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Original Article

Clinical and genetic features of Australian families with long QT syndrome: A registry-based study

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ABSTRACT

Background: Familial long QT syndrome (LQTS) is a primary arrhythmogenic disorder caused by mutations in ion channel genes. The phenotype ranges from asymptomatic individuals to sudden cardiac arrest and death. LQTS is a rare but significant health problem for which global data should exist. This study sought to provide the first clinical and genetic description of Australian families with LQTS.

Methods: We performed a cross-sectional study to evaluate clinical and genetic features of families with LQTS. We recruited individuals from the Australian Genetic Heart Disease Registry and Genetic Heart Disease Clinic, in Sydney, Australia, and included those with a diagnosis of LQTS according to the most recent consensus statement.

Results: Among 108 families with LQTS, 173 individuals were affected. Twenty-five (32%) probands had a sudden cardiac death (SCD) event (including appropriate implantable cardioverter defibrillator [ICD] therapy, or resuscitated cardiac arrest). There were 64 (82%) probands who underwent genetic testing, and 34 (53%) had a pathogenic or likely pathogenic mutation in. Having a family history of LQTS was significantly associated with identification of a pathogenic result (79% versus 14%, $p < 0.0001$). There were 16 (9%) participants who experienced delay to diagnosis of at least 12 months.

Conclusions: This is the first clinical and genetic study in a large cohort of Australian families with LQTS. Findings from this study suggest that the clinical and genetic features in this population are not dissimilar to those described in North American, European, and Asian cohorts. Global-scale information about families with LQTS is an important initiative to ensure diagnostic and management approaches are applicable to different populations and ethnicities.

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1. Introduction

Familial long QT syndrome (LQTS) is a primary arrhythmogenic disorder caused by ion channel abnormalities leading to abnormal ventricular repolarization and a prolonged QT interval on the

electrocardiogram (ECG) [1]. Clinical manifestations include palpitations, syncope, or cardiac arrest due to *torsade de points* and ventricular fibrillation (VF) [1,2]. Familial LQTS, mostly inherited as an autosomal dominant trait, rarely presents as a recessive trait in the form of Jervell and Lange-Nielsen syndrome [3,4].

Clinical diagnosis is based on the identification of a prolonged QT interval on the ECG, presence or absence of a family history, and absence of QT-prolonging medications [2]. Advances in the understanding of molecular genetics and pathogenesis of genetic heart diseases have contributed extensively to elucidating the role

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of genetics in familial LQTS [5]. Compared with other genetic heart diseases, the yield of genetic testing has been highest in LQTS, and is now an integral part of clinical management of families [6]. Particularly, apart from playing a role in diagnosis, genotype also has potential therapeutic and prognostic implications, with genotype–phenotype correlations shown to explain some of the heterogeneity of the disease [6–8].

At least 15 genes are associated with familial LQTS, with 3 of these genes accounting for 70–75% of cases [5]. Despite advances in the understanding of the molecular basis of LQTS, challenges remain in making the clinical diagnosis. Importantly, between 10–40% of gene carriers have normal QT intervals [9,10]. While molecular genetics has contributed to improvements in some aspects of diagnosis, due to the variability of the QT interval and variable penetrance and expressivity, there is still evidence of significant misdiagnosis and delay in diagnosis [11]. Studies that describe the clinical and genetic features of LQTS have been mainly from Europe, North America, and Asia. To our knowledge, there are no reports of cohorts with LQTS from Australia. With a prevalence of 1:2000–3000 [12,13], LQTS is a rare but significant health problem, and thus, clinical and genetic data from a range of countries and ethnicities are important. This study sought to report the clinical and genetic features of a registry-based cohort of Australian families with LQTS.

2. Materials and methods

2.1. Patient cohort

All probands and relatives with LQTS attending Royal Prince Alfred Hospital (RPAH) Genetic Heart Disease Clinic in Sydney, Australia, or those enrolled in the Australian Genetic Heart Disease (AGHD) Registry were included [14]. The AGHD Registry aims to recruit all Australians with a genetic heart disease, and participants are recruited or self-referred from all states in Australia. Patients meeting expert consensus recommendations for LQTS diagnosis were included [2]. In most cases, the proband was defined as the first affected family member who sought medical advice for LQTS. All studies were conducted in strict accordance with ethics protocols approved by the Human Research Ethics Committee at Royal Prince Alfred Hospital, Sydney (Approval number X11-0077), Australia.

