Yield of genetic screening in inherited cardiac channelopathies: how to prioritize access to genetic testing

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ABSTRACT

Background: Identification of mutations in cardiac ion channel genes concurs to the diagnosis of long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). However, since availability of genetic screening is still limited and reimbursement policies are lacking, there is a need of evidence-based criteria to prioritize access to genetic testing for these diseases.

Methods and Results: We determined the yield of genetic testing and cost per positive genotyping in 1394 consecutive probands. Among the 546 patients referred for LQTS-genes screening, those with clinical diagnosis of LQTS had the highest yield (64%) and lowest cost (US $8418) for each positive genotyping. Among 798 individuals screened for mutation on the SCN5A gene, the highest yield was obtained in patients with Type 1 BrS ECG pattern (51/405; 13%) corresponding to a cost of US $21441 per positive genotyping. In conclusive BrS patients the presence of atrioventricular block (OR: 3.3, CI 1.8-6.1; P=0.0001) increases the yield (23%) of genotyping and reduces its cost (US$ 11700). Among 175 patients screened on RyR2 gene, those with documented bidirectional ventricular tachycardia had the highest incidence (62%) of mutations and the lowest cost (US $5263) per positive genotyping. Genetic screening of unselected family members of sudden cardiac death victims and idiopathic ventricular fibrillation survivors is largely ineffective (yield of 9%) and costly (US$ 71430 per one positive genotyping).

Conclusions: Genotyping can be performed at reasonable cost in individuals with conclusive diagnosis of LQTS and CPVT, and in patients with Type I BrS ECG with atrioventricular block. These patients should be given priority to access genetic testing.

Key words: genetics; long QT syndrome; catecholaminergic VT, Brugada Syndrome
INTRODUCTION

Long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are the three most prevalent inherited cardiac channelopathies (ICC) that cause sudden cardiac death (SCD) in young patients with structurally intact heart. In the last decade, several disease-genes were discovered and genotype-phenotype studies demonstrated that management of affected individuals and family members can be tailored to the genetic substrate. Unfortunately, so far there has been a slow introduction of genetic testing into clinical practice: only few research laboratories accept samples for genetic analysis and commercial genotyping is not widely available besides being expensive. The lack of reimbursement policies further discourages the development of genetic assays for cardiac channelopathies.

In this context, it is important 1) to identify patients who benefit most from genetic testing; 2) to assess the cost of genotyping in different subgroups of patients and 3) to define in which patients the cost per positive genetic testing is more favorable. To address these questions, we performed a retrospective evaluation of the yield of genetic analysis for LQTS, BrS or CPVT based on the population referred to our large clinic of inherited diseases based at the Fondazione Salvatore Maugeri (FSM) in Pavia, Italy.

METHODS

1. Study population

Between September 2001 and September 2006, 1394 consecutive probands with either a clinically confirmed or suspected diagnosis of LQTS, BrS or CPVT or with a personal or family history of idiopathic ventricular fibrillation (IVF)/cardiac arrest
CA)/SCD referred to our center for molecular diagnosis entered the present study. Clinical profiles and results of genetic analysis were input in a searchable custom-made database; each patient was coded with a unique string of letters and numbers so that patient’s identity was unknown to the investigators. Among the 1394 probands, 1219 met criteria for either a “conclusive diagnosis” or a “possible diagnosis” (as defined below) of LQTS, BrS and CPVT; the remaining 175 cases were either survivors of IVF or family member of premature SCD victim (IVF-FMSCD). In these 175 cases, structural heart disease was unable to indentify despite of intensive clinical investigations including coronary artery angiogram.

2. Protocol of genetic screening and grouping of patients

\textit{KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2} genes were analyzed when screening for LQTS using the DHPLC/Sequencing method as previously reported \cite{1}, \textit{SCN5A} was the only gene analyzed in BrS screening and \textit{RyR2} was the gene analyzed in CPVT screening \cite{7,8}.

Patients with “conclusive” or “possible” diagnosis of LQTS, BrS or CPVT were tested for the corresponding genes. Subjects in the IVF-FMSCD group were screened on the \textit{SCN5A} when IVF/SCD occurred at rest or during sleep, or on LQTS-related and \textit{RyR2} genes while the event occurred during stress and emotion. Whenever the amount of DNA available was insufficient to perform a full screening on both LQTS-related genes and the \textit{RyR2} gene, samples were screened for LQTS genes.

