HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

Heart Rhythm Society SM

# *SCN5A* gene variants and arrhythmic risk in Brugada syndrome: An updated systematic review and meta-analysis

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## ABSTRACT

**BACKGROUND** A rare gene variant in *SCN5A* can be found in approximately 20%–25% of patients with Brugada syndrome (BrS).

**OBJECTIVE** The aim of this systematic review and meta-analysis was to evaluate the differences in clinical characteristics of BrS patients with and without *SCN5A* rare variants and the prognostic role of *SCN5A* for ventricular arrhythmias in BrS.

**METHODS** PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from inception to January 2024 to identify all relevant studies. Studies were analyzed if they included patients diagnosed with BrS in whom genetic testing for *SCN5A* variants was performed and arrhythmic outcomes were reported.

**RESULTS** A total of 17 studies with 3568 BrS patients, of whom 3030 underwent genetic testing for *SCN5A* variants, fulfilled the eligibility criteria and were included. Compared with *SCN5A*− patients, *SCN5A*+ BrS patients more frequently had spontaneous type 1 electrocardiogram, history of syncope, and documented arrhythmias. Furthermore, higher PQ and QRS intervals in *SCN5A*+ BrS patients compared with *SCN5A*− have been found. The pooled analysis demonstrated a significant association between the presence of *SCN5A* rare variants in BrS patients and the risk of major arrhythmic events, with a pooled odds ratio of 2.14 (95% confidence interval, 1.53–2.99; $I^2 = 29\%$).

**CONCLUSION** *SCN5A*+ BrS patients showed a worse clinical phenotype compared with *SCN5A*−. The pooled analysis demonstrated a significant association between *SCN5A*+ mutation status and the risk of major arrhythmic events in BrS patients.

**KEYWORDS** Brugada syndrome; Genetics; Sudden cardiac death; *SCN5A*; Ventricular arrhythmias

(Heart Rhythm 2024;■:1–11) 

## Introduction

Brugada syndrome (BrS) is an inherited arrhythmia syndrome associated with a typical electrocardiographic pattern and sudden cardiac death (SCD) in the absence of structural heart disease.[1] *SCN5A* gene encodes for the α-subunit of the cardiac sodium channel (Nav1.5), implicated in sodium current ($I_{Na}$) conductance.[2] A reduction in $I_{Na}$ conductance has been deemed pathogenic for BrS. A reduced conduction reserve in the right ventricular outflow tract (RVOT), at least in part genetically mediated, is responsible for the BrS phenotype. Thus, any reduction of $I_{Na}$ can determine BrS phenotype if it is above the RVOT conduction reserve.[3]

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https://doi.org/10.1016/j.hrthm.2024.04.047

1547-5271/$-see front matter 

A rare gene variant in *SCN5A* can be found in approximately 20%–25% of patients.[4] However, the introduction in 2015 of the American College of Medical Genetics and Genomics (ACMG) classification[5] brought stringency to classification of *SCN5A* variants and association with BrS. In particular, missense variants can be reclassified as pathogenic/likely pathogenic (P/LP) in ≈17% of cases, and most variants are reclassified as a variant of uncertain significance.[6]

Since the first description of the genetic basis for BrS, significant heterogeneity has been found for *SCN5A* as a prognostic factor. The first studies reporting on arrhythmic outcomes for *SCN5A* rare variant carriers did not find an increased risk of events.[7,8] However, recent studies from both Japanese and European cohorts confirmed a worse epicardial substrate and clinical phenotype.[9] This translates into a higher risk of ventricular arrhythmia (VA) for BrS patients carrying *SCN5A* rare variants.[10]

The aim of this systematic review and meta-analysis was to evaluate—from a current up-to-date literature pooled analysis—the differences in clinical characteristics of BrS patients with and without *SCN5A* rare variants and the prognostic role of *SCN5A* for VAs in BrS. A subanalysis based on loss of function (LoF) *SCN5A* variant carriers vs non-LoF *SCN5A* variant carriers vs *SCN5A*− patients was also performed.

## Methods

The study was designed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[11] (Supplemental Table 1). All research was conducted according to a protocol registered in the PROSPERO database (PROSPERO registration: CRD42024506439).

### Data sources and searches

PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from inception to January 2024 to identify all the relevant studies. A basic search strategy was developed for the PubMed database and accordingly modified for the other research databases. The reference list of all identified articles was also reviewed for relevant studies. No restrictions of language, publication date, or age of the participants were applied. Conference abstracts were also checked, and experts were contacted to identify unpublished studies. PROSPERO was also searched to identify possible similar systematic reviews in progress to avoid duplication with our study. The search terms used were *Brugada*, *SCN5A*, and *variant* or *mutation*. The search was conducted by 2 independent investigators (I.D., S.C.); the detailed search strategy is presented in Supplemental Table 2. The study complied with the Declaration of Helsinki as revised in 2013.