2.2. Clinical diagnosis

Clinical diagnosis was based on the recent HRS/EHRA/APHRS expert consensus guidelines [2]. Specifically, a diagnosis was made in the presence of an LQTS risk score ≥ 3.5 in the absence of a secondary cause of QT prolongation, and/or in the presence of an unequivocally pathogenic mutation in one of the LQTS genes, or a QTC ≥ 500 ms in repeated 12-lead ECG without a secondary cause for QT prolongation.

2.3. Genetic analysis

Genetic test results were recorded if testing had been previously performed. An amended version of the updated 2015 American College of Medical Genetics (ACMG) standards and guidelines document was used to determine the pathogenicity of LQTS variants [15]. Key determinants of pathogenicity included rarity ($< 0.05\%$ or absence from the large Exome Aggregation Consortium dataset, <http://exac.broadinstitute.org>), agreement amongst *in silico* tools (CADD [Combined Annotation-Detection Depletion], SIFT [Sorting Intolerant From Intolerant, <http://sift-dna.org/>], Polyphen-2 [Polymorphism phenotyping Ver2 <http://genetics.bwh.harvard.edu/pph2/>], MutationTaster [www.mutationtaster.org]) of a possibly deleterious role, previous association of the variant within LQTS patients, segregation data, as well as available and supportive experimental data. Individuals who did not meet the clinical diagnosis but harbored variants classified as pathogenic or likely pathogenic using this criterion were included after being considered as meeting the expert consensus recommendations. Topological placement of variants was done using a combination of Uniprot (<http://ca.expasy.org/uniprot/>), Human Protein Reference Database (http://www.hprd.org/Motifs_details/CC), and a review of the literature [16].

2.4. Collection of clinical and genetic information

Clinical and genetic information were obtained by review of the medical record and direct correspondence with the treating cardiologist. The QT interval was measured in lead II or V5 and corrected for heart rate according to Bazett's formula (QTc). Where there was more than 1 ECG available, the longest QTc was recorded. A sudden cardiac death (SCD) event was defined as SCD, resuscitated cardiac arrest, or appropriate ICD shock for ventricular tachycardia (VT) or ventricular fibrillation (VF). A family history of LQTS was considered when at least 1 other relative had a clinical diagnosis. Delay to diagnosis was defined as the period between the initial presentation of the symptoms likely attributable to LQTS up to the time of diagnosis in the proband. Delay in diagnosis was only considered when the time to diagnosis was at least 12 months.

2.5. Statistical analysis

Data were analyzed using Prism (version 6.0) and SPSS Statistics (version 20.0). Descriptive statistics were used to describe clinical and genetic features of probands, relatives, and families. Associations between variables and outcome factors were assessed using unpaired *t*-tests for continuous data and chi-square analysis for categorical data. A *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of LQTS probands and families

A total of 219 individuals were identified with a possible, probable, or confirmed diagnosis of LQTS. Thirty-one probands and 15 relatives were excluded from the analysis as they did not meet the HRS/EHRA/APHRS expert consensus guidelines for inclusion. A total of 173 individuals from 108 families with LQTS in the clinical and genetic characterization (Fig. 1). Ancestry data was available for 47 probands; the majority (40 (85%)) of these probands self-reported Northwest European (Caucasian) ancestry. The mean follow-up time for probands was 2 years (0–13 years).

A total of 78 probands (from 108 families; the remaining 30 probands were not enrolled in the AGHD Registry) and 95 relatives meeting diagnostic criteria were identified; the demographic and clinical characteristics are summarized in Table 1. The mean age of probands was 40 ± 18 years and 21 (27%) were males. The mean age at diagnosis was 32 ± 18 years, and the mean corrected QT (QTc) was 515 ± 46 ms. There were 39 (50%) probands who had a documented episode of syncope, and 25 (32%) had experienced an SCD event, including 3 SCD cases, 22 resuscitated cardiac arrests, 1 appropriate ICD therapy for VT, and 4 appropriate ICD therapies for VF. The SCD event was the presenting symptom in 21 (27%) probands. There were 66 (85%) probands on beta-blocker therapy

