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An Opposite-Direction Modulation of the *COMT* Val158Met Polymorphism on the Clinical Response to Intrathecal Morphine and Triptans

Sarah Cargnin,* Francesco Magnani,† Michele Viana,‡ Cristina Tassorelli,‡ Daniela Mittino,§ Roberto Cantello,§ Grazia Sances,‡ Giuseppe Nappi,‡ Pier Luigi Canonico,* Armando A. Genazzani,* William Raffaeli,† and Salvatore Terrazzino*

**Università del Piemonte Orientale "A. Avogadro," Dipartimento di Scienze del Farmaco and Centro di Ricerca Interdipartimentale di Farmacogenetica e Farmacogenomica (CRIFF), Novara, Italy.*
†Fondazione ISAL-Institute for Research on Pain, Torre Pedrera-Rimini, Italy.
‡Headache Science Centre, IRCCS "National Neurological Institute C. Mondino" Foundation, Pavia, Italy.
§Division of Neurology, Maggiore Hospital, Amedeo Avogadro University, Novara, Italy.

Abstract: **Genetic variation in the *COMT* gene is thought to have clinical implications for pain perception and pain treatment. In the present study, we first evaluated the association between *COMT* rs4680 and the analgesic response to intrathecal morphine in patients with chronic low back pain to provide confirmation of previously reported positive findings. Next, we assessed the relationship between rs4680 and headache response to triptans in 2 independent cohorts of migraine patients. In patients with chronic low back pain (n = 74), logistic stepwise regression analysis showed that age (odds ratio [OR]: .90, 95% confidence interval [CI]: .85–.96, *P* = .002) and the presence of the *COMT* Met allele (vs Val/Val, OR: .21, 95% CI: .04–.98, *P* = .048) were predictive factors for lower risk of poor analgesic response to intrathecal morphine. Intriguingly, in migraine patients, the *COMT* rs4680 polymorphism influenced headache response to triptans in the opposite direction. Indeed, in an exploratory cohort of migraine patients without aura (n = 75), homozygous carriers of the *COMT* 158Met allele were found at increased risk to be poor responders to frovatriptan when compared to homozygous patients for the Val allele (OR: 5.20, 95% CI: 1.25–21.57, *P* = .023). In the validation cohort of migraine patients treated with triptans other than frovatriptan (n = 123), logistic stepwise regression analysis showed that use of prophylactic medications (OR: .43, 95% CI: .19–.99, *P* = .048) and *COMT* Met/Met genotype (vs Val/Val, OR: 4.29, 95% CI: 1.10–16.71, *P* = .036) were independent risk factors for poor response to triptans.**

Perspective: ***This study highlights the importance of* COMT *rs4680 in influencing the clinical response to drugs used for chronic pain, including opioid analgesics and triptans. These findings also underline a complex relationship between* COMT *genotypes and pain responder status.***

Key words: *Low back pain, morphine, migraine, triptans, response,* COMT *polymorphism.*

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Address reprint requests to Salvatore Terrazzino, PhD, Università del Piemonte Orientale "A. Avogadro," Dipartimento di Scienze del Farmaco and Centro di Ricerca Interdipartimentale di Farmacogenetica e Farmacogenomica (CRIFF), Largo Donegani, 2, 28100 Novara, Italy. E-mail: terrazzino@pharm.unipmn.it

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The catechol-O-methyltransferase (COMT) enzyme metabolizes catecholamines such as dopamine, adrenaline, and noradrenaline that are involved in modulation of pain.[35,36,57] Genetic variation in the *COMT* gene may therefore contribute to the interindividual variability in human pain phenotypes such as pain sensitivity, chronicity, severity, and response to analgesics.[1,19] The rs4680 G >A variant (Val158Met) in the *COMT* gene causes a substitution from a valine (Val) to a methionine (Met) at amino acid position 158, leading to a 3- to 4-fold reduced enzymatic activity and higher dopamine availability (Met/Met >Val/Met >Val/Val).[5,26]

The *COMT* rs4680 variant has been shown to influence efficacy of morphine used for cancer pain, for which the Met/Met genotype group needs lower morphine doses than the Val/Val genotype group,[28,41,43] possibly explained by an increased density of μ-opioid receptors in Met/Met genotype individuals.[4,58] However, some other reports were unable to demonstrate an involvement of rs4680 on the opioid dose requirement in cancer patients.[20,25] Failure to confirm such an association may be explained by several confounding factors that are inherent features of these studies on cancer patients, including the presence of both neuropathic and somatic pain. Hence, pharmacogenetic studies in noncancer patients may contribute to clarify the relationship between rs4680 and the analgesic response to opioids.

