Spectrum and Frequency of Cardiac Channel Defects in Swimming-Triggered Arrhythmia Syndromes

Grace Choi, MD; Laura J. Kopplin, BS; David J. Tester, BS; Melissa L. Will, BS; Carla M. Haglund; Michael J. Ackerman, MD, PhD

Background—Swimming is a relatively genotype-specific arrhythmogenic trigger for type 1 long-QT syndrome (LQT1). We hypothesize that mimickers of concealed LQT1, namely catecholaminergic polymorphic ventricular tachycardia (CPVT), may also underlie swimming-triggered cardiac events.

Methods and Results—Between August 1997 and May 2003, 388 consecutive, unrelated patients were referred specifically for LQTS genetic testing. The presence of a personal and/or family history of a near-drowning or drowning was determined by review of the medical records and/or phone interviews and was blinded to genetic test results. Comprehensive mutational analysis of the 5 LQTS-causing channel genes, *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), *KCNE1* (LQT5), and *KCNE2* (LQT6), along with *KCNJ2* (Andersen-Tawil syndrome) and targeted analysis of 18 CPVT1-associated exons in *RyR2*, was performed with the use of denaturing high-performance liquid chromatography and direct DNA sequencing. Approximately 11% (43 of 388) of the index cases had a positive swimming phenotype. Thirty-three of these 43 index cases had a "Schwartz" score ($\geq$4) suggesting high clinical probability of LQTS. Among this subset, 28 patients (85%) were LQT1, 2 patients (6%) were LQT2, and 3 were genotype negative. Among the 10 cases with low clinical probability for LQTS, 9 had novel, putative CPVT1-causing *RyR2* mutations.

Conclusions—In contrast to previous studies that suggested universal LQT1 specificity, genetic heterogeneity underlies channelopathies that are suspected chiefly because of a near-drowning or drowning. CPVT1 and strategic genotyping of *RyR2* should be considered when LQT1 is excluded in the pathogenesis of a swimming-triggered arrhythmia syndrome. **(*Circulation*. 2004;110:2119-2124.)**

Key Words: catecholamines ■ tachycardia ■ genes ■ ion channels ■ long-QT syndrome

The congenital long-QT syndrome (LQTS) is predominantly a cardiac channelopathy with approximately 65% to 75% of LQTS owing its pathogenic basis to mutations involving 5 essential cardiac channel subunits.[1,2] 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).[3–8] There are relatively gene-specific triggers for cardiac events in LQTS. Patients with LQT1 usually have cardiac events during exercise, whereas patients with LQT2 and LQT3 are more likely to have events during auditory/emotional stress or rest/sleep.[9] Moreover, swimming appears to trigger events in nearly 15% of children and young adults with symptomatic LQTS, and, according to 2 small case series, swimming-triggered cardiac events appear to be pathognomonic for LQT1.[10–13]

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is another arrhythmogenic channelopathy with at least 50% of CPVT caused by mutations in the *RyR2*-encoded cardiac ryanodine receptor/calcium release channel (CPVT1).[14] Except for the absence of an abnormally prolonged QT interval, CPVT mimics the clinical phenotype of LQTS, particularly LQT1. CPVT may unexpectedly present with sudden cardiac death with physical exertion or emotional stress, and 30% of the patients with CPVT can be misdiagnosed as having LQTS.[14]

In the present study, we sought to determine the spectrum and prevalence of cardiac channel defects among unrelated subjects with a personal and/or family history of a swimming-triggered cardiac event who were referred specifically for LQTS genetic testing because of a presumptive clinical diagnosis of LQTS. On the basis of our previous observations, we hypothesized that LQT1 represents the predominate genotype among the "swimmers" with a high clinical probability for LQTS but that mimickers of concealed LQT1, namely CPVT1, is responsible

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From the Department of Pediatric and Adolescent Medicine/Division of Cardiovascular Disease (G.C., C.M.H., M.J.A.), the Department of Molecular Pharmacology and Experimental Therapeutics (L.J.K., D.J.T., M.L.W., C.M.H., M.J.A.), and the Department of Internal Medicine/Division of Cardiovascular Disease, Mayo Clinic College of Medicine (M.J.A.), Rochester, Minn.

