Circulation: Heart Failure

ORIGINAL ARTICLE

# Genetic Testing Yield and Clinical Characteristics of Hypertrophic Cardiomyopathy in Understudied Ethnic Groups: Insights From a New Zealand National Registry

Nikki J. Earle, PhD; Annika Winbo, MD, PhD; Jackie Crawford, NZCS; Miriam Wheeler, MBChB; Rachael Stiles, PGDipNurs; Tom Donoghue, MNurs; Martin K. Stiles, MBChB, PhD; Ian Hayes, MBChB; Luciana Marcondes, MBChB; Andrew Martin, MBChB; Jonathan R. Skinner, MBChB, MD

**BACKGROUND:** Aotearoa/New Zealand has a multiethnic population. Patients with hypertrophic cardiomyopathy (HCM) are enrolled in the national Cardiac Inherited Diseases Registry New Zealand. Here, we report the characteristics of Cardiac Inherited Diseases Registry New Zealand HCM probands with and without pathogenic or likely pathogenic (P/LP) genetic variants for HCM, and assess genetic testing yield and variant spectrum by self-identified ethnicity.

**METHODS:** Probands with HCM and enrolled in Cardiac Inherited Diseases Registry New Zealand who have undergone clinical genetic testing over a 17-year period were included. Clinical data, family history, and genetic test results were analyzed.

**RESULTS:** Of 336 probands, 121 (36%) were women, 220 (66%) were European ethnicity, 41 (12%) were Māori, 26 (8%) were Pacific people, and 49 (15%) were other ethnicities. Thirteen probands (4%) presented with sudden death and 19 (6%) with cardiac arrest. A total of 134 (40%) had a P/LP variant identified; most commonly in the *MYBPC3* gene (60%) followed by the *MYH7* gene (24%). A P/LP variant was identified in 27% of Māori or Pacific probands versus 43% European or other ethnicity probands ($P$=0.022); 16% of Māori or Pacific probands had a variant of uncertain significance identified, compared with 9% of European or other ethnicity probands ($P$=0.092). Women more often had a P/LP variant identified than men (48% versus 35%; $P$=0.032), and variant-positive probands were younger at clinical diagnosis than variant of uncertain significance/variant-negative probands (39±17 versus 50±17 years; $P$<0.001) and more likely to have experienced cardiac arrest or sudden death events over their lifetime ($P$=0.002).

**CONCLUSIONS:** Carriage of a P/LP variant in HCM probands is associated with presentation at younger age, and cardiac arrest or sudden death events. Māori or Pacific probands were less likely to have a P/LP variant identified than European or other ethnicity probands.

**Key Words:** cardiomyopathies ■ genetic testing ■ heart failure ■ hypertension ■ New Zealand

See Editorial by Dunn

Hypertrophic cardiomyopathy (HCM) is one of the most common inherited heart conditions affecting at least 1 in 500 people,[1] and is a major cause of heart failure, ventricular arrhythmias, and sudden death.[2] Largely considered a Mendelian disease with autosomal dominant inheritance and variable penetrance, clinical

Correspondence to: Nikki J. Earle, PhD, Heart Health Research Group, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. Email n.earle@auckland.ac.nz

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.123.010970.
For Sources of Funding and Disclosures, see page 221.



*Circulation: Heart Failure* is available at www.ahajournals.org/journal/circheartfailure

## WHAT IS NEW?

- Among hypertrophic cardiomyopathy probands from a diverse New Zealand population undergoing clinical genetic testing, including Māori and Pacific peoples, 40% had pathogenic or likely pathogenic genetic variants identified.
- Despite presenting with hypertrophic cardiomyopathy at a younger age and with a greater mean maximum left ventricular wall thickness, Māori and Pacific individuals had a lower yield of pathogenic or likely pathogenic variants and higher yield of variants of uncertain significance than their European or other ethnicity counterparts.
- This study highlights the need for diverse genomic data resources and their potential impact on equitable health care.

## WHAT ARE THE CLINICAL IMPLICATIONS?

- The findings highlight the impact of ethnicity, sex, and age on genetic testing yield and disease severity.
- Clinicians should consider the potential for lower yield of pathogenic or likely pathogenic variants and higher yield of variants of uncertain significance in patients from ethnic groups underrepresented in genomic databases, and the resulting effects on hypertrophic cardiomyopathy diagnosis and management.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ACA** | aborted cardiac arrest |
| **CIDRNZ** | Cardiac Inherited Diseases Registry New Zealand |
| **HCM** | hypertrophic cardiomyopathy |
| **LV** | left ventricular |
| **P/LP** | pathogenic or likely pathogenic |
| **SCD** | sudden cardiac death |
| **VUS** | variants of uncertain significance |

genetic testing for HCM is well established, with 8 sarcomeric genes accounting for >95% of pathogenic or likely pathogenic (P/LP) variants.[3,4] Despite over 30 years passing since the first HCM-related gene was identified,[5] over 50% of those tested do not receive a genetic diagnosis,[6] and the pathogenicity of many detected genetic variants is difficult to determine.

