Detection of sudden death syndromes in New Zealand

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ABSTRACT

AIM: To investigate regional variations in the detection of sudden death syndromes across New Zealand by assessing registrations in the national Cardiac Inherited Diseases Registry New Zealand (CIDRNZ).

METHODS: The CIDRNZ has been a national entity since 2009, with a hub in Auckland and locally funded regional coordinators (Midland, Central) linked with multidisciplinary cardiac genetic teams. Registration is consent-based and voluntary, and involves the collection of clinical/genetic information and permits genetic testing and research. Registry data were extracted from the CIDRNZ in October 2015 and results are expressed as registrations per 100,000 people by district health board area.

RESULTS: The CIDRNZ has 1,940 registrants from 712 families, 46% of whom are definitely or probably affected by cardiac inherited disease. There are clear regional differences in registration frequencies between regions and between the North and South Islands, both for overall registrations (56/100,000 and 14/100,000, respectively; $p<0.001$) and for long QT syndrome registrations (15/100,000 and 6/100,000, respectively; $p<0.001$). Regions with local coordinators have the highest number of registrations.

CONCLUSION: The detection of sudden death syndromes in New Zealand through a cardiac genetic registry is possible but much work is needed to improve regional variation in the detection/reporting of these conditions across the country.

The sudden cardiac death (SCD) of a young person is a devastating event, with the incidence estimated at between one to seven deaths per 100,000 people per year in in 1–35 year olds.[1–3] This equates to about 150 deaths per year in New Zealand. Many studies have shown that 20–50% of SCD in 1–35 year olds are due to inherited heart conditions such as cardiomyopathies and ion channelopathies.[4–6] Since death is largely preventable in these conditions through avoidance of triggers, regular beta blockers, left cardiac sympathectomy or implantable cardiac defibrillators, there is an imperative to find and protect those at risk.[7]

Community-based electrocardiogram (ECG) screening programs for inherited heart conditions are controversial, mostly due to the poor sensitivity and specificity of the ECG.[8,9] However, there is now abundant evidence that pre-symptomatic individuals can be identified through cascade clinical cardiac and genetic screening of relatives of affected individuals, including the investigation and management of families of young sudden cardiac death victims.[4–6,10]

Since 2009, New Zealand has had a national cardiac inherited disease registry that coordinates the cardiac and genetic investigation of sudden unexplained deaths with the national coronial and forensic services, and undertakes family cascade screening of people diagnosed with inherited heart conditions and in those resuscitated in the community for which no cause can be identified.[10] The effectiveness of the registry is proven by the high level of detection of individuals with long QT syndrome in Auckland City where the registry is based and was initially established; approximately one in 4,000 have already been identified, with an anticipated population prevalence of one in 2,000.[10,11]

The national registry coordinator is based in Auckland and works predominantly across Auckland, Waitemata, Counties Manukau and Northland district health boards. National funding for the registry has been sought from the Ministry of Health on a number of occasions over the last ten years but has been denied. Regional coordinators, with local funding, were appointed

in the Midland area (Waikato, Taranaki, Bay of Plenty, Lakes District and Tairawhiti district health boards) and Central (Capital and Coast, Hutt Valley, Hawke's Bay, MidCentral, Wairarapa, Whanganui and Nelson Marlborough district health boards) in 2012 after initial charitable support from Cure Kids. There is no registry coordinator based in the South Island, though referrals including sudden deaths in the South Island are handled through the national office.

The aim of the study reported here was to investigate regional variations in the detection of sudden death syndromes across New Zealand by assessing registrations in the national cardiac inherited disease registry across district health board areas, and to study the detected prevalence of one particular cardiac inherited disease, long QT syndrome, across the country.

Methods

The national registry is known as the Cardiac Inherited Diseases Registry New Zealand (CIDRNZ), which is maintained by the Cardiac Inherited Diseases Group New Zealand. Demographic, clinical and genetic data are stored on a secure web-based database, from which the data for these analyses was extracted on October 1st 2015. Population data of each district health board area was obtained from Statistics New Zealand.[12] Results are expressed as registrations per 100,000 people by district health board area, based on the residential address given at the time of enrolment in the registry.

