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Single Nucleotide Polymorphisms, Associated with Increased Risk of Irritable Bowel Syndrome with Predominant Constipation: A Meta Analysis

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Introduction. Genetic predisposition in combination with environmental factors and the patient's psychological and emotional state play a key role in the development of irritable bowel syndrome (IBS). Studies of association between genetic polymorphisms and IBS can help in understanding the key pathophysiological mechanisms. To date, 11 meta-analyses on this issue have been published, however, none of them comprehensively summarize the data on the prevalence of genetic polymorphisms in IBS with predominant constipation (IBS-C).
Aim: to summarize the published data on the impact of genetic polymorphisms on the risk of IBS-C.
Materials and methods. A literature search was performed in the PubMed and Scopus databases. Identified studies were used for a meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Publications investigating genetic polymorphisms in patients with IBS-C were included in this analysis.
Results. A total of 34 studies met the inclusion criteria. The collected data were sufficient to conduct a meta-analysis on polymorphisms of three of the listed genes: *SLC6A4* (10 articles), *GNB3* (5 articles), *ADRA2A* (4 articles). No significant association was found between the *SLC6A4* (5-HTTLPR) polymorphism, *GNB3* c.825C > T (rs5443) polymorphism and either IBS or IBS-C. It was found that *ADRA2A* 1291C>G polymorphism was significantly associated with both IBS and IBS-C.
Conclusions. Our meta-analysis revealed that *ADRA2A* 1291C>G polymorphism was significantly associated with both IBS and IBS-C in the mixed population. Neither homozygous nor heterozygous variants of the *SLC6A4* (5-HTTLPR) polymorphism and *GNB3* C825T polymorphism were associated with either IBS-C or IBS as a whole.
Keywords: genetic susceptibility, genetic polymorphisms, constipation, irritable bowel syndrome, 5-HTTLPR polymorphism
Conflict of interest: the authors declare no conflict of interest.

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Однонуклеотидные полиморфизмы, ассоциированные с повышенным риском развития синдрома раздраженного кишечника с преобладанием запора: метаанализ

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Введение. Сочетание генетической предрасположенности с факторами окружающей среды и психоэмоциональным состоянием пациента играет ключевую роль в развитии синдрома раздраженного кишечника (СРК). Изучение ассоциации полиморфизмов генов с СРК может помочь в понимании доминирующих патофизиологических механизмов. На сегодня по данной теме опубликовано 11 метаанализов, однако среди них нет ни одного, который исчерпывающе обобщил бы данные о распространенности генетических полиморфизмов среди пациентов с СРК с преобладанием запора (СРК-З).
Цель: обобщение опубликованных данных о влиянии полиморфизмов генов на риск развития СРК-З.
Материалы и методы. Поиск литературы проводился в электронных базах PubMed и Scopus. На основе найденных исследований проводился метаанализ в соответствии с международными рекомендациями «Предпочитаемые элементы отчетности для систематических обзоров и метаанализов» (Preferred Reporting

Items for Systematic Reviews and Meta-Analyses, PRISMA). В анализ включались работы, в которых изучалась ассоциация генетических полиморфизмов у пациентов, страдающих СРК-З.
Результаты. Критериям включения соответствовали 34 исследования. Полученных данных оказалось достаточно для проведения метаанализа по полиморфизмам трех из перечисленных генов: *SLC6A4* (10 статей), *GNB3* (5 статей), *ADRA2A* (4 статьи). Не было выявлено статистически значимой ассоциации полиморфизма 5-HTTLPR гена *SLC6A4* и полиморфизма C825T (rs5443) гена *GNB3* как с СРК, так и с СРК-З. Была выявлена статистически значимая ассоциация полиморфизма 1291C>G гена *ADRA2A* как с СРК, так и с СРК-З.
Выводы. По данным проведенного нами метаанализа выявлена статистически значимая ассоциация полиморфизма 1291C>G гена *ADRA2A* как с СРК, так и с СРК-З в смешанной популяции. Ни гомозиготный, ни гетерозиготный варианты полиморфизма 5-HTTLPR гена *SLC6A4*, а также полиморфизма C825T гена *GNB3* не были ассоциированы ни с СРК-З, ни с СРК в целом.
Ключевые слова: генетическая предрасположенность, генные полиморфизмы, запор, синдром раздраженного кишечника, полиморфизм 5-HTTLPR
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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder manifesting with recurrent abdominal pain at least once a week, associated with two or more of the following criteria: related to defecation, associated with a change in the frequency and form (appearance) of stool. Four subtypes of IBS are described based on the Rome IV criteria: IBS with predominant diarrhea (IBS-D), IBS with predominant constipation (IBS-C), and IBS unclassified (IBS-U) [1].

This disorder is not associated with increased mortality, but significantly reduces patients' quality of life [2].

The current treatment options focus primarily on symptom management and have limited efficacy. No pathogenesis- or etiology-directed treatment has been developed, as certain aspects of the pathogenesis and etiology have not yet been completely elucidated [3]. It is suggested that genetic predisposition in combination with environmental factors and the patient's psychological and emotional state play a key role in the development of irritable bowel syndrome (IBS) [4]. The environmental factors include diet, specifically 'Western' diet, which is high in refined carbohydrates, energy-dense food; social factors (any variable in social environment affecting the behavior, well-being and health of an individual); antibiotics use, etc. [4].

The factors described above induce pathophysiological mechanisms, such as gut microbiota modifications, increased gut permeability, low-grade intestinal inflammation, disruption in the bidirectional neurohumoral signaling within the "microbiota — gut — brain" axis, visceral hypersensitivity, and impaired motor function [1].

Genetic polymorphism or single nucleotide polymorphism (SNP) is defined as the replacement of a single nucleotide by another. The study of genetic polymorphisms can help in understanding the key pathophysiological mechanisms, promoted by environmental exposures. Currently, most of the evidence demonstrates association between IBS and genetic polymorphisms in genes, encoding neurotransmitters and their receptors, such as serotonin transporter gene (*SLC6A4*), catechol-O-methyltransferase gene (*COMT*), guanine nucleotide binding protein β3 subunit gene (*GNB3*), alpha-2A adrenergic receptor gene (*ADRA2A*), alpha-2C adrenergic receptor gene (*ADRA2C*), alpha-2D adrenergic receptor gene (*ADRA2D*), as well as proteins modulating inflammatory response, such as tumor necrosis factor alpha (*TNF*), interleukin-10 (*IL10*), interleukin-6 (*IL6*), interleukin-23R (*IL23R*), transforming growth factor beta-1 (*TGFB1*), TNF superfamily member 15 (*TNFSF15*), namely tumor necrosis factor-like cytokine 1A (*TL1A*) [5].

