ESC Europace (2026) **28**, euag014
https://doi.org/10.1093/europace/euag014

CLINICAL RESEARCH

Clinical profile and prognosis of brugada syndrome *SCN5A* variant carriers with negative sodium channel blocker challenge

Elodie Surget [1,2]*, Gael Clerici [3], Frédéric Sacher [4], Raphael Martins [5], Philippe Maury [6], Isabelle Denjoy [1,2], Aurélie Thollet [7], Julien Barc [8], Jean Jacques Schott [7], Nathalie Drapier[7], Richard Redon [7], Jean Baptiste Gourraud [7], and Vincent Probst [7]

[1]Department of Pediatric Cardiology, Centre Hospitalier Universitaire Robert Debré, Université Paris Cité, 48 boulevard Sérurier, 75019 Paris, France; [2]Department of Cardiology, Reference Center for Inherited Arrhythmic Syndromes, Centre Hospitalier Universitaire Bichat–Claude Bernard, AP-HP, Université Paris Cité, 46 rue Henri Huchard, 75018 Paris, France; [3]Department of Cardiology, CHR La Réunion, Saint-Pierre, France; [4]Department of Cardiology, CHU Bordeaux, Hôpital Cardiologique du Haut-Lévêque, Bordeaux, France; [5]Department of Cardiology, CHU Rennes, Rennes, France; [6]Department of Cardiology, CHU Toulouse, Toulouse, France; [7]Department of Cardiology and Medical Genetics, Institut du Thorax, INSERM, CNRS, Université de Nantes, CHU Nantes, Nantes, France; and [8]Department of Medical Genetics, Institut du Thorax, INSERM, CNRS, Université de Nantes, CHU Nantes, Nantes, France

Received 8 September 2025; accepted after revision 9 January 2026; online publish-ahead-of-print 11 March 2026

Aims Loss-of-function (LOF) variants in *SCN5A* are associated with Brugada syndrome (BrS), progressive conduction slowing, and other arrhythmias. While the prognosis of *SCN5A* carriers with a positive sodium channel blocker challenge (SCBC) is established, data on those with negative SCBC are limited.

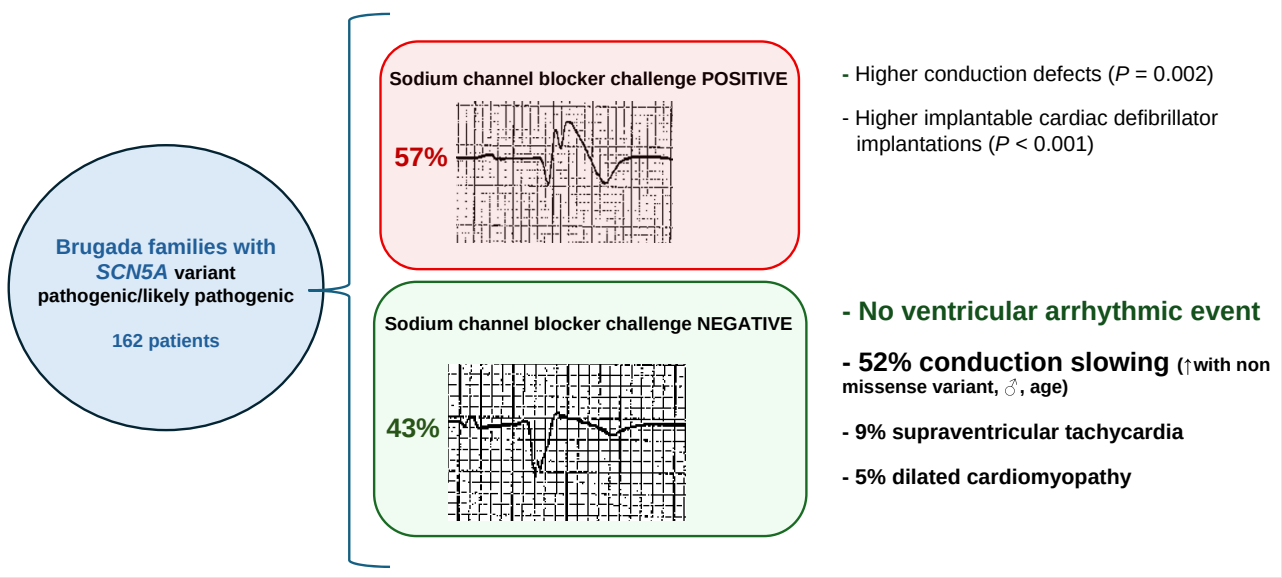
Objective To assess the clinical presentation and prognosis of *SCN5A* variant carriers with negative SCBC, and compare them to relatives with positive SCBC.

Methods and results We retrospectively included patients from five university hospitals (2000–2024) carrying a pathogenic or likely pathogenic *SCN5A* variant and negative SCBC. Relatives with the same variant and positive SCBC were also analysed. Patients with spontaneous type 1 ECG, gain-of-function variants, double variants, or ACMG class 1–3 variants were excluded. Clinical, ECG, genetic, and follow-up data were collected. Conduction slowing was evaluated using the PR interval and QRS duration. The cohort included 162 patients from 43 families (median age 37 ± 19 years, 46% male), of whom 69 (43%) had negative SCBC. Among these 69 patients, 25 (36%) had baseline intraventricular conduction defects, and 19 (28%) had first-degree AV block. After a median follow-up of 75 [40–168] months, 52% of patients developed progressive conduction slowing. Negative SCBC patients had fewer conduction defects (36% vs. 70%, p = 0.002) and ICD implantations (1% vs. 23%, $P < 0.001$). Non-missense variants were associated with more conduction slowing (71% vs. 42%, $P = 0.04$).

Conclusion This multicentre study provides the largest analysis of *SCN5A* carriers with negative SCBC, showing excellent arrhythmic prognosis despite frequent progressive conduction slowing.

* Corresponding author. Tel: +33 1 40 25 77 84, *E-mail address*: elodie.surget@aphp.fr

Graphical Abstract



Keywords SCN5A • SCBC • Ajmaline • Brugada

What's new?

- This is the largest study to date focusing on *SCN5A* variant carriers with a negative sodium channel blocker challenge (SCBC).
- Carriers with a negative SCBC showed **no ventricular arrhythmic events during long-term follow-up.**
- Despite the absence of arrhythmic risk, a substantial proportion of carriers developed progressive conduction slowing over time, with significant PR and QRS prolongation.
- **Variant type influenced phenotype**: Non-missense variants were more frequently associated with conduction slowing than missense variants.
- These findings demonstrate that **SCBC negativity identifies a subgroup with excellent arrhythmic prognosis but ongoing risk of conduction progression**, supporting SCBC as a clinically valuable stratification tool in *SCN5A* carriers.