Registration with the cardiac inherited disease registry

Registration is consent-based and voluntary. When giving consent, each patient, guardian or next-of-kin (for deceased probands), permits the maintenance of clinical and genetic information, genetic testing where appropriate and research into their condition. The information sheets and consent forms have been approved by the multi-regional ethics committee (AKX/02/00/107/AM3).

Referrals to the Cardiac Inherited Diseases Group are received from paediatric/cardiology services or a pathologist in the case of sudden death, and the registry coordinator gathers the relevant clinical information needed for a multidisciplinary case discussion (Figure 1). Each registry coordinator is linked to a cardiac genetic team, with specialist cardiology and clinical genetics.[13] Consent is usually obtained *via* the registry coordinator or by the lead clinician. Once an affected proband has been identified, most cascade testing of family members is arranged *via* regional cardiac genetic clinics, with joint counselling by specialist cardiologists and genetic consultants or associates.

There is also a national hub based in Auckland, which includes additional specialist molecular genetics, cardiac electrophysiology, paediatric cardiology and pathology representation. This multidisciplinary team meets fortnightly with the regional coordinators. The whole national team meets by video conference bi-monthly.

Prior to the national registry being established in 2009, a local registry was established in the Northern region in 2006 and these patients were incorporated into the national registry upon its formation.

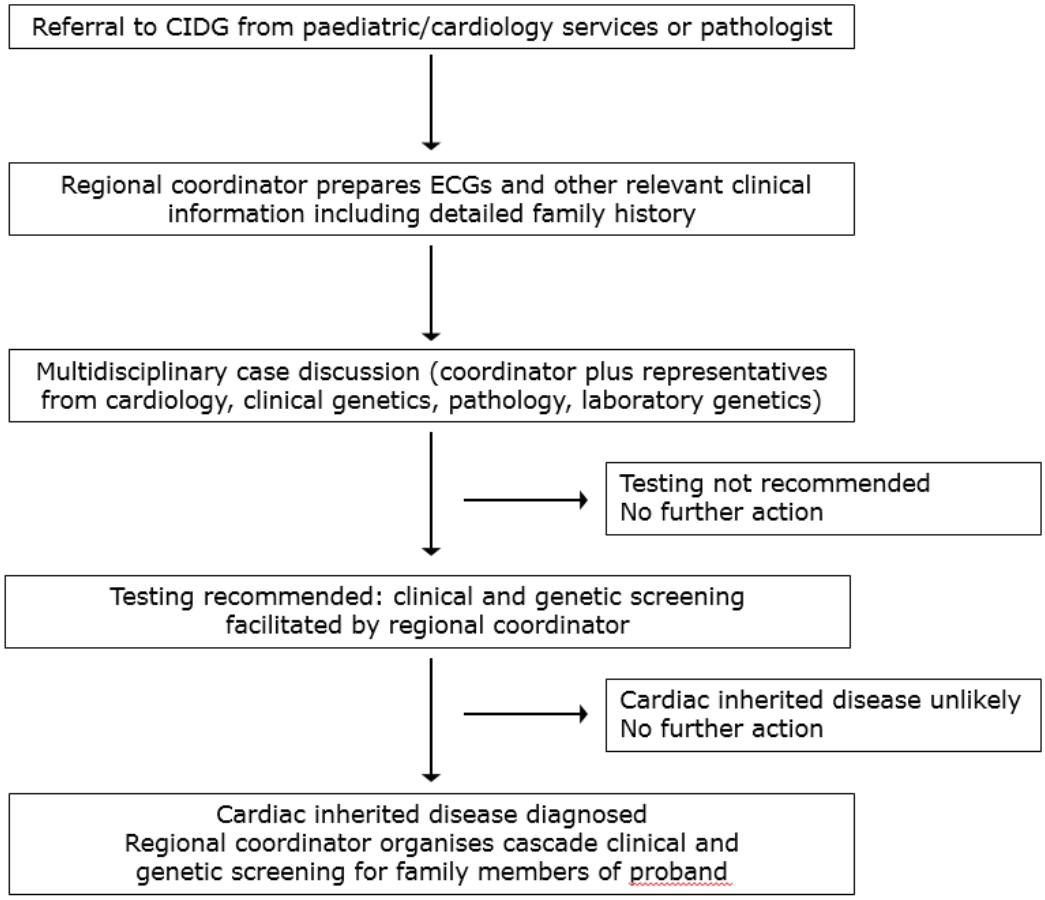
Initial funding of the cardiac inherited disease registry