The LQTS group included all patients tested for LQTS-related genes and it was divided into three subgroups: 1) patients with QTc $\geq$ 470ms were defined as “\textit{Conclusive diagnosis of LQTS (CD-LQTS)}”; 2) patients with 440 $\leq$ QTc < 470ms were defined as “\textit{Possible diagnosis of LQTS (PD-LQTS)}”; and 3) “\textit{IVF-FMSCD}” were either family members of victims of premature SCD or survivors of IVF/CA.
occurring during stress or emotion (Figure 1).

The BrS group included patients tested for the SCN5A gene and it was divided into three subgroups: 1) patients with spontaneous or flecainide/ajmaline induced Type 1 BrS ECG configuration were defined as “Conclusive diagnosis of BrS (CD-BrS)”; 2) patients presenting with Type 2 or Type 3 BrS ECG pattern were defined as “Possible diagnosis of BrS (PD-BrS)” and 3) “IVF-FMSCD” were either family members of victims of premature SCD or survivors of IVF/CA occurring at rest or during sleep (Figure 2).

CPVT group included patients screened for RyR2 mutation and were divided into three subgroups: 1) patients with documented bidirectional or polymorphic ventricular tachycardia (VT) induced by exercise/emotion were defined as “Conclusive diagnosis of CPVT (CD-CPVT)” ; 2) patients with stress or emotion induced syncopal episodes but no documented bidirectional/polymorphic VT were defined as “Possible diagnosis of CPVT (PD-CPVT)” and 3) “IVF-FMSCD” were individuals with normal ECG who were either family members of victims of premature SCD or survivors of IVF/CA occurring during physical stress or emotion (Figure 3).

3. Definitions and terms

**Index case or proband**: all patients in this study are index cases defined as the first member of each family referred to our center. The term “proband” is used as alternative to “index case” with the same meaning.

**Sudden cardiac death (SCD)**: SCD is defined as an unexpected, unexplained death occurring within one hour from the onset of symptoms and manifesting as an abrupt change in a patient’s stable clinical state. “Premature SCD” is defined as SCD occurring before age 40.

**QTc**: QT interval was measured on lead II of standard 12-lead ECG (on lead I or III
whenever measurement on lead II was technically difficult or not available) and corrected according heart rate (Bazett’s formula)\textsuperscript{9}.

**ECG configuration and diagnosis**: An ECG recording showing a J point elevation with coved ST segment elevation $\geq 2$mm and negative T wave in the right precordial leads is defined a Type 1 ECG\textsuperscript{4} and is diagnostic for BrS. An ECG recording characterized by a saddle-back ST segment elevation $\geq 2$mm and positive/biphasic T wave (Type2 ECG) or by a saddle-back ST segment elevation $\leq 1$mm and positive T wave (Type 3 ECG) is non-diagnostic\textsuperscript{4} and indicative of possible presence of BrS.

**Atrioventricular block (AVB)**: In the present study the term AVB refers to a first degree AVB (PR interval $>200$ms).

**Mutation**: A mutation is defined as a DNA change was not present in any of the 300 reference samples (600 alleles) and resulting in a modification of the protein.

**Positive genotyping**: Genotyping or genetic testing is considered “positive” when a mutation considered with high probability causative of the ICC was identified.

4. **Yield of genetic testing and parameters used for cost assessment**

The yield of LQTS, BrS or CPVT genetic testing, defined as the percentage of patients with positive genotyping, was determined. In order to estimate the cost of genetic testing, we used the pricing currently adopted by the commercial genotyping company Familion \textsuperscript{TM} corresponding to: US $5400.00 for LQTS screening that includes analysis of *KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2* genes; US $2700.00 for BrS (screening of the *SCN5A* gene) and to US $3248.73 for CPVT (screening of the *RyR2* gene)\textsuperscript{10, 11}.

