Brugada症候群における下壁側壁誘導でのJ波の出現頻度と臨床的特徴

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【背景】下壁側壁誘導でのJ波を伴う特発性心室細動とBrugada症候群における心電図上の類似性・相違性が指摘されているが，詳細はいまだに不明である．今回，Naチャネル遮断薬負荷試験陽性例における薬物負荷前安静時心電図でのJ波の出現頻度について検討した．【対象と方法】対象は，Naチャネル遮断薬負荷試験にてtype 1 Brugada型心電図が確認された127例(平均年齢51±15歳，男性111例)である．既往の症状や不整脈から対象を4群〔Ⅰ群：非致死性不整脈(n=19)，Ⅱ群：失神(n=28)，Ⅲ群：無症状・Brugada型心電図(n=73)，Ⅳ群：致死性不整脈(n=7)〕に分類し，負荷前安静時心電図におけるJ波の出現頻度について検討した．【結果】J波は下壁側壁誘導で25例(19.7%)，下壁誘導のみで18例(14.2%)，側壁誘導のみで11例(8.7%)に出現し，下壁側壁誘導における各群のJ波の出現頻度には統計学的有意差があった〔Ⅰ群：4例(21.1%)，Ⅱ群：7例(25.0%)，Ⅲ群：9例(12.3%)，Ⅳ群：5例(71.4%)；$p<0.02$〕．何かしらの不整脈あるいは失神などの既往を有するⅠ・Ⅱ・Ⅳ群におけるJ波の出現頻度は，無症状のⅢ群に対して下壁誘導で有意差を認めた〔Ⅰ・Ⅱ・Ⅳ群 vs. Ⅲ群；13(24.1%) vs. 5(6.8%)；$p<0.02$〕が，側壁誘導では有意差を認めなかった．【結論】J波は致死性不整脈の既往を有するⅣ群において高頻度に合併し，また下壁誘導でのJ波は何かしらの不整脈発生基質の存在を反映している可能性が示唆された．

Keywords
- Brugada症候群
- J波
- 下壁側壁誘導

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Ⅰ．はじめに

心電図上のQRSからST部分にかけての軽微な異常，すなわちST上昇とQRS下降脚のノッチやスラーを形成するJ波は，病的意義の乏しい早期再分極所見として認識されている．そのうち，右側胸部誘導や下壁側壁誘導におけるST上昇とJ波は正

The Prevalence and Clinical Characteristics of J Wave in Patients with Brugada Syndrome
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常亜型とみなされている．Brugada症候群における心電図的特徴は右側胸部誘導におけるcoved型ST上昇であるが，同様のST異常を右側胸部誘導以外の下壁誘導などでも認めることがある．また，近年では特発性心室細動(IVF)において下壁側壁誘導でのJ波の合併が報告され，J波と突然死の関連が注目を集めている．Brugada症候群患者の下壁側壁誘導におけるJ波の特徴を明らかにするため，その出現頻度や部位などについて検討した．

Ⅱ．対象と方法

対象は，診断基準に準じた典型的type 1 Brugada型心電図がNaチャネル遮断薬負荷試験にて確認された127例(平均年齢51 ± 15歳，男性111例)である．なお，右側胸部誘導(V_1～V_3誘導)は，1肋間および2肋間高位の右側高位肋間誘導も合わせて全例記録した．Naチャネル遮断薬負荷試験は，既報のごとくピルジカイニドを用い，0.1 mg/kg/分を10分かけて投与した．症例は，臨床状より以下の4群とした[1),2)]．

Ⅰ群(19例)：非致死性不整脈(発作性心房細動，発作性上室頻拍，心房・心室期外収縮など)の既往例．

Ⅱ群(28例)：失神，前失神発作の既往例．

Ⅲ群(73例)：無症状．

Ⅳ群(7例)：致死性心室性不整脈の既往例(持続性心室頻拍，IVF)．

J波は，基線より1 mm (0.1 mV)上昇し下壁誘導(Ⅱ，Ⅲ，aV_F誘導)あるいは側壁誘導(Ⅰ，aV_L，V_4～V_6誘導)にてQRS終末部のノッチまたはスラーを認めるものとし，2誘導以上で認めた場合をJ波ありと定義した．以上の定義にしたがい，ベースライン(薬物負荷投与前)心電図におけるJ波の出現頻度，誘導数および誘導部位について検討した．

心室細動誘発試験：心室細動(VF)誘発試験は，右室心尖部および右室流出路から異なる基本周期(600，400 msec)か最短連結期180 msecでの2連発期外刺激，250 ppmまでの連続刺激，最短連結期200 msecまでにおける3連発期外刺激にて施行した．以上の刺激を行ったにもかかわらず誘発できなかった場合には，β遮断薬(プロプラノロール0.1 mg/kg)を投与して同様の刺激プロトコールで評価した．

表1　各グループにおけるtype 1 Brugada型心電図の出現頻度と心室細動誘発性

	Baseline		After NB		VF induction	
	Standard	+high leads	Standard	+high leads	Control	BB
Ⅰ群 n=19	17%	22%	67%	100%	73%	73% n=11
Ⅱ群 n=28	4%	27%	62%	100%	72%	78% n=18
Ⅲ群 n=73	17%	40%	65%	100%	67%	87% n=15
Ⅳ群 n=7	29%	57%	57%	100%	100% n=7	
Overall n=127	15%	36%	64%	100%	75%	82% n=51

NB：Naチャネル遮断薬，BB：β遮断薬

Ⅲ．結　　果

1．各群におけるtype 1 Brugada型心電図の出現頻度および心室細動誘発性

表1に各群におけるtype 1 Brugada型心電図の出現頻度，VF誘発性を示す．ベースライン(薬物負荷投与前)心電図においては，type 1 Brugada型心電図は通常誘導記録のみで平均15%，高位肋間誘導記録を含めると36%であった．Naチャネル遮断薬負荷下での通常誘導記録では64%であった．VF誘発試験は51症例で施行され，薬物非投与下では75%でVFの誘発が可能であった．薬物投与下においてはβ遮断薬を用いて誘発試験を行い，最終的には82%の症例でVFが誘発された．

2．下壁側壁誘導におけるJ波の出現頻度

J波は，下壁側壁誘導にて25例(19.7%)に認められた．各群のうちわけは，Ⅰ群4例(21.1%)，Ⅱ群7例(25.0%)，Ⅲ群9例(12.3%)，Ⅳ群5例(71.4%)であり，各群におけるJ波の出現頻度には有意差を認めた(図1)．このうち，18例(14.2%)は下壁誘導(Ⅱ，Ⅲ，aV_F誘導)に，11例(8.7%)は側壁誘導(Ⅰ，aV_L，V_4～V_6誘導)に限局して認められた．誘導部位別では各群に有意差は得られなかった(図2)．

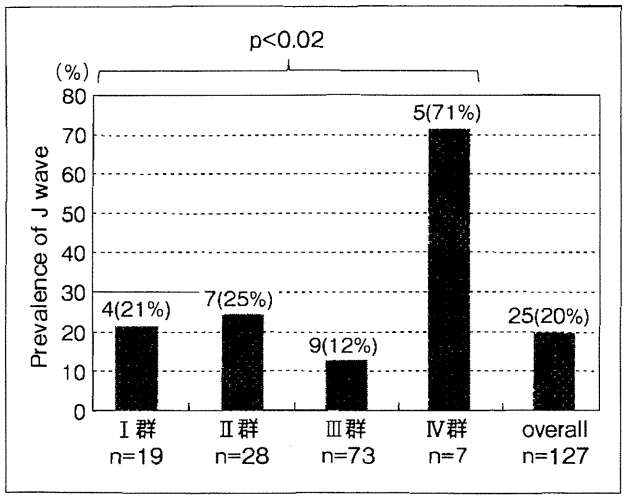

図1　各グループにおけるJ波の出現頻度

表2　各グループにおけるJ波の誘導数

	>7	6	5	4	3	2	1	Prevalence (≥1 lead)
Ⅰ群 n=19	0	0	0	0	**4** (4)	0 (4)	2 (6)	32%
Ⅱ群 n=28	0	0	0	1	**5** (6)	1 (7)	1 (8)	30%
Ⅲ群 n=73	0	0	1	1 (2)	5 (7)	2 (9)	**12** (21)	29%
Ⅳ群 n=7	0	0	0	1	**3** (4)	1 (5)	1 (6)	88%
Overall n=127	0	0	1 (1)	3 (4)	**17** (21)	4 (25)	16 (41)	32%

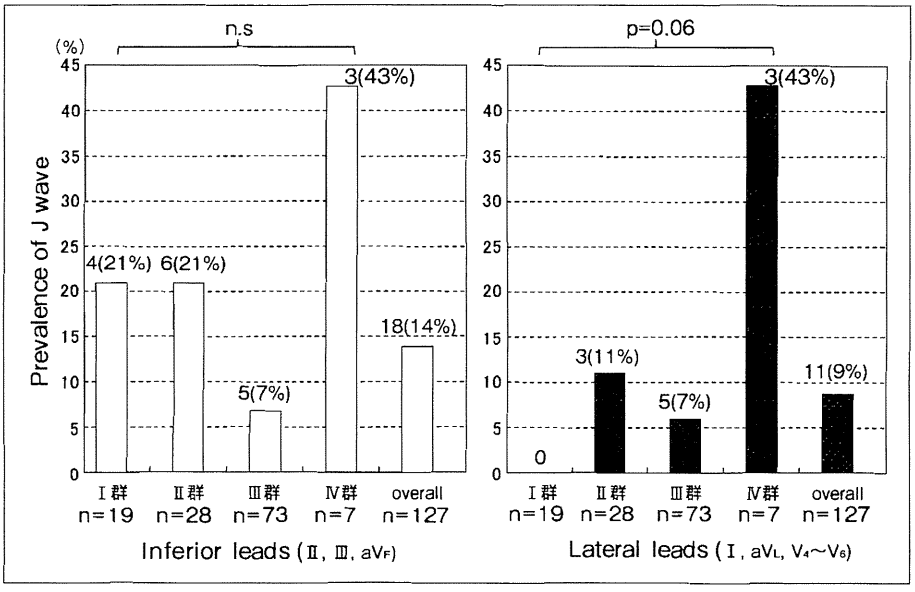

図2
下壁誘導(左)と側壁誘導(右)での各グループによるJ波の出現頻度

3. 各群におけるJ波の誘導数

各群におけるJ波を認めた誘導数を表2に示す．Ⅰ，Ⅱ，Ⅳ群では3つの誘導にJ波を認めることが最も多かったのに対して，Ⅲ群では定義上はJ波なしと判断するひとつの誘導のみにJ波を認める例が最も多かった．また，J波をひとつでも認めた誘導はⅠ，Ⅱ，Ⅲ群では30%前後にすぎなかったのに対して，Ⅳ群では8例中7例(87.5%)と，Ⅳ群におけるJ波の出現頻度は他の群に比して高い割合を示した．

