TPH Gene Polymorphisms Are Associated With Disease Perception and Quality of Life in Women With Irritable Bowel Syndrome

Sang-Eun Jun, RN, PhD1, Ruth Kohen, MD2, Kevin C. Cain, PhD3, Monica E. Jarrett, RN, PhD4, and Margaret M. Heitkemper, RN, PhD4

Abstract

The aims of this exploratory study were to examine whether tryptophan hydroxylase (TPH) gene polymorphisms are associated with psychosocial factors in women with irritable bowel syndrome (IBS). TPH is the rate-limiting enzyme in the biosynthesis of serotonin and has two isoforms, TPH1 and TPH2. Four single nucleotide polymorphisms (SNPs) in the TPH1 gene and one SNP in the TPH2 gene were selected based on previous studies investigating associations between these SNPs and psychiatric or behavioral disorders. One hundred ninety-nine Caucasian women with IBS were included. Results of univariate analysis showed no association between TPH1 and TPH2 gene SNPs and current level of psychological distress or psychiatric illness. However, TPH1 gene SNPs were associated with IBS-related cognitions (rs4537731 and rs21105) and quality of life (rs684302 and rs1800532), in particular the mental health and energy subscales. These associations were independent of the subjects’ levels of gastrointestinal symptoms. These results suggest that patients’ perception of their illness, and of the impact it has on their lives, may be subject to genetic influences, in this case sequence variants in TPH1. However, caution should be used in interpreting these results given the large number of hypothesis tests performed in this exploratory hypothesis-generating study, and the results should be considered tentative until confirmed in an independent sample.

Keywords

irritable bowel syndrome, tryptophan hydroxylase, polymorphism, disease perception, quality of life

Numerous studies have shown that irritable bowel syndrome (IBS), a chronic functional disorder of the gastrointestinal (GI) tract, aggregates in families (Locke, Zinsmeister, Talley, Fett, & Melton, 2000; Saito et al., 2010; Saito et al., 2008). This finding has prompted investigators to consider the role of genetics in this chronic condition. Thus far, researchers have examined over 60 genes for their potential association with IBS (Saito, 2011). Because of the role of serotonin in both the central nervous system and the GI tract, genes involved in the regulation of serotonin (5-hydroxytryptamine, 5-HT) have received particular attention.

The level of 5-HT in the synaptic cleft is regulated by its synthesis as well as its reuptake. Thus, alterations in 5-HT biosynthesis or reuptake change its availability. Clinically, serotonergic drugs (5-HT3 antagonists, 5-HT4 agonists) have been developed and tested for their efficacy in patients with IBS (Saad, 2011; Spiller, 2011). At the same time, animal studies have validated the role of 5-HT in enterochromaffin (EC) cells and enteric neurons on gut motility and visceral sensitivity (Coates, Johnson, Greenwood-Van Meerveld, & Mawe, 2006; Zhao et al., 2011).

Tryptophan hydroxylase (TPH) is the rate-limiting enzyme of 5-HT synthesis; therefore TPH gene variants have been evaluated for possible associations with disorders whose underlying pathophysiology is related to 5-HT. One published Phase II trial of LX1031, a TPH inhibitor, shows clinical benefit in patients with nonconstipating IBS (Brown et al., 2011). However, not all patients benefited, which may reflect dosing or perhaps other differences. For example, Camilleri et al.

1 College of Nursing, Keimyung University, Daegu, South Korea
2 Department of Psychiatry & Behavioral Sciences, University of Washington, Seattle, WA, USA
3 Department of Biostatistics and Office of Nursing Research, University of Washington, Seattle, WA, USA
4 Department of Biobehavioral Nursing and Health Systems, University of Washington, Seattle, WA, USA

Corresponding Author:
Margaret M. Heitkemper, RN, PhD, Department of Biobehavioral Nursing and Health Systems, Box 357266, University of Washington, Seattle, WA 98195, USA.
Email: heit@uw.edu
(2002) showed that patients with the \textit{SERT} 5-HTTLPR l/l genotype were more responsive to alosetron (a 5-HT3 antagonist).

TPH has two isoforms, TPH1 and TPH2, with overall 71% identity in amino acid sequence between them in humans (Walther & Bader, 2003). TPH1 consists of 444 amino acids and is encoded on chromosome 11p15.3-p14 with a length of 29 kbp and composed of 11 exons (Paoloni-Giacobino et al., 2000). TPH2 consists of 490 amino acids and is encoded on chromosome 12q21.1 with a length of 93.6 kbp and composed of 11 exons (Zill, Butterer, Eisenmenger, Bondy, & Ackenheim, 2004). TPH2 is mainly expressed in the brain, while TPH1 is expressed both in the brain and in the periphery such as EC cells in the gut (Walther & Bader, 2003; Zill et al., 2007). In an earlier report we described possible associations between two \textit{TPH1} gene single nucleotide polymorphisms (SNPs), rs4537731 and rs211105, and daily reporting of GI symptoms including diarrhea, bloating, and loose stools in European American women with IBS (\(N = 199\); Jun, Kohen, Cain, Jarrett, & Heitkemper, 2011). In that study we also showed possible associations between a \textit{TPH2} gene SNP in the promoter region, rs4590625, and stool characteristics, such as diarrhea and constipation.

