World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i47.17693

World J Gastroenterol 2014 December 21; 20(47): 17693-17698
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (4): Irritable bowel syndrome

Genetic polymorphism in pathogenesis of irritable bowel syndrome

Cynthia KY Cheung, Justin CY Wu

Cynthia KY Cheung, Justin CY Wu, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China
Author contributions: Cheung CKY and Wu JCY equally contributed to this paper.
Correspondence to: Justin CY Wu, Professor, Institute of Digestive Disease, The Chinese University of Hong Kong, 9/F, Clinical Science Building, Prince of Wales Hospital, Shatin, Hong Kong, China. justinwu@cuhk.edu.hk
Telephone: +852-26323593 Fax: +852-26373852
Received: June 24, 2014 Revised: September 22, 2014
Accepted: December 1, 2014
Published online: December 21, 2014

Abstract

Irritable bowel syndrome (IBS) is a complex symptom-based disorder without established biomarkers or putative pathophysiology. IBS is a common functional gastrointestinal disorder which is defined as recurrent abdominal pain or discomfort that has at least two of the following symptoms for 3 d per month in the past 3 mo according to ROME Ⅲ: relief by defecation, onset associated with a change in stool frequency or onset with change in appearance or form of stool. Recent discoveries revealed genetic polymorphisms in specific cytokines and neuropeptides may possibly influence the frequencies and severity of symptoms, as well as the therapeutic responses in treating IBS patients. This review gives new insights on how genetic determinations influence in clinical manifestations, treatment responses and potential biomarkers of IBS.

Key words: Irritable bowel syndrome; Genetic polymorphism; Cytokines; Serotonin; Psychiatric distress; Endocannabinoids

Core tip: Irritable bowel syndrome (IBS) is a complex symptom-based disorder without established biomarkers or putative pathophysiology. This review gives new insights on how genetic determinations influence in clinical manifestations, treatment responses and potential biomarkers of IBS. Although a number of IBS- related genes have been identified, the majority of the identified genes required further validation as each of them may only contribute to the pathophysiology in 1%-5% in patients with functional gastrointestinal disorders.

Cheung CKY, Wu JCY. Genetic polymorphism in pathogenesis of irritable bowel syndrome. *World J Gastroenterol* 2014; 20(47): 17693-17698 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i47/17693.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i47.17693

INTRODUCTION

Irritable bowel syndrome (IBS) is defined according to ROME Ⅲ criteria as recurrent abdominal pain or discomfort for at least 3 d per month during the previous months with two or more of the following characteristics: relief by defecation, onset associated with a change in the frequency of stools, onset associated with change in form or appearance of stools[1,2]. IBS is often subcategorized according to the predominant stool pattern reported by the patients. These subcategories include constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and so-called mixed stool pattern IBS (IBS-M) which involves both constipation and diarrhea.

The prevalence of IBS ranges from 4.7% to 19.1% in western countries, however the prevalence in eastern countries ranges from 3.7% to 15.7% according to ROME Ⅱ criteria[3]. Although the pathophysiology of IBS still remains unknown, there is growing evidence that genetic contributions, inflammatory activation, psychosocial factors may play important roles to the development of IBS.

Recent studies in genetic polymorphisms reported that cytokines and neuropeptides may be involved in etiology and clinical manifestations of IBS. This review summarizes the recent discoveries in association of genetic polymorphisms and their impacts on the symptom development and severity, pathogenesis as well as treatment responses to IBS.

GENE POLYMORPHISMS

As IBS is a complex symptom based disorder without single identified pathophysiology or biomarker, multiple mechanisms such as motility dysregulation, visceral hypersensitivity, immune activation, psychosocial factors and altered brain-gut axis has been proposed. Although a number of IBS- related genes have been identified, the majority of the identified genes required further validation. Besides, each of them may only contribute to the pathophysiology in 1%-5% in patients with functional gastrointestinal disorders[4]. This review will summarize how genetic determinations may possibly regulate the putative mechanisms mentioned.

