Identification of SEPP1 polymorphisms is not a genetic risk factor for preeclampsia in Chinese Han women

A clinical trial and experimental study

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Abstract

Background: SEPP1 encodes selenoprotein P, which involved in oxidative stress and plays an important role in the development of preeclampsia (PE). The aim of this study was to investigate the association between PE and genetic variants of SEPP1 in Chinese Han women.

Methods: In all, 2434 unrelated pregnant women were recruited, including 1034 PE cases and 1400 normal pregnant controls. TaqMan allelic discrimination real-time PCR method was used to genotype the 2 polymorphisms of rs7579 and rs230813 in SEPP1.

Results: No statistically significant difference in genotypic or allelic frequencies were found at the 2 genetic variants in SEPP1 between PE patients and controls (rs7579: genotype \( \chi^2 = 2.417, P = .299 \) and allele \( \chi^2 = 0.197, P = .671 \), odds ratio 1.049, 95% confidence interval 0.864–1.151; rs230813: genotype \( \chi^2 = 3.273, P = .195 \) and allele \( \chi^2 = 0.252, P = .615 \), odds ratio 0.971, 95% confidence interval 0.846–1.091). There were also no statistically significant differences in genetic distributions between mild/severe PE or early/late-onset PE and control subgroups.

Conclusion: Our data indicate that the 2 genetic variants of rs7579 and rs230813 in SEPP1 may not play a role in the pathogenesis of PE in Chinese Han Women.

Abbreviations: CI = confidence intervals, OR = Odds ratios, PE = preeclampsia.

Keywords: preeclampsia, SEPP1, single-nucleotide polymorphism, susceptibility

1. Introduction

As a multifactorial disease, preeclampsia (PE) characterized by hypertension after 20th week gestation and de novo proteinuria, affects about 2% to 8% of all pregnancies in the world[1] and carries a severe morbidity and mortality risk for both mother and fetus. Numerous studies[2] including immune maladaptation, placental ischemia, inflammation, and endothelial dysfunction about the mechanisms of PE have been investigated; however, it is not fully elucidated. Furthermore, increasing evidence indicates that oxidative stress, which results from abnormal placetation and ischemia injury,[3] may contribute to the pathophysiology of PE.[4,5] On the basis of this hypothesis, several related candidate genes, such as GSTZ1, eNOS, and COMT[6–8] have been investigated whether the genetic polymorphisms in antioxidant enzymes influence the formation of PE. But the results are inconsistent, because of different race and different sample size. Therefore, other studies related to oxidative stress candidate genes involved in PE still remain to be identified.

As 1 of the genes related to oxidative stress, SEPP1 located on chromosome 5q31, encodes selenoprotein P, which contains a selenocysteine residue. The selenocysteine residue C-terminal confers redox function and metal-binding function, acting as antioxidants to decrease oxidative stress and as transport of selenium.[9] Additionally, the up-regulation of selenoprotein P may protect the tissue from the effects of oxidative stress or inflammation.[10] Previous animal study indicated a selenium-free diet caused a PE-like syndrome in pregnant rats, including significantly increased blood pressure, proteinuria, and placent oxidative stress.[11] Moreover, significantly lower levels of the selenoenzymes reductase have been found in placental in PE patients compared with healthy pregnancy controls and lower plasma selenium concentrations in PE patients.[12–14] which were validated in UK pregnant women.[15–17] Epidemiological investi-
gation showed that selenium supplementation may be beneficial in reducing oxidative stress in women at risk of PE among 45 countries.\textsuperscript{[19]}

As a complex multifactorial disorder, PE is the consequence of interactions between genetic and environmental risk factors. More and more studies\textsuperscript{[11]} supported that genetic factors play an important role in the maintenance of PE. Hence, genetic variants in \textit{SEPP1} may affect the activity of these selenoproteins, and subsequently oxidative stress and disease risk. Although the impact of \textit{SEPP1} polymorphisms (rs7579 and rs230813) on multiple complex diseases such as prostate cancer,\textsuperscript{[20,21]} breast cancer,\textsuperscript{[22]} and colorectal cancer\textsuperscript{[23]} has previously been investigated, few studies have focused on the association between \textit{SEPP1} polymorphisms and PE in the Han Chinese population. Therefore, in the present study, we selected the 2 single-nucleotide polymorphisms (SNPs) of \textit{SEPP1} and designed a case-control study to explore their relationship with PE risk in Han Chinese women.

