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RESEARCH ARTICLE

Effects of *CYP24A1* polymorphisms on premature ejaculation: a case–control study

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Abstract. Premature ejaculation (PE) is a common male sexual dysfunction disorder, and is considered to have the genetic predisposition. However, the internal regulation mechanisms is still unclear. Hence, this study intended to explore the effects of genetic polymorphisms of *CYP24A1* on the risk of PE. This case–control study genotyped three SNPs of *CYP24A1* (rs2762934, rs1570669 and rs6068816) from 139 PE patients and 372 healthy men using Agena MassARRAY platform. Collected data was then processed in SPSS 18.0. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in logistic regression analysis to evaluate the associations between *CYP24A1* polymorphisms and the PE risk. The results suggested that allele A of rs1570669 was significantly associated with the increased PE risk (OR=1.38, 95% CI=1.04–1.84, *P*=0.026). Meanwhile, we also identified rs1570669 as a risk factor of PE under the additive model (OR=1.47, 95% CI=1.02–2.11, *P*=0.039) by comparing the genotypic distributions between cases and controls, and genotype AA of rs1570669 was detected to be significantly related with an increased risk of PE under the codominant model (OR=2.26, 95% CI=1.06–4.83, *P*=0.036). This study is the first to proved that the genetic variants of *CYP24A1* played essential role in affecting the susceptibility to PE in Chinese Han.

Keywords. *CYP24A1*; premature ejaculation; single-nucleotide polymorphism; case–control study.

Introduction

Premature ejaculation (PE) is a common male disease characterized by sexual dysfunction, and approximately 20–30% of adult men are suffering from PE (Zhao *et al*. 2018; Bao *et al*. 2019). PE can be classified as primary or secondary, and its clinical features include short ejaculation latency time, poor ejaculation control, and resulting depression (Dai *et al*. 2019). PE has a significant negative impact on sexual satisfaction of patients and their sexual partners, therefore, it is crucial to address the effective treatment for PE. Currently, the commonly used medical treatments including behavioural psychotherapy, surgical treatment and traditional Chinese medicine treatment are still in the exploratory stage (Dai *et al*. 2019). A study on Finnish male twins suggests that 30% of the aetiology of PE is the result of genetic effects (Jern *et al*. 2009; Zhu *et al*. 2013; Huang *et al*. 2016a, b). However, there is no specific genetic variation mechanism to explain the genetic effects of PE, therefore, investigations on the correlation between genetic susceptibility alleles and the risk of PE are still needed.

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Cytochrome P450, family 24, subfamily A, polypeptide 1 (*CYP24A1*) is located on an amplified genome region of 20q13.2 (Cao *et al*. 2020), and encodes the vitamin D 24-hydroxylase and regulates the catabolism of $1,25(OH)_2D_3$ (Carpenter 2017; Yi *et al*. 2020). Studies have shown that androgen deficiency in renal function can enhance the expression of 24 hydroxylase and inhibit the effect of vitamin D, especially in the case of limited androgen supply (Lee *et al*. 2018). We speculate that *CYP24A1* may be involved in PE. In addition, the effects of *CYP24A1* polymorphisms on breast cancer (Wei *et al*. 2019), colorectal cancer (Chen *et al*. 2017; Vidigal *et al*. 2017), lung cancer (Qu *et al*. 2019) and ischemic stroke (Türkanoğlu Özçelik *et al*. 2018) have been studies. However, to the best of our knowledge, the regulation mechanism of *CYP24A1* on PE has not been investigated. But in the related study on the Korean population, researchers found that the genetic variants of *CYP24A1* were associated with prostate cancer (Oh *et al*. 2014). Meanwhile, Luo *et al*. found that in prostate cancer cell lines, *CYP24A1* expression was negatively correlated with promoter DNA methylation (Luo *et al*. 2010). Related epidemiological studies also showed that *CYP24A1* variations were associated with hormone-related diseases (Wang *et al*. 2015). These studies confirmed the relationship of *CYP24A1* and prostate-related and hormone-related diseases, thereby suggesting the potential effect of *CYP24A1* gene polymorphisms on the susceptibility of PE.