4. 症状の有無別にみたJ波

何かしらの不整脈あるいは失神などの症状を有するⅠ群，Ⅱ群，Ⅳ群と症状を有さないⅢ群との間におけるJ波の出現頻度を比較検討した．下壁側壁誘導および下壁誘導においては，有症候例におけるJ波の出現頻度は無症候例と比較して有意に高かったが，側壁誘導におけるJ波の出現頻度には有意差を認めなかった(図3)．

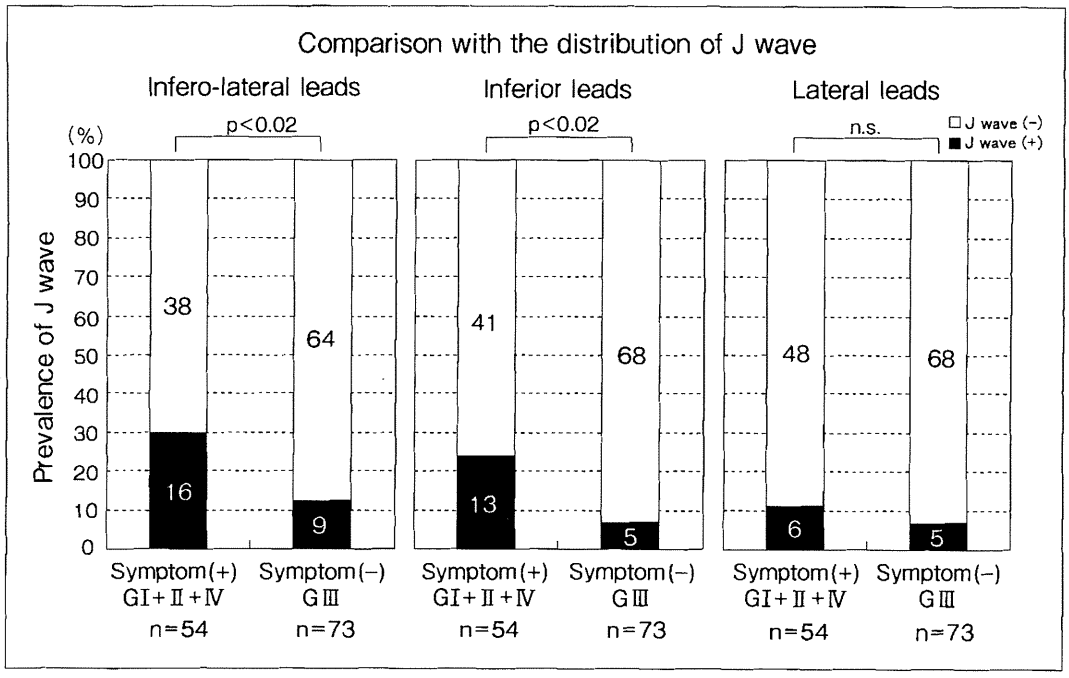

図3　症状の有無別でのJ波の頻度

左：下壁側壁誘導，中：下壁誘導，右：側壁誘導．

Ⅳ．考　　察

Naチャネル遮断薬(ピルジカイニド)負荷試験にて，type 1 Brugada型心電図が証明された127例の安静時心電図におけるJ波の出現頻度について検討した結果，以下の知見を得た．①下壁側壁誘導でのJ波の頻度は，致死性不整脈の既往のあるⅣ群(Brugada症候群)において他群よりも著明に高率であった．②J波の出現誘導数は，何かしらの症候を有するⅠ，Ⅱ，Ⅳ群では3つの誘導で認めることが多かったのに対し，Ⅲ群ではひとつの誘導のみに認めることが最も多かった．③何かしらの症状を有するⅠ，Ⅱ，Ⅳ群と症状を有さないⅢ群との比較では，J波は下壁側壁誘導と下壁誘導においてその出現頻度に有意差を認めたが，側壁誘導での有意差は認められなかった．

IVF例での下壁側壁誘導におけるJ波の合併がHaïssaguerreらによって報告され，従来良性所見と考えられてきたJ波(早期再分極)のなかに，病的なJ波が含まれることが明らかにされつつある[3]．Brugada症候群においてもしばしばJ波が下壁側壁誘導に合併することがあるが，Brugada症候群におけるJ波とIVFにおけるJ波との相違点については不明な点が多い．J波の出現頻度に関しては，HaïssaguerreらがIVF例での下壁側壁誘導において31％にみられたと報告したが，本研究における無症状を含めたBrugada型心電図例での頻度は約20％であった．しかし，VF既往例に限ると，少数例ではあるが当施設で高率(71％)に認められた．Letsasら[4]は，290例のBrugada症候群でのJ波(0.1 mV以上)の出現頻度は12％であり，このうち有症候88例では13例(15％)に認めるにすぎず，有症候例でのJ波を認めた症例と認めない症例において，不整脈イベントの発生を含み臨床的に相違はみられなかったと報告している．2009年にKamakuraら[5]が報告した330例におけるBrugada型心電図の長期予後によると，J波(早期再分極)は全体で10％に認められ，そのうちVF既往例では56例中10例(18％)に出現した．このKamakuraらの研究ではJ波の合併は不整脈イベント発生の予測因子であっ

た．以上のようにBrugada症候群におけるJ波は，既報では10～20％の出現頻度であり，J波自体の意義については統一見解を得ていないのが現状である．J波を認める心電図誘導部位と症状との関連については，Rossoら[6]はIVFと健常者・若年アスリートにみられるJ波との鑑別において，前胸部誘導(V_1～V_6誘導)での診断価値は低いと報告している．本研究においても無症候例では側壁誘導にJ波を認める例が多かったが，有症候例では下壁誘導において有意に多かったことから，IVFに限らず下壁誘導におけるJ波の存在は不整脈の存在を示唆する所見として注目すべきと思われた．

V．おわりに

本研究では，致死性不整脈既往例であるⅣ群でのJ波の合併頻度が，これまでの報告と比較しても高かったが，他群と比べて少数であるため，さらに症例を重ねて検討すべきと思われる．また，安静時心電図における典型的Brugad型type 1心電図は高位肋間誘導部位を含め36％と少なく，いわゆるBrugada signとJ波の出現との関係などについて検討していないため，これについても今後の検討課題である．

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EDITORIAL COMMENTARY

Molecular screening of long-QT syndrome: risk is there, or rare?

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Congenital long QT syndrome (LQTS) is an inherited disorder characterized by the QT interval prolongation of the electrocardiogram (ECG) that is associated with polymorphic ventricular tachycardia, or torsades de pointes (TdP), leading to syncope and sudden cardiac death (SCD). To date, 12 forms of LQTS have been identified in clinically affected LQTS patients, and LQT1, LQT2, and LQT3 syndromes constitute more than 90% of genotyped LQTS patients. More than several hundred LQTS-causing mutations in at least 12 LQTS-susceptibility genes have been identified, and a litany of genotype-phenotype studies about LQT1, LQT2, and LQT3 syndromes have investigated stratification of risk and effective treatment of genotyped patients.

More recently, mutations in regions such as the transmembrane, linker, pore of *KCNQ1* (LQT1-susceptibility gene), and *KCNH2* (LQT2-susceptibility gene) may be defined as high-probability LQTS-causing mutations, indicating the possibility of mutation site-specific management or treatment.[1,2] On the other hand, mutations in *SCN5A* (LQT3 susceptibility gene) are considered variants of uncertain significance since the greatest prevalence of common variants observed occurred in the control population, suggesting a significantly greater degree of genetic background noise in *SCN5A* than in either *KCNQ1* or *KCNH2*.[3]

The prevalence of LQTS previously has been estimated at 1:20,000 to 1:5,000 in the general population. However, recent ECG-guided molecular screening provides a higher prevalence of LQTS, at least 1:2,000 apparently healthy live births.[4] ECG-guided molecular screening can identify most infants affected by LQTS and unmask affected relatives. Of cases diagnosed as sudden infant death syndrome (SIDS), 9.5% carry functionally significant genetic variants in LQTS genes, demonstrating that sudden arrhythmic death is an important contributor to SIDS.[5] On the other hand, examination of relatives of young sudden unexplained death (SUD) victims has a high diagnostic yield, with identification of the disease in 40% of families and ≈9% asymptomatic carriers per family. Molecular genetics can provide significant supportive information.[6]

New Zealand, with a population of 4.2 million people, is a unique country with a national registry of inherited heart disease. Blood spots on Guthrie cards have been collected from newborns since 1969 and are used to screen for diseases of inborn errors of metabolism by the National Testing Centre. Using the Guthrie card, a recent paper[7] from the same group that performed the current study in this issue of *Heart Rhythm*[8] reported the results of screening genes linked to LQTS in 21 cases of SUD in young victims (SUDY), showing that genetic variants were found in eight individuals (38%), six of whom indicate that LQTS was likely the cause of death.

In the current issue of *Heart Rhythm*, Skinner et al[8] aimed at a diagnostic value of postmortem LQT genetic analysis in a prospective study of 1- to 40-year-old SUDY. In 2 years, they found 33 cases of SUDY in their country, all of whom, along with possibly 72% of the family members, underwent ECG and genetic screening of the LQTS gene. They found five (15%) cases with missense mutation from the 33 SUDY, which is lower than the previous retrospective autopsy analysis: >20%. However, if this study includes the two possible LQTS cases, the total becomes seven (21%) of 33, which is a similar frequency. Furthermore, this study includes two possible arrhythmogenic right ventricular cardiomyopathy (ARVC) cases.

In cases of LQTS, the established yield of genetic testing among clinically indisputable cases of LQTS is ≈70%–75%, but these may include a few (up to 10%) false positives, and this background noise rate is ethnically dependent.[3] In this study, one case had a missense mutation T96R in *KCNQ1*, and patch-clamp analysis of this mutant found a significant reduction of I_{Ks}. Although the mother and sister have the same T96R variant, their phenotype was equivocal, and *in silico* analysis showed it to be a benign mutation. Another had a missense mutation of P968L in *KCNH2*, in which the functional and clinical significance have not been investigated. Therefore, importantly, there is a large gap between the postmortem LQTS gene mutation and the direct cause of death in SUDY.