5. **Statistical analysis**

Continuous variables are presented as Mean $\pm$ SD and were tested for normal distribution with one sample Kolmogorov-Smirnov test. Mann-Whitney test was used
to compare continuous variables without a normal distribution. Cost per positive

genotyping was calculated by the following formula:

\[
\text{Cost for one screening} \times \text{Number of screened patients} \\
\text{Cost per positive genotyping} = \frac{\text{Number of patients with positive genotyping}}{\text{Number of patients with positive genotyping}}
\]

As the cost for a specific screening is identical per individual, the comparison of “cost

per positive genotyping” was actually equivalent to the comparison of “yield of

genetic testing”. These comparisons were performed by utilizing Pearson Chi-square

test. Unpaired \(t\)-test for independent sample was used to compare continuous variables

with normal distribution. Binary logistic regression models were used to identify the

predictors of positive genotyping in different subgroups. Statistical analysis was

performed using the SPSS software (SPSS 13.0, Chicago, USA). Two-tailed \(P<0.05\)

was defined as statistical significance.

The authors had full access to and take full responsibility for the integrity of the data.

All authors have read and agree to the manuscript as written.

RESULTS

1. Study Population

**LQTS group**: 304/546 patients (56%) had conclusive LQTS diagnosis (CD-LQTS)

and 160/546 (29%) had a possible LQTS diagnosis (PD-LQTS). Eighty-two patients

in the “IVF-FMSCD” group were screened for LQTS: half of them (41/82) were

family members of premature SCD victims and half were IVF/CA survivors (Figure 1,

Table 1).

**BrS group**: among 798 patients included in this group, 405 (51%) had a conclusive

diagnosis (CD-BrS); 248 (31%) had a possible diagnosis (PD-BrS) and 145 (18%)
were IVF-FMSCD: 71 IVF/CA survivors and 74 family members of premature SCD victims (Figure 2, Table 1).

**CPVT group:** of the 175 patients included in this group, 81 (46%) were CD-CPVT, 21 (12%) were PD-CPVT and the remaining 73 (42%) individuals were classified as IVF-FMSCD: 44 IVF/CA survivors and 29 family members of premature SCD victims (Figure 3, Table 1).

2. Yield and cost of genetic testing for LQTS, BrS and CPVT

**LQTS group:** mutations in the five LQTS-related genes were identified in 220/546 (40%) patients, leading to a cost per one positive genotyping was US $13402 in the entire LQTS group (Figure 4). Most of the genotyped individuals (205/220; 93%) were heterozygous carriers of a single mutation. The remaining 15/220 (7%) individuals were carriers of two mutations. Mutations in the *KCNQ1* or *KCNH2* genes accounted for 85% of positive genotype. Yield of LQTS genetic testing was much higher in the CD-LQTS patients (64%, versus 14% in PD-LQTS and 2% in IVF-FMSCD subgroups). The cost per one positive genotyping was US $8418 in CD-LQTS (P=0.0001 versus PD-LQTS or IVF-FMSCD), US $37565 in PD-LQTS and US $221400 in IVF-FMSCD (P=0.008 versus PD-LQTS) (Figure 4).

**BrS group:** genetic screening of *SCN5A* in these patients identified a mutation in 65/798 (8%) subjects with a cost per one positive genotyping at US $33148 (Figure 5): 51/405 (13%) patients with Type1 BrS ECG configuration (CD-BrS) were genotyped on *SCN5A*, while only 11/248 (4%) PD-BrS patients carried a mutation. Among individuals in the IVF-FMSCD subgroup, the yield of *SCN5A* screening was 2%. The cost per positive genotype in BrS was US $21441 for CD-BrS, US $60872 for PD-BrS (P=0.001 versus CD-BrS) and US $130500 for IVF-FMSCD (P=0.0001 versus CD-BrS; P=0.348 versus PD-BrS) (Figure 5).
**CPVT group:** a RyR2 mutation was detected in 50/81 (62%) CD-CPVT patients, in 1/21 (5%) PD-CPVT case and in 11/73 (15%) individuals from IVF-FMSCD subgroup. The estimated cost per one positive RyR2 genotyping was US $5263 in CD-CPVT group, US $68223 in PD-CPVT (P=0.0001 versus CD-CPVT), and US $21560 in IVF-FMSCD group (P=0.0001 versus CD-CPVT; P=0.381 versus PD-CPVT patients). For the entire CPVT group, the yield of genetic testing was 35% (62/175) and cost per one positive genotyping was US $9170 (**Figure 6**).

**IVF-FMSCD category:** Of all 175 IVF-FMSCD cases, mutation on either of LQTS-related genes, SCN5A or RyR2 was identified in 15 patients, one of whom was overlapped in both LQTS and BrS groups. Accordingly the yield of genetic testing in this IVF-FMSCD entity was 9% (15/175) regardless of etiology and the cost per one positive genotyping was US $ 71430 (**Figure 7**).