Introduction

The voltage-gated cardiac sodium channel NaV1.5 is involved in phase 0 of the action potential and is essential for the initiation and propagation of cardiac depolarization.[1] Mutations in *SCN5A*, which encodes the α-subunit of the cardiac sodium channel, are associated with a wide spectrum of inherited arrhythmic disorders[2–4] Pathogenic loss-of-function (LOF) variants in *SCN5A* reduce INa and may cause Brugada syndrome (BrS),[5] cardiac conduction disease,[6] sick sinus syndrome,[7] atrial fibrillation,[7] and dilated cardiomyopathy.[8] LOF variants in *SCN5A* are frequently identified when genetic testing is performed in patients with unexplained (aborted) cardiac arrest or syncope at rest or during sleep. In addition, cascade screening has led to a growing number of *SCN5A* LOF variant carriers, some of whom may present no abnormalities on baseline ECG. The diagnosis of BrS is based on a specific type 1 ST-segment elevation pattern in the right precordial leads.[9] In patients without a spontaneous type 1 ECG pattern, a sodium channel blocker challenge (SCBC) is commonly used to unmask the ECG pattern.[9,10] While the clinical course and prognosis of patients with *SCN5A* variants and a positive SCBC are well established, those of patients with *SCN5A* variants and a negative SCBC remain poorly defined. The aim of this study was:

(1) to evaluate the clinical presentation of patients with *SCN5A* variants and negative SCBC; and (2) to compare their clinical phenotype with that of carriers of the same variant but with a positive SCBC, to help clinicians in the management and follow-up of these patients.

Methods

Study design and population

We retrospectively included consecutive patients from five university hospitals between 2000 and 2024 who carried a pathogenic or likely pathogenic variant in *SCN5A* (according to ACMG classification[11]) and had a negative SCBC. Their relatives carrying the same variant but with a positive SCBC were also analysed. Patients with a spontaneous type 1 ECG pattern at baseline, gain-of-function variants with prolonged QT interval, double variants, or ACMG class 1, 2, or 3 variants were excluded.

Clinical data, including demographic characteristics, medical history, family history of sudden cardiac death (SCD), and device implantation, were collected from electronic health records. Patients were categorized as symptomatic if they had a history of aborted cardiac arrest (CA), symptomatic or sustained ventricular tachycardia, symptomatic and documented atrial tachyarrhythmia or bradyarrhythmia, or arrhythmogenic syncope. Arrhythmic events—defined as the occurrence of SCD, appropriate ICD shock, sustained ventricular arrhythmia (VA), or syncope suspected to be of VA origin—were evaluated only during the follow-up period after the sodium channel blocker challenge (SCBC), to exclude events that occurred before phenotypic characterization. Clinical follow-up data were collected

prospectively directly from patients or from their referring cardiologists. The study complied with European guidelines for clinical and genetic research. Written informed consent was obtained from all participants.

ECG data and SCBC

The diagnosis of BrS was based on the 2013 criteria: the presence of a typical type 1 ECG pattern, either spontaneous or pharmacologically induced, in at least one right precordial lead (V1, V2, V3) placed in the 2nd, 3rd, or 4th intercostal space. Type 1 ST-segment elevation was defined as a J-wave elevation >0.2 mV, followed by a coved-type ST elevation and a negative T wave.

Before the publication of the recent consensus document on sodium channel blocker testing in Brugada syndrome,[12] SCBC was routinely performed in most participating centres irrespective of SCN5A variant status, often before genetic results were available, in order to establish the phenotypic status of family members. Around 2005, most centres progressively transitioned from flecainide to ajmaline as the preferred agent, in accordance with emerging evidence and subsequent guideline recommendations.

In all patients, the SCBC was performed using intravenous ajmaline or flecainide according to recommended protocols. The test was indicated either for the diagnostic evaluation of a suspected Brugada syndrome, unexplained syncope, or family screening in the context of an identified *SCN5A* variant. After obtaining informed consent, ajmaline was administered at a maximal dose of 1 mg/kg (up to 100 mg) infused over a period of 10 min, with continuous 12-lead ECG and blood pressure monitoring. Flecainide was given intravenously at a maximal dose of 2 mg/kg (up to 150 mg), infused continuously over 10 min, following the same safety precautions and monitoring protocol. SCBC was discontinued in the event of a type 1 ECG pattern, premature ventricular complexes or ventricular tachycardia, marked QRS prolongation (>130 ms of baseline), or the occurrence of second- or third-degree atrioventricular block; in addition, a rapid and abrupt increase in QRS duration, even below the 130% threshold, was considered an indication to immediately stop the test. Upon appearance of these safety criteria, ajmaline administration was immediately stopped, and intravenous sodium bicarbonate was administered when appropriate. After termination of ajmaline administration, continuous ECG monitoring was maintained for a minimum of 60 min, or until complete regression of conduction abnormalities. In families in which other members had previously demonstrated significant QRS widening during sodium channel blocker testing, particular attention was paid to strict QRS monitoring during the test, and in selected high-risk cases, temporary pacing was considered before pharmacological challenge. If the full dose could not be administered and no type 1 pattern occurred, the test was considered inconclusive, and these patients were excluded.

All ECGs were analysed at baseline, during SCBC, and during follow-up. Heart rate, PQ interval, QRS duration, and QT interval were measured. The QT interval was measured using the tangent method and corrected using Bazett's formula. The increase in PQ and QRS duration during SCBC was calculated as: (max PQ during SCBC—baseline PQ) and (max QRS during SCBC—baseline QRS), respectively, where baseline values refer to ECG measurements immediately before drug infusion. Interventricular (IV) conduction defect was defined as complete or incomplete right (RBBB) or left bundle branch block (LBBB), left anterior fascicular block (LAFB), left posterior fascicular block (LPFB), or intraventricular conduction delay. Conduction disease was defined as first-, second-, or third-degree AV block. Progressive conduction delay was defined as PR interval >200 ms, QRS duration >120 ms, and/or sinus node dysfunction (atrial standstill, symptomatic bradyarrhythmia, or sinus arrest >3 s) in the absence of a BrS pattern.

