Σύνδρομο ευερέθιστου εντέρου – Γενετικό & Μοριακό Υπόβαθρο

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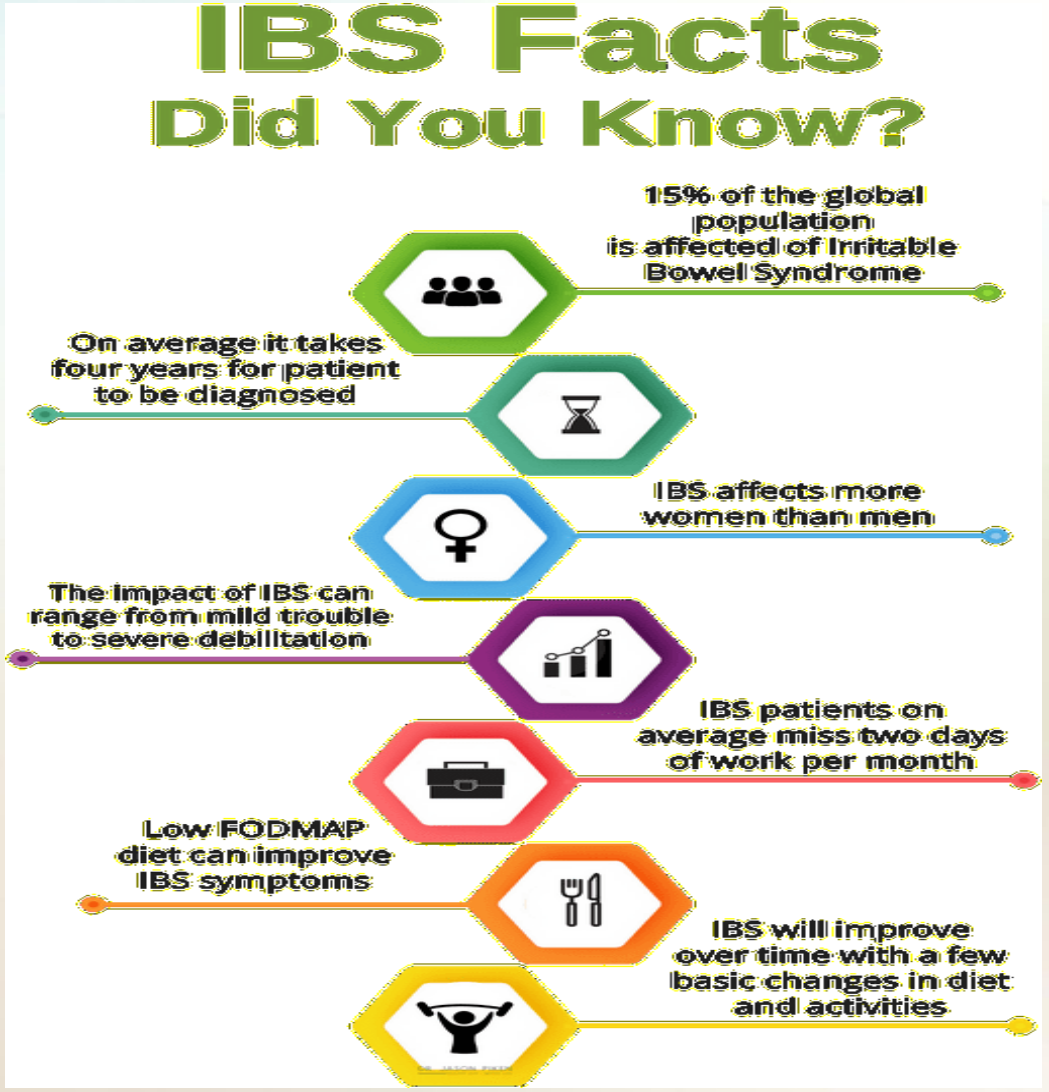
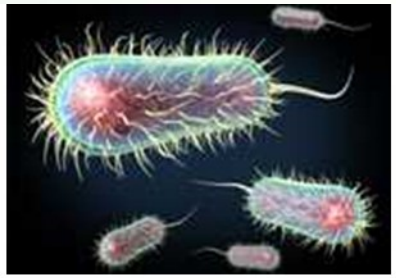
Σύνδρομο ευερέθιστου εντέρου (IBS)

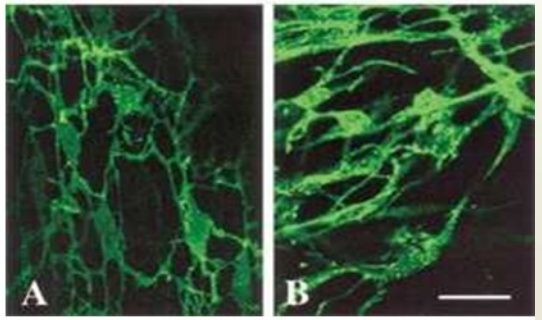
- **Εντερική διαταραχή – Σύνθετο νόσημα – Άγνωστη αιτιολογία**
- **Συνδέεται με αγχωτικά γεγονότα και η αναλογία γυναίκες/άνδρες = 3/1**



1. Post - Infectious IBS



2. Interstitial Cells of Cajal



3. Serotonin Pathway

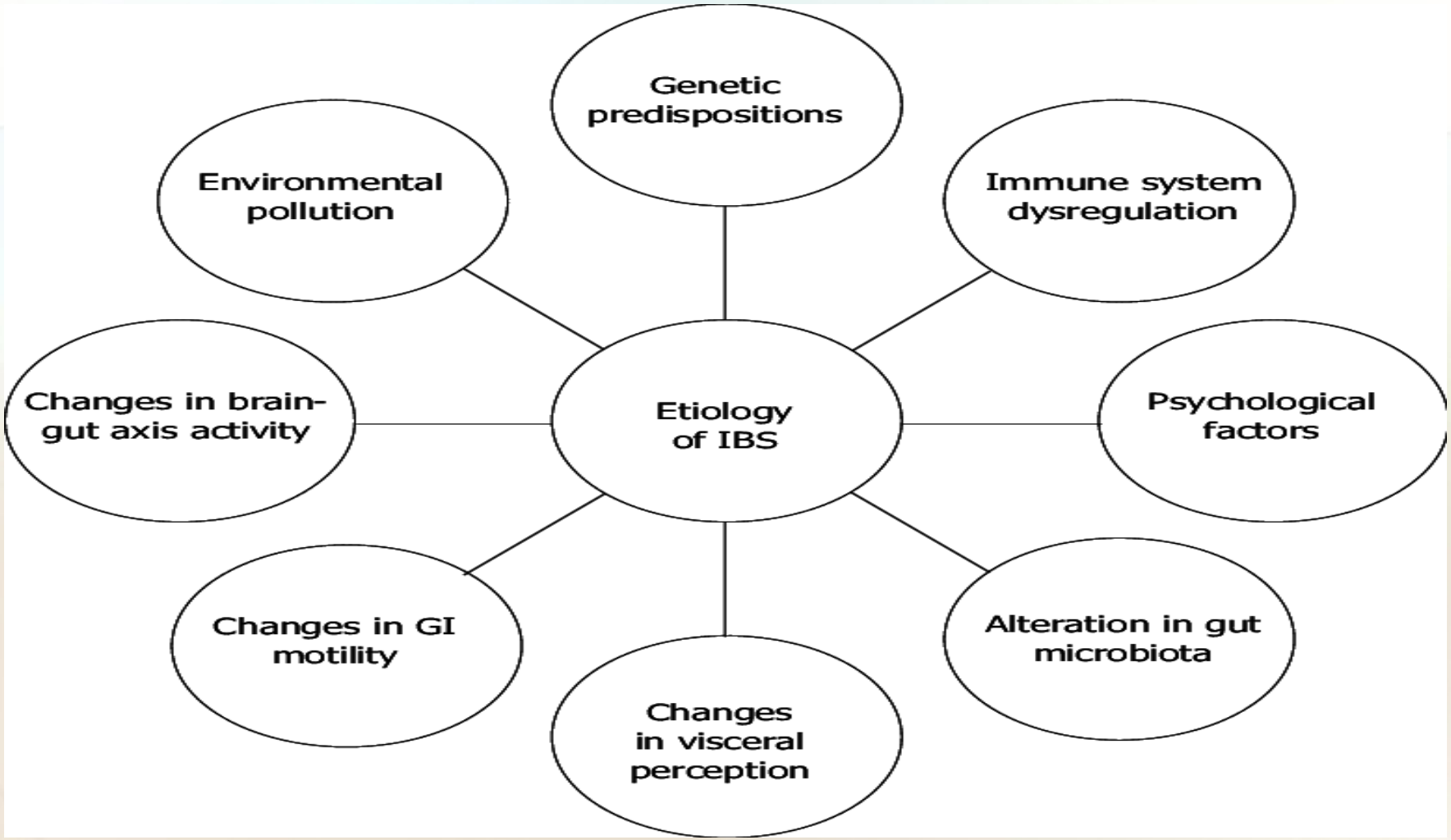
Κύρια σημεία

- Οι γενετικές μελέτες στο IBS βασίζονται σε οικογένειες και μελέτες σε διδύμους, σε προσεγγίσεις με διάφορα υποψήφια γονίδια και σε γενικές μελέτες σύνδεσης γονιδιώματος
- Παρά τα μεγάλα μεγέθη δειγμάτων, την αυξημένη στατιστική ισχύ και τις μετα-αναλύσεις, οι θετικές συσχετίσεις μεταξύ των γονιδιακών πολυμορφισμών και των υποτύπων του IBS είναι ακόμη ασαφείς και πολλοί συσχετισμοί δεν έχουν αναπαραχθεί σε άλλους πληθυσμούς
- Οι επιγενετικές και οι φαρμακογενωμικές αναλύσεις είναι ακόμα στην αρχή
- Ένα σημαντικό πρόβλημα στην έρευνα του IBS είναι η έλλειψη μεγάλων ομογενοποιημένων ομάδων ελέγχου περιπτώσεων που να είναι σύμφωνα με τυποποιημένα και εναρμονισμένα κριτήρια

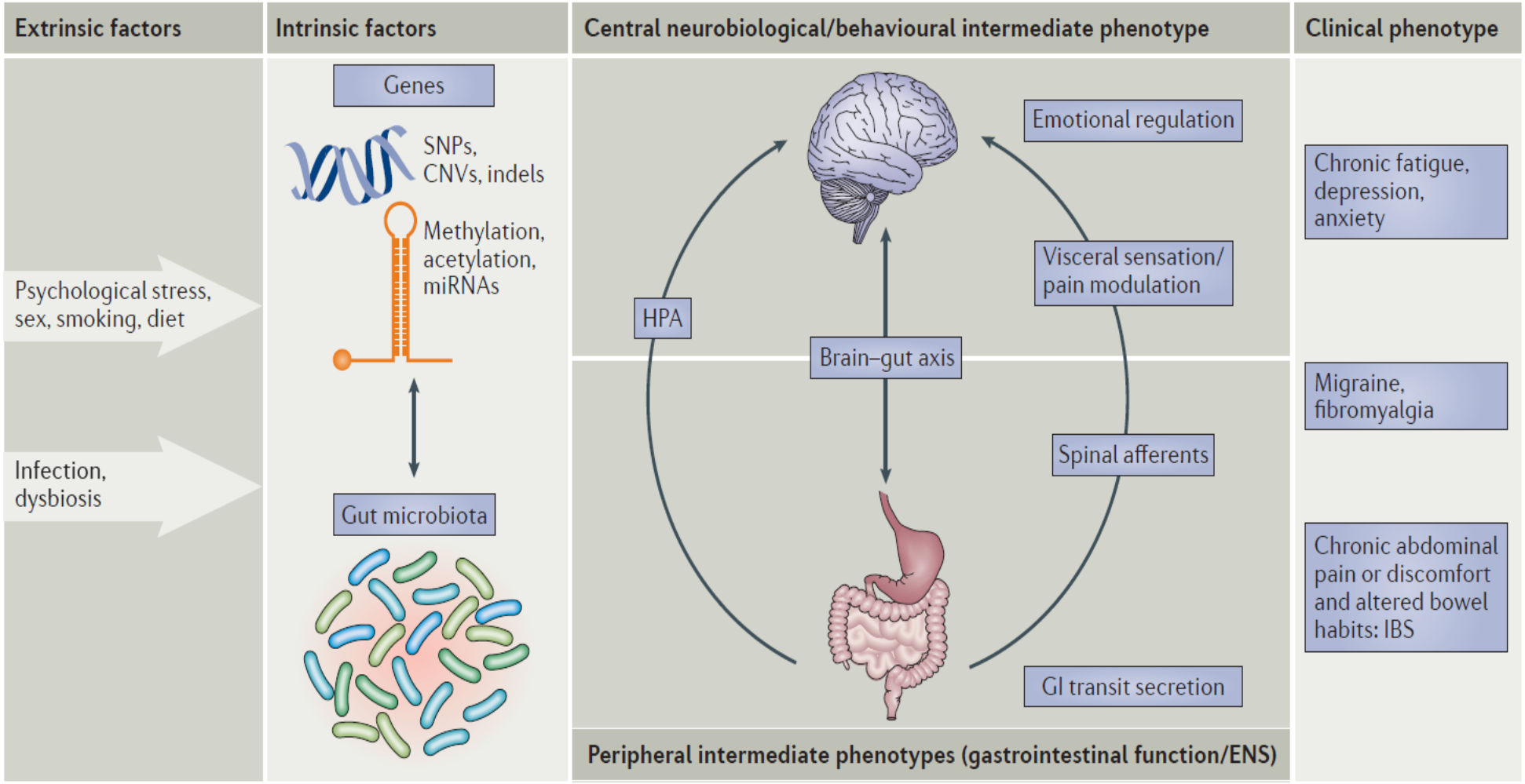
Κληρονομικότητα

- Θετικό οικογενειακό ιστορικό είναι επιβαρυντικός παράγοντας αυξάνοντας 2-3 φορές την πιθανότητα στους απογόνους
- Μελέτες σε διδύμους υποστηρίζουν ότι το IBS μπορεί να είναι μια πολυπαραγοντική διαταραχή γενετικής και περιβαλλοντικής προέλευσης. Μέχρι σήμερα, έχουν γίνει περίπου πέντε μελέτες σε διδύμους και η γενετική κληρονομικότητα στα μονοζυγωτκά κυρίως δίδυμα εκτιμάται σε ~ 22-57%

Αιτιοπαθολογία



Πολλαπλά επίπεδα πολυπλοκότητας σε περιβαλλοντικό και γενετικό ή επιγενετικό επίπεδο συμβάλλουν στην την παθογένεση του IBS και τις σχετιζόμενες συνθήκες



Nat Rev Gastroenterol Hepatol. 2016;13(2):77-87

Γενετικοί πολυμορφισμοί στο serotonergic σύστημα.

