Cyclin D1 and Cyclin E1 Gene Polymorphisms and Their Interaction with Preeclampsia: An Association Study Postprint

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Abstract

Background: Preeclampsia (PE) is a life-threatening multisystem disorder that poses a significant threat to maternal and fetal health.

Objective: To investigate the association between cyclin D1 (CCND1) and cyclin E1 (CCNE1) gene polymorphisms and their interaction with PE, thereby providing a scientific basis for etiological research on PE.

Methods: A case-control study design was employed. Two hundred and two PE patients who presented to the obstetrics departments of the Third Xiangya Hospital of Central South University and Hunan Provincial Maternal and Child Health Hospital between October 2020 and October 2023 were recruited as the case group. Four hundred pregnant women with normal blood pressure who underwent prenatal examinations in the same hospitals during the same period served as the control group. Multivariate Logistic regression analysis was performed to examine the association between CCND1 and CCNE1 gene polymorphisms and PE occurrence, with adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) calculated. Crossover analysis was conducted to explore gene-gene additive interactions in relation to PE. The 3DSNP database was utilized for functional annotation of single nucleotide polymorphism (SNP) loci.

Results: Multivariate Logistic regression analysis revealed that pregnant women carrying the CT/TT genotype at the CCND1 rs1352075 locus had a lower risk of PE compared to those with the CC genotype (dominant model: aOR=0.44, 95%CI=0.20–0.96). The GG genotype at the CCNE1 rs3218070 locus was associated with a higher risk of PE compared to the CC/GC genotype (recessive model: aOR=4.31, 95%CI=1.16–16.04). Analysis using the 3DSNP database demonstrated that in the chromatin open regions of rs1352075 and rs3218070,

there was a relatively high proportion of cell regulatory factor binding sites related to blood vessel and placenta formation. Interaction analysis indicated that the additive interaction between the rs1352075 and rs3218070 loci was not associated with PE occurrence.

Conclusion: The CC genotype at the CCND1 rs1352075 locus and the GG genotype at the CCNE1 rs3218070 locus may be associated with an increased risk of PE.

Full Text

Study on the Association between Polymorphisms and Interaction of CCND1 and CCNE1 Genes with Preeclampsia

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Abstract

Background: Preeclampsia (PE) is a life-threatening multisystemic disorder that significantly endangers maternal and fetal health. **Objective:** To investigate the association between CCND1 (Cyclin D1) and CCNE1 (Cyclin E1) gene polymorphisms, as well as their interactions, with the risk of PE, to provide scientific evidence for its pathogenesis.

Methods: A case-control study was conducted. From October 2020 to October 2023, pregnant women diagnosed with PE (n=202) were recruited from the Xiangya Third Hospital of Central South University and the Hunan Provincial Maternal and Child Health Hospital as the case group, while pregnant women with normal blood pressure were recruited as the control group (n=400). Multivariate Logistic regression analyses were performed to evaluate the association between CCND1 and CCNE1 gene polymorphisms and the risk of PE, with adjusted odds ratios (aOR) and 95% confidence intervals (95%CI) calculated. Interaction analysis was performed to investigate the association between gene-gene interactions and PE risk. Functional annotation of single nucleotide polymorphisms (SNPs) was performed using the 3DSNP database.

Results: Multivariate Logistic regression analysis revealed that pregnant women with the CT/TT genotype at CCND1 rs1352075 had a lower risk of PE compared to those with the CC genotype (dominant model: aOR=0.44, 95%CI=0.20-0.96). Pregnant women with the GG genotype at CCNE1 rs3218070 had a higher risk of PE compared to those with the CC/GC genotype (recessive model: aOR=4.31, 95%CI=1.16-16.04). Analysis based on

the 3DSNP database revealed a higher proportion of cellular regulatory factors related to vascularization and placentation in the open chromatin regions at rs1352075 and rs3218070 binding sites. Interaction analysis showed that the additive interaction between rs1352075 and rs3218070 was not significantly associated with PE risk.

Conclusion: The CCND1 rs1352075 locus harboring the CC genotype and the CCNE1 rs3218070 locus harboring the GG genotype may be associated with an elevated risk of developing PE.

Keywords: Pre-eclampsia; Cyclin D1; Cyclin E1; Single nucleotide polymorphism; Case-control study; Logistic regression analysis

Introduction

Preeclampsia (PE) is a multisystem disease that seriously threatens maternal and infant health, characterized by hypertension with proteinuria or other end-organ dysfunction after 20 weeks of gestation. The incidence of PE in China is 4%-5%. It is estimated that PE causes more than 60,000 maternal deaths and over 500,000 preterm births globally each year. In addition to mortality risk, the risk of serious complications such as placental abruption and disseminated intravascular coagulation is significantly increased in pregnant women with PE. However, aside from terminating the pregnancy, no other effective treatments currently exist. Research into the etiology and risk factors of PE is therefore crucial for reducing disease risk and improving patient prognosis.

