Nobel Med 2024; 20(1): 5-13

A PRELIMINARY VIEW ON NEUROPSYCHIATRIC MANIFESTATIONS IN IRRITABLE BOWEL SYNDROME – SOME GENETIC ASPECTS

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ABSTRACT

Irritable bowel syndrome (IBS) is defined as a chronic disorder characterized by abdominal pain, discomfort and frequent changes in bowel habits and altered gastrointestinal motility, without, however, any known organic causes. Thus, considering our previous experience in this area of research, we are describing here some preliminary aspects regarding the neuropsychiatric manifestations of Irritable Bowel Syndrome and some new genetic aspects on this matter.

Keywords: *Irritable Bowel Syndrome, neuropsychiatric, genetic.*

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DELIVERING DATE: 07 / 03 / 2023 • **ACCEPTED DATE:** 29 / 05 / 2023

İRRİTABL BAĞIRSAK SENDROMUNDA NÖROPSİKİYATRİK BULGULARA İLİŞKİN BİR ÖN BAKIŞ – GENETİK YÖNLER

ÖZET

İrritabl bağırsak sendromu (IBS), bilinen herhangi bir organik neden olmaksızın karın ağrısı, rahatsızlık ve bağırsak alışkanlıklarında sık değişiklikler ve gastrointestinal motilitede değişiklik ile karakterize kronik bir hastalık olarak tanımlanır. Bu nedenle, bu araştırma alanındaki önceki deneyimlerimizi göz önünde bulundurarak, İrritabl Bağırsak Sendromunun nöropsikiyatrik belirtilerine ilişkin bazı ön bilgileri ve bu konudaki bazı yeni genetik yönleri açıklıyoruz.

Anahtar kelimeler: İrritabl Bağırsak Sendromu, nöropsikiyatri, genetik.

INTRODUCTION

Introduction to Irritable Bowel Syndrome - a Functional Gastrointestinal Disorder

Irritable bowel syndrome (IBS) is presently the most common gut-brain interaction disorder in the world, even though its prevalence remains elusive due to the variability in diagnostic criteria and survey methods used in research studies.[1] IBS is defined as a chronic disorder characterised by abdominal pain, discomfort and frequent changes in bowel habits, and altered gastrointestinal motility, without any known organic causes leading to constipation and diarrhoea.[2] As such, IBS is classified as a functional gastrointestinal disorder (FGID), diagnosed almost exclusively on the basis of symptomatic criteria because there are no significant tissue changes or any specific changes in paraclinical markers.

Up to date, the exact pathophysiology of IBS is not fully known, and beyond the physiological context, the psychological and psychosocial factors have been significantly implicated in its causality and maintenance.[3] According to the biopsychosocial model, IBS is the result of interactions between the central nervous system, various psychological factors, and an impaired intestinal motility and sensitivity.[4] Acute and chronic stress, childhood trauma, and a history of abuse significantly affect the severity of symptoms, disease manifestation, and quality of life in patients with IBS.[5] Traumatic life events, such as early maternal separation and sexual abuse, play an important role in the later development of IBS. These suggest the importance to explore the psychiatric component associated with IBS.[6] At least half of patients with IBS can be described as depressed, anxious, or hypochondriac.[7] Psychological, social, and genetic factors contribute to the development of IBS symptoms through several mechanisms, such as modulation of hypothalamic-pituitary-adrenal (HPA) axis activity, hyperactivity of visceral pain receptors, and predisposition to some psychiatric or psychological disorders.[8]

Currently, the 2016 ROME IV clinical diagnostic criteria, the most frequently used in the diagnosis of FGID, refers to the disturbance of the brain-gut axis as a diagnostic criterion of IBS and include besides the three older IBS subtypes-IBS with constipation (IBS-C), with diarrhoea (IBS-D), and mixed IBS (IBS-M)-a new addition, the IBS un-classified (IBS-U), which refers to IBS mechanisms associated with gastro- and neuro-components.[9] However, recently, a newer hypothesis has appeared in the literature proposing the reclassification of IBS towards a peripheral neuropathy instead of a typical functional gastrointestinal syndrome.[10]

