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ORIGINAL RESEARCH

Exploring the Causal Relationship and Molecular Mechanisms Between Fasting Insulin and Androgenetic Alopecia: A Mendelian Randomization Study with Bioinformatics Analysis

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Background: Prior studies have suggested a significant connection between fasting insulin (FI) and androgenetic alopecia (AGA), but the exact cause of this connection and underlying molecular mechanism has not been clarified. In this study, a Mendelian randomization (MR) analysis was utilized to discover the causal associations between FI and AGA.

Methods: Genome-wide association study (GWAS) data for FI and AGA were retrieved, and bidirectional MR analysis was conducted. FI-associated genes were identified through expression quantitative trait loci (eQTL) analysis, with enrichment analysis and a protein-protein interaction (PPI) network used to explore potential pathways and core genes.

Results: Forward MR analysis revealed a significant causal relationship between elevated FI levels and AGA (P=0.027, OR=43.944). Reverse MR analysis found no causal effect of AGA on FI (P=0.808, OR=1.0001). A total of 92 FI-associated genes were analyzed, with enrichment results indicating involvement in glycine, serine, and threonine metabolic pathways. EIF2B4 and NRBP1 were identified as potential core genes linking FI and AGA.

Conclusion: By using MR analysis, this study verified the possible causative connection between FIns and AGA by MR analysis. The core genes EIF2B4 and NRBP1, along with biological processes such as glycosylation and amino acid metabolism, may serve as crucial links.

Keywords: androgenetic alopecia, fasting insulin, Mendelian randomization, GWAS, bioinformatics

Introduction

Androgenetic alopecia (AGA) is an autosomal dominant disorder marked by widespread hair loss with preservation of the frontal hairline in women and a receding frontal hairline in men. Patients with AGA may experience substantial psychological discomfort.[1,2] The disorder is largely caused by the enzyme 5-reductase and the hormone dihydrotestosterone (DHT), which causes hair follicles to shrink and continuous growth cycles to shorter.[3,4] Besides, Hamilton proposed the mutual interplay of androgens, genetic and age factors in the origin of AGA.[5] But up to now, the pathogenesis of androgenic alopecia is still unclear to some extent.

A growing body of literature has revealed associations between androgenic alopecia (AGA) and various metabolic disorders, including metabolic syndrome, insulin resistance, hypertension, dyslipidemia, and obesity.[6,7] Fasting insulin (FI), which refers to the measurement of insulin levels in a fasting state, is a hormone secreted by the pancreas that plays a crucial role in regulating carbohydrate metabolism.[8–10] FI levels are highly susceptible to Insulin resistance (IR) associated with metabolic disorders such as diabetes and metabolic syndrome (MetS).[11] However, the relationship

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between AGA and FI remains poorly understood. Therefore, further investigation into the association between AGA and fasting insulin may contribute to the understanding of AGA pathogenesis.

Mendelian randomization (MR), an instrumental variable analysis method that utilizes genetic variations linked to exposure for determining causal effects on outcomes,[12,13] is generally robust against reverse causation and confounding variables while being strongly related to the relevant exposure.[14,15] Despite previous evidence suggesting that patients with AGA are more prone to cardiovascular diseases, MetS, diabetes mellitus, and hypertension; no study has utilized MR analysis to investigate FI as risk factor associated with AGA prior to this research.[6,16] To address some limitations identified in previous studies, this study aims at examining the association between AGA and FI using MR analysis. To further elucidate the underlying molecular mechanisms, this study also aimed to perform enrichment analysis by single nucleotide polymorphism (SNP) -related genes and construct protein-protein interaction (PPI) networks. The findings offer novel insights into the bidirectional causal relationship and underlying mechanisms between Fins and AGA, thereby providing valuable guidance for preventing the development of AGA.

Materials and Methods

Data Sources and Preprocessing Procedures

The AGA dataset was obtained from the Genome-Wide Association Studies (GWASs) database (https://gwas.mrcieu.ac.uk/), encompassing a total of 212,453 AGA samples and 8,885,805 SNPs specific to the AGA population. For fasting insulin analysis, the sample size comprised 151,013 individuals with genotypic information available for 29,664,438 SNPs and in the sample. This study is a secondary analysis based on publicly available genetic databases, utilizing exclusively de-identified aggregate data from published Genome-Wide Association Studies (GWAS). In accordance with Article 32, Clause 2 of the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (issued on February 18, 2023), this research is exempt from ethical review.