2. Materials and methods

2.1. Subjects

A total of 2434 Chinese Han women (1034 cases, mean age ±SD = 30.69 ± 4.47 years) and 1400 controls, mean age ±SD = 30.98 ± 3.37 years) were recruited from the Affiliated Hospital of Qingdao University, Binzhou Medical University Hospital, Yantai Qianhai Hospital, and Liaocheng People’s Hospital between January 2012 and November 2015. The present study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University and informed consent was obtained from all participants. The inclusion criteria of PE were according to the American College of Obstetricians and Gynecologists (ACOG) 2013 criteria.\textsuperscript{[24]} It defined as de novo hypertension (above 140 mm Hg systolic blood pressure or above 90 mm Hg diastolic blood pressure on 2 or more occasions at least 6 hours apart) and detectable urinary protein (above 300 mg/24h, above 30 mg/dL or above a positive urine dipstick) after 20th gestational weeks. Women with PE associated with chronic hypertension, multiple pregnancies, cancer, cardiovascular, autoimmune, renal, and hepatic diseases were excluded. The control group is composed of singleton normal pregnant women, which is in the third trimester of normal pregnancy and without any fatal disorder, or pathological states. To further investigate the association between \textit{SEPP1} variants and PE, all PE patients were divided into 2 subgroups: mild PE (n = 181) and severe PE (n = 853).

2.2. Genotyping

DNA was extracted from venous blood, which were collected on EDTA from all participants, using Qiagen DNA extraction kits (Qiagen, Hilden, Germany). \textit{SEPP1} genotyping was carried out by the TaqMan allelic discrimination real-time PCR. The rs7579 primers were 5’-CCTTCAAACTAATTTTATATG-3’ (forward) and 5’- ACATACTCCCAATTTAGTCTAGAC-3’ (reverse); rs230813 primers were 5’- GCCTCAGGGTCTCGCAGAAAGCTA-3’ (forward) and 5’- GTGAGGTTTTCTCTTCCCTGGACTGTGGTT-3’ (reverse), which were synthesized by Applied Bio-systems of Life Technologies (ABI, NY). The total volume of the reaction mixture was 25 µL and contained 1.25 µL 20× SNP Genotyping Assay, 12.5 µL 2× PCR Master Mix, and 11.25 µL DNA and DNase-free water. The amplification condition is 95°C for 3 minutes, followed by 45 cycles of 95°C for 15 seconds and 60°C for 1 minute, and then the fluorescent signals from VIC/FAM-labeled probes were detected by each cycle. Amplifications were carried out in C1000\textsuperscript{®}thermal cycler and CFX96\textsuperscript{®}real-time system (Bio-Rad, CA), and discrimination of genotypes was conducted using Bio-Rad CFX manager software 3.0.

2.3. Statistical analysis

Statistical analysis was carried out by SPSS 22.0 (SPSS Inc., Chicago, IL). Hardy–Weinberg equilibrium using the goodness-of-fit chi-square test was tested in control group. Comparisons between 2 groups were made by Student \textit{t} test for clinical characteristics, and were described by the mean ± standard error (SE) or percentage. Allele and genotype frequencies between the 2 groups were analyzed by Pearson chi-square test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to express the risk between case and control groups. Statistical significance was calculated at the \textit{P} value < .05 level. The power analysis was calculated using the program Power and Sample Size Calculations (PS, Version 3.1.2).