IBS Neuropsychiatric Comorbidities

Neurosychiatric comorbidities, such as neurosis, anxiety, depression, cognitive dysfunctions are frequently reported in IBS with high prevalence. Guthrie *et al*. found that 44% of their patients with IBS had psychiatric comorbidities, mainly due to depression and anxiety.[11] A one year screening of 345 patients diagnosed with IBS revealed in almost half of these the association of mental disorders with IBS, with anxiety and depression being the most common ones.[12] The wide range of neuropsychiatric symptoms suggests a common pathway and a bidirectional association in patients with FGID and affective comorbidities; this is occasionally doubled by the neurodegeneration of various brain regions, such as significant activation of the amygdala, thinning of the insular and anterior cingulate cortex, and increase in hypothalamic grey matter, often accompanied by dysbiosis of the gut microbiota as a main factor.[4] Changing sleep patterns, especially altered REM sleep, may be observed in patients with IBS because of a serotonin 5-hydroxytryptamine (5-HT)-associated CNS dysfunction. In addition, treatments, such as antidepressants and anxiolytics, targeting serotonergic transmission in the CNS have been reported to be effective in treating IBS symptoms.[13]

Psychiatric disorders have complex aetiologies that involve interactions between multiple genetic and non-genetic risk factors, however, major neuropsychiatric disorders are hereditary and there is growing evidence these disorders sharing overlaps between basic molecular and cellular sets.[14] Gandal *et al*. performed transcriptomic profiling of molecular brain-based phenotypes across 5 major psychiatric disorders - autism, schizophrenia, bipolar disorder, depression, and alcoholism - using 700 cerebral cortical samples and found patterns of shared and distinct gene expression perturbations across these conditions.[14]

In the case of schizophrenia, the hereditary nature of the disorder varies owing to the difficulty of separating the effects of genes from the epigenetic effects of the environment.[15] It is possible that multiple genes are involved in the disease aetiology, each with a small effect and unknown transmission and expression. Several potentially responsible genes have been proposed, such as NOTCH4 (Notch 4 receptor) and histone protein (loci) sectors, including variations in the number of copies.[16] Occurence of IBS cases in patients with schizophrenia was reportedly around 17%-19%, but the actual prevalence of IBS symptoms may be much higher, as these results depend on the individual reporting of symptoms.[8,17,18]

Autism, with an estimated heritability of approximately 90%, is a complex genetic disorder, the result of simultaneous genetic variations.[19] The high prevalence of gastrointestinal disorders in people with autism can be correlated with the increasing severity of autistic symptoms.[20] A recent genomic study on very large populations of autistic persons identified and confirmed several genetic susceptibility loci, such as NCAM1, CADM2, PHF2/FAM120A, DOCK9, CKAP2/TPTE2P3 and BAG6, relevant also to IBS as well as mood and anxiety disorders.[21] The gastrointestinal disturbances in autism remain yet a subject of debate on whether they present a potential cause of the syndrome.

The prevalence of anxiety and depression in patients with IBS seeking treatment in healthcare units has been investigated previously, however few studies have evaluated the prevalence of IBS in psychiatric patients. Among the latter, there are some reports on the increased prevalence ranging from 27 to 47% of IBS in patients with depression.[7,22,23]

