The Impact of Congenital Long QT Syndrome on First Nations Children and Youth in Northern British Columbia

by

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BSc, McGill University, 2018

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Supervisory Committee

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Abstract

Background: Long QT syndrome (LQTS) is a cardiac condition which predisposes individuals to syncope, seizures, and sudden cardiac death. There is a high prevalence of congenital LQTS in a First Nations community in Northern British Columbia due to the founder variant p.V205M in the *KCNQ1* gene. Additionally, two other variants of interest are present in this population: the *KCNQ1* p.L353L variant, previously noted to modify the phenotype of LQTS in adults, and the *CPT1A* p.P479L variant, a metabolic variant common in Northern Indigenous populations associated with hypoglycemia and sudden unexpected infant death.

Methods: We performed a mixed methods study to better understand the impact of LQTS in children and youth in this First Nations community. To learn about the clinical impact of LQTS, and better understand the effects of the *KCNQ1* and *CPT1A* variants in children, we used statistical analysis to compare the cardiac phenotypes of 211 First Nations children with and without the p.V205M, p.L353L and p.P479L variants, alone and in combination. Ordinary Least Squares linear regression was used to compare the highest peak corrected QT interval (QTc). The peak QTc is an electrocardiogram measurement used in risk stratification of LQTS patients. Logistic regression was used to compare the rates of syncope and seizures experienced in childhood.

Additionally, to learn about the lived-experience of LQTS, we interviewed one young First Nations adult about her experiences growing up with LQTS as a teenager. From this interview, we conducted a qualitative case study analysis using Interpretative Phenomenological Analysis. All

research was done in partnership with the First Nations community using community-based participatory methods.

Results: We found that the p.V205M variant conferred a 22.4ms increase in peak QTc ($p<0.001$). No other variants or variant interaction effects were observed to have a significant impact on peak QTc. No association between the p.V205M variant and loss of consciousness (LOC) events (syncope and seizures) was observed (OR(95%CI)=1.3(0.6-2.8); p=0.531). However, children homozygous for p.P479L were found to experience 3.3 times more LOC events compared to non-carriers (OR=3.3(1.3-8.3); p=0.011). With regard to the qualitative portion of the thesis, four superordinate (main) themes emerged from the case study: Daily life with Long QT Syndrome, Interactions with Medical Professionals, Finding Reassurance, and The In-Between Age. We found that even though our participant was asymptomatic and felt that she was not impacted by LQTS in her daily life, she considered certain elements of the condition to be stressful, such as taking a daily beta-blocker.

Conclusion: These results suggest that while the *KCNQ1* p.V205M variant is observed to significantly prolong the peak QTc, the *CPT1A* p.P479L variant is more strongly associated with LOC events in children from this community. More research is needed to further determine the effect of these variants; however, our preliminary findings suggest management strategies, such as whether beta-blockers are indicated for p.V205M carriers, may need to be reassessed. The importance of developing a holistic, well-balanced approach to medical care, taking into consideration the personal perspectives and unique medical circumstances of each child is exemplified in this study.

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List of Abbreviations

BC – British Columbia

CBPR – Community-based participatory research

CPT1 – Carnitine palmitoyltransferase 1

ECG – Electrocardiogram

FAP – Familial adenomatous polyposis

IPA – Interpretative phenomenological analysis

LOC – Loss of consciousness

LQTS – Long QT syndrome

OR – Odds ratio

TRC – Truth and Reconciliation Commission

QTc – QT interval correct for heart rate

Acknowledgments

First and foremost, I would like to thank the Gitxsan Nation for the privilege to collaborate and study in partnership with their community. I would also like to extend my gratitude to the research participants without whom this study would not be possible.

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Dedication

For those in rural, remote and Northern communities.

Chapter 1. Introduction

This thesis is part of the ongoing story of long QT syndrome (LQTS) in Northern British Columbia (BC). In 2004, the Aboriginal Health Program at BC Women's Hospital met with various First Nations communities throughout BC with the aim to better understand local healthcare concerns. One of these meetings was held in the Gitxsan First Nation's community in Northern BC and yielded unexpected results. Instead of hearing about common diseases such as diabetes and cancer, the Gitxsan voiced that their major concern was the high prevalence of LQTS, a rare heart condition in their community.

The findings from this meeting were conveyed to Dr. Laura Arbour, a physician and health researcher with extensive experience working with Indigenous communities. A community-based participatory research approach was arranged to explore LQTS in the region, in collaboration with a research advisory board, composed of Gitxsan health society members, local healthcare professionals, community members and an Elder.

Through this research, it was found that LQTS affects approximately 1 in 250 people in the Gitxsan community[1] compared to an estimated 1 in 2000 people in the general population.[2] As the cause of LQTS can be genetic in nature, genetic sequencing on the five genes known then to cause LQTS was done within this population and found that a novel variant called p.V205M in the *KCNQ1* gene was responsible for the increased rates of LQTS.

