SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome

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Short title: Genetic background in Brugada syndrome

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ABSTRACT

Background: Mutations in SCN5A are identified in about 20-30% of probands affected by Brugada syndrome (BrS). However, in familial studies the relationship between SCN5A mutations and BrS remains poorly known. The aim of this study was to investigate the association of SCN5A mutations and BrS in a group of large genotyped families.

Methods and results: Families were included if at least 5 family members were carriers of the SCN5A mutation identified in the proband. Thirteen large families composed of 115 mutation carriers were studied. The signature type I ECG was present in 54 mutation carriers (BrS-ECG+) (47%). In 5 families, we found 8 individuals affected by BrS, but with a negative genotype (mutation-negative BrS-ECG+). Among these 8 mutation-negative BrS-ECG+ individuals, 3, belonging to 3 different families, had a spontaneous type I ECG, while 5 had a type I ECG only after administration of sodium channel blockers. One of these 8 individuals had also experienced syncope. Mutation carriers had, on average, longer PR and QRS intervals than non-carriers, demonstrating that these mutations exerted functional effects.

Conclusions: Our results suggest that SCN5A mutations are not directly causal to the occurrence of a BrS-ECG+ and that genetic background may play a powerful role in the pathophysiology of BrS. These findings add further complexity to concepts regarding the causes of BrS, and are consistent with the emerging notion that the pathophysiology of BrS includes various elements beyond mutant sodium channels.

Key Words: Brugada syndrome; SCN5A mutation, genetics; arrhythmia.
Introduction

Brugada syndrome (BrS) is an inherited arrhythmia syndrome with an increased risk of sudden death resulting from polymorphic ventricular tachycardia (VT) and/or ventricular fibrillation (VF) in the absence of gross structural abnormalities.\(^1\) BrS is associated with ST-segment elevation in the right precordial ECG leads, which have such a characteristic shape (so-called type I ECG, here abbreviated as "BrS-ECG+", see Methods) that their presence is required for the diagnosis. A BrS-ECG+ may occur spontaneously or be provoked by sodium channel blocking drugs. Although BrS and a BrS-ECG+ are intimately linked, not all patients with a BrS-ECG+ are at risk of ventricular fibrillation, as individuals with a BrS-ECG+ exhibit marked phenotypic variability, ranging from sudden death victims to individuals in whom a BrS-ECG+ is found by chance, but who remain asymptomatic.\(^2\) The phenotypic variability has spawned studies aimed at finding modifying factors such as gender, age and other environmental factors.\(^3,4\) Recent experimental studies support a role of the genetic background, although clinical observations indicate that the risk of sudden death of a BrS patient is not increased if otherwise unexplained sudden death has occurred in his/her family.\(^5,6\)

Mutations in the SCN5A gene, which encodes the pore-forming subunit of the cardiac voltage-gated sodium channel, are found in 20-30% of BrS patients.\(^7,8\) Five other genes (GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3) have been associated with BrS, but the prevalence of variants in these genes is yet unknown.\(^9-12\) SCN5A mutations may also lead to progressive cardiac conduction defects (PCCD), long QT syndrome type 3, or atrial standstill.\(^13-15\) Cardiac conduction defects (PCCD) and BrS are both associated with a loss of function of the mutant sodium channel.
Accordingly, "overlap" families who present a mixed phenotype with features of both diseases exist. The causality of SCN5A mutations in PCCD was proven by linkage analysis. In contrast, SCN5A mutations in BrS were discovered by a candidate gene approach and linkage data are still lacking, with the exception of a large overlap family in which the causal mutation is linked with a mixed phenotype. Of note, not only is the proportion of SCN5A mutation carriers low, but, conversely, BrS-ECGs+ were reported among members of SCN5A-positive BrS families who did not carry the familial SCN5A mutation. Clearly, the association between BrS and SCN5A mutations is complex. In the present study, we set out to investigate this association in a larger group of families.

Methods

This retrospective study was conducted at the center of reference for rare arrhythmic diseases of Nantes University Hospital and at the Academic Medical Center, University of Amsterdam, in accordance with the local guidelines for genetic research and with the approval of the local medical ethics committees. Informed written consent was obtained from all patients.

