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Identifying therapeutic targets for primary ovarian insufficiency through integrated genomic analyses

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Abstract

Background Primary ovarian insufficiency (POI) is a disorder characterized by the premature decline in ovarian function, leading to significant fertility and health impacts on women under 40. The unclear etiology of POI hinders the development of effective treatments, highlighting the need for novel therapeutic targets.

Methods This study employed genome-wide association analysis (GWAS) integrated with expression quantitative trait loci (eQTL) data from the GTEx and eQTLGen databases. Mendelian randomization (MR) and colocalization analyses were conducted to investigate causal relationships between genetic variants and POI and to identify potential therapeutic targets.

Results We identified 431 genes with available index cis-eQTL signals, of which four (HM13, FANCE, RAB2A, and MLLT10) were significantly associated with POI. Colocalization analysis revealed strong evidence for FANCE and RAB2A, indicating their potential as therapeutic targets. Subsequent druggability assessments identified FANCE and RAB2A as promising candidates for POI treatment, supported by their involvement in DNA repair and autophagy regulation, respectively.

Conclusions Our study establishes a causal link between specific genes and POI, highlighting FANCE and RAB2A as potential drug targets. These findings provide a foundation for future research and therapeutic development, aiming to improve outcomes for women with POI. Validation in further trials is necessary to confirm these potential targets.

Keywords Primary ovarian insufficiency, Genome-wide, Mendelian randomization, Therapeutic target

Background

Primary ovarian insufficiency (POI) is a disorder characterized by a decline in ovarian function, loss of oocytes and folliculogenesis, and elevated gonadotropin levels, typically occurring in women under 40 years of age [1]. POI significantly affects women's fertility and quality of life [2]. The global prevalence of POI is approximately 3.7% and is increasing [3]. POI results from a premature decrease in ovarian follicles, accelerated follicle destruction, or a poor follicular response to gonadotropins. The pathogenesis remains inconclusive, with various factors implicated, including genetic, autoimmune,

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toxic, metabolic, infectious, and iatrogenic factors [1]. Hormone replacement therapy (HRT) is the primary pharmacological treatment for POI, yet scientific evidence supporting its efficacy in restoring ovarian function is lacking [4]. Research indicates that three out of four women with POI retain ovarian follicles, albeit in a dormant state [5]. Consequently, there is an urgent need for novel drugs to awaken dormant primordial follicles. However, the unclear etiology of POI presents a barrier to drug development.

Although the exact mechanism underlying POI remains unknown, numerous studies have identified genetic factors as the most commonly implicated cause, offering potential targets for therapeutic interventions [6, 7]. Currently, the most commonly recognized genetic causes of POI include X chromosome abnormalities, notably Turner syndrome (13% of cases) [8], and FMR1 premutations (3–15% of cases) [9]. A clinical study involving 27 POI patients identified FMR1 premutations as a potential target for treating occult POI [10]. Similarly, a multicenter observational study involving 291 POI patients identified seven genes (USP36, VCP, WDR33, PIWIL3, NPM2, LLGL1, and BOD1L1) as potential targets for POI treatment [11]. However, it is essential to recognize that these results stem from observational studies, making them susceptible to confounding variables and reverse causation. Additionally, the constraints of observational studies limit the investigation of causal relationships between different genetic variants and POI, underscoring the necessity for more rigorous research approaches.

Genome-wide association analysis (GWAS) is pivotal for identifying single nucleotide polymorphisms (SNPs) and novel genetic variants associated with diseases. Nevertheless, the risk loci identified via GWAS are predominantly in non-coding regions of the genome, complicating their interpretation [12]. In contrast, expression quantitative trait loci (eQTL) studies quantify gene expression levels across the genome, offering an unbiased view of gene expression regulation [13]. Combining eQTL data with GWAS findings facilitates the identification of target genes driving the GWAS signal at specific loci [12]. In our study, we employed eQTL as an exposure tool in Mendelian randomization (MR) to examine causal links between genetic variants and POI. Moreover, we performed colocalization analyses to identify potential therapeutic targets for POI.