Correspondence to Dr Michael J. Ackerman, Long QT Syndrome Clinic and the Sudden Death Genomics Laboratory, Guggenheim 501, 200 First St SW, Rochester, MN 55905. E-mail ackerman.michael@mayo.edu

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for a significant minority of subjects who have a positive swimming phenotype.

Methods

Study Cohort

Between August 1997 and May 2003, 388 consecutive, unrelated patients (260 female subjects) were referred to the Sudden Death Genomics Laboratory at Mayo Clinic, Rochester, Minnesota, for LQTS genetic testing (average age at diagnosis, 23±16 years; average QTc, 482±57 ms). The presence of a personal and/or family history of cardiac events during swimming was determined by review of the medical records and/or phone interviews and was blinded to the status of genetic testing. Near-drowning or drowning was characterized as a survival or death, respectively, from syncope or cardiac arrest that occurred immediately after diving or during recreational or competitive swimming. Previously, we reported a small case series involving 6 unrelated patients with a positive swimming phenotype.[13]

Cardiac Channel Gene Screen

After we received written informed consent from the patients or their parents, blood samples were obtained from the index cases for this institutional review board–approved study. Genomic DNA extraction from peripheral blood lymphocytes was performed with the use of the Purgene DNA extraction kit (Gentra, Inc). Comprehensive mutational analysis of the 5 LQTS-causing channel genes, *KCNQ1/KVLQT1* (LQT1), *KNCNH2/HERG* (LQT2), *SCN5A* (LQT3), *KCNE1/mink* (LQT5), and *KCNE2/MiRP1* (LQT6), was performed by means of exon-targeted amplification by polymerase chain reaction, denaturing high-performance liquid chromatography, and automated DNA sequencing.[15] In addition, *KCNJ2*, responsible for Andersen-Tawil syndrome (ATS1, previously annotated as LQT7), was analyzed.[16] The primers and polymerase chain reaction conditions for *KCNJ2* were designed by our laboratory and are available on request. A targeted analysis of *RyR2* restricted to 18 exons (8, 14, 15, 44 to 47, 49, 83, 88, 90, 93, 97, 100 to 103, and 105) known to host type 1 CPVT (CPVT1)–causing mutations was conducted.[14,17,18] For mutations involving LQTS-causing potassium channels, 1488 reference alleles derived from 4 ethnic groups were analyzed.[15] For the cardiac sodium channel, 1658 alleles were examined. For potential *KCNJ2*- or *RyR2*-disease–causing variants, 400 reference alleles obtained from 100 healthy white subjects and 100 healthy black subjects were analyzed.

Statistical Analysis

All continuous variables were reported as mean±SD. A 2-tailed Fisher exact test was used to compare the prevalence of swimming-triggered cardiac events for each genotype. A Kruskal-Wallis test was used to compare the heart rate–corrected QT interval (QTc) across the various genotypes. A probability value of <0.05 was considered to be statistically significant.

Results

Among this cohort of 388 consecutive, unrelated index cases (260 female subjects; average age at diagnosis, 23±16 years; average QTc, 482±57 ms) referred for LQTS genetic testing, 43 index cases (11%, 27 female) had a personal (n=27) and/or family history (n=20) of a near-drowning or drowning (Table). In total, 49 individuals (index cases and relatives, 27 female) had a swimming-triggered cardiac event, including 8 cases of fatal drowning (cases 7, 12, 23, 32 to 34, 37, and 42; Table). The average age at the time of drowning/near-drowning was 12±6 years (range, 4 to 39 years). Among those in whom the location of the event was recorded, the majority took place in a swimming pool (33 of 35, 91%) while actively swimming. Two events occurred while breath-holding in the water, and one occurred while diving. In >80% of this swimming cohort, the near-drowning or drowning was the sentinel event in the family.

