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ORIGINAL ARTICLE

Genotype-Phenotype Correlation of *SCN5A* Genotype in Patients With Brugada Syndrome and Arrhythmic Events

Insights From the SABRUS in 392 Probands

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BACKGROUND: Brugada syndrome (BrS) is associated with mutations in the cardiac sodium channel gene, *SCN5A*. However, genetic studies of patients with BrS with arrhythmic events have been limited. We sought to compare various clinical, ECG, and electrophysiological parameters according to *SCN5A* genotype in a large cohort of BrS probands with first arrhythmic event.

METHODS: Survey on Arrhythmic Events in Brugada Syndrome is a survey of 10 Western and 4 Asian countries, gathering 678 patients with BrS with first arrhythmic event. Only probands were included, and *SCN5A* genotype adjudicated. Patients without appropriate genetic data were excluded. Associations of genotype with clinical features were analyzed.

RESULTS: The study group comprised 392 probands: 92 (23.5%) *SCN5A+*(44 pathogenic/likely pathogenic [P/LP] and 48 variants of unknown significance) and 300 (76.5%) *SCN5A–*. *SCN5A* missense variants and the patients hosting them were similar regardless of adjudication. A higher proportion of patients with P/LP were pediatric (<16 years) compared with *SCN5A–* (11.4% versus 3%, P=0.023). The proportion of females was higher among patients with P/LP compared with *SCN5A–* (18.2% versus 6.3%, P=0.013). P/LP probands were more likely to have a family history of sudden cardiac death compared with *SCN5A–* (41.9% versus 16.8%, P<0.001). A higher proportion of patients with P/LP were White compared with *SCN5A–* (87.5% versus 47%, P<0.001). Ethnicity (odds ratio, 5.41 [2.8–11.19], P<0.001) and family history of sudden cardiac death (odds ratio, 2.73 [1.28–5.82], P=0.009) were independent variables associated with P/LP genotype following logistic regression.

CONCLUSIONS: The genetic basis of BrS has a complex relationship with gender, ethnicity, and age. Probands hosting a P/LP variant tended to experience their first arrhythmic event at a younger age and to have events triggered by fever compared with patients with *SCN5A–*. In addition, they were more likely to be White and to have family history of sudden cardiac death. Among females, a P/LP variant suggests an increased risk of being symptomatic. This association should be further studied on an ethnically specific basis in large prospectively collected international cohorts.

Key Words: Brugada syndrome ■ ethnic groups ■ genotype ■ mutation ■ sudden cardiac death

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Nonstandard Abbreviations and Acronyms

AE	arrhythmic event
BrS	Brugada syndrome
EPS	electrophysiological study
SABRUS	Survey on Arrhythmic Events in Brugada Syndrome
SCD	sudden cardiac death
VUS	variant of uncertain significance

Brugada syndrome (BrS) is an inherited channelopathy associated with increased risk of malignant ventricular tachyarrhythmias and sudden cardiac death (SCD).[1] The condition typically affects apparently healthy young males in their 40's who exhibit a typical spontaneous or drug-induced ST elevation in at least one of the right precordial ECG leads (V1 through V3). The clinical phenotype and its manifestations have been reviewed in detail elsewhere.[2]

The *SCN5A* gene was the first associated with the disease[3] and encodes the alpha-subunit of the cardiac sodium channel Nav1.5, responsible for the sodium inward current (INa). Implicated rare pathogenic variants (mutations) in *SCN5A* exhibited a reduction of INa, and consequently led to slowing of conduction. Rare variants in >20 genes encoding other channels or channel interacting proteins have also been linked to BrS.[4] Disease-gene associations were, however, recently re-evaluated by an expert consortium of the Clinical Genomic Resource. This panel concluded that only the *SCN5A* gene has a rigorous enough level of genetic and experimental evidence to offer any confidence regarding disease causality.[5] The remaining heritability of BrS appears to be due to common genetic variation,[6] suggesting a complex oligogenic architecture underlying genetic susceptibility to BrS.[7]

