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Genetic epidemiology of irritable bowel syndrome

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Abstract

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder characterized by presence of abdominal pain or discomfort associated with altered bowel habits. It has three main subtypes - constipation predominant IBS (C-IBS), diarrhea predominant IBS (D-IBS) and IBS with mixed features

of both diarrhea as well as constipation (M-IBS). Its pathophysiology and underlying mechanisms remain elusive. It is traditionally believed that IBS is a result of multiple factors including hypersensitivity of the bowel, altered bowel motility, inflammation and stress. Initial studies have shown familial aggregation of IBS suggesting shared genetic or environmental factors. Twin studies of IBS from different parts of world have shown higher concordance rates among monozygotic twins than dizygotic twins, and thus suggesting a genetic component to this disorder. Multiple studies have tried to link single-nucleotide polymorphisms (SNPs) to IBS but there is little evidence that these SNPs are functional. Various molecules have been studied and investigated by the researchers. Serotonin, a known neurotransmitter and a local hormone in the enteric nervous system, has been most extensively explored. At this time, the underlying gene pathways, genes and functional variants linked with IBS remain unknown and the promise of genetically-determined risk prediction and personalize medicine remain unfulfilled. However, molecular biological technologies continue to evolve rapidly and genetic investigations offer much promise in the intervention, treatment and prevention of IBS.

Key words: Irritable bowel syndrome; Single-nucleotide polymorphism; Serotonin; Familial aggregation; Genetics

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Core tip: Irritable bowel syndrome (IBS) is believed to result from interplay of several factors including hypersensitivity of the bowel, altered bowel motility, inflammation and stress. Familial aggregation of cases and twin studies underscore the genetic basis of IBS. Different researchers have studied several candidate genes but the evidence so far linking IBS to specific genes is inconsistent and weak. Genome wide association studies that can examine several common genetic variants are needed to design newer drugs and

diagnostic methods.

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder with a worldwide prevalence rates ranging between 7%-21%^[1]. It is a clinical diagnosis that does not require diagnostic testing unless needed to exclude other diagnostic possibilities. It is characterized by presence of abdominal pain or discomfort associated with altered bowel habits. Rome III criteria that assess the relationship between abdominal pain or discomfort, stool form and change in bowel frequency is the most accepted criteria used in clinical practice for making a clinical diagnosis^[2]. Three clinical types have been recognized based on altered bowel motility and the resulting predominant feature - constipation predominant IBS (C-IBS), diarrhea predominant IBS (D-IBS) and IBS with mixed features of both diarrhea as well as constipation (M-IBS).

The genetic basis of IBS has been suggested by familial aggregation and twin studies. Furthermore, over the last decade, several candidate genes have been identified that are potentially linked to IBS. This review will further elaborate on our current understanding of genetic epidemiology of IBS.

GENETIC EPIDEMIOLOGY OF IBS

Familial aggregation of IBS

Mankind is familiar with IBS for more than a century but its pathophysiology and underlying mechanisms remain elusive. It is traditionally believed that IBS is a result of multiple factors including hypersensitivity of the bowel, altered bowel motility, inflammation and stress. Initial studies have shown familial aggregation of IBS suggesting that genes or shared environmental exposures contribute to the development of IBS (Table 1). In one of the earlier studies by Whorwell *et al.*^[3] while investigating the non colonic symptoms of IBS, investigators found that 33% of IBS patients had a family member with IBS as compared to only 2% in the control group ($P < 0.0001$). In an interesting study by Levy *et al.*^[4] it was revealed that children of parents who had IBS made 20% more ambulatory care visits than the children of parents without IBS ($P = 0.0001$). In the same study, researchers also showed that these children who had a parent with IBS made 50% more visits for gastrointestinal symptoms as compared to