Large genotyped BrS families in which five or more family members carried a SCN5A mutation were included for the present investigation. An individual was defined as affected by BrS if he/she displayed a BrS-ECG at baseline or after provocation with a class I antiarrhythmic drug (BrS-ECG+). A BrS-ECG+ was defined as a coved-type ST-segment elevation ≥0.2mV at its peak followed (without isoelectric separation) by a negative T-wave in two or more right precordial leads. Either intravenous ajmaline (1 mg/kg body weight at a rate of 10 mg/min) or flecainide (2 mg/kg body weight in 10
min with a maximum of 150 mg) were used for drug testing. Drug challenge was not performed in patients younger than 16 years of age and in those showing severe conduction defect at rest. Underlying structural heart disease was excluded by echocardiography, chest roentgenogram, and exercise testing. Laboratory tests excluded acute ischemia and metabolic or electrolyte disturbances.

ECG parameters that were analyzed, before and after drug testing, were: heart rate (HR), PQ interval (in lead II), QRS duration, maximal ST elevation (right precordial leads) and QTc duration in V4 (Bazett’s formula).

**Genetic analysis**

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28 exons of SCN5A were amplified by polymerase chain reaction utilizing intronic primers.\(^8\) Polymerase chain reaction products were screened for a SCN5A mutation using denaturing high performance liquid chromatography (dHPLC)-DNA sequencing. DNA variants were disease causing mutations, rather than polymorphisms, if they were present in highly conserved regions of SCN5A and absent in 200 control individuals. Annotation of mutations was based on the cDNA reference sequence GenBank NM_198056. Sequencing of the SCN5A gene was performed in probands and in all mutation-negative BrS-ECG+ patients.

**Statistical analysis**

ECG parameters were compared with Student's \(t\)-test. Clinical data are expressed as mean value ± SD for continuous data or proportions for categorical data. A \(p\) value <0.05 was considered significant.
RESULTS

Clinical and electrocardiographic results.

Among a total of 444 genotyped probands with BrS-ECGs+ in whom molecular screening was conducted in our international multicenter database, 118 (26%) carried an SCN5A mutation. Thirteen of them, each with a different mutation (Table 1), belonged to large families with ≥5 SCN5A-positive members. For the present analysis, all the screened members of these thirteen families were included and constitute the study population (n=264) (Table 2). A history of sudden cardiac death at young age was present in 3 families. In the 13 probands, the workup which led to the diagnosis of BrS was conducted because of: 1) unexplained syncopal episode (n=4), 2) ECG performed due to chest pain (n=2), 3) ECG performed because of palpitations (n=2), 4) ECG performed for other reason (n=4), 5) ECG performed because of a family history of sudden death (n=1). Eleven out of 13 probands had a spontaneous BrS-ECG+ (type I), while one showed a BrS-ECG+ only after drug provocation (family D) (Figure 1). The last proband (family L) suffered from sudden cardiac death during car racing; his brother also died during car racing from sudden cardiac death and that second event initiated familial screening.

Genetic analysis of the probands’ relatives identified a total of 115 carriers (Figure 1) of the familial SCN5A mutation and 149 mutation negative relatives (mutation negative unaffected individuals not shown in Figure 1). Totally, a spontaneous BrS-ECG+ was present in 21 of 115 mutation carriers (18%) and in 3 of the non-carriers. Provocation testing, performed in 67 mutation carriers and 63 non-carriers, was positive in 33 additional mutation carriers and in 5 non-carriers. Thus, among carriers
of the familial mutation the penetrance of the BrS phenotype increased from 18% at baseline to 61% after drug testing (54/88 patients). Twenty-five mutation carriers received an implantable cardioverter/defibrillator (ICD).

At baseline, mutation carriers had, on average, significantly longer PR (193±37 vs. 162±29 ms, p<0.00001) and QRS intervals (113±20 vs. 95±14 ms, p<0.0001), compared with the non-carriers (Table 2). There was a higher proportion of patients affected by a first degree AV block among carriers (27/115, 23%) than among non-carriers (4/149, 3%, p<0.001) and a higher proportion of patients affected by a complete right bundle branch block among carriers (23/115, 20%) than among non-carriers (5/149, 3%, p<0.001).

