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"Better Late Than Never"—Late-Onset Genotype-Negative Congenital Long QT Syndrome: Case Report and Review

Clement Tan[1] | Vaikunthan Thanabalasingam[1,2] | Chaminda Sella Kapu[1] | Zhihua Zhang[1,3]

[1]Department of Cardiology, Coronary Care Unit & Cardiac Catheterisation Laboratory, Mackay Base Hospital, Mackay, Queensland, Australia | [2]Jaffna Teaching Hospital, Jaffna, Sri Lanka | [3]College of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia

Correspondence: Clement Tan (clement.tan@health.qld.gov.au)

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ABSTRACT

Congenital long QT syndrome (LQTS) is a genetic disorder causing prolonged QT intervals and an increased risk of arrhythmias and sudden cardiac death. With 25% of cases lacking known genetic mutations, diagnosis and treatment can be challenging. We present a successfully managed case of late-onset genotype-negative phenotype-positive LQTS presenting as palpitations, complicated by a single event of polymorphic ventricular tachycardia, followed by a review of the literature. This case underscores the gaps in understanding congenital long QT syndrome, especially in genotype-negative cases, and highlights the need for ongoing research for risk assessment and effective management to prevent fatal cardiac events.

1 | Introduction

Congenital long QT syndrome (LQTS) is an inherited cardiovascular disorder characterized by impairment of the cardiac repolarization phase due to genetic mutations [1, 2]. This leads to a heart rate corrected QT interval (QTc) prolongation and an increased risk of life-threatening ventricular arrhythmias, syncope, seizures, and sudden cardiac death (SCD)—typically in young healthy individuals [2, 3]. Presentation within older ages is extremely rare, but has been sparsely described in case reports [1, 4].

LQTS remains an important disease due to its lethality. Patients with symptoms that have insufficient workup can often be left without therapy, leading to increased mortality risks of approximately 20% [5]. The treatment for LQTS, now readily available, nullifies the mortality risks when treated appropriately [3]. At present, LQTS has an average prevalence of 1 in 7500 individuals. In LQTS, a positive family history is often present in 40% of cases, and SCD can be noted in up to 30% of cases [4]. Despite being a heavily researched cardiac disease in aspects of molecular biology and genetics, there remain large knowledge gaps in the disease of LQTS. At present, approximately 75% of these genetic variations have been identified. This allows for appropriate classification, identification of the genotype–phenotype correlation, risk stratification, and specific therapies. However, 25% of LQTS cases remain elusive in their genotype, hence hampering phenotypical recognition and the inability to correctly investigate, stratify, and treat [6–8].

We describe a rare occurrence of a late onset of genotype-negative LQTS in an elderly adult male who presented with palpitations. During his admission, a more sinister light is shed on his positive family history. Albeit the first presentation, this diagnosis is better late than never in ensuring treatment to prevent SCD. A brief review of available literature on LQTS will follow the case. The CARE guidelines have been used for this case report [9].

2 | Case History

A 69-year-old gentleman presented to the emergency department for a day history of palpitations and shortness of breath. His

Summary

- There is much left unknown regarding congenital long QT syndrome, especially in the field of the rare and elusive genotype-negative cases.
- These gaps in our understanding may impede our ability to diagnose and manage; hence, this case aims to contribute further to this field and potentially help mitigate these challenges in the future.

medical history is only notable for atrial fibrillation. His atrial fibrillation occurred 4 years ago and was concluded to be triggered by social alcohol intake, to which he has now ceased but remains on anticoagulation and rate control drugs. These include Apixaban 5 mg twice daily and Bisoprolol 1.25 mg once daily. He works as an electrician, is a nonsmoker and nondrinker. At the emergency department, he examined well with a temperature of 36.8, blood pressure of 147/97, pulse rate of 62 beats per minute (bpm), saturations at 100% on room air, and a respiratory rate of 18 breaths per minute. His heart sounds were dual with no appreciable murmurs, lungs were clear to auscultation, and abdomen and calves were soft and nontender. He was then admitted under cardiology for observation of his palpitations.

3 | Investigation

Serial electrocardiograms (ECGs) done showed atrial fibrillation (AF) with a rate of 58 bpm, a couple of premature ventricular complexes (PVCs) and a pre-existing left bundle branch block. Of significance was his QTc segment measuring 470 milliseconds (msec) to 510 msec—with the Bazzett's formula. The admission ECG is shown in Figure 1. There were no acquired causes that accounted for his prolonged QTc. The blood investigations done for him showed no significant findings; more importantly, his B-type natriuretic peptide and cardiac troponin I (cTnI) were within normal limits—the relevant results can be found in Table 1.

