Psychological Distress and Quality of Life in Participants Undergoing Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy Caused by *TMEM43* p.S358L: Is It Time to Offer Population-Based Genetic Screening?

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Keywords

Arrhythmogenic right ventricular cardiomyopathy · Distress · Quality of life · Population-based genetic screening

Abstract

Purpose: We have identified 27 families in Newfoundland and Labrador (NL) with the founder variant *TMEM43* p.S358L responsible for 1 form of arrhythmogenic right ventricular cardiomyopathy. Current screening guidelines rely solely on cascade genetic screening, which may result in unrecognized, high-risk carriers who would benefit from preemptive implantable cardioverter-defibrillator therapy. This pilot study explored the acceptability among subjects to *TMEM43* p.S358L population-based genetic screening (PBGS) in this Canadian province. **Methods:** A prospective cohort study assessed attitudes, psychological distress, and health-related

quality of life (QOL) in unselected individuals who underwent genetic screening for the *TMEM43* p.S358L variant. Participants ($n = 73$) were recruited via advertisements and completed 2 surveys at baseline, 6 months, and 1 year which measured health-related QOL (SF-36v2) and psychological distress (Impact of Events Scale). **Results:** No variant-positive carriers were identified. Of those screened through a telephone questionnaire, >95% felt positive about population-genetic screening for *TMEM43* p.S358L, though 68% reported some degree of anxiety after seeing the advertisement. There were no significant changes in health-related QOL or psychological distress scores over the study period. **Conclusion:** Despite some initial anxiety, we show support for PBGS among research subjects who screened negative for the *TMEM43* p.S358L variant in NL. These findings have implications for future PBGS programs in the province.

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited, autosomal dominant cardiomyopathy which can lead to ventricular arrhythmias and sudden cardiac death (SCD) [1]. Its prevalence in the general population is estimated to be between 1/2,000 and 1/5,000, but variability in presentation and insensitive clinical tests make an accurate prevalence difficult to establish [2]. One form of ARVC, caused by the *TMEM43* p.S358L pathogenic variant, was discovered in Newfoundland and Labrador (NL) and demonstrates complete penetrance and a sex-influenced phenotype [3, 4]. Males present with a severe form of the disease, exhibiting cardiac symptoms and SCD at a much younger age compared to females [4]. Placement of an implantable cardioverter-defibrillator (ICD) for both primary prevention (based on variant testing alone) and secondary prevention (based on variant analysis and clinical evidence of ventricular arrhythmias) confers a significant survival benefit in *TMEM43* p.S358L carriers [5]. The most substantial benefit is seen in primary prevention for male carriers, where placement of an ICD leads to a survival increase of 31 years [5]. Identifying carriers through population-based genetic screening (PBGS) could improve survival not only through placement of an ICD, but through earlier counseling of safe exercise practices given the association of ventricular arrhythmias with moderate to high-intensity exercise [6]. The lifelong risk of ventricular arrhythmias and SCD highlights the importance of identifying all individuals at risk of carrying the *TMEM43* p.S358L variant who would benefit from placement of a lifesaving ICD.

Due to a major founder effect in the island's population, we have identified 27 multigenerational multiplex families with the *TMEM43* p.S358L pathogenic variant that predates the peopling of the island of Newfoundland [7]. New families or extended branches of known families are often ascertained following the death of a young relative, followed by cascade genetic screening to identify gene carriers [8]. Cascade genetic screening works well within families, where the only requirement for testing is relatedness to the proband (often a deceased relative) irrespective of clinical symptoms. However, identifying new ARVC families in the absence of a severe clinical event is unlikely due to (a) variability of expression resulting in minimal clinical signs and symptoms (especially in women), (b) misattribution of SCD to other causes (e.g., accidents), (c) uninformative family structure (small family, mostly females), and (d) lack of local tertiary-level diagnostic testing [9, 10]. Relying solely on cascade ge-

netic screening may result in unidentified *TMEM43* p.S358L carriers in the population. If this is indeed the case, PBGS for *TMEM43* p.S358L may serve as an additional screening tool in this population where a high burden of disease coexists with lifesaving prophylactic treatment [5–7, 11].

