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

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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 which investigated 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 (GI) 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*, one of two alternate rate-liming enzymes of serotonin biosynthesis. 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 has prompted investigators to consider the role of genetics in this chronic condition. Thus far over 60 genes have been

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examined for their potential association with IBS (Saito, 2011). Because of the role of serotonin in both the central nervous system (CNS) 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 re-uptake. Thus, alterations in 5-HT biosynthesis or reuptake change its availability. Clinically, serotonergic drugs (5-HT_3 antagonists, 5-HT_4 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 non-constipating IBS (Brown et al., 2011). However, not all patients benefitted which may reflect dosing or perhaps other differences. For example, Camilleri et al (2002) showed that patients with the SERT 5-HTTLPR l/l genotype were more responsive to alosetron (a 5-HT_3 antagonist).

TPH has two isoforms, TPH1 and TPH2, with overall 71% identity in amino acid sequence between them in humans (Walther & Bader, 2003). TPH1consists 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), while 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, Buttner, Eisenmenger, Bondy, & Ackenheil, 2004). TPH2 is mainly expressed in the brain, while TPH 1is 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 *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). This study also showed possible associations between a *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 and increased frequency of psychopathologic disorders, abnormal personality traits, psychological distress and sexual abuse (Farnam, Somi, Sarami, & Farhang, 2008; Morken, Lind, Valeur, Wilhelmsen, & 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. Variants of the *TPH* genes have been investigated for possible association 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(C. 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 *TPH* gene polymorphisms with cognitive, psychological, and psychiatric factors in IBS patients. Therefore, the aims of this study were to examine whether *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. Four SNPs in the *TPH1* gene and one

SNP in the *TPH2* gene were selected for genotyping. These specific SNPs were selected because they are among those shown in the literature cited above to be related to psychological disorders or distress. *TPH1* SNPs are rs4537731 (-6526A/G), rs684302, rs21105, and rs1800532 (A218C) and the *TPH2* SNP is rs4570625 (-709G/T). For convenience, all SNPs were numbered by their location 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 *Rome III* criteria (Drossman et al., 2006). Recruitment was conducted through community advertisement. Subjects were excluded if they 1) had a history of co-existing 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 the following medications more than 3 days a week: antibiotics, anticholinergics, cholestyramine, narcotics, colchicines, docusate, an enema preparation, iron supplements, or laxatives. The protocol for this study was approved by the University of Washington's institutional review board and all the patients gave written informed consent. The HapMap project (http://www.hapmap.org) results showed the minor allele frequencies of all the selected SNPs are different across ethnicity and our data also showed similar patterns with the HapMap results (data not shown). The only ethnic group with a large enough sample size for a reasonable analysis was Caucasians, thus in this report analysis is restricted 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) met criteria for diarrhea-predominant and 26% (n = 52) met criteria 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 BSI (Brief Symptom Inventory) 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 ranged from 0 (*not at all*) to 4 (*extremely*) and profiled into 9 subscales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and a global index (Global Severity Index, GSI) as a mean score of all items. The internal consistency in this sample, as measured by Cronbach's alpha, was α=0.94 for the Global Severity Index, α=0.79 for Anxiety, and α=0.79 for Depression.

History of mental disorders was assessed 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 DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) and ICD-10 (International Classification of Disease, 10th revision) mental disorders. The CIDI mood-disorders module (depression as

single and recurrent episode, dysthymia and mania), anxiety-disorders module (panic disorder with our without agoraphobia, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, phobias including social phobia, and post-traumatic stress disorder) and suicidal ideation module (recurrent thoughts of death, suicidal ideation and suicide attempt) were used 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*) over 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 2 subscales: pain and bowel performance anxiety. The 6 additional items had been part of the original version and the correlation between the extended version and the standard version was 0.99 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 this study, the internal consistency was $\alpha = 0.942$ for the total score, $\alpha = 0.685$ for pain, $\alpha = 0.941$ for bowel performance anxiety.

Illness impact and Quality of life—The IBS specific quality of life (IBS-QOL) is a 31-item questionnaire with 9 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"; or "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". The scales were transformed to standard scales of 0 (*poor quality of life*) to 100 (*highest quality of life*). A total score was computed by averaging all except sexual relations because this was missing for a large portion of the sample. Internal consistency for subscales ranged from $\alpha = 0.745$ to $\alpha = 0.916$.

Daily Diary—The mean score of GI symptoms was measured by a daily dairy which subjects filled in for 28 days (Jun et al., 2011). Symptoms include abdominal pain, diarrhea, constipation, bloating, and intestinal gas. They were rated from 0 (not present), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe).

