**Cell Reports Medicine, Volume 3** 

# Supplemental information

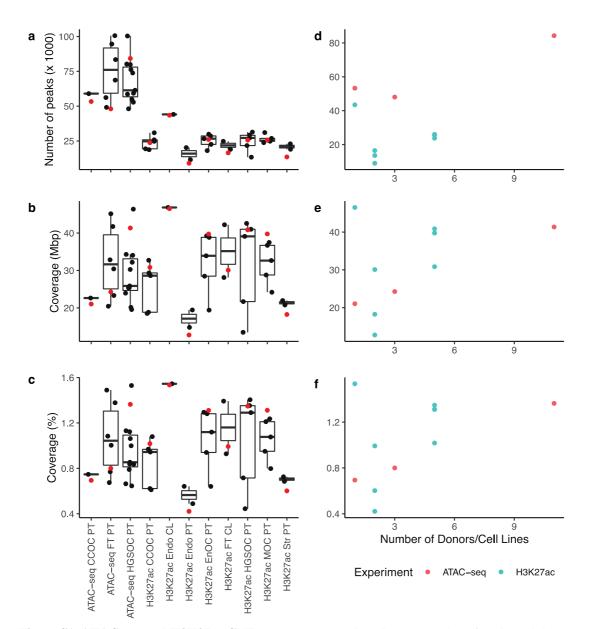
# A multi-level investigation of the genetic

### relationship between endometriosis

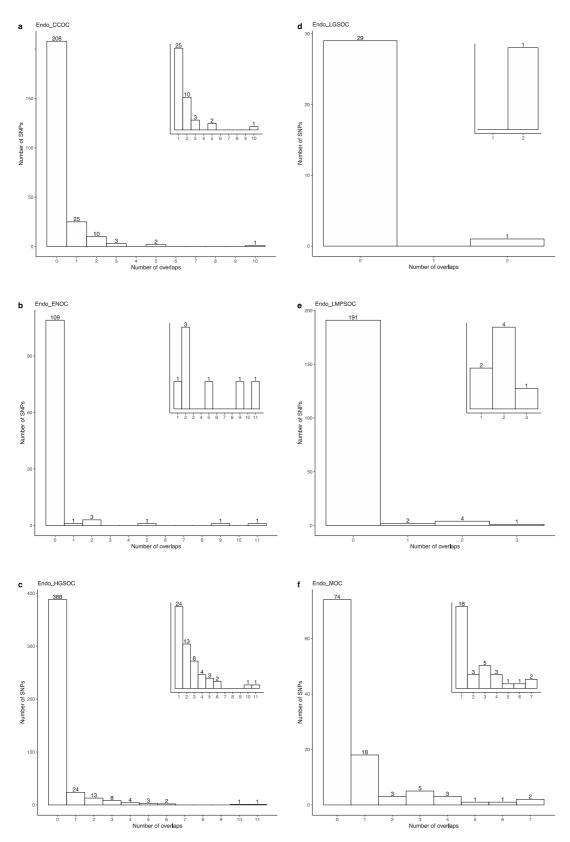
## and ovarian cancer histotypes

Sally Mortlock, Rosario I. Corona, Pik Fang Kho, Paul Pharoah, Ji-Heui Seo, Matthew L. Freedman, Simon A. Gayther, Matthew T. Siedhoff, Peter A.W. Rogers, Ronald Leuchter, Christine S. Walsh, Ilana Cass, Beth Y. Karlan, B.J. Rimel, Ovarian Cancer Association Consortium, International Endometriosis Genetics Consortium, Grant W. Montgomery, Kate Lawrenson, and Siddhartha P. Kar