Most of the published research on the genetic architecture of HCM comes from cohorts from America, Europe, and more recently, Australia and Asia. Wider diversity in genomic research is needed to aid variant interpretation, and support health equity. Aotearoa/New Zealand has a multiethnic population with the genomes of New Zealanders reflecting multiple waves of migration. Settled by Māori (the Indigenous people of New Zealand) during the 13th century Polynesian migration,[7] settlers from Europe followed in the 19th century, with subsequent ongoing immigration from around the world, particularly the Pacific (Western and Eastern Polynesia) and South and South East Asia. Māori and Pacific population groups have not been previously studied with respect to the genetics of HCM.

The Cardiac Inherited Diseases Registry New Zealand (CIDRNZ) is a national consent-based registry that coordinates the cardiac and genetic investigation of sudden unexplained deaths and of families with suspected inherited heart conditions.[8] Recent investigations in CIDRNZ probands with long-QT syndrome identified that probands with Polynesian ancestry (Māori and Pacific people) are more likely to experience serious cardiac events, yet less likely to have disease-causing variants identified during diagnostic genetic testing.[9]

Here, in CIDRNZ probands with HCM who have undergone diagnostic genetic testing as part of their clinical care, we compare the characteristics of those with and without P/LP variants and assess genetic testing yield and variant spectrum by self-identified ethnicity.

# METHODS

The CIDRNZ has been described in detail previously and is summarized here.[8] Probands with suspected disease are referred to the Cardiac Inherited Diseases Group for genetic testing from a range of specialists, with phenotypic data reviewed by the national multidisciplinary team before approval for testing.

## Study Cohort

This study includes unrelated CIDRNZ probands with a clinical diagnosis of HCM who had undergone genetic testing for HCM-related genes between January 2003 and August 2020. Testing was performed at one of the University of Auckland (New Zealand), LabPLUS Auckland (New Zealand), National Health Service Oxford University Hospitals (United Kingdom) or Invitae (United States). The clinical diagnosis was formally assessed using the current diagnostic criteria including clinical ECG and echocardiographic assessment,[10] with discussion of each case at the multidisciplinary Cardiac Inherited Diseases Group meeting before any genetic testing being undertaken. Referred cases were reviewed to exclude more common phenocopies such as cardiac amyloidosis. In the presence of chronic hypertension, a decision to test was based on the combination of cardiac magnetic resonance imaging findings in keeping with HCM and family history. The term proband is defined as the first individual with clinically suspected HCM in a family without known HCM.

## Study Data

Data were extracted from the CIDRNZ database on August 28, 2020. Self-reported ethnicity was categorized into European (New Zealand European, other European), Māori, Pacific peoples (including Samoan, Tongan, Cook Island Māori, Fijian), and

other (Chinese, Indian, other Asian, South–East Asian, Middle Eastern). Self-reported ethnicity is the preferred measure of ethnicity in New Zealand and does not depend on any additional metrics, nor does it take mixed ancestry into account. Clinical data not available via CIDRNZ was obtained by medical record review including echocardiographic data (from the most recent ECG) and incidence of septal reduction therapy (alcohol septal ablation or surgical septal myectomy).

Over the 17 years of retrospective data, this study includes clinically recommended molecular genetic testing has advanced with increasing numbers of genes tested. Thus, the number of genes tested per proband has increased over the study period and ranges from 8 to 50 cardiomyopathy-related genes (Table S1).

Variants in genes with definitive or moderate evidence of disease association were included as potentially HCM causing.[11] Variant classification reported here was performed by the relevant accredited testing laboratory according to the American College of Medical Genetics guidelines[12] and reviewed by the Cardiac Inherited Diseases Group multidisciplinary team. For patients tested before 2015, where results were reported without American College of Medical Genetics classification (n=96), variants were classified using the VarSome American College of Medical Genetics implementation search engine in July 2021 (www.varsome.com). For this study, variant positive was defined as P/LP, class IV to V variants.[12] Variants of uncertain significance (VUS; class III) were also recorded, and all variants were classified and described at the DNA level (substitution, deletion, intronic, duplication, or deletion-insertion), and at the protein level (substitution [missense or nonsense], frameshift, deletion, or splice).[13]

Data were collected with the ethics requirement that patients' data are confidential; however, summarized deidentified data may be available from the corresponding author on reasonable request.