**Results in the families with individuals who had a BrS-ECG+ but did not carry the familial mutation (mutation negative BrS ECG+)**

In 5 of the 13 studied families, 8 individuals showed a BrS-ECG+, but did not carry the familial mutation (mutation negative BrS-ECG+ individuals) (Figure 2). Among them, 3 (each from a different family) had a spontaneous BrS-ECG+, whereas 5 had a BrS-ECG+ only after drug testing. One was symptomatic (syncope) (d2), while the other 7 were asymptomatic (3 men and 4 women). Drugs or factors leading to acquired Br-ECG+ have been excluded in these 8 individuals.24,27

These 5 families were composed of 44 mutation positive and 61 mutation negative subjects in total (mutation negative BrS subjects not shown in Figure 1). Also in this subgroup, mutation positive individuals had, on average, significantly longer PR intervals (180±32 ms vs. 158±25 ms, p=0.001) and QRS durations (107±18 ms vs. 94±15 ms, p<0.0001) than mutation negative individuals. Among the
non-carriers of these families there were no significant differences in conduction parameters between the subjects showing a BrS ECG and the ones without ST segment elevation (PR: 165±18 ms vs. 157±26 ms, p=0.3; QRS: 98±14 ms vs. 94±15 ms, p=0.4).

EPS was performed in 5 BrS-ECG non-mutation patients. The mean HV interval was 50 ms. Ventricular tachyarrhythmias were inducible in 3 (1 with a spontaneous BrS-ECG and 2 with a BrS-ECG induced by ajmaline). Signal averaged ECG was performed in all the mutation negative BrS-ECG+ patients and was negative in all. An ICD was implanted in these 3 patients. No arrhythmic event was registered during a 52±42 months follow-up period.

Genetic analysis in the mutation negative BrS-ECG+ patients.
To make sure that the Brugada syndrome phenotype identified in these patients was not related to another mutation of the SCN5A gene we have performed a complete sequencing of the SCN5A gene. This sequencing failed to identify any mutation.

DISCUSSION
We set out to investigate the association between the occurrence of a BrS-ECG+ and carriership of a SCN5A mutation. For this purpose, we studied 13 families with BrS-ECGs+ in whom at least 5 family members carried the familial SCN5A mutation. We found that this association is complex, as BrS-ECGs+ were only found in 18% of mutation carriers at baseline and in 61% after drug testing, and conversely, 8 individuals had a BrS-ECG, but did not carry the familial mutation.