Genotype-phenotype correlation of *SCN5A* mutation in patients with BrS has been the subject of numerous studies. Chen et al[8] recently reported a meta-analysis and found that *SCN5A* mutation carriers had a younger age at onset of symptoms, higher spontaneous type-1 ECG pattern and more pronounced conduction and repolarization abnormalities; in addition, the presence of *SCN5A* mutations was associated with an increased risk of major arrhythmic events (AEs) in both Asians and Whites. However, all studies included in this meta-analysis involved patients with BrS with various clinical presentations, with only a small proportion of patients with documented AEs.

Survey on Arrhythmic Events in Brugada Syndrome (SABRUS)[9–12] is the largest multicenter Survey on AEs in BrS, including 678 patients with BrS with documented AEs. The present study sought to assess the correlation of various clinical, ECG, and EP parameters with *SCN5A* mutation status in a large cohort of patients with first AE. To avoid selection bias of including affected family members, only probands were studied.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The authors declare that all supporting data are available within the article (Data Supplement). The full methods are available in the Data Supplement. The study was approved by the Research Ethics Boards of all participating institutions.

RESULTS

The study group comprised 392 SABRUS probands: 92 (23.5%) *SCN5A+* and 300 (76.5%) *SCN5A–*. The overall demographics of the entire cohort are presented in Table 1. The demographic, clinical, ECG, and electrophysiological study (EPS) results of the study patients according to *SCN5A* genotype status are presented in Table 2 and Table I in the Data Supplement.

Age at Time of AE

Patients with P/LP variants were significantly younger than the *SCN5A–* group (36.6±17.2 versus 42.2±14.0 years old, P=0.018; Table 2). Most patients in both groups were >16 years old, however, a higher proportion of pediatric patients (<16 years) were observed in the P/LP group compared with the *SCN5A–* group (11.4% versus 3%, P=0.023). Figure displays *SCN5A* genotype according to age group at time of AE. The highest proportion of *SCN5A+* patients was observed in the pediatric age group (P<0.05).

Gender and Ethnicity

The proportion of females was significantly higher among the P/LP compared with the *SCN5A–* groups (18.2% versus 6.3% respectively, P=0.013; Table 2). Additionally, the proportion of P/LP in females (29.6%) was also significantly higher than that in males (11.36%; P=0.0063). Out of the 392 study group patients, 205 (52.3%) were White, 162 (41.3%) were of Asian ethnicity, and the remainder 25 patients (6.4%) were of other or unknown ethnicity. When studying Asian and White ethnicity, a significantly higher proportion of P/LP patients were White compared with *SCN5A–* patients (87.5% versus 47%, P<0.001); however, the opposite was observed for Asian patients (12.5% versus 53% P<0.001). Moreover, a pathogenic or likely pathogenic *SCN5A* variant was present in only 5 (3%) of all Asian patients compared with 31 (15.1%) of all White patients (P<0.001).

Family History

Although most study patients did not have a family history of SCD (77.3%), P/LP probands had a higher percentage of such a family history than *SCN5A–* probands (41.9% versus 16.8%, respectively; P<0.001).

Table 1. Demographics of the Entire Cohort (392 Patients)

		Study group
Number of patients		392
Patient age at AE, y	Age (mean±SD)	41.5±14.7
	Patients <16 y	18 (4.6)
	16≥ patients ≤70	369 (94.1)
	Patients >70 y	5 (1.3)
Gender		
	Male	360 (91.8)
	Female	32 (8.2)
Ethnicity		
	White	205 (52.3)
	Asian	163 (41.6)
	Other/unknown	24 (6.1)
Mode of AE documentation		
	Group A	267 (68.1)
	Group B	125 (31.9)
Family history of SCD		
	Yes	75 (19.1)
	No	303 (77.3)
	Unknown	14 (3.6)
History of syncope		
	Yes	139 (35.5)
	No	253 (64.5)
Presence of fever during AE		
	Yes	19 (4.9)
	No	306 (78)
	Unknown	67 (17.1)
Spontaneous type-1 BrS-ECG		
	Yes	260 (66.3)
	No	132 (33.7)
VF inducibility		
	EPS performed	219 (55.9)
	Inducible	136 (62.1)
	Not inducible	83 (37.9)

AE indicates arrhythmic event; SCD, sudden cardiac death; BrS-ECG, Brugada syndrome ECG; and VF, ventricular fibrillation.

