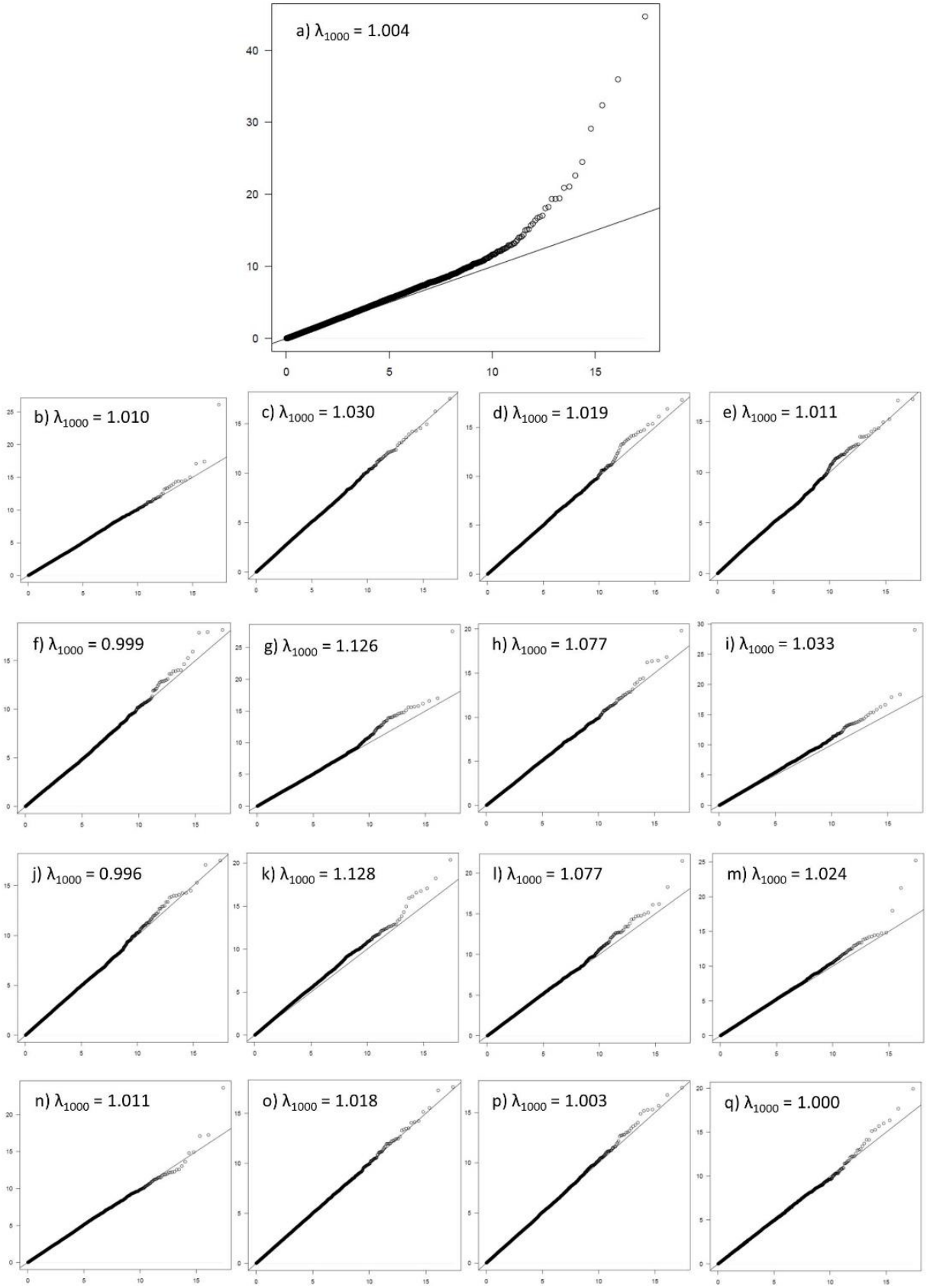
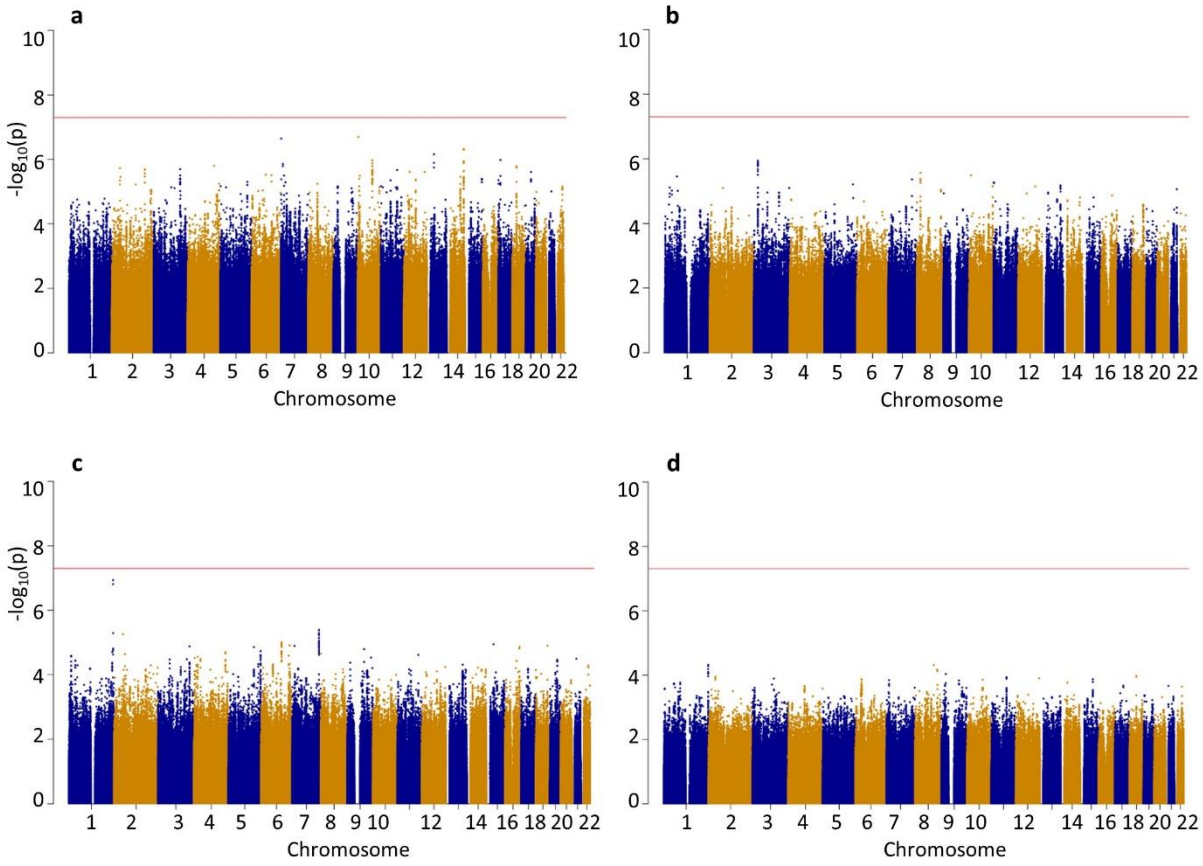
Supplementary Information
Identification of nine new susceptibility loci for endometrial cancer. O'Mara et al.