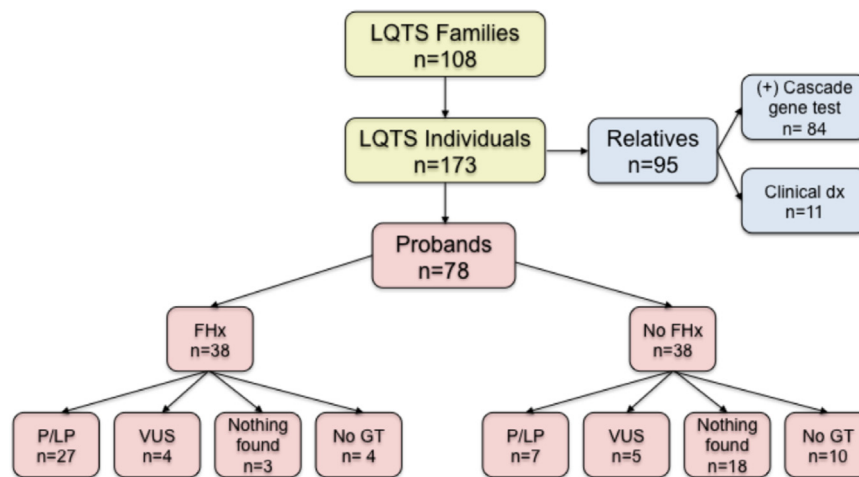


Fig. 1. Flow chart of genetic testing outcomes in LQTS families. A total of 173 individuals from 108 families were identified for inclusion in this study. LP, likely pathogenic; P, pathogenic; VUS, variant of uncertain significance; FHx, family history; GT, genetic testing; dx, diagnosis.

Table 1
Demographic and clinical characteristics of the cohort with LQTS.

Variable	Probands	Relatives	p-value
n	78	95	–
Mean age (years)	40 ± 18	34 ± 22	0.038
Mean age at diagnosis (years)	32 ± 18	25 ± 22	0.027
Male (n, %)	21 (27)	44 (46)	0.009
North West European Ethnicity (n, %)	40 (85)	45 (47)	Not applicable
Delay to dx (n, %)	13 (17)	3 (3)	0.002
Mean QTc (ms)	515 ± 46	479 ± 41	< 0.0001
QTc ≥ 500 ms (n, %)	43 (61)	27 (29)	< 0.0001
Documented syncope (n, %)	39 (50)	11 (12)	< 0.0001
ICD in situ (n, %)	40 (51)	15 (16)	< 0.0001
SCD event (n, %)	25 (32)	2 (2)	< 0.0001
Appropriate ICD therapy for VF (n, %)	4 (10)	1 (6)	0.113
Appropriate ICD therapy for VT (n, %)	1 (3)	1 (6)	0.889
SCD	3 (4)	0	< 0.0001
OHCA	22 (28)	1 (1)	< 0.0001
Beta Blocker therapy (n, %)	66 (85)	79 (83)	0.838
Family history of LQTS (n, %)	38 (49)	95 (100)	Not applicable
Genetic test (n, %)	64 (82)	84 (88)	0.238
Pathogenic or Likely Pathogenic genetic result (n, %)	34 (53)	83 (99)	Not applicable

SCD event, including sudden cardiac death, resuscitated cardiac arrest and appropriate VT/VF ICD therapy; ICD, implantable cardioverter defibrillator; mean ± standard deviation (SD).

and 40 (51%) with an ICD. Thirty-eight (49%) probands reported a family history of LQTS.

Of the 108 families (including families where the proband was not known to the center), 70 (65%) had a family history of LQTS (i.e. 2 or more individuals with a clinical diagnosis of LQTS). Thirty-three (31%) families had a history of SCD and 26 (24%) reported a history of epilepsy, sudden infant death syndrome, unexplained drowning, miscarriage, frequent “blackouts”, or hearing loss.

3.2. Genetic characteristics of LQTS families

Genetic testing was performed in 88 (81%) families with a pathogenic or likely pathogenic result identified in 68 (77%). The mean number of affected family members per family in a 3 generational family pedigree was 4 (median, 2; range, 0–28). Of 64 probands tested, 34 (53%) had a pathogenic or likely pathogenic mutation identified. Amongst the probands, the median number of genes screened was 6. There were 4 probands with multiple gene variants identified, including 1 with a likely pathogenic and a pathogenic *KCNQ1* mutation in *cis*, 1 with a pathogenic *KCNH2*

mutation and an additional variant of uncertain significance (VUS) in *KCNH2* in *trans*, 1 proband with a likely pathogenic variant in *KCNQ1* and a VUS in *CACNA1C*, and 1 proband with a *KCNJ2* VUS in addition to a likely pathogenic *KCNH2* variant.