Table 1

| Case                              | Control                          | t   | P     |
|-----------------------------------|----------------------------------|-----|-------|
| Age, y                            | 30.69 ± 4.47                     | 30.98 ± 3.73 | -1.638 | .102  |
| Age of menarche, y                | 14.01 ± 1.18                     | 14.02 ± 1.25 | -0.056 | .955  |
| Number of abortion                | 0.62 ± 0.93                      | 0.61 ± 0.85  | 0.367  | .713  |
| Gestational age at admission, wks | 33.09 ± 4.40                     | 39.19 ± 1.37 | -47.41 | .000  |
| Gestational age at delivery, wks  | 35.80 ± 3.14                     | 39.42 ± 1.15 | -38.54 | .000  |
| Fetal birth weight, g             | 2507 ± 939                       | 3399 ± 342.3 | -31.61 | .000  |
| Systolic blood pressure, mm Hg    | 160.99 ± 18.70                   | 114.72 ± 8.67 | 78.53  | .000  |
| Diastolic blood pressure, mm Hg   | 104.63 ± 13.72                   | 73.50 ± 7.70  | 70.88  | .000  |
| White blood cell, ×10\textsuperscript{12}/L | 9.64 ± 2.92   | 9.01 ± 2.43  | 5.84   | .000  |
| Neutrophil, ×10\textsuperscript{9}/L | 7.15 ± 2.58   | 6.86 ± 2.20  | 2.93   | .003* |

*Statistically significant difference: cases versus controls.
Table 2
Genotypic and allelic distributions in case and control groups.

| Genotype | Case (n=1034) | Control (n=1400) | χ² | P | OR (95% CI) |
|----------|--------------|-----------------|----|---|-------------|
| rs7579   |              |                 |    |   |             |
| Genotypes |             |                 |    |   |             |
| GG       | 538 (52.03) | 718 (51.29) | 0.254 | .881 |
| AG       | 421 (40.72) | 583 (41.64) |    |    |             |
| AA       | 75 (7.25)  | 99 (7.07)  |    |    |             |
| Alleles  |             |                 |    |   |             |
| G        | 1497 (72.39) | 2019 (72.11) | 0.047 | .828 |
| A        | 571 (27.61) | 781 (27.89) | (0.893–1.151) |    |
| Dominant models |         |                 |    |   |             |
| GG       | 538 (52.03) | 718 (51.29) | 0.132 | .716 |
| AG + AA  | 406 (47.97) | 622 (48.71) | (0.877–1.210) |    |
| Recessive models |     |                 |    |   |             |
| AA       | 75 (7.25)  | 99 (7.07)  | 0.030 | .863 |
| AG + GG  | 959 (92.75) | 1301 (92.93) | (0.753–1.403) |    |
| rs230813 |              |                 |    |   |             |
| Genotypes |             |                 |    |   |             |
| CC       | 161 (15.57) | 202 (14.43) | 3.273 | .195 |
| CG       | 475 (45.94) | 695 (49.64) |    |    |             |
| GG       | 398 (38.49) | 503 (35.93) |    |    |             |
| Alleles  |             |                 |    |   |             |
| C        | 707 (36.54) | 1099 (50.25) |    |    |             |
| G        | 1277 (61.46) | 1701 (63.75) | (0.864–1.091) |    |
| Dominant models |         |                 |    |   |             |
| GG       | 398 (38.49) | 503 (35.93) | 1.675 | .196 |
| CG + CC  | 636 (61.51) | 897 (36.47) | (0.945–1.318) |    |
| Recessive models |     |                 |    |   |             |
| CC       | 161 (15.57) | 202 (14.43) | 0.611 | .434 |
| CG + GG  | 873 (84.43) | 1198 (85.57) | (0.874–1.369) |    |

CI = confidence interval, OR = odds ratio.

