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**Molecular basis of the irritable bowel syndrome**

Vaiopoulou A *et al*. IBS and genetics

Anna Vaiopoulou, Georgios Karamanolis, Theodora Psaltopoulou, George Karatzias, Maria Gazouli

**Anna Vaiopoulou, Maria Gazouli,** Department of Basic Medical Science, Laboratory of Biology, School of Medicine, University of Athens, 11527 Athens, Greece

**Georgios Karamanolis, George Karatzias,** Gastroenterology Unit, 2nd Department of Surgery, "Aretaieio" University Hospital, School of Medicine, University of Athens, 11527 Athens, Greece

**Theodora Psaltopoulou,** Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, University of Athens, 11527 Athens, Greece

**Author contributions**: Gazouli M and Karamanolis G designed the study; Vaiopoulou A, Karatzias G and Psaltopoulou T performed research at the literature; Vaiopoulou A and Gazouli M analyzed data; Vaiopoulou A, Gazouli M and Karamanolis G wrote the paper.

**Correspondence to: Maria Gazouli, Assist Professor,** Department of Basic Medical Science, Laboratory of Biology, School of Medicine, University of Athens, Michalakopoulou 176, 11527 Athens, Greece. mgazouli@med.uoa.gr

**Telephone:** +30-210-7462231 **Fax:** +30-210-7462231

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**Abstract**

Irritable bowel syndrome (IBS) is a functional disorder characterized by abdominal pain, discomfort and bloating. The pathophysiology of IBS is poorly understood, but the presence of psychosocial basis is now known. There is an increasing number of publications supporting the role of genetics in IBS. Most of the variations are found in genes associated with the brain-gut axis, revealing the strong correlation of brain-gut axis and IBS. miRNAs, which play critical roles in physiological processes, are not well studied in IBS. However, so far there is found an involvement of alterations in miRNA expression or sequence, in IBS symptoms. IBS phenotype is affected by epigenetic alteration and environment. Changes in DNA and histone methylation are observed in patients who suffered childhood trauma or abuse, resulting in altered gene expression, such as the glucocorticoid receptor gene. Finally, diet is another factor associated with IBS, which may contribute to symptom onset. Certain foods may affect on bacterial metabolism and epigenetic modifications, predisposing to IBS.

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**Key words:** Irritable bowel syndrome; Gastrointestinal diseases; Genetics; Epigenetics; Diet

**Core tip:** Irritable bowel syndrome (IBS) is a multifactorial disease, whose development and phenotype are related to both genetic and epigenetic factors. Gene polymorphisms and epigenetic modifications affect the function of brain-gut axis and are responsible for many of the symptoms of the disease. The relationship between environmental factors and IBS shows the effect of environment on gene expression alteration by epigenetic modification.

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**INTRODUCTION**

Irritable bowel syndrome (IBS) is amongst the most widely recognized functional gastrointestinal disorders and is remarkably prevalent in the general population, affecting as many as 5%-20% of people worldwide[1]. The prevalence of IBS is slightly higher in women, with a variable influence of age across studies. Symptom based criteria is applied to diagnose the entity. The presence of chronic or recurrent abdominal pain or discomfort, relieved by defecation and associated with an altered bowel habit, in the absence of any underlying structural or biochemical abnormalities, identifies patients with IBS[2].

The syndrome has been subdivided into different subgroups based on the predominant bowel habit; diarrhea-predominant (D-IBS), constipation-predominant (C-IBS), or a mixture of both diarrhea and constipation (M-IBS). The use of these subgroups has received acceptance by most clinical investigators, as it commonly dictates symptomatic pharmacological management[3]. However, the value of this categorization is under consideration, knowing that each IBS patient could switch from one subgroup to another over time.

There is a significant variability in the clinical presentation of patients with IBS and they could differ by predominant stool type, severity and frequency of pain/discomfort and comorbidities including psychological distress and somatic complaints[4]. Moreover, IBS symptoms can fluctuate over time. The severity and intensity of IBS symptoms vary from very mild in patients who do not seek medical attention to very severe one that may significantly affect quality of life with the same degree of impairment as major chronic disorders. Despite the fact that a minority of IBS patients chooses to consult a physician, IBS is a clinical problem of considerable cost for the health care system because of its high prevalence and the chronic or recurrent nature of symptoms[5].

The pathophysiology of IBS is largely unknown and it is generally considered a multifactorial disorder. Among the putative mechanisms involved in the pathogenesis of IBS, there is evidence to support the key role of heritability and genetics factors. It is recognized that psychological factors and stress appear to be the primary drivers of symptoms in IBS patients. There is a hypothesis that IBS patients have a certain personality with predisposition to develop the disease. Dimensions of personality that are important in clinical practice include response to stress, attitude toward illness, health and medical treatment. These constitutional features may have genetic origins that may be influenced by early environmental experiences.

