Community detection of long QT syndrome with a clinical registry: An alternative to ECG screening programs?

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BACKGROUND Long QT syndrome (LQTS) prevalence is estimated at 4 of 10,000 based on community electrocardiogram (ECG) screening, about which there is disagreement regarding efficacy, accuracy, cost-effectiveness, and practicality. Family studies of autosomal dominant conditions such as LQTS have revealed 8–9 gene-positive family members per proband.

OBJECTIVE To evaluate a cardiac/genetic registry and family screening program as a tool to identify LQTS in the community.

METHODS Possible LQTS probands were referred to the New Zealand Cardiac Inherited Disease service. The registry was first established in the northern region (population 2.03 million), including central Auckland (population 0.46 million). After clinical evaluation, genetic testing and family cascade screening were initiated. Genotype-positive individuals were classified as definite LQTS, and others were classified as definite or probable LQTS by clinical and ECG criteria.

RESULTS One hundred twelve probands were identified (presentation: 7 sudden death, 82 cardiac event, 16 ECG abnormality, and 7 sudden death of a family member). Following cascade screening, 309 patients with LQTS were identified (248 definite and 61 probable). Two hundred twenty patients had LQTS-causing mutations identified (120 [55%] LQT1, 78 [35%] LQT2, 19 [9%] LQT3, 1 [0.5%] LQT 5, and 2 [1%] LQT7). Thus far, an average of 2.1 definitely or probably affected family members have been identified per proband. The community detection rate is 1.5 of 10,000 for the whole region and 2.2 of 10,000 in Auckland.

CONCLUSIONS A high level of community detection of LQTS is possible using a clinical registry. With adequate resourcing, this has the potential to be an effective alternative to community ECG screening.

KEYWORDS Long QT syndrome; ECG screening; Sudden cardiac death; Genetic testing

ABBREVIATIONS CIDG = Cardiac Inherited Diseases Group; **ECG** = electrocardiogram; **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

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Introduction

Sudden unexpected death has a devastating effect on families and communities, particularly when it occurs in the young. Yet if presymptomatic individuals with an inherited risk can be identified in the community, lifesaving interventions can be provided.[1] One cause of sudden death in the young with a prevalence estimated at 4 of 10,000 is long QT syndrome (LQTS), characterized by prolonged ventricular repolarization and susceptibility to life-threatening arrhythmias.[2]

For LQTS and other causes of sudden cardiac death (SCD) in the young, much discussion surrounds the value of electrocardiogram (ECG) screening of the general pediatric population or specific populations considered to be at a higher risk.[3–7] The ECG, however, is neither sensitive nor specific, both of which are essential requirements of any clinical screening program.[8] Consequently, children are referred for further assessment that may be unwarranted, increasing the financial costs and anxiety associated with uncertain diagnoses.[9]

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An alternative approach is to identify probands and then exhaustively screen family members. With an autosomal dominant disease such as LQTS, half the targeted population would be affected individuals and so the overdiagnosis from poor test specificity is reduced, particularly when supported by genetic testing.

A consent-based clinical registry for patients with LQTS has been in operation in the northern region of New Zealand since 2003 (with ethics committee approval). Since the establishment of the registry, there have been efforts to raise awareness of LQTS among clinicians and the public. The LQTS registry is part of a wider inherited heart disease registry run by the Cardiac Inherited Diseases Group (CIDG), a network of clinicians and scientists. This report addresses the question as to whether this LQTS registry (and thus others like it) can identify LQTS in the community at a high enough frequency that it might be a viable alternative to community ECG-based screening programs.

Methods

New Zealand has a population of 4.43 million and a relatively large geographical area with a density of 16 people per square kilometer.[10] The northern region (defined in this report as the 5 northernmost district health board areas Northland, Auckland, Waitemata, Counties Manukau, and Waikato), in which the CIDG and the LQTS registry are based, comprises nearly half of New Zealand's population (2.03 million) and includes the cities of Auckland and Hamilton.

