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ORIGINAL COMMUNICATION

New evidence for involvement of *ESR1* gene in susceptibility to Chinese migraine

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Abstract Migraine is a common and disabling nervous system disease with a significant genetic predisposition. The sex hormones play an important role in the pathogenesis of migraine. However, the conclusions of the previous genetic relation studies are conflicting. The aim of this study is to determine whether variants in genes involved in estrogen receptor and estrogen hormone metabolism are related to Chinese migraine. By employing a case–control approach, 8 SNPs in the *ESR1*, *ESR2,* and *CYP19A1* genes are studied in a cohort of 494 migraine cases and 533 controls. In addition, genotyping is performed using Sequenom MALDI-TOF mass spectrometry iPLEX platform. Univariate and multivariate analyses are carried out by logistic regression. The corresponding haplotypes are studied with the Haploview software and gene–gene interaction is assessed using the Generalized Multifactor Dimensionality Reduction (GMDR) analysis. There are significant differences in allelic distributions for rs2234693 and rs9340799 in *ESR1* gene between patients with migraine and control subjects. Univariate logistic analysis shows that rs2234693 and rs9340799 are risk factors for migraine, but multivariate analysis reveals that only rs2234693 is significant associated with migraine. In the subgroup analysis, rs2234693 in *ESR1* gene is found associated with menstrually related migraine. Further haplotypic analysis shows that rs2234693–rs9340799 TA haplotype serves as risk haplotype for migraine. The GMDR analysis identifies rs2234693 in ESR1 alone to be a crucial candidate in migraine susceptibility. This study is in agreement with the previous studies that variants in the *ESR1* gene are associated with migraine suggesting that it plays a role in the migraine process.

Keywords Migraine · Polymorphism · *ESR1* · *ESR2* · *CYP19A1* · China

Introduction

Migraine is a common neurovascular disease that incurs a heavy burden on Chinese society affecting the lives of millions [25]. In general, two types of migraine, migraine without aura (MO) and migraine with aura (MA), are classified according to the criteria declared by the International Headache Society [10]. Although the exact pathogenesis of migraine remains undetermined, recent genetic advances have shown that several genes are linked to migraine, including hormonal, neuronal, vascular, and pain pathways [22].

Over the past years, epidemiological and clinical studies have shown that sex hormones play an important role in the migraine process. A Population-Based Door-to-Door Survey from China showed that migraine prevalence was 2.1-fold higher among women than men [24]. And comparing with that on men, women migraine experienced more frequent, longer lasting, and more painful attacks [15]. Moreover, the frequency of headache attacks was increased in women during the peri-menopause compared with premenopause [17]. Therefore, investigation of genes involved in sex hormone receptor pathways and metabolism may

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provide valuable insights into the genetic susceptibility to migraine.

Estrogen receptor 1 (*ESR1* or *ER-alpha*) and estrogen receptor 2 (*ESR2 or ER-beta*) are widely expressed in various human brain regions [1]. In addition, cytochrome P450, family 19, subfamily A, polypeptide 1 (*CYP19A1*) are involved in the final step of estrogen synthesis. Gene variants located in *ESR1*, *ESR2*, and *CYP19A1* gene have become the focus of such research. However, many results were conflicting and could not be replicated in other independent populations [14, 21]. Considering the current issues and the relation between sex hormone and migraine, we investigated multilocus from sex hormone receptor pathways and metabolism in a Chinese population of migraineurs and matched controls. The study was conducted in a large sample involving 1027 individuals from a single institution in southern Fujian province of China.

Methods

Subjects

The study population consisted of 494 unrelated migraine patients and 533 unrelated non-headache healthy volunteers. All migraine patients were recruited in the headache specialized clinic at the Department of Neurology of the First Affiliated Hospital of Xiamen University between April 2010 and August 2015. In addition, diagnosis was based on the International Classification of Headache Disorders (ICHD-III beta) for migraine [10]. Subjects with tumor, a history of depression, or other co-morbid psychiatric disorders were excluded. The controls were recruited from the nurses underwent blood test in our hospital or attendees at the physical examination department who can provide a history of headache. The two groups, recruited from the same geographic areas, were matched for age and sex and written consent was obtained from all participants, where the study was approved by the hospital ethics committee.

