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A Population-Based Registry of Patients With Inherited Cardiac Conditions and Resuscitated Cardiac Arrest

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ABSTRACT

BACKGROUND The relative proportion of each cardiac inherited disease (CID) causing resuscitated sudden cardiac arrest (RSCA) on a population basis is unknown.

OBJECTIVES This study describes the profile of patients with CIDs presenting with RSCA; their data were collected by the national Cardiac Inherited Diseases Registry New Zealand (CIDRNZ).

METHODS Data were collated from CIDRNZ probands presenting with RSCA (2002 to 2018).

RESULTS CID was identified in 115 (51%) of 225 RSCA cases: long QT syndrome (LQTS) (n = 48 [42%]), hypertrophic cardiomyopathy (HCM) (n = 28 [24%]), Brugada syndrome (BrS) (n = 16 [14%]), catecholaminergic polymorphic ventricular tachycardia (CPVT) (n = 9 [8%]), arrhythmogenic right ventricular cardiomyopathy (ARVC) (n = 9 [8%]), and dilated cardiomyopathy (n = 5 [4%]). Seventy-one (62%) of 115 were male. Of 725 probands from the CIDRNZ with CID, the proportion presenting with RSCA was: CPVT, 9 (53%) of 17; BrS, 16 (33%) of 49; ARVC, 9 (25%) of 36; LQTS, 48 (20%) of 238; dilated cardiomyopathy, 5 (9%) of 58; and HCM, 28 (8%) of 354. Incident activity was: normal everyday activities, 44 (40%); exercising, 33 (30%); concurrent illness, 13 (12%); sleeping, 10 (9%); drugs/medication, 9 (8%); and emotion, 2 (2%). LQTS and CPVT predominated in those <24 years of age, 30 (77%) of 39; cardiomyopathies and BrS predominated in those >24 years of age, 49 (64%) of 76. For those >40 years of age, HCM was the most common (33%) CID. A genetic diagnosis in patients with CID was made in 48 (49%) of 98 tested. Diagnosis by age range was as follows: age 1 to 14 years, 78%; age 15 to 24 years, 53%; age 25 to 39 years, 54%; and age >40 years, 26%.

CONCLUSIONS The commonest CID identified after RSCA was LQTS; the most common CID cause of RSCA for those >40 years of age was HCM. CPVT was the CID most likely to present with RSCA and HCM the least. Genetic yield decreases with age. Only one-third of RSCA cases due to CID occurred while exercising.
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Sudden cardiac death (SCD) in young people occurs most commonly during sleep or at rest. Data from Australia, New Zealand, and Denmark have shown that for those <30 years of age, most cases have nothing to find at autopsy, with 10% to 30% of these being ascribed to cardiac ion channelopathies such as long QT syndrome (LQTS). For those >30 years of age, coronary artery disease predominates (1,2). Public knowledge about basic life support, improved access to automated external defibrillators, and fast response from emergency medical services aim to decrease the occurrence of fatal outcomes, and this knowledge has led to increasing numbers resuscitated from a cardiac arrest arriving to the hospital and surviving (3,4).

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Advances in genetic testing have occurred over the same time period and have facilitated family screening for cardiac inherited disease (CID), providing a foundation for clinical and genetic registries (5,6). There is some provisional evidence from relatively small studies of the outpatient investigation of families in tertiary centers that the profile of CIDs among survivors of cardiac arrest differ from that of sudden death victims (7). Furthermore, the prevalence of identifiable CIDs is much higher (8). New Zealand is an unusually favorable place to provide a perspective on prevalence of such conditions from a population perspective, having a nationwide registry of cardiac inherited heart conditions combined with a national registry and clinical service for the investigation of young sudden death and resuscitated sudden cardiac arrest (RSCA) (9–11). New Zealand also has an advanced program aiming to improve access to advisory external defibrillators (12). Although we reported previously on cardiac genetic investigation of sudden unexplained death (13), our group has not yet reported on the profile of RSCA in our population except in the context of arrhythmogenic cardiomyopathy (14).

The goal of the current study was to describe the profile of the CIDs identified in individuals who first presented with RSCA, investigated by using a national standardized approach and referred to the national cardiac genetic registry. The aim was to study trends in diagnosis according to age and report activity or incident triggers at the time of the RSCA, and describe the relative likelihood of each case of CID to present with RSCA.

METHODS

Data were extracted from the national Cardiac Inherited Diseases Registry New Zealand (10). Data are collected prospectively for this registry, which is used for clinical service and to facilitate family screening. Patients are investigated and managed by regional services across New Zealand's National Health Service (15). The design of the study and main results are summarized in the **Central Illustration**. A nationally agreed algorithm for the investigation of RSCA (established by Heart Rhythm New Zealand and the Cardiac Inherited Diseases Group) is shown in **Figure 1**.

