HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2022 July 15.

Published in final edited form as:

Am J Cardiol. 2021 July 15; 151: 51–56. doi:10.1016/j.amjcard.2021.04.010.

Frequency of Irritable Bowel Syndrome in Patients with Brugada Syndrome and Drug-Induced Type 1 Brugada Pattern

Anil S. Sarica, MD[a], **Serhat Bor, MD**[b], **Mehmet N. Orman, PhD**[c], **Hector Barajas-Martinez, PhD**[d], **Jyh-Ming Jimmy Juang, MD, PhD**[e], **Charles Antzelevitch, PhD**[d,f,g], **Can Hasdemir, MD**[a]

[a]Department of Cardiology, Ege University School of Medicine, Izmir, Turkey

[b]Division of Gastroenterology, Ege University School of Medicine, Izmir, Turkey

[c]Department of Biostatistics and Medical Informatics, Ege University School of Medicine, Izmir, Turkey

[d]Department of Cardiovascular Research, Lankenau Institute for Medical Research, Wynnewood, Pennsylvania

[e]Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

[f]Lankenau Institute for Medical Research and Lankenau Heart Institute, Wynnewood, Pennsylvania

[g]The Jefferson Medical College, Philadelphia, Pennsylvania

Abstract

Irritable bowel syndrome (IBS) is one of the most widely recognized functional bowel disorders (FBDs) with a genetic component. *SCN5A* gene and *SCN1B* loci have been identified in

Address for Correspondence: Can Hasdemir, M.D., Ege University School of Medicine, Department of Cardiology, Bornova, Izmir, 35100 Turkey, Phone: +90 232 390-4001, FAX: +90 232 343-5392, can.hasdemir@yahoo.com.
First author's present address: Bayburt State Hospital, Bayburt, Turkey

CRediT Author Statement

Anil S. Sarica: Formal analysis, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing

Serhat Bor: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration

Mehmet N. Orman: Formal analysis, Visualization

Hector Barajas-Martinez: Investigation, Writing - Review & Editing

Jyh-Ming Jimmy Juang: Investigation, Writing - Review & Editing

Charles Antzelevitch: Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Funding acquisition

Can Hasdemir: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

population-based IBS cohorts and proposed to have a mechanistic role in the pathophysiology of IBS. These same genes have been associated with Brugada syndrome (BrS). The present study examines the hypothesis that these two inherited syndromes are linked. Prevalence of FBDs over a 12 months period were compared between probands with BrS/drug-induced type 1 Brugada pattern (DI-Type 1 BrP) (n=148) and a control group (n=124) matched for age, female sex, presence of arrhythmia and co-morbid conditions. *SCN5A/SCN1B* genes were screened in 88 patients. Prevalence of IBS was 25% in patients with BrS/DI-Type 1 BrP and 8.1% in the control group ($p=2.34\times10^{-4}$). On stepwise logistic regression analysis, presence of current and/or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; p=0.033) was a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. We identified 8 putative *SCN5A/SCN1B* variants in 7 (12.3%) patients with BrS/DI-Type 1 BrP and 1 (3.2%) patient in control group. Five out of 8 (62.5%) patients with *SCN5A/SCN1B* variants had FBDs. In conclusion, IBS is a common co-morbidity in patients with BrS/DI-Type 1 BrP. Presence of current and/or history of migraine are a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs. Frequent co-existence of IBS and BrS/DI-Type 1 BrP necessitates cautious use of certain drugs among the therapeutic options for IBS that are known to exacerbate the Brugada phenotype.

Keywords

J Wave Syndromes; Functional Bowel Disorders; Irritable Bowel Syndrome; Epidemiology; Genetics

Introduction

Irritable bowel syndrome (IBS) based on the Rome III diagnostic criteria is one of the most widely recognized functional bowel disorders (FBDs), with more than 10% of the global adult population reporting symptoms compatible with the condition in population-based surveys.[1,2] Previous reports suggest that there may be distinct, as well as, shared genetic underpinnings for IBS.[3] Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome characterized by a distinct ST-segment elevation in the right precordial leads in the absence of structural heart disease.[4,5] Loss-of-function and gain-of-function variants in *SCN5A* gene and *SCN1B* locus among BrS susceptibility genes, identified in population-based IBS cohorts have been proposed to have a mechanistic role in the pathophysiology of IBS.[6,7] In view of these observations, we extrapolated these findings to our BrS and drug-induced type 1 Brugada ECG pattern (DI-Type 1 BrP) cohort. The present study was designed to determine the period prevalence of FBDs, the prevalence of *SCN5A* and *SCN1B* gene variants, to investigate the demographic and clinical characteristics in probands with BrS/DI-Type 1 BrP and control group and to identify subset of clinical variables/co-morbidities to predict underlying BrS/DI-Type 1 BrP among patients with FBDs.