Table 2. The Demographic, Clinical, ECG, and EPS Results of the Study Patients According to *SCN5A* Genotype Status

		P/LP	*SCN5A*–	*P* value
Number of patients		44	300	
Patient age at AE, y	Age (mean±SD)	36.6±17.2	42.2±14	0.018
	Patients <16 y	5 (11.4)	9 (3.0)	0.023
	Patients ≥16 y	39 (88.6)	291 (97.0)	
Gender				
	Male	36 (91.8)	281 (93.7)	0.013
	Female	8 (18.2)	19 (6.3)	
Ethnicity				
	White	35 (87.5)	134 (47.0)	<0.001
	Asian	5 (12.5)	151 (53.0)	
	Other/unknown	4 (9.1)	15 (5.0)	
Mode of AE documentation				
	Group A	26 (59.1)	212 (70.7)	0.161
	Group B	18 (40.9)	88 (29.3)	
Family history of SCD				
	Yes	18 (41.9)	49 (16.8)	<0.001
	No	25 (58.1)	242 (83.2)	
	Unknown	1 (2.3)	9 (3.0)	1
History of syncope				
	Yes	17 (38.6)	102 (34.0)	0.611
	No	27 (61.4)	198 (66.0)	
Presence of fever during AE				
	Yes	4 (10.3)	11 (4.5)	0.137
	No	35 (89.7)	232 (95.5)	
	Unknown	5 (11.4)	57 (19.0)	0.294
Spontaneous type-1 BrS-ECG				
	Yes	30 (68.2)	197 (65.7)	0.865
	No	14 (31.8)	103 (34.3)	
VF inducibility				
	EPS performed	30 (68.2)	164 (54.7)	0.105
	Inducible	17 (56.7)	103 (62.8)	0.545
	Not inducible	13 (43.3)	61 (37.2)	

AE indicates arrhythmic event; BrS-ECG, Brugada syndrome ECG; EPS, electrophysiological study; P/LP, pathogenic or likely pathogenic variant; SCD, sudden cardiac death; and VF, ventricular fibrillation.

Other Findings

No difference was observed in first AE presentation (group A and group B; *P*=0.161). Furthermore, the proportion of patients with P/LP who had their AE during fever was almost twice than that of *SCN5A*- patients (10.3% versus 4.5%) but the difference was also not statistically significant (*P*=0.137).

No difference was observed between the groups with respect to a prior history of syncope before the AE (38.6% versus 34%, respectively, *P*=0.611). A similar high prevalence of spontaneous type1 BrS-ECG was observed in P/LP and in *SCN5A*– patients (68.2% versus 65.7%, respectively, *P*=0.865). EPS was performed in the same proportion of patients for both groups, with a comparable proportion of patients having inducible ventricular fibrillation during the test (56.7% and 62.8%, respectively, *P*=0.545). No significant difference in the clinical, ECG, and EPS results were observed in respect of the type of *SCN5A* variant (Table II in the Data Supplement).