Dopaminergic system hypersensitivity has been suggested in the pathogenesis of migraine on the basis of pharmacologic evidence supporting the clinical use of dopamine antagonists in the treatment of acute migraine, either as an adjunct treatment for nausea or for migraine itself.[7,27] Although rs4680 does not appear to be involved in the predisposition to migraine,[51] this genetic factor has been involved in the phenotypic expression of migraine without aura (MwoA), with 158Met-allele carriers displaying a higher pain intensity of headache and a higher incidence of the accompanying nausea/vomiting compared to MwoA patients without 158Met allele.[32] Therefore, it is possible that interindividual differences in *COMT* activity might influence efficacy of drugs used for the treatment of migraine pain, including the triptan class of serotonin 5-HT1 B/1D receptor agonists.[11,50] Although controversial results have been reported on the role of the DRD2 NcoI polymorphism in the variability in the therapeutic effects of triptans,[3,16,53] no data are available as to whether an increased dopaminergic tone, as expected in *COMT* Met/Met individuals, might affect headache response to triptans in migraine sufferers.

In the present study, we assess the value of *COMT* rs4680 as a predictive factor for the response to opioids or triptans, 2 classes of medication used to assist in the management of chronic pain. More specifically, we evaluated the association between rs4680 and the analgesic response to intrathecal morphine in patients with chronic low back pain to provide confirmation of previously reported positive findings, whereas the relationship between rs4680 and headache response to triptans was assessed in 2 independent cohorts of migraine patients: 1 exploratory cohort of exclusively MwoA patients treated with frovatriptan and 1 validation cohort of migraine patients treated with other types of triptans.

Methods

Patients With Persistent Chronic Low Back Pain

Patients suffering from chronic low back pain who received intrathecal morphine were enrolled in this study at the Pain Therapy and Palliative Care Unit of Rimini Hospital. The study was approved by the local ethics committees. These patients received intrathecal morphine as a trialing method to evaluate suitability to having an intrathecal drug delivery system implanted.[9,23,38,39] A total of 74 subjects were enrolled between 2008 and 2012 according to the following inclusion/exclusion criteria. Inclusion criteria: 1) patient able to read, understand, and voluntarily sign the informed consent to participation before undergoing any procedure for the study; 2) patient age 18 years or older at study entry; 3) patient affected by chronic low back pain secondary to spinal stenosis and failed back surgery, and eligible to receive implantation of an intrathecal drug delivery system[9,23,38,39]; and 4) patient receiving an intrathecal morphine trialing protocol at a dose of .030 mg. Exclusion criteria: 1) patient who is pregnant or breast-feeding; 2) patient who received an investigational drug within 30 days prior to screening; 3) patient with a known hypersensitivity to opioid drugs; 4) patient for whom the use of opioid analgesia is contraindicated; 5) patient with a preexisting history of psychosis; and 6) patient with a history of drug addiction.

Pain levels were assessed using a visual analog scale (VAS) of 0 to 10 (0 = no pain, 10 = worst pain possible) based on patient self-report at the time of initial assessment (baseline), and at 1 hour after intrathecal administration of morphine. The intrathecal administration of .03 mg of morphine has been previously demonstrated to be effective in inducing pain relief in patients with chronic noncancer pain.[14,40] The presence of side effects commonly associated with opioids was also assessed. Patients were considered good responders to intrathecal morphine if pain reduction was ≥60%, moderate responders if it was ≥40% and <60%, and poor responders if pain reduction was <40%.

Patients With Migraine Pain

A total of 198 Caucasian migraine outpatients of the Novara and Pavia headache centers were enrolled in the study. Patients were diagnosed by 2 neurologists (M.V. and D.M.) after neurological examination and direct interview according to the diagnostic criteria set by the International Headache Society (Headache Classification Subcommittee of the International Headache Society [IHS], 2004) for migraine without aura (MwoA) (IHS code 1.1) and migraine with aura (MwA)—typical aura with migraine headache (IHS code 1.2.1). Exclusion criteria were a headache that fulfilled the diagnostic criteria for a probable medication overuse headache (IHS code 8.2.7) and contraindication to triptan use. Tension-type headache patients and patients with double diagnosis were not enrolled in this study. In the first visit, patients were prescribed 1 of the 6 triptans commercially available in Italy according to the clinician's judgement and were given a diary in which to record the clinical response to the drug in 3 consecutive migraine attacks. If indicated, they were also prescribed a migraine prophylactic therapy. For each of the migraine attacks, the patient was asked to record in the diary the intensity of pain (on a scale from 0 to 3, ie, 0 = absent

pain, 1 = mild pain/no disability, 2 = moderate pain/partial disability, and 3 = severe pain/total disability) at the moment of the triptan intake and after 120 minutes, and the presence and intensity (on a scale from mild to severe) of side effects. The second visit took place after 3 attacks. Good responders were defined as the migraine patients who experienced a ≥2-point reduction in a 4-point scale intensity of pain from 3 (severe) to 0 (absent) 2 hours after triptan administration in at least 2 attacks out of the 3[54]; otherwise, patients were defined as poor responders.