Methods

Two hundred eighty-eight consecutive, unrelated patients and control subjects were included in a single-center, cross-sectional study between September 11th 2018 and November 20th 2018. Sixteen patients were excluded due to following reasons: incomplete filling of

questionnaire (n=6), familial Mediterranean fever (n=3), inflammatory bowel disease (n=2), microscopic colitis (n=1), celiac disease (n=1), diverticular disease/colorectal polyps (n=1), spina bifida (n=1) and drug-induced thyrotoxicosis (n=1). The remaining 272 patients (126 women/146 men; mean age 41.8±11.8 years; range 18 to 72) formed the study population. Period prevalence (past 12 months) of FBDs and demographic/clinical characteristics were compared between probands with BrS/DI-Type 1 BrP (n=148, 62 women/86 men; mean age 42.8±11.4; range 18 to 72) and the control group (n=124, 64 women/60 men; mean age 40.6±12.1; range 18 to 66). Prevalence of putative *SCN5A* and *SCN1B* gene variants were screened in 88 patients. The control group consisted of patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=24, 19 women/5 men; mean age 46.9±11.1; range 20 to 65), atrioventricular accessory pathways (AV-APs, n=42, 17 women/25 men; mean age 36.9±13; range 18 to 66) and "pure" control subjects (n=58, 28 women/30 men; mean age 40.7±10.7 years; range 18 to 63) with ajmaline challenge test negative for type 1 Brugada pattern. All study subjects were of Turkish (Anatolian Caucasian) descent. Study protocol was approved by the ethics committee of Ege University School of Medicine (Authorization Number:18–9/49). All patients agreed to participate in the study and gave written informed consent.

Ege University School of Medicine BrS/DI-Type 1 BrP cohort consisted of 246 patients referred to our tertiary referral hospital between January 2004 and November 2018. BrS was defined according to the J-Wave syndromes expert consensus conference report.[5] Diagnosis of probable/definite BrS, possible BrS, or a nondiagnostic score were assigned scores of ≥3.5, 2 to 3, and <2 points, respectively.[5] Type 1 BrP in V_1 and/or V_2 precordial leads during ajmaline challenge test with an assigned score of zero was defined as DI-Type 1 BrP.[8,9] The proportions of diagnostic types in BrS/DI-Type 1 BrP cohort in the current study were as follows: probable/definite BrS (n=17), possible BrS (n=67), nondiagnostic BrS (n=7) and DI-Type 1 BrP (n=57). Eight patients with the diagnosis of probable/definite BrS received defibrillator for cardiac arrest (n=4), nocturnal agonal respiration (n=3) and unexplained syncope (n=1). The "pure" control group consisted of unrelated subjects with structurally normal hearts, no known heart disease and no history of any type of atrial and/or ventricular arrhythmia.

FBDs were defined according to the Rome III diagnostic criteria.[10] The validated Turkish version of the questionnaire (27 questions) with pre-tested psycholinguistic and psychometric properties was used.[11] FBDs were classified into 5 distinct categories: irritable bowel syndrome (IBS), functional constipation, functional diarrhea, functional abdominal bloating/distention, and unspecified FBD.[10] IBS was subcategorized into four subtypes based on predominant stool pattern: constipation (IBS-C), diarrhea (IBS-D), a mix of constipation and diarrhea (IBS-M), or undefined predominant stool form (IBS-U). Period prevalence of FBDs was defined as the proportion of the study subjects having the characteristics at any point during a given time period of interest (past 12 months).

Presence of current and/or history of familial Mediterranean fever, inflammatory bowel disease, celiac disease, gastrointestinal or other malignancies, diverticular disease, colorectal polyps, prior major abdominal surgery including cholecystectomy, uncontrolled diabetes mellitus, hypo/hyperthyroidism and chronic opiate and/or any other medication use related

with the study were considered as exclusion criteria. Patients were questioned for the presence of “warning” symptoms (rectal bleeding in the absence of documented bleeding hemorrhoids/anal fissures, unintentional weight loss, family history of colorectal cancer) for gastroenterology consultation.