The Genetic Component of Gastrointestinal Disorders Observed in IBS

One of the biggest constraints in searching for candidate IBS genes is the IBS phenotype. Molecular mechanisms for constipation versus diarrhoea, for sporadic IBS versus post-infectious IBS, or even for anxiety-associated IBS versus non-anxiety-associated IBS are likely different.[2] The most studied IBS genes are involved in serotoninergic, adrenergic, inflammation, intestinal barrier, and psychiatric main pathways, owing to the presumed role of the encoded proteins in gastrointestinal or sensory functions, or their potential role in the resistance or response to microbial organisms. Serotonin (or 5-HT) has been extensively studied because of its presence in the intestinal tract and brain. Selective serotonin reuptake inhibitors are one of the most effective antidepressants, and 5-HT receptor agonists and antagonists are known to accelerate and slow the symptoms of IBS gastrointestinal transit and have a positive impact.[24] At the molecular level, abnormalities have been found in the transport system of 5-HT reuptake in patients with IBS.[25] The polymorphic region linked to the 5-HT transporter gene, 5-HTT LPR, is the best-studied functional variant in the field of psychiatry and IBS.[26] In addition to other genetic variants of the serotonin transporter gene (SLC6A4), several studies have examined the functional single nucleotide polymorphisms (SNPs) of 5-HT receptor encoding genes, including HTR2A, HTR3A, HTR3B, HTR3C, and HTR3E, with positive results; thus, the HTR3A-42C>TC/T genotype was more common in patients with IBS-D.[27,28] In a recent study on over 20 genes involved in 5-HT transport out of the 968 IBS cases and controls, 27 SNPs of 9 genes encoding TDO2, HTR2A, and HTR7 were associated with IBS, 32 SNPs of 15 genes encoding HTR4 and HTR7 were associated with IBS-C, and 26 SNPs of seven genes encoding HTR2A were associated with IBS-D, among others.[28] Regarding mood disorders in IBS, Saito *et al*. (2010) evaluated 10 SNPs on 8 genes (FKBP5, COMT, NPY, BDNF, ANKK1, DRD2, OPRM1, and FAAH) but did not report any to be associated with IBS. However, COMT Val158Met was associated with IBS-C, OPRM1 118A>G was associated with IBS-M and IBS-D in women, and the BDNF Val166Met SNP was associated with individuals with IBS accompanied by a psychiatric disorder.[29] These findings are interesting because the COMT variant is related to anxiety, obsessive-compulsive disorder, panic disorder, and cognitive performance, while the OPRM1 variant is related to pain sensitivity, opioid dependence, and social sensitivity.[30,31]

This complex relationship between serotonin, adrenergic receptors, inflammation, the intestinal barrier, and the main psychiatric pathways is shown in Table 1.

Table 1. Description of some genetic variants of some candidate genes for Irritable bowel syndrome (IBS)

Gene	Description	Polymorphism	Association with IBS?	References
Genes involved in serotonin metabolism				
SLC6A4	5-hydroxytryptamine (serotonin) transporter gene	5-HTT LPR (44 bp ins/del) STin2 VNTR - Alela G>T	No; LS, LL α IBS-C Not Gallery Not	Villani A, Saito Y, *et al,* 2004, Camilleri M, Carlson P, *et al,* 2010, Kohen R, Jarrett M, *et al,* 2009 Villani A-C, Lemire M, *et al,* 2010
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, ionotropic	102T>C - 1438G>A H452Y	Not Not Not	Villani A-C, Lemire M, *et al,* 2010, Pata C, Erdal E, *et al,* 2004
HTR3A	5-hydroxytryptamine (serotonin) receptor 3A, ionotropic	-42C>T -25C>T *70C>T *503C>T	CT α IBS-D Not Not Not	Kapeller J, Houghton L, *et al,* 2008
HTR3B	5-hydroxytryptamine (serotonin) receptor 3B, ionotropic	386A>C	AC/CC	Fukudo S, Ozaki N, *et al,* 2009
HTR3C	5-hydroxytryptamine (serotonin) receptor 3C, ionotropic	489C>A	CC α IBS-D	Kapeller J, Houghton L, *et al,* 2009
HTR3E	5-hydroxytryptamine (serotonin) receptor 3E, ionotropic	*76G>A *115T>G *138C>T -189A>G	GA α IBS-D Not Not Not	Kapeller J, Houghton L, *et al,* 2008
TPH1	Tryptophan hydroxylase 2	218A>C 779A>C	Not Not	Villani A-C, Lemire M, *et al,* 2010
TPH2	Tryptophan hydroxylase 2	-473T>A -703G>T 90A>G	Not Not Not	Villani A-C, Lemire M, *et al,* 2010
Genes involved in inflammation				
IL10	Interleukin 10	-1082G>A -819C>T -592A>C	A α IBS; No; G α IBS; GA α IBS Not Not	Villani A, Saito Y, *et al,* 2004, Barkhordari E, Rezaei N, *et al,* 2010, van der Veek PP, *et al,* 2005, Villani A-C, Lemire M, *et al,* 2010
TNFα	Tumour necrosis factor-alpha	-308G>A -238G>A	GA α IBS; No; No G α IBS	van der Veek PP, *et al,* 2005,
				SanthoshS, DuttaA, *et al,* 2010, Barkhordari E, Rezaei N, *et al,* 2010
TGFβ1	Growth factor beta 1	+869T>C -509C>T	Not Not	Gonsalkorale WM, *et al,* 2003 Villani A-C, Lemire M, *et al,* 2010
CARD8	Caspase family member of recruitment 8	Cys10Stop	Not	Villani A-C, Lemire M, *et al,* 2010
TLR4	Toll-like receptor 4	D299G	Not	Villani A-C, Lemire M, *et al,* 2010
TLR5	Toll-like receptor 5	1174C>T	Not	Villani A-C, Lemire M, *et al,* 2010
TLR9+	Toll-like receptor 9	-1237T>C 2848G>A	T α PI-IBS A α PI-IBS	Villani A-C, Lemire M, *et al,* 2010
CD14	CD14 antigen	-159T>C	Not	Villani A-C, Lemire M, *et al,* 2010
NFKB1	Nuclear factor kappa B subunit 1	-94delATTG	Not	Villani A-C, Lemire M, *et al,* 2010
ATG16L1	Autophagy associated 16 as1	T300A	Not	Villani A-C, Lemire M, *et al,* 2010
PTGER4	Prostaglandin E4 receptor	- - -	Not Not Not	Villani A-C, Lemire M, *et al,* 2010