3. **Predictors of positive LQTS, BrS and CPVT genetic testing**

Binary logistic regression analysis was performed to identify indicators of positive genotyping in each disease (**Table 2**).

**LQTS group:** logistic analysis was conducted in CD-LQTS and PD-LQTS groups but not in IVF-FMSCD as too few mutation carriers were present in this group. We entered in the model the following variables: gender, family history of SCD, syncope and occurrence of CA. However, none of these variables was associated with an increased rate of positive genotyping.

**BrS group:** we ran logistic regression in CD-BrS and PD-BrS patients by including the following variables: gender, family history of SCD, syncope, occurrence of CA and presence of AVB at ECG. The only variable predicting the identification of a mutation in the SCN5A gene among patients with Type 1 BrS ECG was the presence of AVB (OR 3.3; CI 1.8-6.1; P=0.0001). When the analysis was conducted in PD-BrS
patients, results indicated that in addition to AVB (OR 11.0; CI 2.6-46.7; P=0.001), a history of syncope was associated with higher probability of carrying a mutation in the SCN5A gene (OR 7.8; CI 1.5-40.9; P=0.015). 27/117 (23%) CD-BrS with AVB patients carried a SCN5A mutation lowering the cost per one positive genotyping to US $11700; while only 24/288 (8%) CD-BrS without AVB cases were identified having SCN5A mutation resulting in a cost per positive genotyping at US $32400 (Figure 8). Interestingly, in the small group of patients with PD-BrS and AVB, the yield of genetic testing was as high as 27% (6/22) which was associated with a cost per one positive genotyping at US $9900; while only 5/226 (2%) PD-BrS individuals without AVB were SCN5A mutation carriers and the cost per one positive genotyping in this subgroup was US $122040 (P=0.0001 versus PD-BrS with AVB). Analysis was not performed in IVF-FMSCD population as too few mutation carriers were present in this subgroup.

**CPVT group**: we established a logistic regression model only for CD-CPVT patients by including these variants: gender, family history of SCD, CA episode and early occurrence (defined as < 10 years of age) of the exercise or emotion induced event. Results showed that male gender (OR 5.0; CI 1.3-19.0; P=0.018) and CA (OR 4.1; CI 1.0-15.7; P=0.042) were predictors of the presence of a RyR2 mutation. Analysis was not performed in PD-CPVT and IVF-FMSCD individuals because too few mutation carriers were present in these subgroups.

**DISCUSSION**

Screening for mutations in genes that encode cardiac ion channels associated with LQTS, BrS and CPVT is primarily sought in clinically affected patients to tailor risk stratification and management and to further identify family members 1-7. The
importance of knowing the molecular substrate in patients with ICC is recognized and highlighted in the guidelines for the prevention of SCD developed by the American Heart Association, the American College of Cardiology and the European Society of Cardiology. However, genetic analysis is not yet available at most clinical centers and it is still mainly performed in finite research laboratories. Furthermore, the development of diagnostic genotyping is limited by the fact that in most countries reimbursement policies have not been defined. Thereby the few structures that provide genetic testing are supposed to focus on screening patients with profiles indicating a higher probability to be positively genotyped. On the contrary, however, we have recently observed an increase in the number of requests of genetic testing to confirm uncertain clinical diagnosis of ICC, to identify the cause of CA in individuals with a structurally intact heart and to screen family members of victims of premature SCD with negative autopsy. The yield of genotyping in these patients remains unknown.

Data derived from our large genotyping practice show that patients with a “Conclusive diagnosis” of a cardiac channelopathy represent only half of the population referred for genotyping although account for 80-90% of final positive molecular diagnosis (mutation identified). While a mutation is identified in more than 60% of patients with CD-LQTS or CD-CPVT at an acceptable cost per positive genotyping (US $8418 and US $5263, respectively; Figure 4, Figure 6), BrS patients with Type I ECG have a much lower yield of genetic testing (13% with a cost per positive genotyping of US $21441; Figure 5). Nevertheless, if the screening was limited in patients with CD-BrS and AVB, the yield of genotyping was considerably improved to 23% and the cost per positive genotyping decreased to US $11700 (Figure 8). This observation is in agreement with the report by Smits et al who...
found that the SCN5A-related patients have greater defects in impulse propagation (longer PR and HV intervals at baseline and greater QRS prolongations upon sodium channel blocker challenge) than non-SCN5A-related patients. Considering that mutation screening in BrS is important to identify affected family members and not for directing management, it seems reasonable to prioritize access to genotyping those patients with Type 1 BrS ECG and AVB.

