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Psychological Distress in Fibromyalgia Patients: A Role for Catechol-*O*-Methyl-Transferase Val158Met Polymorphism

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Objective: Fibromyalgia (FM) has been related to biochemical alterations, central pain sensitization and psychological distress. Among genetic and environmental hypotheses, a role was suggested for catechol-*O*-methyl-transferase (COMT), a modulator in the metabolism of monoaminergic neurotransmitters. ***Method:*** This study compared the COMT Val158Met enzyme polymorphism (rs4680) of 198 FM patients to 99 pain-free controls. Psychological and functional aspects were assessed through investigating anxiety, depression, catastrophizing, perceived health, and functional status. ***Results:*** The distribution of the COMT Val158Met polymorphism was similar in FM and controls. Out of 198 patients, 137 were able to stop medication before evaluation. In these patients, the COMT Val158Met genotype was associated with specific psychological profiles. The Met/Met subgroup scored systematically worse on all psychological and functional variables. All variables displayed a "genotype-trend effect" with the Met/Met and Val/Val subgroups at the two ends of the scores. Genotypes distribution in the 61 patients unable to stop medication was significantly different from that of patients able to stop medication and controls ($p = .002$ and $p = .018$, respectively) with an increase in the proportion of the Met/Met genotype associated to the lowest COMT activity. These results suggest a possible role of COMT Val158Met polymorphism in the psychological distress observed in FM. ***Conclusions:*** The association of COMT genotype with psychological distress may be of importance as identifying subgroups is a challenge in the diagnosis and treatment of fibromyalgia patients. This association may contribute to open new perspectives into the understanding of the pathophysiology of fibromyalgia and stress-related genes.

Keywords: fibromyalgia, psychological distress, chronic pain, catechol-*O*-methyl-transferase (COMT) polymorphism

The etiology and pathogenesis of fibromyalgia (FM) remain unclear despite extensive research. This chronic musculoskeletal pain condition is characterized by generalized pain, a predictable pattern of tender points, stiffness, fatigue and disturbed sleep; it has been related to biochemical alterations, central pain sensitization and psychological distress (Wolfe et al., 1990; Desmeules et al., 2003; Yunus, 2007). Although FM patients generally appear to be well, they often experience severe functional impairments, psychological suffering, and a resulting negative quality of life, thus leading FM to be a highly incapacitating chronic pain syndrome.

Various psychosocial factors and behavioral aspects have been associated with FM. These include emotional distress and depression and their contribution to the health care seeking behavior of these patients (Kersch et al., 2001; Hughes, Martinez, Myon, Taïeb, & Wessely, 2006). Although no common psychopathological profile was associated with FM, it has been described as one of the forms of affective spectrum disorder, a group of psychiatric and medical conditions (Aaron et al., 1996; Hudson et al., 2000). A premorbid lifestyle has been described as globally overactive whereas low activity levels, social withdrawal, and emotional distress are most often observed and described by the patients after FM onset (Van Houdenhove, Neerinckx, Onghena, Lysens, & Vertommen, 2001). Psychological factors have been shown to influence pain severity in FM and to modulate the severity of perceived distress (Hassett, Cone, & Sigal, 2000). Taken together, psychosocial data point to the heterogeneity of FM patients and to possible subgroups of patients (Thieme, Turk, & Flor, 2004; Giesecke et al., 2005).

FM-related symptoms are often found in members of FM patient families and there is evidence that polymorphisms of genes in the monoaminergic systems might play a role in the etiology of this