After this discovery, additional outreach clinics in Northern BC were established to assist these families affected by LQTS. As a result of this increased care, LQTS is now recognized early in this community and commonly diagnosed in childhood. As such, the aim of this thesis is to learn about the impact of long QT syndrome on Gitxsan children and youth in order to better inform

healthcare practices and ease this journey for future children diagnosed with LQTS. This thesis explores the impact of LQTS from a mixed-methods approach, drawing from both quantitative and qualitative methodologies. Dr. Arbour's research partnership with the Gitxsan Nation continues to this day, and this study is part of her ongoing work with the community.

Chapter 2. Background

This thesis brings together a unique combination of disciplines and knowledge. The aim of this background section is to offer tools and guidance to the reader which they may draw upon to better understand the intersectional space between genetics, cardiology and Indigenous health that this study occupies.

2.1. Indigenous Peoples

2.1.1. Indigenous Peoples in Canada

The term Indigenous refers to three distinct and diverse groups of people within Canada: First Nations, Inuit and Métis. Indigenous peoples compose approximately 5% of the total Canadian population.[3] Statistics Canada reported the population of Canadian Indigenous peoples to have grown 42.5% from 2006 to 2016. In addition to an increase in birth rates, a large part of this growth is due to an increase in Indigenous status identification.[4]

2.1.2. Indigenous Peoples Health

Colonization, cultural oppression, and systemic racism have contributed to the health disparities that exist between Indigenous and non-Indigenous peoples in Canada.[5,6] Indigenous peoples experience a lower life expectancy,[7] a higher rate of infant mortality,[8] a higher rate of chronic disease,[9] and reduced mental health.[3] Research suggests that many measurements of Indigenous health are improving, but at a slower rate than the general population; thus, the health gap between Indigenous and non-Indigenous peoples is thought to be widening.[10] It is important

to recognize however, that these measurements of health stem from a Western perspective and are not inclusive of overall Indigenous well-being.[11,12]

In recognition of past historical injustices towards Canadian Indigenous peoples, the Truth and Reconciliation Commission of Canada (TRC) was formed. In 2015, the TRC made specific Calls to Action relevant to this thesis project. The 18th Call to Action directly appeals to the municipal, provincial, federal and Indigenous governments to recognize that the current health of Indigenous peoples is a direct result of past Canadian Government policies, such as residential schools.[5] The 19th Call to Action emphasizes the importance of establishing measurable goals, in consultation with Indigenous peoples, to resolve these health inequities. Additionally, the 22nd Call to Action emphasizes the importance of recognizing Indigenous healing practices in the treatment of Indigenous peoples.[5] This thesis aims to embody many of the TRC's Calls to Action by working with the Gitxsan Nation to address a health concern identified to be of importance to the community.

2.1.3. Genetic Research and Indigenous Peoples

One of the healthcare disparities experienced by Indigenous peoples is that of genetic healthcare. Genomic technologies that are becoming regularly available to most Canadians are less accessible to Indigenous peoples.[13] Moreover, the genetic counseling which is offered to Indigenous peoples originates from a Western perspective, and little research has been done into the Indigenous peoples' perspectives of genetic testing.[14] As such, more research is needed to improve services offered to Indigenous peoples; however, care must be taken to ensure this research is done in an ethical, respectful and culturally appropriate manner.[15]

There are numerous examples of healthcare research performed in Indigenous communities which resulted in egregious ethics violations.[15,16] For example, over 800 blood samples taken from the Nuu-chah-nulth peoples of British Columbia for the purposes of arthritis research were instead used to determine the ancestry of the Nuu-chah-nulth Nation.[17,18] Genetics health research in particular requires particular care as DNA samples have the potential to be misused for ancestry or status determination purposes as demonstrated above. Moreover, DNA samples from saliva or blood, like any biological sample, are often considered sacred within Indigenous cultures,[19] and community guidance regarding the creation, care and return of such samples is paramount. Specific concerns regarding genetics research include: lack of community involvement, disregard towards cultural beliefs, issues surrounding DNA sample ownership and a general impression of exploitation of Indigenous communities.[15]

In an effort to prevent future violations, guidelines have been published regarding genetics research with Indigenous peoples. A community-based participatory research approach is recommended, where the Indigenous community involved in the research is consulted throughout the entire research process.[15] Moreover, the potential risk of stigmatization may be of concern to communities due to the historical context of oppression,[6] and potential harm towards both the individual participant and an entire community should be considered.[20] The research must reflect the needs of the community and provide opportunities of benefit for the Nation, such as capacity development, improved healthcare, resources and education. The biological DNA samples must be handled with respect and should be considered property of the individual and the community, and thereby "on loan" to the researcher. Lastly, the research results must be shared with the community for their own use.[15]

2.1.4. The Gitxsan Nation

This study is conducted in partnership with the Gitxsan Nation, a First Nations group located in what is now commonly referred to as north-western British Columbia. The Gitxsan people have inhabited this traditional territory for over 10,000 years and approximately 70% of registered Gitxsan people live on five reserves – Sik-e-dakh (Glen Vowell), Gitwangak (Kitwanga), Gitsegukla, Gitanmaax, and Kispiox – and two provincial municipalities – Hazelton and New Hazelton.[21] Collectively known as the *The Hazeltons*, this region is located roughly 300 kilometers east of Prince Rupert (Figure 2.1).[14]

Figure 2.1. Traditional territory of the Gitxsan Nation.[14]

Traditional territory of the Gitxsan Nation is illustrated in yellow.

