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Identification of a common genetic substrate underlying postpartum cardiac events in congenital long QT syndrome

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KEYWORDS
Long QT syndrome;
Postpartum period;
Sudden death;
Genetic testing

OBJECTIVES The aim of this study was to elucidate the genetic basis for long QT syndrome (LQTS) in patients with a personal or family history of postpartum cardiac events.

BACKGROUND The postpartum period is a time of increased arrhythmogenic susceptibility in women with LQTS.

METHODS Between August 1997 and May 2003, 388 unrelated patients (260 females, average age at diagnosis, 23 years, and average QTc, 482 ms) were referred to Mayo Clinic's Sudden Death Genomics Laboratory for LQTS genetic testing. Comprehensive mutational analysis of the 5 LQTS-causing channel genes was performed. The postpartum period was defined as the 20 weeks after delivery. Cardiac events included sudden cardiac death, aborted cardiac arrest, and syncope. The presence of a personal and/or family history of cardiac events during postpartum period was determined by review of the medical records and/or phone interviews and was blinded to the status of genetic testing.

RESULTS Fourteen patients (3.6% of cohort) had personal (n = 4) and/or family history (n = 11) of cardiac events during the defined postpartum period. Thirteen of 14 patients (93%) possessed an LQT2 mutation and 1 had an LQT1 mutation. Postpartum cardiac events were found more commonly in patients with LQT2 (13 of 80, 16%) than in patients with LQT1 (1 of 103, <1%, $P = .0001$).

CONCLUSIONS There is a relatively gene-specific molecular basis underlying cardiac events during the postpartum period in LQTS. Along with previous gene-specific associations involving swimming and LQT1 as well as auditory triggers and LQT2, this association between postpartum cardiac events and LQT2 can facilitate strategic genotyping.

The congenital long QT syndrome (LQTS) comprises the first genetically defined type of arrhythmia to be understood at the molecular level as a primary cardiac channelopathy.[1–3] To date, 6 LQTS genes have been identified: *KCNQ1* (*KVLQT1*, LQT1), *KCNH2* (*HERG*, LQT2), *SCN5A* (LQT3), *ANKB* (*Ankyrin-B*, LQT4), *KCNE1* (*minK*, LQT5), and *KCNE2* (*MiRP1*, LQT6).[4–9] There are relatively gene-specific triggers for cardiac events in LQTS. Patients with LQT1 usually have cardiac events during exercise (62%), whereas LQT2 and LQT3 patients are more likely to have events during rest/sleep (29% and 39%).[10] Moreover, swimming appears to trigger events in nearly 15% of children and young adults with symptomatic LQTS, and swimming-

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Table 1 Fourteen index cases who experienced personal and/or family history of cardiac events during postpartum period

Case No.	Relationship to case	No. of cardiac events	Type of cardiac event	Time from delivery (weeks)	LQTS genotype	Mutation	Location
1	Self	1	Aborted cardiac arrest	16	LQT2	I31S*	N-terminal
2	Family member (1)	1	Syncope	8	LQT2	T65P	N-terminal
3	Family member (1)	1	SCD	8	LQT2	Y475del*	S2/S3
4	Family member (1)	1	SCD	8	LQT2	G572S*	S5
5	Family member (1)	1	Aborted cardiac arrest	16	LQT2	N588D	S5/Pore
6	Family member (1)	1	SCD	12	LQT2	N633S	Pore/S6
7	Family member (2)	1	SCD	12	LQT2	V822M	cNBD
8	Family member (1)	1	Syncope	6	LQT2	D837G*	C-terminal
9	Self‡	2	Syncope/SCD	8, 0§	LQT2	P910fs/16*	C-terminal
10	Self	2	Syncope/syncope	8, 12	LQT2	R920fs/51	C-terminal
11	Family member (2)	1	Aborted cardiac arrest	8	LQT2	N996I*	C-terminal
12	Self	2	Syncope/aborted cardiac arrest†	4, 20	LQT2	R1005fs/50*	C-terminal
13	Family member (1)	1	SCD	10	LQT2	R1033fs/23*	C-terminal
14	Family member (1)	1	SCD	20	LQT1	T322A*	Pore/S6

Family member = number in () indicates relatedness to the index case, (1) denotes a first-degree relative, either mother or sister; (2) indicates a second-degree relative, either aunt or niece; LQTS = long QT syndrome; SCD = sudden cardiac death.
* Denotes a novel LQTS-causing mutation.
† This patient received an appropriate shock by an implantable cardioverter defibrillator due to ventricular fibrillation.
‡ This patient also had a second-degree relative (maternal aunt) with postpartum sudden cardiac death.
§ Cardiac events occurred 1 hour after delivery.

triggered cardiac events almost universally denote the presence of LQT1.[11–13] In contrast, the majority of cardiac events triggered by auditory stimuli such as the doorbell and alarm clock occur in patients with LQT2.[14] Rashba and colleagues [15] reported that the 40 weeks after the birth of a baby are associated with increased risk for cardiac events in women with LQTS, but the genetic underpinnings for such postpartum-triggered cardiac events were unknown. The objective of this study was to determine the genetic basis for LQTS in patients with a personal or family history of cardiac events occurring postpartum.