For these 43 index cases with a positive swimming phenotype, the QTc was 485±68 ms (range, 402 to 700 ms). Overall, 39 of 43 swimming-positive index cases (91%) had a putative arrhythmia syndrome–causing variant (Table). Thirty-three of the 43 subjects had a clinical diagnostic score (ie, Schwartz score ≥4)[19] that suggested high clinical probability for the diagnosis of LQTS. Among this subset with high clinical probability LQTS, 28 of 33 (85%) harbored mutations in *KCNQ1* (LQT1, Figure 1), 2 of 33 had an LQT2-causing *KCNH2* variant, and 3 were genotype negative. None of the variants identified were observed in >1400 reference alleles.[15] No isolated mutations involving *SCN5A*, *KCNE1*, *KCNE2*, or *KCNJ2* were identified.

The near-drowning or drowning was the sentinel event for all 16 LQT1 probands with a swimming-triggered cardiac event. Five of these individuals (cases 10, 11, 15, 19, and 25; Table) had subsequent LQTS-related events: 1 with another near-drowning, 2 with exertional syncope, 1 with syncope during emotional stress, and 1 with drug-induced cardiac arrest. Thirteen of the 28 LQT1 index cases had a family history of a swimming-triggered cardiac event, of which 8 were the sentinel event. One of these relatives (case 18) had exertional syncope before her near-drowning. Notably, 4 index cases (cases 4, 12, 18, and 24) had exertional syncope before their relative's near-drowning or fatal drowning. In the 2 cases of LQT2, the near-drowning was the sentinel and only known LQTS-related event for case 29. Case 30 had presented with seizures starting at 4 years of age, had an unexplained episode of syncope at age 9, and had the near-drowning at age 11.

Overall, 28 of the 103 unrelated index cases genotyped for LQT1 had a positive history of a swimming-triggered cardiac event, compared with 2 of 80 index cases with LQT2. Thus, the gene specificity associated with near-drownings/drownings in the setting of congenital LQTS was 10-fold greater in patients with LQT1 genotype than LQT2 genotype (27% versus 2.5%, $P<0.0001$) in this study cohort.

Consistent with our hypothesis that CPVT1 and LQT1 may mimic one another, novel, putative CPVT1-causing variants in *RyR2* were detected in 9 of 43 swimming-positive index cases (21%) overall and in 9 of the 10 cases in which there was insufficient clinical evidence to warrant the diagnosis of LQTS (Table). Each *RyR2* variant involved highly conserved residues and localized to regions of previously reported CPVT1-causing mutations. None of these variants were observed in 400 reference alleles. Among the 9 *RyR2*-positive index cases (cases 31 to 39, Table), the near-drowning or drowning was the sentinel event in 8 cases. For case 39, a relative died suddenly and without explanation during sleep before the near-drowning that occurred in both the proband and a third-degree relative. To our knowledge, only 1 of the 9 index cases (case 37) has had a subsequent event, which was another near-drowning.

There was a significant difference in the mean QTc between the 4 groups: LQT1 (511±67 ms), LQT2 (490±14 ms), CPVT1 (413±13 ms), and genotype negative (462±23

