Genetic testing in Polynesian long QT syndrome probands reveals a lower diagnostic yield and an increased prevalence of rare variants

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BACKGROUND New Zealand has a multiethnic population and a national cardiac inherited disease registry (Cardiac Inherited Disease Registry New Zealand [CIDRNZ]). Ancestry is reflected in the spectrum and prevalence of genetic variants in long QT syndrome (LQTS).

OBJECTIVE The purpose of this study was to study the genetic testing yield and mutation spectrum of CIDRNZ LQTS probands stratified by self-identified ethnicity.

METHODS A 15-year retrospective review of clinical CIDRNZ LQTS probands with a Schwartz score of $\geq$2 who had undergone genetic testing was performed.

RESULTS Of the 264 included LQTS probands, 160 (61%) reported as European, 79 (30%) NZ Māori and Pacific peoples (Polynesian), and 25 (9%) Other ethnicities, with comparable clinical characteristics across ethnic groups (cardiac events in 72%; age at presentation 28$\pm$19 years; corrected QT interval 512$\pm$55 ms). Despite comparable testing (5.3$\pm$1.4 LQTS genes), a class III–V LQTS variant was identified in 35% of Polynesian probands as compared with 63% of European and 72% of Other probands ($P<.0001$). Among variant-positive CIDRNZ LQTS probands (n=148), Polynesians were more likely to have non-missense variants (57% vs 39% and 25% in probands of European and Other ethnicity, respectively; $P=.005$) as well as long QT syndrome type 1-3 variants not reported elsewhere (71% vs European 22% and Other 28%; $P<.0001$). Variants found in multiple probands were more likely to be shared within the same ethnic group; $P<.01$).

CONCLUSION Genetic testing of Polynesian LQTS probands has a lower diagnostic yield, despite comparable testing and clinical disease severity. Rare LQTS variants are more common in Polynesian LQTS probands. These data emphasize the importance of increasing the knowledge of genetic variation in the Polynesian population.

KEYWORDS Long QT syndrome; Ethnicity; Genetic testing; Mutation spectrum; Variants; Genetic variation

(Heart Rhythm 2020;17:1304–1311)

Introduction

Long QT syndrome (LQTS) is an inherited cardiac disease characterized by a prolongation of the QT interval on the surface electrocardiogram and a propensity for life-threatening arrhythmias, which is caused by pathogenic sequence variants in genes encoding cardiac ion channels and related proteins.[1] Among various identified LQTS-related genes, 3 genes—*KCNQ1*, *KCNH2*, and *SCN5A*—account for the vast majority of molecularly defined LQTS cases (corresponding to long QT syndrome

Dr Winbo is funded by the Hugh Green Foundation, Cure Kids, and the Auckland Medical Research Foundation. Dr Skinner receives salary support from Cure Kids. The rest of the authors report no conflicts of interest. [1]Present address: Department of Pathology, Sidra Medicine, Doha, Qatar.

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1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2020.03.015

type 1 , type 2 , and type 3 [LQT1, 2, and 3], respectively).[2,3] A molecular genetic diagnosis remains elusive in 20%–25% of definite LQTS cases despite testing known LQTS genes.[4]

Ancestry is known to be reflected in the spectrum and prevalence of genetic variants in LQTS genes.[5–7] In New Zealand, a consent-based national cardiac inherited disease registry (Cardiac Inherited Disease Registry New Zealand [CIDRNZ]) permits research and coordinates the cardiac and genetic investigation of families with suspected inherited cardiac disease.[8] New Zealand (Aotearoa) is a multiethnic society, settled by Māori during the 13th century Polynesian migration,[9] with a second 19th century immigration wave of settlers from Europe (in Māori referred to as Pākehā, meaning New Zealanders of European ancestry), followed by mixed continued immigration, with a marked increase during the past decades. Of the 1940 CIDRNZ registrants as of October 1, 2015 (self-identified ethnicity reported in 78%), 69% identified as New Zealand European or Other European, 25% as Polynesian (18% Māori, 7% Pacific Islander), and 6% as Other ethnicities. These proportions are similar to those in the general population (http://archive.stats.govt.nz/Census/2013-census/profile-and-summary-reports/quickstats-culture-identity.aspx).[8,10]

It remains unknown whether ancestry is reflected in the spectrum and prevalence of pathogenic LQTS sequence variants in people of Polynesian ancestry. It is also unknown whether there are ethnicity-related inequities with regard to receiving molecular genetic testing and/or the extent of cascade screening in New Zealand LQTS families.

Here, using CIDRNZ data spanning 15 years, we assess overall diagnostic processing of New Zealand LQTS proband families in order to determine genetic testing yield and the resulting mutation spectrum stratified by self-identified ethnicity.

Methods

The CIDRNZ has been previously described in detail.[8,10,11] Probands are referred for genetic testing by specialist cardiac electrophysiologists affiliated to the New Zealand national Cardiac Inherited Diseases Group. When cases are referred by other cardiologists, or forensic pathologists (after a sudden unexplained death), the referral is vetted by the national multidisciplinary team with review of phenotypic data before approving or declining genetic testing.