Methods

Study design

The study design is illustrated in Fig. 1. Cis-eQTL data were obtained from the Genotype-Tissue Expression (GTEx, https://gtexportal.org/home/) database[14] and the eQTLGen consortium (https://www.eqtlgen.org/)[15]. POI GWAS data were sourced from the FinnGen study (https://www.finngen.fi/en)[16]. As this research reanalyzed previously collected and published data, no further ethics approval was required.

Acquisition of eQTL and GWAS Summary Data

Cis-eQTL data were utilized from GTEx V8 and the eQTLGen consortium [14, 15]. The GTEx V8 dataset included 838 primarily European participants and spanned 49 tissues or cell types. Specifically, cis-eQTL data from the ovary ($n=167$) and whole blood ($n=670$) were extracted within the GTEx V8 dataset. The eQTLGen consortium provided cis-eQTL data from peripheral blood samples of 31,684 participants. A PeQTL threshold of $<5\times10^{-8}$ was applied to all cis-eQTL. POI GWAS data were derived from the FinnGen study's R11 dataset, comprising 599 cases and 241,998 controls [16]. All participants in this dataset were of European descent.

MR Analysis

We utilized the SMR software tool (version 1.3.1) to conduct SMR analysis on cis-eQTL and GWAS data, aiming to identify gene-POI associations [17]. To address potential pleiotropy between exposure and outcomes, we performed an instrument-dependent heterogeneity (HEIDI) test on the cis-eQTL and GWAS data. A $P_{HEIDI} < 0.05$ indicates significant interlocking pleiotropy between two distinct genetic variants, leading to their exclusion from the study. Additionally, a two-sample MR analysis was conducted using gene-indexed SNPs, employing the Wald ratio and delta method to calculate odds ratios (OR) and 95% confidence intervals (CI) between genes and POI [17]. A Bonferroni-corrected $P<0.05$ was used as the threshold to establish a causal relationship between genes and GWAS [18].

Colocalization analysis

The coloc R package was employed to perform colocalization analyses, assessing the impact of linkage disequilibrium on gene-POI associations [19]. Colocalization, using a Bayesian approach, produced posterior probabilities for five hypotheses: PP.H0 indicates no association with either trait; PP.H1 indicates an association with trait 1 only (gene expression); PP.H2 indicates an association with trait 2 only (POI trait); PP.H3 indicates an association with both traits but different causal variants for each; and PP.H4 indicates an association with both traits with the same causal variant [20]. We applied default priors: $p1=1\times10^{-4}$, $p2=1\times10^{-4}$, $p12=1\times10^{-5}$. Low PP.H3 and PP.H4 combined with high PP.H0, PP.H1, and/or PP.H2 indicate limited power in the colocalization analysis. Therefore, we restricted our analysis to genes with PP.H3+PP.H4≥0.8 [21].