Is it "irritable brain" or "irritable bowel"?

Genetic alterations on irritable bowel syndrome

Gene	Polymorphism	Ref.
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]

World J Gastroenterol. 2014; 20(2): 376–383

Gene	SNP database number (RS)	*HGVS* nomenclature	Functional variant	General or mixed IBS	IBS subtype	Association with comorbid disorder or other quantitative traits	Case Group (*n*)	Control Group (*n*)	Country of origin	Reference (see main text for details and reference list)
SNPs in genes in serotonergic pathways										
SLC6A4	rs4795541*	g.28564359_28564360insG	c.-1950_-1949insC	No association			1034	1377	USA, UK, Turkey, China, Korea	34
					LS genotype with IBS-D		54	91	Turkey	38
					SS genotype with IBS-C and LS genotype with IBS-D					
					SS genotype with IBS-D		194	448	USA	35
					SS genotype with IBS-D		190	437	Korea	36
					S allele with M-IBS, but not IBS overall		50	53	USA	39
					SS genotype with IBS-C		151	100	India	40
					SS genotype with IBS-D	Higher 5-HT level in rectal biopsies	150	252	India	37
					SS genotype with IBS		119	238	China	44
				No association			33	56	Korea	41
				No association			256	120	USA	33
					LL genotype with IBS-C		81	48	China	42
					LL genotype with IBS-C		87	96	China	43
				LL genotype with the total IBS, IBS-C and IBS-M			99	171	Korea	32
						SS genotype with depression in IBS; LL	133	-	USA	47

Adrenergic and opioidergic system		
α_2-adrenergic receptor	α2C del 322-325, deletion	[19]
	α2A-1291C > G	[19,84]
COMT	α2A-1291 C > G	[20]
	$Val^{158}Met$	[21,22]
CNR1	(AAT)n triplet repeat	[23]
	rs806378	[24]
CRH-R1	rs7209436	[27]
	rs242924	[27]
BDNF	$Val^{166}Met$	[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]
	2848 G> A	[84]
IL1R	Pst-I 1970C > T	[86]
IL4	-590C > T	[84,87]
	-33T	[87]
IL6	-174G > C	[84,86]

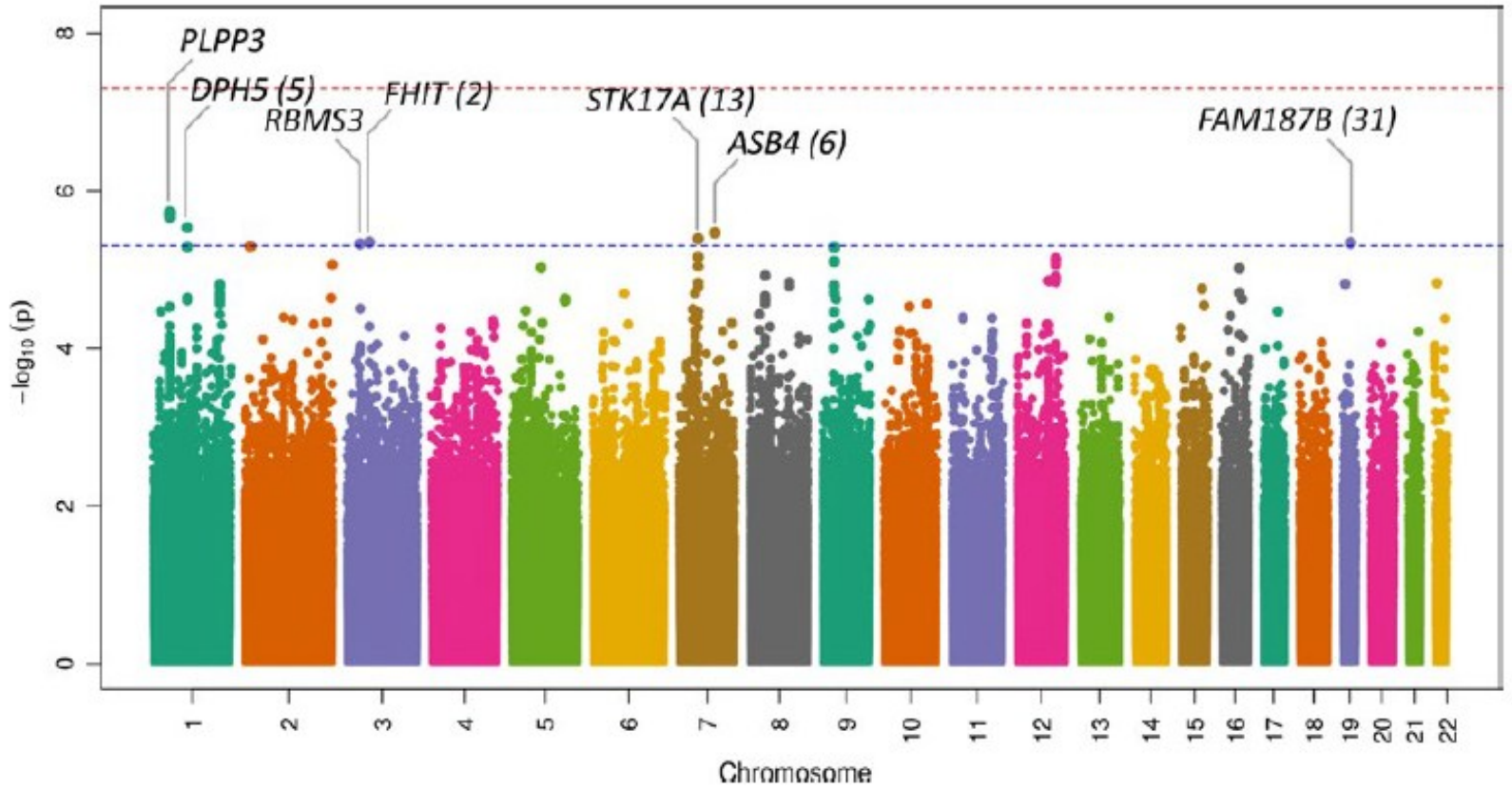
	rs352139	g.32236372T>C	c.2848G>A	A allele with PI-IBS						
SNPs in genes involved in barrier integrity										
CDH1	rs16260	g.68737131C>A	c.-160C>A		A allele with PI-IBS		228	581	Canada	94
CDC42	rs17837965	g.22394625A>G	c.-176-5962A>G		With IBS-C		935	639	USA, UK, Sweden	82
SNPs in genes involved in bile acid synthesis, transport and excretion										
KLB	rs17618244	g.39448529G>A	p.R728Q		G allele (Arg728) with IBS-D	Accelerated transit in IBS-D	435	279	USA	131
						G allele with increased bile acids synthesis and excretion	94	30	USA	135
FGFR4	rs351855	g.177093242G>A	c.1097+65G>A,			Colonic transit in IBS-D	435	279	USA	131
	rs1966265	g.177089630G>A	c.28G>A							

*This SNP represents a polymorphic region consisting of an indel, for example either an insertion or a deletion, of 43 or 44 nucleotides, respectively. This SNP is commonly

GWAS

- ✓ Η παθοφυσιολογία του συνδρόμου ευερέθιστου εντέρου (IBS) είναι περίπλοκη και εξακολουθεί να είναι ελάχιστα κατανοητή. Είναι γνωστό ότι υπάρχει κληρονομική συνιστώσα, αλλά οι προσπάθειες «κυνηγιού» γονιδίων δεν έχουν εντοπιστεί ακόμα το σαφή γενετικό τόπο κινδύνου για το IBS.

- ✓ Επτά γονιδιωματικές περιοχές, που φιλοξενούν 64 υποψήφια γονίδια έχουν εντοπιστεί. Η λειτουργική ανάλυση αυτών των γονιδίων έδειξαν τη ρύθμιση της δραστηριότητας των διαύλων ιόντων ως πιο πιθανή οδός που επηρεάζει τον κίνδυνο IBS.


PLPP3
DPH5 (5)
RBMS3
FHIT (2)
STK17A (13)
ASB4 (6)
FAM187B (31)
−log10 (p)
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Chromosome

Function	Gene	Polymorphism	Endophenotype	PMID
Neurotransmission				
Serotonin biosynthesis	Tryptophan hydroxylase (*TPH1* and *TPH2* isoforms)	rs4537731, rs211105, rs4570625	IBS-D, IBS-C	21073637, 24060757
Serotonin reuptake; Seretonin receptors	Serotonin reuptake transporter (*SERT* or *SLC6A4*); 5-HT receptor 3A (*HTR3A*)	5-HT transporter linked promoter region (5-HTT LPR) deletion; rs25531; rs1062613	IBS-C, IBS; IBS-D, symptom severity and anxiety	12135035, 15361494, 17040410, 17564628, 17074108, 17241856, 18511740, 19426812, 19125330; 19125330, 24069428, 24512255, 21420406.
Adrenergic receptors, Catecholamine metabolism	Adrenergic receptors alpha (*ADR2A*, *ADR2C*, *ADRA1D*), Catechol-o-methyl transferase (*COMT*)	alpha(2C) Del 322–325; alpha(2A) −1291; rs1556832, val158met	IBS-C, severity, alterations in brain regions, IBS	19833115, 26288143
Neuropeptide receptors	Neuropeptide S receptor1 (*NPSR1*)	rs2609234, rs6972158, rs1379928, rs1379928	colonic transit, pain and gas	21437260
Cannabinoid mechanisms	Cannabinoid receptor1, (*CNR1/CB1*), Fatty acid amide hydrolase (*FAAH*), Corticotropin-releasing hormone binding protein (*CRHBP*)	AAT repeat frequency, rs806378 C385A, rs10474485	IBS, abdominal pain, IBS-D, colonic motility, transit time, emotional abnormalities	19732772
Barrier function, Immune and Inflammatory Mediators				
Barrier function, adhesion	Toll-like receptor 9 (*TLR9*), Cadherein 1 (*CDH1*)	rs5743836	PI-IBS, epithelial cell barrier function	20044998
Cytokines	Interleukin (*IL*)-*6*, *IL-10*, Tumor necrosis factor-alpha (*TNFα*), *IL-8*, *TNFSF15*	rs1800870, rs1800872, rs6478108, rs6478109, rs7848647, rs4263839	PI-IBS, IBS, IBS-D, innate immune response	20044998; 22837345
Ion Channels and Bile acids				
	Voltage-gated sodium channel NaV 1.5 (*SCN5A*), G protein-coupled bile acid receptor 1 (*GPBAR1*), Klotho Beta (*KLB*)	rs11554825, rs17618244	IBS, colonic transit, fecal bile acid	20044998, 21752155, 16279907, 23595519, 12477767, 15765388, 20337945, 22158028, 24409078, 22684480, 21636646, 25824902

Table 1 *shows genetic changes associated with IBS and IBS endophenotypes. PMID, PubMed ID; IBS-D, IBS diarrhea subtype; IBS-C, IBS constipation subtype.*