Serotonergic system

Serotonin (5-HT) is one of the most abundant neurotransmitter molecules in the gastrointestinal tract. It is stored in the secretory granules of enterochromaffin (EC) cells in the enteric nervous system, and its release is believed to be responsible for eliciting appetite regulation[5], gut motility[6] and visceral sensitivity[7]. Abnormal levels and activities of 5-HT had been reported in functional gastrointestinal (GI) disorders such as functional dyspepsia (FD)[8] and IBS. Increased plasma 5-HT levels were found in female IBS-D patients[9-11] while decreased postprandial plasma serotonin levels have been reported in IBS-C patients[10]. Excessive 5-HT release in the bowel may lead to diarrhea, nausea and vomiting. Studies reported that single nucleotide polymorphisms (SNPs) in serotonin modulators showed significant associations with IBS. First, tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin[12]. The two isoforms TPH1 and TPH2 showed associations to clinical manifestations in patients with IBS. TPH1 is located on chromosome 11p15.3-p14 and composed of 11 exons[13] and mainly expressed in gut and peripheral organs. TPH2 is located at chromosome 12q21.1 and composed of 11 exons[14] and mainly expression in CNS and peripheral neurons[15]. Homozygous for minor allele (GG) of rs4537731 in promoter region of TPH1 reported more severe diarrhea, bloating, and a trend of more watery stool compared to two genotype groups(AA and AG genotypes) in IBS patients[16]. Genotypes reported with a minor allele (GT and GG genotypes) of rs211105 in intron 3 of TPH1 also reported more severe diarrhea symptoms and trend of more watery stool. Homozygous for the minor allele (T) of TPH2 rs4570625 reported more days with both very hard and watery stools compared to other genotype groups (GG and GT genotypes) in the promoter region of TPH2[16].

Serotonin reuptake transporter (SERT) is a protein that removes serotonin from the sites of action and recycles serotonin back into presynaptic neurons. SERT is located on the chromosome 17q11.2-q1. Wang *et al*[17] showed that the homozygous genotype (L/L) in the promoter region of SERT (L variant bp-1440 to +22) can increase the mRNA and protein level expression of SERT promoter activity in the colonic mucosa. Yeo *et al*[18] found that a strong genotypic association was established between SERT promoter deletion/deletion genotype and female IBS-D patients. Fukudo *et al*[19] further reported SERT linked promoter region polymorphism with long (L, 528bp) and short (S, 484bp) forms showed different levels of brain activation after colorectal distention. This functional gene polymorphism may partially predict the individual effect of long-lasting neural processing from visceral organs. Camilleri *et al*[20] also reported that genetic polymorphisms at the SERT promoter influence response to a 5-HT3 antagonist in D-IBS patients. Kohen *et al*[21] reported that the carriers of rare G allele in polymorphism rs25531 of SERT linked promoter region showed threefold increase in odds ratio of IBS compared to healthy controls.

The 5-HT transporter gene linked polymorphic regions (5-HTTLPR), which is a 43bp insertion/ deletion polymorphism in the 5' flanking promoter region. It is 1.2 kb upstream of the transcription start site. Jarrett *et al*[22] showed the functional polymorphism(insertion or deletion of 44bp) in the 5-HTTLPR that was associated with depression and anxiety traits[23]. Furthermore, the 5-HTTLPR short allele has been found associated with increased visceral sensitivity in IBS[24]. Moreover, the L/L genotype was significantly associated with IBS, IBS-C and IBS-M patients in Korean population[25]. These may suggest that 5-HTTLPR might play a key role in IBS by modulation of SERT at transcriptional level.

Serotonin modulates visceral sensitivity by its action on 5-HT3 receptors. 5-HTR3 receptor A subunit (5-HTR3A), playing a key role in receptor formation, has been associated with depression and anxiety related trait. A functional polymorphism in 5-HTR3A subunit C-42C>T(rs1062613) was associated with more severe dyspeptic symptoms[26], increased anxiety, amygdala responsiveness and severity of IBS[27].

The 5-HT2A receptor subunit A (5-HTR2A) was believed to play a significant role in the genesis of various neuropsychiatric diseases. 5-HTR2A was reported to be responsible in regulating the perception of abdominal pain and smooth muscle contraction in gastrointestinal tract[28,29]. Markoutsaki *et al*[30] reported that the carriers of A allele of the -1438(G/A) polymorphism[31] and homozygote C allele of the 102 T/C polymorphisms in 5-HTR2A had higher risks of IBS[31]. Pata *et al*[31] showed that T/T genotype of 102 T/C polymorphism in 5-HTR2A may be associated with more severe pain in patient with IBS.

Cholecystokinin

Cholecystokinin (CCK) is released by endocrine I cells within the duodenal and jejunal mucosa for stimulating protein and fat digestion. It also served as a hunger suppressant[32]. Elevated plasma CCK level was reported to be associated with patients with post-infectious IBS. Plasma CCK level was correlated with postprandial dyspeptic

symptoms in these patients[33]. Study by Park *et al*[34] showed that polymorphism in CCK receptor intron 1 (779 T>C) was associated with constipation predominant IBS(IBS-C) and mixed IBS(IBS-M) in Korean population.

Catechol-O-methyltransferase

Catechol-*O*-methyltransferase (COMT) is involved in the inactivation of the catecholamine neurotransmitters. Altered COMT activities by different polymorphisms were related to chronic pain conditions such fibromyalgia[35] whereas the COMT Val158Met polymorphism had been associated to panic disorder[36] as well as IBS (Val/Val carriers showed a trend of smaller proportion of hard stools and higher occurrence of postprandial defecation)[37].