3. Results

3.1. Demographic and clinical characteristics

The comparison of demographic and clinical characteristics between cases and controls were shown in Table 1. No statistically significant differences were found in age, age of menarche, and abortion numbers between the 2 groups (all P > .05). However, PE group had earlier admission gestational age, delivery gestational age, lower fetal birth weight, higher blood pressure, and higher levels of white blood cell and neutrophil (all P < .001).

3.2. Analysis of genotypic and allelic frequencies

The control groups in our study were in accordance with the Hardy-Weinberg equilibrium (for 7579, χ² = 1.738, P = .187; for 230813, χ² = 2.417, P = .125). The genotypic and allelic frequencies of rs7579 and rs230813 between cases and controls (for rs7579, χ² = 2.417, P = .197, OR = 1.049, 95% CI 0.945–1.140; for rs230813, χ² = 2.351, P = .187; for rs7579, χ² = 0.938, P = .626 by genotype; χ² = 2.417, P = .197, OR = 1.049, 95% CI 0.744–1.206 by allele). For rs7579, χ² = 0.938, P = .626 by genotype; χ² = 2.417, P = .197, OR = 1.049, 95% CI 0.744–1.206 by allele. For rs230813, χ² = 2.351, P = .187 by genotype; χ² = 0.938, P = .626 by allele. For rs7579, χ² = 0.938, P = .626 by genotype; χ² = 2.417, P = .197, OR = 1.049, 95% CI 0.744–1.206 by allele. For rs230813, χ² = 2.351, P = .187 by genotype; χ² = 0.938, P = .626 by allele.

To further investigate the association between SEPP1 variants and PE, all PE patients were divided into mild PE (n = 181) and severe PE (n = 853) groups. Table 3 shows no statistically significant difference in mild/severe PE and controls (mild PE vs control: for rs7579, χ² = 5.757, P = .038 by genotype; χ² = 2.417, P = .197 by allele; for rs230813, χ² = 1.369, P = .049 by genotype; χ² = 2.417, P = .197 by allele; severe PE vs control: for rs7579, χ² = 1.318, P = .076 by genotype; χ² = 2.417, P = .197 by allele; for rs230813, χ² = 1.369, P = .049 by genotype; χ² = 2.417, P = .197 by allele).
P = .674, OR 1.029, 95% CI 0.900–1.178 by allele. For rs230813, \( \chi^2 = 1.333, P = .460 \) by genotype; \( \chi^2 = 0.423, P = .516 \), OR 0.960, 95% CI 0.848–1.086 by allele. We also divided cases early-onset PE (529 cases) and late-onset PE (505 cases). Table 4 shows no statistically significant difference in early-onset/late-onset PE and controls (early-onset PE vs control: for rs7579, \( \chi^2 = 1.277, P = .528 \) by genotype; \( \chi^2 = 0.332, P = .564 \), OR 0.955, 95% CI 0.817–1.117 by allele. For rs230813, \( \chi^2 = 1.467, P = .480 \) by genotype; \( \chi^2 = 0.000, P = .989 \), OR 0.999, 95% CI 0.846–1.155 by allele; late-onset PE vs control: for rs7579, \( \chi^2 = 0.271, P = .873 \) by genotype; \( \chi^2 = 0.902, P = .342 \), OR 1.082, 95% CI 0.920–1.273 by allele; for rs230813, \( \chi^2 = 3.076, P = .215 \) by genotype; \( \chi^2 = 0.637, P = .425 \), OR 0.941, 95% CI 0.812–1.092 by allele).

4. Discussion

Preeclampsia is 1 of the most common and severe pregnancy-specific syndrome, and remains a severe morbidity and mortality risk for both mother and fetus worldwide, especially in low-income and middle-income countries. Furthermore, PE women have a greater risk of developing hypertension, stroke, cardiovascular disease (CVD), and chronic kidney disease in their later life. More importantly, numerous strategies to prevent and treat PE have been investigated, but the effect is not satisfactory and the mechanisms of PE are still not fully elucidated. However, more and more evidence supports that placental and systemic oxidative stress plays a crucial role in the development of PE. As we all know, SEPP1 is 1 of the candidate genes that relate to oxidative stress.