**GENETICS AND IBS**

***Gene polymorphisms***

IBS, as a multifactorial disorder, is also associated with altered brain-gut axis[6]. A recent study showed that corticotrophin-releasing hormone (CRH) is involved in stress-related pathophysiology of IBS and in the inflammation of the intestinal mucosa[7]. Polymorphisms in genetic factors may influence these mechanisms, and affect brain-gut interrelations[8-10]. Polymorphisms involve the serotonergic, adrenergic and opioidergic systems, and genes encoding proteins with immunomodulatory and/or neuromodulatory features[9,10].

***Serotonergic system***

Serotonin [5-hydroxytryptamine (5-HT)] controls gastrointestinal secretion, motility, and visceral perception by activating at least five types of receptors[10]. Alterations in 5-HT levels and signaling are present in IBS patients which may induce diarrhea, nausea, and vomiting[11,12]. So far, only a few gene polymorphisms are associated with IBS. Polymorphisms in promoter of serotonin reuptake transporter (*SERT*) gene effect on transcription activity and influence 5-HT reuptake efficiency. In a recent study, among 9 polymorphisms in promoter region of SERT, only one polymorphism (insertion/deletion polymorphism) was associated with diarrhea in women with IBS. The deletion polymorphism decreases expression of the sodium-dependent serotonin transporter and, thus, reduces reuptake of serotonin[13]. Another study showed a lower prevalence of the SS genotype (homozygosity for deletion) in IBS and, particularly, in D-IBS, but this was only observed in male patients[14]. (Table 1)

This polymorphism is also correlated with behavioral traits and psychiatric disorders and IBS patients homozygous for the deletion present significantly higher risk for depressive episodes[15]. Another study also associated insersion/deletion polymorphism with anxiety. Long allele (insertion) in females is implicated with negative emotion but acts contrary in males[16]. This allele influences the efficacy of tegaserod treatment. IBS patients carrying the long allele respond poorly to treatment[17].

***Adrenergic and opioidergic systems***

Autonomic system has an important role in gastrointestinal motility, acting via adrenergic receptors. Genetic variations in α2-adrenergic receptor may change sensory and motor function in IBS[18]. α2C Del 322–325 deletion, a variation resulting in a loss-of-function phenotype, is associated with C-IBS (constipation IBS)[19]. The α2A -1291 C>G is associated with D-IBS, but no with C-IBS[20] (Table 1).

A polymorphism (Val158Met) in cathechol-*O*-methyltransferase, an enzyme metabolizing catecholamines, showed association with IBS[21]. Patients carrying this polymorphism have a reduced response to pain[22] (Table 1).

Alterations in cannabinoid receptor genes are also analysed and associated with IBS. A polymorphic (AAT)n triplet repeat in the 3-flanking region of the cannabinoid receptor 1 (CNR1) gene is related with IBS and severity of abdominal pain in IBS[23] (Table 1).

Additionally, single nucleotide polymorphisms (SNPs) in CRH receptor 1 (CRH-R1), which plays a critical role in stress-induced pathophysiology of IBS, were studied for moderating IBS phenotype and negative emotion in IBS patients (Table 1). Findings of this study showed association between SNPs and IBS moderation, but no association was found with negative emotion[24]. Genetic variation rs806378 in CNR1 is associated with colonic transit in D-IBS and sensation rating of gas[25] (Table 1). This polymorphism is also correlated with treatment effectiveness of nonselective cannabinoid receptor agonist, dronabinol[26,27].

***Cytokines***

Several studies have reported cytokine gene polymorphisms in IBS. Interleukin (IL)-10-1082 G/G, a high producer IL-10 genotype, correlated with lower risk for developing IBS[28,29](Table 1). Gene single nucleotide polymorphisms (SNPs) of IL-8 and IL-10 were also analyzed by Romero-Valdovinos *el al*[30] and an association between alleles IL-8+ 396G and IL-10-1082A and IBS was found. These findings were confirmed by other study[31] (Table 1). TNF alpha (-308 G/A) polymorphism and IBS are correlated, and G/G genotype may increase risk of IBS. G/A genotype has a protective role[28] (Table 1). A study evaluating GNβ3 825C>T polymorphism in IBS showed significant interactions between gastrointestinal infection and T allele in the development of IBS, suggesting gene–environment interactions[32] (Table 1). However, another study replicated none of these results[33]. Another IL-10 polymorphism associated with IBS is IL-10-819 T>C. The frequency of IL10 -819 CC genotype was significantly higher in D-IBS[34](Table 1).

***miRNAs AND IBS***

miRNAs are small (21-23 nucleotides) single-stranded RNA molecules[35,36]. miRNAs are not translated into proteins and have regulatory function, such as translational repression of targeted mRNAs[37]. miRNAs form RISC (RNA-induced silencing complex), which can prevent the expression of proteins, either by activating endonuclease that degrades mRNAs or by blocking translation[38]. miRNAs are connected with physiological processes such as cell division and death[39], cellular metabolism[40], intracellular signaling[41], immunity[42] and cell movement[43]. Thus, altered miRNA expression can affect these critical processes, and as a result, lead to various pathological and occasionally malignant outcomes.

