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COMT Val158Met Polymorphism and Symptom Improvement Following a Cognitively-Focused Intervention for Irritable Bowel Syndrome

Claire J. Han, PhD, RN [Research Assistant],
Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle

Ruth Kohen, MD [Associate Professor],
Department of Psychiatry & Behavioral Sciences, University of Washington, Seattle

Psychiatrist Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA

Sangeun Jun, PhD, RN [Assistant Professor],
College of Nursing, Keimyung University Daegu, South Korea

Monica E. Jarrett, PhD, RN [Professor],
Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle

Kevin C. Cain, PhD [Research Scientist],
Department of Biostatistics and Office of Nursing Research, University of Washington, Seattle

Robert Burr, MSEE, PhD [Research Professor], and
Department of Biostatistics and Office of Nursing Research, University of Washington, Seattle

Margaret M. Heitkemper, PhD, RN, FAAN [Professor]
Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle

Abstract

Background—Our nurse-delivered Comprehensive Self-Management (CSM) program, a cognitive behavioral therapy intervention, is effective in reducing gastrointestinal and

Corresponding Author: Margaret M. Heitkemper, PhD, RN, FAAN, Department of Biobehavioral Nursing and Health Systems, Box 357266, University of Washington, Seattle, WA, 98195 (heit@u.washington.edu).
Claire J. Han, PhD, RN, is Research Assistant, Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle.
Ruth Kohen, MD, is Associate Professor, Department of Psychiatry & Behavioral Sciences, University of Washington, Seattle, and Psychiatrist, Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA.
Sangeun Jun, PhD, RN, is Assistant Professor, College of Nursing, Keimyung University Daegu, South Korea.
Monica E. Jarrett, PhD, RN, is Professor, Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle.
Kevin C. Cain, PhD, is Research Scientist, Department of Biostatistics and Office of Nursing Research, University of Washington, Seattle.
Robert Burr, MSEE, PhD, is Research Professor, Department of Biostatistics and Office of Nursing Research, University of Washington, Seattle.
Margaret M. Heitkemper, PhD, RN, FAAN, is Professor, Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle.

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Supplemental Digital Content 1. Contains four supplement tables that include *COMT* genotype. .doc

psychological distress symptoms in patients with irritable bowel syndrome (IBS). Findings from non-IBS studies indicate that the catechol-O-methyltransferase (*COMT*) Val158Met polymorphism may moderate the efficacy of cognitive behavioral therapy. It is unknown whether this *COMT* polymorphism is associated with symptom improvements in patients with IBS.

Objective—We tested whether this *COMT* Val158Met polymorphism influences the efficacy of our two-month CSM intervention.

Methods—We analyzed data from two published randomized controlled trials of CSM. The combined European-American sample included 149 women and 23 men with IBS (CSM, n =111; Usual Care [UC], n = 61). The primary outcomes were daily reports of abdominal pain, depression, anxiety, and feeling stressed measured three and six months after randomization. Secondary outcomes were additional daily symptoms, retrospective psychological distress, IBS quality of life, and cognitive beliefs about IBS. The interaction between *COMT* Val158Met polymorphism and treatment group (CSM vs. UC) in a generalized estimating equation model tested the main objective.

Results—At three months, participants with at least one Val allele benefited more from CSM than did those with the Met/Met genotype (p = .01 for anxiety and feeling stressed, and p < .16 for abdominal pain and depression). The moderating effect of genotype was weaker at six months.

Discussion—Persons with at least one Val allele may benefit more from CSM than those homozygous for the Met allele. Future studies with larger and more racially diverse samples are needed to confirm these findings.

RCT Registration—Parent studies were registered at ClinicalTrials.gov (NCT00167635 and NCT00907790).

Keywords

catechol-O-methyltransferase (*COMT*) polymorphism; cognitive behavioral therapy; digestive signs and symptoms; irritable bowel syndrome; self-management

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder characterized by abdominal pain or discomfort associated with altered bowel habits including constipation, diarrhea or mixed diarrhea/constipation. In clinical practice IBS is most commonly diagnosed using Rome criteria (Drossman & Dumitrascu, 2006). The etiology of IBS is thought to be heterogeneous, and may be related, at least in part, to genetic factors (Makker, Chilimuri, & Bella, 2015). Self-management programs are effective behavioral interventions for many patients with IBS (Lackner et al., 2007). Our nurse-delivered Comprehensive Self-Management (CSM) intervention was developed and tested in three randomized controlled trials (RCTs) (Heitkemper et al., 2004; Jarrett et al., 2016; Jarrett et al., 2009). Our CSM intervention is based on an IBS biopsychosocial conceptual model (Drossman & Dumitrascu, 2006); and is grounded in cognitive behavioral therapy (CBT) and includes cognitively focused strategies (Barney, Weisman, Jarrett, Levy, & Heitkemper, 2010). In the CSM intervention, participants learn to recognize dietary triggers, use relaxation techniques and problem-solving approaches, learn to revise false beliefs, manage pain, and practice good sleep habits (Barney et al., 2010). In previous studies (Heitkemper et al., 2004; Jarrett et al., 2016; Jarrett et al., 2009), the CSM intervention was

delivered either in person or by telephone. In all trials, the CSM group were compared to a usual care (UC) group who were recontacted for the follow-up assessments. No significant difference was found based on the delivery approach. The CSM intervention was more effective at reducing GI and psychological symptoms, enhancing quality of life (QOL), and improving cognitions about IBS when compared to UC (Jarrett et al., 2016; Jarrett et al., 2009).

