Further Insights in the Most Common SCN5A Mutation Causing Overlapping Phenotype of Long QT Syndrome, Brugada Syndrome, and Conduction Defect

Christian Veltmann, MD; Hector Barajas-Martinez, PhD FHRS; Christian Wolpert, MD; Martin Borggrefe, MD; Rainer Schimpf, MD; Ryan Pfeiffer, BS; Gabriel Cáceres, MS; Elena Burashnikov, BS; Charles Antzelevitch, PhD, FHRS, FACC, FAHA; Dan Hu, MD, PhD, FHRS, FAHA

Background—Phenotypic overlap of type 3 long QT syndrome (LQT3), Brugada syndrome (BrS), cardiac conduction disease (CCD), and sinus node dysfunction (SNd) is observed with SCN5A mutations. SCN5A-E1784K is the most common mutation associated with BrS and LQT3. The present study examines the genotype–phenotype relationship in a large family carrying SCN5A-E1784K and SCN5A-H558R polymorphism.

Methods and Results—Clinical work-up, follow-up, and genetic analysis were performed in 35 family members. Seventeen were SCN5A-E1784K positive. They also displayed QTc prolongation, and either BrS, CCD, or both. One carrier exhibited SND. The presence of SCN5A-H558R did not significantly alter the phenotype of SCN5A-E1784K carriers. Fourteen SCN5A-E1784K patients underwent implantable cardioverter-defibrillator (ICD) implantation; 4 developed VF and received appropriate ICD shocks after 8±3 months of follow-up. One patient without ICD also developed VF after 6.7 years. These 5 cases carried both SCN5A-E1784K and SCN5A-H558R. Functional characterization was achieved by expressing SCN5A variants in TSA201 cells. Peak (I_{Na,P}) or late (I_{Na,L}) sodium currents were recorded using whole-cell patch-clamp techniques. Co-expression of SCN5A-E1784K and SCN5A-WT reduced I_{Na,P} to 70.03% of WT, shifted steady-state inactivation by −11.03 mV, and increased I_{Na,L} from 0.14% to 1.86% of I_{Na,P}. Similar changes were observed when SCN5A-E1784K was co-expressed with SCN5A-H558R.

Conclusions—We demonstrate a strong genotype-phenotype correlation with complete penetrance for BrS, LQTS, or CCD in the largest family harboring SCN5A-E1784K mutation described so far. Phenotype of LQTS is present during all decades of life, whereas CCD develops with increasing age. Phenotypic overlap may explain the high event rate in carriers. (J Am Heart Assoc. 2016;5:e003379 doi: 10.1161/JAHA.116.003379)

Key Words: Brugada syndrome • channelopathies • conduction defect • electrophysiology • genetics • long QT syndrome

Mutations in the SCN5A gene have been associated with long QT syndrome (LQTS) type 3, Brugada syndrome (BrS), sick sinus syndrome, and cardiac conduction disease (CCD). Some of these mutations can cause an overlapping electrocardiographic phenotype. SCN5A-E1784K was first described in clinical cases presenting with mild bradycardia, LQTS, and sudden cardiac death (SCD). Recently, this mutation was associated with the phenotype of BrS, LQTS, and sick sinus syndrome. The SCN5A-E1784K mutation has been recognized as the most common LQT3 mutation and accounts for up to 34% of LQT3 cases. In vitro studies suggest that this common SCN5A mutation causes the mixed phenotype by enhanced sodium channel inactivation, a negative shift of steady-state sodium channel inactivation, and enhanced tonic block in response to sodium channel blockers.

Polymorphisms have been shown to modulate SCN5A mutations in the sense of either aggravation of the channelopathy or rescue of the pathophysiologic effect of the mutation. SCN5A-H558R is a common polymorphism and has been shown to restore normal sodium channel function in the case of specific mutations and to enhance sodium channel dysfunction in others.
The objective of the present study was to elucidate clinical spectrum and electrocardiographic phenotype in a large European family with familial SCD and carrying the SCN5A-E1784K mutation and the common polymorphism SCN5A-H558R. Furthermore, the electrophysiologic effects of the SCN5A-H558R polymorphism on the SCN5A-E1784K mutation were studied both in vitro and in vivo.

Methods

Clinical Analysis

The European family studied consisted of 76 family members (Figure 1). All members were encouraged to undergo a complete clinical work-up and follow-up. The work-up included medical and family history, physical examination, 12-lead baseline and stress ECG, and echocardiogram. ECGs were analyzed by 2 independent cardiologists blended to genotype status. In case of abnormal findings, invasive cardiologic investigations were performed. All members were invited to participate in an ajmaline challenge test and genetic screening for causative mutations. The clinical and genetic studies were approved by the local human ethics committees and performed after written informed consent was obtained from all participants. All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Genetic Analysis

Genomic DNA was prepared from peripheral blood lymphocytes of the patient. Genomic DNA was extracted from peripheral blood lymphocytes using a commercial kit (Gentra System; Puregene, Valencia, CA). All exons and intron borders of the susceptibility genes (SCN5A, SCN1-4B, GPD1L, CACNA1C, CACNB2b, CACNA2D1, KCNE3-5, KCNJ8, ABCC9), including the alternative splice variants, were amplified and analyzed by direct sequencing. Polymerase chain reaction products were purified with a commercial enzyme (ExoSAP-IT; USB, Cleveland, OH) and directly sequenced from both directions using an Applied Biosystems 3100 Genetic Analyzer (Applied Biosystem, Foster City, CA). Comprehensive open-reading frame/splice site mutational analysis was then performed.