This study was approved by the ethics committees of the institutions involved (Istituto C. Mondino Pavia and Ospedale Maggiore della Carità, Novara) and it met the requirements of the Declaration of Helsinki. Informed consent was obtained from all patients before participation in the study.

COMT *Val158Met Genotyping*

Genomic DNA was extracted from peripheral blood by using the QiaAmp DNA Mini Kit (Qiagen, Valencia, CA). Polymerase chain reactions (PCRs), conducted in a total volume of 30 μL containing 100 ng of genomic DNA, were performed using .4 μM of each couple of the following primers: Fw: 5′-TCG TGG ACG CCG TGA TTC AGG-3′; Rev: 5′-AGG TCT GAC AAC GGG TCA GGC-3′. After 33 cycles of PCR amplification (denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, extension at 72°C for 30 seconds), amplification products of 217 bp in length were electrophoresed in 2% agarose gel and visualized after staining with ethidium bromide. The PCR products (10 μL) harboring the single-nucleotide polymorphisms were digested overnight at 37°C by 2 U of NlaIII (New England Biolabs, Milano, Italy). Wild-type *COMT* Val/Val was characterized by 136, 81 bp fragments, heterozygotes (Val/Met) by 138, 96, 81, and 40 bp fragments, and homozygotes for the Met allele (Met/Met) by 96, 81, 40 bp sized fragments. All PCR reactions were set up in a dedicated PCR area with dedicated pipettes and reagents. For quality control purposes, each PCR and restriction enzyme digestion included negative as well as positive controls. For validation, about 10% of the samples were re-genotyped. The results were reproducible, with no discrepancies in genotyping.

Statistical Analysis

Data were summarized and presented in the form of mean, standard deviation, and percentage as descriptive statistics. The Hardy-Weinberg equilibrium was verified in each patient cohort using the chi-square test as implemented in the Finetti program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Patients were dichotomized in 2 groups on the basis of drug response status: responders (good and moderate) and poor responders. In a preliminary analysis, the Armitage test for linear trend in proportions was performed on genotype frequency data to assess the dosage effect of possessing 0, 1, or 2 copies of the Met allele (ie, an additive effect) on drug responses rates (analgesic response to intrathecal morphine or headache response to triptans). Next, the magnitude of the effect (effect size) of categorical or continuous variables (age) on the risk of poor drug responses was evaluated by unconditional logistic regression analysis (univariate analysis). Odds ratios (ORs) and their 95% confidence intervals (CIs) were used as estimates of relative risk. Finally, a binary logistic regression model, weighted for multilevel data and with forward stepwise selection of the variables (with input *P* values set at .15), was tested to investigate the dependence of drug response status on a set of explanatory variables. A $P < .05$ was considered statistically significant. All clinical and genotype data were managed with the statistical software package SYSTAT for Windows (version 12; Systat Software Inc, Chicago, IL).

Results

Analgesic Response to Intrathecal Morphine in Patients With Chronic Low Back Pain

Of the 74 patients with persistent chronic low back pain (age, 60.7 ± 16.1 years), 34 (45.9%) were males and 40 (54.1%) females (Table 1). The percentages of patients with good, moderate, and poor analgesic response to intrathecal morphine were 74.3%, 9.5%, and 16.2%, respectively. Distribution of *COMT* genotypes (Val/Val: n = 19; Val/Met: n = 44; Met/Met: n = 11) was in Hardy-Weinberg equilibrium ($P = .08$). The analgesic response rate according to *COMT* Val/Met genotype distribution is presented in Fig 1A. The analysis on dichotomized responses (good and moderate vs poor response) showed a significant better response across the 3 genotypes according to the number of copies of the Met allele carried (Armitage trend test; $P = .018$) with 100% of the patients with Met/Met experiencing response (good or moderate) to intrathecal morphine compared to 68.4% of responders in patients with Val/Val genotype ($P = .037$). As none of the patients with Met/Met responded poorly to intrathecal morphine, Val/Met and Met/Met genotypes were combined to estimate the impact of *COMT* genotypes on the risk of poor intrathecal morphine response. The univariate logistic regression analysis (Table 1) showed that patients with poor response to intrathecal morphine differed from responders (good or moderate) for younger age (OR: .91, 95% CI: .86–.96, $P = .001$) and lower frequency of the Met allele compared to Val/Val genotype (OR: .26, 95% CI: .07–.96, $P = .043$). Given that *COMT* activity may be under hormonal control[17,56] and our cohort was composed of a similar proportion of males and females, we conducted separate analyses for each gender. The sex-specific analysis of the data showed a trend in both male and female carriers of the Met allele toward a lower risk to be poor responders to intrathecal morphine (Table 1), but in both groups the effect of *COMT* genotype did not reach statistical significance, probably because of the small number of patients. The 2-way analysis of covariance adjusted for age revealed that the interaction between *COMT* genotype (Met