These observations may suggest that carriership of a SCN5A mutation is not causal
to the occurrence of a BrS-ECG+. Historically, the putative role of SCN5A mutations in BrS is derived from the identification of loss-of-function mutations in many BrS syndrome patients throughout the world. In general, affected families are small and genetic linkage data are lacking, with exception of a large family with an overlap syndrome where a sodium channel mutation co-segregated with a complex phenotype. If gene-negative, phenotype-positive patients (as present in 5 of these 13 families) would have been found in the initial years of the genotyping efforts in this disease entity, a causal role for SCN5A would have been probably refuted. Biophysical (patch-clamp) studies of the aberrant gene products (cardiac sodium channels) have consistently demonstrated that their altered functional properties are compatible with the BrS phenotype. All BrS-associated SCN5A mutants reported at present exhibit net loss-of-function which is generally regarded as the inciting pathophysiological mechanism of BrS (yet, whether reduced sodium channel function acts by exacerbating spatial inhomogeneities in depolarization or in repolarization to cause the signature ST elevations of BrS is still controversial). Among mutations found in our 13 families (Table 1), two mutations introduce wrong splice sites (c.612-2A>G and c.3963+2T>C), two are frameshift mutations (c.3816delG and c.1983-1993dup), one mutation introduces a premature stop codon (p.Arg535X), and one mutation causes an in-frame insertion (p.1570- Phe1571inslle). These mutations are all likely to produce non-functional sodium channels as usually identified in the Brugada syndrome. The seven remaining mutations are missense mutations, four of which have been biophysically studied (p.Glu161Lys, p.Gly752Arg, p.Gly1408Arg, p.Arg225Trp) and have shown to produce a strong decrease in peak sodium current. Although no functional data is available for the remaining 3 missense
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mutations (p.Ser1382Ile, p.Leu839Pro, p.Asn1722Asp), we found that mutation carriers have, on average, longer PR intervals and QRS durations than non-carriers. These findings are consistent with previous reports\textsuperscript{17,30} and suggest that the mutant channels produce less sodium current, as sodium current reduction causes cardiac conduction slowing. Thus, the apparent lack of association between carriership of a \textit{SCN5A} variant and a BrS-ECG+, as observed in our study population, cannot be explained by the fact that these \textit{SCN5A} variants are no disease-causing mutations. Then the mutations identified in the There is also no reason to believe that the subjects with BrS-ECG+ who do not carry the familial \textit{SCN5A} mutation, have no true BrS. Indeed, among the genotype-negative phenotype-positive patients, 3 in 3 different families had a spontaneous BrS-ECG+, whereas 5 had a BrS-ECG+ only after sodium channel blockers. We have found no other clinical abnormalities to explain the electrocardiographic aspect of BrS. One of these individuals was symptomatic with syncope before the study. Finally, the EPS induced VF in 3/5 of these patients as previously reported in BrS.\textsuperscript{8,34,35}

A novel notion to emerge from our observation that some patients have a BrS-ECG+, but do not carry the familial \textit{SCN5A} mutation, is that modulating factors within the studied families (genetic background) are sufficiently powerful to evoke a BrS-ECG+. These observations are in line with emerging experimental studies which indicate that disparate genetic backgrounds confer disparate susceptibilities to the effects of a single loss-of-function mutant sodium channel.\textsuperscript{6} Clearly, the relevant elements in the genetic background may encompass all proteins and molecules that play a role in the pathophysiology of BrS. For instance, such genes may include not only those that encode ion channel subunits, but also those that encode molecules
that modify cardiac structure (e.g., fibrosis), thereby facilitating arrhythmias. Hence, it seems conceivable that the genetic background in some families is so strongly conducive to the occurrence of a BrS-ECG+ that a BrS-ECG+ occurs even in the absence of a SCN5A mutation or drug provocation (spontaneous BrS-ECG+). This might point to the fact that a loss-of-function SCN5A mutation, on its own, might not be sufficient to cause BrS but could act like a revelatory factor as sodium channel blocker challenge.

Limitations

All the genes known to be involve in the occurrence of the Brugada syndrome have not been sequenced. Then it is possible that other gene mutations are responsible for the Brugada within the families presented in the study. A provocation testing has not been performed in all the family members, then it is possible that we have underestimated the frequency of the Brugada syndrome within these families.

Conclusion.

We provide novel clinical evidence to suggest that genetic background may play a powerful role in the pathophysiology of BrS. These findings add further complexity to concepts regarding the causes of BrS, and are consistent with the emerging notion that the pathophysiology of BrS includes various elements beyond mutant sodium channels that produce reduced sodium current.
Acknowledgments

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Disclosures

None.
References


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Table 1: Summary of the phenotype-genotype relationship in the study group (n=13 families).