Cure Kids provided the initial funding for a prospective evaluation of long QT syndrome molecular autopsy for sudden unexplained death in 2006. The diagnostic success of this program (30% when including family cardiac testing) led, in 2008, to the Ministry of Justice funding ongoing testing for such cases through the then Chief Coroner for New Zealand (Judge Neil Maclean). The National Forensic Pathology Service and the Cardiac Inherited Diseases Group manage this national budget for molecular autopsy of sudden unexplained death in young people.

Results

There were 1,940 registrants in the national cardiac inherited disease registry from 712 families (Table 1) since 2006 when the registry was established. These registrants originate from 133 sudden death investigations, 290 families with a proband with a cardiac ion channelopathy (238 Long QT syndrome, 36 Brugada syndrome, 13 catecholaminergic polymorphic ventricular tachycardia, three progressive cardiac conduction disorder), 257 families with

Figure 1: Process for referral and investigation through the Cardiac Inherited Diseases Group for probands with suspect inherited cardiac disease.



a cardiomyopathy (202 hypertrophic cardiomyopathy, 28 arrhythmogenic right ventricular cardiomyopathy, 27 dilated cardiomyopathy) and 32 resuscitated sudden death investigations. Forty-six percent of registrants were classified as being definitely or probably clinically affected by an inherited cardiac disease, regardless of genetic testing status. 1,206 (62%) registrants underwent genetic screening, with a disease-causing mutation confirmed in 40% of those tested.

The distribution of registrations per 100,000 residents in each district health board area varies widely throughout the country, ranging from 0/100,000 in West Coast to 104/100,000 in Auckland (Figure 2). Notably, the average number of registrations for the North Island and South Island differ significantly (56/100,000 and 14/100,000, respectively; $p<0.001$).

Registrations have markedly increased in the past 2.5 years in regions with coordinators in place. The Midland and Central coordinators were employed late 2012, and a coordinator has been in place in the Northern region since 2006. From January 2013 until the current data from October 2015, in the Midland region, the numbers of registered patients increased by 28/100,000 resident population (from 31/100,000 to 59/100,000). In the Central area, registrations increased 12/100,000 (16/100,000 to 28/100,000), and in the Northern region, the registrations increased 24/100,000 (43/100,000 to 67/100,000). In the remainder of the South Island, where there has been no registry coordinator, registrations have increased only 6/100,000 (7/100,000 to 13/100,000).

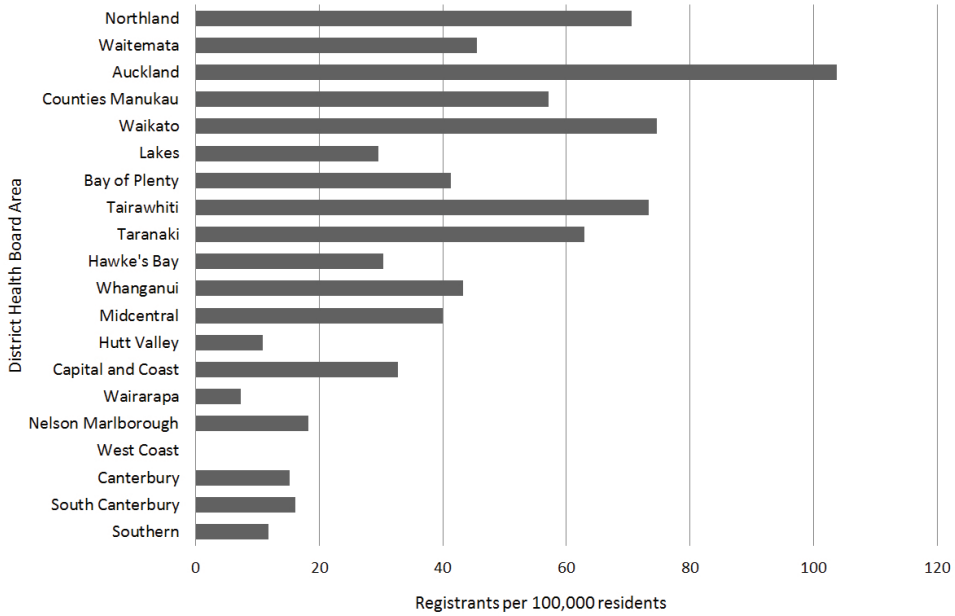
Long QT syndrome is the inherited cardiac disease with the highest number of registrants in the New Zealand registry (41%). The numbers of registrants with clinically diagnosed long QT syndrome varies widely between different district health board areas, and again there is significant disparity in the number of registered patients between the North and South Islands (15/100,000 and 6/100,000, respectively; $p<0.001$) (Figure 3).