Voltage-gated sodium channel

Voltage-gated sodium channel (Na_v) was present in gastrointestinal smooth muscles. These missense mutations were found in tetrodotoxin-resistant sodium channel (SCN5A) in 13 out of 584 patients with irritable bowel syndrome. It was more prevalent in Diarrhea -predominant IBS patients. And these mutations showed disruption in Na_v 1.5 function with decreased peak currents and mechanosensitivity[4,38].

Guanine nucleotide binding protein beta polypeptide 3

Guanine nucleotide binding protein (G-protein) beta polypeptide 3 (GNB3) encodes the beta3 subunit of heterotrimeric G-protein. G-protein is responsible for various functions such as ion channel, motility and contraction. Lee *et al*[39] reported that a polymorphism in C825T has been associated with IBS-C patients in South Korea. Although no association was found between C825T with the overlapping of IBS and FD patients by Kim *et al*[40], an association was reported between dyspeptic symptoms and homozygous 825T allele of GNB3 protein in the H Pylori-negative Japanese population[41]. Oshima *et al*[42] also revealed epigastric pain syndrome(EPS) was correlated with homozygous 825T allele in GNB3 protein of patients with FD. Moreover, Saito *et al*[43] showed that an interaction was found between GNB3 825T allele and gastrointestinal infection of IBS in western population.

Endocannabinoid system

Endocannabinoids serve as synaptic circuit breakers and regulate multiple physiological and pathological conditions including nociception (pain sensation), appetite, lipid metabolism, gastrointestinal motility, cardiovascular modulation, motor activity, mood, and memory. Cannabinoids suppress behavioral responses to noxious stimulation and nociceptive processing through activation of cannabinoid CB receptor 1 (CNR1) and CB receptor 2 (CNR2) subtypes[44]. Wong *et al*[45] reported polymorphism of rs806378 (CT/TT genotype) in CB(1) receptor was associated with IBS patients having a modest delay in colonic transit. Camilleri *et al*[46] also showed that TT group had the fastest colonic transit at 24 and 48 h. Besides, there was a significant association of CNR1 in rs806378 with sensation rating of gas, but not pain sensation in various IBS subtypes. Park *et al*[47] and colleagues found a different distribution of allelic frequency of AAT repeats in the *CNR1* gene between healthy controls and IBS patients. They also reported a significant association of CNR1 >10/>10 genotype with IBS.

Psychiatric distress

Research has implicated that a combination of genetic and environmental risk factors (*e.g.*, Early life adversity, traumatic experiences) in the pathogenesis of mood disorders such as depression[48]. While strong association was established between psychological distress and functional gastrointestinal diseases[49], an established biopsychosocial model was suggested where early life stress may predispose HPA axis dysfunction and develop functional gastrointestinal symptoms[50]. The prevalence of depression and anxiety disorder was 37.1% and 31.4% respectively in Indian population with IBS[51]. Lee *et al*[52] also reported that IBS is also strongly associated with generalized anxiety disorder in Chinese population. Chronic widespread pain related to fibromyalgia and chronic fatigue is associated with IBS and major depressive disorder. Sato *et al*[53] showed that TT genotype of rs7209436 and rs242924 in Corticotrophin-releasing hormone was significantly more common in patients with IBS than in healthy controls. Corticotrophin-releasing hormone carries a potential risk for depression. These polymorphisms were also associated with bowel pattern in these IBS patients. Besides, polymorphisms in 5-HTTLPR, intron 2 (STin2 VTNR) of SERT were also correlated with depressive episodes and IBS[22].

Neuropeptide S (NPS) is a 20 amino acids peptide that selectively binds and activates an orphan G-protein coupled receptor, Neuropeptide S receptor 1 (NPSR1). It is expressed on the intestinal epithelium. This neuropeptide S system is involved in stress responses, anxiety, and nociception through selectively inhibiting the evoked release of serotonin and norepinephrine the frontal cortex, by acting directly on serotonin and norepinephrine nerve terminals[54]. NPSR1 polymorphisms were reported to be associated with colonic transit rate (rs2609234, rs6972158 and rs1379928) and visceral pain(rs1379928)[55].