Genetic analysis

The SCN5A gene was screened in all probands, while relatives underwent targeted testing for the familial variant identified in the corresponding proband. Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28 exons of SCN5A were amplified by polymerase chain reaction (PCR) employing intronic primers. PCR products were initially screened for variants using denaturing high-performance liquid chromatography (dHPLC) or high-resolution melting (HRM) analysis. Samples with abnormal profiles were subsequently subjected to DNA sequencing for variant confirmation. Variants were annotated according to the SCN5A cDNA reference sequence (GenBank NM_198056). The study was conducted in accordance with European guidelines for clinical and genetic research and was approved by institutional ethics committees. Written informed consent was obtained from all participants before inclusion.

Statistical analysis

Continuous variables were expressed as mean ± SD or median [IQR] according to distribution. Comparisons between groups were made using the Student's *t*-test or Wilcoxon rank-sum test for continuous variables, and the Chi² test or Fisher's exact test for categorical variables. Correlations were assessed using Pearson's or Spearman's method. A *P*-value <0.05 was considered statistically significant. Analyses were performed using R++ software.

Results

Study population

The study included 162 consecutive patients from 43 families (median age 37 ± 19 years), of whom 74 (46%) were male. SCBC was positive in 93 (57%) patients and negative in 69 (43%). Ajmaline was used in 131 (81%) and flecainide in 31 (19%), with the SCN5A variant status unknown before SCBC in 92% of patients tested with flecainide. Overall, 54 patients underwent SCBC before 2005 and 108 after the protocol transition favouring ajmaline, while 75 patients were tested before 2009 and 87 thereafter. In the combined cohort, 18 (11%) were probands, and 13 (8%) were symptomatic. Population characteristics are summarized in *Table 1*. An example of a family with the same *SCN5A* variant but different SCBC responses is shown in *Figure 1*.

It is important to note that SCBC was prematurely terminated for safety reasons in two patients because of marked conduction abnormalities occurring during the test. Both patients were tested using ajmaline. In one patient, significant conduction abnormalities developed during SCBC despite the absence of baseline conduction disturbances. In the second patient, who already presented severe baseline conduction abnormalities (QRS duration 190 ms), conduction further worsened during SCBC and degenerated into ventricular fibrillation. These patients were excluded from the main analysis but are reported separately due to their more severe phenotype.

Clinical characteristics and prognosis of negative SCBC

Among the 69 patients with negative SCBC, 25 (36%) had baseline IV conduction defects (complete RBBB in 2, incomplete RBBB in 10, complete LBBB in 1, incomplete LBBB in 2, LAFB in 3, atypical IV bundle branch block in 6, bifascicular block in 1), and 19 (28%) had first-degree AV block (*Table 1*). Sinus node dysfunction was present in three patients.

After a median follow-up of 75 [40–168] months, 36 (52%) patients (58% male, mean age 52 ± 20 years) had conduction slowing (Tables *2* and *3*). In the 40 patients (58%) with available follow-up ECGs, PQ and QRS durations significantly increased (188 ± 31 ms vs. 177 ± 33 ms, $P < 0.001$ and 107 ± 22 ms vs. 99 ± 15 ms, $P < 0.001$). Occurrence of conduction slowing was associated with an older age (52 ± 20y vs. 37 ± 17y, *P* 0.003) and male sex (58% vs. 30%, $P = 0.03$) (*Table 3*).

Table 1 Clinical characteristics of the study population

		Groups		Combined cohort
		Negative SCBC	Positive SCBC	
Total		69 (43%)	93 (57%)	162
Age (years)		40 ± 19	35 ± 19	37 ± 19
Sex (male)		31 (45%)	43 (46%)	74 (46%)
Syncope		3 (4%)	13 (14%)	16 (10%)
Proband		2 (3%)	16 (17%)	18 (11%)
Familial history of SCD		29 (42%)	37 (40%)	66 (41%)
ECG parameters at inclusion				
HR (bpm)		68 ± 15	68 ± 11	68 ± 13
PQ (ms)		180 ± 30	186 ± 37	184 ± 34
QRS (ms)		102 ± 16	101 ± 15	101 ± 15
QTc (ms)		418 ± 32	406 ± 38	411 ± 36
Conduction abnormalities at inclusion				
IV conduction defect		25 (36%)	50 (54%)	75 (46%)
Conduction disease		19 (28%)	31 (33%)	50 (31%)
Symptomatic		6 (9%)	7 (7%)	13 (8%)
SVT		6 (9%)	4 (4%)	10 (6%)
Future arrhythmic events		0	2/92 (2%)	2/158 (1%)
SCD or aborted CA		0	1 (1%)	1 (0.6%)
Appropriate ICD shock		0	1 (1%)	1 (0.6%)
VA		0	0	0
Arrhythmogenic syncope		0	0	0
Device		2 (3%)	21 (23%)	23 (14%)
PM		1 (1%)	0	1 (1%)
ICD		1 (1%)	21 (23%)	22 (14%)
Dilated cardiomyopathy		3 (5%)	0	3 (2%)
Death		3 (4%)	6 (6%)	9 (6%)
Variant type	Missense	45 (65%)	67 (72%)	112 (69%)
	Non missense	24 (35%)	26 (28%)	50 (31%)
Molecule used	Ajmaline	53 (77%)	78 (84%)	131 (81%)
	Flecainide	16 (23%)	15 (16%)	31 (19%)

This table summarizes demographic and baseline ECG characteristics, including heart rate, PQ and QRS intervals, and presence of conduction abnormalities. Comparisons between SCBC-negative and SCBC-positive patients are shown. Values are presented as mean ± SD or as *n* (%). SCBC, sodium channel blocker challenge; SCD, sudden cardiac death.

In the negative SCBC group, one patient (2%) experienced syncope due to paroxysmal high-degree AV block and sinus node dysfunction, requiring pacemaker implantation; however, this patient was of advanced age, and a degenerative mechanism cannot be excluded as a confounding factor. Another patient received an ICD for severe progression of IV conduction defect and multiple family histories of SCD. Three patients (5%) developed dilated cardiomyopathy, and six (9%) had supraventricular tachycardia (SVT), including atrial fibrillation ($n = 3$), atrial flutter ($n = 2$), and focal atrial tachycardia ($n = 1$). Three patients (3%) died, one from cardiac cause (heart failure). Importantly, no ventricular arrhythmic events were observed during follow-up.

After a mean follow-up of 108 ± 84 months, compared with positive SCBC patients (Tables 4 and 7) negative SCBC patients had less IV conduction defect (36% vs. 70%, $P = 0.002$) and ICD implantations (23% vs. 1%, $P < 0.001$).

