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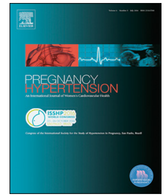
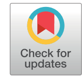


The relationship between DNA repair genes (XPA, XPF, XPG) polymorphism and the risk of preeclampsia in Chinese Han Women



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ABSTRACT

Our study aimed to investigate the association between polymorphism of three core genes belonging to NER pathway and preeclampsia (PE) risk in Chinese Han Women. The DNA used in our experiment was extracted from 1004 cases and 1274 normal pregnant women. All single nucleotide polymorphisms (SNPs) were analyzed with TaqMan allelic discrimination real-time PCR. Our findings showed the genotype and allele frequency of XPA rs1800975, XPF rs1799801, XPG rs17655 in case group has no significant differences compared with control group (all $P > 0.05$). However, we found the genotype of rs1799801 in the control group was significantly different from severe PE group in cases ($P < 0.05$). Moreover, the genotype frequency of rs1800975 and rs1799801in the early-onset PE were significantly different from control group (all $P < 0.05$). These results indicated that the polymorphism of the three SNPs had no significant correlation with risk of PE as a whole. However, we found XPA rs1800975 played a role in the development of early-onset PE, and XPF rs1799801 was associated with severe PE and early-onset PE. So we may need to continue to increase the sample size to clarify their relationship.

1. Introduction

Preeclampsia (PE) is a multisystem disorder that occurs in pregnant women, which affects about 5–8% of pregnant women in the world. It is characterized by hypertension (> 140/90 mmHg) and end-organ dysfunction at ≥20 weeks of gestation and so causes serious maternal and fetal morbidity and mortality [1]. Abnormal placentation which can be caused by many factors such as oxidative stress, inflammation, deficient heme oxygenase expression, autoantibodies against the angiotensin receptor and so on are thought to be associated with the development of PE [1,2]. In addition, there is evidence that genetic factors play an important role in the pathogenesis of PE, and the interaction between genes and the environment accounts for more than half of the causes [3].

Although the integrity of genetic material is constantly threatened by environmental agents (chemicals and radiation) and byproducts of cellular metabolic processes (for example, reactive oxygen species, alkylating agents, intrinsic chemical instability), DNA can still be stable because of the human evolution to perfect gene repair system, including nucleotide excision repair (NER), the direct reversal of damage, double-strand break repair (DSB), base excision repair (BER), and interstrand crosslink repair [4]. NER is the most common repair mechanism in terms of a variety of types of gene damage among all repair systems, which involves at least eight core genes (XPA, ERCC3/XPB, XPC, ERCC2/XPD, XPE/DDB1, ERCC4/XPF,. ERCC5/XPG, ERCC1) [5].

XPA, the xeroderma pigmentosum group A gene, encoding a zinc-finger DNA-binding protein, participates in the modulation of damage recognition and maintains genomic integrity at NER pathway. XPA A23G polymorphism (rs1800975) is an A to G substitution in the 5′-end noncoding region [6]. A large number of studies have shown that this nucleotide polymorphism is associated with lung cancer. Wu et al. demonstrated that individuals with GG and AG genotypes of this polymorphism had a higher DNA repair capacity than those who carried AA genotype [7]. XPF, the xeroderma pigmentosum complementation

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group F, is located on chromosome 16p13.12 and contains 11 exons. The XPF encoding protein which consists of 916 amino acids is a rate-limiting enzyme. XPF constitutes a close heterodimer with resection repair cross-complement 1 (ERCC1) as a structurally specific endonuclease that plays an important role in catalyzing the 5 'incision during DNA resection and removes DNA double-strand breaks, 3′single-stranded flaps, immunoglobulin class switch recombination, and DNA interstrand crosslinks [8,9]. XPF 30028 T/C polymorphism (rs1799801), though not altering amino acids (Ser835Ser), was reported to influence the enzyme function, and be related to cancer [8]. XPG, Xeroderma pigmentosum group G which is located on chromosome 13q22-q33, encodes a structure-specific endonuclease including 1,186-amino acid. The protein cleaves the damaged DNA strand at the 3′ side of the damaged site, and participates in the 5′ incision regulated by the XPF/ERCC1 heterodimer, as well as stabilizes the DNA repair complex of the damaged DNA [10,11]. XPG Asp1104His (rs17655 G > C) polymorphism is a non-synonymous SNP (nsSNP) located in exon15. Several studies have investigated the its function [5]. Therefore, the three single-nucleotide polymorphisms may have functional significance.

We used case-control study to explore the relationship between the three SNPs and the pathogenesis of PE. To the best of our knowledge, The study is the first attempt to investigate the association between the XPA rs1800975/XPF rs1799801/XPG rs17655 polymorphisms and risk of PE in Chinese Han Women.