control group ($P = 0.0001$). In the study by Locke *et al.*^[5], a survey of people residing in Olmsted county of Minnesota with functional gastrointestinal disorders showed higher odds (OR = 2.3; 95%CI: 1.3-3.9) of reporting a relative with gastrointestinal symptoms among these individuals. Studies by Kalantar *et al.*^[6] and Saito *et al.*^[7] are the other examples where relatives of IBS patients and controls were interviewed and it was determined that statistically higher percentage of IBS patients' relatives had IBS as compared to control patients' relatives (17% vs 7%, OR = 2.7; 95%CI: 1.2-6.3 and 37% vs 16%, $P = 0.002$ respectively). In another study by Saito *et al.*^[8] besides showing aggregation of IBS cases among family members, lack of any association in spouses was also shown. In a recent large nationwide case cohort study from Sweden, a higher odds ratio of IBS was found in first, second and third degree relatives of IBS patients (OR for first degree relatives: 1.75-1.90, for second degree relatives: 1.10-1.78 and third degree relatives: 1.11)^[9]. These studies further support the concept of shared genes or shared environmental exposures.

Similarly, twin studies have also demonstrated the role of genes in IBS. The first twin study from Australia by Morris-Yates *et al.*^[10] and another study involving Swedish twin pairs by Svedberg *et al.*^[11] emphasized the genetic basis of IBS. Studies by Levy *et al.*^[12] and Bengtson *et al.*^[13] involving 281 twin pairs in United States and 3334 twin pairs in Norway respectively showed higher concordance rate for IBS among monozygotic twins than in dizygotic twins (17.2% vs 8.4%, $P = 0.03$; 22.4% vs 9.1%, $P = 0.011$ respectively). In the study by Lembo *et al.*^[14], 986 twin pairs from Minnesota twin registry were surveyed and their results concur with results of the studies from the other countries and showed the higher rate of IBS among monozygotic twins. Though all these twin studies mentioned above underscore the genetic basis of IBS, the study by Mohammed *et al.*^[15] did not come to the same conclusion and found no difference in concordance rates between monozygotic and dizygotic twins.

CANDIDATE GENE STUDIES AND IBS

Serotonin and IBS

Many investigators have focused on specific candidate genes and whether variation in these genes is associated with IBS. Serotonin (5-hydroxytryptamine, 5-HT) is the most widely studied molecule due to its role in brain-gut axis and abundance in the gastrointestinal tract. Majority of body serotonin is present in gastrointestinal tract where it is synthesized mainly by enterochromaffin cells (EC cells) and some of it by myenteric plexus neurons. Serotonin is a known neurotransmitter and a local hormone in the enteric nervous system. It is released from EC cells in response to variety of stimuli and exerts its local

Table 1 Familial aggregation studies

Authors (Year)	Number of IBS patients	Conclusion
Whorwell <i>et al</i> ^[3] (1986)	100	Significant number of IBS patient had another family member with IBS
Levy <i>et al</i> ^[4] (2000)	373	Children of parents with IBS made more visits for gastrointestinal symptoms
Locke <i>et al</i> ^[5] (2000)	643	People with functional gastrointestinal disorders had higher odds of reporting a relative with similar symptoms
Kalantar <i>et al</i> ^[6] (2003)	181	IBS prevalence was higher among IBS patients' relatives
Saito <i>et al</i> ^[7] (2008)	50	Statistically higher percentage of IBS patients' relatives had IBS
Saito <i>et al</i> ^[8] (2010)	477	50% of IBS patients had at least another relative with IBS
Waehrens <i>et al</i> ^[9] (2015)	51952	Increased risk of IBS among first, second and third degree relatives of IBS patients

IBS: Irritable bowel syndrome.

paracrine effects through serotonin receptors. There are seven serotonin receptors identified so far named as 5-HT1 to 5-HT7. Out of these seven receptors, 5HT1 to 5-HT4 and 5HT7 play a key role in mediating intestinal responses. The effect of serotonin molecule initiated after its binding to serotonin receptor is eventually terminated by its uptake through a serotonin reuptake transporter (SERT)^[16].