Overnight, he was placed on telemetry, which noted a handful of runs of PVCs and a sudden entry into a broad complex tachycardia pattern, later determined to be polymorphic ventricular tachycardia (VT) commencing as a R on T phenomenon. The medical emergency team (MET) was alerted by staff members monitoring the telemetry, and the patient was found to be completely asymptomatic and completely unaware of what had happened. The episode lasted 18 s, where he remained asymptomatic before, during, and after the arrhythmic event. No intervention was done at that time. The sequence of ECG strips acquired from the telemetry, along with the polymorphic ventricular tachycardia, can be found in Figure 2.

Other investigations done the following day included a transthoracic echocardiogram (TTE) and a coronary angiogram. His TTE was significant for a mild bi-atrial enlargement, dilated ventricles with a mildly reduced ejection fraction of 43%, aortic sclerosis, and without any structural concerns. His coronary angiogram showed mild left circumflex coronary artery disease, but has otherwise, non-obstructive coronary artery disease. His cardiac magnetic resonance imaging (CMR) returned normal.

4 | Treatment

The current active issues for addressing were heart failure with mildly reduced ejection fraction (HFmrEF), and most significantly, albeit short, his polymorphic VT episode. In the aspect of his HFmrEF, given that he was already on a regular dose of Bisoprolol, the other 3 pillars of heart failure were also started. These included Spironolactone 25 mg, Dapagliflozin 10 mg, and perindopril 2.5 mg once daily.

Pertaining to the concerning episode of polymorphic VT, his history was thoroughly revisited. His history of presenting complaint was again unremarkable apart from a day's history of palpitations and shortness of breath. Each of these palpitations was seemingly associated with exertion at his job, each resolving spontaneously. He does not report any chest pains at any point in time. His family history was alarming for three cardiac events in three other different individuals. There was no known congenital deafness within the family. Despite the family pedigree being highly suggestive of an inherited arrhythmogenic

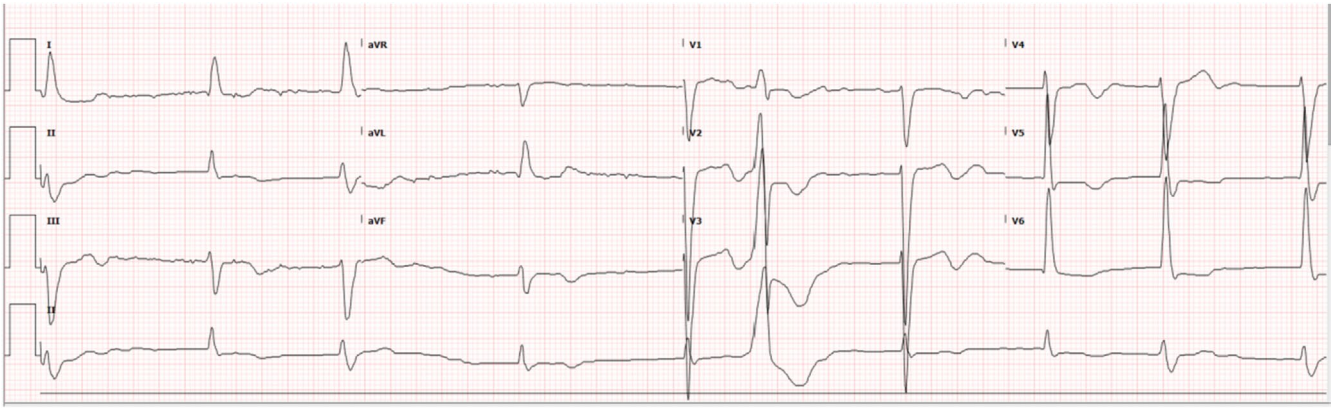


FIGURE 1 | 12 lead ECG admission ECG showing atrial fibrillation with a ventricular rate of 57 bpm, a single premature ventricular complex, and a QTc of 502 ms.

TABLE 1 | Laboratory values and reference ranges for relevant investigations.

