Identification of a *TNNT2*-related cardiac disorder following investigations for causes of a sudden cardiac arrest in a patient with a clinical diagnosis of probable long QT

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1. Introduction

Sudden cardiac arrest (SCA) in young and clinically idiopathic individuals are often caused by concealed inherited cardiac conditions[1].
When the genetic cause is identified, this enables offering pre-symptomatic genetic testing to relatives and potential targeted treatment to SCA survivors. When SCA survivors present a clinical phenotype which can explain the SCA, testing has been generally guided by this phenotype[1]. However, a genetic diagnosis is often unsuccessful.
The proband here is a 39-year-old woman, who survived a sudden cardiac arrest (SCA) at age 28. She had an ICD implanted following a diagnosis of congenital LQT (long QT). She started nadolol, but stopped this 4 years later. She has not required any ICD therapy.

2. Methods

An earlier 5-gene LQT panel had not identified any pathogenic variants. Wales's current practice is to offer testing for a 51-gene molecular autopsy panel to VF arrest survivors and post-mortem cases where genetic testing is appropriate, even if there is a phenotype identified. It includes a 10-gene LQT panel. All such cases have an MDT discussion, involving the Cardiology and Clinical Genetics departments, and appropriate genetic counselling.

3. Results

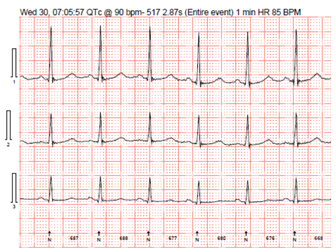
Molecular autopsy panel testing for this patient showed a pathogenic *TNNT2* variant. Pathogenic *TNNT2* variants are mostly associate with autosomal dominant cardiomyopathies[2,3], though arrhythmic events can be the presenting feature [3,4]. Age of onset can range from childhood to adult[3,5].

pathogenic *TNNT2* variant
NM_001001430.2:c.517C>T
p.(Arg173Trp)

Result prompted clinical review

- Echocardiogram showed moderately reduced left ventricular systolic function, EF (ejection fraction) ~40%
- Holter monitoring showed QTc of 458 ms at 57 bpm, 474 ms at 75 bpm and 515 ms at 90 bpm.
- Abnormal T-wave morphology following ventricular escape beats

Patient has both signs of dilated cardiomyopathy (DCM) and LQT phenotype



QT = 420ms

QTc (Bazett's) = 509ms

Figure 2. Proband's Holter monitoring – ECG sections

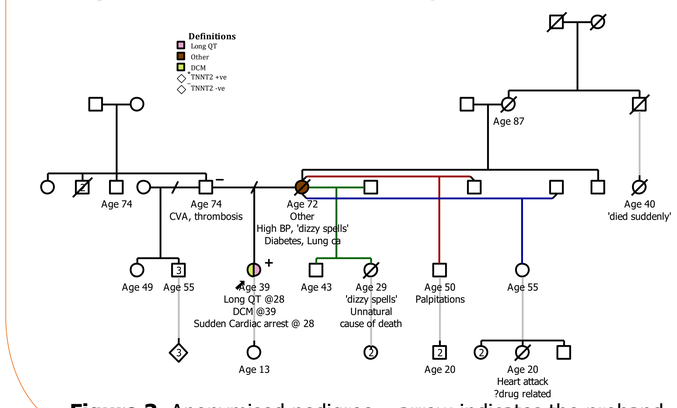
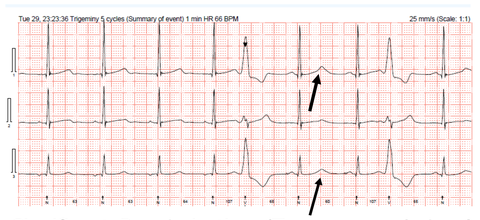


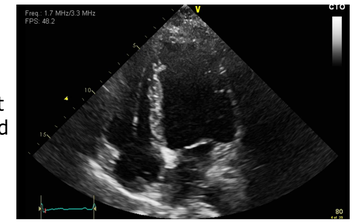
Figure 3. Anonymised pedigree – arrow indicates the proband



Significant Repolarisation (T wave morphology) changes caused by post VPB pause

Pre-symptomatic Testing (PST) for relatives:

- Proband's father does not have the pathogenic *TNNT2* gene variant.
- Ongoing arrangements for testing a tissue sample from the proband's mother
- Proband's daughter on waiting list to be seen in Genetics



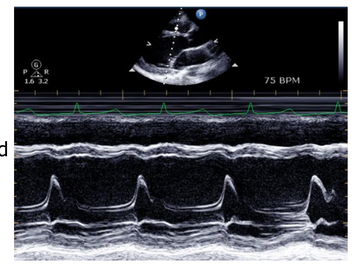


Figure 1. Proband's echocardiogram showing an apical 4-chamber view. It shows the ICD lead in the right ventricle. The LV can be seen to be mildly dilated.

M-mode demonstrating left ventricular enlargement and reduced systolic function (estimated EF 40%)
Images kindly provided by Dr Zaidi and Dr Wilson (Consultant Cardiologists).

4. Discussion and Conclusions

The *TNNT2* variant does not explain the patient's LQT, but is a reason for her SCA. It has enabled us to offer predictive testing for the *TNNT2* variant as well as LQT screening to all first-degree relatives. Though unexpected, this finding is not unique. Research studies have shown that survivors of SCA, who did not show any diagnostic cardiac structural changes, can often have pathogenic variants identified in cardiomyopathy genes [1].
This result demonstrates the value of a wider molecular autopsy panel following a cardiac arrest, even when there is an apparent phenotype. We suggest that restricted phenotype-guided genetic testing in SCA, as initially occurred in this case, may be overly limiting.

5. Refences

1) Isbister *et al* (2021) "Concealed Cardiomyopathy" as a Cause of Previously Unexplained Sudden Cardiac Arrest. International Journal of Cardiology. Feb 1;324:96-101.
2) Watkins *et al.* (1995) Mutations in the Genes for Cardiac Troponin T and *a* –Tropomyosin in Hypertrophic Cardiomyopathy. The New England Journal of Medicine. 332(16): 1058-1064
3) Campbell et al. (2013) Whole Exome Sequencing Identifies a Troponin T Mutation Hot Spot in Familial Dilated Cardiomyopathy. PLoS ONE 8(10): e78104.
4) Ramchand *et al* (2020) Prospective Evaluation of the Utility of Whole Exome Sequencing in Dilated Cardiomyopathy J Am Heart Assoc 9:e013346.
5) Quiat *et al* (2020) Retrospective Analysis of Clinical Genetic Testing in Pediatric Primary Dilated Cardiomyopathy: Testing Outcomes and the Effects of Variant Reclassification J Am Heart Assoc 9:e016195.