

A *KCNQ1* V205M missense mutation causes a high rate of long QT syndrome in a First Nations community of northern British Columbia: a community-based approach to understanding the impact

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Purpose: Hereditary long QT syndrome is named for a prolonged QT interval reflecting predisposition to ventricular arrhythmias and sudden death. A high rate in a remote, northern Canadian First Nations community was brought to attention. **Methods:** Two severely affected index cases and 122 relatives were ascertained using community-based participatory research principles. Genetic sequencing of five known genes responsible for long QT syndrome was carried out on the index cases, leading to the identification of a novel missense mutation. Functional properties of the identified mutation were studied in transfected mouse *Itk* cells using whole cell patch clamp techniques. Corrected QT interval measurements were obtained from participants and subsequent genotyping of relatives was carried out. **Results:** In the two index cases, a novel missense mutation (V205M) was identified in the S3 transmembrane helix of KvLQT1, the pore forming domain of the I_{Ks} channel complex. In transfected mouse *Itk*-cells the V205M mutation suppressed I_{Ks} by causing a dramatic depolarizing shift in activation voltage coupled with acceleration of channel deactivation. Twenty-two mutation carriers had a significantly higher mean corrected QT interval than noncarriers (465 ± 28 milliseconds vs. 434 ± 26 milliseconds, $P < 0.0001$); however, 30% of carriers had a corrected QT interval below 440 milliseconds. **Conclusion:** A novel *KCNQ1* mutation in this founder population likely confers increased susceptibility to arrhythmias because of decreased I_{Ks} current. Even with a common mutation within a relatively homogenous population, clinical expression remains variable, exemplifying the multifactorial nature of long QT syndrome, and supporting the difficulty of definitive diagnosis without genetic testing. A community participatory approach enabled a comprehensive evaluation of the impact. *Genet Med* 2008;10(7):545–550.

Key Words: long QT syndrome, *KCNQ1*, V205M, North American Indian, community-based participatory research

Long QT syndrome (LQTS), which can be acquired or congenital, results from delayed repolarization of cardiac ventricular action potentials, and is characterized by a prolongation in the QT interval of the electrocardiogram (ECG). It can be as-

sociated with a serious multifocal ventricular tachyarrhythmia, *torsades de pointes*,¹ which may lead to syncope and sudden death. Genetically heterogeneous, at least eight different genes are known to be responsible for the congenital form.^{2,3} Although considered to be inherited in an autosomal dominant pattern because a single mutation may alter channel function, compound mutations⁴ and common polymorphisms⁵ also play a role in the pathogenesis of congenital LQTS, illustrating the complex etiology.⁶ Genetic predisposition may play an important role in acquired drug-induced LQTS⁷ and furthermore a number of common medications increase the risk of a cardiac event for those with congenital LQTS.⁸ Treatment is effective in reducing mortality and consists of avoidance of QT prolonging drugs, the use of beta blockers and/or implanted cardioverter-defibrillators.^{8,9}

Congenital LQTS is relatively rare, affecting an estimated 1 in 5,000–10,000 people,¹⁰ but it is disproportionately prevalent in a Canadian First Nations community of 5500 people in

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northern British Columbia (the Gitksan), whose ancestors are said to have resided there for thousands of years without European contact until 1860. Forty individuals had been diagnosed as likely having the condition, and another 200 were considered at risk. Although founder mutations have been previously reported in Finland¹¹ and South Africa,¹² hereditary LQTS has not been reported in North American Aboriginal populations. Although a report from the Strong Heart Study found that prolonged corrected QT interval (QTc) was an independent predictor for all causes of mortality for a large American Indian cohort, congenital LQTS per se was not discussed.¹³

Through a community initiated study of 124 participants identified because they either had LQTS or had a relative diagnosed with LQTS, we identified a novel missense mutation (valine substitution with methionine at position 205, V205M) in the S3 transmembrane region of *KCNQ1*, the α -subunit for the slow delayed rectifier potassium channel, I_{Ks} . The V205M mutation was present in 22 individuals in three separate kindreds who are of the same First Nation, suggesting a frequency of at least 1 in 250 people in this remote community.

