RESEARCH ARTICLE

Contribution of polymorphisms in *ESR1*, *ESR2*, *FSHR*, *CYP19A1*, *SHBG* and *NRIP1* genes to migraine susceptibility in Turkish population

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Abstract

Migraine, a highly prevalent headache disorder, is regarded as a polygenic multifactorial disease. Single-nucleotide polymorphisms (SNPs) in the genes that involved in sex hormone metabolism may comprise risk for migraine, but the results of previous genetic association studies are conflicting. The aim of this study was to evaluate genetic variants in genes involved in oestrogen receptor and oestrogen hormone metabolism in a Turkish population. A total of 12 SNPs in the *ESR1*, *ESR2*, *FSHR*, *CYP19A1*, *SHBG* and *NRIP1* genes were genotyped in 142 migraine cases and 141 nonmigraine controls, using a BioMark 96.96 dynamic array system. In addition, gene–gene interactions were analysed using generalized multifactor dimensionality reduction (GMDR) methods. According to GMDR analysis, our results indicated that there was a significant association between migraine and gene–gene interaction among the *CYP19A1*, *FSHR*, *ESR1* and *NRIP1*. Single-gene variant analysis showed that a significant association was observed between the TT genotype of rs10046 and migraine susceptibility. When the analysis was performed only in women, the GG genotype of rs2229741 was different between migraineurs and controls. When the female migraine patients were divided into two groups, migraine related to menstruation (MRM) or migraine not related to menstruation (MNRM), GG genotype of rs726281 was significantly associated with MRM. These results suggested that rs10046 could play a potential role in migraine susceptibility in Turkish population. Also, the rare GG genotype of rs726281 appears to influence migraine susceptibility in a recessive manner in MRM subgroup of female patients. In addition, variant GG genotype of rs2229741 may reduce the risk of migraine in Turkish women.

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Introduction

Migraine is characterized by recurrent headache attacks accompanied by nausea, vomiting and sensitivity to light, sound or smell (Haut *et al.* 2006). The mean one-year prevalence of the migraine is reported to be highest in Europe (14.9%) followed by Southeast Asia (10.9%) and America (10.6%) (World Health Organization 2011). Generally, two types of migraine, migraine without aura (MO) and migraine with aura (MA) are referred and about one-third of migraine patients describe an aura before or during the migraine headache. Patients are usually classified according to the criteria declared by the International Headache Society (Society 2004).

Genetic and environmental factors are involved in migraine pathophysiology. The fluctuating sex hormones are one of the major contributing factors in the migraine headache attacks. This hormonal theory is particularly related to high oestrogen levels and oestrogen withdrawal in women (Somerville 1971). Migraine has been observed more common in women than men, and the ratio of women who experience menstruation-related migraine ranged from 50 to 60% (Lipton and Bigal 2005; Brandes 2006). These evidences support the hormonal theory and indicate the association of female sex steroids with migraine, but the underlying mechanism is not well established.

Oestrogen receptor 1 (ESR1 or ER-alpha) and oestrogen receptor 2 (ESR2 or ER-beta) are widely distributed throughout the brain. Therefore, oestrogens can influence

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multiple neuronal functions in a site-dependent and receptor-dependent manner (Laflamme *et al.* 1998). Nuclear receptor interacting protein 1 (NRIP1) negatively regulates the transcription of oestrogen receptors, particularly *ESR1*. Moreover, *ESR2* is more sensitive to repression by NRIP1. Interestingly, oestrogens also regulate *NRIP1* gene expression (Docquier *et al.* 2013). Genetic variations that affect the synthesis of oestrogen, oestrogen receptors or transport of oestrogen may influence the susceptibility to migraine. Oestrogen synthesis begins with the follicle stimulating hormone (FSH) stimulation through the FSH receptor (FSHR). High FSH levels and low oestrogen levels have been associated with the improvement of migraine in postmenopausal women (Wang *et al.* 2003). Cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1 or enzyme aromatase) is involved in the final step of oestrogen biosynthesis. Genetic variation in the *CYP19A1* gene has been associated with the circulating oestrogen levels (Haiman *et al.* 2007). The level of circulating hormones may also depend on the concentration of sex hormone-binding globulin (SHBG) which binds and transports sex steroids (Hammond 1995).

A detailed understanding of the genetic variations in the *ESR1*, *ESR2*, *FSHR*, *CYP19A1*, *SHBG* and *NRIP1* genes may provide useful insights in the field of migraine pathophysiology. Genetic association studies have been conducted to decipher the putative relation between polymorphisms in these genes and migraine (Colson *et al.* 2004, 2006; Kaunisto *et al.* 2006; Oterino *et al.* 2006, 2008; Corominas *et al.* 2009; Joshi *et al.* 2010; Ghosh *et al.* 2012). However, the results of these studies were contradictory or have not been replicated. In the present study, we investigated 12 single-nucleotide polymorphisms (SNPs) in the *FSHR* (rs6166), *SHBG* (rs6259), *CYP19A1* (rs10046), *NRIP1* (rs2229741), *ESR1* (rs2234693, rs726281, rs2295193, rs3798577, rs1801132 and rs2228480) and *ESR2* (rs1255998 and rs4986938) in migraine patients and healthy controls.

Materials and methods

Study subjects

The study group consisted of 142 unselected and unrelated patients with migraine. All migraine patients were registered at the outpatient clinic of the Department of Neurology at Dicle University, Medical Faculty in Diyarbakır, Turkey between June 2011 and June 2013 were included in this study. Migraine was diagnosed according to the International Classification of Headache Disorders criteria (Society 2004). Patients with obesity, diabetes and other neurologic or psychiatric disorders were excluded. The control group consisted of 141 volunteers who applied to the other outpatients at Dicle University. A complete medical history was recorded and they were examined. The controls were genetically unrelated to the patients, and they had no clinical evidence for migraine, no history of migraine, no family history of migraine or other neurological and psychiatric diseases. In addition, they had no history of diabetes mellitus, hypertension, organic or genetic disorders. The mean age, sex, and ethnicity of the control group were matched with the study group. All participants were of Turkish origin, from the same geographical area (southeastern region of Turkey). This case–control study was approved by the Ethics Committee of Dicle University, Medical Faculty and each subject provided written informed consent.

Genotyping

We have reviewed the literature about SNPs in the neurological and psychiatric disorders and those reported in English literature. Particularly, SNPs that have association with the migraine phenotype and/or sex hormone metabolism have been selected. In addition, SNPs in the genes related to oestrogen metabolism were confirmed using the NCBI SNP database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db1/4snp). Genomic DNA was extracted from whole blood using DNA isolation kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The DNA concentration was determined using a Nano-Drop spectrophotometer (Thermo-Scientific, Waltham, USA) and samples were stored at -20°C until polymerase chain reaction (PCR). The genotype was determined from each individual patient and controls by using the Fluidigm dynamic array system. Polymorphisms were analysed from the genomic DNA using a 96.96 dynamic array on the BioMark HD system (Fluidigm, south San Francisco, USA). The Digital PCR Analysis software (Fluidigm, south San Francisco, USA) was used to process the data after the reaction. Chambers that yielded signals were detected and counted.