It is well documented that patients with IBS report symptoms suggesting an increased frequency of psychopathological disorders, abnormal personality traits, psychological distress, and sexual abuse (Farnam, Somi, Sarami, & Farhang, 2008; Morken, Lind, Valeur, Wilhelmson, & Berstad, 2009; Seres et al., 2008). The comorbidity of mood disorders with IBS necessitates attention to psychological distress as an important mediating variable in symptom experiences. Researchers have investigated variants of the \textit{TPH} genes for possible associations with migraine without aura (Jung et al., 2010) and psychological disorders such as major depression (Gizatullin, Zaboli, Jonsson, Asberg, & Leopardi, 2006), suicidal behavior (Galfalvy, Huang, Oquendo, Currier, & Mann, 2009), bipolar disorder (Chen, Glatt, & Tsuang, 2008), attention-deficit/ hyperactivity disorder (Halmoy et al., 2010), and anger-related personality traits (Rujescu et al., 2002).

Given the high psychiatric comorbidity in IBS, it is of interest to investigate a possible association of \textit{TPH} gene polymorphisms with cognitive, psychological, and psychiatric factors in IBS patients. Therefore, the aims of the present study were to examine whether \textit{TPH} gene polymorphisms are associated with psychosocial factors in women with IBS across four domains: current psychological distress, cognitive beliefs about IBS, disease-specific quality of life (QOL), and lifetime history of mental disorders. We selected four SNPs in the \textit{TPH1} gene and one SNP in the \textit{TPH2} gene for genotyping because they are among those shown in the literature cited above to be related to psychological disorders or distress. The \textit{TPH1} SNPs are rs4537731 (-6526A/G), rs684302, rs21105, and rs1800532 (A218C), and the \textit{TPH2} SNP is rs4570625 (-709G/T). For convenience, we numbered all SNPs by their locations within the genes.

**Materials and Methods**

**Subjects**

DNA samples and survey data were assembled from three studies of IBS carried out in Washington State (Jarrett et al., 2009; Jarrett et al., 2007; Motzer, Jarrett, Heitkemper, & Tsuji, 2002). All participants had a prior diagnosis of IBS made by a health care provider and currently met \textit{Rome III} criteria (Drossman et al., 2006). We recruited participants through community advertisement. Subjects were excluded if they (1) had a history of coexisting GI pathology (e.g., inflammatory bowel disease) or surgery (e.g., bowel resection), renal or reproductive pathology (e.g., endometriosis), severe fibromyalgia, infectious disease (e.g., hepatitis B or C), or severe cardiovascular disease or (2) were currently taking any of the following medications more than 3 days a week: antibiotics, anticholinergics, cholestyramine, narcotics, colchicines, docusate, an enema preparation, iron supplements, or laxatives. The University of Washington’s institutional review board approved the protocol for this study, and all the patients gave written informed consent. The HapMap project (http://www.hapmap.org) results showed that the minor allele frequencies of all the selected SNPs differ across ethnicities, and our data showed patterns similar to the HapMap results (data not shown). The only ethnic group with a large enough sample size for a reasonable analysis in the present study was Caucasian; thus we restrict analysis in this report to only those women who identified themselves as Caucasian. This resulted in an analysis set of 199 women with IBS, of which 20% (\(n = 41\)) met criteria for constipation-predominant, 44% (\(n = 88\)) for diarrhea-predominant, and 26% (\(n = 52\)) for mixed IBS.

**Genotyping**

Genomic DNA was extracted from buffy coat preparations (Miller, Dykes, & Polesky, 1988) using Puregene DNA Purification kits (Gentra Systems, Inc., Minneapolis, MN). Genotyping was done using Applied Biosystems (ABI, Foster City, CA) TaqMan custom genotyping assays and an ABI 7300 Real-time PCR System as shown in our previous report (Jun et al., 2011). The minor allele frequencies in our sample for SNP1 to SNP5 were 0.39, 0.44, 0.21, 0.42, and 0.18, respectively.

**Measures**

**Current psychological distress.** The Brief Symptom Inventory (BSI) has 53 items that ask how much a certain problem has bothered the subject over the last 7 days (Derogatis, 1993). Each item of the BSI is rated on a 5-point scale that ranges from 0 (\textit{not at all}) to 4 (\textit{extremely}) and profiled into one of nine subscales—somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism—and a global severity index (GSI) as a mean score of all items. The internal consistency in the present sample, as measured by Cronbach’s alpha, was \(\alpha = .94\) for the GSI, \(\alpha = .79\) for anxiety, and \(\alpha = .79\) for depression.
History of mental disorders. We assessed history of mental disorders using the World Health Organization Composite International Diagnostic Interview (CIDI). This instrument is a fully structured diagnostic interview administered via a computer to derive diagnoses of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and International Classification of Disease, 10th revision (ICD-10) mental disorders. We used the CIDI mood-disorders module (depression as single and recurrent episode, dysthymia, and mania), anxiety-disorders module (panic disorder with or without agoraphobia, agoraphobia, generalized anxiety disorder, obsessive–compulsive disorder, phobias including social phobia, and posttraumatic stress disorder), and suicidal ideation module (recurrent thoughts of death, suicidal ideation, and suicide attempt) in this study (Andrews & Peters, 1998).