Despite these overall group differences, not all patients improved following the CSM program. The mean percent of participants with at least 50% improvement in overall symptoms, including abdominal pain and psychological distress, was 60% (Jarrett et al., 2016; Jarrett et al., 2009). The odds ratios (*OR*s) for the probability of 50% improvement of symptoms in each CSM group relative to UC group were all greater than 2.3, and almost all are statistically significant at three and six months (Jarrett et al., 2016; Jarrett et al., 2009). A later analysis of these data based on heart rate variability showed that participants with higher vagal tone and reduced sympathovagal balance at baseline had greater symptom reduction, suggesting that autonomic nervous system arousal may be important in learning and incorporating new self-management strategies (Jarrett et al., 2016).

Catechol-O-methyltransferase (COMT) is an enzyme involved in the degradation of the catecholamine neurotransmitters, e.g., norepinephrine and dopamine. COMT plays important roles in neurocognitive processes such as pain and emotions. (Antypa, Drago, & Serretti, 2013). The Val158Met polymorphism (rs4680) of the *COMT* gene leads to a substitution of valine (Val) by methionine (Met). The Met allele has one third to one fourth of the enzymatic activity of the Val allele (Lachman et al., 1996). For example, the lower activity of Met allele has been associated with increased risk for fibromyalgia, and more severe pain and lower pain sensitivity thresholds in those with fibromyalgia (Desmeules et al., 2014). This functional polymorphism has been also associated with cognitive performance and psychiatric conditions (Witte & Flöel, 2012) as well as pain processing and sensitivity (Tammimaki & Mannisto, 2012). The direction of the associations of *COMT* genotype with cognitive performance depends on the type of cognitive task employed. The Met allele is associated with stable cognitive performance in relation to working memory and attention while the Val allele is associated with better performance on tasks that require cognitive flexibility (Witte & Flöel, 2012).

Previous association studies of *COMT* Val158Met with the diagnosis and severity of IBS have been inconsistent. In elderly Chinese patients diagnosed with IBS based on Rome III criteria, the Met allele was more prevalent (12.9 % of 66 IBS patients) compared to a healthy comparison group (6.5% of 115 controls) and associated with diarrhea (Wang, Wu, Qiao, & Zhang, 2014). By contrast, researchers in Sweden (Karling et al., 2011) found that the occurrence of the Val/Val genotype was more common (30% of 70 patients with IBS [Rome III criteria]) compared to a control group who were representative of the general population without IBS (20% of 867 controls). Karling et al. (2011) found increased stool frequency among Val/Val homozygous patients compared to other *COMT* genotype carriers. Hall and colleagues (Hall et al., 2012) in the U.S. studied 262 IBS patients (based on Rome II criteria, 96% European-American) and found that Met/Met homozygotes had the greatest reduction of IBS symptom severity including abdominal pain to a placebo acupuncture

intervention at 3 weeks following treatment (Hall et al., 2012). These results suggest some associations of *COMT* Val158Met with IBS symptoms, particularly symptom severity, pain and bowel pattern. However, this association is likely complex and remains to be clarified.

In addition to a potential association of *COMT* Val158Met with cognitions, pain and psychological distress, the results of three studies suggest that the *COMT* gene may be related to therapeutic responses. In a study of 62 healthy male Caucasian volunteers in Germany, a nocebo response to both drug (immunosuppressive drug) and placebo (lactulose powder) treatment was augmented among Val allele carriers (Wendt et al., 2014). Two other studies showed associations between the *COMT* Val158Met polymorphism and CBT responses. In cocaine-dependent mostly European-American women and men, Carroll et al. (2015) found a better response (i.e., reduced relapse, following a web-delivered CBT among Val allele carriers) compared to Met/Met homozygotes. Similarly, in a Swedish study of Caucasian women and men with a panic disorder (Lonsdorf et al., 2010), Val allele carriers had a better response to CBT. Given the findings of these studies, it can be conjectured that the presence of a Val allele may be associated with the greater efficacy of CSM in patients with IBS.

To examine the potential moderating effect of *COMT* Val158Met polymorphism on the efficacy of CSM for symptoms, we used data from two RCTs that tested CSM versus UC (Jarrett et al., 2016; Jarrett et al., 2009). Consistent with prior studies showing a better response to CBT among Val allele carriers of the *COMT* Val158Met polymorphism (Carroll et al., 2015; Lonsdorf et al., 2010), we aimed to test whether the efficacy of the CSM intervention is influenced by the *COMT* Val158Met polymorphism. We hypothesized that IBS patients with the Val/Val or Val/Met genotype would respond better to CSM than Met/Met homozygotes. To test this, we analyzed daily reports of abdominal pain, depression, anxiety, and feeling stressed in study participants as primary outcome measures. Additional daily diary symptoms, retrospective psychological distress, IBS specific QOL, and cognitive beliefs about IBS measures were examined as secondary outcomes.