PBGS has historically been used for preconception counseling in couples at risk of transmitting genetic disease as well as in the newborn period for identification of autosomal recessive conditions. However recently, research has focused on the utility of PBGS for carrier detection of autosomal dominant conditions which clinically present in early adulthood. These conditions include BRCA-related hereditary breast and ovarian cancer (HBOC), hereditary nonpolyposis colorectal cancer (HNPCC), and familial hypercholesterolemia (FH). As a group, these have been classified as Tier 1 genetic conditions by the Centers of Disease Control and Prevention (CDC), for which early identification and intervention have a meaningful clinical impact [12]. Many studies have supported the use of PBGS in high-risk populations – BRCA1/2 screening for HBOC in Ashkenazi Jewish women [13–20], MLH1/MSH2/MSH6/PMS2 screening for HNPCC in women diagnosed with endometrial cancer [21], and APOB/LDLR/PCSK9 screening for FH in South Africans [22] as well as in the general population [23–25]. These studies also highlight that a significant number of newly identified carriers, some of which have a diagnosis of cancer related to their underlying genetic variant [25], do not meet clinical criteria for genetic screening based on local guidelines [13–15, 19, 21–23, 25]. Similar to the CDC Tier 1 genetic conditions, it is likely that many *TMEM43* p.S358L carriers remain unidentified in the province due to the innate inadequacies of cascade genetic screening in conjunction with NL's founder population. The purpose of this study was to explore the acceptability of pathogenic variant-specific PBGS for *TMEM43* p.S358L in NL.

Materials and Methods

Study Design

This was a prospective cohort study which assessed (1) the impact of PBGS for the *TMEM43* p.S358L variant on psychological distress and quality of life (QOL) up to 1-year post-genetic testing and (2) public attitudes towards this method of detection.

Study Population

All individuals who had at least 1 grandparent from NL and who could provide informed consent were eligible.

Participant Recruitment

The majority of study participants were recruited through advertisements on television, radio, and in community newspapers in geographical regions of the island of Newfoundland known to have families with ARVC. A small proportion of participants had heard about the study through a family member or friend and had contacted the Provincial Medical Genetics Program directly, while others had expressed their interest in participating while visiting the genetics clinic for an unrelated reason. Before determining eligibility, the coordinator (author CS) asked the potential participants (a) how did you hear about the study and (b) 2 closed-ended Likert survey items assessing their attitude towards population sampling. This included (1) on a scale of 1 (not) to 5 (very), how anxious were you after seeing the advertisement and (2) on a scale of 1 (not) to 5 (very), do you think identifying people with a potentially serious heart condition using an advertisement in a newspaper is a good idea. In this way, public attitudes were recorded even in those who chose to not take part in the study or were ineligible. For those eligible and willing, the coordinator collected contact information and mailed a study package, including an introduction letter and a consent form. Those ineligible or not wishing to continue were thanked for their time.

Variant Testing

A cardiac Genetic Counselor (GC) (author FC) contacted the participant within 2 weeks to review the consent form. Participants were then offered an appointment at which the GC provided in depth counseling about ARVC caused by *TMEM43* p.S358L. This included an explanation of the possible results of the genetic test, implications for themselves and family members, and a discussion of psychosocial issues related to genetic screening. It was explained that any individual found to have the *TMEM43* p.S358L variant would be referred to Eastern Health's Cardiac Genetic Clinic for management. All potential participants were informed that a copy of their DNA test result would be provided to their primary care physician. Following counseling, if the participant wished to continue, a spit sample from which DNA could be extracted was obtained. DNA was extracted from saliva as per recognized protocols [26, 27] and determination of the presence or absence of the *TMEM43* p.S358L variant was assessed using Sanger sequencing [3].

Quantitative Assessments

Demographic information was obtained initially by the GC. Participants were asked to complete 2 surveys at baseline, 6 months, and 1 year to measure health-related QOL and psychological distress. Follow-up surveys were completed by mail. Validated measures included the SF-36v2 and the Impact of Events Scale (IES), both used extensively to assess psychological well-being across numerous health conditions.

The SF-36v2 contains 36 questions which assess health-related QOL. The sections of the SF-36v2 include physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Scaled scores were transformed to a 0–100 scale; lower scores reflect higher levels of disability and higher scores reflect lower levels of disability [28].

