Multi-Tissue Transcriptome-Wide Association Study Identifies Genetic Mechanisms Underlying Endometrial Cancer Susceptibility

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1. Background

- Endometrial cancer is the most commonly diagnosed gynaecological cancer in developed countries.
- Although genome-wide association studies (GWAS) have identified genetic risk variants associated with endometrial cancer, our understanding about mechanisms underlying endometrial cancer susceptibility remains largely unknown.
- The goal of this study is to integrate endometrial cancer GWAS with expression quantitative trait loci (eQTL) datasets by transcriptome-wide association study (TWAS) to elucidate candidate genes for endometrial cancer.

2. Data and Methods

- Endometrial Cancer GWAS meta-analysis of 12,906 endometrial cancer cases and 108,979 controls of European descent [1].
- eQTL datasets for 48 tissues from the Genotype-Tissue Expression Project (GTEx v7).
- GWAS and eQTL datasets were integrated by TWAS analysis and subsequent colocalization. Prioritised genes were assessed for drug-gene similarities and pleiotropy associations.

3. Results: MultiXcan Analysis

- TWAS analysis by MultiXcan [2] prioritised 20 candidate genes for endometrial cancer at FDR<0.05 (**Figure 1**).

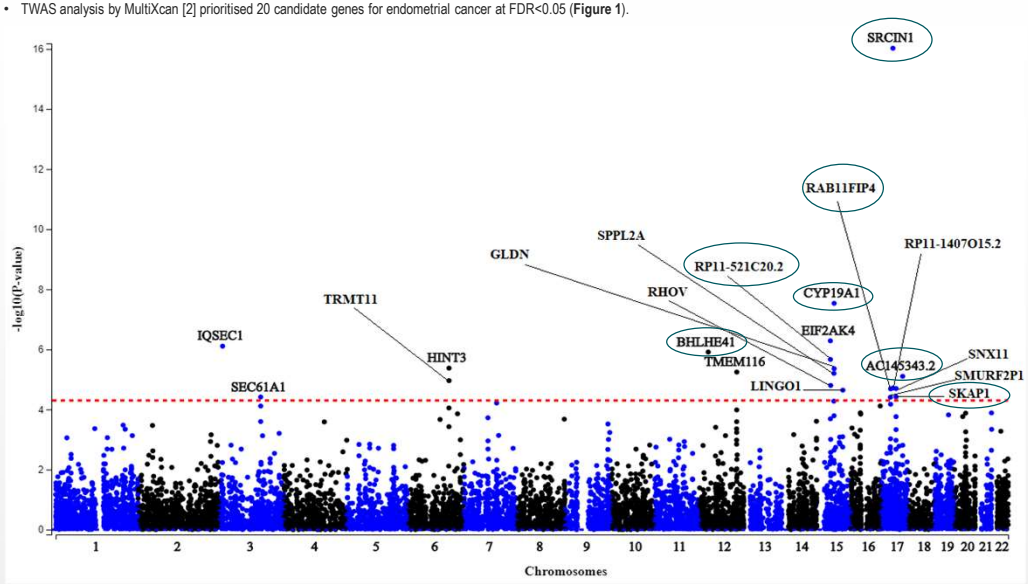

Figure 1: Manhattan plots of MultiXcan analysis, using eQTL data for 48 tissues. Red dotted line represents FDR < 0.05 significance threshold, which is equivalent to ~ P value 5 ×10^{-5}. Genes in circle were supported by colocalization analysis of GWAS signals and eQTL signals

4. Results: Colocalization Analysis

- 7 out of 20 TWAS candidate genes showed colocalization within the same region (e.g. **Figure 2**).