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syndrome (Buskila, Sarzi-Puttini, & Ablin, 2007). These polymorphisms are not specific for FM and are associated with other functional somatic disorders and emotional distress (Diatschenko et al., 2005; Domschke, Deckert, O'Donovan, & Glatt, 2007). Among the several genetic hypotheses, a possible role has been suggested for catechol-*o*-methyl-transferase (COMT), a key modulator in the metabolism of endogenous monoaminergic neurotransmitters (Campbell, Dunnette, Mwaluko, Van Loon, & Weinshilboum, 1984) and hence of opioidergic neurotransmitters, since an enhanced monoaminergic activity can upregulate opioid receptors by decreasing the level of endorphins (Chen, Aloyo, & Weiss, 1993; Unterwald, Rubenfeld, & Kreek, 1994; Zubieta et al., 2003). The COMT enzyme possesses a frequent nonsynonymous polymorphism (Pacifici & Fraccia, 1995) that encodes for the substitution of valine (Val) by methionine (Met) at codon 158 (Val158Met) and is associated with a fourfold reduction in the activity of the COMT (Lotta et al., 1995). Individuals with the Val/Val genotype have the highest activity of COMT, those with the Met/Met genotype have the lowest activity of COMT, and heterozygous individuals are intermediate [Diatchenko et al., 2005; Nackley et al., 2006). Under normal conditions, COMT deficiency does not appear to significantly affect brain monoamine levels despite relevant changes in their metabolites (Huotari et al., 2002). However, when an acute stress is imposed on the system, notably under conditions in which the monoamine system is challenged, the COMT deficiency can be uncovered in a pattern consistent with gene–environment interaction. This might well be the case in fibromyalgia (Martinez-Lavin & Hermosillo, 2000; Martinez-Lavin et al., 2002).The COMT Val158Met polymorphism has been linked to a decrease in pain tolerance in healthy volunteers (Zubieta et al., 2003). Studies on healthy volunteers have also shown greater brain activation in the limbic region of Met/Met carriers in reaction to an emotionally challenging situation such as the presentation of unpleasant stimuli (Zubieta et al., 2003; Smolka et al., 2005, 2007; Drabant et al., 2006). Longitudinal studies have shown that COMT polymorphisms might play a role in the pathogenesis of some chronic pain syndromes in women (Diatchenko et al., 2005). Moreover, an association with COMT polymorphism has been suggested in FM (Gürsoy et al., 2003; Vargas-Alarcon et al., 2007).

Our study aimed to compare COMT genotype of FM patients to pain-free healthy controls and to assess the possible relationship between psychological and genetic factors. Drawing from the literature, a greater proportion of COMT deficient allele is expected in FM patients as compared with control participants; furthermore the severity of emotional distress in FM patients may be associated with this COMT Val158Met polymorphism.

Materials and Methods

Population

Patients meeting the criteria of the American College of Rheumatology for FM were included (Wolfe et al., 1990). The patients enrolled in this study were referred to the Multidisciplinary Pain Centre at the Geneva University Hospitals by their internists or rheumatologists. Participation in the study was proposed to FM patients included in a neurophysiological investigation assessing central sensitization. This investigation required the interruption for at least four to seven half-lives of analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs], opioids) or coanalgesics (antidepressants, anticonvulsants) acting on central processing of nociceptive stimuli; rescue analgesics with a short half-life (e.g., acetaminophen) were allowed up to 24 hours before neurophysiological examination. Patients who did not succeed to stop medication or refused to stop for fear of an increase of their symptoms were also included, but were classified in a different subgroup, potentially more severely affected. Noninclusion criteria were specific medical disorders (e.g., inflammatory, infectious, neurological diseases, or fractures).

The control group was constituted by asking the patients to come with someone from their close social circle (friends but not family) and by advertising the study in the general population. Controls matched to cases for age and gender were included; further inclusion criteria were the absence of any acute or chronic health problems and of medication acting either on mood or on pain. A medical evaluation was carried out to assess the absence of chronic medical disorders affecting the peripheral or central nervous system, of a chronic painful condition, or of medication intake. These participants underwent the same procedures as FM patients. All the participants of this study were Caucasians.

The protocol was approved by the local ethics committee and prior written informed consent was obtained from all participants.

