

Genetic Contribution of Catechol-*O*-methyltransferase Polymorphism in Patients with Migraine without Aura

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Background: Recent genetic association studies have investigated the possible genetic role of the dopaminergic system in migraine. Catechol-*O*-methyltransferase (COMT) is an enzyme that plays a crucial role in the metabolism of dopamine and its genetic polymorphism is associated with three- to fourfold variation of enzymatic activity.

Objectives: The objective of this study was to elucidate the role of the COMT polymorphism in the genetic susceptibility to migraine and its phenotypic expression in patients with migraine without aura (MWOA).

Methods: Ninety-seven patients with MWOA and 94 healthy volunteers were included in the study. After amplifying COMT genes by the polymerase chain reaction, we assessed their genotype frequencies and allele distributions by based on restriction fragment length polymorphisms. We classified all MWOA patients into two groups according to their COMT genotype: with the L allele ($N = 43$), and without this allele ($N = 54$).

Results: The genotype frequency and allele distribution of the COMT polymorphism did not differ between MWOA patients and the control group. During migraine attacks, MWOA patients with the L allele showed a higher pain intensity of headache ($P = 0.001$) and a higher incidence of the accompanying nausea/vomiting (94% vs 75%; $P = 0.026$) compared with MWOA patients without the L allele.

Conclusions: Although the COMT polymorphism does not appear to be involved in predisposition to the development of MWOA, this genetic factor could be involved in the phenotypic expression of MWOA.

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Key Words : Catechol-*O*-methyltransferase, Migraine without aura, Polymorphism, Dopamine

INTRODUCTION

Many investigators have reported that dopaminergic neurotransmission is altered in migraineurs.¹⁻⁴ The frequency and severity of attacks in migraineurs decreases after the development of Parkinson's disease, and serum levels of dopamine increase in patients with migraine without aura (MWOA).^{5,6} Clinical trials involving treatment with dopamine receptor antagonists for migraine provide strong evidence for the involvement of dopa-

mine.^{7,8} The accompanying symptoms during the migraine attack (nausea, vomiting, dizziness, and orthostatic faintness) may be related to dopaminergic activation.⁹⁻¹¹

Migraine shows strong familial aggregation and presumably has a genetic basis, but the type and number of genes involved are currently unclear.¹²⁻¹⁴ Recent genetic association studies have investigated the possible genetic role of the dopaminergic system in migraine. Catechol-*O*-methyltransferase (COMT) is an enzyme that inactivates catecholamines or catechol-containing drugs. The gene encoding for COMT has been mapped to chromosome

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22q11.¹⁵ Several studies indicate that the genetic polymorphism due to a G→A substitution at codon 158 of the COMT gene, leading to a valine-to-methionine substitution, results in differences in COMT activity: a valine at codon 158 results in a heat-stable, high-activity COMT variant, whereas a methionine at this position results in heat-labile, low-activity variants.^{16,17} The potential role of this functional polymorphism of COMT in Parkinson's disease and other neuropsychiatric disorders, including schizophrenia and bipolar affective disorders, has already been investigated.¹⁷⁻²⁰ However, few studies have examined the association between COMT polymorphisms and migraine.²¹ Moreover, no study has investigated the phenotypic expression of dopamine-related accompanying symptoms.

We therefore investigated the possible role of COMT enzyme polymorphism in the genetic susceptibility to migraine and its phenotypic expression.

SUBJECTS AND METHODS

Subjects

All subjects included in this study were identified from a larger pool of subjects involved in an ongoing prospective study of the genetic contribution to headache at the headache clinic of the Catholic university of Korea. Ninety-seven patients with MWOA consecutively recruited from the headache clinic, and 94 healthy normal subjects without MWOA agreed to participate in this study. None of the participants were from the same family. The migraine patients and healthy control group were closely age matched. Given the known effects of gender on this gene system, only women were included in this study. This study was approved by the institutional ethical committee of our institute, and written informed consent was obtained from all participating subjects.

