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A genetic association study of single nucleotide polymorphisms in *GNβ3* and *COMT* in elderly patients with irritable bowel syndrome

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Statistical Analysis C
Data Interpretation D
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Background: Several polymorphisms have been reported to be associated with irritable bowel syndrome (IBS), including C825T, the single nucleotide polymorphism (SNP), responsible for a truncated G protein β3 subunit (*GNβ3*), and the Vall158Met substitution in catechol-O-methyltransferase (*COMT*). We investigated the association between these mutations and the prevalence of IBS in 66 elderly Chinese patients.

Material/Methods: Sixty-six patients (over age 60 years) were diagnosed with IBS according to the Rome III criteria, and divided into 3 groups based on symptom presentation. The groups consisted of 7 patients with constipation, 46 patients with diarrhea, and 13 patients with both or neither symptoms. We enrolled 115 age-matched individuals without IBS as the control group. All patients were evaluated by using the Geriatric Depression Scale, disease progression was recorded, and *GNβ3* and *COMT* were genotyped by PCR.

Results: There was no significant difference in *GNβ3* C825T genotype distribution and allele frequency between the 2 groups. In contrast, compared with control subjects, COMT 158Met was significantly more prevalent in the IBS group (P=0.040) and significantly more prevalent in patients with diarrhea (P=0.029). 158Met was also more prevalent in those patients who had experienced symptoms for over 5 years (P=0.022).

Conclusions: In elderly Chinese patients, the 158Met SNP in COMT is associated with IBS pathogenesis, but the *GNβ3*-C825T SNP is not associated with IBS pathogenesis.

MeSH Keywords: Dental Care for Elderly • Single Nucleotide Polymorphisms • Irritable Bowel Syndrome

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Background

Irritable bowel syndrome (IBS) is a heterogeneous, idiopathic, gastrointestinal syndrome characterized by abdominal pain or discomfort, diarrhea, and/or constipation. A questionnaire survey conducted in students from a Chinese university found that only 5.7% of respondents could be diagnosed with IBS [1], but epidemiological surveys in India, Iran, Japan, and other Asian countries suggest that IBS is more prevalent in elderly people than in young adults [2–4]. Questionnaires and related testing of elderly people in Hong Kong diagnosed 13.1% with IBS [3], and epidemiological investigation in the Songjiang district of Shanghai found a prevalence of 9.4% in adults aged 60–79 years old and 10.2% in those over 80 years of age [4].

Although the etiology of IBS is currently unknown, several hypotheses have been proposed for its pathogenesis. The development of IBS may involve visceral abnormalities, genetic susceptibility, a neuro-immunological disorder, and/or psychological factors. IBS shows a familial tendency [5], and the mutations involved in genetic susceptibility to IBS have recently received particular attention [6,7]. However, identifying genetic markers of IBS is complicated by the multi-factorial pathophysiology of this syndrome. It is hypothesized that exposure to certain environmental factors, such as infection or severe psychological stress, may induce IBS in genetically susceptible individuals. Polymorphisms in the 5-hydroxytryptamine (5-HT) transporter or receptors, adrenergic system, and mitochondrial genome have been highlighted as potentially contributing to abnormalities in IBS patients, including enhanced perception of gut stimuli, altered gastrointestinal motor function, and psychiatric symptoms [8,9].

Several neurotransmitter receptors involved in the regulation of gastrointestinal motility, such as the 5-HT receptor, adrenergic receptor, and cannabinoid receptor, are G protein-coupled receptors. One G protein subunit, G protein beta polypeptide 3 (*GNβ3*), is a component of several G protein complexes, and thus polymorphisms in the *GNβ3* gene impact signal transduction from several receptors [10,11]. A common single nucleotide polymorphism substitution of C with T at position 825 within exon 10 of the *GNβ3* gene (rs5443) results in a truncated GNβ3 splice variant with enhanced G protein activation [11]. This polymorphism has been reported to be overrepresented in patients diagnosed with some forms of IBS [12–17].