Statistical analysis

We have compared the genotype and allele frequencies of SNPs under additive model between migraine patients and control group; further analyses for genotypes based on dominant and recessive models were conducted. Chi-square or Fisher exact tests were used to compare genotype and allele distributions between the study and control groups; $P < 0.05$ was considered statistically significant. Bonferroni corrections for multiple comparisons were performed. For the age variable, which obtains a continuous value, the normality test was conducted using Kolmogorov–Smirnov test. The age variable was compared between the two groups using a student's *t*-test. The data were given as mean $\pm$ standard deviation (SD) and frequency. Two-tailed tests were used unless otherwise stated. Goodness-of-fit χ^2 test was used to assess deviations from Hardy–Weinberg equilibrium (HWE) in control group. The gene–gene interactions were investigated by generalized multifactor dimensionality reduction (GMDR) (Lou *et al.* 2007). All possible combinations from two-locus to 12-locus SNPs were examined. We explored gene–gene interaction on migraine presence using logistic

Table 1. Demographic characteristics of study participants.

Parameter	Migraine patient n =142	Healthy controls n =141	P
Age (years), (mean ± SD)	31.32 ± 9.79	30.21 ± 6.67	0.269
Gender			
Female (n, %)	107 (75.4%)	103 (73.0%)	0.658
Male (n, %)	35 (24.6%)	38 (27.0%)	
Migraine types			
MA (n, %)	24 (16.9%)	NA	
MO (n, %)	118 (83.1%)		
Familial history			
Positive (n, %)	80 (56.3%)	NA	
Negative (n, %)	62 (43.7%)		

MA, migraine with aura; MO, migraine without aura; NA, not assessed; SD, standard deviation.

regression model adjusted for covariates. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Statistical analyses were performed with SPSS 15.0 (Chicago, USA) and open-resource GMDR software package (ver. 0.9).

Power analysis

Statistical power was calculated as 77.9% based on the genotyping results of rs10046. The ratio of TT genotype of rs10046 in the migraine group (28.2%) and in the control group (16.3%) and a free web-based tool were used for power calculation (https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx).

Results

Clinical characteristics of the subjects

In this study, the mean age of the 142 subjects in patient group (35 males and 107 females) was 31.32 ± 9.79 SD, while the mean age of the 141 subjects in control group (38 males and 103 females) was 30.21 ± 6.67 SD. There was no significant difference in age or sex between the groups ($P = 0.269$, $P = 0.658$, respectively). The number of patients described migraine with aura was 24 (16.9%) and migraine without aura was 118 (83.1%). In addition, 80 patients (56.3%) described positive familial history but 62 patients (43.7%) had no familial history. The demographic characteristics of the groups are shown in table 1.

Comparison of the genotype and allele distributions

The genotype distributions confirmed to HWE in the controls ($P > 0.05$). Minor allele frequency (MAF) values are given in table 2. A significant association was detected between rs10046 polymorphism and migraine. The frequency of the rare TT genotype of rs10046 was significantly higher in migraine group compared to control group ($P = 0.046$). Also, when CC and CT genotypes were combined and compared against TT genotype (recessive model) in the groups, a significant association was observed ($P = 0.016$, ORs (95% CIs) = 0.50 (0.27–0.92)). The CC and CT genotypes were more frequent in controls (n =118, 83.7%) than in migraine group ($n = 102$, 71.8%). The frequency of T allele of rs10046 polymorphism in migraine group was slightly higher than control group, but no significant difference was observed between two groups ($P = 0.129$; table 3).

Table 2. MAF in different populations.

SNP	Chromosome (position)	MAF in 1000 genomes (allele)	MAF in present study	MAF (population)	Literature
FSHR (rs6166)	2 Chr (49189921)	0.41 (C)	0.46	0.42 (Caucasian origin Spanish)	Oterino *et al.* (2008)
SHBG (rs6259)	17 Chr (7536527)	0.07 (A)	0.04	0.18 (Chinese women)	Cui *et al.* (2005)
CYP19A1 (rs10046)	15 Chr (51502986)	0.36 (A)	0.44	0.49 (Mostly European Whites)	Haiman *et al.* (2007)
				0.51 (Caucasian origin Spanish)	Oterino *et al.* (2008)
				0.25 (north Indian)	Ghosh *et al.* (2012)
NRIP1 (rs2229741)	21 Chr (16340289)	0.40 (C)	0.56	0.61 (Caucasian origin Spanish)	Oterino *et al.* (2008)
ESR1 (rs2234693)	6 Chr (152163335)	0.45 (C)	0.49	0.66 (north Indian)	Joshi *et al.* (2010)
				0.47 (Caucasian origin Australian)	Colson *et al.* (2006)
ESR1 (rs726281)	6 Chr (152302578)	0.45 (A)	0.66	Not found	Not found
ESR1 (rs2295193)	6 Chr (152453094)	0.31 (G)	0.39	Not found	Not found
ESR1 (rs3798577)	6 Chr (152421130)	0.46 (C)	0.45	Not found	Not found
ESR1 (rs1801132)	6 Chr (152265522)	0.28 (G)	0.25	0.81 (Spanish)	Oterino *et al.* (2006)
				0.23 (Finnish)	Kaunisto *et al.* (2006)
				0.37 (north Indian)	Joshi *et al.* (2010)
				0.19 (Caucasian origin Spanish)	Corominas *et al.* (2009)
SR1 (rs2228480)	6 Chr (152420095)	0.19 (A)	0.14	0.28 (East coast of Australia)	Colson *et al.* (2004)
				0.18 (Spanish)	Oterino *et al.* (2006)
				0.14 (Caucasian origin Spanish)	Corominas *et al.* (2009)
ESR2 (rs1255998)	14 Chr (64693871)	0.37 (C)	0.80	Not found	Not found
ESR2 (rs4986938)	14 Chr (64699816)	0.26 (T)	0.39	Not found	Not found

MAF; minor allele frequency.

Table 3. Distribution of alleles and genotypes among the groups.