To date, from 2007 to 2019, 11 meta-analyses were published. Among them, the meta-analysis, performed by S. Zhu et al. (2019) is the largest. It includes 28 studies. This meta-analysis summarizes the data on polymorphisms in the eight of the most extensively studied genes to date [5]. It has been confirmed that the rs4263839 and rs6478108 polymorphisms in the *TNFSF15* gene are associated with an increased risk of IBS, while the rs1800896 polymorphism in the *IL10* gene is associated with a reduced risk of this disease in the general population. Polymorphisms in the remaining six genes (*SLC6A4, COMT, IL6, IL23R, GNB3, TNF*) did not show a significant association with the risk of IBS [5]. Another two

meta-analyses included data on genes encoding pro-inflammatory and anti-inflammatory cytokines. Meta-analysis by B. Czogalla et al. (2015) also demonstrated an association between the rs4263839 polymorphism in the *TNFSF15* gene and an increased risk of IBS (and IBS-C in particular) in the USA and UK populations [6]. Meta-analysis by M. Bashashati et al. (2012) included studies on association between IBS and genetic polymorphisms in *IL10*, *TGFB1*, *TNF* genes. It demonstrated the association between IBS and the *IL10* rs1800870 (-1082A/G) polymorphism in the general population, and the *TNF* 308G/A polymorphism in the Asian population [7].

In addition, a number of meta-analyses studied polymorphisms in certain genes. Thus, association between the risk of IBS and the 5-HTTLPR and VNTR polymorphisms in the serotonin transporter gene (*SLC6A4*) was studied in five meta-analyses [8–12]. The obtained data were controversial. M. Bashashati et al. (2017) did not find an increased risk of IBS in patients with *IL6* rs1800795 (-G174C) polymorphism, and Z.G. Pan et al. (2014) did not reveal association with *GNB3* C825T polymorphism [13, 14]. Meta-analysis, performed by S.Y. Qin et al. (2013) demonstrated association between *IL10* rs1800870 (-1082A/G) polymorphism and an increased risk of IBS in the European, but not Asian, population [15].

However, despite the significant number of meta-analyses, to date there was no meta-analysis that comprehensively summarizes data on the prevalence of genetic polymorphisms among patients with IBS-C.

The aim of this meta-analysis is to critically assess published data on the impact of polymorphisms in the above genes on the IBS-C risk.

Materials and methods

A search of the literature on IBS and genetic polymorphisms was carried out in the PubMed and Scopus electronic databases using the following search algorithms: ("irritable bowel genetics") and ("irritable" AND bowel AND syndrome AND genetics"), respectively. The search for studies took place on December 29, 2022, and covered the time period from 1978 to 2023 inclusive. A total of 1634 publications were found in the PubMed database and 829 — in the Scopus database.

Identified studies were used for a meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Publications investigating genetic polymorphisms in patients with IBS-C were included in this analysis.

Inclusion criteria for studies in the meta-analysis were as follows: 1) study in a group of humans; 2) the presence of a separate group of IBS-C patients; 3) availability of information on the clinical diagnoses in the study groups; 4) availability of information on gene polymorphisms associated with IBS-C; 5) access to the full text of the article.

Studies were excluded if: 1) there was no separate group of patients with IBS-C; 2) the identified literature source was not an original experimental article (i.e. abstracts, reviews, comments, etc.).

Two independent investigators include studies in the meta-analysis. Disagreements between reviewers were resolved by consensus and the thorough review of the full text article or by the decision of a third reviewer.

Studies were included in the meta-analysis regardless of the date of their conduct and the original language. In the first stage of study selection, titles and abstracts were reviewed and, if the selection criteria were met, full-text articles were analyzed using the following data: 1) first author's name; 2) year of publication; 3) country and ethnicity of participants; 4) number of participants in the control group and study group; 5) composition of the study group; 6) analysis of SNP in a specific gene and its distribution between the groups; and 7) conclusions about the association between SNPs and IBS.

Statistical processing of data was carried out using the special CMA (Comprehensive Meta Analysis) software [16]. A random effects model was used for analysis [17]. The relative risks of IBS, and in particular IBS-C, were assessed by calculating odds ratios (OR) with 95% confidence intervals (95% CI). Cochran's *Q* test was used to assess heterogeneity of studies. The heterogeneity of the observed effect was assessed by calculating the *I*-squared value, and the variance of the effect size was assessed by calculating the tau-squared value and tau.

Results

Two authors performed screening and included 34 studies in the systematic review, of which 14 were included in the quantitative analysis and 20 — in the qualitative analysis (Fig. 1). All included publications contained data on the association of 25 polymorphisms in 23 genes with IBS-C. A review of the literature references of previously published meta-analyses was performed and no articles matching the search conditions were found. In most studies, DNA was extracted from blood cells, in 4 studies — directly from WBCs, in 3 studies — from rectal mucosa biopsies, in