All participants were interviewed clinically and examined physically and neurologically by an experienced neurologist. Psychiatric interviews were performed by a psychiatrist, and patients with personality or major psychiatric disorders were excluded according to DSM-IV

criteria. During the interview, detailed data were obtained regarding clinical symptoms and headache variables using a structured questionnaire. The diagnosis of MWOA was made based on the operational diagnostic criteria of the International Headache Society (ICHD-II [International Classification of Headache Disorders]).²² We did not include patients suffering migraine with aura, because there were too few of them in the pool of subjects from which they were selected.

Determination of the COMT genotype

Blood samples were collected into heparinized tubes and stored at -80°C before isolation of DNA. Genomic DNA was isolated and amplified by the polymerase chain reaction (PCR) using the specific oligonucleotide primers 5'-CTC ATC ACC ATC GAG ATCAA-3' and 5'-GAT GAC CCT GGT GAT GTGG-3'. PCR reaction mixtures contained 50 ng of genomic DNA, 50 pmol of each primer, 10 mM Tris-HCL, 50 mM KCl, 50 mM MgCl₂, 0.01% Tween 20, each of dATP, dCTP, dGTP, and dTTP at 0.2 and 2.5 units of *Taq* polymerase in a total volume of 100 μL. The following cycling conditions were used: (1) an initial denaturation at 95°C for 3 min; (2) three cycles of denaturation at 94°C for 30 s, touch-down annealing at 65°C for 1 min, and synthesis at 72°C for 1 min; (3) 34 cycles of denaturation at 94°C for 30 s, annealing at 63°C for 1 min, and synthesis at 72°C for 1 min; and (4) a final extension at 72°C for 10 min. PCR was conducted in a thermal cycler (BioRad, Richmond, California).

The resulting PCR products were subjected to restriction digestion for 3 h at 37°C using 5 U *Nla*III (New England BioLabs, Beverly, Massachusetts). The digested products were separated at 150 V for 2 h on a 4% NuSieve 3:1 agarose gel (FMC Bio-Products, Rockland, Maine) containing 0.5 g/mL ethidium bromide. The gel was visualized under UV light using a gel electrophoresis visualization system (Vilber Lourmat, Marne La Vallée, France). The COMT-Met/Met genotype (L/L) was represented by 54-, 67-, and 71-bp fragments, COMT-Met/Val (L/H) by 54-, 71-, and 85-bp fragments, and COMT-Val/Val (H/H) by 54-, 67-, 71-, and 85-bp fragments. The 18-bp fragment was

Table 1. Distributions of genotypes and allele frequencies of the catechol-*O*-methyltransferase (COMT) polymorphism in patients with migraine without aura (MWOA) and in controls

Subject group	Genotype distribution (%)			Allele frequency (%)			
	<i>N</i>	L/L (Met/Met)	L/H (Met/Val)	H/H (Val/Val)	<i>N</i>	L (Met)	H (Val)
MWOA	97	6 (6%)	37 (38%)	54 (56%)	194	49 (25%)	145 (75%)
Control	94	9 (10%)	38 (40%)	47 (50%)	188	56 (30%)	132 (70%)

Genotype distribution: $\chi^2 = 1.05$ (two degrees of freedom), $P = 0.059$

Allele frequency: $\chi^2 = 0.983$ (one degree of freedom), $P > 0.05$

difficult to visualize because of both its small size and its comigration with the similarly sized primer residue; however, detection of this fragment was not critical to determining the genotypes. Genotyping was based upon independent scoring of the results by two reviewers who were unaware of the case/control status.