Sympathetic dysfunction of the adrenergic nerves has also been associated with the pathogenesis of some cases of IBS [18–20]. Dysfunction of catechol-O-methyltransferase (COMT), an enzyme capable of degrading catecholamines such as dopamine, norepinephrine, and epinephrine, appears to play a role in the pathogenesis of some cases of IBS [18–20]. A common single nucleotide polymorphism substitution at position 1947 in exon 4 of the *COMT* gene results in the substitution of Valine 158 with Methionine in the COMT protein (A/A genotype) [18], which reduces the activity of COMT by about 4-fold [21,22]. However, COMT with Val 158 (G/G genotype) appears to have higher activity. Recent studies have demonstrated that *COMT* gene polymorphisms are correlated to chronic pain and depression [23]. Although IBS patients often have abdominal pain accompanied by anxiety or depression, few studies have investigated the relationship between *COMT* gene polymorphisms and IBS. Preliminary investigations have found that individuals with 2 copies of the gene producing COMT with valine at position 158 are over-represented in groups diagnosed with IBS [19,20].

We sought to determine whether these single nucleotide polymorphisms in *GNβ3* and *COMT* were associated with IBS in elderly Chinese patients. Due to the likely multi-factorial nature of IBS, we sub-divided patients diagnosed with IBS according to their symptoms and determined the frequency of these SNPs in these groups and an age-matched control group unaffected by gastrointestinal disease.

Material and Methods

Subjects

Between March and December 2012, 66 patients over 60 years old were enrolled at Huashan Hospital (Shanghai, China). All patients were diagnosed with IBS according to the Rome III diagnostic criteria [24] and were further subdivided into 3 groups based on symptom presentation: 1) IBS with constipation (IBS-C), 2) IBS with diarrhea (IBS-D), and 3) IBS with both symptoms (IBS-M). Other lower gastrointestinal diseases were ruled-out by colonoscopy. Patients with liver, gallbladder or pancreatic disease, diabetes, hyperthyroidism, cancer, or any other disease were excluded by examination of medical records, physical examination, ultrasound, and blood biochemical analysis. Patients with history of abdominal surgery or adverse drug reactions, including constipation and diarrhea, were also excluded from this study.

We enrolled 115 age-matched subjects without IBS as a control group during the same period at routine annual physical examination. Subjects in the control group defecated once or twice a day, or once every 2 days, producing yellow, soft, solid stools, and did not experience hard bowel movements, abdominal pain, or discomfort.

All participants provided written informed consent, and the study was approved by the Ethics Committee of Huashan Hospital, Fudan University [2012(229)].

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Table 1. *GNβ3* and *COMT* polymorphism primers.

SNP	Primer 5'---3'	Probe 5'---3'	Annealing temperature
rs5443	GNB3 Loaded-469F: 5-TCCCACGAGAGCATCATCTG-3 GNB3 Loaded-548R: 5-TCGTCGTAGCCAGCGAATAGT-3	GNB3 probe 1 5-Fam-CATCACGTCcGTGGCCTTCTC-TAMRA-3 GNB3 probe 2 5-HEX-CATCACGTCtGTGGCCTTCTCC-TAMRA-3	60°C
rs4680	COMT Loaded-471F: 5- ATCACCCAGCGGATGGTGG-3 COMT Loaded-531R: 5- ACGGGTCAGGCATGCACAC-3	COMT probe 1 5-Fam-TTTCGCTGGCaTGAAGGACAA-TAMRA-3 COMT Probe2 5-HEX-TTTCGCTGGCgTGAAGGACA-TAMRA-3	60°C

Survey and information collection

The demographic characteristics and medical history of all participants were recorded. A professionally trained physician evaluated all participants with the Geriatric Depression Scale (GDS), a set of 30 polar questions used to quantify participant emotional state during the preceding week. For each question, a positive response is assigned 1 point, and a negative response is assigned no points. A cumulative score above 10 indicates depressive symptoms.