Since some participants did not complete all of the questionnaires, there are differences in the number of subjects reported for each questionnaire.

Statistical analysis

Hardy-Weinberg equilibrium was tested using Pearson's Chi-square tests. Analysis of covariance (ANCOVA) was used 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 (ANOVA). We tested 30 hypotheses and 5 SNPs; to adjust for multiple comparisons, a p-value of less than 0.05/150 = 0.0003 would be considered to be significant. Because of the exploratory nature of our study, however, the results were presented without correction for multiple testing and should be interpreted with this in mind. All p-values were two-sided and $p < 0.05$ was considered statistically significant.

Results

The total sample included 199 women with IBS. Demographic characteristics are shown in Table 1. Only unrelated Caucasian women were included in the analysis. Participants in this study were relatively well educated, with 66% 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. Likewise, we found no association between *TPH* gene polymorphisms and lifetime history of mental health disorders measured by CIDI in the IBS group. These results are shown in Tables 2 and 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). The SNP5 of *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, analyses were repeated while excluding all subjects taking such medications. The results did not change substantially from those reported here, with one exception: In the subset of patient not taking antidepressant or antianxiety medications, there was a significant ($p=0.018$) association between SNP4 on the THP2 gene and GSI, with GSI being higher in GG than in GT subjects.

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 GSI and the severity of GI symptoms were controlled for, while those between *TPH1* SNPs and IBS-related cognitions remained with modest changes. This might indicate that the link between *TPH1* polymorphisms and cognitions or illness impact on QOL was not mediated by current psychological or GI distress.

CS-FBD is a cognitive scale which was 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 have been considered important factors impacting symptom severity and 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 the 5-HT synthesis, variations in *TPH* genes may lead to dysfunction of the serotonin system. A recent study demonstrated that 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 has failed to find this association in US patients with major depression (Galfalvy et al., 2009). *TPH2* gene polymorphisms have also been found to be associated with 5-HIAA concentrations in the CSF (Zhou et al., 2005). In addition, 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, our results found no association between negative cognitions about IBS and the*TPH2* gene SNP. It may be that cognitive measures related to depression, cognitive control, and hyperactivity are influenced to a greater degree than the negative appraisal of IBS measured in this sample. However, our data do provide evidence for the association of *TPH1* gene polymorphisms with negative cognition about IBS symptoms, especially as they relate to perception of pain and anxiety over bowel movements. We also saw that *TPH* 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). This is in keeping with prior findings that inhibition of TPH, which would also 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. The SNP1 of *TPH1* gene 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 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.).

TPH2 gene polymorphisms have been investigated for associations with various cognitive or/and emotional and behavioral traits (Waider, Araragi, Gutknecht, & Lesch, 2011). The minor (T) allele carriers of *TPH2* gene SNP5 were reported to have a greater functional MRI (fMRI) 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). SNP5 has been also associated with 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, 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, only one SNP was tested for THP2. Even though SNP5 has been tested in its association with many psychiatric and behavioral studies and showed high LD with other functional TPH2 SNPs which are associated with CSF5-HIAA levels, it does not cover all of the haploblocks of TPH2 gene. Therefore further studies are suggested 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, results were presented 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 interaction 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 is particularly relevant in IBS, since a history of psychological trauma and higher levels of daily stress have been repeatedly shown to be positively associated with GI symptoms (Jarrett et al., 1998). Therefore, further studies are needed to examine possible interactions between 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.

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Table 1

Demographic Characteristics

	IBS (n = 199)
Age, mean (sd) [a§]	40.0 (14.0)
Married/ partnered (%) [b]	41%
Education, bachelor's or higher (%) [b]	66%
Occupation [c]	
Professional	40%
Technical, service and sales	25%
Students	10%
Other	25%
Psychological distress [d]	
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)
Predominant Bowel Pattern (Rome III) [§]	
Constipation	41 (21%)
Diarrhea	89 (45%)
Mixed	52 (26%)
Unsubtyped	17 (9%)

[§] reported in the previous paper

Table 2

Association between *TPH* Gene Polymorphisms and Current Psychological Distress in Women with Irritable Bowel Syndrome