Selected SNPs and genotyping

Eight loci in the three genes involved in sex hormone receptor pathways and metabolism were selected: rs10046 (*CYP19A1*), rs4646 (*CYP19A1*), rs1801132 (*ESR1*), rs2228480 (*ESR1*), rs2234693 (*ESR1*), rs9340799 (*ESR1*), rs4986938 (*ESR2*), and rs1256049 (*ESR2*). Genomic DNA was extracted from peripheral blood lymphocytes using the TIANamp Blood DNA Kit (Tiangen Biotech, Beijing, China) and stored at −80 °C for genotyping. All subjects were genotyped for SNPs using Sequenom's iPLEX Assay technology as reported [23].

Statistical analysis

The public statistics Web tool http://ihg.gsf.de/cgi-bin/hw/hwa1.pl was used to verify Hardy–Weinberg equilibrium (HWE) for observed genotype frequencies of each SNP. Age difference between two groups was assessed by the Student's *t* test. Differences in the genotype and allele frequencies between the patients and controls were compared through the Chi-squared test. And to estimate the risk of migraine with every single locus, the odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated using univariate and multivariate binary logistic regression with adjustments for age and gender. Statistical analysis was performed using the Statistical Package for the Social Sciences version 23.0 (SPSS, version 23.0) for Windows. The estimation of haplotype frequency and the analysis of its effect on migraine were performed using Haploview 4.2. The gene–gene interactions were investigated by generalized multifactor dimensionality reduction (GMDR). All possible combinations from 1-locus to 8-locus SNPs were examined. A two-tailed *P* value ≤ 0.05 was considered statistically significant. The Bonferroni correction was used to adjust the significance level of multiple comparisons. Power was calculated by Power and Sample Size Calculations Version 3.0 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

Results

Characteristics of patients

The mean age of the 494 migraine patients (61 males and 433 females) was 35.3 ± 10.1 years, while the mean age of the 533 subjects in control group (57 males and 476 females) was 34.8 ± 8.9 years. There was no significant difference in age or sex between the two groups ($P = 0.340$ and $P = 0.406$, respectively). The number of patients described migraine with aura was 74 (15.0 %), migraine without aura was 420 (85.0 %), and menstrually related migraine (MRM) was 126 (25.5 %).

Comparison of the genotype and allele distributions

The genotypic and allelic distributions of all SNPs were shown in Table 1. The genotypes of all SNPs in controls followed the Hardy–Weinberg equilibrium ($P > 0.05$). Significant differences in genotypic distributions were observed in the polymorphisms of rs2228480 and rs2234693 in ESR1 between migraine cases and controls ($P = 0.027$ and $P = 0.000$, respectively). However, there was no significant difference in allelic distribution for rs2228480 between two groups ($P = 0.180$), and the allelic

Table 1 Genotype and allele frequencies of gene polymorphism in Chinese migraine case–control population