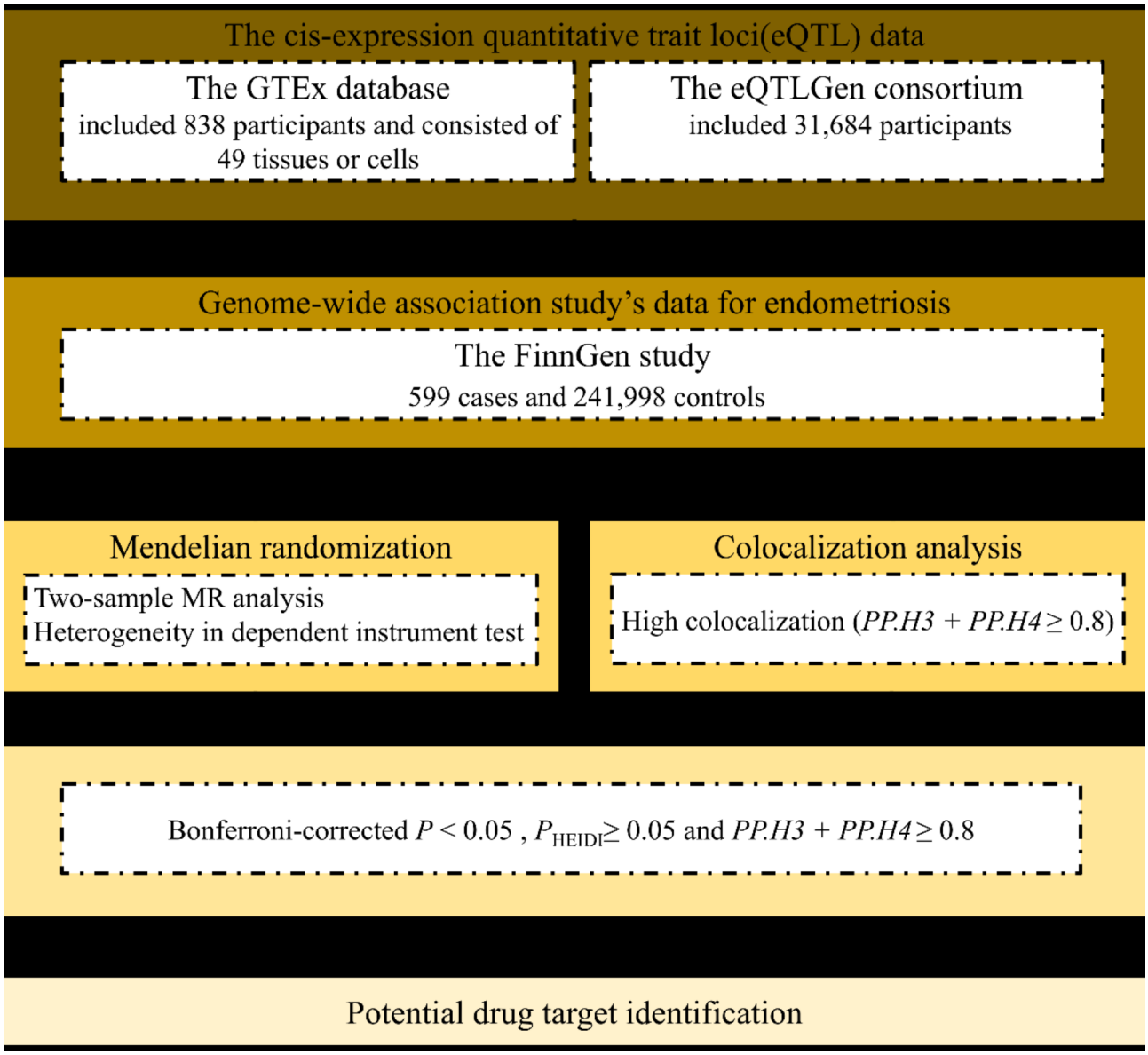

Fig. 1 Study design. PP.H3, the posterior probability of H3; PP.H4, the posterior probability of H4; HEIDI, instrument-dependent heterogeneity; MR, Mendelian Randomization

Potential drug target identification

To evaluate the druggability of the genes, we queried Online Mendelian Inheritance in Man (OMIM), the DrugBank database, the Drug-Gene Interaction database (DGIdb), and the Therapeutic Target Database (TTD) to identify mutations linked to phenotypic abnormalities. Our evaluation criteria included: (1) approval for marketing or involvement in clinical trials, (2) preclinical development stage, and (3) considered druggable, even if not documented in the database but recognized as a potential drug target by our team [22].

Results

Genome-wide MR analysis

GWAS loci are often located in non-coding regions of the genome, making it difficult to interpret their functions [23]. Cis-eQTL analysis helps determine whether non-coding loci identified by GWAS affect gene expression, elucidating the relationship between gene expression and genetic variation and identifying potential candidate genes [24]. In this study, we explored the association between 431 genes with available index cis-eQTL signals and the risk of POI outcomes using a two-sample MR analysis (Supplementary Table S1). Associations with $P_{\mathrm{HEIDI}} < 0.05$ were deemed likely due to pleiotropy, resulting in the exclusion of 57 genes from the analysis. By

applying a bonferroni-corrected *P* threshold of 0.05, we identified four genes with statistical significance. The MR analysis outcomes are illustrated in Fig. 2. Our findings predicted that HM13, FANCE, RAB2A, and MLLT10 were significantly associated with a reduced risk of POI (Table 1).