Table 1. Logistic Regression Analysis Evaluating the Association Between *COMT* rs4680 and Clinical Variables With Analgesic Response to Intrathecal Morphine

Variable	Total Patients N = 74 (%)	Responders (Good or Moderate) n = 62 (%)	Poor Responders n = 12 (%)	OR (95% CI)	P value
Univariate analysis					
Sex					
Female	40 (54.1)	33 (53.2)	7 (58.3)	1	
Male	34 (45.9)	29 (46.8)	5 (41.7)	.81 (.23–2.84)	.745
Age at study entry (years), mean ± SD	60.7 ± 16.1	63.8 ± 14.4	44.4 ± 15.4	.91 (.86–.96)	.001
COMT rs4680 (total sample)					
Val/Val	19 (25.7)	13 (21.0)	6 (50.0)	1	
Val/Met	44 (59.5)	38 (61.3)	6 (50.0)		
Met/Met	11 (14.9)	11 (17.7)	0 (0)	.26 (.07–.96)*	.043
COMT rs4680 (females only)					
Val/Val	11 (27.5)	8 (24.2)	3 (42.9)	1	
Val/Met	21 (52.5)	17 (51.5)	4 (57.1)		
Met/Met	8 (20.0)	8 (24.2)	0 (0)	.43 (.08–2.32)*	.325
COMT rs4680 (males only)					
Val/Val	8 (23.5)	5 (17.2)	3 (60.0)	1	
Val/Met	23 (67.6)	21 (72.4)	2 (40.0)		
Met/Met	3 (8.8)	3 (10.3)	0 (0)	.14 (.02–1.06)*	.057
Multivariate stepwise logistic regression analysis					
Age				.90 (.85–.96)	.002
*COMT*_Met allele carriers vs Val/Val				.21 (.04–.98)	.048

NOTE. Some percentages may not add up to 100% because of rounding.
*Met allele carriers vs Val/Val.

carriers vs Val/Val) and gender on the analgesic response to intrathecal morphine was not significant ($P = .515$). In the logistic stepwise regression analysis (Table 1), age (OR: .90, 95% CI: .85–.96, $P = .002$) and the presence of the *COMT* Met allele (vs Val/Val, OR: .21, 95% CI: .04–.98, $P = .031$) were selected as significant independent predictors for lower risk of poor analgesic response to intrathecal morphine.

Headache Response to Frovatriptan in Patients Without Aura (MwoA)

Demographic and clinical data of MwoA patients treated with frovatriptan, in the overall cohort (n = 75) and after stratification for headache response status, are shown in Table 2. Eighty-four percent of the study population was female (63/75), the average age in the cohort was 40.9 years ± 11.3, and 56% of patients (42/75) used prophylactic medications. Thirty-four of the 75 patients (45.3%) were poor responders to frovatriptan. Distribution of *COMT* genotypes was in accordance with Hardy-Weinberg equilibrium ($P = .72$). Sex, age, and use of prophylactic medications were similarly distributed between good and poor responders to frovatriptan ($P = .78$, $P = .31$, $P = .36$, respectively). The headache response rate of MwoA patients to frovatriptan after stratification for *COMT* Val/Met genotypes is shown in Fig 1B. The Armitage trend test showed a significant worse headache response across the 3 genotypes according to the number of copies of the Met allele carried ($P = .017$), and 31.6% of migraine patients with Met/Met experienced response to frovatriptan, whereas the response rate was higher in the Val/Val group (70.6% of responders, $P = .019$). In the univariate analysis (Table 2), homozygous carriers of the *COMT* 158Met allele were found at increased risk to be poor responders to frovatriptan when compared to homozygous patients for the Val allele (OR: 5.20, 95% CI: 1.25–21.57, $P = .023$). Similar results were obtained when analysis was restricted to women. The relationship between rs4680 polymorphism and poor response to frovatriptan remained significant after adjustments for sex, age, and use of prophylactic medications (Met/Met vs Val/Val, OR: 5.73, 95% CI: 1.33–24.67, $P = .019$).