## Clinical Events

The most serious clinical event recorded in CIDRNZ for each proband was condensed into the following categories: (1) no symptoms, (2) nonspecific symptoms (palpitations, dizziness, shortness of breath, chest pain, and atrial fibrillation), (3) syncope (including loss of consciousness with or without seizures, documented polymorphic ventricular tachycardia, and near drowning without need for resuscitation), and (4) a composite of aborted cardiac arrest (ACA) and sudden cardiac death (SCD; likely life-threatening ventricular arrhythmias requiring cardiopulmonary resuscitation or defibrillator cardioversion, including near drowning and sudden death).[9]

## Statistical Methods

Baseline characteristics of groups were described using means SD or median (interquartile range) for continuous variables and n (percent) for categorical variables. Association testing was performed using *t* test, ANOVA, Wilcoxon rank-sum test or Kruskal-Wallis test for continuous variables and $\chi^2$ test or Fisher exact test for categorical variables.

To assess the lifetime burden of ventricular arrhythmias, the date of first occurrence of the composite outcome of ACA (including appropriate implantable cardioverter defibrillator therapy) or SCD was used to create cumulative event curves (from birth) stratified by variant status (presence/absence of a P/LP variant), with those unaffected censored at the date of data extraction. Cumulative incidence curves were estimated using Kaplan-Meier methods and the between-group difference was evaluated using a log-rank test.

A *P* value of <0.05 was deemed statistically significant. Statistical analyses were performed using R, version 4.2.2, and packages.[14]

## Ethics Approval

The CIDRNZ is approved by an institutional review committee (Health and Disability Ethics Committees, Wellington, AKX/02/00/107/AM03 and MEC/05/10/130); registrants have given informed consent.

# RESULTS

A total of 336 probands from CIDRNZ had undergone genetic testing for HCM over the 17-year study period, with 36% women and 64% men, and a mean age of clinical diagnosis of 46±18 years (Table 1). Two hundred and twenty (66%) probands were of European ethnicity, 41 (12%) Māori, 26 (8%) Pacific peoples, and 49 (15%) other ethnicities (Table 2; Figure 1). With a median of 16 genes tested per proband (range, 8–50), 134 (40%) probands were variant-positive (ie, carriers of a P/LP variant). Variant-positive probands had a younger age of clinical diagnosis compared with VUS or variant-negative probands (39±17 versus 51±17 years; *P*<0.001). This was also evident by age group categories with 67% of those clinically diagnosed age ≤24 years being variant-positive compared with 54% of those aged 25 to 39 years, and 29% of those aged ≥40 years (*P*<0.001). Women were more likely to be variant positive than men, 48% and 35% variant-positive, respectively (*P*=0.032). The mean maximum left ventricular (LV) wall thickness on ECG was greater in variant-positive probands than VUS or variant-negative probands (20±6 versus 18±6 mm; *P*=0.048; Table 1). Among all probands, 16% had a recorded family history of sudden death, with this identified in 20% of variant-positive probands and 12% of VUS or variant-negative probands (*P*=0.063). The most common reason for referral to Cardiac Inherited Diseases Group was a symptom or cardiac event (65%).

Cascade genetic screening was documented in 57% of families with a variant-positive proband (Table 2). In families where this occurred, a median of 3 additional family members underwent genetic testing (range, 1–16) and a median of 2 additional variant-positive family members were identified per family (range, 1–8).

## Cardiac Arrest or SCD Events

Forty-four (13%) probands had experienced ACA/SCD events. Of these, 13 events were a first presentation with SCD, 19 were a first presentation with ACA, and the remaining 12 were ACA/SCD events, which occurred following clinical diagnosis with HCM. Of the 13 probands referred for molecular autopsy from pathology services following presentation with sudden death, 5 were variant-positive, with 2 having an identical Class V splice site variant in the *TNNI3* gene