**Abbreviations**

**ACA:** aborted cardiac arrest

**BrS:** Brugada syndrome

**ECG:** electrocardiogram

**ICD:** implantable cardioverter-defibrillator

**LoF:** loss of function

**MAEs:** major arrhythmic events

**P/LP:** pathogenic/likely pathogenic

**RVOT:** right ventricular outflow tract

**SCD:** sudden cardiac death

**VA:** ventricular arrhythmia

### Eligibility and exclusion criteria

We included cohort (prospective or retrospective) and case-control studies of patients diagnosed with BrS in whom genetic testing for *SCN5A* variants was performed. BrS was defined as the presence of a spontaneous type 1 electrocardiogram (ECG) or a type 1 ECG induced by pharmacologic provocation with sodium channel blockers, in accordance with the guidelines applicable at the time of each study.[12,13] Studies were included if they reported rare variants in *SCN5A* gene. A subanalysis was performed for studies reporting P/LP variants following current ACMG guidelines.[5] Studies were considered eligible if differences between rare *SCN5A* variant carriers (*SCN5A*+) and noncarriers (*SCN5A*− or control group) were analyzed, along with data on arrhythmic events observed during the follow-up. LoF *SCN5A* variant carriers vs non-LoF *SCN5A* variant carriers vs *SCN5A*− patients were also analyzed in a prespecified subanalysis. The exclusion criteria were the following: case reports and case series with fewer than 10 individuals; certain publication types (letters, reviews, editorials, abstracts); and duplicate data, defined as studies with populations from the same registries. No age restrictions were applied. In case of duplicate publications, we included the study with the largest sample size or longest follow-up. Individuals who tested positive for *SCN5A* but who did not receive a diagnosis of BrS were excluded.

### Study selection

The results of the searches from all the databases were imported into a reference management software (EndNote X9 for Windows; Thomson Reuters, Toronto, Ontario, Canada). After the removal of duplicate records, 2 reviewers (I.D. and S.C.) independently screened titles and abstracts, and full texts were investigated for eligible studies. Disagreements between the reviewers regarding abstract selection were solved by a third reviewer (L.P.).

### Quality assessment

Two reviewers (I.D. and S.C.) analyzed the quality of the full texts on the basis of the Newcastle-Ottawa quality assessment scale in 3 domains: recruitment and selection of the participants, comparability between the groups, and ascertainment of the outcome of interest in the studies.[14] A study with a total score of 7 or higher was considered to have low risk of bias, whereas studies with a score of 6 or less were considered to have high likelihood of bias. The assessments were done independently by the 2 authors (I.D. and S.C.), and any disagreements were resolved by a third reviewer (L.P.).

### Data extraction

One reviewer (S.C.) extracted data independently, and a second reviewer (I.D.) verified the data. Data items that were

extracted included title and first author, year of publication, country/region of participant recruitment, study design, and total number of participants with BrS. Characteristics of participants included mean age, sex, and *SCN5A* variant carrier status; history of documented VA, syncope, and aborted cardiac arrest (ACA); family history of SCD; spontaneous type 1 ECG; presence of implantable cardioverter-defibrillator (ICD); mean follow-up duration; electrocardiographic characteristics (P wave, PR interval, QRS, and QTc duration); electrophysiologic characteristics (presence of late potentials, VA inducibility during electrophysiology study, abnormal substrate size); and follow-up data. Major arrhythmic events (MAEs) during the follow-up were defined as follows: ventricular tachycardia/fibrillation (VT/VF) or appropriate ICD shock or ACA or SCD.

### Statistical analysis

Continuous variables were expressed as mean ± SD or median and 25%–75% interquartile range. Summary estimates of continuous variables were reported as the mean difference, whereas estimates of categorical variables were reported as odds ratios (ORs) with 95% confidence intervals (CIs). DerSimonian-Laird random effects model meta-analysis was chosen because of anticipated clinical and methodologic heterogeneity between the studies. Pooled results of the meta-analysis were visualized in a forest plot along with the 95% CIs. Heterogeneity was assessed with Cochran *Q* test, and the degree of heterogeneity was quantified by the $I^2$ and $tau^2$ statistics. Heterogeneity was classified as low, moderate, and high for $I^2$ statistic values of $\leq$25%, 50%, and $\geq$75%, respectively. A prespecified subgroup analysis was also performed. Subgroups were defined according to patients' clinical characteristics as well as by functional classification of *SCN5A* mutations. Metaregression analysis was conducted to investigate the effect of various factors on the results of the prognostic role of *SCN5A* mutation status in MAEs. Statistical significance was considered a result of *P* value < .10. Publication bias was assessed by a funnel plot and Egger regression test with a significance level of .1. All statistical values were presented with a 95% CI and a 2-tailed *P* value at significance level of .05. All analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) by using the meta and metafor packages.[15]

## Results

### Search results

After removal of duplicates, 985 studies were evaluated on the basis of their title and abstract. Of the initial pool of 985 studies, 899 were excluded during the title and abstract screening phase because of the identification of specific publication types lacking sufficient data for analysis or studies unrelated to the study theme. Of the 86 studies that were assessed for eligibility by full-text screening, 17 studies were excluded as case reports and 44 studies did not report the outcome of interest or they did not have a control group. A total of 16 studies included populations from the same registry, so only the study with follow-up data or with the largest number of participants was included in our analysis. In particular, 8 studies were excluded for duplicate patients. Eventually, 17 studies with 3568 BrS patients (Figure 1), of whom 3030 underwent genetic testing for *SCN5A* variants, fulfilled the eligibility criteria and were included in the systematic review and meta-analysis[7–9,16–29] (Table 1).

### Study and patient characteristics

Of the 17 studies, 8 were conducted at single-center locations; the remaining studies were multicenter. Four studies consisted of an Asian population[20,21,23,24] and 12 studies of a White population[7–9,16,17,19,22,25–29]; 1 study included a mixed population.[18] Regarding age groups, 1 study encompassed a population aged <19 years,[17] another study focused specifically on children younger than 12 years,[25] 1 study included a mixed population with patients <16 years old,[29] and the rest of the studies consisted of an adult population.