Gene	SNP	Genotype	Migraine patients		Healthy controls		*P*	ORs (95% CIs)
			$n = 142$	%	$n = 141$	%		
FSHR	rs6166	AA/AG/GG	27/84/31	19.0/59.2/21.8	40/71/30	28.4/50.3/21.3	0.163	
	Alleles	A/G	138/146	48.6/51.4	151/131	53.5/46.5	0.238	0.82 (0.58–1.16)
	Recessive	AA+AG/GG	111/31	78.2/21.8	111/30	78.7/21.3	0.907	0.97 (0.53–1.77)
	Dominant	AA/AG+GG	27/115	19.0/81.0	40/101	28.4/71.6	0.064	0.59 (0.33–1.07)
SHBP	rs6259	GG/AG/AA	132/10/0	93.0/7.0/0	130/11/0	92.2/7.8/0	0.808	
	Alleles	G/A	274/10	96.5/3.5	271/11	96.1/3.9	0.811	1.11 (0.43–2.88)
	Recessive	GG+AG/AA	142/0	100.0/0	141/0	100.0/0	–	–
	Dominant	GG/AG+AA	132/10	93.0/7.0	130/11	92.2/7.8	0.807	1.12 (0.42–2.96)
CYP19A1	rs10046	CC/CT/TT	37/65/40	26.1/45.7/28.2	38/80/23	27.0/56.7/16.3	**0.046**	
	Alleles	C/T	139/145	48.9/51.1	156/126	55.3/44.7	0.129	0.77 (0.55–1.09)
	Recessive	CC+CT/TT	102/40	71.8/28.2	118/23	83.7/16.3	**0.016**	0.50 (0.27–0.92)
	Dominant	CC/CT+TT	37/105	26.1/73.9	38/103	27.0/73.0	0.865	0.96 (0.54–1.67)
NRIP1	rs2229741	GG/GA/AA	33/82/27	23.2/57.7/19.1	46/66/29	32.6/46.8/20.6	0.140	
	Alleles	G/A	148/136	52.1/47.9	158/124	56.0/44.0	0.351	0.85 (0.61–1.21)
	Recessive	GG+GA/AA	115/27	81.0/19.0	112/29	79.4/20.6	0.743	1.10 (0.59–2.06)
	Dominant	GG/GA+AA	33/109	23.2/76.8	46/95	32.6/67.4	0.078	0.63 (0.36–1.09)
ESR1	rs2234693	CC/CT/TT	31/74/37	21.8/52.1/26.1	35/69/37	24.9/48.9/26.2	0.813	
	Alleles	C/T	136/148	47.9/52.1	139/143	49.3/50.7	0.740	0.95 (0.67–1.33)
	Recessive	CC+CT/TT	105/37	73.9/26.1	104/37	73.8/26.2	0.971	1.01 (0.57–1.77)
	Dominant	CC/CC+TT	31/111	21.8/78.2	35/106	24.9/75.1	0.552	0.85 (0.47–1.52)
	rs726281	AA/AG/GG	50/66/26	35.2/46.5/18.3	65/57/19	46.1/40.4/13.5	0.157	
	Alleles	A/G	166/118	58.5/41.5	187/95	66.3/33.7	0.053	0.71 (0.50–1.02)
	Recessive	AA+AG/GG	116/26	81.7/18.3	122/19	86.5/13.5	0.266	0.69 (0.35–1.38)
	Dominant	AA/AG+GG	50/92	35.2/64.8	65/76	46.1/53.9	0.062	0.64 (0.38–1.05)
	rs2295193	AA/AG/GG	62/62/18	43.7/43.7/12.6	52/67/22	36.9/47.5/15.6	0.480	
	Alleles	A/G	186/98	65.5/34.5	171/111	60.6/39.4	0.232	1.23 (0.86–1.76)
	Recessive	AA+AG/GG	124/18	87.4/12.6	119/22	84.4/15.6	0.479	1.27 (0.62–2.63)
	Dominant	AA/AG+GG	62/80	43.7/56.3	52/89	36.9/63.1	0.245	1.33 (0.80–2.20)
	rs3798577	TT/TC/CC	40/72/30	28.2/50.7/21.1	42/71/28	29.7/50.4/19.9	0.941	
	Alleles	T/C	152/132	53.5/46.5	155/127	55.0/45.0	0.729	0.94 (0.67–1.33)
	Recessive	TT+TC/CC	112/30	78.9/21.1	113/28	80.1/19.9	0.791	0.93 (0.50–1.71)
	Dominant	TT/TC+CC	40/102	28.2/71.8	42/99	29.7/70.3	0.764	0.92 (0.54–1.60)
	rs1801132	CC/CG/GG	73/56/13	51.4/39.4/9.2	82/46/13	58.2/32.6/9.2	0.472	
	Alleles	C/G	202/82	71.1/28.9	210/72	74.5/25.5	0.371	0.84 (0.57–1.24)
	Recessive	CC+CG/GG	129/13	90.8/9.2	128/13	90.8/9.2	0.984	1.01 (0.42–2.42)
	Dominant	CC/CG+GG	73/69	51.4/48.6	82/59	58.2/41.8	0.254	0.76 (0.46–1.25)
	rs2228480	GG/AG/AA	116/22/4	81.7/15.5/2.8	102/37/2	72.3/26.3/1.4	0.066	
	Alleles	G/A	254/30	89.4/10.6	241/41	85.5/14.5	0.153	1.44 (0.85–2.45)
	Recessive	GG+AG/AA	138/4	97.2/2.8	139/2	98.6/1.4	0.684	0.50 (0.06–3.21)
	Dominant	GG/AG+AA	116/26	81.7/18.3	102/39	72.3/27.7	0.061	1.71 (0.94–3.11)
ESR2	rs1255998	CC/CG/GG	106/32/4	74.6/22.6/2.8	93/40/8	66.0/28.3/5.7	0.216	
	Alleles	C/G	244/40	85.9/14.1	226/56	80.1/19.9	0.067	1.51 (0.95–2.41)
	Recessive	CC+CG/GG	138/4	97.2/2.8	133/8	94.3/5.7	0.228	2.09 (0.55–8.47)
	Dominant	CC/CG+GG	106/36	74.6/25.4	93/48	66.0/34.0	0.109	1.52 (0.88–2.63)
	rs4986938	GG/GA/AA	55/63/24	38.7/44.4/16.9	50/71/20	35.5/50.4/14.2	0.584	
	Alleles	G/A	173/111	60.9/39.1	171/111	60.6/39.4	0.946	1.01 (0.71–1.44)
	Recessive	GG+GA/AA	118/24	83.1/16.9	121/20	85.8/14.2	0.528	0.81 (0.41–1.62)
	Dominant	GG/GA+AA	55/87	38.7/61.3	50/91	35.5/64.5	0.568	1.15 (0.69–1.92)

–, No statistics computed; ORs (95% CIs), odds ratios (95% confidence intervals). Bold values indicate statistical significance, $P < 0.05$.