Patients are referred to the registry at the discretion of the managing clinical team when a CID is diagnosed or suspected, or no cause has been found after RSCA. The case is reviewed by the national multidisciplinary team, and further phenotyping, family screening, and targeted genetic testing are performed if required and appropriate. When a new proband is referred, written consent is obtained for data storage and de-identified research and publication into their condition. National ethical approval includes the publication of clinical audits such as this (Health and Disability Ethics Committees, Wellington, AKX/02/00/107/AM03), and this publication has been approved by the host institutions' research office at Auckland District Health Board. Clinical and demographic data are entered by a regional coordinator and reviewed by the senior clinical team. After centralized multidisciplinary review, a level of confidence in the putative clinical diagnosis is categorized as unlikely, possible, probable, or definite.

Diagnoses are made following international guidelines for each condition current at the time of the diagnosis or at the time of clinical review as we have previously reported (details are given in the Supplemental Methods) (14,16,17).

The registry has a high profile nationally for the investigation of such cases, with representation within the large regional hospitals (18). Because genetic testing has matured over the years of the registry's existence since 2002, consistent with international experience, there was not a single gene list used over this time (13). However, for example, every LQTS participant had at least *KCNQ1*, *KCNH2*, and *SCN5A* analyzed, and every participant with hypertrophic cardiomyopathy (HCM) had at least 8 genes analyzed (*MYH7, MYBPC3, TNNT2, TPM1, TNNI3, MYL2, MYL3,* and *ACTC*).

Data were audited on November 1, 2018. Patients were eligible when the most severe event they had experienced was RSCA, defined as requiring cardiopulmonary resuscitation (CPR), with or without

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

BrS = Brugada syndrome

CID = cardiac inherited disease

CPR = cardiopulmonary resuscitation

CPVT = catecholaminergic polymorphic ventricular tachycardia

DCM = dilated cardiomyopathy

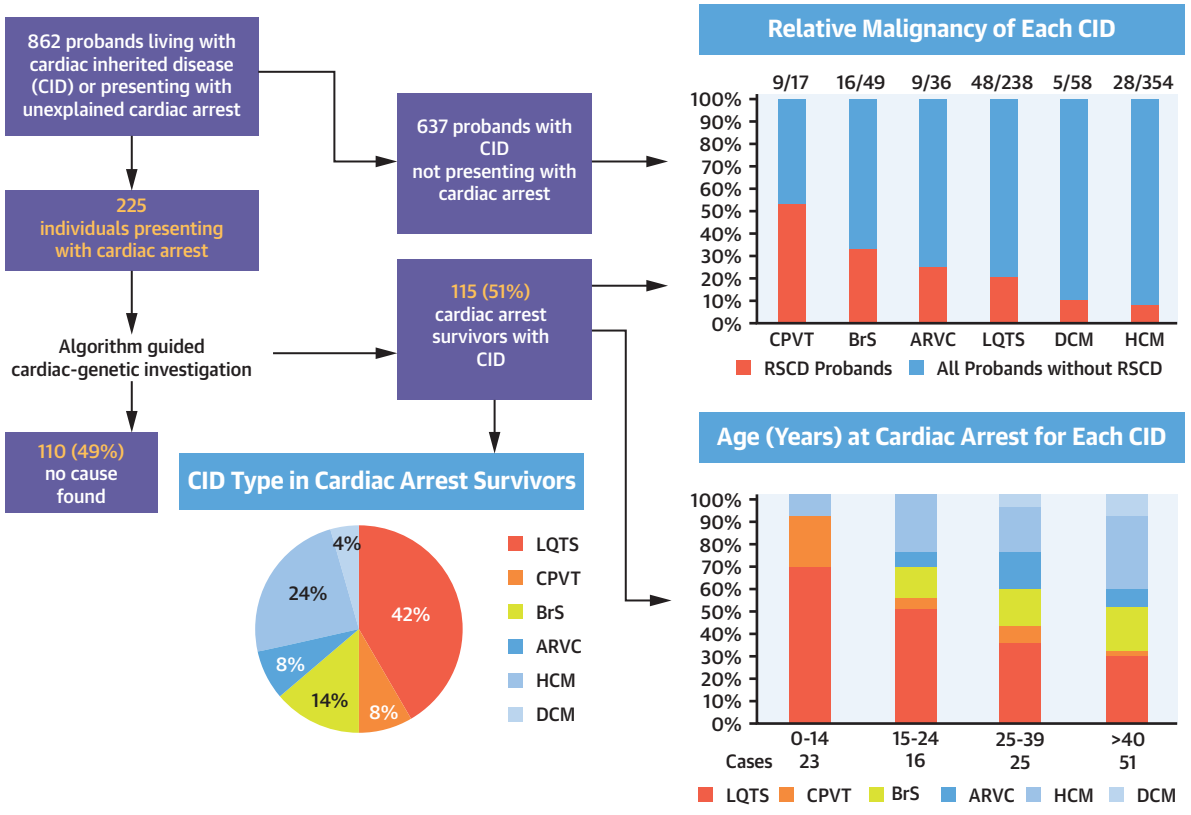
HCM = hypertrophic cardiomyopathy

LQTS = long QT syndrome

RSCA = resuscitated sudden cardiac arrest

SCD = sudden cardiac death

CENTRAL ILLUSTRATION **Summarizing the Patient Groups and the Principal Subanalyses of the Current Study**