Patient Data

Case No.	Relationship to Case*	Sex	Age of Episode	Location	Activity	Genotype	Mutation	Location
1	S†	F	19	Pool	Swimming	LQT1	AAPdel71–73‡	N-term
						LQT1	V524G‡	C-term
2	FM1†	F	8	Pool	Swimming	LQT1	M159sp	S2
3	FM1	M	20	Ocean	Swimming	LQT1	V162fs/72‡	S2
4	FM3†	F	19	Pool	Swimming	LQT1	L191fs/90	S2/S3
						LQT1	V524G‡	C-term
5	S	M	N/A	N/A	N/A	LQT1	L191fs/90	S2/S3
6	FM3	F	N/A	Pool	Swimming	LQT1	L191fs/90	S2-S3
7	S	M	12	N/A	Swimming	LQT1	S225L	S4
8	S	F	15	Pool	Swimming	LQT1	I235N‡	S4
9	FM1	M	6	Pool	Swimming	LQT1	R243C	S4/S5
10	S	F	12	Pool	Swimming	LQT1	V254M	S4/S5
11	S	F	11	Pool	Swimming	LQT1	V254M	S4-S5
12	FM1	M	13	Pool	Swimming	LQT1	R259L‡	S4/S5
13	FM3†	N/A	12	Pool	Swimming	LQT1	G269S	S5
						LQT3	A572D	IS6-IIS1
14	S	M	4	Pool	Swimming	LQT1	G269D	S5
						LQT1	R293C‡	S5-PORE
15	S	F	4	Pool	Swimming	LQT1	Y278H‡	S5
						LQT1	A302V‡	PORE
16	S	M	9	Pool	Swimming	LQT1	T312I	PORE
17	S	F	8	Pool	Swimming	LQT1	G314D‡	PORE
18	FM3	F	7	Pool	N/A	LQT1	Y315C	PORE
19	S/FM2	F/F	5/15	Pool	Swimming	LQT1	T322A‡	PORE/S6
20	S†	M	10	Pool	Swimming	LQT1	F339del‡	S6
21	S	M	8	Pool	Swimming	LQT1	P343S‡	S6
22	FM1	F	N/A	N/A	N/A	LQT1	A344V	S6
23	FM3†	M	N/A	N/A	N/A	LQT1	SP/A344/G-A	S6
24	FM1	M	7	Pool	Swimming	LQT1	SP/A344/G-A	S6
25	S	F	13	Pool	Swimming	LQT1	R366W	C-term
26	FM1	F	N/A	Pool	Swimming	LQT1	R539W	C-term
27	S	M	8	Pool	Swimming	LQT1	S546L‡	C-term
28	S	F	10	Lake	Breath-holding	LQT1	I567S‡	C-term
29	S	F	11	N/A	Swimming	LQT2	V131fs/185‡	N-term
30	S	F	11	N/A	Swimming	LQT2	T613M	PORE
31	S	M	17		Swimming	CPVT1	P164S‡	N-term
32	S	M	11	Pool	Swimming	CPVT1	R414L‡	N-term
33	FM1/FM1/FM1	F/M/M	13/17/10	Pool	N/A	CPVT1	I419F‡	N-term
34	S/FM3	F/M	14/7	Pool	Swimming	CPVT1	A2403T‡	FKBP 12.6
35	FM1	F	39	Pool	N/A	CPVT1	F4499C‡	TM6-TM7
36	S	M	15	Lake	Swimming	CPVT1	A4510T‡	TM7
37	S	M	11	Pool	Swimming	CPVT1	G4671R‡	TM9-TM10
38	S/FM1	F/F	14/16	Pool	Breath-holding	CPVT1	I4848V‡	TM12
39	S/FM3	F/M	13,N/A	Pool	N/A	CPVT1	I4848V‡	TM12
40	S	F	12	Pool	Swimming	Negative	...	...
41	FM2	M	N/A	Pool	Coming out	Negative	...	...
42	S	F	8	Pool	Diving	Negative	...	...
43	FM1	F	15	Pool	Swimming	Negative	...	...

*S indicates Self; FMx, family member, where x=degree of relatedness. For example, if the family member were the index case's daughter, the second column would read FM1. FM2 would indicate a maternal uncle for example and FM3 would denote a cousin. N/A, not available.

†Denotes the 6 cases previously reported.[12]

‡Denotes a mutation that is novel to this patient cohort and not previously reported.