To further explore the underlying effect of three candidate single-nucleotide polymorphisms (SNPs) of *CYP24A1* on the PE risk, we carried out this case–control study and collected blood samples of PE patients and healthy controls for genotyping, and tried to provide theoretical basis of a more optimized genetic treatment regimen for patients of Chinese Han.

Materials and methods

Study population

A total of 511 subjects were recruited in this study comprising 139 PE patients and 372 healthy controls. PE patients were diagnosed according to the definition of International Society for Sexual Medicine (ISSM) (Gao *et al*. 2017). Patients with other diseases such as endocrine disease, neurological disease and cancers were excluded. Meanwhile, cases treated by drugs including antidepressants, topical anesthetics and other drugs were also excluded. All the patients were from Hainan Provincial People's Hospital. The healthy controls were from the Hainan General Hospital who came for heath checkup, and had no major medical disease or family history of PE. All participants were informed of the purpose and the procedure of this study, and signed the informed consent for blood donation. This study was permitted by Hainan General Hospital and followed the declaration guideline of Helsinki.

Data collection

Participants' information, including age, premature ejaculation diagnostic tool (PEDT Score), IIEF-5 score (international index of erectile function), and health status, was obtained through questionnaire surveys and medical records. We also collected clinical features such as ejaculation latency (sec), leptin, 5-hydroxytryptamine (5-HT) and folic acid.

SNP selection and genotyping

According to the criteria of minor allele frequency (MAF) > 0.05 and $r^2 > 0.80$, three variants of *CYP24A1* (rs2762934, rs1570669 and rs6068816) were randomly selected in the 1000 Genomes Project database (https://www.internationalgenome.org/). The extended primers of these SNPs were designed by the Agena Bioscience Assay Design Suite V2.0 software and the MassARRAY iPLEx platform (Agena Bioscience), and are displayed in table 1. Genomic DNA were obtained through the whole blood samples of all participants using GoldMag-Beads kit (GoldMag, Xi'an, Shaanxi, China), and spectrometry (Beckman, Fullerton, USA) was applied for DNA concentration. SNP genotyping and data collection were performed by the Agena MessARRAY platform and Agena Bioscience TYPER software (Agena Bioscience, San Diego, USA), respectively. Finally, annotations of selected SNPs were predicted by RegulomeDB to evaluate their potential effects (Boyle *et al*. 2012).

Bioinformatics analysis

RegulomeDB (http://regulome.stanford.edu/index) and HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) were used to predict the potential functions of the candidate SNPs.

Statistical analysis

The collected data was then statistically analysed by SPSS 18.0, Microsoft Excel and PLINK software. Independent-sample T test and Mann–Whitney U test were used to analysis the differences in ages and clinical indexes between PE patients and health men. The allele frequencies in cases and controls were calculated by χ^2 test. The correlations between candidate SNPs and PE risk were evaluated by logistic regression analysis under different genetic models including codominant, dominant, recessive and additive models, and the associations were represented by odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting confounding factors such as age. The Fisher's exact test was used to assess the Hardy–Weinberg equilibrium (HWE) of

Table 1. Sequences of oligonucleotide primers.

SNP	1st-PCRP	2nd-PCRP	UEP-DIR	UEP
rs2762934	ACGTTGGATGTCTCTTGTAGCCTGGTTCTC	ACGTTGGATGTACCTCCTATGGGTTGTCAC	R	gggtTCACCAAGCTAGGTGCTATT
rs1570669	ACGTTGGATGTCCAGTGAATTCCATTCCTG	ACGTTGGATGAGTTCTTGAAAAGTTGTGCC	R	TTATTTGATAACTTTTTAACCTAATGA
rs6068816	ACGTTGGATGAAAGCTGTTATCAGCGGTCC	ACGTTGGATGATCCTAGCATGTGGAAAAGC	R	TGGAAAAGCTCCCTGA

SNP, single-nucleotide polymorphism; PCRP, polymerase chain reaction primer; UEP-DIR, unique base extension primer direction; F, forward; R, reverse; UEP, unique base extension primer. Sequences are written in the *5′–3′* (left to right) orientation.