Cognitive beliefs. The Cognitive Scale for Functional Bowel Disorders (CS-FBD) contains items related to cognitions about bowel function and personal characteristics relevant to IBS (Toner et al., 1998). Each item is rated on a 7-point scale, ranging from 1 (strongly disagree) to 4 (neither agree/disagree) to 7 (strongly agree). Typical items are, “I often worry there might not be a toilet available when I need it,” and “I often feel this abdominal pain will never go away.” We included 6 items in addition to the original 25 in order to calculate two subscales: pain and bowel performance anxiety. The six additional items had been part of the original version of the instrument, and the correlation between the extended version and the standard version was .99 in our study. A total cognitive score was the mean of all 31 items, with higher scores indicating more negative cognition regarding IBS symptoms and consequences. For the present study, the internal consistency was \( \alpha = .942 \) for the total score, \( \alpha = .685 \) for pain, and \( \alpha = .941 \) for bowel performance anxiety.

Illness impact and quality of life. The IBS-specific Quality of Life (IBS-QOL) instrument is a 31-item questionnaire with nine subscales: emotional, mental health, sleep, energy, physical functioning, diet, social role, physical role, and sexual relations (Hahn, Kirchdoerfer, Fullerton, & Mayer, 1997). Example items are “How often during the past 4 weeks did your IBS make you feel worried?” scored from 0 (none of the time) to 6 (all of the time) and “During the past 4 weeks, how much of the time did you feel emotionally worn out and tired because of IBS?” scored from 1 (every day) to 5 (none). We transformed the scales to standard scales of 0 (poor quality of life) to 100 (highest quality of life). We computed a total score by averaging all subscales except sexual relations because answers to this portion were missing for a large portion of the sample. Internal consistency for subscales ranged from \( \alpha = .745 \) to \( \alpha = .916 \).

Daily diary. We measured the mean score of GI symptoms using a daily dairy that participants filled in for 28 days (Jun et al., 2011). Participants rated the symptoms of abdominal pain, diarrhea, constipation, bloating, and intestinal gas with fractures.

### Table 1. Participant Demographic Characteristics (N = 199).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)*</td>
<td>40.0 (14.0)</td>
</tr>
<tr>
<td>Married/partnered (%)</td>
<td>41</td>
</tr>
<tr>
<td>Education, bachelor’s degree or higher (%)</td>
<td>66</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td>Professional 40, Technical, service, and sales 25, Student 10, Other 25</td>
</tr>
<tr>
<td>Psychological distress, mean (SD)</td>
<td>Somatization 0.49 (0.45), Obsessive–compulsive 0.86 (0.68), Interpersonal sensitivity 0.55 (0.62), Depression 0.46 (0.53), Anxiety 0.56 (0.55), Hostility 0.38 (0.38), Phobic anxiety 0.20 (0.49), Paranoid ideation 0.34 (0.48), Psychoticism 0.27 (0.42), Global Symptom Index 0.47 (0.39)</td>
</tr>
<tr>
<td>Predominant bowel pattern (Rome III), n (%)*</td>
<td>Constipation 41 (21), Diarrhea 89 (45), Mixed 52 (26), Unsubtypeated 17 (9)</td>
</tr>
</tbody>
</table>


Hardy–Weinberg equilibrium was tested using Pearson’s \( \chi^2 \) tests. We used analysis of covariance to assess the association of BSI scores and CS-FBD scores with individual SNPs, adjusting for age as a covariate because scores were correlated with age. Associations with IBS-QOL scores of individual SNPs were tested by analysis of variance. We tested 30 hypotheses and 5 SNPs; to adjust for multiple comparisons, a \( p \) value of less than .05/150 = .0003 would be considered to be significant. Because of the exploratory nature of our study, however, we present the results without correction for multiple testing, and they should be interpreted with this in mind. All \( p \) values were two-sided and \( p < .05 \) was considered statistically significant.

### Results

The total sample included 199 women with IBS. Demographic characteristics appear in Table 1. Only unrelated Caucasian women were included in the analysis. Participants in this study were relatively well educated, with more than a majority reporting a bachelor’s degree or higher.
None of the TPH gene polymorphisms were statistically significantly associated with current psychological distress as measured by GSI scores in women with IBS. Similarly no associations were found with the individual subscales of the BSI (Table 2). Likewise, we found no association between TPH gene polymorphisms and lifetime history of mental health disorders measured by CIDI in the IBS group (Table 3).

In contrast, SNP1 and SNP3 in the TPH1 gene were associated with IBS-related negative cognitions (Table 4). These associations did not change substantially when controlling for GSI and mean score of GI symptoms (abdominal pain, diarrhea, constipation, bloating, and intestinal gas). SNP5 of the TPH2 gene did not show any association with IBS-related cognitions.