There is evidence that patients with IBS have defects in serotonergic signaling. Almost four decades ago, it was discovered that patients with IBS have more number of EC cells as compared to controls^[17,18]. Since then numerous studies have explored the relationship between EC cells, serotonin and IBS. Study by Bearcroft *et al*^[19] demonstrated that patients with D-IBS have higher blood levels of serotonin. Similarly studies by Dunlop *et al*^[20] and Atkinson *et al*^[21] have shown higher blood levels of serotonin in D-IBS patients and lower blood levels of serotonin in C-IBS patients. These authors also measured the levels of 5-HIAA (5-hydroxyindoleacetic acid), a 5-HT metabolite, in the rectal mucosal biopsy specimens and blood to obtain 5-HT/5-HIAA ratios as a surrogate marker for serotonin turnover. Based on analysis of 5-HT/5-HIAA ratios in blood and mucosal biopsies, serotonin release defects in C-IBS and serotonin uptake defects in D-IBS were suggested. In the search for an explanation to these differences SERT functions, polymorphism of SERT gene has been extensively investigated.

The SERT gene, also known as solute carrier family 6 member 4 (SLC6A4), was mapped to chromosome 17q11.2 by Ramamoorthy *et al*^[22] in 1993. Polymorphic loci that affect the expression and function of SERT gene have been identified. There is a GC base pair rich repetitive sequence located at 5' regulatory end of the SERT gene and is labeled as 5-HT transporter

linked promoter region (5-HTT LPR). Polymorphism due to deletion or insertion of 44 base pairs in this region resulting in a long (L) and short (S) allele was first discovered by Heils *et al*^[23]. Another common polymorphism of SERT gene results from a variable number of 17 base pair repeats (VNTR: variable number tandem repeats) in the intron 2 of gene^[24]. VNTR has 4 alleles described with 9, 10, 11 and 12 repeats.

The evidence on the relationship between different genotypes and their phenotypic expression comes from a study conducted by Lesch *et al*^[25]. Lesch *et al*^[25] found that S/S genotype as compared to other genotypes L/L and S/L had less 5-HT uptake resulting in higher blood levels of 5-HT. Based on studies from Dunlop *et al*^[20] and Atkinson *et al*^[21] where defects in serotonin uptake were suggested in D-IBS, S/S genotype was expected to be associated with D-IBS. Several researchers have explored the association between IBS and SERT gene since then but have come up with conflicting results. In 2002 for the first time, Pata *et al*^[26] demonstrated higher percentage of C-IBS patients to have S/S genotype and D-IBS to have L/S genotype. In the same year Camilleri *et al*^[27] investigated the association between SERT polymorphism and response to Alosetron (5-HT3 receptor antagonist) and found higher response rates to the drug in IBS individuals with L/L genotype. According to the study by Lee *et al*^[28] in the Korean population there was no association between IBS and SERT gene polymorphism. However, another Korean study by Park *et al*^[29] found significantly higher frequency of S/S genotype among patients with D-IBS, contrary to results of study by Pata *et al*^[26] mentioned above. Similarly, in the North American study by Yeo *et al*^[30] S/S genotype was found to be associated with D-IBS female patients but Saito *et al*^[31] found a significantly higher number of S/S genotype with M-IBS patients. In the study involving Indian IBS patients a significant association was found between S/S genotype and C-IBS^[32]. In a Chinese study by Li *et al*^[33] allele frequency of the L/L genotype was significantly higher in the C-IBS group. In the same study, researchers also demonstrated poor response to Tegaserod (5HT4 partial selective agonist) associated with L/L genotype.