A total of 306 patients and control subjects were initially contacted by telephone at random in order to question their interest to participate in the study. Eighteen patients declined to participate. All patients and control subjects interested in participating in the study were invited to our medical center and informed about the questionnaire in a face-to-face interview. Participants were encouraged to complete the questionnaire by themselves and mark the most suitable answer in each question by taking enough time. The final category of the FBDs of each patient was classified based on the flowchart of the questionnaire by co-authors (ASS and SB) blinded to the groups of study population. All patients and control subjects with the diagnosis of FBDs based on the questionnaire were subsequently further questioned for confirmation for the diagnosis and the category of FBDs, subtypes of IBS and history of gastrointestinal work-up after completion of the questionnaire.

History of co-morbid conditions such as structural heart diseases, diabetes mellitus, systemic hypertension, epilepsy and migraine were obtained in all participants. Lifetime prevalence of migraine was defined as the proportion of the study subjects who, at some point in life has ever had migraine. Ajmaline challenge test (Gilurytmal®, CARINOPHARM GmbH, Germany) was performed according to the J-Wave syndromes expert consensus conference report.[5]

Genetic screening and analysis for *SCN5A/SCN1B* gene variants were performed in 88 patients (44 women/44 men; mean age 41±13 years): 57 with BrS/DI-Type 1 BrP and 31 control subjects. *SCN5A/SCN1B* gene variants were screened and analyzed by target gene in-depth sequencing by using the Agilent SureSelect Target Enrichment Kit (Agilent Genomics, Santa Barbara, CA, USA) and Illumina Hi-Seq 4000 machine. The identified variants were confirmed by Sanger sequencing. We compared the allele frequency of each identified variant in public databases including 1000 Human Genome Project Database (1000G), Genome Aggregation Database (gnomAD version 2.0.2) and NHLBI GO Exome Sequencing Project (ESP). Sorting Intolerant From Tolerant (SIFT) and Polymorphism Phenotyping-2 (PolyPhen-2) bioinformatics algorithms were used to assess the potential functional impacts of identified mutations. A rare variant was defined as a variant with a minor allele frequency of <0.01%.

Normally distributed variables were presented as mean ± standard deviation and compared using Student’s *t*-test. Non-normally distributed variables were presented as median and compared using Mann-Whitney *U* test. Categorical variables were compared using Pearson’s chi-squared and Fisher’s exact test. Comparisons were performed using Pearson’s chi-squared test and univariate logistic regression analysis. In order to identify the predictors for underlying BrS/DI-Type 1 BrP among patients with FBDs, multiple (full model) and backward method of stepwise logistic regression analysis were performed with clinical variables demonstrating significant association on univariate logistic regression analysis. $P < 0.05$ (two-sided) was considered statistically significant.

Results

There were a total of 94 (34.5%) patients with FBDs diagnosed based on the initial flowchart of the questionnaire in the whole study population. The diagnosis of FBDs was dropped out in 3 out of 94 (3.2%) patients and 5 out of 94 (5.3%) patients had a change in the category of FBDs following subsequent questioning of each patient with FBDs by co-authors.

Prevalence of FBDs (43.2% versus 21.8%, $p=1.86\times10^{-4}$) and IBS (25% versus 8.1%, $p=2.34\times10^{-4}$) was higher in patients with BrS/DI-Type 1 BrP compared to the control group, respectively (Table 1). Prevalence of functional constipation, functional diarrhea, functional abdominal bloating/distension and combination of functional constipation/diarrhea/abdominal bloating-distension were not statistically different between patients with BrS/DI-Type 1 BrP and the control group.

The BrS/DI-Type 1 BrP cohort was matched to the control group in terms of age, female sex, presence of arrhythmia and co-morbid conditions (Table 1). The BrS/DI-Type 1 BrP cohort had higher lifetime prevalence of migraine (64.9% versus 29.8%, $p=8.64\times10^{-9}$) compared to the control group (Table 1). None of the patients and control subjects had "warning" symptoms.