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More than half of SUDY in this issue died during sleep, but only 22% died during light activity. It is well-known that the majority of LQT1 patients have events precipitated by physical exercise, whereas LQT2 patients are more likely to develop arrhythmia after emotion and LQT3 patients tend to be symptomatic at rest or during sleep. A recent nationwide survey in Japan showed that the LQTS genes were confirmed in 29 (71%) of 41 infants available for genetic testing. Furthermore, life-threatening arrhythmias at perinatal periods mostly occurred in LQT2 and LQT3 or no known mutation.[9] Another postmortem genetic testing in 49 autopsy-negative SUDY at the Mayo Clinic[10] also discovered 10 LQTS-associated mutations such as LQT1 (n = 5), LQT2 (n = 3), and LQT3 (n = 2) and found them to be far more common among women than men, whereas sudden death occurred during sleep (n = 5), exertion (n = 2), auditory arousal (n = 1), and undetermined (n = 2). The current study is consistent with those previous studies; thus half of the SUDY occur during sleep or light activity, suggesting arrhythmic death by LQT2 or LQT3.

What can we learn from the genetic screening? Genetic screening for the high-risk family member helps us to diagnose and treat the LQT carrier of remaining family members using beta-blockade therapy. In this issue, as well as in the previous report,[10] the authors tell us that once the proband has been genotyped, we should investigate genetic testing to minimize the risk of SUDY in the remaining asymptomatic family members. Recently, it was shown that 20%–30% of drug-induced LQTS have an LQTS gene mutation.[11,12] In a silent mutation carrier of the LQTS gene with a normal QT interval at baseline, QT prolongation may be suddenly unmasked by taking medicine with a I_{Kr} blocking effect.[13] On the other hand, sudden death of a sibling promoted more aggressive treatment but did not predict risk of death or aborted cardiac arrest in patients with LQTS.[14]

Prevention of life-threatening arrhythmias in LQTS can be done with beta-blockers, and such treatment is generally well accepted by patients. Hofman et al[15] recently noted that 65% of mutation-carrying relatives of LQTS probands were prophylactically treated with medication.

Taking all of these considerations into account, the current issue of *Heart Rhythm* sends an important message to investigate the cases of SUDY, and postmortem molecular screening helps us to understand the distribution of potentially inherited arrhythmic diseases and to diagnose and treat relatives for prevention of SUDY.

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Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

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Objectives This study was designed to assess the clinical course and to identify risk factors for life-threatening events in patients with long-QT syndrome (LQTS) with normal corrected QT (QTc) intervals.

Background Current data regarding the outcome of patients with concealed LQTS are limited.

Methods Clinical and genetic risk factors for aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years were examined in 3,386 genotyped subjects from 7 multinational LQTS registries, categorized as LQTS with normal-range QTc (≤440 ms [n = 469]), LQTS with prolonged QTc interval (>440 ms [n = 1,392]), and unaffected family members (genotyped negative with ≤440 ms [n = 1,525]).

Results The cumulative probability of ACA or SCD in patients with LQTS with normal-range QTc intervals (4%) was significantly lower than in those with prolonged QTc intervals (15%) ($p < 0.001$) but higher than in unaffected family members (0.4%) ($p < 0.001$). Risk factors ACA or SCD in patients with normal-range QTc intervals included mutation characteristics (transmembrane-missense vs. nontransmembrane or nonmissense mutations: hazard ratio: 6.32; $p = 0.006$) and the LQTS genotypes (LQTS type 1:LQTS type 2, hazard ratio: 9.88; $p = 0.03$; LQTS type 3:LQTS type 2, hazard ratio: 8.04; $p = 0.07$), whereas clinical factors, including sex and QTc duration, were associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (female age >13 years, hazard ratio: 1.90; $p = 0.002$; QTc duration, 8% risk increase per 10-ms increment; $p = 0.002$).

Conclusions Genotype-confirmed patients with concealed LQTS make up about 25% of the at-risk LQTS population. Genetic data, including information regarding mutation characteristics and the LQTS genotype, identify increased risk for ACA or SCD in this overall lower risk LQTS subgroup. (J Am Coll Cardiol 2011;57:51–9) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACA = aborted cardiac arrest
ECG = electrocardiographic
LQTS = long-QT syndrome
LQT1 = long-QT syndrome type 1
LQT2 = long-QT syndrome type 2
LQT3 = long-QT syndrome type 3
QTc = corrected QT interval
SCD = sudden cardiac death

Congenital long-QT syndrome (LQTS) is an inherited channelopathy characterized by a prolonged corrected QT interval (QTc) at rest that is associated with an increased predisposition for polymorphic ventricular arrhythmias and sudden cardiac death (SCD) in young subjects without structural heart disease (1). To date, more than 500 mutations have been identified in 12 LQTS-susceptibility genes, with the long-QT syndrome type 1 (LQT1), long-QT syndrome type 2 (LQT2), and long-QT syndrome type 3 (LQT3) genotypes constituting more than 95% of genotype-positive LQTS and approximately 75% of all LQTS (2). Risk assessment in affected patients with LQTS relies primarily on a constellation of electrocardiographic (ECG) and clinical factors, including QTc interval and age-sex interactions (3–6). In addition, there is increasing evidence that genetic information and the molecular and cellular properties of the LQTS-causative mutation may identify subjects with increased risk for cardiac events (7–10). Despite these recent advances, however, currently there are limited data regarding the clinical course and risk factors for life-threatening events in patients with LQTS with normal resting QTc values, so-called silent mutation carriers, concealed LQTS, or normal-QT interval LQTS.

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In the present study we used combined data from 7 national LQTS registries to: 1) compare the clinical courses of patients with LQTS and normal-range QTc intervals to those of patients with prolonged QTc intervals and of genotype-negative unaffected family members; and 2) identify specific clinical and genetic risk factors for life-threatening cardiac events in patients with LQTS with normal-range QTc intervals.

Methods

Study population. The study population comprised 3,386 genotyped subjects drawn from the Rochester, New York, enrolling center (center 1) of the International LQTS Registry (n = 2,630), the Netherlands LQTS Registry (n = 391), and the Japanese LQTS Registry (n = 205), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project from Denmark (n = 90), Italy (n = 28), Israel (n = 25), and Sweden (n = 17). Patients were derived from 552 proband-identified *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) families. The proband in each family had otherwise unexplained, diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had: 1) >1 LQTS identified mutation (n = 70); 2) Jervell and Lange-Nielsen syndrome with deafness and 2 *KCNQ1* mutations or 1 known *KCNQ1* mutation and congenital deafness (n = 2); and 3) no identified mutation on genetic testing with prolonged QTc interval (>440 ms [n = 428]).

Data collection and end point. Routine clinical and rest ECG parameters were acquired at the time of enrollment in each of the registries. Measured parameters on the first recorded electrocardiogram included QT and R-R intervals in milliseconds, with QT interval corrected for heart rate using Bazett's (11) formula. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical histories, ECG findings, therapies, and events during long-term follow-up. Data common to all LQTS registries involving genetically tested subjects were electronically merged into a common database for the present study. In addition, information regarding QT interval–prolonging medications and triggers for cardiac events was collected through a specific questionnaire for patients enrolled the U.S. portion of the registry.

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising aborted cardiac arrest (ACA; requiring external defibrillation as part of the resuscitation or internal defibrillation in patients with implantable cardioverter-defibrillators) or LQTS-related SCD (abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep). In the multivariate models, follow-up was censored at age 41 years to avoid the influence of coronary disease on the occurrence of cardiac events. We also evaluated a secondary end point that included the occurrence of a first cardiac event of any type during follow-up (comprising syncope [defined as transient loss of consciousness that was abrupt in onset and offset], ACA, or SCD).

Phenotype characterization. For the purpose of this study, the QTc interval was categorized as normal range (≤440 ms) or prolonged (>440 ms) according to accepted criteria for the phenotypic definition of LQTS (12). Using this definition, the study population were categorized into 3 genotype and QTc subgroups: 1) LQTS with normal-range QTc interval (n = 469), comprising patients identified to have LQT1 to LQT3 mutations with QTc intervals ≤440 ms; 2) LQTS with prolonged QTc interval (n = 1,392), comprising patients with LQT1 to LQT3 mutations with QTc intervals >440 ms; and 3) unaffected family members (n = 1,525), comprising registry subjects from genotype-positive proband-identified families who were genetically tested and found to be negative for the LQTS-associated mutation, with QTc intervals ≤440 ms (i.e., genetically and phenotypically unaffected family members).

Genotype characterization. The *KCNQ1*, *KCNH2*, and *SCN5A* mutations were identified with the use of standard genetic tests performed in academic molecular genetics laboratories, including the Functional Genomics Center, University of Rochester Medical Center, Rochester, New York; Baylor College of Medicine, Houston, Texas; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota; Boston Children's Hospital, Boston, Massachusetts; the Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; the Department of Clinical Genetics, Academic Medical Center, Amsterdam, the Netherlands; and the Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Genetic alterations of the amino acid sequence were characterized by location and by the type of the specific mutation. The transmembrane region of each of the 3 LQTS channels was defined as: 1) amino acid residues from 120 through 355 in the *KCNQ1*-encoded Kv7.1 channel (S1 to S6 region); 2) amino acid residues from 398 through 657 (S1 to S6 region) in the *KCNH2*-encoded Kv11.1 channel; and 3) amino acid residues 129 through 417, 713 through 940, 1201 through 1470, and 1523 through 1740 in the *SCN5A*-encoded Nav1.5 channel (13). On the basis of prior studies that demonstrated the functional and clinical importance of missense mutations that are located in the transmembrane region of these LQTS-associated channels (9,10), mutation categories were pre-specified in the primary analysis as transmembrane-missense (mutations of the missense type in any of the 3 transmembrane regions described previously) versus nontransmembrane or nonmissense (i.e., any other identified LQT1 to LQT3 mutation that was not transmembrane-missense).

Statistical analysis. The clinical characteristics of study patients were compared by genotype and QTc categories using chi-square tests for categorical variables and *t* tests and Mann-Whitney-Wilcoxon tests for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first life-threatening event and the cumulative event rates by risk groups and risk factors, and groups were compared using the log-rank test.

Cox proportional hazards regression analysis was carried out in the total study population and separately in the subset of patients with genotype-positive LQTS. Pre-specified covariates in the total population model included the 3 genotype and QTc categories, sex, and time-dependent beta-blocker therapy. The models comprising genotype-positive patients included the following pre-specified covariates: QTc category (normal range [≤440 ms] vs. prolonged [>440 ms]), the LQT1 to LQT3 genotypes, mutation location and type, sex, QTc duration (assessed both as a continuous measure [per 10-ms increase] and as a categorical covariate [dichotomized at the median value of each QTc category and assessed in separate models]), time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative. The effect of each covariate on outcome in each QTc category (i.e., in patients with LQTS with normal-range and prolonged QTc intervals) was assessed using interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal and prolonged QTc categories were obtained using these interactions. To avoid violation of the proportional hazards assumption due to sex-risk crossover during adolescence, we used an age-sex interaction term in the multivariate models.