**Table 1. Clinical Characteristics of 336 Cardiac Inherited Diseases Registry New Zealand Probands With Hypertrophic Cardiomyopathy Who Have Had Molecular Genetic Testing Performed**

| | Whole group, n=336 | Variant positive, n=134 (40%) | VUS, n=34 (10%) | Variant negative, n=168 (50%) | *P* value* |
|---|---|---|---|---|---|
| Age at diagnosis, y; mean±SD | 46±18 | 39±17 | 47±17 | 54±16 | <0.001 |
| Female sex, n (%) | 121 (36) | 58 (43) | 10 (29) | 53 (32) | 0.031 |
| Family history of SCD, n (%) | 52 (16) | 27 (20) | 3 (9) | 22 (13) | 0.063 |
| Reason for referral | | | | | |
| Incidental ECG/echocardiogram abnormality | 46 (14) | 17 (13) | 2 (6) | 27 (16) | 0.818 |
| Symptom/cardiac event† | 218 (65) | 89 (66) | 19 (56) | 110 (65) | 0.716 |
| Family with SCD or suspected HCM | 59 (17) | 23 (17) | 13 (38) | 23 (14) | 0.998 |
| Pathology referral after SCD | 13 (4) | 5 (3) | 0 | 8 (5) | 0.998 |
| Echocardiogram‡ | | | | | |
| Maximum LV wall thickness, mm; mean±SD | 19±6 | 20±6 | 19±6 | 17±6 | 0.048 |
| LVOT obstruction at rest, n (%) | 75 (25) | 22 (17) | 6 (18) | 47 (28) | 0.066 |
| Therapy | | | | | |
| ICD implanted | 87 (26) | 40 (30) | 8 (24) | 39 (23) | 0.187 |
| Septal reduction therapy | 41 (13) | 15 (12) | 2 (6) | 24 (14) | 0.824 |
| Genetics | | | | | |
| Genes tested, median (IQR) | 16 (13–19) | 16 (12–19) | 18 (16–19) | 16 (13–19) | 0.200 |

HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LV, left ventricular; LVOT, left ventricular outflow tract; SCD, sudden cardiac death; and VUS, variant of uncertain significance.

*Test is variant positive vs VUS/variant-negative combined.

†Includes resuscitated cardiac arrest.

‡Echocardiogram data unavailable for 33 probands.

(c.550-1G>A; Table S2). Of the 19 probands who presented with resuscitated cardiac arrest, 9 were variant positive.

There was a significantly higher incidence of ACA/SCD events (from birth) in variant-positive compared with VUS or variant-negative probands (Figure 2; log-rank test; *P*=0.002).

## Variant Details

Eighty-seven different P/LP variants from 11 genes were identified among the 134 variant-positive probands, with 1 variant presented per proband (Table S3). Seventy-one (82%) of these P/LP variants were only found once, with the other 16 P/LP variants accounting for variants identified in the remaining 63 probands. Most common were variants in the *MYBPC3* gene (44 different variants identified in 80 [60%] variant-positive probands) followed by the *MYH7* gene (25 different variants identified in 32 [24%] variant-positive probands).

For 128 of the 134 (96%) variant-positive probands, the P/LP variants were identified in genes that were included on the first and smallest diagnostic gene panel (comprising the *MYH7*, *MYBPC3*, *MYL2*, *MYL3*, *TNNT2*, *TPM1*, *ACTC1*, and *TNNI3* genes; Table S1).

## Clinical Characteristics and Testing Results by Ethnicity

Genetic testing results and clinical characteristics by ethnic group are summarized in Figure 1. Probands of Māori or Pacific ethnicity had a younger mean age at clinical diagnosis when compared with those of non-Māori/non-Pacific ethnic groups (42±17 versus 47±17 years, respectively; *P*=0.042) and greater mean maximum LV wall thickness (21±6 versus 19±6 mm, respectively; *P*=0.006). The presence of a family history of SCD varied significantly across all ethnic groups (*P*=0.012; Table 2), with Māori or Pacific probands more likely to have a family history of SCD recorded compared with non-Māori/non-Pacific probands (27% versus 13%; *P*=0.008).

Probands of Māori and Pacific ethnicity were less likely to have a P/LP variant identified (22% and 35%, respectively; Table 2) compared with European or other ethnicity probands (43% and 39%, respectively; Māori or Pacific [27%] versus non-Māori/non-Pacific [43%]; *P*=0.022). This difference in testing yield is despite no significant difference in the mode of presentation (reasons for clinical referral) or in numbers of genes tested across ethnic groups (Table 2; Table S4).

The frequency of cascade genetic screening varied by ethnic group (*P*=0.045; Table 2), and was highest in probands of Māori ethnicity where it was performed in 78% of variant-positive families.

## Variants of Uncertain Significance

Thirty-four probands (10%) only had a VUS identified with 25 different variants found (Table S5).

