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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. 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.

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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.
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. 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, gut motility and visceral sensitivity. Abnormal levels and activities of 5-HT had been reported in functional gastrointestinal (GI) disorders such as functional dyspepsia (FD) and IBS. Increased plasma 5-HT levels were found in female IBS-D patients while decreased postprandial plasma serotonin activity, pathogenesis as well as treatment responses to IBS. 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. 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 and mainly expressed in gut and peripheral organs. TPH2 is located at chromosome 12q21.1 and composed of 11 exons and mainly expression in CNS and peripheral neurons. 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. 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.

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 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 found that a strong genotypic association was established between SERT promoter deletion/deletion genotype and female IBS-D patients. Fukudo et al 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 also reported that genetic polymorphisms at the SERT promoter influence response to a 5-HT3 antagonist in D-IBS patients. Kohen et al 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 showed the functional polymorphism (insertion or deletion of 44bp) in the 5-HTTLPR that was associated with depression and anxiety traits. Furthermore, the 5-HTTLPR short allele has been found associated with increased visceral sensitivity in IBS. Moreover, the L/L genotype was significantly associated with IBS, IBS-C and IBS-M patients in Korean population. These may suggest that 5-HTTLPR might play a significant role in IBS by modulation of SERT at transcriptional level.

Serotonin modulates visceral sensitivity by its action on 5-HT3 receptors. 5-HT3 receptor A subunit (5-HT3A), playing a key role in receptor formation, has been associated with depression and anxiety related trait. A functional polymorphism in 5-HT3A subunit C-42>C->T(rs1062613) was associated with more severe dyspeptic symptoms increased anxiety, amygdala responsiveness and severity of IBS.

The 5-HT2A receptor subunit A (5-HT2RA) was believed to play a significant role in the genesis of various neuropsychiatric diseases. 5-HT2RA was reported to be responsible in regulating the perception of abdominal pain and smooth muscle contraction in gastrointestinal tract. Markouatski et al reported that the carriers of A allele of the -1438(G/A) polymorphism and homozygote C allele of the 102 T/C polymorphisms in 5-HT2RA had higher risks of IBS. Kata et al showed that T/T genotype of 102 T/C polymorphism in 5-HT2RA 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. Elevated plasma CCK level was reported to be associated with patients with post-infectious IBS. Plasma CCK level was correlated with postprandial dyspeptic 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.
symptoms in these patients. Study by Park et al. 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 whereas the COMT Val158Met polymorphism had been associated to panic disorder as well as IBS (Val/Val carriers showed a trend of smaller proportion of hard stools and higher occurrence of postprandial defecation).

**Voltage-gated sodium channel**

Voltage-gated sodium channel (Na+) is 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+ 1.5 function with decreased peak currents and mechanosensitivity.

**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. 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., an association was reported between dyspeptic symptoms and homozygous 825T allele of GNB3 protein in the H Pylori-negative Japanese population. Oshima et al. also revealed epigastric pain syndrome (EPS) was correlated with homozygous 825T allele in GNB3 protein of patients with FD. Moreover, Saito et al. showed that an interaction was found between GNB3 825T allele and gastrointestinal infection in IBS of 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. Wong et al. reported polymorphism of rs806378 (CT/TT genotype) in CB1 receptor was associated with IBS patients having a modest delay in colonic transit. Camilleri et al. 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. 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. While strong association was established between psychological distress and functional gastrointestinal diseases, an established biopsychosocial model was suggested where early life stress may predispose HPA axis dysfunction and develop functional gastrointestinal symptoms. The prevalence of depression and anxiety disorder was 37.1% and 31.4% respectively in Indian population with IBS. Lee et al. 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. showed that TT genotype of rs7209436 and rs424924 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.

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. NPSR1 polymorphisms were reported to be associated with colonic transit rate (rs2609234, rs6972158 and rs1379928) and visceral pain (rs1379928).

**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 G1 mucosa. Studies reported significant associations between functional polymorphisms in these genes among IBS patients. Tumour necrosis factor alpha (TNFa) 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 TNFa -308 G/A showed no difference in frequencies between Indian IBS patients and healthy volunteers, Barkhordari et al. showed that polymorphism of TNFa 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[14] 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[15].

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[56] 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[57]. Moreover, there was significant difference in frequencies shown in IL-6 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[58]. 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[60].

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[61], Romero-Valdivinos et al[62] 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[63].

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.

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