Female migraine patients were divided into two subgroups; first group consist of MRM group ($n = 38$) and second group consist of MNRM group ($n = 69$). There was a nominal significance in the genotype distribution of rs726281 between two groups ($P = 0.043$) which was not maintained after Bonferroni adjustment. When we use recessive model (AA and AG genotypes were combined and compared against GG genotype), rare GG genotype was higher in the MRM group ($P = 0.014$; OR (95% CI) = 3.75 (1.24–11.33)). Allele frequency of rs726281 was also different between MRM and MNRM groups. Allele A is significantly higher in MNRM group ($P = 0.027$; OR (95% CI) = 1.90 (1.03–3.50), table 4).

When SNPs were evaluated only in women participants, the genotype distribution of *NRIP1* rs2229741 was different between female patients ($n = 107$) and healthy female

Table 4. Allele and genotype frequencies for each of the associated SNPs in the sub-groups of female patients.

Gene	SNP	Alleles 1	Alleles 2	Genotype (n, %) MNRM, $n = 69$ 11	12	22	MRM, $n = 38$ 11	12	22	Allele 2 versus 1 OR (95% CIs)	P	Recessive 11 + 12 versus 22 OR (95% CIs)	P	Dominant 11 versus 12 + 22 OR (95% CIs)	P
FSHR	rs6166	A	G	15 (21.7)	37 (53.6)	17 (24.6)	9 (23.7)	23 (60.5)	6 (15.8)	0.81 (0.44–1.47)	0.450	0.57 (0.21–1.61)	0.286	0.89 (0.35–2.29)	0.817
SHBP	rs6259	G	A	65 (94.2)	4 (5.8)	0 (0)	34 (89.5)	4 (10.5)	0 (0)	1.86 (0.38–9.18)	0.458				
CYP19A1	rs10046	C	T	18 (26.1)	33 (47.8)	18 (26.1)	10 (26.3)	18 (47.4)	10 (26.3)	1.25 (0.68–2.32)	0.437	1.01 (0.41–2.49)	0.979	0.99 (0.40–2.43)	0.979
NRIP1	rs2229741	G	A	14 (20.3)	43 (62.3)	12 (17.4)	6 (15.8)	23 (60.5)	9 (23.7)	1.24 (0.68–2.26)	0.449	1.47 (0.56–3.90)	0.433	1.36 (0.48–3.88)	0.568
ESR1	rs2234693	C	T	19 (27.5)	34 (49.3)	16 (23.2)	6 (15.8)	22 (57.9)	10 (26.3)	1.35 (0.74–2.46)	0.298	0.49 (0.18–1.36)	0.169	0.85 (0.34–2.11)	0.718
	rs726281	A	G	29 (42.0)	34 (49.3)	6 (8.7)	11 (28.9)	17 (44.7)	10 (26.3)	1.90 (1.03–3.50)	**0.027**	3.75 (1.24–11.33)	**0.014**	1.78 (0.76–4.15)	0.181
	rs2295193	A	G	25 (36.2)	33 (47.8)	11 (15.9)	18 (47.4)	15 (39.5)	5 (13.2)	0.74 (0.39–1.39)	0.313	0.80 (0.26–2.50)	0.699	0.63 (0.28–1.41)	0.261
	rs3798577	T	C	17 (24.6)	41 (59.4)	11 (15.9)	12 (31.6)	18 (47.4)	8 (21.1)	0.96 (0.53–1.76)	0.897	1.41 (0.51–3.87)	0.508	0.71 (0.29–1.70)	0.440
	rs1801132	C	G	38 (55.1)	24 (34.8)	7 (10.1)	20 (52.6)	17 (44.7)	1 (2.6)	0.88 (0.44–1.74)	0.687	0.24 (0.03–2.02)	0.157	1.10 (0.49–2.44)	0.808
	rs2228480	G	A	54 (78.3)	14 (20.3)	1 (1.4)	33 (86.8)	3 (7.9)	2 (5.3)	0.77 (0.27–2.13)	0.590	3.78 (0.33–43.09)	0.253	0.55 (0.18–1.64)	0.276
ESR2	rs1255998	C	G	51 (73.9)	16 (23.2)	2 (2.9)	28 (73.7)	9 (23.7)	1 (2.6)	1.00 (0.42–2.36)	0.996	0.91 (0.08–10.32)	0.936	1.01 (0.41–2.49)	0.979
	rs4986938	G	A	30 (43.5)	27 (39.1)	12 (17.4)	12 (31.6)	21 (55.3)	5 (13.2)	1.10 (0.64–2.17)	0.581	0.72 (0.23–2.22)	0.566	1.67 (0.72–3.83)	0.228

MNRM, migraine not related to menstruation; MRM, migraine related to menstruation. *The significance was not maintained after the Bonferroni adjustment, $P < 0.016$ ($\alpha = 0.05/3$).
Bold values indicate statistical significance, $P < 0.05$.

controls ($n = 103$; $P = 0.032$). The variant GG genotype was higher in female controls (32.0%) than female migraineurs (18.7%). However, the significance was not maintained after Bonferroni adjustment. Although, there was no difference for the allele frequency of rs2229741 in women, a significant association was found when AA and AG genotypes compared with the variant GG genotype (recessive model) ($P = 0.026$; OR (95% CI) = 2.05 (1.08–3.88), table 5). In addition, we analysed the association for 12 SNPs between MA and MO subgroups. As shown in table 6, the most significant association was observed under the recessive model for rs1801132 and rs2295193 ($P = 0.010$ and $P = 0.043$, respectively), (table 6). On the other hand, we compared the male and female patients, a significant difference was observed under the dominant model for *NRIP1* rs2229741 ($P = 0.025$). However, there were no statistically significant differences in the frequencies of the alleles and genotypes of the other variants between the male and female patients (table 7).

Gene–gene interactions in the migraine patients and controls

For the gene–gene interaction, GMDR analyses were run to investigate the impacts of combinations of the 12 SNPs on migraine disease using the two-locus to 12-locus model, with adjustment for covariates (sex and age). The summary of gene–gene interaction models are listed in table 8. With covariate adjustments, the best model for migraine disease, included rs10046, rs6166, rs2229741 and rs726281, was scored 7/10 for cross validation consistency and 9/10 by the sign test ($P = 0.0107$). According to GMDR results, we divided the migraine samples into low-risk and high-risk genotype combination groups. When the subjects had a genotype combination as in light gray boxes, we put them into the low-risk group, but other combinations as in dark gray boxes indicate the high-risk group (figure 1). The analysis of other combinations of genotypes did not reach the statistical significance level.

