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Supplemental information

Splicing annotation of endometrial cancer GWAS risk loci reveals potentially causal variants and supports a role for *NF1* and *SKAP1* as susceptibility genes

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SUPPLEMENTAL FIGURES

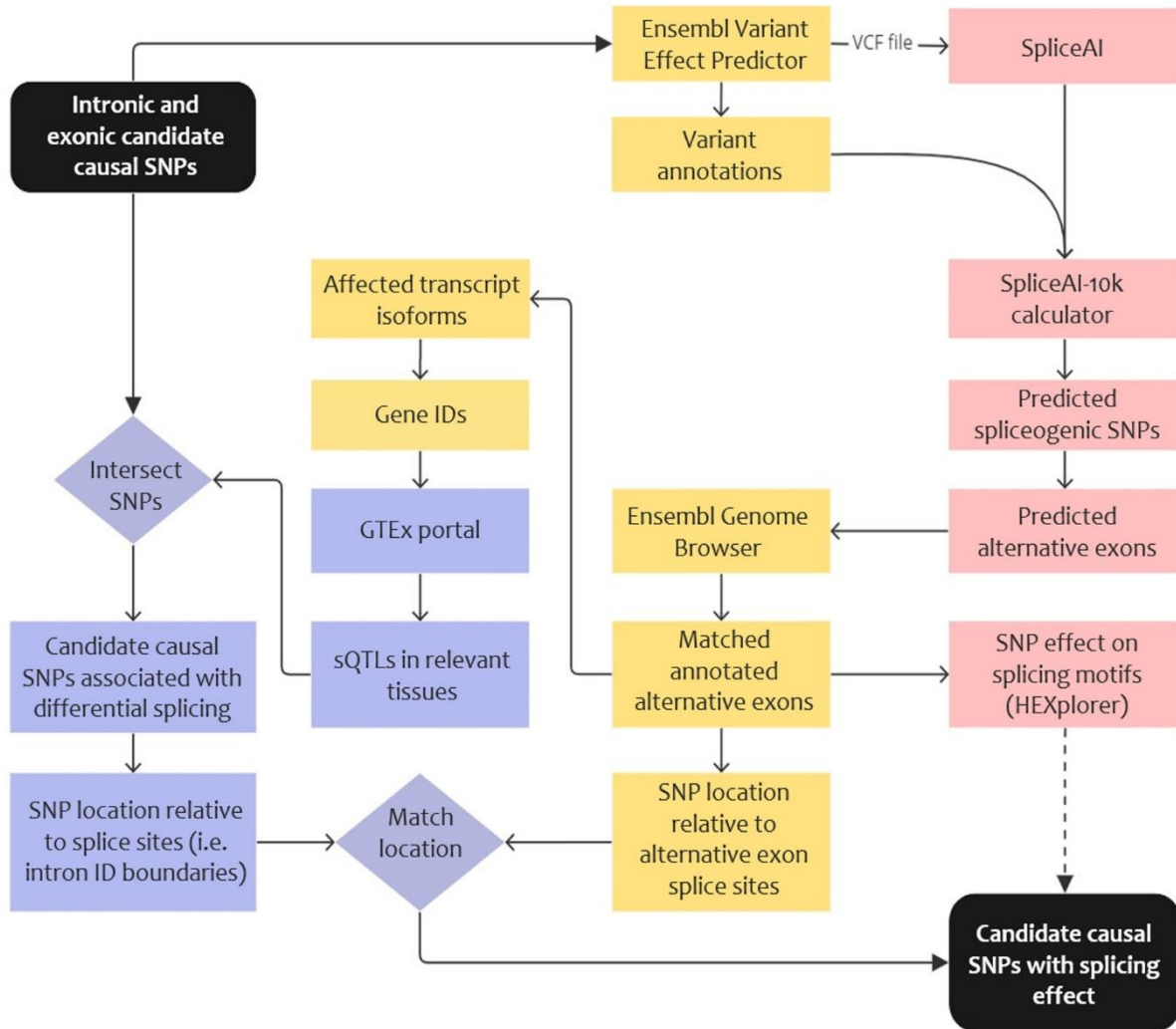
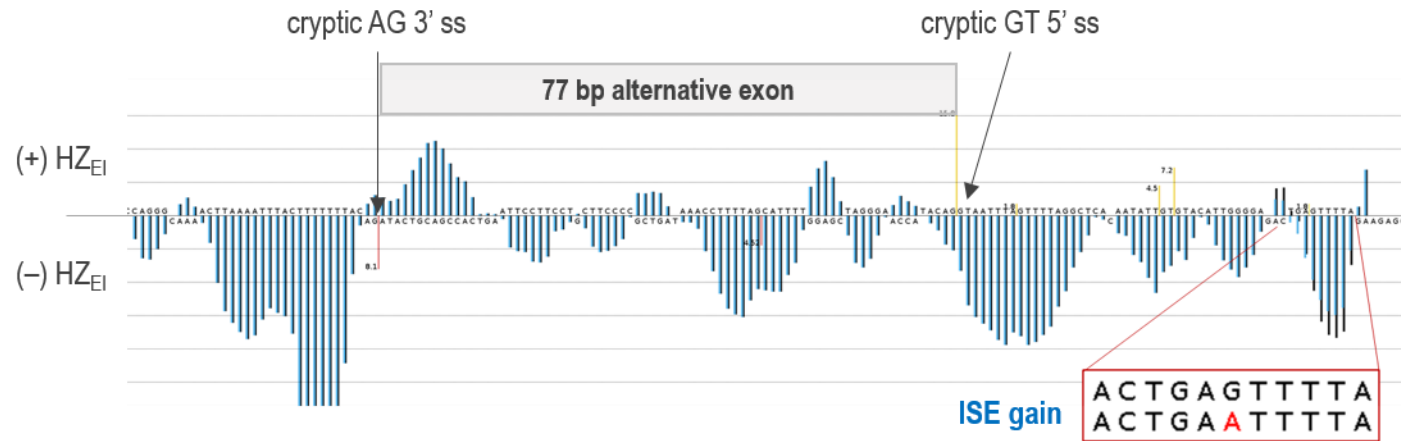