Another polymorphism pertaining to a single nucleotide polymorphism locus, rs25531 that is located immediately upstream of 5-HTTLPR was described by Kohen *et al*^[34]. It has two - A and G alleles. Hu *et al*^[35] showed that A variant of L allele (designated as L_A) yields higher SERT expression as compared to G variant of L allele (designated as L_G). This implies that L_G (G variant of rs25531 with L allele) actually behaves as the low expressing S allele. With respect to VNTR polymorphism, one study^[36] found a significant association between the VNTR polymorphism and IBS but other studies by Yeo *et al*^[30], Pata *et al*^[26] and Li *et al*^[33] did not find any significant association.

To investigate the possible association between IBS subtypes and SERT polymorphism, Van Kerkhoven *et al.*^[37] conducted a meta-analysis of eight studies in 2007 that found no significant association between SERT polymorphism and IBS subtypes. Another meta-analysis conducted in 2013 that included more recent studies conducted since the first meta-analysis by Van Kerkhoven *et al.* in 2007, concluded a positive association between SERT polymorphism and C-IBS^[38]. In another meta-analysis from 2013 performed by Areeshi *et al.*^[39] that included twelve studies comprising 2068 IBS patients, no association was found between SERT polymorphism and IBS overall. However, when the studies were stratified according the country of origin, significant association was found in American and Asian studies. The most recent meta-analysis with the largest sample size, involving 25 studies comprising of 3443 IBS patients found a positive association between SERT polymorphism and IBS but this association was found only in the East Asian population and not in the Caucasian population^[40]. One probable explanation for this ethnic difference, as evidenced by this meta-analysis, could be the significantly lower frequency of L allele among the East Asian population as compared to Caucasian controls.

Besides the most widely studied polymorphism involving SERT LPR discussed above, several other polymorphism loci have been explored. These include polymorphisms of gene involving other serotonin receptors - 5-HT_{2A} gene^[41-43] and 5-HT_{3E} gene^[44] and yet again the studies have yielded either conflicting results or need further validation in other ethnic groups.

Tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT biosynthetic pathway has two isoforms - TPH1 and TPH2 encoded by genes on chromosome 11 and 12 respectively. Jun *et al.*^[45] found no association between TPH1 gene single nucleotide polymorphism and risk of developing IBS, however found significant association with severity as well as number of days with diarrhea in IBS patients. TPH2 gene polymorphism was also tested and shown to be associated with reduced risk of having IBS but statistically this difference was barely significant. Similar to this study by Jun *et al.*, no association was found between genotype frequencies and IBS in the study conducted by Grasberger *et al.*^[46]. But the CC genotype was found to be more prevalent in IBS-D patients in the study. Researchers that investigated the colonic mucosa levels of TPH1 mRNA in IBS patients found significantly reduced TPH1 mRNA levels in both IBS subtypes^[47].

CYTOKINES AND IBS

Cytokines are important mediators of inflammatory and immune responses. Cytokines have an established role in the inflammation of gastrointestinal tract, however the role in IBS is not yet clear. Genes involving

various cytokines and inflammatory pathways have been studied. These involve genes for tumor necrosis factor-alpha (TNF- α), Transforming growth factor beta 1 (TGF- β 1), interleukin-8 (IL-8) and interleukin-10 (IL-10). Production of these cytokines is under the genetic control and based on polymorphism involving genes coding these cytokines, high and low cytokine producing alleles been identified.