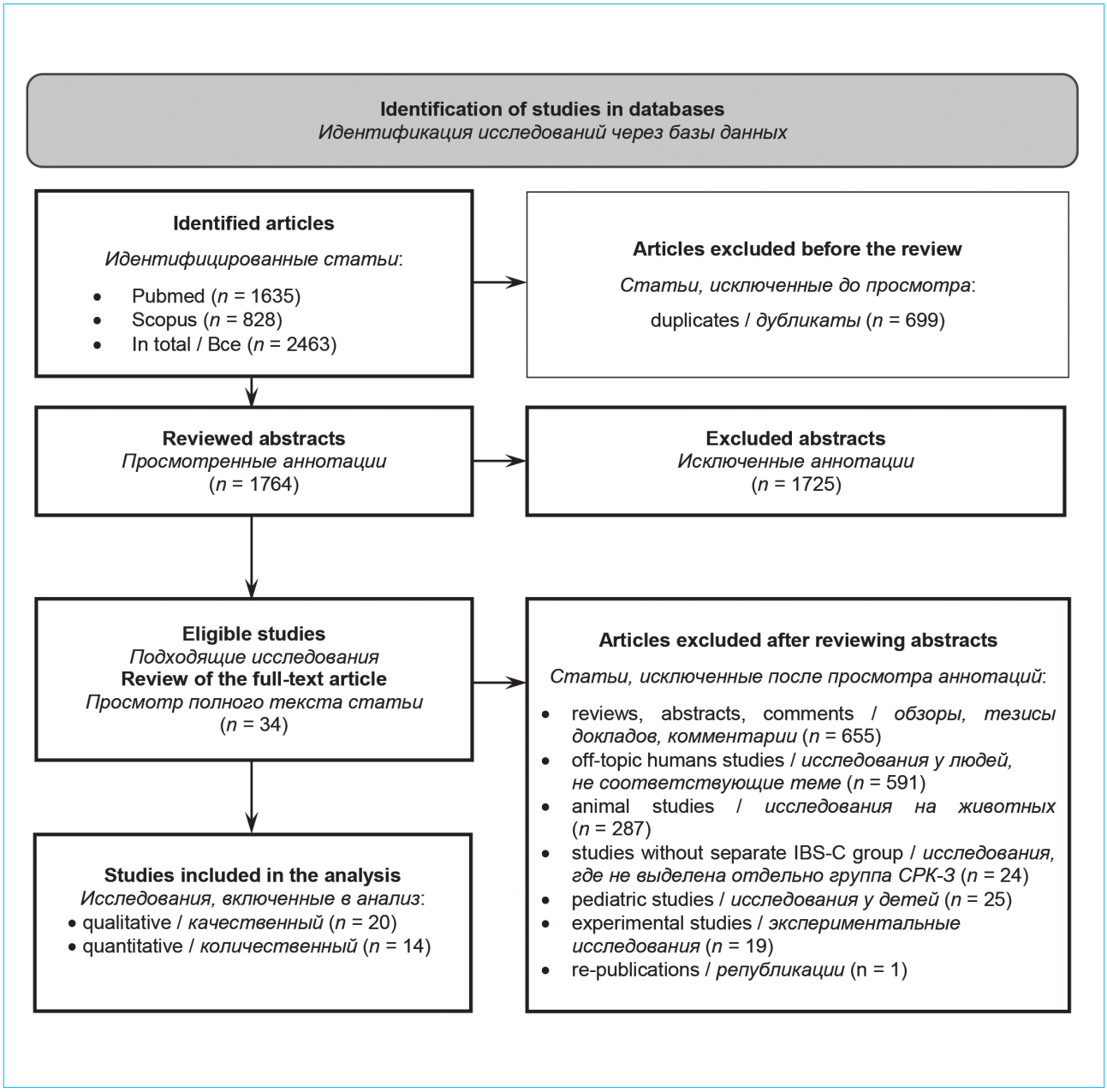

Figure 1. Study flowchart

Рисунок 1. Блок-схема исследования

2 studies — from saliva, and in one study — from the buccal epithelium. In all included studies, gene polymorphisms were identified by PCR.

The majority of data was focused on polymorphisms in the *SLC6A4* gene (*SERT*) (10 articles); *GNB3* gene (5 articles); *ADRA2A*, *IL10*, *TNF*, gene (4 articles); *CNR1* gene (3 articles). Two articles addressed polymorphisms in the *ADRA2C*, *TNFSF15* and *TPH1* genes. One article each described polymorphisms in the *LCT (LPH), CASR, TGR5, FAAH, TPH2, 5-HT2A, CRHR1, TRPV1, NXPH1, CDC42, COMT, CRHR2, MCM6* genes.

Thus, the collected data were sufficient to conduct a meta-analysis on polymorphisms of 3 of the listed genes: *SLC6A4*, *GNβ3*, and *ADRA2A*. Other polymorphisms and their association with IBS and IBS-C were not analyzed in this meta-analysis due to the small number of studies on each of them.

5-HTTLPR polymorphism in the SLC6A4 gene, reducing the expression of the serotonin transporter (SERT) on the presynaptic membrane, as a risk factor of IBS-C

A total of 10 studies included 1456 IBS patients, of whom 558 have IBS-C, and 1489 healthy

Table. Articles included in the analysis
Таблица. Статьи, включенные в анализ

Article ***Статья***	**Year** ***Год***	**Country** ***Страна***	**IBS** ***СРК***	**IBS-C** ***СРК-З***	**CG** ***КГ***	**Serotonin transporter** ***Транспортер серотонина***	**Receptors for neurotransmitters** ***Рецепторы к нейромедиаторам***	**Cytokines** ***Цитокины***	**Others** ***Прочие***
Kim et al. [18]	2004	USA *США*	256	90	120	*SLC6A4* (5-HTTLPR)	*ADRA2A (1291C>G)* *ADRA2C* (Del 322–325)	–	–
van der Veek et al. [19]	2005	Netherlands *Нидерланды*	111	24	162	–	–	*TNF* (G-308A) *IL10* (G-1082A)	–
Andresen et al. [20]	2006	USA *США*	233	82	152	–	–	–	*GNB3* (C825T)
Park et al. [21]	2006	South Korea *Южная Корея*	190	54	437	*SLC6A4* (5-HTTLPR)	–	–	–
Li et al. [22]	2007	China *Китай*	87	44	96	*SLC6A4* (5-HTTLPR; VNTR)	–	–	–
Saito et al. [23]	2007	USA *США*	50	5	53	*SLC6A4* (5-HTTLPR)			*GNB3* (C825T)
Camilleri et al. [24]	2008	USA *США*	122	49	39	*SLC6A4* (5-HTTLPR)	*ADRA2A (1291C>G)* *ADRA2C* (Del 322–325)	–	*GNB3* (C825T)
Truedsson et al. [25]	2009	Sweden *Швеция*	131	35	299	–	–	–	*OXT* (rs61333010) *OXTR* (rs3806675; rs1465386; rs1042778; rs968389)
Sikander et al. [26]	2009	India *Индия*	151	44	100	*SLC6A4* (5-HTTLPR)	–	–	–
Niesler et al. [27]	2010	Germany *Германия*	196	99	92	*SLC6A4* (5HTTLPR; VNTR)	–	–	–
Markoutsaki et al. [28]	2010	Greece *Греция*	124	43	238	–	*5-HT2A* (–1438 (G/A); 102 (C/T))	–	–
Sikander et al. [29]	2010	India *Индия*	151	44	100	–	*ADRA2A (1291C>G)*	–	–

Table continuation.
Продолжение таблицы.