Cancer is one of human diseases clearly associated with miRNA regulation. miRNAs may involve in tumor development as tumor suppressors or oncogenes. They also play roles in tumor invasion and metastasis. Down-regulation of miR-15 and miR-16 is correlated with the pathogenesis of B-cell chronic lymphocytic leukemia[44]. In addition, miR-125b, miR-145, miR-21, and miR-155 expression is associated with the increased risk of breast cancer[45]. The implication of miRNAs in immune-related diseases, such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), and type I/II diabetes is also known. In MS, miR-34a, miR-155 and miR-326 are overexpressed[46]. In SLE, increased risk of disease development is associated with decreased expression of miR-46a[47]. Several studies show that miRNAs regulate critical pathways in inflammation, such as pathways correlated with nuclear factor kappa beta. miR-155 and miR-146 are the best characterized miRNAs which are implicated in immune-diseases[46,48,49].

The role of miRNAs in IBS is not well studied. The first association of miRNAs and IBS was from Kapeller *et al*[50]. This study showed that the variation c.\*76G>A (rs62625044) in the 3΄ untranslated region (UTR) of the serotonin receptor type 3 subunit genes HTR3E correlates with D-IBS. This functional variation is located in the miRNA-510 target site of the gene. The co-localization of HTR3E and miR-510 in enterocytes of the gut epithelium and the presence of cis-regulatory variation show the regulation of serotonin receptor gene expression by miRNA.

Next evidence came from Zhou *et al*[51], who evaluated the miRNA expression in blood microvesicles (circular membrane fragments that are shed from the cell surfaces and accompanies cell activation) and gut tissues in D-IBS patients and IBS patients with normal membrane permeability. They found that miR-29a expression was increased in blood microvesicles in the small bowel and colon tissues of IBS patients with increased permeability. miR-29a is complementary in the 3΄ UTR of the glutamine synthetase gene. These results suggest the role of glutamine synthetase in the intestinal membrane permeability and the role of miR-29a in regulation of glutamine synthetase and intestinal membrane permeability.

**EPIGENETICS AND IBS**

Phenotype is the combination of DNA sequence, epigenetic DNA modifications and environmental factors. The presence of epigenetic changes in monozygotic twins, leading to phenotypic alterations, suggests a potential role of epigenetics in IBS[52]. DNA methylation and histone modification are the most common epigenetic mechanisms. DNA methylation usually silences gene expression[53]. However, histone acetylation or methylation may activate or not gene transcription[54].

IBS is associated with early life trauma or abuse, and this condition leads to negative health outcomes and behaviors in adults. Childhood trauma influences somatic symptoms and neural network development and neuroendocrine system development[55-57]. In a recent study, IBS patients showed enhanced cortisol response to a visceral stressor. The hypothalamic-pituitary-adrenal (HPA) axis hyperresponsiveness to stressor is more related to early adverse life events rather than to the presence of IBS[55].

Early childhood trauma decreases glucocorticoid receptor expression by hypermethylation of glucocorticoid receptor gene[58]. Altered glucocorticoid receptor gene expression, which mediates the negative feedback of the HPA axis, reduces the capability of HPA to deal effectively with stress. In animal model of IBS, animals exposed to perinatal stress had methylation of glucocorticoid receptor promoter, decreased gene expression and prolonged elevation of corticosterone levels[59].

The impact of early adverse life events on developing IBS or other diseases is being explored lately. Gluckman *et al*[60] developed a hypothesis that epigenetic processes, including DNA methylation and histone modification, partially mediate developmental plasticity. Another group searched for a mechanism that link the social environment early in life and long-term epigenetic programming of behavior and responsiveness to stress. They took into account data suggesting that DNA methylation is a dynamic process and postmitotic cells may change methylation pattern responding to different environmental stimuli. This study showed that maternal licking and grooming in the rat triggered activation of 5-HT receptors, activation of the transcription factor nerve growth factor-induced gene A and acetylation of the promoter of the glucocorticoid receptor (mediated by a histone acetyl transferase), leading to differential epigenetic programming of the glucocorticoid receptor[61].

Alterations in acetylation motif change behavior in adult offsprings. Except maternal care, diet may also affect behavioral plasticity[62]. Maternal separation acts as a stressor and helps adult rats to develop intestinal mucosal dysfunction, increased HPA axis responses, and anxiety-like behavior[63].

Finally, early life stress increases the levels of proinflammatory cytokines. In IBS patients, levels of IL-6 and IL-8 were high, as a result of epigenetic glucocorticoid alterations[64,65]. Upregulation of proinflammatory cytokines influences tryphophan metabolism, resulting on changes of 5-HT activity[66]. The kyneurenin:tryptophan ratio, which shows tryptophan catabolism, is increased in IBS patients with severe symptoms, and they were more likely to have depression or anxiety.