The studies included a total population of 3568 patients with BrS. Genetic testing was performed in 3030 patients who were included in this systematic review. The remaining 538 patients were excluded. Of the 3030 patients, 750 (24.7%) patients tested positive and 2280 (75.3%) patients tested negative for *SCN5A* variants. Overall, most BrS patients were male (72%) with a mean age of 39.9 ± 11.8 years. A history of syncope and ACA was reported in 21% and 8% of the cases, respectively. Spontaneous type 1 ECG BrS pattern was present in 50% of the patients. In addition, 25% reported a family history of sudden death, and a VA was documented in 9% of them. An ICD was implanted in 40% of the cases. Detailed patient and study characteristics can be found in Table 1.

### Clinical, electrocardiographic, and electrophysiologic parameters of SCN5A+ vs SCN5A− patients

Meta-analysis results of the differences between *SCN5A*+ and *SCN5A*− patients are summarized in Table 2. *SCN5A*+ patients were younger at the time of diagnosis (40.9 ± 3.2 years vs 44.7 ± 2.9 years; $P = .002$). There was no significant difference in the proportions of male patients between the groups (66% vs 74%; $P = .2$). *SCN5A*+ patients experienced syncope and ACA more frequently than *SCN5A*− patients (39% vs 29% [$P < .001$] and 16% vs 10% [$P = .04$], respectively). Moreover, a higher proportion of *SCN5A*+ patients presented with spontaneous type 1 ECG and had history of documented VA (45% vs 40% [$P < .001$] and 27% vs 18% [$P = .002$], respectively). No differences were observed in the family history of SCD and history of AF between the groups.

As shown in Table 2, meta-analysis of the electrocardiographic and electrophysiologic parameters showed prolonged P wave, PR interval, QRS, and QTC durations as well as larger abnormal substrate size before and after provocation test in the *SCN5A*+ group compared with the *SCN5A*− group. No difference was observed in VA inducibility during electrophysiology study. Forest plots of these meta-analyses are presented in Supplemental Figures 1–16.

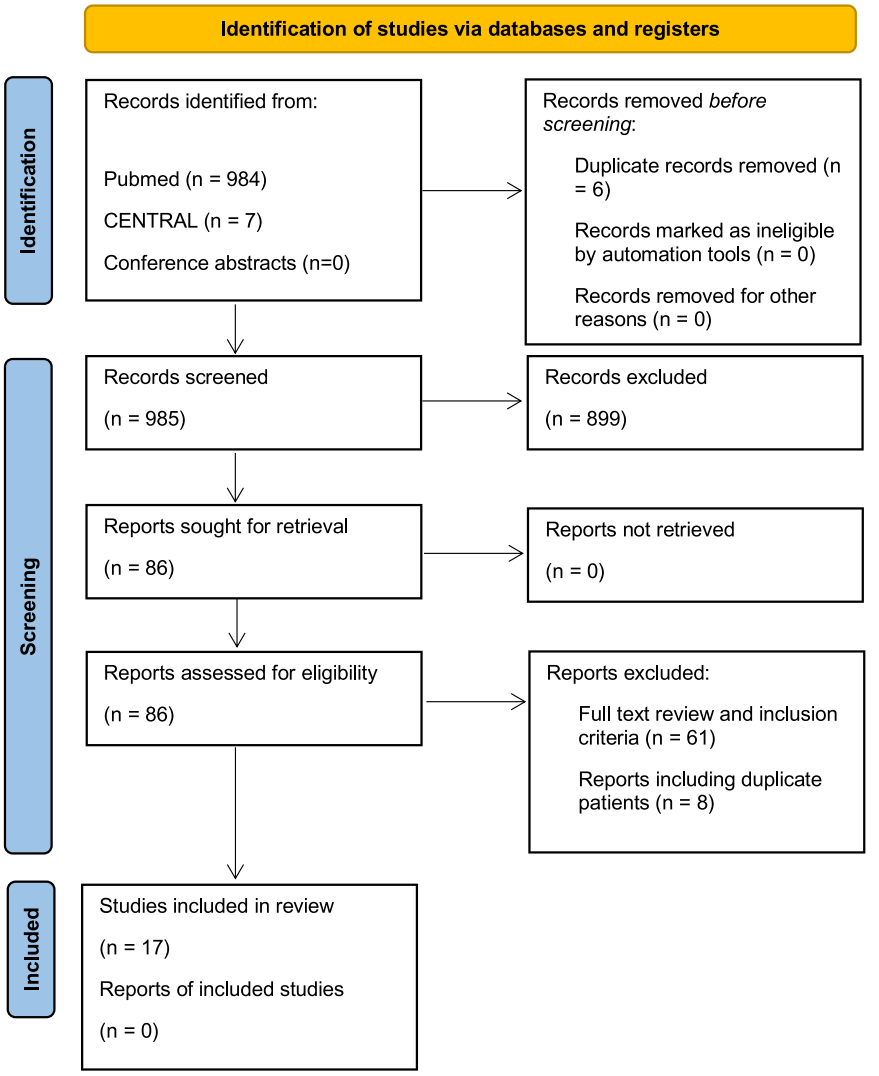


**Figure 1**
Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the study selection process.

### *MAEs during follow-up*

In total, 12 studies including 1914 BrS patients (537 *SC5NA*+ and 1377 *SCN5A*−) reported the occurrence of MAEs in the 2 groups at a mean follow-up of 59.6 ± 20 months. As shown in Figure 2, the pooled analysis demonstrated a significant association between the presence of *SCN5*A rare variants in BrS patients and the risk of MAEs, with a pooled OR of 2.14 (95% CI, 1.53–2.99, $I^2$ = 29%).