The results of genotyping in patients in whom the diagnosis of LQTS, BrS or CPVT is suspected but cannot be conclusively established prompt several considerations. Obviously, in this setting the answer provided by genetic testing is clinically important despite the considerable costs that range between US $37565 per one positive genotyping in LQTS, to US $60872 in BrS and to US $68223 in CPVT.

Facing the decision of whether it is reasonable to apply genotyping in these patients, it is critical to remember that a negative result of genetic testing in any of the three arrhythmogenic syndromes does not exclude the presence of the disease and that therefore only a positive genetic diagnosis is informative. Furthermore, cost is not the only determinant of whether it is worth offering genetic screening: the significance of a positive genotyping is in fact clearly different in BrS versus in LQTS. In the latter, identification of a mutation directs treatment strategy and therefore it may be worth accepting a higher expenditure given the benefit derived from being able to implement gene-specific therapies. Based on these considerations, it seems appropriate to recommend that whenever a diagnosis to LQTS, BrS or CPVT is suspected but unconfirmed, clinical evaluation of family members prior to genetic screening should be undertaken. Evaluation of family members may allow identifying clinically affected individuals who should be then referred for molecular testing as “proband” of that family and with a higher probably of being successfully genotyped.
Whenever the screening of family members is not informative, the clinician should weight the cost of the analysis versus the value of a positive genotyping in the patient and his/her family.

Among IVF/CA survivors and family members of SCD victims, genetic screening is often the “last hope” to establish the cause of IVF/CA or SCD. Unfortunately, our data show that yield of genetic analysis in this population is very low for both LQTS (2% associated with a cost per positive genotyping of US $221400) and BrS (2% associated with a cost per positive genotyping of US $130500) while it has a relative higher yield and more reasonable cost in CPVT (15% of genotyped individuals corresponding to a cost per positive genotyping of US $21560). Putting together, the yield of genetic testing was only 9% in all 175 IVF-FMSCD cases with a cost per one detected-mutation at US $71430. The reasons accounting for the higher yield of RyR2 screening in IVF-FMSCD may be related to the high lethality of CPVT and to the fact that sudden cardiac death is often the first manifestation of the disease. It seems therefore reasonable to recommend screening RyR2 gene for mutation in IVF/CA survivors when the event occurred during exercise/emotion and in family members of SCD victim when the proband died during a high adrenergic state.

CONCLUSION

Our data suggest that genetic testing can be performed at reasonable cost in individuals with conclusive clinical diagnosis of LQTS and CPVT and therefore these patients should have a priority to access genetic screening. Conversely, screening for SCN5A mutation in unselected patients with diagnosis of BrS is less cost-effective; however, the yield of genotyping increases substantially in patients with Type I BrS ECG and AVB suggesting that this subset of BrS patients should be screened. Finally,
our data show that, unexpectedly, the screening of family members of SCD victim and of IVF/CA survivors on LQTS and BrS genes is largely ineffective and costly. On the contrary, the search for mutations on the RyR2 gene in the entity of family members of SCD victims and IVF survivors with effort/emotion-related events leads to an acceptable yield and cost per positive genotyping.
Sources of Funding for This Study: This work was supported by Telethon, Italy (Grant No. GGP04066) and by funds from the Ministero dell’Università e della Ricerca Scientifica e Tecnologica to Prof. Silvia G. Priori (Ricerca Finalizzata 2003/180, FIRB RBNE01XMP4_006 and RBLA035A4X_002, PRIN 2006055828_002).

Disclosures: The authors have no conflicts of interest to report.
Reference


features differentiate SCN5A-related patients from non-SCN5A-related patients. J Am Coll Cardiol. 2002; 40:350-356


Legends for Figures:

**Figure 1:** Flowchart describing the study population and the yield of genotyping in the different subgroup of patients screened for mutations on genes associated with LQTS.

**Figure 2:** Flowchart describing the study population and the yield of genotyping in the different subgroup of patients screened for mutations on gene associated with BrS.