Blood sample collection and DNA extraction

Two mL of peripheral intravenous blood was drawn from participants. Genomic DNA was extracted using QIAamp mini-spin columns (Qiagen, USA) according to the manufacturer's instructions and separated by agarose gel electrophoresis for SNP determination.

SNP genotyping

The SNP sequences of GNB C825T (rs 5443) and COMT Val158Met (rs 4680) were based on the Gene Bank databases. Primers and probes were designed using ABI Primer Express Software v2.0 and synthesized by Invitrogen, as detailed in Table 1. The PCR reaction was carried out in a StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) and subjected to 95°C for 2 min, then 40 cycles of 95°C for 10 s, followed by 53°C for 45 s. Fluorescence was measured by the Real-Time PCR System and data was converted by SDS 2.0 software. SNP genotype was determined by the fraction of VIC and FAM PCR amplification products.

Statistical analysis

The chi-square test and Hardy-Weinberg equilibrium theory were used to compare the genotype and allele frequency between the IBS and control groups, and between IBS subgroups. Chi-square test and Fisher's exact test were used to assess the relationship between clinical factors and genotype. Unconditional logistic regression analysis and crossover analysis were used to analyze the risk factors for IBS disease by gene polymorphism. Statistical analysis was performed with SPSS 13.0 statistical software and *P*-values <0.05 was considered statistically significant.

Results

Genotype frequency of *GNβ3* C825T and COMT V158M

Participant demographics are shown in Table 2. The genomic distribution of the *GNβ3* C825T and COMT Val158Met polymorphisms in the control group did not significantly deviate from the Hardy-Weinberg equilibrium ($P > 0.05$).

Genotype distribution and allele frequency of *GNβ3* gene C825T

GNβ3 genotyping determined that the C allele frequency was 85.6% in the IBS group and 89.1% in the control group, and the T allele frequency was 14.4% in the IBS group and 10.9% in the control group (Table 3). The CC genotype of *GNβ3* was found in 75.8% of those enrolled in the IBS group (50 instances) in comparison to 80% of the control group (92 instances). The CT genotype was present in 19.7% (13 instances) of the IBS group and 18.3% (21 instances) of the control group, and the TT genotype was present in 4.5% (3 instances) of the IBS group and 1.7% (2 instances) of the control group (Table 4). There was no statistically significant difference between allele frequency (P=0.323) or the genotype distribution (P=0.534) between the IBS and control groups.

Genotype distribution and allele frequency of COMT Val158Met

COMT genotyping determined that the G allele frequency was 87.1% in the IBS group and 93.5% in the control group, and the A allele frequency was 12.9% in the IBS group and 6.5% in the control group (Table 5). The GG genotype of COMT was

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Table 2. Demographics of participants.

	IBS group (n=66)	Control group (n=115)	P-value
Age (years)	74.5±6.1	74.3±5.8	0.826
Gender (male/female)	56/10	89/26	0.226
Body Mass Index (kg/m²)	23.9±3.1	23.6±3.2	0.512
Hypertension, n (%)	40 (60.6)	56 (53.0)	0.324
Marital status			
Living with spouses, n (%)	40 (60.6)	83 (72.2)	0.108
Widowed, n (%)	23 (34.8)	28 (24.3)	0.131
Divorced, n (%)	2 (3.1)	2 (1.7)	0.965
Unmarried, n (%)	1 (1.5)	2 (1.7)	0.623
GSD score above 10, n (%)	27 (40.9)	32 (30.4)	0.153

Table 3. Allele frequencies of *GNβ3* C825T.

Allele frequencies	IBS group	Control group		
C (%)	113 (85.6)	205 (89.1)	X^2=0.978	*P*=0.323
T (%)	19 (14.4)	25 (10.9)		

Table 4. Genotype distribution of *GNβ3* gene C825T site.

Genotype	IBS group	Control group	*P*-value
CC, n (%)	50 (75.8)	92 (80.0)	
CT, n (%)	13 (19.7)	21 (18.3)	
TT, n (%)	3 (4.5)	2 (1.7)	0.534*

* Using Fisher exact test.