There was no statistical difference in terms of mean age (41.7±10.7 years versus 43.8±11.2 years, p=0.387), female sex (46.9% versus 51.9%, p=0.664) and co-morbid conditions (31.3% versus 15%, p=0.155) among patients with FBDs with BrS/DI-Type 1 BrP and the control group, respectively. Patients with BrS/DI-Type 1 BrP and FBDs had higher lifetime prevalence of migraine (71.9% versus 48.1%, p=0.030) compared to the control group with FBDs, respectively. Prevalence of IBS (57.8% versus 37%, p=0.070) and combination of functional constipation/diarrhea/abdominal bloating-distension (42.2% versus 63%, p=0.070) was not statistically different between patients with BrS/DI-Type 1 BrP and the control group, respectively, among patients with FBDs.

Univariate, multivariable logistic regression analysis and multivariable backward method of stepwise logistic regression analysis were performed to identify subset of clinical variables to predict underlying BrS/DI-Type 1 BrP among patients with FBDs. On stepwise logistic regression analysis, presence of current or history of migraine (OR of 2.75; 95% CI: 1.08 to 6.98; p=0.033) was a predictor of underlying BrS/DI-Type 1 BrP.

We identified 8 putative variants in *SCN5A* (n=4) and *SCN1B* (n=4) genes in 7 out of 57 patients with BrS/DI-Type 1 BrP and 1 out of 31 patients in control group (12.3% versus 3.2%, p=0.158), respectively. Demographic, clinical and *SCN5A* and *SCN1B* variant characteristics are presented in Table 2. The prevalence of *SCN5A* and *SCN1B* variants in BrS/DI-Type 1 BrP patients with FBDs (n=25) was not statistically different from control group (n=7) (20% versus 0%, p=0.56), respectively.

Discussion

There are several important aspects of the correlation between IBS and BrS/ DI-Type 1 BrP. First is the high prevalence of IBS among patients with BrS/ DI-Type 1 BrP and the epidemiology of both diseases; second is the clinical implications of co-morbidity of IBS; third is the clinical implications of migraine as a predictor of underlying BrS/DI-Type 1 BrP among patients with FBDs; and fourth is the underlying genetic characteristics and the mechanistic link between FBDs and BrS/DI-Type 1 BrP.

An analysis from a global epidemiological study for functional gastrointestinal disorders, including data from 29,609 adults surveyed in 14 countries, estimated a 10.1% prevalence of IBS based on the Rome III diagnostic criteria.[2] The prevalence of IBS was 9.8% in Turkish population.[2] The world-wide prevalence of a Brugada ECG pattern (type1/2/3) in general population is estimated to be 0.5 to 1.6 per 1000.[5] The prevalence of DI-Type 1 BrP in Turkish population was 4.8%.[9] Prevalence of IBS among patients with BrS/DI-Type 1 BrP was 25% in our study. The 25% of the 4.8% of the Turkish population with BrS/DI-Type 1 BrP (~1% of the general population) may have co-occurring IBS and BrS/DI-Type 1 BrP. Prevalence of IBS in Turkish general population and in our control group is ~10%. If these results could be extrapolated to the entire IBS population, we estimate that there would be nearly 1 in every 10 patients with IBS in general population may have underlying BrS/DI-Type 1 BrP. As a result, each patient with BrS/DI-Type 1 BrP should be questioned routinely for the presence and severity of symptoms of IBS or vice versa during history taking.

The coexistence of IBS and BrS/DI-Type 1 BrP is of potential clinical relevance for the appropriate management of patients in terms of cautious use of certain drugs known to exacerbate the Brugada phenotype.[12] Among the therapeutic options for IBS, certain drugs (prescribed off-label) with cardiac I_{Na} channel blocking properties such as tricyclic antidepressants and certain selective serotonin reuptake inhibitors (fluoxetine and paroxetine) used for abdominal pain are classified as “to be avoided” or “preferably avoided” in patients with BrS.[12] Drugs (not listed in the international database) with potential cardiac I_{Na} and I_{Ks}/I_{Kr} channel blocking properties such as certain opioid agonists (loperamide) used for diarrhea is known to be a pro-arrhythmic agent.[13]

Patients with IBS often have co-morbidities.[14] A high lifetime prevalence of migraine in patients with BrS/DI-Type 1 BrP has been recently reported.[15] Our current study showed that the lifetime prevalence of migraine was higher (64.9% versus 29.8%) in patients with BrS/DI-Type 1 BrP compared to the control group. Lifetime prevalence of migraine was even higher (71.9% versus 48.1%) in patients with BrS/DI-Type 1 BrP and FBDs compared to the control group with FBDs. Bidirectional co-morbidity of IBS, BrS/DI-Type 1 BrP and migraine may represent a genetic overlap. The identification of genetic overlap and specific genetic variants shared across these disorders can be used to assess the validity of the clinical diagnosis and classification of patients.

