MAOA and TNF-β Gene Polymorphisms are Associated with Photophobia but not Osmophobia in Patients with Migraine

Masakazu Ishii[1], Shino Usami[1,2], Hajime Hara[3], Atsuko Imagawa[3], Yutaka Masuda[4,5], Shunichi Shimizu[1]

Abstract-

Purpose: Photophobia and osmophobia are typical symptoms associated with migraine, but the contributions of gene polymorphisms to these symptoms are not fully elucidated. We investigated whether the gene polymorphisms are involved in photophobia and osmophobia in patients with migraine.

Methods: Ninety-one migraine patients and 119 non-headache healthy volunteers were enrolled. The 12 gene polymorphisms were determined by polymerase-chain-reaction (PCR) and PCR restriction-fragment-length polymorphism analysis.

Results: Photophobia and osmophobia were observed in 49 (54%) and 31 patients (34%), respectively. Distributions of monoamine oxidase A (*MAOA*) *T941G* and tumour necrosis factor-β (*TNF-β*) *G252A* polymorphisms were significantly different between patients with photophobia and controls. However, no gene polymorphism differences were observed between patients with osmophobia and controls.

Conclusion: The *MAOA T941G* and *TNF-β G252A* gene polymorphisms appear to contribute to photophobia but not to osmophobia. We propose that different gene polymorphisms are responsible for photophobia and osmophobia symptoms during migraine.

Key Words: gene polymorphism, migraine, photophobia, osmophobia.

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From the [1]Department of Pharmacology, Toxicology and Therapeutics, Division of Physiology and Pathology, Showa University School of Pharmacy, Tokyo, Japan; [2]Usami Neurosurgery Clinic/Institute, Tokyo, Japan; [3]Department of Neurology, Showa University Fujigaoka Rehabilitation Hospital, Kanagawa, Japan; [4]Department of Research and Development for Innovative Medical Needs, Showa University School of Pharmacy, Tokyo, Japan; [5]Department of Anesthesiology, Showa University School of Medicine, Tokyo, Japan.

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Correspondence to: Masakazu Ishii, PhD. Department of Pharmacology, Toxicology and Therapeutics, Division of Physiology and Pathology, Showa University School of Pharmacy 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan.
E-mail: masakazu@pharm.showa-u.ac.jp

INTRODUCTION

Migraine is a common neurological disorder that is typically characterised by severe pain on either one or both sides of the head and disturbances in vision. During migraine attacks, patients often complain of increased sensitivity to their surroundings including sensitivity to light (photophobia) and odour (osmophobia). In a Japanese study, Takeshima et al. [1] showed that 43.9% and 17.9% patients with migraine with aura (MA) and those with migraine without aura (MO), respectively, had photophobia. In addition, Saisu et al. [2] reported that 63% patients with migraine have concurrent osmophobia (MA, 71%; MO, 57%). Compared with the Japanese population, in Western populations the prevalence of photophobia and osmophobia is approximately 90% [3,4] and 20%–40%, respectively [5-7]. Although differences in prevalence of photophobia and osmophobia were observed, these associated symptoms were observed in many patients.

In our previous study, we focused on the gene polymorphisms that are related to the onset of migraine, and reported that gene polymorphisms such as monoamine oxidase A *(MAOA) T941G*, methylenetetrahydrofolate reductase *(MTHFR) C677T* and tumour necrosis factor-β *(TNF-β) G252A* independently contribute to the pathogenesis of migraine [8]. Moreover, personality traits including neuroticism and conscientiousness are also involved in the pathogenesis of migraine [8]. Park et al.[9] investigated a harm avoidance personality dimension and polymorphisms in serotonin (5-HT) transporter protein gene in patients with MO and demonstrated that the harm avoidance personality and a variable number of tandem repeat polymorphisms within intron 2 (VNTR) of the serotonin (5-HT) transporter *(5-HTTVNTR)* independently contribute to MO in patients. Thus, it appears that migraine is a multifactorial disease. Therefore, to determine the pathophysiology of migraine, it is very important to investigate the contributions of gene polymorphisms to associated symptoms of photophobia and osmophobia.

Photophobia is elicited when 5-HT levels are depleted [10]. However, it is not known whether there is an association between 5-HT-related gene polymorphisms and photophobia or osmophobia. Recently, using a genotype–phenotype assay, Liu et al.[11] suggested that *MTHFR C677T*, a 5-HT-unrelated gene polymorphism, is associated with osmophobia but not photophobia. In contrast, Azimova et al.[12] demonstrated a positive association between *MTHFR C677T* and photophobia. Thus, the association between *MTHFR C677T* and photophobia is controversial. However, it is possible that multiple factors, such as 5-HT-related and -unrelated gene polymorphisms, contribute to the onset of photophobia and osmophobia during migraines.