Nine probands had a VUS in a known LQTS gene in which co-segregation studies had not been completed to clarify causation. In addition, there were 18 relatives enrolled in the AGHDR (without the proband) resulting in a total of 62 variants (pathogenic, likely pathogenic, and VUS) in this cohort of affected individuals (Supplementary Table 1). Of the relatives who underwent cascade testing, 29 variants were identified in *KCNQ1* (47%), 22 in *KCNH2* (35%), 3 in *SCN5A* (5%), 4 variants in *CACNA1C* (6%), 2 in *KCNE2* (3%), and 2 in *KCNJ2* (3%). Characteristics of these variants are summarized in Table 2. The majority of variants identified were missense mutations, (74%) classified as likely pathogenic (53%). Of the variants in this cohort, 18 (29%) were novel and not previously published in the literature. The compendium of LQTS variants from this cohort by genomic location, nucleotide, protein change, and region are summarized in the Supplementary Table 1.

3.3. Factors associated with a greater mutation pick-up rate in LQTS probands

A family history of LQTS was a significant predictor of a positive genetic result, with a causative variant identified in 27 (79%) of those with a positive family history of LQTS compared to 3 (14%) of those with no apparent history or reportedly affected relatives ($p < 0.0001$). Further, the QTc interval was significantly longer in probands with a pathogenic or likely pathogenic variant than in those where no variant was identified following genetic testing (excluding VUS; 523 ± 55 ms versus 496 ± 23 ms, $p = 0.045$). Other clinical characteristics and basic demographics were not associated with a positive genetic result (Table 3).

3.4. Genotype–phenotype correlation

There were no significant differences when comparing probands with *KCNQ1*, *KCNH2*, or variants in *SCN5A*, *CACNA1C*, *KCNJ2*, and *KCNE2* (excluding VUS). Although the numbers were small, when comparing probands with 1 pathogenic or likely pathogenic variant versus those with 2 variants, the QTc was significantly longer in probands with 2 versus 1 variant (578 ± 79 versus 513 ± 45 , $p = 0.028$), irrespective of the variant classification (Table 4). The location of mutations in the transmembrane or pore

Table 2

Summary of variants identified in Australian families with LQTS.

	KCNQ1	KCNH2	SCN5A	CACNA1C	KCNE2	KCNJ2	Total
Total (n)	29	22	3	4	2	2	62
Probands	22	9	2	3	2	1	39
Mean age (years)	34 ± 18	41 ± 17	36 ± 45	26 ± 12	45 ± 11	39	–
Male (n, %)	7 (32)	4 (44)	1 (50)	1 (33)	0	0	–
Syncope (n, %)	9 (41)	6 (67)	1 (50)	3 (100)	0	1	–
Mean QTc (ms)	520 ± 53	515 ± 41	524 ± 79	497 ± 17	578 ± 88	529	–
Appropriate ICD therapy for VF (n, %)	0	0	0	0	1 (50)	NA	–
Appropriate ICD therapy for VT (n, %)	0	0	0	0	0	NA	–
Beta Blocker (n, %)	17 (77)	6 (67)	1 (50)	1 (33)	2 (100)	1	–
Pathogenic (n, %)	9 (31)	4 (18)	2 (67)	0	0	0	15 (24)
Likely pathogenic (n, %)	16 (55)	14 (64)	1 (33)	1 (25)	1 (50)	0	33 (53)
Uncertain (n, %)	4 (14)	4 (18)	0	3 (75)	1 (50)	2 (100)	14 (23)
Missense (n, %)	24 (83)	12 (55)	2 (67)	4 (100)	2 (100)	2 (100)	46 (74)
Nonsense (n, %)	3 (10)	5 (23)	0	0	0	0	8 (13)
Frameshift (n, %)	2 (7)	2 (9)	0	0	0	0	4 (6)
Splice site (n, %)	0	2 (9)	0	0	0	0	2 (3)
In-frame INDELS (n, %)	0	1 (5)	1 (33)	0	0	0	2 (3)
Novel (n, %)	4 (14)	10 (45)	0	2 (50)	1 (50)	1 (50)	18 (29)

Data analysis for age, gender, syncope, QTc, and therapies conducted on probands only. Probands with > 1 variant excluded from this analysis.

Table 3

Genotype positive versus negative probands.

