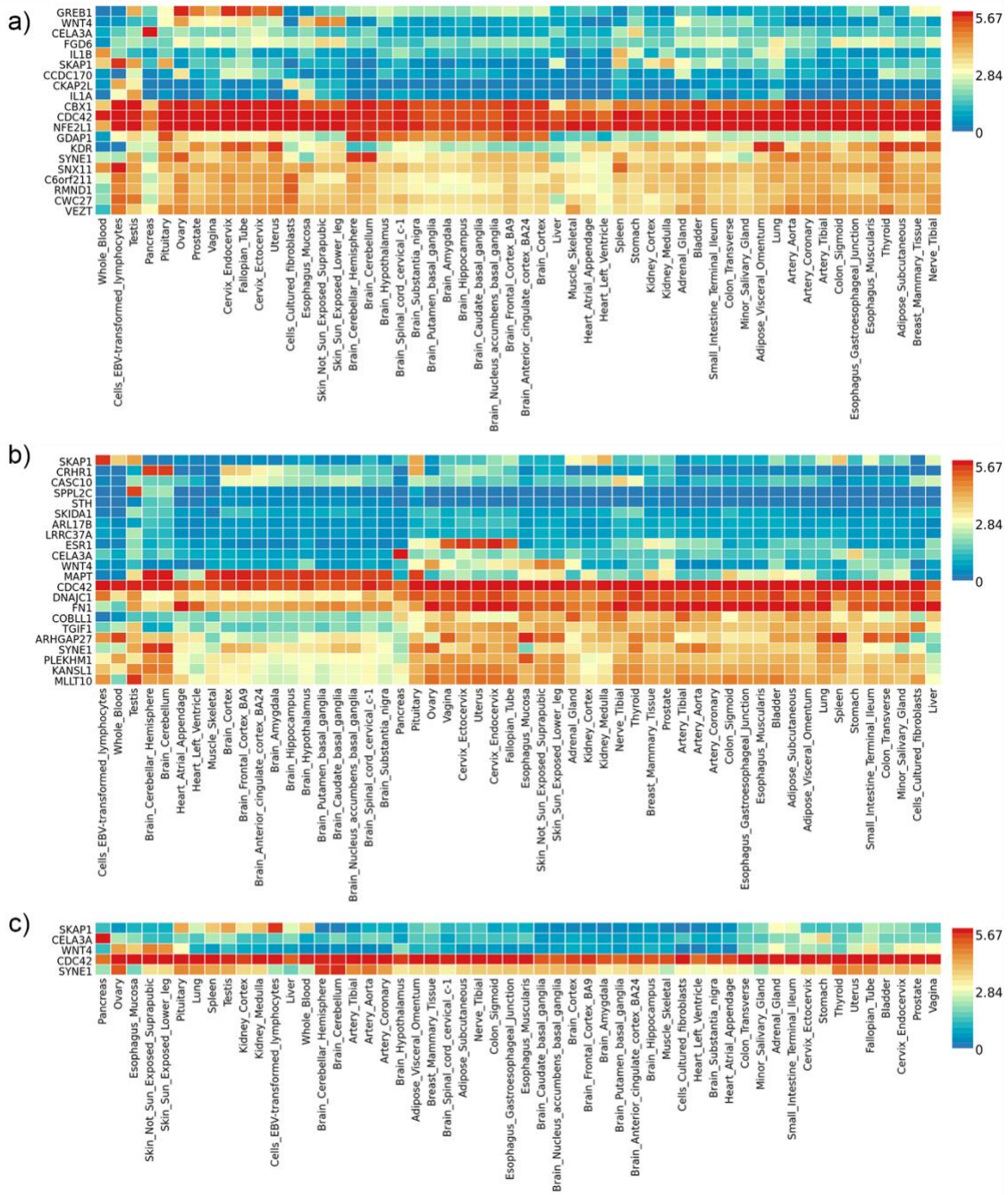
Figure S4. Expression of genes annotated to associated regions. Heatmap, generated in FUMA, of genes annotated to SNPs significantly associated with endometriosis plus (a) clear cell ovarian cancer, (b) high-grade serous ovarian cancer and (c) all three, expressed across 58 tissues from GTEx. Related to Tables 3 and 4 and Table S8.