Genotype-prognosis correlation

All patients carried *SCN5A* heterozygote variants: 153 class 5 ACMG and 9 class 4. Missense variants were present in 112 (69%) patients, and non-missense variants in 50 (31%) (splicing in 20, nonsense in 15, frameshift in 15) (*Table 5*). Among negative SCBC patients, non-missense variants ($n = 24$, 35%) were associated with greater conduction slowing than missense variants ($P = 0.04$). Variants were mostly (44, 76%) located in domains DI to DIV, and 14 localized to the S5, *P*-loop, and S6 regions containing the pore filter of the sodium channel (*Table 6*). Variants in the pore region were not significantly

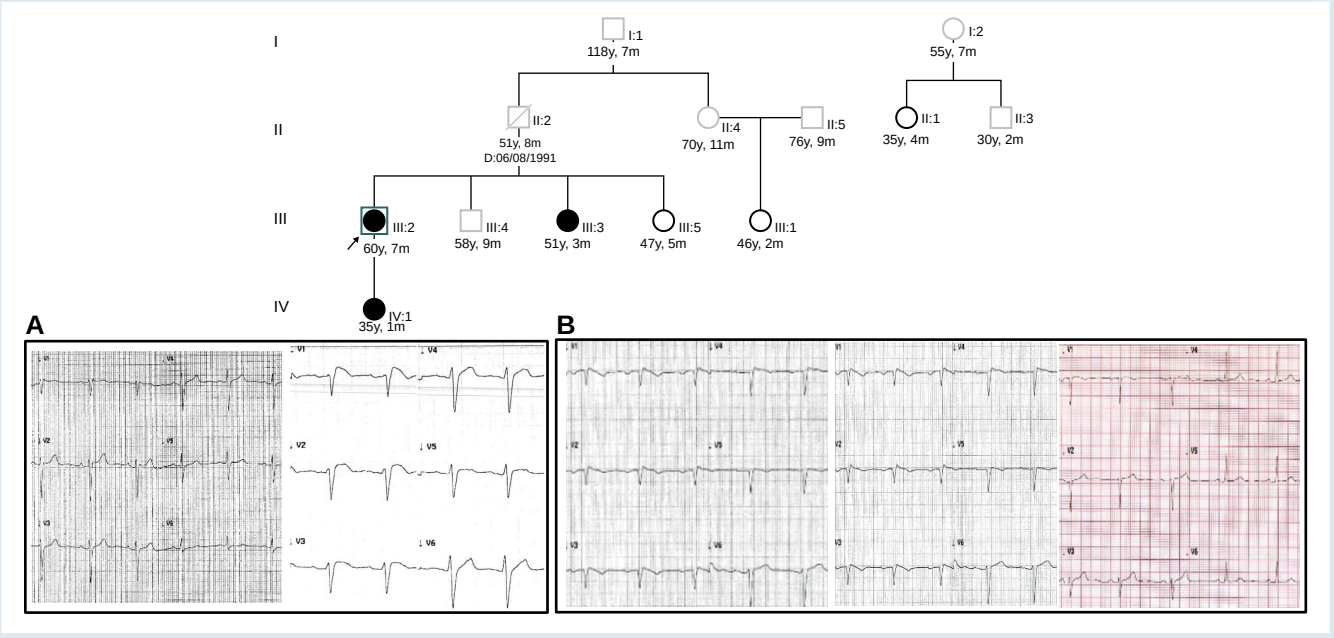


Figure 1 Example of a family with missense SCN5A variant and SCBC negative and positive. Panel A: Patient III:2 : Left: Baseline ECG: HR 54bpm, PQ 182 ms, QRS 87 ms, QTc 388 . Right: Positive Ajmaline test*. Panel B: Patient III:5 : Left: Baseline ECG. Middle: Negative ajmaline test*. Right: baseline ECG 6 years after with the apparition of conduction disease: HR 58bpm, PQ 202 ms, QRS 85 ms, QTc 392. * For ajmaline test, V1 and V2—fourth intercostal space, V3 and V4—third intercostal space, and V5 and V6—second intercostal space.

Table 2 Risk for developing conduction disease in negative SCBC patients

		No conduction slowing *N* = 33 (48%)	Conduction slowing *N* = 36 (52%)	*P*
Clinical characteristics				
Sex (male)		10 (30%)	21 (58%)	**0.03**
Age at the last ECG (years)		37 ± 17	52 ± 20	**0.003**
Proband		1 (3%)	1 (3%)	0.99
Syncope		1 (3%)	2 (6%)	0.99
Familial history of SCD		11 (33%)	18 (50%)	0.2
SVT		2 (6%)	4 (11%)	0.7
ECG parameters under SCBC				
PQ before drug infusion		165 ± 28	194 ± 25	**<0.001**
QRS before drug infusion		94 ± 12	110 ± 16	**<0.001**
PQ max under SCBC		216 ± 39	236 ± 43	**0.03**
QRS max under SCBC		132 ± 22	161 ± 42	**<0.001**
Δ PQ SCBC		51 ± 24	45 ± 34	0.4
Δ QRS SCBC		37 ± 24	50 ± 35	0.1
Variant type	missense	26 (79%)	19 (53%)	**0.04**
	non missense	7 (21%)	17 (47%)	
Variant in pore region (*N* = 58)		7 (22%)	7 (27%)	0.8

The timeline corresponds to the interval between the first ECG and the first occurrence of either new conduction abnormalities or worsening of pre-existing conduction disturbances during follow-up. Values are presented as mean ± SD or as *n* (%). CA, conduction abnormality; SCBC, sodium channel blocker challenge; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VA, ventricular arrhythmia.

Table 3 Evolution of ECG parameters in negative SCBC patients

N = 40	Baseline	Last ECG	*P*
ECG parameters			
HR (bpm)	68 ± 17	68 ± 11	**0.02**
PQ (ms)	177 ± 33	188 ± 31	**<0.001**
QRS (ms)	99 ± 15	107 ± 22	**<0.001**
QTc (ms)	419 ± 33	422 ± 37	**<0.001**
SVT	1 (3%)	5 (13%)	0.1
Conduction abnormalities			
Isolated			
PR > 200ms	7	11	0.3
QRS > 120ms	1	3	0.3
SND	0	0	1
Combined			
↑PR > 200 ms and QRS > 120ms	2	4	0.4
↑PR > 200 ms and SND	0	0	1
↑QRS > 120 ms and SND	0	0	1
↑PR > 200 ms, QRS and SND	0	0	1

This table shows baseline and follow-up PR and QRS intervals, and highlights progression of conduction disturbances in the last ECG available. Values are presented as mean ± SD or as *n* (%). CA, conduction abnormality; HR, heart rate; SCBC, sodium channel blocker challenge; SVT, supraventricular tachycardia.