TPH1, but not TPH2, gene polymorphisms were associated with QOL scores, in particular the mental health and energy subscales (Table 5). These associations were strengthened if GSI and mean GI symptom score were controlled for in the analysis.

Since use of antidepressant or antianxiety medications could affect reports of psychological symptoms, we repeated analyses while excluding all subjects taking such medications. The results did not change substantially from those reported here, with one exception: in the subset of patients not taking antidepressant or antianxiety medications, there was a significant ($p = .018$) association between SNP4 on the TPH1 gene and the GSI, with the GSI being higher in GG than in GT subjects.

### Table 2. Association Between TPH Gene Polymorphisms and Current Psychological Distress as Measured by the BSI in Women With Irritable Bowel Syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Genotype</th>
<th>$p$ Value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPH1 SNP1 (rs4537731)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA (n = 75)</td>
<td>AG (n = 96)</td>
</tr>
<tr>
<td></td>
<td>GG (n = 27)</td>
<td></td>
</tr>
<tr>
<td>GSI</td>
<td>0.49 (0.39)</td>
<td>0.49 (0.43)</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.49 (0.44)</td>
<td>0.51 (0.47)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.50 (0.60)</td>
<td>0.48 (0.53)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.62 (0.64)</td>
<td>0.55 (0.53)</td>
</tr>
<tr>
<td><strong>TPH1 SNP2 (rs684302)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC (n = 63)</td>
<td>CT (n = 97)</td>
</tr>
<tr>
<td></td>
<td>TT (n = 39)</td>
<td></td>
</tr>
<tr>
<td>GSI</td>
<td>0.44 (0.32)</td>
<td>0.49 (0.43)</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.49 (0.46)</td>
<td>0.49 (0.43)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.39 (0.44)</td>
<td>0.51 (0.59)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.49 (0.43)</td>
<td>0.59 (0.60)</td>
</tr>
<tr>
<td><strong>TPH1 SNP3 (rs211105)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT (n = 124)</td>
<td>GT (n = 66)</td>
</tr>
<tr>
<td></td>
<td>GG (n = 9)</td>
<td></td>
</tr>
<tr>
<td>GSI</td>
<td>0.47 (0.37)</td>
<td>0.49 (0.45)</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.48 (0.45)</td>
<td>0.49 (0.46)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.47 (0.54)</td>
<td>0.47 (0.54)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.59 (0.58)</td>
<td>0.53 (0.52)</td>
</tr>
<tr>
<td><strong>TPH1 SNP4 (rs1800532)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC (n = 72)</td>
<td>AC (n = 89)</td>
</tr>
<tr>
<td></td>
<td>AA (n = 38)</td>
<td></td>
</tr>
<tr>
<td>GSI</td>
<td>0.46 (0.35)</td>
<td>0.48 (0.43)</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.49 (0.46)</td>
<td>0.49 (0.43)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.43 (0.45)</td>
<td>0.49 (0.60)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.53 (0.45)</td>
<td>0.56 (0.61)</td>
</tr>
<tr>
<td><strong>TPH2 SNP5 (rs4570625)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG (n = 130)</td>
<td>GT (n = 62)</td>
</tr>
<tr>
<td></td>
<td>TT (n = 6)</td>
<td></td>
</tr>
<tr>
<td>GSI</td>
<td>0.49 (0.39)</td>
<td>0.43 (0.40)</td>
</tr>
<tr>
<td>Somatization</td>
<td>0.52 (0.46)</td>
<td>0.46 (0.44)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.46 (0.52)</td>
<td>0.46 (0.57)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.60 (0.56)</td>
<td>0.51 (0.56)</td>
</tr>
</tbody>
</table>

Note. Data are reported as mean (SD). BSI = Brief Symptom Inventory; GSI = global severity index; SNP = single nucleotide polymorphism; TPH = tryptophan hydroxylase.

$^a p$ Value based on one-way analysis of variance while controlling for age.