SEPP1 locates on chromosome 5q31 and encodes selenoprotein P, which is 1 of the major selenoprotein in plasma, acting as a selenium transport protein and antioxidant. Selenoproteins have previously been associated with risk of various cancers and redox-related diseases, such as prostate, lung, breast, and colorectal cancer. It is reported that oxidative stress causes endothelial dysfunction, which may lead to hypertension through lipid peroxidation and leukocyte activation. As ischemia or reperfusion of placental, PE patients created a hypoxic environment which favors oxidative stress, which can result in the formation of unbalanced free radical, lipid peroxidation, and endothelial dysfunction. Thus, it is important to study genetic variations of the candidate genes that result in susceptibility to oxidative stress. Previous study has suggested that rs7579 in the 3'-untranslated region of SEPP1 has a functional effect which modulates the selenoprotein transport and enzyme activities in the plasma. This variant also influences the proportion of the protein isoform. Previous studies have investigated the association between the rs7579 and risk of many diseases. For instance, Strauss et al demonstrated that rs7579 is associated with aggressive-growing abdominal aortic aneurysm (AAA) and aortoiliac occlusive disease (AIOD). Steinbrecher et al showed a borderline significant association between rs7579 (AA vs GG) and prostate cancer risk in European men. As another tag-SNP of SEPP1, rs230813 locates in the intron variant. It has been reported that it has a relationship with many disorders such as breast cancer.

Takata at al found that rs230813 was significantly associated with malondialdehyde (MDA) concentration, which is a marker of oxidative stress.

On the contrary, SEPP1 is suggested as selenium transport and has a relationship with the content of selenium in body. Selenium is a micronutrient essential for human health, and has the capacity to reduce the risk of PE through selenoproteins/selenoenzymes. Previous studies indicated that PE patients have lower selenium status in toenail or circulating selenium concentrations during pregnancy. Hence, it is possible that genetic variations of SNPs in SEPP1 have the potential to modulate the relationship between selenoprotein and diseases, which may through alters the synthesis of protein isoform. Therefore, we evaluated 2 SNPs in SEPP1 SNPs that have been associated with oxidative stress and PE. To the best of our knowledge, it is the first study on the relationship between SEPP1 and PE susceptibility in Chinese Han women.

In the present study, we conducted the genotypes of 1034 PE patients and 1400 age-matched normal pregnant women, but we did not find any statistically significant difference in genotypic and allelic frequencies of rs7579 and rs230813 in SEPP1 between PE and control groups in Chinese Han population. To further understand the relationship between SEPP1 and PE, we divided the PE patients into mild/severe and early/late-onset subgroups, but found no statistically significant difference. In conclusion, our data suggest that rs7579 and rs230813 in SEPP1 do not play a crucial role in the risk of PE in Chinese Han women.

Although the sample size of our study was large enough and post hoc power calculations (for rs7579 and rs230813 are 5.4%
and 6.2%, respectively) to draw credible conclusions, there were several limitations that should be noted. Firstly, all the cases and controls were recruited from Shandong Province in China; the results may not be representative of other regions or ethnicities. Secondly, other SNPs in the SEPP1 may affect the risk of PE; only 2 SNPs (rs7579 and rs230813) were investigated in our study. Finally, PE is a complex multifactorial disease, which is the consequence of interaction between genetic and environment risk factors and their interaction. Hence, several genetic variants in SEPP1 might not influence gene expression; other genes or environmental factors such as diet, obesity, and stress may contribute to the development of PE. Therefore, studies with more SNPs and functions are needed to be verified in different races and regions to explore the association between SEPP1 polymorphisms and PE.

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