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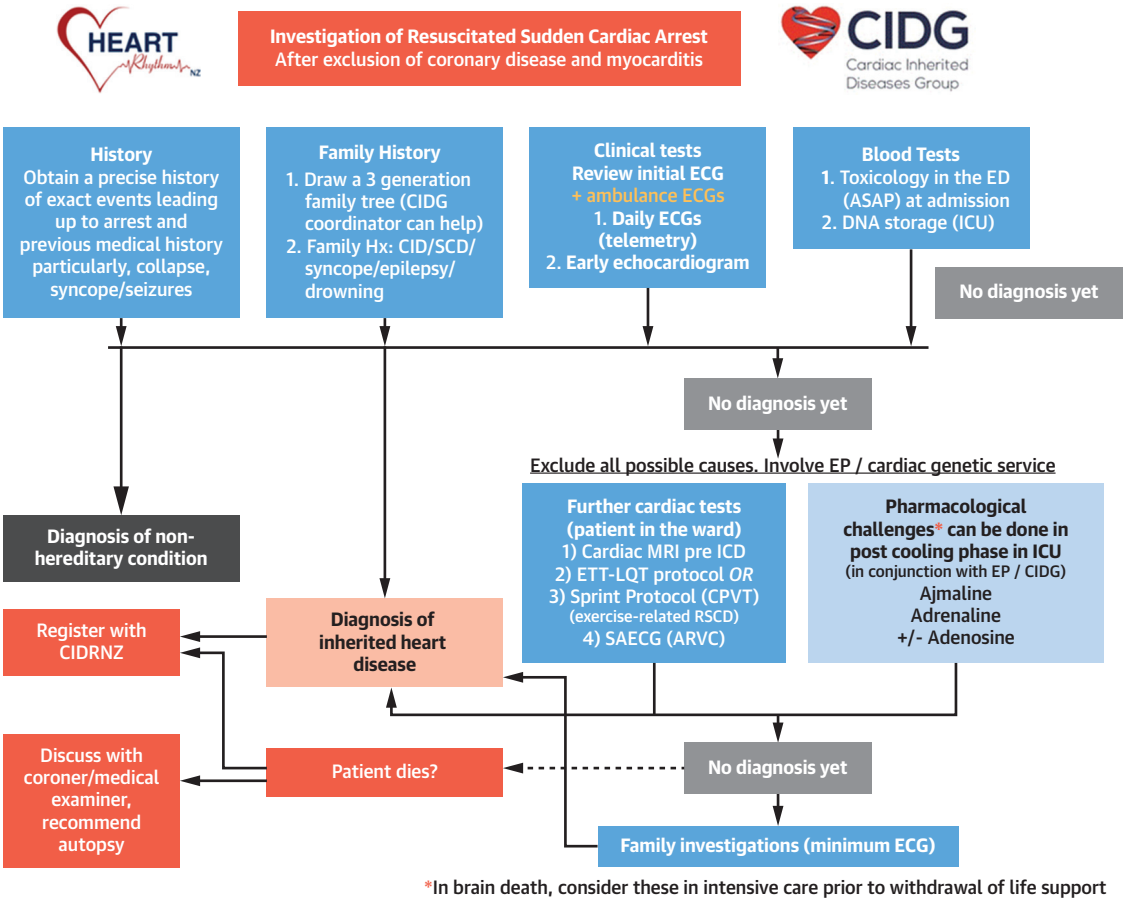
The graphic summarizes the results of this study. The participants are registrants in the Cardiac Inherited Diseases Registry New Zealand, and all participants are probands. The study focuses on the 225 patients who presented following survival of a cardiac arrest. The figure shows the spectrum of cardiac inherited disease (CID) that was ultimately identified in 115 (51% of the total) in the pie graph entitled **CID Type in Cardiac Arrest Survivors**; cardiomyopathies are given in **shades of blue** and the channelopathies in **red/orange/yellow**. The **column graph in the bottom right** shows how the type of disease identified varies by age at presentation. The **graph at the top right** indicates the relative malignancy of each condition by comparing those presenting with cardiac arrest versus 637 others in the registry who presented with less severe symptoms. ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; RSCD = resuscitated sudden cardiac death.

electrical cardioversion. To prevent bias from large family kindreds, probands only are included; that is, only those who presented first with cardiac arrest, and not family members identified through family screening. Diagnostic categories included were LQTS, Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), HCM, dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). Age, sex, and activity at the time of RSCA were collated. We divided activities into 6 categories: exercise, light activity, sleep, substance related (including medical or psychoactive), emotion/pain (including acute grief), and illness. For the purpose of this report, miscellaneous conditions such as mitral valve prolapse and sarcoid disease were excluded as cause known and nonfamilial. Where early repolarization was present, these were considered unexplained. No familial early repolarization, short QT syndrome, or ST-segment depression has been identified to-date in New Zealand.

