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Original Research

Exploration of the Shared Genes and Molecular Pathways between Pre-Eclampsia and Type 2 Diabetes Mellitus via Co-Expression Networks Analysis

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Abstract

Background: Pre-eclampsia is a serious disorder associated with pregnancy, but its etiology remains poorly understood. In this study, we aimed to explore the shared genes and molecular pathways between pre-eclampsia and type 2 diabetes mellitus (T2DM). **Methods**: The record of 2160 pregnant women who had pre-eclampsia risk assessed by placental growth factor (PIGF) levels in Fuyang People's Hospital, China were retrospectively reviewed. The microarray datasets of pre-eclampsia and T2DM were searched in the Gene Expression Omnibus (GEO) and were downloaded for secondary analysis. **Results**: According to the PIGF stratification, the high-risk group had a significantly higher proportion of T2DM than the low-risk group (51/326, 15.6% *vs.* 1.4%, $p < 0.001$). An overlapping geneset containing 30 members between pre-eclampsia and T2DM was identified. The significantly enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were "Rap1 signaling pathway", "Aldosterone synthesis and secretion", "Phosphatidylinositol signaling system", "Neurotrophin signaling pathway", "Aldosterone-regulated sodium reabsorption" and "Insulin signaling pathway". Combined with previous research findings, we infer that impaired PI3K/Akt signaling pathway may be a common pathogenetic factor of T2DM and pre-eclampsia. The gene ontology (GO) analysis confirmed that the shared genes were enriched in several Biological Process (BP) terms directly related to insulin-PI3K-Akt signaling pathways. **Conclusions**: Impaired PI3K/Akt signaling pathway might be a common pathogenetic factor of T2DM and pre-eclampsia. For activating purposes, self-management behaviors, including self-monitoring of blood glucose, healthy diet, physical activity and medication adherence should be highly recommended during nursing practice for pregnant women with pre-existing T2DM.

Keywords: pre-eclampsia; type 2 diabetes mellitus; KEGG; PI3K-Akt

1. Introduction

Pre-eclampsia (PE) is a severe disorder associated with pregnancy, affecting about 4–5% of pregnancies worldwide [1,2]. It is characterized as the onset of hypertension after 20 weeks of pregnancy and is accompanied by proteinuria, which may become a severe disorder causing maternal and fetal morbidity and mortality [2].

The etiology of pre-eclampsia remains poorly understood. It is currently defined as a cumulative placental and maternal dysfunction, triggered by a series of genetic alterations (such as *FLT1*, *MECOM*, *FGF5* and *SH2B3* SNPs) [3,4], maternal and immunological factors (hypertension, kidney disease, diabetes, autoimmune diseases) [2,5]. These factors might increase the risk of abnormal placentation (such as incomplete spiral artery remodeling) and the release of antiangiogenic factors (such as soluble fms-like tyrosine kinase 1, sFLT1 and soluble endoglin, sEng) from the ischemic placenta into the maternal circulation [2,5]. Due to the growing understanding of the pathogenesis, some novel therapeutic strategies, such as administration of recombinant vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) and selective inhibition of sFLT1 have been proposed [2,5]. However, delivery of the fetus remains the only definitive treatment for pre-eclampsia [2].

One previous meta-analysis of genome-wide association scans (GWAS) identified positive genetic correlations between pre-eclampsia and both systolic and diastolic blood pressure, hypertension, coronary artery disease and type 2 diabetes mellitus (T2DM) [4], suggesting that these diseases may share some gene signatures and molecular pathways in common. T2DM is characterized by insulin resistance, with the loss of reactive insulin receptors and weakened downstream signals, resulting in excessive compensatory production of insulin, leading to both hyperglycemia and hyperinsulinemia [6]. Obesity is a shared risk factor for pre-eclampsia and T2DM [6]. A clear understanding of the inter-relational molecular mechanisms might help identify biomarkers for diagnosis, prediction or treatment of pre-eclampsia.

In this study, we aimed to explore the shared genes and molecular pathways between pre-eclampsia and T2DM, using available gene expression datasets from the Gene Expression Omnibus (GEO).

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2. Materials and Methods

2.1 Retrospective Analysis of Data in Our Hospital

This study was approved by the ethics committee of Fuyang People's Hospital, Fuyang, China (Approval No. 2022-176). To characterize the association between the risk of pre-eclampsia in pregnant women with or without pre-existing T2DM, we retrospectively checked the record of 2160 pregnant women who had pregnancy check-ups in Fuyang People's Hospital, China in 2020–2021. Their risk of pre-eclampsia was assessed by serum placental growth factor (PIGF) levels using commercial ELISA kit (batch number: AL3030, PerkinElmer Medical Laboratory, Suzhou, Jiangsu, China). The cut-off values of PIGF were provided by the kit manual according to the pregnant weeks. Risk group stratification was performed according to the specific cutoff values. The low-risk group was defined as the test result $>$ the specific cutoff values, while the high-risk group was defined as the test result $<$ the specific cutoff values. The differences between the parameters were compared using unpaired *t*-test or Fisher's exact test. $p < 0.05$ were considered significantly different.