The “two-stage model” plays an important role in the pathogenesis of PE. The first stage involves abnormalities in trophoblast cell proliferation, differentiation, and invasion, which can lead to impaired vascular remodeling and reduced placental blood supply, resulting in a certain degree of ischemia and hypoxia. In this environment, the placenta secretes anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). The second stage involves persistently elevated serum sFlt-1 and sEng, causing vascular endothelial dysfunction and worsening hypoxia/ischemia, ultimately leading to PE.

The cell cycle is a critical component of cell proliferation, consisting of interphase and mitotic phase (M phase). Interphase includes G1 phase (pre-DNA synthesis), S phase (DNA synthesis), and G2 phase (post-DNA synthesis). The transitions from G1 to S phase and G2 to M phase are key regulatory nodes in cell cycle control because molecular-level changes are most active during these phases and susceptible to external influences. CCND1 and CCNE1 genes play important regulatory roles in controlling cell cycle progression from G1 to S phase. Research indicates that these genes affect trophoblast cell migration and invasion capacity, thereby causing placental dysfunction. However, current research lacks investigation into the association between CCND1 and CCNE1 gene polymorphisms and PE susceptibility. Studies in this area would facilitate early prediction and identification of high-risk populations for PE.

Notably, as a complex disease, PE often does not result from the action of a single gene; gene-gene interactions are also crucial in its development. Therefore, this study aims to explore the association between CCND1 and CCNE1 gene polymorphisms and their interactions with PE susceptibility, providing scientific evidence for PE etiology research.

Methods

Study Population

Pregnant women visiting the obstetrics departments of Xiangya Third Hospital of Central South University and Hunan Provincial Maternal and Child Health Hospital between October 2020 and October 2023 were selected. After obtaining informed consent, pregnant women meeting the inclusion and exclusion criteria for PE were enrolled as the case group, while pregnant women with normal blood pressure receiving prenatal care during the same period served as the control group.

Case group inclusion criteria: (1) Pregnant women diagnosed with PE by obstetric specialists according to the "Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy (2020)" compiled by the Hypertensive Disorders in Pregnancy Group of the Obstetrics and Gynecology Branch of the Chinese Medical Association; (2) No kinship between cases; (3) Voluntary participation and signed informed consent after project notification.

Case group exclusion criteria: (1) History of hypertension, cardiovascular disease, or diseases that may cause hypertension (such as hyperadrenocorticism); (2) Non-spontaneous conception; (3) Multiple pregnancy; (4) Inability to provide blood samples or complete questionnaires for various reasons.

Control group inclusion criteria: (1) Pregnant women diagnosed by obstetric specialists as not having PE or other subtypes of gestational hypertension according to the same guidelines; (2) No kinship between subjects; (3) Voluntary participation and signed informed consent after project notification.

Control group exclusion criteria: Same as the case group.

Demographic and Biosample Data Collection

Demographic data were collected through face-to-face questionnaires, including: basic maternal information (age, education level, pre-pregnancy BMI, and average annual household income); obstetric and reproductive history (gravidity, parity, adverse pregnancy history, pregnancy complication history, planned pregnancy, family history of hypertension); and perinatal environmental exposures (smoking, secondhand smoke exposure, early pregnancy alcohol consumption, early pregnancy tea consumption, environmental pollutants near residence, home renovation, CT/X-ray exposure, and folic acid supplementation).

Within 24 hours of enrollment, 3-5 mL of peripheral venous blood was collected using ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes.

Candidate Gene Selection and Confirmation

The candidate genes for this study were CCND1 and CCNE1. SNP loci were identified and screened through the NCBI dbSNP database (https://www.ncbi.nlm.nih.gov/SNP/) and the 1000Genomes database (https://asia.ensembl.org/index.html). Variants with MAF in Asian & CHS $\geq$ 5% were considered common variants. Haploview software was used to test for Hardy-Weinberg equilibrium of 22 gene loci from the two genes in the control group, with P>0.05 as the criterion for equilibrium. Ultimately, 14 loci from 2 genes were included: CCND1 (rs1352075, rs9344, rs602652, rs7177, rs3212891, rs586459, rs647451, rs678653, rs2510467) and CCNE1 (rs1406, rs3218035, rs3218038, rs3218070, rs3218076).