Discussion

In this study, we evaluated 12 SNPs in *FSHR*, *SHBG*, *CYP19A1*, *NRIP1*, *ESR1* and *ESR2* genes. Although, MAF values of rs726281 (*ESR1*), rs1255998 (*ESR2*) and rs4986938 (*ESR2*) were higher than those values in 1000 genomes most of the MAF values of the studied SNPs were in accordance with previous reports at least one different population or those MAF values in 1000 genomes project. The TT genotype of rs10046 in *CYP19A1* was higher in our study, and it was statistically significant in both recessive and additive model. This polymorphism was targeted previously by Oterino *et al.* (2008) in Caucasians in northern Spain, and they found no difference in genotype distribution between migraine patients and healthy controls (Oterino *et al.* 2008). A significant interaction was reported for *CYP19A1*, rs10046 polymorphism with *ESR1* and *ESR2* gene polymorphisms,

Table 5. Allele and genotype frequencies for each of the associated SNPs between female patients and controls.

				Genotype (n, %)							Allele		Recessive		Dominant	
		Alleles		Female case, $n = 107$			Female control, $n = 103$				2 versus 1		11 + 12 versus 22		11 versus 12 + 22	
Gene	SNP	1	2	11	12	22	11	12	22	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P
FSHR	rs6166	A	G	24 (22.4)	60 (56.1)	23 (21.5)	30 (29.1)	55 (53.4)	18 (17.5)	0.492	0.81 (0.54–1.21)	0.271	1.42 (0.76–2.65)	0.267	1.29 (0.65–2.57)	0.463
SHBP	rs6259	G	A	99 (92.5)	8 (7.5)	0 (0)	95 (92.2)	8 (7.8)	0 (0)	0.937	1.04 (0.35–3.11)	0.938				
CYP19A1	rs10046	C	T	28 (26.2)	51 (47.7)	28 (26.2)	32 (31.1)	53 (51.5)	18 (17.5)	0.301	0.76 (0.51–1.14)	0.163	1.27 (0.70–2.32)	0.432	1.67 (0.86–3.26)	0.128
NRIP1	rs2229741	G	A	20 (18.7)	66 (61.7)	21 (19.6)	33 (32.0)	46 (44.7)	24 (23.3)	**0.032**	0.82 (0.55–1.23)	0.321	2.05 (1.08–3.88)	**0.026**	0.80 (0.41–1.56)	0.516
ESR1	rs2234693	C	T	25 (23.4)	56 (52.3)	26 (24.3)	27 (26.2)	51 (49.5)	25 (24.3)	0.881	0.94 (0.63–1.41)	0.768	0.86 (0.46–1.61)	0.633	1.00 (0.53–1.88)	0.996
	rs726281	A	G	40 (37.4)	51 (47.7)	16 (15.0)	47 (45.6)	44 (42.7)	12 (11.7)	0.455	0.78 (0.51–1.18)	0.217	1.41 (0.81–2.44)	0.225	1.33 (0.60–2.98)	0.482
	rs2295193	A	G	43 (40.2)	48 (44.9)	16 (15.0)	36 (35.0)	49 (47.6)	18 (17.5)	0.715	1.18 (0.78–1.78)	0.416	0.80 (0.46–1.40)	0.434	0.83 (0.40–1.73)	0.620
	rs3798577	T	C	29 (27.1)	59 (55.1)	19 (17.8)	29 (28.2)	54 (52.4)	20 (19.4)	0.918	1.01 (0.68–1.51)	0.950	1.05 (0.58–1.93)	0.865	0.87 (0.45–1.80)	0.757
	rs1801132	C	G	58 (54.2)	41 (38.3)	8 (7.5)	58 (56.3)	36 (35.0)	9 (8.7)	0.858	0.98 (0.62–1.55)	0.921	1.09 (0.63–1.88)	0.759	0.84 (0.31–2.28)	0.738
	rs2228480	G	A	87 (81.3)	17 (15.9)	3 (2.8)	73 (70.9)	29 (28.2)	1 (1.0)	0.071	1.47 (0.80–2.72)	0.188	0.56 (0.29–1.07)	0.076	2.94 (0.3–28.75)	0.331
ESR2	rs1255998	C	G	79 (73.8)	25 (23.4)	3 (2.8)	63 (61.2)	34 (33.0)	6 (5.8)	0.129	1.70 (1.00–2.89)	**0.038**	0.56 (0.31–1.01)	0.050	0.47 (0.11–1.92)	0.280
	rs4986938	G	A	42 (39.3)	48 (44.9)	17 (15.9)	38 (36.9)	49 (47.6)	16 (15.5)	0.921	1.04 (1.69–1.57)	0.833	0.91 (0.52–1.58)	0.725	1.03 (0.49–2.16)	0.944

*The significance was not maintained after the Bonferroni adjustment, $P < 0.016$. Bold values indicate statistical significance, $P < 0.05$.

Table 6. Allele and genotype frequencies for each of the associated SNPs in the subgroups of migraine patients.