Table 1. Description of some genetic variants of some candidate genes for Irritable bowel syndrome (IBS)

Gene	Description	Polymorphism	Association with IBS?	References
IRGM	GTPaseM-linked immunoglobulin	- -	Not Not	Villani A-C, Lemire M, *et al,* 2010
PTPN2	Non-receptor protein tyrosine phosphatase type 1	- -	Not Not	Villani A-C, Lemire M, *et al,* 2010
IL1R	interleukin 1 receptor-like 1	Pst-I 1970C>T	C α IBS	Barkhordari E, Rezaei N, *et al,* 2010
IL4	interleukin 4	-590C>T -33T	No; C α IBS T α IBS	Villani A-C, Lemire M, *et al,* 2010,
IL6	interleukin 6	-174G>C Nt565 -1082 A>G -819T>C -592A>C	C α PI-IBS; G α IBS Not Not Not Not	Villani A-C, Lemire M, *et al,* 2010, Santhosh S, Dutta A, *et al,* 2010,
Genes involved in the intestinal barrier				
SLC22A4	Carrier Family 22 Member 4	167 2C>T	Not	Villani A-C, Lemire M, *et al,* 2010
SLC22A5	Carrier Family 22 Member 5	-207G>C	Not	Villani A-C, Lemire M, *et al,* 2010
CDH1	Cadherin 1	-160C>A -347G>A	A α PI-IBS Not	Villani A-C, Lemire M, *et al,* 2010
ICAM1	Intracellular adhesion molecule 1	K469E G241R	Not Not	Villani A-C, Lemire M, *et al,* 2010
DLG5	MAGUK Protein Discs for large scaffolds 5	R30Q	Not	Villani A-C, Lemire M,*et al,* 2010
ABCB1	Subfamily B ATP binding box member 1	3435C>T -	Not Not	Villani A-C, Lemire M,*et al,* 2010
Genes involved in the adrenergic pathway				
ADRA2A	Alpha 2A adrenoceptor	753C>G -1291C>G	Not G α IBS-C; CG/GG α IBS-D; No	Villani A-C, Lemire M, *et al,* 2010, Kim HJ, Camilleri M, *et al,* 2004, Camilleri M, Carlson P, *et al,* 2010, Sikander A, Rana SV, *et al,* 2010
ADRA2C	Alpha 2C adrenoceptor	Del 332-335	IBS - C	Kim HJ, Camilleri M, *et al,* 2004
Genes involved in psychiatric pathology				
FKBP5	Peptidyl-prolyl cis-trans isomerase	- - -	Not Not Not	Saito Y, Larson J, *et al,* 2010
COMT	Catechol-O-methyltransferase	Val 158Met	Met α IBS - C	Saito Y, Larson J, *et al,* 2010
BDNF	Brain-derived neurotrophic factor	Val 166Met	Met α psychiatric IBS	Saito Y, Larson J, *et al,* 2010
ANKK1	Ankyrin repeat and kinase domain containing 1	-	Not	Saito Y, Larson J, *et al,* 2010
DRD2	The dopamine D2 receptor	Ser311Cys	Not	Saito Y, Larson J, *et al,* 2010
OPRM1	Mu 1 opioid receptor	118A>G	G α IBS-M, IBS-D females	Saito Y, Larson J, *et al,* 2010
Other genes involved				
CNR1	Cannabinoid receptor 1	AAT repeats	Yes	Park J, Choi M, *et al,* 2011
FAAH	Fatty acid amide acid hydrolase	385C>A	Yes	Park J, Choi M, *et al,* 2011
GNβ3	G protein beta 3 subunit	825C>T	Nu, dar posibila interactiunea cu infectia gastrointestinala	Camilleri M, Carlson P, *et al,* 2010, Holtmann G, Siffert W, *et al,* 2004
NPSR1	Neuropeptide S1 receptor	Ile 107Asn Arg241Ser Arg344Gln	Not Not Not	Camilleri M, Carlson P, *et al,* 2010
SCN5A	Sodium channel, Voltage-gated, type V alpha subunit	G298S	IBS - D	Saito YA, Strege PR, *et al,* 2009