RESULTS

A total of 225 cases of RSCA were identified, in whom 123 had a definite or probable CID diagnosis. These cases were reviewed in detail by the senior author

FIGURE 1 The New Zealand National Algorithm for the Investigation of Adults After Resuscitated Sudden Cardiac Arrest



This algorithm was designed by the Cardiac Inherited Diseases Group (CIDG) and Heart Rhythm NZ. The pediatric algorithm, from which the adult algorithm was developed, has been published previously (Skinner et al. [16]). Registration with Cardiac Inherited Diseases Registry New Zealand (CIDRNZ) is consent based, involving next of kin if the patient dies. ARVC = arrhythmogenic right ventricular cardiomyopathy; ASAP = as soon as possible; CID = cardiac inherited disease; CPVT = catecholaminergic polymorphic ventricular tachycardia; ECG = electrocardiogram; ED = emergency department; EP = cardiac electrophysiology services; ETT = exercise tolerance test; Hx = history; ICD = implantable cardioverter-defibrillator; ICU = intensive care unit; LQT = long QT; SAECG = signal-averaged electrocardiogram; SCD = sudden cardiac death.

(J.R.S.); 8 cases were downgraded according to the level of confidence in the diagnosis given the clinical follow-up since the last categorization. This left 115 cases (51% of the total), which form the basis of the current study; 49% of cases remain unexplained.

Of the 115 unrelated cases, 105 (91%) required electrical cardioversion and 10 required CPR only (9%). Distribution by disease is shown in the pie chart in the **Central Illustration**. Overall, the most common CID to present with RSCA was LQTS, representing 42% of all those with RSCA in which a CID was ultimately diagnosed (n = 115). The next most common were HCM (28 of 115 [24%]) and BrS (16 of 115 [14%]). However, when the results are expressed as a percentage of the total number of 752 probands within the registry (**Table 1**) with each condition presenting with RSCA, CPVT was the highest (9 of 17 [53%]), and HCM was the lowest (28 of 354 [8%]). Details are also provided in the **Central Illustration**.

The incidence of RSCA found to be due to a CID between 2003 and 2015 was an average of 5.7 cases per year (Supplemental Table 1). New Zealand's mean population was 4.3 million at this time (19). Supplemental Figure 1 illustrates the incidence of each condition identified in 3-year epochs after 2001. During the latter 6 years, there have been fewer cases of LQTS identified and an increase in cardiomyopathies, particularly HCM.

TABLE 1 All Probands With the 6 Conditions Indicated Within the Cardiac Inherited Diseases Registry New Zealand, With a Clinical Status of Definitely or Probably Affected

Condition	No. of Probands	Age, yrs	Age Range, yrs	Female	Male
LQTS	238	38.8 ± 19.3	0–80	159 (66.8)	79 (33.2)
CPVT	17	35.5 ± 19.9	4–67	12 (70.6)	5 (29.4)
BrS	49	49.9 ± 14.8	16–80	8 (16.3)	41 (83.7)
ARVC	36	53.8 ± 14.6	18–79	7 (19.4)	29 (80.6)
HCM	354	54.0 ± 16.9	0.1–89	131 (37)	223 (63)
DCM	58	48.9 ± 17.2	1–77	20 (34.5)	38 (65.5)
Total	752	48.1 ± 18.9	0–89	337 (44.8)	415 (55.2)

Values are n, mean ± SD, range, or n (%).
ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome.

AGE AND SEX. Across all conditions, the mean age at RSCA was 35 years (range, 1 day to 74 years). Mean age and age range of RSCA for each condition are presented in **Table 2** and are compared according to sex in Supplemental Table 2. The youngest patient had LQTS and torsade de pointes on day 1 of life, with a de novo variant in *KCNH2*. The 2 oldest patients were both 74 years of age; one had ARVC and the other HCM. Mean age was lowest in CPVT (19 years) and highest in DCM (50 years). Overall, the participants were predominantly male (n = 71 [62%]). However, there were striking differences in sex according to disease: male subjects predominated in all 3 cardiomyopathies and BrS, and female subjects predominated in LQTS and CPVT.

The **Central Illustration** and Supplemental Figure 2 describe presentation with RSCA according to disease in age groups. LQTS and CPVT dominate in the 0- to 14-year-old group, and the cardiomyopathies and BrS became progressively more important with age. HCM overtakes LQTS as the leading cause of RSCA after the age of 40 years (17 of 51 [33%]), followed by LQTS (15 of 51 [29%]) and BrS (10 of 51 [20%]).