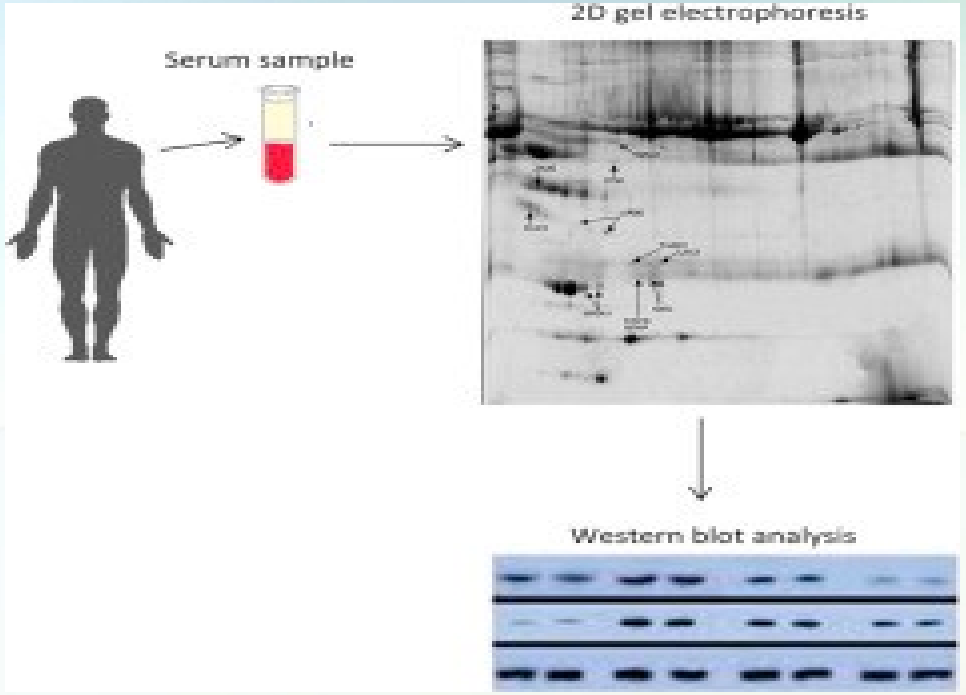
Front. Psychiatry , 14 August 2020

Sec. Psychological Therapy and Psychosomatics

Volume 11 - 2020 | https://doi.org/10.3389/fpsyt.2020.00805

Πρωτεομική

7a-Hydroxy-4-cholesten-3-one (7aHCO or 7aC4) (humans)	2-DE and HPLC-MS/MS	Overexpressed in IBS-D	Bile acid malabsorption
Gelsolin (GSN) (humans)	2-DE and LC-MS/MS	Overexpressed in high pain IBS groups	Homeostasis of GI function and inflammatory response
Trefoil factor 3 (TFF-3) (humans)	2-DE and LC-MS/MS	Overexpressed in all IBS groups	Homeostasis of GI function and inflammatory response
Histamine (humans)	2-DE and MALDI-TOF/MS	Eightfold downregulated in IBS patients after low FODMAP diet	Increases the number of gas-consuming bacteria
Dimethyl sulfide (humans)	2-DE and MS analysis of breath samples	Overexpressed in IBS	
1-Octene (humans)	2-DE and MS analysis of breath samples	Overexpressed in IBS	
3-Methylhexane (humans)	2-DE and MS analysis of breath samples	Overexpressed in IBS	
Benzene (humans)	2-DE and MS analysis of breath samples	Overexpressed in IBS	
Volatile organic metabolites (VOMs) (humans)	GC-MS	Differentiate IBS-D from active IBD	
Short-chain fatty acid cyclohexanecarboxylic acid (humans)	GC-MS	Associated with IBS-D	

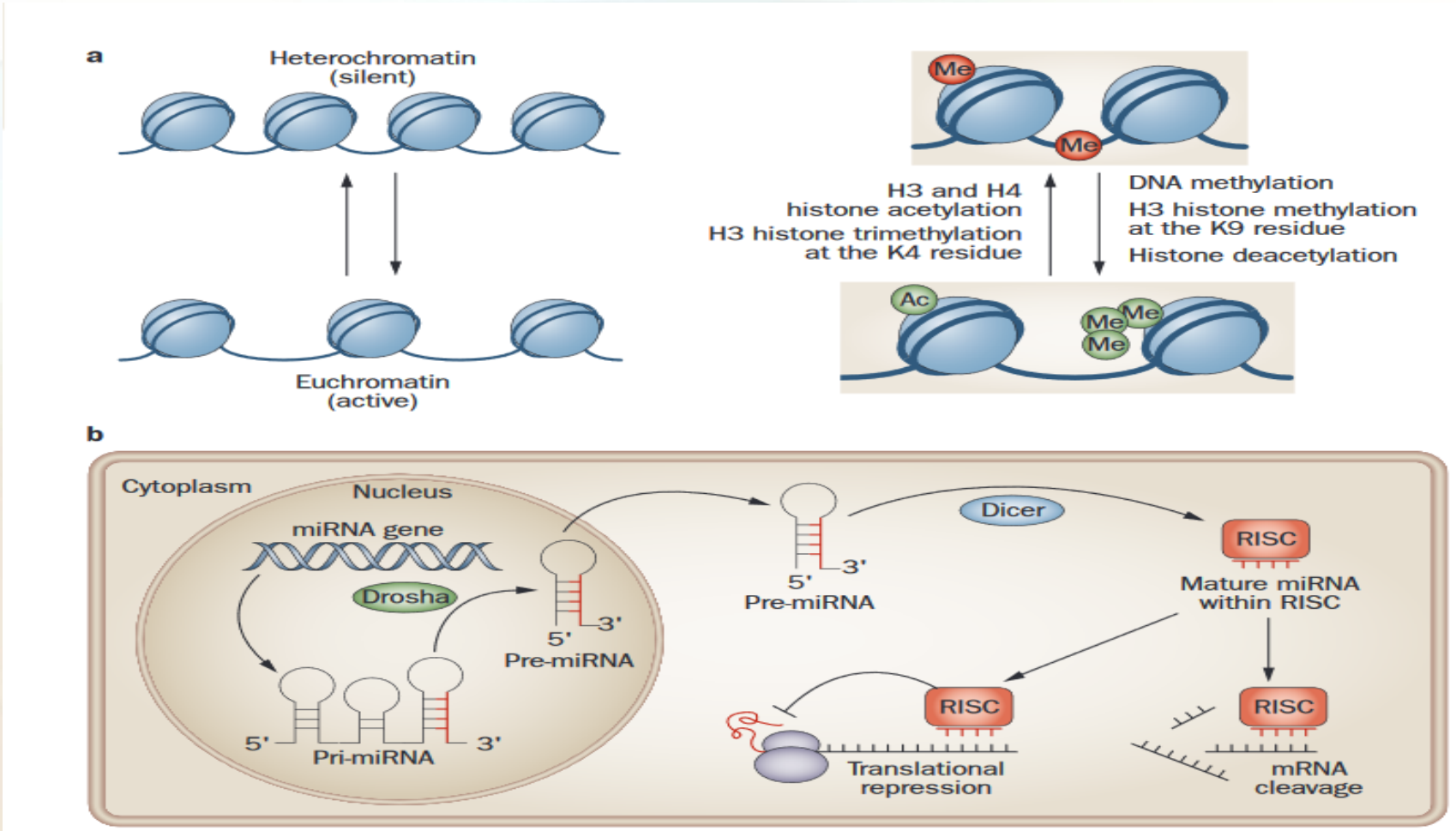


J Proteomics. 2018;188:167-172

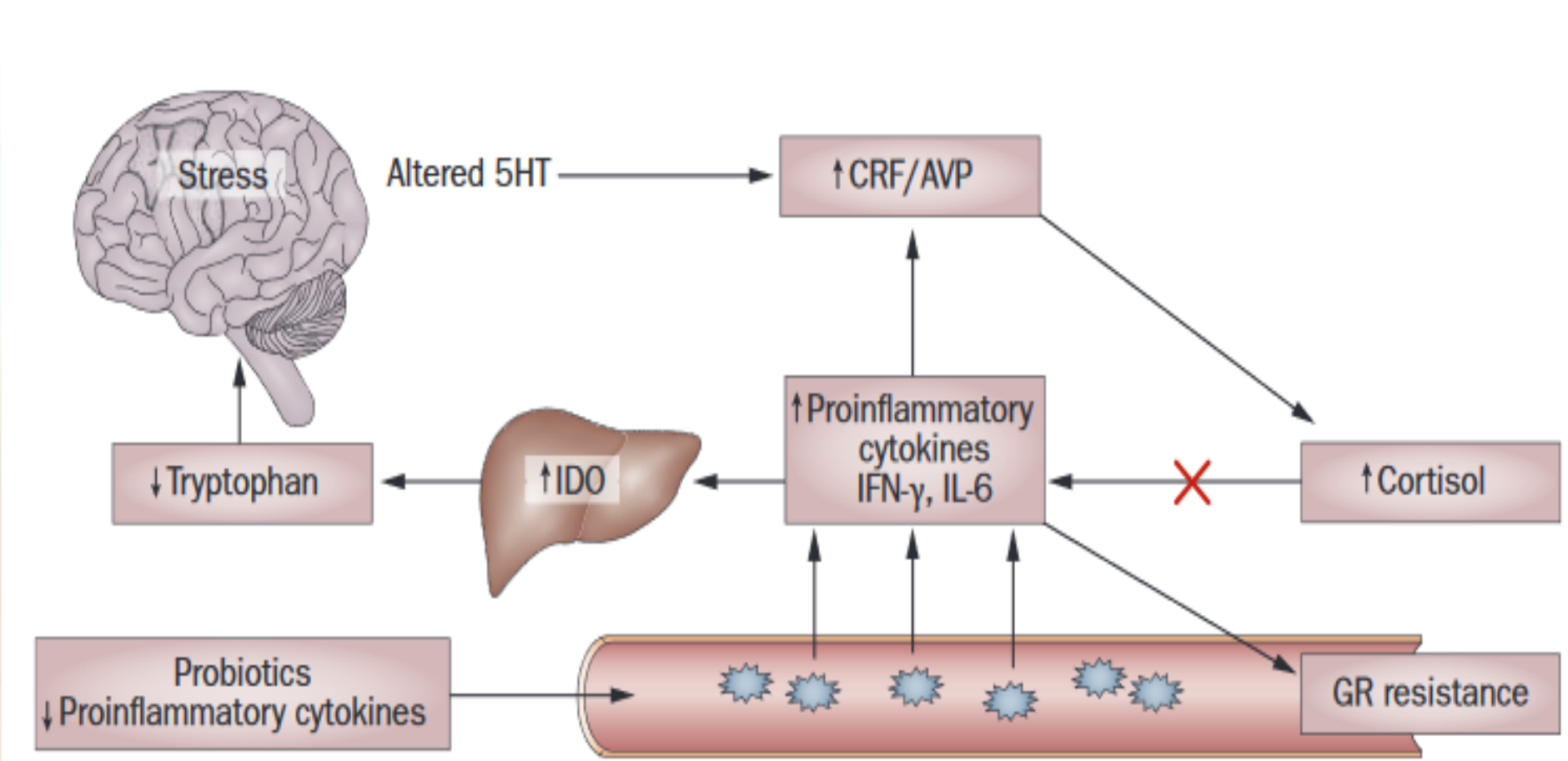
Protein name	Protein symbol	MW	pI	Mascot score	Coverage	Expression levels	
						IBS	Healthy
Ig kappa chain C region	IGKC_HUMAN	11,773.00	5.5	55	54	691.5 ± 72.8*	251.7 ± 61.8
Apolipoprotein E	APOE_HUMAN	36,246.00	5.5	152	47	1307.3 ± 208.4*	566.5 ± 204.3
Clusterin	CLUS_HUMAN	53,031.00	5.9	56	13	2212.5 ± 848.4*	703.4 ± 457.8
Serotransferrin	TRFE_HUMAN	79,294.00	7.0	158	28	2078.5 ± 580.7*	1153.7 ± 493.1
Beta-2-glycoprotein	APOH_HUMAN	39,584.00	9.5	93	26	196.5 ± 62.2*	18.1 ± 1.15
Collagen alpha-1 (XIV) chain	COEA1_HUMAN	194,478.00	5.0	51	4	187.8 ± 72.4*	53.1 ± 4.4
Retinol-binding protein 4	RET4_HUMAN	23,337.00	5.7	128	72	230.9 ± 32.2	1430.2 ± 131.4*
Ig lambda-3 chain C regions	LAC3_HUMAN	11,402.00	7.70	46	46	395.6 ± 70.1*	71.6 ± 31.1