Lee et al. [30]	2010	Korea *Корея*	94	12	88	–	–	*IL10* (1082G/A) *TNF* (308 G/A)	*GNB3* (C825T)
Camilleri et al. [31]	2011	USA *США*	414	157	230	–	–	–	*TGR5* (rs11554825)
Jun et al. [32]	2011	USA *США*	199	41	79	–	–	–	*TPH1* (rs4537731; rs684302; rs211105; rs1800532) *TPH2* (rs4570625)
Park et al. [33]	2011	Korea *Корея*	162	42	423	–	*CNR1* ((AAT)n)	–	–
Zucchelli et al. [34]	2011	USA Sweden *США* *Швеция*	861	261	1131	–	–	*TNFSF15* (rs4263839; rs6478109)	–
Kumar et al. [35]	2012	India *Индия*	150	52	252	–	–	–	*LCT* (C/T-13910; G/A-22018)
Kumar et al. [36]	2012	India *Индия*	150	52	252	*SLC6A4* (5HTTLPR)	–	–	–
Sato et al. [37]	2012	Japan *Япония*	103	32	142	–	–	–	*CRHR1* (rs7209436; rs242924; rs110402)
Song et al. [38]	2012	Korea *Корея*	103	20	80	–	–	–	*TRPV1* (rs222749; rs9894618; rs222747)
Swan et al. [39]	2013	Great Britain *Великобритания*	332	122	179	–	–	*TNFSF15* (rs6478108; rs6478109; rs7848647; rs1407308; rs10982412) *TNF* (rs1800629) *IL10* (rs1800896; rs1800872; rs1143634) *IL1B* (rs1143627)	*CCL11* (rs17809012; rs4795896; rs3744508) *CCL13* (rs81036; rs408121; rs1431991) *NR1D1* (rs12939700; rs3744805; rs2071427)

End of the table.
Окончание таблицы.

Kantar et al. [40]	2013	Turkey *Турция*	100	70	100	–	*ADRA2A* *(1291C>G)*	–	–
Schmulson et al. [41]	2013	Mexico *Мексика*	45	13	92	–	–	*IL10* (-1082G/A) *TNF* (-308G/A)	–
Camilleri et al. [42]	2013	USA *США*	455	154	228	–	*CNR1* (rs806378; (AAT)n)	–	–
Colucci et al. [43]	2013	Italy *Италия*	204	106	200	*SLC6A4* (5-HTTLPR)	–	–	–
Farjadian et al. [44]	2013	Iran *Иран*	50	15	100	*SLC6A4* (5-HTTLPR; VNTR)	–	–	–
Grasberger et al. [45]	2013	USA *США*	422	75	495	–	–	–	*TPH1* (rs7130929)
Wouters et al. [46]	2013	Great Britain USA Canada *Велико- британия США Канада*	1432	443	1526	–	–	–	*NXPH1* (rs2349775) *CDC42* (rs17837965)
Wang et al. [47]	2014	China *Китай*	66	7	115	–	–	–	*COMT* (rs4680) *GNB3* (C825T)
Jiang et al. [48]	2014	China *Китай*	292	99	298	–	*CNR1* (> 10/> 10)	–	*FAAH* (rs324420)
Romero et al. [49]	2015	Germany *Германия*	951	417	794	–	–	–	*CASR* (rs1801725)
Komuro et al. [50]	2016	Japan *Япония*	142	41	142	–	–	–	*CRHR2* (rs4722999; rs3779250; rs2240403; rs2267710; rs2190242, rs2284217; rs2284220)
Almazar et al. [51]	2019	США *USA*	538	58	317	–	–	–	*MCM6* (13910 C/T)

Note: *IBS* — irritable bowel syndrome, IBS-C — irritable bowel syndrome with a predominance of constipation, CG — control group.

Примечание: СРК — синдром раздраженного кишечника, СРК-З — синдром раздраженного кишечника с преобладанием запоров, КГ — контрольная группа.

controls. No significant association was found between the studied polymorphism and either IBS (ls/ss vs. ll; OR = 0.973; 95% CI: 0.734–1.289; p = 0.846) (Fig. 2A) or IBS-C (ls/ss vs. ll; OR = 0.814; 95% CI: 0.612–1.081; p = 0.155) (Fig. 2B).

A more detailed analysis of the association between IBS (IBS-C in particular) and homozygous and heterozygous mutations of the studied polymorphism was carried out in 9 studies. Since the study by M. Camilleri et al. (2008) did not provide separate data on the prevalence of homozygous and heterozygous mutations, it was excluded from further analysis. A total of 1334 IBS patients were included in the analysis, of which 509 patients have IBS-C, and 1450 were healthy controls. Thus, a homozygous mutation was not associated with the risk of either IBS (ss vs. ll/ls; OR = 1.115; 95% CI: 0.812–1.533; p = 0.501) (Fig. 2C) or IBS-C (ss vs. ll/ls; OR = 0.923; 95% CI: 0.648–1.315; p = 0.657) (Fig. 2D). A heterozygous mutation was also not associated with either IBS (ls vs. ll/ls; OR = 0.840; 95% CI: 0.684–1.032; p = 0.096) (Fig. 2E) or IBS-C (ls vs. ll/ ls; OR = 0.922; 95 % CI: 0.427–1.993; p = 0.597) (Fig. 2F). A homozygous variant ll was also not associated with either IBS (ll vs. ss/ls; OR = 1.141; 95% CI: 0.785–1.659; p = 0.489) (Fig. 2G) or IBS-C (ll vs. ss/ls; OR = 1.320; 95% CI: 0.897–1.943; p = 0.159) (Fig. 2H).

C825T (rs5443) polymorphism in the GNB3 gene, increasing the expression of the G-protein beta 3-subunit and neurotransmission via G-protein-coupled receptors (adrenergic, serotonin, cannabinoid), as a risk factor of IBS-C

A total of 5 studies included 537 IBS patients, of whom 155 have IBS-C, and 447 healthy controls. No significant association was found between the studied polymorphism and either IBS (TT/TC vs. CC; OR = 1.102; 95% CI: 0.832–1.460; p = 0.498) (Fig. 3A) or IBS-C (TT/TC vs. CC; OR = 0.955; 95 % CI: 0.623–1.463; p = 0.833) (Fig. 3B).

Further analysis included 415 IBS patients, of whom 106 patients have IBS-C, and 408 were healthy subjects from 4 studies. A homozygous mutation was not associated with the risk of either IBS (TT vs. CC/TC; OR = 1.468; 95% CI: 0.831–2.594; p = 0.186) (Fig. 3C) or IBS-C (TT vs. CC/TC; OR = 1.894; 95% CI: 0.943–3.805; p = 0.073) (Fig. 3D). A heterozygous mutation was also not associated with either IBS (TC vs. CC/TT; OR = 0.923; 95 % CI: 0.688–1.238; p = 0.593) (Fig. 3E) or IBS-C (TC vs. CC/TT; OR = 0.855; 95% CI: 0.533–1.370; p = 0.514) (Fig. 3F).