Genetic Similarities Between IBS and Anxiety Disorder

In a study examining the relationship between IBS and anxiety, 32% of patients with IBS had symptoms of anxiety compared to other psychological manifestations.[32] According to Fadgyas-Stanculete, the visceral sensitivity index is a strong predictor of the severity of specific anxiety in gastrointestinal disorders.[7] Corticotropin-releasing hormone (CRH) plays an important role in the pathophysiology of IBS and regulates the stress response through two CRH receptors (R1 and R2). A polymorphism of the CRHR1 gene (rs110402) and haplotypes have been reported to be associated with IBS.[33,34] Significant associations have been found between CRHR2 genetic polymorphisms and haplotypes and the pathophysiology of IBS and negative emotions in patients with IBS. The involvement of RBFOX1 in the development of anxiety-related conditions, such as generalised anxiety disorder, has been suggested by an independent genome-wide association study that also identified variants in RBFOX1 linked to the anxiety sensitivity index (ASI). Two exons of ITM2B were identified to have significantly higher expression levels in individuals with higher ASI than those in monozygotic twins, an effect replicated in an independent sample. This finding also suggests that both genetic and non-genetic variations are essential for the development of this disorder.[35] Pharmacological studies have specifically delineated the role of the GABA A α3 subunit in anxiety, in accordance with other genetic studies on the GABRA3 receptor gene that also support its potential role in mood disorder phenotypes.[36,37] Clinical genetic studies indicate a considerable heritability in anxiety disorders (ranging 30–67%) in the case of multiple vulnerability genes such as 5-HT1A, 5HTT, MAO-A, COMT, CCK-B, ADORA2A, CRHR1, FKBP5, ACE, RGS2/7, and NPSR1. These genes may partially interact with each other (such as the COMT/5-HT1A complex) and with environmental factors to model the overall risk of disease in a complex genetic model. In addition, epigenetic signatures play a crucial role in increasing the functional impact of anxiety disorder risk genes, such as methylation patterns induced by an altered environmental influences.[38]

A table showing the genetic similarities of IBS with anxiety disorders and a list of candidate genes for anxiety in association with IBS is shown in Table 2.