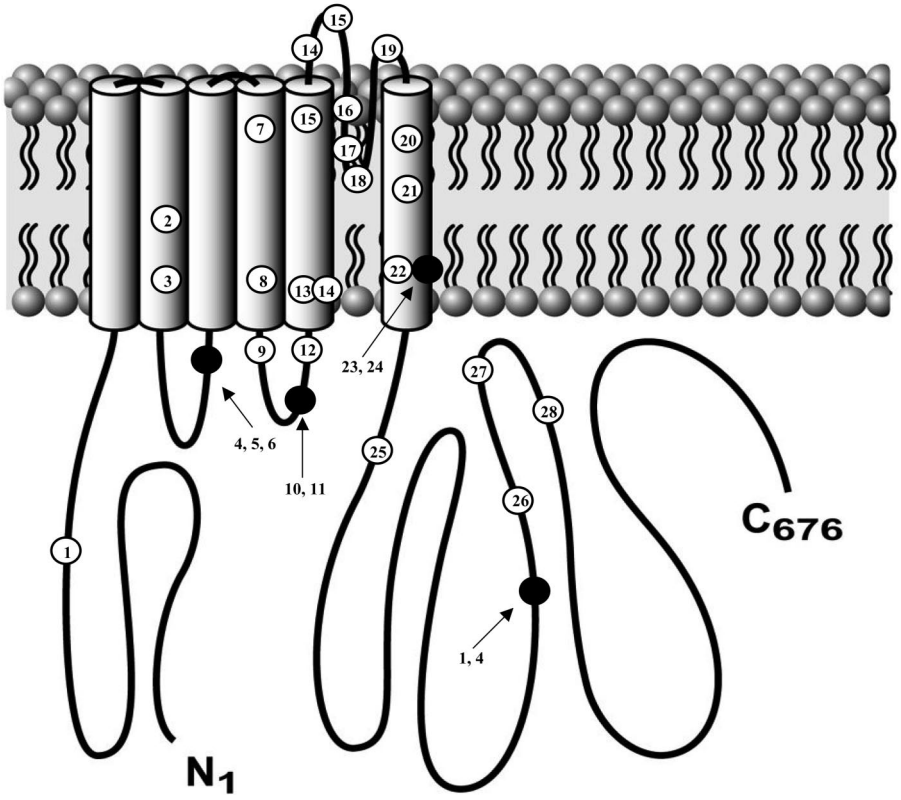

Figure 1. Channel topology of *KCNQ1* with LQT1-associated variants. Depicted is the linear channel topology of the I_{Ks} α-subunit encoded by *KCNQ1* with the approximate location of the pathogenic LQT1-causing mutations indicated. Number within the circle corresponds to the case number in the Table. Solid circles with >1 case number to the side denotes either a case with >1 mutation or the same mutation found in >1 case.

ms, Figure 2, Kruskal-Wallis test, $P<0.001$). Furthermore, the QTc among the 9 CPVT1-positive individuals was less than the 3 other genotypes, either separately or combined ($P\leq0.001$). The swimming-triggered cardiac events tended to occur at a slightly older age (15.2±7.7 years; range, 7 to 39) in individuals hosting a CPVT1-associated *RyR2* variant compared with individuals with LQT1 (10.6±4.6 years; range, 4 to 20; $P<0.04$).

Discussion

Specific triggers for cardiac events have been associated with particular genotypes. Auditory-related events (for example, an alarm or a sudden, unexpected loud noise) and cardiac events occurring in the postpartum period are more apt to occur in an individual with LQT2.[9,12,20] Swimming has been cited as a common arrhythmogenic trigger in LQTS.[10,11]