2.2 GEO Datasets Collection and Processing

We used the keywords "pre-eclampsia" or "type 2 diabetes" to search relevant gene expression datasets in the GEO database (http://www.ncbi.nlm.nih.gov/geo/). The following criteria were applied to identify datasets included for this study: (1) Samples included both disease and healthy controls. (2) Size $>$100 for pre-eclampsia-related gene set, for the accuracy of the Weighted Gene Co-Expression Network Analysis (WGCNA). (3) Size $>$10 for T2DM dataset. (4) Raw data matrix was available for reanalysis. Finally, for pre-eclampsia WGCNA, GSE75010 [7] was selected. For T2DM analysis, GDS3681 [8], GDS3715 [9], GSE25462 [10], GSE19420 [11], GSE18732 [12], GSE15932, GSE13760 [13], GSE9006 [14], GSE25724 [15], and GSE23343 [16] were selected. The normalized series matrix files were downloaded and subjected to log2 transformation. Genes with significant differential expression between the T2DM and healthy control groups were defined as false discovery rate (FDR)-adjusted p value < 0.05. Since 10 datasets were included for T2DM analysis, the genes with FDR-adjusted p value $<$ 0.05 in at least one dataset were considered potential dysregulated genes.

2.3 Weighted Gene Co-Expression Network Analysis (WGCNA)

WGCNA was performed following standard procedures introduced previously [17]. The gene expression profile in GSE75010 was used to calculate the Median Absolute Deviation (MAD) of each gene. The first 50% of the genes with the smallest MAD were eliminated. Then, the GoodSamplesGenes method of R software (v4.2.1, R Core Team 2021, https://www.r-project.org/) package WGCNA was used. The modules with |correlation coefficient| $\geq$0.4 were identified and the genes in these modules were selected for further analyses. The other parameters were set as follows: networkType = "unsigned", minModuleSize = 30, mergeCutHeight = 0.25 and deepSplit = 3.

2.4 Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways

For GO annotation, we used genes in the R software package org. Hs. eg. db (version 3.1.0, https://www.r-project.org/) as the background. For KEGG enrichment analysis, we used KEGG rest API (https://www.kegg.jp/kegg/rest/keggapi.html) to obtain the latest KEGG Pathway gene annotation as the background. The shared genes were mapped genes to the background set for enrichment analysis, by using the R software package clusterProfiler (version 3.14.3). The following parameters were set: minimum gene set: 5; the maximum gene: 5000; p value of $<$0.05 and a FDR q of $<$0.10.

3. Results

3.1 The Association between the Risk of Pre-Eclampsia and Pre-Existing T2DM

The association between the risk of pre-eclampsia and pre-existing T2DM of the 2160 pregnant women was summarized in Table 1. Results showed that the group with T2DM had significantly higher age at the pregnancy (34.4 $\pm$ 7.6 *vs.* 29.1 $\pm$ 5.0, $p < 0.001$). By the PIGF stratification of pre-eclampsia risk, the high-risk group had a significantly higher proportion of T2DM compared to the low-risk group (51/326, 15.6% *vs.* 275/2082, 1.4%, $p < 0.001$) (Table 1).

Table 1. Characterization of the association between T2DM and Pre-eclampsia.

Parameters	T2DM		*p*
	N (n = 2082)	Y (n = 78)	
Age (mean $\pm$ SD)	29.1 $\pm$ 5.0	34.4 $\pm$ 7.6	$<$0.001
PE-risk (by PIGF)			
Low	1807	27	
High	275	51	$<$0.001

PE, Pre-eclampsia; SD, standard deviation; PIGF, placental growth factor; T2DM, type 2 diabetes mellitus; N, No; Y, Yes.

3.2 Information of Included Microarrays

The information of the pre-eclampsia and T2DM datasets were summarized in Table 2, including GSE number, study design, sample number, tissue sources and detection platforms.

Table 2. Information of included microarrays.