Selection of Eligible Instrumental Variable

The selection of appropriate instrumental variables (IVs) is crucial in Mendelian randomization (MR) analysis, which uses genetic variants associated with the exposure to establish causal relationships between the exposure and outcome. To identify eligible IVs, three key assumptions must be satisfied: (1) there should be a strong association between IVs and exposure; (2) the IVs should be independent of confounding factors; and (3) the effect of IVs on the outcome should only occur through their impact on exposure without any alternative pathways. Therefore, potential instruments were restricted to SNPs directly associated with the exposure at a genome-wide significant p-value threshold of $p < 5e\text{-}08$. The identification of exposure factors and filtering of IVs were performed using the twoSampleMR R package[17] and extract instruments function.

Bidirectional Two Sample MR Analysis

Once the eligible IVs were selected, independent SNPs were clumped at a threshold of linkage disequilibrium (LD) at r2 = 0.001 within the window of 10 megabase pairs in order to avoid duplication and biased estimates of causal effects. Next, the IVs from the end result trait were retrieved and synchronized in both exposure and outcome GWAS. In this step, palindromic SNPs with intermediate allele frequency were excluded. Univariable MR analyses were conducted to estimate the overall causal effect of FI on AGA using three methods: Weighted median, Inverse variance weighted (IVW), and Simple mode. The results primarily relied on IVW.

To investigate the direct effects of FI on AGA, multivariable MR analysis was performed as an extension of univariable MR that allows for detecting joint causal effects of multiple risk factors. The IVW method was employed for MR analysis to provide consistent estimates when there is no pleiotropy among instrumental variables. The SNPs used in multivariable MR consisted of combinations from each exposure's IVs. Cochran's Q statistics was utilized to assess heterogeneity across individual SNPs. Sensitivity testing was conducted using three methods: mr_heterogeneity test for assessing heterogeneity where a Q value greater than 0.05 indicates no heterogeneity; Horizontal pleiotropy test

for evaluating horizontal pleiotropy where a p-value greater than 0.05 suggests no horizontal pleiotropy; Leave-One-Out method aimed at identifying outlier values for the effect estimation of each SNP.

Functional Annotation

Target SNPs were focused and the eQTLGen Consortium's SNP database (https://eqtlgen.orgphase1.html) was utilized to identify genes associated with these SNPs. Specifically, the names of target SNPs were input to retrieve their corresponding cis-eQTLs (cis-regulated, https://eqtlgen.org/cis-eqtls.html). Cis-eQTLs primarily refer to genetic variants that are in close proximity to the regulated gene, typically within a 1Mb region upstream or downstream of the gene.

Enrichment Analysis and PPI Network Construction

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were conducted using SangerBox (http://sangerbox.com) and Metascape (https://metascape.org/). The input genes included genes associated with SNPs. A hypergeometric test was used to assess the over-representation of GO terms and KEGG pathways, with p-values adjusted using the Benjamini-Hochberg (BH) method to control the false discovery rate (FDR). Pathways or categories with an adjusted p-value < 0.05 were considered significantly enriched. Protein-protein interaction (PPI) networks were generated using the STRING database (https://string-db.org), with the confidence score threshold set at 0.4 (medium confidence). Disconnected nodes in the network were removed, and the resulting network was visualized and analyzed using Cytoscape software.[18] Hub genes were determined based on network topology parameters calculated using the CytoHubba plugin.

Ethics Statement

This study conducted a secondary analysis using publicly available aggregate summary data obtained from previously published studies. No original data were collected, and no direct involvement with study participants occurred. Ethical approvals for each primary study are documented in the original publications.

Results

Study Design

A schematic representation of the study design is presented in Figure 1.

Genetic Instruments and Forward MR Analysis (FI as Exposure and AGA as Outcome)

The study identified a set of 38 SNPs as IVs for FI. None of these 38 SNPs showed any association with androgenetic alopecia (AGA). Univariable Mendelian randomization analysis revealed a significant causal relationship between FI and AGA, indicating that elevated FI is positively associated with an increased risk of AGA development (P=0.027, OR=43.944) (Table 1).

The scatter plot revealed a positive slope for FI, indicating its role as a risk factor for AGA (Figure 2A). The forest plot data indicated that SNP points for FI were on the right, supporting the notion that it was a risk factor for AGA (Figure 2B). The funnel plot suggested that MR is consistent with Mendel's second law of random grouping (Figure 2C). The sensitivity analysis results indicated that the p-values for fasting insulin were greater than 0.05, suggesting no evidence of heterogeneity. Moreover, the P-value for Horizontal pleiotropy was also greater than 0.05, indicating the absence of horizontal multi-effect. Additionally, the forest plot generated by the leave-one-out method revealed all error lines positioned to the right of zero, implying a lack of deviation points (Figure 2D).

Genetic Instruments and Reverse MR Analysis (AGA as Exposure and FIns as Outcome)

The selection of 63 SNPs as IVs for androgenetic alopecia (AGA) yielded no associations with fasting insulin levels. Univariate Mendelian randomization analysis revealed that AGA was not causally related to fasting insulin levels, despite the initial suggestion of a potential risk (P=0.808, OR=1.0001) (Table 2).