Table 1: Demographic and clinical characteristics of patients enrolled in the national Cardiac Inherited Diseases Registry New Zealand since 2006.

	Total n = 1940
Male sex, n (%)	959 (49)
Ethnicity, n (%)	
NZ European	1050 (54)
Māori	277 (14)
Pacific Islander	106 (5)
Asian	40 (2)
Indian	29 (1)
Other	17 (1)
Not stated or Unknown	421 (22)
Probands, n (%)	712 (37)
Age, med (IQR)	36 (19–54)
Deceased, n (%)	206 (11)
Presenting condition, n (n probands)*	
Long QT syndrome	795 (238 probands)
Hypertrophic cardiomyopathy	436 (202 probands)
Sudden cardiac death	364 (133 probands)
Resuscitated SCD/syncope	65 (32 probands)
Dilated cardiomyopathy	104 (27 probands)
Brugada syndrome	52 (36 probands)
Catecholaminergic polymorphic ventricular tachycardia	35 (13 probands)
Arrhythmogenic right ventricular cardiomyopathy	80 (28 probands)
Progressive cardiac conduction disorder	9 (3 probands)
Clinical status, n (%)	
Definitely affected	607 (31)
Probably affected	283 (15)
Possibly affected	332 (17)
Unlikely to be/not affected	260 (13)
Clinical status undetermined++	458 (24)
Genetic status, n (%)	
Genotype positive	487 (25)
Genotype negative	293 (15)
Testing uninformative	325 (17)
Unclassified variant	101 (5)
Genetic testing not undertaken	734 (38)

NZ = New Zealand; IQR = interquartile range; SCD = sudden cardiac death.
* Classification is according to their categorisation at presentation.
++ This includes victims of SCD and their families where no inherited heart disease diagnosis has yet been made.

Figure 2: New Zealand Cardiac Inherited Disease Registry registrants per 100,000 residents by district health board area.