SNP	Group	Genotypes			*P*	Alleles		*P*
rs10046 (CYP19A1)		GG	GA	AA		G	A	
	Migraine	117 (23.7)	241 (48.8)	136 (27.5)	0.717	475 (48.1)	513 (51.9)	0.510
	Control[a]	123 (23.1)	251 (47.1)	159 (29.8)		497 (46.6)	569 (53.4)	
rs4646 (CYP19A1)		CC	CA	AA		C	A	
	Migraine[a]	223 (45.2)[a]	223 (45.2)	47 (9.6)	0.213	669 (67.8)	317 (32.2)	0.657
	Control	260 (48.8)	213 (40.0)	60 (11.3)		733 (68.8)	333 (31.2)	
rs1801132 (ESR1)		CC	CG	GG		C	G	
	Migraine	117 (23.7)	243 (49.2)	134 (27.1)	0.474	477 (48.3)	511 (51.7)	0.282
	Control	134 (25.1)	272 (51.0)	127 (23.8)		540 (50.7)	526 (49.3)	
rs2228480 (ESR1)		AA	AG	GG		A	G	
	Migraine	36 (7.3)	157 (31.8)	301 (60.9)	**0.027**	229 (23.2)	759 (76.8)	0.180
	Control	19 (3.6)	183 (34.3)	331 (62.1)		221 (20.7)	845 (79.3)	
rs2234693 (ESR1)		CC	CT	TT		C	T	
	Migraine	102 (20.6)	222 (44.9)	170 (34.4)	**0.000**	426 (43.1)	562 (56.9)	**0.003**[b]
	Control	62 (11.6)	267 (50.1)	204 (38.3)		391 (36.7)	675 (63.3)	
rs9340799 (ESR1)		AA	AG	GG		A	G	
	Migraine	298 (60.4)	170 (34.5)	25 (5.1)	0.108	766 (77.7)	220 (22.3)	**0.046**[c]
	Control	349 (65.5)	168 (31.5)	16 (3.0)		866 (81.2)	200 (18.8)	
rs4986938 (ESR2)		CC	CT	TT		C	T	
	Migraine[a]	398 (80.6)	88 (17.8)	8 (1.6)	0.620	884 (89.5)	104 (10.5)	0.612
	Control	433 (81.2)	95 (17.8)	5 (0.9)		961 (90.2)	105 (9.8)	
rs1256049 (ESR2)		CC	CT	TT		C	T	
	Migraine[a]	185 (37.5)	242 (49.1)	66 (13.4)	0.260	612 (62.1)	374 (37.9)	0.493
	Control[a]	221 (41.5)	234 (44.0)	77 (14.5)		676 (63.5)	388 (36.5)	

Bold values denote significance

[a] One subject missing genotypes

[b] Migraine compared with control by C allele: OR = 1.309, 95 % CI 1.096–1.562, $P = 0.003$

[c] Migraine compared with control by G allele: OR = 1.244, 95 % CI 1.003–1.542, $P = 0.046$

distributions of rs2234693 and rs9340799 in *ESR1* were significantly different between migraine patients and controls. In the group of patients, 426 (43.1 %) had the C allele and 526 (56.9 %) had the T allele for the rs2234693 variant, which was significantly higher as compared with that in the controls (OR = 1.309, 95 % CI 1.096–1.562, $P = 0.003$, Power = 0.985). For the rs9340799 variant, the frequency of allele G was 22.3 % (220 G alleles) and allele A was 77.7 % (766 A alleles), which was significantly higher as compared with controls (OR = 1.244, 95 % CI 1.003–1.542, $P = 0.046$, Power = 0.790). Moreover, no significant difference in genotypic and allelic distributions was observed in the other polymorphisms between two groups.

Univariate and multivariate analyses

In the univariate analysis using binary logistic regression (Table 2), two SNPs emerged as independent risks for migraine in the co-dominant genetic model: rs2234693 (OR = 1.308, 95 % CI 1.095–1.562, $P = 0.003$) and rs9340799 (OR = 1.255, 95 % CI 1.010–1.560, $P = 0.040$). For rs2234693 variant, ancestral allele C was identified as risk allele for the allelic distribution shown in Table 1. And using a forward stepwise multivariate analysis for all 8 SNPs, significant risk for migraine was only observed for *ESR1* rs2234693 (OR = 1.272, 95 % CI 1.014–1.597, $P = 0.038$). ESR1 rs9340799 lost the significance.