ADRA2A -1291G>C polymorphism, increasing the expression of alpha-2A adrenergic receptor, as a risk factor of IBS-C

A total of 4 studies included 629 IBS patients, of whom 253 have IBS-C, and 359 healthy subjects. A significant association was found between the studied polymorphism and both IBS (GC/GG vs. CC; OR = 1.361; 95% CI: 1.036–1.789; p = 0.027) and IBS-C (GC/GG vs. CC; OR = 1.510; 95% CI: 1.080–2.110; p = 0.016). Further analysis included 507 IBS patients, of whom 204 patients have IBS-C, and 320 healthy subjects from 3 studies. A homozygous mutation was not associated with the risk of either IBS (GG vs. GC/CC; OR = 1.025; 95% CI: 0.508–2.066; p = 0.945) or IBS-C (GG vs. GC/CC; OR = 1.298; 95% CI: 0.527–3.197; p = 0.571) (Fig. 4C, 4D). Similarly, a heterozygous mutation was not associated with either IBS (GC vs. GG/CC; OR = 1.266; 95% CI: 0.877–1.827; p = 0.209) or IBS-C (GC vs. GG/CC; OR = 1.296; 95% CI: 0.907–1.853; p = 0.155) (Fig. 4E, 4F).

Discussion

Currently, numerous studies have provided a growing body of data that continues to form and expand our understanding of the pathogenesis of IBS. Considering the large number of currently known pathogenic mechanisms involving the nervous, endocrine, immune systems, and intestinal microbiota, the hypothesis of IBS heterogeneity remains unshakable. It is reasonable to assume that IBS is a group of diseases similar in clinical picture, but different in pathogenesis [19]. This hypothesis is supported by the presence of different IBS subtypes, defined on the basis of their clinical picture (IBS-D, IBS-C, IBS-M). The study of genetic polymorphisms in each of the known IBS subtypes can help identify the underlying pathogenetic mechanisms induced by certain environmental exposures [7].

Our meta-analysis focused on IBS-C. The majority of studies focused on neurotransmitter receptors and proteins involved in the synthesis and metabolism of neurotransmitters, as well as proteins involved in neurotransmission. It is suggested that disruption of these processes may play a key role in colonic motility alterations and hypersensitivity development.

Numerous works addressed the association between IBS and *SLC6A4* polymorphism. Replacement of the long “l” allele with the short “s” allele in the 5-HTTLPR locus of the *SLC6A4* gene decreases the expression of the serotonin transporter (*SERT*). Thus, the s/s genotype may decrease serotonin reuptake, increase serotonin