Clinical Measures

The 18 tender points (TP) and the myalgic score (MS) were assessed in patients and controls. In response to a digital force of 4 kg, participants were asked to indicate whether they felt no discomfort (score = 0), tenderness (score = 1), or pain; pain with no flinching or withdrawal was scored 2, and pain with flinching or withdrawal was scored 3. The MS score can range from 0 to 54. FM patients also filled in the regional pain score (RPS). The RPS is a body drawing on which 21 regions are indicated. Participants were asked to assess pain in each region by indicating the level that best described it, from 0 (*no pain*) to 5 (*unbearable pain*), providing a score between 0 and 105. The RPS has been validated with FM patients (Lautenschläger, Seglias, Brückle, & Muller, 1991). Patients' global present pain intensity was recorded on a visual analogue scale (VAS).

Psychological and functional impact aspects were investigated by means of self-reported questionnaires. Presence of anxiety was assessed through the State–Trait Anxiety Inventory (STAI-a [state anxiety] and STAI-b [trait anxiety]). Scores range from 20 (best) to 80 (Spielberger, 1983). Depression was assessed by means of the Beck Depression Inventory (BDI), a specific scale ranging from 0 to 62 with lower values indicating more positive responses (Beck et al., 1988). Both the STAI and the BDI are widely used, reliable, and valid instruments. Catastrophizing cognitions about pain were evaluated by means of the catastrophizing scale of the Coping Strategies Questionnaire ranging from 0 to 36 (best) (Rosenstiel & Keefe, 1983). The Psychological General Well-Being index (PGWB) was used to characterize the psychological dimension of health-related quality of life. It includes 22 items scored from 0 to 5, providing a total score between 0 and 110, with higher values indicating more positive responses (Dupuy, 1984). The SF-36 allowed for the evaluation of perceived health and functional status. It includes eight subscales measuring "general

health," "physical functioning," "role-physical," 'bodily pain,' "social functioning," "role-emotional," "mental health," and "vitality." Scores for each subscale range from 0 to 100 (best; Perneger, Leplège, Etter, & Rougemont, 1995). The Fibromyalgia Impact Questionnaire (FIQ) is a reliable and valid brief 10-item questionnaire measuring FM impact on, among others, physical function, fatigue, or mood, with lower scores indicating less negative impact (Burckhardt, Clark, & Bennett, 1991; Perrot et al., 2003). Assessment of the control group included the same questionnaires, except for the FIQ.

COMT genotyping. Genomic DNA was extracted from 200 μl whole blood using the QIAamp DNA blood mini kit (QIAGEN, Hombrechtikon, Switzerland). The COMT Val158Met polymorphism (rs4680) was genotyped using a commercially available TaqMan SNP genotyping assay (C_25746809_50, Applied Biosystems, Warrington, U.K.). Twenty-five μl reactions were performed using predesigned PCR primers and TaqMan MGB probes (FAM and VIC dye-labeled) according to the manufacturer's instructions in Taqman Universal PCR Master Mix using an iCycler iQ detection system (Bio-Rad, Hercules, CA).

Data analysis procedures. The chi-square test was used to assess the deviation of SNP genotypes from Hardy-Weinberg Equilibrium. Differences in the distribution of sociodemographic, clinical, psychological, and functional impact measures were compared among patients and controls and between patients by chi-square tests (categorical data) and *t* tests (continuous data). Analysis of variance (ANOVA) was used to compare the mean scores in psychological and functional variables. Results are reported as Bonferonni adjusted values. For the SF-36 subscales role physical and role emotional the Mann–Whitney *U* test and the Kruskal-Wallis test were used to take into account the nonparametric distribution of the variables. All analyses were done with SPSS version 15.0 (SPSS, Chicago, IL).

Results

Population

Out of the initial sample of 232 recruited patients, 34 refused to participate or did not show up; among the remaining 198 patients, 137 were labeled as "able to stop medication" (ASM), and 61 as "unable to stop medication" (USM). Ninety-nine control participants were recruited.

Comparison of the sociodemographic characteristics between ASM, USM, and controls are depicted in Table 1. The vast majority of the patients were middle-aged females. Over half of the patients were either on sick-leave or on disability pension, in sharp contrast to controls (see Table 1). The mean duration of FM symptoms was about 10 years and all clinical measures indicated moderate to severe pain in the patients (see Table 2). At the time of the examination patients rated their present pain intensity as a mean of 50 on a 100 mm-VAS. Medication use prior to entering the study showed a high intake of NSAIDs and/or acetaminophen in all the patients. Almost half of the ASM patients were on antidepressant medication and nearly all the USM patients were using antidepressants. This difference was also observed for opioids and for anticonvulsants (see Table 2).