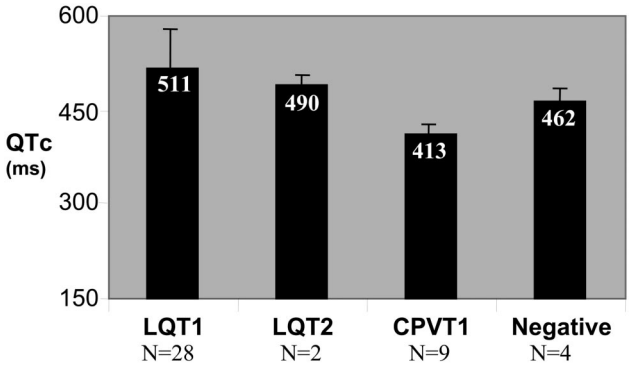

Figure 2. Effect of genotype on QTc. Mean±1 SD QTc of LQT1, LQT2, CPVT1, and genotype-negative subsets are shown.

Previously, our laboratory and Moss and colleagues[12,13,21–23] reported that swimming was an LQT1-specific arrhythmogenic trigger. In our initial retrospective study, we identified 6 unrelated cases with a history of a swimming-triggered cardiac event and elucidated an LQT1-causing mutation in each case.[13] Similarly, Moss and colleagues[12] demonstrated that 3 unrelated families with a positive swimming phenotype each had LQT1.

In the present study, among cases with a high clinical probability of LQTS, the vast majority of cases were indeed LQT1, and a history of a swimming-triggered cardiac event was 10 times more likely to have been elicited among individuals with LQT1 compared with LQT2. A cogent explanation can be proffered for why swimming is a relatively LQT1-specific arrhythmogenic trigger in LQTS. First, swimming combines exertion, voluntary apnea, possible cold-water exposure, and face immersion, resulting in increased sympathetic and parasympathetic activity through activation of the "dive reflex."[24,25] This concomitant activation of both the sympathetic and parasympathetic autonomic system may explain why swimming seems to precipitate premature ventricular contractions.[26] Second, cold-water face immersion has been demonstrated to lengthen QT intervals in normal subjects and occasionally induce T-wave alternans.[27] Third, during epinephrine QT stress testing, individuals with LQT1 demonstrate a paradoxical prolongation in the QT interval caused by mutated *KCNQ1*-encoded I_{Ks} potassium channels.[28,29] Thus, near-drownings or drownings in individuals with LQT1 may represent a convergence of a vulnerable I_{Ks}-deficient host (the substrate), who will have an accentuated QT response and perhaps increased dispersion of refrac-

toriness caused by simultaneous face immersion and sympathetic stimulation while engaging in an activity (swimming) in which premature ventricular contractions caused by early afterdepolarizations (the trigger) are more likely to occur than during dry land activities.

For the entire cohort of index cases referred for LQTS genetic testing chiefly because of a personal or family history of a near-drowning or drowning, more than one third represent pathogenic mechanisms other than LQT1. Interestingly, >20% of the index cases and nearly all of the low-probability LQTS cases harbored putative CPVT1-causing mutations involving the calcium release channel encoded by *RyR2*. To our knowledge, this study represents the first report of swimming-triggered cardiac events in association with CPVT. One case of sudden death while bathing has been reported, but no further details were provided.[30] To what extent swimming represents an arrhythmogenic trigger in CPVT warrants further investigation, as our cohort is likely to contain an ascertainment bias because of our prior work related to swimming and drownings. On the basis of our previous reports associating LQT1 with cardiac events during swimming and the observation that there is incomplete penetrance associated with LQTS in general and LQT1 in particular,[28,31] we surmise that these patients, despite a nondiagnostic QTc, were referred for LQTS genetic testing on the premise that their swimming event may have been triggered by a "concealed" LQT1 substrate.