Since 2003, living probands suspected of having LQTS have been referred to the CIDG by pediatric or cardiology services and victims of unexplained sudden death have been referred by pathologists or the coroner (following collection of a DNA sample at autopsy).[11,12] Each referred case is discussed at a multidisciplinary CIDG meeting and a decision made regarding the need for further clinical and/or genetic testing. When probands are identified, cascade clinical and genetic screening is carried out in family members to identify at-risk presymptomatic individuals. Screening and delivery of results takes place mostly in dedicated multidisciplinary cardiac genetics clinics and includes counseling, obtaining a detailed family medical history, and a 12-lead ECG. All ECGs are measured manually by cardiologists specialized in electrophysiology and familiar with LQTS, and the Bazett formula for LQTS diagnosis is used to correct for heart rate (giving the corrected QT interval [QTc]). Every ECG in this report was checked and reported by the senior author prior to knowledge of the patient's genetic status. The QT interval is measured in leads II and V_5 by using the "teach the tangent" technique, and the longer of the two is taken as representative.[13] If indicated, further investigations such as exercise testing, Holter recordings, echocardiograms, and pharmacological testing are performed.

Genetic screening for LQTS was initially part of a university-based research program but was transferred to a diagnostic clinical service at Auckland City Hospital in 2005. Initially, patients were screened for point mutations in the coding regions of the *KCNQ1*, *KCNH2*, and *SCN5A* genes, but since 2006 a further 3 LQTS-associated genes—*KCNE1*, *KCNE2*, and *KCNJ2*—are routinely screened in all patients. All coding exons of the above genes are amplified by using exon-specific primers and the amplicons are subjected to bidirectional capillary-based dideoxy sequencing.

The focus of mutation screening was largely sequence-based until 2007 when it was decided to screen for rarer deletion and duplication mutations by using the technique termed multiplex ligation-dependent probe amplification. This approach has now been superseded by the simultaneous screening of deletion/duplication mutations in 84 genes implicated in heritable cardiac disorders by using the Comparative Genomic Hybridization array. Patients with clinically definite LQTS who appear to carry no mutations detected by sequencing are subsequently screened for deletion and duplication mutations.

Mutations in the LQTS genes are assessed for pathogenicity by using a multifaceted approach involving evidence from the literature (and mutation databases), in silico analysis with predictive bioinformatic programs, and in vitro analyses. Finally, familial segregation of the mutation among affected relatives of the proband provides strong evidence of pathogenicity but can be hampered by access to other family members. The initial spectrum of mutations seen up to 2005 has been published previously,[14] as have the large gene rearrangements[15] and 11 in vitro evaluations (46% of the novel mutations detected in New Zealand).[12,16,17]

On enrolment in the registry, patients are given a classification of their clinical status based on their ECG, symptoms/events, and family history. Broadly, the classifications are definitely affected (QTc >470 ms for women and >460 ms for men with unequivocal symptomatology, or QTc >480 ms for women and >470 for men without symptoms), probably affected (QTc >440 ms with repolarization abnormalities, suggestive symptoms, or family history), possibly affected (QTc between 420 and 470 ms), or unlikely to be affected (QTc <420 ms). Classifications are made or adjusted in the context of symptomatology and repeated ECGs, exercise tests, and occasionally Holter recordings. This report includes only patients classified clinically as definitely or probably affected with LQTS and genotype-positive patients (included in the definite LQTS subgroup for this analysis).

The CIDG was initially established in the northern region, but cases of LQTS from throughout New Zealand were enrolled from 2009 onward. The location of the registry coordinator in Auckland and the differing lengths of registry operational times (the northern region of the country compared to nationally) have resulted in an uneven distribution of case registrations throughout New Zealand. To allow a more accurate estimation of the prevalence of LQTS identified through the registry, northern region cases alone were included in this analysis.

All patient information is entered into a secure Web-based database. The data that have been used in this report were extracted from the database on June 1, 2012.