Table 1
Sociodemographic Characteristics of Fibromyalgia Patients and Controls

	ASM (n = 137)	USM (n = 61)	Controls (n = 99)	
Female gender (%)	92.7	91.8	90.9	NS
Age (years: mean, *SD*)	50.1 ± 9.7	52.5 ± 10.7	48.9 ± 10.8	NS
Marital status (%)				
Single	12.5	8.2	25.9	NS
Married	59.6	57.4	50	
Divorced	23.5	27.9	20.4	
Widow	4.4	6.6	3.7	
Employment status (%)				
Employed	30.7	13.1	87.5	$p < .0001$
Not working/retired	18.3	26.3	12.5	
Sick-leave	13.1	13.1	0	
Disability pension	38	47.5	0	

Note. ASM = patients able to stop medication progressively; USM = patients unable to stop medication.

Psychological and Functional Scales

The measures of psychological and functional aspects showed major impairments in patients with FM as compared with the control group (see Table 3). Within the FM group, cognitive and emotional aspects were more severely affected in the USM patients with significantly higher values for anxiety, catastrophizing, and depression as indicated by the STAI-B [Trait], CSQ, and BDI scores, respectively. Various subscales addressing functional aspects also yielded statistically significant between-groups differences with the USM patients displaying worse results on the physical function subscale of the FIQ as well as on all four physical subscales of the SF-36 (see Table 3).

The global scores of the FIQ and of the PGWB, and the four mental subscales of the SF-36 did not show significant between-groups differences; however, the scores of the USM patients were always worse than those of the ASM patients (see Table 3). These results indicated that the patients who could not stop their medication intake suffered more severe emotional and functional limitations.

Catechol-*O*-Methyl-Transferase Genetic Polymorphism

The distribution of the COMT polymorphism encoding for the substitution of valine (Val) by methionine (Met) at codon 158 (Val158Met) was consistent with the Hardy-Weinberg equilibrium in controls, ASM patients, and USM patients. As shown in Table 4, genotype distribution was similar in controls and in ASM patients ($p = .583$). In contrast, the Met/Met genotype, associated to the lowest COMT activity, was clearly overrepresented in USM patients while the proportion of the Val/Val genotype (i.e., highest activity of COMT) was markedly decreased in this subgroup ($p = .018$ vs. controls and $p = .002$ vs. ASM, Table 4).

Consistently, the frequency of the A allele (Met) was significantly increased in USM patients as compared with controls and ASM patients ($p = .015$ and $p = .002$, respectively). Moreover, the odds ratios for the A allele were 1.77 (USM vs. control) and 1.96 (USM vs. ASM, Table 4) suggesting a potential association of

Table 2
Clinical Characteristics of Fibromyalgia Patients

	ASM (n = 137)	USM (n = 61)	
Symptom onset (years; mean, range)	9.7 (0.3–48)	10.1 (1–48)	NS
Number of tender points (mean, *SD*)	15.5 ± 2.7	16.3 ± 2.2	$p < .05$
Myalgic score (range 0–54; mean, *SD*)	31.6 ± 9.2	35.4 ± 10.5	$p < .01$
Regional Pain Score (best = 0–105; mean, *SD*)	61 ± 18.2	62.9 ± 17.1	NS
Present pain intensity (VAS; mean, *SD*)	50.6 ± 23.1	50.6 ± 18	NS
Physician global impression (best = 1–5; mean, *SD*)	2.6 ± 0.9	2.6 ± 1.1	NS
Medication use (%)			
NSAIDs and/or acetaminophen	89.1	78.7	NS
Antidepressant	48.9	91.8	$p < .001$
Tricyclics	24.8	24.6	
Serotonin reuptake inhibitors	15.3	47.5	
Noradrenergic reuptake inhibitors	1.5	0	
Others	7.3	19.7	
Anticonvulsants	3.6	13.1	$p < .05$
Opioids	13.1	39.4	$p < .001$
Weak	12.4	32.8	
Strong	0.7	6.6	
Benzodiazepines	31.4	45.9	NS
Neuroleptics	4.4	6.6	NS

Note. ASM = patients able to stop medication progressively; USM = patients unable to stop medication.

this mutant allele with severe emotional and functional impairments in FM patients.