We hypothesized that IBS and BrS/DI-Type 1 BrP co-occur because they share a common genetic background. IBS is known to aggregate in families most likely due to shared genetic

and/or environmental factors.[16,17] BrS and IBS are genetic diseases and share common features such as oligogenic/polygenic genetic architecture, same causal common and/or rare variants and worsening of phenotype by gene dysregulation induced by environmental factors (fever and drugs in patients with BrS and certain foods or beverages and hormones in patients with IBS).[5–7,18,19]

The voltage sensitive and the mechanosensitive Na^+ channels (Nav1.5) encoded by the *SCN5A* gene highly expressed in human cardiac myocytes as well as human intestinal interstitial cells of Cajal (ICC) and smooth muscle cells.[20] Loss-of-function variants in *SCN5A*, *SCN1B*, *SCN2B* and *SCN3B* genes have been causally related to BrS in ~20–25% of cases.[5] There is mounting evidence of the association of sodium-channel defects and functional gastrointestinal disorders.[20] Loss-of-function and gain-of-function variants in *SCN5A* gene have been identified in patients with wide-range of gastrointestinal symptoms, FBDs, and functional dyspepsia.[6,21–24] *SCN5A* missense mutations (mostly loss-of-function) were present in 13 (2.2%) patients with IBS.[6] A greater proportion of patients with *SCN5A* mutation met criteria for IBS-C than for IBS-D. *SCN5A* loss-of-function mutations in patients with IBS have been shown to generate $Na_V1.5$ currents of smaller density and reduced mechanosensitivity.[6] Two out of 7 patients with BrS/DI-Type 1 BrP and *SCN5A/SCN1B* variants in our study population (Patients 1 and 3 in Table 2) had loss-of-function *SCN5A* variant (p.Phe1293Ser) and IBSC. Interestingly, this particular *SCN5A* variant has been previously reported in patients with IBS-C and proposed to have a mechanistic role in the pathophysiology of IBS.[25,26] A recent GWAS meta-analysis from 5 population-based cohorts implicated ion channel genes in the pathogenesis of IBS.[7] Suggestive GWAS signals were identified in 7 genomic regions, harboring 64 gene candidates to affect IBS risk via altered function and/or expression of ion channels. Interestingly, one of the suggestive risk loci was BrS-related *SCN1B* gene.[7] *SCN1B* gene encodes the β1 and β1B subunits of the cardiac sodium channel which is also highly expressed by ICC in the mouse colon.[27]

The major limitations of this study are that the current Rome IV diagnostic criteria were not used in our study because of lack of validation of the questionnaire in Turkish population. Comparative characteristics of IBS and identification of biological and/or clinical variables that point to an underlying type1-BrP among patients with IBS were not possible between BrS/DI-Type 1 BrP cohort and the control group because of relatively low number of patients with IBS in the control group.

In conclusion, recognition of co-existence of BrS/DI-Type 1 BrP and IBS will allow physicians to treat their patients more effectively without exposing them to hidden drug cardiotoxicities. Larger studies are necessary to confirm the co-existence of BrS/DI-Type 1 BrP and IBS and to further define the phenotypical characteristics, the molecular genetic overlap and the role of ajmaline challenge test in these patients.

Acknowledgments

Financial Support: This work was supported by grants from the NIH (HL47678, HL138103 and HL152201), W.W. Smith Charitable Trust and Wistar and Martha Morris Fund