Colocalization analysis

In MR studies, linkage disequilibrium (LD) can affect result accuracy. Colocalization analysis helps distinguish between true causal variants and those merely linked to causal variants, enhancing causal inference accuracy [19]. Evidence suggests that genes supported by both MR and colocalization evidence are more likely to be successful drug targets [25]. We also performed colocalization analyses to examine genes related to POI, investigating whether the genes identified in the FinnGen study shared genetic variants associated with POI. We found strong evidence of colocalization (PP.H3+PP.H4≥0.8) for FANCE and RAB2A (Fig. 3) [21]. However, the posterior probability of HM13 and MLLT10 did not reach strong evidence of colocalization (PP.H3+PP.H4≥0.8), likely due to insufficient samples in GTEx and eQTLGen.

Druggability of identified genes

To determine the potential of genes identified by MR and colocalization analysis as drug targets, we specifically assessed FANCE and RAB2A, which showed strong evidence of colocalization. Although these genes have not been recognized as drug targets for POI in existing studies, they remain promising candidates (Supplementary Table S2). Mutations in FANCE and RAB2A are known to cause monogenic diseases. Specifically, mutations in the FANCE gene lead to Fanconi anemia (FA) [26], whereas no drug information was found for RAB2A. Our MR results suggest that inhibiting FANCE and RAB2A could potentially be a treatment for POI.

Discussion

Our study employed comprehensive genome-wide MR and colocalization analyses to clarify the causal relationships between genes and POI, providing valuable insights into potential therapeutic targets. MR analysis effectively reduced confounding factors in assessing the associations between gene expression and disease. Colocalization analysis confirmed that the eQTL instrument in the MR was not incidentally associated with both traits, thereby ruling out the possibility of the MR effect stemming from alternative causal variants in linkage disequilibrium. Among the genes analyzed, only FANCE and RAB2A exhibited evidence of a shared genetic effect with POI outcomes through both MR and colocalization analyses. FANCE and RAB2A were linked to a reduced risk of POI, highlighting their potential as promising targets for POI treatment.

FANCE is a subunit of the FA pathway, which plays a key role in repairing DNA interstrand cross-links. FA pathway genes encode proteins involved in gonadal development, DNA replication, and DNA repair [27]. Mutations in the FANCE gene cause FA in humans [28]. Our study confirmed that FANCE is associated with a reduced risk of POI and is a risk locus for POI. Interestingly, clinical evidence indicates that female FA patients exhibit reduced fertility, manifesting as POI [29]. Previous studies have shown that FANCE$^{-/-}$ mice exhibit ovarian dysplasia and severely reduced numbers of follicles by five days after birth, resembling women suffering from POI [30]. Animal experiments have also demonstrated that FANCE defects impair the rapid mitotic proliferation of primordial germ cells (PGCs) in mouse embryos, leading to a sharp decrease in PGCs number and abnormal cell cycle distribution [31]. These findings indicate that FANCE is essential for PGC survival, with potential mechanisms involving cell cycle regulation, DNA damage repair, cell death prevention, and the regulation of lysosome and ribosome functions [32].

In FA cells, DNA damage remains unrepaired due to a dysfunctional DNA repair process, causing cells to be blocked in the G2/M phase [33]. When DNA damage occurs in the primordial follicle, it responds by phosphorylating and activating TAp63 [34]. Activation of TAp63 induces the transcription of pro-apoptotic factors such as BH3, PUMA and NOXA. The upregulated expression of these proteins facilitates their interaction with the pro-apoptotic BCL2 family members, BAX and BAK [34]. The translocation of BAX and/or BAK to the oocyte's mitochondria causes mitochondrial dysfunction, release of apoptogenic proteins, and activation of caspase-9 and proteolytic enzymes, collectively triggering apoptosis and cell death [34]. The depletion of oocytes damages fertility and leads to POI [35]. Two rounds of meiosis are vital for oocyte maturation [36]. During the prophase of the first meiosis, fully grown oocytes are arrested in the germinal vesicle (G2) phase [37]. Meiotic resumption marks the initiation of oocyte maturation, characterized by germinal vesicle breakdown (GVBD), followed by meiotic spindle assembly and migration during metaphase I (MI)[38]. Subsequently, cytokinesis occurs, the oocyte extrudes the first polar body, and arrests in the metaphase II (MII) phase [37]. The G2/M phase and the MII phase are two major stages in oocyte meiosis [38]. G2/M cell cycle blockade leads to meiotic recovery failure, chromosome misalignment, increased aneuploidy, abnormal spindle assembly, and severe meiotic defects in oocytes [37, 39, 40]. These issues are the main causes of ovarian aging and reduced female fertility [41].