Four KvLQT1 subunits coassemble with MinK accessory subunits to form the slowly activating and slowly deactivating I_{Ks} in the heart, which modulates the repolarization of cardiac action potentials,^{14,15} particularly during sympathetic activation and tachycardia.¹⁶ LQTS linked to mutations in the *KCNQ1* gene is usually attributed to a decrease or suppression of I_{Ks} by the prevention of efficient protein folding and trafficking to the cell membrane,^{17–20} and less often to modification of the response of I_{Ks} channels to changes in voltage such that their contribution to repolarization is diminished.^{21–23}

Aboriginal communities may be hesitant to participate in genetics research because of past research practices which may not have considered the needs of the community.²⁴ This study demonstrates the merits of carrying out genetics research in a community-based participatory research manner,²⁵ one that was mutually acceptable to the community and to the researchers.

MATERIALS AND METHODS

Study participants

Consistent with the principles of community-based participatory research,²⁶ community members alerted university researchers to the need to investigate a high rate of LQTS. A local research advisory committee consisting of lay community members and medical personnel was struck under the authority of the Gitksan Health Society to advise and govern the research. Research protocols were developed in a participatory manner. Community approval and individual consents were obtained, following University of British Columbia and Northern Health Authority ethics approval. After clinical assessment of two index cases, family members were invited to participate. If not previously carried out, an ECG was done and all ECGs on file were collected for QTc measurements. Genetic Counselors (R.R./S.M.) recorded family histories and obtained

medical records. Blood or saliva was collected for DNA extraction under the stipulation of *DNA on Loan*.²⁴

QTc measurements

For QTc measurements, 12-lead ECG information was used. Analysis was carried out by a cardiologist (S.S.) blinded to the clinical and mutation status of the participant. QTc intervals were determined in all leads using Bazett correction,²⁷ to ensure that representative measurements were being made, but only lead II was used for the analysis. For sinus arrhythmia, the QT interval was taken using an interval which followed an RR interval approximating the average heart rate. The end of the T wave was defined using published criteria.²⁸ For individuals with more than one ECG recording, an average QTc was calculated from their individual ECG records, and this value was used in the determination of the mean QTc of the mutation “carrier” and “noncarrier” groups. However, all QTc determinations are shown graphically. Statistical analysis for comparisons between groups included 95% confidence intervals and Student *t* test, with a value of $P < 0.05$ considered significant. Odds ratios were used when appropriate.

Sequencing of genes and genotyping

DNA was extracted from blood or saliva using standard methods from 124 participants (all samples available). For the two index cases, the entire coding regions of *SCN5A*, *KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2* (62 exons) were polymerase chain reaction (PCR) amplified based on primers and conditions previously published^{29,30} and sequenced on an ABI 3730xl Analyzer (J.E.). Dimethyl sulfoxide or betaine was added when needed to improve PCR amplification.³¹ Genotyping of the identified mutation was performed using a custom Taqman SNP genotyping assay from Applied Biosystems (Foster City, CA) on an ABI Prism 7000 Sequence detection system in the clinically accredited laboratory of one of the investigators (B.C.).

Molecular biology

KCNQ1 and *KCNE1* genes were purchased from Origene Technologies (Rockville, MD). The missense mutation V205M within the third transmembrane (S3) region of the *KCNQ1* gene was constructed using a two-step PCR reaction.

Cell preparation and transfection

Electrophysiology was carried out on transiently transfected mouse *ltk*- cells. One microgram of *KCNQ1* and 2.5 μ g of *KCNE1* accessory subunit DNA was incubated with 1 μ g of pGFP and 3 μ L of LipofectAMINE 2000 (Gibco-BRL) in serum-free OPTI-MEM (Gibco-BRL), and then added to the dishes containing cells in modified Eagle’s medium with 10% fetal bovine serum. Cells were allowed to grow overnight before recording.

Solutions and electrophysiological procedures

Standard patch clamp procedures on cultured cells were used. Patch pipettes contained (in mM): KCl, 130; EGTA, 5;

MgCl₂, 1; HEPES, 10; Na₂ATP, 4; GTP, 0.1; and was adjusted to pH 7.2 with KOH. The bath solution contained (in mM): NaCl, 135; KCl, 5; HEPES, 10; sodium acetate, 2.8; MgCl₂, 1; CaCl₂, 1; and was adjusted to pH 7.4 with NaOH. Throughout the text, data are presented as mean ± SEM. Significance was tested using Student unpaired *t* test or one-way analysis of variance as appropriate and a value of *P* < 0.05 was considered significant.