Dataset ID	Study design	Tissue sources	Array platform
GSE75010	PE placentas (n = 80) *vs.* non-PE placentas (n = 77)	Human placentas	Affymetrix 1.0 ST
GDS3681	T2DM (n = 10) *vs.* control (n = 20)	Human skeletal muscle	Affymetrix U95Av2
GDS3715 (G1)	T2DM (n = 15) *vs.* insulin sensitive (n = 20)	Human skeletal muscle	Affymetrix U95A
GDS3715 (G2)	T2DM (n = 15) *vs.* insulin resistant (n = 20)	Human skeletal muscle	Affymetrix U95A
GSE25462 (G1)	T2DM (n = 10) *vs.* control (no family history of T2DM, n = 15)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE25462 (G2)	T2DM (n = 10) *vs.* control (with family history of T2DM, n = 25)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE19420 (G1)	T2DM before training (n = 10) *vs.* pre-diabetes subjects (n = 12)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE19420 (G2)	T2DM after training (n = 8) *vs.* pre-diabetes subjects (n = 12)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE19420 (G3)	T2DM before training (n = 10) *vs.* normoglycemic controls (n = 12)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE19420 (G4)	T2DM after training (n = 8) *vs.* normoglycemic controls (n = 12)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE18732 (G1)	T2DM (n = 20) *vs.* normal muscle (n = 20)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE18732 (G2)	T2DM (n = 20) *vs.* muscle glucose intolerant (n = 20)	Human skeletal muscle	Affymetrix U133 Plus 2.0
GSE15932	T2DM (n = 8) *vs.* control (n = 8)	Human peripheral blood	Affymetrix U133 Plus 2.0
GSE13760	T2DM (n = 10) *vs.* control (n = 11)	Human arterial tissue	Affymetrix U133 Plus 2.0
GSE9006	T2DM (n = 12) *vs.* control (n = 24)	Human peripheral blood	Affymetrix U133 Plus 2.0
GSE25724	T2DM (n = 6) *vs.* control (n = 7)	Human islets	Affymetrix U133A
GSE23343	T2DM (n = 10) *vs.* control (n = 7)	Human liver biopsies	Affymetrix U133 Plus 2.0

52 weeks of exercise training was conducted in GSE19420.

PE, Pre-eclampsia; T2DM, type 2 diabetes mellitus.

