Observational Study

Medicine®

OPEN

PTX3 Gene 3'UTR polymorphism and its interaction with environmental factors are correlated with the risk of preeclampsia in a Chinese Han population

Ning Xu, MD, Wei Zhang, MD*

Abstract

To investigate the interaction between the single nucleotide polymorphism of the 3' untranslated region (3'UTR) of the *pentraxin 3* (*PTX3*) gene, as well as environmental factors and the preeclampsia risk in a Chinese Han population.

Sanger sequencing was used to analyze rs5853783 and rs73158510 loci of the *PTX3* gene 3'UTR from 235 patients with preeclampsia and 235 control subjects. The plasma PTX3 protein level was measured by enzyme-linked immunosorbent assay (ELISA).

The risk of preeclampsia in the *PTX3* gene rs5853783 locus D allele carriers was 0.72 times higher than that of the I allele carriers (95% CI: 0.60–0.84, $P < .001$). The risk of preeclampsia in the *PTX3* gene rs73158510 locus A allele carriers was 1.36 times higher than in the G allele carriers (95% CI: 1.16–1.55, $P < .001$). The area under the ROC curve (AUC) for the diagnosis of preeclampsia by plasma PTX3 protein levels was 0.906 ($P < .001$). The *PTX3* gene rs5853783 and rs73158510 single nucleotide polymorphisms (SNPs) were associated with plasma PTX3 protein levels. The AUC of plasma PTX3 protein level diagnosis of preeclampsia in *PTX3* gene rs5853783 locus II genotype subjects was up to 0.9371, followed by the ID genotype (AUC = 0.8586); the DD genotype was the lowest (AUC = 0.8154). The AUC of plasma PTX3 protein level diagnosis of preeclampsia in rs73158510 locus GG genotype subjects was 0.9102, GA genotype was 0.8766, and AA genotype was 0.8750.

The rs5853783 and rs73158510 SNPs in the 3'UTR region of the *PTX3* gene are associated with the risk of preeclampsia in a Chinese Han population.

Abbreviations: 3'UTR = 3' untranslated region, AUC = area under the ROC curve, BMI = body mass index, CI = confidence interval, D = insT, ELISA = enzyme-linked immunosorbent assay, HWE = Hardy-Weinberg equilibrium, I = insAT, IL = interleukin, LPS = lipopolysaccharide, MAF = minor allele frequency, OR = odds ratio, PTX3 = pentraxin 3, SNPs = single nucleotide polymorphisms, TNF-α = tumor necrosis factor.

Keywords: gene-environment interaction, *pentraxin 3*, preeclampsia, single nucleotide polymorphism

1. Introduction

Preeclampsia is a unique complication of pregnancy, and its pathogenesis is considered to be closely related to vascular endothelial injury, inflammatory excessive oxidative stress, insulin resistance, as well as genetic factors.[1,2] Clinical signs and symptoms of preeclampsia include visual impairment, headache, upper abdominal pain, thrombocytopenia, and abnormal liver function.[1,3]

Pentraxin 3 (PTX3) is the first discovered long-chain pentameric protein, with a molecular weight of 40 to 50 KD, and is highly conserved in human and mouse evolution.[4,5] PTX3 has a wide range of synthesis and release sites, including neutrophils, dendritic cells, macrophages, activated endothelial cells, smooth muscle cells, fibroblasts, etc.[6,7] At the site of inflammation, the synthesis and release of PTX3 can be induced by interleukin-1 (IL-1), tumor necrosis factor (TNF-α), interleukin 10 (IL-10), lipopolysaccharide (LPS), etc.[7] Under physiological conditions, PTX3 levels in peripheral blood are relatively low; however, in the early stages of inflammation, plasma PTX3 levels can rise rapidly and reach a peak at 6 to 8 h.[4,6] Compared to the plasma C-reactive protein, PTX3 responds more rapidly, exists longer, better represents local inflammatory response, with a less variable plasma concentration than C-reactive protein.[8,9] Thus, PTX3 is a marker for the occurrence and progression of inflammatory responses.

The human *PTX3* gene is located in the q25 region of chromosome 3, containing 3 exons, and expressing 381 amino acids.[10] A variety of single nucleotide polymorphisms (SNPs) in the *PTX3* gene are associated with the occurrence of several

Editor: Daryle Wane.

This work was supported by grants from the Health Science and Technology Plan Medical Key Specialty Disease Project of Hangzhou (20150733Q03).

The authors have no conflicts of interests to disclose.

Department of Obstetrics, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

** Correspondence: Wei Zhang, Department of Obstetrics, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, No. 261, Huansha Road, Hangzhou, Zhejiang, China (e-mail: zhangweihz1983@163.com).*

How to cite this article: Xu N, Zhang W. PTX3 Gene 3'UTR polymorphism and its interaction with environmental factors are correlated with the risk of preeclampsia in a Chinese Han population. Medicine 2020;99:3(e18740).