Methods

Design and Settings

The study used data collected in two RCTs (Jarrett et al., 2016; Jarrett et al., 2009) of women and men with IBS in the Pacific Northwest, U.S. The first RCT (RCT-1) was conducted from 2002 to 2007, and the second RCT (RCT-2) from 2008 to 2013. Both trials have been described in detail elsewhere (Jarrett et al., 2016; Jarrett et al., 2009). In both studies participants provided symptom assessments through a daily diary as well as other questionnaires at baseline, at three months postintervention, and at six months follow up. Diary entries for the 28 days prior to each time point were averaged into a single symptom (e.g., abdominal pain) measure. We collected blood for genetic analysis during the baseline visit. Participants provided written consent for the parent studies, as well as for genetic testing and analyses. All studies were approved by the University of Washington Institutional Review Board. Since both RCTs had similar protocols, recruitment approaches, and sample characteristics, we combined data from both studies for this analysis.

Participants

For both RCT-1 and RCT-2, we enrolled patients with IBS between the ages 18 and 70 years with a prior diagnosis of IBS from a healthcare provider, and who met the latest Rome criteria for IBS at the time of the study (Rome-II for RCT-1; Rome-III for RCT-2) (Drossman & Dumitrascu, 2006). For both, potential participants were recruited through local community advertisements and from targeted mailings to patients in a university-based gastroenterology clinic (Jarrett et al., 2016; Jarrett et al., 2009). Exclusion criteria were the presence of moderate to severe comorbid conditions or surgery that might result in IBS-type symptoms, or who were taking specific medications more than three days a week for IBS (e.g., antibiotics, antidiarrheals, or antispasmodics) or other medications with common GI side effects. Persons with type 1 or type 2 diabetes mellitus, infectious diseases, and bipolar or dementia diagnosis were excluded. After completion of the baseline assessment, eligible participants were randomized to either the CSM or UC group. In this secondary analysis, baseline symptoms and genetic data were available on 172 European-American participants (in the CSM group, women: $n = 97$, men: $n = 14$; in rhw UC group, women: $n = 52$, men: $n = 9$). For this genetic analysis, we restricted our sample to self-reported European Americans only, 84% of total study participants, to avoid population stratification bias.

Interventions

The 60-minute sessions were conducted in person and by telephone using the “IBS Managing Symptoms Workbook” (Barney et al., 2010). The goal was to complete nine sessions in RCT-1 and eight sessions in RCT-2 over 10 to 12 weeks. Each session included a review of the prior week’s homework, two new topics were introduced and practiced, and the next week’s homework assignment introduced. Participants randomized to the UC group were notified that they should continue their current activities until it was time for the first follow-up assessment. At the end of the study, the participants in the UC group were given the workbook used in the CSM intervention. Both groups were compensated for the time to complete the baseline and follow-up assessments.

Measures

Genotyping—Deoxyribonucleic acid (DNA) was isolated from whole blood using buffy coat preparations and Puregene DNA purification kits (Qiagen Sciences LLC, Louisville KY) according to the manufacturer’s instructions. After DNA extraction, the samples were analyzed for the *COMT* Val158Met (rs4680) polymorphism at the Center for Ecogenetics and Environmental Health (CEEH) facility (University of Washington, Seattle) using the TaqMan rs4680 genotyping assay (ThermoFisher Scientific, Waltham, MA).

Baseline characteristics—Demographic data such as age, race and ethnicity, marital status, education, and total annual household income level were collected. IBS specific history, baseline information and health behaviors were assessed using a Health History Questionnaire.

Primary outcomes—Twenty-six symptoms were recorded in a 28-day daily diary prior to the baseline, three months, and six months assessment times. For this analysis, we used symptoms of abdominal pain or discomfort, depression, anxiety, and feeling stressed as

primary outcomes. Each symptom was rated as 0 = *not present*, 1 = *mild*, 2 = *moderate*, 3 = *severe*, or 4 = *very severe*. Daily symptoms were summarized across days as the percent of days with symptoms that was "moderate to very severe" (Jarrett et al., 2009; Levy, Cain, Jarrett, & Heitkemper, 1997). The diary was used to reduce retrospective bias related to recalled symptoms (Lackner et al., 2014). The construct validity was shown when correlated with global scales (Burman, 1995; Hertig, Cain, Jarrett, Burr, & Heitkemper, 2007).