In addition, we further analyzed all the 8 SNPs associated with migraine subgroup susceptibility according to clinical features, including aura, gender, and menstrual status (Table 3). And it was shown that *ESR1* rs2234693 was also a significant risk for MO and female migraine. Moreover, comparing with the female controls, *ESR1* rs2234693 also independently contributed to susceptibility to MRM.

Haplotype analysis

Haplotypes based on the three gene polymorphisms were constructed and only the *ESR1* gene linkage disequilibrium

Table 2 Univariate and multivariate analyses of all SNPs while controlling age and sex

Gene	SNP	Risk allele	Univariate analysis			Multivariate analysis		
			OR	95 % CI	*P*	OR	95 % CI	*P*
CYP19A1	rs10046	A	0.943	0.795–1.118	0.499	0.962	0.749–1.236	0.765
CYP19A1	rs4646	C	1.046	0.870–1.258	0.633	1.016	0.774–1.332	0.911
ESR1	**rs1801132**	G	1.104	0.928–1.313	0.266	1.13	0.947–1.349	0.176
ESR1	**rs2228480**	A	1.157	0.941–1.422	0.167	0.863	0.700–1.064	0.169
ESR1	**rs2234693**	C	1.308	1.095–1.562	**0.003**	1.272	1.014–1.597	**0.038**
ESR1	**rs9340799**	G	1.255	1.010–1.560	**0.040**	1.068	0.809–1.410	0.641
ESR2	**rs4986938**	T	1.080	0.813–1.433	0.596	1.111	0.827–1.491	0.485
ESR2	**rs1256049**	T	1.067	0.892–1.277	0.477	1.097	0.910–1.323	0.332

Bold values denote significance

SNP single nucleotide polymorphism, *OR* odds ratio, *CI* confidence interval

Table 3 Selected susceptibility SNPs for migraine subgroup in multivariate analysis

Subgroup	SNP	Gene	Risk allele	OR	95 % CI	P^a
MO	rs2234693	ESR1	C	1.316	1.093–1.586	**0.004**
MA	rs2228480	ESR1	A	1.561	1.054–2.314	0.026
Female	rs2234693	ESR1	C	1.251	1.036–1.510	**0.020**
Male	rs2234693	ESR1	C	1.839	1.048–3.229	0.034
MRM^2	rs2234693	ESR1	C	1.400	1.048–1.871	**0.023**

After Bonferroni correction, significance was taken at $P \leq 0.05/2$; bold values denote significance

MRM menstrually related migraine; which was compared with the female controls

(LD) block exhibited nominally significant linkage between rs2234693, rs9340799, rs1801132, and rs2228480 (Table 4). After adjusting the Bonferroni correction for multiple comparisons, the TA haplotypes between rs2234693 and rs9340799 were detected to have statistically significant association with migraine ($D' = 1$, $r^2 = 0.391$). Moreover, the TA haplotype was less frequent among migraine cases (56.9 %) than that in controls (63.3 %), which proved that it had a protective effect against migraine (OR = 0.764, 95 % CI 0.640–0.912, $P = 0.0029$). In addition, there were no marked associations between the other four haplotypes and migraine.

Gene–gene interactions analysis

In exploring the gene–gene interactions, GMDR analysis, shown in Table 5, was run to investigate the impacts of combinations of the 8 SNPs on migraine with adjustment for covariates (sex and age). Our GMDR analysis demonstrated *ESR1* rs2234693 polymorphism as the one-factor model in envisaging the migraine risk [testing accuracy = 0.5445, CVC (cross-validation consistency) = 10/10, $P = 0.0107$]. *CYP19A1* rs1046 and *ESR1* rs2234693 constituted the two-factor model; *CYP19A1* rs1046, *ESR1* rs2234693, and *ESR2* rs1256049 polymorphisms

Table 4 Selected ESR1 haplotypic analysis between patients with migraine and controls