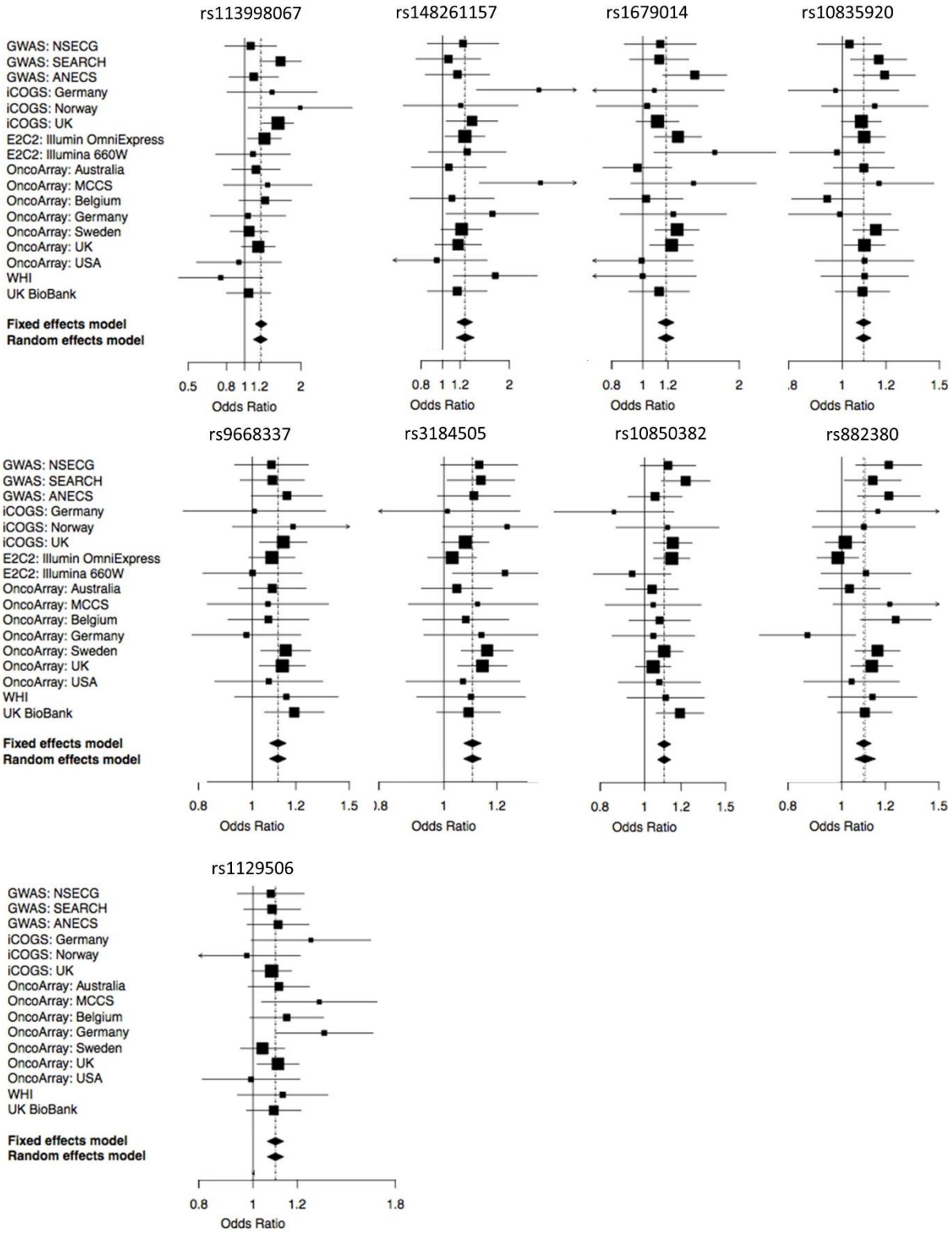


Supplementary Fig. 1. Quantile Quantile plots (33,278 uncorrelated SNPs). a) Meta-analysis of all studies b) NSECG GWAS c) SEARCH GWAS d) ANECS GWAS e) E2C2 OmniExpress f) E2C2 Illumina 660W g) iCOGS Germany h) iCOGS Norway i) iCOGS UK j) OncoArray Australia k) OncoArray Belgium l) OncoArray Germany m) OncoArray Sweden n) OncoArray UK o) OncoArray USA p) WHI q) UK

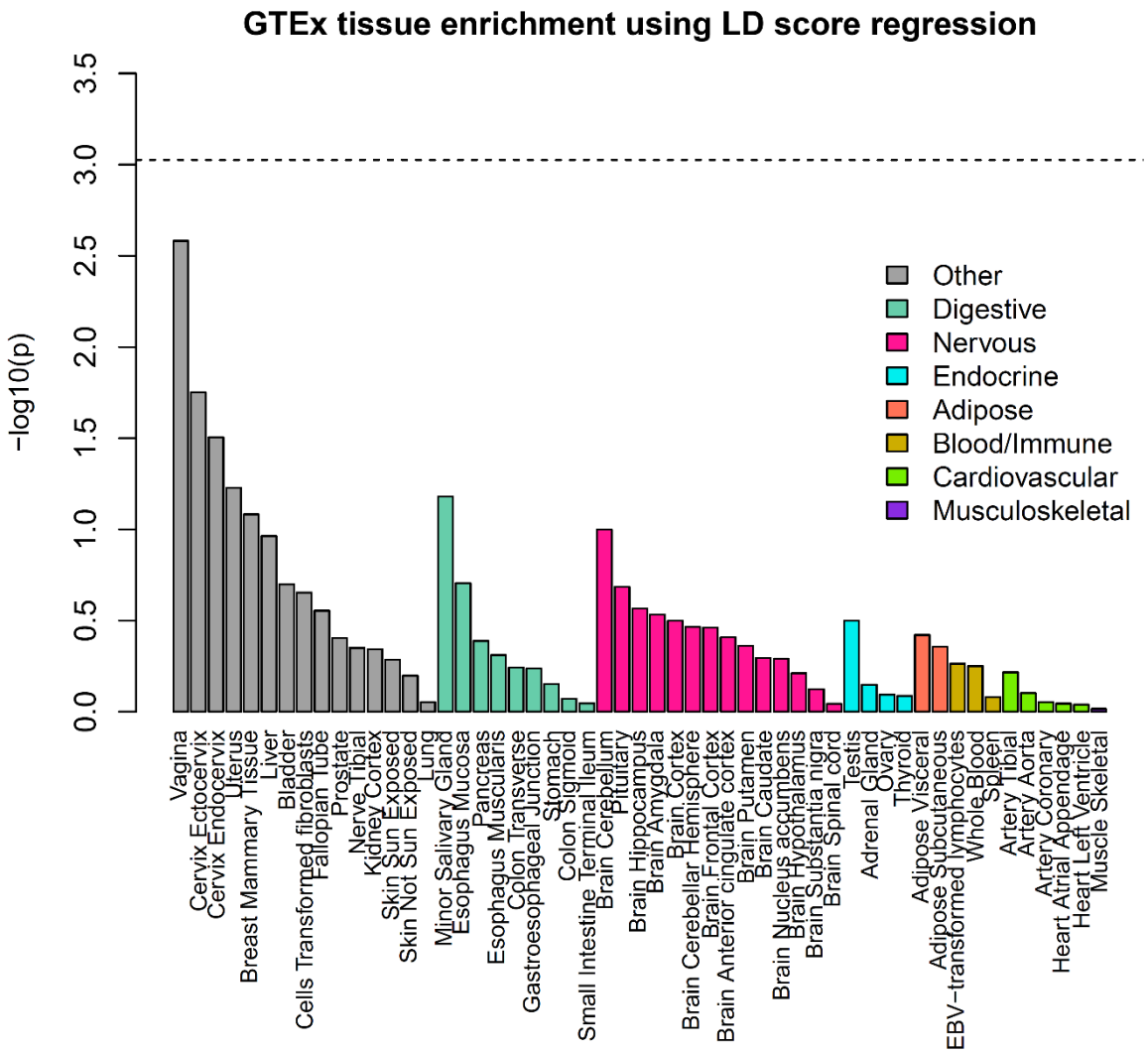
Biobank.