In the present study, to examine the involvement of gene polymorphisms in migraine-associated symptoms of photophobia and osmophobia, the previous data [8] were sub-analyzed by photophobia and osmophobia.

METHODS

Subjects

We included 91 Japanese patients with migraine who were admitted to the Department of Neurology, Showa University Fujigaoka Rehabilitation Hospital, Kanagawa, Japan; the Pain Clinic in Showa University East Hospital, Tokyo, Japan and the Neurosurgery Clinic, Tokyo, Japan between June 2006 and December 2010. Migraine was diagnosed on the basis of the International Classification of Headache Disorders-II [13]. Data on the frequency and characteristics of headaches, age at onset of migraine and family history were collected using a questionnaire. Patients with migraine were then divided into the MA (n = 24) and MO groups (n = 67). In addition, patients were also classified according to whether they experienced headache exacerbation during daily activities, nausea, photophobia and osmophobia [2,14]. Age- and sex-matched healthy volunteers comprised the control group (n = 119). All subjects diagnosed with depression or with a history of other co-morbid psychiatric disorders were excluded. The study was approved by the Ethics Committee for Genome Research, Showa University. All subjects provided informed consent to participate in this study.

Clinical information

Data on the frequency and characteristics of headache, age at the onset of migraine and family history were collected using a questionnaire. Associated symptoms, such as photophobia and osmophobia, were assessed by the ID migraine screener Japanese version [2], which

included four items (headache exacerbation during daily activities, nausea, photophobia and osmophobia). Based on previous study by Lipton et al., [14] we assessed both photophobia and osmophobia using the following rules: "yes" assigned to response of "less than half the time" or "half the time of more".

Genotyping

Gene polymorphisms of the 5-HT transporters *5-HTTLPR (NG_011747)*[15] and *5-HTTVNTR (NG_011747)*[16], *5-HT$_{2A}$* receptor *T102C* (rs6313)[17], *5-HT$_{1B}$* receptor *G861C* (rs6296)[18], monoamine oxidase A (*MAOA*) *VNTR* (NG_008957)[19,20] and *MAOA T941G* (rs6323)[21], methylenetetrahydrofolate reductase *(MTHFR) C677T* (rs1801133)[22], angiotensin-1-converting enzyme *(ACE)* insertion/deletion *(I/D)* (NG_011648)[23], estrogen receptor 1 *(ESR1) G325C* (rs1801132)[24], *G594A* (rs2228480)[25], dopamine receptor 2 *(DRD2) C939T* (rs6275)[26] and tumour necrosis factor-β *(TNF-β) G252A* (rs909253)[27] were studied. Genomic DNA was extracted

Table 1. Backgrounds of subjects

	Control (*n* = 119)		Migraine (*n* = 91)		*p* value
	n	%	n	%	
Age (years)					
mean ± S.D.	40.7 ± 10.4		42.4 ± 10.2		0.227
Sex					
Male	31	26.1	20	22.0	0.495
Female	88	73.9	71	78.0	
Type of migraine					
MA	-		24	26.4	
MO			67	73.6	
Age at onset of migraine					
<10 years			7	7.7	
10-19 years			30	33.0	
20-29 years	-		30	33.0	
30-39 years			17	18.7	
40-49 years			6	6.6	
≥50 years			1	1.1	
Frequency					
Several times/year			21	23.1	
1/month			15	16.5	
2-3/month	-		27	29.7	
≥4/month			21	23.1	
Variable			7	7.7	
Characteristics (multiple answers allowed)					
Throbbing			76	83.5	
Tightness	-		13	14.3	
Feeling of heaviness			26	28.6	
Familiarity with migraine (multiple answers allowed)					
yes			54	59.3	
Mother			37	40.7	
Brother/Sister			9	9.9	
Child	-		11	12.1	
Variable			12	13.2	
no			2	2.2	
no response			1	1.1	

Table 2. Assesment of photophobia and osmophobia by ID Migraine screener Japanese version

	Control (n = 119)		Migraine (n = 91)	
	n	%	n	%
Photophobia				
never	119	100.0	25	27.5
rarely	0	0.0	17	18.7
less than half the time	0	0.0	21	23.1
half the time or more	0	0.0	28	30.8
never, rarely	119	100.0	42	46.2
less than half the time, half the time or more	0	0.0	49	53.8
Osmophobia				
never	119	100.0	42	46.2
rarely	0	0.0	18	19.8
less than half the time	0	0.0	15	16.5
half the time or more	0	0.0	16	17.6
never, rarely	119	100.0	60	65.9
less than half the time, half the time or more	0	0.0	31	34.1