SNPs in the control group. All *P* values in this study were two-tailed and $P<0.05$ was considered statistically significant. All participants were informed of the purpose and the procedure of this study, and signed the informed consent for blood donation. This study was permitted by Hainan General Hospital and followed the declaration guideline of Helsinki.

Results

Differences in clinical indexes between cases and controls

In this study, information of all 511 participants including age and some clinical indexes were collected and then compared between cases and controls (table 2). The mean ages of the case group and the control group were 30.85 ± 6.75 and 41.24 ± 10.78 years old respectively, and we found a significant difference in age between two groups ($P<0.001$). Meanwhile, some clinical indicators including premature ejaculation diagnostic tool (PEDT) score, international index of erectile function (IIEF) score, ejaculation latency time, leptin, 5-hydroxytryptamine (5-HT) and folic acid were also compared between PE patients and healthy men, and significant differences were detected accordingly (all $P<0.05$).

In silico analysis predicted the function of the selected SNPs

To evaluate the possible function of the selected SNPs, we conducted *in silico* analysis using Regulome DB Score and HaploReg. Table 3 showed the basic information and the potential function of the selected SNPs. Regulome DB database allows assessing functional effects of SNPs in noncoding and intergenic regions using known and predicted regulatory elements. The RegulomeDB scores refer

Table 2. Clinical characteristics of cases and controls.

Variables	Case (*n*=139)	Control (*n*=372)	*P*
Age	30.85 ± 6.75	41.24 ± 10.78	<0.001[a]*
PEDT score	18.30 ± 2.11	3.62 ± 3.19	<0.001[b]*
IIEF-5 score	23.45 ± 2.84	23.53 ± 1.33	<0.001[b]*
Ejaculation latency (s)	68.76 ± 32.68	687.49 ± 350.27	<0.001[b]*
Leptin (ng/mL)	1.74 ± 1.92	1.89 ± 1.40	0.040[b]*
5-HT (ng/mL)	40.93 ± 45.65	92.40 ± 97.70	<0.001[b]*
Folic acid (ng/mL)	56.64 ± 47.58	58.39 ± 52.46	0.034[b]*

PEDT, premature ejaculation diagnostic tool; IIEF, international index of erectile function; 5-HT, 5-hydroxytryptamine.
[a]*P* was calculated by *t* test.
[b]*P* was calculated by Mann–Whitney U test.
*$P<0.05$ indicated a significant difference.

Table 3. *In silico* analysis for SNPs function annotation.

SNP	Chromosome	Position	Role	Allele A/B	RegulomeDB rank	HaploReg
rs2762934	20	54154722	3′-UTR	A/G	4	Promoter histone marks, Enhancer histone marks, DNAse, proteins bound, motifs changed
rs1570669	20	54157888	Intron	A/G	5	DNAse, proteins bound, motifs changed
rs6068816	20	54164552	Coding sequence	T/C	2b	DNAse, proteins bound, motifs changed

SNP, single-nucleotide polymorphism, rank 2b, TF binding + any motif + DNase footprint + DNase peak; rank 4, TF binding + DNase peak; rank 5, TF binding or DNase peak.

to the data available for each individual SNP, with lower scores representing a more important function. By HaploReg annotation, we found that the selected SNPs were associated with regulation of promoter histone marks, enhancer histone marks, DNAse, proteins bound, and motifs changed.