References

1. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV. Gastroenterology 2016;150:1262–1279.
2. Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, Whitehead WE, Dumitrascu DL, Fang X, Fukudo S, Kellow J, Okeke E, Quigley EMM, Schmulson M, Whorwell P, Archampong T, Adibi P, Andresen V, Benninga MA, Bonaz B, Bor S, Fernandez LB, Choi SC, Corazziari ES, Francisconi C, Hani A, Lazebnik L, Lee YY, Mulak A, Rahman MM, Santos J, Setshedi M, Syam AF, Vanner S, Wong RK, Lopez-Colombo A, Costa V, Dickman R, Kanazawa M, Keshteli AH, Khatun R, Maleki I, Poitras P, Pratap N, Stefanyuk O, Thomson S, Zeevenhooven J, Palsson OS. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology 2021;160:99–114.e3. [PubMed: 32294476]
3. Saito YA. The role of genetics in IBS. Gastroenterol Clin North Am 2011;40:45–67. [PubMed: 21333900]
4. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391–1396. [PubMed: 1309182]
5. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, Gussak I, Hasdemir C, Horie M, Huikuri H, Ma C, Morita H, Nam GB, Sacher F, Shimizu W, Viskin S, Wilde AA. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Heart Rhythm 2016;13:e295–e324. [PubMed: 27423412]
6. Beyder A, Mazzone A, Strege PR, Tester DJ, Saito YA, Bernard CE, Enders FT, Ek WE, Schmidt PT, Dlugosz A, Lindberg G, Karling P, Ohlsson B, Gazouli M, Nardone G, Cuomo R, Usai-Satta P, Galeazzi F, Neri M, Portincasa P, Bellini M, Barbara G, Camilleri M, Locke GR, Talley NJ, D'Amato M, Ackerman MJ, Farrugia G. Loss-of-function of the voltage-gated sodium channel NaV1.5 (channelopathies) in patients with irritable bowel syndrome. Gastroenterology 2014;146:1659–1668. [PubMed: 24613995]
7. Bonfiglio F, Henström M, Nag A, Hadizadeh F, Zheng T, Cenit MC, Tigchelaar E, Williams F, Reznichenko A, Ek WE, Rivera NV, Homuth G, Aghdassi AA, Kacprowski T, Männikkö M, Karhunen V, Bujanda L, Rafter J, Wijmenga C, Ronkainen J, Hysi P, Zhernakova A, D'Amato M. A GWAS meta-analysis from 5 population-based cohorts implicates ion channel genes in the pathogenesis of irritable bowel syndrome. Neurogastroenterol Motil 2018;30:e13358.
8. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, Aydin M, Pfeiffer R, Burashnikov E, Wu Y, Antzelevitch C. High prevalence of concealed Brugada syndrome in patients with atrioventricular nodal reentrant tachycardia. Heart Rhythm 2015;12:1584–1594. [PubMed: 25998140]
9. Hasdemir C, Juang JJ, Kose S, Kocabas U, Orman MN, Payzin S, Sahin H, Celen C, Ozcan EE, Chen CJ, Gunduz R, Turan OE, Senol O, Burashnikov E, Antzelevitch C. Co-existence of atrioventricular accessory pathways and drug-induced type 1 Brugada pattern. Pacing Clin Electrophysiol 2018;41:1078–1092. [PubMed: 29953624]
10. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology 2016;150:1393–1407.
11. Ozgursoy Uran BN, Vardar R, Karadakovan A, Bor S. The Turkish version of the Rome III criteria for IBS is valid and reliable. Turk J Gastroenterol 2014;25:386–392. [PubMed: 25254520]
12. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM, Priori SG, Tan HL, Hiraoka M, Brugada J, Wilde AA. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm 2009;6:1335–1341. [PubMed: 19716089]
13. Ollitrault P, Dolladille C, Chrétien B, Milliez P, Alexandre J. Cardiovascular Toxicities Associated With Loperamide: Analysis of the World Health Organization Pharmacovigilance Database. Circulation 2021;143:403–405. [PubMed: 33493030]
14. Wongtrakul W, Charoenngam N, Ungprasert P. Increased prevalence of irritable bowel syndrome in migraine patients: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2021 Jan 18. doi:10.1097/MEG.0000000000002065. Online ahead of print.

15. Hasdemir C, Gokcay F, Orman MN, Kocabas U, Payzin S, Sahin H, Nyholt DR, Antzelevitch C. Recognition and clinical implications of high prevalence of migraine in patients with Brugada syndrome and drug-induced type 1 Brugada pattern. J Cardiovasc Electrophysiol 2020;31:3311–3317. [PubMed: 33058326]

16. Saito YA, Zimmerman JM, Harmsen WS, De Andrade M, Locke GR 3rd, Petersen GM, Talley NJ. Irritable bowel syndrome aggregates strongly in families: a family-based case-control study. Neurogastroenterol Motil 2008;20:790–797. [PubMed: 18221250]

17. Waehrens R, Ohlsson H, Sundquist J, Sundquist K, Zöller B. Risk of irritable bowel syndrome in first-degree, seconddegree and third-degree relatives of affected individuals: a nationwide family study in Sweden. Gut 2015;64:215–221. [PubMed: 24694578]