Table 4 Clinical evolution according to SCBC test

	Groups		*P*
	Negative SCBC	Positive SCBC	
Syncope	3 (4%)	13 (14%)	0.06
Symptomatic	6 (9%)	7 (7%)	0.8
ECG parameters at inclusion			
HR (bpm)	68 ± 15	68 ± 11	0.6
PQ (ms)	180 ± 30	186 ± 37	0.5
QRS (ms)	102 ± 16	101 ± 15	0.7
QTc (ms)	418 ± 32	406 ± 38	**0.02**
Conduction abnormalities at inclusion	25 (36%)	50 (54%)	**<0.001**
IV conduction defect	19 (28%)	31 (33%)	0.5
Conduction disease			
Last ECG parameters			
HR (bpm)	68 ± 11	64 ± 8	0.2
PQ (ms)	188 ± 31	191 ± 32	0.7
QRS (ms)	107 ± 22	113 ± 18	**0.03**
QTc (ms)	422 ± 37	423 ± 28	0.5
Last Conduction abnormalities			
IV conduction defect	14 (36%)	31 (70%)	**0.002**
Conduction disease	19 (28%)	31 (33%)	0.5
Device			
PM	1 (1%)	0	0.4
ICD	1 (1%)	21 (23%)	**<0.001**
SVT	6 (9%)	4 (4%)	0.3
Future arrhythmic events	0	2/92 (2%)	0.2
SCD or aborted CA	0	1 (1%)	
Appropriate ICD shock	0	1 (1%)	
VA	0	0	
Arrhythmogenic syncope	0	0	
Dilated cardiomyopathy	3 (5%)	0	0.07
Death	3 (4%)	6 (6%)	0.7

This table includes only post-SCBC events. Values are presented as mean ± SD or as *n* (%). HR, heart rate; ICD, implantable cardiac defibrillator; IV, intraventricular; PM, pacemaker; SVT, supraventricular tachycardia; VA, ventricular arrhythmia.

associated with conduction slowing occurrence (27%, vs. 22%, *P* = 0.8).

Discussion

In this large multicentre cohort, we provide the most comprehensive analysis to date of *SCN5A* variant carriers with a negative SCBC. Our analysis confirms that despite the absence of inducible Brugada ECG patterns, a substantial proportion of these patients exhibit baseline conduction abnormalities and experience progressive conduction disease over long-term follow-up. Moreover, structural cardiac involvement, including dilated cardiomyopathy, was observed, underscoring the clinical heterogeneity and complexity of *SCN5A* LOF variants beyond BrS phenotypes. However, importantly, compared to positive SCBC patients, none of them presented an arrhythmic event. These findings emphasize that a negative SCBC identifies patients with excellent arrhythmic prognosis while still requiring monitoring for conduction and structural abnormalities.

Clinical evolution of negative SCBC

The clinical heterogeneity of *SCN5A* LOF variants has been well established,[2–4,13] with phenotypes ranging from BrS[5] to isolated cardiac conduction disease,[6] atrial arrhythmias,[7] and, more rarely, dilated cardiomyopathy.[8] Most prior studies have focused on BrS patients, often identified by a positive SCBC or spontaneous type 1 ECG pattern[14–16] Our findings strongly support that a negative SCBC identifies a subgroup of *SCN5A* carriers with a favourable arrhythmic prognosis. During a median follow-up of more than 6 years, no patient experienced ventricular arrhythmias or sudden cardiac death, which is reassuring for both clinicians and patients. Although the difference in post-SCBC arrhythmic events between negative and positive SCBC patients is no longer significant after excluding those with prior ventricular arrhythmias, performing the SCBC remains clinically valuable. It allows the identification of two phenotypically distinct groups, with SCBC-positive patients exhibiting more pronounced conduction and electrical abnormalities, challenging

Table 5 Clinical characteristics and evolution in negative SCBC patients according to variant type

	Missense	Non missense	*P*
Total	45 (65%)	24 (35%)	
Syncope	3 (7%)	0	0.5
Symptomatic	5 (12%)	1 (4%)	0.4
Familial history of SCD	17 (38%)	12 (50%)	0.4
ECG parameters			
HR (bpm)	69 ± 17	66 ± 11	0.6
PQ (ms)	173 ± 29	194 ± 29	**0.009**
QRS (ms)	100 ± 14	107 ± 18	0.1
QTc (ms)	421 ± 34	412 ± 27	0.6
ECG parameters under SCBC			
PQ max under SCBC	212 ± 31	253 ± 47	**0.002**
QRS max under SCBC	140 ± 26	161 ± 50	0.06
Δ PQ SCBC	42 ± 25	59 ± 34	**0.05**
Δ QRS SCBC	39 ± 24	52 ± 39	**0.05**
Dilated cardiomopathy	3 (8%)	0	0.5
PCCD	19 (42%)	17 (71%)	**0.04**
IV conduction defect	10 (22%)	15 (63%)	**0.001**
Conduction disease	8 (18%)	11 (46%)	**0.02**
SVT	5 (12%)	1 (4%)	0.4
Device implantation			
PM	1 (2%)	0	0.99
ICD	0	1 (4%)	0.3

Values are presented as mean ± SD or as *n* (%). CA, conduction abnormality; HR, heart rate; ICD, implantable cardiac defibrillator; IV, intraventricular; PM, pacemaker; SCD, sudden cardiac death; SVT, supraventricular tachycardia; VA, ventricular arrhythmia.

recent guidelines[12] that questioned the utility of SCBC in *SCN5A* carriers.

Despite this favourable arrhythmic profile, progressive conduction disease was common. At baseline, more than one third of patients already had conduction abnormalities, and nearly half developed conduction disease during follow-up. Conduction disease development was associated with older age and male sex. The association of male sex with higher conduction disease occurrence aligns with previous studies, indicating sex-specific differences in BrS prognosis.[17] Furthermore, patients without conduction disease were younger, suggesting that with longer follow-up, they might develop conduction disease, and that its prevalence is likely underestimated given the relatively young mean age of the negative SCBC population (40 ± 19 years). In our cohort, six families showed consecutive transmission of a phenotype-negative status, with SCN5A variant carriers remaining phenotype-negative across generations, including negative sodium channel blocker challenges. Although not formally assessed, this observation suggests that phenotype negativity may cluster within specific family lineages. Importantly, although PQ and QRS durations increased during SCBC, this change did not predict future conduction disease progression, since these intervals were already prolonged at baseline in patients who later developed conduction disease. Thus, conduction slowing under SCBC reflects baseline electrophysiological abnormalities rather than a dynamic marker of progression. One patient, who was elderly, developed complete atrioventricular block requiring pacemaker implantation—an evolution that may have been influenced by age-related degenerative conduction changes, representing a potential confounding factor. In addition, SVTs (atrial fibrillation, atrial flutter, or focal atrial tachycardia) were observed in several patients, consistent with prior reports[18] of atrial arrhythmias in *SCN5A* loss-of-function carriers. These observations emphasize the broad electrophysiological spectrum of *SCN5A* variants even in the absence of Brugada phenotypes.