Methods

Study population

Between August 1997 and May 2003, 388 unrelated patients were referred to Mayo Clinic's Sudden Death Genomics Laboratory for LQTS genetic testing because of a clinical suspicion of LQTS. The study was approved by Mayo Foundation's Institutional Review Board. The presence of a personal and/or family history of cardiac events occurring postpartum was determined by review of the medical records and/or phone interviews and was blinded to the status of genetic testing. In an effort to focus on the time period where postpartum-associated physiological alterations are likely present and to minimize ascertainment/recall bias, the postpartum period was defined as the first 20 weeks after delivery.

The standard obstetrical/gynecologic definition of the postpartum period is 4 to 8 weeks, whereas the legal definition for maternal mortality data is the first year after delivery. Cardiac events included sudden cardiac death (SCD), aborted cardiac arrest, and syncope. Comprehensive mutational analysis of the 5 LQTS-causing channel genes: *KCNQ1/KVLQT1* (LQT1), *KCNH2/HERG* (LQT2), *SCN5A* (LQT3), *KCNE1/mink* (LQT5), and *KCNE2/MiRP1* (LQT6) was performed using exon-targeted amplification by polymerase chain reaction, denaturing high performance liquid chromatography, and automated DNA sequencing.[16]

Statistical analysis

All continuous variables were reported as the mean ± SD. A 2-tailed Fisher exact test was used to compare the prevalence of the cardiac events during postpartum in each gene mutation. A P value $< .05$ was considered to be statistically significant.

Results

Among this cohort of 388 unrelated patients (260 females, average age at diagnosis, 23 years, and average QTc, 482 ms), referred for mutational analysis of the LQTS-causing channel genes because of a clinical diagnosis of suspected LQTS, 14 patients (3.6%) had a personal and/or family history of at least one cardiac event during the defined postpartum period (Table 1). Four of these 14 index cases experienced postpartum cardiac events including: appropriate implantable cardioverter defibrillator therapy to terminate ventricular fibrillation during sleep at 4 and 20 weeks postpartum (case 12, Table 1), aborted cardiac arrest result-

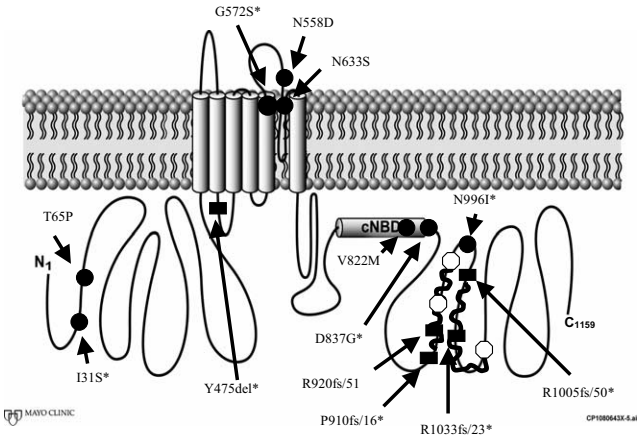

Figure 1 LQT2-causing *KCNH2* mutations and postpartum-triggered cardiac events. Displayed is the linear channel topology of the *KCNH2*-encoded HERG (I_{Kr}) potassium channel and the location of the pathogenic LQT2-causing mutations. Novel mutations are indicated by ***.** Missense mutations are indicated with a **solid circle,** the deletion mutation is indicated by a **solid rectangle,** and the 4 frameshift mutations culminating in premature truncation are indicated by a **solid rectangle followed by a curved line and an octagonal "stop" sign.** Note that the R1005fs/50 and the R1033fs/23 mutations terminate at the same residue.

ing in profound neurological injury at 16 weeks postpartum (case 1, Table 1), and syncope at 8 weeks postpartum in 2 patients (cases 9 and 10). Eleven of 14 probands had a positive family history of a postpartum-triggered cardiac event: SCD in 7 including 5 first-degree relatives (either mother or sister), aborted cardiac arrest in 2, and syncope in 2. The average time from delivery to a cardiac event was 10.5 ± 5.2 weeks (range 1 hour to 20 weeks, median 8 weeks, and mode 8 weeks).