IL-10 gene polymorphism located at position 1082 constituting G to A substitution yields two types of alleles - allele G associated with high production of IL-10 whereas allele A associated with low production of IL-10^[48]. Similarly for TNF- α , allele A and for TGF- β 1, alleles T and G are identified as high producers^[49]. Gonsalkorale *et al.*^[50], found significantly less number of high producer alleles of IL-10 in patients with IBS. Subsequently there were studies that highlighted the relationship between IBS and IL-10^[51,52] but on the other hand others showed no association among the two^[53]. Similarly the studies that explored the role of other cytokines like TNF- α also had conflicting results. Chang *et al.*^[52] did not find any positive association between IBS and TNF- α but van der Veek *et al.*^[53] on the other hand found that high producer genotypes of TNF- α were more prevalent in patients with IBS. Inconsistent findings of these and other studies led to a meta-analysis by Bashashati *et al.*^[54] that comprised of five studies with 529 IBS patients and looked at three cytokines - IL-10, TNF- α and TGF- β 1. The meta-analysis found a decreased risk of IBS among high producer genotypes of IL-10 (1082, G/G), positive correlation between TNF (G/A genotype) and Asian IBS patients and failed to find any significant association between IBS and TGF- β 1 gene polymorphism. Another more recent and larger meta-analysis by Bashashati *et al.*^[55] comprising of nine studies found no difference in blood IL-10 levels and IBS patients but based on gender stratification a significant association was found among men with IBS and lower IL-10 levels. With regards to TNF- α , the meta-analysis found that all IBS subtypes and women had significantly higher blood levels of TNF- α . In another meta-analysis comprising 8 studies with 928 IBS patients, all three known polymorphisms of IL-10 gene - rs1800870 (1082 G/A), rs1800871 (819C/T), and rs1800872 (592A/C) were explored. The meta-analysis concluded that one of the polymorphism was significantly associated with IBS in Caucasians (rs1800870), second (rs1800872) associated with IBS in Asians and third (rs1800871) had no association to IBS^[56].

CANNABINOIDS

Δ 9-Tetrahydrocannabinol, active ingredient of cannabis, acts through two cannabinoid receptors - CB1 and CB2. While CB1 mediates neurotransmitter release in the peripheral and central neuronal pathways, CB2 is associated with immune functions. CB1 receptors are present throughout the gastrointestinal tract

and endocannabinoids mediate their gastrointestinal effects through these receptors. Action of the endocannabinoids is terminated by their uptake and subsequent metabolism by the enzyme fatty acid amide hydrolase (FAAH)^[57]. Gene coding for CB1 receptor has been mapped to chromosome 6 and polymorphism involving AAT triplet microsatellite flanking 3' end has been described in literature^[58]. In a Korean study by Park *et al.*^[59] a significant association was found between IBS and the AAT triplet genotype with more than 10 repeats. Similar results were replicated by another Chinese study conducted by Jiang *et al.*^[60]. These authors also studied another single nucleotide polymorphism (rs324420) involving *FAAH* gene and found that A/A genotype was present less frequently in patients with IBS as compared to healthy controls but the difference was not statistically significant. In another study by Camilleri *et al.*^[61] comprising mainly of Caucasians investigated the association between phenotypic expression (colonic transit and rectal sensation) and genetic variations - AAT polymorphism as well as another polymorphism locus (rs806378) of CB1 receptor gene. The group found no association between AAT repeat polymorphism and phenotypic expression - colonic transit and rectal sensation. However, a significant association between D-IBS and colonic transit as well sensation rating of gas was found.

OTHER MEDIATORS

TNFSF15, also known as TL1a, is a member of tumor necrosis factor super family (TNFSF) of ligands. It binds to death receptor 3 (DR3) and mediates T cell proliferation, secretion of inflammatory cytokines and T cell immune responses. Polymorphism of TNFSF15 gene has been well established to be associated with inflammatory bowel disease. Its association with C-IBS was shown in a study by Zucchelli *et al.*^[62], whereas Swan *et al.*^[63] found it to be associated with D-IBS.

Cholecystokinin (CCK), a gastrointestinal tract peptide hormone acts through two receptors - CCK1 and CCK2. Genetic polymorphism of CCK1 was found more commonly among C-IBS and M-IBS patients in a study by Park *et al.*^[64]. In another study evaluating the effects of a CCK1 antagonist in C-IBS patients, gastric emptying was accelerated but no effect on overall colonic motility was found^[65].