Supporting this observation, the investigation of the association between the severity of psychological and functional aspects in ASM patients and COMT genotypes showed particular profiles according to the patient's COMT Val158Met genotype (see Table 5). The Met/Met subgroup scored worse than the Val/Val subgroup on all psychological and functional variables. The Met/Met subgroup also scored systematically worse than the Val/Met which in turn scored worse than the Val/Val subgroups on all variables, although between group differences did not reach statistical significance except for "social functioning" and "physical functioning" subscales (p = .005 and p = .001, respectively). Figure 1 shows the z-scores for all psychological and functional variables according to the COMT Val158Met polymorphism. Here again, all scales displayed the same "genotype-trend effect" with the Met/Met and Val/Val subgroups at the two far ends of the scores and the Val/Met subgroup in-between.

Table 3
Severity of Psychosocial Aspects in Fibromyalgia Patients Able and Unable to Stop Medication and in Controls

	ASM (N = 137)	USM (N = 61)	Controls (N = 99)
STAI-B (20 = best to 80)	44.5 ± 13.9	**50.0 ± 13.7***	32.4 ± 9.6‡
CSQ (0 = best to 36)	16.4 ± 9.3	**19.5 ± 7.9***	3.4 ± 5.3‡
BDI (0 = best to 60)	15.9 ± 10.4	**18.9 ± 9.6***	4.3 ± 4.0‡
SF36 physical functioning (range 0 to 100 = best)	44.2 ± 22.1	**36.7 ± 18.6***	94.2 ± 12.4‡
SF36 role physical	19.7 ± 28.7	**7.9 ± 19.0***	94.3 ± 17.0‡
SF36 bodily pain	29.1 ± 16.3	**23.9 ± 16.3***	88.3 ± 13.8‡
SF36 general health	36.7 ± 20.5	**30.4 ± 14.8***	82.2 ± 14.7‡
FIQ physical function subscale (0 = best to 10)	4.6 ± 2.4	**5.7 ± 1.8***	—
STAI-A (20 = best to 80)	43.6 ± 15.5	**47.3 ± 14.2**	21.1 ± 7.9‡
PGWB (0 to 110 = best)	49.6 ± 21.0	**47.1 ± 18.5**	85.8 ± 12.4‡
SF36 role emotional	40.6 ± 40.8	**37.7 ± 41.9**	87.5 ± 27.4‡
SF36 mental health	49.1 ± 24.7	**45.3 ± 20.8**	75.4 ± 13.8‡
SF36 vitality	25.5 ± 18.8	**20.8 ± 15.9**	64.2 ± 15.5‡
SF36 social functioning	37.4 ± 22.9	**33.8 ± 20.0**	88.6 ± 14.9‡
FIQ (global score; 0 = best to 100)	54.0 ± 17.0	**54.5 ± 13.8**	—

Note. ASM = able to stop medication; BDI = Beck Depression Inventory; CSQ = Catastrophizing Scale Questionnaire; FIQ = Fibromyalgia Impact Questionnaire; PGWB = Psychological General Well-Being; SF36 = Short Form 36 Health Survey; STAI = State (A) -Trait (B) Anxiety Inventory; USM = unable to stop medication. In bold: most severe scores.
‡ $p < .05$ (FM patients vs. controls). * $p < .05$ (ASM vs. USM).

Discussion

The major finding of this study is a suggested role for COMT Val158Met polymorphism in the psychological vulnerability observed in FM patients. Our results showed that FM patients, when considered globally, were severely affected on all psychological and functional impact measures as compared with a pain-free control population. The differences between FM and controls were not only statistically significant, but also clinically meaningful for all aspects investigating health-related quality of life, physical activities, and mood (anxiety, depression, and catastrophizing).