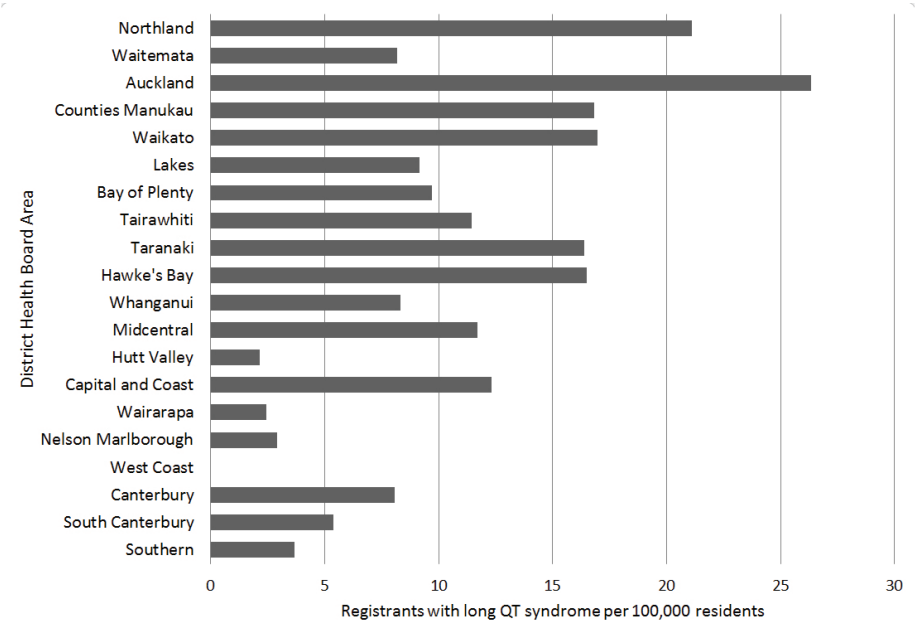
A key measure of the success of a screening program is the number of family members being investigated with genetic testing for a genetic mutation of proven pathogenicity (cascade genetic tests), allowing pre-symptomatic treatment to reduce the risk of sudden death. The numbers of cascade genetic tests performed for long QT syndrome per 100,000 residents by district health board area are shown in Figure 4. These data are dependent on whether a pathogenic mutation has been identified in a family, and the number of family members who are available and have consented for testing. Nevertheless, the variation across regions is clear.

Discussion

These data demonstrate the success of the registry in the identification of individuals at risk of inherited heart conditions across New Zealand. There is a clear difference between regions in the numbers of individuals registered with the national cardiac inherited disease registry.

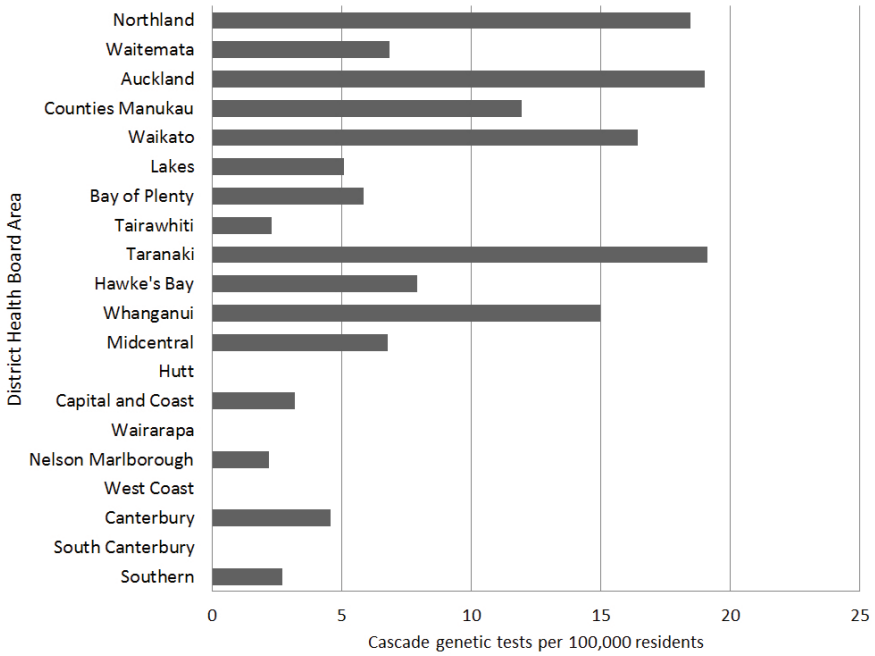
A limitation of the data presented here is that it only includes people registered with CIDRNZ and does not represent every case of inherited heart disease, nor every patient who has undergone a cardiac genetic test in New Zealand. The Northern hub of Genetic Health Service New Zealand (GHSNZ), based

Figure 3: Clinically diagnosed long QT syndrome registrants per 100,000 residents by district health board area.