Cellular Electrophysiologic Analysis

The appropriate nucleotide changes were engineered into human cardiac voltage-dependent sodium channel SCN5A/hNav1.5 in the pcDNA3.1 vector (Invitrogen, Carlsbad, CA) as

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Clinical summary of the affected family. A, Pedigree of the family. B, Baseline ECG of the index patient (proband), who is positive for SCN5A-E1784K and H558R. C, PR interval vs QTc among SCN5A-E1784K carriers. Upper limit of normal values is indicated by dotted lines.
reported previously.\textsuperscript{13,14} Wild-type (WT) and mutant channels were expressed transiently in TSA201 cells for functional study.\textsuperscript{13} The WT \textit{SCN1B} cloned in pRC-CMV were co-expressed in each experimental group. CD\textsubscript{8} beads were used for identification.

Macroscopic \(I_{\text{Na}}\) was measured using a standard whole-cell patch clamp method at a temperature of 22°C to 24°C. The extracellular (bath) solution contained (in mmol/L): 140 NaCl, 5 KCl, 1.8 CaCl\textsubscript{2}, 1 MgCl\textsubscript{2}, 2.8 Na acetate, 10 HEPES, and 10 glucose (pH 7.3 with NaOH). Tetraethylammonium (5 mmol/L) was added to the buffer. The pipette solution contained (in mmol/L): 5 NaCl, 5 KCl, 130 CsF, 1.0 MgCl\textsubscript{2}, 5 EGTA, and 10 HEPES (pH 7.2 with CsOH). Pipettes had resistances between 8 and 2.8 M\(\Omega\) when filled with recording solution. The data were acquired using pClamp 9.2 (Axon Instruments Inc., Union City, CA) and analyzed using Clampfit (Axon Instruments Inc.). The standard voltage clamp protocols and other details are presented with the data and as described in detail previously.\textsuperscript{15} Late \(I_{\text{Na}}\) was recorded in bath solution without and with 25 \(\mu\)mol/L tetrodotoxin. To ensure the accuracy of the value of late \(I_{\text{Na}}\), we only included cells with peak \(I_{\text{Na}}\)\textgreater\=1 nA.

**Statistical Analysis**

Clinical and electrophysiological data were presented as mean\(\pm\)SD and mean\(\pm\)SE, respectively. Before choosing the appropriate statistical test, we checked for normality (Kolmogorov–Smirnov test) and assumption of equal variance (Levene’s test). In case of a non-normality or unequal variance the Wilcoxon signed-rank test, the Mann–Whitney \(U\) test, and the Kruskal–Wallis test were used. Continuous variables among multiple subgroups were analyzed by ANOVA coupled with a Student–Newman–Keuls (SNK) test for electrophysiological study. Chi-square test and Fisher’s exact test were used for comparison of categorical variables. Kaplan–Meier survival curves were generated to compare the outcome according to the underlying genotype. Receiver operating characteristic curves were used to analyze ECG parameters in predicting a positive genotype with the corresponding sensitivity and specificity. A \(P<0.05\) was considered statistically significant. All calculations were performed using SPSS 21 (SPSS Inc, Chicago, IL).

**Results**

**Clinical Analysis**

The proband (III,21), a 47-year-old male of European descent, presented with aborted SCD (or sudden cardiac arrest [SCA]) due to ventricular fibrillation (VF). His basal ECG showed QTC prolongation of 465 ms, first-degree atrioventricular block (AVB), and ST elevation in the right precordial leads with a type-I and type-II Brugada pattern (Figure 1B). He received an implantable cardioverter-defibrillator (ICD).

The family consisted of 76 family members (Figure 1A). The family history revealed aborted SCA of proband’s elder brother (III,18) 3 years ago. The brother exhibited sinus bradycardia, first-degree AVB (PR, 225 ms), and QTC interval of 469 ms without ST-segment elevation in the right precordial leads. He received an ICD and subsequently experienced 4 appropriate ICD shocks due to VF. Furthermore, 3 other family members suffered SCD at the age of 1 year (III,3), 22 years (III,19), and 45 years of age (III,2).

Of the 76 family members, 28 refused genetic analysis and 13 patients died before they could be evaluated. A total of 35 family members (19 males, mean age 29.8\(\pm\)15.9 years) were clinically and genetically evaluated. None of them received Class III anti-arrhythmic drug as medication.

**Genetic Analysis**

Of the 35 genotyped family members, 17 (8 males/47%; mean age 30.6\(\pm\)15.5 years) were carriers of the \textit{SCN5A}-E1784K mutation. Eighteen members (11 males/61%; mean age 29\(\pm\)16.7 years) were negative for the mutation. No significant differences with respect to age and sex were observed.