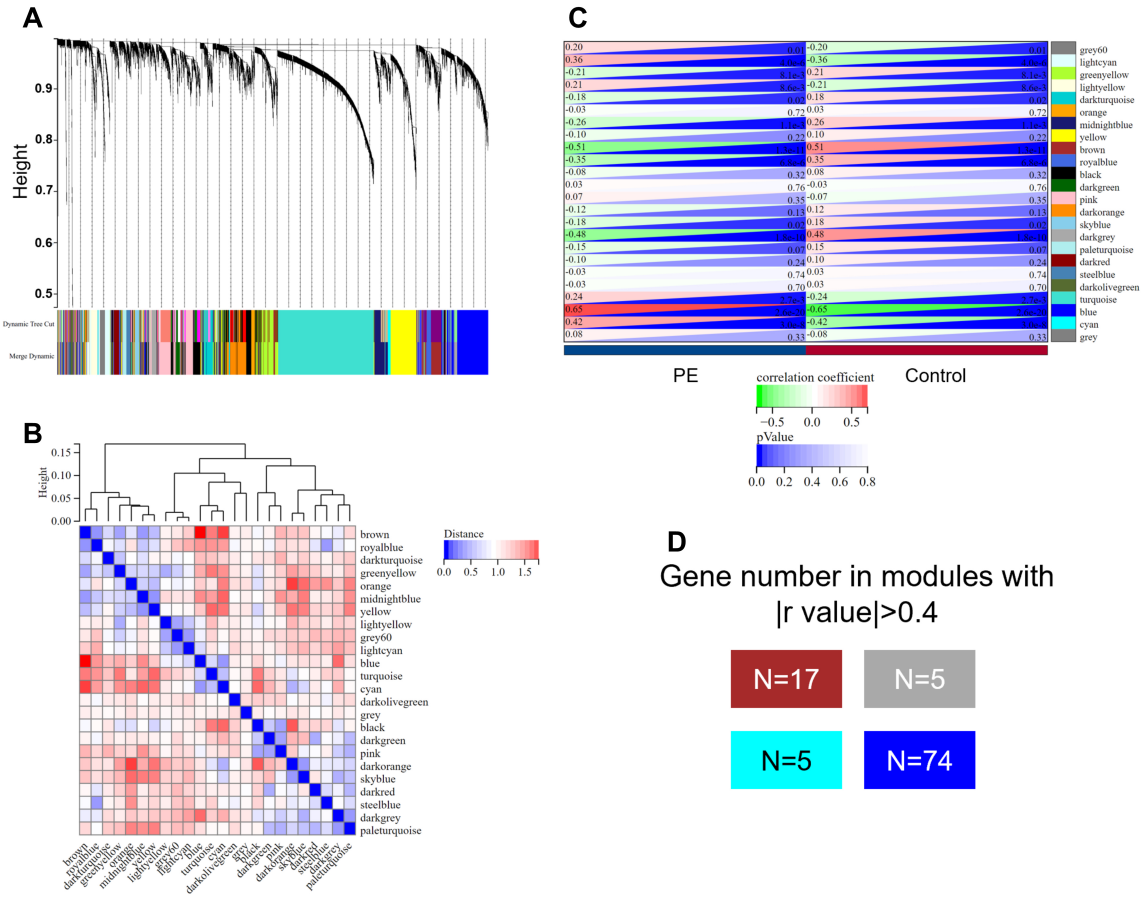

Fig. 1. Weighted gene co-expression network analysis (WGCNA) of genes related in pre-eclampsia. (A,B) The cluster dendrogram (A) and heatmap (B) of co-expression genes in pre-eclampsia in GSE75010. (C) Module-trait relationships in pre-eclampsia in GSE75010. Each cell contains the corresponding correlation and *p*-value. (D) A block matrix showing the modules with |correlation coefficient| ≥0.4 with pre-eclampsia and the number of genes included in each module.

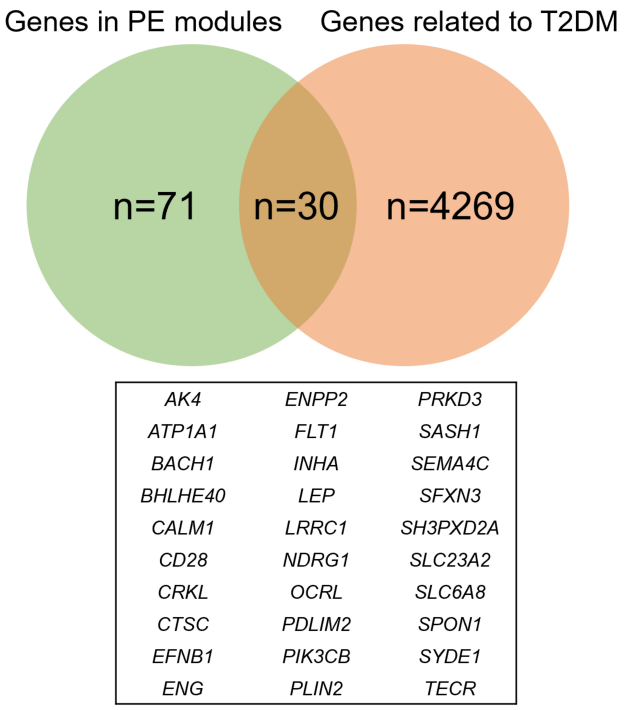

Fig. 2. A Venn plot showing the shared genes between pre-eclampsia and T2DM. PE, Pre-eclampsia; T2DM, type 2 diabetes mellitus.

3.3 Weighted Gene Co-Expression Network Analysis (WGCNA) in Pre-Eclampsia

WGCNA was performed to identify the key modules and genes associated with pre-eclampsia using data from GSE75010. The soft-thresholding power was set to $\beta = 4$ to generate a scale-free gene co-expression network (Fig. 1A). Via the dynamic tree cut algorithm, 24 gene modules were generated (Fig. 1A). The distance matrix of the gene modules was illustrated in Fig. 1B. Then, a heat map was generated to display module-trait relationships on the basis of the Pearson's correlation coefficients (Fig. 1C). By setting |correlation coefficient| $\geq$0.4 we identified four modules (brown, darkgray, cyan and blue) are associated with pre-eclampsia (Fig. 1D). A total of 102 genes were identified in these 4 modules (Fig. 1D, **Supplementary Table 1**).

3.4 Identification of Dysregulated Genes Related to T2DM

For the 10 datasets included to identify dysregulated genes in T2DM, we introduced a strict criteria (FDR-adjusted (adj.) p value < 0.05) for statistical comparison. The genes with FDR-adjusted p value < 0.05 in at least one dataset were considered potential dysregulated genes. Under the strict screening criteria, only 5 datasets contained significantly dysregulated genes (Table 3). By removing the duplicates, a total of 4299 dysregulated genes were identified (**Supplementary Table 2**).

Table 3. The number of dysregulated genes related to T2DM.

Dataset ID	No. of dysregulated genes (adj. $p < 0.05$)
GDS3681	0
GDS3715 (G1)	5
GDS3715 (G2)	144
GSE25462 (G1)	0
GSE25462 (G2)	1
GSE19420 (G1)	0
GSE19420 (G2)	0
GSE19420 (G3)	0
GSE19420 (G4)	0
GSE18732 (G1)	0
GSE18732 (G2)	0
GSE15932	0
GSE13760	0
GSE9006	1652
GSE25724	3576
GSE23343	0

adj, adjusted.