Genetic Similarities Between IBS and Depressive Disorder

Multiple genetic reports have highlighted a higher frequency of the depression comorbidity in patients with IBS. Several studies examining FKBP5 and CHRH1 have shown that variants of these genes moderate the effects of exposure to child abuse, childhood adversity, or adverse life events on adult depression.[39,40] These genes are interesting candidates because they regulate the stress response through the HPA axis.[41] The piccolo presynaptic cytomatrix protein (PCLO) is located in the cytoplasmic matrix of the presynaptic active area and plays a significant role in monoaminergic neurotransmission in the brain. A possible role for this region in the onset of depression was reported by Hek *et al.*, who identified an association between the rs2522833 SNP in PCLO and depression in a Dutch population.[42] The PCLO gene is involved in establishing active synaptic areas and tracking synaptic vesicles.[43] Other subsequent studies found mixed evidence regarding the association between PCLO SNPs and depression.[44] Of particular interest is the association between depression and the polymorphic variants of the apolipoprotein E (APOE) and methylene tetrahydrofolate reductase (MTHFR) genes.[45] These genes have been discussed in the context of the etiopathogenesis of the dysthymic disorder (DD) vascular theory, which claims that DD, as well as other mental illnesses, such as schizophrenia and manic-depressive psychosis, occur due to disruption of the blood supply to neuronal tissue.[46] There may be a continuum of these diseases, which are separated only by a thin line, as, for example, some clinical subtypes of depression are characterised by marked psychotic symptoms (F32.3 in ICD-10).[46] Numerous replication attempts based on 5-HTT LPR or other genetic variants, such as BDNF, monoamine oxidase A (MAOA), FK506 binding protein 51, CRHR1, COMT, have focused on stressful early or childhood life events, as well as child abuses, such as physical abuse, sexual abuse or neglect, as risk factors for adult stage IBS.[47] Several studies have reported an association of the Val66Met polymorphism in BDNF with DD onset, but many attribute the risk of DD to the effect of different allelic variants. For example, Frielingsdorf *et al*. showed that homozygotes with Met alleles had a significantly increased risk of depression, whereas Ribeiro *et al*. defined Val as the allele associated with the risk of depression.[48,49] This inconsistency was analysed in a meta-analysis that combined the results of 14 original studies, but did not confirm an association between the polymorphic variant of BDNF and DD.[50] Other studies showed that the effect of this polymorphism could only be observed in interaction with other polymorphic systems, such as 5-HTT LPR polymorphisms or after exposure to severe stress.[46]

The list of candidate genes for depression associated with IBS is shown in Table 3.

Table 2. List of candidate genes for anxiety, in association with Irritable bowel syndrome

Gene	Description	Polymorphism	Association with IBS?	References
ADORA2A	Adenosine A2A receptor	753>G; -1291>G	Yes	Domschke, K., & Maron, E. (2013). Genetic Factors in Anxiety Disorders. Modern Trends in Pharmacopsychiatry, 24–46.
ACE	Angiotensin-converting enzyme	rs13447447	Not	Domschke, K., & Maron, E. (2013)
CCK-B	Colecistokinina B	rs906895	Yes	Domschke, K., & Maron, E. (2013)
COMT	Catechol-O-methyltransferase	Val158Met	Yes	Domschke, K., & Maron, E. (2013)
CRHR1	Corticotropin-releasing hormone receptor 1	rs110402	Yes	Domschke, K., & Maron, E. (2013), (Komoro H,Sato N, Sasaki A, Suzuki N,Kano M, *et al*, 2016).
CRHR2	Corticotropin-releasing hormone receptor 2	rs4722999	Yes	Komoro H,Sato N, Sasaki A, Suzuki N,Kano M, *et al*, 2016
MAO-A	Monoamine oxidase A	VNTR polymorphism in the promoter region	Not	Gatt JM, Burton KL, Williams LM, Schofield PR.,2015
NPSR1	Neuropeptide S1 receptor	Ile107Asn	Not	Domschke, K., & Maron, E. (2013)
RBFOX1	Fox-1 Homolog 1 RNA Binding	rs17143930	Not	Davies, M. N., Verdi, S., Burri, A., Trzaskowski, M., Lee, M., Hettema, J. M., Spector, T. D. (2015).
ITM2B	Integral membrane protein 2B	rs104894417	Not	Davies, M. N., Verdi, S., Burri, A., Trzaskowski, M., Lee, M., Hettema, J. M., Spector, T. D. (2015).
GABRA3	Gamma-aminobutyric acid type A Alpha 3 receptor	GABA A α3	Yes	Xuan Pham,Cuie Sun, Xiangning Chen, dr. Edwin JCG van den Oord, Michael C. Neale,2009
RGS2/7	G protein signalling regulator	rs148489044	Not	Domschke, K., & Maron, E. (2013)
5-HT1A	The 5-hydroxytryptamine 1A receptor	rs6295	Yes	Domschke, K., & Maron, E. (2013)
SLC6A4	Single carrier family 6 members 4	5-HTT	Yes	Domschke, K., & Maron, E. (2013)
BDNF	Brain-derived neurotrophic factor	Val66Met	Yes	Yuri A. Saito,2012
FKBP5	FKBP prolyl isomerase 5	rs4713916	Not	Domschke, K., & Maron, E. (2013)