**Discussion**

In this exploratory study, we examined possible associations between TPH gene polymorphisms and psychosocial factors in women with IBS. We found significant associations of TPH1, but not TPH2, polymorphisms with IBS-related cognitions and IBS-specific QOL. Interestingly, the associations between TPH1 SNPs and IBS-QOL were strengthened once we controlled for the GSI and severity of GI symptoms, while...
### Table 3. Prevalence of Depressive and Anxiety Disorders by TPH Gene Polymorphisms in Women with IBS.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n (%)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPH1 SNP1 (rs4537731)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type of depressive episodes or dysthymia</td>
<td>33 (43%)</td>
<td>39 (41%)</td>
</tr>
<tr>
<td>Recurrent moderate-to-severe depressive episode</td>
<td>14 (18%)</td>
<td>23 (24%)</td>
</tr>
<tr>
<td>Suicide ideation</td>
<td>22 (31%)</td>
<td>27 (29%)</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>35 (46%)</td>
<td>38 (40%)</td>
</tr>
<tr>
<td>GAD</td>
<td>13 (18%)</td>
<td>13 (14%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>8 (11%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td><strong>TPH1 SNP2 (rs684302)</strong></td>
<td>CC (n = 63)</td>
<td>CT (n = 97)</td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type of depressive episodes or dysthymia</td>
<td>27 (43%)</td>
<td>36 (37%)</td>
</tr>
<tr>
<td>Recurrent moderate-to-severe depressive episode</td>
<td>14 (22%)</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>Suicide ideation</td>
<td>19 (32%)</td>
<td>21 (22%)</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>27 (43%)</td>
<td>37 (38%)</td>
</tr>
<tr>
<td>GAD</td>
<td>8 (13%)</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>9 (15%)</td>
<td>14 (15%)</td>
</tr>
<tr>
<td><strong>TPH1 SNP3 (rs211105)</strong></td>
<td>TT (n = 125)</td>
<td>GT (n = 66)</td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type of depressive episodes or dysthymia</td>
<td>56 (45%)</td>
<td>24 (36%)</td>
</tr>
<tr>
<td>Recurrent moderate-to-severe depressive episode</td>
<td>27 (22%)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>Suicide ideation</td>
<td>32 (26%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>55 (44%)</td>
<td>25 (38%)</td>
</tr>
<tr>
<td>GAD</td>
<td>20 (16%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>16 (13%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td><strong>TPH1 SNP4 (rs1800532)</strong></td>
<td>CC (n = 72)</td>
<td>AC (n = 89)</td>
</tr>
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<td><strong>Depressive disorders</strong></td>
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<td>Suicide ideation</td>
<td>21 (30%)</td>
<td>19 (22%)</td>
</tr>
<tr>
<td><strong>Anxiety disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>30 (42%)</td>
<td>35 (40%)</td>
</tr>
<tr>
<td>GAD</td>
<td>10 (15%)</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>11 (16%)</td>
<td>12 (14%)</td>
</tr>
<tr>
<td><strong>TPH2 SNP5 (rs4570625)</strong></td>
<td>GG (n = 131)</td>
<td>GT (n = 62)</td>
</tr>
<tr>
<td><strong>Depressive disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any type of depressive episodes or dysthymia</td>
<td>60 (46%)</td>
<td>22 (36%)</td>
</tr>
<tr>
<td>Recurrent moderate-to-severe depressive episode</td>
<td>30 (23%)</td>
<td>10 (16%)</td>
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<tr>
<td>Suicide ideation</td>
<td>36 (29%)</td>
<td>15 (25%)</td>
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<tr>
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<tr>
<td>GAD</td>
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<td>8 (14%)</td>
</tr>
<tr>
<td>PTSD</td>
<td>19 (15%)</td>
<td>9 (15%)</td>
</tr>
</tbody>
</table>

Note. History of depressive or anxiety disorders was measured using the World Health Organization Composite International Diagnostic Interview (CIDI). GAD = general anxiety disorder; IBS = irritable bowel disorder; PTSD = posttraumatic stress disorder; SNP = single nucleotide polymorphism; TPH = tryptophan hydroxylase.

*p Value based on χ² test.
those between TPH1 SNPs and IBS-related cognitions showed only modest changes. This finding might indicate that current psychological or GI distress did not mediate the links between TPH1 SNPs and cognitions and illness impact on QOL.

CS-FBD is a cognitive scale developed to evaluate the belief systems of patients as they relate to their functional bowel disorders (Toner et al., 1998). IBS-QOL was designed for use in patients with IBS to evaluate their life quality associated with the symptoms of IBS (Hahn et al., 1997). Dysfunctional cognition or negative cognitions impact symptom severity and the emotional consequences of living with IBS. In this context, the biopsychosocial model of IBS provides a theoretical framework for explaining how cognition might affect IBS symptoms (Drossman et al., 2006; Levy et al., 2006). Within this model, genetic predispositions influence physiological dysfunction (e.g., disturbance in motility and/or visceral sensitivity) and the way in which the individual reacts cognitively to recurrent GI symptoms (e.g., catastrophizing).

It is well known that 5-HT modulates developmental states (Nakamura & Hasegawa, 2007). Since TPH is the rate-limiting enzyme in 5-HT synthesis, variations in TPH genes may lead to dysfunction of the serotonin system. A recent study demonstrated that the SNP rs453771 of the TPH1 gene is positively associated with cerebrospinal fluid (CSF) concentrations of the major serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in healthy European Americans (Andreou et al., 2010). The levels of 5-HIAA were higher in those with the minor allele (G/G and A/G) as compared to those with the A/A genotype. However, another study failed to find this association in U.S. patients with major depression (Galfalvy et al., 2009). Investigators have also found TPH2 gene polymorphisms to be associated with 5-HIAA concentrations in the CSF (Zhou et al., 2005). In addition, the effects of acute tryptophan depletion on brain–gut responses and emotional arousal give support to the idea that serotonin availability plays an important role in IBS-related cognitions (Kilkens, Honig, van Nieuwenhoven, Riedel, & Brummer, 2004; Labus et al., 2011).

Although TPH2 is expressed in the brain and has been shown to be linked to a number of disorders associated with cognition, we found no association between negative cognitions about IBS and the TPH2 gene SNP in the present study. It may be that TPH2 influences cognitive measures related to depression, cognitive control, and hyperactivity to a greater degree than it does the negative appraisal of IBS we measured.