Cytokines

It has become increasingly clear that low-grade inflammation is implicated in the pathophysiology of IBS with subtle changes in pro-inflammatory or anti-inflammatory cytokines in blood or GI mucosa[56,57]. Studies reported significant associations between functional polymorphisms in these genes among IBS patients. Tumour necrosis factor alpha (TNFα) is a cytokine which involved in stimulating systemic inflammation and it is implicated in various diseases such as cancer, depression and inflammatory bowel disease. Although polymorphism in TNFα(-308 G/A) showed no difference in frequencies between Indian IBS patients and healthy volunteers[58], Barkhordari *et al*[59] showed that polymorphism of TNFα at position -308 and -238 were also

significantly higher in IBS patients. TNFSF15 is a member of the TNF (ligand) superfamily which codes for TL1A. It is expressed primarily in macrophage, T cells, and immune cells that are exposed to pro-inflammatory stimuli or microbes. TNFSF15 involves in the defense against pathogens and homeostatic interactions with commensal bacteria in the gut. Study by Zucchelli *et al*[60] showed the Crohn's disease risk allele rs4263839 G in TNFSF15 gene was significantly associated with increased risk of IBS and particularly in IBS-C patients. TNFRSF17 is expressed in mature B lymphocytes and development of B cells. Besides its involvement in inflammatory bowel disease (IBD), SNPs at position -1729G, -2445 and -2493 showed significantly distinct frequencies in patients with lower functional gastrointestinal disorders compared to healthy controls[61].

Interleukins are important modulators in inflammatory responses, they play a vital role in intestinal inflammation. Pro-inflammatory cytokines such as interleukin (IL)-6 and IL-8 has been up-regulated in IBS patients[56]. Although Camilleri *et al*[62] showed no difference in gene polymorphisms of IL-6 was found between subtypes of IBS patients and healthy individuals in American population, IL-6 G allele at position -174 showed higher frequencies in Iranian IBS patients[59]. Moreover, there was significant difference in frequencies shown in IL-8 G allele at position +396 and C allele +781 between IBS patients and healthy controls. Besides, the combinations of IL-8 ATCC haplotypes (at positions -251, +396, +781 and +1633) reported significant association with susceptibility to development of IBS[63]. In Mexican population, IL-8 T allele at position +781 was significantly overexpressed in patients with IBS and IL-8 G allele at position +396 was also associated with IBS[64].

Anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF) β1 also play an important role in the regulation of immune and inflammatory responses. Although no significant difference was found in colonic expression of TGFβ1 in IBS patients[65], Romero-Valdovinos *et al*[63] showed that IL-10 A allele at position 1082 were significantly increased in IBS Mexican patients. IL-10 can inhibit pro-inflammatory cytokines such as tumour necrosis factor beta (TNF-β). IL-10 ACC haplotypes (at positions -1082, -819 and -592) were also associated with development of IBS. IL-10 C allele at position -592 also showed association with higher risk in developing IBS in Mexican population[64].

CONCLUSION

IBS is a complex functional disorder that involves multiple interactions of genetic inheritance, environmental and psychosocial factors. This review summarized the recent discoveries on how genetics may influence on the symptoms severity and subtypes of IBS through modulation of gastrointestinal functions such as gut motility, immune activation and visceral sensation. Further studies are necessary to understand the mechanisms on how genetics may determine the clinical manifestations and therapeutic responses to subset of IBS patients. Besides, biomarker discovery for this complex heterogeneous disorder remains a big challenge. Future studies should be required to search for candidate genes with combinations of gene expression profiling for target treatment and diagnosis for specific subsets of IBS patients.

REFERENCES

1 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

2 **Drossman DA**, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointestin Liver Dis* 2006; **15**: 237-241 [PMID: 17013448]

3 **Kang JY**. Systematic review: the influence of geography and ethnicity in irritable bowel syndrome. *Aliment Pharmacol Ther* 2005; **21**: 663-676 [PMID: 15771752 DOI: 10.1111/j.1365-2036.2005.02396.x]

4 **Saito YA**, Mitra N, Mayer EA. Genetic approaches to functional gastrointestinal disorders. *Gastroenterology* 2010; **138**: 1276-1285 [PMID: 20176021 DOI: 10.1053/j.gastro.2010.02.037]

5 **Curzon G**. Serotonin and appetite. *Ann N Y Acad Sci* 1990; **600**: 521-530; discussion 530-531 [PMID: 2252331]

6 **Spiller R**. Serotonin and GI clinical disorders. *Neuropharmacology* 2008; **55**: 1072-1080 [PMID: 18687345 DOI: 10.1016/j.neuropharm.2008.07.016]

7 **Grundy D**. 5-HT system in the gut: roles in the regulation of visceral sensitivity and motor functions. *Eur Rev Med Pharmacol Sci* 2008; **12** Suppl 1: 63-67 [PMID: 18924445]

8 **Cheung CK**, Lee YY, Chan Y, Cheong PK, Law WT, Lee SF, Sung JJ, Chan FK, Wu JC. Decreased Basal and postprandial plasma serotonin levels in patients with functional dyspepsia. *Clin Gastroenterol Hepatol* 2013; **11**: 1125-1129 [PMID: 23591288 DOI: 10.1016/j.cgh.2013.03.026]