Table 5. Allele frequencies of *COMT* Val158Met.

Allele frequencies	IBS group	Control group		
G (%)	115 (87.1)	215 (93.5)	X^2=4.206	*P*=0.040
A (%)	17 (12.9)	15 (6.5)		

Table 6. Genotype distribution of *COMT* Val158Met.

Genotype	IBS group (n=66)	Control group (n=115)	χ^2	*P*-value
G/G, n (%)	57 (86.4)	101 (87.8)		
G/A, n (%)	1 (1.5)	13 (11.3)		
A/A, n (%)	8 (12.1)	1 (0.9)	15.88	<0.001

found in 86.4% of those enrolled in the IBS group (57 instances) in comparison to 87.8% of the control group (101 instances). The GA genotype was present in 1.5% (1 instance) of the IBS group and 11.3% (13 instances) of the control group, and the AA genotype was present in 12.1% (8 instances) of the IBS group and 0.9% (1 instance) of the control group (Table 6).

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Table 7. Genotype distribution and allele frequency in IBS-C subgroup and the control group.

	IBS-C (n=7) n (%)		Control group (n=115) n (%)		Statistics
GNβ3 genotype					
CC	6	(85.7)	92	(80.0)	
CT	1	(14.3)	21	(18.3)	
TT	0	(0.0)	2	(1.7)	*P*=1.0*
GNβ3 allele					
C	13	(92.9)	205	(89.1)	χ^2=0, P=1.0
T	1	(7.1)	25	(10.9)	
COMT genotype					
G/G	6	(85.7)	101	(87.8)	
G/A	0	(0.0)	13	(11.3)	
A/A	1	(14.3)	1	(0.9)	*P*=0.136*
COMT allele					
G	12	(85.7)	215	(93.5)	*P*=0.254*
A	2	(14.3)	15	(6.5)	

* Using Fisher's exact test.

Table 8. Genotype distribution and allele frequency in IBS-D subgroup and the control group.

	IBS-D (n=46) n (%)		Control group (n=115) n (%)		Statistics
GNβ3 genotype					
CC	36	(78.3)	92	(80.0)	
CT	8	(17.4)	21	(18.3)	
TT	2	(4.3)	2	(1.7)	*P*=0.687*
GNβ3 allele					
C	80	(87.0)	205	(89.1)	χ^2=0.305, P=0.581
T	12	(13.0)	25	(10.9)	
COMT genotype					
G/G	39	(84.8)	101	(87.8)	
G/A	1	(2.2)	13	(11.3)	
A/A	6	(13.0)	1	(0.9)	*P*=0.001*
COMT allele					
G	79	(85.9)	215	(95.3)	χ^2=4.79, *P*=0.0290.052
A	13	(14.1)	15	(6.5)	

* Using Fisher's exact test.

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Table 9. Genotype distribution and allele frequency in IBS-M subgroup and the control group.

	IBS-M (n=13) n (%)		Control group (n=115) n (%)		Statistics
GNβ3 genotype					
CC	8	(61.5)	92	(80.0)	
CT	4	(30.8)	21	(18.3)	
TT	1	(7.7)	2	(1.7)	*P*=0.107*
GNβ3 allele					
C	20	(76.9)	205	(89.1)	χ^2=2.224
T	6	(23.1)	25	(10.9)	P=0.136
COMT genotype					
G/G	12	(92.3)	101	(87.8)	
G/A	0	(0.0)	13	(11.3)	
A/A	1	(7.7)	1	(0.9)	*P*=0.146*
COMT allele					
G	24	(92.3)	215	(93.5)	χ^2=0, *P*=1.0
A	2	(7.7)	15	(6.5)	

* Using Fisher's exact test.

The A allele was found significantly more frequently in the IBS group than in the control group (*P*=0.040), and the genotype distribution also differed significantly between the IBS group and the control group (*P* <0.001).