Genotyping

This study used the MassARRAY matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry system for genotyping. The process involved PCR amplification of DNA sequences containing SNP loci, followed by single-base extension using specific extension primers on PCR products. In the ddNTP reaction system, extension primers only extended and terminated at bases complementary to the SNP locus. Final extension products were analyzed by time-of-flight mass spectrometry, and SNPs were genotyped based on molecular weight differences of different bases. Genotyping was completed by Biomiao Biotechnology (Beijing) Co., Ltd.

Statistical Analysis

A database was established using EpiData 3.0 software, with all questionnaire data double-entered and cross-checked. All statistical analyses were performed using SPSS 26.0 and R Studio v4.2.1. Count data were expressed as relative frequencies, with inter-group comparisons using ^{2} test or Fisher's exact test. Single-factor and multi-factor Logistic regression models were used to analyze the association between each gene locus and PE susceptibility. Risk was expressed as odds ratio (OR) and 95% confidence interval (95%CI). Unless otherwise specified, all hypothesis tests used P<0.05 as the threshold for statistical significance. The 3DSNP database was used for functional annotation of SNP loci to assess their biological functions. Additive interactions between candidate genes were investigated using crossover analysis to comprehensively evaluate the impact of gene-gene interactions on PE development.

Results

Comparison of Baseline Characteristics

A total of 602 subjects were enrolled, including 202 cases and 400 controls. Statistically significant differences were observed between the case and control groups in maternal age at pregnancy, education level, pre-pregnancy BMI, pregnancy complication history, early pregnancy tea consumption, and perinatal secondhand smoke exposure ($P<0.05$) .

Association Analysis of Candidate Genes with PE

Using genotype as the independent variable and PE occurrence as the dependent variable (assigned as: not occurred=0, occurred=1), single-factor and multi-factor Logistic regression analyses were performed. In the multi-factor Logistic regression analysis, variables including pregnancy age, education level, pre-pregnancy BMI, pregnancy complication history, early pregnancy tea consumption, and perinatal secondhand smoke exposure were adjusted, with specific assignments shown in .

For the CCND1 rs1352075 locus, single-factor Logistic regression analysis showed that both the dominant model (OR=0.40, 95%CI=0.20-0.81) and additive model (OR=0.75, 95%CI=0.57-0.99) reduced PE risk ($P<0.05$). Multi-factor Logistic regression analysis revealed that pregnant women carrying the CT/TT genotype had lower PE risk than those with the CC genotype (dominant model: aOR=0.44, 95%CI=0.20-0.96, $P<0.05$) . No association was found between genotypes at rs9344, rs602652, rs7177, rs3212891, rs586459, rs647451, rs678653, and rs2510467 loci and PE occurrence in either single-factor or multi-factor analyses ($P>0.05$).

For the CCNE1 rs3218070 locus, single-factor Logistic regression analysis showed that the recessive model (OR=4.08, 95%CI=1.21-13.72) increased PE risk ($P<0.05$). Multi-factor Logistic regression analysis revealed that pregnant women carrying the GG genotype had higher PE risk than those with the CC/GC genotype (recessive model: aOR=4.31, 95%CI=1.16-16.04) . No association was found between genotypes at rs1406, rs3218035, rs3218038, and rs3218076 loci and PE occurrence in either single-factor or multi-factor analyses ($P>0.05$).

3DSNP Database Functional Annotation Results

The 3DSNP online database was used to conduct comprehensive functional evaluation of candidate SNP loci, including 3D interactions, enhancer and promoter status, transcription factor binding sites, motif changes, and evolutionary conservation. Six-dimensional radar functional plots were constructed to comprehensively understand the functional characteristics of these loci. Results are shown in and [Figure 1: see original paper]: CCND1 rs1352075 had a total score of 110.92, with the highest promoter score (100), followed by transcrip-

tion factor score (8.99), conservation score (0.73), enhancer score (0.54), and motif score (0.53), suggesting this locus primarily regulates CCND1 gene expression through promoter effects. CCNE1 rs3218070 had a motif score of 1.05 and conservation score of 0.32, suggesting this locus primarily participates in CCNE1 gene expression regulation by affecting transcription factor binding site sequence patterns.

[Figure 2: see original paper] shows potential target cell types/subtypes for genetic variants identified by single-cell chromatin accessibility sequencing (scATAC-seq). Results indicated that potential target cell types/subtypes for CCND1 rs1352075 include vascular endothelial cells (20.51%), stromal cells (7.30%), retinal progenitor cells and Müller glial cells (6.74%), etc. Potential target cell types/subtypes for CCNE1 rs3218070 include vascular endothelial cells (14.10%), extravillous trophoblast cells (8.98%), stromal cells (7.69%), etc. These findings reveal that the chromatin open regions of candidate SNP loci contain numerous binding sites for cellular regulatory factors related to vascular and placental formation, suggesting important regulatory roles.