Because almost all the subjects were first-degree and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership (14). All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc., Cary, North Carolina). A 2-sided significance level of 0.05 was used for hypothesis testing.

Results

The spectrum and number of LQT1-associated, LQT2-associated, and LQT3-associated mutations by the pre-specified location and type categories are presented in Online Table 1. Totals of 100, 177, and 41 different mutations were identified in the *KCNQ1*-encoded Kv7.1, *KCNH2*-encoded Kv11.1, and *SCN5A*-encoded Nav1.5 ion channels, respectively. Study patients with identified LQTS mutations exhibited a very wide QTc interval distribution (Fig. 1), ranging from a minimum of 350 ms to a maximum of 800 ms (mean 450 ± 56 ms; median 440 ms; interquartile range: 410 to 480 ms). QTc distribution was similar among the 3 LQTS genotypes. Four hundred sixty-nine LQTS mutation–positive patients exhibited normal-range QTc intervals, constituting 25% of identified cases.

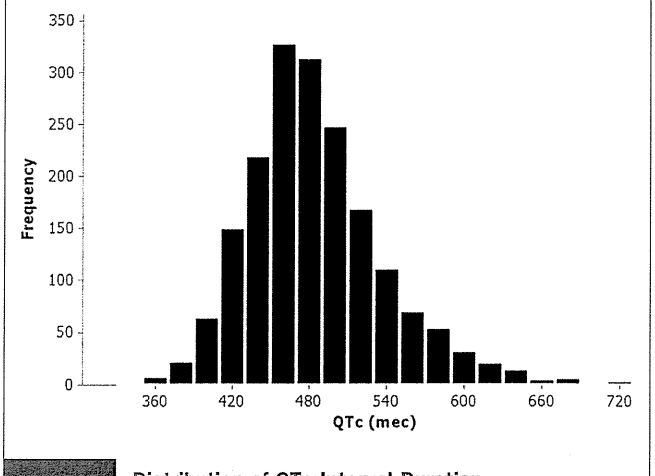

Figure 1 **Distribution of QTc Interval Duration in Genotype-Positive Patients With LQTS**

Distribution of corrected QT (QTc) interval durations in genotype-positive study patients. LQTS = long-QT syndrome.

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Table 1 Baseline and Follow-Up Characteristics of the Study Population by Genotype-Phenotype

Characteristic	Unaffected Family Members (n = 1,525)	Patients With LQTS With Normal-Range QTc Intervals (n = 469)	Patients With LQTS With Prolonged QTc Intervals (n = 1,392)
Female	52%	48%	61%*†
Family history of SCD	8%	12%	19%*†
QTc interval (ms)			
Mean ± SD	412 ± 22	419 ± 20	501 ± 48
Median (IQR)	420 (400–430)	420 (410–440)	490 (470–520)
Proband	8%	8%	29%*†
RR interval (ms)			
Mean ±SD	793 ± 221	888 ± 236	848 ± 214*†
Median (IQR)	800 (640–930)	900 (740–1,040)	840 (700–1,000)*†
Genotype			
LQT1	NA	40%	39%
LQT2	NA	45%	47%
LQT3	NA	16%	14%
Mutation: TM-MS			
Overall	NA	35%	43%
LQT1	NA	45%	61%
LQT2	NA	16%	29%†
LQT3	NA	64%	31%†
Therapies			
Beta-blockers	6.2%	38%	54%*†
Pacemaker	0.3%	0.6%	5%*†
LCSD	0.1%	0.2%	1.4%*†
ICD	0.6%	6%	14%*†
Events			
Syncope	10%	21%	40%*†
ACA	0.2%	1.3%	8.4%*†
SCD	0.1%	1.5%	4.4%*†
ACA/SCD‡§	0.3%	2.8%	11.3%*

*$p < 0.05$ for the comparison among the 3 genotyped categories. †$p < 0.05$ for the comparison between genotype-positive patients with QTc intervals ≤440 ms and genotype-positive patients with QTc intervals >440 ms. ‡Appropriate ICD shocks constituted 0.04% of ACAs in genotype-positive patients with QTc intervals ≤440 ms and 1.4% of ACAs in genotype-positive patients with QTc intervals >440 ms. §Only the first event for each patient was considered.

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LCSD = left cardiac sympathetic denervation; LQT1 = long-QT syndrome type 1; LQT1 = long-QT syndrome type 2; LQT3 = long-QT syndrome type 3; LQTS = long-QT syndrome; MS = missense; NA = not applicable; QTc = corrected QT; SCD = sudden cardiac death; TM = transmembrane.

The clinical characteristics of the total study population by genotype and QTc subgroup are shown in Table 1. The frequency of probands (defined in the registry as the first person in a family, living or deceased, identified to have LQTS by the enrollment center) was highest in patients with prolonged QTc intervals, whereas most patients with normal-range QTc intervals (92%) were asymptomatic at the time of genetic testing. The frequency of female subjects was similar between the unaffected subjects and patients with LQTS with normal-range QTc intervals and higher in patients with prolonged QTc intervals. In mutation carriers, the frequency of the 3 main LQTS genotypes was similar between patients with and without prolonged QTc intervals. However, patients with LQT1 and LQT2 with prolonged QTc intervals had a higher frequency of transmembrane-missense mutations compared with the corresponding genotype carriers who had normal-range QTc intervals. LQTS-related therapies were administered to a significantly higher frequency of patients with prolonged QTc intervals than to subjects in the other 2 subgroups (Table 1).

Clinical course by genotype and QTc subgroup. Kaplan-Meier survival analysis (Fig. 2) demonstrated a relatively low rate of ACA or SCD in patients with LQTS with normal-range QTc intervals (4% at age 40 years and 10% at age 70 years). Event rates were significantly higher in patients with prolonged QTc intervals (15% and 24% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup) and significantly lower in unaffected family members (0.4% and 1% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup and for the overall difference among the 3 subgroups). Notably, life-threatening events in patients with normal-range QTc intervals occurred mostly after age 10 years, whereas patients with prolonged QTc intervals exhibited an earlier onset of life-threatening events (Fig. 2).

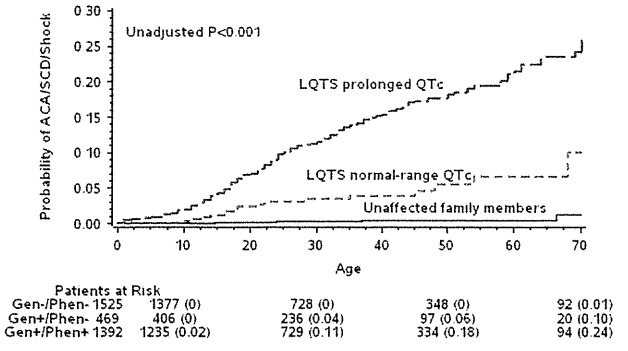

Figure 2 Rate of ACA or SCD by Genotype and QTc Category

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by genotype and corrected QT (QTc) subgroup. LQTS = long-QT syndrome.

After multivariate adjustment for sex, time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative, patients with LQTS with normal-range QTc intervals were shown to have a significant 72% ($p < 0.001$) lower risk for ACA or SCD compared with patients with prolonged QTc intervals but also exhibited a >10-fold increase in the risk for life-threatening events compared with unaffected family members (Table 2). Histories of syncope were present in 62% of patients with LQTS with normal-range QTc intervals who had life-threatening events during follow-up. Accordingly, when the composite secondary end point of a first cardiac event of any type was assessed (comprising mainly non-life-threatening syncopal episodes), patients with normal-range QTc intervals were consistently shown to be at a lower risk compared with those with prolonged QTc intervals (hazard ratio [HR]: 0.47; 95% confidence interval [CI]: 0.33 to 0.59; $p < 0.001$) and at a higher risk compared with unaffected family members (HR: 5.20; 95% CI: 4.19 to 6.44; $p < 0.001$).

Risk factors for ACA or SCD in patients with LQTS with and without prolonged QTc intervals. Interaction-term analysis demonstrated significant differences in risk factors for life-threatening events between the 2 LQTS subgroups (Table 3). In patients with normal-range QTc intervals, the LQT1 and LQT3 genotypes were associated with respective 10- and 8-fold increases in the risk for life-threatening events compared with the LQT2 genotype. In contrast, in patients with prolonged QTc intervals, the LQT1 genotype was associated with one-half the risk of the LQT2 genotype ($p = 0.002$), with a statistically significant genotype–by–QTc subgroup interaction ($p = 0.006$) (Table 3, first row), and the LQT3 genotype showed a similar risk to the LQT2 genotype, without a statistically significant genotype–by–QTc subgroup interaction (Table 3, second row).

The location and type of the LQTS mutation were shown to be significant risk factors for ACA or SCD in patients with normal-range QTc intervals. In this LQTS subset, transmembrane-missense mutations were associated with a pronounced >6-fold ($p = 0.006$) increase in the risk for ACA or SCD compared with nontransmembrane or nonmissense mutations. In contrast, in patients with prolonged QTc intervals, transmembrane-missense mutations were not independently associated with outcomes (Table 3, third row). Notably, when the secondary end point of cardiac events of any type was assessed, transmembrane-missense mutations were shown to be an independent risk factor in both LQTS subgroups (normal-range QTc interval, HR: 1.71; 95% CI: 1.16 to 2.34; prolonged QTc interval, HR: 1.39; 95% CI: 1.17 to 1.65).

Consistent results demonstrating an association between transmembrane-missense mutations and the risk for ACA or SCD in patients with normal-range QTc intervals were shown when the reference group (comprising nontransmembrane or nonmissense mutations) was further divided into 3 subcategories, including nonmissense mutations in the transmembrane region, missense mutations in the nontransmembrane region, and nonmissense mutations in the nontransmembrane region (HR >4.0 for all 3 comparisons). Accordingly, patients with normal-range QTc intervals with transmembrane-missense mutations experienced a relatively high rate of ACA or SCD during follow-up (9% at age 40 years and 21% at age 70 years), whereas patients with normal-range QTc intervals with other mutations had a very low event rate (1% at age 40 years and 5% at age 70 years; log-rank p for overall difference = 0.005) (Fig. 3A). In contrast, in patients with prolonged QTc intervals, there was no statistically significant difference in the rate of ACA or SCD between the 2 mutation categories (16% and 14% at 40 years, respectively, $p = 0.18$) (Fig. 3B).