Secondary outcomes—Eight additional *GI daily symptoms* (i.e., abdominal pain after eating, abdominal distension, intestinal gas, bloating, flatulence, constipation, diarrhea, and urgency), and three *psychological distress symptoms* (i.e., fatigue, sleepiness during the day, and panic) were assessed. Symptoms were summarized as described above. *Retrospective psychological distress* was measured with the 53-item Brief Symptom Inventory (BSI). Each symptom was rated as 0 *(not at all*) to 4 (*extremely*). The Global Severity Index (GSI) is a mean of the nine subscale scores including somatization, anxiety, obsessive-compulsive, phobic anxiety, depression, interpersonal sensitivity, hostility, paranoia, psychoticism) (Derogatis, 1993). For this study, we included depression, anxiety, and GSI scores. In this sample, reliability estimated using Cronbach's alpha was 0.82 for depression scores, 0.83 for anxiety scores, and 0.88 for GSI scores. *IBS-quality of life (IBSQOL)* was measured with the IBSQOL, a 34-item questionnaire with nine scales: sleep, emotional, mental health beliefs, energy, physical functioning, diet, social role, physical role, and sexual relations (Hahn, Kirchdoerfer, Fullerton, & Mayer, 1997). A total score was calculated by averaging all except for items of diet and sexual relations (Jarrett et al., 2009). The diet scale was omitted because participants in the CSM group were encouraged to avoid foods that elicit symptoms. The sexual relations scale was omitted due to low sexual activity by participants (Jarrett et al., 2009). Example questions are, "How often did your IBS make you feel fed up or frustrated" rated 1 = *always*, 2 = *often*, 3 = *sometimes*, 4 = *seldom*, or 5 = *never*; or "My IBS affected my ability to succeed at work/main activity," 1 = *strongly agree* to 5 = *strongly disagree*. The scales are transformed to a standard 0 to 100 scale. Reliability of subscale scores estimated using Cronbach's alpha ranged from 0.74 to 0.97. Finally, The Cognitive Scale for Functional Bowel Disorders (CSFBD) assesses 25 *cognitive beliefs about IBS* with 31 items. The items are rated from 1 = *strongly disagree* to 7 = *strongly agree.* A typical item is, "I often worry that there might not be a bathroom available when I need it." A total score was calculated as the mean of all items, with higher scores indicating more negative cognitions regarding symptoms and consequences. The CSFBD has high concurrent criterion validity, acceptable convergent validity, high content validity and face validity with minimal social desirability contamination (Toner et al., 1998). For this study, the reliability of total scores estimated using Cronbach's alpha was 0.96.

Statistical Analysis

Power analysis—This report uses data from two prior studies. The sample sizes for those prior studies were chosen to have good power for testing a treatment effect of CSM. The analyses in this report involved testing an interaction term, and the effect size was defined as the difference of treatment efficacy (mean change in the CSM group minus mean change in the UC group) in Val allele carriers minus treatment efficacy in Met/Met genotype. The primary analyses involve testing an interaction term, which means effect size is defined as

the difference of treatment efficacy (mean change in the CSM group minus mean change in the UC group) in Val carriers minus treatment efficacy in Met/Met. The primary outcome variables are measured as percent of days with moderate or severe symptom severity. Power depends on the true effect size, which will be different for the different outcomes. Based on the sample size at three months, power would be approximately 52%, 71%, 85%, and 94% for a true effect size of 12, 15, 18, and 21, respectively.

Data Analysis—To compare baseline demographic, symptom and clinical characteristics by *COMT* genotype or between the CSM and UC groups, we used χ^2 tests for categorical data and *t*-test for continuous data. Generalized estimating equation (GEE) models were used to test the interaction effects of intervention and *COMT* genotype. Within each of the CSM and UC group, and for each of the primary and secondary outcome variables, models were fit to test whether the mean change from baseline in outcome variables differed by *COMT* genotype, after controlling for baseline outcome variables, age, gender, and study (RCT-1, RCT-2). Separate analyses were done for outcomes at three months and at six months, and then an analysis which combined data from three and six months was done. Next, models were fit using data from both the CSM and UC groups together, and including main effects and the interaction between *COMT* genotype and group. This interaction term tests whether CSM efficacy (i.e., mean change in outcome variables in the CSM group minus mean change in outcome variables in the UC group) differs by *COMT* genotype. In other words, it tests whether *COMT* genotype moderates the effect of CSM on outcome variables. These models all use *COMT* genotype as a three-level factor (i.e., Val/Val, Val/Met, and Met/Met). Since previous studies showed a better response to CBT among Val allele carriers (Carroll et al., 2015; Lonsdorf et al., 2010), post hoc analyses collapsed Val/Val and Val/Met genotypes into one category to compare to the Met/Met genotype. IBM SPSS 19.0 Statistic version was used and a *p*-value less than .05 was considered statistically significant.

Results

Demographics, Clinical Characteristics, *COMT* Genotype, and Baseline Outcome Variables

Participant characteristics are summarized in Table 1. Of the 172 participants 149 were women (86.6%), 81 (47.1%) were married or partnered, and 77 (44.8%) had professional jobs. The majority had at least a college degree (n = 122; 70.9%) and an average income of greater than $60,000/year ($n$ = 83; 48.2%). In the sample, 49 (28.5%) were constipation predominant, 93 (54%) were diarrhea predominant, 19 (11%) were mixed bowel pattern, and 11 (6.4%) were designated as unknown bowel pattern. The duration since IBS diagnosis was 8.1 years (SD = 4.9). Some participants were taking medications to manage their symptoms, 2–3 times a day, more than 3 days per month. Approximately 21.5% (n = 37) were taking analgesics for pain or discomfort, 21.5% (n = 37) were taking selective serotonin reuptake inhibitors, and 1.7% (n = 3) were taking tricyclic antidepressants for depression or abdominal discomfort. Approximately 12% (n = 20) were taking other psychotropic drugs such as benzodiazepines or gabapentin for anxiety. The *COMT* genotype frequencies were Val/Val (n = 44; 25.6%), Val/Met (n = 87; 50.6%), and Met/Met (n = 41; 23.8%). There were no differences in demographic variables and clinical characteristics by *COMT* genotype.