The \textit{SCN5A}-H558R polymorphism was identified in a total of 18 patients. Nine patients (5 males, mean age 35.1\(\pm\)16.3 years) were positive for both \textit{SCN5A}-E1784K mutation and \textit{SCN5A}-H558R polymorphism, whereas 8 patients (3 males; mean age 25.7\(\pm\)13.9 years) carried only the mutation, but not the polymorphism. Common single nucleotide polymorphisms, V1869M (22.9%) and L1868P (33.1%) in \textit{CACNA1C}, were also found in the proband, which have never been reported as disease-causing or disease-modulating variants.

Out of 18 patients negative for \textit{SCN5A}-E1784K, 9 patients (7 males/78%; mean age 17.6\(\pm\)9.4 years) were carriers of H558R polymorphism. Nine members (4 males/44%; mean age 40.5\(\pm\)14.7 years) were neither carrier of the mutation nor the polymorphism. Patients carrying the polymorphism without mutation were significantly younger than family members negative for both (\(P<0.002\)).

**Electrocardiographic Analysis**

\textit{SCN5A}-E1784K positive versus \textit{SCN5A}-E1784K negative

Electrocardiographic measurements of \textit{SCN5A}-E1784K carriers versus noncarriers are shown in Table 1. Patients positive for \textit{SCN5A}-E1784K exhibited significantly longer PR interval, QRS duration, and QTC interval compared to noncarriers (\(P<0.0001\), \(P=0.03\), \(P<0.0001\), respectively). Ajmaline
challenge was positive in 87% of patients positive for SCN5A-E1784K. In 2 patients, ajmaline administration had to be stopped due to QRS widening >130% and the occurrence of premature ventricular contractions (PVCs). The response to intravenous ajmaline was negative in all SCN5A-E1784K noncarriers.

In the receiver operating characteristic analysis, QRS interval was not found to be predictive for the identification of an SCN5A-E1784K carrier (area under the curve, 0.692). There was good correlation between PR interval and SCN5A-E1784K mutation carrier (area under the curve 0.842). Using a PR interval of 176 ms, sensitivity and specificity for identification of a SCN5A-E1784K carrier was 76.5% and 72.2%. The best correlation was found for QTc interval. The cut-off value of QTc=445 ms identified an SCN5A-E1784K mutation carrier with a sensitivity of 88% and a specificity of 100% (area under the curve 0.993, Figure 2A).

**SCN5A-E1784K and SCN5A-H558R**

Electrocardiographic parameters with respect to mutation and polymorphism are represented in Table 2 and Figure 1C. There were no significant differences within SCN5A-E1784K mutation carriers positive or negative for SCN5A-H558R. Carriers with the mutation and polymorphism exhibited a Brugada saddle-back type ECG (55%) more often than patients without the polymorphism (25%). The response to ajmaline administration was positive in 75% (E1784K+/H558R⁺) and 100% (E1784K⁺/H558R⁻), respectively. QRS widening over 130% and PVCs during ajmaline administration occurred in 2 patients with E1784K⁻/H558R⁻, which led to the interruption of the test.

In patients negative for SCN5A-E1784K mutation, carriers of the polymorphism had a significantly shorter PR interval and QRS duration (P=0.04 and 0.005, respectively). However, patients positive for the polymorphism were significantly younger than patients without the polymorphism (17.6±9.4 versus 40.5±14.7 y/o; P=0.002). In all patients without mutation, ajmaline challenge tests were negative.

**Age and mutation**

The impact of age on the electrocardiographic presentation of the SCN5A-E1784K carriers versus noncarriers is presented in Table 3. Patients were divided in subgroups according to age (age <40 years [mean age 20.4 years] and ≥40 years [mean age 49.3 years]) and presence or absence of SCN5A-E1784K. Among patients positive for the SCN5A-E1784K mutation, RR-interval, PR interval, and QRS duration were significantly longer in patients ≥40 years of age (P=0.007, 0.0001, 0.04). All mutation carriers ≥40 years exhibited a first-degree AVB with a mean PR interval of 231±19 ms. QTc interval was not significantly different between young (<40 years of age) and old (≥40 years of age) mutation carriers (465±15 ms versus 470±19 ms; P=0.55). In noncarriers there were no significant differences between patients in the subgroups <40 and ≥40 years, although an increase of PR interval and QRS duration was observed.

In comparison of patients <40 years with respect to the absence or presence of SCN5A-E1784K, significant differences were found for PR interval and QTc interval. Mutation carriers <40 years had significantly longer PR and QTc intervals compared to noncarriers at the same age (P=0.03 and 0.0001). There was a trend of longer QRS duration in mutation carriers (P=0.07). In older patients (≥40 years), mutation carriers exhibited significantly longer PR, QTc interval, and maximal ST elevation in the right precordial leads (P=0.001, 0.001, and 0.032, respectively). In addition, when SCN5A-H558R was taken into consideration, there is no difference among those with SCN5A-E1784K⁺, no matter in which age subgroup (<40 or ≥40 years, Table 4). When comparing electrocardiographic parameters of SCN5A-E1784K⁺ carriers, the presence or absence of SCN5A-H558R also had a similar distribution with age, except the SCN5A-H558R⁻ group showed a lower heart rate in the older-age subgroup (≥40 years), and the SCN5A-H558R⁺ group showed a higher ST elevation in the younger-age subgroup (<40 years).