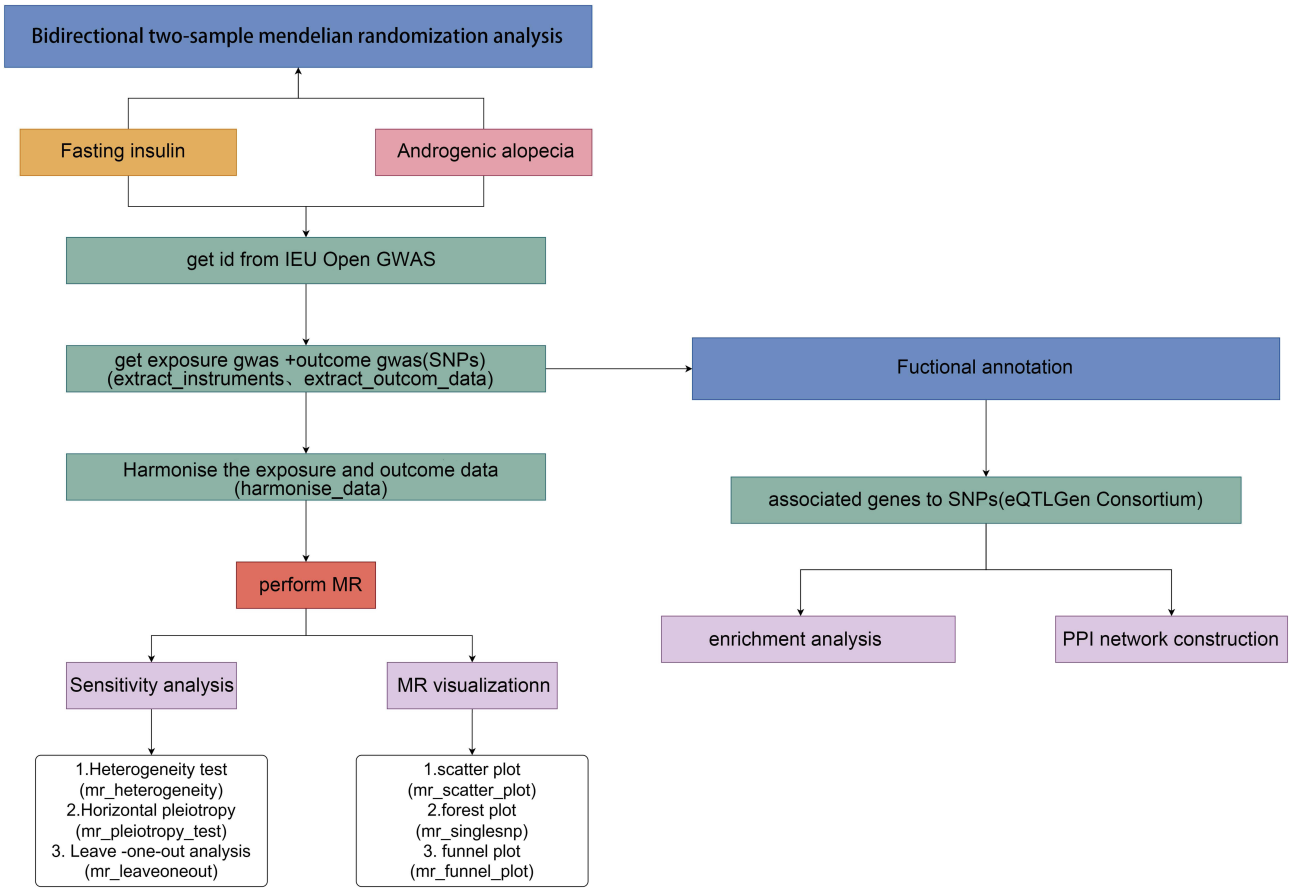

Figure 1 Flow chart of the present study.

The scatter plot indicated a positive slope for the line representing AGA, suggesting that AGA is a risk factor for fasting insulin (Figure 3A). The results of the forest plot supported the notion that AGA was a risk factor for fasting insulin, as evidenced by the SNP points being on the right side (Figure 3B). The funnel plot demonstrated that Mendel's second law of random grouping was consistent with MR analysis (Figure 3C). Sensitivity analysis revealed no heterogeneity, as indicated by Q=0.280. The P-value of horizontal pleiotropy was 0.715, indicating no evidence of horizontal multi-effect. The forest plot of the leave-one-out method claimed that there were no points of deviation (Figure 3D).