	Day of admission	Reference ranges with units
Hemoglobin (Hb)	146	135–180 (g/L)
White Cell Count (WCC)	7.7	4–11 ($\times 10^9$/L)
Platelets (Plt)	211	140–400 ($\times 10^9$/L)
Hematocrit (Hct)	0.42	0.39–0.52
Mean Corpuscular Hemoglobin (MCH)	31.9	27–33 (pg)
Red Cell Count (RCC)	4.57	4.5–6 ($\times 10^{12}$/L)
Mean Corpuscular Volume (MCV)	92	80–100 (fl)
Neutrophils	5.12	2–8 ($\times 10^9$/L)
Lymphocytes	1.66	1–4 ($\times 10^9$/L)
Monocytes	0.74	0.10–1.00 ($\times 10^9$/L)
Eosinophils	0.13	<0.6 ($\times 10^9$/L)
Basophils	0.04	<0.20 ($\times 10^9$/L)
Sodium	144	135–145 (mmol/L)
Potassium	3.8	3.5–5.2 (mmol/L)
Chloride	105	95–110 (mmol/L)
Bicarb	29	22–32 (mmol/L)
Anion Gap (AG)	9	4–13 (mmol/L)
Urea	6.3	2.9–8.2 (mmol/L)
Creatinine	82	64–108 (μmol/L)
Urea/creatinine	77	40–100
GFR	85	>90 (mL/min/1.73m^2)
Calcium Level (Albumin corrected)	2.37	2.10–2.60 (mmol/L)
Phosphate	1.04	0.75–1.50 (mmol/L)
Magnesium	1.18	0.70–1.10 (mmol/L)
Osmolality (Serum)	309	275–295 (mmol/L)
B-type Natriuretic Peptide (BNP)	44	<100 (ng/L)
Cardiac Troponin I (cTnI)	24	<54 (ng/L)
C-Reactive Protein (CRP)	2	<5.0

condition, no formal workup was ever done. His daughters were briefed on LQTS but ultimately declined genetic testing. The extent of the known family pedigree and their cardiac comorbidities and events can also be found in Figure 3.

Schwartz score conducted on the patient scored a total of 5–6 points, scoring 2–3 points for his QTc ranging from 470 to 510 msec since the time of admission, 1 point for his T-wave alternans, and 2 points for his polymorphic ventricular tachycardia episode. Throughout his admission, there have not been any acquired causes of long QTc. Genetic counseling was done for him and his direct family. Genetic testing with entire exome parallel sequencing was also carried out. In the interim, a single coil implantable cardiac defibrillator (ICD) lead was inserted into the right ventricle at a low septal position, with the settings programmed to VVI at 60 bpm. His genetic testing, done using Next-generation sequencing (Illumina NextSeq 550), later returned negative for the arrhythmia gene panel and the extended cardiac structural gene panel. Table 2 further shows the genes tested.

5 | Outcome and Follow-Up

On discharge, he was scheduled to be followed up every 3 months for his ICD checks as well as a cardiology outpatient clinic. At the sixth month mark, he remains well during both his regular clinic follow-up as well as his device checks. All device checks conducted thus far showed no VT detected and no ICD shocks delivered.

6 | Discussion

This case presents an unusual case of the lesser-known form of LQTS, genotype-negative phenotype-positive LQTS, through an episode of polymorphic ventricular tachycardia manifesting in a completely asymptomatic elderly man up until now. He was admitted for a run of palpitations, which later uncovered a worrying family history for SCD and a high resultant Schwartz score. In addition, the uniqueness of the late onset of this case suggests a strong unknown, including gene–gene interactions and transmitted epigenetic contributions that are partly accessible through thorough clinical evaluation in genotype-negative phenotype-positive LQTS.

LQTS was first described in the 1950s after a family with deafness and ECG abnormalities was discovered, now known as Jervell and Lange-Nielsen syndrome. Within the next decade, similar ECG abnormalities in a family without deafness were found, now known as Romano–Ward syndrome [6]. Then, a two-entity disease was coined. However, as the 1990s came along, further subdivisions came about after genetic defects were discovered that led to specific phenotypes. Since then, sequencing of genes has become increasingly affordable over the last decade, which led to a boom in interest pertaining to deoxyribonucleic acid (DNA) diagnostics [8]. The current goal of genomic sequencing remains to predict lifetime risk of conditions and targeted therapies [10]. It is through the rise of sequencing that a greater understanding of genotype–phenotype correlations in LQTS was brought about [6, 8]. However, despite these continual advancements, approximately a quarter of LQTS patients are still classed as genotype negative phenotype positive. This is due to undiscovered monogenic genes or complex polygenic interactions [6, 10]. It still remains a consensus amongst clinicians that a negative genetic test does