Patient II,6, the mother of the proband, was an obligate mutation carrier. Repetitive ECG recordings at the age of 64, 75, 77, 78, and 81 were available (Figure 3). She developed progressive conduction disease with increasing age. At the age of 75, the patient showed first-degree AVB and 3 years later second-degree AVB. Consecutively, a DDD pacemaker was implanted due to symptomatic bradycardia due to sinus node dysfunction (SND) and second-degree AVB. Furthermore, intermittent ST-segment elevation in lead V1 (typical saddle-back type for the BrS), was visible (Figure 3B).

**Table 1.** Electrocardiographic Parameters of SCN5A-E1784K Carriers Versus Noncarriers

| Parameter          | E1784K⁺ n=17 | E1784K⁻ n=18 | P Value |
|--------------------|-------------|-------------|---------|
| RR, ms             | 920±258     | 865±168     | 0.46    |
| PR, ms             | 196±31      | 162±17      | <0.0001 |
| QRS, ms            | 100±20      | 87±13       | 0.03    |
| QTc, ms            | 467±16      | 408±17      | <0.0001 |
| ST elevation V1, mV| 0.04±0.07   | 0.01±0.03   | 0.11    |
| ST elevation V2, mV| 0.04±0.07   | 0.01±0.03   | 0.08    |
| ST elevation V3, mV| 0.02±0.05   | 0.04±0.02   | 0.2     |
| Brugada type II/III| 7           | 0           | 0.0008  |
| Ajmaline positive   | 13/15 (87%)*| 0/11 (0%)   | <0.0001 |

*Two had to be stopped due to QRS widening >130% and the occurrence of premature ventricular contractions.

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Treatment and follow-up

The index patient (III,21) and his brother (III,18) received an ICD for secondary prophylaxis after successful resuscitation. The asymptomatic sisters of the proband (III,20 and III,22) with the electrocardiographic phenotype of LQTS and BrS were implanted with an ICD for primary prophylaxis after diagnosis due to the strong family history of SCD. All patients with a positive genotype were advised to avoid medication and circumstances, including fever, that might aggravate the phenotype and increase the risk for cardiac events according to www.crediblemeds.org and www.brugadadrugs.org.16

A total of 14 patients (82%) positive for SCN5A-E1784K mutation and the clinical phenotype of LQTS underwent ICD implantation. Three patients refused prophylactic ICD implantation. Including the index patient, 4 family members had VF and SCA and received adequate ICD shocks (2 males; mean age 40 years).

Figure 2. A, Receiver operating characteristic curve for PR interval, QRS duration, and QTc interval for the identification of SCN5A-E1784K carriers vs noncarriers. The best correlation was found for QTc interval (area under the curve 0.993). B, Kaplan–Meier event-free survival curves for SCN5A-E1784K mutation carrier vs noncarriers are displayed. Noncarriers had no cardiac events. Four mutation carriers developed sudden cardiac arrest and ventricular fibrillation beyond the age of 40 years.

Table 2. Demographic and Electrocardiographic Parameters with Respect to Mutation and Polymorphism

|                | E1784K+ n=17 | E1784K- n=18 | P Value | E1784K+ n=17 | E1784K- n=18 | P Value |
|----------------|--------------|--------------|---------|--------------|--------------|---------|
| Male sex (%)   | 5 (56%)      | 3 (38%)      | 0.46    | 7 (78%)      | 4 (44%)      | 0.15    |
| Age, y         | 35.1±16.3    | 25.7±13.9    | 0.22    | 17.6±9.4     | 40.4±14.6    | 0.002   |
| RR, ms         | 911±215      | 930±315      | 0.88    | 822±196      | 909±132      | 0.29    |
| PR, ms         | 208±34       | 183±22       | 0.94    | 154±15       | 170±16       | 0.04    |
| QRS, ms        | 102±24       | 98±16        | 0.78    | 80±8         | 96±12        | 0.005   |
| QTc, ms        | 464±17       | 470±15       | 0.42    | 412±15       | 404±20       | 0.34    |
| QT dispersion, ms | 44±20      | 36±24        | 0.74    | 29±14        | 28±16        | 0.95    |
| QTp-e dispersion, ms | 43±24  | 51±25        | 0.52    | 38±18        | 34±15        | 0.44    |
| ST elevation in V1, mV | 0.05±0.08 | 0.04±0.07    | 0.74    | 0.11±0.25    | 0.11±0.33    | 1.0     |
| ST elevation in V2, mV | 0.03±0.05 | 0.06±0.09    | 0.46    | 0            | 0.02±0.03    | 0.35    |
| ST elevation in V3, mV | 0.01±0.03 | 0.03±0.06    | 0.42    | 0.01±0.02    | 0.02±0.04    | 0.33    |
| Brugada type II/III | 5 (55%)   | 2 (25%)      | 0.2     | 0            | 0            | 1.0     |
| Ajmaline positive | 6/8 (75%)   | 7/7 (100%)   | 0.2     | 0/7          | 0/4          | 1.0     |
age 47.3±3 years) after a mean follow-up of 8±3 months (Figure 4). Clinical characteristics of patients with adequate ICD therapies or SCA during follow-up are presented in Table 5. One male patient (III,16), who refused an ICD implantation, also developed VF and SCA after 6.7 years of follow-up. All 5 patients were ≥40 years of age, had positive