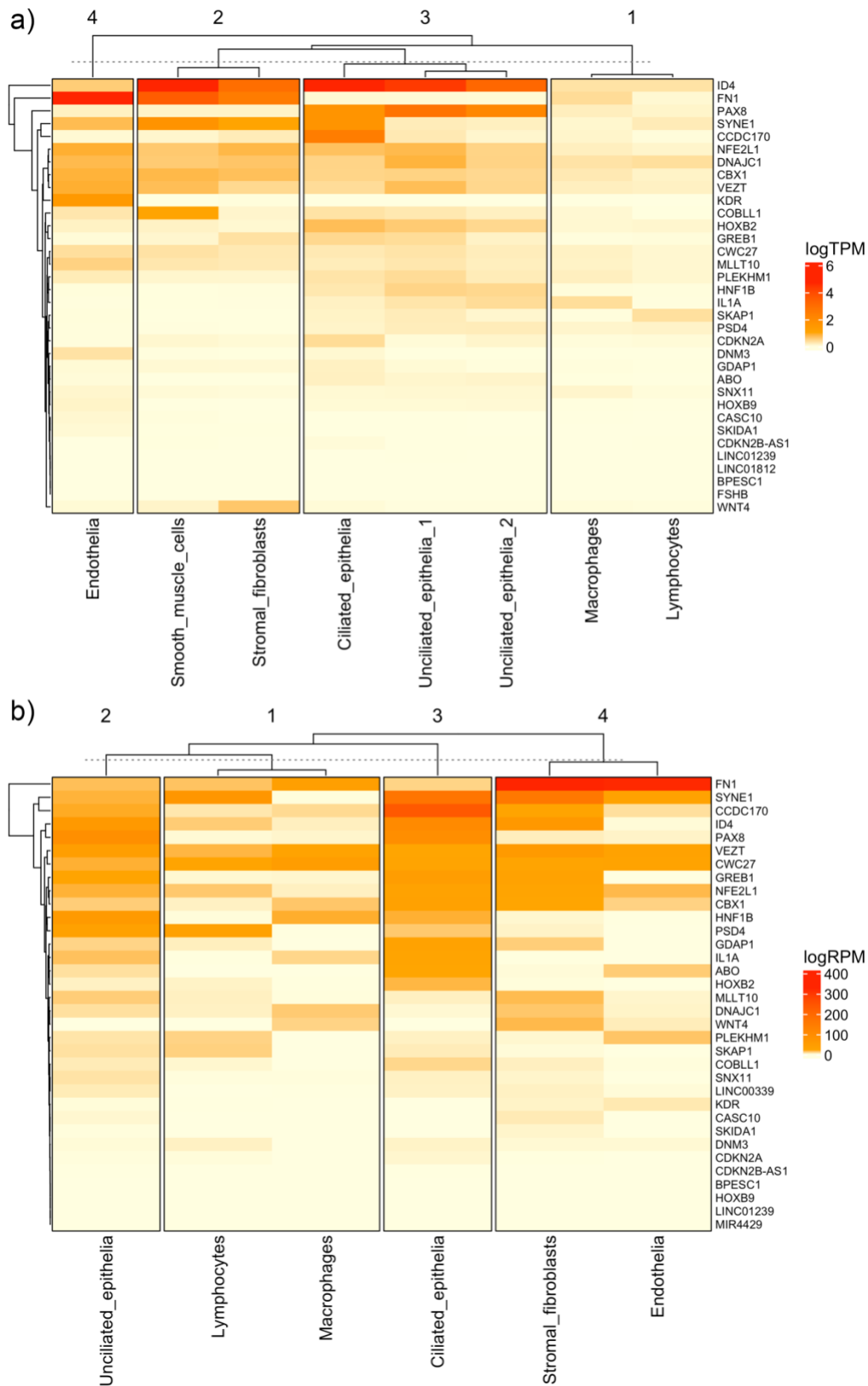**Figure S5. Endometrial single-cell expression of target genes.** Heatmaps showing the expression of target genes in eight cell types identified from single-cell sequencing of endometrial samples by Wang et al. 2020 [GSE111976]. Counts from both the 10x dataset (a), generated using the 10x Chromium system, and C1 dataset (b), generated using Fluidigm C1 medium chips, were plotted. Related to Tables 4 and 6.