### *Subgroup, sensitivity, and metaregression analysis*

A subgroup analysis based on the age and ethnicity of the participants was conducted (Figures 3 and 4). *SCN5A*+ mutation status was associated with an elevated risk of MAEs both in adults BrS (>19 years; OR, 1.97; 95% CI, 139–2.79; $I^2$ = 28%) and in the BrS population younger than 19 years (OR, 5.88; 95% CI, 1.58–21.92; $I^2$ = 0%). *SCN5A* mutation status was predictive of MAEs in the Asian population (OR, 2.2; 95% CI, 1.2–4.07; $I^2$ = 0%); however, results were marginally not statistically significant in the non-Asian cohort (OR, 2.05; 95% CI, 0.85–4.97; $I^2$ = 48%). Three of the included studies evaluated the risk of MAEs on the basis of LoF *SCN5A* variant carriers. Pooled results demonstrated that LoF *SCN5A*+ mutation status was associated with an elevated risk of MAEs compared with non-LoF *SCN5A*+ BrS patients (OR, 4.05; 95% CI, 1.54–10.64; $I^2$ = 0%) as well as in comparison with *SCN5A*− patients (OR, 3.4; 95% CI, 1.59–7.6; $I^2$ = 38%; Supplemental Figures 17 and 18). There was no association between non-LoF *SCN5A*+ vs *SCN5A*− BrS patients and the risk of MAEs (OR, 0.9; 95% CI, 0.13–5.9; $I^2$ = 49%; Supplemental Figure 19). In a sensitivity analysis based on the ACMG classification, *SCN5A*+ mutation status was associated with an elevated risk of MAEs both with ACMG classification (OR, 2.19; 95% CI, 1.47–3.27; $I^2$ = 0%) and without (OR, 2.48; 95% CI, 0.98–6.31; $I^2$ = 48%), with the latter marginally not reaching statistical significance (Supplemental Figures 20 and 21).

Metaregression analysis was conducted to investigate the effect of various factors on the results of the prognostic role of *SCN5A* mutation status in MAEs. Supplemental Table 3 shows

**Table 1** Main characteristics of included studies

| Author, year | Origin | Participants | No. | Design | Age (y) | Male sex | Follow-up (mo) | *SCN5A*+ | Spontaneous type 1 ECG | History of syncope | History of ACA | History of documented VT/VF | ICD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Eckardt, 2005 | Multicenter/4 European university hospitals | BrS patients with spontaneous or drug-induced type 1 ECG | 212 | Pro | 45 ± 6 | 152 (72) | 40 ± 50 | 57/183 (31) | 125 (59) | 65 (31) | 24 (11) | NR | 113 (53) |
| Nishii, 2010 | Multicenter/4 Japanese hospitals | BrS patients from January 1997 to December 2009 | 108 | Pro | 46.8 ± 11.6 | 105 (97) | 71.9 ± 41.3 | 17/108 (16) | 71 (33) | 42 (39) | NR | 23 (21) | 49 (45) |
| Amin, 2011 | Single center/The Netherlands | BrS patients with *SCN5A* mutation analysis performed | 214 | Retro | 45.6 ± 1.6 | 133 (62) | 43.8 ± 3.2 | 78/214 (36) | 49 (23) | 67 (31) | 0 (0) | 24 (11) | 65 (30) |
| Maury, 2013 | Multicenter/4 French university hospitals | BrS patients with spontaneous or drug-induced type 1 ECG | 325 | Retro | 47 ± 13 | 258 (79) | 48 ± 34 | 42/189 (22) | 143 (44) | NR | NR | NR | 135 (42) |
| García-Molina, 2013 | Single center/Spain | BrS patients with spontaneous or drug-induced type 1 ECG (only probands) | 76 | Pro | 41.8 ± 13.7 | 65 (86) | NR | 8/76 (10) | 43 (50) | 10 (13) | 3 (4) | NR | 9 (12) |
| Rudic, 2016 | Single center/ Germany | BrS patients with *SCN5A* mutation analysis and CMR performed | 81 | Retro | 43 ± 12 | 56 (69) | 105 (69–125)[a] | 16/81 (20) | 37 (46) | 23 (28) | 2 (2) | NR | NR |
| Calò, 2016 | Multicenter/4 Italian tertiary cardiology centers | BrS patients with spontaneous type 1 ECG without history of cardiac arrest since 1999 | 347 | Pro | 45 ± 13.1 | 272 (78) | 48 ± 38.6 | 32/107 (30) | 347 (100) | 14 (4) | 0 (0) | 0 (0) | 98 (28) |
| Andorin, 2016 | Multicenter/16 European centers | BrS patients <19 years of age with spontaneous or drug-induced type 1 ECG | 106 | Retro | 11.1 ± 5.7 | 58 (55) | 54 (15–99)[a] | 58/75 (77) | 36 (34) | 15 (14) | 4 (4) | 2 (2) | 22 (21) |
| Makarawate, 2017 | Single center/ Thailand | Symptomatic BrS patients with ICD implantation from 2008 to 2011 | 40 | Pro | 43 (22–66)[a] | 39 (98) | 24 (13–52)[a] | 13/40 (33) | 29 (73) | NR | 29 (73) | NR | 40 (100) |

(*continued*)