**Table 2. Molecular Genetic Testing Results in Probands With Hypertrophic Cardiomyopathy From Cardiac Inherited Diseases Registry New Zealand by Self-Reported Ethnic Group**

| All probands | | | | | | |
|---|---|---|---|---|---|---|
| | All n=336 | Māori n=41 (12%) | Pacific n=26 (8%) | European n=220 (66%) | Other n=49 (15%) | *P* value* |
| Age at diagnosis, y; mean±SD | 46±18 | 42±17 | 42±19 | 46±18 | 50±12 | 0.081 |
| Family history of SCD, n (%) | 52 (16) | 13 (32) | 5 (19) | 30 (14) | 4 (8) | 0.012 |
| Cardiac arrest or SCD event | 44 (13) | 7 (17) | 2 (8) | 32 (15) | 3 (6) | 0.293 |
| Reason for referral | | | | | | |
| Incidental ECG/echocardiogram abnormality | 46 (14) | 3 (7) | 6 (23) | 29 (13) | 8 (16) | 0.300 |
| Symptom/cardiac event† | 218 (65) | 26 (63) | 13 (50) | 148 (67) | 31 (63) | 0.368 |
| Family with SCD or suspected HCM | 59 (17) | 8 (20) | 7 (27) | 35 (16) | 9 (18) | 0.551 |
| Pathology referral after SCD | 13 (4) | 4 (10) | 0 | 8 (4) | 1 (2) | 0.149 |
| Echocardiogram‡ | | | | | | |
| Maximum LV wall thickness, mm; mean±SD | 19±6 | 21±6 | 21±7 | 19±5 | 17±6 | 0.003 |
| LVOT obstruction at rest, n (%) | 75 (25) | 7 (17) | 6 (23) | 55 (26) | 9 (18) | 0.481 |
| Genetics | | | | | | |
| Genes tested, median (IQR) | 16 (13–19) | 19 (13–26) | 16 (13–19) | 16 (12–19) | 18 (13–19) | 0.059 |
| **Variant-positive probands** | | | | | | |
| | All, n=134 | Māori, n=9 (22%) | Pacific, n=9 (35%) | European, n=97 (44%) | Other, n=19 (39%) | |
| Cascade screening undertaken in family, n (%) | 77 (57) | 7 (78) | 4 (44) | 60 (62) | 6 (32) | 0.045 |
| Family members tested, median (IQR) | 3 (2–5) | 3 (1.5–3) | 4 (2–7) | 3 (2–5) | 2 (2–2.75) | 0.179 |
| Variant positive identified per family | 2 (1–3) | 2 (1.5–3) | 1 (1–2) | 2 (1–3) | 1.5 (1–2.75) | 0.865 |
| Variant types (protein level) | | | | | | |
| Substitution, n (%) | | | | | | |
| Missense | 80 (60) | 6 (67) | 6 (75) | 53 (55) | 15 (79) | 0.216 |
| Nonsense | 7 (5) | 0 | 0 | 6 (6) | 1 (5) | 0.999 |
| Frameshift | 17 (13) | 1 (11) | 2 (22) | 13 (13) | 2 (11) | 0.999 |
| Deletion | 6 (5) | 0 | 0 | 6 (6) | 0 | … |
| Splice site | 23 (17) | 2 (22) | 1 (13) | 19 (13) | 1 (5) | 0.479 |
| **Probands with variants of uncertain significance** | | | | | | |
| | All, n=34 | Māori n=8 (20%) | Pacific, n=3 (11%) | European, n=16 (7%) | Other, n=7 (14%) | |

IQR indicates interquartile range; LVOT, left ventricular outflow tract; and SCD, sudden cardiac death.
*Comparison across 4 ethnic group categories.
†Includes resuscitated cardiac arrest.
‡Echo data unavailable for 33 probands.

Sixteen percent of Māori or Pacific probands had only a VUS identified compared with 9% of non-Māori/non-Pacific probands (*P*=0.092). The frequency of the presence of VUS did not significantly differ when compared across all ethnic groups (*P*=0.074). The most common VUS identified in this cohort was in the troponin T2 (cardiac type) gene *TNNT2* c.571-1G>A, which was found in 6 probands of Māori (n=4) or Pacific (n=2) ethnicity. Though sufficient family testing to enable co-segregation analysis for this variant has not been performed, these 6 probands had confirmed clinical disease with a mean age of diagnosis of 33 years, wall thickness ranging from 20 to 30 mm, and 3 of the 6 had an implantable cardioverter defibrillator implanted.

## DISCUSSION

Here, we report for the first time the clinical profile and diagnostic genetic testing yield for a multiethnic group of HCM probands from Aotearoa/New Zealand, population 5.1 million. A P/LP genetic variant was found in 40% of probands. Variant-positive probands were younger at clinical diagnosis and more likely to have experienced ACA/SCD events than VUS or variant-negative probands.