Headache Response to Other Triptans in Migraineurs

In order to validate the generality of our findings, we studied an independent cohort of migraine patients treated with triptans other than frovatriptan. Demographic and clinical data of the second cohort of migraine patients (n = 123) are shown in Table 3. Seventy-seven percent of the study population was female (95/123), and the average age in the cohort was 38.3 years ± 10.2, 90.2% of whom were affected by MwoA and 9.8% by MwA. The triptans prescribed were rizatriptan (n = 34), eletriptan (n = 34), almotriptan (n = 25), sumatriptan (n = 21), and zolmitriptan (n = 9). Sixty-five of 123 patients (54.2%) were on prophylactic medication, whereas for 3 patients the data on the use of preventive medication were lacking. Poor response to triptans was observed in 30.1% of migraine patients (37/123). The genotype frequency distribution of rs4680 was in accordance with Hardy-Weinberg

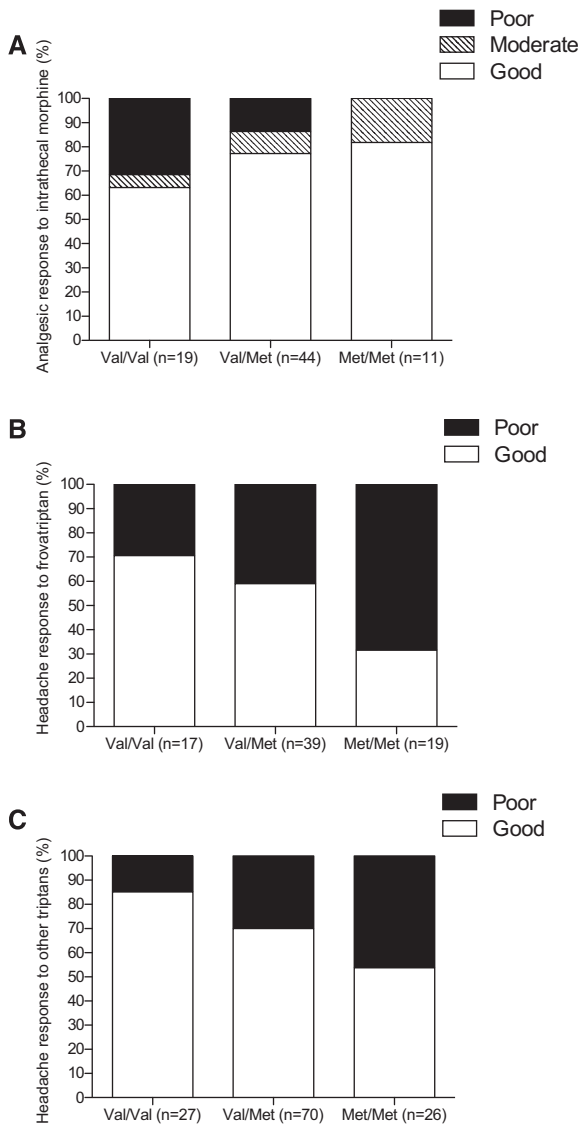

Figure 1. **(A)** Analgesic response rate to intrathecal morphine according to *COMT* Val158Met genotype distribution in patients with chronic low back pain. Comparison of responders (good and moderate) with Armitage trend test across the 3 genotypes ($P = .018$). **(B)** Headache response rate to frovatriptan according to *COMT* Val158Met genotypes in migraine patients without aura (Armitage trend test across the 3 genotypes, $P = .017$). **(C)** Headache response to triptans other than frovatriptan in an independent cohort of migraineurs (Armitage trend test; $P = .013$).

equilibrium expectations ($P = .12$). Fig 1C shows headache response rates after stratification for the *COMT* Val/Met genotypes, in the validation cohort of migraine patients. The analysis revealed again a significantly worse headache response across the 3 genotypes according to the number of copies of the Met allele carried (Armitage trend test, $P = .013$); that is, 53.8% of the patients with Met/Met experienced response to triptans other than frovatriptan, whereas the response rate was higher in the Val/Val genotype (85.5% of responders, $P = .013$). In the univariate analysis (Table 3), patients undergoing prophylactic treatment (n = 120) were found to be at lower risk to be poor responders, as compared to patients who were not on prophylactic treatment (OR: .44, 95% CI: .2–.99, $P = .046$). All other demographic and clinical variables considered were similarly distributed when comparing good and poor responders to triptans (Table 3). In addition, homozygous carriers of 158Met allele were more frequently poor responders to triptans when compared to homozygous patients for the Val allele (OR: 4.93, 95% CI: 1.33–18.31, $P = .017$), and similar results were obtained when analysis was limited to women (Table 3). In the logistic stepwise regression analysis (Table 3), use of prophylactic medications (OR: .43, 95% CI: .19–.99, $P = .048$) and *COMT* Met/Met genotype (vs Val/Val, OR: 4.29, 95% CI: 1.10–16.71, $P = .036$) were selected as independent risk factors for poor response to triptans (Table 3).