**DIET, NUTRIGENOMICS/NUTRIGENETICS AND IBS**

It is well documented, that the interplay between genes and diet may be reflected in susceptibility to various diseases[67]. Scientific studies have demonstrated the effectiveness of dietary therapies in alleviating the symptoms and even in altering the progression of inflammatory and autoimmune disorders[68,69]. Concerning the IBS, even if many patients recognize the impact of specific diet in symptom occurrence, limited population-based studies have evaluated the importance of diet in IBS and its role remains uncertain[70-72]. Diet may contribute to symptom onset through several mechanisms such as food allergy and intolerance. Additionally, certain food may alter the composition of the luminal milieu, directly or indirectly through effects on bacterial metabolism. Diet is known also to influence the epigenetic modification of genes[73]. Finally, IBS symptoms may develop following exposure to food-born pathogens[72]. Furthermore, an increase probability of developing IBS is associated with the inheritance of a number of contributory genetic polymorphisms, as well as with the altered expression of certain genes[74]. The variant forms of genes often result in an abnormal response to normal gut bacteria that may be changed through inappropriate diet or environment. Shifts in the bacterial makeup of the human gut microbiota have been associated with gut disorders including IBS[75]. In the field of nutritional research, 2 terms have been established: nutrigenetics which aims to study how genotype determines optimal dietary requirements for health on an individual basis, and nutrigenomics which studies the effect on diet on DNA structure and gene expression[76]. However, the most of the nutrigenetic/nutrigenomic work has focused on cardiovascular disease, type II diabetes mellitus or inflammatory bowel disease[77,78] and no study has be done on IBS. Low FODMAPs diet, that is elimination of fermentable Oligo-, Di- and Mono-saccharides, and Polyols from diet, is an area of intense investigation for symptoms’ alleviation[79,80]. FODMAPs’ ingestion could result in the symptomatology of these patients, because they are osmotically active, they are fermented and through bacterial overgrowth can cause bloating, pain and the sequence of symptomatology in IBS. Thus, the application of these approaches in the field of IBS research is open. It is hoped that the nutrigenetics/nutrigenomics implementation will promote the understanding of diet-gene interactions and facilitate a better characterization of individual IBS patients for further identification of nutritional patterns that allow personalized therapies.

**CONCLUSION**

IBS is a multifactorial disease, whose development and phenotype are related to both genetic and epigenetic factors. Most factors involve in pathogenesis by causing changes in gene expression. Gene polymorphisms and epigenetic modifications affect the function of brain-gut axis and are responsible for many of the symptoms of the disease. IBS is one of the diseases where the environmental influence is strong. Early life incidents and diet habits play an important role in disease development. The relationship between environmental factors and IBS shows the effect of environment on gene expression alteration by epigenetic modification.

**REFERENCES**

1 **Talley NJ**. Scope of the problem of functional digestive disorders. *Eur J Surg Suppl* 1998; **582**: 35-41 [PMID: 10029363]

2 **Drossman DA**, Corazziari E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, Whitehead WE. Rome III: The Functional Gastrointestinal Disorders. McLean, VA: Degnon Associates, Inc; 2006

3 **Whitehead WE**, Drossman DA. Validation of symptom-based diagnostic criteria for irritable bowel syndrome: a critical review. *Am J Gastroenterol* 2010; **105**: 814-20; quiz 813, 821 [PMID: 20179688 DOI: 10.1038/ajg.2010.56]

4 **Adeyemo MA**, Spiegel BM, Chang L. Meta-analysis: do irritable bowel syndrome symptoms vary between men and women? *Aliment Pharmacol Ther* 2010; **32**: 738-755 [PMID: 20662786 DOI: 10.1111/j.1365-2036.2010.04409.x]

5 **Gralnek IM**, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterology* 2000; **119**: 654-660 [PMID: 10982758]

6 **Fukudo S**, Hongo M. On the organ choice in psychosomatic disorders. Irritable bowel syndrome: a disorder of abnormal brain-gut interactions. *Jpn J Psychosom Med* 1999; **39**: 159-166

7 **Fukudo S**. Role of corticotropin-releasing hormone in irritable bowel syndrome and intestinal inflammation. *J Gastroenterol* 2007; **42** Suppl 17: 48-51 [PMID: 17238026]

8 **Saito YA**, Petersen GM, Locke GR, Talley NJ. The genetics of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; **3**: 1057-1065 [PMID: 16271334 DOI: 10.1111/j.1572-0241.2008.02048.x]

9 **Adam B**, Liebregts T, Holtmann G. Mechanisms of disease: genetics of functional gastrointestinal disorders--searching the genes that matter. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 102-110 [PMID: 17268545]

10 **Cervio E**, Rondanelli M, Balestra B, Dellabianca A, Agazzi A, Giacosa A, Tonini M. [Recent insights into the pathogenesis of abdominal symptoms in functional bowel disorders]. *Recenti Prog Med* 2007; **98**: 69-73 [PMID: 17439064]

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 **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]

13 **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]