Gene Set Enrichment Analyses

The eQTLGen Consortium identified a total of 92 genes associated with SNPs specific to FIns. Enrichment analysis results from Metascape (Figure 4A and B) revealed their involvement in translation, endoplasmic reticulum to Golgi

Table 1 Mendelian Randomization Analysis of Fasting Insulin Levels (Exposure) and AGA (Outcome)

Outcome	Exposure	Method	nSNP	b	pvalue	or
Androgenic alopecia || id:finn-b-L12_ALOPECANDRO	Fasting insulin || id:ebi-a-GCST90002238	Weighted median	38	5.476	0.021	238.821
Androgenic alopecia || id:finn-b-L12_ALOPECANDRO	Fasting insulin || id:ebi-a-GCST90002238	**Inverse variance weighted**	38	3.783	**0.027**	43.944
Androgenic alopecia || id:finn-b-L12_ALOPECANDRO	Fasting insulin || id:ebi-a-GCST90002238	Simple mode	38	3.777	0.404	43.694

Notes: Bold font denotes key results in this table, including: The main analytical method (Inverse Variance Weighted, IVW), central to Mendelian randomization analysis; p-values.

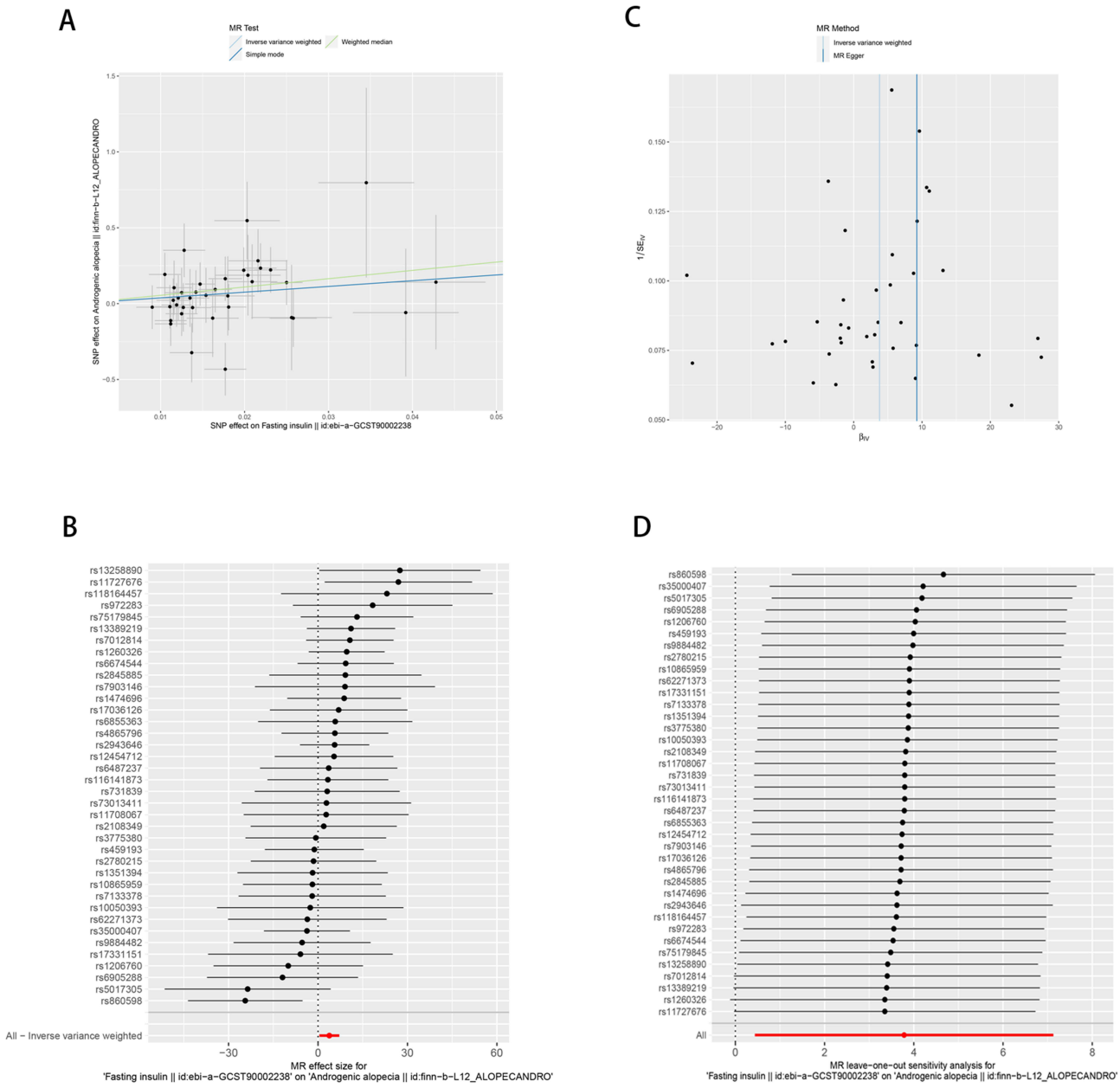

Figure 2 (**A**) The causality of FI on AGA risk. (**B**) Forest plot showing the effect of FI on AGA. (**C**) Funnel plot to assess the heterogeneity of FI. (**D**) Leave-one-out analysis of the effect of FI on AGA.