9 **Houghton LA**, Atkinson W, Whitaker RP, Whorwell PJ, Rimmer MJ. Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome. *Gut* 2003; **52**: 663-670 [PMID: 12692050]

10 **Atkinson W**, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2006; **130**: 34-43 [PMID: 16401466 DOI: 10.1053/j.gastro.2005.09.031]

11 **Bearcroft CP**, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut* 1998; **42**: 42-46 [PMID: 9505884]

12 **Lovenberg W**, Jequier E, Sjoerdsma A. Tryptophan hydroxylation: measurement in pineal gland, brainstem, and carcinoid tumor. *Science* 1967; **155**: 217-219 [PMID: 6015530]

13 **Ledley FD**, Grenett HE, Bartos DP, van Tuinen P, Ledbetter DH, Woo SL. Assignment of human tryptophan hydroxylase locus to chromosome 11: gene duplication and translocation in evolution of aromatic amino acid hydroxylases. *Somat Cell Mol Genet* 1987; **13**: 575-580 [PMID: 2889273]

14 **Zill P**, Baghai TC, Zwanzger P, Schüle C, Eser D, Rupprecht R, Möller HJ, Bondy B, Ackenheil M. SNP and haplotype analysis of a novel tryptophan hydroxylase isoform (TPH2) gene provide evidence for association with major depression. *Mol Psychiatry* 2004; **9**: 1030-1036 [PMID: 15124006 DOI: 10.1038/sj.mp.4001525]

15 **Zill P**, Büttner A, Eisenmenger W, Möller HJ, Ackenheil M, Bondy B. Analysis of tryptophan hydroxylase I and II mRNA expression in the human brain: a post-mortem study. *J Psychiatr Res* 2007; **41**: 168-173 [PMID: 16023677 DOI: 10.1016/j.jpsychires.2005.05.004]

16 **Jun S**, Kohen R, Cain KC, Jarrett ME, Heitkemper MM. Associations of tryptophan hydroxylase gene polymorphisms with irritable bowel syndrome. *Neurogastroenterol Motil* 2011; **23**: 233-239, e116 [PMID: 21073637 DOI: 10.1111/j.1365-2982.2010.01623.x]

17 **Wang YM**, Chang Y, Chang YY, Cheng J, Li J, Wang T, Zhang QY, Liang DC, Sun B, Wang BM. Serotonin transporter gene promoter region polymorphisms and serotonin transporter expression in the colonic mucosa of irritable bowel syndrome patients. *Neurogastroenterol Motil* 2012; **24**: 560-565, e254-e255 [PMID: 22435794 DOI: 10.1111/j.1365-2982.2012.01902.x]

18 **Yeo A**, Boyd P, Lumsden S, Saunders T, Handley A, Stubbins M, Knaggs A, Asquith S, Taylor I, Bahari B, Crocker N, Rallan R, Varsani S, Montgomery D, Alpers DH, Dukes GE, Purvis I, Hicks GA. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut* 2004; **53**: 1452-1458 [PMID: 15361494 DOI: 10.1136/gut.2003.035451]

19 **Fukudo S**, Kanazawa M, Mizuno T, Hamaguchi T, Kano M, Watanabe S, Sagami Y, Shoji T, Endo Y, Hongo M, Itoyama Y, Yanai K, Tashiro M, Aoki M. Impact of serotonin transporter gene polymorphism on brain activation by colorectal distention. *Neuroimage* 2009; **47**: 946-951 [PMID: 19426812 DOI: 10.1016/j.neuroimage.2009.04.083]

20 **Camilleri M**, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, McKinzie S, Urrutia R. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002; **123**: 425-432 [PMID: 12145795]

21 **Kohen R**, Jarrett ME, Cain KC, Jun SE, Navaja GP, Symonds S, Heitkemper MM. The serotonin transporter polymorphism rs25531 is associated with irritable bowel syndrome. *Dig Dis Sci* 2009; **54**: 2663-2670 [PMID: 19125330 DOI: 10.1007/s10620-008-0666-3]

22 **Jarrett ME**, Kohen R, Cain KC, Burr RL, Poppe A, Navaja GP, Heitkemper MM. Relationship of SERT polymorphisms to depressive and anxiety symptoms in irritable bowel syndrome. *Biol Res Nurs* 2007; **9**: 161-169 [PMID: 17909168 DOI: 10.1177/1099800407307822]

23 **Sen S**, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *Am J Med Genet B Neuropsychiatr Genet* 2004; **127B**: 85-89 [PMID: 15108187 DOI: 10.1002/ajmg.b.20158]

24 **Camilleri M**, Busciglio I, Carlson P, McKinzie S, Burton D, Baxter K, Ryks M, Zinsmeister AR. Candidate genes and sensory functions in health and irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**: G219-G225 [PMID: 18511740 DOI: 10.1152/ajpgi.90202.2008]