Supplementary Tables

Table S1. Mendelian Randomization results for the association between genetic liability to each epithelial ovarian cancer (EOC) histotype and endometriosis risk. Related to Table 2. The primary IVW analysis results are in bold font.

Exposure	Method	nsnp	pval	OR	OR_lci95	OR_uci95
Using genetic variants associated with each EOC histotype at P< 5e-8						
High-grade Serous	**Inverse variance weighted**	**14**	**0.59**	**1.03**	**0.93**	**1.14**
High-grade Serous	MR Egger	14	0.64	0.95	0.75	1.19
High-grade Serous	Weighted median	14	0.95	1.00	0.92	1.08
Low Malignant Potential Serous	**Inverse variance weighted**	**3**	**0.31**	**1.04**	**0.97**	**1.11**
Low Malignant Potential Serous	MR Egger	3	0.95	1.01	0.78	1.31
Low Malignant Potential Serous	Weighted median	3	0.52	1.03	0.95	1.11
Mucinous	**Inverse variance weighted**	**4**	**0.06**	**1.09**	**1.00**	**1.20**
Mucinous	MR Egger	4	0.14	7.35	1.37	39.31
Mucinous	Weighted median	4	0.01	1.12	1.03	1.21
Using genetic variants associated with each EOC histotype at P < 1e-5 (because no variants were associated with endometrioid and Low-grade serous EOC risks at P < 5e-8 and only one variant was associated with clear cell EOC risk at P < 5e-8 in our data set, precluding the use of IVW, weighted median and MR-Egger methods, all of which require at least three variants in the genetic instrument for MR)						
Clear Cell	**Inverse variance weighted**	**21**	**0.41**	**1.01**	**0.98**	**1.05**
Clear Cell	MR Egger	21	0.16	1.06	0.98	1.14
Clear Cell	Weighted median	21	0.14	1.03	0.99	1.08
Endometrioid	**Inverse variance weighted**	**11**	**0.17**	**0.95**	**0.88**	**1.02**
Endometrioid	MR Egger	11	0.75	1.04	0.82	1.32
Endometrioid	Weighted median	11	0.75	0.98	0.89	1.08
Low-grade Serous	**Inverse variance weighted**	**26**	**0.68**	**0.99**	**0.97**	**1.02**
Low-grade Serous	MR Egger	26	0.39	0.98	0.92	1.03
Low-grade Serous	Weighted median	26	0.72	0.99	0.96	1.03
nsnp: number of SNPs included as instruments pval: Mendelian Randomisation P-value OR: odds ratio OR_lci95: lower 95% confidence interval odds ratio OR_uci95: upper 95% confidence interval odds ratio						

Table S7. Index SNPs for independent loci from the cross-trait meta-analysis containing SNPs intersecting with biofeatures. Related to Figure 1 and Figure S2.