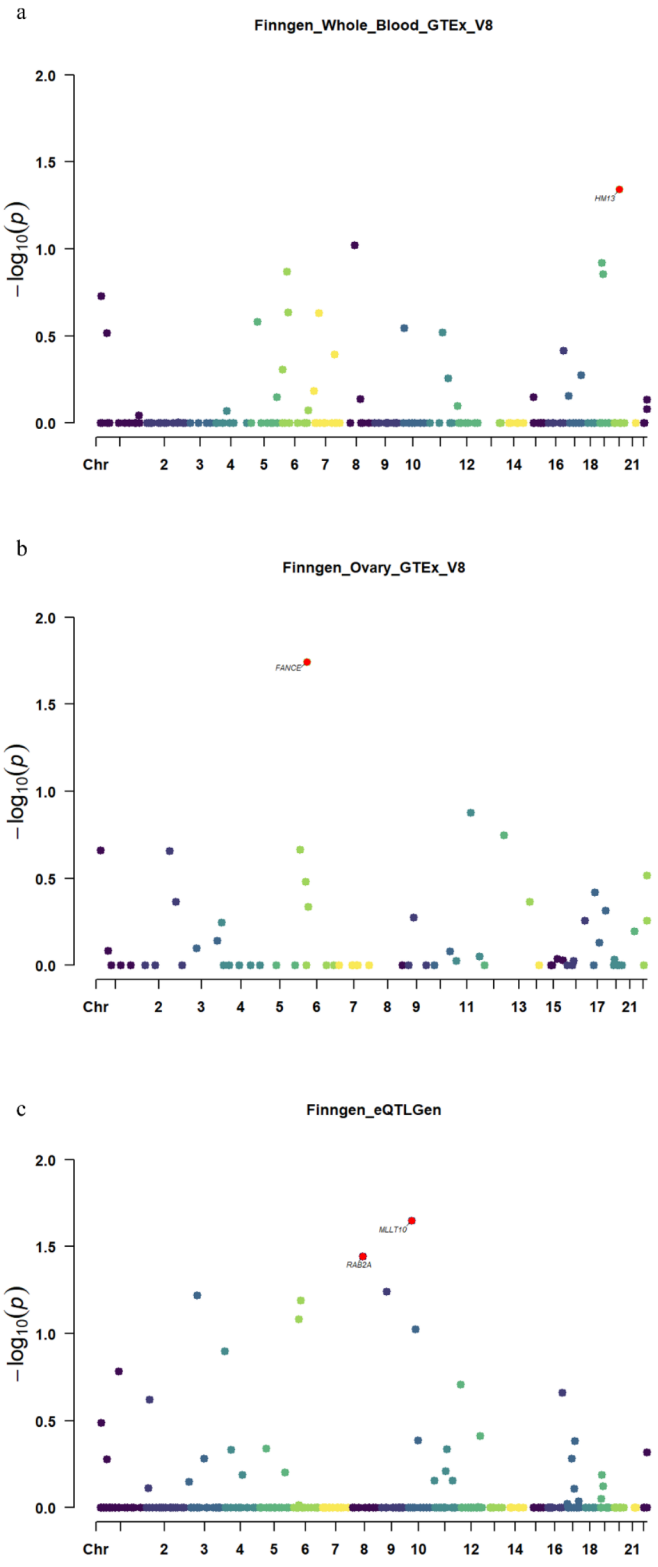

Fig. 2 Manhattan plots for associations of genome-wide with POI in MR analysis. Labelled and red genes refer to MR findings with $P_{HEIDI} \geq 0.05$ and Bonferroni-corrected $P < 0.05$. (**a**) Associations of genetically predicted genes levels from Finngen_Whole_Blood_GTEx_V8 with POI; (**b**) Associations of genetically predicted genes levels from Finngen_Ovary_GTEx_V8 with POI; (**c**) Associations of genetically predicted genes levels from Finngen_eQTLGen with POI

Table 1 The mendelian randomization and colocalization results of cis-eQTL datasets and POI GWAS