This study includes clinical CIDRNZ LQTS probands (the first identified/registered individual with suspected LQTS in a family without known relation to any other New Zealand LQTS family) with a Schwartz score of ≥ 2[12] who had completed recommended genetic testing. Data were extracted from the secure CIDRNZ web-based database on February 28, 2018, coded on the basis of self-reported ethnicity, and retrospectively reviewed.

CIDRNZ self-reported ethnicity categories include subsets (in parentheses), here condensed into 3 main categories: (1) European (New Zealand European and Other European), (2) Polynesian (Māori, Cook Island Māori, Niuean, Other Pacific Islander, Samoan, and Tongan), and (3) Other (African, Chinese, Indian, Latin American Hispanic, and Middle Eastern). The self-reported ethnicity categories do not take multiethnicity into account.

Over the 15 years that this retrospective study covers (2003–2018), the recommended molecular genetic testing has changed several times, starting with testing only LQT1–3 genes in a research setting and progressing to clinically accredited laboratories with large multigene panels, with diagnostic techniques ranging from Sanger sequencing to multiplex ligation–dependent probe amplification.[9] This study focuses on LQT1–3 genes, and clinical LQTS probands with an identified possibly pathogenic sequence variant in a minor LQTS gene ($\sim$2% of probands, most notably probands presenting with LQT7, Andersen-Tawil syndrome or LQT8, Timothy syndrome) were excluded.

The critical assessment of the pathogenicity of the identified sequence variants has similarly improved over the last 15 years. Since pathogenicity criteria include previous documentation, including segregation and experimental data, variants found in a genetically relatively unstudied group (such as Polynesian peoples) are more likely not to reach pathogenicity thresholds. Hence, inclusion criteria for "variant-positive" was the identification of a class III–V sequence variant (III, variant of uncertain significance; IV, likely pathogenic; V, pathogenic), classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines using VarSome: the human genomic variant search engine (https://varsome.com) (as of March 23, 2019). Thus, the term *variant-positive* is not meant to imply pathogenicity or even functional abnormality, nor does it reflect our clinical practice. Sequence variants were classified using the standard nomenclature.[13]

There are no published Polynesian control genome data available for comparison. We used 110 control chromosomes from non-LQTS patients in order to assess the frequency of variants identified in Polynesian CIDRNZ LQTS probands. The genomes of 55 Māori and Pacific peoples are a combination of those who took part in the Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients (n=43)[14] and a study focusing on the genetic causes of gout and related conditions (n=12).[15] The whole-genome resequencing for these individuals was aligned and variant called using an adaptation of the Genome Analysis ToolKit (v3.6) best practices pipeline (https://doi.org/10.5281/zenodo.2564243 and https://doi.org/10.1101/201178). Variants with a minor allele frequency of $\geq$1% in the Polynesian control chromosomes were excluded and regarded as possible Polynesian population–specific polymorphisms, irrespective of ACMG class.

With regard to molecular genetic testing, we noted for each LQTS proband (1) the number of LQTS-related genes tested, (2) whether a class III–V sequence variant had been detected, (3) the number of additional family members tested in families where a class III–V sequence variant had been identified, and (4) the number of additional variant-positive family members detected in the same families.

For each class III–V sequence variant, we noted (1) LQTS subtype, (2) variant type, (3) variant location, (4) pathogenicity classification according to the ACMG guidelines, (5) whether the variant had been previously described outside New Zealand using VarSome (as of March 23, 2019), (6) whether the variant was unique or shared between ≥2 CIDRNZ probands, and (7) whether variants found in >1 proband were shared within or between ethnic groups (European, Polynesian, and Other).

Multiple clinical data in the CIDRNZ database were reviewed. These data included most severe clinical event, age at clinical diagnosis (in years), and the longest recorded corrected QT (QTc) interval (in milliseconds; measured by an experienced cardiologist in leads II and V_5 from 12-lead resting electrocardiograms using the tangent technique to determine the end of the T wave and corrected using $QTc = QT/\sqrt{R\text{-}R}$).[16] QTc assessments within 48 hours of cardiac arrest, while undergoing cerebral cooling or on QT-prolonging medications, were excluded.

Clinical presentations were condensed into 4 categories: (1) no symptoms, (2) nonspecific symptoms (palpitations, dizziness, shortness of breath, and chest pain), (3) syncope (likely ventricular arrhythmia including loss of consciousness with or without seizures, documented polymorphic ventricular tachycardia, and near drowning without need for resuscitation), and (4) 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).

Data were summarized and presented as total number plus percentage for proportions and mean ± SD for continuous variables. Pearson correlations (χ^2 test) were calculated between continuous variables/covariates. Association testing for continuous variables was performed by analysis of variance. For all analyses, a 2-tailed P value of <.05 was considered statistically significant. Statistical analyses were performed with GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla, CA; www.graphpad.com). Images were constructed using Open Source software Inkscape (https://inkscape.org).

Ethics approval

The study was approved by an institutional review committee (Health and Disability Ethics Committees, Wellington, AKX/02/00/107/AM03 and MEC/05/10/130) and all subjects provided written informed consent.

Data sharing

Data were collected with the ethics requirement that patients' data are confidential and will not be shared. Any questions should be directed to the corresponding author.