Figure S1. Flow diagram of analyses to identify candidate causal SNPs with splicing effect. Splicing predictions (pink) are supported by evidence from Ensembl variant/transcript annotations (yellow) and sQTL analysis results (blue). The broken arrow indicates positive prediction of splicing effect with matched Ensembl-annotated alternative exons/transcripts, but no evidence of splicing effect from sQTL analysis.

C. *NF1* c.8377+1709G>A (rs7502834)



D. *SKAP1* c.481G>A (rs2278868)

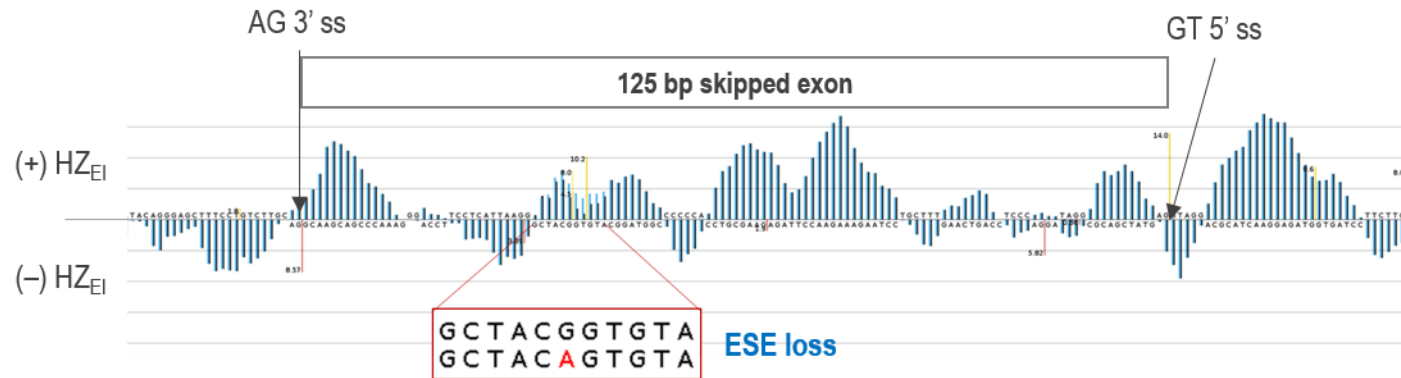
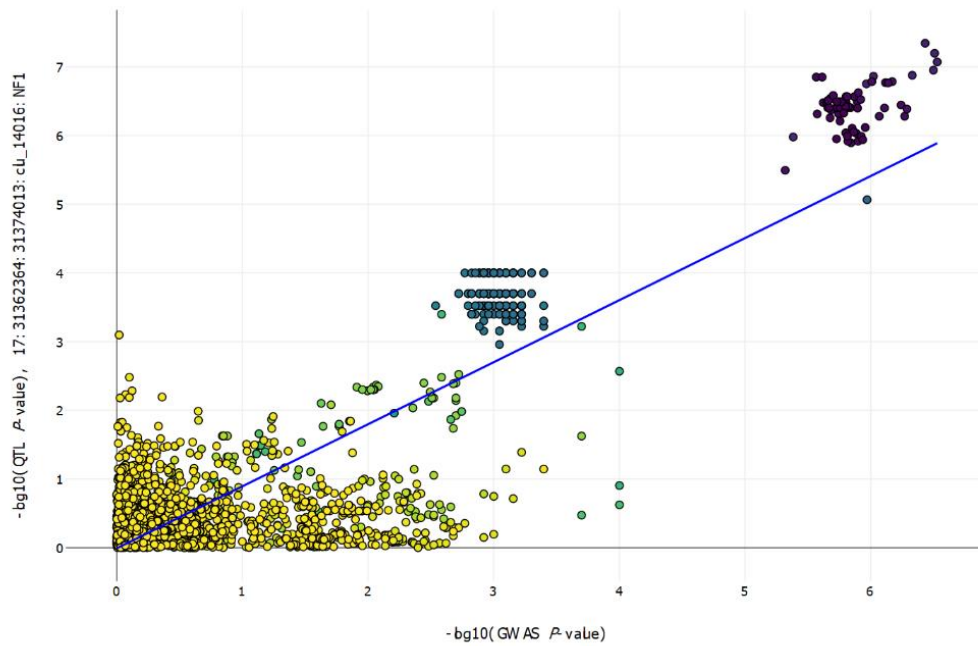