Baseline primary and secondary outcomes did not vary except for intestinal gas by *COMT* genotype (Table 1), or between UC and CSM groups (Supplemental Digital Content 1, see Supplement Table 1).

Differences in Mean Changes of Symptoms by *COMT* Genotype on Primary Outcomes

Table 2 presents the mean changes in symptoms at each follow-up timepoint (three and six months) by *COMT* genotype within the UC and CSM groups separately. In the UC group, Val/Met heterozygotes showed an increase in depressive symptoms at three months, compared to both homozygote groups ($p = .03$). In the CSM group, reductions in anxiety and feeling stressed were observed among the Val/Val and Val/Met genotype groups at three months, with the greatest symptom reductions among Val/Val homozygotes ($p = .009$ for anxiety and $p = .02$ for feeling stressed). Similar differences were present at six months, but were no longer statistically significant. We also observed a trend towards greater reduction in abdominal pain in CSM participants with the Val/Val and Val/Met genotypes compared to Met/Met heterozygotes at six months ($p = .06$). The differences in mean changes of symptoms by *COMT* genotype at the combined three and six month timepoints were not significant within either the UC or CSM group (data available upon request).

COMT Genotype Moderates Efficacy of CSM Intervention on Primary Outcomes

The results of testing whether *COMT* genotype moderates the intervention effect of CSM versus UC for the four primary symptom outcomes are shown in Table 3. We found significant *COMT* genotype by CSM intervention interactions for anxiety ($p = .01$) and feeling stressed ($p = .01$) at three months. The coefficient for the interaction term measures the magnitude of this interaction effect for both of the Val carrier groups (Val/Val and Val/Met) versus the reference category of Met/Met homozygotes. For example, the estimated coefficient of −20.6 at three months for feeling stressed means that among participants with the Val/Met genotype, the efficacy of CSM, defined as mean change from baseline to three months in feeling stressed for the CSM group minus the mean change for the UC group, is 20.6 points lower than for Met/Met homozygotes. Negative change is reflective of symptom improvement. Thus, this negative coefficient indicates that participants with the Val/Met genotype benefited more from the CSM intervention than did Met/Met homozygotes ($p = .003$). However, this moderating effect of *COMT* on CSM efficacy was much weaker at six months. The interaction effects between intervention and *COMT* genotype were not statistically significant for the primary outcomes at the combined time points (data available upon request).

Post Hoc Analysis

Based on the results in Table 3, it appeared that the benefit of CSM is least in the Met/Met genotype group and greater in those with one or more Val allele. Thus, we performed an additional post hoc analysis, in which Val/Val and Val/Met genotype carriers were combined into one group and compared to Met/Met homozygotes. The Val allele carriers showed a better psychological distress response to the CSM intervention than those with the Met/Met genotype (Table 4). This analysis confirmed a *COMT* genotype×CSM intervention interaction on anxiety and feeling stressed at three months, along with a borderline

significant interaction on depression at six months (Table 4) and at the combined time points (p = .05 for anxiety, p = .03 for feeling stressed; data available upon request).

COMT Genotype Moderates Efficacy of CSM Intervention on Secondary Outcomes

For secondary outcome measures (Supplemental Digital Content 1, see Supplement Tables 2A & 2B), there were significant interaction effects between *COMT* genotype and CSM intervention on abdominal distension, constipation, and retrospective psychological distress (i.e., depression, anxiety, and GSI) at three months (Supplemental Digital Content 1, see Supplement Table 2A). There was also a significant interaction (p = .05 for abdominal distension) at the combined timepoints (data available upon request. When we categorized *COMT* genotype as two groups (Val allele carriers vs. Met/Met homozygotes), similar results were observed. There were significant interaction effects on abdominal distension, intestinal gas, constipation, and retrospective psychological distress at three months (Supplemental Digital Content 1, see Supplement Table 3) and the combined time points (data not shown). *COMT* genotype did not influence CSM efficacy in other secondary outcomes (i.e., diarrhea, flatulence, urgency, fatigue, sleepiness during the day, panic, IBSQOL, and cognitive beliefs about IBS at three months and six months; (Supplemental Digital Content 1, see Supplement Tables 2A, 2B, and 3), and the combined time points (data available upon request).

Discussion

The findings reported here contribute to our understanding of the relationship between response to the CSM intervention and a gene associated with dopamine and catecholamine metabolism. This is the first study conducted in patients with IBS demonstrating that the *COMT* Val158Met polymorphism could influence response to a cognitively focused behavioral program. The parent RCTs showed the efficacy of CSM in IBS symptom reduction and enhancement of QOL (Jarrett et al., 2016; Jarrett et al., 2009). This study provides new evidence about a genetic factor that might reveal information about the pathophysiology of IBS, as well as a predictive factor in terms of symptom improvement following a nonpharmacologic therapy. We found that the functional Val158Met polymorphism of *COMT* was related to CSM intervention outcomes with respect to psychological distress and several GI symptoms (i.e., abdominal distension, constipation, and intestinal gas). For these measures we observed that participants who carried at least one Val allele derived greater benefits from CSM compared to those with the Met/Met genotype. Our findings are consistent with the results of two previous studies where *COMT* genotype was found to have a moderating effect on CBT outcomes (Carroll et al., 2015; Lonsdorf et al., 2010).