Thirteen of the 14 postpartum-positive probands (93%) harbored mutations in *KCNH2* (LQT2) including 8 novel mutations and 5 previously published mutations. One individual (7%) had a novel pore mutation in *KCNQ1* (LQT1). Four of the 13 *KCNH2* mutations localized to either the channel pore or transmembrane spanning domains while 9 resided in the cytoplasmic N- or C-terminal regions (non-pore regions, Table 1, Figure 1). The severity of cardiac events (aborted cardiac arrest or SCD vs. syncope) was not significantly different between non-pore and pore mutations in the *KCNH2*-encoded HERG potassium channel (data not shown). None of the mutations identified were observed in over 1,400 reference alleles.[17]

Overall, 13 of the 80 index cases (16%) genotyped for LQT2 had a positive history of a cardiac event postpartum compared with 1 of 103 index cases with LQT1 and none of the remaining genotype positive individuals. Thus, the gene specificity of cardiac events during postpartum period in probands or family members was significantly greater in patients with LQT2 genotype than LQT1 genotype (16% vs. <1%, $P = .0001$) in this study cohort (Figure 2). Within this cohort of 388 unrelated patients, there was no personal or family history of a postpartum-triggered event among the 16 index cases with LQT3 or the single case of LQT5. There were no cases of LQT6.

Discussion

Although bringing in a new life is typically associated with great anticipation and excitement, new mothers with LQTS also enter into a period of increased vulnerability for a life-threatening arrhythmia during this postpartum period.[15] Among this cohort of 388 unrelated patients referred for LQTS genetic testing, nearly 4% had a positive personal and/or family history of a postpartum cardiac event. Of the 260 females referred for LQTS genetic testing, 4 (1.5%) have had and survived a postpartum cardiac event. Over 90% of this postpartum-positive subset was found to harbor mutations in *KCNH2* responsible for LQT2. Because of the small numbers of LQT3 (n = 16), LQT5 (n = 1), and LQT6 (n = 0) genotypes represented in this substantial unrelated patient cohort, one cannot conclude from this study that perhaps women with such a genotype are somehow protected against cardiac events during the postpartum period.

KCNH2 (*HERG*; chromosome 7q35-36) encodes the alpha subunit underlying delayed rectifier potassium channels (I_{Kr}) in the heart that mediate phase 3 repolarization.[18,19] Mutations of the HERG channel result in decreased I_{Kr} which is the electrophysiologic phenotype in LQT2 patients.[20] Previously, Moss and colleagues [21] reported that patients with mutations in the channel pore of HERG had a more severe phenotype than those harboring non-pore mutations. In our study, the majority of postpartum-positive LQT2 patients had non-pore mutations despite their severe phenotype underscoring the profound heterogeneity in the clinical expression of LQTS.

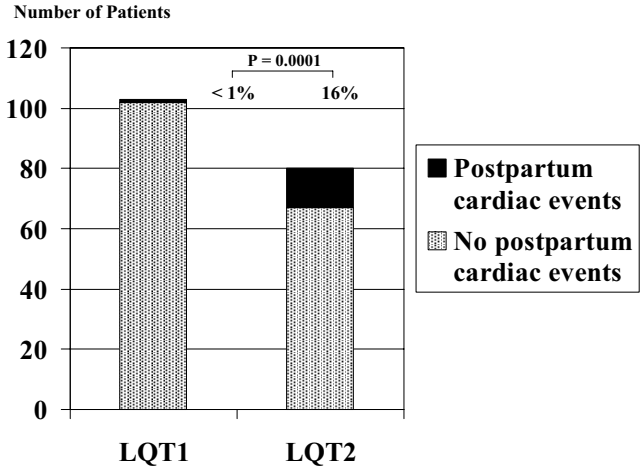

Figure 2 Gene-specificity of postpartum-triggered cardiac events. Thirteen of 80 unrelated patients (16%) with LQT2 had personal and/or a family history of cardiac events during the postpartum period, which was significantly greater than 1 of 103 patients (<1%) with LQT1 ($P = .0001$).

Precisely why the postpartum period is preferentially arrhythmogenic to those with an underlying LQT2 substrate is unknown. Previously, Rashba and colleagues [15] reported on pregnant women with LQTS and found that the 40 weeks after delivery of a baby posed a far greater risk for cardiac events than either the 40 weeks of pregnancy or the 40 weeks before conception. However, the pathogenetic mechanism underlying this association was unknown.