18. Bezzina CR, Barc J, Mizusawa Y, Remme CA, Gourraud JB, Simonet F, Verkerk AO, Schwartz PJ, Crotti L, Dagradi F, Guicheney P, Fressart V, Leenhardt A, Antzelevitch C, Bartkowiak S, Borggrefe M, Schimpf R, Schulze-Bahr E, Zumhagen S, Behr ER, Bastiaenen R, Tfelt-Hansen J, Olesen MS, Kääb S, Beckmann BM, Weeke P, Watanabe H, Endo N, Minamino T, Horie M, Ohno S, Hasegawa K, Makita N, Nogami A, Shimizu W, Aiba T, Froguel P, Balkau B, Lantieri O, Torchio M, Wiese C, Weber D, Wolswinkel R, Coronel R, Boukens BJ, Bézieau S, Charpentier E, Chatel S, Despres A, Gros F, Kyndt F, Lecointe S, Lindenbaum P, Portero V, Violleau J, Gessler M, Tan HL, Roden DM, Christoffels VM, Le Marec H, Wilde AA, Probst V, Schott JJ, Dina C, Redon R. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet 2013;45:1044–1049. [PubMed: 23872634]

19. Aiba T. Recent understanding of clinical sequencing and gene-based risk stratification in inherited primary arrhythmia syndrome. J Cardiol 2019;73:335–342. [PubMed: 30910390]

20. Verstraelen TE, Ter Bekke RM, Volders PG, Masclee AA, Kruimel JW. The role of the SCN5A-encoded channelopathy in irritable bowel syndrome and other gastrointestinal disorders. Neurogastroenterol Motil 2015;27:906–913. [PubMed: 25898860]

21. Locke GR 3rd, Ackerman MJ, Zinsmeister AR, Thapa P, Farrugia G. Gastrointestinal symptoms in families of patients with an SCN5A-encoded cardiac channelopathy: evidence of an intestinal channelopathy. Am J Gastroenterol 2006;101:1299–1304. [PubMed: 16771953]

22. Braak B, Klooker TK, Scholvinck D, Hofman N, Wilde A, Boeckxstaens GE. Abdominal symptoms in patients with long QT syndrome and a “gain of function” mutation in the Nav1.5 sodium channel. Gastroenterology 2008;134:A-683.

23. Saito YA, Strege PR, Tester DJ, Locke GR 3rd, Talley NJ, Bernard CE, Rae JL, Makielski JC, Ackerman MJ, Farrugia G. Sodium channel mutation in irritable bowel syndrome: evidence for an ion channelopathy. Am J Physiol Gastrointest Liver Physiol 2009;296:G211–218. [PubMed: 19056759]

24. Jung KT, Park H, Kim JH, Shin DJ, Joung BY, Lee MH, Jang YS. The Relationship Between Gastric Myoelectric Activity and SCN5A Mutation Suggesting Sodium Channelopathy in Patients With Brugada Syndrome and Functional Dyspepsia - A Pilot Study. J Neurogastroenterol Motil 2012;18:58–63. [PubMed: 22323988]

25. Beyder A, Farrugia G. Ion channelopathies in functional GI disorders. Am J Physiol Gastrointest Liver Physiol 2016;311:G581–G586. [PubMed: 27514480]

26. Strege PR, Mazzone A, Bernard CE, Neshatian L, Gibbons SJ, Saito YA, Tester DJ, Calvert ML, Mayer EA, Chang L, Ackerman MJ, Beyder A, Farrugia G. Irritable bowel syndrome patients have SCN5A channelopathies that lead to decreased NaV1.5 current and mechanosensitivity. Am J Physiol Gastrointest Liver Physiol 2018;314:G494–G503. [PubMed: 29167113]

27. Lee MY, Ha SE, Park C, Park PJ, Fuchs R, Wei L, Jorgensen BG, Redelman D, Ward SM, Sanders KM, Ro S. Transcriptome of interstitial cells of Cajal reveals unique and selective gene signatures. PLoS One 2017;12:e0176031.