25 **Choi YJ**, Hwang SW, Kim N, Park JH, Oh JC, Lee DH. Association Between SLC6A4 Serotonin Transporter Gene Lainked Polymorphic Region and ADRA2A -1291C& gt; G and Irritable Bowel Syndrome in Korea. *J Neurogastroenterol Motil* 2014; **20**: 388-399 [PMID: 24917480 DOI: 10.5056/jnm14020]

26 **Mujakovic S**, ter Linde JJ, de Wit NJ, van Marrewijk CJ, Fransen GA, Onland-Moret NC, Laheij RJ, Muris JW, Grobbee DE, Samsom M, Jansen JB, Knottnerus A, Numans ME. Serotonin receptor 3A polymorphism c.-42C & gt; T is associated with severe dyspepsia. *BMC Med Genet* 2011; **12**: 140 [PMID: 22014438 DOI: 10.1186/1471-2350-12-140]

27 **Kilpatrick LA**, Labus JS, Coveleskie K, Hammer C, Rappold G, Tillisch K, Bueller JA, Suyenobu B, Jarcho JM, McRoberts JA, Niesler B, Mayer EA. The HTR3A polymorphism c. -42C& gt; T is associated with amygdala responsiveness in patients with irritable bowel syndrome. *Gastroenterology* 2011; **140**: 1943-1951 [PMID: 21420406 DOI: 10.1053/j.gastro.2011.03.011]

28 **Tokunaga A**, Saika M, Senba E. 5-HT2A receptor subtype is involved in the thermal hyperalgesic mechanism of serotonin in the periphery. *Pain* 1998; **76**: 349-355 [PMID: 9718253]

29 **Kim DY**, Camilleri M. Serotonin: a mediator of the brain-gut connection. *Am J Gastroenterol* 2000; **95**: 2698-2709 [PMID: 11051338 DOI: 10.1111/j.1572-0241.2000.03177.x]

30 **Markoutsaki T**, Karantanos T, Gazouli M, Anagnou NP, Karamanolis DG. 5-HT2A receptor gene polymorphisms and irritable bowel syndrome. *J Clin Gastroenterol* 2011; **45**: 514-517 [PMID: 21325954 DOI: 10.1097/MCG.0b013e318205e13b]

31 **Pata C**, Erdal E, Yazc K, Camdeviren H, Ozkaya M, Ulu O. Association of the -1438 G/A and 102 T/C polymorphism of the 5-Ht2A receptor gene with irritable bowel syndrome 5-Ht2A gene polymorphism in irritable bowel syndrome. *J Clin Gastroenterol* 2004; **38**: 561-566 [PMID: 15232358]

32 **Cremonini F**, Camilleri M, McKinzie S, Carlson P, Camilleri CE, Burton D, Thomforde G, Urrutia R, Zinsmeister AR. Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005; **100**: 652-663 [PMID: 15743365 DOI: 10.1111/j.1572-0241.2005.41081.x]

33 **Dizdar V**, Spiller R, Singh G, Hanevik K, Gilja OH, El-Salhy M, Hausken T. Relative importance of abnormalities of CCK and 5-HT (serotonin) in Giardia-induced post-infectious irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2010; **31**: 883-891 [PMID: 20132151 DOI: 10.1111/j.1365-2036.2010.04251.x]

34 **Park SY**, Rew JS, Lee SM, Ki HS, Lee KR, Cheo JH, Kim HI, Noh DY, Joo YE, Kim HS, Choi SK. Association of CCK(1) Receptor Gene Polymorphisms and Irritable Bowel Syndrome in Korean. *J Neurogastroenterol Motil* 2010; **16**: 71-76 [PMID: 20535329 DOI: 10.5056/jnm.2010.16.1.71]

35 **Gürsoy S**, Erdal E, Herken H, Madenci E, Alaşehirli B, Erdal N. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int* 2003; **23**: 104-107 [PMID: 12739038 DOI: 10.1007/s00296-002-0260-5]

36 **Domschke K**, Deckert J, O'donovan MC, Glatt SJ. Meta-analysis of COMT val158met in panic disorder: ethnic heterogeneity and gender specificity. *Am J Med Genet B Neuropsychiatr Genet* 2007; **144B**: 667-673 [PMID: 17357147 DOI: 10.1002/ajmg.b.30494]

37 **Karling P**, Danielsson Å, Wikgren M, Söderström I, Del-Favero J, Adolfsson R, Norrback KF. The relationship between the val158met catechol-O-methyltransferase (COMT) polymorphism and irritable bowel syndrome. *PLoS One* 2011; **6**: e18035 [PMID: 21437260 DOI: 10.1371/journal.pone.0018035]