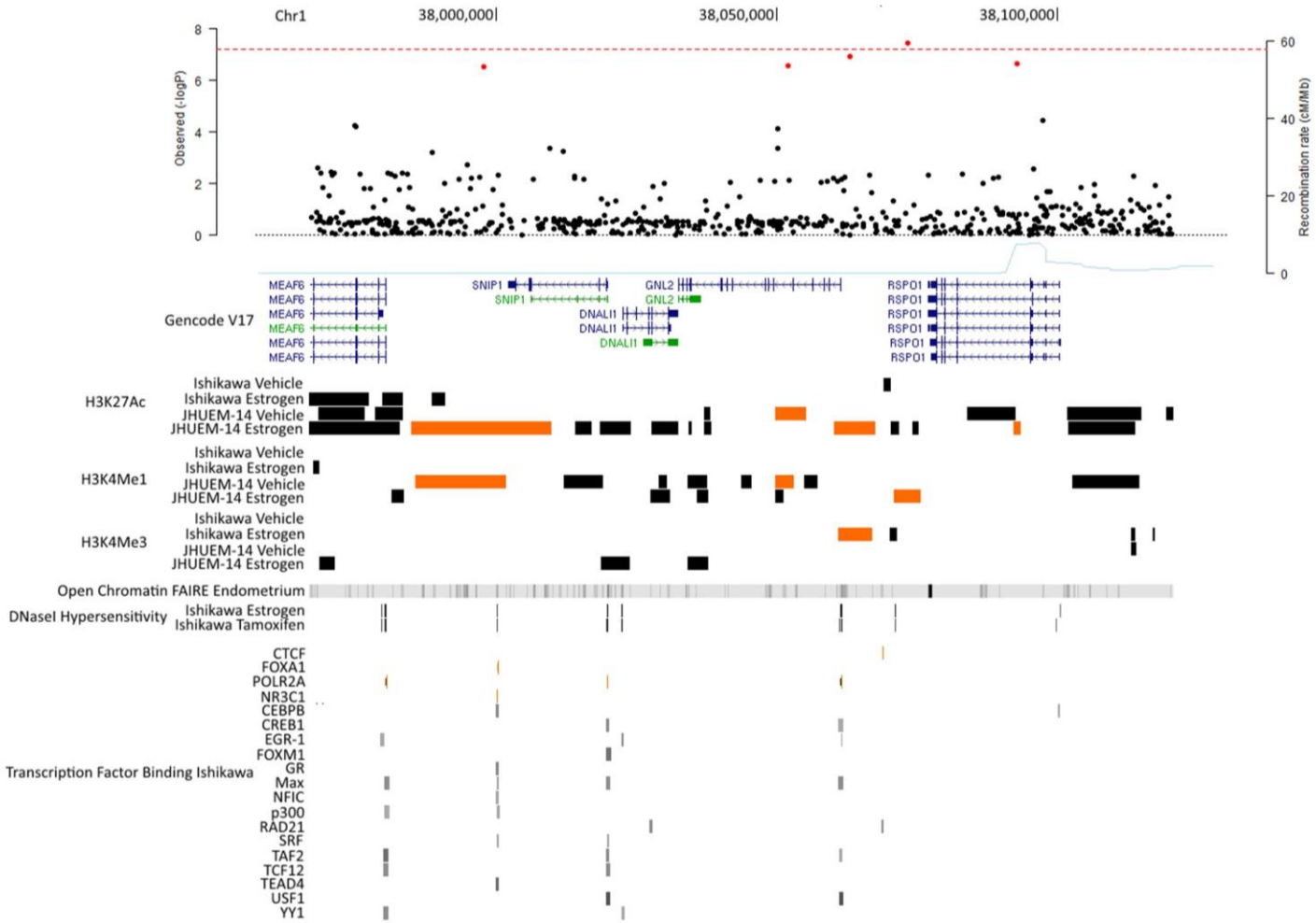
Supplementary Fig. 2. Manhattan plot of the analyses of specific endometrial cancer non-endometrioid histological subtypes comparing to 108,979 controls. Genetic variants are plotted according to chromosome and position (X-axis) and statistical significance (Y-axis). The red line marks the $5x10^{-8}$ GWAS significance threshold. a) Serous carcinoma (434 cases) b) Carcinosarcoma (164 cases) c) Clear cell carcinoma (128 cases) d) Mucinous carcinoma (49 cases).



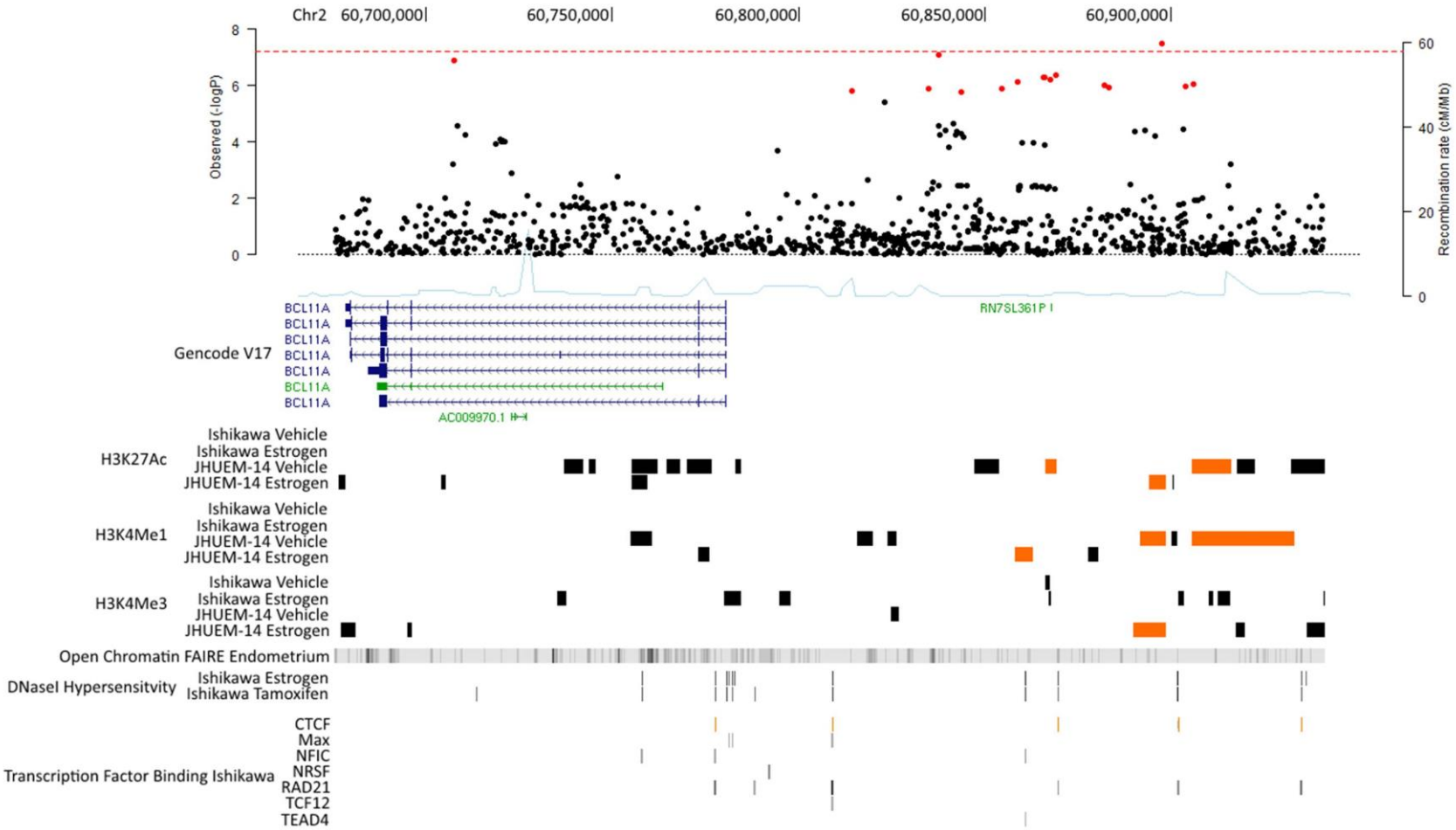
Supplementary Fig. 3. Forest plots for the nine new endometrial cancer susceptibility loci. Details of the individual studies are given in Supplementary Data 1.