Received: 30 July 2019 / Received in final form: 8 December 2019 / Accepted: 14 December 2019

http://dx.doi.org/10.1097/MD.0000000000018740

diseases. For example, Zandifar et al[11] indicated that the *PTX3* gene rs3816527 polymorphism is associated with the susceptibility to migraine in men. In addition, He et al[12] reported a significant correlation between *PTX3* rs1840680 polymorphism and the susceptibility to pulmonary aspergillosis in patients with COPD. To date, there are only a few studies have investigated *PTX3* gene polymorphisms in preeclampsia. In the present study, we selected two SNP loci in the 3' untranslated region (3'UTR) of the *PTX3* gene with a minor allele frequency (MAF) above 0.05, that is, rs5853783 and rs73158510. A case-control study was conducted to investigate the association of these two SNP loci with the risk of preeclampsia.

2. Materials and methods

2.1. Subjects

A cohort of 235 patients with preeclampsia (case group) was recruited from the Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine between March 2016 and October 2018, with ages ranging from 18 to 39 years (mean, 28.18 ± 5.50 years), and gestational age ranging from 35 to 39 weeks (mean, 38.04 ± 1.05 weeks). Another cohort of 235 healthy pregnant women were randomly selected as the control group, aged 20 to 40 years (mean, 28.87 ± 6.08 years), and gestational age was 35 to 42 weeks (mean, 38.11 ± 1.41 weeks). The inclusion criteria were as follows:

(1) Han nationality;
(2) age ≥ 18 years;
(3) complete medical records;
(4) diagnostic criteria for preeclampsia in accordance with the American College of Obstetricians and Gynecologists (ACOG) guide.[13]

The exclusion criteria were as follows:

(1) other complications during pregnancy;
(2) history of chronic hypertension, heart disease, kidney disease, diabetes, and liver disease before pregnancy.

All subjects signed the informed consent form and the study was approved by the Medical Ethics Committee of the Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. The recruitment was performed in accordance with the World Medical Association Declaration of Helsinki.

2.2. Genotyping

Plasma genomic DNA was extracted using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden Germany) according to the manufacturer's instructions and stored at −80°C. The DNA fragment containing the rs5853783 and rs73158510 loci of the *PTX3* gene 3'UTR was amplified by polymerase chain reaction (PCR) using the extracted genomic DNA as a template. The PCR primers were: 5'-TGG CCA GAG ATG AAT TTT ACA TTG G-3' (forward); 5'-TCT TCT CAA AAA CGT GAC ATT CG-3' (reverse). 5'-CGA ATG TCA CGT TTT TGA GAA GAT A-3' (forward); 5'-ACG AGT TTG CTC CAA AAC ATC T-3' (reverse). The PCR mixture contained 12.5 μL PCR mix (Elpis-Biotech), 1 μL (10 pmol) each of the primers, 1 μL genomic DNA, and 1.5 μL double distilled water. The PCR conditions were as follows: pre-denaturation at 94°C for 2 minutes, denaturation at 94°C for 1 minute, annealing at 60°C for 40 seconds, and extension at 72°C for 4 minutes, in a total of 30 cycles. After PCR, Sanger sequencing was performed using GENEWIZ (North Brunswick, NJ), and the genotypes were determined by comparing the sequencing results with the sequences in the NCBI database.

2.3. Enzyme-linked immunosorbent assay (ELISA)

A quantitative sandwich ELISA was performed to test the plasma PTX3 protein levels using 3 ml of whole blood collected from participants. Plasma PTX3 protein levels were determined using an ELISA kit (R&D Systems, Inc., Minneapolis, America) according to the manufacturer's instructions. The minimum detectable dose of the kit is 0.007 to 0.116 ng/ml.

2.4. Statistical analysis

In the present study, statistical analysis was performed using SPSS 22.0 (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean ± SD, and statistically analyzed using the *t* test. Categorical variables were expressed as n(%) and statistically analyzed using the χ^2 test. Fisher Exact Test was used to compare the genotype distribution of *PTX3* gene SNPs between the case and control groups. χ^2 test was performed to test whether the genotype distribution was consistent with the Hardy-Weinberg equilibrium (HWE), based on the distribution of allele frequencies and genetic models (additive, dominant, and recessive models) to determine the correlation between *PTX3* gene SNPs and the risk of preeclampsia. The odds ratio (OR) and 95% confidence interval (CI) were used in an unconditional logistic regression analysis, adjusted for age, gestational age, pre-pregnancy body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and family history of hypertension. Multi-factor dimensionality reduction (MDR) was performed to assess the SNPs of *PTX3* gene and its interaction with environmental factors. All tests were 2-tailed, with $P < .05$ considered as significant differences.

3. Results

3.1. Demographic information

The demographic information of the case group and the control group are shown in Table 1. There was no significant difference in age and gestational age between the case and the control groups

Table 1

Comparison of demographic characteristics between the case and control groups.

Parameters	Case (n = 235)	Control (n = 235)	*P* value
Age (years, mean ± SD)	28.18 ± 5.50	28.87 ± 6.08	.19
Gestational age (weeks, mean ± SD)	38.04 ± 1.05	38.11 ± 1.41	.39
Pre-pregnant BMI (kg/m^2, mean ± SD)	24.10 ± 4.28	22.26 ± 3.81	<.001
SBP (mmHg, mean ± SD)	170.21 ± 25.39	112.41 ± 14.34	<.001
DBP (mmHg, mean ± SD)	103.74 ± 15.40	71.49 ± 9.06	<.001
Family history of hypertension [n(%)]			<.001
Yes	105 (44.68%)	42 (17.87%)	
N	130 (55.32%)	193 (82.13%)	

BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation.