Table 3. Gene polymorphisms

		Control (n = 119)		Photophobia (n=49)			Osmophobia (n=31)		
		n	%	n	%	p value	n	%	p value
5-HTTLPR	s/s	73	61.3	27	55.1		16	51.6	
(NG_011747)	s/l	38	31.9	18	36.7		13	41.9	
	l/l	4	3.4	4	8.2		2	6.5	
	s/xl	3	2.5	0	0.0		0	0.0	
	l/xl	1	0.8	0	0.0		0	0.0	
	s/s, s/l, s/xl	114	95.8	45	91.8	0.451	29	93.5	0.634
	l/l, l/xl	5	4.2	4	8.2		2	6.5	
5-HTTVNTR	12/12	98	82.4	37	75.5		28	90.3	
(NG_011747)	12/10	18	15.1	9	18.4		2	6.5	
	12/9	3	2.5	1	2.0		0	0.0	
	10/10	0	0.0	2	4.1		1	3.2	
	12/12	98	82.4	37	75.5	0.310	28	90.3	0.411
	12/10,12/9,10/10	21	17.6	12	24.5		3	9.7	
5-HT_{2A} T102C	T/T	27	22.7	12	24.5		9	29.0	
(rs6313)	T/C	67	56.3	27	55.1		16	51.6	
	C/C	25	21.0	10	20.4		6	19.4	
	T/T	27	22.7	12	24.5	0.802	9	29.0	0.461
	T/C, C/C	92	77.3	37	75.5		22	71.0	
5-HT_{1B} G861C	G/G	34	28.6	9	18.4		6	19.4	
(rs6296)	G/C	63	52.9	32	65.3		20	64.5	
	C/C	22	18.5	8	16.3		5	16.1	
	G/G	34	28.6	9	18.4	0.168	6	19.4	0.301
	G/C, C/C	85	71.4	40	81.6		25	80.6	

Table 3. Gene polymorphisms

			Control (n = 119)		Photophobia (n = 49)			Osmophobia (n=31)		
			n	%	n	%	p value	n	%	p value
MAOAVNTR		s/s	34	28.6	18	36.7		13	41.9	
(NG_008957)	female	s/l	38	31.9	20	40.8		11	35.5	
		l/l	16	13.4	3	6.1		1	3.2	
	male	s	23	19.3	7	14.3		4	12.9	
		l	8	6.7	1	2.0		2	6.5	
		s, s/s, s/l	95	79.8	45	91.8	0.069	28	90.3	0.292
		l, l/l	24	20.2	4	8.2		3	9.7	
MAOA T941G		T/T	26	21.8	7	14.3		6	19.4	
(rs6323)	female	T/G	44	37.0	15	30.6		8	25.8	
	male	G/G	18	15.1	19	38.8		11	35.5	
		T	10	8.4	0	0.0		2	6.5	
		G	21	17.6	8	16.3		4	12.9	
		T, T/T, T/G	80	67.2	22	44.9	0.007*	16	51.6	0.107
		G, G/G	39	32.8	27	55.1		15	48.4	
MTHFR C677T		C/C	37	31.1	23	46.9		14	45.2	
(rs1801133)		C/T	61	51.3	19	38.8		10	32.3	
		T/T	21	17.6	7	14.3		7	22.6	
		C/C	37	31.1	23	46.9	0.051	14	45.2	0.141
		C/T, T/T	82	68.9	26	53.1		17	54.8	
ACE I/D		I/I	49	41.2	19	38.8		11	35.5	
(NG_011648)		I/D	48	40.3	26	53.1		17	54.8	
		D/D	22	18.5	4	8.2		3	9.7	
		I/I, I/D	97	81.5	45	91.8	0.105	28	90.3	0.292
		D/D	22	18.5	4	8.2		3	9.7	
ESR1 G325C		G/G	14	11.8	11	22.4		6	19.4	
(rs1801132)		G/C	62	52.1	20	40.8		14	45.2	
		C/C	43	36.1	18	36.7		11	35.5	
		G/G	14	11.8	11	22.4	0.077	6	19.4	0.268
		G/C, C/C	105	88.2	38	77.6		25	80.6	
ESR1 G594A		G/G	78	65.5	38	77.6		23	74.2	
(rs2228480)		G/A	26	21.8	11	22.4		8	25.8	
		A/A	15	12.6	0	0.0		0	0.0	
		G/G, G/A	104	87.4	49	100.0	0.006*	31	100.0	0.041*
		A/A	15	12.6	0	0.0		0	0.0	
DRD2 C939T		C/C	29	24.4	7	14.3		6	19.4	
(rs6275)		C/T	61	51.3	30	61.2		16	51.6	
		T/T	29	24.4	12	24.5		9	29.0	
		C/C	29	24.4	7	14.3	0.148	6	19.4	0.557
		C/T, T/T	90	75.6	42	85.7		25	80.6	
TNF-β G252A		G/G	11	9.2	10	20.4		6	19.4	
(rs909253)		G/A	56	47.1	18	36.7		13	41.9	
		A/A	52	43.7	21	42.9		12	38.7	
		G/G	11	9.2	10	20.4	0.048*	6	19.4	0.114
		G/A, A/A	108	90.8	39	79.6		25	80.6	