**Table 1** Continued

| Author, year | Origin | Participants | No. | Design | Age (y) | Male sex | Follow-up (mo) | *SCN5A*+ | Spontaneous type 1 ECG | History of syncope | History of ACA | History of documented VT/VF | ICD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Robyns, 2018 | Single center/ Belgium | BrS patients and controls with *SCN5A* mutation analysis performed | BrS cohort = 83 (total cohort = 156) | Retro | 42.8 ± 14.6 | 49 (59) | 56.1 ± 65.9 | 44/83 (53) | 32 (39) | NR | NR | NR | 33 (40) |
| Ishikawa, 2021 | Multicenter/ Japan | 2 independent BrS cohorts (probands) and 1 control cohort with *SCN5A* mutation analysis performed | BrS cohort-I = 415 | Retro | 46 ± 14 | 403 (97) | 72 (1–279)[b] | 60/415 (14) LoF mutations = 45 Non-LoF mutations = 15 | 299 (72) | 99 (23) | 88 (21) | NR | 241 (58) |
| Ciconte, 2021 | Single center/ Italy | BrS patients (probands) with *SCN5A* mutation analysis performed undergoing EPS | 195 | Retro | 42.7 ± 12.2 | 156 (80) | NR | 49 (25) | 43 (22) | 79 (41) | 23 (12) | 75 (38) | 75 (38) |
| Righi, 2021 | Single center/ Italy | BrS patients <12 years of age between 2007 and 2018 | 43 | Retro | 7.2 ± 2.6 | 25 (58) | 47.6 ± 36.8 | 14/39 (36) | 13 (30) | 2 (5) | 0 (0) | NR | 3 (6) |
| Pham, 2023 | Single center/ Vietnam | BrS patients from January 2017 to April 2022 with *SCN5A* mutation analysis performed | 117 | Retro | 47.5 ± 12.4 | 114 (97) | NR | 30/117 (26) | 83 (71) | 45 (38) | 7 (6) | 7 (8) | 86 (74) |
| Rossi, 2023 | Multicenter/ 5 Italian centers | BrS patients with spontaneous or drug-induced type 1 ECG without history of cardiac arrest or VT/VF | 372 | Retro | 44 ± 15 | 257 (69) | 48 (27–84)[a] | 55/167 (33) | 185 (50) | 94 (25) | 0 (0) | 0 (0) | 89 (24) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pannone, 2023 | Single center/ Belgium | BrS patients from 1992 to 2022 with reclassification of *SCN5A* gene variants (adults = 437, children = 63) | 500 | Pro | 38.9 ± 16.9 | 245 (49) | 84 (45.7–138)[a] | 104 (21) LoF mutations = 35 Non-LoF mutations = 69 | 87 (17.4) | 159 (31.8) | 29 (5.8) | NR | 197 (39.4) |
| Chen, 2023 | Multicenter | Fever-induced BrS patients with next-generation sequencing for *SCN5A* gene variants | 216 | Retro | 41.7 ± 17.5 | 210 | 50.5 (32.5–81.5)[a] | 77/198 (39) P/LP = 59 B/LB/VUS = 18 | 120 (46) | 89 (34) | | 32 (12) | NR |

Categorical variables are presented as n (%) or n/N (%). Continuous variables are presented as mean ± SD unless otherwise indicated.
ACA = aborted cardiac arrest; B/LB/VUS = benign/likely benign/variant of uncertain significance; BrS = Brugada syndrome; CMR = cardiac magnetic resonance; ECG = electrocardiogram; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; LoF = loss of function; NR = not reported; P/LP = pathogenic/likely pathogenic; Pro = prospective; Retro = retrospective; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Median (interquartile range).
[b]Median (range).

the factors studied in the metaregression analysis. Proportions of male sex, spontaneous type 1 ECG, history of syncope, history of ACA, ICD implantation, proband status, and age of the participants were found to have no effect on the main analysis results.

### Publication bias and grading of evidence

The publication bias of the different studies included in the meta-analysis was explored with funnel plots. Although a total of 17 studies were included in this systematic review, most measured outcomes were included in <10 studies, with only the end point of MAEs included in >10 studies. Consequently, only the end point of MAEs in the total population was examined. Egger test showed no significant publication bias ($P = .7$; Supplemental Figure 22). On the Newcastle-Ottawa quality assessment scale, only 1 study scored 5/9 and another 2 studies 6/9 and were considered to have high risk of bias, whereas the rest of the studies were considered to have low risk. The quality of evidence was considered low (Supplemental Tables 4 and 5).

## Discussion

The main findings of this study can be summarized as follows:

- *SCN5A*+ patients showed a worse clinical phenotype compared with *SCN5A*− patients.
- The pooled analysis demonstrated a significant association between the presence of *SCN5A* rare variants in BrS patients and the risk of MAEs, with a pooled OR of 2.14 (95% CI, 1.53–2.99; $I^2 = 29\%$).
- LoF *SCN5A*+ mutation status was associated with an elevated risk of MAEs compared with non-LoF *SCN5A* variant carriers and *SCN5A*− patients. There was no difference in MAEs between non-LoF variant carriers and *SCN5A*− BrS patients.

### Role of SCN5A in BrS clinical phenotype

Following the current expert consensus, according to the ClinGen curation of all BrS-associated genes, only *SCN5A* is associated with BrS (definitive evidence); all other genes have been classified as disputed.[30] In this systematic review and meta-analysis, including >3000 BrS patients, *SCN5A* rare variant carriers were associated with a worse clinical phenotype. In particular, compared with *SCN5A*− patients, *SCN5A*+ BrS patients presented more frequently with spontaneous type 1 ECG, history of syncope, documented VA, and ACA. Furthermore, differences in electrocardiographic characteristics, such as longer PQ and QRS intervals in *SCN5A*+ BrS patients compared with *SCN5A*− patients have been found, consistent with previous studies.[31] This can be explained by a reduction in $I_{Na}$ in *SCN5A* rare variant carriers, especially in LoF variants, with slow conduction in both atria and ventricles, as demonstrated by recent electrocardiography imaging studies.[32,33] Notably, a prolonged transatrial conduction time has been demonstrated in *SCN5A*+ patients, and this might relate to a higher risk of atrial tachyarrhythmias.[32] On the other hand, a prolonged