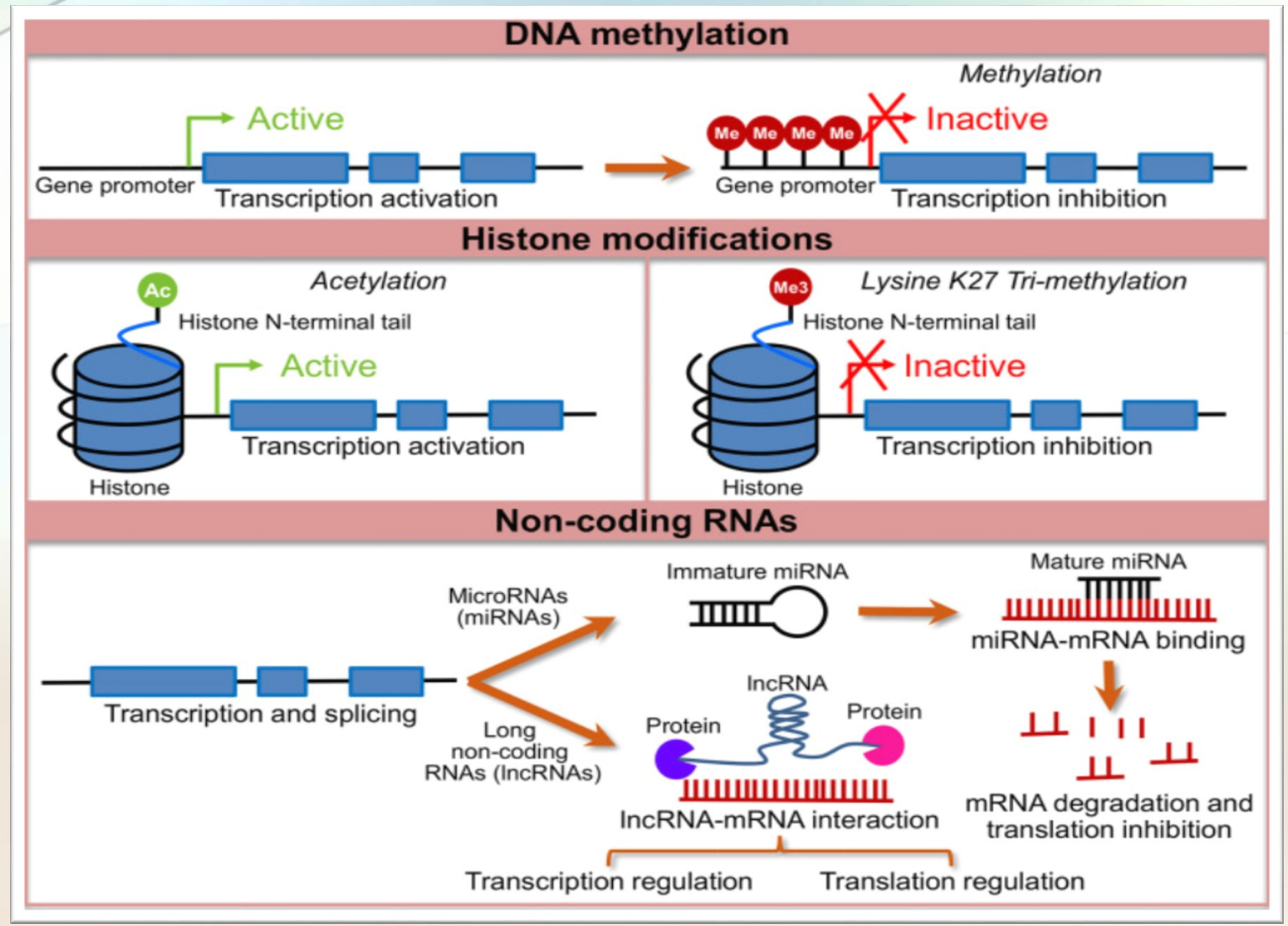
Επιγενετικές αναλύσεις

Nat Rev Gastroenterol Hepatol. 2010;7(8):465-71.



Epigenetic model of IBS




DNA methylation
Methylation
Active
Inactive
Me
Me
Me
Me
Gene promoter
Transcription activation
Gene promoter
Transcription inhibition
Histone modifications
Acetylation
Ac
Histone N-terminal tail
Active
Transcription activation
Histone
Lysine K27 Tri-methylation
Me3
Histone N-terminal tail
Inactive
Transcription inhibition
Histone
Non-coding RNAs
MicroRNAs
(miRNAs)
Immature miRNA
Mature miRNA
miRNA-mRNA binding
Transcription and splicing
Long
non-coding
RNAs (lncRNAs)
lncRNA
Protein
Protein
lncRNA-mRNA interaction
mRNA degradation and
translation inhibition
Transcription regulation
Translation regulation

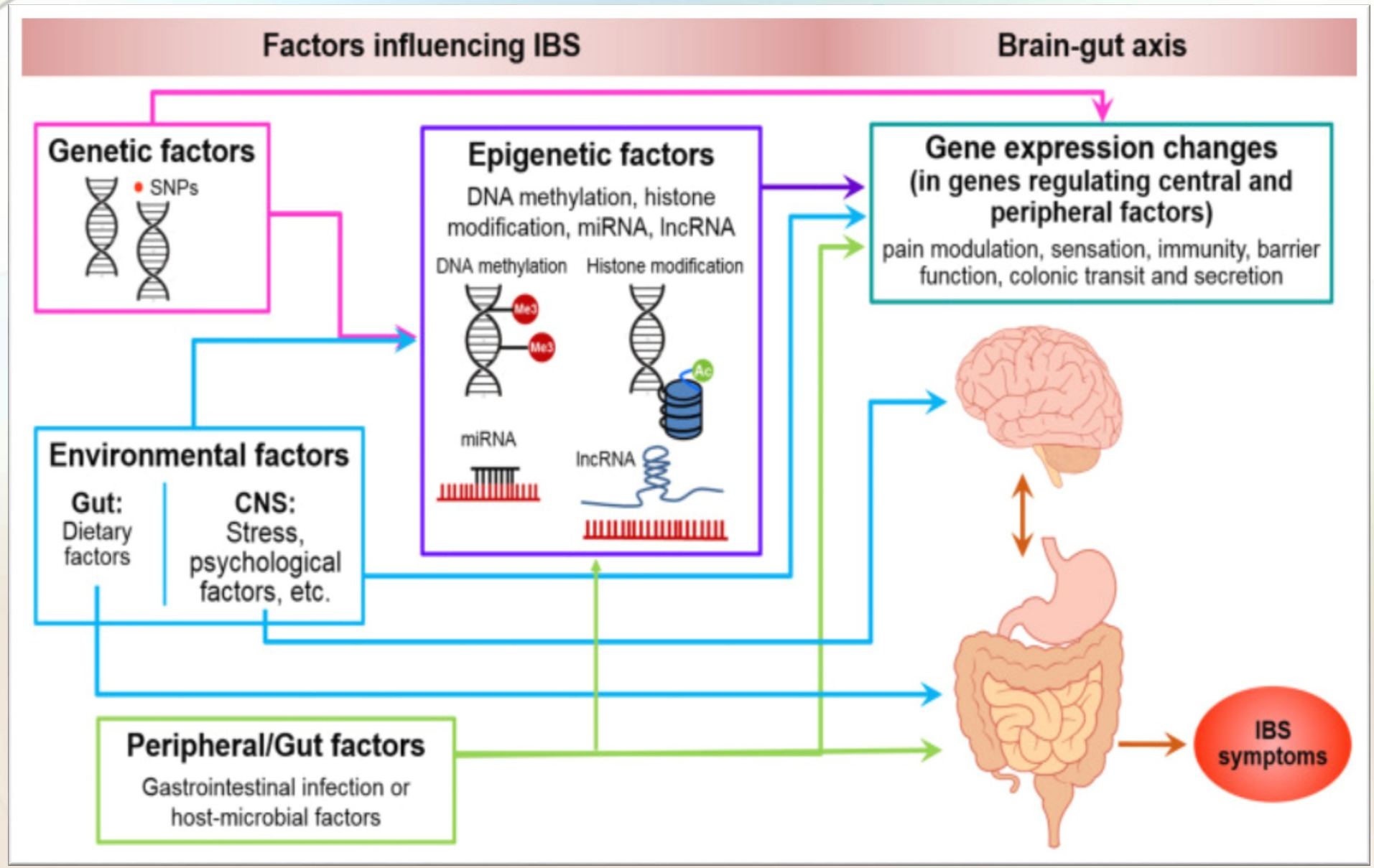

Factors influencing IBS
Brain-gut axis
Genetic factors
SNPs
Epigenetic factors
DNA methylation, histone modification, miRNA, lncRNA
DNA methylation
Histone modification
Me3
Me3
Ac
miRNA
lncRNA
Gene expression changes
(in genes regulating central and peripheral factors)
pain modulation, sensation, immunity, barrier function, colonic transit and secretion
Environmental factors
Gut:
Dietary factors
CNS:
Stress, psychological factors, etc.
Peripheral/Gut factors
Gastrointestinal infection or host-microbial factors
IBS symptoms

Table 2 Gene methylations involved in IBS mechanisms

Methylated Genes	Expression (↓ or ↑)	Regulation &/or observed function	Biomarkers analysed	Clinical condition and samples analysed (*n*); (human, cells and animal model); biological sources	Reference
Human studies					
SSPO, GSTM1, GSTM5, TPPP	↑	Association of *SSPO* methylation with high HADs and PSS scores	HAD and PSS scores	IBS-D (*n* 10), IBS-C (*n* 8), IBS-M (*n* 9), HC (*n* 23); whole blood (PBMCs)	[20]
ADCYAP1	↓				
AKAP12; PRKAR1B	↑				
Animal studies					
GR, CRF	GR↑, CRF↓	Increase visceral pain	VMR to CRD; GR, CFR expression	WAS rat model & HC; amygdala tissue	[137]
H3K9 methylation in the promoter region of claudin-1, ZOs, and occludin	↑	IL-6 promotes H3K9me2/me3, preventing GR transcriptional factors binding on the TJs genes promoter region; with the consequent increase in permeability and visceral pain	IL-6, GR, claudin-1, ZOs, occludin	WAS rat model & HC	[71]
GR (NC3R1), CNR1	↑	WAS increased DNMT1-mediated CNR1 methylation	VMR to CRD, GR, TRPV1, CNR1	WAS rat model & HC	[21]

CNR1 cannabinoid receptor 1, *COX2* cyclooxygenase-2, *CRD* colorectal distension, *CRF* corticotropin-releasing factor, *DNMT1* DNA methyltransferases 1, *GR* glucocorticoid receptor, *HC* healthy control, *IFNγ* interferon γ, *IL-1β* interleukin-1β *IL-6* interleukin-6, *IL-8* interleukin-8, *IkB* inhibitor of kB, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *PBMCs* peripheral blood mononuclear cells, *PSS* perceived stress scale, *VMR* visceromotor response, *WAS* water-avoidance stress

Functional category	Gene	Sample	IBS vs controls	Phenotype	PMID
DNA methylation					
Oxidative stress	Glutathione-S-transferases mu 5 (*GSTM5*)	PBMCs	Hyper-methylated	IBS-D	26670691
Neuronal genes	SCO-Spondin (*SSPO*)	PBMCs	Hyper-methylated	IBS; HAD[#] depression	26670691
	Tubulin polymerization promoting protein (*TPPP*)	PBMCs	Hyper-methylated	IBS-C	26670691
	SSX family member 2 interacting protein (*Ssx2ip*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Par-3 family cell polarity regulator (*Pard3*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Vinculin (*Vcl*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Glucocorticoid receptor (*Nr3c1*)	MS Amygdala/DRG[%] neurons in WAS[$]	Hyper-methylated	Visceral hypersensitivity	25263804; 23084728
	Corticotropin-releasing factor (*Crf*)	Amygdala/DRG neurons in WAS[$]	Hypo-methylated	Visceral hypersensitivity	23084728
	Cannabinoid receptor 1(*Cnr1*)	DRG[%] neurons in WAS[$]	Hyper-methylated	Visceral hypersensitivity	25263804
Histone modifications					
Neuronal genes	Transient receptor potential cation channel subfamily V member 1 (*Trpv1*)	DRG[%] neurons in WAS[$]	Increased histone (H3) acetylation	Visceral hypersensitivity	25263804
	Brain derived neurotrophic factor (*Bdnf*)	Neonatal inflammation	histone acetylene transferase (HAT)	Visceral sensitivity	28439935
Calcium channels	*Cacna1c*	Neonatal inflammation	Reduced interaction with histone deacetylase 3 (HDAC3)	Altered motility and diarrhea	23886858

Table 2A shows epigenetic changes, including DNA methylation and histone modifications associated with IBS or IBS models. [#]HAD, hospital anxiety depression scale; PMID, PubMed ID; [$]WAS, water avoidance stress; [%]DRG, dorsal root ganglia; IBS-D, IBS diarrhea subtype; IBS-C, IBS constipation subtype; Hyper-methylation, increased methylation; Hypo-methylation, decreased methylation.