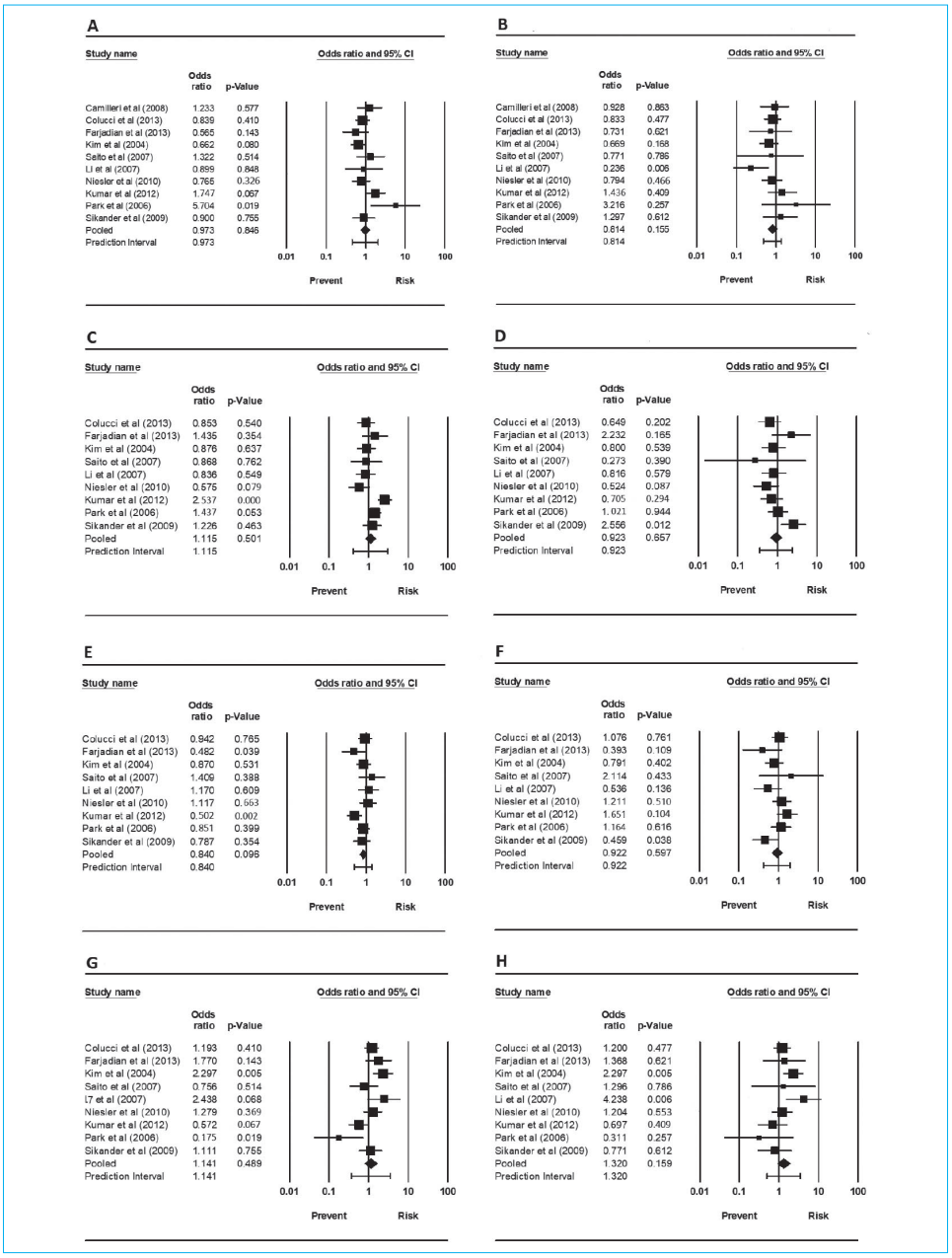

Figure 2. Risk of developing IBS and IBS-C in patients with the 5-HTTLPR polymorphism of the *SLC6A4* gene; forest plots demonstrate the association of the risk of developing: A — IBS with 5-HTTLPR polymorphism without division into variants (ls/ss) (I^2 = 13.38 %); B — IBS-C with 5-HTTLPR polymorphism without division into variants (ls/ss) (I^2 = 4.63 %); C — IBS with a homozygous variant (ss) of the 5-HTTLPR polymorphism (I^2 = 0 %); D — IBS-C with a homozygous variant (ss) of the 5-HTTLPR polymorphism (I^2 = 4.63 %); E — IBS with a heterozygous variant (ls) of the 5-HTTLPR polymorphism (I^2 = 5.02 %); F — IBS-C with a heterozygous variant (ls) of the 5-HTTLPR polymorphism (I^2 = 0 %); G — IBS with homozygous variant (ll) of the 5-HTTLPR polymorphism (I^2 = 24.1 %); H — IBS-C with homozygous variant (ll) of the 5-HTTLPR polymorphism (I^2 = 4.35 %); in all graphs, heterogeneity does not exceed 25 %

Рисунок 2. Риск развития СРК и СРК-З у пациентов с полиморфизмом 5-HTTLPR гена *SLC6A4*; лесовидные графики демонстрируют ассоциацию риска развития: А — СРК с полиморфизмом 5-HTTLPR без разделения на варианты (ls/ss) (I^2 = 13,38 %); В — СРК-З с полиморфизмом 5-HTTLPR без разделения на варианты (ls/ss) (I^2 = 4,63 %); С — СРК с гомозиготным вариантом (ss) полиморфизма 5-HTTLPR (I^2 = 0 %); D — СРК-З с гомозиготным вариантом (ss) полиморфизма 5-HTTLPR (I^2 = 4,63 %); Е — СРК с гетерозиготным вариантом (ls) полиморфизма 5-HTTLPR (I^2 = 5,02 %); F — СРК-З с гетерозиготным вариантом (ls) полиморфизма 5-HTTLPR (I^2 = 0 %); G — СРК с гомозиготным вариантом (ll) полиморфизма 5-HTTLPR (I^2 = 24,1 %);

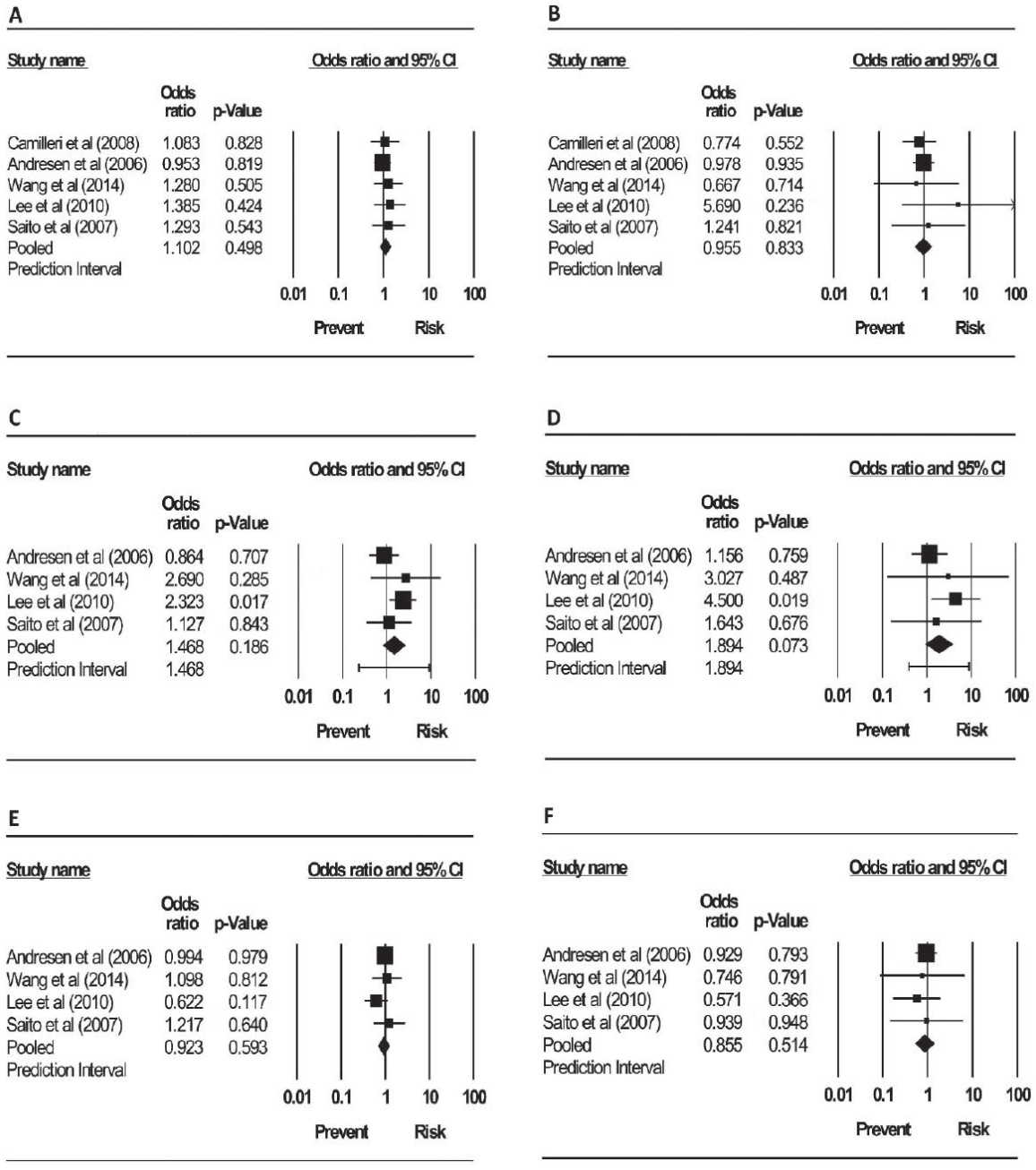

Figure 3. Risk of developing IBS and IBS-C in patients with the C825T polymorphism of the *GNB3* gene; forest plots demonstrate the association of the C825T polymorphism of the *GNB3* gene and the risk of developing: A — IBS without division into polymorphism variants (TT/TC; I^2 = 0 %); B — IBS-C without division into polymorphism variants (TT/TC; I^2 = 0 %); C — IBS with homozygous variant (TT; I^2 = 0 %); D — IBS-C with homozygous variant (TT; I^2 = 0 %); E — IBS with heterozygous variant (TC; I^2 = 0 %); F — IBS-C with heterozygous variant (TC; I^2 = 0 %); in all graphs, heterogeneity does not exceed 25 %