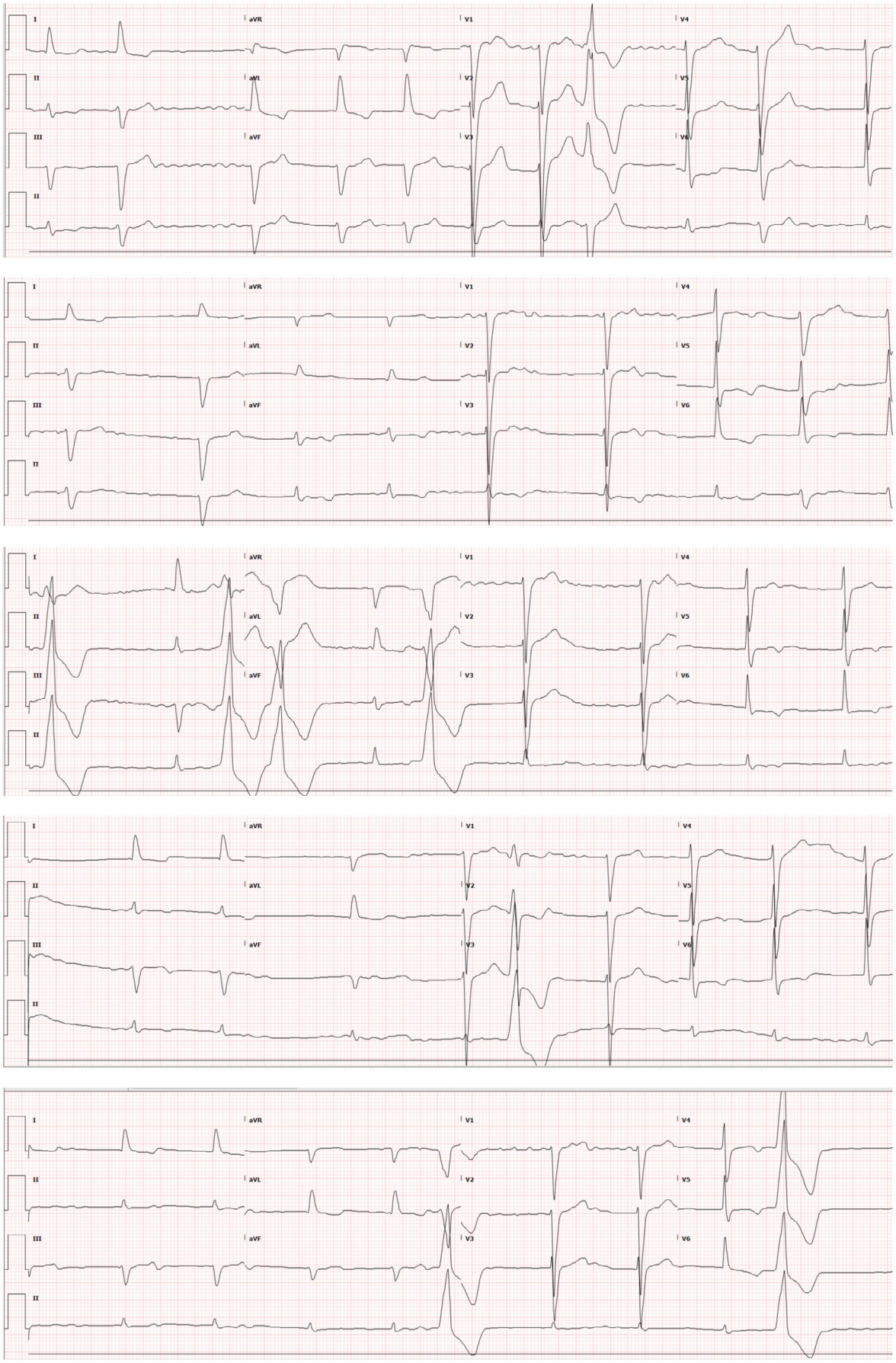
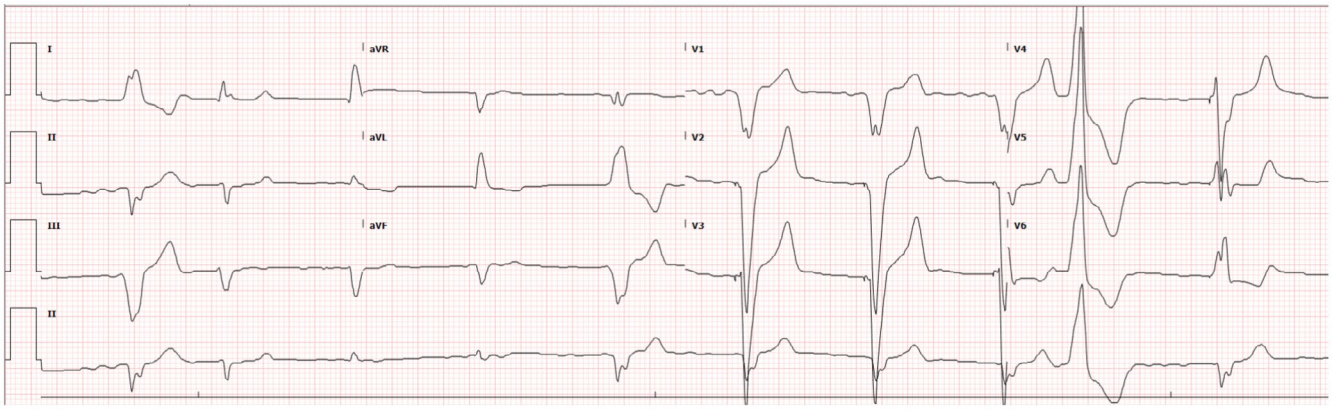