National population data were taken from the most recent Statistics New Zealand estimates (as on June 2012), and regional district health board-based population data were taken from June 2011 projections.[10,18] Statistical analysis was performed by using R version 2.14.1; χ^2 or Fisher exact tests were used to test for differences between groups.

Results

Eighty-five probands with definite LQTS and 27 probands with probable LQTS were enrolled in the registry (Figure 1). The reasons for referral were as follows: 7 (6%) sudden unexplained deaths, 7 (6%) sudden unexplained deaths of family members, 82 (73%) cardiac events, and 16 (14%) incidental ECG abnormalities. A further 163 definite and 34 probable cases were identified through family screening, giving a total of 309 cases of LQTS in the northern region of New Zealand. Baseline characteristics of all patients are shown in Table 1: 184 (60%) were women, the median age at enrolment was 30 years (interquartile range 12–45 years; range 0.01–88 years), and ethnicities were as follows: 204 (66%) Caucasians, 68 (22%) New Zealand Maori, 16 (5%) Pacific Islanders, and 21 (7%) other/unknown. The median QTc was 480 ms (interquartile range 460–513). Thirty-two percent of the patients had a QTc of $\geq$500 ms, 11% of the patients had a QTc of $\leq$440 ms, and 5% of the patients had a QTc of $<$420 ms. The proportion of genotype-positive patients with a QTc of $\leq$440 ms was also 11%.

The population of the northern region of New Zealand is 2.03 million; with 309 patients with LQTS identified, this equates to a prevalence of 1.5 of 10,000. Within the northern region, the registry and tertiary arrhythmia and genetic services are based in central Auckland (ie, the Auckland district health board area) with a population of 0.46 million. One hundred cases of LQTS were identified here, giving a detected prevalence of 2.2 of 10,000 ($P < .0001$ compared to the rest of the region). The distribution of prevalence by the ethnic group is uneven. For example, the prevalence of LQTS is 1.6 of 10,000 among those of Maori ancestry but is 0.5 of 10,000 and 0.1 of 10,000 among those of Pacific Islander and Asian ancestry, respectively.

From the 112 probands identified in the northern region, 237 family members with LQTS (203 definite and 34 probable) were identified (186 within the northern region and 51 outside), giving an average of a further 2.1 affected family members identified per proband. These numbers differ slightly from the total identified in the northern region (Figure 1), as 8 probands from outside the region had affected relatives living within the region.

Two hundred twenty patients were positive for 63 different LQTS-causing mutations (120 *KCNQ1*, 78 *KCNH2*, 19 *SCN5A*, 1 *KCNE1*, and 2 *KCNJ2*; Supplementary Table 1). Two patients carried 2 LQTS-causing mutations. Of the 29 patients with clinically definite LQTS but no mutations identified, genetic screening was uninformative in 12 patients and 17 patients did not undergo testing (either because they declined or because genetic screening in family members was uninformative). Sixty-six gene-positive probands were identified in the region, resulting in 151 gene-positive and 179 gene-negative cascade tests. The details of the identified mutations are in Supplementary Table 1, along with evidence of their