Рисунок 3. Риск развития СРК и СРК-З у пациентов с полиморфизмом С825Т гена *GNB3*; лесовидные графики демонстрируют ассоциацию полиморфизма С825Т гена *GNB3* и риска развития: А — СРК без разделения на варианты полиморфизма (ТТ/ТС; I^2 = 0 %); В — СРК-З без разделения на варианты полиморфизма (ТТ/ТС; I^2 = 0 %); С — СРК с гомозиготным вариантом (ТТ; I^2 = 0 %); D — СРК-З с гомозиготным вариантом (ТТ; I^2 = 0 %); Е — СРК с гетерозиготным вариантом (ТС; I^2 = 0 %); F — СРК-З с гетерозиготным вариантом (ТС; I^2 = 0 %); во всех графиках гетерогенность не превышает 25 %

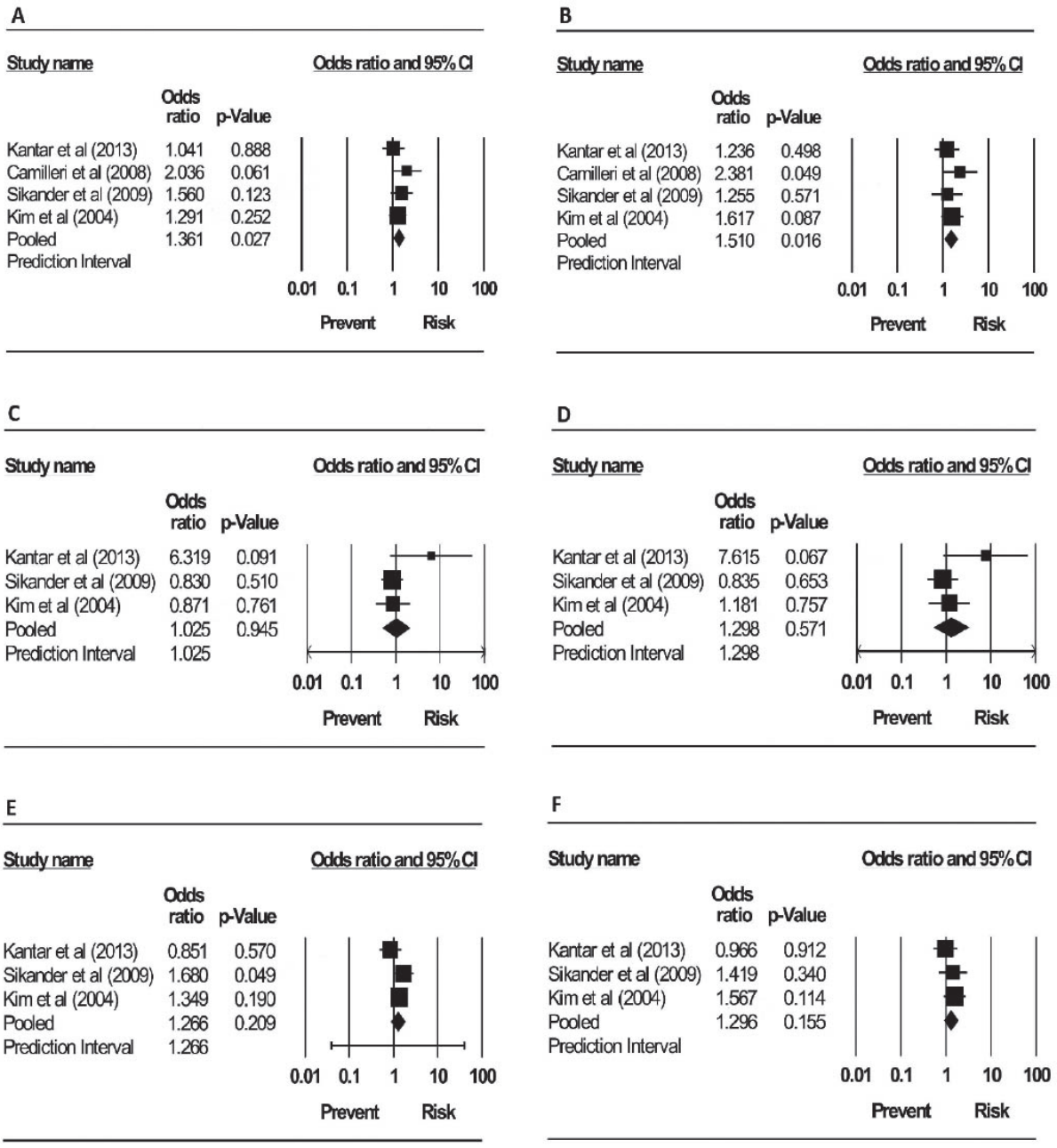

Figure 4. Risk of developing IBS and IBS-C in patients with the (1291C>G) polymorphism of the *ADRA2A* gene; forest plots demonstrate the association of the (1291C>G) polymorphism of the *ADRA2A* gene and the risk of developing: A — IBS without division into polymorphism variants (GG/GC; I^2 = 0 %); B — IBS-C without division into polymorphism variants (GG/GC; I^2 = 0 %); C — IBS with homozygous variant (GG; I^2 = 26.79 %); D — IBS-C with homozygous variant (GG; I^2 = 21.50 %); E — IBS with heterozygous variant (GC; I^2 = 0 %); F — IBS-C with heterozygous variant (GC; I^2 = 0 %); in all graphs, heterogeneity does not exceed 25 %