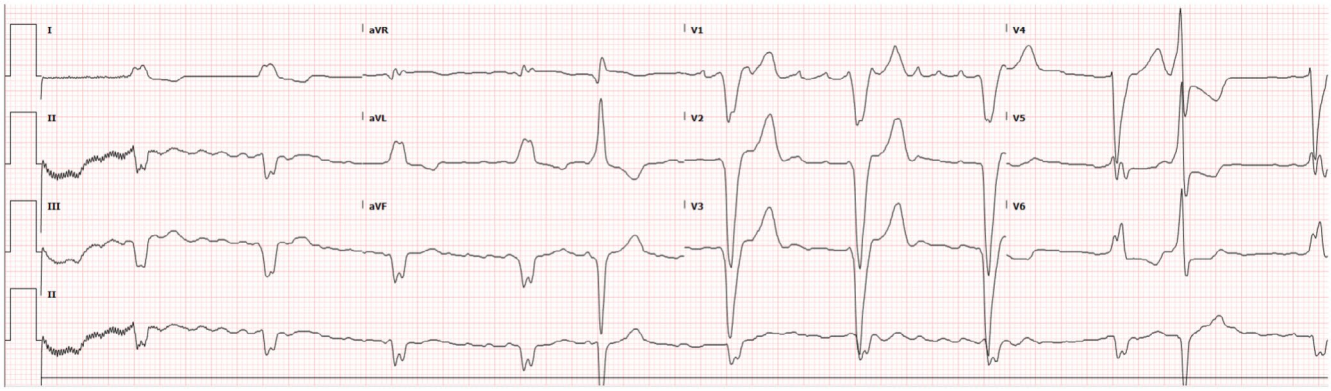


