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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.

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 [Polymorhism 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

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