Genotype distribution and allele frequency of *GNβ3* C825T and COMT Val158Met in IBS subgroups

IBS patients were divided into subgroups according to symptom presentation. Seven patients (10.6%) had constipation (IBS-C), 46 patients (69.7%) had diarrhea (IBS-D), and 13 patients (19.7%) had both symptoms (IBS-M) (Tables 7–9). No statistically significant differences in *GNβ3* genotype or allele frequency were found between the control group and any of the IBS subgroups (Tables 7–9). However, the genotype distribution of COMT Val158Met differed significantly between the control and IBS-D groups (*P*<0.001) (Table 8), and this subgroup had a higher A allele frequency (*P*=0.029) when compared with the control group (Table 8). No significant difference in COMT genotype distribution or allele frequency was detected between the IBS-M or IBS-C subgroups and the control group (Tables 7 and 9).

The association between gene polymorphism and the duration of IBS

As indicated in Table 10, IBS patients were subdivided into 2 subgroups based on the duration of their IBS symptoms; 39.4% of enrolled IBS patients had symptoms for longer than 5 years, and 60.6% for less than 5 years.

Although no difference was detected in the genotype distribution or allele frequency of *GNBβ3*-C825T, the allele frequency of COMT 158A was elevated in patients with IBS symptoms for longer than 5 years (*P*=0.022, Table 10).

Gene – gene interaction analysis

After applying non-conditional logistic regression analysis and adjusting for sex, age, and GDS score, crossover analysis showed that the effect of the *GNβ3* gene or the *COMT* gene was not statistically significant among IBS patients (*P*>0.05, Table 11). Interaction analysis indicated no interaction between the *GNβ3* gene and the *COMT* gene in IBS patients (*P*>0.05, Table 12).

Discussion

In this study we found that COMT 158Met allele, encoding an enzyme with reduced activity [21,22], was significantly associated with IBS in elderly Chinese patients, and was particularly significantly associated with IBS accompanied by diarrhea and IBS that had persisted for longer than 5 years. We also found that IBS patients were significantly less likely to possess heterozygous COMT genes than the control patients.

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Table 10. The relationship between genotype and duration of IBS patients.

	Duration ≥5 years (n=26) n (%)		Duration <5 year (n=40) n (%)		Statistics
GNβ3 genotype					
CC	22	(84.6)	30	(75.0)	
CT	3	(11.5)	8	(20.0)	
TT	1	(3.8)	2	(5.0)	*P*=0.780*
GNβ3 allele					
C	47	(90.4)	68	(85.0)	χ^2=0.814, P=0.367
T	5	(9.6)	12	(15.0)	OR=1.659, 95%CI: 0.548–5.021
COMT genotype					
G/G	20	(76.9)	37	(92.5)	
G/A	1	(3.8)	0	(0.0)	
A/A	5	(9.2)	3	(7.5)	*P*=0.127*
COMT allele					
G	41	(78.8)	74	(92.5)	χ^2=5.236, *P*=0.022
A	11	(21.2)	6	(7.5)	

* Using Fisher's exact test.

Table 11. Crossover analysis of the impact of *GNβ3* and *COMT* polymorphism on IBS risk.

GNβ3	*COMT*	β	Wald value	OR	*P*-value
CC	G/G		0.618		0.892
CC	G/A+A/A	0.082	0.026	1.085	0.873
CT+TT	G/G	0.215	0.300	1.240	0.584
CT+TT	G/A+A/A	0.621	0.372	1.860	0.542

Table 12. *GNβ3* and *COMT* polymorphism and IBS interaction analysis.

Gene	β	Wald value	OR	*P*-value
GNβ3	0.276	0.070	1.318	0.791
COMT	0.380	0.123	1.463	0.726
GNβ3×COMT	0.112	0.015	1.119	0.902

The frequency of COMT 158Met in the IBS group was significantly higher than that in the control group, suggesting that the Met allele predisposes elder people to IBS, and the Val allele protects against IBS. Our results are consistent with previous reports that found that sympathetic dysfunction of the adrenergic nerves is associated with the pathogenesis of some cases of IBS [18–20], but inconsistent with another study that found the COMT 158Val allele to be significantly associated with pathogenesis of IBS and increased frequency of defecation [23].