Genotypic characteristics and annotations of selected SNPs

Detailed information such as the position and role of selected SNPs are displayed in table 4. The results confirmed that all the SNPs in the control group conform to HWE ($P>0.05$) and MAFs < 0.05. Meanwhile, the allele A of rs1570669 was found to be related with the increased PE risk by comparing the allele distributions of the two groups (OR=1.38, 95% CI=1.04–1.84, $P=0.026$). We further predicted the functional effects of SNPs via RegulomeDB, and rs6068816 was assigned a rank of 2b which indicate TF binding + any motif + DNase Footprint + DNase peak. *CYP24A1* rs2762934 and rs1570669 got scores of 4 and 5, respectively, and were likely to affect TF binding and/or DNase peak.

Association of CYP24A1 polymorphisms with the PE susceptibility

The association of *CYP24A1* polymorphisms and the PE risk was further evaluated by logistic regression analysis under different genetic models, and the results are shown in table 5. *CYP24A1* rs1570669 was detected as a risk factor of PE under the additive model (OR=1.47, 95% CI=1.02–2.11, $P=0.039$), whereas homozygous AA was found to be significantly associated with an increased PE risk under the codominant model (OR=2.26, 95% CI=1.06–4.83, $P=0.036$). However, no further significant associations of rs2762934 and rs6068816 polymorphisms and the PE risk were detected based on the current data.

Association between the clinical indexes and CYP24A1 polymorphisms

To further explore the relationship between genotype distributions of each SNP with clinical indictors of PE patients, we carried out relevant studies and summarized the results in table 6. However, no significant correlation was found between *CYP24A1* genetic polymorphisms and clinical indexes of PE including PEDT score, IIEF-5 score, ejaculation latency time, leptin, 5-HT and folic acid.

Discussion

CYP24A1 is considered as an essential enzyme involved in the degradation of vitamin D. During the metabolism of vitamin D, 25(OH)D is converted into $125(OH)_2D_3$ by 1α-hydroxylase encoded by *CYP27B1* and then released into the

Table 4. Detailed information of SNPs in *CYP24A1* and functional annotation by RegulomeDB.

Gene	SNP	Allele A/B	MAF		*P*-HWE	ORs (95% CI)	*P*
			Case	Control			
CYP24A1	rs2762934	A/G	0.112	0.101	0.562	1.13 (0.72–1.76)	0.593
CYP24A1	rs1570669	A/G	0.412	0.336	0.296	1.38 (1.04–1.84)	0.026*
CYP24A1	rs6068816	T/C	0.352	0.366	0.823	0.94 (0.70–1.26)	0.687

MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval.
*$P < 0.05$ indicated a significant difference.

Table 5. Association of *CYP24A1* polymorphisms with the PE risk.

SNP	Model	Genotype	Cases	Controls	OR(95% CI)	*P*
rs2762934	Codominant	AA	2 (1.4%)	2 (0.5%)	1.32 (0.11–15.67)	0.825
		AG	27 (19.4%)	71 (19.1%)	0.89 (0.48–1.66)	0.710
		GG	109 (78.4%)	299 (80.4%)	1	–
	Dominant	AA-AG	29 (20.9%)	73 (19.6%)	0.91 (0.49–1.67)	0.749
		GG	109 (78.4%)	299 (80.4%)	1	–
	Recessive	AA	2 (1.4%)	2 (0.5%)	1.35 (0.11–15.98)	0.811
		AG-GG	136 (97.8%)	370 (99.5%)	1	–
	Additive	–	–	–	0.93 (0.53–1.65)	0.805
rs1570669	Codominant	AA	23 (16.5%)	37 (9.9%)	2.26 (1.06–4.83)	0.036*
		AG	66 (47.5%)	174 (46.8%)	1.35 (0.78–2.34)	0.278
		GG	47 (33.8%)	158 (42.5%)	1	–
	Dominant	AA-AG	89 (64.0%)	211 (56.7%)	1.53 (0.91–2.56)	0.108
		GG	47 (33.8%)	158 (42.5%)	1	–
	Recessive	AA	23 (16.5%)	37 (9.9%)	1.92 (0.96–3.85)	0.067
		AG-GG	113 (81.3%)	332 (89.2%)	1	–
	Additive	–	–	–	1.47 (1.02–2.11)	0.039*
rs6068816	Codominant	TT	21 (15.1%)	51 (13.7%)	0.77 (0.35–1.67)	0.500
		TC	53 (38.1%)	170 (45.7%)	0.59 (0.35–1.01)	0.053
		CC	61 (43.9%)	151 (40.6%)	1	–
	Dominant	TT-TC	74 (53.2%)	221 (59.4%)	0.63 (0.38–1.03)	0.067
		CC	61 (43.9%)	151 (40.6%)	1	–
	Recessive	TT	21 (15.1%)	51 (13.7%)	0.99 (0.47–2.06)	0.976
		TC-CC	114 (82.0%)	321 (86.3%)	1	–
	Additive	–	–	–	0.78 (0.54-1.12)	0.180