3.5 The Common Gene Signatures in Pre-Eclampsia and T2DM

By comparing the genes in PE modules and dysregulated genes related to T2DM, we identified an overlapping geneset containing 30 members (Fig. 2). We hypothesized that these genes are highly related to the pathogenesis of both pre-eclampsia and T2DM.

To explore the potential regulatory pathways of the 30 shared genes, we conducted KEGG and GO analysis. The significantly enriched KEGG pathways were "Rap1 signaling pathway", "Aldosterone synthesis and secretion", "Phosphatidylinositol signaling system", "Neurotrophin signaling pathway", "Aldosterone-regulated sodium reabsorption" and "Insulin signaling pathway" (Fig. 3, Table 4).

In GO analysis, only significantly enriched GO-Biological Process (BP) terms and GO-Molecular Function (MF) terms were identified by applying FDR-adjusted q value < 0.1 as the selecting criteria. The top 10 significantly enriched GO-BP terms were "Positive regulation of cellular protein metabolic process", "Positive regulation of protein metabolic process", "Positive regulation of protein phosphorylation", "Positive regulation of phosphatidylinositol 3-kinase signaling", "Positive regulation of phosphorylation", "Phosphate-containing compound metabolic process", "Positive regulation of intracellular signal transduction", "Phosphorus metabolic process", "Positive regulation of phosphorus metabolic process", and "Positive regulation of phosphate metabolic process" (Fig. 4A, Table 5).

The top 10 significantly enriched GO-MF terms were "cofactor transmembrane transporter activity", "carboxylic acid transmembrane transporter activity", "organic acid transmembrane transporter activity", "sodium ion transmembrane transporter activity", "organic anion transmembrane transporter activity", "SH3/SH2 adaptor activity",

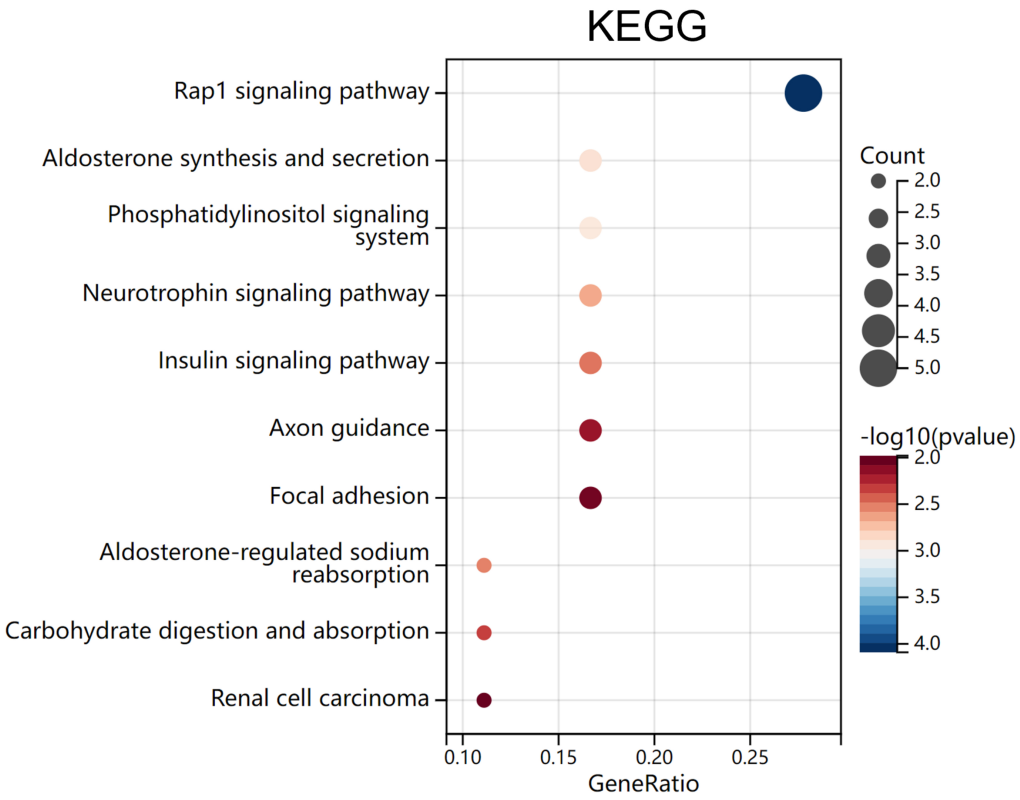

Fig. 3. Bubble plots of KEGG analysis. The significantly enriched (adj. $p < 0.10$) KEGG pathways of the 30 shared genes.