NZMJ 18 November 2016, Vol 129 No 1445
ISSN 1175-8716

Figure 4: Cascade genetic tests carried out for families with a definitive genetic diagnosis of long QT syndrome per 100,000 residents.



in Auckland, performs all of its tests for inherited heart disease through CIDRNZ (this does not include Marfan syndrome or other dysmorphic syndromes such as Noonan syndrome, nor familial hypercholesterolaemia). The Central and South Island hubs of GHSNZ, while performing some testing through CIDRNZ, also carry out cardiac genetic assessment and testing outside of the registry; this may relate to ease-of-access to the collaborative service through the regional coordinator. Neither hub has an additional database which enables this additional genetic testing or the diagnostic rate for cardiac conditions to be collated efficiently at this stage. The South Island hub of GHSNZ, as the most recently established hub of GHSNZ, has had a small number of referrals with cardiac inherited disease, so the data presented here is likely to be representative of the total for the region. The Central hub of GHSNZ based in Wellington has had a more active program, which started before CIDRNZ existed,[14] and manages some large long QT syndrome pedigrees. Total numbers detected may be significantly higher in that region than what is reported here. There is a possibility that management and genetic testing of families with cardiac inherited disease might also occur through district health board cardiology departments, general practice or in the private sector although genetic testing is likely to be limited by cost.

The data demonstrate that in regions with registry coordinators, the frequencies of registration and detection are higher, and the data also reflect the length of time the coordinators have been in place. Prior to the appointment of the Midland coordinator, relative proximity to the original single Auckland coordinator permitted the referral and investigation of many families, and this has accelerated following the appointment of the local coordinator. The variability within the Northern region with high rates in central Auckland is due to historical reasons (the registry began in central Auckland), and because tertiary paediatric cardiology services are located at Starship Hospital. Given it is known that death can be prevented in these conditions and that many sudden deaths or cardiac arrests occur as the first presentation of disease,[15,16] this raises the possibility that death from these conditions has been more likely in regions where registrations are fewer, particularly in the South Island. The recent agreement to fund a coordinator in the South Island is likely to increase registration and detection and reduce the likelihood of deaths from these conditions in this region.

The establishment of a regional registry coordinator, with cardiology and genetics

supervision, has a number of positive effects locally. The profile of cardiac inherited disease is raised, and local education to medical, nursing and paramedical staff leads to increased referral of appropriate cases. Obtaining a three-generation family history alone has a high diagnostic hit-rate in resuscitated sudden cardiac death, and dilated cardiomyopathy in particular.[17] A registry coordinator increases the outreach of services: specialist cardiologists and clinical geneticists may be inadequately resourced to recruit family members to the registry or to offer cascade screening. A coordinator can work with the family and tests can be organised for review by a specialised cardiac genetic team. Forensic pathologists benefit from a local team with whom they can discuss cases which might benefit from a molecular autopsy and family cardiac investigation.[18–20]

Funding for the regional coordinators must still be found from within the regions, and no additional funding is available for genetic testing; some district health boards are more reluctant than others to permit such testing, which can have high initial costs. The Ministry of Health has been resistant to requests for national funding of cardiac inherited disease services despite its own investigation in 2008 (under the National Service and Technology Review process) finding that "a national registry of inherited heart diseases is essential". On the plus side, however, we have recently been advised that from July 2016, the Ministry of Health will fund one day a week of national clinical leadership, together with full funding for a national registry coordinator and a database administrator.

New Zealand's national cardiac inherited disease registry and clinical service network was established as one of the first in the world, and such a program potentially obviates the need for controversial and expensive national ECG screening programs advocated by some European countries and Japan.[8,9] Unfortunately, published population-level international data on the investigation and detection of inherited heart disease are scarce, meaning comparison with the New Zealand rates of registration and detection is not currently possible. The data presented here show that the registry is effective in facilitating the detection of these conditions, but there is still much to be done to improve regional variation in the detection of inherited heart conditions across the country, most particularly in the South Island. The registry and its associated clinical program require further investment to permit equity of access across New Zealand.

Competing interests:
Nil.

Acknowledgements:
The Cardiac Inherited Diseases Group is generously supported by Cure Kids. The Heart Trust (Waikato and Bay of Plenty) funded CIDRNZ in the Midland region for the first two years.

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