38 **Abecasis GR**, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012; **491**: 56-65 [PMID: 23128226 DOI: 10.1038/nature11632]

39 **Lee HJ**, Lee SY, Choi JE, Kim JH, Sung IK, Park HS, Jin CJ. G protein beta3 subunit, interleukin-10, and tumor necrosis factor-alpha gene polymorphisms in Koreans with irritable bowel syndrome. *Neurogastroenterol Motil* 2010; **22**: 758-763 [PMID: 20337945 DOI: 10.1111/j.1365-2982.2010.01496.x]

40 **Kim HG**, Lee KJ, Lim SG, Jung JY, Cho SW. G-Protein Beta3 Subunit C825T Polymorphism in Patients With Overlap Syndrome of Functional Dyspepsia and Irritable Bowel Syndrome. *J Neurogastroenterol Motil* 2012; **18**: 205-210 [PMID: 22523731 DOI: 10.5056/jnm.2012.18.2.205]

41 **Tahara T**, Arisawa T, Shibata T, Wang F, Nakamura M, Sakata M, Hirata I, Nakano H. Homozygous 825T allele of the GNB3 protein influences the susceptibility of Japanese to dyspepsia. *Dig Dis Sci* 2008; **53**: 642-646 [PMID: 17717746 DOI: 10.1007/s10620-007-9923-0]

42 **Oshima T**, Nakajima S, Yokoyama T, Toyoshima F, Sakurai J, Tanaka J, Tomita T, Kim Y, Hori K, Matsumoto T, Miwa H. The G-protein beta3 subunit 825 TT genotype is associated with epigastric pain syndrome-like dyspepsia. *BMC Med Genet* 2010; **11**: 13 [PMID: 20102604 DOI: 10.1186/1471-2350-11-13]

43 **Saito YA**, Larson JJ, Atkinson EJ, Ryu E, Almazar AE, Petersen GM, Talley NJ. The role of 5-HTT LPR and GNβ3 825C& gt; T polymorphisms and gene-environment interac-