Functional category	Gene	Sample	IBS vs controls	Phenotype	PMID
DNA methylation					
Oxidative stress	Glutathione-S-transferases mu 5 (*GSTM5*)	PBMCs	Hyper-methylated	IBS-D	26670691
Neuronal genes	SCO-Spondin (*SSPO*)	PBMCs	Hyper-methylated	IBS; HAD[#] depression	26670691
	Tubulin polymerization promoting protein (*TPPP*)	PBMCs	Hyper-methylated	IBS-C	26670691
	SSX family member 2 interacting protein (*Ssx2ip*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Par-3 family cell polarity regulator (*Pard3*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Vinculin (*Vcl*)	Colon of WAS[$]	Hyper-methylated	Visceral hypersensitivity	30106160
	Glucocorticoid receptor (*Nr3c1*)	MS Amygdala/ DRG[%]neurons in WAS[$]	Hyper-methylated	Visceral hypersensitivity	25263804; 23084728
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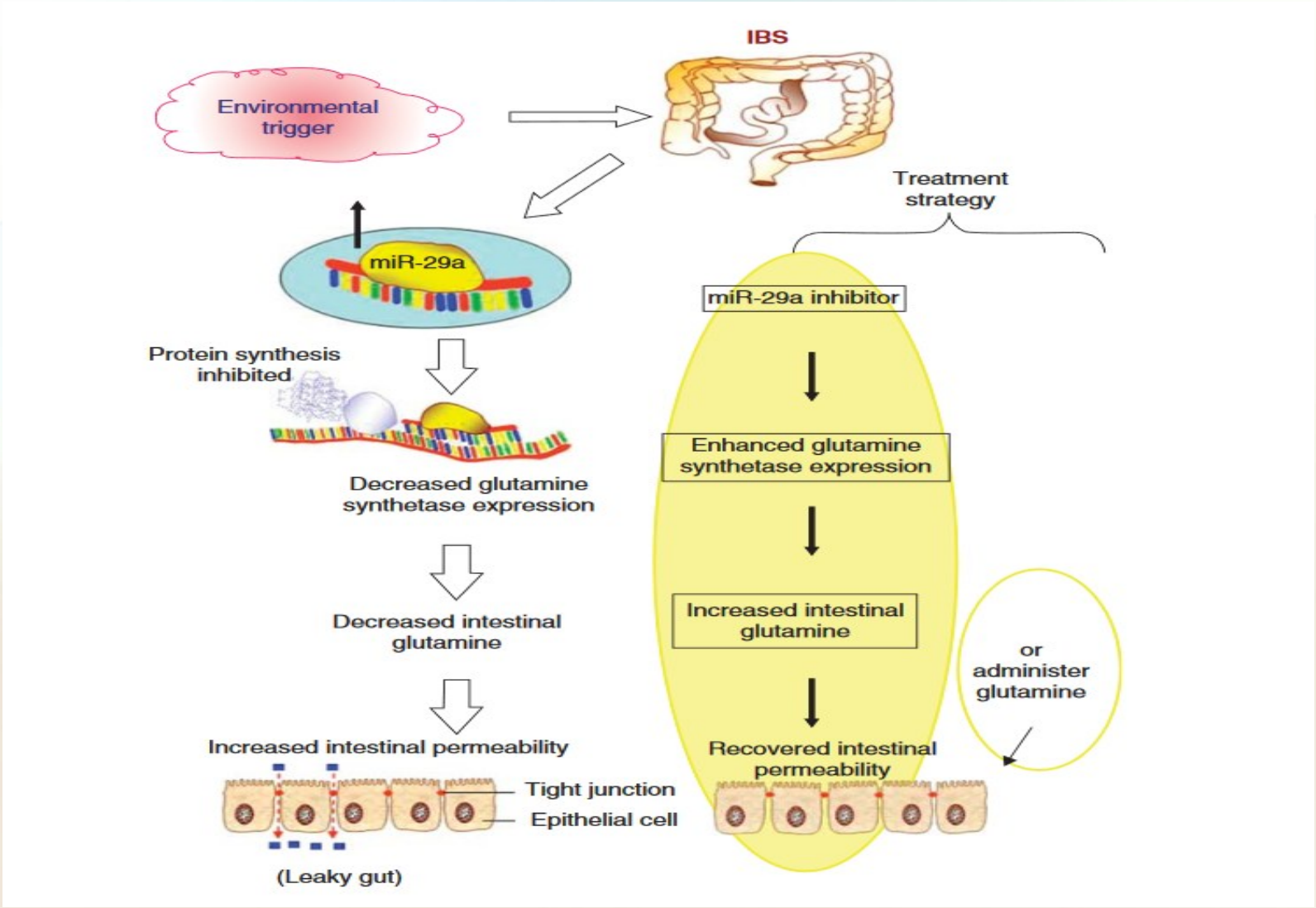
Calcium channels	*Cacna1c*	Neonatal inflammation	Reduced interaction with histone deacetylase 3 (HDAC3)	Altered motility and diarrhea	23886858

miRNAs



Expert Opin. Biol. Ther. (2011)11(8):991-995

Micro RNA	Target	Population studied	Results	Suggested mechanism	Potential clinical applicability
miRNA-24	Serotonin reuptake transporter (SERT)	10 IBS patients and 10 healthy patients; IBS mouse model	miRNA-24 upregulated in IBS patients and intestinal mucosa of mice	miRNA-24 inhibits SERT expression and aggravates IBS	miRNA-24 inhibitor
miRNA-29	NFKB-repressing factor(NKRF) and claudin-1 genes	183 IBS and 36 HC	Increased levels of miRNA-29 and reduced levels of NKRF and claudin-1 in patients with IBS-D	miRNA-29 targets and reduces claudins and NKRF, which increases intestinal permeability	miRNA-29 inhibitors for IBS with increased permeability
		Mir 29 knock-out mice	Decreased intestinal hyperpermeability in Mir-29 knockout mice		
	Glutamine synthetase gene *GLUL*	19 IBS-D and 10 HC	Increased miRNA-29a in IBS-D patients with increased intestinal permeability (42% of IBS-D patients)	miRNA-29a increases membrane permeability by decreasing GLUL gene expression and glutamine level	miRNA-29 inhibitor and glutamine for IBS with increased intestinal permeability
miRNA-150 and miRNA-342-3p	Multiple targets including telomerase-related proteins dyskerin, and prosurvival protein kinase AKT2	5 IBS-D, 5 IBS-C, 2 IBS-M, and 31 HC	Increased level of miRNA-150 and miRNA-342-3p in IBS	Inflammatory, pain, and motility pathways	Possible role as biomarkers
miRNA-199	Transient receptor potential vanilloid type 1 (TRPV1) signaling	45 IBS-D and 40 HC	Decreased colonic miRNA-199 correlates with visceral pain in patients with IBS-D	miRNA-199a decreases visceral pain via inhibition of TRPV1 signaling	miRNA-199 precursors for pain in IBS
		Visceral hypersensitivity rat models	Reduced miRNA-199a in rat DRG and colon tissue associated with visceral hypersensitivity		
miRNA-510	5-HT_3 receptor type 3 subunit gene HTR3E	98 IBS-D, 99 IBS-C and 100 HC (UK); 119 IBS-D and 195 HC (Germany)	*HTR3E* variant c. *76G>A, associated with female IBS-D	Variant of HTR3E reduces binding and inhibitory effect of miRNA-510, thus increasing expression of 5-HT3E protein in IBS-D	Unclear clinical impact of miRNA-510 in IBS

HC, healthy controls; NFKB, Nuclear factor-κB; NKRF, NFKB- repressing factor; DRG, Dorsal root ganglia.

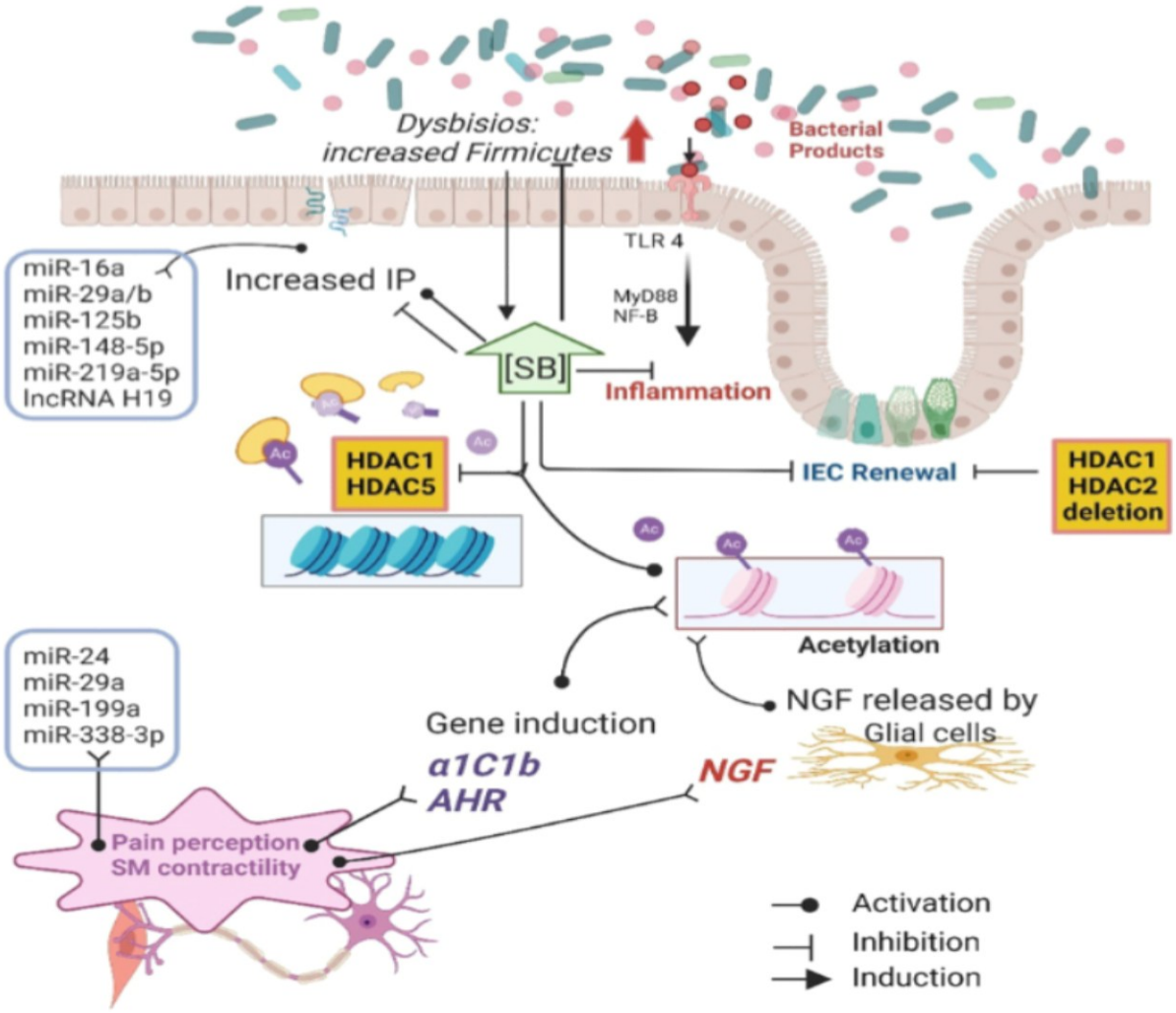


Fig. 1 Epigenetic factors involved in gut–brain axis dysregulation – Histone acetylation and miRNA expression triggering biomolecular pathways involved in IBS. The underlying hypothesis envisages miRNA such as miR-24 and miR-29a having a direct involvement in pain perception and increased IP. An akin effect is induced by SB, a great HDAC inhibitor, produced at high levels by *Firmicutes*. In contrast, high SB levels were shown to restore IP and dysbiosis. Increased histone acetylation elicits NGF production by enteric glial cells resulting in higher SM contractility and pain perception. High SB levels reduce TLR4-mediated inflammation and, allegedly by a dose-dependent mechanism, both impair and restore intestinal permeability. *AHR* aromatic hydrocarbon receptor, *IEC* intestinal epithelial cells, *NGF* nerve growth factor, *SB* sodium butyrate, *VIP* vasoactive intestinal protein