Table 4. Association Between TPH Gene Polymorphisms and Cognition About IBS.

<table>
<thead>
<tr>
<th>TPH1 SNP1 (rs4537731)</th>
<th>Genotype Mean (SD)</th>
<th>p Valuea</th>
<th>p Valueb</th>
</tr>
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<tbody>
<tr>
<td>CS-FBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA (n = 71)</td>
<td>4.03 (1.2)</td>
<td>.03*</td>
</tr>
<tr>
<td></td>
<td>AG (n = 91)</td>
<td>4.53 (1.0)</td>
<td>.04*</td>
</tr>
<tr>
<td></td>
<td>GG (n = 27)</td>
<td>4.51 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA (n = 71)</td>
<td>4.10 (1.4)</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>AG (n = 91)</td>
<td>4.50 (1.3)</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>GG (n = 27)</td>
<td>4.80 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Bowel movement anxiety</td>
<td></td>
<td>3.68 (1.5)</td>
<td>.03*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.33 (1.4)</td>
<td>.03*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.21 (1.4)</td>
<td></td>
</tr>
<tr>
<td>TPH1 SNP2 (rs684302)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS-FBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC (n = 48)</td>
<td>4.51 (1.0)</td>
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</tr>
<tr>
<td></td>
<td>CT (n = 80)</td>
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<td>.31</td>
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<td>TT (n = 29)</td>
<td>4.13 (1.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC (n = 48)</td>
<td>4.62 (1.4)</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>CT (n = 80)</td>
<td>4.29 (1.4)</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>TT (n = 29)</td>
<td>4.26 (1.1)</td>
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<tr>
<td>Bowel movement anxiety</td>
<td></td>
<td>4.36 (1.3)</td>
<td>.11</td>
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<td></td>
<td></td>
<td>4.07 (1.6)</td>
<td>.15</td>
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<td>TPH1 SNP3 (rs211105)</td>
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<tr>
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<td></td>
<td>TT (n = 96)</td>
<td>4.18 (1.1)</td>
<td>.05*</td>
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<td>GT (n = 55)</td>
<td>4.57 (1.2)</td>
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<td></td>
<td>GG (n = 6)</td>
<td>4.90 (0.8)</td>
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<tr>
<td>Pain</td>
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<tr>
<td></td>
<td>TT (n = 96)</td>
<td>4.18 (1.3)</td>
<td>.27</td>
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<tr>
<td></td>
<td>GT (n = 55)</td>
<td>4.63 (1.4)</td>
<td>.35</td>
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<tr>
<td></td>
<td>GG (n = 6)</td>
<td>5.28 (1.1)</td>
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<tr>
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<td>3.89 (1.4)</td>
<td>.16</td>
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<tr>
<td></td>
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<td>4.35 (1.5)</td>
<td>.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.67 (1.2)</td>
<td></td>
</tr>
<tr>
<td>TPH1 SNP4 (rs1800532)</td>
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<td></td>
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<tr>
<td>CS-FBD</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>CT (n = 53)</td>
<td>4.57 (1.0)</td>
<td>.04*</td>
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<tr>
<td></td>
<td>CT (n = 53)</td>
<td>4.63 (1.4)</td>
<td>.27</td>
</tr>
<tr>
<td></td>
<td>AC (n = 76)</td>
<td>4.26 (1.4)</td>
<td>.35</td>
</tr>
<tr>
<td></td>
<td>AA (n = 28)</td>
<td>4.25 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Bowel movement anxiety</td>
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<td>4.40 (1.3)</td>
<td>.08</td>
</tr>
<tr>
<td></td>
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<td>.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.67 (1.2)</td>
<td></td>
</tr>
<tr>
<td>TPH2 SNP5 (rs4570625)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS-FBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG (n = 107)</td>
<td>4.38 (1.1)</td>
<td>.07</td>
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<td></td>
<td>GT (n = 45)</td>
<td>4.24 (1.1)</td>
<td>.87</td>
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<td>TT (n = 5)</td>
<td>4.41 (2.1)</td>
<td></td>
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<tr>
<td>Pain</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>GG (n = 107)</td>
<td>4.41 (1.4)</td>
<td>.95</td>
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<td>GT (n = 45)</td>
<td>4.35 (1.3)</td>
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<td>TT (n = 5)</td>
<td>4.40 (1.9)</td>
<td></td>
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<td>4.13 (1.4)</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.96 (1.4)</td>
<td>.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.05 (2.7)</td>
<td></td>
</tr>
</tbody>
</table>

Note. Cognition about IBS was measured with the Cognitive Scale for Functional Bowel Disorders (CS-FBD). Total mean score and mean scores on the pain and bowel movement anxiety subscales are provided here. Higher scores indicate worse cognition. IBS = irritable bowel syndrome; SNP = single-nucleotide polymorphism; TPH = tryptophan hydroxylase.

*p Value based on one-way analysis of variance while controlling for age.

Significant association, p ≤ .05.