RESULTS

Study population demographics

Index case No. 1 was 38 years at presentation, and had been resuscitated from an apparent cardiac arrest which occurred during a competitive sports activity. She had a previous history of syncope and palpitations. Index case No. 2 also had a history of frequent palpitations, with brief episodes of altered consciousness and weakness. A prolonged QTc was noted at age 37. Both were managed with implanted defibrillators. Although both were Gitksan from the same community, there was no knowledge of being related within four generations known to them (Fig. 1 A and B). They were both found to have the V205M mutation as a result of a G to A substitution in exon 4 of the *KCNQ1* gene (Fig. 1C), a mutation predicted to be pathogenic. Both of the index cases also had a polymorphism in *KCNE1*, G38S, which is not thought to modify the QT interval.³² No other mutations were detected in both index cases in the three other LQTS genes screened (*SCN5A*, *KCNH2*, *KCNE2*), although a number of polymorphisms in each were detected. One hundred twenty-two additional community participants were genotyped for the presence of V205M *KCNQ1*. Twenty relatives carried the V205M mutation (total

22) and 102 were without the mutation. One additional kindred, not known to be related to the other two, but with affected individuals harboring the V205M mutation, is not shown. Of the 22 individuals with mutations, eight were previously considered definitively affected by their physicians, four were considered “borderline,” and six were considered unlikely to have a mutation. Four had not been previously assessed. Of the 102 individuals without mutations, one individual was thought to be affected by her clinician after presenting with a moderately elevated QTc and palpitations. For that individual, in addition to genotyping for the V205M mutation, the coding regions of *SCN5A*, *KCNQ1*, *KCNH2*, *KCNE1* and *KCNE2* (62 exons) were sequenced as was carried out for the two index cases. Although no mutations were detected, one common polymorphism (*SCN5A* H558R), thought to occasionally predispose to Brugada-like ECG changes,³³ was found.

Of the 22 with V205M mutations, 21 had available ECGs for review (total 78) and of the noncarriers, 64 had available ECGs (total 86) (Fig. 2A). The age range for those with the mutation was 18–69 years (mean 44.3), and for those without the mutation was 3–81 years (mean 33.4). There were 20 individuals without mutations who were younger than 18 years. There was no difference in the QTc between those below 18 years and those above (431 ± 3 milliseconds vs. 437 ± 4 milliseconds, *P* = 0.33). Of those with the mutation, 77% were women compared with 56% without (OR, 2.2; 95% CI, 0.9–5.6). There was no difference between the QTc of male and female noncarriers (430 ± 4 milliseconds vs. 437 ± 4 milliseconds, *P* = 0.13, respectively). There was no difference between the male carriers and noncarriers (430.3 ± 10 milliseconds vs. 430.1 ± 4 milliseconds, *P* = 0.98) but there was a significant difference between male and female carriers (430.3 ± 10 milliseconds vs. 470.9 ± 6 milliseconds, *P* = 0.02). Adult females with mutations (*n* = 18) were also compared with adult females without mutations (*n* = 40) and found to have the most significant difference in QTc measurement (471 ± 6 milliseconds vs. 438 ± 4 milliseconds, *P* < 0.0001). Although all mutation

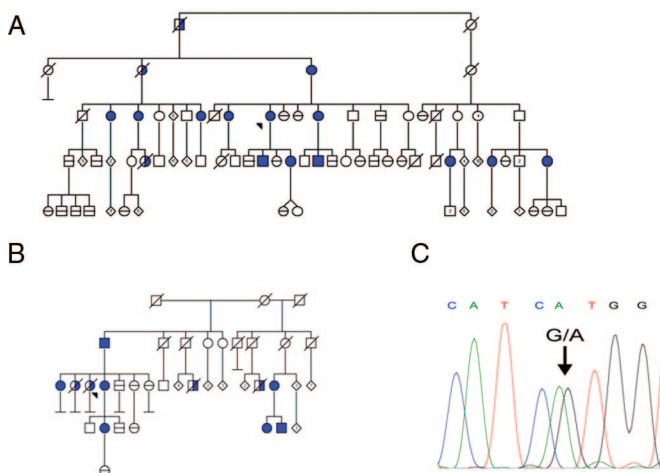


Fig. 1. Simplified family pedigree of index case families, representing two of three kindreds from the same community with the V205M mutation. A, Index case No. 1 extended family. B, Index case No. 2 immediate family. The index cases are identified with arrows. Presence of V205M mutation confirmed by genotyping is designated by the filled symbols, absence of the V205M mutation is designated by a horizontal line through the symbol. Unexplained death is designated with half-filled symbols with oblique line designating death. C, DNA sequencing of *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* genes of the index cases revealed a G to A substitution in exon 4 of the *KCNQ1* gene that results in mutation of valine 205 to methionine.