Рисунок 4. Риск развития СРК и СРК-З у пациентов с полиморфизмом (1291C>G) гена *ADRA2A*; лесовидные графики демонстрируют ассоциацию полиморфизма (1291C>G) гена *ADRA2A* и риска развития: A — СРК без разделения на варианты полиморфизма (GG/GC; I^2 = 0 %); B — СРК-З без разделения на варианты полиморфизма (GG/GC; I^2 = 0 %); C — СРК с гомозиготным вариантом (GG; I^2 = 26,79 %); D — СРК-З с гомозиготным вариантом (GG; I^2 = 21,50 %); E — СРК с гетерозиготным вариантом (GC; I^2 = 0 %); F — СРК-З с гетерозиготным вариантом (GC; I^2 = 0 %); во всех графиках гетерогенность не превышает 25 %

concentrations on the surface of the intestinal epithelium, and, therefore, accelerate the colonic motility and secretion, leading to diarrhea. The l/l genotype is associated with higher serotonin reuptake, which may lead to constipation, associated with slower secretion and motility [24, 36]. In the studies by H.J. Kim et al. (2004) that included USA patients and by Y. Li et al. (2007) that included Chinese patients, there was a significant association between the l/l genotype and IBS-C. The H.J. Kim's study also demonstrated a significant association between this genotype and IBS, while the Y. Li's study did not find such an association [18, 22]. On the contrary, the study by A. Sikander et al. (2009) demonstrated an association between the s/s genotype and IBS-C, but no significant association with IBS was found [26]. Our meta-analysis of 10 studies did not identify a significant association between either IBS-C or IBS and any variant of the 5-HTTLPR genotype. Our findings are consistent with those obtained in the meta-analyses by S. Zhu et al. (2019), Z.F. Zhang et al. (2014), and L.A. Van Kerkhoven et al. (2007) [5, 10, 12]. However, meta-analyses by Z. Jia et al. (2019) and Z.F. Zhang et al. (2014) demonstrated an association between the l/l genotype and IBS-C in the populations of East Asia and China, respectively [8, 10]. This association may not have been confirmed in the meta-analysis by S. Zhu et al. (2019) due to the fact that the authors did not perform subgroup analysis by IBS subtypes, and in our meta-analysis — due to the lack of analysis by ethnicity. A meta-analysis by M.Y. Areeshi et al. (2013) assessed the association between a polymorphism and a reduced risk of IBS and demonstrated a significant association of the l/s genotype with a reduced risk of this disease [11].

Serotonin receptors are also involved in the regulation of motor function and the development of visceral sensitivity. Six classes of serotonin receptors out of 13 discovered (*5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4* and *5-HT7*) were found in the GI tract. The study by T. Markoutsaki et al. (2010) demonstrated that the AA genotype or allele A of the -1438 (G/A) polymorphism in the *5-HT2A* gene were more common among in IBS patients than in healthy individuals, however, no significant association was found among subgroups, including those with IBS-C [28].

The alpha-adrenergic receptors (*ADRA*) are G-protein coupled receptors and include three subtypes (2A, 2B, 2C) [24]. *ADRA2A* receptors are the most abundant subtype and located on the presynaptic membrane, regulating the release of norepinephrine via a negative feedback mechanism [29]. The 1291C>G polymorphism is a replacement, complete or partial, of the C allele with the G allele. This polymorphism increases function of the agonist-activated receptor (norepinephrine). *ADRA2A* are receptors of the visceral afferent neurons, therefore, their functional modifications may alter the neurotransmission from GI receptors, including colonic receptors, to the brain [18]. The study by M. Camilleri et al. (2008) revealed a significant association between the studied polymorphism and IBS-C, but not IBS, in the USA population [24]. The study by A. Sikander et al. (2009) [29] revealed a significant association with IBS in the USA population, but not with IBS-C in the Indian population. Our meta-analysis revealed a significant association of the studied polymorphism (combined GG and GC genotypes) with both IBS and IBS-C. At the same time, separate analysis for each genotype did not reveal a significant association of either GG or GC in patients with IBS or IBS-C. It may be related to the smaller number of studies included in further analysis (3 out of 4). We exclude the study by M. Camilleri et al. (2008) from the further analysis due to the lack of data on the association of genotypes GG and GC with IBS and IBS-C separately [24]. Previously, no meta-analyses of studies focused on this polymorphism were performed.

Subtype 1 and 2 cannabinoid receptors (*CNR1, CNR2*) are also located in the gastrointestinal mucosa, and their activation slows intestinal motility and gastric emptying, and there is also evidence of their involvement in the regulation of visceral sensitivity. Studies conducted in China, Korea and the USA demonstrated a significant association between the (AAT)n polymorphism in the *CNR1* gene and IBS, while no significant differences in the frequency of this polymorphism in different subgroups were found [33, 42, 48]. Meta-analyses on this polymorphism were not conducted due to the small number of studies.

Some neurotransmitter receptors (serotonin, cannabinoid and adrenergic) involved in the regulation of gastrointestinal motility are coupled with G-protein. One of the G-protein subunits, G-protein beta polypeptide 3 (*GNB3*), is a component of several G-protein complexes, and therefore *GNB3* polymorphisms affect signal transduction from the above receptors [20]. The C825T polymorphism is a cytosine (C) to a thymine (T) substitution at position 825 located in exon 10 of the *GNB3* gene. It increases the G protein activity and neurotransmission from associated receptors [24]. An association between this polymorphism and IBS has been reported. The study by H.J. Lee et al. (2010) reported significant association between the T/T genotype of this polymorphism and IBS/IBS-C in the Korean population

[30]. Our meta-analysis of 5 studies did not reveal a significant association of either homozygous or heterozygous C825T polymorphism with IBS and IBS-C. Our data are consistent with the results of the meta-analysis by Z.G. Pan et al. (2014) [14].

A low-grade inflammation is another important factor involved in the pathogenesis of IBS. Two meta-analyses revealed a significant association with polymorphisms in the *TNFSF15* gene, encoding the proinflammatory tumor necrosis factor-like cytokine 1A (*TL1A*). *TL1A* is produced by dendritic cells and stimulates T-cells to produce IL-22, IL-17, and IFN-γ [5, 6]. The rs1800896 polymorphism in the *IL10* gene is associated with a reduced risk of IBS in a mixed population, while the rs1800870 polymorphism in the same gene, on the contrary, increases the risk of IBS [5, 7, 15]. There are also meta-analysis data on the association of *TNF* gene polymorphism with IBS in the Asian population.

A limitation of this systematic review is the relatively small number of studies included, since we analyzed only those studies that assessed the association of gene polymorphisms with IBS-C, in addition to IBS. Because of this, the number of included studies was somewhat smaller than in meta-analyses focused on the association of genetic polymorphisms with IBS. This made it difficult to conduct analyzes within each ethnic group. Some genes potentially associated with IBS were not presented in this article for the same reason. Studies in children were not included in this analysis.

Conclusion

Our meta-analysis revealed that *ADRA2A* 1291C>G polymorphism was significantly associated with both IBS and IBS-C in the mixed population. Neither homozygous nor heterozygous variants of the 5-HTTLPR polymorphism of the *SLC6A4* gene and C825T polymorphism of *GNB3* gene were associated with either IBS-C or IBS as a whole.

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