*p Value based on one-way analysis of variance while controlling for age, score on the global severity index of the Brief Symptom Inventory and gastrointestinal symptoms (abdominal pain, diarrhea, constipation, bloating, and intestinal gas).
in this sample. However, our data do provide evidence for an association of TPH1 gene polymorphisms with negative cognitions about IBS symptoms, especially as they relate to perception of pain and anxiety over bowel movements. We also saw that TPH1 gene polymorphisms influence IBS-related QOL. For SNP1, the allele (A) we found to be associated with better cognition and higher QOL has previously been associated with lower serotonin levels (Andreou et al., 2010). These findings, together, are in keeping with prior findings that inhibition of TPH, which would cause lower serotonin levels, leads to symptom improvement in patients with IBS (Camilleri, 2011). Several studies have shown associations between TPH1 SNPs and personality traits or psychiatric disorders. SNP1 of TPH1 has been linked to suicidal behavior in patients with mood disorders (Abbar et al., 2001; Bellivier, Chaste, & Malafosse, 2004), anger–aggression-related traits (Rujescu et al., 2002) and schizophrenia (Watanabe, Nunokawa, Kaneko, & Someya, 2007). SNP4 has been shown to moderate

### Table 5. Association Between TPH Gene Polymorphisms and IBS-QOL.

<table>
<thead>
<tr>
<th>IBS-QOL Measure</th>
<th>Genotype mean (SD)</th>
<th>p Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TPH1 SNP1 (rs4537731)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL-total</td>
<td>AA (n = 71)</td>
<td>71.7 (13.5)</td>
<td>67.8 (14.6)</td>
</tr>
<tr>
<td>Emotional</td>
<td>58.5 (20.3)</td>
<td>79.6 (16.2)</td>
<td>62.3 (18.3)</td>
</tr>
<tr>
<td>Mental health</td>
<td>82.2 (16.0)</td>
<td>75.6 (22.1)</td>
<td>83.5 (13.1)</td>
</tr>
<tr>
<td>Energy</td>
<td>72.4 (21.4)</td>
<td>80.1 (19.4)</td>
<td>66.7 (20.8)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>83.0 (14.9)</td>
<td>61.9 (23.5)</td>
<td>79.2 (18.9)</td>
</tr>
<tr>
<td>Social role</td>
<td>67.1 (22.7)</td>
<td>72.2 (25.6)</td>
<td>63.2 (25.6)</td>
</tr>
<tr>
<td><strong>TPH1 SNP2 (rs684302)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL-total</td>
<td>CC (n = 59)</td>
<td>67.9 (13.3)</td>
<td>69.5 (15.0)</td>
</tr>
<tr>
<td>Emotional</td>
<td>57.5 (19.7)</td>
<td>55.7 (20.4)</td>
<td>59.8 (21.3)</td>
</tr>
<tr>
<td>Mental health</td>
<td>80.5 (14.2)</td>
<td>79.6 (17.0)</td>
<td>86.5 (13.9)</td>
</tr>
<tr>
<td>Energy</td>
<td>63.5 (20.2)</td>
<td>66.5 (22.6)</td>
<td>78.0 (19.9)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>77.2 (18.2)</td>
<td>80.1 (19.4)</td>
<td>82.6 (16.3)</td>
</tr>
<tr>
<td>Social role</td>
<td>60.2 (25.8)</td>
<td>64.4 (23.1)</td>
<td>69.3 (19.3)</td>
</tr>
<tr>
<td><strong>TPH1 SNP3 (rs211105)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL-total</td>
<td>TT (n = 119)</td>
<td>71.4 (13.5)</td>
<td>66.9 (14.6)</td>
</tr>
<tr>
<td>Emotional</td>
<td>58.9 (20.4)</td>
<td>54.0 (20.0)</td>
<td>54.9 (20.9)</td>
</tr>
<tr>
<td>Mental health</td>
<td>82.7 (15.2)</td>
<td>78.6 (16.6)</td>
<td>79.4 (15.1)</td>
</tr>
<tr>
<td>Energy</td>
<td>71.6 (21.5)</td>
<td>62.1 (21.0)</td>
<td>58.3 (22.5)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>81.0 (17.1)</td>
<td>77.8 (20.5)</td>
<td>75.0 (20.4)</td>
</tr>
<tr>
<td>Social role</td>
<td>66.4 (22.4)</td>
<td>61.0 (24.3)</td>
<td>54.2 (28.5)</td>
</tr>
<tr>
<td><strong>TPH1 SNP4 (rs1800532)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL-total</td>
<td>CC (n = 68)</td>
<td>66.9 (13.7)</td>
<td>70.5 (14.7)</td>
</tr>
<tr>
<td>Emotional</td>
<td>55.0 (21.1)</td>
<td>57.5 (19.2)</td>
<td>60.1 (21.5)</td>
</tr>
<tr>
<td>Mental health</td>
<td>78.0 (16.1)</td>
<td>81.5 (15.5)</td>
<td>86.7 (14.0)</td>
</tr>
<tr>
<td>Energy</td>
<td>62.9 (20.6)</td>
<td>67.3 (22.3)</td>
<td>78.8 (19.6)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>77.4 (17.9)</td>
<td>80.3 (19.6)</td>
<td>82.3 (16.3)</td>
</tr>
<tr>
<td>Social role</td>
<td>59.8 (25.5)</td>
<td>65.5 (23.1)</td>
<td>68.6 (19.1)</td>
</tr>
<tr>
<td><strong>TPH2 SNP5 (rs4570625)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QOL-total</td>
<td>GG (n = 127)</td>
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<td>71.6 (11.6)</td>
</tr>
<tr>
<td>Emotional</td>
<td>55.5 (19.6)</td>
<td>60.2 (21.6)</td>
<td>57.5 (24.8)</td>
</tr>
<tr>
<td>Mental health</td>
<td>81.0 (15.5)</td>
<td>81.8 (16.5)</td>
<td>78.0 (17.7)</td>
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<tr>
<td>Energy</td>
<td>66.6 (23.4)</td>
<td>71.1 (17.1)</td>
<td>60.0 (28.5)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>77.7 (19.8)</td>
<td>83.6 (14.5)</td>
<td>83.3 (21.2)</td>
</tr>
<tr>
<td>Social role</td>
<td>63.4 (23.9)</td>
<td>65.7 (21.9)</td>
<td>60.0 (35.0)</td>
</tr>
</tbody>
</table>