($P > .05$). The proportion of pre-pregnancy BMI, SBP, DBP, and subjects with a family history of hypertension were significantly higher in the case group than in the control group ($P < .05$).

3.2. Association of PTX3 gene 3'UTR SNPs with preeclampsia

We analyzed the genotype and allele frequencies of the 3'UTR rs5853783 and rs73158510 loci from 235 cases of preeclampsia patients and 235 control subjects (Table 2). The frequency distribution of the rs5853783 and rs73158510 loci of the *PTX3* gene in the control group was consistent with the HWE ($P > .05$). Using the II genotype of the *PTX3* gene rs5853783 locus as a reference, both ID and DD genotypes were protective factors for preeclampsia (OR = 0.76, 95% CI: 0.62–0.93, $P = .01$; OR = 0.50, 95% CI: 0.29–0.78, $P = .01$; respectively). In addition, the risk of preeclampsia was dramatically reduced in both dominant and recessive models (OR = 0.50, 95% CI: 0.35–0.72, $P < .001$; OR = 0.57, 95% CI: 0.33–0.89, $P = .01$; respectively). The risk of preeclampsia in rs5853783 locus D allele carriers was 0.72 times higher than in the I allele carriers (95% CI: 0.60–0.84, $P < .001$) (Table 2). Moreover, based on the GG genotype of *PTX3* gene rs73158510 locus, both GA and AA genotypes were high risk factors for preeclampsia (OR = 1.30, 95% CI: 1.05–1.57, $P = .02$; OR = 1.74, 95% CI: 1.17–2.08, $P = .01$; respectively). The risk of preeclampsia was significantly increased in both the dominant and recessive models (OR = 1.36, 95% CI: 1.12–1.62, $P < .01$; OR = 1.62, 95% CI: 1.09–1.93, $P = .02$; respectively). The risk of preeclampsia in the *PTX3* gene rs73158510 locus A allele carriers was 1.36 times higher than in the G allele carriers (95% CI: 1.16–1.55, $P < .001$) (Table 2).

3.3. Stratified analyses

In the present study, a stratified analysis to test the correlation between the *PTX3* gene 3'UTR SNP and the risk of preeclampsia was performed. Hence, we divided all participants into the following sub-groups: younger reproductive age (age $\leq$ 35 years) and advanced reproductive age (age > 35 years), non-obesity (BMI $\leq 24\,kg/m^2$) and obesity (BMI $> 24\,kg/m^2$), as well as with family history and without family history of hypertension. The results demonstrated that in subjects with younger reproductive age, non-obesity, and with a family history of hypertension, the risk of preeclampsia in the *PTX3* gene rs5853783 locus D allele carriers (ID/DD) was significantly lower than that of the type II genotype ($P < .05$). However, in subjects with advanced reproductive age, obesity, and without a family history of hypertension, there was no significant difference in the risk of preeclampsia between the *PTX3* gene rs5853783 locus D allele carriers (ID/DD) and the II genotype carriers ($P > .05$) (Table 3). These findings indicate that the correlation between the risk of preeclampsia and the *PTX3* gene rs5853783 locus SNP can be affected by several factors including age, pre-pregnancy BMI, and a family history of hypertension.

Similarly, in subjects with younger reproductive age, advanced reproductive age, non-obesity, and without a family history of hypertension, the risk of preeclampsia in *PTX3* gene rs73158510 locus A allele carriers (GA/AA) was significantly lower than in the GG genotype carriers ($P < .05$). However, in obese subjects, with a family history of hypertension, no significant difference was observed in the risk of preeclampsia between the *PTX3* gene rs73158510 locus A allele carriers (GA/AA) and the GG genotype carriers ($P > .05$) (Table 4). These findings indicate that the correlation between the risk of preeclampsia and the *PTX3* gene rs73158510 locus SNP was affected by BMI and a family history of hypertension.

3.4. Multi-factor dimensionality reduction (MDR) analysis of the interaction between PTX3 gene SNPs and environmental factors

Further, we performed MDR to analyze the interaction between *PTX3* gene rs5853783 and rs73158510 loci SNPs and environmental factors, that is, age, pre-pregnancy BMI, and family history of hypertension. We observed that there was a positive interaction between *PTX3* gene rs5853783 SNP and age, BMI, as well as a family history of hypertension. There was a positive interaction between the *PTX3* gene rs73158510 SNP and age, as well as a family history of hypertension; however, there was a negative interaction between the *PTX3* gene rs73158510 SNP and the pre-pregnancy BMI (Fig. 1A). In addition, the interaction between the *PTX3* gene rs73158510

Table 2

Correlation between the 3'UTR genotype and allele frequency of *PTX3* gene and preeclampsia risk.