14 **Niesler B**, Kapeller J, Fell C, Atkinson W, Möller D, Fischer C, Whorwell P, Houghton LA. 5-HTTLPR and STin2 polymorphisms in the serotonin transporter gene and irritable bowel syndrome: effect of bowel habit and sex. *Eur J Gastroenterol Hepatol* 2010; **22**: 856-861 [PMID: 19561511 DOI: 10.1097/MEG.0b013e32832e9d6b]

15 **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]

16 **Mizuno T**, Aoki M, Shimada Y, Inoue M, Nakaya K, Takahashi T, Itoyama Y, Kanazawa M, Utsumi A, Endo Y, Nomura T, Hiratsuka M, Mizugaki M, Goto J, Hongo M, Fukudo S. Gender difference in association between polymorphism of serotonin transporter gene regulatory region and anxiety. *J Psychosom Res* 2006; **60**: 91-97 [PMID: 16380315]

17 **Li Y**, Nie Y, Xie J, Tang W, Liang P, Sha W, Yang H, Zhou Y. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci* 2007; **52**: 2942-2949 [PMID: 17394071]

18 **Viramontes BE**, Malcolm A, Camilleri M, Szarka LA, McKinzie S, Burton DD, Zinsmeister AR. Effects of an alpha(2)-adrenergic agonist on gastrointestinal transit, colonic motility, and sensation in humans. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G1468-G1476 [PMID: 11705752]

19 **Kim HJ**, Camilleri M, Carlson PJ, Cremonini F, Ferber I, Stephens D, McKinzie S, Zinsmeister AR, Urrutia R. Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. *Gut* 2004; **53**: 829-837 [PMID: 15138209]

20 **Sikander A**, Rana SV, Sharma SK, Sinha SK, Arora SK, Prasad KK, Singh K. Association of alpha 2A adrenergic receptor gene (ADRAlpha2A) polymorphism with irritable bowel syndrome, microscopic and ulcerative colitis. *Clin Chim Acta* 2010; **411**: 59-63 [PMID: 19833115 DOI: 10.1016/j.cca.2009.10.003]

21 **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]

22 **Zubieta JK**, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003; **299**: 1240-1243 [PMID: 12595695]

23 **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]

24 **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]

25 **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]

26 **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]

27 **Wong BS**, Camilleri M, Busciglio I, Carlson P, Szarka LA, Burton D, Zinsmeister AR. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. *Gastroenterology* 2011; **141**: 1638-47.e1-7 [PMID: 21803011 DOI: 10.1053/j.gastro.2011.07.036]

28 **Bashashati M**, Rezaei N, Bashashati H, Shafieyoun A, Daryani NE, Sharkey KA, Storr M. Cytokine gene polymorphisms are associated with irritable bowel syndrome: a systematic review and meta-analysis. *Neurogastroenterol Motil* 2012; **24**: 1102-e566 [PMID: 22897390 DOI: 10.1111/j.1365-2982.2012.01990.x]

29 **Hua MC**, Chao HC, Yao TC, Lai MW, Huang JL; PATCH Study Group. Investigation of interleukin-10 promoter polymorphisms and interleukin-10 levels in children with irritable bowel syndrome. *Gut Liver* 2013; **7**: 430-436 [PMID: 23898383 DOI: 10.5009/gnl.2013.7.4.430]

30 **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]

31 **Gonsalkorale WM**, Perrey C, Pravica V, Whorwell PJ, Hutchinson IV. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003; **52**: 91-93 [PMID: 12477767]

32 **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 interactions in irritable bowel syndrome (IBS). *Dig Dis Sci* 2012; **57**: 2650-2657 [PMID: 22855291]

33 **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]

34 **Shiotani A**, Kusunoki H, Kimura Y, Ishii M, Imamura H, Tarumi K, Manabe N, Kamada T, Hata J, Haruma K. S100A expression and interleukin-10 polymorphisms are associated with ulcerative colitis and diarrhea predominant irritable bowel syndrome. *Dig Dis Sci* 2013; **58**: 2314-2323 [PMID: 23595519 DOI: 10.1007/s10620-013-2677-y]

35 **Mehler MF**, Mattick JS. Noncoding RNAs and RNA editing in brain development, functional diversification, and neurological disease. *Physiol Rev* 2007; **87**: 799-823 [PMID: 17615389]

36 **Farh KK**, Grimson A, Jan C, Lewis BP, Johnston WK, Lim LP, Burge CB, Bartel DP. The widespread impact of mammalian MicroRNAs on mRNA repression and evolution. *Science* 2005; **310**: 1817-1821 [PMID: 16308420]

37 **Dinan TG**. MicroRNAs as a target for novel antipsychotics: a systematic review of an emerging field. *Int J Neuropsychopharmacol* 2010; **13**: 395-404 [PMID: 19849891 DOI: 10.1017/S1461145709990800]

38 **Hobert O**. Gene regulation by transcription factors and microRNAs. *Science* 2008; **319**: 1785-1786 [PMID: 18369135 DOI: 10.1126/science.1151651]