FIGURE 2 | 12 lead sequential ECGs showing atrial fibrillation with varying QTc of 458–506 ms. Repeated premature ventricular complexes seen as coinciding with an R on T phenomenon giving rise to the polymorphic ventricular tachycardia (final image).





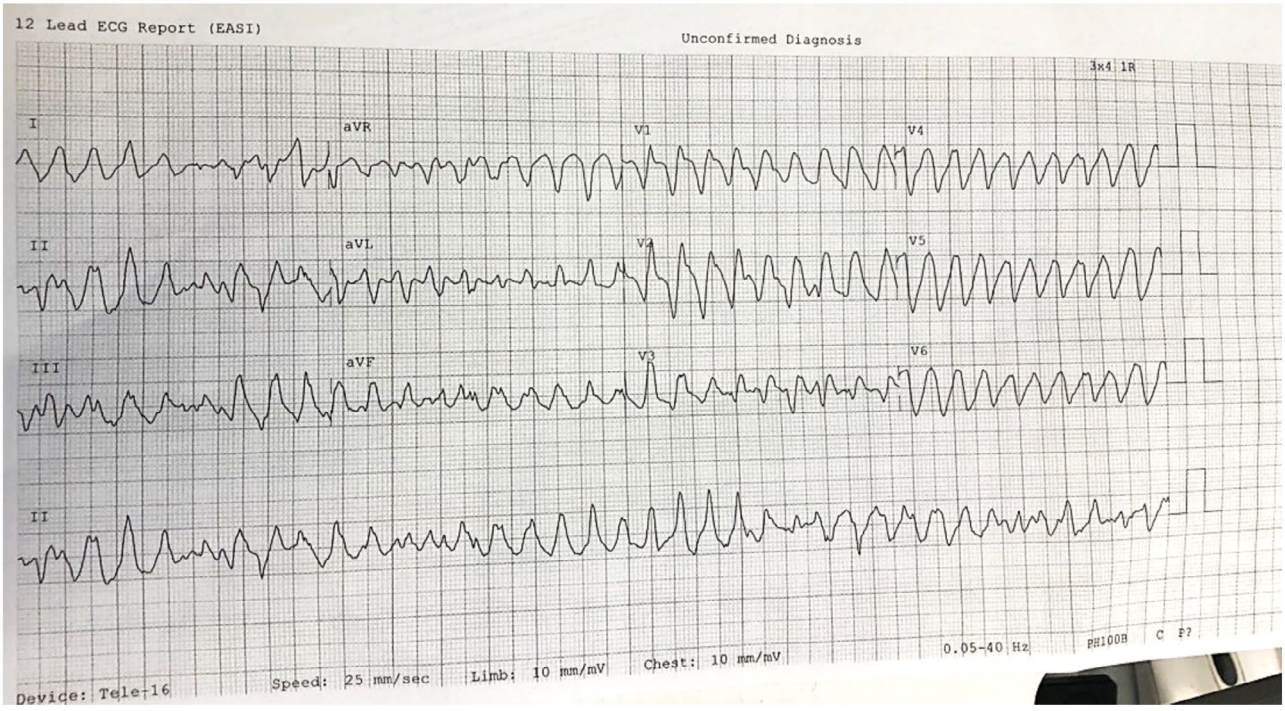


FIGURE 2 | (Continued)

not exclude LQTS in patients with undeniable phenotypes present [6, 7, 10, 11].

At present, mutations have been identified in 17 genes, with LQTS Type 1, LQTS Type 2, and LQTS Type 3 genotypes being the commonest, accounting for 95% of all genotype-positive LQTS and approximately 75% of all patients with LQTS [4, 6, 11]. The clinical genome resource has, however, carried out an analysis using metrics to derive seven genes with strong genetic evidence for LQTS, as these all encode ion channels in cardiac myocytes involved in the repolarization phase [12]. A mutational analysis study conducted for common LQTS genes detected that

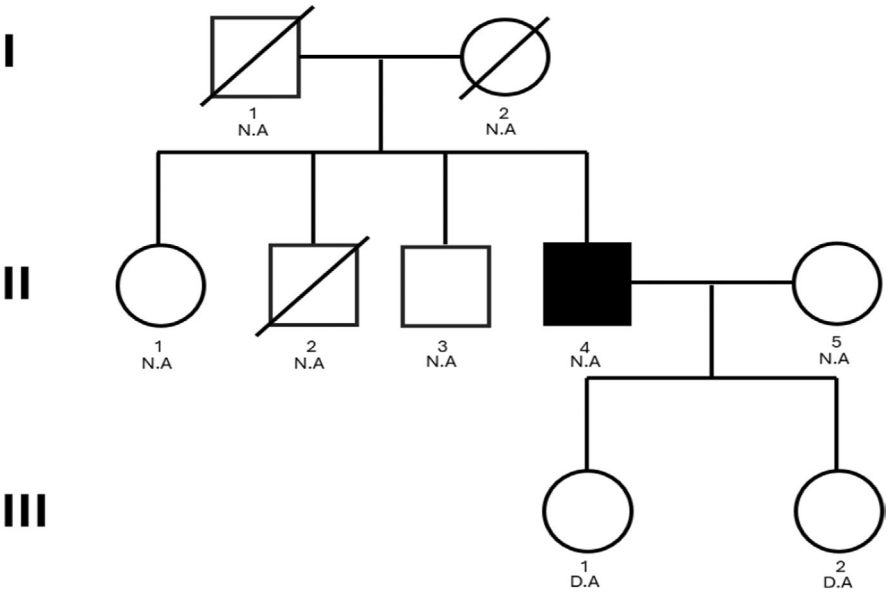


FIGURE 3 | Family pedigree. The solid black filled box indicates the affected individual. Symbol "N.A" (not analyzed) indicate individuals with unknown genotype or phenotype. Symbol "D.A" (decline analysis) indicate individuals that could be at risk but declined testing. I.1: Deceased in 70s from cardiac event. I.2: Death in 90s from natural causes. II.1: Atrial septal defect, no surgical closure required. II.2: Deceased at 58 years from SCD while having meal. II.3: Out of hospital cardiac arrest at 45 years, required implantable of implantable cardiac defibrillator (ICD) subsequently, given diagnosis of cardiomyopathy with QTS, no genetic testing. II.5: No cardiac events of note.