Enzyme catechol-o-methyltransferase (COMT) that degrades the catecholamines including adrenaline, noradrenaline and dopamine is another possible molecule related to IBS. Both, COMT gene polymorphism as well as IBS, have been shown to be associated with pain^[66] and anxiety^[67]. On these grounds the relationship between COMT gene polymorphism and IBS was also explored. Karling *et al.* found that val/val allele of COMT gene encoding high COMT activity enzyme was more common among D-IBS patients. On the contrary, Chinese researchers

Wang *et al.*^[68] found val/val allele to be protective against IBS, whereas the other allele met/met encoding reduced COMT activity enzyme significantly associated with elderly D-IBS patients. Interestingly in another study by Hall *et al.*^[69] investigating the placebo effect, the cases with allele (met/met) were found to be most responsive to placebos.

Single nucleotide polymorphism C825T on gene encoding β -3 subunit of the guanine nucleotide binding protein (GN β 3) was also explored. Studies from United States by Andresen *et al.*^[70] and Saito *et al.*^[71] found no relationship between this polymorphism and IBS patients. On the contrary, significant relationship among the GNB3 polymorphism and Korean as well Greek IBS patients was shown by Lee *et al.*^[72] and Markoutsaki *et al.*^[73] respectively. But other Korean study^[74] as well as study from China did not show any association of the same polymorphism to IBS^[68].

Hypothalamic hormone, corticotropin releasing hormone (CRH), which mediates its effects through two receptors - CRH1 and CRH2 has also been studied. Sato *et al.*^[75] explored three single nucleotide polymorphism of CRH1 gene and found significant association with IBS symptoms.

Mediators of autonomic system also have been implicated in pathogenesis of IBS. Association between autonomic dysregulation and IBS has been already shown in other studies^[76,77]. α 2-adrenergic receptors that are present on both presynaptic as well as postsynaptic locations and have three subtypes - 2A, 2B and 2C, are encoded by gene on chromosome 10. A 12 base pair deletion polymorphism of adrenergic receptor 2C (denoted α 2C Del 322-325) and another single nucleotide polymorphism involving adrenergic receptor 2A gene (C1291G) were studied by Kim *et al.*^[78] Both the polymorphisms were found to have significantly higher odds (odds ratio 2.48 and 1.66 respectively) to be associated with C-IBS. In contrast, Sikander *et al.*^[79] in Indian IBS patients and Choi *et al.*^[80] in Korean IBS patients found an association between adrenergic receptor 2A gene polymorphism and D-IBS. Whereas in the study by Camilleri *et al.*^[81] no association was found between adrenergic receptor 2A gene polymorphism and IBS. Cholinergic muscarinic receptor type 3 gene polymorphism (rs3738435) was investigated by Onodera *et al.*^[82] Though no association was found between the polymorphism and different IBS subtypes, researchers found the polymorphism to be associated with the duration of disease.

So far the expedition to find a genetic basis for IBS has included wide array of studies ranging from epidemiological familial aggregation studies to gene polymorphism testing studies. Though these studies in several ways have shown the possible hereditary component of IBS but most of the studies have provided only weak evidence between the two. In the last decade gene search studies have focused more on detecting gene polymorphisms. Several possible gene polymorphisms have been shown to be associated