39 **Ng R**, Song G, Roll GR, Frandsen NM, Willenbring H. A microRNA-21 surge facilitates rapid cyclin D1 translation and cell cycle progression in mouse liver regeneration. *J Clin Invest* 2012; **122**: 1097-1108 [PMID: 22326957 DOI: 10.1172/JCI46039]

40 **Rayner KJ**, Esau CC, Hussain FN, McDaniel AL, Marshall SM, van Gils JM, Ray TD, Sheedy FJ, Goedeke L, Liu X, Khatsenko OG, Kaimal V, Lees CJ, Fernandez-Hernando C, Fisher EA, Temel RE, Moore KJ. Inhibition of miR-33a/b in non-human primates raises plasma HDL and lowers VLDL triglycerides. *Nature* 2011; **478**: 404-407 [PMID: 22012398 DOI: 10.1038/nature10486]

41 **Zhang P**, Bill K, Liu J, Young E, Peng T, Bolshakov S, Hoffman A, Song Y, Demicco EG, Terrada DL, Creighton CJ, Anderson ML, Lazar AJ, Calin GG, Pollock RE, Lev D. MiR-155 is a liposarcoma oncogene that targets casein kinase-1α and enhances β-catenin signaling. *Cancer Res* 2012; **72**: 1751-1762 [PMID: 22350414 DOI: 10.1158/0008-5472.CAN-11-3027]

42 **Taganov KD**, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A* 2006; **103**: 12481-12486 [PMID: 16885212]

43 43 **Png KJ**, Halberg N, Yoshida M, Tavazoie SF. A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. *Nature* 2012; **481**: 190-194 [PMID: 22170610 DOI: 10.1038/nature10661]

44 **Calin GA**, Dumitru CD, Shimizu M, Bichi R, Zupo S, Noch E, Aldler H, Rattan S, Keating M, Rai K, Rassenti L, Kipps T, Negrini M, Bullrich F, Croce CM. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci U S A* 2002; **99**: 15524-15529 [PMID: 12434020]

45 **Iorio MV**, Ferracin M, Liu CG, Veronese A, Spizzo R, Sabbioni S, Magri E, Pedriali M, Fabbri M, Campiglio M, Ménard S, Palazzo JP, Rosenberg A, Musiani P, Volinia S, Nenci I, Calin GA, Querzoli P, Negrini M, Croce CM. MicroRNA gene expression deregulation in human breast cancer. *Cancer Res* 2005; **65**: 7065-7070 [PMID: 16103053]

46 **Junker A**, Krumbholz M, Eisele S, Mohan H, Augstein F, Bittner R, Lassmann H, Wekerle H, Hohlfeld R, Meinl E. MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47. *Brain* 2009; **132**: 3342-3352 [PMID: 19952055 DOI: 10.1093/brain/awp300]

47 **Löfgren SE**, Frostegård J, Truedsson L, Pons-Estel BA, D'Alfonso S, Witte T, Lauwerys BR, Endreffy E, Kovács L, Vasconcelos C, Martins da Silva B, Kozyrev SV, Alarcón-Riquelme ME. Genetic association of miRNA-146a with systemic lupus erythematosus in Europeans through decreased expression of the gene. *Genes Immun* 2012; **13**: 268-274 [PMID: 22218224 DOI: 10.1038/gene.2011.84]

48 **Jopling CL**, Yi M, Lancaster AM, Lemon SM, Sarnow P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* 2005; **309**: 1577-1581 [PMID: 16141076]

49 **Lanford RE**, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME, Kauppinen S, Ørum H. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. *Science* 2010; **327**: 198-201 [PMID: 19965718 DOI: 10.1126/science.1178178]

50 **Kapeller J**, Houghton LA, Mönnikes H, Walstab J, Möller D, Bönisch H, Burwinkel B, Autschbach F, Funke B, Lasitschka F, Gassler N, Fischer C, Whorwell PJ, Atkinson W, Fell C, Büchner KJ, Schmidtmann M, van der Voort I, Wisser AS, Berg T, Rappold G, Niesler B. First evidence for an association of a functional variant in the microRNA-510 target site of the serotonin receptor-type 3E gene with diarrhea predominant irritable bowel syndrome. *Hum Mol Genet* 2008; **17**: 2967-2977 [PMID: 18614545 DOI: 10.1093/hmg/ddn195]

51 **Zhou Q**, Souba WW, Croce CM, Verne GN. MicroRNA-29a regulates intestinal membrane permeability in patients with irritable bowel syndrome. *Gut* 2010; **59**: 775-784 [PMID: 19951903 DOI: 10.1136/gut.2009.181834]

52 **Haque FN**, Gottesman II, Wong AH. Not really identical: epigenetic differences in monozygotic twins and implications for twin studies in psychiatry. *Am J Med Genet C Semin Med Genet* 2009; **151C**: 136-141 [PMID: 19378334 DOI: 10.1002/ajmg.c.30206]

53 **Mehler MF**. Epigenetics and the nervous system. *Ann Neurol* 2008; **64**: 602-617 [PMID: 19107999 DOI: 10.1002/ana.21595]