Gene-Gene Interaction and PE Susceptibility

This study used crossover analysis to investigate additive interactions between candidate gene loci and their association with PE. Covariates included variables showing statistical differences in demographic analysis and potential environmental confounders associated with PE risk: pregnancy age, education level, pre-pregnancy BMI, pregnancy complication history, early pregnancy tea consumption, and perinatal secondhand smoke exposure. The final SNP loci included were CCND1 rs1352075 and CCNE1 rs3218070. As shown in , no additive interaction was found between rs1352075 and rs3218070 after controlling for confounding factors.

Discussion

This study evaluated 14 loci in CCND1 and CCNE1 genes for association with PE risk. Results showed that the CC genotype at CCND1 rs1352075 and the GG genotype at CCNE1 rs3218070 may be associated with increased PE risk. These findings provide scientific evidence for PE etiology research and may contribute to PE prevention and early identification of high-risk populations, which is significant for reducing PE incidence, decreasing PE-related disease burden, and improving maternal and infant health.

CCND1 is the initiating factor for cell cycle start and a sensor for growth factors. This study found that CCND1 rs1352075 polymorphism was associated with reduced PE risk, consistent with NUZZO et al. who reported significantly downregulated CCND1 expression in placental mesenchymal stem cells (PDMSC) from PE patients. Further research demonstrated that altered Cyclin D1-p16INK4C/p18INK4C pathways in PE-PDMSC lead to abnormal villous structures, participating in PE development. Multiple studies have shown that

CCND1 is enriched in PE-related pathways such as AMP-dependent protein kinase (AMPK) and FoxO1 signaling pathways. Additionally, CCND1 overexpression has been found to promote tumor angiogenesis in various cancers. Given the similarities between PE and cancer pathogenesis, including establishment of vascular networks, growth promotion, and immunosuppression regulation, these findings suggest CCND1 may play an important regulatory role in PE pathogenesis. Bioinformatics analysis revealed that rs1352075 has high activity in promoter regions of cell types closely related to placental development and umbilical vein formation, suggesting it may be an important gene expression regulatory region with key roles in CCND1 regulation. scATAC-seq indicated this locus may function in vascular endothelial cells and stromal cells, which are crucial for maintaining vascular and other tissue formation and function. These findings further support the important role of rs1352075 in PE pathogenesis.

CCNE1 is an important regulator for cell entry into S phase. This study found that CCNE1 rs3218070 polymorphism was associated with increased PE risk. Current research on CCNE1 and PE is limited. DELOIA et al. demonstrated that CCNE1 plays a major role in villous trophoblasts and may participate in trophoblast terminal differentiation. GAO et al. found significantly reduced CCNE1 mRNA and protein levels in umbilical vein endothelial cells from PE patients, suggesting that downregulated CCNE1 expression may participate in PE development by affecting cell proliferation, migration, and invasion. AKCORA et al. reported significantly reduced CCNE1 phosphorylation levels in placentas from PE women compared to controls. Although 3DSNP database scores indicated rs3218070 has weaker function in 3D genome structure, scATAC-seq revealed numerous binding sites for vascular and placental formation-related regulatory factors at this locus, suggesting important roles in CCNE1 expression regulation. These findings indicate CCNE1 rs3218070 may be a functional genetic variant with significant impact on CCNE1 expression regulation, representing an important target for studying gene expression mechanisms and developing novel therapies.

This study explored potential interactions between CCND1 and CCNE1 genes through crossover analysis. No additive interaction was found between rs1352075 and rs3218070. However, considering the important roles of these genes in cell cycle regulation, future studies should expand the population to include different regions and ethnicities to further explore the role of candidate genes in PE pathogenesis. Extensive research on gene-gene interactions will help better explain the complex pathogenesis of PE and provide new clues for precision medicine and personalized treatment.

Compared with previous studies, this study has several strengths: it explored the association between maternal CCND1 and CCNE1 gene polymorphisms and PE occurrence; it examined interactions among multiple SNP loci in these genes and their relationship with PE risk. These findings provide new directions for PE prediction and intervention, with potential to reduce PE incidence and improve maternal and infant health. However, this study has limitations: due

to ethical restrictions, placental tissues were not obtained for studying CCND1 and CCNE1 gene expression, limiting in-depth exploration of PE pathogenesis; the study only examined two cell cycle-related genes, and future research should expand the gene scope to investigate associations between more cell cycle regulatory genes and PE pathogenesis.

In summary, this study found that CCND1 rs1352075 and CCNE1 rs3218070 polymorphisms are associated with PE susceptibility. The CC genotype at CCND1 rs1352075 and the GG genotype at CCNE1 rs3218070 may be associated with increased PE risk.

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