				Genotype (n, %)							Allele		Recessive		Dominant	
		Alleles		MO, $n = 118$			MA, $n = 24$				2 versus 1		11 + 12 versus 22		11 versus 12 + 22	
Gene	SNP	1	2	11	12	22	11	12	22	P	OR (95% CIs)	P	ORs (95% CIs)	P	OR (95% CIs)	P
FSHR	rs6166	A	G	24 (20.3)	69 (58.5)	25 (21.2)	3 (12.5)	15 (62.5)	6 (25.0)	0.660	1.26 (0.65–2.47)	0.461	1.24 (0.44–3.45)	0.680	1.79 (0.49–6.49)	0.569
SHBP	rs6259	G	A	111 (94.1)	7 (5.9)	0 (0)	21 (87.5)	3 (12.5)	0 (0)	0.373	0.46 (0.10–2.34)	0.380				
CYP19A1	rs10046	C	T	33 (28.0)	48 (40.7)	37 (31.4)	4 (16.7)	17 (70.8)	3 (12.5)	**0.024**	0.86 (0.44–1.67)	0.633	0.31 (0.09–1.11)	0.061	1.94 (0.62–6.11)	0.250
NRIP1	rs2229741	G	A	26 (22.0)	70 (59.3)	22 (18.6)	7 (29.2)	12 (50.0)	5 (20.8)	0.675	0.91 (0.46–1.76)	0.754	1.15 (0.39–3.41)	0.780	0.69 (0.26–1.83)	0.451
ESR1	rs2234693	C	T	25 (21.2)	62 (52.5)	31 (26.3)	6 (25.0)	12 (50.0)	6 (25.0)	0.919	0.90 (0.46–1.76)	0.747	1.07 (0.39–2.93)	0.897	1.24 (0.45–3.45)	0.680
	rs726281	A	G	40 (33.9)	59 (50.0)	19 (16.1)	10 (41.7)	7 (29.2)	7 (29.2)	0.131	1.11 (0.57–2.18)	0.734	2.15 (0.78–5.88)	0.150	0.72 (0.29–1.76)	0.468
	rs2295193	A	G	49 (41.5)	51 (43.2)	18 (15.3)	13 (54.2)	11 (45.8)	0 (0)	0.110	0.51 (0.23–1.10)	0.063	0.85 (0.78–0.91)	**0.043**	0.60 (0.25–1.45)	0.255
	rs3798577	T	C	34 (28.8)	58 (49.2)	26 (22.0)	6 (25.0)	14 (58.3)	4 (16.7)	0.702	0.97 (0.50–1.89)	0.921	0.71 (0.22–2.25)	0.557	1.21 (0.44–3.32)	0.705
	rs1801132	C	G	63 (53.4)	48 (40.7)	7 (5.9)	10 (41.7)	8 (33.3)	6 (25.0)	**0.013**	2.00 (1.00–4.00)	**0.031**	5.29 (1.59–17.52)	**0.010**	1.60 (0.66–3.90)	0.295
	rs2228480	G	A	93 (78.8)	21 (17.8)	4 (3.4)	23 (95.8)	1 (4.2)	0 (0)	0.141	0.15 (0.01–1.08)	**0.036**	0.97 (0.93–0.99)	1.000	0.16 (0.02–1.26)	0.078
ESR2	rs1255998	C	G	85 (72.0)	29 (24.6)	4 (3.4)	21 (87.5)	3 (12.5)	0 (0)	0.254	0.36 (0.08–1.29)	0.086	0.97 (0.93–0.99)	1.000	0.39 (0.10–1.32)	0.112
	rs4986938	G	A	46 (39.0)	52 (44.1)	20 (16.9)	9 (37.5)	11 (45.8)	4 (16.7)	0.987	1.03 (0.52–2.02)	0.938	0.98 (0.31–3.18)	0.973	1.07 (0.43–2.63)	0.892

*The significance was not maintained after the Bonferroni adjustment, $P < 0.016$; MO, migraine without aura; MA, migraine with aura. Bold values indicate statistical significance $P < 0.05$

Table 7. Allele and genotype frequencies for each of the associated SNPs in female and male patients.

Gene	SNP	Alleles		Genotype (n, %)						Allele		Recessive		Dominant	
				Female case, $n = 107$			Male case, $n = 35$			2 versus 1		11 + 12 versus 22		11 versus 12 + 22	
		1	2	11	12	22	11	12	22	OR (95 CIs)	P	OR (95 CIs)	P	ORs (95 CIs)	P
FSHR	rs6166	A	G	24 (22.4)	60 (56.1)	23 (21.5)	3 (8.6)	24 (68.6)	8 (22.9)	1.36 (0.76–2.43)	0.269	1.08 (0.43–2.69)	0.866	3.08 (0.87–10.96)	0.070
SHBP	rs6259	G	A	99 (92.5)	8 (7.5)	0 (0)	33 (94.3)	2 (5.7)	0 (0)	0.76 (0.11–3.98)	0.728				
CYP19A1	rs10046	C	T	28 (26.2)	51 (47.7)	28 (26.2)	9 (25.7)	14 (40.0)	12 (34.3)	1.19 (0.67–2.11)	0.533	1.47 (0.65–3.34)	0.354	1.02 (0.42–2.45)	0.958
NRIP1	rs2229741	G	A	20 (18.7)	66 (61.7)	21 (19.6)	13 (37.1)	16 (45.7)	6 (17.1)	0.65 (0.36–1.17)	0.128	0.84 (0.31–2.30)	0.745	0.39 (0.17–0.90)	**0.025**
ESR1	rs2234693	C	T	26 (24.3)	56 (52.3)	25 (23.4)	11 (31.4)	18 (51.4)	6 (17.1)	0.76 (0.43–1.36)	0.332	0.70 (0.30–1.62)	0.404	0.67 (0.25–1.82)	0.439
	rs726281	A	G	40 (37.4)	51 (47.7)	16 (15.0)	10 (28.6)	15 (42.9)	10 (28.6)	1.58 (0.89–2.82)	0.098	2.27 (0.92–5.63)	0.071	1.49 (0.65–3.43)	0.343
	rs2295193	A	G	43 (40.2)	48 (44.9)	16 (15.0)	19 (54.3)	14 (40.0)	2 (5.7)	0.58 (0.30–1.10)	0.075	0.34 (0.07–1.58)	0.154	0.57 (0.26–1.22)	0.144
	rs3798577	T	C	29 (27.1)	59 (55.1)	19 (17.8)	11 (31.4)	13 (37.1)	11 (31.4)	1.21 (0.68–2.14)	0.496	2.12 (0.89–5.06)	0.085	0.81 (0.35–1.86)	0.621
	rs1801132	C	G	58 (54.2)	41 (38.3)	8 (7.5)	15 (42.9)	15 (42.9)	5 (14.3)	1.53 (0.83–2.83)	0.146	2.06 (0.63–6.78)	0.225	1.58 (0.73–3.41)	0.244
	rs2228480	G	A	87 (81.3)	17 (15.9)	3 (2.8)	29 (82.9)	5 (14.3)	1 (2.9)	0.92 (0.34–2.40)	0.859	1.02 (0.10–10.13)	0.987	0.90 (0.33–2.46)	0.837
ESR2	rs1255998	C	G	79 (73.8)	25 (23.4)	3 (2.8)	27 (77.1)	7 (20.0)	1 (2.9)	0.87 (0.36–2.04)	0.733	1.02 (0.10–10.13)	0.987	0.84 (0.34–2.05)	0.696
	rs4986938	G	A	42 (39.3)	48 (44.9)	17 (15.9)	13 (37.1)	15 (42.9)	7 (20.0)	1.14 (0.63–2.04)	0.643	1.32 (0.49–3.52)	0.573	1.09 (0.49–2.41)	0.824

Bold values indicate statistical significance $P < 0.05$.

and the rs10046 polymorphism is suggested as a risk factor for migraine in north Indian population (Ghosh *et al*. 2012, 2014).