Results

Of the 264 CIDRNZ LQTS probands fulfilling the inclusion criteria, 160 (61%) reported as European, 79 (30%) Polynesian, and 25 (9%) Other ethnicities. There was no significant difference in the severity of clinical presentation across ethnic groups (Figure 1A); however, probands identifying as Polynesian were less likely to have a variant-positive

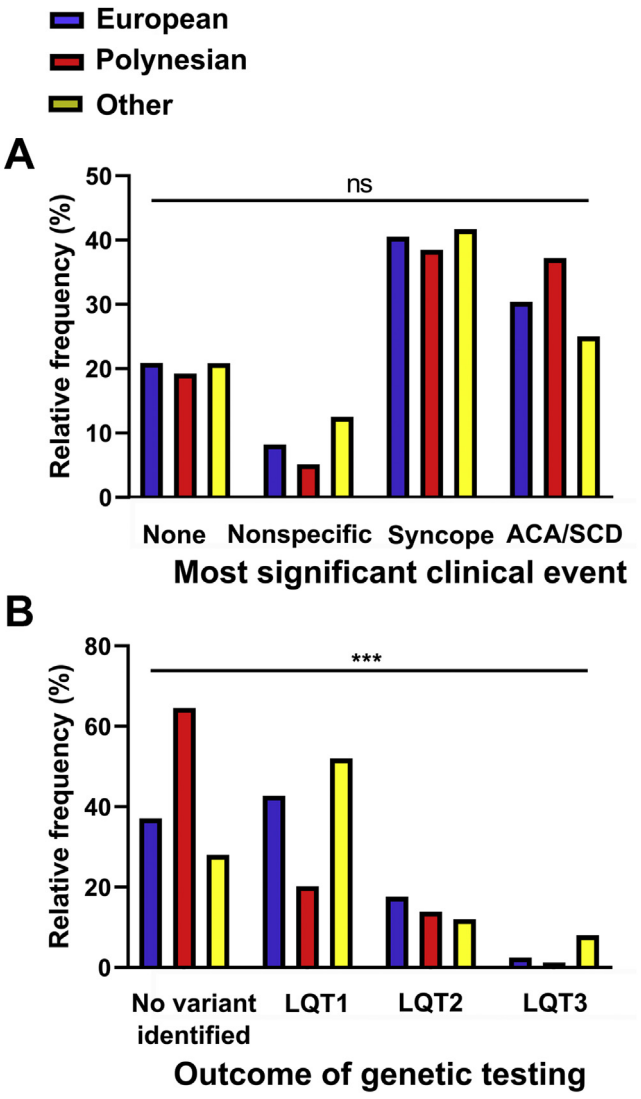

Figure 1 Clinical presentation and genetic testing outcome in 264 CIDRNZ LQTS probands. Clustered bar graphs (relative frequency [%]): European n=160 (*blue*), Polynesian n=79 (*red*), Other n=25 (*yellow*). **A:** The most severe clinical events recorded in CIDRNZ LQTS probands, stratified by ethnicity. None: incidental or isolated findings of QT prolongation on the surface electrocardiogram. Nonspecific: palpitations, dizziness, shortness of breath, chest pain, atrial fibrillation (and/or QT prolongation). Syncope: loss of consciousness, with or without seizures, documented polymorphic ventricular tachycardia, or near drowning without need for resuscitation. ACA/SCD: aborted cardiac arrest, near drowning requiring cardiopulmonary resuscitation/defibrillator cardioversion, and sudden cardiac death; ns = not significant (P=.573). **B:** The outcome of recommended molecular genetic testing in 264 CIDRNZ LQTS probands, stratified by ethnicity. A significant association between ethnicity and testing outcome was seen (P=.0006). The proportion of probands with an identified class III–V variant in LQT1–3 genes after testing (variant-positive) was significantly lower for probands identifying as Polynesian (35% vs 63% and 72% in probands of European and Other ethnicity, respectively, P<.0001). LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

Table 1 Clinical characteristics and molecular genetic testing performed in 264 CIDRNZ LQTS probands

Variable	All	European	Polynesian	Other	*P**
All LQTS probands	(n=264)	(n =160 [61%])	(n=79 [30%])	(n=25 [9%])	
Age at presentation (y)	28±19	29±19	27±19	26±17	.592
QTc interval (ms)	512±55	513±57	512±48	508±63	.912
Schwartz score†	3.6±1.0	3.6±1.0	3.6±1.0	3.5±1.0	.802
Genes tested	5.3±1.4	5.3±1.5	5.5±0.9	5.1±1.9	.342
Variant-positive	(n=148)	(n=102 [69%])	(n=28 [19%])	(n=18 [12%])	
Age at presentation (y)	26±19	28±19	22±15	23±18	.243
QTc interval (ms)	**519±47**	516±47	523±44	529±55	.545
Schwartz score	**3.7±1.0**	3.7±1.0	3.9±1.0	3.7±0.9	.632
Genes tested	5.0±1.5	4.9±1.4	5.4±1.3	4.9±2.2	.379
Family members tested	4.9±5.7	5.3±5.8	5.0±6.9	2.5±2.5	.159
Variant-positive family members identified/proband	2.6±3.2	2.8±3.3	2.6±3.5	1.4±1.9	.225
No variant identified	(n=116)	(n=58 [50%])	(n=51 [44%])	(n=7 [6%])	
Age at presentation (y)	30±19	31±20	29±20	34±12	.851
QTc interval (ms)	**504±62**	508±71	506±50	457±52	.122
Schwartz score	**3.4±1.1**	3.5±1.0	3.5±1.1	3.0±1.2	.515
Genes tested	5.7±1.1	5.8±1.4	5.6±0.6	5.7±0.8	.466

Values are presented as mean ± SD.