Figure S2. HEXplorer profile of alternatively spliced exons affected by candidate causal endometrial cancer GWAS variants in *NF1* and *SKAP1*. Blue (wild type) and black (variant) vertical lines represent HEXplorer¹ exon–intron Z-scores (HZ_{EI} score); exonic splicing enhancer (ESE) and intronic splicing silencer (ISS) motifs have positive scores, while exonic splicing silencer (ESS) and intronic splicing enhancer (ISE) motifs have negative scores. Red vertical lines below the x-axis represent AG 3' splice site (ss). Yellow vertical lines above the x-axis represent GT 5' ss. Variant nucleotides within the altered splicing motifs are in red font.

NF1

QTL-GWAS P -value Correlation: Spearman rho=0.328, Pearson's r=0.828



SKAP1

QTL-GWAS P -value Correlation: Spearman rho=0.43, Pearson's r=0.739

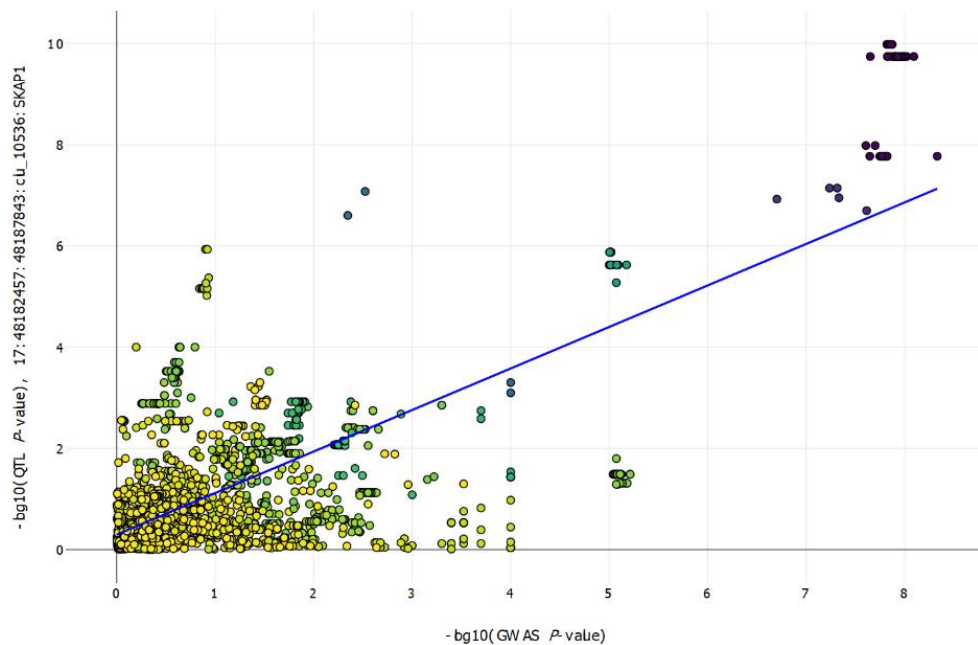


Figure S3. GWAS data and sQTL colocalization analysis. Each point is a variant at the locus. The x-axis is the $-\log_{10}(P\text{-value})$ for endometrial cancer risk from O'Mara et al. (2018),² and the y-axis is the $-\log_{10}(P\text{-value})$ for the sQTL association in subcutaneous adipose tissue for *NF1*, or in EBV-transformed lymphocytes for *SKAP1* in GTEx v8.

SUPPLEMENTAL REFERENCES

1. Erkelenz, S., Theiss, S., Otte, M., Widera, M., Peter, J.O., and Schaal, H. (2014). Genomic HEXploring allows landscaping of novel potential splicing regulatory elements. *Nucleic Acids Research* 42, 10681-10697.
2. O'Mara, T.A., Glubb, D.M., Amant, F., Annibaldi, D., Ashton, K., Attia, J., Auer, P.L., Beckmann, M.W., Black, A., Bolla, M.K., et al. (2018). Identification of nine new susceptibility loci for endometrial cancer. *Nature Communications* 9, 3166.