P/LP Variants Compared With VUS

Patients with a variant of uncertain significance (VUS; n=48) were similar in their clinical characteristics to patients who harbored P/LP variants (n=44; Table III in the Data Supplement) except for a family history of

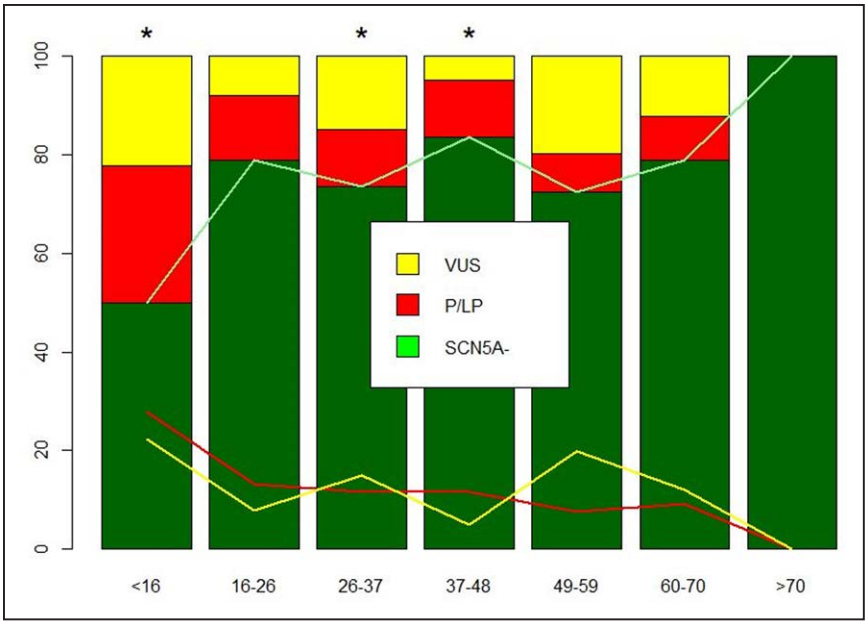

Figure. *SCN5A* genotype according to age group at time of arrhythmic event (AE).
Relative proportions of *SCN5A* genotype according to age groups. Bars represent the relative proportion; straight line represent each colors proportion. P/LP indicates pathogenic and likely pathogenic; *SCN5A*–, genotype negative; and VUS, variant of uncertain significance. *$P<0.05$ for Fisher exact comparison of each age group against the rest of the cohort.

SCD (18.2% versus 41.9%, respectively, $P=0.02$). Furthermore, there was no difference in the transmembrane topological location of missense variants deemed P/LP compared with VUS (14/18 [78%] versus 31/41 [76%] $P=1$). An additional comparison of the VUS group to the SCN5A– group (Table IV in the Data Supplement) yielded a difference in ethnicity ($P<0.001$) with a trend towards a younger age (<16 years) for the VUS group ($P=0.089$).

Multivariate Analysis

A logistic regression was performed for prediction of a P/LP *SCN5A* variant (P/LP versus *SCN5A*–; Table 3). The 2 independent factors observed were ethnicity, with Whites having an odds ratio of 5.09 (1.97–15.8; $P=0.002$) for a P/LP variant and family history of SCD with an odds ratio of 2.73 (1.28–5.82; $P=0.009$) for an LP/P variant. White ethnicity was also observed as an independent factor when comparing patients with VUS to the *SCN5A*– group (Table V in the Data Supplement).

DISCUSSION

The present study, conducted in the largest BrS population with first AE ever reported, aimed to assess various clinical, ECG and EPS parameters according to *SCN5A* genotype. There are 3 main findings: (1) probands hosting a P/LP variant experience their first AE at a younger age than *SCN5A*– patients with a particular importance in the pediatric age group; (2) P/LP probands are characterized by higher proportions of females, Whites and a positive family history of SCD, the latter 2 factors being independent at multivariable analysis; (3) probands hosting P/LP variants were similar although not identical to those hosting a VUS, as was the topological location of missense P/LP and VUS variants.

This last finding reflects that a rare *SCN5A* variant in a definite case of BrS has a higher a priori likelihood of being disease associated than represent background population genomic variation.[13,14] Nonetheless, there are still benign variants among the VUS group that weaken some of the associations identified in the comparison of the P/LP group with the VUS group.