Our results support the hypothesis of a role for COMT in the increase of psychological vulnerability in FM in the patients able to stop medication. Indeed, those patients with a low COMT activity displayed the most severe psychological and functional impact scores whereas, in sharp contrast, those with the highest COMT activity had the best scores. Although the associations between the psychological variables and COMT genotype subgroups did not reach statistical significance, they were consistent and suggested a dose-response form of association between the activity level of COMT and the psychological variables. Recent studies have investigated whether psychological variables such as

Table 4
COMT Val158Met Genotypes' and Alleles' Distributions in Controls, ASM and USM Patients

COMT rs4680 G > A	Genotypes[a]				Alleles[a]			
	GG	GA	AA	*p*-value[b]	G	A	*p*-value[b]	OR [95% CI][c]
Controls	30 (30.3)	44 (44.4)	25 (25.3)	0.583[d]	104 (52.5)	94 (47.5)	0.573[d]	0.9 [0.62–1.3][d]
ASM	41 (30.1)	68 (50)	27 (19.9)	0.018[d]	150 (55.1)	122 (44.9)	0.015[d]	1.77 [1.12–2.8][d]
USM	8 (13)	31 (50.8)	22 (36.1)	0.002[e]	47 (38.5)	75 (61.5)	0.002[e]	1.96 [1.27–3.03][e]

[a] Number of genotypes (frequencies, %) or alleles. [b] Chi-square test. [c] Odds ratio for allele A. [d] Versus controls. [e] Versus ASM.

catastrophizing and COMT genotype may influence clinical pain ratings in patients undergoing surgery for musculoskeletal complaints (George et al., 2008). The results showed that high pain catastrophizing and a low COMT activity were associated with higher preoperative pain ratings, and an increased chance of experiencing persistent pain following surgery. Another study evaluating the association between COMT and symptoms related to a whiplash after a car accident suggests that COMT genetic variations affecting stress response system function influence the severity of pain report as well as the length of physical and psychological recovery (McLean et al., 2011). A 3-year longitudinal study in healthy female volunteers further demonstrated an association between COMT polymorphism, pain sensitivity, and the risk of developing temporomandibular pain, a chronic musculoskeletal pain condition (Diatchenko et al., 2005). Furthermore in FM a recent study showed that patients with a low COMT activity experienced a greater decline in positive affect when suffering intense pain (Finan et al., 2010).

Our study also allowed the identification of a subgroup of patients unable to stop medication. These patients displayed the worst scores on all clinical, psychological, and functional dimensions, despite the persistence of medication intake including antidepressants in more than 90% of them. The COMT Met/Met genotype, resulting in low enzyme activity, was significantly overrepresented in these patients. These results are consistent with the trends observed in the association between the COMT genotype and the severity of the psychological and functional impact of the disease and further underscore a role for COMT Val158Met polymorphism in the psychological distress observed in FM patients.

Our data are in line with those of studies showing that the low-activity Met158 allele is associated with higher risk for anxiety-related behaviors (Enoch, Xu, Ferro, Harris, & Goldman, 2003), with a lower emotional resilience against negative mood states in healthy participants (Smolka et al., 2005), and with maladaptive coping and pain in FM (Finan et al., 2011).

Though the findings of our study offer further perspectives in the possibility to subgroup patients with FM, the limitations of its design and outcomes should be acknowledged.