Outcomes datasets	Outcomes	SMR datasets	Gene	OR (95%CI)	*P*-value	Bonferroni-corrected *P*	P_{SMR}	P_{HEIDI}	Colocalization Analysis PP.H4.abf_conditional
Finngen R11	POI	Whole_Blood_GTEx_V8	HM13	0.76 (0.66–0.88)	0.0003	0.046	0.0004	0.26	0.78
		Ovary_GTEx_V8	FANCE	0.82 (0.72–0.93)	0.0003	0.018	0.002	0.66	0.86
		eQTLGen	RAB2A	0.73 (0.62–0.86)	0.0001	0.036	0.000	0.54	0.91
			MLLT10	0.74 (0.64–0.86)	0.00008	0.022	0.000	0.06	0.01

Note: CI, confidence interval; OR, odds ratio; HEIDI, instrument-dependent heterogeneity

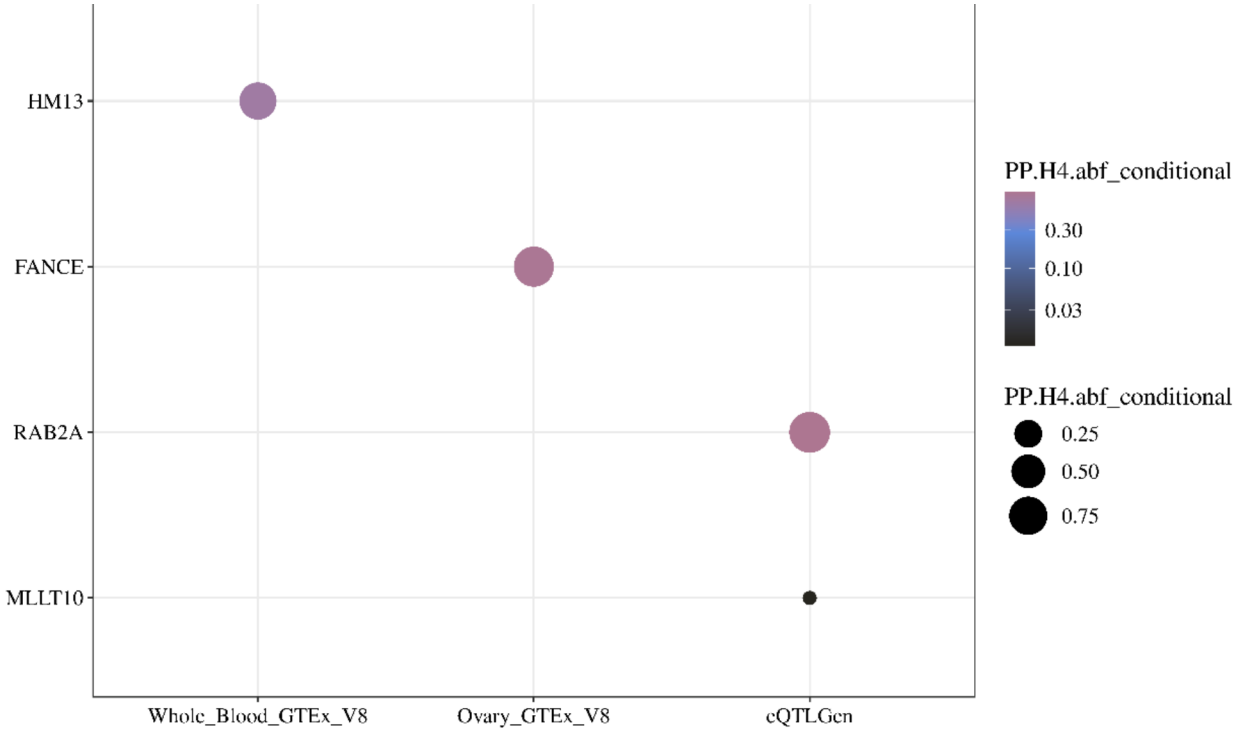

Fig. 3 High support evidence for colocalization between genes and POI. The size and colour of circle indicate the for PP.H3 + PP.H4

RAB2A, a member of the Rab family, is localized to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) transport complex and regulates ERGIC transport within the cell membrane [42]. Our findings indicate that genetically predicted RAB2A is inversely associated with the risk of POI. The HEIDI test and colocalization analysis further ruled out the possibility of horizontal pleiotropy. While current studies show that RAB2A is associated with sperm viability and motility function in men [43], the mechanism of premature ovarian aging in females with POI remains unclear.