The psychological stress, changes in sex hormone levels, lactation, alteration of sleep pattern, alteration of life style related to taking care of baby, and abrupt, intense new auditory stimuli (i.e., a crying baby) that are present postpartum may provide arrhythmogenic trigger(s) to women with LQT2. Generally, females have faster resting heart rates and longer QTc than males [22] and a higher risk for syncope and sudden death in LQTS.[23] Estrogen and progesterone may be arrhythmogenic [24] and may play a critical role in cardiac repolarization.[25] Changes involving the sex hormones of estrogen, progesterone, and prolactin during pregnancy and postpartum period could potentially increase the risk of cardiac events. However, levels of estrogen and progesterone are extremely low postpartum and would not likely mediate this LQT2 predilection for postpartum cardiac events. With respect to prolactin, Altemus and colleagues[26] demonstrated that lactating women had increased vagal contribution to heart rate regulation, and postpartum women who were not lactating had evidence of elevated sympathetic and decreased parasympathetic nervous system activity.

Lanfranchi and colleagues[27] demonstrated a divergent sex-related effect on the RR interval during rapid eye movement (REM) sleep with women having an accentuated QTc during REM compared with men. Sleep disturbance was greatest during the first postpartum month, particularly for first-time mothers, and there was improvement in sleep characteristics by the third month postpartum.[28] These 2 findings, perhaps, explain why most cardiac events occurred around 8 weeks postpartum in our study. Finally, auditory stimuli such as an alarm clock triggers cardiac events preferentially in patients with LQT2.[14,29,30] Akin to an alarm clock, we speculate that perhaps a babies cry startling a LQT2 women during REM sleep may be arrhythmogenic. This speculation is buttressed by observations by Shimizu and Antzelevitch[31] whereby beta-adrenergic stimulation transiently increased action potential duration, transmural dispersion, and the incidence of torsades de pointes in a pharmacologic in vitro model of LQT2.

Study limitations

First, although we extensively reviewed all sources of data including phone interviews and medical records, it is possible that the ~4% prevalence of cardiac events occurring postpartum is an underestimate. Importantly, the genetic testing was performed independent of a subject's postpartum phenotype, minimizing the potential for bias. Second, because of the unavailability of appropriately archived tissue, a molecular autopsy [32] was not performed on each decedent who experienced SCD postpartum to confirm the presence of the same pathogenic LQTS-causing mutation established in the living proband in our cohort. However, the LQTS-causing mutation has been confirmed in 6 of 10 positive family history only cases (cases 2, 5, 6, 8, 13, and 14) by molecular autopsy or determination of its obligate presence through the subsequent voluntary participation of relatives to the index case. Although it seems quite reasonable to assume that the decedent shared the same mutation in the remaining cases, we cannot exclude the possibility of a non-LQTS sudden death such as pulmonary thromboembolism or the possibility that other LQTS-causing mutations or channel polymorphisms may have been additionally present in the decedent.

Conclusions

Approximately 4% of this LQTS cohort had a positive history of a cardiac event during the postpartum period, most commonly during the first 2 months after delivery. Mutations in *KCNH2* (LQT2) were present in the majority of families experiencing postpartum sudden death, aborted cardiac arrest, or syncope. Along with swimming and LQT1 and auditory triggers and LQT2, this association between postpartum cardiac events and LQT2 can facilitate strategic genotyping. The precise triggers that render a woman with LQT2 susceptible to a life-threatening arrhythmia after giving birth warrant further investigation.

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References

1. Ackerman MJ, Clapham DE. Ion channels—basic science and clinical disease. N Engl J Med 1997;336:1575–1586.
2. Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. Mayo Clin Proc 1998;73:250–269.
3. Keating MT, Sanguinetti MC. Molecular and cellular mechanisms of cardiac arrhythmias. Cell 2001;104:569–580.
4. Curran M, Atkinson D, Timothy K, Vincent GM, Moss AJ, Leppert M, Keating M. Locus heterogeneity of autosomal dominant long QT syndrome. J Clin Invest 1993;92:799–803.
5. Schott JJ, Charpentier F, Peltier S, Foley P, Drouin E, Bouhour JB, Donnelly P, Vergnaud G, Bachner L, Moisan JP. Mapping of a gene for long QT syndrome to chromosome 4q25-27. Am J Hum Genet 1995;57:1114–1122.

6. Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, Keating MT. Coassembly of K(V)LQT1 and minK (IsK) proteins to form cardiac I(Ks) potassium channel. Nature 1996;384:80–83.
7. Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, Van Raay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Towbin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 1996;12:17–23.
8. Bennett PB, Yazawa K, Makita N, George AL Jr. Molecular mechanism for an inherited cardiac arrhythmia. Nature 1995;376:683–685.
9. Mohler PJ, Schott JJ, Gramolini AO, Dilly KW, Guatimosim S, du Bell WH, Song L-S, Haurogne K, Kyndt F, Ali ME, Rogers TB, Lederer WJ, Escande D, Le Marec H, Bennett V. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature 2003;421:634–639.
10. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
11. Garson A Jr, Dick M 2nd, Fournier A, Gillette PC, Hamilton R, Kugler JD, Van Hare GF III, Vetter V, Vick GW III. The long QT syndrome in children: an international study of 287 patients. Circulation 1993; 87:1866–1872.
12. Moss AJ, Robinson JL, Gessman L, Gillespie R, Zareba W, Schwartz PJ, Vincent GM, Benhorin J, Heilbron EL, Towbin JA, Priori SG, Napolitano C, Zhang L, Medina A, Andrews ML, Timothy K. Comparison of clinical and genetic variables of cardiac events associated with loud noise versus swimming among subjects with the long QT syndrome. Am J Cardiol 1999;84:876–879.
13. Ackerman MJ, Tester DJ, Porter CJ. Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc 1999;74:1088–1094.
14. Wilde AA, Jongbloed RJ, Doevendans PA, Duren DR, Hauer RN, van Langen IM, van Tintelen JP, Smeets HJ, Meyer H, Geelen JL. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). J Am Coll Cardiol 1999;33:327–332.
15. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, Schwartz PJ, Andrews M. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome: LQTS Investigators. Circulation 1998;97:451–456.
16. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. Mayo Clin Proc 2002;77:413–421.
17. Ackerman MJ, Tester DJ, Jones G, Will MK, Burrow CR, Curran M. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc 2003;78:1479–487.
18. Trudeau MC, Warmke JW, Ganetzky B, Robertson GA. HERG, a human inward rectifier in the voltage-gated potassium channel family. Science 1995;269:92–95.
19. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. Cell 1995;81:299–307.
20. January CT, Gong Q, Zhou Z. Long QT syndrome: cellular basis and arrhythmia mechanism in LQT2. J Cardiovasc Electrophysiol 2000; 11:1413–1418.
21. Moss AJ, Zareba W, Kaufman ES, Gartman E, Peterson DR, Benhorin J, Towbin JA, Keating MT, Priori SG, Schwartz PJ, Vincent GM, Robinson JL, Andrews ML, Feng C, Hall WJ, Medina A, Zhang L, Wang Z. Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. Circulation 2002;105:794–799.
22. Rautaharju PM, Zhou SH, Wong S, Calhoun HP, Berenson GS, Prineas R, Davignon A. Sex differences in the evolution of the electrocardiographic QT interval with age. Can J Cardiol 1992;8:690–695.
23. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A Jr. The long QT syndrome: prospective longitudinal study of 328 families. Circulation 1991;84:1136–1144.
24. Romhilt DW, Chaffin C, Choi SC, Irby EC. Arrhythmias on ambulatory electrocardiographic monitoring in women without apparent heart disease. Am J Cardiol 1984;54:582–586.
25. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. Circulation 1996;94:1471–1474.
26. Altemus M, Redwine LS, Leong YM, Frye CA, Porges SW, Carter CS. Responses to laboratory psychosocial stress in postpartum women. Psychosom Med 2001;63:814–821.
27. Lanfranchi PA, Shamsuzzaman AS, Ackerman MJ, Kara T, Jurak P, Wolk R, Somers VK. Sex-selective QT prolongation during rapid eye movement sleep. Circulation 2002;106:1488–1492.
28. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. Obstet Gynecol 2000;95:14–18.
29. Wellens HJ, Vermeulen A, Durrer D. Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. Circulation 1972;46:661–665.
30. Nakajima T, Misu K, Iwasawa K, Tamiya E, Segawa K, Matsuo H, Hada K. Auditory stimuli as a major cause of syncope in a patient with idiopathic long QT syndrome. Jpn Circ J 1995;59:241–246.
31. Shimizu W, Antzelevitch C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2, and LQT3 models of the long QT syndrome. J Am Coll Cardiol 2000;35:778–786.
32. Ackerman MJ, Tester DJ, Porter CJ, Edwards WD. Molecular diagnosis of the inherited long-QT syndrome in a woman who died after near-drowning. N Engl J Med 1999;341:1121–1125.