**Figure 3:** Flowchart describing the study population and the yield of genotyping in the different subgroup of patients screened for mutations on gene associated with CPVT.

**Figure 4:** Yield of genetic testing, defined as percentage of patients with positive genotyping (left Y axis, red bars), and cost in US $ per one positive genetic screening (right Y axis, blue bars) in patients screened for mutations in genes associated with LQTS. The actual number of positively / negatively genotyped patient is also reported in the bars. *: P=0.0001 compared to CD-LQTS; ^: P=0.008 compared to PD-LQTS.

**Figure 5:** Yield of genetic testing, defined as percentage of patients with positive genotyping (left Y axis, red bars), and cost in US $ per one positive genetic screening (right Y axis, blue bars) in patients screened for mutations in gene associated with BrS. The actual number of positively / negatively genotyped patient is also reported in the bars. *: P=0.001 compared to CD-BrS; ^: P=0.348 compared to PD-BrS.

**Figure 6:** Yield of genetic testing, defined as percentage of patients with positive...
genotyping (left Y axis, red bars), and cost in US $ per one positive genetic screening (right Y axis, blue bars) in patients screened for mutations in gene associated with CPVT. The actual number of positively / negatively genotyped patient is also reported in the bars. *: P=0.0001 compared to CD-CPVT; ^: P=0.381 compared to PD-CPVT.

Figure 7: Yield of genetic testing (left Y axis, red bar) and cost in US $ per one positive genotyping (right Y axis, blue bar) in all IVF-FMSCD patients. The actual number of positively / negatively genotyped patient is also reported in the bars.

Figure 8: Yield (left Y axis, red bars) and cost in US $ per one positive genetic screening (right Y axis, blue bars) in CD-BrS patients according to the presence / absence of atrioventricular block. The actual number of positively / negatively genotyped patient is also reported in the bars. *: P=0.0001 compared to CD-BrS with AVB.

Abbreviations:

(LQTS: long QT syndrome; BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; SCD: sudden cardiac death; CA: cardiac arrest; IVF: idiopathic ventricular fibrillation; VT: ventricular tachycardia; CD: conclusive diagnosis; PD: possible diagnosis; FSMCD: family members of sudden cardiac death victims; AVB: atrioventricular block; FSM: Fondazione Salvatore Maugeri)
### Long QT Syndrome (N=546)

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<td>Grouping based on QTc interval †</td>
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<tr>
<td>CD-LQTS (%); QTc (ms)</td>
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<td>PD-LQTS (%); QTc (ms)</td>
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<td>Syncope (%)</td>
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### Brugada Syndrome (N=798)

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### Catecholaminergic Polymorphic VT Group (N=175)

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<td>Cardiac arrest (%)</td>
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<td>Positive Genotyping (%)</td>
<td>62 (35)</td>
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*: P=0.0001 for the Mann-Whitney test for QTc.
§: Conduction abnormalities included atrioventricular block and/or right bundle branch block.
†: See text for definition.
### Table 2  Logistic Regression Analysis to Identify Predictor to a Positive Genotyping in LQTS, BrS and CPVT Groups

<table>
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<td>Syncope</td>
<td>1.2</td>
<td>0.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Cardiac Arrest *</td>
<td>1.1</td>
<td>0.4</td>
<td>3.4</td>
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<td>PD LQTS (N=160)</td>
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<tr>
<td>Male Gender</td>
<td>0.5</td>
<td>0.2</td>
<td>1.4</td>
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<td>Family History of SCD</td>
<td>1.1</td>
<td>0.5</td>
<td>2.1</td>
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<tr>
<td>Syncope</td>
<td>1.1</td>
<td>0.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Cardiac Arrest *</td>
<td>2.1</td>
<td>0.2</td>
<td>25.3</td>
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<td><strong>BrS Group</strong></td>
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<td>CD-BrS (N=405)</td>
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<td>Male Gender</td>
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<td>2.7</td>
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<tr>
<td>Family History of SCD</td>
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<td>0.3</td>
<td>1.4</td>
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<td>Syncope</td>
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<td>0.5</td>
<td>2.0</td>
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<tr>
<td>Cardiac Arrest</td>
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<td>0.3</td>
<td>2.1</td>
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<tr>
<td>Atrioventricular Block</td>
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<td>1.8</td>
<td>6.1</td>
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<tr>
<td>PD-BrS (N=248)</td>
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<td></td>
<td></td>
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<tr>
<td>Male Gender</td>
<td>1.6</td>
<td>0.1</td>
<td>20.7</td>
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<tr>
<td>Family History of SCD</td>
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<td>0.9</td>
<td>24.4</td>
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<tr>
<td>Syncope</td>
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<td>1.5</td>
<td>40.9</td>
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<td>3</td>
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<tr>
<td>Atrioventricular Block</td>
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<td>46.7</td>
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<td><strong>CPVT Group</strong></td>
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<td>CD-CPVT (N=81)</td>
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<td>Male Gender</td>
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<td>19.0</td>
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<td>Family History of SCD</td>
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<td>5.8</td>
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<tr>
<td>Cardiac Arrest</td>
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<td>1.0</td>
<td>15.7</td>
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<td>First Cardiac Arrest / Syncope at Age &lt; 10</td>
<td>1.8</td>
<td>0.6</td>
<td>5.7</td>
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**Abbreviations:**