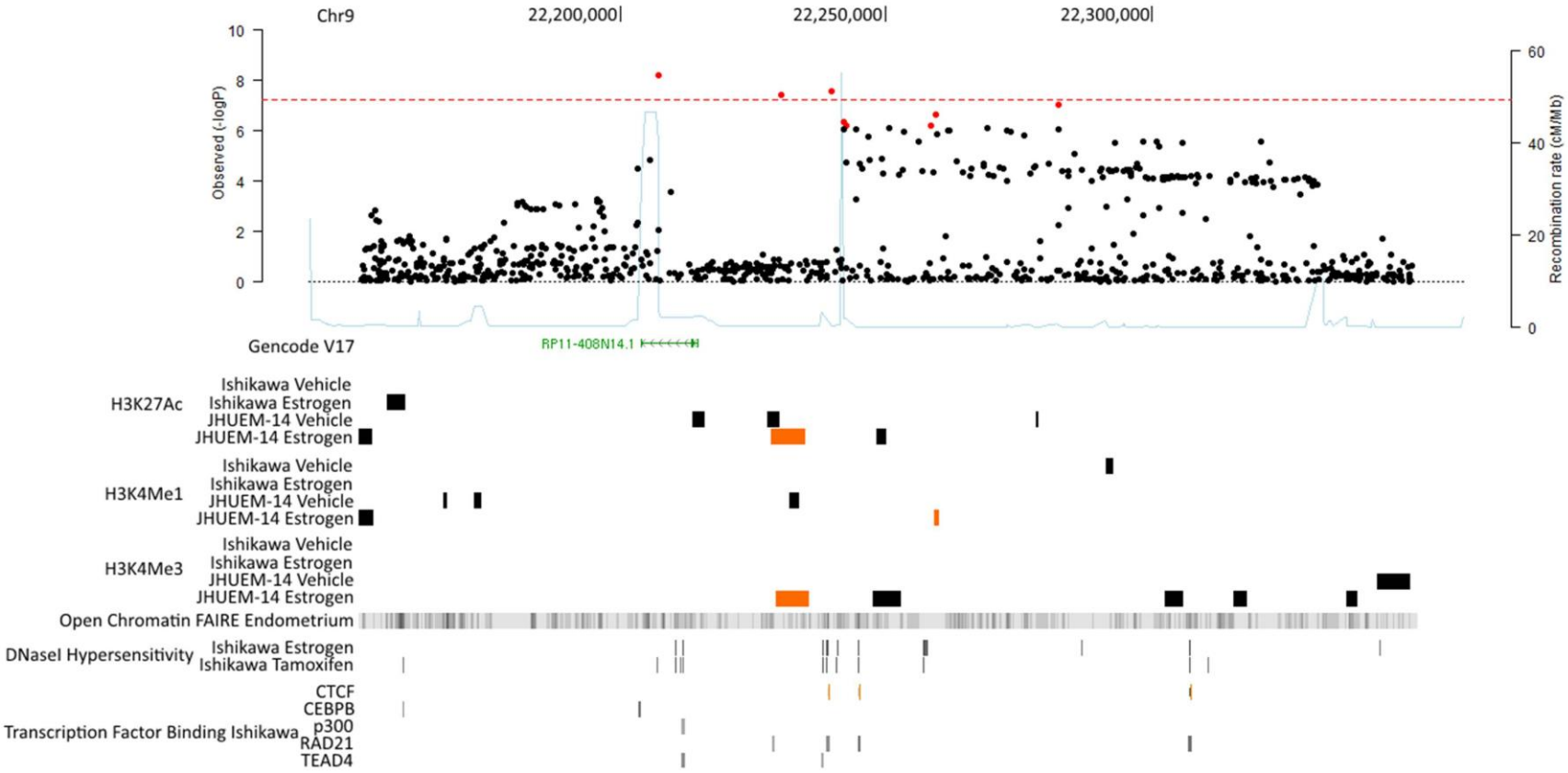
Supplementary Fig. 4. GTEx tissue enrichment using LD score regression. The dashed line represents Bonferroni-corrected significance for the number of tissues tested.



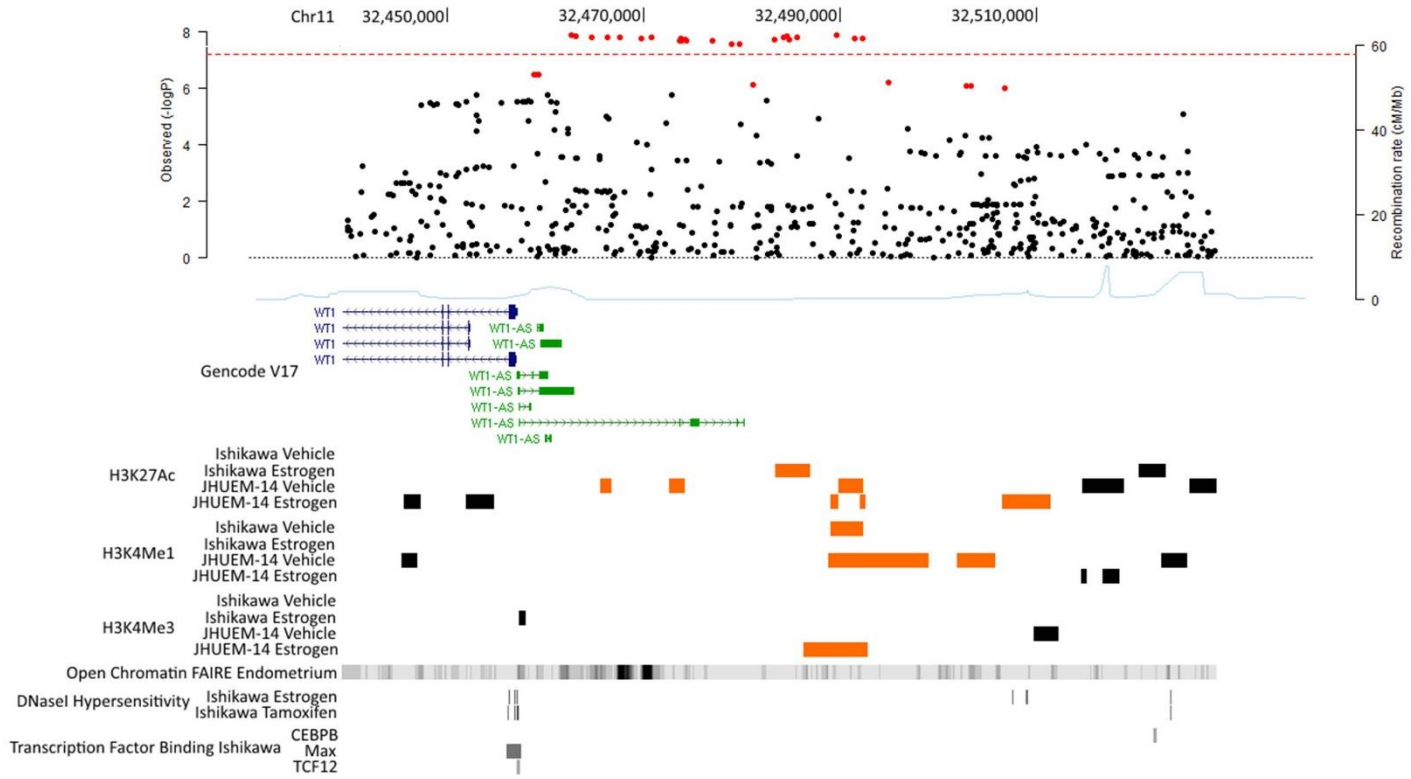
Supplementary Fig. 5. Regional association plots and genomic featured at the 1p34.3 region. ccrSNPs are denoted by red dots. All five ccrSNPs are coincident with histone marks identified in endometrial cancer cells (highlighted in orange). The risk allele of the ccrSNP rs114240971 is associated with increased *CDCA8* expression in all (p=0.0019) and endometrioid (p=0.00078) TCGA endometrial tumours (ST3). rs114240971 is an intergenic variant coincident with histone marks characteristic of enhancers: H3K4Me1 in estrogen-stimulated JHUEM-14 and H3K27Ac in uterus and vagina. *CDCA8* is an essential regulator of mitosis and cell division, and knockdown of expression suppresses cancer cell proliferation [1,2]. In ovarian cancer, and *CDCA8* has been identified as an oncogene [3] and risk variation associates with *CDCA8* expression in TCGA ovarian tumours [4].