The IES is a 15-item scale which assesses an individual's level of psychological distress in response to an identifiable event [29] – in this case, the event was defined as undergoing predic-

Fig. 1. Reported anxiety levels upon seeing or hearing advertisements designed to inform potential participants about the genetic screening study for *TMEM43* p.S358L on television, radio, and/or in community newspapers by 63 individuals who inquired about the study (21 males, 42 females). No significant differences were noted.

Fig. 2. Opinions on the use of advertisements on television, radio, and/or in community newspapers from 84 individuals (28 males and 56 females) who inquired about the genetic screening study for *TMEM43* p.S358L. No significant differences were noted.

tive genetic testing for the *TMEM43* p.S358L variant. Each question is scored on a Likert scale based on the participant's response and weighted between not at all = 0 and often = 5 [29]. The range of global scores falls between 0 and 75 [29]. Two subscales were created, including an Intrusive Subscale and an Avoidant Subscale which range from 0 to 35 and 0–40, respectively [29]. The intrusive subscale identifies if an individual is experiencing intrusive thoughts, nightmares, feelings, or imagery associated with the event; the Avoidant Subscale identifies if an individual is actively avoiding thoughts and feelings associated with the event [29].

Statistical Analysis

Descriptive statistics, in the form of frequency (proportion) and mean $\pm$ standard deviation, were conducted on categorical and continuous variables, respectively. χ^2 analyses and logistic re-

Table 1. Characteristics of the study population ($n = 73$)

	Male	Female	Total
Sample size, n (%)	23 (31.5)	50 (68.5)	73
Age mean, years $\pm$ SD	50 $\pm$ 14	53 $\pm$ 13	52 $\pm$ 13
Education, n (%)*			
<High School	1 (4)	5 (10)	6 (8)
High school	4 (17)	11 (23)	15 (21)
College diploma	13 (57)	18 (38)	31 (44)
University degree	5 (22)	14 (29)	19 (27)
Missing data	0	2	2
Personal history of cardiac condition, n (%)	4 (17)	12 (24)	16 (22)
Family history of SCD, n (%)	17 (74)	44 (88)	61 (84)
Prior knowledge of ARVC, n (%)	11 (48)	20 (40)	31 (43)
History of genetic testing, n (%)	2 (9)	3 (6)	5 (7)

SCD, sudden cardiac death; ARVC, arrhythmogenic right ventricular cardiomyopathy. * (%) represents the valid percentage.

gressions were used to identify categorical and continuous variables which were predictive of anxiety levels after seeing the study advertisement. Data from the SF-36v2 questionnaires were scored using the QualityMetric Health Outcomes Scoring Software Version 4.5. A repeated measures, linear mixed-effect model was performed to compare the means of the transformed scores for each component of the SF-36v2 and IES between the 3 time points (baseline, 6 months, and 1 year). The statistical software program SPSSv20 was used for all analyses and a p value ≤ 0.05 was considered statistically significant.

Results

Demographic Data

Ninety-four individuals inquired about the study, the majority of whom completed the 2 initial screening questions (Fig. 1, 2). Population-genetic screening for *TMEM43* p.S358L was considered a somewhat (15%) or a very good idea (80%), with a minority (3%) describing it as a poor method of screening. A degree of anxiety after seeing the advertisement was reported by 68% of participants, with 23% feeling very anxious and 17% feeling extremely anxious. Most respondents (58%) felt moderate anxiety or less after seeing the advertisement. There were no significant differences between male and female respondents on opinions surrounding the advertisement or anxiety levels after seeing the advertisement.

Seventy-three individuals continued beyond the first phone call and provided a spit sample for testing. No *TMEM43* p.S358L carriers were identified. DNA test results were provided to participants at a median of 3-month post sample being obtained. All but 1 participant received

their genetic results in 6 months or less. Characteristics of the study population are in Table 1. The mean age was 52 years, 69% ($n = 50$) were female, and the majority had a post-secondary education (71%). Through a self-report survey item, 84% indicated that a family member had passed away due to SCD. Extended family histories were fully explored with the GC during genetic counseling and 3 individuals were referred to the Eastern Health Cardiac Genetic Clinic for further evaluation, clinical screening, and follow-up. Thirty-one participants (43%) stated they were familiar with ARVC primarily because there was an ARVC diagnosis within their extended family; in all cases, the affected family member was related via a distant marriage, and likely reflects the close-knit communities in these regions. Only 5 individuals (7%) had undergone genetic testing in the past and had done so through other genetic research studies. There were no significant differences in baseline characteristics between male and female participants.