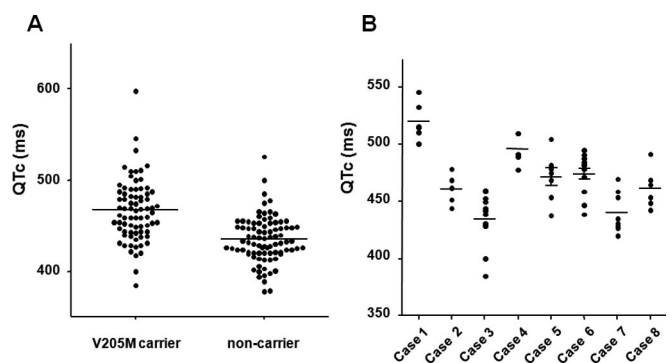


Fig. 2. The V205M mutation prolongs the QTc. A, QTc intervals determined at rest for mutation carriers and noncarriers. Each point represents one QTc determination. Measurement of QTc was carried out on 78 ECGs from 21 carriers and 86 ECGs from 64 noncarriers, as described in “Methods.” The short horizontal bars represent the mean QTc of individuals which were 465 ± 4 milliseconds and 434 ± 3 milliseconds, in carriers and noncarriers, respectively. QTc variations among eight V205M carriers are shown in (B).

carriers had a significantly higher mean QTc than all noncarriers (465 ± 28 milliseconds vs. 434 ± 26 milliseconds, $P < 0.0001$) (Fig. 2A), 30% of carriers had at least one QTc below 440 milliseconds. Figure 2B depicts eight cases with more than five ECGs, demonstrating substantial inpatient variability for QTc. Although a QTc of >430 milliseconds had a sensitivity for mutation positive status of 88%, the specificity was only 46%. On the other hand, a QTc of >466 milliseconds conferred a specificity of 86%, but had $<50\%$ sensitivity.

The V205M mutation alters activation and deactivation properties of I_{Ks} channels

Wt and mutant *KCNQ1* channels were coexpressed with the accessory β -subunit *KCNE1* in *ltk-* cells, as they possess no endogenous K^+ channel activity. The responses of Wt and mutant I_{Ks} channels to voltage were characterized and compared by recording ionic currents at 35°C from cells expressing Wt *KCNQ1+KCNE1* (Fig. 3A) and V205M *KCNQ1+KCNE1* (Fig. 3B) during 2 second depolarizations. Outward currents were recorded positive to -10 mV in the Wt channels (Fig. 3C), but strikingly, current activation was slowed and shifted to more depolarized potentials in the presence of the V205M mutation, appearing positive to $+20$ mV (Fig. 3C). The voltage dependence of activation was determined by measuring the half-activation voltages ($V_{1/2}$) for Wt and

V205M channels, and was shifted from $+10.4$ to $+44.1$ mV in the V205M channels.

In addition to modulating I_{Ks} channel activation properties, the V205M mutation accelerated the rate of channel deactivation (Fig. 3D, tail currents). It is clear that the V205M mutation accelerated deactivation at all the potentials tested compared with Wt channels. These data suggest that the V205M mutation reduces I_{Ks} channel availability by shifting the voltage dependence of activation to more depolarized potentials, in addition to slowing the rate of activation and accelerating the rate of channel deactivation.

DISCUSSION

The majority of *KCNQ1* mutations typically produce a loss of function by disrupting protein folding, assembly, and/or trafficking to the membrane.^{17–20} In contrast, the V205M mutation exhibited markedly slowed activation and accelerated deactivation (Fig. 3). The half-activation potential was depolarized >30 mV without altering the slope factor. This impairs the physiological ability of I_{Ks} channels to respond to rapid heart rhythms by beat-to-beat summation of current levels and may lead to a reduction of the overall repolarization reserve in affected hearts.³⁴ Similar electrophysiological findings (a depolarizing shift of activation) have been reported for the