Female subjects with RSCA due to LQTS were significantly older than male subjects ($p < 0.01$). Their mean age was 34 years (range, 0 to 64 years) versus 20 years (range, 0 to 52 years). A similar trend in CPVT (23 years [4 to 49] vs. 10 years [5 to 13]) was not statistically significant ($p = 0.23$), and there was no significant age/sex difference in HCM ($p = 0.78$). There were no female subjects with RSCA due to DCM or ARVC and only 1 of 16 with BrS.

ETHNICITY. People of European descent comprised 79 (69%) of the cases. Seventeen participants were of Māori descent (15%), followed by participants from the Pacific Islands (n = 13 [11%]), Asia (n = 4 [3%]), and India (n = 2 [2%]). These proportions broadly correlate with the ethnic composition of New Zealand.

ACTIVITY AT TIME OF RSCA. Details of the activity at time of RSCA were available in 111 cases. Forty-four (40%) were categorized as light activity, comprising everyday activities, 6 of whom were awake but resting (e.g., on the couch/bed, watching television, passenger in a car); 21 others were at home, eating, talking on the telephone, or getting ready in the morning; and 17 were performing regular activities outside the house (e.g., driving a car, at school, working, in restaurant/bar/mall, running errands).

Thirty-three RSCA events (30%) occurred during exercise, 15 with LQTS, 8 with HCM, 6 with CPVT, 2 with ARVC, and 1 each with DCM and BrS (**Figure 2**). This included 9 participants while swimming, all of whom had LQTS. Eight of these had a pathogenic variant in *KCNQ1*, and the remaining subject had a variant of uncertain significance in *SCN5A*.

The third most frequent category was illness (13 cases [12%]). Here we grouped people with viral symptoms (whether respiratory or gastrointestinal), patients affected with myocardial infarction or chest pain, a woman with sepsis during pregnancy and another in the postpartum period with fever, and 2

TABLE 2 Probands Within the Cardiac Inherited Diseases Registry New Zealand With the 6 Conditions Indicated Who Had Experienced RSCA (Participants Forming the Basis of This Report)

Condition	No. of Probands	Age, yrs	Age Range, yrs	Female	Male	CPR Only	Cardioversion
LQTS	48	28.6 ± 18.7	0–64	29 (60)	19 (40)	9	39
CPVT	9	19.0 ± 14.6	4–49	6 (67)	3 (33)		9
BrS	16	42.1 ± 15	17–68	1 (6)	15 (94)		16
ARVC	9	41.2 ± 15.6	22–74	0 (0)	9 (100)		9
HCM	28	42.5 ± 18.6	0.1–74	8 (29)	20 (71)	1	27
DCM	5	50.4 ± 11.3	38–63	0 (0)	5 (100)		5
Total	115	35.1 ± 19.1	0–74	44 (38)	71 (62)	10	105

Values are mean ± SD, range, or n (%), unless otherwise indicated.
CPR = cardiopulmonary resuscitation; RSCA = resuscitated sudden cardiac arrest; other abbreviations as in Table 1.

subjects after surgery. Seven participants in this group had LQTS, and 4 had BrS.

Ten individuals were sleeping. Four had BrS and 3 had HCM; none had a genetic diagnosis. Three had LQTS: 2 male subjects (*KCNH2* and *CACNA1C*) and 1 female subject (testing uninformative), all <1 year of age.

Nine participants (6 with LQTS) experienced RSCA while under the influence of various drugs or medications: 5 of them with prescribed medications (3 under general anesthesia) and 4 under the influence of illegal drugs or alcohol.

The final category was emotion. One patient with profound grief had LQTS (variant of uncertain significance in *KCNQ1*) and another who was acutely embarrassed in public had BrS (*SCN5A*).

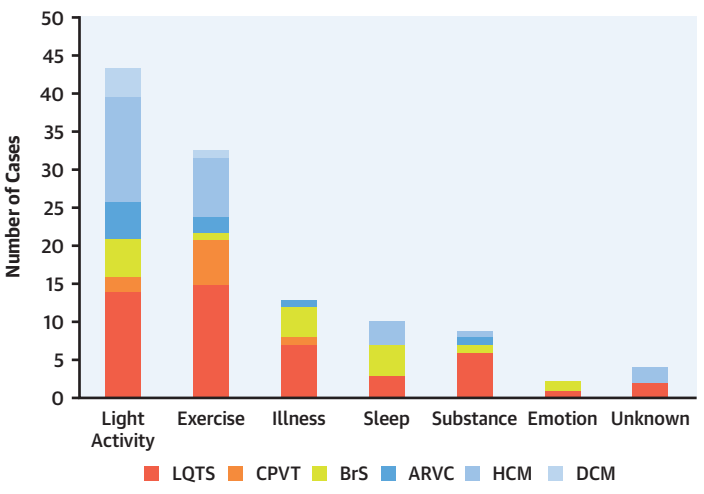
GENETIC RESULTS. Genetic analysis was performed and available for 98 participants (**Table 3**, Supplemental Table 3). There was a 49% yield with class 4 or 5 variants using the criteria described by the American College of Medical Genetics (20). Variants of uncertain significance were reported in 13%, and 38% had an uninformative test result. No genetic results were available in 17 cases for a variety of reasons, including patient unwillingness to take the test and loss of contact with the patient.