The generalizability of these results to other patients with FM may be questioned due to the distribution of COMT Val158Met genotype that does not allow to distinguish FM patients (considered as a whole) from pain-free controls. Our results regarding the distribution parallel those of the HUNT (Nord-Trøndelag Health Survey) study (Hagen, Pettersen, Stovner, Skorpen, & Zwart, 2006). This very large epidemiological study investigating 3048 patients suffering from various chronic musculoskeletal pain complaints showed no association between COMT Val158Met polymorphism and these complaints, including the 332 women suffering widespread pain. A smaller study showed the same absence of association in various neuropathic pain conditions (Armero et al.,

Table 5
Severity of Psychosocial Aspects in Fibromyalgia Patients Able to Stop Medication According to Their COMT Val158Met Genotype

	Met/Met (n = 27)	Val/Met (n = 68)	Val/Val (n = 41)
STAI-B (range 20 = best to 80)	**51.9 ± 16.3**	42.6 ± 13.1	44.6 ± 13.6
STAI A (range 20 = best to 80)	**49.8 ± 16.7**	42.8 ± 15.1	42.4 ± 15.5
CSQ (range 0 = best to 36)	**19 ± 10.7**	16.5 ± 8.9	14.9 ± 9.3
BDI (range 0 = best to 60)	**20.3 ± 13.3**	15.6 ± 10.8	14.6 ± 7.6
PGWB (range 0 to 110 = best)	**44.3 ± 20.0**	49.9 ± 21.8	52.5 ± 20.3
SF36 physical functioning (range 0 to 100 = best; mean, *SD*]	**41.4 ± 17.1**	42.3 ± 22.7	50.1 ± 23.6
SF36 role physical	**5.8 ± 10.7**	17.9 ± 24.9	31.9 ± 37.1
SF36 bodily pain	**24.7 ± 11.5**	27.8 ± 15.5	33.8 ± 18.8
SF36 general health	36.7 ± 20.0	**34.9 ± 22.4**	39.6 ± 17.3
SF36 role emotional	**22.2 ± 32.8**	41.7 ± 40.4	46.9 ± 43.6
SF36 mental health	**43.7 ± 21.6**	50.1 ± 24.9	49.6 ± 26.1
SF36 social functioning	**28.8 ± 19.9**	35.1 ± 22.8	46.6 ± 22.4
SF36 vitality	**20.8 ± 11.9**	24.4 ± 19.9	29.6 ± 19.2
FIQ (global score; range 0 = best to 100)	**57.2 ± 11.8**	54.5 ± 17.2	51.1 ± 19

Note. In bold: most severe scores.