TABLE 2 | Cardiac panels and respective genes tested.

Cardiac Arrhythmia Gene Panel	AKAP9, ALG10, ANK2, CACNA1C, CALM1; CALM2, CALM, CASQ2, CAV3, HCN4, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, RYR2, SCN48, SCNSA, SNTA1, TECRL, TRDN
Cardiac Structural Gene Panel	ABCC9, ACTC1, ACTN2, ALPK, BAG, CACNA1C, CRP3, DES, DMD, DSC2, DSG2, DSP, EMD, FHL1, FHOD3, FLNC, GLA, HCN4, JPH2, JUP, LAMP2, LDB3, LMNA, MYBPC, MYH6, MYH7, MYL2, MYL3, NEXN, NKX2-5, PKP2, PLN, PROM 16, PRKAG2, PTPN11, RAF1, RIT1, RBM20, RYR2, SCNSA, TAFAZZIN, TCAP, TMEM43, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TTN, TTR, VCL

missense mutations were the commonest at 72%; this is followed by frameshift mutations at 10%, in-frame deletions, nonsense and splice-site mutations each spanning approximately 5% [13].

Typically, the QTc is largely determined by the duration of the ventricular action potential, which depends on a sequence of ion channel activity, the influx and efflux of ions causing relative depolarization and repolarization [3, 4]. In LQTS, these ion channels become affected by genetic variations either in the ion channels themselves, accessory subunits, or upstream/downstream proteins that modulate ion channel functions, causing the prolonged QTc and the predisposition to SCD [4, 6]. The genotype–phenotype relationships for the three most common subtypes have been well described. In brief, LQTS Type 1 and LQTS Type 2 are based on the loss-of-function of potassium channel genes KCNQ1 and KCNH2, respectively. While LQTS Type 3 is based on a gain-of-function of inward sodium channel gene SCN5A [4, 6].

A consensus from the Heart Rhythm Society, European Heart Rhythm Association, and Asian Pacific Heart Rhythm Society has been laid out for the clinical approach toward diagnosing LQTS. The first step would be assessing the clinical presentation of a patient through thorough history taking. This would include past medical history, family history, and collateral history. The basic workup of bloods, ECGs, and relevant cardiac imaging is also crucial. Next, causes of acquired LQTS need to be ruled out through thorough medication reviews, electrolyte optimization, and reviewing necessary cardiac imaging. Once ruled out, the QTc can now be formally calculated using specific formulae, such as Bazett, Framingham, and the Hodges formulae, for completion of the Schwartz score [7]. The Schwartz score corresponds to the probability of LQTS and guides the next step. A Schwartz score ≤ 1.0 would have a low probability of LQTS. A Schwartz score of 1.5–3.0 would mean an intermediate probability, while a score ≥ 3.5 would be a high probability [3, 4, 6]. The current consensus suggests that if the Schwartz score is within 1.5–3.0, then a provocative testing should be undertaken to assess QTc under strenuous settings. Whereby a Schwartz score of ≥ 3.5 should score one a genetic testing. The exception to the use of the Schwartz score would be a confirmed QTc of ≥ 500 msec on repeated ECGs after ruling out acquired causes—a genetic testing is recommended in the first instance for such groups [6].

Once diagnosed with LQTS, the focus of management is to identify those at high risk for cardiac events. The evaluation of the QTc and thorough history incorporated within the Schwartz score contributes to this. An alternative to this is the 1–2–3-LQTS-Risk, an online calculator designed specifically

for LQTS Type 1 to 3, currently validated for predicting 5-year life-threatening cardiac events [7, 14] In certain settings, a team of genetic specialists may often be beneficial for counseling of family members of LQTS patients to aid medical and personal decision making [3, 7]. For genotype-negative individuals with highly suggestive family history and clinical status, a management strategy should be undertaken in a shared decision between the patient and treating clinician—with focus on risks rather than mutation-specific outcomes [8, 15].