Though *COMT* polymorphism has been associated with pain and psychological distress in patients with other chronic diseases (Gatt, Burton, Williams, & Schofield, 2014; Scheggia, Sannino, Luisa Scattoni, & Papaleo, 2012; Tammimaki & Mannisto, 2012), our study showed only one difference (i.e., intestinal gas) in baseline symptom severity by *COMT* genotype. These results are similar to Karling et al. (2011) findings in a Swedish IBS cohort who showed no differences in severity of abdominal pain, bloating and psychological

distress by *COMT* genotype. Hall et al. (2015) in U.S. participants with IBS (*N* = 82, 94% European-American) found no significant differences in severity of GI symptoms or anxiety by *COMT* genotype.

Our secondary analyses also showed no differences in baseline abdominal pain severity by *COMT* genotype. IBS is a heterogeneous condition with a variety of phenotypic characteristics in relation to visceral hypersensitivity (e.g., pain related to meals, diarrhea, constipation, and mixed bowel patterns) and is associated with several risk factors including prior intestinal infection, epigenetic modifications due to early adverse life events, and chronic inflammation (Makker et al., 2015). Therefore, there is likely diversity in the pathophysiological mechanisms accounting for somatic nociceptive and visceral pain (Karling et al., 2011). As such, the activity of *COMT* may influence pain sensitivity differently in IBS as compared to other chronic pain disorders (Karling et al., 2011; Sikandar & Dickenson, 2012). In addition, abdominal pain could be also influenced by a number of other genotypes such as those involved in serotonin and immune pathways (Camilleri, 2013). For example, Colucci et al. (2013) studied IBS patients and found that *s* allele (low-producing) carriers of serotonin reuptake transporter gene (*SERT)* had higher abdominal pain severity than the *l/l* allele (high-producing) carriers. Therefore, additional, large sample studies are warranted to examine the associations of *COMT* polymorphism with pain in IBS.

In our study, the *COMT* genotype by CSM interactions on psychological distress may reflect the way in which *COMT* genotype shapes signal transmission through dopamine D1 and D2 receptors (Witte & Flöel, 2012). The Met allele is associated with increased tonic dopamine transmission (Witte & Flöel, 2012). It can be conjectured that this would result in greater tonic stimulation of dopamine D1 receptors in the prefrontal cortex, an area important for regulating attention and distraction, impulse control and organization of emotional reactions (Gao et al., 2016). In contrast, the Val allele is associated with increased phasic dopamine transmission and cognitive flexibility. This cognitive flexibility is proposed to be a key factor of response to CBT, due to greater activation of dopamine D2 type receptors (Carroll et al., 2015; Witte & Flöel, 2012). Thus, the greater cognitive flexibility conveyed by the Val allele may be associated with an improved learning capacity required to incorporate CSM strategies of self-management.

The stronger *COMT* genotype by CSM intervention interactions at three months compared to six months follow up suggests that the genotype influence may wane with time or that the stronger interaction at three months is influenced by proximity of the participant to their interaction with the nurse therapist (Fairman, 2010). An analyses of interview data from 81 participants in our RCT-2 (Jarrett et al., 2016) revealed that 94% of 81 participants in the CSM group continued to use at least six of CSM strategies at 12 months follow up (Zia, Barney, Cain, Jarrett, & Heitkemper, 2016). This may suggest that the *COMT* genotype contributes to the initial learning and incorporation of behavior change, but that over time, its contribution are less important to sustaining behavior learned in the CSM intervention.

In IBS, there is increasing evidence that environmental factors, especially early childhood adverse events, may play an important role in symptom phenotypes and gene expression (O'Mahony et al., 2009). A study of adult Spanish twins (Goldberg et al., 2013) showed that

a history of childhood maltreatment was significantly associated with enhanced cognitive performance in participants with Met/Met genotype but not Val/Met and Val/Val groups, suggesting that there may be *COMT* gene-environment interaction related to cognition. Other daily life stressors such as finances, child care, and the lack of family/social supports that are associated with IBS symptoms (Hertig et al., 2007; Levy et al., 1997) may also influence the expression of *COMT* (Collip et al., 2011). Many of our participants reported stress related to finances, lack of family support and job instability as major daily stressors. Thus, both early childhood, as well as adult stressors, need to be considered in future trials.

Limitations

There are several limitations in this study. First, the sample size was relatively small. To reduce variability of race/ethnicity, only those who self-reported European-American participants were included. Due to this, the results cannot be generalized to other racial/ethnic groups (Fiocco et al., 2010; Humphreys, Scheeringa, & Drury, 2014). Second, although both men and women were included, the sample was predominantly female. Third, we did not perform gene expression studies, which would help to clarify the functional significance of our observations. For these reasons, the results of this study should be interpreted with caution. Our results suggest that while *COMT* Val158Met has no relationship to daily abdominal pain perception; it is associated with who is likely to experience a decrease in daily psychological distress following a cognitively focused therapy. This effect needs to be confirmed with future follow-up studies in more diverse and larger populations. Further research will be required to fully understand the mechanisms of interaction between *COMT* genotype and CBT. These studies will likely include other genetic polymorphisms, along with measures of gene expression (transcriptomics), or proteomics to examine protein changes. The interactions among *COMT* genotype, time, intervention, and environmental factors (e.g., gene × treatment × environment) should be also considered in future studies.