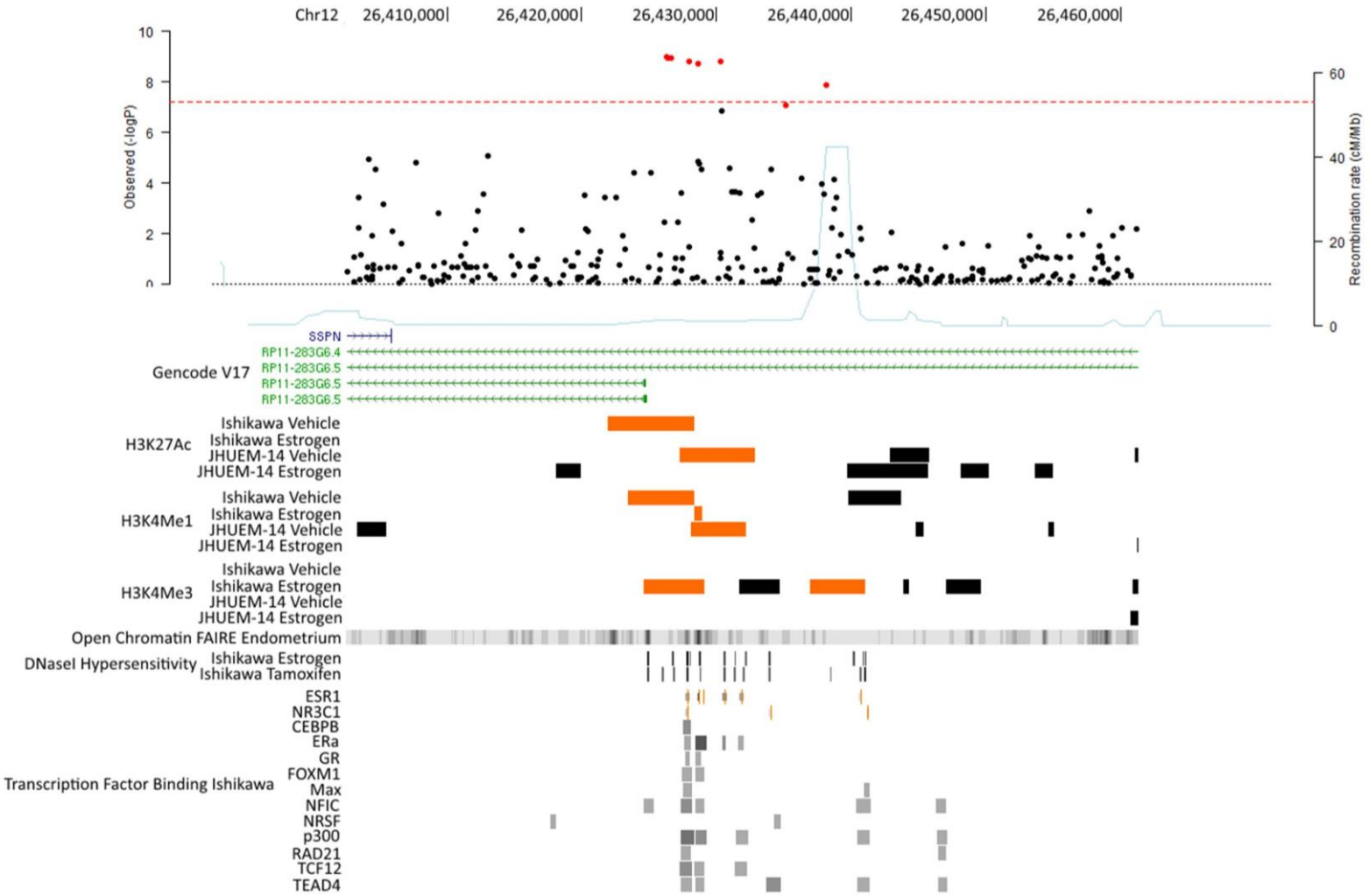
Supplementary Fig. 6. Regional association plots and genomic feature intersects for 2p16.1 region. ccrSNPs are denoted by red dots. Five of the 16 ccrSNPs are coincident with histone marks identified in endometrial cancer cells (highlighted in orange). The lead ccrSNP, rs148261157, is an intergenic variant located in an active chromatin region delineated by H3K27Ac, H3K4Me1 and H3K4Me3 in JHUEM-14 cells.



Supplementary Fig. 7. Regional association plots and genomic feature intersects for 9p21.3 region. ccrSNPs are denoted by red dots. Three of the eight ccrSNPs are coincident with DHS or histone marks in endometrial cancer cell lines (histone marks highlighted in orange). The lead ccrSNP, rs1679014, is a lncRNA (RP11-408N14.1) intronic variant located in a DNaseI hypersensitivity site (DHS) in Ishikawa cells.