SNP, single-nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.
P value was calculated by logistic regression analysis with adjustment for age.
*$P<0.05$ indicates statistical significance.

Table 6. Association analysis on clinical indexes of PE and *CYP24A1* genetic polymorphisms.

SNP		PEDT score	IIEF-5 score	Ejaculation latency (sec)	Leptin (ng/mL)	5-HT (ng/mL)	Folic acid (ng/mL)
rs2762934	AA	17.00	23.00	90.00	–	–	–
	AG	19.20 ± 1.20	23.95 ± 3.15	79.29 ± 30.25	1.39 ± 2.39	40.02 ± 48.82	59.44 ± 61.25
	GG	18.20 ± 2.06	23.33 ± 2.80	66.00 ± 33.10	1.73 ± 1.79	39.08 ± 44.48	56.51 ± 45.66
	P	0.095	0.677	0.319	0.650	0.958	0.877
rs1570669	AA	18.61 ± 0.98	24.06 ± 2.18	55.77 ± 31.88	1.67 ± 2.67	47.62 ± 42.92	94.74 ± 68.37
	GA	18.40 ± 2.24	23.09 ± 3.22	72.05 ± 34.03	1.50 ± 1.34	39.97 ± 48.95	47.85 ± 42.85
	GG	18.21 ± 1.98	23.50 ± 2.67	72.80 ± 29.09	1.98 ± 2.31	42.99 ± 46.32	57.70 ± 43.48
	P	0.774	0.466	0.244	0.759	0.936	0.106
rs6068816	TT	18.31 ± 2.63	22.08 ± 3.75	77.60 ± 16.73	2.13 ± 1.81	44.35 ± 53.24	63.79 ± 49.38
	CT	18.14 ± 2.38	23.59 ± 2.72	69.42 ± 40.60	1.93 ± 2.21	38.32 ± 43.46	63.13 ± 56.90
	CC	18.36 ± 1.79	23.64 ± 2.66	64.74 ± 29.15	1.52 ± 1.78	42.52 ± 48.03	49.94 ± 40.51
	P	0.887	0.193	0.522	0.714	0.946	0.656

PEDT, premature ejaculation diagnostic tool; IIEF, international index of erectile function; 5-HT, 5-hydroxytryptamine.

blood circulation, which is further degraded by 25-hydroxyvitamin D 24-hydrolytic enzyme encoded by *CYP24A1* (Yi *et al*. 2020). Therefore, *CYP24A1* has irreplaceable clinical values in diseases regulated by vitamin D. In this case–control study, we analysed the associations between genetic variants of *CYP24A1* and PE risk by establishing the genetic models, and concluded that rs1570669 of *CYP24A1* may be a risk factor in increasing the susceptibility to PE. Meanwhile, low serum vitamin D levels remain an important risk factor for PE (Abd El Aal *et al*. 2018), and this finding supported our conclusions to a certain extent. Meanwhile, Canat *et al*. (2019) also proved that low levels of vitamin D in serum is associated with an increased likelihood of PE (Canat *et al*. 2019). Combined with our findings, we hypothesized that *CYP24A1* may accelerate the degradation of vitamin D in blood, thereby increasing the risk of PE.