**Table 2** Clinical, electrocardiographic, and electrophysiologic differences between *SCN5A*+ and *SCN5A*− patients

| | *SCN5A*+ | | *SCN5A*− | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No. | Mean ± SD or No. (%) | No. | Mean ± SD or No. (%) | No. of studies | Statistical value (95% CI) | *P* | $I^2$, % |
| Clinical characteristics | | | | | | | | |
| Age, y | 408 | 40.9 ± 3.2 | 1137 | 44.7 ± 2.9 | 10 | MD = −3.95 (−6.38 to −1.51) | .002 | 77 |
| Male sex | 511 | 339 (66) | 1429 | 1061 (74) | 10 | OR = 0.82 (0.57–1.18) | .2 | 26 |
| History of syncope | 423 | 167 (39) | 1400 | 399 (29) | 8 | OR = 1.6 (1.16–2.21) | <.001 | 36 |
| History of ACA | 251 | 40 (16) | 1052 | 110 (10) | 5 | OR = 2.04 (1.24–3.34) | .04 | 0 |
| History of VT/VF | 174 | 47 (27) | 460 | 83 (18) | 4 | OR = 2.06 (1.29–3.28) | .002 | 0 |
| Family history of SCD | 497 | 165 (33) | 1477 | 312 (21) | 10 | OR = 1.51 (0.9–2.53) | .15 | 74 |
| ICD implantation | 448 | 201 (45) | 1335 | 571 (43) | 9 | OR = 1.37 (1.08–1.74) | .009 | 0 |
| History of AF | 215 | 38 (18) | 744 | 103 (14) | 6 | OR = 1.58 (0.90–2.76) | .1 | 0 |
| Electrocardiographic characteristics | | | | | | | | |
| Spontaneous type 1 ECG | 464 | 211 (45) | 1395 | 558 (40) | 10 | OR = 1.83 (1.32–2.53) | <.001 | 33 |
| P wave duration, ms | 180 | 126.3 ± 17.6 | 638 | 104.6 ± 10.4 | 3 | MD = 21.8 (6.94–36.66) | .004 | 95 |
| PR interval duration, ms | 437 | 192.4 ± 17.6 | 995 | 164.5 ± 12.5 | 8 | MD = 29.04 (19.89–38.19) | <.001 | 94 |
| QRS duration, ms | 327 | 109.5 ± 6 | 804 | 98.1 ± 8.8 | 7 | MD = 11.08 (7.70–14.47) | <.001 | 0 |
| QTc interval duration, ms | 268 | 416.4 ± 13.5 | 566 | 409 ± 20 | 5 | MD = 6.5 (−8.64 to 21.66) | .4 | 89 |
| Electrophysiologic characteristics | | | | | | | | |
| VT/VF inducibility during EPS | 159 | 89 (60) | 672 | 441 (66) | 6 | OR = 0.81 (0.55–1.20) | .31 | 26 |
| Abnormal substrate size, $cm^2$ | 126 | 9.7 ± 1.2 | 267 | 5.6 ± 0.7 | 2 | MD = 4.14 (3.65–4.62) | <.001 | 0 |
| Abnormal substrate size after provocation, $cm^2$ | 126 | 19.7 ± 1 | 267 | 12.8 ± 1.3 | 2 | MD = 6.65 (5.74–7.56) | <.001 | 0 |

ACA = aborted cardiac arrest; AF = atrial fibrillation; CI = confidence interval; ECG = electrocardiogram; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; MD = mean difference; OR = odds ratio; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

activation time has been demonstrated in the RVOT of *SCN5A* rare variant carriers and is associated with VAs in BrS.[33,34] Furthermore, longer fractionated and delayed epicardial potentials at invasive mapping have been found in *SCN5A*+ patients, and severity of abnormal substrate is a predictor of arrhythmic prognosis in BrS.[9,33,35] This study further confirmed, from a pooled analysis, a larger substrate size in *SCN5A* rare variant carriers, both at baseline and after provocation testing.

### *Prognostic role of* SCN5A *in BrS*

Results of previous studies on the role of *SCN5A* for arrhythmic prognosis have been inconsistent. Early studies did not find significant differences in MAEs between *SCN5A*+ and *SCN5A*− patients, whereas recent literature has consistently shown higher arrhythmic risk for *SCN5A*+. In analyzing these discrepancies, different points should be considered.