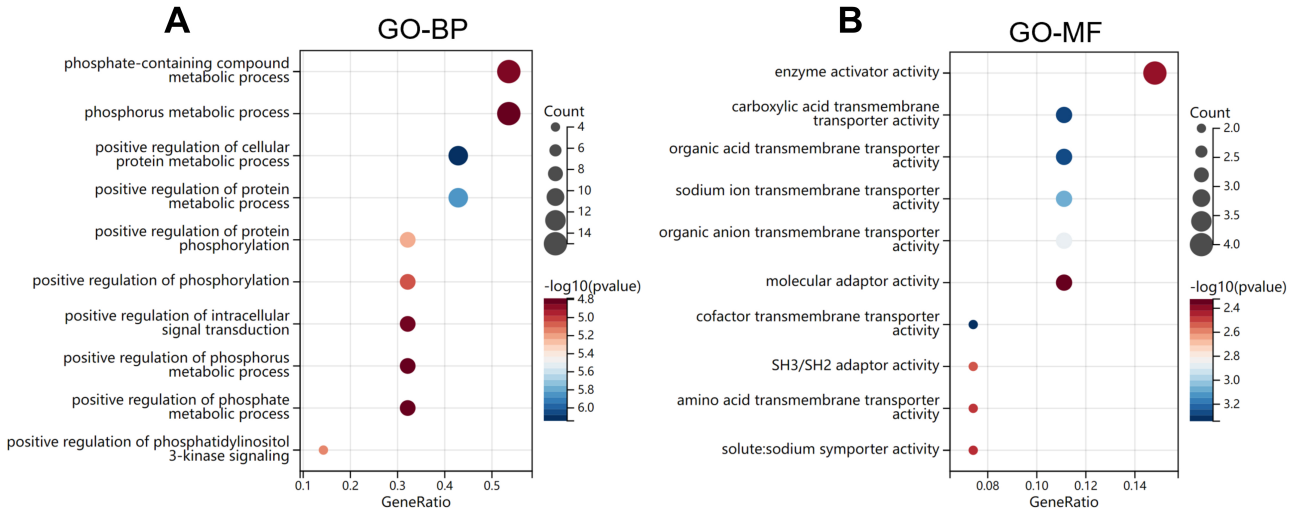

Fig. 4. Bubble plots of GO analysis. (A,B) The significantly enriched (adj. $p < 0.10$) GO-BP (A) and GO-MF (B) terms of the 30 shared genes.

"amino acid transmembrane transporter activity", "solute: sodium symporter activity", "enzyme activator activity" and "molecular adaptor activity" (Fig. 4B, Table 6).

4. Discussion

The molecular pathogenesis of pre-eclampsia remains to be fully revealed. The cooccurrence of pre-eclampsia and T2DM has been previously documented. T2DM has been considered a risk factor for pre-eclampsia. Besides, there is compelling epidemiological evidence that women with pre-eclampsia during pregnancy, including increased risk of essential hypertension, coronary artery disease, and T2DM later in life [18]. Obesity is a shared risk factor for both pre-eclampsia and T2DM [6]. Although the epidemiological association was confirmed, the underlying mechanisms at the genetic level have not been explored. In the general

Table 4. The enrichment of the 30 shared genes in KEGG pathways.

ID	Description	Generatio	BgRatio	*p* value	*p* adjust	*q* value	Gene ID	Count
hsa04015	Rap1 signaling pathway	5/18	210/7914	8.11×10^{-5}	0.012241	0.009642	*CALM1/CRKL/FLT1/PIK3CB/PRKD3*	5
hsa04925	Aldosterone synthesis and secretion	3/18	98/7914	0.001313	0.068047	0.053603	*ATP1A1/CALM1/PRKD3*	3
hsa04070	Phosphatidylinositol signaling system	3/18	99/7914	0.001352	0.068047	0.053603	*CALM1/OCRL/PIK3CB*	3
hsa04722	Neurotrophin signaling pathway	3/18	119/7914	0.002294	0.086149	0.067862	*CALM1/CRKL/PIK3CB*	3
hsa04960	Aldosterone-regulated sodium reabsorption	2/18	37/7914	0.003104	0.086149	0.067862	*ATP1A1/PIK3CB*	2
hsa04910	Insulin signaling pathway	3/18	137/7914	0.003423	0.086149	0.067862	*CALM1/CRKL/PIK3CB*	3

Table 5. The enrichment of the 30 shared genes in top 10 GO-BP terms.