To further explore the relationship between *CYP24A1* and PE, we genotyped three candidate SNPs of *CYP24A1*

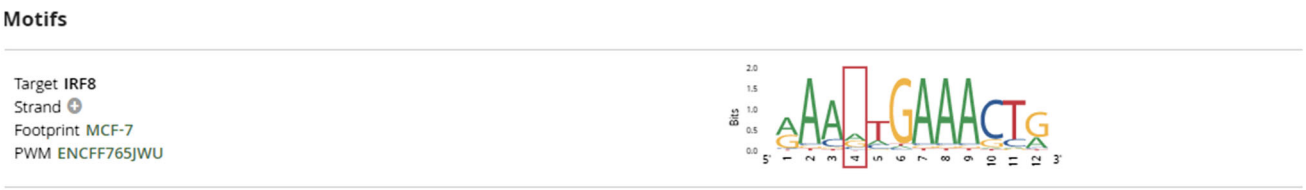

Figure 1. Motif predicts transcription factor binding sites.

of PE patients and healthy men, and compared the differences in allele and genotype distributions between them, and finally found a risk allele A in rs1570669. The analysis based on the genetic models also confirmed that carriers with homozygous AA had a higher risk PE than GG carriers. This site have been studied on breast cancer and ischemic stroke in Chinese Han, but rs1570669 is believed to be primarily involved in reducing the disease risk (Fuhrman *et al*. 2013; Yang *et al*. 2020). Besides, a relevant meta-analysis of GWAS illustrated that rs1570669 is significantly correlated with serum calcium concentration (O'Seaghdha *et al*. 2013) and Carpenter *et al*. (2017) also explained the potential role of *CYP24A1* mutation in the tolerance of calcium homeostasis. However, the specific regulation mechanism of rs1570669 on serum calcium concentration and vitamin D has not been elaborated. Therefore, further studies on the correlation between rs1570669 and vitamin D metabolism should be carried out to enrich the regulation mechanism of *CYP24A1* on PE.

HaploReg shows that the CYP24A1rs1570669 polymorphism is regulated by DNase, protein binding, and motif changes. The RegulomeDB database indicates that the RANK of rs1570669 is 5, which may affect TF binding or DNase peak. We used motifs to predict transcription factor binding sites and found that it could bind to IRF8 (figure 1). Fuhrman *et al*. (2013) study defined rs1570669 as a protective factor for breast cancer. Our results also suggest an association between rs1570669 and an increased risk of PE under different genetic models. At present, studies on the susceptibility of vitamin D related genes mainly focus on cancer and hormone-related diseases, but the specific regulatory mechanism is still unclear. Meanwhile, our study on the coding gene of steroid derivative vitamin D and PE is the first to date.

However, the sample size is not large enough to collect sufficient statistical data is one of the limitations in this study. Moreover, the lack of sample information also causes the impossibility to further analysis the impact of environmental and genetic multifactor regulation on the development of PE. In the following studies, in addition to expanding the sample size and integrating the sample information, we also need to explore the correlation between SNPs of *CYP24A1* and vitamin D concentration to further explain the hereditary effects of *CYP24A1* on the susceptibility to PE.

Conclusion

In summary, this case–control study firstly proved that *CYP24A1* rs1570669 polymorphisms were significantly associated with the increasing risk of PE in the populations of Chinese Han under the allelic, codominant and additive models. Our findings could provide a theoretical basis for reducing the risk of PE from a genetic perspective.

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Authors' contributions

Conceptualization: FW, DFL and WFW; data curation: FW and DFL; formal analysis: FW, JXC and CQP; methodology: DFL, ZYW and HSF; software: JBX, MY, SWM and LYZ; manuscript writing: FW and DFL; manuscript editing: WFW.

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