In probands in whom a class III–V sequence variant was detected, the mean QTc interval was longer (P=.03) and Schwartz score higher (P=.03), and these values are given in boldface.

CIDRNZ = Cardiac Inherited Disease Registry New Zealand; LQTS = long QT syndrome; QTc = corrected QT.

*Comparison across ethnic groups by 1-way analysis of variance.

†Schwartz score: ≥1.5 intermediate probability for LQTS; ≥3.5 high probability for LQTS.[12]

test result (35% vs European 63% or Other 72%; P<.0001) (Figure 1B). Among all probands, 72% had a history of cardiac events (syncope or ACA/SCD). Variant-positive Polynesian probands were more likely to have experienced cardiac events than European variant-positive probands (89% vs 68%; P=.03).

The clinical characteristics of the CIDRNZ LQTS probands and their molecular genetic testing results, stratified by ethnicity and genetic testing outcome, are presented in Table 1.

Among CIDRNZ LQTS probands, there were no significant differences in clinical characteristics, Schwartz score, or number of genes tested across ethnic groups (Table 1). A class III–V sequence variant in a LQTS-associated gene was identified in 148 probands (56%). Among variant-positive probands, 102 reported as European, 28 Polynesian, and 18 Other ethnicities (see Table 1). In LQTS families where a class III–V sequence variant had been identified, the extent of cascade screening (4.9±6 family members per proband; range 0–35 family members per proband) and the extent of additional variant-positives detected (2.6±3 per proband; range 0–14 per proband) were comparable across all groups (Table 1). Overall, variant-positive probands had a longer QTc interval and higher Schwartz score than did probands in whom no variant had been identified (519±47 ms vs 504±62 ms; P=.03 and 3.7±1 vs 3.4±1; P=.03). Among variant-positive CIDRNZ probands, irrespective of ethnicity, the majority were of LQT1 genotype (66%), followed by LQT2 (28%) and LQT3 (5%) (Figure 1B).

The protein location (for single nucleotide variants) and pathogenicity classification according to ACMG guidelines for all class III–V sequence variants in LQT1 (*KCNQ1*), LQT2 (*KCNH2*), and LQT3 (*SCN5A*) genes, stratified by CIDRNZ LQTS proband ethnicity, are shown in Figures 2A–2C, with further details in Online Supplemental Table 1 [S1 Table]. Among the variant-positive CIDRNZ probands, the identified LQT1–3 variants were 20% of unknown significance, 49% probably pathogenic, and 32% pathogenic. For each LQTS subgroup, the proportion of class III–V variants was LQT1 16%, 53%, 31%; LQT2 32%, 29%, 39%; and LQT3 86%, 14%, 0%. There was no significant difference in variant class across the ethnic groups (European 4.1±0.7, Polynesian 4.3±0.8, and Other 4.2±0.8; P=.473, when comparing the mean values allocated for each variant class) (Figure 3A). The clinical presentation of CIDRNZ probands with class III LQT1–3 variants is presented in Online Supplemental Table 2 [S2 Table].

Of all the identified class III–V LQT1–3 sequence variants (n=103), the majority were missense variants (67%) (see Online Supplemental Table 1). There was a significant association between variant type and ethnicity across all groups, with Polynesian probands being more likely to have non-missense nucleotide variants (57% vs 25% and 39% in probands of European and Other ethnicity, respectively; P=.005) (Figure 3B).

Thirty-two percent of variant-positive CIDRNZ LQTS probands had a sequence variant not reported outside New Zealand. Polynesian probands were more likely to have a sequence variant not reported elsewhere (71% vs European 22% and Other 28%; P<.0001) (Figure 3C).

The majority of class III–V LQT1–3 sequence variants identified in CIDRNZ LQTS probands were found in a single