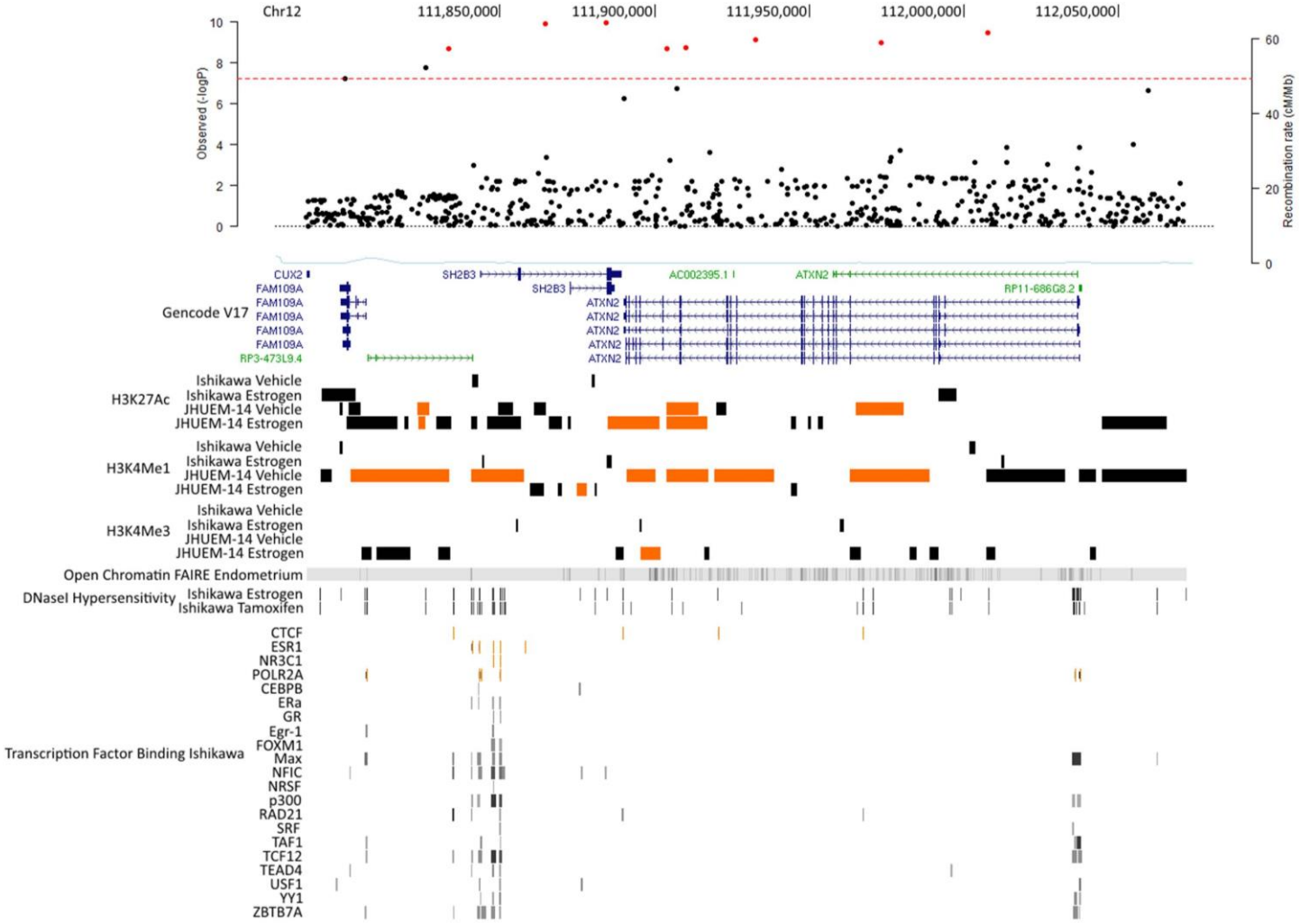


Supplementary Fig. 8. Regional association plots and genomic feature intersects for 11p13 region. ccrSNPs are denoted as red dots. 15 of the 33 ccrSNPs are coincident with histone marks identified in endometrial cancer cell lines (highlighted in orange). Notably, ccrSNPs are associated with the expression of multiple genes in normal and tumour endometrial tissues. The risk alleles of ccrSNPs are associated with increased *CCDC73* in tumour (p=0.039-0.00049) and normal (p=0.048-0.0076) TCGA endometrial tissue (ST3). *CCDC73* encodes coiled-coil domain-containing protein 73 but the function of this protein remains unknown. Risk alleles are also associated with RCN1 expression in normal (p=0.046-0.0052), endometrioid (p=0.034-0.0011) and all tumour (p=0.0056-0.00084) TCGA endometrial tissues (ST3). *RCN1* encodes reticulocalbin 1, a calcium-binding protein that binds oncoproteins such as JAK2 and MYC (https://www.ncbi.nlm.nih.gov/gene/5954). In uterine sarcoma cells, overexpression of RCN1 contributes to doxorubicin-resistance [5] and expression of RCN1 enhances survival of irradiated epithelial cancer cells under hypoxic conditions [6]. The risk alleles of four ccrSNPs are associated with increased *WT1-AS* expression in normal endometrium (p<0.001; ST3). These variants are located ~1kb downstream of a *WT1-AS* promoter delineated by H3K4Me3 in estrogen-treated Ishikawa cells. *WT1-AS* is a long non-coding RNA that overlaps the 5' UTR of *WT1* and strongly correlates with *WT1* expression in TCGA endometrial tumour samples. Indeed, *WT1-AS* can induce *WT1* expression [7] and upregulate WT1 protein levels [8]. *WT1* encodes Wilms tumor protein which appears to act as an oncogene in many tumours and plays an important role in the cellular mesenchymal-epithelial balance [9].



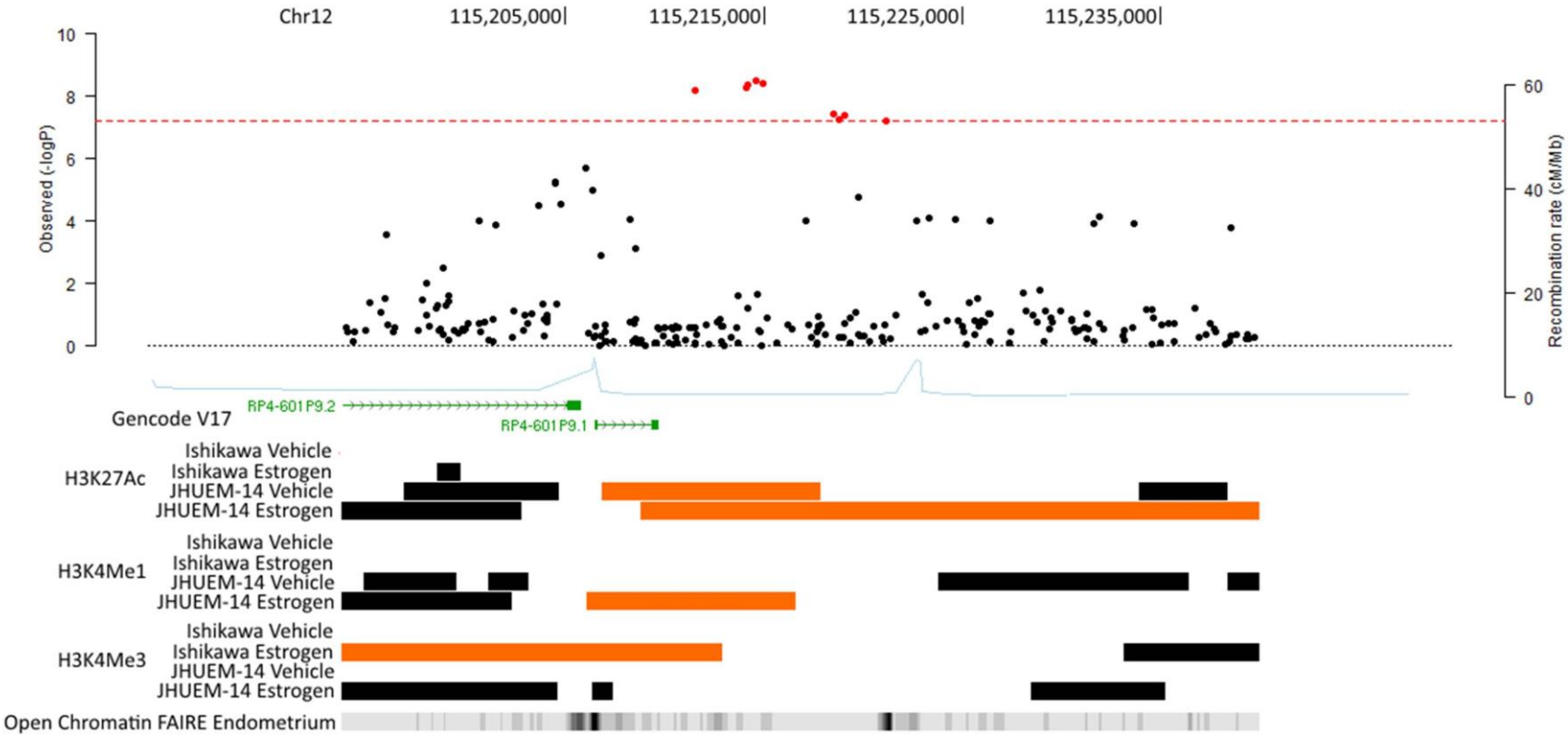
Supplementary Fig. 9. Regional association plots and genomic featured at the 12p12.1 region. All nine ccrSNPs (denoted by red dots) are located in the intronic region of a lncRNA (RP11-283G6.5) that is downregulated in breast tumours[10]. All but one of the ccrSNPs are located in regions of active chromatin delineated by histone marks in endometrial cancer (highlighted in orange). Furthermore, two ccrSNPs, rs7959150 and rs7974900, appear to be located in an endometrial cancer enhancer. These variants are coincident with DHS and/or H3K4Me1 and H3K27Ac enhancer marks in endometrial cancer cells. Moreover, in Ishikawa cells, these variants are coincident with regions bound by transcription factors associated with enhancers such as p300, Era, FOXM1

and RAD21.