Table 3. Logistic Regression of Prediction of Pathogenic/Likely Pathogenic SCN5A Variants vs *SCN5A* Negative

Parameter	OR (95% CI)	*P* value
Age at first AE <16 y	2.95 (0.76–10.74)	0.102
Male gender	0.59 (0.22–1.79)	0.328
White	5.09 (1.97–15.8)	0.002
Family Hx SCD	2.73 (1.28–5.82)	0.009

AE indicates arrhythmic event; OR, odds ratio; SCD, sudden cardiac death.

Previous Studies

Most previous prognostic studies did not find that *SCN5A* genotype influenced AE rate. These included large European surveys[15–18] and concluded that patients with BrS who carry a pathogenic *SCN5A* variant have more pronounced cardiac conduction defects than patients with BrS without. In addition, patients with loss of function alleles causing haploinsufficiency showed more severe conduction disorders but no increased risk of SCD.[19] Moreover, a meta-analysis of the main BrS databases available reported no difference in the risk of life-threatening arrhythmias in *SCN5A* genotype positive subjects.[20]

In contrast, in a recent Japanese study of BrS probands, 97% of whom were male, Yamagata et al[21] showed that the presence of a pathogenic *SCN5A*

variant, using quite stringent criteria, was a significant predictor of AEs. Additionally, 2 recent meta-analyses obtained new insights when comparing patients with BrS harboring an *SCN5A* variant to those without. The first performed by Yang et al[22] intended to elucidate the effect of *SCN5A* genotype on patients with BrS of mixed ethnicity with symptoms and undergoing EPS. They concluded that in symptomatic patients or those with a negative EPS, the presence of an *SCN5A* variant conferred a higher risk of AEs. Ethnicity was not examined. The second meta-analysis by Chen et al[8] observed that positive *SCN5A* genotype was associated with an elevated risk of major AEs in both White and Japanese patients. None of these studies re-evaluated *SCN5A* variants according to ACMG criteria.[23]

Present Study

The present study is unique and different from previous publications due to the large cohort of BrS probands with a documented AE. Our patient cohort, therefore, has preselected higher risk enabling several important observations. We were also able to re-evaluate *SCN5A* variants systematically for pathogenicity according to ACMG criteria.

Age at Time of AE

Our study observed a younger age at time of AE in probands with a P/LP *SCN5A* variant. This result is in concordance with the meta-analysis by Chen et al[8] where mutation carriers had a younger age at symptom presentation. We found that the younger age derived from a higher proportion of pediatric patients harboring a *SCN5A* variant. A similar observation was previously reported in a prospective study by Andorin et al.,[24] where 9 of the 10 pediatric patients who had a life-threatening AE during follow up were found to carry the *SCN5A* mutation (90%). Our results as well as those of Andorin et al[24] should encourage further prospective studies in larger groups of pediatric patients.

Gender

In a previous analysis,[11] we observed that the proportion of male patients with SABRUS with *SCN5A* variants was slightly higher than that of a large cohort of asymptomatic male patients with BrS (27.8% versus 20.8%, $P<0.001$). However, in female patients with SABRUS the proportion with *SCN5A* variants was markedly higher than in asymptomatic female patients with BrS (47.6% versus 26.8%, $P<0.001$), suggesting, for the first time, that *SCN5A* genotype could represent an important risk marker for AE in females and to a lesser extent in male patients. In the whole patient group, an *SCN5A* mutation was found almost twice as much in females (48% versus 28% in males; $P=0.007$). In our present study involving probands only, a significantly higher proportion of P/LP *SCN5A* variant carriers was observed in the female cohort compared with males (more than twice as much), strengthening the hypothesis that *SCN5A* variants are an important risk marker for AE in females, as well as genetic susceptibility to BrS. These results highlight the important role that sex hormones play in BrS phenotype, resulting in opposite effects on the age of presentation and at onset of AEs. Testosterone plays a crucial role in Brugada male phenotype influencing the age at onset of AE in adulthood.[25–27] Females, however, experience AEs at younger and older ages, in association with greater genetic susceptibility in the form of *SCN5A* variants. However, when estrogen levels are higher after puberty and before menopause, there may be a protective effect as observed by Song et al.[28]