Table 3. Demographic and Electrocardiographic Parameters with Respect to Mutation and Age

| E1784K* | E1784K* |
|---------|---------|
| n=17    | n=18    |
| <40     | ≥40     | <40     | ≥40     | <40     | ≥40     |<40     | ≥40     |<40     | ≥40     |
| n=11    | n=6     | n=14    | n=4     | P Value |<40     | ≥40     |<40     | ≥40     |<40     | ≥40     |
| Male sex| 5 (45%) | 3 (50%) | 1.0     | 9 (64%) | 2 (50%) | 1.0     |
| Age, y  | 20.4±7.3| 49.3±4.1| 0.0001  | 21.7±10.0| 55.1±3.6| 0.001   |
| RR, ms  | 804±219 | 1132±182| 0.007   | 837±164  | 960±166  | 0.19    |
| PR, ms  | 176±12  | 231±19  | 0.0001  | 166±10   | 181±12   | 0.02    |
| QRS, ms | 91±14   | 117±21  | 0.03    | 84±11    | 94±7     | 0.1     |
| QTc, ms | 465±15  | 470±19  | 0.55    | 408±18   | 407±17   | 0.96    |
| QT dispersion, ms | 36±21 | 48±22 | 0.29 | 25±11 | 39±15 | 0.13 |
| QTp-e dispersion, ms | 45±26 | 50±21 | 0.70 | 32±14 | 39±16 | 0.32 |
| Max. ST, mV | 0.03±0.06 | 0.13±0.08 | 0.02 | 0.01±0.03 | 0.02±0.05 | 0.63 |
| Brugada type II/III | 0 | 5 (83%) | 0.001 | 0 | 0 | 1.0 |
| Ajmaline positive | 7/9 (78%) | 6/6 (100%) | 0.2 | 0/9 | 0/2 | 1.0 |

Table 4. Electrocardiographic and Demographic Parameters with Respect to Genotype and Age

| E1784K* H558R* | E1784K* H558R* |
|----------------|----------------|
| n=4 | n=5 | P Value |<40 | ≥40 |<40 | ≥40 | P Value |<40 | ≥40 | P Value |
| Male sex | 2 | 3 | 1.0 | 3 | 0 | 0.0 | 7 | 0 | — | 2 | 2 | 1.0 |
| Age, y | 18.5±5.6 | 48.3±3.7 | 0.0001 | 21.6±8.3 | 54.4 | 0.25 | 14.9±5.1 | 42.1 | 0.02 | 28.6±5.1 | 55.1±3.6 | 0.22 |
| RR, ms | 718±154 | 1065±89 | 0.02 | 854±246 | 1467 | 0.25 | 818±109 | 845 | 0.56 | 867±95 | 960±166 | 1.0 |
| PR, ms | 176±8 | 233±21 | 0.02 | 177±15 | 225 | 0.25 | 154±15 | 160 | 0.7 | 161±14.7 | 182±12 | 1.0 |
| QRS, ms | 89±17 | 111±25 | 0.286 | 98±16 | 106 | 0.05 | 79±7 | 73 | 1.0 | 92±12 | 101±13 | 0.22 |
| QTc, ms | 461±19 | 465±17 | 1.0 | 467±13 | 495 | 0.25 | 411±15 | 417 | 0.73 | 400±23 | 407±18 | 0.67 |
| QT dispersion, ms | 32±15 | 53±19 | 0.06 | 38±25 | 22 | 0.75 | 25±4 | 41 | 0.11 | 19±10 | 39±15 | 0.22 |
| QTp-e dispersion, ms | 34±24 | 50±23 | 0.29 | 51±27 | 50 | 1.0 | 34±4 | 45 | 0.19 | 26±12 | 39±14 | 0.44 |
| Max. ST, mV in V1, mV | 0 | 0.09±0.09 | 0.19 | 0.01±0.04 | 0.2 | 0.25 | 0.01±0.03 | 0 | 0.56 | 0 | 0.02±0.05 | 1.0 |
| Max. ST, mV in V2, mV | 0 | 0.05±0.05 | 0.19 | 0.03±0.07 | 0.2 | 0.25 | 0 | 0 | 0.56 | 0 | 0.02±0.07 | 1.0 |
| Max. ST, mV in V3, mV | 0 | 0.02±0.04 | 0.73 | 0.01±0.04 | 0.15 | 0.25 | 0 | 0 | 0.56 | 0 | 0.02±0.04 | 1.0 |
| Brugada type II/III | 0 | 4 (80%) | 0.02 | 0 | 1 | 0.005 | 0 | 0 | 1.0 | 0 | 0 | 1.0 |
| Ajmaline positive | 1/3 | 5/5 | 0.17 | 6/6 | 1/1 | 1.0 | 0/6 | 0/1 | 1.0 | 0/2 | 0/2 | 1.0 |
ajmaline challenge, first-degree AVB, and prolonged QTc interval. SCN5A-E1784K mutation and SCN5A-H558R polymorphism were found in each of them. Patients negative for SCN5A-E1784K mutations revealed no cardiac events (Figure 2B). A total of 6 stored intracardiac electrograms of adequate ICD therapies were analyzed in 4 cases. Patient III,18 had 2 episodes of VF. Mean basic cycle length before the inducing PVC was 770 and 576 ms. The VF-inducing PVC was coupled with 86% and 89% of the previous basic cycle length. Patients III,20 and III,22 had 1 and 2 adequate ICD shocks during follow-up, respectively. Basic cycle lengths were 888 ms in patient III,20 and 776 and 754 ms in patient III,22. Coupling interval of the VF-triggering PVC was 52% in these 2 cases. The proband (III,21) also developed VF during follow-up. In his case, basic cycle length was 720 ms and the inducing PVC was short-coupled with 290 ms (40%).