	Genotype			
***TPH1* SNP1 (rs4537731)**	**AA (n = 75)**	**AG (n = 96)**	**GG (n = 27)**	**p-value[a]**
GSI	0.49 (0.39)	0.49 (0.43)	0.38 (0.24)	0.39
Somatization	0.49 (0.44)	0.51 (0.47)	0.41 (0.41)	0.60
Depression	0.50 (0.60)	0.48 (0.53)	0.33 (0.31)	0.38
Anxiety	0.62 (0.64)	0.55 (0.53)	0.46 (0.36)	0.37
TPH1 SNP2 (rs684302)	CC (n = 63)	CT (n = 97)	TT (n = 39)	
GSI	0.44 (0.32)	0.49 (0.43)	0.48 (0.39)	0.67
Somatization	0.49 (0.46)	0.49 (0.43)	0.49 (0.49)	1.00
Depression	0.39 (0.44)	0.51 (0.59)	0.46 (0.53)	0.38
Anxiety	0.49 (0.43)	0.59 (0.60)	0.63 (0.60)	0.38
TPH1 SNP3 (rs211105)	TT (n = 124)	GT (n = 66)	GG (n = 9)	
GSI	0.47 (0.37)	0.49 (0.45)	0.34 (0.18)	0.54
Somatization	0.48 (0.45)	0.49 (0.46)	0.49 (0.59)	0.79
Depression	0.47 (0.54)	0.47 (0.54)	0.26 (0.26)	0.48
Anxiety	0.59 (0.58)	0.53 (0.52)	0.48 (0.50)	0.68
TPH1 SNP4 (rs1800532)	CC (n = 72)	AC (n = 89)	AA (n = 38)	
GSI	0.46 (0.35)	0.48 (0.43)	0.48 (0.38)	0.93
Somatization	0.49 (0.46)	0.49 (0.43)	0.47 (0.49)	0.98
Depression	0.43 (0.45)	0.49 (0.60)	0.46 (0.54)	0.76
Anxiety	0.53 (0.45)	0.56 (0.61)	0.64 (0.60)	0.62
TPH2 SNP5 (rs4570625)	GG (n = 130)	GT (n = 62)	TT (n = 6)	
GSI	0.49 (0.39)	0.43 (0.40)	0.47 (0.42)	0.54
Somatization	0.52 (0.46)	0.46 (0.44)	0.21 (0.25)	0.23
Depression	0.46 (0.52)	0.46 (0.57)	0.64 (0.55)	0.71
Anxiety	0.60 (0.56)	0.51 (0.56)	0.34 (0.36)	0.45

GSI, Global Severity Index

[a] p value based on one way analysis of variance with controlling for age

Table 3

Prevalence of Depressive and Anxiety Disorders by *TPH* Gene Polymorphisms

	Genotype			
***TPH1* SNP1 (rs4537731)**	**AA (n = 76)**	**AG (n = 96)**	**GG (n = 27)**	**p-value[a]**
Depressive disorders				
Any type of depressive episodes or dysthymia, n (%)	33 (43%)	39 (41%)	11 (41%)	0.93
Recurrent moderate-to-severe depressive episode, n (%)	14 (18%)	23 (24%)	4 (15%)	0.49
Suicide ideation, n (%)	22 (31%)	27 (29%)	4 (15%)	0.31
Anxiety disorders				
Any anxiety disorder, n (%)	35 (46%)	38 (40%)	9 (33%)	0.47
GAD, n (%)	13 (18%)	13 (14%)	2 (8%)	0.44
PTSD, n (%)	8 (11%)	17 (18%)	4 (15%)	0.43
***TPH1* SNP2 (rs684302)**	CC (n = 63)	CT (n = 97)	TT (n = 40)	
Depressive disorders				
Any type of depressive episodes or dysthymia, n (%)	27 (43%)	36 (37%)	20 (50%)	0.37
Recurrent moderate-to-severe depressive episode, n (%)	14 (22%)	16 (17%)	11 (28%)	0.32
Suicide ideation, n (%)	19 (32%)	21 (22%)	13 (34%)	0.27
Anxiety disorders				
Any anxiety disorder, n (%)	27 (43%)	37 (38%)	18 (45%)	0.71
GAD, n (%)	8 (13%)	15 (16%)	5 (13%)	0.85
PTSD, n (%)	9 (15%)	14 (15%)	6 (15%)	1.00
***TPH1* SNP3 (rs211105)**	TT (n = 125)	GT (n=66)	GG (n=9)	
Depressive disorders				
Any type of depressive episodes or dysthymia, n (%)	56 (45%)	24 (36%)	3 (33%)	0.45
Recurrent moderate-to-severe depressive episode, n (%)	27 (22%)	13 (20%)	1 (11%)	0.74
Suicide ideation, n (%)	32 (26%)	19 (30%)	2 (25%)	0.86
Anxiety disorders				
Any anxiety disorder, n (%)	55 (44%)	25 (38%)	2 (22%)	0.36
GAD, n (%)	20 (16%)	8 (13%)	0 (0%)	0.39
PTSD, n (%)	16 (13%)	11 (18%)	2 (25%)	0.53
***TPH1* SNP4 (rs1800532)**	CC (n = 72)	AC (n = 89)	AA (n = 39)	p-value[a]
Depressive disorders				
Any type of depressive episodes or dysthymia, n (%)	29 (40%)	34 (38%)	20 (51%)	0.37
Recurrent moderate-to-severe depressive episode, n (%)	15 (21%)	15 (17%)	11 (28%)	0.34
Suicide ideation, n (%)	21 (30%)	19 (22%)	13 (35%)	0.27
Anxiety disorders				
Any anxiety disorder, n (%)	30 (42%)	35 (40%)	17 (44%)	0.89
GAD, n (%)	10 (15%)	13 (15%)	5 (13%)	0.97