Among the 28 LQTS patients with RSCA who were class 4 and 5 variant positive, the genotypes were as follows: *KCNQ1*, 18 (64%) (12 female subjects; mean age 21 years); *KCNH2*, 5 (18%) (3 female subjects; mean age 27 years); *SCN5A*, 4 (14%) (3 male subjects; mean age 27 years); and *CACNA1C*, 1 (4%).

Testing yield overall was higher among younger participants (78% for the population up to 14 years of age) and decreased with age. For those >40 years of age, the yield was 26%. There was a statistically significant difference between groups aged 0 to 14 years and >40 years ($p = 0.0003$) (**Figure 3**). The statistical test used was analysis of variance followed by a Tukey test.

FACTORS POTENTIALLY LEADING TO MISSING THE PRESENCE OF A CID FOLLOWING RSCA. Confounding factors can potentially lead clinicians away from a hereditary cause for RSCA. Among LQTS participants, a male patient presented with RSCA at age 23 years after a drug binge, with prolonged QTc on arrival at hospital. The astute clinical team did not assume it was the drugs alone; the QTc did not completely resolve, and the patient was determined to carry a pathogenic missense variant in *KCNQ1*. A 44-year-old man with a history of coronary artery disease experienced RSCA while performing everyday activities; he was determined to have a pathogenic frameshift variant in *MYBPC3* with definite but only modest echocardiographic and electrocardiogram features of HCM. Another male subject with LQTS experienced an episode at 48 years of age after an appendectomy, with sleep apnea, type 2 diabetes, and obesity as comorbidities; he has a pathogenic variant in *KCNH2*. A woman >50 years of age experienced her first symptom as ventricular fibrillation with a myocardial infarction. Her QTc did not resolve. A *KCNQ1* pathogenic variant was found and co-segregates within the family.

FIGURE 2 Activity (Total Numbers) at the Time of Resuscitated Sudden Cardiac Arrest Among 115 Survivors With a CID



The **colors** show each type of cardiac inherited disease (CID). Cardiomyopathies are **shades of blue**, and ion channelopathies are **red/orange/yellow**. Substance indicates substance abuse, medication, or drug taken. BrS = Brugada syndrome; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; other abbreviations as in **Figure 1**.

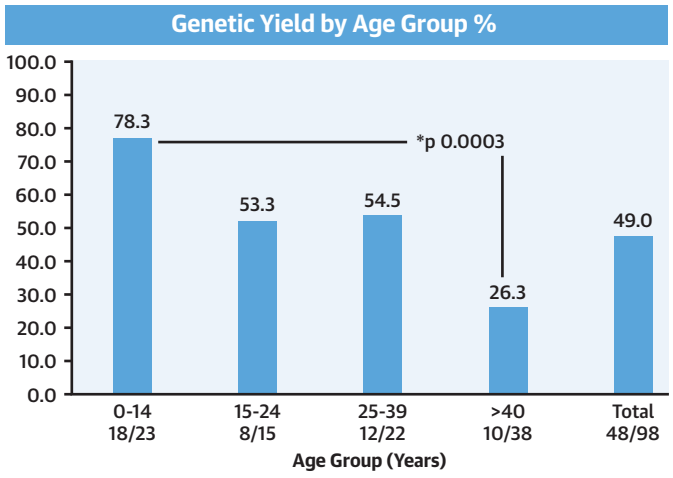
TABLE 3 Genetic Testing Results Among 115 Probands Experiencing RSCA in the Cardiac Inherited Diseases Registry New Zealand

Condition	Genotype Positive*	Testing Uninformative	Unclassified Variant	Unknown	Total
LQTS	28 (58)	15 (31)	5 (10)	0 (0)	48
CPVT	5 (56)	3 (33)	1 (11)	0 (0)	9
BrS	1 (5)	10 (63)	3 (19)	2 (13)	16
ARVC	4 (44)	1 (11)	0 (0)	4 (44)	9
HCM	9 (32)	6 (21)	4 (14)	9 (32)	28
DCM	1 (20)	2 (40)	0 (0)	2 (40)	5
Total	48 (42)	37 (32)	13 (11)	17 (15)	115

Values are n (%) unless otherwise indicated. *Pathogenic (class V) or likely pathogenic (class IV) variant identified.

Abbreviations as in **Tables 1 and 2**.