2. Materials and methods

2.1. Subjects

We performed a multicenter case-control study case-control study. The study consisted of 1004 cases and 1274 normal pregnant women which were recruited from The Affiliated Hospital of Qingdao University, The Hospital of Yantai Yuhuangding, Binzhou Medical University Hospital, Maternal and Child Health Care of Zaozhuang, Linyi People's Hospital, and Liaocheng People’s Hospital. The diagnostic criteria for PE referred to a report of the American College of Obstetricians and Gynecologists’ Task Force on Hypertension in Pregnancy are defined as a persistent systolic blood pressure ≥ 140 mmHg, or a diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation in a woman whose previously blood pressure is normal, and proteinuria C of 300 mg or higher in 24-hour after 20 weeks of gestation [12]. All participants are selected from single pregnancy and non-smoking pregnant women. Patients with systemic lupus erythematosus, diabetes mellitus, history of hypertension were excluded. Control group was selected from the normal pregnant population and excluded the pregnant women with cardiac disease, chronic hypertension, hepatic diseases, renal disease, diabetes mellitus, transfusion, autoimmune disease, and obstetric complications (for example, placenta previa, premature rupture of the membranes, artificial insemination, threatened abortion). Macrosomia in the present gestation were also excluded. Case group matched with control group in mean age (Case group: 30.72 ± 4.18, control group: 30.73 ± 5.87). For this study, we collected detailed clinical information, including gestational age at delivery, gestational age at admission, the number of gravidity and abortions, routine urinary, coagulation convention, blood routine and biochemical analysis. We conducted the study approved by the local ethics committee. In addition, all participants have given informed consent.

2.2. Genetic studies

Genomic DNA was extracted from 300 μL peripheral venous blood using Qiagen DNA extraction kit (Qiagen, Hilden, Germany). The rs1800975/rs1799801/rs17655 polymorphisms were analyzed by the TaqMan allelic discrimination real-time PCR. The synthesis of Taqman probes and primers were performed by Applied Biosystems of Life Technologies (New York, USA). The rs1800975 primer sequences were 5′-GGGAGCTAGGTCCTCGGAGTGGGCC-3′(forward) and 5′-GAGATGG CGGCGGCCGACGGGGCTT-3′(reverse), the rs1799801 sequences were 5′-CAGCACTGGCCATTACAGCAGATTC-3′(forward) and 5′-GAAACCCT TCCCGAGTCAGAGAAGT-3′(reverse), and the rs17655 primer sequences were 5′- TTCATTAAAGATGAACTTTCAGCAT-3′(forward) and 5′- TTCACTTGAAGATCCATCAGATGAT-3′(reverse). The reaction system with 25 μL reaction volume containing 12.5 μL of 2 × PCR Master Mix, 1.25 μL of 20 × SNP, 11.25 μL of DNA and DNase-free water. The amplification containing C1000™ thermal cycler and CFX96™ real-time system (Bio-Rad, California, USA) is as follows: 95 °C for 3 min; 45 cycles of 95 °C for 15 s and 60 °C for 1 min. The genotypes were distinguished by identifying the fluorescent signals from VIC/FAM-labeled probes.

2.3. Statistical analysis

All statistical data were analyzed by SPSS V 22.0 software. The differences in clinical characteristics and demographic data (for example, Maternal age, gestational age, blood pressure, number of gravidity and so on) between case and control groups were analyzed by T-test. The Pearson’s chi-square test was used to compare the differences in genotypic and allelic frequencies between case and control groups. Furthermore, Hardy–Weinberg balance tested by chi-square test, was used to detect whether the control group had a population representation. The odds ratios (ORs) and 95% confidence intervals (CIs) were used to indicate the relative risk degree. The result was considered statistically significant with P value < 0.05.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of PE and normal pregnant women are shown in Table 1. There was no significant difference between the case group and the control group in age (case group: 30.73 ± 5.87, control group: 30.72 ± 4.18; $P > 0.05$). And there was no difference in the number of abortions ($P > 0.05$). As shown in Table 1, the results are different in other ways. On the gestational age of delivery and admission, the case group was significantly earlier than the control group ($P < 0.001$). Birth weight of neonatus of the two groups were also significantly different, the weight of the newborns in the case group was lower than that in the control group ($P < 0.001$). The mean systolic/diastolic blood pressure from the case group was higher compared with healthy pregnant women

Table 1
Demographic and clinical characteristics of the preeclampsia cohort and normal pregnant women.

	Control	Preeclampsia	t	p-value
Maternal age (years)	30.72 ± 4.18	30.73 ± 5.87	−0.237	0.813
Gestational age (weeks)	39.24 ± 1.35	35.57 ± 3.38	193.652	P < 0.001
Gestational age at delivery (weeks)	39.46 ± 1.14	36.06 ± 3.03	195.757	P < 0.001
Gravidity (times)	2.84 ± 1.31	2.96 ± 1.49	−3.051	0.002
Abortion (times)	1.80 ± 0.99	1.87 ± 0.96	−1.262	0.207
Birth weight (Kg)	3.44 ± 0.34	2.85 ± 0.95	915.831	P < 0.001
Systolic blood pressure (mmHg)	115.57 ± 9.73	163.13 ± 19.89	−861.054	P < 0.001
Diastolic blood pressure (mmHg)	74.28 ± 7.67	106.27 ± 14.47	−630.786	P < 0.001

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