Associations of migraine phenotypes with COMT genotypes

We classified all patients with MWOA into two groups according to their COMT genotype: those with the L allele ($N = 44$, L/L and L/H genotype) and those without this allele ($N = 53$, H/H genotype). The physical variables of the patients' headaches were evaluated according to the pain index of headache intensity, as measured on a visual analog scale (scale anchored with 0 and 10, where 0 means no pain at all and 10 means pain as bad as it can be), the headache frequency (per month), and the duration of each headache attack (hours) during the previous 6 months. Clinical manifestations associated with MWOA (location, quality, aggravation by activity, nausea/vomiting, phonophobia/photophobia, and dizziness) were assessed during this evaluation. Photophobia and phonophobia (0, at least one present; 1, both present) as well as nausea and vomiting (0, not present; 1, at least one present) were combined into a single index variable for later analysis.

Data analysis

Comparisons of genotype distribution and allele frequency were performed on raw frequencies using a chi-squared test. A chi-squared analysis of the Hardy-

Weinberg equilibrium for the genotypes was conducted to determine whether the allele frequencies were stable within the patients and controls. Comparisons of clinical symptoms and physical variables of migraine according to the COMT allele were performed using the *t*-test for parametric variables and the chi-squared test for non-parametric variables. SPSS statistical software (version 10.0; SPSS, Chicago, Illinois, USA) was used for all the analyses, with a probability value of $P < 0.05$ considered significant.

RESULTS

The genotype distributions in patients with MWOA and controls did not deviate from those expected based on the Hardy-Weinberg equilibrium. Table 1 indicates that the COMT genotype distribution and allele frequencies did not differ significantly between MWOA patients and controls.

The pain intensity of headache was significantly higher in patients with the L allele than in those without this allele. Variables including the headache frequency and duration of headache attack did not differ significantly between the two groups (Table 2). Nausea or vomiting accompanying migraine attacks was more frequent in patients with L allele than in those without this allele (94% vs 75%, $P = 0.026$). Although the tendency to experience dizziness during a migraine attack was higher in patients with the L allele than in those without this allele (63% vs 47%), the difference was not statistically significant (Table 2).

Table 2. Clinical symptoms of patients with MWOA according to their COMT polymorphism

Characteristic	Total	MWOA with L allele	MWOA without L allele	<i>P</i>
Number of subjects	97	43	54	
Headache frequency (per month)	5.42±3.03	5.42±2.76	5.43±3.27	> 0.05
Duration of each attack (hours)	14.32±8.81	15.20±8.43	13.58±9.17	> 0.05
Average intensity of pain (VAS)	8.18±1.70	8.96±1.11	7.52±1.84	0.001
Incidence of symptoms				
Unilateral headache	61%	64%	60%	> 0.05
Throbbing pain	82%	85%	79%	> 0.05
Nausea/vomiting	84%	94%	75%	0.03
Phonophobia/photophobia	44%	46%	43%	> 0.05
Dizziness	54%	63%	47%	> 0.05

VAS; visual analog scale

Table 3. Summary of association studies investigating dopamine-related genes in migraine

Gene	Migraine type	Sample size	Significance	Source
DRD ₂	MWA	52	<i>P</i> < 0.005	Peroutka et al. ²⁴
	MWOA	77	NS	
	MWOA	22	<i>P</i> = 0.004	Del Zompo et al. ²⁵
	MWA/MWOA	102	NS	Dichgans et al. ²⁶
	MWA/MWOA	177	NS	Lea et al. ²⁷
DRD ₁	MWA/MWOA	262	NS	Shepherd et al. ²⁸
DRD ₃	MWA/MWOA	252	NS	Shepherd et al. ²⁸
	MWOA	50	NS	Del Zompo et al. ²⁵
DRD ₄	MWOA	50	NS	Del Zompo et al. ²⁵
	MWOA	202	<i>P</i> < 0.002	Mochi et al. ²⁹
	MWA	186	NS	
DRD ₅	MWA/MWOA	273	NS	Shepherd et al. ²⁸
DβH	MWA/MWOA	284	<i>P</i> = 0.006	Lea et al. ²⁷
	MWA/MWOA	284	NS	
	MWA/MWOA	388	NS	Mochi et al. ²⁹
DAT	MWA/MWOA	388	NS	Mochi et al. ²⁹
MAO-A	MWA/MWOA	119	NS	Marziniak et al. ³¹
	MWOA	80	<i>P</i> = 0.042	Filic et al. ³⁰
MAO-B	MWOA	80	NS	
COMT	MWA/MWOA	62	<i>P</i> = 0.013	Ermin Erdal et al. ²¹
	MWOA	97	NS	Present study