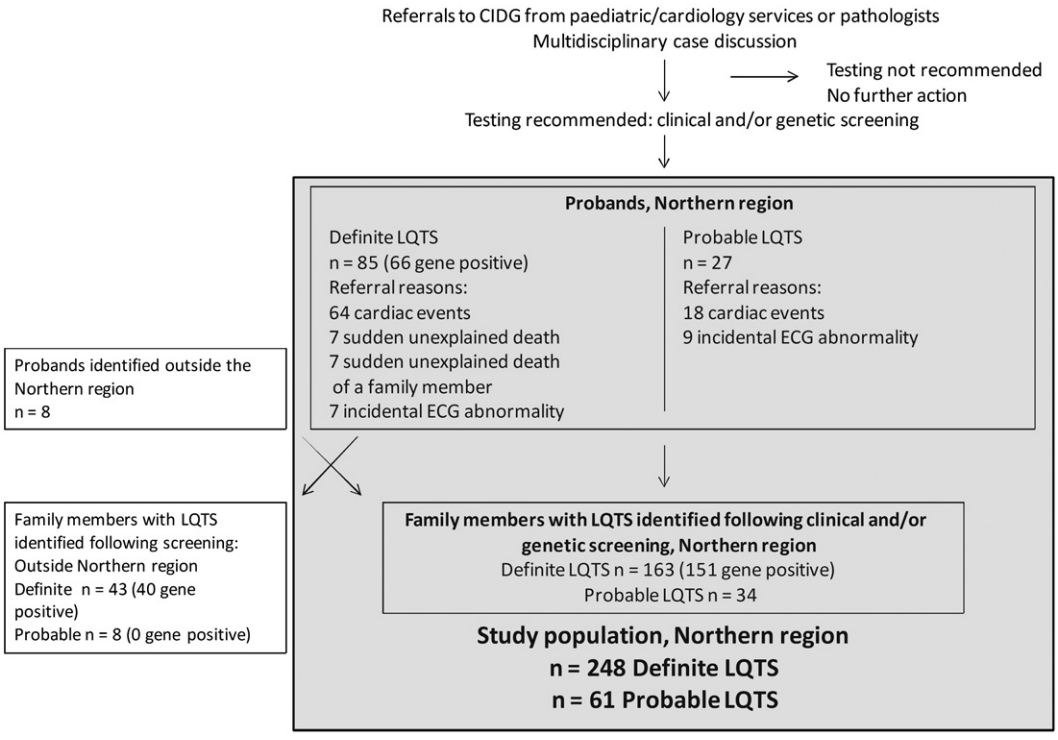

Figure 1 Individuals with long QT syndrome (LQTS) in the northern region of New Zealand: derivation of the study population. CIDG = Cardiac Inherited Diseases Group.

Table 1 Baseline characteristics of patients with LQTS in the northern region of New Zealand

	Total	Total definite LQTS	Total probable LQTS
N	309	248	61
Probands, n (%)	112 (36)	85 (34)	27 (44)
Sex: Woman, n (%)	184 (60)	149 (60)	35 (57)
Age (y), median (IQR)	30 (12–45)	26 (11–44)	30 (14–45)
Ethnicity, n (%)			
Caucasian	204 (66)	169 (68)	35 (57)
Maori	68 (22)	48 (19)	20 (33)
Pacific Islander	16 (5)	12 (5)	4 (7)
Other/unknown	21 (7)	19 (8)	2 (3)
Reason for referral, n (%)			
Sudden death	7 (2)	7 (3)	0 (0)
Cardiac event not sudden death	82 (27)	64 (26)	18 (29)
Incidental ECG abnormality	16 (5)	7 (3)	9 (15)
Family member with sudden death	40 (13)	39 (16)	1 (2)
Family member with LQTS	164 (53)	131 (53)	33 (54)
Most significant clinical event, n (%)			
Sudden death	14 (5)	13 (5)	1 (2)
Resuscitated sudden cardiac death	34 (11)	26 (11)	8 (13)
Loss of consciousness	72 (23)	58 (23)	14 (23)
Presyncope/palpitations	14 (5)	11 (4)	3 (5)
None	175 (56)	140 (57)	35 (57)
ECG			
QTc (ms), median (IQR)	480 (460–513)	482 (461–520)	469 (459–490)
QTc $\geq$500 ms (%)	32	37	13
QTc $\leq$440 ms (%)	11	12	7

ECG = electrocardiogram; IQR = interquartile range; LQTS = long QT syndrome; QTc = corrected QT interval.

pathogenicity. Twenty-four (38%) of the mutations identified have not been reported outside of New Zealand. Twenty-four (38%) of the mutations have been associated with sudden unexplained death in the young in New Zealand, and a further 10 (16%) with documented torsades de pointes or resuscitated SCD. Mutations were detected in 70% of the probands who underwent genetic screening.