Polymorphisms in *ESR1* and *ESR2* genes have been targeted in several genetic association studies for migraine susceptibility. The rs2234693 (intron 1 Pvu II alteration) in *ESR1* gene has been evaluated in north Indian population, and this polymorphism conferred a risk for migraine (Joshi *et al.* 2010). However, no association has been reported between rs2234693 and migraine in a case–control study conducted in Caucasian origin of Australian population (Colson *et al.* 2006). In terms of rs1801132 (C325G alteration in exon 4) in the *ESR1* gene and migraine susceptibility, a nominal association has been reported in a large Finnish population and GG genotype has been found higher in migraine patients (Kaunisto *et al.* 2006). The rs2228480 (G594A alteration in exon 8) in *ESR1* gene has been evaluated in Australian population (Caucasian origin), and an association has been reported between this polymorphism and migraine susceptibility where an A allele carriers suggested to have a higher risk of migraine (Colson *et al.* 2004). The evaluated six SNPs (rs2234693, rs2228480, rs1801132, rs3798577, rs726281 and rs2295193) in *ESR1* and two SNPs in *ESR2* (rs1255998 and rs4986938) gene in the present study may not be associated with migraine in Turkish population. In addition, the analysed SNPs in *FSHR*, *SHBG* or *NRIP1* could not be associated with migraine in the comparisons of all migraineurs and controls in our study.

The frequency of migraine alters depending on contraceptive usage or during the pregnancy, lactation and menopause (Serva *et al.* 2011). For this reason, the association of sex steroids with migraine is broadly accepted. Supporting this hormonal theory, the gene variants involved in oestrogen metabolism and oestrogen receptors have been associated with menstruation-related migraine previously (Rodriguez-Acevedo *et al.* 2014). When we evaluated the influence of 12 polymorphisms on migraine attacks related to menstruation in the female sub-groups (MRM and MNRM), genotype distribution in recessive model and allele frequency of rs726281 in *ESR1* was significantly different between MRM and MNRM, and G allele showed increased risk for MRM. To our knowledge, rs726281 in *ESR1* have not been targeted for migraine susceptibility so far. This association may be related to pain modulators including dopamine, noradrenaline and adrenaline (catecholamines). Since, *ESR1* is functionally related in the catechol-o-methyltransferase (COMT) pathway by downregulating its transcription. COMT inactivates these pain modulators and reduced COMT activity may lead to higher total plasma catecholamine level (Smith *et al.* 2014). Recently, minor G allele of the rs726281 in *ESR1* gene was associated with reduced COMT activity in a dose-dependent manner, which means, two copies of G allele cause more reduction in the COMT activity (Smith *et al.* 2014). Interestingly, total plasma catecholamine level was found higher in people awoke with migraine (Hsu *et al.* 1977). Although, we did not evaluate COMT activity in this

Table 8. Best gene–gene interaction models identified by the GMDR.

Best model	Training balanced accuracy	Testing balanced accuracy	Sign test (P)*	Cross-validation consistency
(rs726281 rs4986938)	0.6217	0.5212	4 (0.8281)	7/10
(rs726281 rs4986938 rs2295193)	0.684	0.5622	6 (0.3770)	8/10
(rs10046 rs726281 rs6166 rs2229741)	0.7657	0.5985	**9 (0.0107)**	7/10
(rs10046 rs726281 rs6166 rs2229741 rs3798577)	0.8384	0.5451	6 (0.3770)	3/10
(rs10046 rs726281 rs4986938 rs6166 rs2229741 rs3798577)	0.9085	0.5577	7 (0.1719)	4/10
(rs10046 rs726281 rs4986938 rs6166 rs2229741 rs2234693 rs3798577)	0.9547	0.4764	4 (0.8281)	3/10

*Adjusted for sex and age. Bold value indicates statistical significance $P < 0.05$.

study, our results support the association of rs726281 with menstruation-related migraine attacks. Recently, rs4986938, located in the 3′ UTR of *ESR2*, has been associated with menstruation-related migraine in which the migraine attacks occur on day 1 ± 2 of menstruation in at least two out of three menstrual cycles (Rodriguez-Acevedo *et al.* 2014). In addition, G allele of rs4986938 has been reported to be a risk factor for menstrual migraine (Rodriguez-Acevedo *et al.* 2014).

The rs10046 polymorphisms in the *CYP19A1* have been associated with circulating oestrogen levels (Haiman *et al.* 2007). In the subgroup analysis, between female patients and female controls, Oterino *et al.* (2008) reported a difference in the genotype distribution of rs10046 in *CYP19A1*, and CC genotype has been found higher in female patients or in female patients with aura (Oterino *et al.* 2008). In Finnish female population, the genotype distribution of rs1801132 in *ESR1* has been found different only in females sub-group and two minor alleles increased the risk for migraine with aura (Kaunisto *et al.* 2006). Similarly, in a Spanish cohort, rs1801132 polymorphism was reported to be associated with migraine in women, and women carrying the C allele have a higher risk of migraine (Oterino *et al.* 2006). According to our results, it seems that GG genotype of rs2229741 in *NRIP1* has a protective effect on migraine in women, and this may indicate an association between migraine and *NRIP1* in women in the recessive model (GA + AA). The rs2229741 polymorphism in *NRIP1* gene has been targeted by Oterino *et al.* (2008) but no difference has been found between whole migraineurs and controls. Taking into account the role of *NRIP1* on oestrogen-regulated genes including oestrogen receptor expression (Docquier *et al.* 2013), the effect of rs2229741 polymorphism on migraine susceptibility may be more remarkable in female.

The rs1255998 is located in the 3′ UTR of the *ESR2* gene. In Japanese women, the GC genotype of rs1255998 was associated with significantly lower circulating estradiol concentrations (Sowers *et al.* 2006). In our study, G allele of rs1255998 in *ESR2* seems to be associated with an increased risk for migraine in women.

The genetic association studies, conducted for migraine susceptibility, have included the rs6166 polymorphism in the *FSHR* gene. A significant gene–gene interaction between *ESR2* and *ESR1*, and *FSHR* haplotypes has been observed for migraine, and the *FSHR* gene variant rs6166 has been reported to be associated with migraine in women (Oterino *et al.* 2008). However, no association was reported between rs6166 and migraine susceptibility in women in a study that conducted recently (Rodriguez-Acevedo *et al.* 2014). In the present study, we did not find a difference between female cases and controls for rs6166.

SHBG level has been found higher in women who carry A allele of the rs6259 in *SHBG* gene, and responsible for the low oestradiol level (Cui *et al.* 2005). Alteration in the circulating hormone levels due to the SHBG levels may influence migraine susceptibility. However, we did not find a difference between migraine and control groups for the genotype distribution or allele frequency of rs6259.

In comparison of MO and MA patients, a statistical significance was obtained in the genotype distribution of rs10046 in *CYP19A1*, but it was not maintained after Bonferroni adjustment. However, sample size was not appropriate to relate this polymorphism with MA. Similarly, the ratio of GG genotype of rs1801132 in *ESR1* was higher in MA patients, and G allele has an increased risk for migraine with aura. To our knowledge, other SNP, rs2295193 in *ESR1* has not been targeted in migraine association studies. Absence of any subject with GG or AA genotype in the MA phenotype for the rs2295193 and rs2228480 polymorphisms respectively did not allow us to make a prediction, although the significant differences were found for rs2295193 and rs2228480.