No.	Haplotype	Frequency	Case *n* (%)	Control *n* (%)	OR (95 % CI)	*P*
1	TA–	0.602	562 (56.9)	675 (63.3)	0.764 (0.640–0.912)	**0.0029**
2	CG–	0.205	221 (22.4)	200 (18.8)	1.248 (1.007–1.546)	0.0429
3	TAC–	0.285	258 (26.1)	327 (30.6)	0.799 (0.659–0.968)	0.0238
4	CGG–	0.092	105 (10.6)	84 (7.8)	1.390 (1.029–1.878)	0.0310
5	TACA	0.225	200 (20.3)	262 (24.6)	0.779 (0.632–0.960)	0.0193

The order of SNPs in estimated analysis of haplotypes frequency: rs2234693, rs9340799, rs1801132, and rs2228480

After Bonferroni correction, significance was taken at $P = 0.05/3$ for No. 1, 2; $P = 0.05/6$ for No. 3, 4; $P = 0.05/12$ for No. 5

Bold values denote significance

Table 5 GMDR analysis for exploring high-order interactions with migraine

Model	Training balanced accuracy	Testing balanced accuracy	Sign test (*P*)	CVC[a]
rs2234693 (*ESR1*)	0.5451	0.5445	9 (**0.0107**)	10/10
rs1046(*CYP19A1*), rs2234693 (*ESR1*)	0.5623	0.5186	6 (0.3770)	6/10
rs4646(*CYP19A1*),rs2234693(*ESR1*), rs1256049(*ESR2*)	0.5795	0.4904	5 (0.6230)	4/10

Bold value indicates statistical significance $P < 0.05$

CVC cross-validation consistency

represented the three-factor interaction model, but both of them did not reach the statistical significance level.

Discussion

Recent advancement in molecular biology has suggested genetic factors and their extensive interactions modulated the disease susceptibility [11]. Hence, in this study, we aimed to investigate the individual and synergistic effect of gene variations involved in sex hormone receptor pathways and metabolism to modulate migraine susceptibility using three multi-analytical approaches: multiple regression, haplotype analysis, and generalized multifactor dimensionality reduction (GMDR). Multiple logistic regression could exclude confounding factors, haplotype analysis is an effective way of improving detection power comparing with single markers, and GMDR improves the identification of multilocus genotype combinations (higher order gene–gene interactions) predicting the disease vulnerability for complex and multifactorial diseases [16].

Our single locus analysis showed that rs2234693 and rs9340799 in *ESR1* gene were significantly associated with migraine. However, in the multivariate analysis, *ESR1* rs9340799 lost the significance, which indicated that this locus was a potential confounder to the migraine susceptibility. Then, the haplotype analysis also showed that *ESR1* rs2234693 in combination with rs9340799 as the important factor enhancing the migraine risk. Most importantly, the GMDR analysis revealed that *ESR1* rs2234693 alone was the best candidate with highest testing accuracy and CVC. All these analyses indicated ESR1 rs2234693 as the major risk factor for Chinese migraine susceptibility.

The rs2234693 polymorphism is located at intron 1 of *ESR1* gene and possibly affects receptor function by changing *ESR1* expression levels or altering its pre-mRNA splicing [2]. This locus has been targeted in several genetic association studies for migraine susceptibility, but the conclusions in these studies are inconsistent and controversial. A report from north Indian concluded that the rs2234693 TT and CT genotype significantly increased the risk of migraine [12], which was in contrast to ours. However, no association has been reported in other two case–control studies conducted in Australian and Turkish population [3, 6]. Given these results, a meta-analysis was performed to clarify the issue (Fig. 1), which can effectively increase sample size by combining data, reduce random errors, and enhance the statistical power of analysis [7]. The above three research data and ours were included in the study, and the result revealed that risk allele C was a borderline association with migraine (OR = 1.04, 95 % CI 0.92–1.17). However, there was statistical heterogeneity among all the included studies ($P < 0.001$, $I^2 = 88$ %), which may be due to sample size and ethnic group differences. When the study from India was excluded (*P* of HWE in their controls = 0.07), heterogeneity became acceptable ($P = 0.27$, $I^2 = 23$ %) and the result showed that the frequency of risk allele C was significantly higher in migraine than in control (OR = 1.20, 95 % CI 1.05–1.38). Based on the statistical data, it can be speculated that the *ESR1* rs2234693 polymorphism may have major contribution to the pathogenesis of migraine. Therefore, further functional studies are needed to investigate the functions of this allele.