	Case (n = 235)	Control (n = 235)	HWE *p*	*P*	OR (95% CI)*
rs5853783					
II	145 (61.70%)	105 (44.68%)	0.24		1.00 (reference)
ID	77 (32.77%)	98 (41.70%)		.01	0.76 (0.62–0.93)
DD	13 (5.53%)	32 (13.62%)		.01	0.50 (0.29–0.78)
Dominant model				<.001	0.50 (0.35–0.72)
Recessive model				.01	0.57 (0.33–0.89)
I	367 (78.09%)	308 (65.53%)			1.00 (reference)
D	103 (21.91%)	162 (34.47%)		<.001	0.72 (0.60–0.84)
rs73158510					
GG	155 (65.96%)	186 (79.15%)	0.51		1.00 (reference)
GA	65 (27.66%)	45 (19.15%)		.02	1.30 (1.05–1.57)
AA	15 (6.38%)	4 (1.70%)		.01	1.74 (1.17–2.08)
Dominant model				<.01	1.36 (1.12–1.62)
Recessive model				.02	1.62 (1.09–1.93)
G	375 (79.79%)	417 (88.72%)			1.00 (reference)
A	95 (20.21%)	53 (11.28%)		<.001	1.36 (1.16–1.55)

CI = confidence interval, D = insT, HWE = Hardy-Weinberg equilibrium, I = insAT, OR = odds ratio, 3'UTR = 3' untranslated region.
* Adjusted by age, gestational age, pre-pregnant BMI, SBP, DBP, family history of hypertension.

Table 3

Stratified analysis of the correlation between *PTX3* gene rs5853783 locus SNP and the risk of preeclampsia.

	Case (n = 235)	Control (n = 235)	*P*	OR (95% CI)
Age (years)				
≤35				
II	125 (60.39%)	84 (43.52%)		1.00 (reference)
ID/DD	82 (39.61%)	109 (56.48%)	.001	0.72 (0.58–0.88)
>35				
II	20 (71.43%)	21 (50.00%)		1.00 (reference)
ID/DD	8 (28.57%)	21 (50.00%)	.13	0.57 (0.26–1.13)
Pre-pregnant BMI (kg/m^2)				
≤24				
II	98 (60.12%)	43 (38.05%)		1.00 (reference)
ID/DD	65 (39.88%)	70 (61.95%)	<.001	0.69 (0.56–0.86)
>24				
II	47 (65.28%)	62 (50.82%)		1.00 (reference)
ID/DD	25 (34.72%)	60 (49.18%)	.07	0.68 (0.44–1.03)
Family history of hypertension				
Yes				
II	71 (67.62%)	17 (40.48%)		1.00 (reference)
ID/DD	34 (32.38%)	25 (59.52%)	.004	0.71 (0.56–0.91)
No				
II	74 (56.92%)	88 (45.60%)		1.00 (reference)
ID/DD	56 (43.08%)	105 (54.40%)	.06	0.76 (0.57–1.01)

Adjusted by age, gestational age, pre-pregnant BMI, SBP, DBP, family history of hypertension.
BMI = body mass index, CI = confidence interval, D = insT, I = insAT, OR = odds ratio, SNP = single nucleotide polymorphism.

SNP and the rs5853783 SNP was the highest, followed by age, family history of hypertension, and pre-pregnancy BMI (Fig. 1B).

3.5. Abnormal elevation of plasma PTX3 levels in patients with preeclampsia

To detect the plasma PTX3 protein levels in all participants, ELISA was performed. The results showed that plasma PTX3 protein levels were significantly higher in patients with preeclampsia than in the control group ($P < .001$) (Fig. 2A). Next, we analyzed the receiver operating characteristic (ROC) curve of plasma PTX3 protein level diagnosis of preeclampsia and found that the area under the curve (AUC) was 0.906 ($P < .001$) (Fig. 2B).

3.6. Association of PTX3 gene rs5853783 and rs73158510 SNPs with plasma PTX3 protein levels

Then, we analyzed the correlation between PTX3 protein levels in plasma and rs5853783 and rs73158510 loci SNPs in the case and control groups. The results demonstrated that in both case and control

Table 4

Stratified analysis of the correlation between *PTX3* gene rs73158510 SNP and the risk of preeclampsia.

	Case (n = 235)	Control (n = 235)	*P*	OR (95% CI)
Age (years)				
≤35				
GG	140 (67.63%)	151 (78.24%)		1.00 (reference)
GA/AA	67 (32.37%)	42 (21.76%)	.02	1.28 (1.03–1.54)
>35				
GG	15 (53.57%)	35 (83.33%)		1.00 (reference)
GA/AA	13 (46.43%)	7 (16.67%)	.02	2.17 (1.15–3.54)
Pre-pregnant BMI (kg/m^2)				
≤24				
GG	103 (63.19%)	91 (80.53%)		1.00 (reference)
GA/AA	60 (36.81%)	22 (19.47%)	.003	1.38 (1.12–1.64)
>24				
GG	52 (72.22%)	95 (77.87%)		1.00 (reference)
GA/AA	20 (27.78%)	27 (22.13%)	.48	1.20 (0.76–1.79)
Family history of hypertension				
Yes				
GG	69 (65.71%)	31 (73.81%)		1.00 (reference)
GA/AA	36 (34.29%)	11 (26.19%)	.45	1.11 (0.87–1.34)
No				
GG	86 (66.15%)	155 (80.31%)		1.00 (reference)
GA/AA	44 (33.85%)	38 (19.69%)	.006	1.50 (1.12–1.95)

Adjusted by age, gestational age, pre-pregnant BMI, SBP, DBP, family history of hypertension.
BMI = body mass index, CI = confidence interval, OR = odds ratio, SNP = single nucleotide polymorphism.