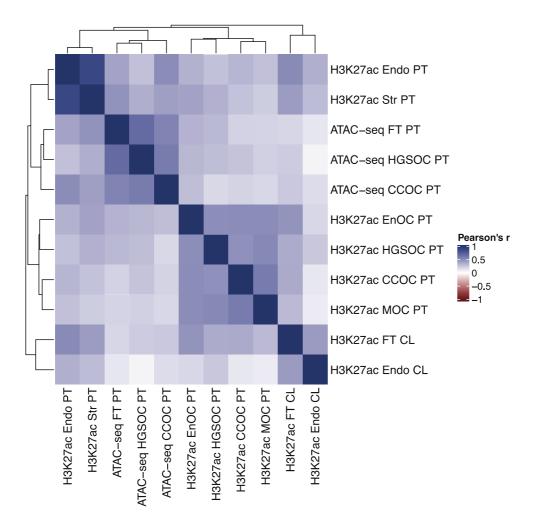
#### **Supplementary Figures**



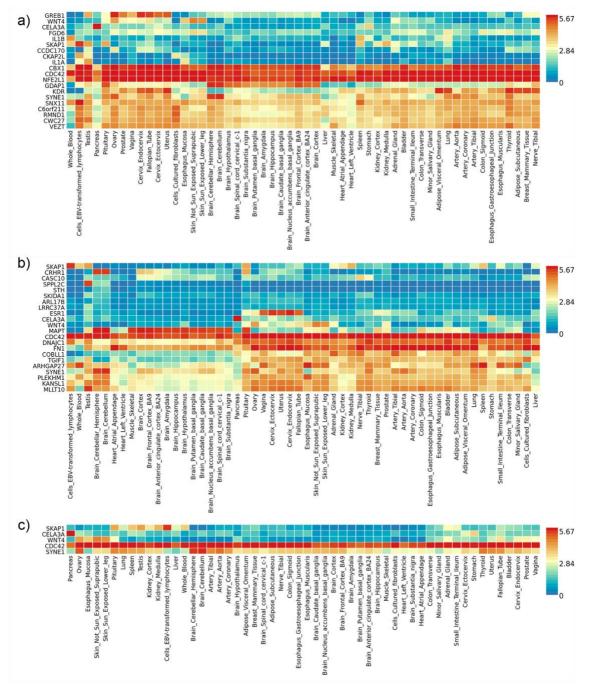
**Figure S1. ATAC-seq and H3K27ac ChIP-seq coverage and peaks.** (a) Number of peaks and (b) genome coverage in Mbp and (c) genome coverage in percentage for sample peak sets (black dots) and consensus peak sets (red dots). (d) Number of peaks (e) and genome coverage in Mbp and (g) genome coverage in 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.



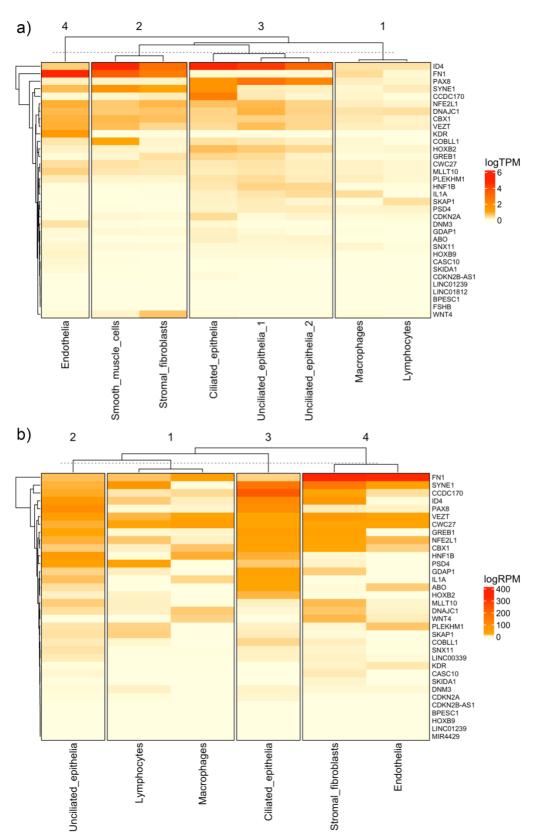
**Figure S2.** Associated SNPs overlap biofeatures. Histogram of number of SNPs associated with endometriosis and (a) clear cell ovarian cancer (CCOC), (b) endometrioid ovarian cancer (ENOC), (c) high-grade serous ovarian cancer (HGSOC), (d) Low-grade serous ovarian cancer (LGSOC), (e) low malignant potential serous ovarian cancer (LMPSOC) and (f) mucinous ovarian cancer (MOC), that overlap *n* biofeatures. Inset histograms show the number of overlaps  $\geq 1$ . 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		
and the COND in 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,								

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

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

**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.

								-	
Endometriosis         F8633634         Chr9         F36135000         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         0.000         9           Clear Cell + Endometriosis         rs71575922         chr6         152554014         SYNE1         6         0         0.000         3           Clear Cell + Endometriosis         rs566679         chr9         22634893         LINC01239         3         0         0.000         2           Endometriois         rs56318008         chr1         22470407         LINC00339         10         0         0.000         2           Endometrioid + Endometriois         rs6475610         chr9         22141894         CDKN2B-AS1         5         0         0.000         2           High-grade Serous + Endometriosis         rs6908034         chr6         19773930         ID4         3         0         0.000         3           High-grade Serous + Endometriosis         rs13000026         chr2	High-grade Serous + Endometriosis	rs111610638	chr6	152449994	SYNE1	4	1	20.00	5
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	High-grade Serous + Endometriosis	rs635634	chr9	136155000	ABO	9	1	10.00	10
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Endometriosisrs5666/9chr9 $22634893$ LINC01239300.003Clear Cell + Endometriosisrs78103255chr875311331GDAP1200.002Endometrioid + Endometriosisrs56318008chr122470407LINC003391000.0010Endometrioid + Endometriosisrs6475610chr922141894CDKN2B-AS1500.002Endometriois + 		rs71575922	chr6	152554014	SYNE1	6	0	0.00	6
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Endometriosis 1307000002 Cm3 130849545 Di ESCI 2 0 0.00 2	Mucinous + Endometriosis	rs67808862	chr3	138849543	BPESC1	2	0	0.00	2
nOverlap: number of SNPs in locus intersecting biofeature.									