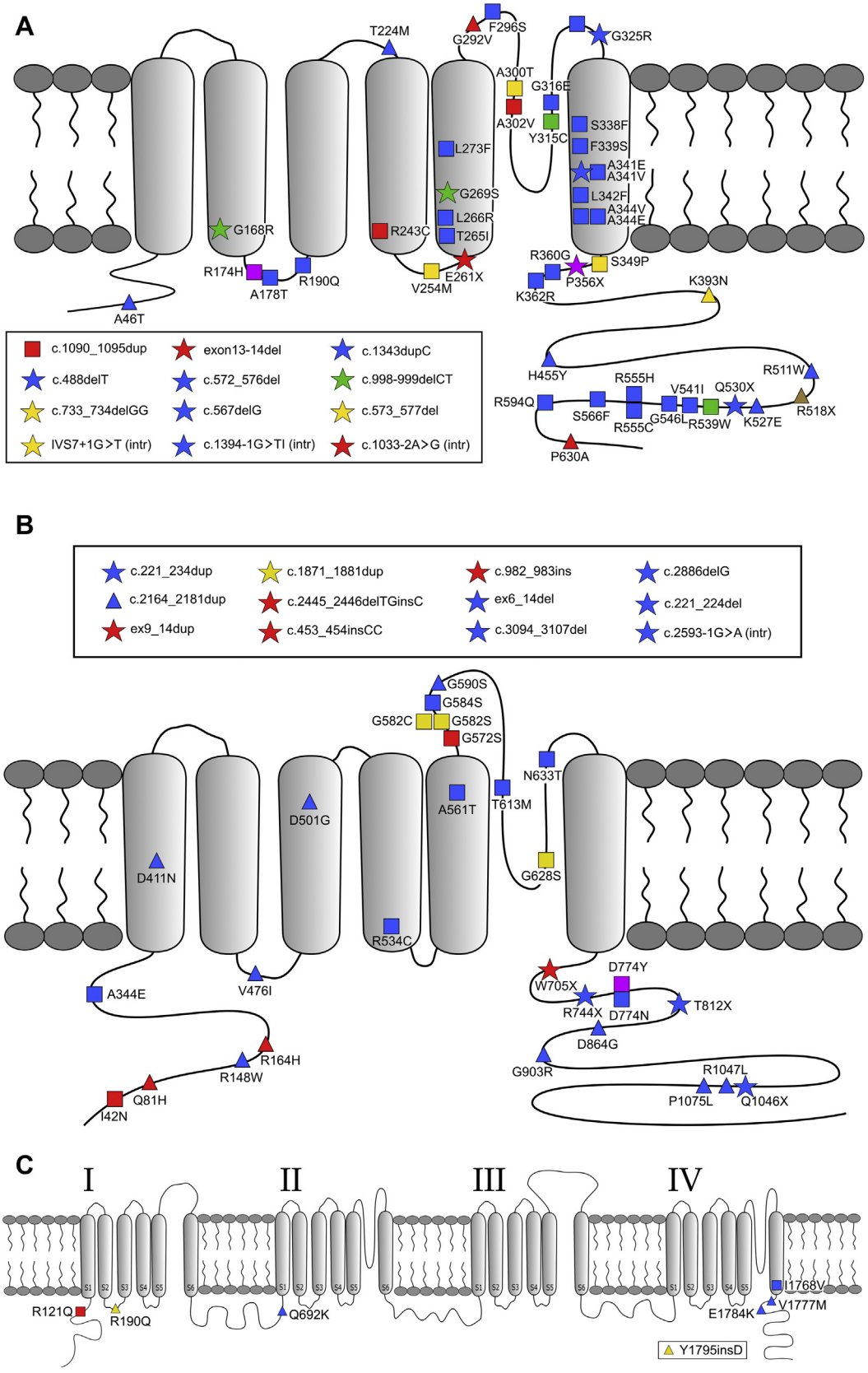

Figure 2 LQT1, LQT2, and LQT3 variant location and classification. Overview of the *KCNQ1* (**A**), *KCNH2* (**B**), and *SCN5A* (**C**) encoded potassium and sodium channels, including the location and amino acid changes in class III–V single nucleotide variants identified in CIDRNZ LQTS probands, stratified by ethnicity. Nonsense single nucleotide variants are depicted in the format 'R518X'-Arg-518-*stop codon. Frameshift and splice site variants (insertions, deletions, duplications, and intronic sequence variants within ±2 of a canonical splice site) are included in the insets. *Triangle*, class III; *square*, class IV; *star*, class V. *Blue*, European; *red*, Polynesian; *yellow*, *Other, green*, European and *Other, purple,* European and Polynesian; *brown*, all ethnicities; LQTS = long QT syndrome; LQT1 = long QT syndrome type 1; LQT2 = long QT syndrome type 2; LQT3 = long QT syndrome type 3.