54 **Mehler MF**. Epigenetic principles and mechanisms underlying nervous system functions in health and disease. *Prog Neurobiol* 2008; **86**: 305-341 [PMID: 18940229 DOI: 10.1016/j.pneurobio.2008.10.001]

55 **Videlock EJ**, Adeyemo M, Licudine A, Hirano M, Ohning G, Mayer M, Mayer EA, Chang L. Childhood trauma is associated with hypothalamic-pituitary-adrenal axis responsiveness in irritable bowel syndrome. *Gastroenterology* 2009; **137**: 1954-1962 [PMID: 19737564 DOI: 10.1053/j.gastro.2009.08.058]

56 **Creed F**, Tomenson B, Guthrie E, Ratcliffe J, Fernandes L, Read N, Palmer S, Thompson DG. The relationship between somatisation and outcome in patients with severe irritable bowel syndrome. *J Psychosom Res* 2008; **64**: 613-620 [PMID: 18501262 DOI: 10.1016/j.jpsychores.2008.02.016]

57 **Anda RF**, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, Dube SR, Giles WH. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci* 2006; **256**: 174-186 [PMID: 16311898]

58 **Meaney MJ**, Szyf M, Seckl JR. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. *Trends Mol Med* 2007; **13**: 269-277 [PMID: 17544850]

59 **Coutinho SV**, Plotsky PM, Sablad M, Miller JC, Zhou H, Bayati AI, McRoberts JA, Mayer EA. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol Gastrointest Liver Physiol* 2002; **282**: G307-G316 [PMID: 11804852]

60 **Gluckman PD**, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008; **359**: 61-73 [PMID: 18596274 DOI: 10.1056/NEJMra0708473]

61 **Szyf M**, McGowan P, Meaney MJ. The social environment and the epigenome. *Environ Mol Mutagen* 2008; **49**: 46-60 [PMID: 18095330]

62 **McGowan PO**, Meaney MJ, Szyf M. Diet and the epigenetic (re)programming of phenotypic differences in behavior. *Brain Res* 2008; **1237**: 12-24 [PMID: 18694740 DOI: 10.1016/j.brainres.2008.07.074]

63 **Gareau MG**, Jury J, Yang PC, MacQueen G, Perdue MH. Neonatal maternal separation causes colonic dysfunction in rat pups including impaired host resistance. *Pediatr Res* 2006; **59**: 83-88 [PMID: 16326990]

64 **Clarke G**, Quigley EM, Cryan JF, Dinan TG. Irritable bowel syndrome: towards biomarker identification. *Trends Mol Med* 2009; **15**: 478-489 [PMID: 19811951 DOI: 10.1016/j.molmed.2009.08.001]

65 **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]

66 **Clarke G**, Fitzgerald P, Cryan JF, Cassidy EM, Quigley EM, Dinan TG. Tryptophan degradation in irritable bowel syndrome: evidence of indoleamine 2,3-dioxygenase activation in a male cohort. *BMC Gastroenterol* 2009; **9**: 6 [PMID: 19154614 DOI: 10.1186/1471-230X-9-6]

67 **Ferguson LR**, Shelling AN, Lauren D, Heyes JA, McNabb WC. Nutrigenomics and gut health. *Mutat Res* 2007; **622**: 1-6 [PMID: 17568628]

68 **Stamp LK**, James MJ, Cleland LG. Diet and rheumatoid arthritis: a review of the literature. *Semin Arthritis Rheum* 2005; **35**: 77-94 [PMID: 16194694]

69 **Peña AS**, Crusius JB. Food allergy, coeliac disease and chronic inflammatory bowel disease in man. *Vet Q* 1998; **20 Suppl 3**: S49-S52 [PMID: 9689726]

70 **Dinan TG**, Cryan J, Shanahan F, Keeling PW, Quigley EM. IBS: An epigenetic perspective. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 465-471 [PMID: 20585338 DOI: 10.1038/nrgastro.2010.99]

71 **Eswaran S**, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am* 2011; **40**: 141-162 [PMID: 21333905 DOI: 10.1016/j.gtc.2010.12.012]

72 Morcos A, Dinan T, Quigley EM. Irritable bowel syndrome: role of food in pathogenesis and management. J Dig Dis. 2009 Nov; 10(4): 237-46 doi: 10.1111/j.1751-2980.2009.00392.x

73 **Kallio P**, Kolehmainen M, Laaksonen DE, Kekäläinen J, Salopuro T, Sivenius K, Pulkkinen L, Mykkänen HM, Niskanen L, Uusitupa M, Poutanen KS. Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study. *Am J Clin Nutr* 2007; **85**: 1417-1427 [PMID: 17490981]

74 **Karantanos T**, Markoutsaki T, Gazouli M, Anagnou NP, Karamanolis DG. Current insights in to the pathophysiology of Irritable Bowel Syndrome. *Gut Pathog* 2010; **2**: 3 [PMID: 20465787 DOI: 10.1186/1757-4749-2-3]