<table>
<thead>
<tr>
<th>Family number</th>
<th>Mutation (nucleotide)</th>
<th>Mutation (amino acid)</th>
<th>Mutation carriers</th>
<th>Mutation positive BrS-ECG+</th>
<th>Mutation positive BrS-ECG-</th>
<th>Mutation positive phenotype undetermined</th>
<th>Mutation negative BrS-ECG+</th>
<th>Type of mutation</th>
</tr>
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<tr>
<td>A</td>
<td>c.612-2A&gt;G</td>
<td>-</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>3</td>
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<tr>
<td>B</td>
<td>c.4222G&gt;A</td>
<td>p.Gly1408Arg</td>
<td>14</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>Missense 31</td>
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<tr>
<td>C</td>
<td>c.673C&gt;T</td>
<td>p.Arg225Trp</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>Missense 32</td>
</tr>
<tr>
<td>D</td>
<td>c.5164A&gt;G</td>
<td>p.Asn1722Asp</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>Missense</td>
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<td>E</td>
<td>c.3963+2T&gt;C</td>
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<td>0</td>
<td>wrong splice 16</td>
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<td>F</td>
<td>c.4145G&gt;T</td>
<td>p.Gly1382Ile</td>
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<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>Missense 29</td>
</tr>
<tr>
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<td>c.2516T&gt;C</td>
<td>p.Leu839Pro</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>Missense</td>
</tr>
<tr>
<td>H</td>
<td>c.2254G&gt;A</td>
<td>p.Gly752.Arg</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>Missense 29,30</td>
</tr>
<tr>
<td>I</td>
<td>c.1983-1993dup</td>
<td>p.Ala665GlyfsX16</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>J</td>
<td>c.1603C&gt;T</td>
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<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>non sense 29</td>
</tr>
<tr>
<td>K</td>
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<td>p.Ala1223ProfsX7</td>
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<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>frame shift, stop</td>
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<tr>
<td>L</td>
<td>p.1570-Phe1671insIle</td>
<td>-</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>1</td>
<td>0</td>
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</tr>
<tr>
<td>M</td>
<td>c.481G&gt;A</td>
<td>p.Glu161Lys</td>
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<td>7</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>Missense 23,23</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>115</td>
<td>54</td>
<td>55</td>
<td>6</td>
<td>8</td>
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</tr>
</tbody>
</table>
**Table 2:** PR and QRS duration in the 13 families (264 members). BrS: Brugada Syndrome

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>PR interval (ms)</th>
<th>QRS interval (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation positive BrS-ECG+</td>
<td>54</td>
<td>194±37</td>
<td>113±18</td>
</tr>
<tr>
<td>Mutation positive not BrS-ECG+</td>
<td>61</td>
<td>193±37</td>
<td>113±21</td>
</tr>
<tr>
<td>Mutation carriers (total)</td>
<td>115</td>
<td>193±37*</td>
<td>113±20**</td>
</tr>
<tr>
<td>Mutation negative BrS-ECG+</td>
<td>8</td>
<td>158±25</td>
<td>94±15</td>
</tr>
<tr>
<td>Mutation negative not BrS-ECG+</td>
<td>141</td>
<td>162±31</td>
<td>94±14</td>
</tr>
<tr>
<td>Mutation negative subjects (total)</td>
<td>149</td>
<td>162±29*</td>
<td>95±14**</td>
</tr>
</tbody>
</table>

total = 264  *p<0.00001  **p<0.001

**Figure Legends**

**Figure 1.** Pedigrees of the 13 SCN5A-related Brugada syndrome families. Squares represent males, circles females. Probands are indicated by an arrow. Family members affected by the Brugada syndrome phenotype (BrS-ECG+) before or after provocation challenge are represented with a left-half filled symbol. Family members affected by progressive cardiac conduction disease (PCCD) are represented with a right half-filled symbol. Mutation carriers without Brugada syndrome phenotype (mutation negative BrS-ECG -) are in white. Patients with undetermined phenotype are shown with grey symbol and unknown genotype is indicated by ?. Family members carriers of a SCN5A mutation are indicated with + and non-carriers with -. The non-carriers of the SCN5A mutation but affected by the Brugada syndrome are circled (mutation negative BrS-ECG +). Patients who underwent sodium channel blocker testing are indicated with a T. Unaffected mutation-negative individuals are...
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not shown.

Figure 2. Electrocardiographic patterns in the mutation negative members affected by the Brugada syndrome phenotype (mutation negative BrS-ECG +). Only leads V1 and V2 are reported for each patient. Patients a1, a2 and m1 had a spontaneous Brugada syndrome phenotype and the ECG presented here has been recorded before sodium channel blocker challenge, while a type 1 BrS-ECG was revealed after sodium channel blocker administration in patients a3, d1, d2, f1 and i1 (ECGs were recorded at maximum dose of sodium channel blocker).
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