Clinical and ECG factors, including sex and QTc duration, were shown to be associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (Table 3, rows 4 to 6). In contrast, in patients

Table 2 Multivariate Analysis: Risk for ACA or SCD Among the 3 Genotype and QTc Categories*

Genotype and QTc Subgroup	HR	95% CI	p Value
LQTS with prolonged QTc interval vs. unaffected family members	36.53	13.35–99.95	<0.001
LQTS with normal-range QTc interval vs. unaffected family members	10.25	3.34–31.46	<0.001
LQTS with normal-range QTc interval vs. LQTS with prolonged QTc interval	0.28	0.16–0.49	<0.001

*Model also adjusted for sex (female age >13 years) and time-dependent beta-blocker therapy.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Table 3 Risk Factors for ACA or SCD in Patients With LQTS by QTc Interval Category*

	LQTS and Normal-Range QTc Interval		LQTS and Prolonged QTc Interval		
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value	p Value for Interaction
Genotype					
LQT1 vs. LQT2	9.88 (1.26–37.63)	0.03	0.53 (0.35–0.79)	0.002	0.006
LQT3 vs. LQT2	8.04 (0.85–36.03)	0.07	1.07 (0.70–1.63)	0.77	0.08
Mutation location and type					
TM-MS vs. non-TM-MS	6.32 (1.71–23.33)	0.006	1.24 (0.88–1.76)	0.22	0.02
Sex					
Female age >13 yrs vs. male age >13 yrs	1.32 (0.42–4.17)	0.64	1.90 (1.26–2.86)	0.002	0.53
QTc interval (ms)					
Per 10-ms increase	1.20 (0.81–1.78)	0.35	1.08 (1.05–1.10)	<0.001	0.58
≥Median vs. <median†	1.03 (0.36–2.98)	0.95	2.96 (2.06–4.26)	<0.001	NA

*Cox proportional hazards regression modeling was carried out in models that included all patients with genotype-positive LQTS (n = 1,861). Covariates in the models included QTc category (≤440 ms vs. >440 ms), genotype, mutation location and type, sex, QTc interval (assessed as a continuous measure [per 10-ms increase]), time-dependent beta-blocker therapy, and a family history of SCD; the effect of each covariate in patients with normal-range (≤440 ms) and those with prolonged (>440 ms) QTc intervals was assessed by interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal-range and prolonged QTc interval groups were obtained using these interactions. Virtually identical results for all pre-specified risk factors were also obtained from the models that did not include appropriate ICD shocks as part of the composite end point. †Results were obtained from separate models that assessed the risk associated with QTc values greater than or equal to the median in patients with LQTS with normal-range QTc intervals (median 420 ms) and prolonged QTc intervals (median 500 ms).

Abbreviations as in Tables 1 and 2.

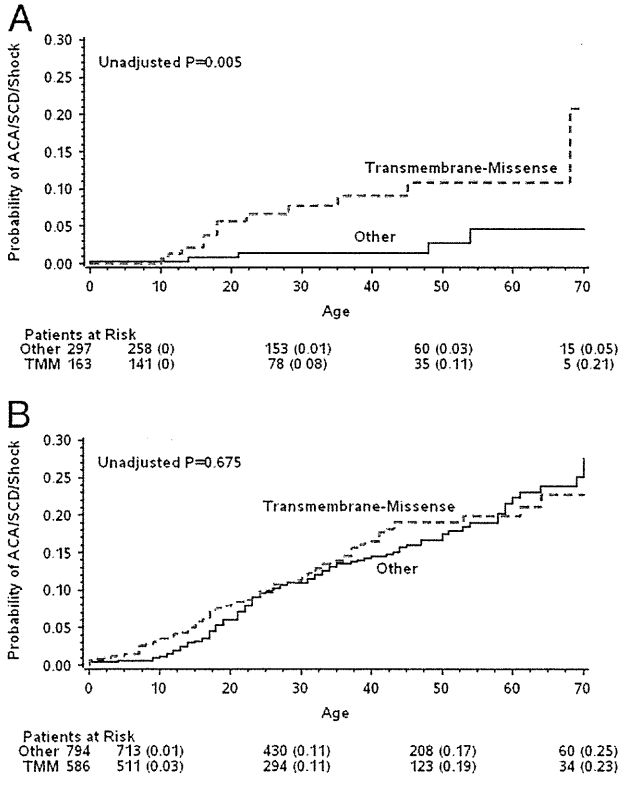

Figure 3 Rate of ACA or SCD in Patients With Normal-Range and Prolonged QTc Intervals by Mutation Location and Type

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by mutation location and type in patients with long-QT syndrome (LQTS) with **(A)** corrected QT (QTc) intervals ≤440 ms and **(B)** QTc intervals >440 ms.

with normal-range QTc intervals, sex was not a significant risk factor, and QTc duration was not independently associated with a significant increase in the risk for ACA or SCD when assessed as a continuous measure or when dichotomized at the median value (≥420 ms).

As suggested previously (15), the presence of a family history of SCD in any first-degree relative was not shown to be an independent predictor of ACA or SCD in patients with either normal-range QTc intervals (HR: 0.89; 95% CI: 0.63 to 1.25; p = 0.50) or prolonged QTc intervals (HR: 1.40; 95% CI: 0.32 to 6.17; p = 0.65) after adjustment for genetic and clinical factors.

Beta-blocker therapy was administered to 38% of patients who had normal-range QTc intervals compared with 54% of the patients who had prolonged QTc intervals (p < 0.001) (Table 1). Treatment with beta-blockers was associated with an overall significant 25% reduction in the risk for ACA or SCD in the total study population (95% CI: 0.70 to 0.80; p < 0.001), with similar effects in patients with normal-range QTc intervals and those with prolonged QTc intervals (p for beta-blocker–by–LQTS subset interaction = 0.45).

Characteristics of fatal or near-fatal cases with a normal-range QTc intervals. The characteristics of patients with normal-range QTc intervals who experienced ACA or SCD during follow-up are shown in Table 4. The mean age at occurrence of the lethal or near-lethal event in this population was 25.9 ± 4.5 years. Nine of the patients (53%) who experienced events were women, and 4 (24%) were treated with beta-blockers are the time of the events. In patients with normal-range QTc intervals with available data regarding therapies and triggers at the time of the events, none were reported as being treated with a QT interval–prolonging drugs at the time of ACA or SCD, and the majority of the lethal or near-lethal events were not associated with exercise or arousal triggers (Table 4).

Table 4 Characteristics of ACA and SCD Cases With Normal-Range QTc Intervals

Case	Event	Event Age (yrs)	Female	QTc Interval (ms)	BB†	LCSD†	PM†	ICD†	QT PD	Trigger*	Genotype	Mutation Location and Type
1	SCD	0.5	–	390	–	–	–	–	–	NA	LQT3	Non-TM-MS
2	ACA	10		430	–	–	–	–	–	Exercise	LQT1	TM-MS
3	ACA/shock	11	+	400	–	–	–	+	–	Non-E/A	LQT1	TM-MS
4	SCD	13	–	440	+	–	–	–	NA	NA	LQT1	TM-MS
5	ACA	14	–	410	–	–	–	–	–	Exercise	LQT1	Non-TM-MS
6	SCD	16	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
7	ACA	16	+	440	–	–	–	–	–	Arousal	LQT1	TM-MS
8	SCD	18	–	430	+	–	–	–	–	Non-E/A	LQT1	TM-MS
9	ACA	18	+	410	–	–	–	–	–	Exercise	LQT1	TM-MS
10	SCD	21	+	380	–	–	–	–	–	Arousal	LQT2	Non-TM-MS
11	SCD	22	–	440	–	–	–	–	NA	NA	LQT1	TM-MS
12	SCD	28	–	410	–	–	–	–	–	Exercise	LQT1	TM-MS
13	ACA	35	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
14	ACA	46	+	440	+	–	–	–	NA	NA	LQT2	TM-MS
15	SCD	48	–	430	+	–	–	–	–	Non-E/A	LQT2	Non-TM-MS
16	ACA	54	+	420	–	–	–	–	–	Non-E/A	LQT3	Non-TM-MS
17	SCD	69	–	380	–	–	–	–	NA	NA	LQT1	TM-MS

*Data regarding triggers for cardiac events and treatment with QT interval–prolonging medications were available for study patients who were enrolled in the U.S. portion of the International LQTS Registry.
†At time of event. ‡Implanted or performed before event.
BB = beta-blocker therapy; E/A = exercise/arousal trigger for event; NA = not available; PM = pacemaker; QT PD = QT interval–prolonging drug; other abbreviations as in Tables 1 and 2.

Discussion

In this study, we assessed the clinical courses and risk factors for life-threatening events in LQTS patients with genetically-confirmed LQTS who do not exhibit the disease's phenotypic hallmark of QT interval prolongation, otherwise referred to as concealed LQTS, normal–QT interval LQTS, or genotype-positive/ECG phenotype–negative LQTS. Similar to prior studies (16), we have shown that patients with LQT1 to LQT3 exhibit a wide QTc distribution, with approximately 25% having QTc intervals well within the normal range. The rate of ACA or SCD in patients with LQTS with normal-range QTc intervals was shown to be very low (4% from birth through age 40 years, corresponding to an approximate event rate of 0.13% per year). Comparatively, however, this very low risk subset of the LQTS population still exhibited a >10-fold increase in the risk for life-threatening events compared with genetically and phenotypically unaffected family members. Importantly, predictors of life-threatening events were shown to be significantly different between LQTS patients with and without prolonged QTc intervals. In the latter LQTS subgroup, genetic data, including knowledge of genotype and mutation characteristics, were shown to identify the risk for ACA or SCD, whereas in the former LQTS subgroup, female sex in the post-adolescence period and QTc duration were identified as the predominant risk factors for life-threatening events.

The clinical courses of patients with LQTS are variable because of incomplete penetrance (17). They are influenced by age, genotype, sex, environmental factors, therapy, and possibly other modifier genes (1–10). Recent studies from the International LQTS Registry that assessed the risk for life-threatening events in patients with LQTS have consistently demonstrated that ECG and clinical risk factors, including the QTc interval and age-sex interactions, identify increased risk in the LQTS population (3–5). These studies, however, included mainly phenotype-positive patients with LQTS with QTc intervals ≥ 450 ms. Thus, the effect of genetic data on outcomes in these studies was not statistically significant after adjustment for the ECG and clinical factors. The present study population, comprising 1,861 genetically confirmed patients with the LQT1 to LQT3 genotypes, extends the data derived from prior studies and demonstrates that risk factors for life-threatening events are significantly different between patients with LQTS with and without QTc prolongation. Consistent with prior studies, we have shown that in patients with LQTS who exhibit prolonged QTc durations, ECG information and clinical factors can be used to identify the risk for life-threatening events. In contrast, in mutation-positive subjects with normal-range QTc intervals, genetic factors, including knowledge of the LQTS genotypes and the mutation location and type, identified patients who were at an increased risk for ACA or SCD after adjustment for ECG and clinical data.