Table 2 Genotype-positive patients with LQTS type 1–3: mode of presentation among probands and most significant clinical event among all mutation carriers

	LQT1 (*KCNQ1*)	LQT2 (*KCNH2*)	LQT3 (*SCN5A*)
Probands, n	39	20	7
Mode of presentation, n (%)			
Sudden death	3 (8)	3 (15)	1 (14)
Family member with sudden death	4 (10)	2 (10)	0 (0)
Cardiac event	27 (69)	15 (75)	5 (72)
Incidental ECG abnormality	5 (13)	0 (0)	1 (14)
All genotype positive, n	120	78	19
Most significant clinical event, n (%)			
Sudden death	4 (3)	4 (5)	2 (11)
Resuscitated sudden death	8 (8)	5 (6)	4 (21)
Loss of consciousness	27 (23)	18 (23)	2 (11)
Presyncope/palpitations	4 (3)	6 (8)	1 (5)
None	76 (63)	45 (58)	10 (52)

There were no significant differences between groups.

ECG = electrocardiogram; LQTS = long QT syndrome; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

A higher proportion of probands with LQT type 3 (LQT3) presented with a cardiac arrest (sudden death or resuscitated sudden death) than those with LQT type 1 (LQT1) or LQT type 2 (LQT2): 6 of 7 (86%) LQT3, 9 of 39 (23%) LQT1, and 3 of 20 (15%) LQT2 ($P = .002$). Of the genotype-positive patients who experienced symptoms, cardiac arrest was more common in patients with LQT3 than in patients with LQT1 or LQT2 (occurring in 6 of 9 [67%], 12 of 44 [27%], and 9 of 33 [27%], respectively) but this was not statistically significant ($P = .08$) (Table 2). Near drowning occurred in 10% of the patients with *KCNQ1* mutations but did not occur in any of the other genotypes.

Some cases (13%) defined as probable LQTS had a recorded QTc in excess of 500 ms (Table 1). These cases were not defined as definite because subsequent ECGs were less convincing, the heart rate was particularly fast or slow, and/or there were other factors that might have affected the QT interval. These factors include suspicion of myocardial injury, uncertainty of core body temperature, close time relationship to a significant cardiac event, or the uncertain influence of medications or natural remedies.

Discussion

We have demonstrated that a clinical LQTS registry incorporating diagnostic genetic testing can facilitate identification of many patients with LQTS, including victims of sudden unexplained death and their families. Community-based ECG screening elsewhere has led to an estimated prevalence of LQTS of 4 of 10,000.[2] The registry and

program we describe, which has been in existence for 9 years, has thus far detected 1.5 of 10,000 individuals with LQTS in the northern region of New Zealand and 2.2 of 10,000 in central Auckland. The higher detection frequency in central Auckland probably relates to the proximity of New Zealand's largest arrhythmia service and the location of the registry and coordinator.

The data from the New Zealand registry suggest that LQTS in New Zealand has a similar clinical and genetic profile to that in other regions, so it seems likely that such an approach could be applicable in other countries. For example, LQT1 mutations are most common (55%), followed by LQT2 (35%) and LQT3 (9%).[14] The mutation detection frequency of 70% among probands undergoing genetic screening is similar to previous studies of cohorts with LQTS.[19] A slight difference is that only 11% of the patients with mutations had a QTc within normal limits ($\leq$440 ms), a proportion that is less than the 25% found in a large group of international patients with LQTS.[20]

The fact that we have already detected over half of the expected prevalence in central Auckland might lead to the erroneous conclusion that our family cascade screening has been particularly successful. In fact, for each proband registered in the northern region, on average only 2.1 family members with LQTS have been identified. On the basis of other examples of sudden death and screening for autosomal dominant disorders such as familial hypercholesterolemia, we expected to identify 8–9 gene carriers per proband.[21,22]

If barriers to identifying affected family members were removed (see Limitations) and we could identify 8 family members for every genotype-positive proband identified in central Auckland (n = 30), then the expected LQTS prevalence would be approximately 5.3 of 10,000, which is higher than previous estimates based on population-based ECG screening.