Numerous studies have shown that ovarian aging is associated with mitochondria, oxidative stress, DNA damage, protein homeostasis, aneuploidy, apoptosis, and autophagy [44]. Previous research has demonstrated that RAB2A regulates autophagosome-lysosome fusion [45]. RAB2 may regulate autophagy initiation through three mechanisms: (1) Transporting Golgi-derived ATG9+vesicles to phagophore assembly sites. (2) Recruiting ULK1 to phagophore assembly sites, as ULK1 appears soluble and forms a diffused cytosolic pattern in the absence of RAB2A. (3) Facilitating ULK1 activation to propagate signals for autophagy initiation [45]. Autophagy plays a crucial role in oocyte development. Under normal circumstances, oocytes cannot actively induce mitophagy to clear damaged mitochondria. However, oocyte mitophagy can be initiated by drugs or abnormal environmental stimuli, affecting the developmental ability of oocytes [46]. Based on our findings and literature reports, we hypothesize that high expression of RAB2A may induce abnormal autophagy in oocyte mitochondria, resulting in a decrease in the number and quality of oocytes, ultimately leading to POI. However, this hypothesis requires further study as no correlation has been reported in the literature yet.

The strength of our study lies in employing MR and colocalization analyses to evaluate gene causality in POI records through genetic variation. MR analysis reduces

biases from confounders and reverse causation, thereby increasing the reliability of causality results. Colocalization analysis is instrumental in revealing the pleiotropic effects of specific loci on multiple traits, avoiding LD and identifying potential therapeutic targets. Additionally, we utilized extensive GWAS data, allowing the simultaneous examination of numerous genes and variants. This cost-effective and efficient method thoroughly investigates the gene-disease relationship. Our study integrated multiple databases, enhancing the robustness of our findings. Focusing on European populations minimized bias related to ethnic disparities.

Nonetheless, certain limitations should be acknowledged. Firstly, our colocalization analyses are constrained by the availability of outcomes from existing studies, limiting the examination of undiscovered genetic variants. Moreover, the reliance on instrumental variants in colocalization analysis can introduce bias if these variants correlate with unmeasured variables. Finally, while focusing on specific ethnicities reduces racial bias, it also limits the generalizability of our findings to diverse ethnic groups.

Conclusion

Our study has successfully established a causal relationship between genes and POI through comprehensive genome-wide MR and colocalization analyses. We identified FANCE and RAB2A as potential drug targets for POI treatment. However, these findings require validation in future trials.

Abbreviations

POI	Primary ovarian insufficiency
HRT	Hormone replacement therapy
GWAS	Genome-wide association analysis
SNP	Single nucleotide polymorphisms
eQTL	expression quantitative trait loci
MR	Mendelian randomization
HEIDI	Instrument-dependent heterogeneity
CI	Confidence intervals
OR	Odds ratios
OMIM	Online Mendelian Inheritance in Man
DGIdb	The Drug-Gene Interaction database
TTD	Therapeutic Target Database
HM13	Histocompatibility minor 13
FANCE	FA complementation group E
RAB2A	RAB2A, member RAS oncogene family
MLLT10	MLLT10 histone lysine methyltransferase DOT1L cofactor
LD	Linkage disequilibrium
FA	Fanconi anemia
PGCs	Primordial germ cells
BH3	BCL2 homology 3
PUMA	p53-upregulated modulator of apoptosis
G2	Germinal vesicle
GVBD	Germinal vesicle breakdown
MI	Metaphase I
MII	Metaphase II
ERGIC	Endoplasmic reticulum-Golgi intermediate compartment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-024-01524-y.

Supplementary Material 1

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Author contributions

Conceptualization, HD, PZ and ZH; Formal analysis, HD; Methodology, HD and XL; Resources, ZH and JZ; Supervision, JZ; Visualization, HD and PZ; Writing-original draft, HD; Writing-review & editing, PZ, XL, JZ, and ZH. All authors reviewed the manuscript.

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Data availability

All data analysed in this study can be obtained by a reasonable request to corresponding authors.

Declarations

Competing interests

The authors declare no competing interests.

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