Conclusion

Taken together, our results suggest that IBS patients carrying at least one Val allele of the *COMT* have a better response, at least short term, in particular greater reduction in psychological distress, to a CSM intervention compared to Met/Met homozygotes. This could be useful in clinical practice to identify those individuals who are most likely to benefit from a cognitive-behavioral intervention in IBS. Further research on the *COMT* Val158Met polymorphism in larger and more diverse samples of patients with IBS is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline Primary and Secondary Outcomes by *COMT* Genotype

	Val/Val (*n* = 44)		Val/Met (*n* = 87)		Met/Met (*n* = 41)		
Scale/item	***M***	**(*SD*)**	***M***	**(*SD*)**	***M***	**(*SD*)**	***p***
Daily Symptom Severity[a]							
Abdominal pain	40.6	(27.7)	34.9	(23.9)	39.9	(26.5)	.41
Depression	5.9	(11.0)	9.3	(13.4)	9.6	(16.2)	.36
Anxiety	19.9	(27.7)	15.9	(18.8)	19.9	(21.1)	.42
Feeling stressed	26.9	(23.1)	24.7	(25.0)	28.2	(26.7)	.74
Abdominal pain after eating	30.6	(27.4)	28.5	(22.7)	33.9	(31.6)	.55
Abdominal distension	29.3	(28.6)	30.6	(27.8)	41.5	(35.3)	.11
Intestinal gas	36.4	(30.4)	40.7	(28.6)	53.2	(31.4)	.03
Bloating	28.4	(25.9)	30.5	(26.4)	40.6	(36.2)	.11
Flatulence	42.2	(30.8)	45.0	(27.4)	51.1	(32.3)	.36
Constipation	18.4	(19.6)	23.3	(24.1)	23.5	(27.5)	.49
Diarrhea	15.6	(22.6)	15.1	(21.4)	16.8	(22.6)	.92
Urgency	22.1	(26.2)	17.5	(22.7)	23.2	(25.8)	.39
Fatigue	31.2	(25.2)	35.2	(27.6)	39.4	(30.9)	.41
Sleepiness during the day	23.2	(24.1)	27.2	(24.8)	27.7	(30.2)	.65
Panic	4.4	(11.5)	4.2	(7.1)	4.8	(11.8)	.06
Retrospective Psychological Distress[b]							
Depression	0.4	(0.4)	0.5	(0.5)	0.5	(0.4)	.79
Anxiety	0.6	(0.6)	0.5	(0.5)	0.7	(0.6)	.50
Global Severity Index (GSI)	0.5	(0.4)	0.5	(0.3)	0.5	(0.4)	.83
IBS Quality of Life[c]	70.1	(13.7)	70.0	(13.9)	69.1	(12.7)	.93
Cognitive Beliefs about IBS[d]	4.8	(1.0)	4.4	(0.1)	4.5	(1.1)	.13

Note. *N* = 172; UC: *n* = 61, CSM: *n* = 111. *COMT* = catechol-O-methyltransferase; CSM = comprehensive self-management; IBS = irritable bowel syndrome; *SD* = standard deviation; UC = usual care.

[a]Based on daily diary (percent of days with moderate to very severe symptom rating); scores can range from 0–100.

[b]Brief Symptom Inventory (BSI); scores can range from 0–4.

[c] Scores can range from 0–100.

[d] Scores can range from 0–7; high scores reflect negative attitudes.

TABLE 2

Mean Changes in Primary Outcomes by *COMT* Genotype Within Usual Care and Comprehensive Self-Management Groups

		Val/Val		Val/Met		Met/Met		
Group	**Time/outcome**	***M***	**(*SD*)**	***M***	**(*SD*)**	***M***	**(*SD*)**	***p***
UC	3 months[a]							
	Abdominal pain	−4.4	(12.6)	0.7	(23.1)	−10.3	(16.5)	.36
	Depression	−1.7	(5.6)	5.5	(17.8)	0.5	(10.9)	.03
	Anxiety	−6.1	(12.6)	6.5	(21.7)	−4.7	(14.1)	.06
	Feeling stressed	−8.1	(18.3)	2.2	(21.6)	−10.0	(14.8)	.08
	6 months[b]							
	Abdominal pain	−8.3	(25.4)	−0.1	(24.7)	−3.9	(22.4)	.63
	Depression	5.4	(11.3)	3.2	(20.2)	−2.2	(10.5)	.25
	Anxiety	0.6	(17.5)	5.4	(21.4)	1.7	(14.5)	.89
	Feeling stressed	0.6	(24.3)	2.9	(24.6)	−2.3	(15.1)	.86
CSM	3 months							
	Abdominal pain	−22.2	(29.2)	−15.7	(21.1)	−13.3	(23.2)	.86
	Depression	−1.3	(9.0)	−1.2	(13.1)	4.6	(15.8)	.13
	Anxiety	−10.3	(18.2)	−4.3	(16.1)	5.8	(20.1)	.01
	Feeling stressed	−13.5	(21.6)	−4.1	(21.1)	1.4	(22.5)	.02
	6 months							
	Abdominal pain	−26.7	(29.1)	−14.9	(21.9)	−10.9	(20.4)	.06
	Depression	−0.3	(12.2)	−3.2	(9.6)	2.8	(14.9)	.26
	Anxiety	−11.4	(27.7)	−5.5	(20.4)	−3.4	(20.6)	.66
	Feeling stressed	−15.4	(26.9)	−7.5	(21.6)	−6.6	(18.9)	.53

Note. Mean changes were calculated from baseline to each time point. Differences in mean changes were evaluated by *COMT* genotype at each time point within UC and CSM groups. *COMT* = catechol-O-methyltransferase; CSM = comprehensive self-management; *SD* = standard deviation; UC = usual care.