A unique feature of this work is the inclusion of Māori and Pacific peoples, population groups who have not previously been studied with respect to HCM. Māori or Pacific probands had a younger age at clinical diagnosis, greater mean LV wall thickness, and were more likely to have a family history of SCD, yet were less likely than

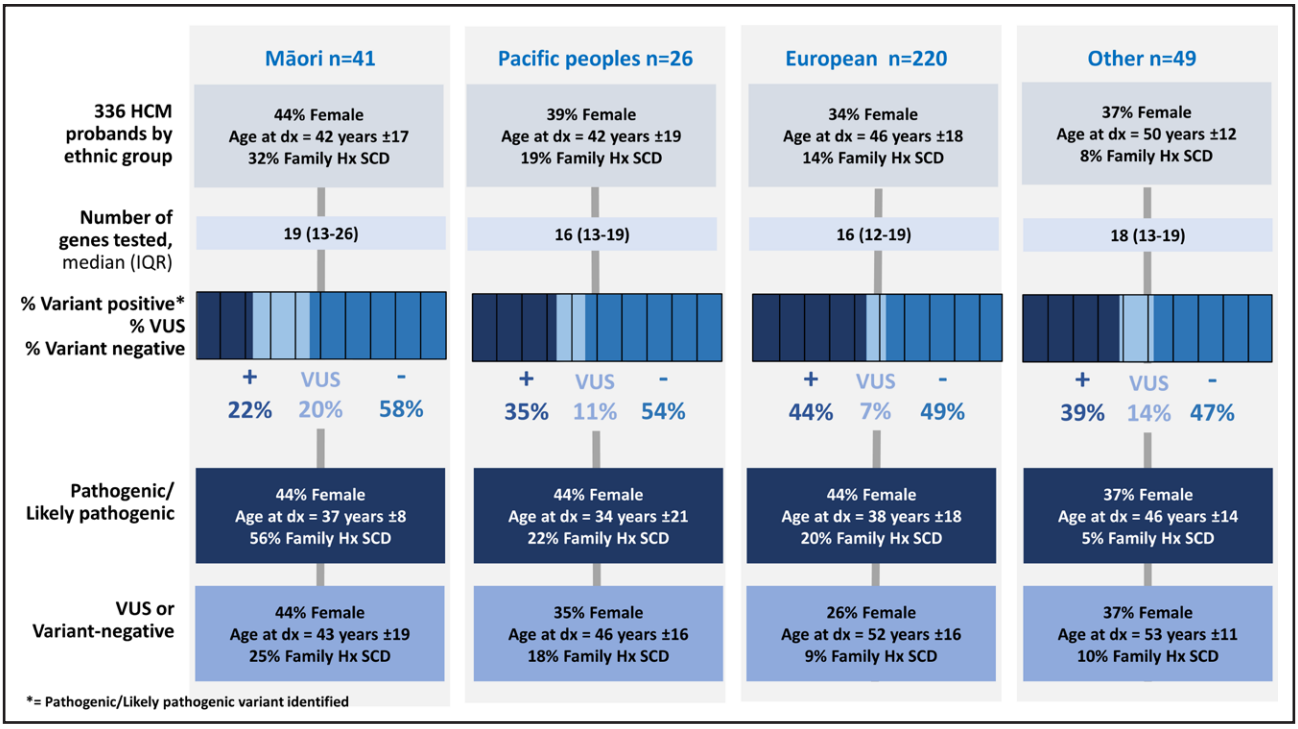


**Figure 1. Summary of the population groups and key results of the current study.**
Dx indicates diagnosis; HCM, hypertrophic cardiomyopathy; Hx, history; IQR, interquartile range; SCD, sudden cardiac death; and VUS, variant of uncertain significance. *Pathogenic or likely pathogenic variant identified.

European or other ethnicity probands to have a P/LP variant identified.