Genotype-phenotype correlation

Few studies have specifically analysed *SCN5A* variant carriers with a negative SCBC[19–21] Bezzina et al.[22] and Probst et al.[20] described families in which conduction disease predominated without BrS ECG patterns, often linked to truncating variants. Our results corroborate these findings: among negative SCBC patients, those with non-missense variants (including truncating and splicing variants; $n = 24$, 35%) had significantly more conduction disease (71% vs. 42%, $P = 0.04$) and longer PQ intervals during SCBC (253 ± 47 ms vs. 212 ± 31 ms, $P = 0.02$). This aligns with functional studies indicating that such variants generally result in haploinsufficiency or non-functional channels, leading to marked conduction slowing[23–25] In contrast, missense variants often have variable functional effects, sometimes involving mixed loss- and gain-of-function properties. Notably, Crotti et al.[26] reported that some missense *SCN5A* variants may lead to isolated conduction slowing or atrial arrhythmias without typical Brugada ECG patterns, supporting the heterogeneity of functional consequences. From a mechanistic perspective, the absence of BrS ECG pattern despite significant conduction slowing may reflect uniform conduction delay without the right ventricular outflow tract heterogeneities required to unmask a Brugada phenotype.

In our study, variants were mostly (44, 76%) located in domains DI to DIV, and 14 were localized to the S5, *P*-loop, and S6 regions containing the pore filter of the sodium channel. Although patients with conduction disease appeared to have more variants in the pore region, this difference was not significant (27% vs. 22%, $P = 0.8$). This finding contrasts with other studies showing an association between pore variants and arrhythmic events.[27] This lack of significance may be explained by the relatively small sample size in our study.

Structural cardiac involvement

An additional observation was the occurrence of dilated cardiomyopathy in three patients with negative SCBC. Although rare, this finding is consistent with prior reports linking *SCN5A* LOF variants to overlap syndromes,[13] especially for variants located in the S3–S4 linker or pore-forming segments. Our data support the notion that dilated cardiomyopathy, although infrequent, should be considered in the long-term surveillance of *SCN5A* variant carriers, regardless of SCBC results.

Implications for clinical management

In SCBC-negative *SCN5A* variant carriers, no ventricular arrhythmias were observed during follow-up. Nevertheless, some patients developed progressive conduction abnormalities, supraventricular arrhythmias, or, more rarely, dilated cardiomyopathy, highlighting the need for ongoing clinical surveillance. Routine intensive arrhythmic monitoring (e.g. Holter) is generally not

Table 6 Identified variants in the SCN5A gene in negative SCBC patients

Nucleotide change	Protein change	Variant type	No. of patients	No of SCBC-	No of SCBC+	ACMG Class	Domain localization
c.612-2A > G	NA	splicing	1	1	0	5	N-terminal
c.617del	p.Thr206Lysfs*22	frameshift	3	2	1	5	N-terminal
c.673C > T	p.Arg225Trp	missense	9	8	1	5	Domain I—segment S1
c.718G > A	p.Val240Met	missense	1	1	0	5	Domain I—segment S1–S2 linker
c.1036G > T	p.Glu346*	nonsense	2	1	1	5	Domain I—segment S6
c.1603C > T	p.Arg535*	nonsense	4	2	2	5	Domain I—segment S6
c.1983_1993dup	p.Ala665Glyfs*16	frameshift	11	2	9	5	Domain II—S2–S3 linker
c.2204C > T	p.Ala735Val	missense	6	2	4	5	Domain II—segment S4
c.2254G > A	p.Gly752Arg	missense	9	2	7	5	Domain II—segment S4–S5 linker
c.2516T > C	p.Leu839Pro	missense	1	1	0	5	Domain II—segment S5–S6 linker
c.2633G > A	p.Arg878His	missense	5	2	3	5	Domain II—segment S6
c.3694C > T	p.Arg1232Trp	missense	22	5	17	5	Domain III—segment S6
c.3840 + 1G > A	NA	splicing	2	1	1	5	Intron between exons 21–22
c.3963 + 2T > C	NA	splicing	9	7	2	5	Intron between exons 22–23
c.4140C > G	p.Asn1380Lys	missense	3	1	2	5	Domain IV—N-terminus
c.4145G > T	p.Ser1382Ile	missense	3	3	0	5	Domain IV—N-terminus
c.4222G > A	p.Gly1408Arg	missense	1	1	0	5	Domain IV—segment S1
c.4299G > T	p.Gly1433Gly	missense	1	1	0	5	Domain IV—segment S2
c.4534C > T	p.Arg1512Trp	missense	2	1	1	4	Domain IV—segment S4
c.4719C > T	p.Gly1573=	splicing	6	2	4	5	Domain IV—S4–S5 linker
c.4747C > T	p.Arg1583Cys	missense	2	1	1	4	Domain IV—segment S5
c.4810G > A	p.Val1604Met	missense	6	2	4	5	Domain IV—segment S5–S6 linker
c.4885C > T	p.Arg1629*	nonsense	5	2	3	5	Domain IV—segment S6
c.4895G > A	p.Arg1632His	missense	4	1	3	5	Domain IV—segment S6
c.4912C > T	p.Arg1638*	nonsense	1	1	0	5	Domain IV—segment S6
c.4981G > A	p.Gly1661Arg	missense	1	1	0	4	C-terminal
c.5015C > A	p.Ser1672Tyr	missense	4	1	3	5	C-terminal
c.5083C > T	p.Gln1695*	nonsense	3	1	2	5	C-terminal
c.5164A > G	p.Asn1722Asp	missense	10	4	6	5	C-terminal
c.5350G > A	p.Glu1784Lys	missense	13	4	9	5	C-terminal
c.5368G > A	p.Asp1790Asn	missense	6	1	5	5	C-terminal
c.5461del	p.Leu1821Cysfs*13	frameshift	1	1	0	5	C-terminal
c.5596G > A	p.Gly1866Arg	missense	3	2	1	4	C-terminal

This table provides a detailed overview of all SCN5A variants detected in the cohort, including variant type and predicted pathogenicity. Columns indicate: No. of patients = total number of carriers of the variant in the study; No. of SCBC– = number of SCBC-negative patients carrying the variant; No. of SCBC + = number of SCBC-positive patients carrying the variant. This allows comparison of variant distribution according to SCBC response.

required; periodic ECG every 3–5 years in stable patients appears appropriate, with escalation to Holter or loop recorder if conduction worsening is detected.