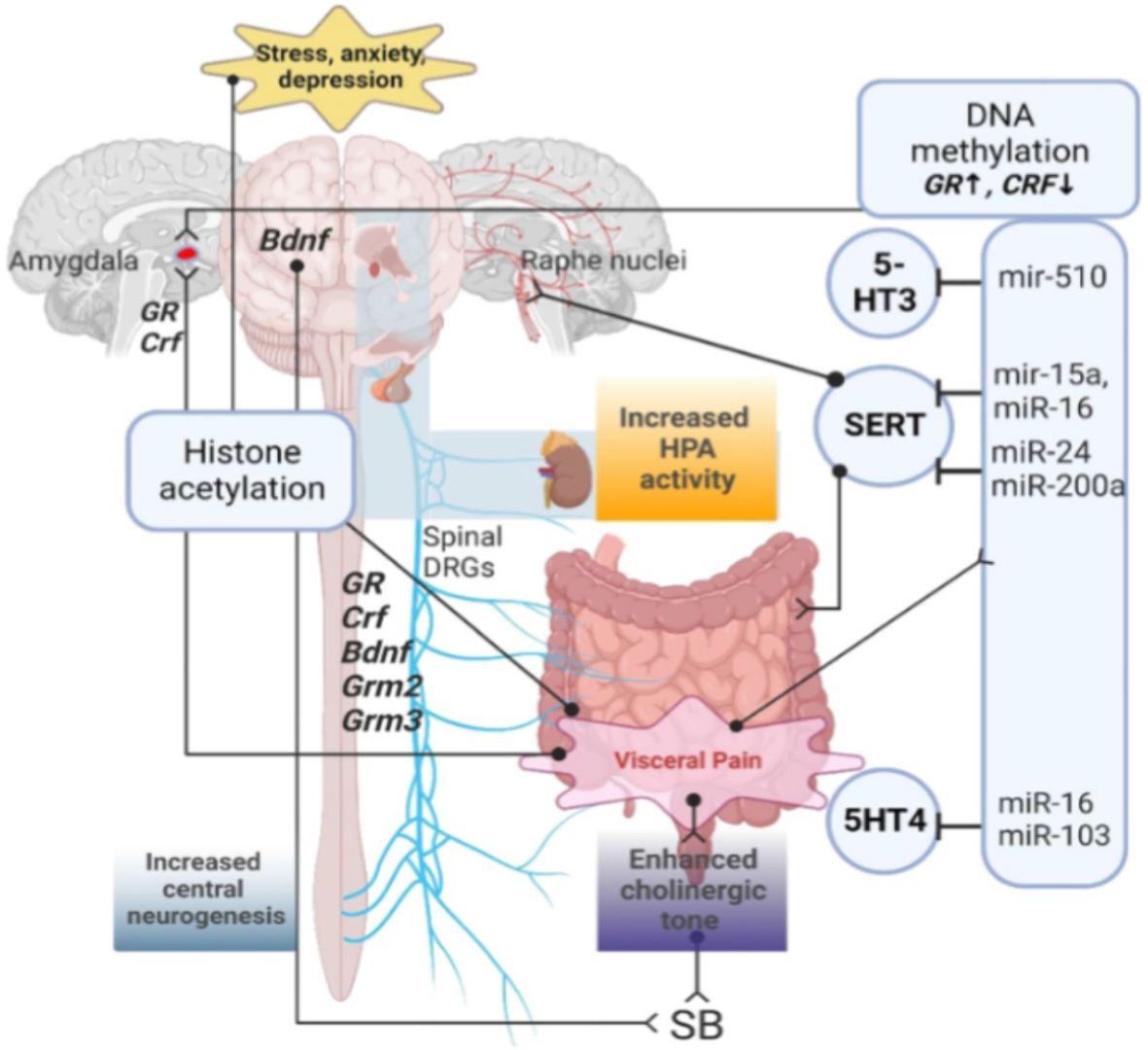


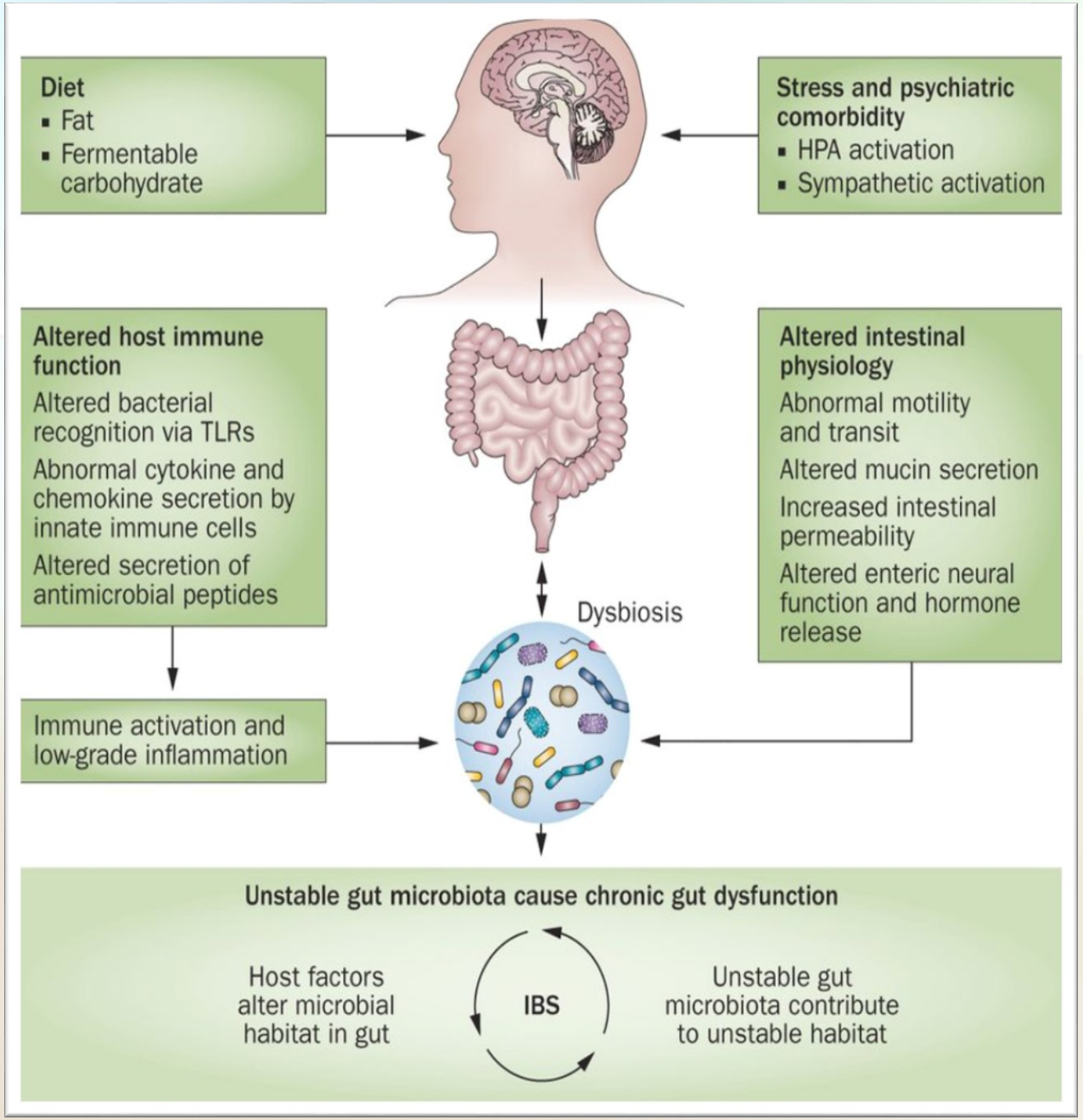
Fig. 2 Epigenetic factors involved in brain-gut axis dysregulation. The scheme reports gene acetylation and miRNAs evoking visceral pain by interacting with key players of serotonergic (i.e., 5-HT3, 5-HT4, SERT), cholinergic, HPA response, and neurogenesis. *SERT* serotonin transporter, *SB* sodium butyrate, *GR* glucocorticoid receptor, *CRF* corticotropin-releasing factor, *BDNF* brain-derived neurotrophic factor, *GRM* glutamate receptor genes

Μικροβίωμα

F1000Res. 2018; 7: F1000 Faculty Rev-1029

Studies demonstrating gut microbiota in subjects diagnosed with IBS in comparison to normal healthy subjects with no IBS type symptoms.

Microorganisms	Quantity	Study
Bifidobacteria	Decreased	Si et al., Rajilić-Stojanović et al. Kerckhoffs et al.
Bacteroidetes	Increased	Rangel et al., Carroll et al.
	Decreased	Jeffery et al. Krogius-Kurikka et al.
Actenobacteria	Decreased	Krogius-Kurikka et al.
Lactobacillus	Increased	Tana et al., Carroll et al.
	Decreased	Malinen et al., Chassard et al.
Aerobicbacteria	Decreased	Carroll et al.
Faecalibacterium spp	Decreased	Rajilić-Stojanović et al.
Coliformis	Decreased	Balsari et al.
Enterobacteriaceae	Increased	Si et al, Carroll et al. Chassard et al.
Clostridium coccoides	Increased	Swidsinski et al.
Proteobacteria	Increased	Carroll et al. Krogius-Kurikka et al.
Veillonella	Increased	Tana et al.
Ruminococcus torques/bromii	Increased	Rajilić-Stojanović et al. Lyra et al.
Firmicutes	Increased	Jeffery et al., Sundin et al.
Aerobes	Increased	Mättö et al.
Eubacteriumrectable	Increased	Swidsinski et al.
Pseudomonas aeruginosa	Increased	Kerckhoffs et al.
Dorea	Increased	Rajilić-Stojanović et al.


Diet
▪ Fat
▪ Fermentable carbohydrate
Stress and psychiatric comorbidity
▪ HPA activation
▪ Sympathetic activation
Altered host immune function
Altered bacterial recognition via TLRs
Abnormal cytokine and chemokine secretion by innate immune cells
Altered secretion of antimicrobial peptides
Altered intestinal physiology
Abnormal motility and transit
Altered mucin secretion
Increased intestinal permeability
Altered enteric neural function and hormone release
Dysbiosis
Immune activation and low-grade inflammation
Unstable gut microbiota cause chronic gut dysfunction
Host factors alter microbial habitat in gut
IBS
Unstable gut microbiota contribute to unstable habitat