We found no significant difference in the percentage of patients with a GDS score above 10 in the IBS group and the control group, no significant difference in the genotype distribution or allele frequency of *GNβ3*-C825T between the IBS and the control group, and no interaction between the *GNβ3*

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gene and the *COMT* gene in IBS patients. No difference in the genotype distribution and allele frequency of *GNβ3*-C825T was detected when IBS patients were further subdivided according to symptom presentation and persistence of symptoms. Our findings concerning *GNβ3*-C825T further support the results of case-control studies conducted in the United States in 2007 [15] and in Korea in 2012 [12]. However, several additional studies found different results in other populations. A 2011 study in a Greek population found the *GNβ3*-825T allele encoding a G protein that mediates enhances activation [11] to be closely associated with the occurrence of IBS [13]. A 2001 study conducted in a Caucasian population found that *GNβ3*-825C was associated with increased defecation frequency [25], and Korean studies in 2010 and 2012 found *GNβ3*-825T to be associated with IBS with constipation in adults [14] and children [16], and *GNβ3*-825C to be associated with IBS with diarrhea in children [16]. We did not detect a statistically significant association of particular *GNβ3* or *COMT* genotypes with IBS with constipation, but our analysis may have been limited by sample size because we enrolled only a small number of patients (7) who experienced IBS with constipation.

The inconsistent results of these studies may be partially explained to be relatively small sample sizes. For example, both Kim [12] and Saito [15] subdivided small populations (60 and 50 IBS patients, respectively) into CC, CT, and TT genotype subgroups, resulting in a smaller size in each group. The studies that found association between *GNβ3*-C825T and IBS were conducted in ethnic Koreans [14] and Greeks [13]. Fang et al. performed a correlation study between the *GNβ3*C825T polymorphism and functional dyspepsia (FD) in a Han Chinese population, and found that this polymorphism is not a risk factor for the onset of FD [3]. Currently, both FD and IBS are thought to share a similar pathogenesis, and both are categorized as functional gastrointestinal diseases (FGID). Therefore, one can speculate that the C825T polymorphism of *GNβ3* may not be a risk factor for the pathogenesis of IBS in the Chinese population.

Conclusions

We found that the COMT val158met single nucleotide polymorphism was associated with susceptibility to IBS, and the Met allele was over represented in patients diagnosed with IBS with diarrhea or IBS that had persistsed for longer than 5 years. However, no evidence for a correlation between *GNβ3* C825T single nucleotide polymorphisms and the pathogenesis of IBS was found among this population of elderly IBS patients. To further validate genetic markers of IBS, larger cohorts will need to be enrolled, as identifying genetic markers of IBS is complicated by the multi-factorial pathophysiology of this heterogeneous syndrome.

Conflict of interest

The authors declare that they have no conflict of interest.

References:

1. Chang FY, Lu CL, Chen TS: The current prevalence of irritable bowel syndrome in Asia. J Neurogastroenterol Motil, 2010; 16: 389–400
2. Masud MA, Hasan M, Khan AK: Irritable bowel syndrome in a rural community in Bangladesh: prevalence, symptoms pattern, and health care seeking behavior. Am J Gastroenterol, 2001; 96: 1547–52
3. Feng XW, Xu S: Epidemiological analysis of Hong Kong SAR older people with irritable bowel syndrome. Chengde Medical Science, 2009; 26: 43–45
4. Feng S, Reading J, Huiqing Z: Epidemiological investigations of irritable bowel syndrome patients in Songjiang community. Chinese Journal of Digestion, 2010; 31: 663-8
5. Saito YA, Zimmerman JM, Harmsen WS et al: Irritable bowel syndrome aggregates strongly in families: a family-based case-control study. Neurogastroenterol Motil, 2008; 20: 790–97
6. Saito YA: The role of genetics in IBS. Gastroenterol Clin North Am, 2011; 40: 45–67
7. Camilleri M, Katzka DA: Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Genetic epidemiology and pharmacogenetics in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol, 2012; 302: G1075–84
8. Yeo A, Boyd P, Lumsden S et al: Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. Gut, 2004; 53: 1452–58
9. Colucci R, Gambaccini D, Ghisu N et al: Influence of the serotonin transporter 5HTTLPR polymorphism on symptom severity in irritable bowel syndrome. PLoS One, 2013; 8: e54831
10. Oshima T, Toyoshima F, Nakajima S et al: Genetic factors for functional dyspepsia. J Gastroenterol Hepatol, 2011; 26(Suppl.3): 83–87
11. Siffert W, Rosskopf D, Siffert G et al: Association of a human G-protein beta3 subunit variant with hypertension. Nat Genet, 1998; 18: 45–48
12. Kim HG, Lee KJ, Lim SG et al: G-Protein Beta3 Subunit C825T Polymorphism in Patients With Overlap Syndrome of Functional Dyspepsia and Irritable Bowel Syndrome. J Neurogastroenterol Motil, 2012; 18: 205–10
13. Markoutsaki T, Karantanos T, Gazouli M et al: Serotonin transporter and G protein beta 3 subunit gene polymorphisms in Greeks with irritable bowel syndrome. Dig Dis Sci, 2011; 56: 3276–80
14. Lee HJ, Lee SY, Choi JE et al: G protein beta3 subunit, interleukin-10, and tumor necrosis factor-alpha gene polymorphisms in Koreans with irritable bowel syndrome. Neurogastroenterol Motil, 2010; 22: 758–63
15. Saito YA, Locke GR III, Zimmerman JM et al: A genetic association study of 5-HTT LPR and GNbeta3 C825T polymorphisms with irritable bowel syndrome. Neurogastroenterol Motil, 2007; 19: 465–70
16. Park CS, Uhm JH: Polymorphisms of the Serotonin Transporter Gene and G-Protein beta3 Subunit Gene in Korean Children with Irritable Bowel Syndrome and Functional Dyspepsia. Gut Liver, 2012; 6: 223–28
17. Evans A, Jun SE, Heitkemper M: IBS symptoms: It's in the genes. Am J Gastroenterol, 2010; 105: S491-S2
18. Syvanen AC, Tilgmann C, Rinne J, Ulmanen I: Genetic polymorphism of catechol-O-methyltransferase (COMT): correlation of genotype with individual variation of S-COMT activity and comparison of the allele frequencies in the normal population and parkinsonian patients in Finland. Pharmacogenetics, 1997; 7: 65–71
19. Hall KT, Lembo AJ, Kirsch I et al: Catechol-O-methyltransferase val158met polymorphism predicts placebo effect in irritable bowel syndrome. PLoS One, 2012; 7: e48135
20. Karling P, Danielsson A, Adolfsson R, Norrback KF: No difference in symptoms of irritable bowel syndrome between healthy subjects and patients with recurrent depression in remission. Neurogastroenterol Motil, 2007; 19: 896–904

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21. Lotta T, Vidgren J, Tilgmann C et al: Kinetics of human soluble and membrane-bound catechol O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry, 1995; 34: 4202–10
22. Lachman HM, Papolos DF, Saito T et al: Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics, 1996; 6: 243–50
23. Choung RS, Locke GR III, Zinsmeister AR et al: Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: a psychological component is the rule. Am J Gastroenterol, 2009; 104: 1772–79
24. Drossman DA: Rome III: the new criteria. Chin J Dig Dis, 2006; 7: 181–85
25. Talley NJ, Howell S, Poulton R: The irritable bowel syndrome and psychiatric disorders in the community: is there a link? Am J Gastroenterol, 2001; 96: 1072–79

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]