Table 2 Candidate genes associated with irritable bowel syndrome

Gene studied	Polymorphism
Serotonin or 5-HT reuptake transporter (SERT) gene - <i>SLC6A4</i>	5-HTT LPR - S and L alleles ^[23] rs25531 - A and G alleles ^[34] VNTR - alleles with 9, 10, 11 and 12 repeats ^[24]
5HT2A	1438 (G/A) and 102 (C/T) ^[41]
5HT3A	c.-42C>T ^[85]
5HT3E	rs62625044 - 76 (G/A) ^[44]
Tryptophan hydroxylase 1 (TPH1)	rs4537731 - 6526 (A/G) ^[45] rs684302 rs21105 rs1800532 - 218 (A/C) rs1799913 - 779 (A/C)
Tryptophan hydroxylase 2 (TPH2)	rs4570625 - 709 (G/T) ^[45]
Tumor necrosis factor- α (TNF- α)	308 (G/A) ^[53]
Transforming growth factor beta 1 (TGF- β 1)	869 (T/C) ^[54] 915 (G/C) ^[54]
Interleukin-10 (IL-10)	rs1800870 - 1082 (G/A) ^[50] rs1800871 - 819 (C/T) ^[53] rs1800872 - 592 (A/C) ^[56]
Cannabinoid receptor 1 (CB1)	AAT triplets ^[59] rs324420 ^[60] rs806378 ^[61] rs4263839 ^[62]
Tumor necrosis factor super family 15 (TNFSF15)	
Cholecystokinin 1 (CCK1)	779 (T/C) ^[64]
Catechol-o-methyltransferase (COMT)	rs 4680 - 158 (Val/Met) ^[68]
Guanine nucleotide binding protein (GN β 3)	rs 5443 - 825 (C/T) ^[66]
Corticotropin releasing hormone receptor 1 (CRH1)	rs110402 ^[75] rs242924 rs7209436
α 2-adrenergic receptor 2A	1291 (C/G) ^[80]
α 2-adrenergic receptor 2C	Del 322-325 ^[78]
Cholinergic muscarinic receptor type 3	rs3738435 ^[82]

with IBS as a result of growing interest in gene polymorphisms. Even though the *P* values of these small studies show strength of association between the polymorphism tested and IBS but it cannot be taken as equivalent to genetic basis of IBS.

Genome-wide association studies

In addition to candidate gene-based association studies, association studies have also been conducted in a systematic, genome-wide manner. Genome wide association studies (GWAS) utilize high throughput genotyping techniques to assay hundreds of thousands of the most common form of genetic variation, the single-nucleotide polymorphism (SNP) and relate genotypes at these variants to the phenotypes of diseases and other traits^[83]. This approach permits the interrogation of much of the common variation in the entire genome in thousands (or even hundreds of thousands) of unrelated individuals, achieving a higher positional resolution than is reasonably possible. In the first and so far the only GWAS by Weronica *et*

al linkage was shown between IBS and two genes mapped to locus 7p22.1. The two genes mapped to this locus were KDEL receptor 2 gene (*KDEL2*) and glutamate receptor ionotropic delta 2 interacting protein (GRID2IP)^[84,85].

FUTURE DIRECTIONS

The field of genetics exploring the underlying potential IBS genes is rapidly evolving. However, huge gaps in our understanding of this complex disorder remain and need further study. Genetic research efforts that are focused on studying the candidate gene polymorphism have so far provided the weak evidence at the best. Gene linkage studies and genome wide association studies are needed to understand the deficiencies in our current knowledge. In the future studies, it will be also of importance to explore how the environment influences these newly discovered genes.

IBS is a complex functional gastrointestinal disorder that poses a great challenge to both, the affected patients and the physicians treating the ones affected. Historically, underlying pathophysiology is believed to be interplay of hypersensitive gut with key contributions from psychological, social and environmental factors. Genetic basis has also been suggested by familial aggregation of cases as well as high concordance rate among monozygotic twins than dizygotic twins. Gene hunt efforts, so far, have explored several potential candidate genes (Table 2) and shown association between polymorphic gene loci and different IBS phenotypes. While studies so far have been less than emphatic in their results due to small sample sizes, varying criteria used to diagnose IBS, heterogeneity of methods used and ethnic differences of the participants tested, there is convincing evidence that a proportion of IBS are due to additive genetic effects. As an alternative to current gene specific candidate driven approach, larger and non-candidate gene driven studies in the form of GWAS are needed to understand this common and complex disorder. Such genome wide studies may provide much needed insight into the genetic susceptibility of IBS and could aid in development of novel therapeutic strategies to diagnose, treat and prevent this disorder.

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