Family History of SCD

For the first time, our study observed a significant association between P/LP *SCN5A* genotype in probands and a family history of SCD. This correlation is intuitive in that there may be a greater chance of genetic heritability of BrS and, therefore, risk of having BrS in families with *SCN5A* variants. Our data also, therefore, suggest that this results in a more severe form of the disease in family members, potentially due to a more penetrant genetic lesion. Our results contrast with those of Yamagata et al,[21] who did not observe such a difference. Moreover, the meta-analysis by Yang et al[22] did not find an association between family history of SCD and future AE in subjects harboring *SCN5A* variants. Finally, the most recent meta-analysis by Chen et al[8] also did not find a difference in the family history of SCD according to genotype. We speculate that these differences could be due to our population being already high-risk (ie, all with AEs) and the use of ACMG criteria to determine pathogenicity.

Ethnicity

Ethnicity was an independent and consistent predictor for a *SCN5A* variant, whether P/LP or VUS. Whites had a significantly higher chance (odds ratio, 5.41) of harboring a P/LP variant. BrS is more prevalent in Asian countries,[29] however, the proportion of Asian patients with rare *SCN5A* variants is lower.[12] This was observed for the entire SABRUS cohort[12] as well as for probands in the present study. Chen et al[8] described that *SCN5A* genotype was associated with an elevated risk of AEs in both Asian and White patients. In our study, the discrepancy in *SCN5A* variants between Asian and White patients, all with AEs, could theoretically be attributed to relative higher susceptibility of Asian patients to BrS due to environmental effects and a different genetic architecture of oligogenic risk[30] that may already place them at

a higher risk, rendering a rare *SCN5A* variant less important in Asian BrS patients.

Supportive data for relevant differences in genetic architecture between Asian and White patients have been identified previously. A promoter region haplotype for the *SCN5A* gene was found to be common in the Japanese population yet absent in Whites and Blacks. This caused reduced expression of *SCN5A* and was associated with increased conduction abnormalities in general population and patients with BrS.[31] More recently, Juang et al[32] reported that common single nucleotide polymorphisms previously associated with BrS in the white and Japanese populations[6] were also overrepresented in Taiwanese patients with BrS when compare to the Taiwanese general population in a genome wide association study. However, their cumulative effect on disease risk was greatest in patients with *SCN5A*– BrS. This was not noted in the previous genome wide association study,[6] suggesting that there may be a stronger effect in the Taiwanese population. Furthermore, in the Thai population, rare *SCN5A* variants were only found in 6% of cases but low frequency and common genetic variation appeared to be significant contributors.[33]

Our results support the observation that different ethnic groups have differing genetic architecture associated with risk in BrS. The clinical implication of such an observation, if validated in prospective studies, could imply that risk stratification in BrS should be studied separately for each ethnic group.

Study Limitations

The present study has several limitations including its retrospective nature. Moreover, we did not test for the presence of several ECG characteristics known to correlate with *SCN5A* mutation carriers, such as conduction disturbances[19] and presence of late potentials on signal-averaged ECG.[34]

SUMMARY

The genetic basis of BrS is oligogenic, in which *SCN5A* plays a critical role, and has a complex relationship with gender, ethnic origin, and age. Furthermore, when a VUS is identified in *SCN5A* in a severely affected individual, it is more likely to be disease associated than benign. Nonetheless, when evaluation with ACMG criteria indicates that a variant is pathogenic or likely pathogenic, the associations with ethnicity, age, gender, and family history of SCD are at their strongest. Probands hosting a P/LP variant tended to experience their first AE at a younger age and to have events triggered by fever compared with *SCN5A*– patients. In addition, they were more likely to be White and to have a positive family history of SCD. Among females, a P/LP variant suggests an increased risk of being symptomatic. This association should be further studied on an ethnically specific basis in large prospectively collected international cohorts.

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None.

Supplemental Materials

Supplemental Methods
Supplemental Tables I–VI
Supplemental Figures I–II

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