On the other hand, it is tempting to speculate on an underlying pathophysiological mechanism whereby swimming could be distinctly arrhythmogenic to a CPVT1 host as well. Generally, it is assumed that the arrhythmias in CPVT are precipitated by delayed afterdepolarizations (DADs) and triggered activity rather than early afterdepolarizations (EADs), as in LQTS.[32–35] The increased leak of calcium from sarcoplasmic reticulum (SR) into cytoplasm through mutated RyR2 channels would activate the electrogenic Na/Ca exchanger, depolarizing the membrane, and give rise to DADs. β-Adrenergic stimulation would be expected to further increase the calcium concentration of SR and increase the propensity for DADs. This physiological mechanism is consistent with the clinical observation that exertion is the most common trigger in CPVT.[14] However, the relatively slower heart rate that is seen during swimming compared with other exertional activities caused by concomitant vagal activation would presumably attenuate calcium loading of the SR, thereby decreasing DADs. Perhaps mutated RyR2 channels exhibit a different response to cytoplasmic calcium.

Specifically, it is conceivable that the dependence of calcium-induced calcium release on cytoplasmic calcium is steeper and that the increased amount of calcium entering the cytoplasm through L-type calcium channels during the comparatively longer cycle lengths seen with swimming opens mutated RyR2 channels to a higher degree, offsetting the lower degree of SR loading, thereby providing a setting in which the vulnerable CPVT1 host has a genetically derived susceptibility for DADs while engaging in an activity (swimming) that has an intrinsic propensity for EADs.

Regardless of the underlying arrhythmogenic mechanism, *RyR2* (CPVT1) joins *KCNQ1* (LQT1) as the two most common genetic causes underlying swimming-triggered cardiac events among families with a suspected channelopathy. It remains to be determined whether mutations in *RyR2* and a CPVT1-mediated dysrhythmia may provide cause and manner of death for sentinel event, autopsy-negative, unexplained drownings among families without a family history suspicious for a heritable arrhythmia syndrome.

Limitations

There remain 4 cases with a positive swimming phenotype that have eluded identification of a pathogenic substrate after comprehensive mutational analysis of the 5 channel genes implicated in LQTS and a targeted analysis of *RyR2*. The *KCNJ2*-encoded inwardly rectifying potassium channel underlying ATS1 (formerly annotated as LQT7) has been analyzed, and no mutations have been identified in these 4 subjects. Three of the 4 subjects had a Schwartz score $\geq$4, suggesting high clinical probability for LQTS. Thus, along with 25% to 35% of LQTS families, their novel LQTS-pathogenic mechanism awaits discovery.

Given the striking observation that 9 of the 10 cases with low clinical probability for the diagnosis of LQTS hosted novel CPVT1 variants, it is possible that this single genotype-negative/LQTS phenotype–negative swimmer has a CPVT1-associated mutation residing elsewhere in *RyR2*. In this study, we targeted only the 18 protein-encoding exons of *RyR2* that were implicated previously in CPVT1. However, *RyR2* contains 85 additional protein-encoding exons (more than the entire LQTS cardiac channel gene screen) that could be analyzed. Alternatively, this individual may host a mutation in the *CASQ2*-encoded calsequestrin 2, which has been associated with the very rare form of autosomal recessive CPVT previously reported in 7 Bedouin families.[36]

Conclusions

As further studies identify additional pathogenic genes for cardiac arrhythmias, a genetic basis for an unexplained drowning may be established. In previous studies, genetic testing for those who had a near-drowning or drowning in the setting of familial LQTS revealed that a swimming-triggered event was pathognomonic for LQT1. This study demonstrates that there is indeed genetic heterogeneity when a channelopathy is suspected chiefly because of a near-drowning or drowning. LQT1 was identified in the majority of swimming-related cases, accounting for two thirds of the entire cohort and nearly all of the cases in which the clinical probability of LQTS was high. Notably, potential CPVT1-causing mutations in *RyR2* were identified in 90% of those cases lacking sufficient clinical evidence for LQTS. Thus, CPVT1 should be considered and genetic testing for *RyR2* performed in the setting of a swimming-triggered event and a clinical suspicion of an arrhythmia syndrome, particularly when the diagnostic criteria for LQTS has not been reached. *RyR2* now joins *KCNQ1* as candidate genes for a molecular autopsy of sentinel-event unexplained drownings.

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