75 **de Wouters T**, Doré J, Lepage P. Does our food (environment) change our gut microbiome ('in-vironment'): a potential role for inflammatory bowel disease? *Dig Dis* 2012; **30** Suppl 3: 33-39 [PMID: 23295690 DOI: 10.1159/000342595]

76 **DeBusk RM**, Fogarty CP, Ordovas JM, Kornman KS. Nutritional genomics in practice: where do we begin? *J Am Diet Assoc* 2005; **105**: 589-598 [PMID: 15800562]

77 **Low YL**, Tai ES. Understanding diet-gene interactions: lessons from studying nutrigenomics and cardiovascular disease. *Mutat Res* 2007; **622**: 7-13

78 **Gruber L**, Lichti P, Rath E, Haller D. Nutrigenomics and nutrigenetics in inflammatory bowel diseases. *J Clin Gastroenterol* 2012; **46**: 735-747 [PMID: 22941427 DOI: 10.1097/MCG.0b013e31825ca21a]

79 **Halmos EP**, Power VA, Shepherd SJ, Gibson PR, Muir JG. A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome. *Gastroenterology* 2013; Epub ahead of print [PMID: 24076059]

80 **de Roest RH**, Dobbs BR, Chapman BA, Batman B, O'Brien LA, Leeper JA, Hebblethwaite CR, Gearry RB. The low FODMAP diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: a prospective study. *Int J Clin Pract* 2013; **67**: 895-903 [PMID: 23701141 DOI: 10.1111/ijcp.12128]

81 **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]

82 **Fukudo S**, Ozaki N, Watanabe S, Kano M, Sagami Y, Shoji T, Endo Y, Kanazawa M, Hongo M. Impact of serotonin-3 receptor gene polymorphism on brain activation by rectal distention in human. *Gastroenterology* 2009; **136**(5 Suppl 1): A-170

83 **Kapeller J**, Houghton L, Walstab J, Boenisch H, Rappold G, Niesler B. A coding variant in the serotonin receptor 3C subunit is associated with diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2009; **136**(5 Suppl 1): A-155–156

84 **Villani AC**, Lemire M, Thabane M, Belisle A, Geneau G, Garg AX, Clark WF, Moayyedi P, Collins SM, Franchimont D, Marshall JK. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology* 2010; **138**: 1502-1513 [PMID: 20044998 DOI: 10.1053/j.gastro.2009.12.049]

85 **Saito Y**, Larson J, Atkinson E, Ryu E, Elder AAE, Lee RM, Petersen GM. A candidate gene association study of functional “psychiatric” polymorphisms in irritable bowel syndrome. *Gastroenterology* 2010; **138**(5, Suppl 1): 348

86 **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]

87 **Barkhordari E**, Rezaei N, Mahmoudi M, Larki P, Ahmadi-Ashtiani HR, Ansaripour B, Alighardashi M, Bashashati M, Amirzargar AA, Ebrahimi-Daryani N. T-helper 1, T-helper 2, and T-regulatory cytokines gene polymorphisms in irritable bowel syndrome. *Inflammation* 2010; **33**: 281-286 [PMID: 20177758 DOI: 10.1007/s10753-010-9183-6]

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**Table 1 Genetic alterations on irritable bowel syndrome**

|  |  |  |
| --- | --- | --- |
| **Gene** | **Polymorphism** | **Reference** |
| **Serotonergic system** | | |
| SERT promoter | 5-HTTLPR, deletion | [13-17] |
|  | rs25531 | [81] |
| HTR3A | −42C>T | [50] |
| HTR3B | 386A>C | [82] |
| HTR3C | 489C>A | [83] |
| HTR3E | rs62625044 | [50] |
| **Adrenergic and opioidergic system** | | |
| α2-adrenergic receptor | α2C del 322-325, deletion | [19] |
|  | α2A −1291C>G | [19, 84] |
| COMT | α2A -1291 C>G | [20] |
| Val158Met | [21, 22] |
| CNR1 | (AAT)n triplet repeat | [23] |
|  | rs806378 | [24] |
| CRH-R1 | rs7209436 | [27] |
|  | rs242924 | [27] |
| BDNF | Val166Met | [85] |
| OPRM1 | 118A>G | [85] |
| **Cytokines** | | |
| IL-10 | -1082 A>G | [28-30] |
|  | 396 T>G | [30] |
|  | -819T>G | [34] |
| TNF alpha | -308G>A | [28] |
|  | −238G>A | [86] |
| GNβ3 | 825C>T | [32] |
| *TLR9*+ | −1237T>C | [84] |
|  | 2848G>A | [84] |
| IL1R | Pst-I 1970C>T | [86] |
| IL4 | −590C>T | [84, 87] |
|  | −33T | [87] |
| IL6 | −174G>C | [84, 86] |

SERT: Serotonin reuptake transporter; COMT: Cathechol-*O*-methyltransferase;

CNR1: Cannabinoid receptor 1; CRH-R1: CRH receptor 1; IL: Interleukin; TNF: Tumor necrosis factor.