vesicle-mediated transport, diseases of glycosylation, and amino acid metabolic processes. KEGG enrichment analysis results from Sangerbox (Figure 4C) indicated significant enrichment in the MAPK signaling pathway, glycine, serine and threonine metabolism, carbon metabolism, Rap1 signaling pathway, and Ras signaling pathway. Additionally, GO

Table 2 Mendelian Randomization Analysis of AGA (Exposure) and Fasting Insulin Levels (Outcome)

Outcome	Exposure	Method	nSNP	b	pval	or
Fasting insulin || id:ebi-a-GCST90002238	|| id:finn-b-L12_ALOPECANDRO	Weighted median	62	0	0.631	0.9997
Fasting insulin || id:ebi-a-GCST90002238	|| id:finn-b-L12_ALOPECANDRO	**Inverse variance weighted**	62	0	**0.808**	1.0001
Fasting insulin || id:ebi-a-GCST90002238	|| id:finn-b-L12_ALOPECANDRO	Simple mode	62	0	0.664	0.9995

Notes: Bold font denotes key results in this table, including: The main analytical method (Inverse Variance Weighted, IVW), central to Mendelian randomization analysis; p-values.

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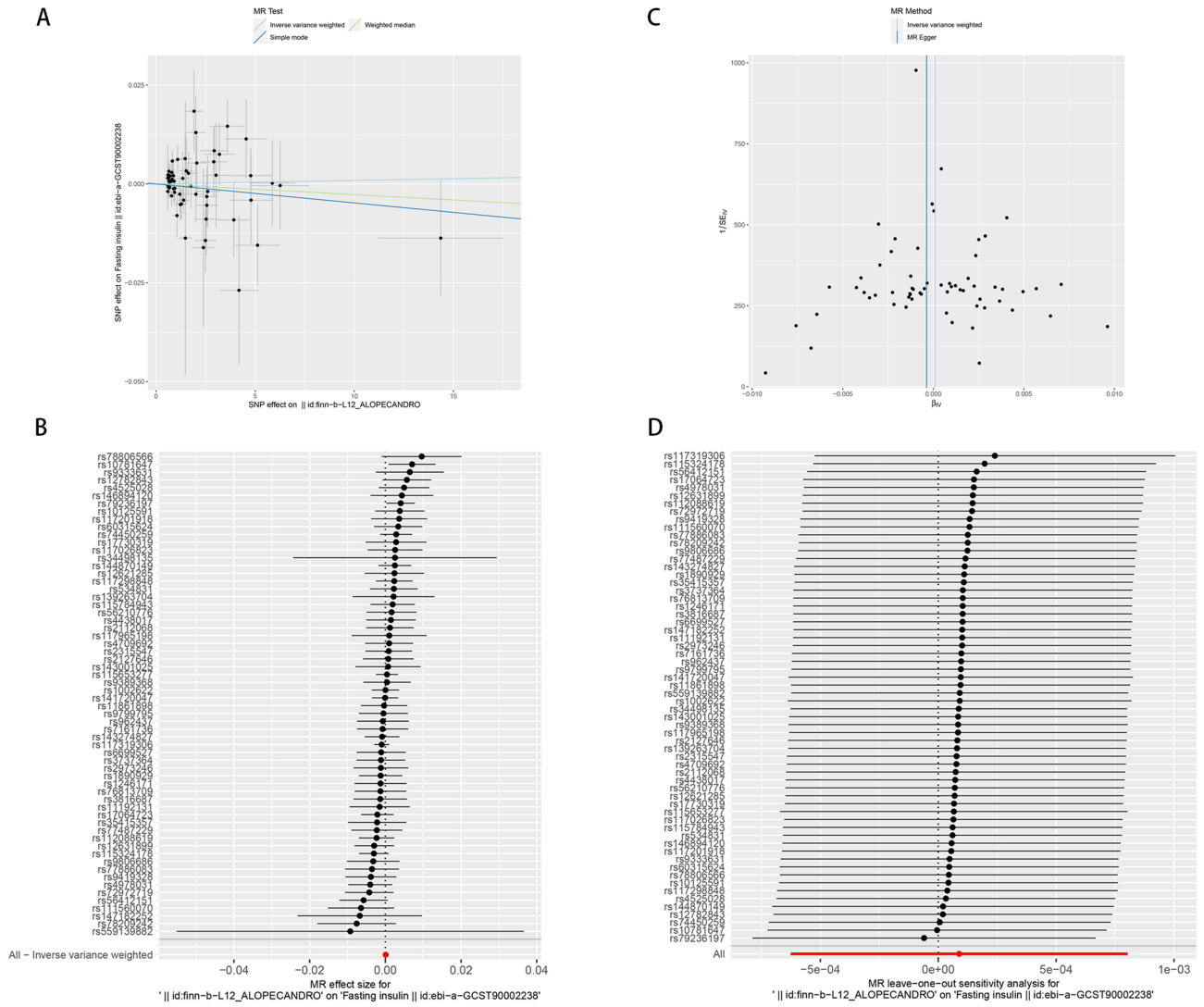