	Genotype			
***TPH1* SNP1 (rs4537731)**	**AA (n = 76)**	**AG (n = 96)**	**GG (n = 27)**	**p-value[a]**
PTSD, n (%)	11 (16%)	12 (14%)	6 (16%)	0.90
***TPH2* SNP5 (rs4570625)**	GG (n = 131)	GT (n = 62)	TT (n = 6)	
Depressive disorders				
Any type of depressive episodes or dysthymia, n (%)	60 (46%)	22 (36%)	1 (17%)	0.18
Recurrent moderate-to-severe depressive episode, n (%)	30 (23%)	10 (16%)	1 (17%)	0.54
Suicide ideation, n (%)	36 (29%)	15 (25%)	2 (33%)	0.86
Anxiety disorders				
Any anxiety disorder, n (%)	55 (42%)	24 (39%)	3 (50%)	0.83
GAD, n (%)	19 (15%)	8 (14%)	1 (17%)	0.96
PTSD, n (%)	19 (15%)	9 (15%)	1 (17%)	1.00

IBS, irritable bowel disorder; GAD, general anxiety disorder; PTSD, posttraumatic stress disorder

[a] p value based on Chi-square test.

Table 4

Association between *TPH* gene polymorphisms and cognition about IBS. Higher scores indicate worse cognition.

	Genotype				
***TPH1* SNP1 (rs4537731)**	**AA (n = 71)**	**AG (n = 91)**	**GG (n = 27)**	**P value[a]**	**P value[b]**
CS-FBD, mean (sd)	4.03 (1.2)	4.53 (1.0)	4.51 (1.3)	**0.03**	**0.04**
Pain	4.10 (1.4)	4.50 (1.3)	4.80 (1.6)	0.07	0.09
Bowel movement anxiety	3.68 (1.5)	4.33 (1.4)	4.21 (1.4)	**0.03**	**0.03**
TPH1 SNP2 (rs684302)	CC (n=48)	CT (n=80)	TT (n=29)		
CS-FBD, mean (sd)	4.51 (1.0)	4.32 (1.2)	4.13 (1.0)	0.31	0.31
Pain	4.62 (1.4)	4.29 (1.4)	4.26 (1.1)	0.33	0.29
Bowel movement anxiety	4.36 (1.3)	4.07 (1.6)	3.65 (1.2)	0.11	0.15
TPH1 SNP3 (rs211105)	TT (n=96)	GT (n=55)	GG (n=6)		
CS-FBD, mean (sd)	4.18 (1.1)	4.57 (1.2)	4.90 (0.8)	**0.05**	**0.03**
Pain	4.18 (1.3)	4.63 (1.4)	5.28 (1.1)	**0.04**	**0.02**
Bowel movement anxiety	3.89 (1.4)	4.35 (1.5)	4.67 (1.2)	0.10	0.11
TPH1 SNP4 (rs1800532)	CC (n=53)	AC (n=76)	AA (n=28)		
CS-FBD, mean (sd)	4.57 (1.0)	4.26 (1.2)	4.14 (1.0)	0.16	0.21
Pain	4.63 (1.4)	4.26 (1.4)	4.25 (1.2)	0.27	0.35
Bowel movement anxiety	4.40 (1.3)	4.01 (1.6)	3.67 (1.2)	0.08	0.13
TPH2 SNP5 (rs4570625)	GG (n=107)	GT (n=45)	TT (n=5)		
CS-FBD, mean (sd)	4.38 (1.1)	4.24 (1.1)	4.41 (2.1)	0.74	0.87
Pain	4.41 (1.4)	4.35 (1.3)	4.40 (1.9)	0.95	0.90
Bowel movement anxiety	4.13 (1.4)	3.96 (1.4)	4.05 (2.7)	0.78	0.81

[a] p value based on one way analysis of variance with controlling for age

[b] p value based on one way analysis of variance with controlling for age, GSI and GI symptoms (abdominal pain, diarrhea, constipation, bloating, intestinal gas)

Table 5

Association between *TPH* gene polymorphisms and IBS-specific QOL. Higher scores indicate better QOL.