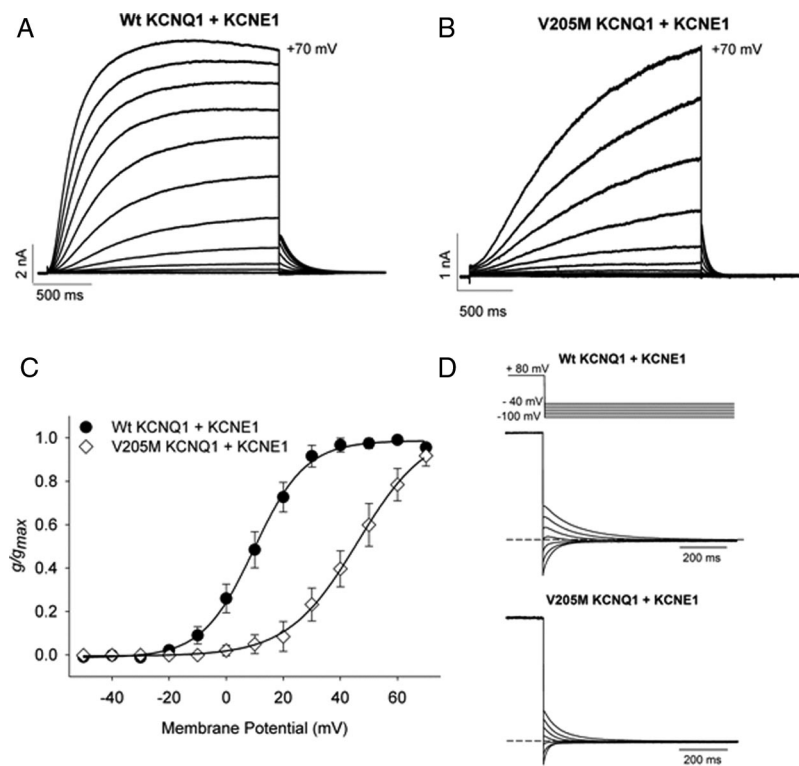


Fig. 3. The V205M mutation results in a depolarizing shift in the voltage dependence of I_{Ks} activation. Wt *KCNQ1+KCNE1* (A) and V205M *KCNQ1+KCNE1* (B) ionic currents were recorded at 35°C during 2 seconds depolarizing pulses to between -50 mV and $+70$ mV followed by a 2 seconds repolarizing pulse to -50 mV. C, g - V relationships were constructed by plotting the peak tail currents at -50 mV and the data were fitted to a single Boltzmann function. The $V_{1/2}$'s of activation were 10.4 ± 3.2 mV ($n = 7$) and 44.1 ± 5.0 mV ($n = 6$) with slope factors of 8.5 ± 0.7 mV and 9.9 ± 1.1 mV for Wt *KCNQ1+KCNE1* ($n = 7$) and V205M *KCNQ1+KCNE1* ($n = 6$), respectively. D, Ionic currents were recorded from cells expressing Wt *KCNQ1+KCNE1* and V205M *KCNQ1+KCNE1* during 2 seconds depolarizing pulses to $+80$ mV at 35°C followed by repolarizing pulses to potentials between -40 mV and -100 mV in 10 mV increments.

Q357R mutation in the S6 region,²¹ R294H in S4,²² and R555C in the C-terminus,²³ but the effect of the V205M mutation on the kinetics of I_{Ks} channels reported here is much more severe. Although four other mutations (D202H, I204M, S209F and V215M) have been detected in the S3 region of *KCNQ1* genes of patients with LQTS,³⁵ none of these mutations have yet been characterized. Any reduction of I_{Ks} because of inherited mutations in the *KCNQ1* genes could result in an increased risk for ventricular arrhythmia during periods of elevated sympathetic activity such as exercise and emotion¹ consistent with the findings in index case No. 1, who experienced cardiac arrest during an episode of emotional stress while exercising.