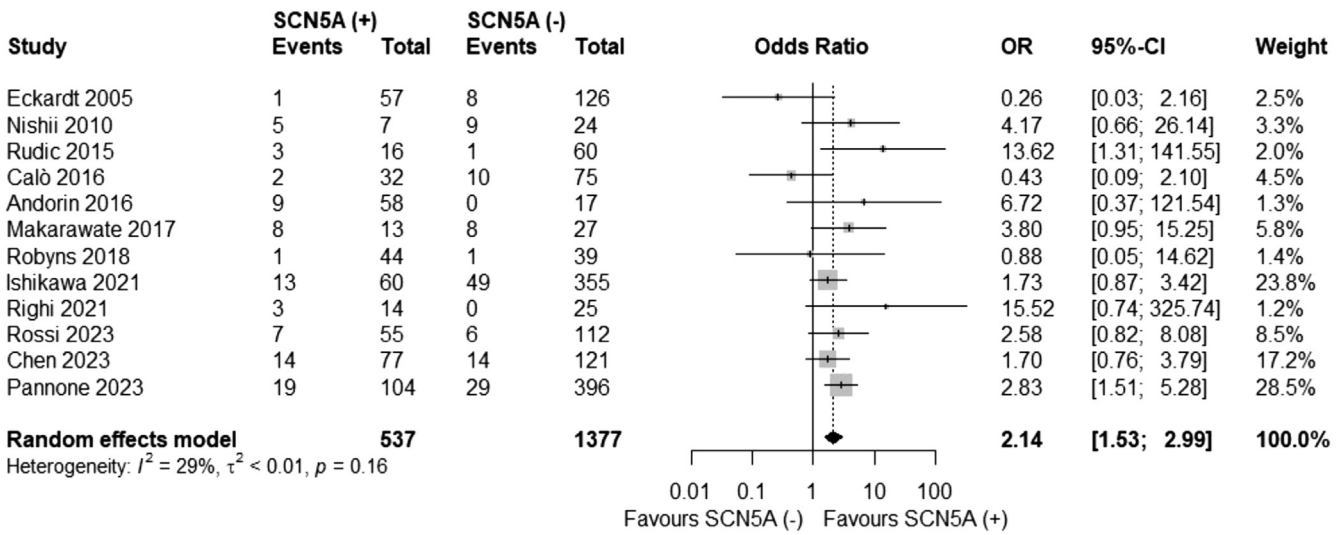


**Figure 2**
Forest plot of major arrhythmic events between *SCN5A*+ and *SCN5A*− patients. CI = confidence interval; OR = odds ratio.

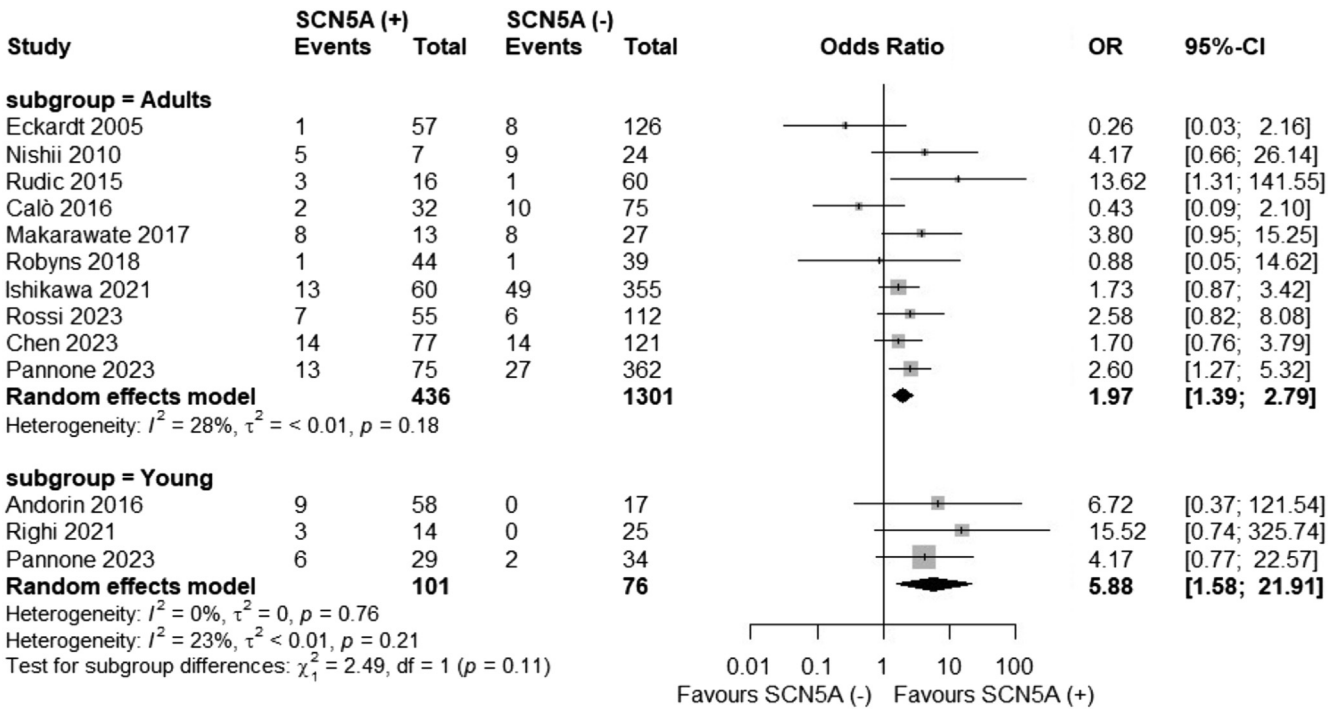


**Figure 3**
Subgroup analysis of major arrhythmic events between *SCN5A*+ and *SCN5A*− based on the age of Brugada syndrome patients. CI = confidence interval; OR = odds ratio.

### Classification of variants

Most included studies reported rare variants in *SCN5A* gene, but only a few studies reported P/LP variants following ACMG guidelines.[5] In 2015, the ACMG reviewed the criteria for the definition of P/LP variants. In a reappraisal of 408 known *SCN5A* variants, only 17% of missense variants were reclassified as P/LP for BrS by the novel ACMG guidelines.[6] Most missense P/LP variants were thus reclassified to variant of