ID	Description	Generatio	BgRatio	*p* value	*p* adjust	*q* value	Gene ID
GO:0032270	Positive regulation of cellular protein metabolic process	12/28	1458/17910	7.2×10^{-7}	1.3×10^{-3}	8.7×10^{-4}	*CALM1/CD28/CRKL/CTSC/ENG/ENPP2/FLT1 /LEP/PIK3CB/SASH1/SEMA4C/SPON1*
GO:0051247	Positive regulation of protein metabolic process	12/28	1548/17910	1.4×10^{-6}	1.3×10^{-3}	8.7×10^{-4}	*CALM1/CD28/CRKL/CTSC/ENG/ENPP2/FLT1 /LEP/PIK3CB/SASH1/SEMA4C/SPON1*
GO:0001934	Positive regulation of protein phosphorylation	9/28	907/17910	6.1×10^{-6}	3.1×10^{-3}	2.1×10^{-3}	*CALM1/CRKL/ENG/ENPP2/FLT1/LEP /PIK3CB/SASH1/SEMA4C*
GO:0014068	Positive regulation of phosphatidylinositol 3-kinase signaling	4/28	81/17910	7.3×10^{-6}	3.1×10^{-3}	2.1×10^{-3}	*CD28/FLT1/LEP/PIK3CB*
GO:0042327	Positive regulation of phosphorylation	9/28	955/17910	9.2×10^{-6}	3.1×10^{-3}	2.1×10^{-3}	*CALM1/CRKL/ENG/ENPP2/FLT1/LEP /PIK3CB/SASH1/SEMA4C*
GO:0006796	Phosphate-containing compound metabolic process	15/28	3115/17910	1.5×10^{-5}	3.1×10^{-3}	2.1×10^{-3}	*AK4/ATP1A1/CALM1/CRKL/ENG/ENPP2/FLT1 /INHA/LEP/OCRL/PIK3CB/PRKD3/SASH1 /SEMA4C/TECR*
GO:1902533	Positive regulation of intracellular signal transduction	9/28	1019/17910	1.6×10^{-5}	3.1×10^{-3}	2.1×10^{-3}	*CALM1/CD28/CRKL/ENG/FLT1/LEP/PIK3CB /SASH1/SEMA4C*
GO:0006793	Phosphorus metabolic process	15/28	3139/17910	1.6×10^{-5}	3.1×10^{-3}	2.1×10^{-3}	*AK4/ATP1A1/CALM1/CRKL/ENG/ENPP2/FLT1/INHA /LEP/OCRL/PIK3CB/PRKD3/SASH1/SEMA4C/TECR*
GO:0010562	Positive regulation of phosphorus metabolic process	9/28	1025/17910	1.6×10^{-5}	3.1×10^{-3}	2.1×10^{-3}	*CALM1/CRKL/ENG/ENPP2/FLT1/ LEP/PIK3CB/SASH1/SEMA4C*
GO:0045937	Positive regulation of phosphate metabolic process	9/28	1025/17910	1.6×10^{-5}	3.1×10^{-3}	2.1×10^{-3}	*CALM1/CRKL/ENG/ENPP2/FLT1/LEP/ PIK3CB/SASH1/SEMA4C*

Table 6. The enrichment of the 30 shared genes in top 10 GO-MF terms.

ID	Description	Generatio	BgRatio	*p* value	*p* adjust	*q* value	Gene ID
GO:0051184	Cofactor transmembrane transporter activity	2/27	20/16967	4.6×10^{-4}	4.6×10^{-2}	2.9×10^{-2}	*SLC23A2*/*SLC6A8*
GO:0046943	Carboxylic acid transmembrane transporter activity	3/27	98/16967	4.9×10^{-4}	4.6×10^{-2}	2.9×10^{-2}	*SFXN3*/*SLC23A2*/*SLC6A8*
GO:0005342	Organic acid transmembrane transporter activity	3/27	99/16967	5.1×10^{-4}	4.6×10^{-2}	2.9×10^{-2}	*SFXN3*/*SLC23A2*/*SLC6A8*
GO:0015081	Sodium ion transmembrane transporter activity	3/27	117/16967	8.3×10^{-4}	5.7×10^{-2}	3.6×10^{-2}	*ATP1A1*/*SLC23A2*/*SLC6A8*
GO:0008514	Organic anion transmembrane transporter activity	3/27	139/16967	1.4×10^{-3}	7.5×10^{-2}	4.7×10^{-2}	*SFXN3*/*SLC23A2*/*SLC6A8*
GO:0005070	SH3/SH2 adaptor activity	2/27	52/16967	3.1×10^{-3}	7.6×10^{-2}	4.8×10^{-2}	*CD28*/*CRKL*
GO:0015171	Amino acid transmembrane transporter activity	2/27	55/16967	3.4×10^{-3}	7.6×10^{-2}	4.8×10^{-2}	*SFXN3*/*SLC6A8*
GO:0015370	Solute: sodium symporter activity	2/27	56/16967	3.6×10^{-3}	7.6×10^{-2}	4.8×10^{-2}	*SLC23A2*/*SLC6A8*
GO:0008047	Enzyme activator activity	4/27	419/16967	4.1×10^{-3}	7.6×10^{-2}	4.8×10^{-2}	*CALM1*/*CTSC*/*OCRL*/*SYDE1*
GO:0060090	Molecular adaptor activity	3/27	216/16967	4.8×10^{-3}	7.6×10^{-2}	4.8×10^{-2}	*CD28*/*CRKL*/*SASH1*

population, pre-eclampsia presents a greater risk in nulliparae. However, in patients with type I diabetes, the incidence of pre-eclampsia was similar among nulliparae and multiparae [19]. This phenomenon might also be true for other types of pregestational diabetes. Therefore, there might be a common genetic basis promoting pre-eclampsia in diabetes. In this study, we explored the key gene modules of pre-eclampsia using the WGCNA. This method can identify the key co-expression modules relevant to the clinical traits [20].