DRD; dopamine receptor gene, DβH; dopamine beta hydroxylase gene, DAT; dopamine transporter gene, MAO; monoamine oxidase gene, MWA; migraine with aura

NS; *P* > 0.05

DISCUSSION

Interest in the contribution of dopaminergic pathways to migraine biogenesis stems from reports of the induction of migraine by dopaminergic agonist at doses

that do not appear to affect nonmigraineurs.^{10,23} Migraine association studies investigating dopamine-related candidate genes have produced some interesting but as yet inconclusive results (Table 3).^{21,24-31} A recent analysis of the association between COMT polymorphism and migraine in a Caucasian population revealed that the

frequency of the L/L genotype was higher in migraine patients.²¹ However, in the present study we found no differences in the genotype distribution and allele frequency of the COMT polymorphism between patients with MWOA and controls. The interactions of the dopaminergic system are complex, and the control of dopamine activity may be determined by various enzymes involved in dopamine metabolism. Therefore, this possibility could be considered in addition to ethnic differences.³²⁻³⁶

In this study, the pain intensity of headache was higher and the associated nausea and/or vomiting was more common in patients with the L allele. The higher dopaminergic activity could presumably result from the COMT activity being lower in individuals with the L allele than in those without this allele. With regard to migraine headache, basal ganglia and dopaminergic neurotransmission are well known to be involved in the regulation of nociception.³⁷ Administration of L-dopa facilitates the perception of pain in rats, and L-dopa agonists can induce pain in Parkinson's patients.^{38,39} Dopamine antagonists are commonly and successfully used to reduce pain intensity of headache in acute migraine, which is additional to their antiemetic effect.^{7,8,40,41} Symptoms accompanying migraine, such as nausea, vomiting, and dizziness, may be mediated by dopaminergic activation.⁹⁻¹¹ Different expression of the D₂ family receptor in the brainstem has been frequently reported in patients with migraine, which may be due to these receptors regulating visceral function, including gastrointestinal motility and blood pressure.^{42,43} D₂, D₃, and D₄ receptors have been detected in intermediate and medial subnuclei among the nucleus of the solitary tract and in the dorsal motor nucleus of the vagus. D₃ receptors are also found in the area postrema. Peripheral D₂ receptors are located presynaptically on sympathetic nerves and ganglia, and may be the mechanism by which dopaminergic stimulation induces dizziness or orthostatic hypotension.⁴⁴ Del Zompo, et al. studied genetic aspects of dopamine receptor polymorphism in migraine patients, and considered that "dopaminergic migraineurs" - selected based on the presence of both nausea and vomiting during the pain phase of migraine - could be differentiated from "nondopaminergic

migraineurs".²⁵ In their study, although no association was detected between dopamine receptor polymorphism and migraine in the overall groups, the allelic distribution differed significantly according to the existence of dopaminergic symptoms.²⁵ Considering those studies, our results suggest that genetic factors of dopaminergic system are involved in the associated clinical manifestation of MWOA. The COMT polymorphism may be of potential pharmacological importance regarding individual differences in the metabolism of dopaminergic drugs in patients with MWOA. Moreover, antidopaminergic drugs may be useful as an antimigraine treatment in patients who are refractory to primary treatment and have prominent accompanying dopaminergic symptoms.

In conclusion, our results do not confirm an association of MWOA with the COMT gene, but they do suggest that allelic variation in COMT is involved in the phenotypic expression of migraine in some individuals.

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