Figure 3 (**A**) The causality of AGA on FI risk. (**B**) Forest plot showing the effect of AGA on FI. (**C**) Funnel plot to assess the heterogeneity of AGA. (**D**) Leave-one-out analysis of the effect of AGA on FI.

enrichment analysis results shown in Figure 4D demonstrated their association with catalytic activity, ATP binding, and oxidoreductase activity. Furthermore, a protein-protein interaction network was constructed using STRING and Cytoscape for the 92 genes. As depicted in Figure 4E, the degree value of each gene is represented by the color intensity of its corresponding circle; EIF2B4 and NRBP1 were found to have the highest degree values.

Discussion

This study utilized a Mendelian randomization (MR) approach to investigate the causal relationship between fasting insulin (FI) levels and androgenetic alopecia (AGA), a condition traditionally characterized by androgen sensitivity and hair follicle miniaturization. Our findings suggest that elevated FI levels are a causal risk factor for AGA; however, no evidence was found to support a reverse causal relationship, where AGA might influence FI levels. This unidirectional causality highlights the systemic influence of metabolic dysregulation on AGA, reframing the condition as one potentially linked to broader metabolic health disturbances.

AGA is a multi-factorial disorder involving the interplay of genetic predispositions, hormone regulation (eg, androgen receptor signaling), and local tissue-level disturbances.[19,20] Increasing evidence indicates that systemic factors, particularly those related to metabolic health, can amplify androgen-driven miniaturization of hair follicles.[21,22] Elevated FI,