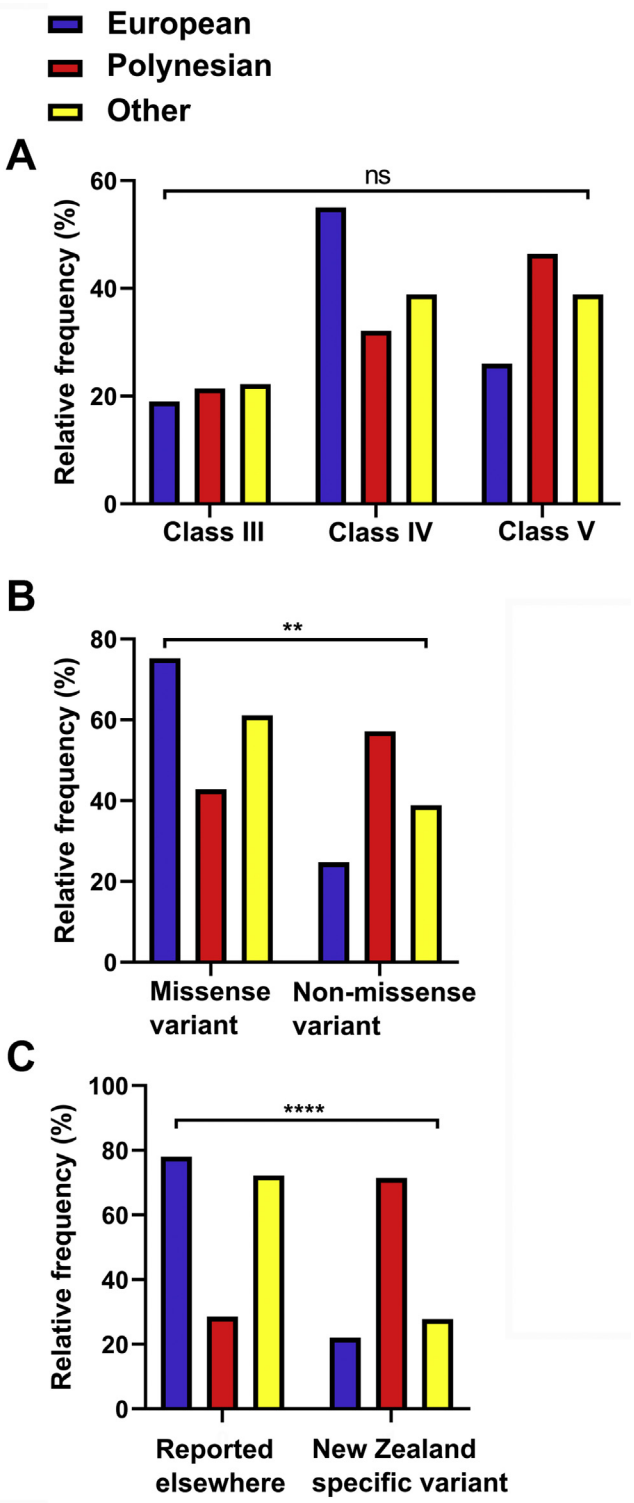

Figure 3 Variants identified in Polynesian LQTS probands were more likely rare. Clustered bar graphs (relative frequency %): European n=102 (*blue*), Polynesian n=28 (*red*), Other n=18 (*yellow*) for probands with a class III–V LQT1–3 variant. **A:** There was no significant difference between ethnicity groups with regard to the variant class according to the American College of Medical Genetics and Genomics guidelines identified in CIDRNZ LQTS probands (P=.190). **B:** Polynesian probands were more likely to have non-missense (splice site, nonsense, frameshift, and in-frame insertion/deletions) variants (57% vs 25% and 39% in probands of European and Other ethnicity, respectively; P=.005). **C:** Polynesian probands were more likely to have a sequence variant not reported outside New Zealand (71% vs European 22% and Other 28%; P<.0001). LQTS = long QT syndrome.

proband (78%), and 23 (22%) were found in ≥2 probands and were termed *shared variants*. Of the 23 shared variants, 14 (61%) were shared within the same ethnic group. A shared variant was identified in 70 (44%) variant-positive CIDRNZ LQTS probands (European 48%, Polynesian 50%, and Other 32%). Only the worldwide common hot-spot class III *KCNQ1*/R518X variant, identified in 5 probands, was found in all ethnic groups. The pattern of variant sharing among CIDRNZ LQTS probands, within and across ethnic groups, is shown in Figure 4.

Discussion

We report the diagnostic testing yield for LQTS1–3 in CIDRNZ LQTS probands, stratified by self-reported ethnicity, over a 15-year period. The largest ethnic groups living in New Zealand are Pākehā, meaning New Zealanders of European ancestry, and Māori and Pacific Island peoples (or Pasifika) of Polynesian ancestry, together constituting 91% of CIDRNZ LQTS probands. This study revealed that genetic testing of Polynesian probands was almost half as likely to reveal a class III–V LQT1–3 sequence variant, despite these probands presenting with similar parameters of disease severity and undergoing comparable diagnostic testing as non-Polynesian New Zealand LQTS probands. Moreover, we found that variant-positive Polynesian LQTS probands were more likely to have experienced syncope and life-threatening cardiac events, to have variants of a non-missense type, and to have variants not reported elsewhere.

Significant ethnicity-dependent differences in the frequency of arrhythmia-associated sequence variants and polymorphisms have been previously reported.[5–7] In a study assessing *KCNQ1* and *KCNH2* variants in 744 healthy individuals, 86% (42 of 49) were ethnicity specific and found exclusively in Asians (n=2), Hispanics (n=2), African Americans (n=26), or in those of European

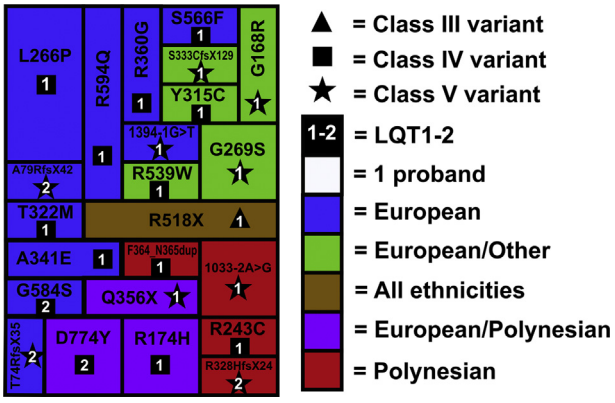

Figure 4 Variants identified in >1 proband were more likely shared within ethnic groups. Illustration depicting the pattern of variant sharing among CIDRNZ LQTS probands, within and across ethnic groups, including identifiers for LQTS subtype, variant class, and variant denominations (amino acid change). There were 23 class III–V LQTS variants that were identified in >1 proband (in total 70 probands, with 2–8 probands sharing each variant). Variants were preferentially shared within ethnic groups (P<.01). LQTS = long QT syndrome.