(LQTS: long QT syndrome; BrS: Brugada syndrome; CPVT: catecholaminergic polymorphic ventricular tachycardia; SCD: sudden cardiac death; CD: conclusive diagnosis; PD: possible diagnosis; IVF: idiopathic ventricular fibrillation; FMSCD: family members of sudden cardiac death victims; VT: ventricular tachycardia)
Workflow and Yield of genotyping in LQTS group

Patients referred for LQTS genetic testing at FSM between 2001 and 2006, N=546

- Patients with prolonged QTc (Conclusive Diagnosis of LQTS), N=304
  - Positive genotyping, N=195
  - Negative genotyping, N=109
- Patients with borderline QTc (Possible Diagnosis of LQTS), N=160
  - Positive genotyping, N=23
  - Negative genotyping, N=137
- Patients with normal QTc, N=82
  - IVF / CA survivor, N=41
  - FM of SCD victim, N=41
    - Positive genotyping, N=2
    - Negative genotyping, N=80

Figure 1
Workflow and Yield of genotyping in BrS group

Patients referred for BrS genetic testing at FSM between 2001 and 2006, N=798

Patients with Type 1 BrS ECG configuration (Conclusive Diagnosis of BrS), N=405
  - Positive genotyping, N=51
  - Negative genotyping, N=354

Patients with Type 2/3 BrS ECG configuration (Possible Diagnosis of BrS), N=248
  - Positive genotyping, N=11
  - Negative genotyping, N=237

Patients without BrS ECG configuration, N=145
  - IVF / CA survivor, N=71
  - FM of SCD victim, N=74
    - Positive genotyping, N=3
    - Negative genotyping, N=142
Workflow and Yield of genotyping in CPVT group

Patients referred for CPVT genetic testing at FSM between 2001 and 2006, N=175

- Patients with documented exercise or emotion induced bidirectional or polymorphic VT (Conclusive Diagnosis of CPVT), N=81
  - Positive genotyping, N=50
  - Negative genotyping, N=31
- Patients with exercise or emotion induced syncope (Possible Diagnosis of CPVT), N=21
  - Positive genotyping, N=1
  - Negative genotyping, N=20
- Patients without exercise or emotion induced VT or syncope, N=73
  - IVF / CA survivor, N=44
  - FM of SCD victim, N=29
  - Positive genotyping, N=11
  - Negative genotyping, N=62
Figure 5

- **Negative Genotyping**
- **Positive Genotyping**
- **Cost Per One Positive Genotyping**

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Patients</th>
<th>Cost Per One Positive Genotyping (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD-BrS</td>
<td>21,441</td>
<td>33,148</td>
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<tr>
<td>PD-BrS</td>
<td>60,872*</td>
<td>130,500^</td>
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<tr>
<td>IVF-FMSCD</td>
<td>142</td>
<td>237</td>
</tr>
<tr>
<td>ALL BrS</td>
<td>733</td>
<td>51</td>
</tr>
</tbody>
</table>

*Note: Costs are approximate estimates for illustrative purposes.*
Yield of Genetic Screening in Inherited Cardiac Channelopathies: How to Prioritize Access to Genetic Testing
Rong Bai, Carlo Napolitano, Raffaella Bloise, Nicola Monteforte and Silvia G. Priori

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