Health-Related QOL: SF-36v2

A repeated measures, linear mixed-effect model did not show any significant differences in the means of the transformed scores for each component of the SF-36v2 in participants who underwent genetic screening over the study period (Table 2).

Psychological Distress Levels: IES

The mean global and subscale scores for the IES were low and did not significantly change between baseline, 6 months, and 1 year using a repeated measures, linear mixed-effect model (Table 3).

Table 2. SF-36v2 section scores (0–100) at baseline, 6 months and 1 year post-genetic testing for *TMEM43* p.S358L

SF-36v2 section	Time of follow-up						
	baseline	6 months	1 year	baseline to 6 months		baseline to 1 year	
				CI	<i>p</i> value	CI	<i>p</i> value
Physical functioning	79.9±2.4	81.9±2.8	80.6±3.1	−6.9 to −2.9	0.420	−6.1 to −4.8	0.802
Role physical	84.1±2.6	82.5±3.2	83.3±3.4	−4.1 to −7.4	0.575	−5.5 to −7.1	0.803
Bodily pain	69.9±2.8	69.5±3.2	66.8±3.5	−5.1 to −6.0	0.868	−3.0 to −9.3	0.308
General health	66.9±2.4	64.4±2.8	64.5±3.0	−2.2 to −7.2	0.295	−2.8 to −7.7	0.362
Vitality	59.8±2.5	58.5±3.0	59.0±3.2	−3.7 to −6.4	0.602	−4.8 to −6.5	0.767
Social functioning	82.0±2.7	80.0±3.2	85.6±3.5	−3.8 to −8.2	0.462	−10.2 to −3.1	0.289
Role emotional	88.9±2.0	87.6±2.5	89.3±2.8	−3.6 to −6.2	0.594	−5.8 to −5.0	0.881
Mental health	77.3±2.5	73.8±2.8	77.0±3.0	−0.5 to −7.4	0.086	−4.1 to −4.7	0.893

Data presented as mean ± standard error. Data analyzed using a repeated measures, linear mixed-effect model.

Table 3. IES section scores at baseline, 6 months, and 1 year post-genetic testing for *TMEM43* p.S358L

IES section	Time of follow-up						
	baseline	6 months	1 year	baseline to 6 months		baseline to 1 year	
				CI	<i>p</i> value	CI	<i>p</i> value
Intrusive subscale range 0–35	5.5±0.9	4.9±1.2	4.6±1.3	−1.8 to −3.0	0.635	−1.7 to −3.6	0.493
Avoidant subscale range 0–40	6.1±1.1	5.4±1.3	5.7±1.5	−1.9 to −3.2	0.604	−2.5 to −3.3	0.780
Global subscale range 0–75	11.0±1.9	10.1±2.4	9.6±2.7	−4.0 to −5.9	0.700	−4.1 to −6.9	0.617

Data presented as mean ± standard error. Data analyzed using a repeated measures, linear mixed-effect model. IES, impact of event scale.

Discussion

This is the first study to assess public attitudes and the psychological impact of PBGS for the *TMEM43* p.S358L pathogenic variant causing 1 form of ARVC. Despite some anxiety reported after seeing the study advertisement, we demonstrated public support for PBGS, consistent with other studies [16–20, 24]. All participants tested negative for the *TMEM43* p.S358L variant and did not experience any significant adverse psychological effect measured by the SF36-v2 and IES up to 1 year following genetic testing, a situation mirrored in previous PBGS studies for BRCA1/2 [16].

We did not identify any carriers of the *TMEM43* p.S358L variant and cannot comment on the impact of being identified as a carrier via this method on psychological distress and QOL. It is likely that being identified as a carrier of *TMEM43* p.S358L could affect QOL based

on the previous research which highlights several areas of concern including employment restrictions, large financial burdens, and insurability post-genetic testing [30]. Furthermore, those screening positive for the *TMEM43* p.S358L variant would have to choose whether to have placement of an ICD, which, although demonstrably life-saving [5], is also known to impact psychological and physical well-being [31, 32]. Young ICD patients with genetic forms of heart disease (including ARVC) have reported increased levels of depression, anxiety, and post-traumatic stress, and show decreased scores on QOL measures in the short-term [33–35]. Additional distress may also be caused by the burden of the risk of transmission to subsequent generations. The increase in survival of >30 years in males provided with an ICD for prophylaxis, >20 years in males with an ICD following clinical ventricular tachyarrhythmia's, and >2 years in females has likely allowed psychological sequelae to this disease

to be recognized; historically, early SCD secondary to lethal arrhythmias or progressive cardiac dysfunction was the overwhelming impact on families and individuals.