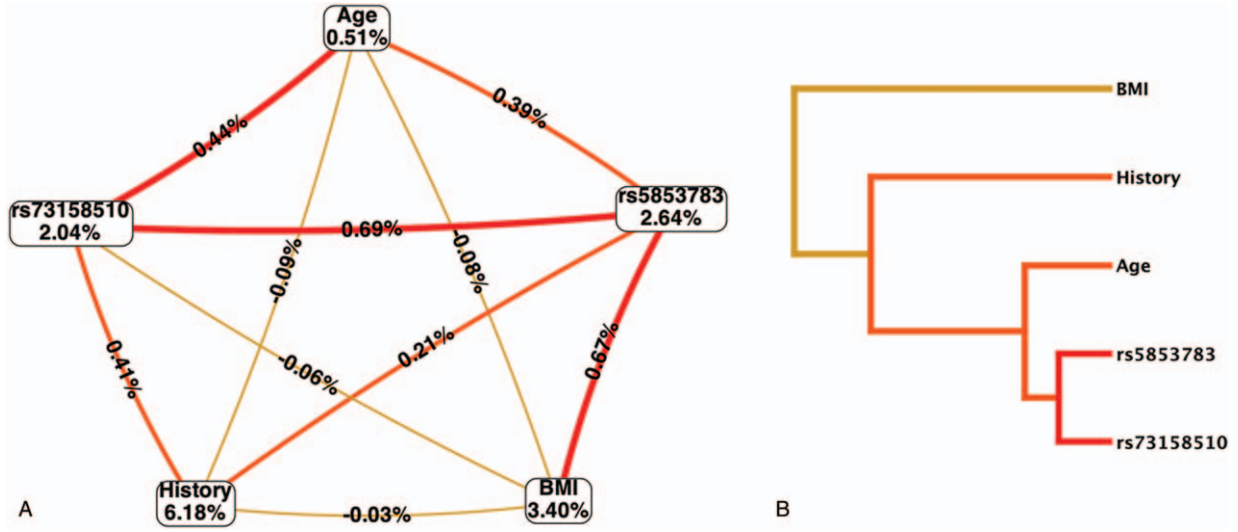

Figure 1. Interaction between the *PTX3* gene rs5853783 and rs73158510 SNPs and subject's age, pre-pregnant body mass index, and family history of hypertension. (A) The circle graph, the percentage at the bottom of each factor represents its entropy, and the percentage on each line represents the percentage of interaction between the 2 factors. The red line indicates a positive interaction and the yellow line indicates a negative interaction. (B) The tree graph. The red line represents a stronger interaction, the orange line represents a weaker interaction. The closer location between the 2 factors represents a stronger interaction.

groups the plasma levels of PTX3 protein were significantly higher in rs5853783 locus II genotype carriers than in the ID genotype, and the DD genotype was the lowest ($P < .05$) (Fig. 3A and B). Moreover, the plasma levels of PTX3 protein in rs73158510 locus GG genotype carriers were significantly lower than in the GA genotype, and the AA genotype was the highest ($P < .05$) (Fig. 3C and D).

3.7. PTX3 gene SNPs affected the diagnostic efficacy of preeclampsia by plasma PTX3 protein levels

Finally, we analyzed the ROC curve of plasma PTX3 protein level diagnosis of preeclampsia in different genotypes of the *PTX3* gene rs5853783 and rs73158510. The results indicated that the AUC of plasma PTX3 protein level diagnosis of preeclampsia in the *PTX3* gene rs5853783 locus II genotype subjects was up to 0.9371, followed by the ID genotype (AUC = 0.8586), and DD genotype was the lowest (AUC = 0.8154), with a statistically significant difference ($P < .05$) (Fig. 4A). The AUC of plasma PTX3 protein level diagnosis of preeclampsia in rs73158510 locus GG genotype subjects was 0.9102; the GA genotype was 0.8766, and AA genotype was 0.8750, with a statistically significant difference observed ($P < .05$) (Fig. 4B).

4. Discussion

Here, we conducted a case-control study to investigate the correlation between SNPs of 2 loci with minor allele frequencies above 0.05 in the *PTX3* gene 3'UTR (ie, rs5853783 and rs73158510) and the risk of preeclampsia in 235 patients with preeclampsia and 235 control subjects. We observed an increased risk of preeclampsia occurrence, as well as the plasma levels of PTX3 protein, in subjects carrying the rs5853783 locus I allele and the rs73158510 locus A allele of the *PTX3* gene. Based on