Comparison	rsID	Chr	Position (bp)	Nearest gene or gene with functional evidence	nOverlap = 0	nOverlap > 0	nOverlap > 0 (%)	Total SNPs
High-grade Serous + Endometriosis	rs7217120	chr17	46484755	*SKAP1*	220	26	10.57	246
Mucinous + Endometriosis	rs4849174	chr2	113973467	*PAX8*	42	26	38.24	68
Clear Cell + Endometriosis	rs10167914	chr2	113563361	*IL1A*	18	12	40.00	30
Clear Cell + Endometriosis	rs11674184	chr2	11721535	*GREB1*	50	12	19.35	62
High-grade Serous + Endometriosis	rs12037376	chr1	22462111	*LINC00339*	36	9	20.00	45
High-grade Serous + Endometriosis	rs7084454	chr10	21821274	*MLLT10*	85	7	7.61	92
High-grade Serous + Endometriosis	rs11658063	chr17	36103872	*HNF1B*	6	6	50.00	12
Mucinous + Endometriosis	rs11674184	chr2	11721535	*GREB1*	23	5	17.86	28
Clear Cell + Endometriosis	rs11651755	chr17	36099840	*HNF1B*	2	4	66.67	6
Clear Cell + Endometriosis	rs12700667	chr7	25901639	*AK057379*	9	4	30.77	13
Endometrioid + Endometriosis	rs10445377	chr17	46214168	*SKAP1*	60	4	6.25	64
High-grade Serous + Endometriosis	rs7570979	chr2	11717429	*GREB1*	17	4	19.05	21
LMP Serous + Endometriosis	rs10445377	chr17	46214168	*SKAP1*	61	4	6.15	65
Clear Cell + Endometriosis	rs61768001	chr1	22465820	*LINC00339*	20	3	13.04	23
LMP Serous + Endometriosis	rs35713035	chr17	46501710	*SKAP1*	119	3	2.46	122
Clear Cell + Endometriosis	rs4516787	chr4	56010165	*KDR*	74	2	2.63	76
Endometrioid + Endometriosis	rs11031005	chr11	30226356	*FSHB*	27	2	6.90	29
Mucinous + Endometriosis	rs10167914	chr2	113563361	*IL1A*	4	2	33.33	6
Clear Cell + Endometriosis	rs1971256	chr6	151816011	*CCDC170*	0	1	100.00	1
Clear Cell + Endometriosis	rs1311245	chr5	64272107	*CWC27*	1	1	50.00	2
Clear Cell + Endometriosis	rs7309252	chr12	95687497	*VEZT*	6	1	14.29	7
Clear Cell + Endometriosis	rs8069263	chr17	46286778	*SKAP1*	8	1	11.11	9
Endometrioid + Endometriosis	rs1971256	chr6	151816011	*CCDC170*	5	1	16.67	6
High-grade Serous + Endometriosis	rs1250244	chr2	216297796	*FN1*	0	1	100.00	1
High-grade Serous + Endometriosis	rs10048393	chr18	3476253	*AX721193*	2	1	33.33	3

High-grade Serous + Endometriosis	rs111610638	chr6	152449994	*SYNE1*	4	1	20.00	5
High-grade Serous + Endometriosis	rs635634	chr9	136155000	*ABO*	9	1	10.00	10
Low-grade Serous + Endometriosis	rs10445377	chr17	46214168	*SKAP1*	27	1	3.57	28
Clear Cell + Endometriosis	rs17803970	chr6	152553718	*SYNE1*	9	0	0.00	9
Clear Cell + Endometriosis	rs71575922	chr6	152554014	*SYNE1*	6	0	0.00	6
Clear Cell + Endometriosis	rs566679	chr9	22634893	*LINC01239*	3	0	0.00	3
Clear Cell + Endometriosis	rs78103255	chr8	75311331	*GDAP1*	2	0	0.00	2
Endometrioid + Endometriosis	rs56318008	chr1	22470407	*LINC00339*	10	0	0.00	10
Endometrioid + Endometriosis	rs6475610	chr9	22141894	*CDKN2B-AS1*	5	0	0.00	5
Endometrioid + Endometriosis	rs495590	chr1	172122809	*DNM3*	2	0	0.00	2
High-grade Serous + Endometriosis	rs6908034	chr6	19773930	*ID4*	3	0	0.00	3
High-grade Serous + Endometriosis	rs62065444	chr17	43565599	*PLEKHM1*	3	0	0.00	3
High-grade Serous + Endometriosis	rs1981046	chr9	22173407	*CDKN2B-AS1*	2	0	0.00	2
High-grade Serous + Endometriosis	rs13000026	chr2	165558884	*COBLL1*	1	0	0.00	1
LMP Serous + Endometriosis	rs4654785	chr1	22491843	*LOC105376850*	5	0	0.00	5
LMP Serous + Endometriosis	rs10748858	chr10	105639514	*OBFC1*	4	0	0.00	4
LMP Serous + Endometriosis	rs11031005	chr11	30226356	*FSHB*	2	0	0.00	2
Low-grade Serous + Endometriosis	rs77294520	chr2	11660955	*GREB1*	1	0	0.00	1
Low-grade Serous + Endometriosis	rs584336	chr6	152616173	*SYNE1*	1	0	0.00	1
Mucinous + Endometriosis	rs6546324	chr2	67856490	*LINC01812*	3	0	0.00	3
Mucinous + Endometriosis	rs67808862	chr3	138849543	*BPESC1*	2	0	0.00	2
nOverlap: number of SNPs in locus intersecting biofeature.								