These findings also reopen the debate on the utility of SCBC in *SCN5A* carriers. Although recent guidelines[12] have questioned its role due to potential safety concerns, SCBC can differentiate two phenotypically distinct populations. In our study, two patients were excluded from analysis because SCBC could not be safely completed: in one patient, significant conduction abnormalities appeared during SCBC that were absent at baseline; in the other

Table 7 Evolution of ECG parameters in positive SCBC patients

	Baseline	Last ECG	*P*
ECG parameters			
HR (bpm)	68 ± 11	64 ± 8	**0.002**
PQ (ms)	186 ± 37	191 ± 32	**<0.001**
QRS (ms)	101 ± 15	113 ± 18	**<0.001**
QTc (ms)	406 ± 38	423 ± 28	**<0.001**

This table shows baseline and follow-up PR and QRS intervals, and highlights progression of conduction disturbances in the last ECG available. Values are presented as mean ± SD or as *n* (%). CA, conduction abnormality; HR, heart rate; SCBC, sodium channel blocker challenge; SVT, supraventricular tachycardia.

patient, who had severe baseline conduction abnormalities (QRS 190 ms), conduction worsened during SCBC and degenerated into ventricular fibrillation, highlighting that SCBC should be avoided in patients with severe baseline conduction disturbances. Importantly, both prematurely terminated sodium channel blocker challenges occurred during ajmaline administration. No patient with known severe baseline conduction abnormalities underwent flecainide testing. Given the prolonged half-life of flecainide, sodium channel blocker testing with flecainide should be avoided in SCN5A loss-of-function variant carriers presenting baseline conduction disturbances. Although the transition to ajmaline occurred around 2005, the two SCBCs prematurely terminated for safety reasons were performed later (in 2014 and 2016), illustrating that adverse conduction responses may still occur despite protocol optimization. The issue of stopping criteria during ajmaline challenge remains debated. Batchvarov et al.[28] reported that in a substantial proportion of positive tests, QRS prolongation >130% preceded the development of a diagnostic type 1 pattern, suggesting that overly strict stopping rules might theoretically reduce test sensitivity. However, ventricular tachyarrhythmias induced by sodium channel blockers are unpredictable, difficult to control, and may be life-threatening. From our perspective, marked or rapidly progressive QRS widening represents a key safety signal and a prerequisite for malignant arrhythmias, justifying immediate test termination. This conservative approach is supported by a large safety series of ajmaline testing,[29] in which a very low incidence of serious complications was observed when consensus-based stopping criteria and monitoring protocols were strictly applied.

In clinical practice, patients carrying SCN5A loss-of-function variants are systematically advised to avoid drugs with sodium channel–blocking properties,[30] as listed on BrugadaDrugs.org,[31,32] even in the absence of a provocable Brugada phenotype. However, we currently lack prospective data assessing the effects of these medications on conduction parameters or clinical outcomes in SCBC-negative SCN5A carriers.

Limitations

Our study has several limitations, including its retrospective design and potential selection bias, as patients were recruited from tertiary referral centres which may not represent the broader population of *SCN5A* variant carriers. A potential selection bias must be acknowledged. This study specifically focused on SCN5A variant carriers with at least one family member presenting a discordant SCBC result, which inherently limited the number of eligible patients. The total number of patients undergoing SCBC with or without SCN5A variants during the same period was substantially larger. Additionally, reliance on electronic health records for data collection may have introduced information bias or missing data. Importantly, some negative SCBC patients lacked follow-up ECGs, and these patients generally underwent less intensive clinical surveillance and fewer complementary examinations compared to positive SCBC patients. This reduced follow-up intensity might have led to an underestimation of the true prevalence of conduction disease progression and arrhythmic events in the negative SCBC group. Moreover, heterogeneity in follow-up duration and evolving management strategies over the study period could have influenced the observed outcomes. Importantly, some patients underwent SCBC using flecainide, which is less sensitive than ajmaline in unmasking Brugada ECG patterns; consequently, drug-induced Brugada changes may have gone undetected in certain negative-SCBC patients tested with flecainide. Finally, the relatively young mean age of the negative SCBC cohort (40 ± 19 years) limits extrapolation to older populations, and longer-term follow-up is needed to fully assess disease progression in this subgroup.

Conclusion

In summary, this study demonstrates that carriers of *SCN5A* variants with a negative SCBC have an excellent arrhythmic prognosis, with no ventricular events observed during long-term follow-up. Nevertheless, they frequently develop progressive conduction disease, occasionally severe enough to require pacing, and in rare cases, may develop dilated cardiomyopathy. These findings highlight the importance of distinguishing negative from positive SCBC patients, as their prognoses differ fundamentally. Negative SCBC patients can be reassured regarding arrhythmic risk, but should remain under periodic—though potentially less frequent—surveillance focused on conduction and structural progression.

Conflict of interest: None declared.

Funding

No Funding.

Data availability

The data underlying this article cannot be shared publicly due to patient privacy and ethical restrictions. The anonymized data will be made available to qualified researchers upon reasonable request to the corresponding author.

References

1. Pierre M, Djemai M, Poulin H, Chahine M. Nav1.5 knockout in iPSCs: a novel approach to study NaV1.5 variants in a human cardiomyocyte environment. *Sci Rep* 2021;**11**:17168.
2. Laurent G, Saal S, Amarouch MY, Béziau DM, Marsman RFJ, Faivre L *et al.* Multifocal ectopic purkinje-related premature contractions: a new SCN5A-related cardiac channelopathy. *J Am Coll Cardiol* 2012;**60**:144–56.
3. Mizusawa Y, Horie M, Wilde AAM. Genetic and clinical advances in congenital long QT syndrome. *Circ J Off J Jpn Circ Soc* 2014;**78**:2827–33.
4. Wilde AAM, Amin AS. Clinical Spectrum of SCN5A mutations: long QT syndrome, brugada syndrome, and cardiomyopathy. *JACC Clin Electrophysiol* 2018;**4**:569–79.
5. Probst V, Wilde AAM, Barc J, Sacher F, Babuty D, Mabo P *et al.* SCN5A mutations and the role of genetic background in the pathophysiology of brugada syndrome. *Circ Cardiovasc Genet* 2009;**2**:552–7.
6. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M *et al.* Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet* 1999;**23**:20–1.
7. Savio-Galimberti E, Darbar D. Atrial fibrillation and SCN5A variants. *Card Electrophysiol Clin* 2014;**6**:741–8.