The study sample is small, and we do not know if findings generalize to a wider population. Referrals to the Genetic Cardiac Clinic have increased for *TMEM43* p.S358L testing (pers comm, FC), and anecdotally the demand from the public appears to be very high. This is reflected in the number of people who responded to this research project who declared a family history of SCD. Perhaps unsurprisingly, there was significant loss to follow-up in our study population of noncarriers, potentially creating a selection bias in those respondents who completed follow-up surveys. Nonetheless, we showed it was acceptable to provide PBGS for the *TMEM43* p.S358L variant and demonstrated that this form of screening is perceived favorably by the public despite some degree of anxiety.

Newfoundland's founder population makes it an ideal location for PBGS not only for ARVC caused by *TMEM43* p.S358L but also for other hereditary forms of cardiac disease with high prevalence. Although the aim of our study was to assess the impact of PBGS for *TMEM43* p.S358L on psychological health and QOL, our findings beg the question of whether PBGS for *TMEM43* p.S358L should be implemented in NL to identify at risk carriers. As elucidated in the 1960s, the features which make a disease suitable for population screening include a disease with a high prevalence in a recognized population, the ability to identify asymptomatic carriers through noninvasive testing, and the availability of treatments which, when provided early, improve prognosis [11]. While most screening programs to date utilize noninvasive tests such as pap smears, mammograms, and fecal immunochemistry to identify at risk individuals, there has been a push toward offering genetic-based population screening for several hereditary conditions. Of these, the CDC has recognized HBOC, HNPCC, and FH as Tier 1 genetic conditions for which early identification and intervention results in a clinically significant outcome [12]. ARVC caused by *TMEM43* p.S358L is a classic example of a CDC Tier 1 genetic condition – a disease which affects a distinct population that can be identified through genetic screening and has a proven impact on survival when treatment is offered [12]. The discovery of *TMEM43* p.S358L in NL has also led the American College of Medical Genetics and Genomics (ACMG) to classify *TMEM43* as one of the “ACMG 59” – genes where specific variants are known to cause disorders with clinical phenotypes that are serious, and where clinical action is available and acceptable [36]. Detecting p.S358L in the *TMEM43* gene by exome or ge-

nome sequencing is now recognized as an actionable finding as disease outcome is modified substantially by early, presymptomatic treatment with an ICD [36].

In conclusion, we show acceptance of PBGS among research subjects who screened negative for the *TMEM43* p.S358L variant in NL with minimal impact on anxiety levels, health-related QOL, and psychological distress. Although we were not able to identify any new carriers due to a small sample size, we believe that PBGS for the *TMEM43* p.S358L variant could serve as an additional screening tool in NL to detect carriers who would benefit from lifesaving treatment with an ICD. Our local infrastructure, which includes the Cardiac Genetics Program and Electrophysiology Department, makes PBGS for this pathogenic variant potentially feasible.

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Statement of Ethics

This research was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans – TCPS 2 and the World Medical Association Declaration of Helsinki. All participants have given their written informed consent. The Health Research Ethics Board (HREB) of NL (File Ref # 12.138) approved this study.

Conflict of Interest Statement

The authors wish to declare that they have none to disclose.

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Author Contributions

Cassidy Brothers and Kathleen Hodgkinson contributed equally to the manuscript: Kathleen Hodgkinson and Holly Etchegary were co-supervisors for Cassidy Brothers research project. Terry-

Lynn Young (molecular genetics), Daryl Pullman (bioethics and GE³LS), and Sean Connors (clinical electrophysiology) were all leads for the SCD research project and involved in the manuscript preparation. Fiona Curtis was the GC. Charlene Simmonds was the Research Manager/Coordinator/Assistant and oversaw data collection and storage. Jim Houston (RA) completed genetic testing for the TMEM43 mutation from participant samples in Terry-Lynn Young's laboratory. Hensley H. Mariathas helped with statistical analysis.

Data Availability Statement

All data generated or analyzed for the study are available upon request to the corresponding author.

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