Variable	Genotype positive (LP/P)	Genotype negative	p-value
n (excluding VUS/ no testing)	34	21	–
Mean age (years)	37 ± 19	43 ± 18	0.261
Mean age at diagnosis (years)	28 ± 19	35 ± 19	0.193
Male (n, %)	12 (35)	4 (19)	0.205
Mean QTc (ms)	523 ± 55	496 ± 23	0.045
QTc (ms) ≥ 500 (n, %)	16 (47)	10 (48)	0.433
Documented syncope (n, %)	17 (50)	8 (38)	0.244
SCD event (n, %)	11 (32)	8 (38)	0.671
ICD in situ (n, %)	15 (44)	13 (62)	0.207
Family history of LQTS (n, %)	27 (79)	3 (14)	< 0.0001

SCD event, including sudden cardiac death, resuscitated cardiac arrest and appropriate VT/VF ICD therapy; ICD, implantable cardioverter defibrillator; LP, likely pathogenic; P, pathogenic; mean ± standard deviation (SD). Those with a VUS were removed from this analysis.

regions was not associated with poorer prognosis, though the numbers were small in each subgroup.

3.5. Delay to diagnosis

There were 16 (9%) participants (probands and relatives) who experienced a delay in diagnosis, including 11 who were initially misdiagnosed (Supplementary Table 2). Specifically, 8 were misdiagnosed with epilepsy, 1 with catecholaminergic polymorphic ventricular tachycardia (CPVT), 1 with nocturnal seizures, and 1 with anxiety. Of the 16 who experienced a delay in diagnosis, 4 (25%) had a likely pathogenic or pathogenic variant in *KCNH2*, with 1 participant found to have a VUS in *KCNH2*, 4 (25%) carrying likely pathogenic or pathogenic variants in *KCNQ1*, as well as 1 additional participant with a VUS in *KCNQ1*. One participant had a VUS in *KCNJ2* and 1 carried a likely pathogenic variant in *CACNA1C*. Two participants from the misdiagnosed group had indeterminate genetic testing and 2 had not had genetic testing at the time of analysis. The mean delay to diagnosis was 8 years (1–20 years). In this group, the earliest investigation year recorded was 1973 and the most recent was 2010. Importantly, the mean delay decreased

Table 4

Compound heterozygosity in Australian families with LQTS.

Variable	1 pathogenic variant	≥ 2 variant ^a	p-value
n	30	4	–
Mean age (years)	38 ± 19	35 ± 14	0.801
Mean age at diagnosis (years)	29 ± 19	26 ± 17	0.788
Male (n, %)	11 (37)	1 (25)	0.646
Mean QTc (ms)	513 ± 45	578 ± 79	0.0269
QTc (ms) ≥ 500 (n, %)	12 (40)	4 (100)	0.0773
Documented syncope (n, %)	15 (50)	2 (50)	0.842
SCD event (n, %)	10 (33)	1 (25)	0.747
ICD in situ (n, %)	14 (47)	1 (25)	0.428
Family history of LQTS (n, %)	24 (80)	3 (75)	0.823

SCD event, including sudden cardiac death, resuscitated cardiac arrest and appropriate VT/VF ICD therapy; ICD, implantable cardioverter defibrillator; mean ± standard deviation (SD).

^a Includes those with any rare variant, i.e. VUS, likely pathogenic and pathogenic.

over time, from a mean of 12 years when the first presentation was before the year 2000, to 5 years from the year 2000 onwards.

3.6. More severe phenotype in probands compared to relatives

The characteristics of relatives are summarized alongside probands in Table 1. There were significant differences in the clinical and demographic variables between relatives and probands. Relatives were younger ($p=0.038$), diagnosed at a younger age ($p=0.027$), and were more likely to be of male sex ($p=0.009$). Relatives had shorter QT intervals ($p<0.0001$), less documented syncope ($p<0.0001$), and fewer SCD events ($p<0.0001$). Fifteen (16%) relatives had an ICD *in situ*, including 1 who had experienced an appropriate ICD shock for VF and 1 who had experienced an ICD shock for VT. There was no difference in terms of beta-blocker use between relatives and probands (83% versus 85% $p=0.838$).

The mean QTc for probands with a pathogenic or likely pathogenic result was 523 ± 55 ms (458–660) and for probands without a genetic result was 496 ± 23 ms (460–540) ($p=0.045$). Relatives with known and genotyped LQTS exhibited wide-ranging QT intervals 479 ± 41 ms (400–620) ($p<0.0001$) (Supplementary Fig. 1). Sixteen (20%) genotyped relatives for whom QTc was available had a QTc interval within the normal range of ≤ 440 ms.