8. Ge J, Sun A, Paajanen V, Wang S, Su C, Yang Z *et al.* Molecular and clinical characterization of a novel SCN5A mutation associated with atrioventricular block and dilated cardiomyopathy. *Circ Arrhythm Electrophysiol* 2008;**1**:83–92.
9. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C *et al.* HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;**10**:1932–63.
10. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D *et al.* Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;**111**:659–70.
11. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med Off J Am Coll Med Genet* 2015;**17**:405–24.
12. Behr ER, Winkel BG, Ensam B, Alfie A, Arbelo E, Berry C *et al.* The diagnostic role of pharmacological provocation testing in cardiac electrophysiology: a clinical consensus statement of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC, the ESC Working Group on Cardiovascular Pharmacotherapy, the Association of European Paediatric and Congenital Cardiology (AEPC), the Paediatric & Congenital Electrophysiology Society (PACES), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2025;**27**:euaf067.
13. Porretta AP, Probst V, Bhuiyan ZA, Davoine E, Delinière A, Pascale P *et al.* SCN5A overlap syndromes: an open-minded approach. *Heart Rhythm* 2022;**19**:1363–8.
14. Nishizaki M, Sakurada H, Yamawake N, Ueda-Tatsumoto A, Hiraoka M. Low risk for arrhythmic events in asymptomatic patients with drug-induced type 1 ECG. Do patients with drug-induced Brugada type ECG have poor prognosis? (Con). *Circ J Off J Jpn Circ Soc* 2010;**74**:2464–73.
15. Gourraud J-B, Barc J, Thollet A, Le Marec H, Probst V. Brugada syndrome: diagnosis, risk stratification and management. *Arch Cardiovasc Dis* 2017;**110**:188–95.
16. Therasse D, Sacher F, Petit B, Babuty D, Mabo P, Martins R *et al.* Sodium-channel blocker challenge in the familial screening of Brugada syndrome: safety and predictors of positivity. *Heart Rhythm* 2017;**14**:1442–8.
17. Asatryan B, Yee L, Ben-Haim Y, Dobner S, Servatius H, Roten L *et al.* Sex-related differences in cardiac channelopathies. *Circulation* 2021;**143**:739–52.
18. Conte G, Bergonti M, Probst V, Morita H, Tfelt-Hansen J, Behr ER *et al.* Atrial arrhythmias in inhEriTed aRrhythmIa syndromes: results from the TETRIS study. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2024;**26**:euae288.
19. Meregalli PG, Tan HL, Probst V, Koopmann TT, Tanck MW, Bhuiyan ZA *et al.* Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. *Heart Rhythm* 2009;**6**:341–8.
20. Probst V, Kyndt F, Potet F, Trochu J-N, Mialet G, Demolombe S *et al.* Haploinsufficiency in combination with aging causes *SCN5A*-linked hereditary Lenègre disease. *J Am Coll Cardiol* 2003;**41**:643–52.
21. Zumhagen S, Veldkamp MW, Stallmeyer B, Baartscheer A, Eckardt L, Paul M *et al.* A heterozygous deletion mutation in the cardiac sodium channel gene SCN5A with loss- and gain-of-function characteristics manifests as isolated conduction disease, without signs of Brugada or long QT syndrome. *PLoS One* 2013;**8**:e67963.
22. Bezzina CR, Rook MB, Groenewegen WA, Herfst LJ, van der Wal AC, Lam J *et al.* Compound heterozygosity for mutations (W156X and R225W) in SCN5A associated with severe cardiac conduction disturbances and degenerative changes in the conduction system. *Circ Res* 2003;**92**:159–68.
23. Clatot J, Ziyadeh-Isleem A, Maugenre S, Denjoy I, Liu H, Dilanian G *et al.* Dominant-negative effect of SCN5A N-terminal mutations through the interaction of Na(v)1.5 α-subunits. *Cardiovasc Res* 2012;**96**:53–63.
24. Tan HL, Bink-Boelkens MT, Bezzina CR, Viswanathan PC, Beaufort-Krol GC, van Tintelen PJ *et al.* A sodium-channel mutation causes isolated cardiac conduction disease. *Nature* 2001;**409**:1043–7.
25. Viswanathan PC, Balser JR. Inherited sodium channelopathies: a continuum of channel dysfunction. *Trends Cardiovasc Med* 2004;**14**:28–35.
26. Crotti L, Brugada P, Calkins H, Chevalier P, Conte G, Finocchiaro G *et al.* From gene-discovery to gene-tailored clinical management: 25 years of research in channelopathies and cardiomyopathies. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2023;**25**:euad180.
27. Itoh H, Shimizu M, Mabuchi H, Imoto K. Clinical and electrophysiological characteristics of Brugada syndrome caused by a missense mutation in the S5-pore site of SCN5A. *J Cardiovasc Electrophysiol* 2005;**16**:378–83.
28. Batchvarov VN, Govindan M, Camm AJ, Behr ER. Significance of QRS prolongation during diagnostic ajmaline test in patients with suspected Brugada syndrome. *Heart Rhythm* 2009;**6**:625–31.
29. Veltmann C, Wolpert C, Sacher F, Mabo P, Schimpf R, Streitner F *et al.* Response to intravenous ajmaline: a retrospective analysis of 677 ajmaline challenges. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2009;**11**:1345–52.
30. Merino JL, Tamargo J, Blomström-Lundqvist C, Boriani G, Crijns HJGM, Dobrev D *et al.* Practical compendium of antiarrhythmic drugs: a clinical consensus statement of the European Heart Rhythm Association of the European Society of Cardiology. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2025;**27**:euaf076.
31. Postema PG, Wolpert C, Amin AS, Probst V, Borggrefe M, Roden DM *et al.* Drugs and brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm* 2009;**6**:1335–41.
32. Postema PG, Neville J, de Jong JSSG, Romero K, Wilde AAM, Woosley RL. Safe drug use in long QT syndrome and Brugada syndrome: comparison of website statistics. *Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol* 2013;**15**:1042–9.