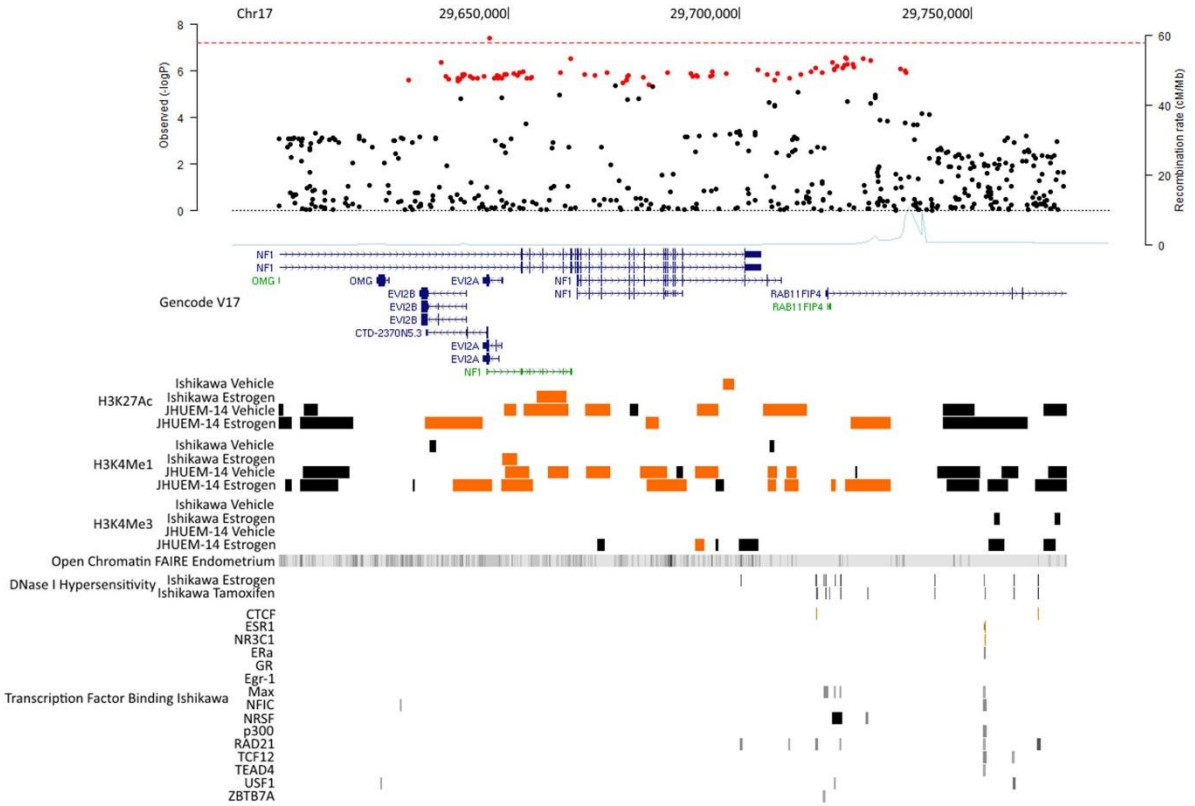


Supplementary Fig. 10. Regional association plots and genomic featured at the 12p24.11 region. ccrSNPs are denoted by red dots. All but one of the eight ccrSNPs are coincident with histone marks identified in endometrial cancer cells (highlighted in orange). The risk alleles of four ccrSNPS are associated with decreased *SH2B3* expression in blood ($p \leq 5.02 \times 10^{-19}$, ST3), including the lead variant at this locus, rs3184504 (Trp262Arg), which causes a substitution in the pleckstrin homology domain of SH2B3. Relevantly, SH2B3 is a negative regulator of the oncoproteins c-KIT and JAK2 and also of processes related to

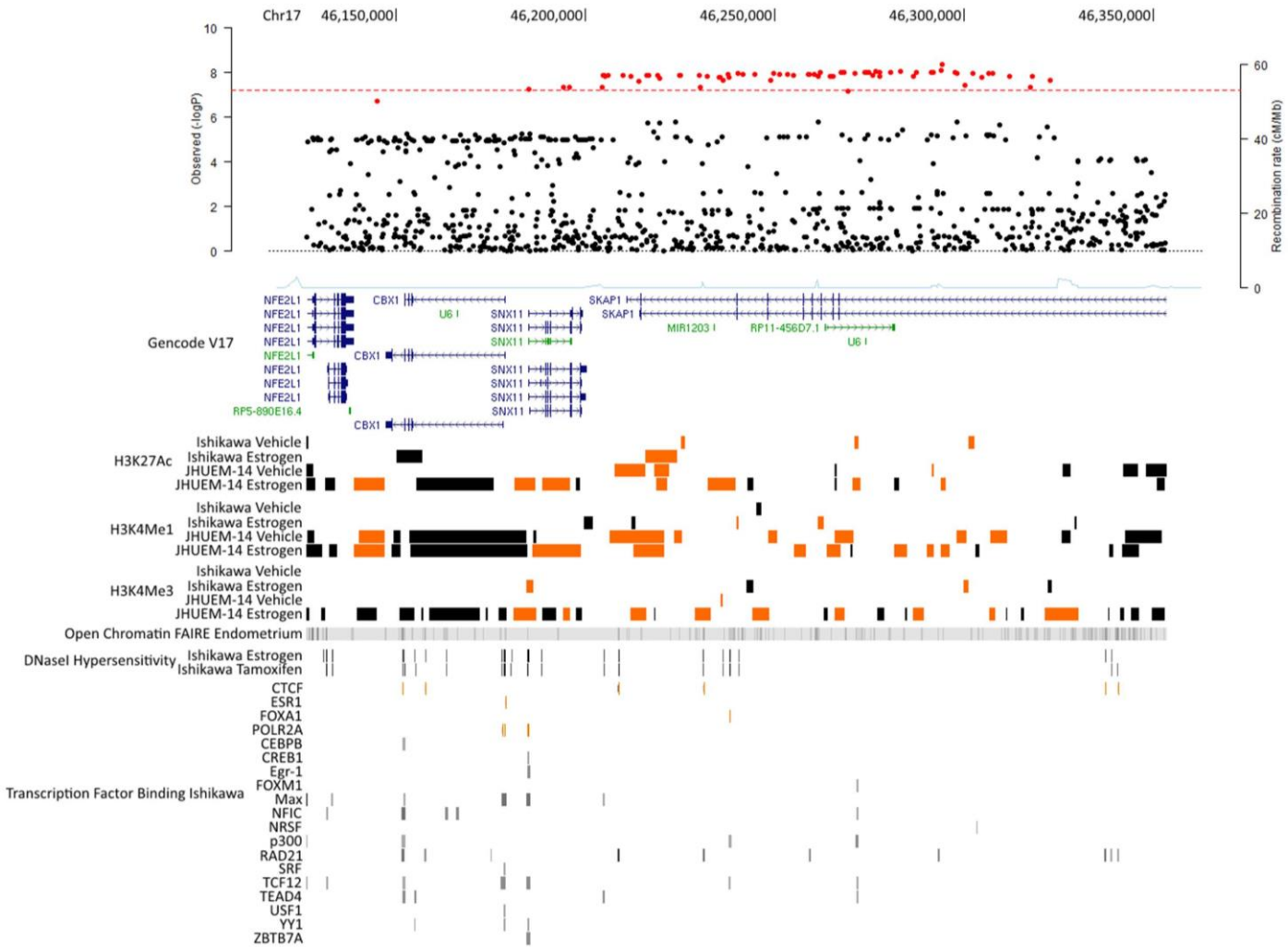
angiogenesis and neovascularisation [11].