IBS: Irritable bowel syndrome

Table 3. List of candidate genes for depression, in association with Irritable bowel syndrome

Gene	Description	Polymorphism	Association with IBS?	References
APOE	Apolipoprotein E	rs121918392	Not	Maria Shadrina, Elena A. Bondarenko, şi Petr A. Slominsky (2018)
CDH18	Cadherin 18	rs550027191	Not	Terracciano *et al* (2010)
SLC6A15	Solute carrier family 6, neutral amino acid transporter, member 15	rs1545843	Not	Maria Shadrina, Elena A. Bondarenko, and Petr A. Slominsky, 2018
SLC6A3	Soil-bearing family 6 members 3	40-bp VNTR	Yes	Gatt JM, Burton KL, Williams LM, Schofield PR.,2015
SLC6A4	Serotonin transporter gene	44-bp Ins/Del (5-HTTLPR)	Yes	Gatt JM, Burton KL, Williams LM, Schofield PR., 2015
DRD4	The D4 dopamine receptor	rs1800443	Not	Erin C. Dunn, Ruth C. Brown, Yael Dai, Jonathan Rosand, 2015
GNB3	G protein beta 3 subunit	rs5443	Yes	Maria Shadrina, Elena A. Bondarenko and Petr A. Slominsky, 2018
FKBP5	FK506 binding protein 51	rs3800373	Not	Erin C. Dunn, Dr. Ruth C. Brown, Yael Dai, BA, Dr Jonathan Rosand, Nicole R. Nugent, 2015
HOMER1	Homer 1 protein	rs9943849	Not	Rietschel *et al* (2010); Maria Shadrina, Elena A. Bondarenko, şi Petr A. Slominsky (2018)
CRHR1	Corticotropin-releasing hormone receptor 1	rs242939	Yes	Erin C. Dunn, Dr. Ruth C. Brown, Yael Dai, BA, Dr Jonathan Rosand, Nicole R. Nugent, 2015
MTHFR	Methylenetetrahydrof folate reductase	rs1801133	Not	Maria Shadrina, Elena A. Bondarenko, and Petr A. Slominsky,2018
COMT	Catecol- O- metiltransferaza	Val158Met	Yes	Sullivan *et al* (2009)
PCLO	Cytomatrix protein prescribed Piccolo	rs2522833	Yes	Sullivan *et al* (2009); Maria Shadrina, Elena A. Bondarenko, şi Petr A. Slominsky (2018)
PDE9A	Phosphodiesterase A	rs13050655	Not	Lewis *et al* (2010)
BDNF	Brain-derived neurotrophic factor	Val66Met	Yes	Yuri A. Saito, 2012
BICCI	Bicaudal counterpart C1	rs9416742	Not	Lewis *et al* (2010); Maria Shadrina, Elena A. Bondarenko, şi Petr A. Slominsky (2018)

IBS: Irritable bowel syndrome

CONCLUSION

IBS is a functional gastrointestinal syndrome which, in addition to digestive tract impairments, may be closely accompanied by significant neuropsychiatric comorbidities, such as autism, anxiety, or depression. The neuropsychiatric component of IBS has emerged in recent years to an extent that the diagnostic criteria have been modified to include it as a defining symptom. Accordingly, neuropsychiatric disorders and IBS may share some common genetic traits, and various gene polymorphisms may be involved in the development of the disorder. Genetic studies of the various clinical forms of IBS could be the most promising direction of research in the recent future.

*The authors declare that there are no conflicts of interest.

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