The varying prevalence across the different ethnic groups residing in northern New Zealand is likely to be a result of barriers to registration rather than a true reflection of differences in prevalence, though some genetic variation may exist as seen in cohorts with LQTS elsewhere.[23] Such barriers include unequal rates of access to and engagement with medical services as well as language difficulties and spiritual and cultural beliefs about disease.

Effective screening programs must be able to reliably identify the condition with a safe and inexpensive test.[8] The largest ECG screening program reported to date is that of more than 44,000 Italian newborns screened between the ages of 15 and 25 days.[2] Intense debate surrounds such programs, specifically the ideal age for screening, whether adequate prophylactic treatments are available for infants (particularly with LQT3), and the impact of false-positive tests.[24,25] While a Task Force of the European Society of Cardiology has endorsed newborn ECG screening,[26] this has not been widely adopted. A recent science advisory group of the American Heart Association stated a lack of evidence to support such a strategy in a North American context.[27] Nevertheless, it is interesting that in their report, Schwartz et al[2] advanced the hypothesis that the true prevalence of LQTS may be near 5 of 10,000 (1 in 2000), which would accord with our projections presented here if we had an ideal family screening system.

A community infant ECG screening program in New Zealand would raise significant resource issues, particularly given the limited number of experts in this area. An international survey of physicians found that fewer than 50% of the cardiologists and 40% of the noncardiologists were able to calculate the QTc correctly in patients with LQTS.[28] There is only 1 pediatric electrophysiologist in New Zealand to assess the equivocal ECGs from the more than 60,000 newborns each year.

Limitations

The main limitation of this study is that many factors would have led to the underestimation of the true community prevalence of LQTS. Not every individual with LQTS in the specified area will be enrolled in the CIDG, and many families have, for many reasons, had incomplete family screening. Conversely, a small number of individuals diagnosed as having LQTS may ultimately prove not to have LQTS, even given the relatively strict criteria used in this study.

Multiple reasons may underlie our lower frequency of detection. In approximately a quarter of families where LQTS was identified, there were significant social, logistic, or genetic reasons why family members could not, or would not, undergo screening. New Zealand does not have a genetic nondiscrimination act such as in the United States; health and other insurance companies may ask for genetic test results and decline insurance because of them. Other reasons may be more universal: the unknown whereabouts or paternity of the father of the proband, small family size, adoption, unwillingness of the local physicians to engage in the screening process, and SCD of likely carriers prior to the initiation of screening. There were also 2 de novo mutations (found only in the affected proband and not present in either parent).

The registry has very limited resources—a single part-time coordinator for the whole of New Zealand covers a range of cardiac inherited diseases and sudden death investigations. Subsequently, family members initially unwilling to engage and give consent for genetic or clinical testing cannot always be reappraised or offered repeat clinic appointments if they do not attend. A familial hypercholesterolemia screening program in the Netherlands used nurse specialist home visits to increase participation.[22] They and others have found that family members invited for cascade screening are more likely to participate when invited by a medical professional, rather than a family member.[22,29] In New Zealand, privacy laws preclude information sharing with family members and obtaining medical information without consent, making it difficult to contact extended family members directly.

Conclusions

A high level of community detection of LQTS is possible by using a clinical registry with an active program to detect

probands and screen their families. In some areas, this has detected more than half of the anticipated prevalence, despite the limited resources of the registry and only partially successful family screening. This detection frequency can be expected to increase in time as further family cascade screening takes place, particularly if resources are increased to facilitate this outcome. We suggest that this approach has the potential to be an effective alternative to community ECG screening.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2012.10.043.

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