Sex was not a significant risk factor for cardiac events in patients with normal-range QTc intervals. Furthermore, patients with normal-range QTc intervals displayed a similar frequency of women as unaffected family members, whereas the frequency of women was significantly higher among patients with prolonged QTc intervals. These findings are in accordance with earlier evidence of longer QTc intervals in LQTS women than in men (18), resulting in a marked female predominance in phenotypically affected patients (3–5). The biologic basis for this sex difference might be the down-regulation of expression of cardiac potassium-channel genes by female

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sex hormones, which have been shown to prolong the QT interval in both congenital and drug-induced LQTS (19,20). These hormonal effects may explain the present findings of a lower frequency of LQTS women with normal-range QTc intervals.

Recent genotype-phenotype studies have shown that missense mutations located in the transmembrane region, which is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk for cardiac events compared with mutations that are located in other regions of the LQTS channel (9,10). The present study also shows that transmembrane-missense mutations are associated with a significantly higher risk for cardiac events of any type (predominated by syncopal episodes) in patients with LQTS with both normal-range and prolonged QTc intervals. However, our findings suggest that data regarding mutation characteristics are important for the assessment of life-threatening events (comprising ACA and SCD) mainly in patients with normal-range QTc intervals, in whom information derived from ECG and clinical data is more limited. In this LQTS subset, missense mutations located in the transmembrane region were shown to be associated with a >6-fold increase in the risk for life-threatening events and with a clinically meaningful rate of ACA or SCD (9%) from birth through age 40 years.

The mechanisms relating to the occurrence of life-threatening ventricular tachyarrhythmias in phenotype-negative patients with LQTS are not clear. In the present study, none of the patients with normal-range QTc intervals who experienced ACA or SCD took QT interval–prolonging medications at the time of the events. Furthermore, most events in patients with normal-range QTc intervals were not related to exercise or arousal triggers (Table 4). An ECG tracing from a patient with the LQT1 genotype who developed arrhythmic events despite a normal-range QTc interval showed spontaneous generation of polymorphic ventricular tachycardia without preceding extrasystolic pauses or sudden sinus rate acceleration (Fig. 4), possibly explaining the occurrence of ACA or SCD in study patients with normal-range QTc intervals who were treated with beta-blockers at the time of the events.

Study limitations. Most study patients did not undergo comprehensive genetic testing for all currently known mutations that may predispose to arrhythmic risk. Thus, it is possible that the coexistence of modifier genes affected the outcomes of patients with LQTS with normal-range QTc intervals who experienced life-threatening cardiac events. In addition, to provide an estimation of event rates among unaffected family members, we included in the control group subjects who were both genotype negative and also had normal-range QTc intervals (and excluded genotype-negative subjects with prolonged QTc intervals due to possible unidentified mutations in this subset). Therefore, the overall frequency of genotype-positive subjects in the total population may not represent the true penetrance of LQTS in affected families.

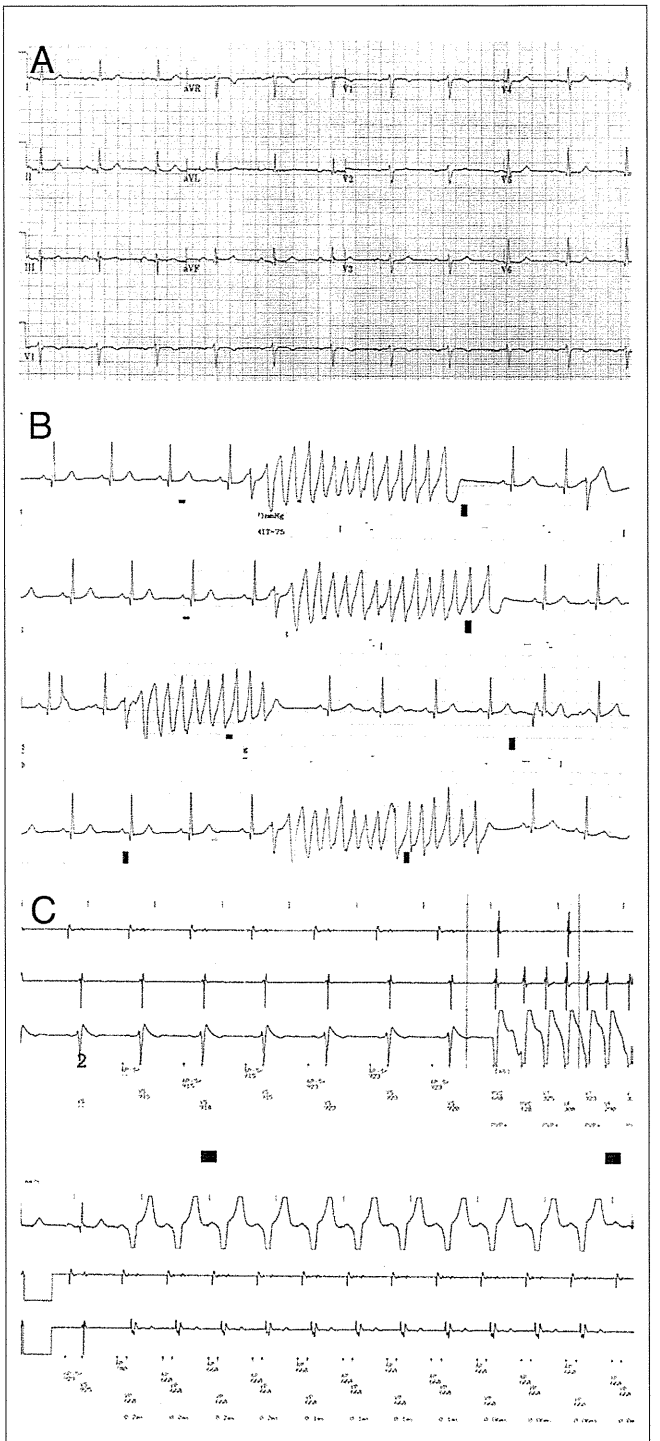

Figure 4 **Polymorphic Ventricular Tachycardia in a Patient With a Normal-Range QTc Interval**

Spontaneous generation of polymorphic ventricular tachycardia in a patient with long-QT syndrome type 1 with a normal-range corrected QT (QTc) interval. **(A)** The patient had a QTc duration of 410 ms on baseline electrocardiography. **(B)** Electrocardiographic tracing at the time of arrhythmic event demonstrates sinus rate with an RR interval of 1,000 ms without significant QT prolongation before the arrhythmia. **(C)** The patient was treated with nadolol and received an implantable cardioverter-defibrillator but continued to exhibit arrhythmic episodes that were recorded on implantable cardioverter-defibrillator interrogation.

The threshold value of 440 ms for the definition of a normal-range QTc in the present study was based on the diagnostic criteria for LQTS proposed by Schwartz et al. (12), which define a prolonged QTc interval as ≥450 ms in male patients and ≥460 ms in female patients. We chose to use a uniform approach by selecting 440 ms as the upper limit of normal rather than having separate phenotypic definitions for male and female patients. It should also be noted that 2.5% of infants and 10% to 20% of adults exceed this cutoff (21). Thus, the 440-ms value is not meant to suggest an LQTS diagnosis on its own.

Conclusions

The present study shows that patients with LQTS who exhibit normal-range QTc intervals constitute approximately 25% of the LQTS population and have a significantly lower risk for life-threatening events compared with phenotypically affected patients but also exhibit a significant increase in the risk of ACA or SCD compared with unaffected family members. Missense mutations in the transmembrane regions of the ion channels, mainly in patients with LQT1 and LQT3, were shown to identify patients with normal-range QTc intervals who have an increased risk for ACA or SCD. In contrast, increments in QTc duration were not shown to be significantly associated with increased risk for life-threatening events in this population. These findings suggest that: 1) risk assessment in phenotype-negative family members of LQTS probands should include genetic testing, because a positive genetic test result in a family member with a normal-range QTc interval implies an overall >10-fold increase in the risk for ACA or SCD compared with a negative test result in an unaffected family member; 2) genetic data may be used to identify phenotype-negative patients with LQTS who are at increased risk for fatal ventricular tachyarrhythmias independently of QTc duration; and 3) LQTS mutation–positive patients with normal-range QTc intervals who are identified as having increased risk for life-threatening events on the basis of genotype and mutation characteristics (i.e., LQT1 and LQT3 with transmembrane-missense mutations) should be carefully followed and receive a similar management strategy as phenotype-positive patients with LQTS, including avoidance of QT-prolonging medications (22), routine therapy with beta-blockers, and possibly implantable cardioverter-defibrillator therapy in those who remain symptomatic despite medical therapy. Conversely, patients with the lowest risk profile of already low risk, concealed LQTS (i.e., concealed LQT2 and non-transmembrane-missense LQT1 and LQT3) may represent the nominally near zero risk subpopulation(s) of LQTS in need of only preventative health recommendations such as QT drug avoidance.

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Key Words: corrected QT interval ▪ long-QT syndrome ▪ sudden cardiac death.

APPENDIX

For a table about *KCNQ1*, *KCNH2*, and *SCN5A* mutations by amino acid coding, frequency, location, and type, please see the online version of this article.

CARDIOVASCULAR DISEASE

Use of Mutant-Specific Ion Channel Characteristics for Risk Stratification of Long QT Syndrome Patients

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Inherited long QT syndrome (LQTS) is caused by mutations in ion channels that delay cardiac repolarization, increasing the risk of sudden death from ventricular arrhythmias. Currently, the risk of sudden death in individuals with LQTS is estimated from clinical parameters such as age, gender, and the QT interval, measured from the electrocardiogram. Even though a number of different mutations can cause LQTS, mutation-specific information is rarely used clinically. LQTS type 1 (LQT1), one of the most common forms of LQTS, is caused by mutations in the slow potassium current (I_{Ks}) channel α subunit KCNQ1. We investigated whether mutation-specific changes in I_{Ks} function can predict cardiac risk in LQT1. By correlating the clinical phenotype of 387 LQT1 patients with the cellular electrophysiological characteristics caused by an array of mutations in KCNQ1, we found that channels with a decreased rate of current activation are associated with increased risk of cardiac events (hazard ratio = 2.02), independent of the clinical parameters usually used for risk stratification. In patients with moderate QT prolongation (a QT interval less than 500 ms), slower activation was an independent predictor for cardiac events (syncope, aborted cardiac arrest, and sudden death) (hazard ratio = 2.10), whereas the length of the QT interval itself was not. Our results indicate that genotype and biophysical phenotype analysis may be useful for risk stratification of LQT1 patients and suggest that slow channel activation is associated with an increased risk of cardiac events.