Electrophysiology Study

Peak sodium current of SCN5A-E1784K

The SCN5A-E1784K mutation and the SCN5A-H558R polymorphism were reproduced in vitro on the SCN5A (hH1c) background in order to study the functional consequences of the mutation both with and without the presence of the polymorphism. We expressed WT+WT, E1784K+WT, and E1784K+H558R channels in TSA201 cells for whole-cell voltage-clamp measurements. Figure 5A represents a typical Na⁺ current. Compared to the WT+WT group, the current

Figure 3. Basal ECGs of patient II,6. The ECGs show QTc prolongation, intermittent saddle-back type Brugada ECG in the right precordial leads, and progressive conduction disease. The patient developed second-degree atrioventricular block at the age of 78 years. A, Age 64: PR 193 ms, QRS 85 ms, QTc 461 ms. B, Age 75: PR 205 ms, QRS 94 ms, QTc 467 ms. C, Age 77: PR 229 ms, QRS 95 ms, QTc 472 ms. D, Age 78: Second-degree AV block, QRS 104 ms, QTc 465 ms. E, Age 81: DDD pacemaker ECG.
amplitude was moderately but significantly reduced for E1784K+WT. When H558R co-expressed with E1784K, the loss of function was slightly more prominent (Figure 5B). The maximum current amplitude was 665.14±87.60 pA/pF for WT+WT, 465.82±50.60 pA/pF for E1784K+WT, and 375.82±65.50 pA/pF for E1784K+H558R (Figure 5C). The voltage of peak sodium current was similar, and there was no difference of activation among the different groups (Figure 5D). Steady-state inactivation was shifted to much more negative potentials by the mutation, but were not further shifted in the presence of the H558R polymorphism (Figure 5E);

$$V_{1/2} = -92.48 \pm 0.82 \text{ mV} \quad \text{and} \quad k = 5.98 \pm 0.30 \text{ mV} \quad \text{for} \quad \text{WT+WT; } V_{1/2} = -103.51 \pm 1.34 \text{ mV} \quad \text{and} \quad k = 7.14 \pm 0.46 \text{ mV} \quad \text{for} \quad \text{E1784K+WT; and } V_{1/2} = -106.54 \pm 1.78 \text{ mV} \quad \text{and} \quad k = 6.89 \pm 0.65 \text{ mV} \quad \text{for} \quad \text{E1784K+H558R. } P \leq 0.001 \text{ is for difference in } V_{1/2} \text{ between WT and the other 2 groups. No significant difference in } k \text{ was observed among all groups (} P=0.134).$$

**Late sodium current of SCN5A-E1784K**

E1784K and H558R channels were also evaluated for late $I_{Na}$ (Figure 6A). TTX-sensitive currents were compared at the end of a 300-ms depolarization, and values were obtained by

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**Table 5. Clinical and Demographic Data of Patients with Sudden Cardiac Arrest or Ventricular Fibrillation during Follow-Up**

| Patient | Sex | Event   | Age With Event (y) | E1784K | H558R | PR | GRS | QTc | Ajmaline Test | ICD Implantation | CI (ms) | CI/Basic CL (%) |
|---------|-----|---------|--------------------|--------|-------|----|-----|-----|---------------|----------------|---------|-----------------|
| III,16  | Male| SCA, VF | 60.8               | +      | +     | 248| 132| 487 | Positive      | Refused       | N/A     | N/A            |
| III,18  | Male| SCA, VF | 47.1               | +      | +     | 256| 136| 468 | Positive      | Yes           | 663     | 86.1%          |
|         |     |         |                    |        |       |    |     |     |               |               | 515     | 89.4%          |
| III,20  | Female| SCA, VF | 50                 | +      | +     | 238| 105| 456 | Positive      | Yes           | 460     | 51.8%          |
| III,21  | Male| SCA, VF | 47.5               | +      | +     | 205| 108| 465 | Positive      | Yes           | 290     | 40.3%          |
| III,22  | Female| SCA, VF | 44.5               | +      | +     | 218| 107| 469 | Positive      | Yes           | 410     | 52.8%          |
|         |     |         |                    |        |       |    |     |     |               |               | 390     | 51.7%          |

CI indicates coupling interval of the first beat of polymorphic VT; CL, cycle length; ICD, implantable cardioverter-defibrillator; N/A, not available; SCA, sudden cardiac arrest; VF, ventricular fibrillation.
subtracting the values before and after TTX. Summary data for late INa, presented as percent of peak INa, were significantly higher when E1784K was expressed (1.86±0.23% co-expressed with WT, n=7; 1.89±0.25% co-expressed with H558R, n=10), compared with the WT group (0.14±0.02%, n=22; Figure 6B). Moreover, late INa amplitude recorded from the E1784K channel, with WT or H558R, was also obviously larger than in WT. Late INa density was 1.30±0.29 pA/pF (n=22) for WT+WT channels, 9.91±2.48 pA/pF (n=7) for E1784+WT and 8.53±1.63 pA/pF (n=10) for E1784+H558R mutant channels (Figure 6C). H558R variant did not significantly alter increased late INa produced by SCN5A-E1784K mutation.