Table 1

Demographic and Clinical Characteristics, Prevalence of Functional Bowel Disorders and Gastrointestinal Work-Up Characterisitcs in Patients with Brugada Syndrome/Drug-Induced Type 1 Brugada Electrocardiographic Pattern and Conrol Group

Variable	Patients with BrS/DI-Type 1 BrP (n=148)	Control Group (n=124)	P-value
Demographic and Clinical Characteristics			
- Age (years)	42.8±11.4	40.6±12.2	0.135
- Women	62 (41.9%)	64 (51.6%)	0.109
- Presence of Arrhythmia	75 (50.7%)	66 (53.2%)	0.675
- Presence of Co-Morbid Conditions	46 (31.1%)	17 (25.8%)	0.430
- Presence of Migraine	96 (64.9%)	37 (29.8%)	8.64×10^{-9}
Categories of Functional Bowel Disorders			
- Functional Bowel Disorders	64 (43.2%)	27 (21.8%)	1.86×10^{-4}
- Irritable Bowel Syndrome	37 (25%)	10 (8.1%)	2.34×10^{-4}
- Constipation subtype	17 (45.9%)	7 (70%)	0.177
- Diarrhea subtype	11 (29.7%)	1 (10%)	0.204
- Mix of Constipation and Diarrhea subtype	6 (16.2%)	1 (10%)	0.624
- Undefined subtype	3 (8.1%)	1 (10%)	1.000
- Functional Constipation	5 (3.4%)	2 (1.6%)	0.460
- Functional Diarrhea	3 (2%)	2 (1.6%)	0.80
- Functional Abdominal Bloating/Distension	19 (12.8%)	13 (10.5%)	0.548
- Functional Constipation/Diarrhea/Abdominal Bloating/ Distension	27 (18.2%)	17 (13.7%)	0.312
Gastrointestinal Work-Up in Patients with Functional Bowel Disorders *			
- History of Gastointestinal Consultations and Work-Up	38 (59.4%)	12 (44.4%)	0.191
- History of Upper Endoscopy	24 (37.5%)	9 (33.3%)	0.706
- History of Colonoscopy	11 (17.2%)	2 (7.4%)	0.223

Data are given as mean ± SD, number of patients and percentages.

* = By Primary Care Physician and/or Gastroenterologist, BrS = Brugada syndrome, DI-Type 1 BrP = Drug-Induced Type 1 Brugada ECG pattern.

Table 2

Summary of Demographic, Clinical and *SCN5A/SCN1B* Gene Variant Characteristics

Patient No.	Age	Sex	Cardiac D_x	Type of FBDs	Gene	Exon	Type and Function of Mutation	Change in Nucleotide	Change in Amino Acid	MAF (1000genome)	MAF (ESP)	MAF (gnomAD)	SIFT-Prediction
1	31	M	BrS	IBS-C	SCN5A	22	Missense LofF	c.3878T>C	p.Phe1293Ser	NA	NA	0.0005892	Tolerated
2	32	F	BrS	IBS-C	SCN1B	NA	Intronic Unknown	IVS5+36G>A	NA	NA	NA	NA	NA
3	34	F	BrS	IBS-C	SCN5A	22	Missense LofF	c.3878T>C	p.Phe1293Ser	NA	NA	0.0005892	Tolerated
4	35	F	DI-Type 1 BrP	Functional AB/D	SCN1B	5	Missense Unknown	c.638G>A	p.Gly213Asp	0.0002	0	0.00001768	Damaging
5	44	M	BrS	IBS-D	SCN5A	27	Missense Unknown	c.4789G>A	p.Val1597Met	NA	NA	0.0000177	Damaging
6	45	F	BrS	None	SCN1B	4	Missense Unknown	c.503T>C	p.Val168Ala	0	0	NA	Tolerated
7	57	M	BrS	None	SCN1B	3	Missense LofF	c.259G>C	p.Glu87Gln	0	0	0.000003978	Tolerated
8	58	F	Control	None	SCN5A	17	Missense Unknown	c.3067C>T	p.Arg1023Cys	NA	NA	0.00002018	Tolerated

BrS = Brugada Syndrome, DI-Type 1 BrP = Drug-Induced Type 1 Brugada Pattern, D_X = Diagnosis, ESP = Exome Sequencing Project, Functional AB/D = Abdominal Bloating/Distension, FBD = Functional Bowel Disorders, gnomAD = Genome Aggregation Database, IBS-C = Irritable Bowel Syndrome Constipation, IBS-D = Irritable Bowel Syndrome Diarrhea, LofF = Loss of Function, MAF = Minor Allele Frequency, 1000 genome = 1000 Human Genome Project Database, Polyphen-2 = Polymorphism Phenotyping 2, SIFT = Sorting Intolerant From Tolerant