INTRODUCTION

The slow potassium current (I_{Ks}) mediates cardiac repolarization. Mutations in the α subunit KCNQ1 of the I_{Ks} channel cause long QT syndrome (LQTS) type 1 (LQT1) (*1*), with risk of sudden death as a result of ventricular fibrillation. The identification of the gene responsible for this syndrome has allowed in vitro characterization of mutation-related changes in the assembled channel. Current risk stratification of LQT1 subjects is performed mainly with clinical parameters such as age, gender, and the QT interval; mutation-specific risk stratification is rarely used to guide therapy (*2–5*). Mutations with an autosomal dominant effect on channel function are associated with higher cardiac risk than those that impair channel function through haploinsufficiency (*6*). In addition, missense mutations and mutations in the transmembrane region of KCNQ1 are associated with a higher risk for cardiac arrhythmias (*6*). The mechanisms underlying these associations are unknown. Previous studies of a few mutations reported a poor correlation between decreased I_{Ks} magnitude and the QTc (corrected QT) interval in patients harboring the mutation (*7–9*).

Recently, we showed that KCNQ1 mutations in highly conserved amino acids in the transmembrane region of human voltage-gated K^+ channels were associated with a high risk for cardiac events in the LQT1 subjects (*10*). Conserved amino acid residues are believed to control important aspects of channel function such as conduction and voltage gating of activation and deactivation (*11*, *12*). Here, we have set out (i) to investigate the association of conventional measures of ion channel function (ion channel current magnitude, rate of current activation and deactivation, voltage dependence, and maximal conductance) with QTc interval; (ii) to determine whether ion channel dysfunction contributes to the risk of cardiac events in LQT1 patients independent of the standard phenotypic risk factors, including QTc duration; and (iii) to investigate the mechanism underlying mutant-specific increase in cardiac risk by evaluating electrophysiological parameters in the action potential of cardiomyocytes in silico.

RESULTS

Population and mutation characteristics

The clinical characteristics of the study patients are shown in Table 1. This population was drawn from the International Long QT Registry (see Materials and Methods for details). All patients were genetically confirmed carriers of a single LQTS-causing mutation in the *KCNQ1* gene and were enrolled over the past 20 to 30 years. Clinical follow-up data for these patients were used to relate altered cellular electrophysiology to cardiac risk. To be able to confidently estimate the mutation-specific clinical course and include as many different mutations as possible, we included only mutations that affected 10 patients or more. A total of 17 mutations present in 387 LQT1 patients drawn from four LQTS international registries were included in the study. Most of the mutations were found in more than one family (59%), eight were found in two or more registries, two mutations were found in more than one family in the same registry, and seven mutations

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Table 1. Patient characteristics by mutations. *n*, number of patients; GTNF, genotype-negative family members.

Mutation	*n*	Families	Registries (1 = United States, 2 = Netherlands, 3 = Japan, 4 = Denmark)	Gender (% males)	QTc (ms), median (range)	β-Blockers started (%)	References
G168R	68	7	1	41	475 (410–660)	35	(*46*, *47*)
Y184S	14	3	2	43	470 (450–520)	64	(*48*)
S225L	14	4	1, 2	29	475 (450–500)	36	(*7*)
R243C	13	5	1, 3	15	495 (420–680)	38	(*19*, *49*)
V254M	62	4	1, 4	48	500 (450–590)	53	(*9*)
L266P	24	5	1	25	490 (390–580)	33	—
G269S	41	5	1, 3	49	480 (410–650)	46	(*50*)
W305S	16	1	1	38	430 (390–480)	69	(*51*)
T312I	17	2	1	47	500 (410–600)	60	—
G314S	19	5	1, 2, 3	53	485 (420–630)	32	(*52*)
Y315C	10	1	1	40	450 (440–470)	20	(*7*, *50*)
A341E	10	1	1	40	460 (410–700)	50	(*9*, *50*)
A341V	21	6	1, 2, 3	38	490 (410–560)	57	(*9*, *18*, *22*, *23*, *53*, *54*)
S349W	15	3	1	53	450 (390–510)	53	—
R591H	19	3	1, 3	53	470 (420–600)	47	(*55*, *56*)
R594Q	14	4	1, 2	43	455 (400–760)	43	(*55*)
D611Y	10	1	3	50	410 (370–460)	0	(*57*)
GTNF (WT)	48	90	1	47	420 (340–550)	8	—

(41%) were found in just one family in one registry. QT prolongation among carriers of the same mutation is variable. To correlate conventional measures used for clinical risk stratification with functional cellular expression measurements, we calculated the median QTc prolongation (QTc_m) in the carrier population for each individual mutation. QTc_m was significantly prolonged for all but one mutation (D611Y). QTc is missing for 67 patients who died before QTc could be evaluated. At least nine patients were used to calculate the median QTc for each mutation studied.

Only missense mutations were used in this study because nonsense mutations are not expected to produce functional mutant channel subunits, and missense mutations carry higher risk in the LQT1 population (*6*). Nonsense mutations are expected to be nonfunctional and, when coexpressed with wild-type (WT) subunits, not to affect the function of wild-type KCNQ1. We also evaluated the effect of nonsense mutations (0.5 WT) (Table 2) and compared it to the effect of the 17 missense mutations. Nonsense mutations had a mild functional effect, consistent with the published milder clinical phenotype of nonsense mutations (*6*). The location of the mutations included in our study is shown in Fig. 1.

Electrophysiological parameters were obtained from expression of wild-type and mutant human KCNQ1 channel subunits together with the auxiliary KCNE1 subunit in *Xenopus laevis* oocytes at room temperature. Wild-type and mutant KCNQ1 subunits were expressed at a 1:1 ratio to mimic the dominant nature of the disease, where both alleles are expressed in patients. The oocyte system allowed control of the expression level in each individual cell, producing low variability in currents. Four mutant channels (G168R, S225L, R243C, and V254M) were also expressed in the human embryonic kidney (HEK) 293T mammalian cell line and yielded currents with the same activation and deactivation rates as in the oocyte system (fig. S2). Currents were decreased in the mammalian cells by ~30% for all mutants tested, but the proportion between mutant and wild-type currents was maintained. Our results indicate that channel expression in *Xenopus laevis* oocytes can be used to study the rate of activation, deactivation impairment of I_{Ks}, and relative changes in current, and that it offers lower cell to cell variability, which is particularly important when a large number of mutants are being studied.

Changes in channel current (I_{mut}/I_{WT}), channel rate of activation ($\tau_{act}/\tau_{act\text{-}WT}$), and channel rate of deactivation ($\tau_{deact}/\tau_{deact\text{-}WT}$) were obtained for channels expressing mutant KCNQ1 subunits (Table 2). All 14 mutations found in the transmembrane region (S1 to S6 domains) displayed a partial dominant-negative response ($I_{mut}/I_{WT} < 1$). Consistent with a dominant-negative response, these mutations also showed significant changes in other channel gating parameters. Changes in maximal conductance ($G_{max}/G_{max\text{-}WT}$) and voltage dependence obtained from the Boltzmann fit of channel voltage dependence of activation curve ($\Delta V_{1/2}$ and k/k_{wt}) are shown in table S1.

Correlation of QTc prolongation in mutation carriers with mutation-specific electrophysiology

Prolonged QTc_m in the population was associated with channels with smaller currents (I_{mut}) and slower activation (τ_{act}), but there was no

Table 2. Changes in ion channel parameters caused by LQT1 mutation. Mutant channel subunits are expressed together with WT subunits and the auxiliary KCNE1 subunits at a ratio of 0.5 Q1WT/0.5 Q1mut/1.0 E1. Values are normalized by the values measured in the channels that mimic the haploinsufficient phenotype (0.5 WT). The WT channel is also measured as a comparison (WT). *n*, number of cells measured; *I*, activated current measured at +40 mV after 4-s depolarization; τ_{act}, single exponential fit of the activation current; τ_{deact}, single exponential fit of the current deactivation.

Mutation	I/I_{WT}			$\tau_{act}/\tau_{act\text{-}WT}$			$\tau_{deact}/\tau_{deact\text{-}WT}$		
	n	Mean	SE	*n*	Mean	SE	*n*	Mean	SE
WT	36	1.39*	±0.08	38	0.93*	±0.03	52	1.02	±0.03
0.5 WT	94	1.00	±0.03	94	1.00	±0.02	96	1.00	±0.02
G168R	24	0.39*	±0.02	25	1.21*	±0.04	24	0.90	±0.04
Y184S	18	0.71*	±0.08	18	1.14*	±0.03	18	1.02	±0.03
S225L	22	0.61*	±0.05	24	1.33*	±0.05	23	0.74*	±0.03
R243C	30	0.42*	±0.03	34	1.18*	±0.03	35	0.79*	±0.02
V254M	24	0.39*	±0.02	27	1.82*	±0.08	26	1.13*	±0.04
L266P	24	0.29*	±0.02	25	1.25*	±0.04	25	0.83*	±0.03
G269S	24	0.52*	±0.03	26	1.16*	±0.03	27	0.68*	±0.03
W305S	37	0.38*	±0.02	37	1.19*	±0.06	39	0.71*	±0.03
T312I	20	0.20*	±0.02	21	1.30*	±0.05	21	0.76*	±0.03
G314S	32	0.32*	±0.02	17	1.25*	±0.06	20	0.90*	±0.03
Y315C	24	0.62*	±0.04	24	1.03	±0.04	24	0.78*	±0.03
A341E	27	0.41*	±0.04	28	1.15*	±0.06	30	0.93	±0.03
A341V	24	0.56*	±0.07	26	1.21*	±0.04	26	0.78*	±0.03
S349W	25	0.73*	±0.06	27	1.31*	±0.05	29	1.00	±0.04
R591H	25	0.95	±0.10	25	0.97	±0.03	32	0.99	±0.02
R594Q	26	0.99	±0.03	25	0.94	±0.04	30	0.97	±0.03
D611Y	27	1.47*	±0.03	25	0.87	±0.06	28	0.95	±0.07

*$P \leq 0.05$, significantly different from the channel mimicking the haploinsufficient phenotype (0.5 WT).