According to the WHO report in 2011, the lowest migraine prevalence has been found in Africa (World Health Organization 2011). Interestingly, the rs3798577 (CC genotype) polymorphism in *ESR1* gene has been associated with lower circulating oestradiol concentrations in African American women (Sowers *et al.* 2006). Therefore, rs3798577 (CC genotype) may have a protective effect on migraine attacks in women. However, our results did not support this effect. Interestingly, the genotype distribution of the rs2229741 in *NRIP1* gene was significantly different in the dominant model between female and male subgroups.

It is also important to disclose gene–gene interactions to explain the migraine pathophysiology. The interaction between *CYP19A1* and *ESR1* has been reported previously (Ghosh *et al.* 2014). In the present study, according to the

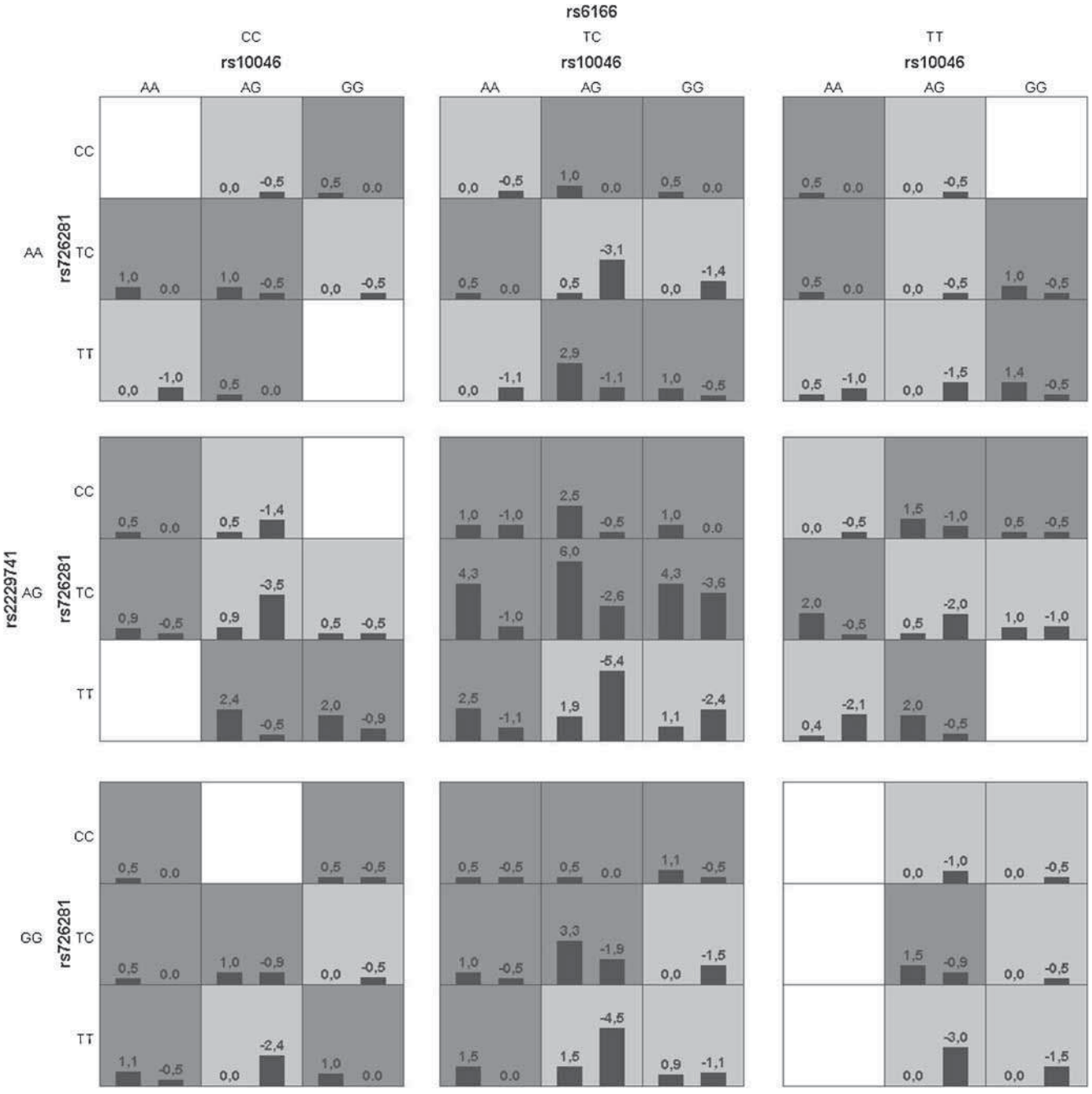

Figure 1. The best model that is identified comprises rs10046 in *CYP19A1*, rs6166 in *FSHR*, rs726281 in *ESR1* and rs2229741 in *NRIP1* ($P < 0.05$). In each cell, the left bar represents a positive score and the right bar a negative score. Dark shading indicates high-risk cells and light shading indicates low-risk cells. Boxes without shade are empty cells.

GMDR analysis, an interaction has been confirmed among the *CYP19A1*, *FSHR*, *ESR1* and *NRIP1*.

The small sample size, particularly less number of participants in subgroups, is the limitation of the present study. The limitations of the genotype association studies about migraine susceptibility have been summarized elsewhere (Schürks *et al.* 2010). First of all, ethnicity and sex differences among study populations may lead to contradictory results. The sample size and allele frequencies should be used to determine the power of the genetic association study. Moreover, several hundred patients and controls should be included in the study to detect at least moderate association. To have adequate power in the subgroup analysis, sample size should be increased, and minor allele frequency should not be low. The results of the study should be stratified by gender, migraine with aura and menstruation-related migraine status.

In conclusion, to our knowledge, this is the first study that investigated the association with the *FSHR*, *ESR1*, *ESR2*, *SHBP*, *CYP19A1* and*NRIP1* gene polymorphisms in Turkish

migraine patients. Our data suggested that *CYP19A1* rs10046 plays a potential role in migraine susceptibility in a Turkish population. In addition, the GG genotype of rs2229741 in *NRIP1* strikingly reduced the risk of migraine in Turkish women, and the rare GG genotype in *ESR1* rs726281 appears to influence susceptibility in a recessive manner in MRM subgroup in female patients. Moreover, a gene–gene interaction among the polymorphisms rs10046 in *CYP19A1*, rs6166 in *FSHR*, rs726281 in *ESR1* and rs2229741 in *NRIP1* may be associated with migraine disease. Further prospective comprehensive studies with more patients are necessary to verify our results.

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