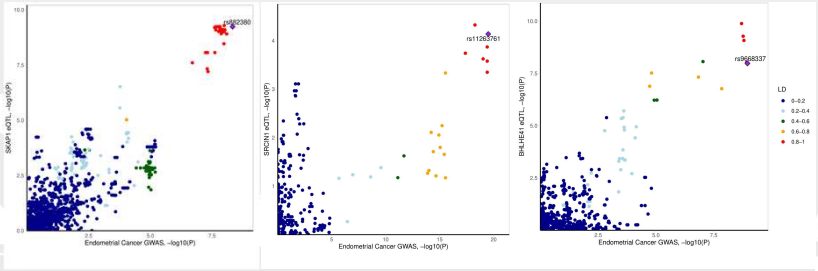

Figure 2: Examples of colocalization plots between GWAS signals and eQTL signals

5. Results: Drug-Gene Expression Similarity Analysis

- Drug-gene expression similarity was assessed for the 49 TWAS-identified genes (FDR<15%) using the Connectivity Map database [3].
- 14 candidate drug compounds were identified with opposing connectivity scores, including tubulin inhibitors, a drug class already in use for treatment of advanced endometrial cancer (**Table 1**).
- Nine candidate drug compounds were $Na^{+/}$ K^{+}-ATPase inhibitors; $Na^{+/}$ K^{+}-ATPase inhibitors have demonstrated anti-cancer activity in experimental models but have shown limited efficacy in clinical studies
- Ca^{2+}-ATPase inhibitor thapsigargin has demonstrated strong anti-proliferative effects in endometrial cancer cell lines but not selective for cancer cells
- Calcium channel activator cinacalcet has been approved for treating hypercalcemia and secondary hyperparathyroidism, could potentially be repurposed for endometrial cancer treatment

Table 1: Candidate drug targets identified from Connectivity Map

Connectivity score	Drug	Drug class	Clinically tested (phase) or approved for
-95.60	nocodazole	Tubulin inhibitor	No
-95.34	vincristine	Tubulin inhibitor	Acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin and non-Hodgkin lymphoma (approved)
-94.75	strophanthidin	Na+/ K+ -ATPase inhibitor	No
-94.45	cinacalcet	Calcium channel activator	Hypercalcemia and secondary hyperparathyroidism (approved)
-94.40	digitoxigenin	Na+/ K+- ATPase inhibitor	No
-93.97	periplocymarin	Na+/ K+ -ATPase inhibitor	No
-93.34	proscillaridin	Na+/ K+ -ATPase inhibitor	No
-93.06	thapsigargin	Ca^{2+}- ATPase inhibitor	No
-92.92	cinobufagin	Na+/ K+- ATPase inhibitor	Liver cancer and gastrointestinal neoplasm (Phase IV)
-92.46	digitoxin	Na+/ K+- ATPase inhibitor	Cystic fibrosis and sarcoma (Phase II)
-92.35	digoxin	Na+/ K+- ATPase inhibitor	Heart failure and atrial fibrillation (approved
-92.33	ouabain	Na+/ K+- ATPase inhibitor	No
-92.21	bufalin	Na+/ K+- ATPase inhibitor	Pancreatic cancer (Phase II)
-90.84	BNTX	Opioid receptor antagonist	No

*Candidate drug targets defined as chemical compounds with a Connectivity Score < -90.

6. Results: Phenome-wide lookup using CTG-VIEW

- Phenome-wide lookup using CTG-VIEW [4] highlighted 3 TWAS-identified candidate genes (*CYP19A1*, *AC145343.2* and *RAB11FIP4*) with potential pleiotropic effects on traits related to endometrial cancer risk factors, such as cardiovascular phenotypes, diabetes and hormone levels
- 3 TWAS-identified candidate genes also associate with traits related to bone health, haematopoiesis and liver function, providing avenues for future study

6. Discussion

- TWAS analysis identified 7 candidate endometrial cancer susceptibility genes, and provided evidence to support previously identified candidate genes.
- 3 out of 7 genes exhibit pleiotropy for several endometrial cancer risk factors, which may aid in understanding the biological mechanisms of endometrial cancer
- By comparing genetically predicted endometrial cancer gene expression with drug-induced gene expression profiles from Connectivity Map database, 14 drug repurposing candidates including tubulin inhibitors, a drug class already in use for treatment of advanced endometrial cancer
- TWAS-identified genes will be prioritised for assessment of their effect in cellular studies.

7. Acknowledgement and References

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References: [1] O'Mara et al 2019 *Nat Commun*; [2] Barbeira et al 2019 *Plos Genet*; [3] Subramanian et al 2017 *Cell*; [4] Cuellar-Partida et al 2019 *bioRxiv*.

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