

Integrative Functional Genomics Identifies Candidate Brain and Pituitary Regulatory Mechanisms of Reproductive Aging

Suzan Farhang-Sardroodi¹, Amin Madani^{2,3}, and Frank Rudzicz^{4,5}

¹*Department of Pharmacology & Toxicology, Temerty Faculty of Medicine, University of
Toronto, Toronto, Ontario, Canada*

²*Department of Surgery, University of Toronto, Toronto, Ontario, Canada*

³*Surgical Artificial Intelligence Research Academy, University Health Network, Toronto, Ontario,
Canada*

⁴*Faculty of Computer Science, Dalhousie University, Halifax, Nova Scotia, Canada*

⁵*Vector Institute for Artificial Intelligence, Toronto, Ontario, Canada*

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Supplemental Figures

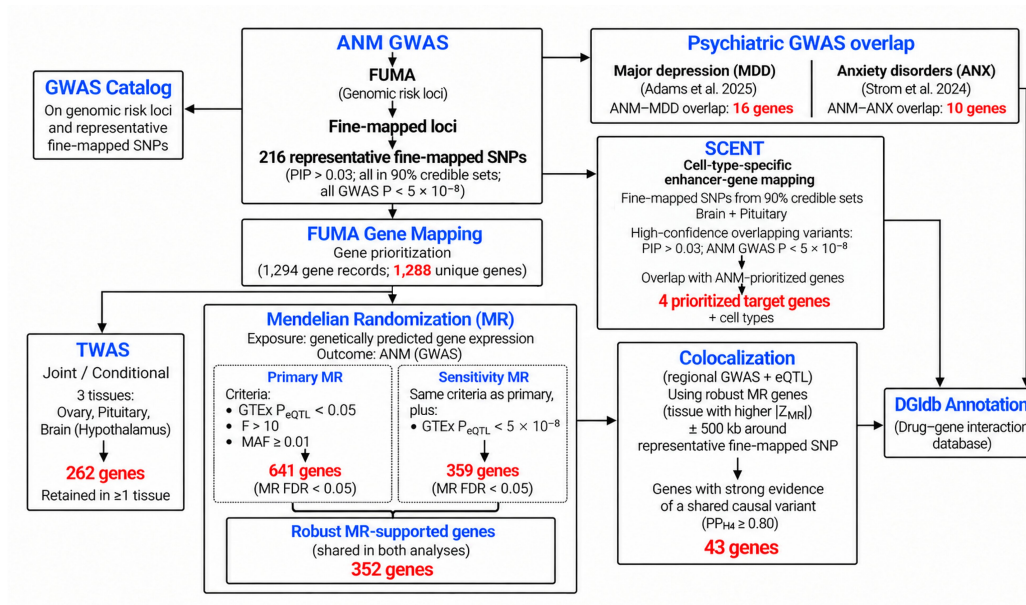


Figure S1: Overview of the integrative analytical workflow and key findings for age at natural menopause (ANM).

Supplemental Tables

Table S1. Genomic risk loci associated with ANM and assessment of previously reported menopausal-timing associations.

Table S2. Fine-mapping of ANM genomic risk loci and prioritized representative variants.

Table S3. Multi-layer xQTL annotation of ANM-prioritized genes.

Table S4. Transcriptome-wide association analysis of ANM.

Table S5. Mendelian randomization analysis of ANM-prioritized genes using GTEx v8 eQTL data.

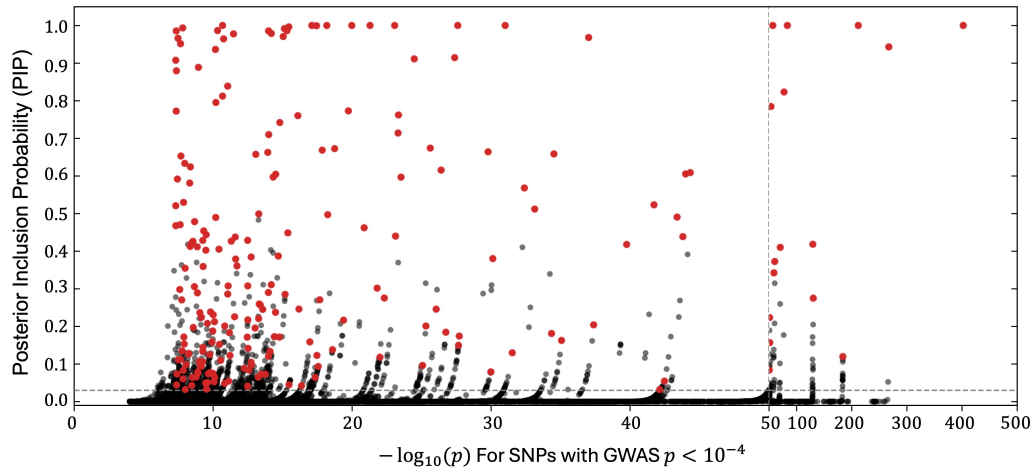


Figure S2: Posterior inclusion probabilities of fine-mapped ANM variants. Posterior inclusion probability (PIP) is plotted against GWAS association strength ($-\log_{10} P$). Red points indicate the 216 representative fine-mapped variants retained for downstream analyses, whereas black points indicate the remaining fine-mapped variants. The horizontal dashed line denotes the PIP threshold of 0.03. The vertical dashed line indicates the x-axis compression breakpoint at $-\log_{10}(P) = 50$.

Table S6. Colocalization analysis of ANM associations with GTEx v8 eQTL signals and pharmacological annotation.

Table S7. SCENT regulatory associations converging with prioritized ANM genes.

SCENT associations were restricted to fine-mapped variants within the 90% ABF credible sets with posterior inclusion probability (PIP) > 0.03 and genome-wide significant ANM association ($P < 5 \times 10^{-8}$). Only SCENT target genes that overlapped the independently prioritized ANM gene set are shown. Variants are ordered by decreasing PIP.

ID	SNP	Chr	MAF	A1	A2	GWAS P	PIP	SCENT Peak	Gene	Cell Type	SCENT β	SCENT FDR
1	rs2277339	12	0.104	G	T	6.439×10^{-84}	1.000	chr12-56751580-56752583	<i>HSD17B6</i>	Brain: INHNEU	-16.414	0.0022
2	rs9911630	17	0.335	G	A	1.902×10^{-51}	0.127	chr17-43035818-43036640	<i>NBR1</i>	Brain: OPC	0.679	0.0119
3	rs1384292	2	0.452	C	G	4.891×10^{-8}	0.521	chr2-212536138-212539590	<i>ERBB4</i>	Pituitary: Lactotrope	1.211	0.0230
4	rs1132803	17	0.223	G	A	1.513×10^{-10}	0.030	chr17-81702778-81703733	<i>HGS</i>	Brain: OPC	1.067	0.0453

Table S8. Integrated functional genomic evidence for ANM-prioritized genes.

Table S9. Gene-level overlap of ANM with MDD and anxiety and pharmacological annotation.