4. Discussion

4.1. Main findings

To our knowledge, this is the first clinical and genetic report of Australian families with LQTS. The key clinical and genetic characteristics of Australian families are not dissimilar to those previously described for European, North American, and Asian cohorts with LQTS. Global information about families with LQTS is an important initiative to ensure diagnostic, and management approaches are applicable to different populations and ethnicities. Further, delay in diagnosis and gene carriers with normal QT intervals emphasize the diagnostic challenges that LQTS can present in clinical practice, and highlight the importance of genetic testing in the management of these families.

4.2. Genetic testing outcomes in LQTS

Genetic testing of probands in our LQTS cohort had a yield of 53%, less than that reported in the literature of 65–75% [7]. In the current study, the genetic testing yield was higher (79%) in those with a positive family history of LQTS, emphasizing the importance of obtaining a comprehensive 3-generation pedigree where possible, consistent with recent findings of family history being a predictor of a positive genetic result in other genetic heart diseases such as hypertrophic cardiomyopathy [17,18]. In services where funding restrictions exist, identification of individuals with LQTS with a high pre-test probability of a variant being identified is valuable and represents the most cost-effective strategy [19,20]. The current study also contributes to the compendium of LQTS-associated genetic variants published in the literature. Eighteen (29%) novel variants were identified in the current cohort, which was primarily of Caucasian origin, highlighting that many families still harbor unique “private” mutations. Given the increasing complexities associated with classifying genetic variants so as to provide families with meaningful information and data that contributes and may aid in this challenging process is valuable.

4.3. Clinical challenges of LQTS diagnosis

Our study highlights and reinforces the complexity of clinical diagnosis of LQTS. Delay in diagnosis is a documented issue that has been observed in several cohorts with LQTS [11,21], as well as in other inherited arrhythmogenic syndromes [22]. In the current study, 9% of participants experienced a diagnostic delay of at least 12 months. Given that the first investigation dates ranged from the 1970s up until 2010, the finding highlights the diagnostic challenge LQTS can present. This seemed particularly true if probands presented with recurrent syncope or ‘seizure-like activity’ and whose primary investigations suggested neurological differential diagnoses rather than cardiac. In a New Zealand study of LQTS patients, delay in diagnosis was frequent in up to 31 (39%) of patients with LQTS [23]. The tendency toward recurrent syncope or “seizure-like activity” can set patients up for a diagnostic odyssey with LQTS not recognized early as a cause for symptoms. Adding further complexity to this issue is a recent study in which the authors suggest that 15% of patients with LQTS presenting with blackouts or seizure-like activity had electroencephalography (EEG) identified epileptiform activity [24]. It is suggested that EEG activity and epilepsy are more frequent in patients with a *KCNH2* (LQT2) mutation. EEG reports were not available in the current study, but taken together with other reports in the literature, provide preliminary support for a neuro-cardiac link with *KCNH2* encoded potassium channels that are expressed both in the brain and the heart. This further reinforces the need for continued

education and awareness among primary care physicians, as well as emergency physicians and general cardiologists.

4.4. Australian LQTS in the international context

The main characteristics of LQTS in the international literature, including demographics, SCD events, genotype frequencies, and normal QTc intervals in genotyped patients, were also demonstrated in this Australian cohort. The current study aligned with larger international studies [6,10,25] and, therefore, allows available evidence to be extrapolated to an Australian context. The AGHD Registry represents the largest genetic heart disease population in Australia [14]. Indeed, the current study is a reminder of the need for cooperative, collaborative efforts in genetic heart disease research, where a lack of randomized controlled trials upon which to base disease management guidelines exist. Collaborative initiatives and truly international cohorts with LQTS are therefore critical to address fundamental questions relating to diagnosis, risk stratification, clinical management, and genotype-guided management.

4.5. Study limitations

Although this is the first study to provide insight into the clinical and genetic features of Australian families with LQTS, this cohort is not truly population-based. Recruiting from the AGHD Registry is likely to have introduced sampling bias whereby those individuals enrolled represent a more severe spectrum of disease. Statistical analysis was limited by the relatively small sample size and highlights the value of a large collaborative initiative.

5. Conclusions

LQTS is a rare but significant health problem, the most tragic outcome of which is SCD. To our knowledge, this is the first cohort study to describe the clinical and genetic characteristics of Australian families with LQTS. The study highlights the complex challenges in the clinical diagnosis of LQTS. Coupled with continued difficulties in clinical diagnosis, the key role of genetic testing is further emphasized. By reporting and contributing to the compendium of LQTS associated variants, this data may provide valuable information to LQTS groups globally, with the ultimate goal to improve the diagnosis and management of families with LQTS.

Conflict of interest

All authors declare no conflicts of interest related to this study.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.joa.2016.02.001>.

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