This is the first description of a founder mutation causing LQTS in a North American Aboriginal community, and as in other groups, the diagnosis of LQTS in family members of affected individuals presented a significant clinical challenge.^{36,37} Here, it was exacerbated because of a large number of individuals who had QTc measurements in the borderline range with 30% of carriers having at least one QTc below 440 milliseconds. Although it has been suggested that a QTc of 430 milliseconds is a reasonable screening cut-off for diagnosing affected relatives of mutation carriers with acceptable sensitivity and specificity,³⁷ this was not true in our relatively homogeneous population. The specificity at that QTc was <50% for our population, suggesting a baseline increased QTc in non-mutation carriers. Although not specifically studied in this community, a baseline increase in QTc may be associated with obesity and diabetes, both common in North American Native populations.¹³ In this study, the highly significant difference in QTc between mutation positive and negative participants, and especially mutation positive and negative women, clinically supports the *in vitro* confirmation of pathogenesis, but may not be helpful for individual clinical assessments of those at risk.

The paucity of men with mutations in our study is consistent with other observations,³⁸ and may be a result of transmission distortion³⁹ or ascertainment bias in that women may be more severely clinically affected,³⁸ and more apt to enter a study such as this. It is also possible that men at high risk are more hesitant to learn their mutation status. Several men in the community known to be at 50% risk have not come forward for testing. The fact that there are so few mutation positive men in our study limits any assumptions that men with mutations are less likely to have an elevated QTc, although our preliminary results suggest that possibility. More research on the impact of *KCNQ1* V205M on men in this community is indicated.

Although QTc length may be helpful in predicting risk of a cardiac event in LQTS,⁴⁰ the marked inpatient variability with resting ECG in our mutation carriers illustrates the difficulty in interpreting mutation status and subsequent risk based on any single QTc measurement. In reviewing the number of unexpected deaths apparent in these families, and in reviewing the case studies of those who have presented symptomatically, the seriousness of the presence of the V205M *KCNQ1* mutation as a *predisposition* to LQTS cannot be ignored, although the presence of this mutation alone may be insufficient to de-

clare that an individual has LQTS. More research is needed to determine whether functional polymorphisms in *KCNQ1* and other genes responsible for LQTS might contribute to the variable presentation evident in this community, and typically seen in families of those with LQTS.⁴⁻⁶ Nongenetic mechanisms underlying the variability in expression of the condition, also need to be considered.⁴¹

Aboriginal communities may hesitate to participate in genetic research that will not have a direct impact on the health of their community.²⁴ This community recognized that addressing LQTS was a health care priority, directed the initiation of this study, and has continued to be involved in the implementation and governance. A community-based approach enabled the research⁴² and is in keeping with the current Canadian Institutes for Health Research Guidelines for Health Research Involving Aboriginal People.⁴³

The impact of LQTS in this community was profound in that local health care providers and consultant cardiologists were often unable to predict which community members were at risk for arrhythmias, resulting in general population avoidance of QT prolonging medications, many of which are commonly used in day to day clinical practice. Furthermore, several individuals were being treated medically on speculation that their borderline QTc was reflective of congenital LQTS, especially if they had close relatives with LQTS. Because the closest tertiary care center (Vancouver) is 1200 km from Hazelton, defining the mutation and confirming pathogenesis has provided a valuable and inexpensive diagnostic test for those with features of LQTS and who are related to mutation carriers. Nonetheless, clinical monitoring of those with the mutation will remain a challenge in this remote community. To date, all mutation carriers have been referred to a cardiologist for assessment of the need for medical or interventional therapy. Continued monitoring is through the local hospital and health centers. Furthermore, portable automatic defibrillators have now been made available throughout the community. Further community education strategies are planned.

Although 22 individuals with V205M mutations have been identified to date, suggesting a rate of at least 1/250 definitively affected individuals in this community, the expanded family histories with added information of mutation status reveal that at least 40 more individuals are at 50% risk of having a mutation and another 80 are at 25% risk. This suggests the mutation positive rate could reach higher than 1/100 in this and surrounding communities. The broader community impact will become known once random community screening for the mutation is implemented. Newborn screening has also been considered,⁴⁴ but population specific evidence of increased risk of death in infancy and early childhood will inform that decision. Ongoing monitoring of those with and without mutations will shed light on the comparative risk of sudden death, and of the merits of treating mutation carriers with beta blockers or defibrillators.

A community-based approach to the study of LQTS in a northern British Columbia First Nations community has led to the identification of a novel LQTS mutation, V205M *KCNQ1*,

and an understanding of its pathogenesis. The delineation of this founder mutation will now allow definitive diagnosis of a predisposition to LQTS and appropriate management to reduce the risk of serious cardiac events. Ongoing studies will provide further insight into variable clinical expression, while optimum screening and management strategies are explored to further benefit this community.

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