ancestry (n=12).[7] The 2 most common polymorphisms identified, while found in all ethnic groups, were significantly more common in those of European ancestry.[7] In LQTS patients and controls, the prevalence of rare *SCN5A* gene variants was the highest in African Americans (4.5%).[4] Similarly, of the 829 healthy individuals, 49% of the identified *SCN5A* variants were found only in African Americans.[6] Specifically, an *SCN5A* gene variant associated with increased arrhythmia risk was found in 13% of African Americans and in none of the Asians or those of European ancestry.[5]

While the common occurrence of a variant tends to infer that it is benign, previous studies on LQTS founder populations have shown that certain pathogenic variants may become relatively common in a population subset.[17–19] Founder effects occur when a small number of individuals are kept relatively isolated by factors such as regional isolation and/or there is preference to find spouses within a specific group. The enrichment of genetic variants in such population groups may be substantial,[20] and known genetic subgroups may well harbor an enrichment of genetic variants of clinical relevance.[19] Our finding that class III–V LQT1–3 variants are more likely to be shared exclusively within the same ethnic group and the finding of an ethnicity-specific LQT3 polymorphism (R1193Q) in 2 Polynesian LQTS probands, also present in 4.5% of Polynesian controls, support founder effects on the migration of the ancestral populations of the NZ Māori and Pacific peoples populations of New Zealand.

There is a paucity of knowledge on the background genetic variation in the Polynesian population, including arrhythmia-associated genes.[21,22] Defining the relevant population burden of genetic variants in LQTS-related cardiac ion channel genes is crucial for the proper interpretation of genetic test results.[7] As an example, the R1193Q variant mentioned above was initially thought to be possibly pathogenic, because of its absence in available control populations (of European ancestry). Knowledge of the background variation in populations constitutes a resource for epidemiological and functional investigation of variant effects on the repolarization properties of cardiac tissues, including susceptibility to lethal cardiac arrhythmias.[7] Our previous and current findings from New Zealand LQTS probands suggest significant differences in the frequency of genetic variants in Polynesian peoples.[23] As a consequence, we stress the importance of increasing the knowledge of background variation in this population.

The most striking finding of this study is that a class III–V sequence variant in a major LQTS gene was found in only 35% of Polynesian LQTS probands as compared with 63%–72% of non-Polynesian CIDRNZ probands undergoing comparable molecular genetic testing. As this study includes probands who were selected on suspicion of LQTS on the basis of comparable clinical characteristics and Schwartz scores, it is unlikely that our finding should reflect a true lower prevalence of LQTS in Polynesian peoples. It is well established that even when including major and minor LQTS genes, a pathogenic sequence variant remains elusive in ~20%–25% of probands with clinically definite LQTS.[4] It is also well established that the majority of our collective association data have been derived from studies of predominantly European populations. Recent fine-mapping studies including additional ethnic groups (not Māori or Pacific peoples) have shown significant associations between ethnicity and variance in various genes influencing the heritable QT interval length.[24,25] While the major LQTS genes, and several other genes, are associated with the QT interval length across ethnic groups, the authors have concluded that additional, novel, and possibly population-specific signals exist that correspond to new loci of interest.[25] To identify and characterize these new loci may further illuminate the genetic and molecular mechanisms underlying the QT interval length. We suggest that association studies in genotype-negative Polynesian families with definite LQTS may identify new loci of importance to cardiac repolarization.

As in other LQTS studies, the majority of sequence variants in New Zealand probands were of a missense type, were found in a single proband, and a third were novel.[4,26] Among the probands of European ancestry, 75% of variants identified were missense, which is similar to previous reports of 72%[3] and 70%,[2,26] respectively. However, among Polynesian probands, only 43% of variants identified were missense, and Polynesian probands were significantly more likely to have "radical" variants (57%). Radical variants, including splice site, nonsense, frameshift, and in-frame insertion/deletions, typically result in a drastically altered or truncated, and often nonfunctional, protein product.[4] In a study including 388 LQTS probands and >1300 healthy controls for each gene, radical variants in LQT1–3 genes were shown to have an estimated predictive value of >99% regardless of location.[4] The high frequency of radical variants in the variant-positive Polynesian CIDRNZ probands could potentially explain the significantly higher frequency of syncope and ACA/SCD in this group.

Conclusion

Genetic testing in Polynesian probands is half as likely to identify a class III–V LQTS sequence variant, despite these patients presenting with similar parameters of disease severity and undergoing comparable diagnostic testing. Variant-positive Polynesian probands are more likely to experience syncope and life-threatening cardiac events, and their variants are more likely to be rarer, non-missense, and not reported outside New Zealand.