Discussion

SCN5A-E1784K is a frequently reported mutation in patients with LQT3 syndrome. It was first described as a congenital LQTS mutation caused by a defect in sodium channel inactivation giving rise to a small, persistent current.6 These
characteristics were confirmed by several subsequent studies. In 2000, Priori and co-workers reported that flecainide not only shortens the QT interval, but can also induce a BrS phenotype in SCN5A-E1784K carriers. Two years later, it was confirmed by the same group that SCN5A-E1784K is associated with BrS in a study of 200 subjects diagnosed with BrS. Recently, it has been reported as a mutation causing phenotypic overlap. Of 41 SCN5A-E1784K carriers, 93% had LQT3, 22% had BrS, and 39% had SND.

Here, we report on the clinical and electrocardiographic phenotypes of a large white family carrying the SCN5A-E1784K mutation and examine the modulatory effect of the common polymorphism H558R. Carriers of SCN5A-E1784K showed a strong genotype–phenotype correlation in this family, with a penetrance of 100% with respect to a prolonged QT interval. Additionally, 13 of 15 patients (87%) presented with the Brugada phenotype and 7% with SND. We demonstrate, for the first time, an association of SCN5A-E1784K with progressive CCD in mutation carriers above the age of 40 years. These electrocardiographic features are consistent with our finding of a loss of function of INa,P and a gain of function of INa,L.

**Genotype–Phenotype Correlation of SCN5A-E1784K**

Compared to previous studies, patients positive for SCN5A-E1784K were found to exhibit the clinical phenotype of LQT 3 syndrome. In the present cohort, the QTc cut-off of 445 ms was able to differentiate carriers from noncarriers with a sensitivity of 88% and a corresponding specificity of 100%. These findings are in line with in vitro studies showing a gain of function of late INa. In the present study, SCN5A-E1784K was associated with a 7.6-fold higher late INa density of E1784K compared with WT+WT channels. These electrophysiologic findings are comparable to those of previous studies.

Priori et al reported overlapping clinical phenotypes of LQT3 syndrome and BrS. Thirteen patients with SCN5A mutations and LQTS received intravenous flecainide. Three of 13 patients were carriers of SCN5A-E1784K. Following flecainide administration, 6 of 13 patients developed a loss of function of INa,P and a gain of function of INa,L.

![Figure 6](image)

**Figure 6.** Functional expression studies evaluating the characteristics of late INa for WT+WT, E1784K+WT, and E1784K+H558R. A, Representative TTX-sensitive sodium current traces obtained by subtraction, recorded during a 300-ms depolarization to −20 mV from −120 mV (left panel). Amplified traces showing late INa (right panel). B and C, Bar graph of relative late INa (% of peak INa) and late INa density (pA/pF) among 3 groups. Statistically significant differences (*P<0.05) were observed between E1784K+WT/E1784K+H558R and WT+WT in both panels (n=7, 10, 22 for each group). No statistically significant difference was observed between E1784K+WT and E1784K+H558R. For values see text.
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Brugada phenotype; 1 of the 3 patients (33%) was an SCN5A-E1784K carrier. In a larger study focusing on SCN5A-E1784K, Makita et al described an overlap of LQT3 and BrS in 9 of 41 mutation carriers. Only 1 SCN5A-E1784K carrier showed spontaneous Brugada type 1 ECG. In the present study, the overlap of LQT3 and Brugada phenotype was much greater. At baseline, 7/17 SCN5A-E1784K carriers revealed a saddle-back-type ECG pattern. Following intravenous ajmaline, a diagnostic Brugada type-I ECG could be unmasked in 13/15 mutation carriers, whereas none of the SCN5A-E1784K-negative family members displayed a Brugada pattern. In our study the overlap of LQT3 and Brugada phenotype was significantly higher than in the study by Makita et al (87% versus 22%, respectively). The main difference between these 2 studies was the sodium channel blocker used. In previous studies, flecainide and pilsicainide were used to unmask the Brugada ECG pattern. In the present study, ajmaline was used. We have previously shown that ajmaline is significantly more sensitive than flecainide in provoking the Brugada phenotype. This may explain the higher overlap of Brugada and LQT3 phenotypes in the present study.