Note. Quality of life measured with IBS-specific Quality of Life questionnaire. Total mean score and subscale scores are reported. Higher scores indicate better QOL. GI = gastrointestinal; GSI = global severity index; IBS-QOL = Irritable Bowel Syndrome-Specific Quality of Life (QOL); SNP = single nucleotide polymorphism; TPH = tryptophan hydroxylase.

*a Significant association, p ≤ .05.

b p Value based on one-way analysis of variance.

*p Value based on one-way analysis of variance with controlling for GSI and GI symptoms (abdominal pain, diarrhea, constipation, bloating, and intestinal gas).
the influence of social support on depressive symptoms (Jokela, Raikkonen, Lehtimaki, Rontu, & Keltikangas-Jarvinen, 2007) and has been associated with bipolar disorder and alcohol dependence (Chen et al., 2012).

Researchers have investigated TPH2 gene polymorphisms for associations with various cognitive and/or emotional and behavioral traits (Waider, Araragi, Gutknecht, & Lesch, 2011). The minor (T) allele carriers of the TPH2 gene SNP5 had a greater functional MRI response of the amygdala, a structure critically involved in the modulation of emotional behaviors, to emotional stimuli (Brown et al., 2005; Canli, Congdon, Gutknecht, Constable, & Lesch, 2005). Investigators have also found associations between SNP5 and affective disorders (Harvey et al., 2004) and the modulation of negative emotionality such as neuroticism and harm avoidance (Gutknecht et al., 2007; Reuter, Kuepper, & Hennig, 2007). However, we saw no associations between SNP5 and psychological distress, lifetime prevalence of psychiatric disorders, IBS-related cognitions, or quality of life. One reason for our negative finding might be the combination of our small sample size and the relatively low minor allele frequency for this SNP (18%), which might have made subtle effects difficult to detect. Another possible explanation is that different cognitive mechanisms with different etiologies come into play in IBS as opposed to primarily psychiatric problems. Also, we only tested one SNP for the THP2 gene. Even though SNP5 has shown associations with many psychiatric and behavioral disorders and high linkage disequilibrium (LD) with other functional TPH2 SNPs that are associated with CSF5-HIAA levels, it does not cover all of the haploblocks of the TPH2 gene. Therefore we suggest that further studies are needed to test associations between other TPH2 SNPs and psychosocial factors in IBS.

Our study has several limitations. Due to our small sample size, our report of genetic associations must be interpreted with caution until confirmed in a larger sample. Because of the exploratory nature of our study, we presented our results without correction for multiple testing. Because of our small sample size we focused on the main effects of genetic polymorphisms on psychosocial factors in IBS without taking possible gene–environment interactions into account. Nonetheless, studies on depression give evidence that often genetic vulnerabilities only reveal themselves in the context of social stressors (Caspi et al., 2003; Grabe et al., 2005). This association with social stressors is particularly relevant in IBS, since research has repeatedly shown that a history of psychological trauma and higher levels of daily stress are positively associated with GI symptoms (Jarrett et al., 1998). Therefore, further studies are needed to examine the effects of possible interactions among stress, life events, and TPH gene polymorphisms on psychological distress and IBS symptoms.

In conclusion, in this exploratory hypothesis-generating study we report a possible association of variants in the TPH1 gene with negative cognitions and reduced QOL in women with IBS. These associations were independent of experienced levels of GI distress, thus indicating a possible mechanism whereby genetic factors might influence the onset and course of IBS by limiting patients’ ability to cope with their symptoms. This study reinforces the concept of IBS as a biopsychosocial illness and indicates the necessity of individualized approaches in providing nursing care such as cognitive behavioral treatment tailored to the patients’ appraisal of their illness.

**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Canli, T., Congdon, E., Gutknecht, L., Constable, R. T., & Lesch, K. P. (2005). Amygdala responsiveness is modulated by tryptophan