tions in irritable bowel syndrome (IBS). *Dig Dis Sci* 2012; **57**: 2650-2657 [PMID: 22855291 DOI: 10.1007/s10620-012-2319-9]
44 **Guindon J**, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets* 2009; **8**: 403-421 [PMID: 19839937]
45 **Wong BS**, Camilleri M, Eckert D, Carlson P, Ryks M, Burton D, Zinsmeister AR. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. *Neurogastroenterol Motil* 2012; **24**: 358-e169 [PMID: 22288893 DOI: 10.1111/j.1365-2982.2011.01874.x]
46 **Camilleri M**, Kolar GJ, Vazquez-Roque MI, Carlson P, Burton DD, Zinsmeister AR. Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**: G553-G560 [PMID: 23306084 DOI: 10.1152/ajpgi.00376.2012]
47 **Park JM**, Choi MG, Cho YK, Lee IS, Kim SW, Choi KY, Chung IS. Cannabinoid receptor 1 gene polymorphism and irritable bowel syndrome in the Korean population: a hypothesis-generating study. *J Clin Gastroenterol* 2011; **45**: 45-49 [PMID: 20505532 DOI: 10.1097/MCG.0b013e3181dd1573]
48 **Klengel T**, Binder EB. Gene-environment interactions in major depressive disorder. *Can J Psychiatry* 2013; **58**: 76-83 [PMID: 23442893]
49 **Levy RL**, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, Creed F. Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology* 2006; **130**: 1447-1458 [PMID: 16678558 DOI: 10.1053/j.gastro.2005.11.057]
50 **Drossman DA**. Gastrointestinal illness and the biopsychosocial model. *J Clin Gastroenterol* 1996; **22**: 252-254 [PMID: 8771417]
51 **Kabra N**, Nadkarni A. Prevalence of depression and anxiety in irritable bowel syndrome: A clinic based study from India. *Indian J Psychiatry* 2013; **55**: 77-80 [PMID: 23439939 DOI: 10.4103/0019-5545.105520]
52 **Lee S**, Wu J, Ma YL, Tsang A, Guo WJ, Sung J. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: a community study. *Aliment Pharmacol Ther* 2009; **30**: 643-651 [PMID: 19552631 DOI: 10.1111/j.1365-2036.2009.04074.x]
53 **Sato N**, Suzuki N, Sasaki A, Aizawa E, Obayashi T, Kanazawa M, Mizuno T, Kano M, Aoki M, Fukudo S. Corticotropin-releasing hormone receptor 1 gene variants in irritable bowel syndrome. *PLoS One* 2012; **7**: e42450 [PMID: 22957021 DOI: 10.1371/journal.pone.0042450]
54 **Raiteri L**, Luccini E, Romei C, Salvadori S, Calò G. Neuropeptide S selectively inhibits the release of 5-HT and noradrenaline from mouse frontal cortex nerve endings. *Br J Pharmacol* 2009; **157**: 474-481 [PMID: 19371348 DOI: 10.1111/j.1476-5381.2009.00163.x]
55 **Camilleri M**, Carlson P, Zinsmeister AR, McKinzie S, Busciglio I, Burton D, Zucchelli M, D'Amato M. Neuropeptide S receptor induces neuropeptide expression and associates with intermediate phenotypes of functional gastrointestinal disorders. *Gastroenterology* 2010; **138**: 98-107.e4 [PMID: 19732772 DOI: 10.1053/j.gastro.2009.08.051]
56 **Dinan TG**, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, O'Mahony S, Shanahan F, Keeling PW. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology* 2006; **130**: 304-311 [PMID: 16472586 DOI: 10.1053/j.gastro.2005.11.033]
57 **Ohman L**, Isaksson S, Lindmark AC, Posserud I, Stotzer PO, Strid H, Sjövall H, Simrén M. T-cell activation in patients with irritable bowel syndrome. *Am J Gastroenterol* 2009; **104**: 1205-1212 [PMID: 19367268 DOI: 10.1038/ajg.2009.116]
58 **Santhosh S**, Dutta AK, Samuel P, Joseph AJ, Ashok Kumar J, Kurian G. Cytokine gene polymorphisms in irritable bowel syndrome in Indian population--a pilot case control study. *Trop Gastroenterol* 2010; **31**: 30-33 [PMID: 20860222]
59 **Barkhordari E**, Rezaei N, Ansaripour B, Larki P, Alighardashi M, Ahmadi-Ashtiani HR, Mahmoudi M, Keramati MR, Habibollahi P, Bashashati M, Ebrahimi-Daryani N, Amirzargar AA. Proinflammatory cytokine gene polymorphisms in irritable bowel syndrome. *J Clin Immunol* 2010; **30**: 74-79 [PMID: 19844779 DOI: 10.1007/s10875-009-9342-4]
60 **Zucchelli M**, Camilleri M, Andreasson AN, Bresso F, Dlugosz A, Halfvarson J, Törkvist L, Schmidt PT, Karling P, Ohlsson B, Duerr RH, Simren M, Lindberg G, Agreus L, Carlson P, Zinsmeister AR, D'Amato M. Association of TNFSF15 polymorphism with irritable bowel syndrome. *Gut* 2011; **60**: 1671-1677 [PMID: 21636646 DOI: 10.1136/gut.2011.241877]
61 **Chae SC**, Yu JI, Oh GJ, Choi CS, Choi SC, Yang YS, Yun KJ. Identification of single nucleotide polymorphisms in the TNFRSF17 gene and their association with gastrointestinal disorders. *Mol Cells* 2010; **29**: 21-28 [PMID: 20016944 DOI: 10.1007/s10059-010-0002-6]
62 **Camilleri M**, Carlson P, McKinzie S, Zucchelli M, D'Amato M, Busciglio I, Burton D, Zinsmeister AR. Genetic susceptibility to inflammation and colonic transit in lower functional gastrointestinal disorders: preliminary analysis. *Neurogastroenterol Motil* 2011; **23**: 935-e398 [PMID: 21752155 DOI: 10.1111/j.1365-2982.2011.01749.x]
63 **Romero-Valdovinos M**, Gudiño-Ramírez A, Reyes-Gordillo J, Martínez-Flores WA, Ramírez-Miranda ME, Maravilla P, Olivo-Díaz A. Interleukin-8 and -10 gene polymorphisms in irritable bowel syndrome. *Mol Biol Rep* 2012; **39**: 8837-8843 [PMID: 22740130 DOI: 10.1007/s11033-012-1745-2]
64 **Olivo-Diaz A**, Romero-Valdovinos M, Gudiño-Ramirez A, Reyes-Gordillo J, Jimenez-Gonzalez DE, Ramirez-Miranda ME, Martinez-Flores WA, Martinez-Hernandez F, Flisser A, Maravilla P. Findings related to IL-8 and IL-10 gene polymorphisms in a Mexican patient population with irritable bowel syndrome infected with Blastocystis. *Parasitol Res* 2012; **111**: 487-491 [PMID: 22287022 DOI: 10.1007/s00436-012-2830-0]
65 **Sun X**, Lan C, An Y, Sun Y. Colonic expression of Runx3 protein and TGF-β(1) and their correlation in patients with irritable bowel syndrome. *Asian Pac J Trop Med* 2011; **4**: 547-549 [PMID: 21803306 DOI: 10.1016/S1995-7645(11)60143-0]

P- Reviewer: Shaffer EA, Wittmann T
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327