[a]Sample sizes at 3 months were UC: $n = 57$ and CSM: $n = 104$.

[b]Sample sizes at 6 months were UC: $n = 57$, CSM: $n = 101$.

TABLE 3

Interaction of Intervention with *COMT* Genotype for the Primary Outcomes

					p	
Time/outcome	***COMT* genotype**[a]	***b***[b]	**(*SE*)**	**95% CI**	***b***	**Interaction**[c]
3 months[d]						
Abdominal pain	Val/Val	−6.1	(7.4)	[−20.5, 8.3]	.41	.31
	Val/Met	−10.9	(7.1)	[−24.9, 3.1]	.13	
Depression	Val/Val	−3.4	(4.9)	[−12.9, 6.2]	.49	.15
	Val/Met	−10.1	(5.8)	[−21.4, 1.3]	.08	
Anxiety	Val/Val	−12.0	(6.5)	[−24.7, 0.7]	.06	.01
	Val/Met	−21.6	(7.2)	[−35.7, −7.5]	.003	
Feeling stressed	Val/Val	−15.1	(6.9)	[−28.8, −1.4]	.03	.01
	Val/Met	−20.6	(6.9)	[−34.2, −6.9]	.003	
6 months[e]						
Abdominal pain	Val/Val	−8.5	(9.9)	[−27.9, −11.0]	.40	.67
	Val/Met	−7.1	(8.9)	[−24.8, 10.5]	.43	
Depression	Val/Val	−10.2	(6.0)	[−22.0, 1.6]	.09	.14
	Val/Met	−10.5	(5.9)	[−22.0, 0.9]	.07	
Anxiety	Val/Val	−5.0	(8.3)	[−21.3, 11.2]	.54	.69
	Val/Met	−6.4	(7.5)	[−21.1, 8.2]	.39	
Feeling stressed	Val/Val	−10.5	(8.9)	[−28.1, 7.1]	.24	.47
	Val/Met	−6.4	(7.5)	[−21.1, 8.2]	.39	

Note. CI = confidence interval; *COMT* = catechol-O-methyltransferase; CSM = comprehensive self-management; *SE* = standard error; UC = usual care.

[a] Met/Met group is a reference category.

[b] β = the extent to which the intervention effect (“mean change in the CSM group” minus “mean change in the UC group”) is stronger in those with Val/Val and Val/Met vs. Met/Met homozygotes (reference group).

[c] *COMT* × Intervention (UC vs. CSM).

[d] Sample sizes at 3 months were UC: $n = 57$ and CSM: $n = 104$.

[e] USample sizes at 6 months were UC: $n = 57$ and CSM: $n = 101$.

TABLE 4

Interaction of Intervention with *COMT* Genotype (Val Allele Carriers vs. Met/Met Homozygotes) for the Primary Outcomes

Time/outcome	*COMT* genotype[a]	*b*[b]	(*SE*)	95% CI	*p*[c]
3 months[d]					
Abdominal pain	Val/Val + Val/Met	−9.2	(5.0)	[−21.9, 3.5]	.16
Depression	Val/Val + Val/Met	−7.9	(5.2)	[−18.1, 2.3]	.13
Anxiety	Val/Val + Val/Met	−18.3	(6.5)	[−31.0, −5.4]	.005
Feeling stressed	Val/Val + Val/Met	−18.6	(6.3)	[−30.9, −6.3]	.003
6 months[e]					
Abdominal pain	Val/Val + Val/Met	−7.4	(8.6)	[−24.3, 9.4]	.39
Depression	Val/Val + Val/Met	−10.5	(5.3)	[−20.9, 0.01]	.05
Anxiety	Val/Val + Val/Met	−5.9	(7.0)	[−19.7, 7.8]	.40
Feeling stressed	Val/Val + Val/Met	−7.7	(6.9)	[−21.2, 5.8]	.26

Note. CI = confidence interval; *COMT* = catechol-O-methyltransferase; CSM = comprehensive self-management; *SE* = standard error; UC = usual care.

[a] Met/Met group is a reference category.

[b] Coefficient gives the extent to which the intervention effect ("mean change in the CSM group" minus "mean change in the UC group") is stronger in those with Val allele carriers versus Met/Met homozygotes (reference group).

[c] For the *COMT* × Intervention (UC vs. CSM) interaction.

[d] Sample sizes at 3 months were UC: $n = 57$ and CSM: $n = 104$.

[e] Sample sizes at 6 months were UC: $n = 57$ and CSM: $n = 101$.