Discussion

Experimental pain studies have consistently shown that individuals with low *COMT* activity have low tolerance to pain. For instance, healthy volunteers with the *COMT* Met/Met genotype displayed higher sensory and affective ratings of pain and a higher regional density of μ-opioid receptors in the brain as measured by ligand–positron emission tomography.[58] Moreover, in a functional neuroimaging study, homozygous subjects for the Met allele exhibited a higher blood oxygen level–dependent response in the anterior cingulate cortex to painful laser stimulation compared to carriers of the Val allele.[29] In chronic clinical pain, the effect of *COMT* on pain sensitivity and modulation has been suggested to depend on the pain conditions.[51] Indeed, in neuropathic and cancer-related pain, *COMT* variation does not play a large role,[2,41,45] whereas in chronic musculoskeletal pain and migraine, low *COMT* activity appears to increase incidence and/or pain symptoms.[19,32] On the other hand, the genetic background may also influence the analgesic response to various pharmacotherapies; however, the specific genetic variations underlying interindividual differences in analgesic drug responses remain poorly elucidated. As genetic variation in the *COMT* gene may have clinical implications not only for pain perception but also for pain treatment, in the present study we have addressed a possible contribution of rs4680 in the *COMT* gene to the individual variability in the response to morphine or triptans, 2 classes of medication used to control pain in patients with chronic low back pain and migraine, respectively.

Our results provide evidence in patients with chronic low back pain that rs4680 significantly influences the response to intrathecal morphine, with the analgesic outcome being inversely proportional to the enzyme activity: better response rate in patients with lower *COMT* activity (Met/Met) and worse response in patients with higher *COMT* activity (Val/Val). These results support a higher efficacy of intrathecal morphine therapy in patients with Met/Met genotype. Therefore, our findings are in the same direction of previous studies reporting that cancer patients with Met/Met genotype require less morphine than patients with

Table 2. Univariate Logistic Regression Analysis Evaluating the Association Between *COMT* rs4680 and Clinical Variables With Response to Frovatriptan in Migraine Patients Without Aura

Variable	Total Patients N = 75 (%)	Good Responders n = 41 (%)	Poor Responders n = 34 (%)	OR (95% CI)	P value
Sex					
Female	63 (84.0)	34 (82.9)	29 (85.3)	1	
Male	12 (16.0)	7 (17.1)	5 (14.7)	.84 (.24–2.92)	.781
Age at study entry (years), mean ± SD	40.9 ± 11.3	41.9 ± 11.1	39.3 ± 11.5	.98 (.94–1.02)	.309
Use of prophylactic medications					
No	33 (44.0)	20 (48.8)	13 (38.2)	1	
Yes	42 (56.0)	21 (51.2)	21 (61.8)	1.54 (.61–3.88)	.361
COMT rs4680 (total sample)					
Val/Val	17 (22.7)	12 (29.2)	5 (14.7)	1	
Val/Met	39 (52.0)	23 (56.1)	16 (47.0)	1.67 (.49–5.67)	.411
Met/Met	19 (25.3)	6 (14.6)	13 (38.2)	5.20 (1.25–21.57)	.023
COMT rs4680 (females only)					
Val/Val	13 (20.6)	10 (29.4)	3 (10.3)	1	
Val/Met	34 (54.0)	19 (55.9)	15 (51.7)	2.63 (.61–11.30)	.193
Met/Met	16 (25.4)	5 (14.7)	11 (37.9)	7.33 (1.38–38.88)	.019

NOTE. Some percentages may not add up to 100% because of rounding.

Val/Val genotype to achieve the same level of analgesia.[28,41,43]

The use of intrathecal drug delivery systems in chronic nonmalignant pain is indicated in those patients in whom traditional administration routes are poorly effective or in those who cannot tolerate high doses because of systemic side effects.[9,23,39] However, the efficacy of intrathecal morphine treatment is hampered by the large variability and unpredictability in individual response. Although the factors explaining variability in opioid efficacy are still largely unknown, clinical features and types of pain,[8,38] as well as polymorphisms in genes encoding drug targets,[47] drug metabolizing enzymes, and/or drug transporters,[48] have been suggested to contribute to the large interindividual variability in the efficacy of intrathecal morphine administration. At present, there is no agreement regarding the intraspinal screening method that will be most predictive of patients' long-term response to intrathecal morphine. Thus, given the results presented here, we propose that *COMT* Val158Met polymorphism should be evaluated further to investigate whether it can predict efficacy of chronic intrathecal morphine therapy.