Beta-blockers are recommended for all asymptomatic LQTS individuals with pathogenic variants, even with a normal QTc interval. An ICD is generally not recommended for asymptomatic patients who have not tried beta-blockers but may be considered for those with very high risk, such as having multiple pathogenic variants, though a family history of LQTS-related SCD alone does not warrant an ICD [3, 4, 7].

Nearly 1 in 4 symptomatic patients still experience at least one nonfatal cardiac event [16]. Hence, symptomatic LQTS patients should aim for complete symptom control with beta-blockers, which are the primary treatment, and an ICD may be needed for those with cardiac arrest or beta-blocker –resistant symptoms. For high-risk individuals who cannot use an ICD or tolerate beta-blockers, left cardiac sympathetic denervation (LCSD) is recommended, while sodium channel blockers may be used for specific genetic variants. Ensuring compliance with beta-blocker therapy is crucial for effective management [3, 4, 6, 7].

The current stance of genetic testing in LQTS is that it offers very little to no incremental information from testing. With a quarter of LQTS cases remaining genotype-negative, much of the disease—such as gene interactions and epigenetic factors—needs further study. A detailed family history can help assess the pretest probability for genetic testing, which is currently recommended for individuals with a positive family history and a known mutation, and patients with a high clinical likelihood of LQTS or QTc prolongation without symptoms [7, 8, 10]. However, multiple a priori arguments have been put forth that because the inherited impairment in cardiac repolarization is evident through clinical criteria for LQTS, genetic testing may again offer little additional benefit compared to a thorough family history and clinical evaluation [8, 15, 17].

The success rate for genetic testing of LQTS is proportionate to the clinical phenotype, that is, more severe symptoms have a higher likelihood of detecting an LQTS mutation [10, 18]. The yield for genetic testing is approximately 58%–83% for those with high clinical probability solely off their Schwartz score, indicating that a significant number of LQTS patients would still remain without identified mutations, much like this case report [10, 18]. A false negative rate of 25% attributable to mutation detection failures poses a large risk of misclassification and thus management [17, 18].

When it pertains to the testing of relatives or family members of LQTS patients, those with a history of SCD or genotype-positive LQTS are more likely to participate in screening. In contrast, those related to a genotype-negative case are less likely to participate in screening. Despite this, the effectiveness in identifying at-risk individuals is still largely similar across both genotype-positive and genotype-negative individuals [10, 11].

Significant challenges in genetic testing remain for LQTS. Gene testing for LQTS often encounters background noise from nondisease-related genetic variants, with identifying missense variants being more common in people with LQTS than in healthy controls [15, 17]. This suggests that current genetic databases used as test panels may be contaminated with benign variants mistaken for harmful ones. The complexity associated with the molecular structure of channel proteins involved in LQTS may cause known or unknown variants to interact in ways not fully understood [1, 8]. This makes risk predictions and predictions of impact in genotype–phenotype correlations extremely challenging. Even in LQTS, a well-studied genetic heart condition, many past gene-disease associations are now seen as questionable or based on limited evidence. This underscores the need for updating and curating genetic and disease data to enhance clinical care and support future research and precision medicine efforts [12].

Currently, vectorcardiographic tools are being developed to enhance the classification of repolarization beyond just the QT interval duration, with detailed analysis of the QT response in early infancy potentially providing new insights. Additionally, next-generation sequencing is revolutionizing genotyping by enabling comprehensive analysis of not only primary LQTS genes but also other potential modifiers and mutations [7, 8, 17].

7 | Conclusion

This case provides an important lesson that despite being a heavily researched cardiovascular disease, there is plenty left unknown about LQTS, especially in the genotype-negative phenotype-positive populations. One must remain vigilant in assessing risk, as risk does not remain static over time and could be modified by several different factors that can occur throughout life. The importance of understanding the essentials of LQTS diagnosis and management is critical in minimizing unnecessary fatal cardiac events.

Author Contributions

Clement Tan: conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing – original draft, writing – review and editing. **Vaikunthan Thanabalasingam:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, writing – original draft, writing – review and editing. **Chaminda Sella Kapu:** formal analysis, project administration, supervision, writing – original draft, writing – review and editing. **Zhihua Zhang:** supervision, writing – review and editing.

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Ethics Statement

This case report was conducted and written in accordance with the Townsville Hospital and Health Service Human Research Ethics Committee EX/2024/QTHS/111425. No institutional approval was required for the publishing of this case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

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