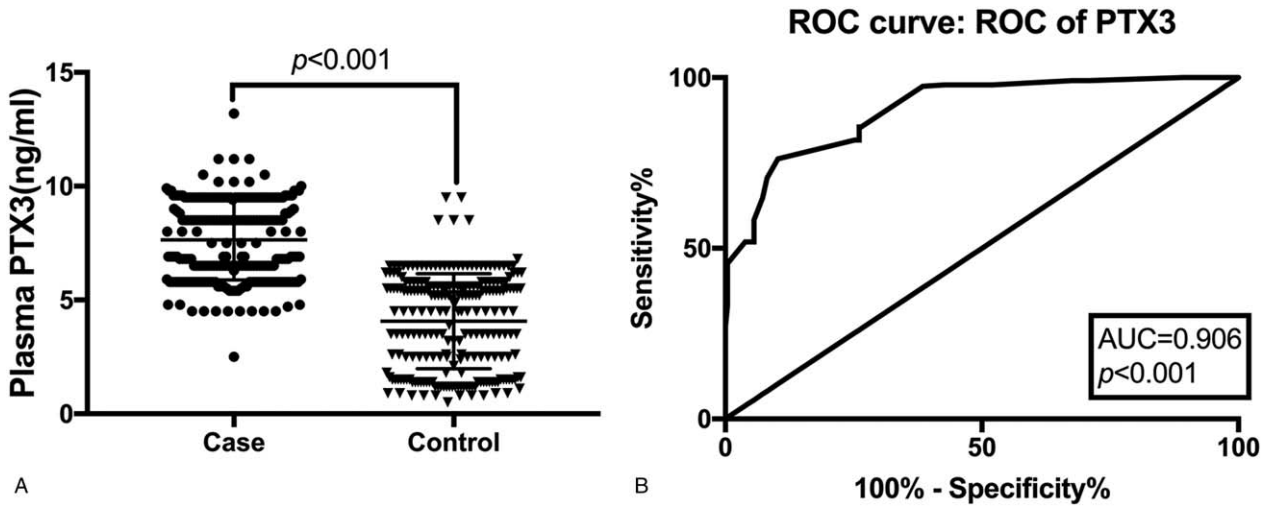

Figure 2. Plasma PTX3 levels detected by ELISA. (A) plasma PTX3 protein levels in the case and control groups. (B) The receiver operating characteristic curve of plasma PTX3 level diagnosis of preeclampsia.