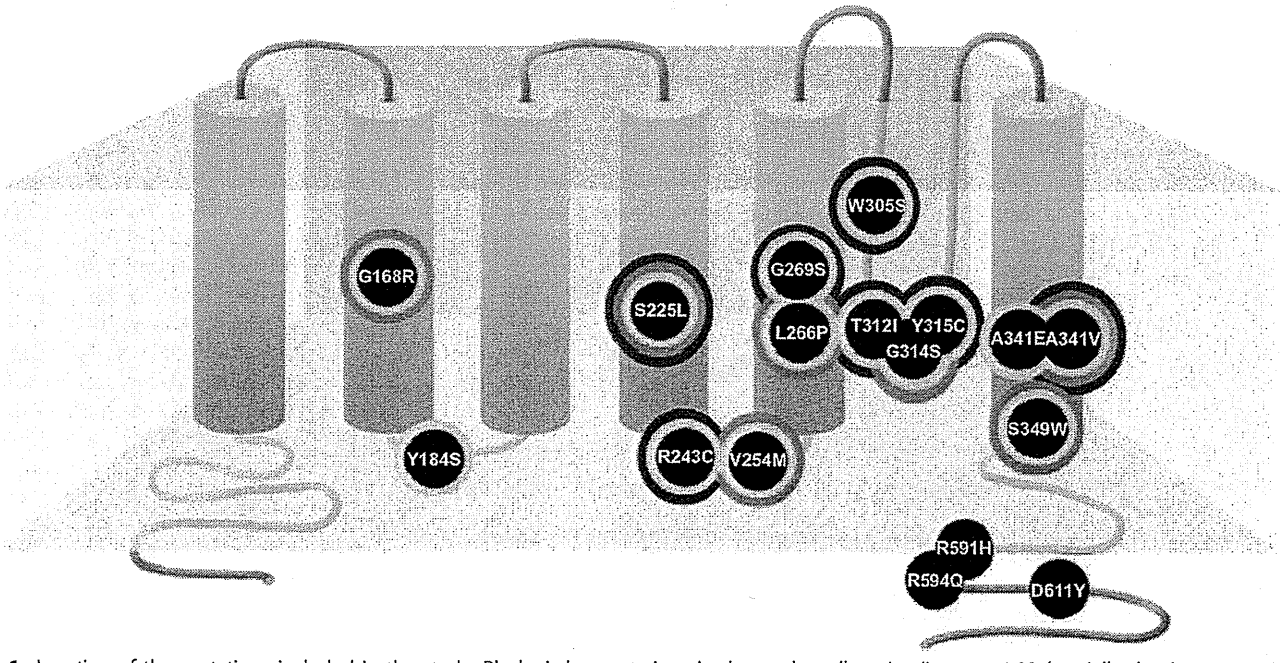

Fig. 1. Location of the mutations included in the study. Black circles, mutations in the study; yellow, $I_{mut}/I_{Kact\text{-}WT}$ <1.00 (partially dominant-negative); green, $\tau_{act}/\tau_{act\text{-}WT}$ >1.20 (increased more than 20%); blue, $\tau_{deact}/\tau_{deact\text{-}WT}$ <0.80 (decreased more than 20%).

correlation with changes in channel deactivation (τ_{deact}) (Fig. 2). In a multivariate regression model, with QTc_m as a function of changes in current (I_{mut}/I_{WT}) and channel rate of activation ($\tau_{act}/\tau_{act\text{-}WT}$), only the decrease in current contributed independently to the QTc_m ($P = 0.016$), whereas channel rate of activation did not ($P = 0.25$). QTc_m showed limited or no correlation to the changes caused by the mutations in the voltage dependence of activation of the channel and maximal conductance (see table S2).

Contribution of mutation-specific electrophysiology to the risk of cardiac events

We tested for the association of channel parameters with cardiac events, which included syncope (transient loss of consciousness that is abrupt in onset and offset), aborted cardiac arrest (ACA) requiring defibrillation, and sudden cardiac death (SCD) (unexpected sudden death without a known cause), whichever occurred first. Mutant channels with slower activation were significantly associated with an increased rate of cardiac events before age 30 ($P = 0.02$), whereas the association with a decrease in channel current was not significant ($P = 0.06$) (Fig. 2). Kaplan-Meier event-free survival rate showed limited or no correlation with the mutation-induced changes in the voltage dependence of activation and maximal conductance (see table S2).

In a multivariate Cox analysis, the median increase in rate of activation ($\tau_{act}/\tau_{act\text{-}WT} > 1.20$) contributed to cardiac risk both univariately and independently of conventional risk markers such as individual patient QTc, gender, and treatment with β-adrenergic receptor blockers (Table 3A and Fig. 3A). The median decrease in I_{mut} and τ_{deact} was 50 and 20%, respectively. Neither changes in current {I_{mut}/I_{WT}: hazard ratio (HR) = 1.07 [95% confidence interval (CI), 0.76 to 1.52], $P = 0.69$} nor deactivation time [$\tau_{deacct}/\tau_{deacct\text{-}WT}$: HR = 1.28 (95% CI, 0.90 to 0.63), $P = 0.55$] contributed in the multivariate models.

Individual QTc is the main clinical parameter used in the assessment of cardiac risk for LQTS patients. A baseline QTc of more than 500 ms is an independent risk factor for cardiac events in LQTS (*2*, *13*). In a secondary analysis shown in Table 3B, we excluded subjects with a severely prolonged QTc, defined as QTc ≥500 ms. A QTc of ≥500 ms was found in 108 of 327 patients with a known QTc. In addition, 67 patients were obligate carriers of a mutation but died before having an electrocardiogram (ECG) recorded; they were also excluded from this analysis. The remaining 212 patients were included. Mutant channels with slow channel activation ($\tau_{act}/\tau_{act\text{-}WT} > 1.20$) remained a strong predictor for cardiac events in patients with QTc <500 ms, whereas a more pronounced QTc prolongation (QTc ≥470 ms) did not predict increased risk of cardiac events (see Table 3B and Fig. 3B).

The KCNQ1(V254M) mutant subunit strongly affected the channel activation time ($\tau_{act}/\tau_{act\text{-}WT} = 1.82$). To classify the mutations into slow-activating ($\tau_{act}/\tau_{act\text{-}WT}$

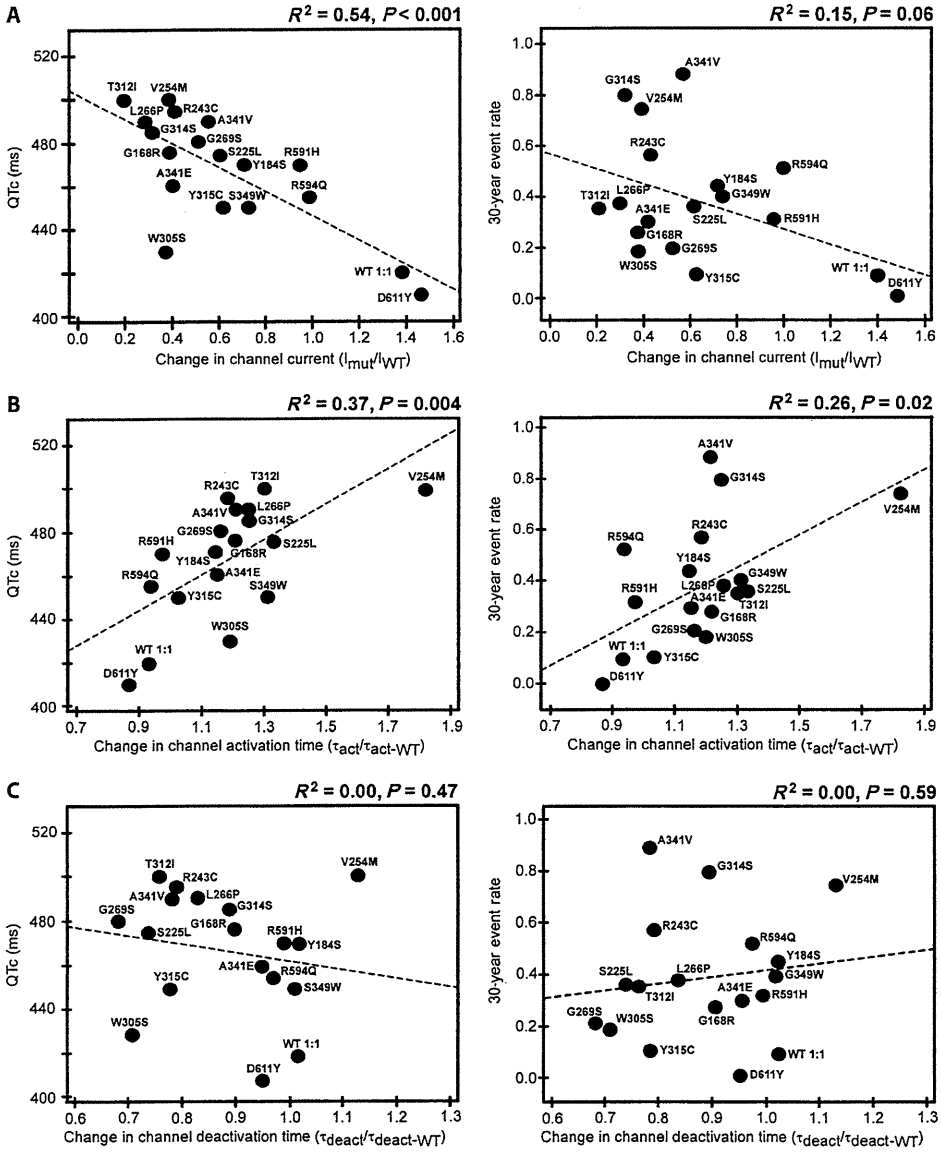

Fig. 2. Results from simple linear regression. Simple linear regression between ion channel characteristics and either the observed median QTc (left) or the observed 30-year Kaplan-Meier survival rates (right) for carriers of each mutation. (**A**) Correlation between changes in ion channel current (I_{mut}/I_{WT}) and median QTc (left) or 30-year Kaplan-Meier survival rates (right). (**B**) Correlation between rate of current activation ($\tau_{act}/\tau_{act\text{-}WT}$) and median QTc (left) or 30-year Kaplan-Meier event rates (right). (**C**) Correlation between changes in rate of current deactivation ($\tau_{deact}/\tau_{deact\text{-}WT}$) and median QTc (left) or 30-year Kaplan-Meier event rates (right).