Moreover, in the subgroup analysis, *ESR1* rs2234693 was also found associated with MO and female migraineurs, which may be due to MO and women accounted for a big proportion in our subjects. Accordingly, no correlation was found between all the 8 SNPs and MA or male migraineurs, which might be because of the small size of the sample in the subgroup. Most importantly, *ESR1* rs2234693 was also observed as a significant risk for MRM, which indicated that there was a link between genetic and clinical phenotypes.

Furthermore, the effects of other polymorphisms in *ESR1, ESR2,* and *CYP19A1* genes on migraine have been explored in several studies. A study conducted in the Norfolk Island population found that three haplotypes in *ESR1* gene were associated with migraine [20]. In addition, a positive association of *ESR1* rs1801132 (325C>G) with migraine was primarily reported in a Spanish population [18, 19], but other epidemiological studies in Caucasian populations failed to replicate the result [3, 5, 6, 13]. In

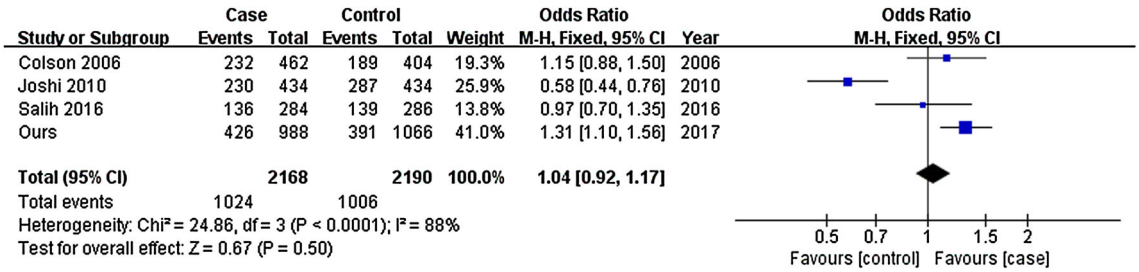

Fig. 1 Meta-analysis of ESR1 rs2234693 allele C for migraine

terms of rs2228480 (594G>A) in the *ESR1* gene and migraine susceptibility, report from Australian population suggested that A allele carriers had a higher risk of migraine [4], but this association did not appear in the other studies [5, 6, 8, 13, 18]. And a recent meta-analysis indicated that both of these two variants conferred increased susceptibility to migraine [14]. In addition, there were no significant associations observed for *ESR2* polymorphisms in the previous studies [6, 8, 19]. *CYP19A1* is located in short arm of chromosome 15 (15q21) and codes for aromatase enzyme which catalyzes the final step of estrogen biosynthesis. Among the three study populations investigating the association between the *CYP19A1* polymorphism and migraine, there was a statistically significant positive association in two study populations [6, 8, 9], and the remaining one found that it interacts with *ESR1* gene to be a contributing factor in migraine susceptibility [19]. These mixed and contradictory results were inconsistent with ours, which may be due to differences in ethnicity and sample sizes.

In conclusion, to our knowledge, this is the first association study that investigated the *ESR1*, *ESR2,* and *CYP19A1* gene polymorphisms in Chinese migraine patients. Our data suggested that *ESR1* rs2234693 plays a potential role in migraine susceptibility in a Chinese population, especially for MRM migraine. Further prospective comprehensive studies with more large-scale samples are necessary to verify our results.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The work was approved by ethics committee of the First Affiliated Hospital of Xiamen University.

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