Late sodium channel blockers, including mexiletine, flecainide, ranolazine, and GS-6615 have been used in patients with LQT3 for primary and secondary prevention. These agents reduced QTc and are expected to lower the arrhythmogenic risk. In population studies, there is no functional effect of H588R detectable in heterologous expression systems in vitro. In patients with SCN5A mutations, the presence of H588R has diverse effects on the cellular and clinical phenotype. H588R has been shown to restore defective sodium channel function and/or trafficking of specific mutations (ie, R282H, T512I, D1275N, D1690N, M1766L, V1951L, and P2006A) by modifying INa,P and/or INa,L.8,10,37–40 It is reported to improve ECG characteristics (QRS duration, J-point elevation, and “aVR sign”) and clinical phenotype of BrS among carriers of SCN5A mutations.12 In contrast, the sodium channel defects of other mutants (ie, E161K, R222Q, G400A, A572D, P1298L, R1632H, and I1835T) are aggravated in the SCN5A-H588R background.13,36–41 In the case of other SCN5A mutations, including the missense and deletion mutants (ie, L212P, T220I, F1617Del, T187I, R878C, and G1408R), as well as the truncated mutants (ie, W1421X, K1578fs/52, R1623X), sodium currents are not significantly affected by H588R.

In the present study, we evaluated the potential effect of SCN5A-H588R both in vitro and in vivo. When comparing electrocardiographic parameters of SCN5A-E1784K carriers, the presence or absence of SCN5A-H588R had no significant effect on PR, QRS, and QTc or the expression of a Brugada phenotype. In the in vitro study, co-expression of SCN5A-E1784K with H588R produced no significant effect on peak or late INa,L although there was a tendency to a further reduction of INa,P. Above all, this kind of discrepancy of in vitro and...
in vivo study may result from several possibilities. First, there are some other underlying mechanisms or modulating background among carriers, which are not present in the cell system used for experimental study. If we had been aware of those factors, we could conduct further investigation. Secondly, the intermittent severe phenotype, such as VT/VF or SCA, likely to be induced or triggered by certain acute conditions (ischemia, stress, fever, hypoxia, change of pH, etc), will not be duplicated in the normal in vitro study. Lastly, despite the chance being very small, there is still the possibility of coincidence. One of the evidences to support this assumption is that patients with SCA or VF during follow-up are the oldest carriers of SCN5A-E1784K, so the effect of aging on the mutant carriers could not be totally excluded.

Aging and Sodium Channel

There is some experimental evidence showing that sodium channels may decline with age. Huang et al demonstrated interesting results indicating an age-dependent alteration in expression and function of sodium current in rat heart.42 Atrial fibrillation, a main arrhythmia significantly contributing to morbidity and mortality in elderly patients, has been correlated with enhanced age-dependent atrial fibrosis. Henry and his group showed decreased Nav1.5 expression and slowed conduction velocity by reduction of sodium channel expression and augmentation of fibrosis among an aged rat atrial fibrillation model. The effect was reversed by relaxin treatment in all aged animals with atrial fibrillation.43 Although the role of aging on genetic variants in SCN5A remains unclear, it is reasonable to speculate that decreased sodium channel and increased fibrosis caused by aging will lead to a more serious phenotype for SCN5A mutation, such as what we observed in our SCN5A-E1784K family.

Risk of SCD

All 5 patients with SCA carried both the SCN5A-E1784K mutation and H558R polymorphism, and their phenotype presented as a combination of long QT interval, CCD, and type I Brugada ECG following ajmaline challenge, suggesting that SCN5A-H558R aggravated the SCN5A-E1784K-associated phenotype under certain conditions. Interestingly, the mechanism of induction of ventricular tachyarrhythmias was different in the 4 patients, whose intracardiac electrograms were available. In 1 male patient, the coupling interval that triggered VF was 90% of the mean previous cycle length. This late coupled PVC suggests that prolonged QT interval is the underlying mechanism for SCA. However, in 2 female patients and the proband the coupling interval was short (40–52%), which indicates BrS as the responsible pathology for sudden death. From these findings, we cannot conclude which phenotype is the responsible one for SCA in these patients. Possibly, both mechanisms are responsible within the same patient; thus, circumstances and drugs provoking either phenotype in these patients should be avoided.

Conclusions

We demonstrate high penetrance for LQTS, BrS, and CCD in a large family harboring the SCN5A-E1784K mutation. Prolonged QT interval was present at all ages, whereas CCD developed after the fourth decade of life. Moreover, at least 87% of SCN5A-E1784K carriers displayed ST-segment elevation diagnostic of BrS. This reveals one of the highest penetrances in a family with BrS syndrome reported by far. SCD/SCA cases occurred mainly after the fourth decade of life in carriers of both E1784K and H558R, displaying overlapping phenotypes of LQTS, BrS, and CCD. In vivo and in vitro studies showed no statistically significant differences in the electrocardiographic phenotypes or I_{Na} characteristics between E1784K with and without H558R.

Author Contributions

Hu, Veltmann, and Antzelevitch designed the study. Veltmann, Hu, Borggreve, Wolpert, Schimpf, coordinated and collected the clinical evaluations. Hu and Antzelevitch supervised and coordinated the genetic and electrophysiology study. Pfeiffer and Cáceres did the genetic screening. Burashnikov provided the plasmids. Hu and Barajas-Martinez performed the electrophysiology laboratory work. Hu and Barajas-Martinez organized and summarized the genetic database. Veltmann, Hu, and Barajas-Martinez analyzed the data. Veltmann, Hu, and Antzelevitch wrote the manuscript. All co-authors contributed to editing of the manuscript.

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All authors have no financial or other considerations to disclose. All authors take responsibility for all aspects of the
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