		IBS-QOL Mean (sd)			
***TPH1* SNP1 (rs4537731)**	**AA (n = 71)**	**AG (n = 91)**	**GG (n = 27)**	**P value[a]**	**P value[b]**
QOL-total	71.7 (13.5)	67.8 (14.6)	70.5 (12.6)	0.219	0.456
Emotional	58.5 (20.3)	54.4 (20.7)	62.3 (18.3)	0.124	0.228
Mental Health	82.2 (16.0)	79.6 (16.2)	83.5 (13.1)	0.403	0.609
Energy	72.4 (21.4)	64.6 (22.1)	66.7 (20.8)	0.075	0.113
Physical functioning	83.0 (14.9)	77.2 (20.5)	79.2 (18.9)	0.158	0.213
Social role	67.1 (22.7)	61.9 (23.5)	63.2 (25.6)	0.435	0.851
TPH1 SNP2 (rs684302)	CC (n = 59)	CT (n = 94)	TT (n = 37)		
QOL-total	67.9 (13.3)	69.5 (15.0)	73.5 (11.5)	0.533	0.086
Emotional	57.5 (19.7)	55.7 (20.4)	59.8 (21.3)	0.515	0.694
Mental Health	80.5 (14.2)	79.6 (17.0)	86.5 (13.9)	0.070	0.092
Energy	63.5 (20.2)	66.5 (22.6)	78.0 (19.9)	**0.005**	**0.002**
Physical functioning	77.2 (18.2)	80.1 (19.4)	82.6 (16.3)	0.434	0.389
Social role	60.2 (25.8)	64.4 (23.1)	69.3 (19.3)	0.226	0.353
TPH1 SNP3 (rs211105)	TT (n = 119)	GT (n = 62)	GG (n = 9)		
QOL-total	71.4 (13.5)	66.9 (14.6)	67.2 (12.8)	0.098	0.058
Emotional	58.9 (20.4)	54.0 (20.0)	54.9 (20.9)	0.220	0.196
Mental Health	82.7 (15.2)	78.6 (16.6)	79.4 (15.1)	0.223	0.358
Energy	71.6 (21.5)	62.1 (21.0)	58.3 (22.5)	**0.008**	**0.002**
Physical functioning	81.0 (17.1)	77.8 (20.5)	75.0 (20.4)	0.465	0.496
Social role	66.4 (22.4)	61.0 (24.3)	54.2 (28.5)	0.183	0.109
TPH1 SNP4 (rs1800532)	CC (n = 68)	AC (n = 86)	AA (n = 36)		
QOL-total	66.9 (13.7)	70.5 (14.7)	73.5 (11.6)	0.055	**0.042**
Emotional	55.0 (21.1)	57.5 (19.2)	60.1 (21.5)	0.472	0.461
Mental Health	78.0 (16.1)	81.5 (15.5)	86.7 (14.0)	**0.027**	**0.026**
Energy	62.9 (20.6)	67.3 (22.3)	78.8 (19.6)	**0.002**	**<0.001**

	IBS-QOL Mean (sd)				
***TPH1* SNP1 (rs4537731)**	**AA (n = 71)**	**AG (n = 91)**	**GG (n = 27)**	**P value[a]**	**P value[b]**
Physical functioning	77.4 (17.9)	80.3 (19.6)	82.3 (16.5)	0.457	0.510
Social role	59.8 (25.5)	65.5 (23.1)	68.6 (19.1)	0.176	0.381
TPH2 SNP5 (rs4570625)	GG (n = 127)	GT (n = 57)	TT (n = 5)		
QOL-total	68.9 (14.6)	71.6 (11.6)	69.5 (21.1)	0.464	0.519
Emotional	55.5 (19.6)	60.2 (21.6)	57.5 (24.8)	0.424	0.390
Mental Health	81.0 (15.5)	81.8 (16.5)	78.0 (15.7)	0.852	0.990
Energy	66.6 (23.4)	71.1 (17.1)	60.0 (28.5)	0.324	0.346
Physical functioning	77.7 (19.8)	83.6 (14.5)	83.3 (21.2)	0.140	0.107
Social role	63.4 (23.9)	65.7 (21.9)	60.0 (35.0)	0.773	0.897

[a] p value based on one way analysis of variance

[b] p value based on one way analysis of variance with controlling for GSI and GI symptoms (abdominal pain, diarrhea, constipation, bloating, intestinal gas)