FIGURE 3 Genetic Testing Yield in Cardiac Arrest Survivors Identified With a Cardiac Inherited Disease



This column graph displays the yield of actionable (pathogenic or likely pathogenic) genetic results per age group among 98 resuscitated sudden cardiac arrest survivors with a cardiac inherited disease. *The p value indicates significant difference between age groups.

DISCUSSION

The Cardiac Inherited Diseases Registry New Zealand, and the associated clinical service, has been in existence for >15 years. Its primary purpose has been to facilitate the detection of inherited cardiac conditions and to offer genetic testing and cascade family screening. Registration is consent based, and referral is at the discretion of clinicians.

The investigation of RSCA has matured over this time. The use of provocative testing has increased (21), and cardiac magnetic resonance imaging has become standard before placement of an implantable cardioverter-defibrillator unless there is a diagnosis that is beyond doubt. The investigation is based around a nationally agreed algorithm (**Figure 1**) that requires the exclusion of acquired disease, particularly coronary artery disease in adults and congenital or infectious disease in children, before referral (22).

OVERVIEW OF THE RESULTS. A CID was diagnosed in one-half of the RSCA cases either before or after referral. Among those with CID, cardiac ion channelopathies accounted for two-thirds, with the largest group being LQTS. Although HCM has the highest prevalence of these cardiac inherited conditions in the general population, the proportion with RSCA is the lowest in this registry, with 28 cases per 354 probands (8%). Despite being the least malignant of these 6 conditions, its high prevalence results in HCM being the most common CID to present with RSCA in those >40 years of age. Some caution is needed, however, because we have observed that non-coronary DCM is less likely to be referred to the service, and we suspect that familial DCM is underdiagnosed (23), especially in adults (18). Furthermore, some patients with arrhythmogenic cardiomyopathy with predominant left ventricular disease (e.g., due to LMNA or FLNC mutations) may thus have escaped referral. The most malignant condition was CPVT, with one-half of the cases presenting with RSCA; it is, fortunately, also the least common condition.

YIELD OF GENETIC TESTING IN PATIENTS WITH A CID. Younger individuals (i.e., those <14 years of age) had the highest yield of genetic testing (78%). The genetic testing yield fell markedly with age, coinciding with the transition from channelopathy to cardiomyopathy as the predominant CID. The yield of genetic testing in patients >40 years of age was 26%. These findings are similar to those of a population-based study of sudden death from Denmark, which suggests that about one-half of cases in 1- to 18-year-olds have a CID, a proportion that falls sharply with increasing age (24).

The diagnostic yield of genetic testing in phenotype-negative RSCA survivors undergoing whole-exome-based evaluation as part of the Canadian CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry) study was recently reported at 17% (25). This outcome is not too different from the finding of 27% for those who had died in Australia and New Zealand (1). This figure of 27% is almost certainly too high, as some variants became reclassified downward over the intervening 3 years since that report. However, the identification of a clinical phenotype increases the performance of genetic tests, reflected in the overall genetic yield of 49% in the current study.

LOW PREVALENCE OF HCM IN THE YOUNG RSCA CASES. Many studies of sudden death in athletes (26,27) have erroneously led to a common misunderstanding that HCM is the most common cause of sudden death in the young overall. A more recent report of sudden death in U.S. college athletes during sports showed that HCM was by far the most common lesion, particularly among African-American male subjects (28). Another US report of SCD in 14- to 18-year-old athletes found that autopsy-negative cases were slightly more common than those with HCM (18% vs. 14%) (29).

In striking contrast, a regional registry from the United Kingdom of 357 sudden deaths in athletes

found that only 6% had HCM and 42% were autopsy negative (5). Furthermore, the largest population-based study of sudden unexpected death to-date found that HCM was a rare cause of SCD for those <24 years of age (1). The current study of RSCA confirms that HCM is, on a population basis, an uncommon cause of RSCA in those <24 years of age, but it does become the most common CID cause of RSCA for those >40 years of age. It is important to note that there are few people of African ancestry, who seem especially prone to HCM-related athletic death, in New Zealand. For this reason, the incidence of RSCA due to CID may be higher in the United States than in New Zealand. Approximately 6 per 1 million per year in New Zealand would translate to ~2000 cases per year in the United States by population size alone.

LONG QT SYNDROME. The age and sex trends in LQTS for RSCA in this study broadly mirror those in a study of sudden death in New Zealand (13). Over a similar time period to that study and in the same population, the mean age at death with LQTS variant-positive sudden unexplained death was 16 years in male subjects and 23 years in female subjects, compared with 20 and 34 years, respectively, for RSCA.

In New Zealand, female subjects with LQTS are significantly over-represented in the registry (67% vs. 33% male subjects) (9), with similar proportions presenting with RSCA here (60% vs. 40%). LQTS reportedly has a higher prevalence among women (16,30), but it has also been suggested that this represents prolongation of the QT interval resulting from being female, and not necessarily LQTS per se (31). However, it has long been established that young male subjects and adult women are the at-risk groups generally in LQTS (32,33), and this has been confirmed in the current study.