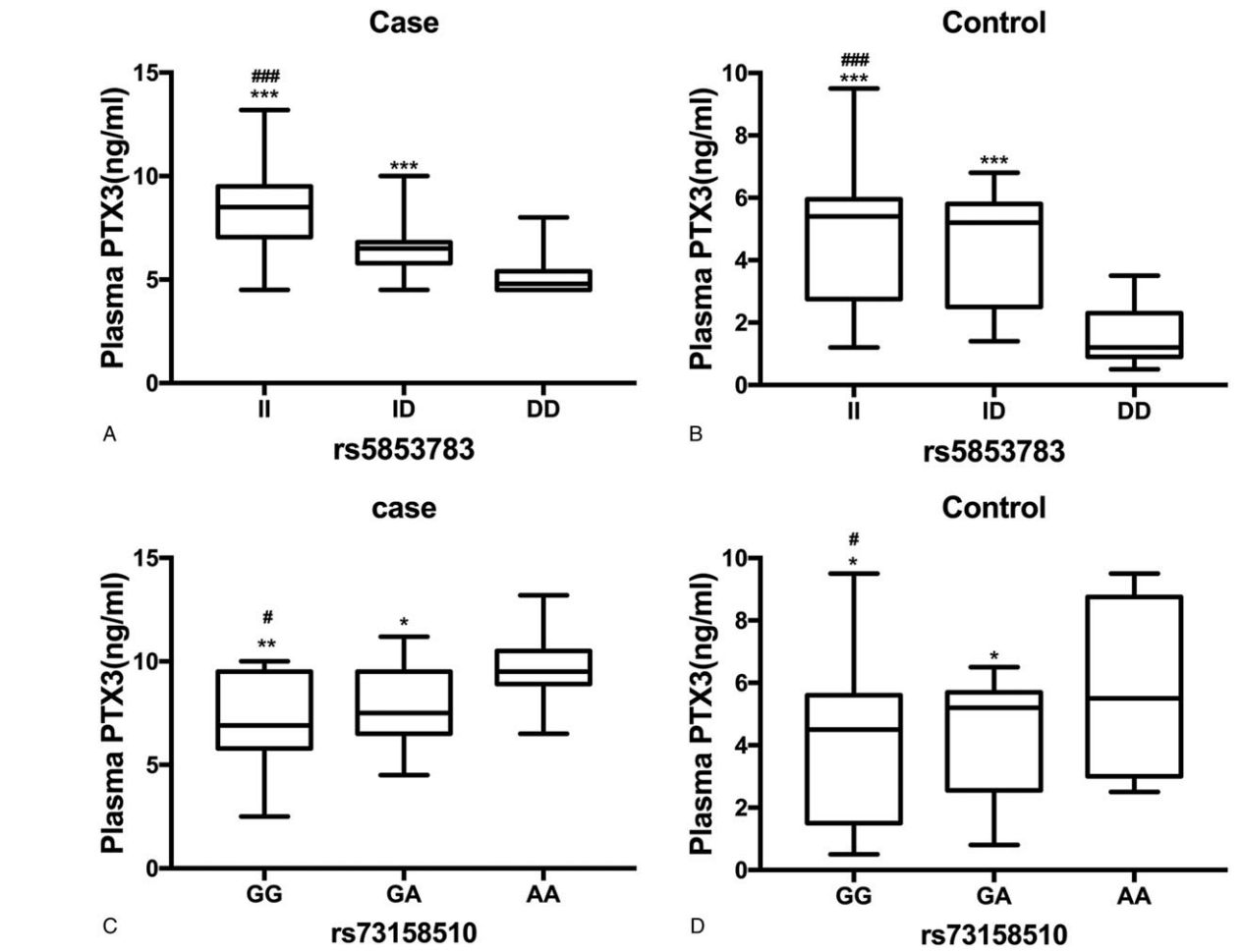

Figure 3. Correlation of *PTX3* gene rs5853783 and rs73158510 SNPs with plasma levels of PTX3 protein. (A) Comparison of plasma PTX3 protein levels between different genotypes of the *PTX3* gene rs5853783 in the case group. (B) Comparison of plasma PTX3 protein levels between different genotypes of the *PTX3* gene rs5853783 in the control group. (C) Comparison of plasma PTX3 protein levels between different genotypes of the *PTX3* gene rs73158510 in the case group. (d) Comparison of plasma PTX3 protein levels between different genotypes of the *PTX3* gene rs73158510 in the control group.

these findings, it is probable that the rs5853783 and rs73158510 SNPs in the 3'UTR of the *PTX3* gene are associated with the risk of preeclampsia in a Chinese Han population.

Preeclampsia is a disease unique to pregnancy, clinically characterized by hypertension, proteinuria, and edema, which are common complications of a hypertensive disorder during pregnancy. Indeed, preeclampsia is a typical representative of the hypertensive disorder in pregnancy.[3,14] Preeclampsia is often accompanied by systemic multiple organ damage or multi-function failure, and these complications seriously endanger maternal and fetal safety.[15,16] Previously, studies have investigated the etiology and pathogenesis of hypertensive disorder in pregnancy, suggesting that preeclampsia may be affected by the interaction of multiple genes and environmental factors.[17–19]

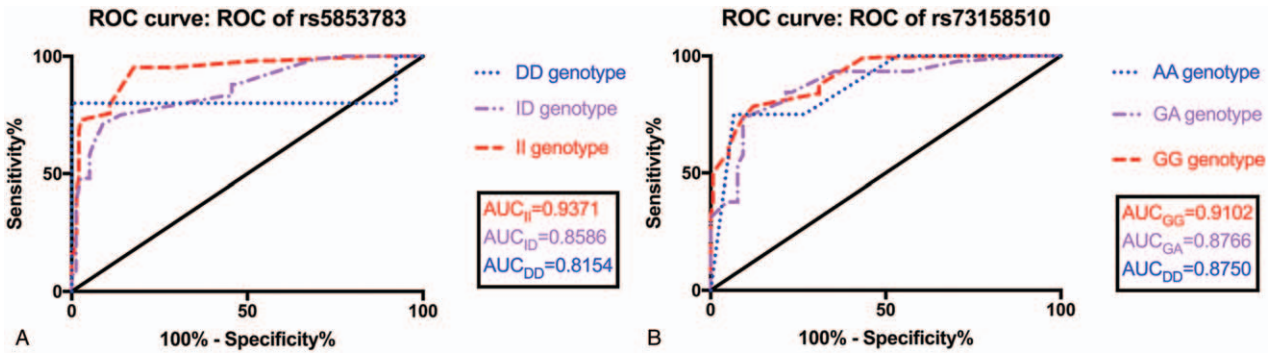

Figure 4. Correlation between *PTX3* gene rs5853783 and rs73158510 SNPs with the plasma PTX3 protein levels in the diagnosis of preeclampsia.

In the present study, we observed that plasma PTX3 protein levels were significantly higher in preeclampsia patients than in the control subjects. Based on the ROC analysis, we reported that the AUC of plasma PTX3 protein level diagnosis of preeclampsia was increased to 0.906, suggesting that PTX3 may be a potential marker of preeclampsia and is of great value in the diagnosis of preeclampsia.

There are a variety of SNP loci in the 3'UTR of the *PTX3* gene. In the present study, we selected 2 SNP loci with MAF > 0.05. Our analyses demonstrated that after adjusting for age, gestational age, pre-pregnancy BMI, SBP, DBP, and family history of hypertension, the D allele of rs5853783 locus was a protective factor for preeclampsia, and the *PTX3* gene rs73158510 locus A alleles was a risk factor for preeclampsia. Further, by measuring the plasma PTX3 protein levels in the participants, we revealed that the plasma PTX3 protein level of the rs5853783 locus D allele carriers was significantly lower than that observed in I allele carriers in both patients with preeclampsia and the control subjects, and the plasma PTX3 protein level of the *PTX3* gene rs73158510 A allele carriers was significantly higher than that in the G allele carriers. This indicated that the *PTX3* gene rs5853783 and rs73158510 loci SNP were associated with plasma PTX3 protein levels. Based on the above findings, we hypothesized that the correlation between the *PTX3* gene rs5853783 and rs73158510 SNPs and the risk of preeclampsia may due to abnormal expression of the PTX3 protein, and in the subjects with the high-risk allele, the PTX3 protein was highly expressed. Given that both the rs5853783 and the rs73158510 loci are located in the 3'UTR of the *PTX3* gene, and the 3'UTR of the gene is a binding site for microRNAs to regulate the gene expression, we speculate that the rs5853783 and rs73158510 SNPs may affect the regulations of PTX3 protein expression through microRNAs; however, there is no direct evidence in the current study to support this hypothesis.