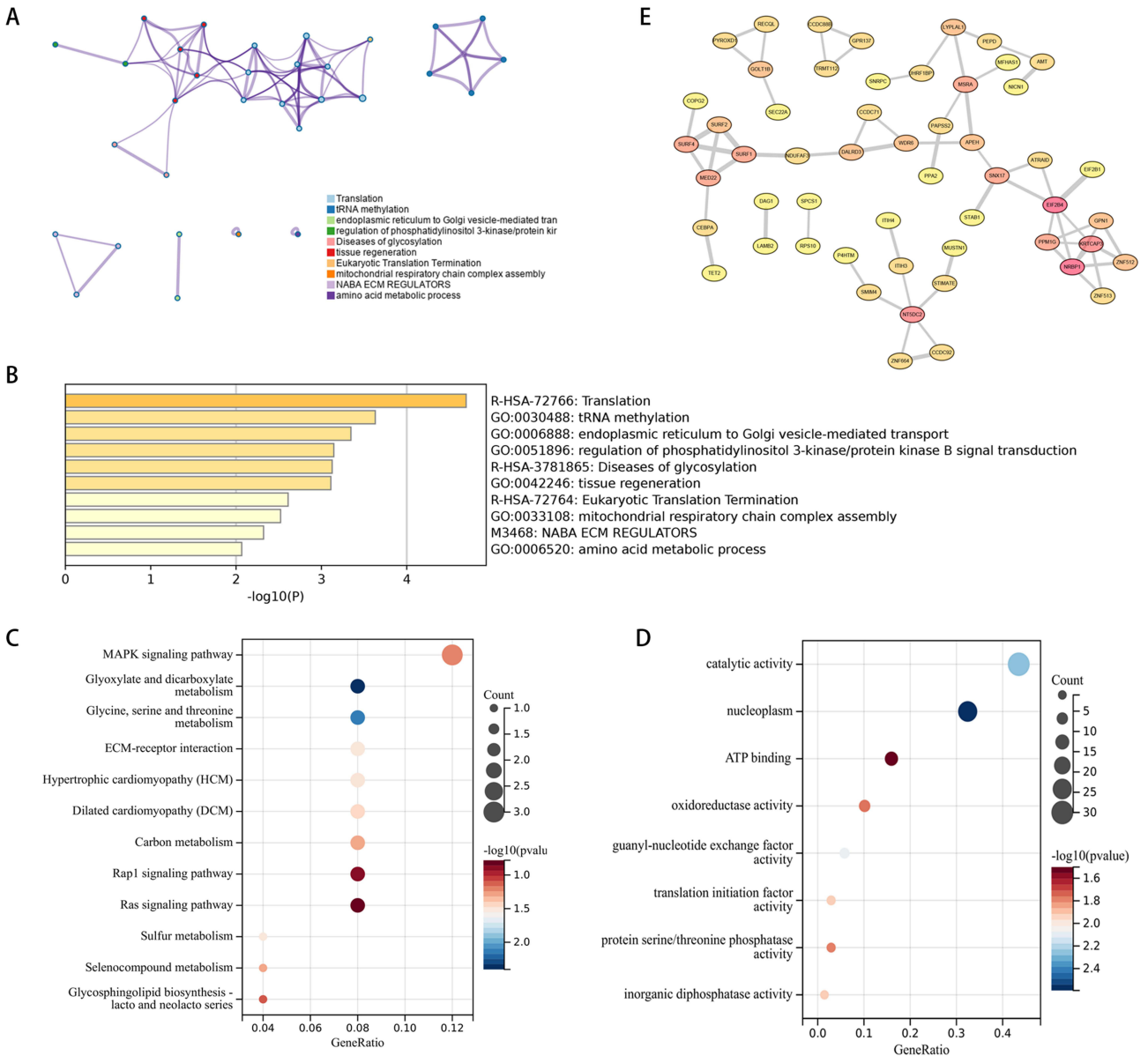

Figure 4 Biological enrichment and PPI network analysis. (**A** and **B**) Visual function enrichment analysis by Metascape. (**C** and **D**) KEGG and GO enrichment analysis by Sangerbox. (**E**) PPI diagram of the common target network.

a proxy for insulin resistance (IR), is inherently tied to systemic inflammatory responses, lipid imbalances, and oxidative stress, all of which contribute to a hostile environment for hair follicle growth and maintenance.[23,24] These metabolic disturbances can impair follicular stem cell function, dysregulate the hair follicle cycling process, and lead to progressive follicular miniaturization and hair thinning, which are hallmarks of AGA.[25,26] While previous studies have established correlations between IR and AGA,[16,27–29] our findings provide compelling evidence for a direct causative link from elevated FI to the development of AGA, underscoring the importance of viewing AGA as not merely a localized disorder but also one influenced by systemic metabolic factors.

At the molecular level, this study identified 92 genes associated with fasting insulin-related Single Nucleotide Polymorphisms (SNPs). Enrichment analyses implicated several metabolic pathways, including glycine, serine, and threonine metabolism, as well as glyoxylate and dicarboxylate metabolism. These pathways are essential for regulating cellular energy homeostasis, redox balance, and the synthesis of critical biomolecules, thereby maintaining healthy tissue microenvironments. Dysregulation of these pathways may disrupt the delicate balance of pro-growth and pro-

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inflammatory signals within the hair follicle, resulting in follicular damage and cycling disruption. Among the identified genes, two key genes, EIF2B4 and NRBP1, were highlighted. EIF2B4 codes for a subunit of eukaryotic initiation factor 2B (EIF2B), which is indispensable for protein synthesis under stress conditions. Mutations in EIF2B4 have been linked to disorders of metabolic stress, such as hyperinsulinemic hypoglycemia, and dysregulated insulin signaling.[30,31] Similarly, NRBP1, an adapter protein involved in transcriptional and metabolic regulation, has been associated with metabolic traits like diabetes, obesity, and dyslipidemia.[32] Although there is limited direct evidence linking these genes to AGA, their roles in metabolic regulation, oxidative stress, and redox balance strongly suggest that they may increase the metabolic burden on hair follicles in individuals with elevated FI. Such mechanisms may exacerbate hair follicle vulnerability by disrupting tissue microenvironments, amplifying microinflammatory responses, and impairing hair follicle stem cell function, all of which are consistent with the known pathophysiology of AGA. Furthermore, while the association between androgen hypersensitivity and genes directly related to dihydrotestosterone (DHT) signaling is well established,[33] systemic metabolic disturbances, such as insulin resistance, may compound the localized androgen-driven stressors within the follicular milieu, adding another layer to the disease complexity.

The relationship uncovered between FI and AGA has broader implications, particularly regarding systemic metabolic health and its interplay with dermatological conditions. For example, androgen-driven tissue changes in AGA, such as follicular miniaturization and microinflammation, may share overlapping molecular mechanisms with other inflammatory skin disorders like seborrheic dermatitis and psoriasis, or even systemic conditions such as metabolic syndrome.[34] Future research could examine whether the metabolic stress responses involving EIF2B4, NRBP1, or related pathways contribute to these shared pathological processes, opening avenues for therapeutic interventions that target both systemic metabolic dysfunction and local tissue manifestations. Clinically, individuals with AGA and coexisting metabolic disorders, such as obesity, insulin resistance, or type 2 diabetes, could benefit from early interventions targeting insulin sensitization and systemic inflammation.[35–37] Lifestyle modifications combined with insulin-sensitizing therapies (eg, metformin, GLP-1 receptor agonists) and anti-inflammatory treatments could not only slow the progression of AGA but also address the broader cardiometabolic risks associated with FI. This integrative treatment approach emphasizes the need to conceptualize AGA within the broader framework of systemic metabolic health, highlighting the dual benefits of treating systemic conditions while reducing hair loss.