We also provide for the first time evidence that allelic variation of the *COMT* rs4680 polymorphism affects headache response to triptans in patients with migraine pain. Intriguingly, the impact of rs4680 on headache response to triptans was in the opposite direction. Indeed, frovatriptan-treated patients with the Met/Met genotype showed a poorer headache response than patients with the Val/Val genotype, and similar results were obtained in a second cohort of migraine patients treated with other types of triptans. Altogether, our results highlight a role of rs4680 as response-modifying gene variant in relation to morphine or to triptan therapy. In addition, our study suggests that the *COMT* rs4680 variant, affecting catecholaminergic neurotransmission, may influence the individual response to different classes of drugs used for chronic pain, irrespective of their primary molecular target. The better response to opioids in Met/Met carriers has been previously explained by an increased amount of regional μ-opioid receptors[4,58] as a compensatory mechanism in response to lower content of enkephalin within the peripheral neurons of these individuals.[22,41] In contrast, the lower rate of response to triptans in migraineurs with Met/Met genotype is an entirely novel finding, for which data on possible molecular mechanisms are missing. We can speculate that in migraine subjects, the lower activity of *COMT* is associated with a reduced metabolization of catecholamines, such as norepinephrine and epinephrine, thereby leading to a potentiation of pain signaling through the downstream stimulation of β2- and β3-adrenergic receptor pathways.[31] The more aggressive phenotype described by Park et al[32] in Met/Met migraine patients may therefore represent a consequence of a genetic predisposition, and the poorer response to triptans just reflects the failure to control more intense attacks. Alternatively, a complex interplay between enhanced adrenergic and dopaminergic activity in different parts of the nociceptive system might explain the complicated actions of low *COMT*.[1,19] On the other hand, the possible contribution of *COMT* rs4680 in migraine pain therapy stems from reports supporting the usefulness of dopamine antagonists in the treatment of acute migraine, either as an adjunct treatment for nausea or for the migraine itself.[7,27,49] Given that *COMT* inactivates norepinephrine and dopamine, but not 5-hydroxytryptamine (5-HT), our data support the possibility that triptans are less effective in migraine patients with a higher catecholaminergic tone, as expected in patients with Met/Met genotype. Noteworthy is that the combination of sumatriptan with the dopaminergic antagonist metoclopramide has been reported to

Table 3. Logistic Regression Analysis Evaluating the Association Between *COMT* rs4680 and Clinical Variables With Response to Triptans Other Than Frovatriptan in Migraine Patients

Variable	Total Patients N = 123 (%)	Good Responders n = 86 (%)	Poor Responders n = 37 (%)	OR (95% CI)	P value
Univariate analysis					
Sex					
Female	95 (77.2)	68 (79.0)	27 (73.0)	1	
Male	28 (22.8)	18 (21.0)	10 (27.0)	1.40 (.57–3.41)	.461
Age at study entry (years), mean ± SD	38.3 ± 10.2	38.0 ± 10.3	38.8 ± 10.4	1.007 (.97–1.04)	.715
Diagnosis					
MwoA	111 (90.2)	79 (91.9)	32 (86.5)	1	
MwA	12 (9.8)	7 (8.1)	5 (13.5)	1.76 (.52–5.97)	.362
Triptan					
Rizatriptan	34 (27.6)	21 (24.4)	13 (35.1)	1	
Eletriptan	34 (27.6)	27 (31.4)	7 (18.9)	.42 (.14–1.23)	.115
Almotriptan	25 (20.3)	17 (19.8)	8 (21.6)	.76 (.26–2.26)	.621
Sumatriptan	21 (17.1)	13 (15.1)	8 (21.6)	.99 (.32–3.05)	.992
Zolmitriptan	9 (7.3)	8 (9.3)	1 (2.7)	.20 (.02–1.81)	.152
Use of prophylactic medications (n = 120)					
No	55 (45.8)	34 (40.0)	21 (60.0)	1	
Yes	65 (54.2)	51 (60.0)	14 (40.0)	.44 (.2–.99)	.046
COMT rs4680 (total sample)					
Val/Val	27 (22.0)	23 (26.7)	4 (10.8)	1	
Val/Met	70 (56.9)	49 (57.0)	21 (56.8)	2.46 (.76–8.00)	.134
Met/Met	26 (21.1)	14 (16.3)	12 (32.4)	4.93 (1.33–18.31)	.017
COMT rs4680 (females only)					
Val/Val	23 (24.2)	20 (29.4)	3 (11.1)	1	
Val/Met	52 (54.7)	38 (55.9)	14 (51.9)	2.46 (.63–9.56)	.195
Met/Met	20 (21.1)	10 (14.7)	10 (37.0)	6.67 (1.49–29.79)	.013
Multivariate stepwise logistic regression analysis					
Prophylaxis_Yes				.43 (.19–.99)	.048
*COMT*_Val/Met				2.27 (.69–7.51)	.180
*COMT*_Met/Met				4.29 (1.10–16.71)	.036