Trends according to ethnicity in LQTS are noteworthy. In a recent report of autopsy-negative sudden death from New Zealand, none of the 31 Māori subjects were LQTS rare variant carriers, compared with 21 (33%) of 64 European subjects (13). However, it is clear from the current study that Māori subjects do indeed have LQTS, forming 21% of the RSCA cohort (10 of 48). These data suggest that Māori subjects may have different clinical and genetic LQTS profiles from those of European subjects.

COMPARING CID FOUND IN RSCA VERSUS CID FOUND IN SUDDEN UNEXPLAINED DEATH. Overall, the biggest difference between RSCA and SCD nonsurvivors (1) is that most who survived RSCA experienced their event usually during the day and undergoing some sort of activity, whereas those who died usually did so at night or at rest. The latter were mostly unwitnessed and with no chance of CPR. RSCA due to CPVT rarely if ever occurs during sleep. The CPVT registry has also shown that 25% of cardiac events due to CPVT happen during quiet activity but generally not when asleep (34). HCM was more common in RSCA survivors >24 years of age than among sudden death victims, consistent with findings from a tertiary referral center in the Netherlands (7).

Cardiac arrest due to HCM usually occurs during activity, is often witnessed, and is thus commonly survived, whereas cardiac arrest due to LQTS and BrS commonly occurs at night, during sleep or at rest, and is less likely to be survived.

The fact that most RSCA occurred during routine daily activities reinforces the message that these patients need protection at all times; avoiding sport would not have prevented most of the events. However, the widespread training for and early application of CPR and increased automated external defibrillators in schools and sports fields such as promoted by Project Adam in the United States (35) will still save lives (36), as will devices placed strategically in places of population movement and high incidence of RSCA (12).

STUDY LIMITATIONS. Referral to cardiac genetic registry and clinical service depends on the clinicians' decision in each region of the country and therefore is variable. We thus cannot state with certainty that the entire population with either unexplained RSCA or CID-associated RSCA has been captured by this report. The detection of CID across New Zealand is somewhat variable by region, even with its truly national clinical service, with input from all centers and a nationally agreed investigative algorithm (15). There is also likely to be a bias toward referring cases in which a genetic diagnosis is more likely (e.g., LQTS, CPVT, HCM), rather than cases in which it is less likely (e.g., DCM, BrS). LQTS also has a high profile in New Zealand due to previous published research. The apparent decreasing incidence of RSCA due to LQTS may be due to the effective cascade screening program, leading to the protection of those at risk (9). The DCM group with RSCA comprises 5 participants (of 58 probands in the registry). Although we encourage such referrals, we suspect that many clinicians still do not consider the familial nature of this condition in the same way as the likes of HCM or LQTS. Furthermore, our understanding of the genetic basis for DCM is maturing, and many cases have additional potentially acquired causes that likely reduce the number of referrals (37). However, to counter this, New Zealand has had a nationally agreed algorithm for

the investigation of RSCA in place for some years, as recently recommended (38).

CONCLUSIONS

The application of a multidisciplinary algorithmic approach to the investigation of RSCA can lead to the detection of a large proportion with inherited cardiac conditions. The most common activity established at the time of occurrence of RSCA in individuals with a CID is normal everyday light activity, followed by exercise. Various forms of illness and substance abuse can unmask an underlying inherited pro-arrhythmic risk. Overall in the registry, CPVT was the condition most likely to present with RSCA but was the least common, and HCM was the least likely to present with RSCA but was the most common. Cardiac ion channelopathies predominate as a cause of RSCA in those <24 years of age, particularly LQTS. Male subjects tend to present younger than female subjects. With increasing age, cardiomyopathies become more common; over the age of 40 years, HCM is the most common inherited condition identified following RSCA. Genetic testing yield is very high in children and falls with increasing age.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: When patients with acquired cardiac disease are excluded, systemic evaluation leads to diagnosis of inherited heart conditions in approximately one-half of those resuscitated from cardiac arrest. Long QT syndromes and catecholaminergic polymorphic ventricular tachycardia were common among younger victims, while hypertrophic cardiomyopathy was the most frequent underlying condition in those over age 40 years. Two-thirds of patients with inherited heart conditions were not exercising at the time of cardiac arrest.

TRANSLATIONAL OUTLOOK: Since one-half of patients referred for genetic testing after resuscitation from cardiac arrest elude diagnosis, further research is needed to identify other predisposing conditions.

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KEY WORDS cardiomyopathies, channelopathies, hypertrophic cardiomyopathy, genetic testing, long QT syndrome, registry, resuscitated sudden cardiac arrest

APPENDIX For supplemental Methods, tables, and figures, please see the online version of this paper.