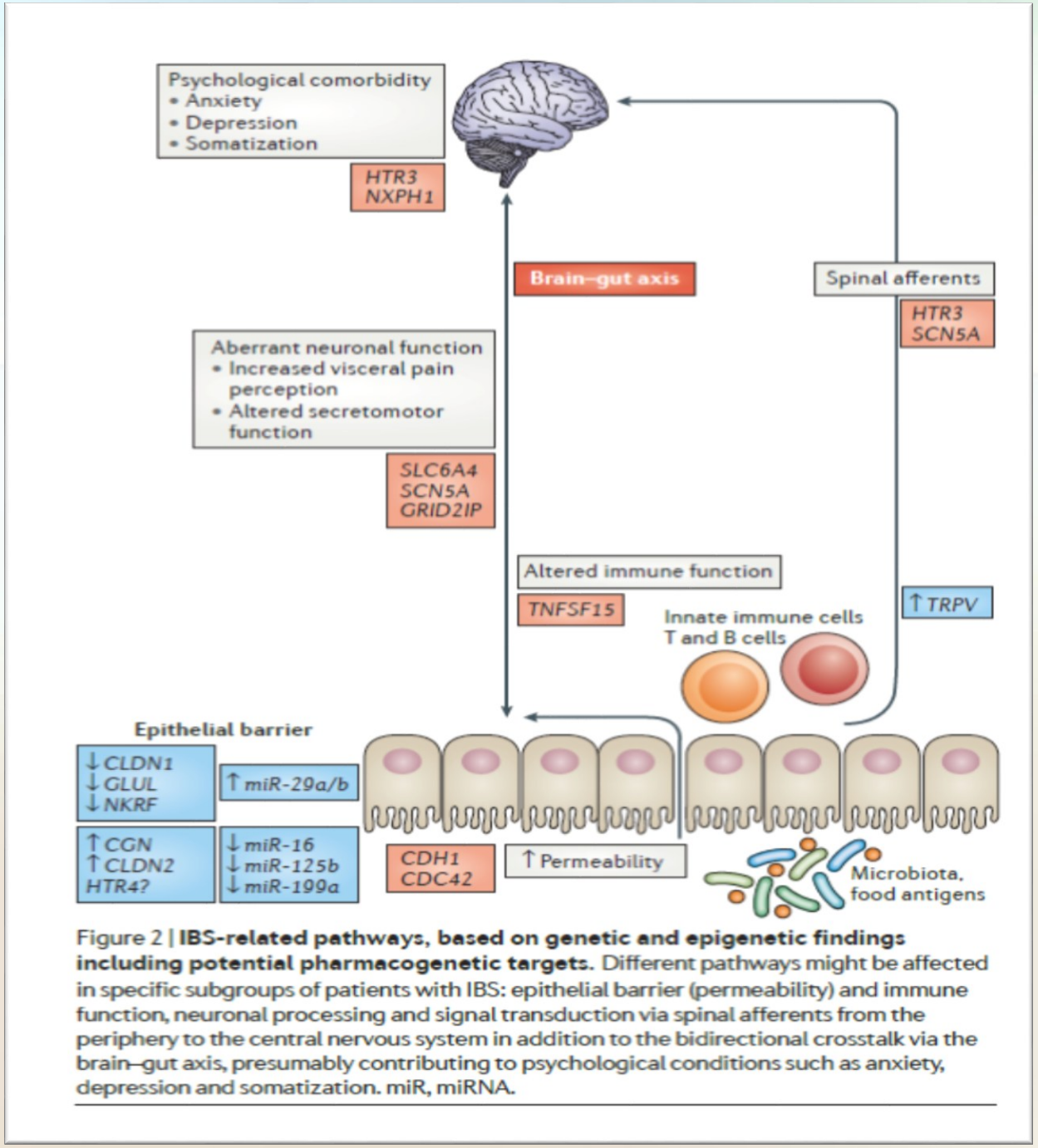
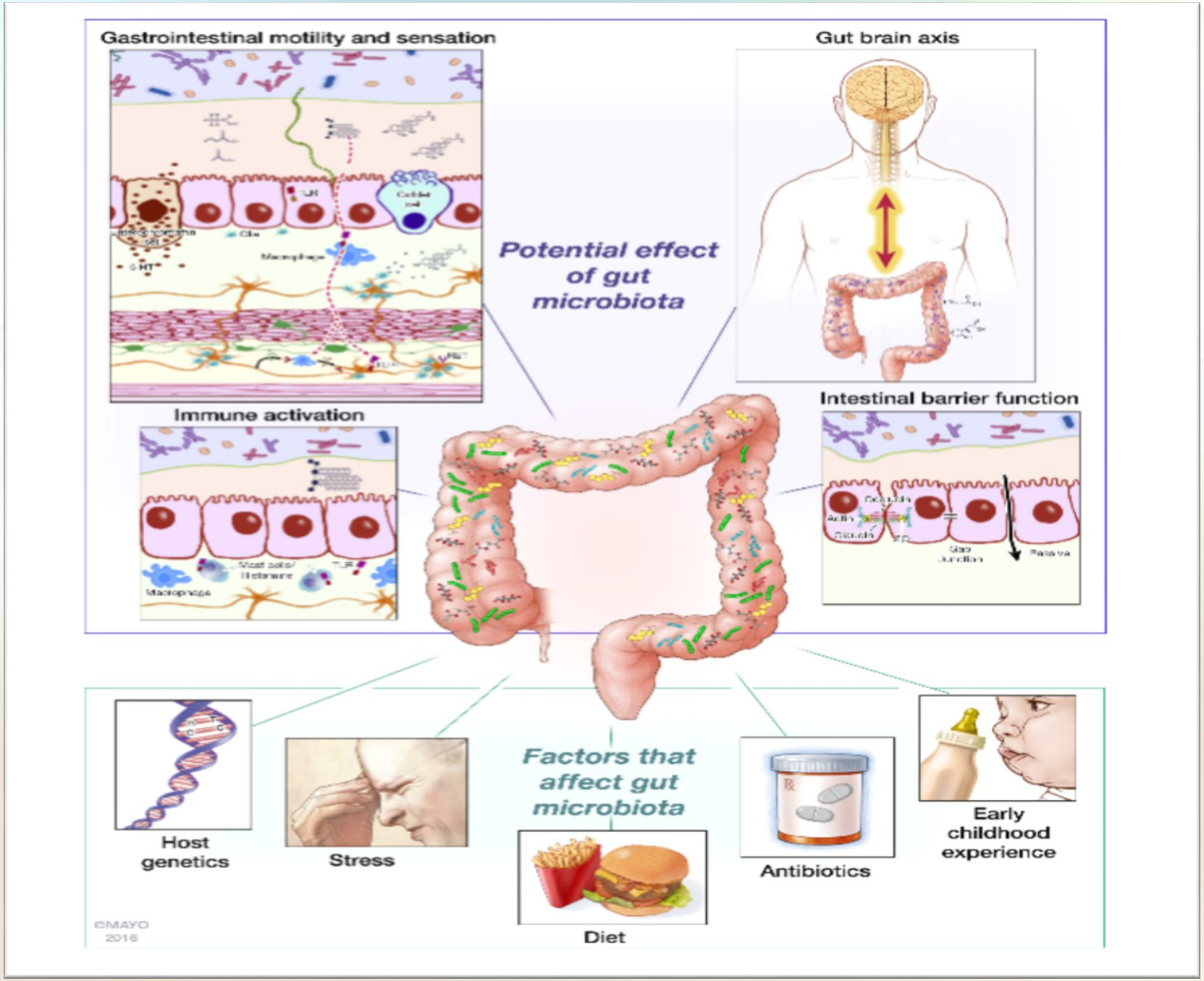
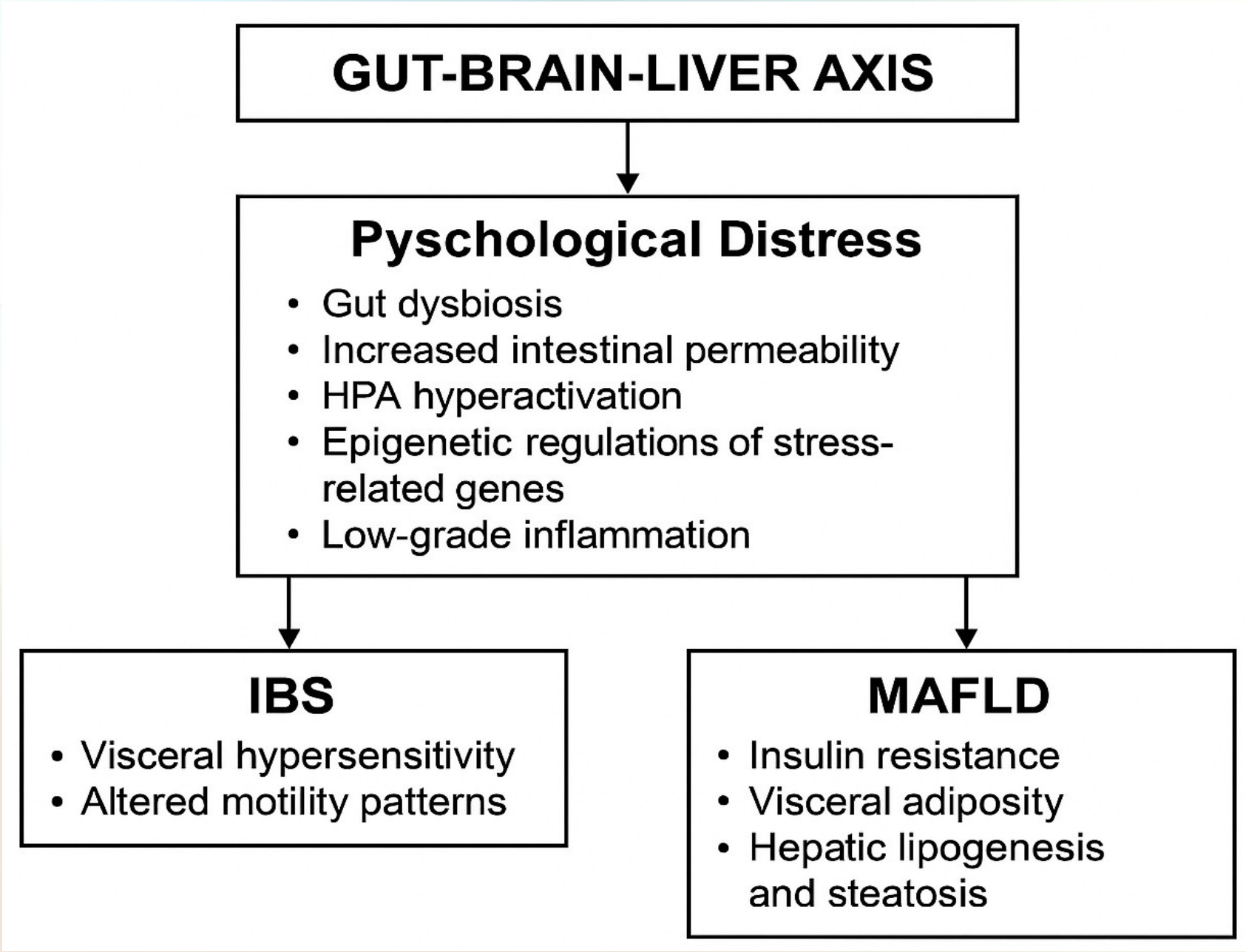


Figure 2 | **IBS-related pathways, based on genetic and epigenetic findings including potential pharmacogenetic targets.** Different pathways might be affected in specific subgroups of patients with IBS: epithelial barrier (permeability) and immune function, neuronal processing and signal transduction via spinal afferents from the periphery to the central nervous system in addition to the bidirectional crosstalk via the brain–gut axis, presumably contributing to psychological conditions such as anxiety, depression and somatization. miR, miRNA.



Am J Physiol Gastrointest Liver Physiol312: G52–G62, 2017


GUT-BRAIN-LIVER AXIS
Pyschological Distress
• Gut dysbiosis
• Increased intestinal permeability
• HPA hyperactivation
• Epigenetic regulations of stress-related genes
• Low-grade inflammation
IBS
• Visceral hypersensitivity
• Altered motility patterns
MAFLD
• Insulin resistance
• Visceral adiposity
• Hepatic lipogenesis and steatosis

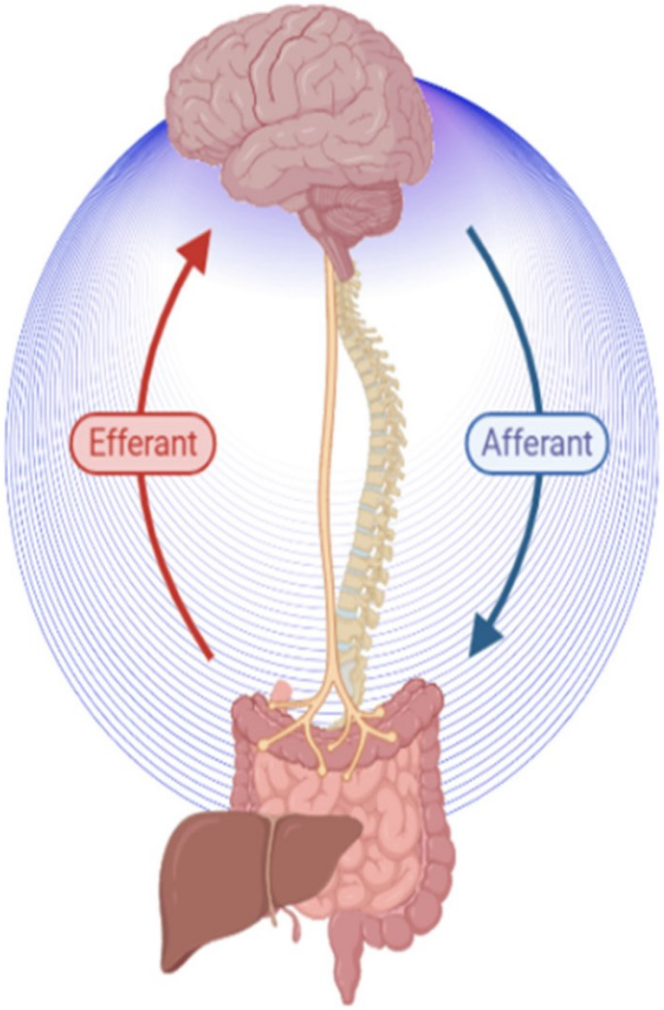
GUT-LIVER-BRAIN AXIS

IBS

Visceral hypersensitivity
Altered motility patterns
Persistent gut–brain signaling abnormalities

NAFLD

Insulin resistance
Visceral adiposity
Hepatic lipogenesis and steatosis
Kupffer cell activation



Common Pathways

Chronic psychological distress (e.g., anxiety, early life trauma)
HPA axis hyperactivation → CRH, ACTH, cortisol
Serotonin alterations
ANS dysregulation (↓ vagal tone)
Altered serotonin signaling
Epigenetic regulation of stress-related genes (e.g., FKBP5, NR3C1)

Low-grade systemic inflammation

↑ IL-6, IL-1β, TNF-α, CRP
TLR4 activation

Microbial dysbiosis

↓ Short-chain fatty acids (SCFAs)
↑Intestinal permeability/LPS translocation
→ systemic & hepatic inflammation
↑ LPS translocation

Livers **2025**, *5*(3), 43; https://doi.org/10.3390/livers5030043

Διατροφή

- **FODMAP** ="Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols

Oligosaccharides: fructans and galactooligosaccharides (GOS)

Disaccharides: lactose

Monosaccharides: fructose

Polyols: sorbitol and mannitol

low FODMAP diet improves IBS symptoms

Diet & IBS

- Relationship between diet and abdominal symptoms is well recognized
- From the patient's perspective, the most frequently perceived cause for symptoms is food intolerance
- Up to 50% of patient's with IBS symptoms worsen after a meal
- 60% of patients with IBS believe they have a food allergy

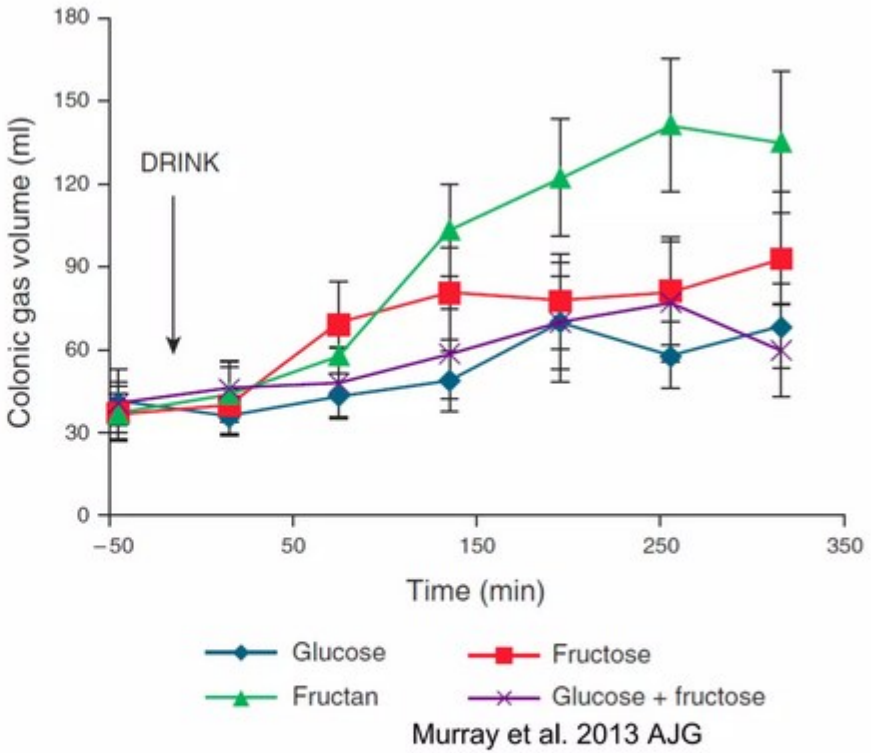
Lea et al. Gastroenterol Clin North Am 2005;34:247-55

FOODS THAT MAY *TRIGGER* IBS SYMPTOMS

- Apples 
- Beans
- Broccoli 
- Cabbage
- Caffeine
- Cauliflower
- Gum, beverages, or foods sweetened w. fructose or sorbitol
- Chocolate 
- Dairy products 
- Fatty foods
- Margarine
- Nuts 
- Orange & grapefruit juices 
- Wheat products