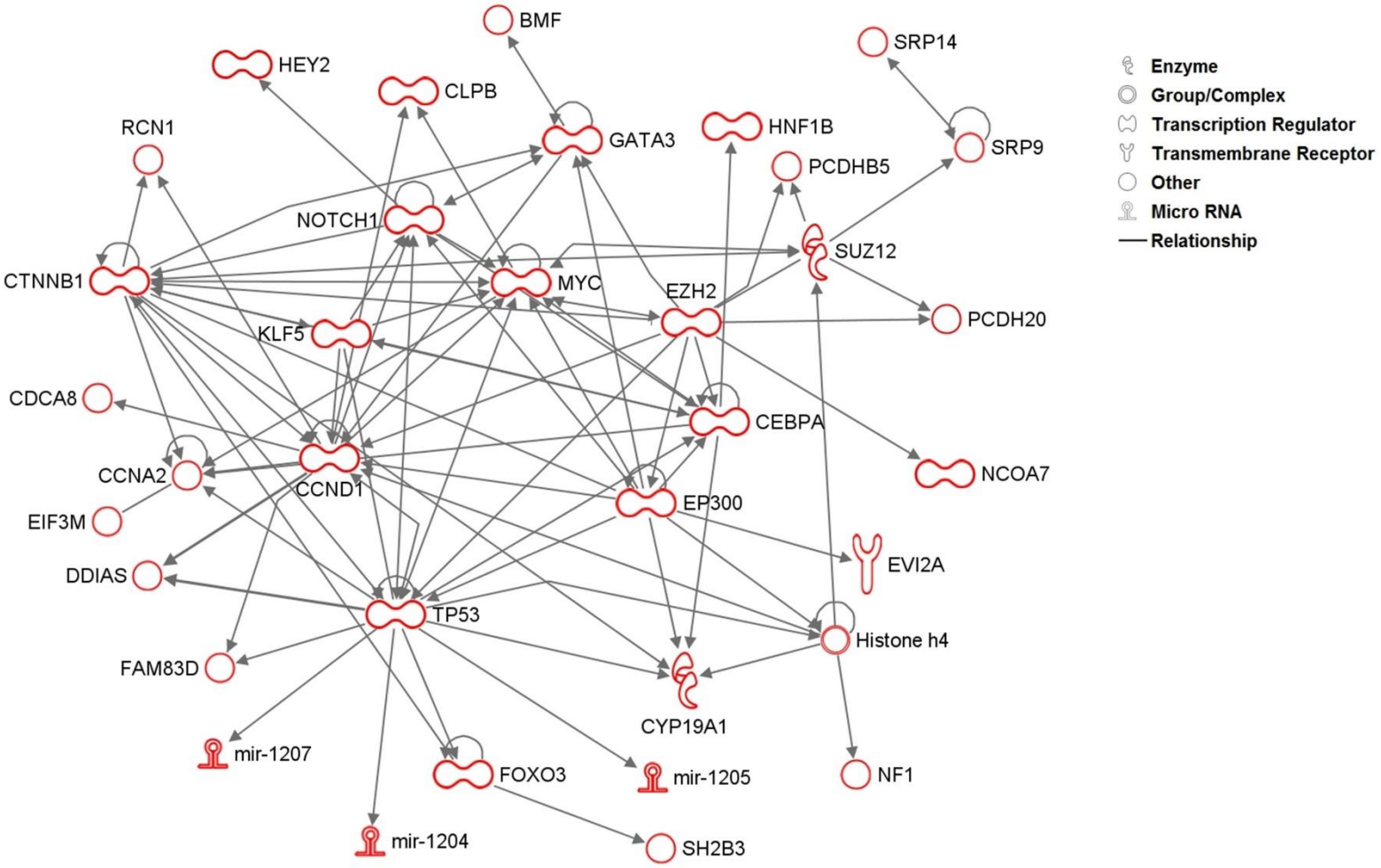
Supplementary Fig. 11. Regional association plots and genomic featured at the 12p24.21 region. All nine ccrSNPs (denoted by red dots) are located in an intergenic region of active chromatin delineated by H3K4Me1, H3K4Me3 and H3K27Ac marks in endometrial cancer cells (highlighted in orange).



Supplementary Fig. 12. Regional association plots and genomic featured at the 17q11.2 region. ccrSNPs are denoted by red dots. 56 of the 80 ccrSNPs are located in either a DHS or histone mark in endometrial cancer cells (histone marks highlighted in orange). The risk alleles of 40 ccrSNPs are associated with decreased *EVI2A* and *NF1* expression in blood ($p \leq 1.68 \times 10^{-36}$; ST3), while the lead (*EVI2A* Ser23Ser) ccrSNP associated with increased *NF1* expression in TCGA endometrial tumours ($p = 7.28 \times 10^{-6}$; ST3). Little is known about the function of EVI2A although it has been proposed that it may play a role in interactions between cancer cells and the extracellular matrix [12]. *NF1* encodes neurofibromin, a tumour suppressor that acts a negative regulator of the oncogenic RAS proteins [13]. Consistent with the function of NF1, a number of *NF1* truncating (putative driver) mutations have been observed in TCGA endometrial tumours, as well as significant deletion in a region encompassing *NF1* and *EVI2A* (GISTIC q-value = 7.19×10^{-8}; data accessed from cBioPortal). Nominal associations were also observed between the risk alleles of 26 ccrSNPs and decreased *SUZ12* expression in normal endometrium (p=0.0076-0.0026, ST3). *SUZ12* encodes a transcription factor required for transcriptionally repressive H3K27 methyltransferase activity [14] and is located at a recurrent chromosomal breakpoint in endometrial stromal sarcoma where *SUZ12* fuses with *JAZF1* [15]. This *SUZ12-JAZF1* fusion abolishes H3K27 methyltransferase activity and has an oncogenic effect by activating genes that are normally repressed [16].



Supplementary Fig. 13. Regional association plots and genomic featured at the 17q21.32 region. ccrSNPs are denoted by red dots. 53 of the 75 ccrSNPs are located in either a DHS or histone mark in endometrial cancer cells (histone marks highlighted in orange). The risk alleles of 30 ccrSNPs are associated with increased *SNX11* expression in blood ($p \leq 8.70 \times 10^{-12}$, ST3) and includes a variant located in the 5'UTR of *SNX11* that is coincident with H3K4Me3 (characteristic of promoters) in both estrogen-treated endometrial cancer cell lines. *SNX11* encodes a vesicular trafficking protein that is involved in nuclear translocation and angiogenesis [17].



Supplementary Fig. 14. Network analysis of candidate causal genes for endometrial cancer using Ingenuity Pathway Analysis.

Supplementary Table 1. Details for antibodies used for ChIP-seq experiments.

Antibody	Catalogue Number	Concentration	Amount Used
Anti-H3K4Me1	Abcam #ab8895	1 µg/µL	5 µg
Anti-H3K4Me3	Abcam #ab8580	1 µg/µL	5 µg
Anti-H3K27Ac	Abcam #ab4729	1 µg/µL	5 µg

Supplementary Note 1. ECAC Study Collaborators

The ANECS Group comprises*:* AB Spurdle, PM Webb, J Young (QIMR Berghofer Medical Research Institute); Consumer representative: L McQuire; Clinical Collaborators: NSW: S Baron-Hay, D Bell, A Bonaventura, A Brand, S Braye, J Carter, F Chan, C Dalrymple, A Ferrier (deceased), G Gard, N Hacker, R Hogg, R Houghton, D Marsden, K McIlroy, G Otton, S Pather, A Proietto, G Robertson, J Scurry, R Sharma, G Wain, F Wong; Qld: J Armes, A Crandon, M Cummings, R Land, J Nicklin, L Perrin, A Obermair, B Ward; SA: M Davy, T Dodd, J Miller, M Oehler, S Paramasivum, J Pierides, F Whitehead; Tas: P Blomfield, D Challis; Vic: D Neesham, J Pyman, M Quinn, R Rome, M Weitzer; WA: B Brennan, I Hammond, Y Leung, A McCartney (deceased), C Stewart, J Thompson; Project Managers: S O'Brien, S Moore; Laboratory Manager: K Ferguson; Pathology Support: M Walsh; Admin Support: R Cicero, L Green, J Griffith, L Jackman, B Ranieri; Laboratory Assistants: M O'Brien, P Schultz; Research Nurses: B Alexander, C Baxter, H Croy, A Fitzgerald, E Herron, C Hill, M Jones, J Maidens, A Marshall, K Martin, J Mayhew, E Minehan, D Roffe, H Shirley, H Steane, A Stenlake, A Ward, S Webb, J White.

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SEARCH collaborators include: Caroline Baynes, Don Conroy, Patricia Harrington, Sue Irvine, Craig Luccarini, Rebecca Mayes.

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ABCTB collaborators: Rosemary Balleine, Robert Baxter, Stephen Braye, Jane Carpenter, Jane Dahlstrom, John Forbes, Soon Lee, Debbie Marsh, Adrienne Morey, Nirmala Pathmanathan, Allan Spigelman, Nicholas Wilcken, Desmond Yip. Samples are made available to researchers on a non-exclusive basis.

BCEES: Allyson Thomson, Christobel Saunders, Terry Slevin, BreastScreen Western Australia, Elizabeth Wylie, Rachel Lloyd.

BSUCH collaborator: Peter Bugert

ESTHER collaborators: Christa Stegmaier, Katja Butterbach, Katarina Cuk.

GC-HBOC collaborators: Stefanie Engert, Heide Hellebrand, Sandra Kröber and LIFE - Leipzig Research Centre for Civilization Diseases (Markus Loeffler, Joachim Thiery, Matthias Nüchter, Ronny Baber).

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Supplementary Note 3. Acknowledgements

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