* p<0.05

from whole blood using NucleoSpinÒ Blood QuickPure (NIPPON Genetics Co., Ltd, Tokyo, Japan). Each gene polymorphism was determined according to previous protocols [15-27]. Primer sequences, restriction enzymes and expected fragment sizes of approximately 12 gene polymorphisms are shown in our previous report [8]. The polymerase chain reaction (PCR) products or restriction enzyme-treated PCR fragments were run with positive controls on 3% agarose gels and stained with ethidium bromide.

Statistical analyses

The genotype frequencies were tested using the public statistical web tool http://www.oege.org/software/hwe-mr-calc.shtml for Hardy–Weinberg equilibrium (HWE). Genotype distributions that deviated from the HWE were identified ($p > 0.05$). A power analysis was performed (http://www.dssresearch.com/toolkit/spcalc/power_a1.asp) using Cohen's criteria[28] as follows: (i) a small effect size of ≥ 0.2 and < 0.5, (ii) a medium effect size of ≥ 0.5 and <0.8 and (iii) a large effect size of ≥ 0.8 (alpha = 5%).

Results are expressed as means ± SD. We used univariate analyses and Student's t-test for continuous variables, and χ^2 or Fisher's exact tests were used for categorical variables. Values of $p < 0.05$ were considered statistically significant. The analyses were performed using Excel Statistics (Excel Toukei) 2008 for Windows (Social Survey Research Information Co., Tokyo, Japan).

RESULTS

Patients

In this study, 91 patients with migraine [males, 20 (22.0%); females, 71 (78.0%); age, 42.4 ± 10.2 years] were included (Table 1). Of these 91 patients, 24 (26.4%) experienced MA and 67 (73.6%) experienced MO (Table 1). The control group comprised 119 healthy volunteers [males, 31 (26.1%); females, 88 (73.9%); age, 40.7 ± 10.4 years] (Table 1).

Clinical features are shown in Tables 1 and 2. The age at onset of migraine was highest from 10 to 19 years and from 20 to 29 years (Table 1). Throbbing in the expression of headache was observed in 83.6% patients (Table 1). A family history of migraine was apparent in 59.3% patients (Table 1). The prevalence of photophobia and osmophobia in association with migraine was 53.8% and 34.1%, respectively (Table 2).

Genotyping

The genotypic distributions of all subjects are presented in Table 3. Only the genotype distribution of the *ESR1 G594A* polymorphism was not consistent with the HWE of controls ($p < 0.001$). This may be because of methodological reasons such as the small sample size used in this non-population-based study.

Significant differences between patients with migraine with photophobia and controls for genotypic distributions of *MAOA T941G* [T (male) plus T/T (female) plus T/G (female) vs. G (male) plus G/G (female), $p = 0.007$] and *ESR1 G594A* (G/G plus G/A vs. A/A, $p = 0.001$) and *TNF-β G252A* (G/G vs. G/A plus A/A, $p = 0.048$) were observed (Table 3). No significant differences in genotypic distributions between patients with migraine with photophobia and controls were observed for polymorphisms of *5-HTTLPR, 5-HTTVNTR, 5-HT$_{2A}$ T102C, 5-HT$_{1B}$ G861C, MAOA VNTR, MTHFR C677T, ACE I/D, ESR1 G325C* and *DRD2 C939T* (Table 3). The genotypic distribution of *ESR1 G594A* was significantly different between patients with migraine with osmophobia and controls (Table 3).

Using an alpha error of 5%, post hoc analysis for *MAOA T941G* and *TNF-β G252A* polymorphisms in patients with photophobia showed that our sample size had a power of 0.77 (medium) and 0.51 (medium), respectively.