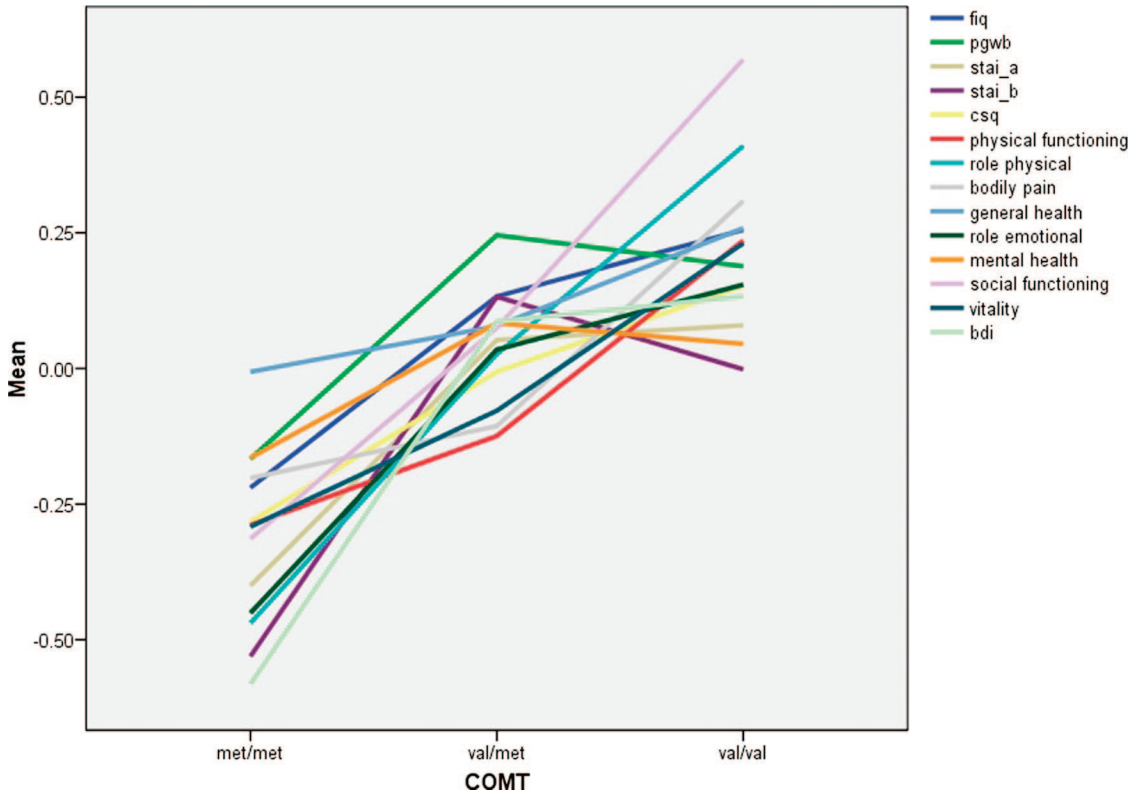

Figure 1. COMT Val158Met genotypes and psychological and functional measures in FM patients without medication (expressed as % and corrected standardized means). Scores from all scales were corrected so that negative standardized means (z-scores) expressed the worst and positive standardized means the best psychosocial and functional measures on all scales.

2005). However, these studies did not control for medication intake and our results showed that this intake may act as a crucial confounding variable. Beside controlling for medication intake, our study allowed for an assessment free of the medication intake bias expected to influence the scores of the questionnaires evaluating psychological status. Indeed, the severity of these scores in our study indicates a high psychological and functional impact of FM. These values are comparable to those in other FM studies (Mannerkopi, Nyberg, Ahlmen, & Ekdahl, 2000; Baumgartner, Finckh, Cedraschi, & Vischer, 2002; Desmeules et al., 2003) and they underline the emotional distress, functional impairments, and poor quality of life that patients with FM experience (Katon, Sullivan, & Walker, 2001; Cedraschi et al., 2004). The values are also very close to those of other studies for clinical characteristics and medication intake (Gowans, De Hueck, Voss, Silaj, & Abbey, 2004; Passard et al., 2007). The recruitment of the control group may have been an issue because it was partly constituted by asking patients to bring someone from their close circle of friends. However, the values of the subscales of the SF-36 were within the range of those for healthy individuals living in the same environment (Richard et al., 2000). The same was true for the scales investigating psychological dimensions, including anxiety, depression, and catastrophizing (Richard et al., 2000).

Our results suggest an association between genetic variations of monoamine neurotransmitter system and psychological and functional variables. The theoretical framework of our study included the role of the altered dopaminergic activity related to COMT Val158Met enzyme polymorphism and its influence on psychological aspects through the opioidergic system in the limbic region (Zubieta et al., 2003; Finan et al., 2011). COMT, as the major catecholamine-clearing pathway, is also implicated in autonomic activity. Autonomic dysfunction is frequent in patients with fibromyalgia. It has been suggested that persistent autonomic dysfunction induces both somatic and psychological complains such as insomnia, irritable bowel, anxiety, and fatigue (Martınez-Lavın & Vargas, 2009). Furthermore catecholamines such as norepinephrine are sympathetic neurotransmitters and a number of patients who suffer FM have norepinephrine-evoked pain (Martınez-Lavın et al., 2002); they also experience various functional symptoms that could be related to and maintained by autonomic dysfunction, and as such it would have been of interest to measure circulating catecholamine levels in the study participants.

The association of COMT genotype with increased psychological distress (i.e., anxiety, catastrophizing, depression) may be of importance as identifying subgroups is a challenge in the diagnosis and treatment of fibromyalgia patients. This association in FM patients may contribute to open new perspectives into the understanding of the pathophysiology of FM and stress-related genes. When it comes to therapeutic perspectives, the role of COMT polymorphism in the severity of the expression of the pain syn-

drome needs to be considered as it may influence the effect of drugs acting on the monoaminergic pathway.

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