Mechanism of action of FODMAP

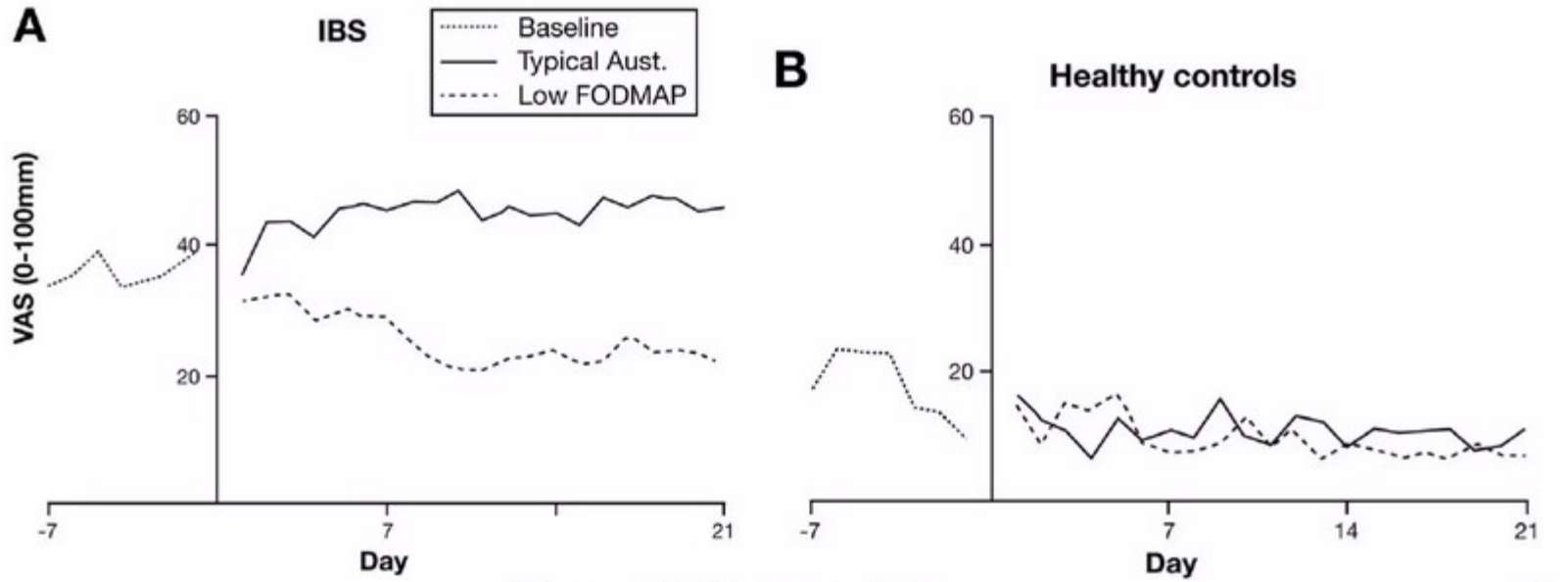
FODMAPs can increase fermentation in the colon leading to increased gas production



Murray et al. 2013 AJG

Other mechanisms of action have been proposed, but require more robust scientific evaluation

- Symptoms improved in patients with IBS
- No difference for healthy controls



Halmos et al. 2014 Gastroenterology

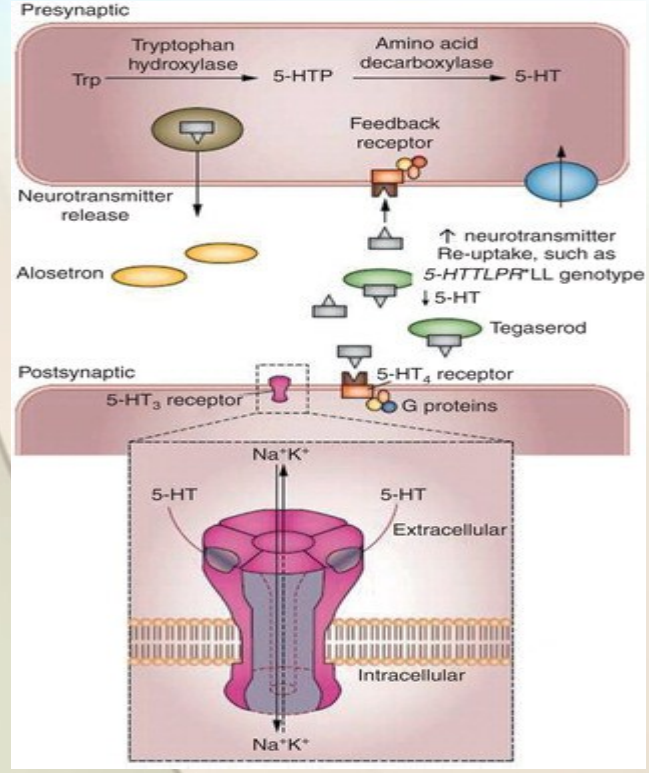
Potential long-term safety concerns

Dietary modifications have potential to:

- Reduce nutritional adequacy / food variety
  - Data-to-date suggests nutritional adequacy is largely maintained
- Reduce quality-of-life
  - Studies to date have shown improvement in quality-of-life
- Alter the microbiota
  - Studies have shown alterations in the microbiota, with some reductions in fecal *Bifidobacteria* noted, but the implications of this are not fully understood

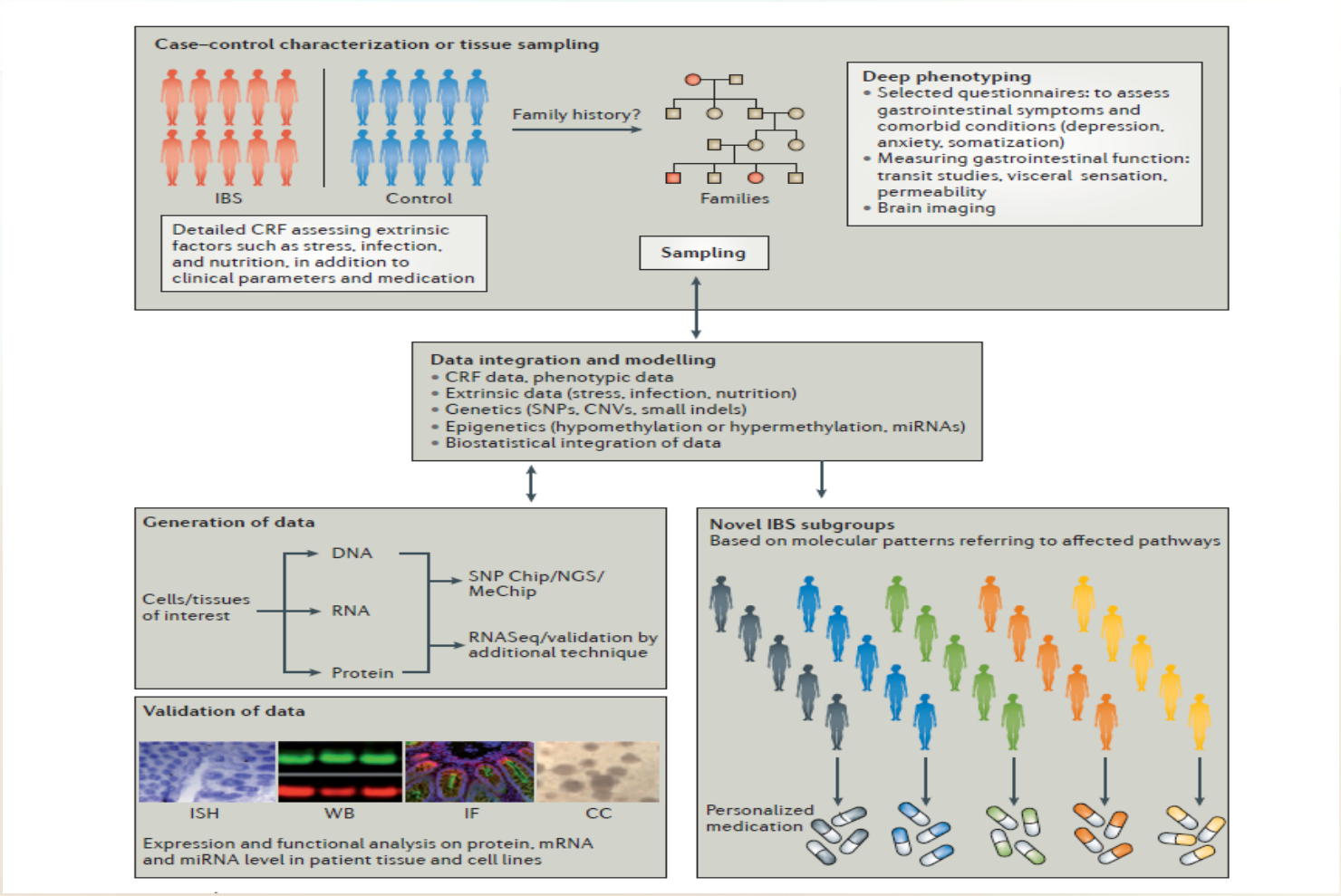
Φαρμακογονιδιωματική

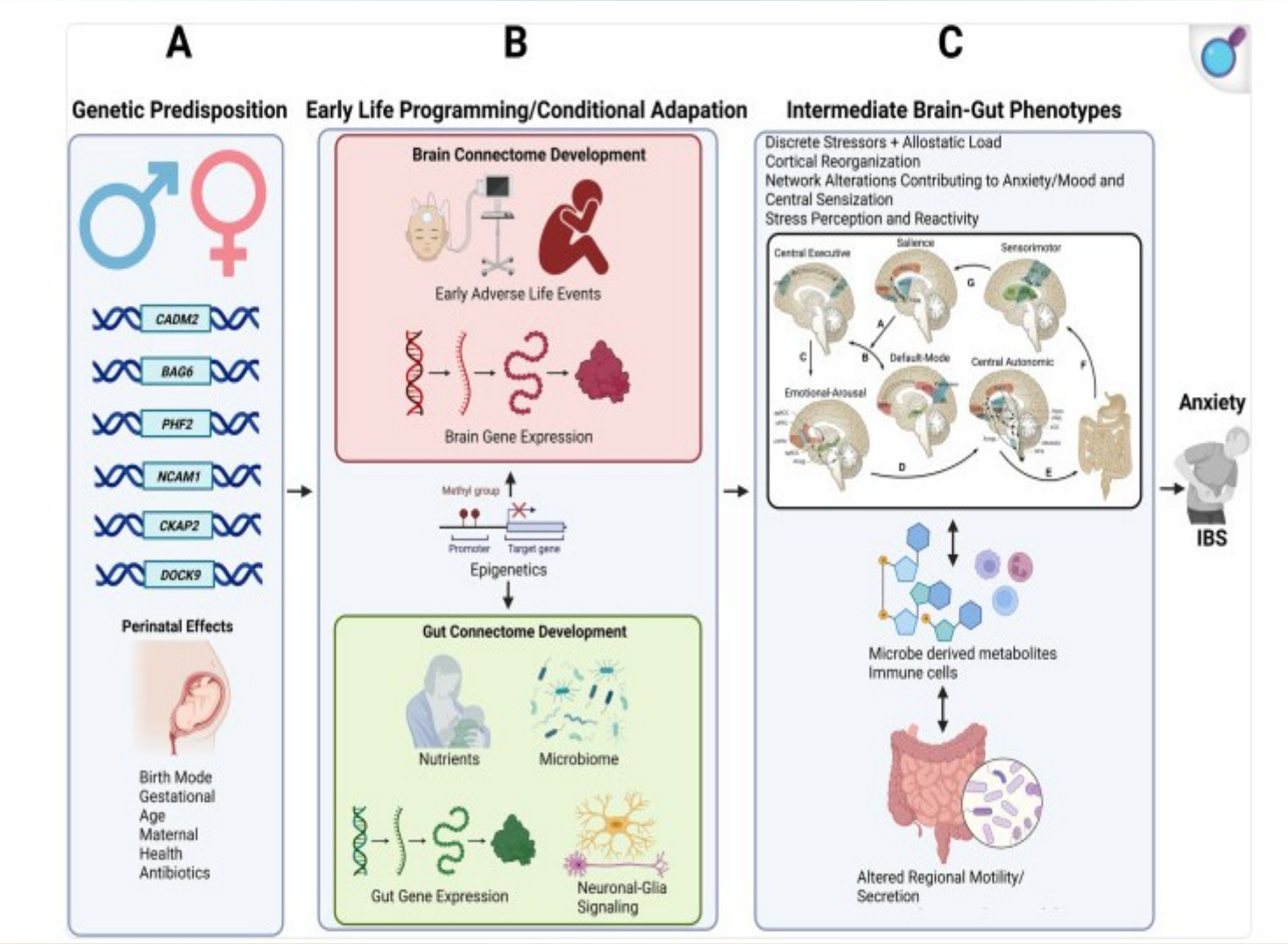
- Genetic variations in drug metabolism, polymorphisms at CYP2D6 affects tricyclic antidepressants and selective serotonin-reuptake inhibitors



5-HTTLPR LL are also less responsive to the 5-HT4 agonist, tegaserod

Future approach in IBS genetics or epigenetics research





Mol Psychiatry. 2023 Feb 2;28(4):1451–1465. doi: 10.1038/s41380-023-01972-w