DISCUSSION

We present novel findings that gene polymorphisms for *MAOA T941G* and *TNF-β G252A* contribute to photophobia but not to osmophobia in patients with migraine. We have therefore identified two potential gene polymorphisms associated with the symptoms of migraine. In addition, we propose that different gene polymorphisms may underpin the pathophysiology of photophobia and osmophobia during migraines.

Ethnicity may influence the prevalence of photophobia and osmophobia symptoms in individuals with migraine. Consistent with previous studies performed in Asian populations[1,29,30], the Japanese patients

with migraine in our study had a lower frequency of photophobia (53.8%) compared with those in previous Western studies (approximately 90%)[3,4]. Numerous epidemiological studies performed in the Asia population have also reported on the prevalence of photophobia is approximately 20%–60% patients with migraine[1,29,30]. Thus, racial differences may have caused discrepancies in the pathophysiology of photophobia. In contrast, we found a similar frequency for osmophobia in our study (34.1%) compared with that in Western studies (20%–40%) [5-7]. A relatively high proportion of Japanese patients with migraine (63%) were found to have concurrent osmophobia[2], although the reason for this is unclear.

Serotonergic mechanisms may play an important role during migraines. Headache may be initiated by low plasma 5-HT levels and associated vasodilation, which is known to be one of the origins of headache. Depletion of tryptophan, a precursor of 5-HT, increases not only headache but also the occurrence of photophobia [10]. In addition, tryptophan demonstrated suppressive effect in a feline model of photosensitive epilepsy [31]. Thus, serotonergic mechanisms may play important roles in either epilepsy or migraine. Oxidase deamination of 5-HT is catalysed by MAOA, and MAOA is located on the X chromosome at Xp.11.3-Xp11.4 [32]. Several polymorphisms, including *MAOA T941G* and *MAOA VNTR*, have been identified in the MAOA coding sequence [19,33]. Although the *T941G* polymorphism did not express a change in the coding protein, it is significantly associated with low (T) and high (G) catalyse activity [19]. The *MAOA T941G* polymorphism is associated with mood disorders, such as major depressive or bipolar disorders [34]; however, we could not find any report demonstrating the relation between *MAOA T941G* polymorphism and photophobia. Hotamisligil and Breakfield [21] showed that MAOA activity is lower in *T941 MAOA* polymorphisms than in *G941 MAOA* polymorphisms. In this study, we found that G and G/G polymorphisms are higher in patients with migraine with photophobia than in controls. Taken together, it is possible that serotonergic mechanisms contribute to photophobia, and it would be pertinent to determine whether plasma 5-HT levels are lower in patients with migraine with photophobia or in controls.

In this study, a genetic association of the G allele for *TNF-β G252A* polymorphism with photophobia was observed in patients with migraine. We had previously suggested that the *TNF-β G252A* gene polymorphism independently contributes to the onset of migraine [8]. Asuni et al. [27] also reported that the G allele for *G252A TNF-β* gene polymorphism is associated with MO. Abraham et al.[25] showed that the G allele is associated with a high TNF-α production in lymphoblastoid cell lines. Cytokines are important mediators of inflammatory pathways, and serum levels of pro-inflammatory cytokines such as TNF-α increase in patients during migraines [36]. Therefore, the *TNF-β G252A* polymorphism and increased production of TNF-α seem to be associated with photophobia during migraines. Because the *G252A* polymorphism of *TNF-β* is a silent mutation, the *TNF-β G252A* gene polymorphism may have linkage disequilibrium with other functional mutations.

Although osmophobia often occurs with photophobia during a migraine, we found no association of gene polymorphisms and osmophobia in patients with migraine. Liu et al.[11] reported that female patients with migraine with the CT genotype of *MTHFR C677T* are more likely to suffer from osmophobia compared with male patients. However, we did not find any gender differences in the *MTHFR C677T* genotypic distribution between patients with migraine with osmophobia and controls. Future studies are needed to collect more subjects and determine the pathogenesis of osmophobia in patients with migraine.

The sample size is the biggest limitation of this study. Since the distribution of MA in this study population (26.4%) seems higher than the distribution of MA in Asian population (12.0%-12.5%) [1,37], the distribution of MA is yet another limitation. However, we could find that that *MAOA T941G* and *TNF-β G252A* gene polymorphisms are associated with photophobia in patients with migraine. These findings are consistent with our previous report that gene polymorphisms are important in the pathogenesis of migraines [8]. Future studies using larger population samples are required to determine the pathogenesis of photophobia and osmophobia in individuals suffering from migraine.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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