Māori or Pacific peoples have, to date, essentially been unrepresented in publicly accessible genomic databases. With such data being an important source of evidence for pathogenicity (or benignity) in variant classification,[12] there is a risk of variant misclassification, misdiagnosis, and potential effects on health equity.[15,16] In the current study, 16% of Māori or Pacific probands had only a VUS identified. The inability to compare these variants against population genomic data may be hindering more precise classification of VUS in these patients. To enable more equitable and precise interpretation, efforts to assemble resources of genomic data for Māori and Pacific peoples are underway, with a strong focus on appropriate governance and use of data.[17] The Aotearoa

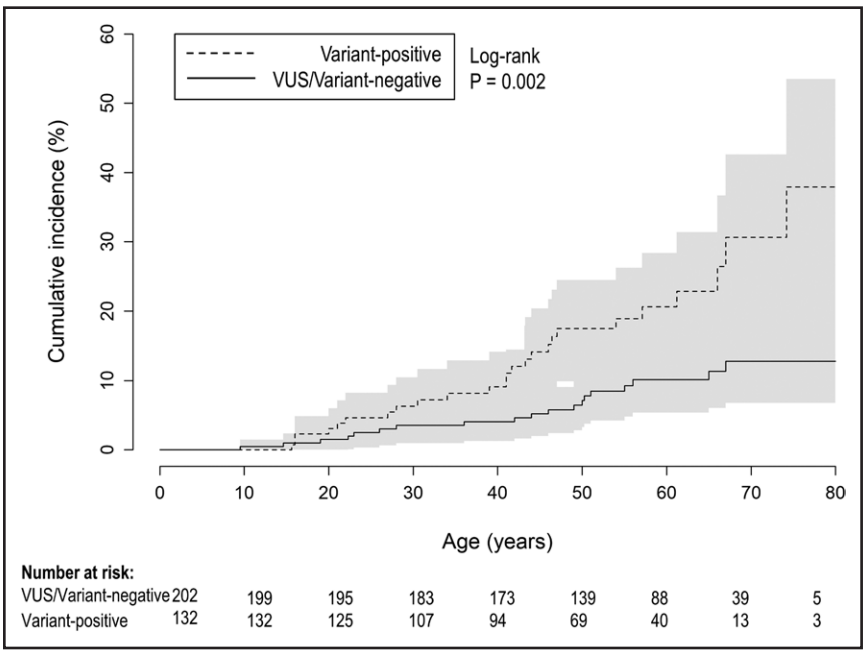


**Figure 2. Presence of a pathogenic or likely pathogenic variant is associated with cardiac arrest or sudden cardiac death events in hypertrophic cardiomyopathy probands.**
Data for curves represent the cumulative incidence of sudden cardiac death, resuscitated cardiac arrest, or appropriate implantable cardioverter defibrillator therapy events from birth, stratified by variant status with shading representing 95% CIs. VUS indicates variant of uncertain significance.

Variome project aims to catalog genetic variants to support disease diagnosis and research into health care conditions relevant and important to Māori and Pacific peoples and to develop a database of sequence variation in Māori. The data from the current study are further evidence of the need for these resources.

The higher rates of family history of SCD for Māori and Pacific probands may not represent SCD due to HCM only; Māori and Pacific New Zealanders are known to be at higher risk of death from ischemic heart disease than European New Zealanders[18,19] and this is likely reflected in our data. Similarly, the greater mean LV wall thickness found among Māori and Pacific probands could reflect more prevalent LV hypertrophy or larger heart size among Polynesian individuals[20,21] rather than true HCM, and this may be contributing to lower genetic testing yield in these patients.

This registry cohort has a similar age and sex profile to other published HCM registries or cohorts, as well as similar associations between variant-positive status and particular clinical characteristics. Among the Sarcomeric Human Cardiomyopathy Registry comprising 4591 patients from 8 centers in Europe and North and South America, the mean age of diagnosis for registrants was 45.8 years and 37% were women.[22] This compares with 46 years and 36% women in the current study, with both registries describing a younger age of clinical diagnosis (a marker for disease severity) for variant-positive patients. Similarly, genotyped patients with P/LP sarcomeric variants in the Sarcomeric Human Cardiomyopathy Registry were at significantly higher lifetime risk for ventricular arrhythmias, as were variant-positive patients from a cohort of 203 patients with HCM in Japan.[23]

An overall testing yield of 40% for P/LP variants in CIDRNZ probands was similar to that found in Sarcomeric Human Cardiomyopathy Registry (42% of probands), to a cohort of 629 probands undergoing genetic testing for HCM in Australia (39%),[24] to 378 patients undergoing testing in Belgium (37%)[25] and 112 probands undergoing testing in Japan (44%).[26] In a different cohort of 224 Singaporean patients with HCM undergoing testing, the yield for P/LP variants was lower at 18%, with a higher proportion of VUS (24%).[4] Variant-positive CIDRNZ probands had a greater mean LV wall thickness, consistent with several other international HCM cohorts.[23,25,27–29]