NOTE. Some percentages may not add up to 100% because of rounding.

provide relief in some migraine patients who failed to achieve adequate relief with a triptan alone.[46] It is therefore tempting to speculate that *COMT* rs4680 genotyping could be useful to identify patients at higher risk of poor response to triptan monotherapy who can benefit from a combination therapy (triptan + DRD2 antagonist).[34]

Although the similarities of 5-HT1B/1D receptor agonists outweigh their differences, important differences exist in the pharmacokinetic profile of triptans. For instance, bioavailability of oral formulations ranges between 14% (sumatriptan) and 69% (almotriptan), and their elimination half-life ranges from 2 hours (sumatriptan and rizatriptan) to 26 hours (frovatriptan).[37] In addition, the beneficial effect of triptans in patients with migraine may be related to their multiple mechanisms of action at peripheral and/or central sites implicated in the pathophysiology of migraine.[13] In this regard, triptans as a class display a poor blood-brain barrier penetration with brain-plasma partition coefficients ($K_{p,brain}$) well below 1, when compared with typical marketed central nervous system drugs (eg, diphenhydramine with a $K_{p,brain}$ of 9).[18,33] In contrast, the relatively hydrophilic triptan, sumatriptan, has been regarded either to be incapable of crossing the blood-brain barrier or to cross it to a lower extent than other triptans.[55] Given the wide variety of drug treatments received by migraine patients because of the naturalistic setting of our study, it was not possible to conduct a rigorous analysis of the possible differential effect of *COMT* rs4680 on headache response to the different triptans. However, it should be noted that the effect size of *COMT* genotype in patients treated with the long-acting triptan (frovatriptan) was similar to that observed in patients treated with the fast-acting triptans (eletriptan, rizatriptan, almotriptan, sumatriptan, and zolmitriptan). In addition, the significance of *COMT* genotype was retained in both univariate (Met/Met vs Val/Val, OR: 5.04, 95% CI: 1.87–13.60, $P = .001$) and fully adjusted multivariate analysis (Met/Met vs Val/Val, OR: 4.09, 95% CI: 1.43–11.67, $P = .008$), when patients receiving sumatriptan were excluded from the combined analysis of the 2 migraine cohorts.

We recognize some limitations in our study. First, the *COMT* Val158Met polymorphism alone cannot fully account for the variation in enzyme activity as *COMT* haplotypes have been shown to influence *COMT* function[30] and to explain the effects on pain perception or opioid efficacy to a greater extent than rs4680 alone.[10,42,52] In addition, rs740603 and haplotypes containing

single-nucleotide polymorphisms in intron 1, but not rs4680, have been associated with adverse effects of morphine.[45] Thus, further studies in larger populations in which *COMT* haplotype analyses can be better evaluated are required to replicate and extend the current findings. In addition, we also recognize that polymorphisms in other genes encoding for drug-metabolizing enzymes, drug transporters, or drug targets may be also involved in the individual variability of clinical response to opioids or triptans.[6,12,21,24,44] Therefore, approaches based on multiple genetic markers, along with demographic and clinical characteristics of patients, are required to characterize the joint effects of multiple genes in predicting the clinical response to opioid analgesics or triptans. Another potential limitation of this study is the absence of placebo-treated groups. Because we do not know the rate of nonspecific or non-drug-attributable responses, we cannot exclude the possibility that some patients in the responder group were subjected to a placebo effect, which in a very recent paper also has been observed with rs4680.[15] Nonetheless, given the confirmatory nature of the study conducted in morphine-treated patients and the consistent association that emerged in the exploratory/validation study of triptan-treated migraine patients, we feel that the presence of placebo groups may not have significantly affected our results. In addition, the observational design of the study conducted in triptan-treated patients reflects the conditions of migraine management in primary care, in which triptans are the first-line treatment and placebo is not used. Finally, given the limited number of male patients in our cohorts, larger studies are required to evaluate gender-specific effects of *COMT* Val158Met polymorphism on the efficacy of morphine or triptans.

In conclusion, the current results highlight the importance of *COMT* rs4680 genotype in influencing the clinical response to drugs used for chronic pain, including opioid analgesics and triptans. The opposite direction of rs4680's effect on the clinical response to these classes of drugs in 2 different pain conditions reveals a complex relationship between *COMT* genotypes and pain responder status, which appears to be drug-specific and likely to reflect the multifaceted interaction between different pain states and the catecholaminergic neurotransmission.

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