To identify dysregulated genes related to T2DM, we compared the expression profile in ten previous microarrays, based on a strict statistical comparison. Via comparison of the overlapping gene set, we identified 30 shared genes. More importantly, we found that these 30 genes were enriched in multiple KEGG terms that might be related to both pre-eclampsia and T2DM. Among the 6 KEGG pathways, "Aldosterone synthesis and secretion" and "Aldosterone-regulated sodium reabsorption" are closely associated, while "Insulin signaling pathway" and Phosphatidylinositol signaling system" are closely related.

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in regulating blood pressure and volume [21]. Dysregulation of this system is closely associated with the development of T2DM [22]. In patients with primary hyperaldosteronism, excessive aldosterone reduces insulin secretion in isolated islets and impairs insulin sensitivity in skeletal muscle and adipocytes [23], leading to a significantly higher risk of T2DM. However, this trend might not be readily transferable to a general population since T2DM cases in a general population are not associated with elevated aldosterone [24]. Normal pregnancy is associated with increased circulating renin, angiotensin II, and aldosterone [25], for an expansion of maternal plasma volume. In the mice model, aldosterone is required for optimal fetal development via maintaining the expression of PIGF and the proliferation of trophoblasts [26]. However, no significant alteration in aldosterone levels is observed in pre-eclampsia cases until proteinuria occurs [27]. Therefore, aldosterone-related pathways might not be the common signaling pathway between T2DM and pre-eclampsia.

In normal physiological conditions, insulin binds to its receptor and initiates sequential phosphorylation events that activate the PI3K/AKT signaling pathway [28]. Activated PI3K/AKT signaling promotes glucose transport, glycogen synthesis and protein synthesis in skeletal muscle, enhances lipid biosynthesis and inhibits lipolysis in adipose tissue and reduces hepatic glucose production and glycogenolysis, increases the synthesis of glycogen and fatty acids in the liver [29]. However, in patients with T2DM, insulin resistance was associated with blunted response to insulin in organs and weakened PI3K-Akt signaling [29]. Decreased expression of placental PI3K, Akt, and p-Akt at the protein level in pre-eclamptic placentas was observed in some previous studies [30–32]. In addition, decreased expression of p-Akt was associated with increased circulating sEng in pre-eclampsia [31].

It is worth noticing that increased total phospholipid content was observed in pre-eclamptic placental tissues in T2DM cases compared to controls [33]. This might be an excessive compensatory production due to the reduced PI3K-Akt activation in T2DM cases. By performing GO analysis, we confirmed that the shared genes were enriched in several MF terms directly related to insulin-PI3K-Akt signaling pathways, such as "Positive regulation of phosphatidylinositol 3-kinase signaling", "Phosphate-containing compound metabolic process" and "Positive regulation of intracellular signal transduction". Based on these findings, we infer that impaired PI3K/Akt signaling pathway may be a common pathogenetic factor of T2DM and pre-eclampsia.

The intervention strategies for T2DM are associated with PI3K/Akt activating effects. For example, Metformin, a first-line therapeutic drug for T2DM, can activate IRS2/PI3K/Akt signaling transduction [34]. Exercise training might also enhance IGFI-R/PI3K/Akt signaling in diabetic rat models [35,36]. Therefore, self-management behaviors, including self-monitoring of blood glucose, healthy diet, physical activity and medication adherence should be highly recommended during nursing practice for pregnant women with pre-existing T2DM.

5. Conclusions

In summary, this study identified that impaired PI3K/Akt signaling pathway might be a common pathogenetic factor of T2DM and pre-eclampsia. For activating purposes, self-management behaviors, including self-monitoring of blood glucose, healthy diet, physical activity, and medication adherence should be highly recommended during nursing practice for pregnant women with pre-existing T2DM.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

ZFD and RL—the study design; ZFD, LLC, RJ and RL—data collection; ZFD and LLC—data analysis; ZFD, RJ and RL—data interpretation and drafting of the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Fuyang People's Hospital, Fuyang, China (Approval No. 2022-176). All participants gave written informed consent prior to entering the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5004073.

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