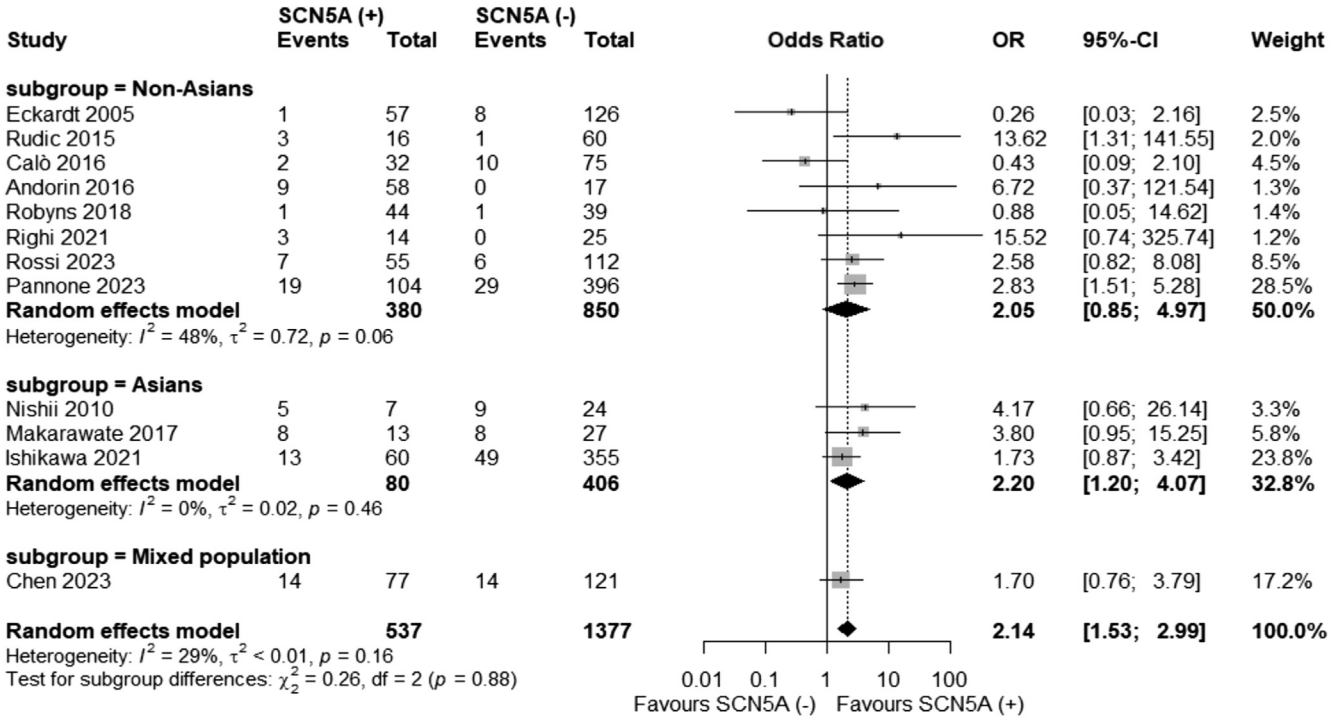


**Figure 4**
Subgroup analysis of major arrhythmic events between *SCN5A*+ and *SCN5A*− based on the ethnicity of Brugada syndrome patients. CI = confidence interval; OR = odds ratio.

uncertain significance. Standard implementation of such guidelines may lead to a conservative interpretation, especially for missense variants, and this might increase the false-negative rate. However, subanalysis comparing studies reporting P/LP *SCN5A* variants following ACMG guidelines vs studies reporting rare *SCN5A* variants without ACMG guidelines showed no difference in *SCN5A* as an arrhythmic prognosticator for MAEs.

### LoF variants vs non-LoF variants

Three of the included studies evaluated the risk of MAEs on the basis of LoF *SCN5A* variant carriers vs non-LoF variants vs *SCN5A*−. Pooled results demonstrated that LoF *SCN5A*+ mutation status was associated with an elevated risk of MAEs compared with both non-LoF *SCN5A*+ and *SCN5A*− BrS patients. There was no difference in the arrhythmic risk between non-LoF *SCN5A*+ and *SCN5A*− patients. Thus, differences in the distribution of LoF and non-LoF *SCN5A* variants in the population cohorts might explain the inconsistencies between different studies, including differences between Asian and non-Asian cohorts. The results of this study further strengthen the role of *SCN5A* testing for family screening and risk stratification in BrS. Furthermore, the role of predicted LoF variants or functional analysis for missense *SCN5A* variants is of major clinical relevance.

The main limitation of the study is consistency in reporting of rare *SCN5A* variants. This might have evolved after introduction of the ACMG classification in 2015. However, the subanalysis performed for variants classification strategy showed no differences. In addition, the diagnosis of BrS in the included studies relied on various consensus statements and guidelines, which evolved over time, potentially introducing selection bias. Another limitation is the lack of functional classification of *SCN5A* variants across all studies. Variants in non-*SCN5A* genes were outside the scope of this research. Nonetheless, the prognostic role of LoF variants in genes other than *SCN5A* may not be negligible.

## Conclusion

In BrS, *SCN5A*+ patients exhibited a worse clinical phenotype compared with *SCN5A*− patients. The pooled analysis demonstrated a significant association between *SCN5A*+ mutation status and the risk of MAEs in BrS patients; LoF *SCN5A*+ mutation status was associated with an elevated risk of MAEs compared with both non-LoF *SCN5A*+ and *SCN5A*− BrS patients.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2024.04.047.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: A.S. received research grants from Daiichi Sankyo and Bayer and has received speaker fees from Menarini and Bayer. M.L.M. is a consultant for AtriCure. P.B. received compensation for teaching purposes from Biotronik. G.C. received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, Boston Scientific, and Acutus Medical. C.dA. receives research grants on behalf of the center from Biotronik, Medtronic, Abbott, LivaNova, Boston Scientific, AtriCure, Philips, and Acutus; and received compensation for teaching purposes and proctoring from Medtronic, Abbott, Biotronik, LivaNova, Boston Scientific, AtriCure, and Acutus Medical Daiichi Sankyo. The remaining authors have nothing to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Data Availability: The data underlying this article will be shared on reasonable request to the corresponding author.

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