Future studies aim to elucidate the associated microRNAs and confirm the effect of the *PTX3* gene rs5853783 and rs73158510 on the regulation of the PTX3 protein expression by these microRNAs in vitro. In addition, the correlations between more relevant genes and environmental factors on the risk of preeclampsia needs to be evaluated. Furthermore, although SNPs of the rs5853783 and rs73158510 loci in the 3'UTR of the *PTX3* gene were found to be related to preeclampsia in a Chinese Han population, the calculated OR value only demonstrated a weak correlation due to the small sample size. Hence, it is necessary to verify these observations with a larger sample size. More importantly, large-scale, multi-regional, and multi-ethnic systematic studies are imperative to better understand the pathogenesis of preeclampsia.

In summary, the rs5853783 and rs73158510 SNPs in the 3'UTR of the *PTX3* gene are associated with the risk of preeclampsia in the Chinese Han population, and the specific mechanisms need to be evaluated in future studies.

Author contributions

Conceptualization: Wei Zhang.
Data curation: Ning Xu.
Formal analysis: Ning Xu.
Funding acquisition: Wei Zhang.
Investigation: Wei Zhang.
Methodology: Ning Xu.
Writing – original draft: Ning Xu.
Writing – review & editing: Wei Zhang.

References

[1] Ramos JGL, Sass N. Costa SHM: preeclampsia. Rev Bras Ginecol Obstet 2017;39:496–512.
[2] El-Sayed AAF. Preeclampsia: A review of the pathogenesis and possible management strategies based on its pathophysiological derangements. Taiwan J Obstet Gynecol 2017;56:593–8.
[3] Mayrink J, Souza RT, Feitosa FE, et al. Incidence and risk factors for Preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. Sci Rep 2019;9:9517.
[4] Peri G, Introna M, Corradi D, et al. PTX3, a prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. Circulation 2000;102:636–41.
[5] Mantovani A, Garlanda C, Doni A, et al. Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 2008;28:1–3.
[6] Garlanda C, Bottazzi B, Bastone A, et al. Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol 2005;23:337–66.
[7] Bottazzi B, Garlanda C, Salvatori G, et al. Pentraxins as a key component of innate immunity. Curr Opin Immunol 2006;18:10–5.
[8] Malaponte G, Libra M, Bevelacqua Y, et al. Inflammatory status in patients with chronic renal failure: the role of PTX3 and pro-inflammatory cytokines. Int J Mol Med 2007;20:471–81.
[9] Boehme M, Kaehne F, Kuehne A, et al. Pentraxin 3 is elevated in haemodialysis patients and is associated with cardiovascular disease. Nephrol Dial Transplant 2007;22:2224–9.
[10] Bottazzi B, Vouret-Craviari V, Bastone A, et al. Multimer formation and ligand recognition by the long pentraxin PTX3. Similarities and differences with the short pentraxins C-reactive protein and serum amyloid P component. J Biol Chem 1997;272:32817–23.
[11] Zandifar A, Iraji N, Taheriun M, et al. Association of the long pentraxin PTX3 gene polymorphism (rs3816527) with migraine in an Iranian population. J Neurol Sci 2015;349:185–9.
[12] He Q, Li H, Rui Y, et al. Pentraxin 3 gene polymorphisms and pulmonary aspergillosis in chronic obstructive pulmonary disease patients. Clin Infect Dis 2018;66:261–7.
[13] American College of Obstetricians and Gynecologists; Task Force on Hypertension in PregnancyHypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013;122: 1122–31.
[14] Xia H, Zhang R, Sun X, et al. Risk factors for preeclampsia in infertile Chinese women with polycystic ovary syndrome: a prospective cohort study. J Clin Hypertens (Greenwich) 2017;19: 504–9.
[15] Eastabrook G, Brown M, Sargent I. The origins and end-organ consequence of pre-eclampsia. Best Pract Res Clin Obstet Gynaecol 2011;25:435–47.
[16] Ramachandran R, Yadav AK, Anakutti H, et al. Utility of serology in the diagnosis of pre-eclampsia and haemolytic uraemic syndrome in pregnancy-related acute kidney injury. Nephrology (Carlton) 2018;23: 602–3.
[17] Roberts CT. IFPA Award in Placentology Lecture: complicated interactions between genes and the environment in placentation, pregnancy outcome and long term health. Placenta 2010;31 Suppl: S47–53.
[18] Kang L, Chen CH, Yu CH, et al. An association study of interleukin-4 gene and preeclampsia in Taiwan. Taiwan J Obstet Gynecol 2014;53: 215–9.
[19] Wu X, Yang K, Tang X, et al. Folate metabolism gene polymorphisms MTHFR C677T and A1298C and risk for preeclampsia: a meta-analysis. J Assist Reprod Genet 2015;32:797–805.