Acknowledgments

We gratefully acknowledge all the members of the Cardiac Inherited Disease Group not included as authors here, who have as clinicians referred many cases and worked with us to establish the phenotype. We also thank members of the clinical and molecular genetic services across New Zealand.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2020.03.015.

References

1. Skinner JR, Winbo A, Abrams D, Vohra J, Wilde AA. Channelopathies that lead to sudden cardiac death: clinical and genetic aspects. Heart Lung Circ 2019; 28:22–30.
2. Kapplinger JD, Tester DJ, Salisbury BA, et al. Spectrum and prevalence of mutations from the first 2,500 consecutive unrelated patients referred for the FAMILION long QT syndrome genetic test. Heart Rhythm 2009;6:12971303.
3. Splawski I, Shen J, Timothy KW, et al. Spectrum of mutations in long-QT syndrome genes: KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. Circulation 2000;102:1178–1185.
4. Kapa S, Tester DJ, Salisbury BA, et al. Genetic testing for long-QT syndrome: distinguishing pathogenic mutations from benign variants. Circulation 2009; 120:1752–1760.
5. Splawski I, Timothy KW, Tateyama M, et al. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. Science 2002; 297:1333–1336.
6. Ackerman MJ, Splawski I, Makielski JC, et al. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. Heart Rhythm 2004;1:600–607.
7. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. Mayo Clin Proc 2003;78:1479–1487.
8. Earle NJ, Crawford J, Hayes I, et al. Development of a cardiac inherited disease service and clinical registry: a 15-year perspective. Am Heart J 2019; 209:126–130.
9. Kayser M, Brauer S, Cordaux R, et al. Melanesian and Asian origins of Polynesians: mtDNA and Y chromosome gradients across the Pacific. Mol Biol Evol 2006;23:2234–2244.
10. Earle N, Crawford J, Gibson K, et al. Detection of sudden death syndromes in New Zealand. N Z Med J 2016;129:67–74.
11. Marcondes L, Crawford J, Earle N, et al. Long QT molecular autopsy in sudden unexplained death in the young (1-40 years old): lessons learnt from an eight year experience in New Zealand. PLoS One 2018;13:e0196078.
12. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation 2011;124:2181–2184.
13. Antonarakis SE; Nomenclature Working Group. Recommendations for a nomenclature system for human gene mutations. Hum Mutat 1998;11:1–3.
14. Becker MA, Fitz-Patrick D, Choi HK, et al. An open-label, 6-month study of allopurinol safety in gout: the LASSO study. Semin Arthritis Rheum 2015; 45:174–183.
15. Krishnan M, Major TJ, Topless RK, et al. Discordant association of the CREBRF rs373863828 A allele with increased BMI and protection from type 2 diabetes in Māori and Pacific (Polynesian) people living in Aotearoa/New Zealand. Diabetologia 2018;61:1603–1613.
16. Waddell-Smith K, Gow RM, Skinner JR. How to measure a QT interval. Med J Aust 2017;207:107–110.
17. Brink PA, Crotti L, Corfield V, et al. Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population. Circulation 2005;112:2602–2610.
18. Winbo A, Diamant UB, Rydberg A, Persson J, Jensen SM, Stattin EL. Origin of the Swedish long QT syndrome Y111C/KCNQ1 founder mutation. Heart Rhythm 2011;8:541–547.
19. Winbo A, Stattin EL, Nordin C, et al. Phenotype, origin and estimated prevalence of a common long QT syndrome mutation: a clinical, genealogical and molecular genetics study including Swedish R518X/KCNQ1 families. BMC Cardiovasc Disord 2014;14:22.
20. Einarsdottir E, Egerbladh I, Beckman L, Holmberg D, Escher SA. The genetic population structure of northern Sweden and its implications for mapping genetic diseases. Hereditas 2007;144:171–180.
21. Merriman TR, Wilcox PL. Cardio-metabolic disease genetic risk factors among Maori and Pacific Island people in Aotearoa New Zealand: current state of knowledge and future directions. Ann Hum Biol 2018;45:202–214.
22. Robertson SP, Hindmarsh JH, Berry S, et al. Genomic medicine must reduce, not compound, health inequities: the case for Hauora-enhancing genomic resources for New Zealand. N Z Med J 2018;131:81–89.
23. Earle N, Yeo Han D, Pilbrow A, et al. Single nucleotide polymorphisms in arrhythmia genes modify the risk of cardiac events and sudden death in long QT syndrome. Heart Rhythm 2014;11:76–82.
24. Seyerle AA, Young AM, Jeff JM, et al. Evidence of heterogeneity by race/ethnicity in genetic determinants of QT interval. Epidemiology 2014;25:790–798.
25. Avery CL, Wassel CL, Richard MA, et al. Fine mapping of QT interval regions in global populations refines previously identified QT interval loci and identifies signals unique to African and Hispanic descent populations. Heart Rhythm 2017;14:572–580.
26. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Compendium of cardiac channel mutations in 541 consecutive unrelated patients referred for long QT syndrome genetic testing. Heart Rhythm 2005;2:507–517.