Despite providing novel insights, this study has limitations that should be acknowledged. The genetic markers analyzed were primarily derived from European populations, which may not fully capture the genetic diversity of other ethnic groups. Both FI levels and AGA prevalence have shown significant ethnic and geographic variability, with previous studies noting distinct differences in FI levels and the prevalence of AGA across Asian, European, and African populations.[38,39] Thus, future research should validate these findings in multi-ethnic cohorts, considering population-specific differences in genetic architecture and environmental exposures. Additionally, while this study focused on systemic metabolic factors, the tissue-specific pathophysiology of AGA, particularly the cellular heterogeneity within the hair follicle, requires further exploration. The hair follicle is a complex mini-organ composed of multiple compartments, including dermal papilla cells, outer root sheath keratinocytes, and follicular stem cells,[40,41] each of which may respond differently to systemic metabolic perturbations. Advanced techniques such as single-cell transcriptomics and spatial transcriptomics hold promise for identifying cell-type-specific contributions of metabolic stressors and delineating how elevated FI impacts different follicular populations.[42,43] For instance, single-cell analyses could reveal how insulin resistance disrupts stem cell niche function while promoting pro-inflammatory states in adjacent compartments. Integrating these molecular-level findings with large-scale genetic and epidemiological studies will help bridge the gap between mechanistic research and population-level observations, offering a comprehensive understanding of AGA pathogenesis. Lastly, functional validation of EIF2B4 and NRBP1 in the context of AGA remains crucial. Future studies should employ both in vitro models, such as dermal papilla cultures under hyperinsulinemic conditions, and in vivo metabolic stress models to clarify the specific roles of these genes in AGA pathology and identify potential therapeutic targets.

In conclusion, this study highlights the systemic underpinnings of AGA, emphasizing how metabolic disturbances, such as elevated FI levels, can exacerbate hair follicle susceptibility to androgen-driven miniaturization. By reframing AGA as a condition influenced by systemic metabolic health, this research opens new avenues for targeted therapeutic

interventions that address both systemic and localized disruptions. Moving forward, synergizing insights from population genetics, molecular biology, and advanced genomic technologies will be critical in developing personalized treatment strategies, ultimately improving the management of AGA in diverse populations.

Strengths and Limitations

The MR study design represents a significant strength of this investigation, as it effectively addresses reverse causality and minimizes confounding in observational studies. Additionally, it facilitates of potential causal relationships between FI and AGA. Furthermore, our study reinforces its findings through secondary analytical approaches and sensitivity analyses, thereby enhancing the reliability of our conclusions. Moreover, we meticulously selected instrumental variables from recent GWAS data to mitigate weak instrumental bias. Lastly, we identified genes linked to fasting insulin-specific SNPs and conducted functional enrichment analysis and core gene identification to provide a molecular basis for the aforementioned causal relationship.

However, there were also some limitations. First, the data from GWASs of this study came from European, so that the similar study should be investigated in other populations. Moreover, the clinical application of the aforementioned findings necessitates additional data from a larger sample size and further comprehensive clinical observation.

Conclusion

This study, for the first time, demonstrated a causal link between fasting insulin (FI) levels and androgenetic alopecia (AGA), identifying EIF2B4 and NRBP1 as key mediators linking metabolic dysfunction to hair follicle damage. These findings expand the understanding of AGA beyond localized follicular changes to systemic metabolic influences, highlighting potential therapeutic targets for patients with concurrent metabolic disorders. In dermatology, this research offers a novel perspective by integrating systemic metabolism into hair disorder pathogenesis. Clinically, it provides potential molecular targets for future therapeutic strategies, particularly for patients with comorbid metabolic disorders and hair loss. However, the study has limitations, including a lack of population diversity and incomplete functional validation of the identified genes. Future studies should focus on addressing these limitations to improve the generalizability and clinical translation of these findings.

Data Sharing Statement

The datasets generated and analysed during the current study are available in the IEU open gwas project [https://gwas.mrcieu.ac.uk/], and the GWAS ID are finn-b-L12_ALOPECANDRO, and ebi-a-GCST90002238, respectively.

Author Contributions

Zhiming Li and Yibin Fan should be considered co-correspondence. Xiaoxia Ding and Zicheng Bai contributed equally to this work and should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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