The finding that women comprised less than half of this cohort, yet were significantly more likely to be variant-positive than men, is consistent with an analysis by sex in 3788 genotyped patients from Sarcomeric Human Cardiomyopathy Registry, where women were 17% more likely to have a sarcomeric variant identified than men, and an analysis by Ingles et al. identifying female sex as an independent predictor of a positive genetic test result.[28,30] Further investigation is needed into sex differences in our cohort to explore the possible role of biases in wall thickness diagnostic criteria, treatment, and sex-gene interactions affecting penetrance and disease severity.[31]

The VUS *TNNT2* c.571-1G>A was identified in 6 CIDRNZ probands of Māori or Pacific ethnicity, and is an illustration of the challenges of variant curation in these populations. It is only present in the South Asian subpopulation of the gnomAD database, but at a frequency greater than that expected for an HCM-associated variant (0.016%).[32] However RNA studies have shown it to cause a splicing defect with an in-frame deletion (p.[Gln191del]).[33] Determining whether the variant is a common Polynesian polymorphism via publicly available reference data is not possible, so due to these difficulties in classification this variant retains a class III classification in CIDRNZ patients.

Large-scale sequencing efforts to identify variants associated with inherited heart conditions in population cohorts (in contrast to those with known or suspected diseases such as in CIDRNZ) have further highlighted the need for genomic reference databases in understudied populations. Following the sequencing of 4810 healthy people in Singapore and the identification of P/LP inherited heart disease variants, several variants that were previously identified as pathogenic in European populations were downgraded to VUS. High allele frequencies of these variants indicated they may be common polymorphisms in this cohort (comprising Chinese, Malay, and Indian participants).[34]

Cascade genetic testing was performed in 57% of HCM probands' families, with a median of 3 additional family members tested and 2 being variant-positive. Cascade testing was most common in families of Māori ethnicity (78%), and least common in those with other ethnicity (32%). On the basis of other autosomal dominant disorders such as familial hypercholesterolemia, we might expect to identify 8 to 9 variant-positive family members per proband.[35,36] For a disease with age-related penetrance such as HCM; however, the utility and consequences of cascade genetic screening in children in particular differs to inherited heart conditions with more likely pediatric-onset such as long-QT syndrome. Cascade screening for pathogenic HCM-associated variants in early life enables clinical monitoring of variant-positive individuals to enable early intervention, and the release of noncarriers from such monitoring.[37] However, the option of regular clinical screening only may be preferential for some parents, leading to the lower uptake of testing found here, particularly in Aotearoa/New Zealand where insurance companies can legally request genomic test results in underwriting decisions, potentially resulting in genomic discrimination.[38]

## Limitations

This study uses registry-derived data and thus is prone to selection bias for registry-based studies, including both

referral and survival bias. Although CIDRNZ is a national registry, we cannot confirm complete capture of all probands in NZ undergoing genetic testing for HCM, with referral to CIDRNZ known to vary by region.[39]

## Conclusions

Genetic testing yield for HCM varies by self-reported ethnicity in a New Zealand population, with the yield of P/LP variants lower—and the burden of VUSs higher—among probands with self-reported Māori or Pacific ethnicity than among probands with European or other ethnicity. Across the HCM cohort as a whole, genetic testing yield for a P/LP variant was 40%. The yield was higher in women, in probands clinically diagnosed at a younger age, and in those with greater mean maximum LV wall thickness, similar to results from other cohorts.

## ARTICLE INFORMATION

Received June 19, 2023; accepted December 7, 2023.

### Affiliations

Departments of Medicine (N.J.E.) and Physiology (A.W.), University of Auckland, New Zealand. Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand (N.J.E., J.C., L.M.). Department of Cardiology, Auckland City Hospital, New Zealand (M.W., A.M.). Department of Cardiology, Waikato Hospital, Hamilton, New Zealand (R.S., M.K.S.). Department of Cardiology, Wellington Hospital, New Zealand (T.D.). Genetic Health Service New Zealand, Northern Hub, Auckland (I.H.). Heart Centre for Children, Children's Hospital at Westmead, Sydney Children's Hospital Network, NSW, Australia (J.R.S.). Department of Paediatric and Adolescent Medicine, University of Sydney, NSW, Australia (J.R.S.).

### Acknowledgments

This article is presented on behalf of the Cardiac Inherited Diseases Group. The authors thank all the members not included as authors here, who have referred many cases and worked to help establish the phenotype, as well as members of the clinical and molecular genetic services across Aotearoa/New Zealand. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

### Sources of Funding

Dr Earle is supported by an Auckland Medical Research Foundation postdoctoral fellowship.

### Disclosures

None.

### Supplemental Material

Tables S1–S5

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