Gitxsan people share a unique worldview which shapes how they interpret and interact with the world around them, including their perspectives of health and well-being.[14] As described by Rhea Joseph, a Gitxsan Dietician and Health Policy Advisory to the Native Brotherhood of BC:

> "Among the Gitksan and Wet'suwet'en, there is no mother tongue word for health. However, they do have a word for strength, which is interchangeable [with] health. They also speak of well-being. This well-being is associated with high self-esteem, a feeling of being at peace and being happy... This includes education. It includes employment. It includes land claims. It includes resource management. All of these lead back to wellness and well-being."[22]

Similar to other Indigenous peoples, the Gitxsan view health holistically. The Gitxsan perspective of health has previously been illustrated in a Medicine Wheel (Figure 2.2).[14] The Medicine Wheel is a concept shared by many Indigenous peoples and informs an Indigenous philosophy of healing. It depicts four equal and separate elements of health: physical, mental, emotional and spiritual. These parts are interconnected, and balance of these elements contributes to overall well-being.[23] Although the Medicine Wheel is a concept shared among many Indigenous peoples, variations of the concept exist in different communities and some Indigenous groups may not share the concept of the Medicine Wheel at all. The Gitxsan holistic view of health includes the four key quadrants Medicine Wheel, as well as three added layers of family, community and creation.[14]

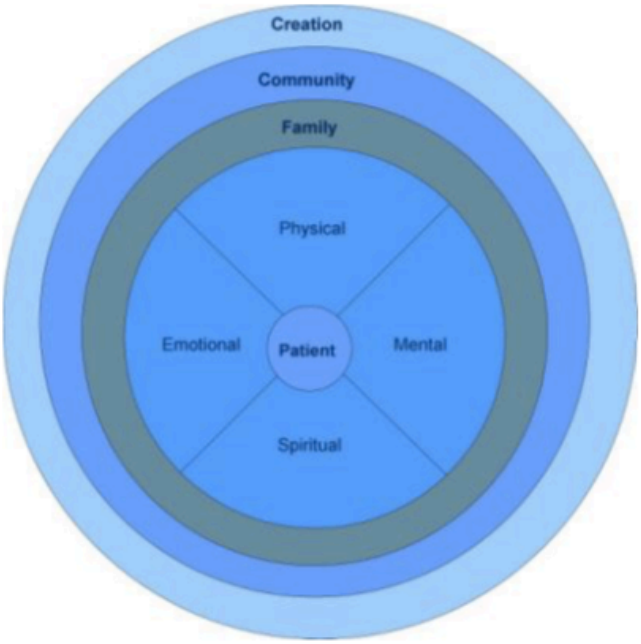


Figure 2.2. Gitxsan holistic view of health.[14] The patient is depicted in the center of the circle, surrounded by the four equally important and interconnected elements of health: physical, mental, emotional and spiritual. Additional layers of family, community and creation encompass the four quadrants.

2.2. Long QT Syndrome

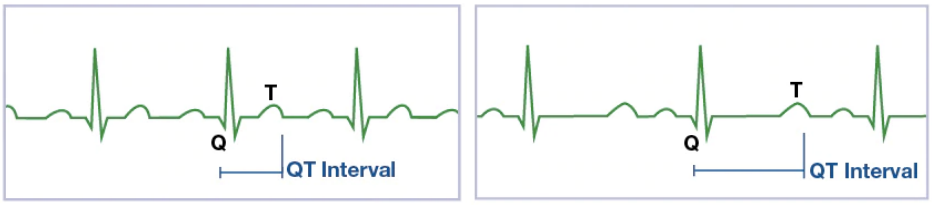
2.2.1. Overview

Long QT Syndrome (LQTS) is an electrical cardiac condition characterized by an abnormality in the cardiac cycle. This abnormality (a prolonged QT interval corrected for rate as shown on the electrocardiogram) predisposes individuals to ventricular arrhythmias, syncope (fainting), seizures and sudden cardiac death; however, treatments exist to reduce these effects.[24] LQTS can be inherited or acquired, and typically affects 0.05% of the population[2]; however, it is

observed at an increased prevalence within the Gitxsan population due to the genetic variant p.V205M in the *KCNQ1* gene.[1]

2.2.2. Pathophysiology

An electrocardiogram (ECG) is a visualization of the heart's electrical activity. Components of the ECG have different labels and represent different parts of the cardiac cycle (heartbeat).[25] For example, the QT interval, represents the time it takes for the ventricles of the heart to push blood to the rest of the body and then reset electrically for the next heartbeat. As the name suggests, the hallmark characteristic of LQTS is that the QT interval is prolonged (Figure 2.3).[25]



A) A normal QT interval. B) A prolonged QT interval.

Figure 2.3. Electrocardiogram comparison of normal and LQTS affected heart rhythms.[26]

A prolonged QT interval can lead to a ventricular arrhythmia known as torsades de pointes (TdP) or "twisting of the points." TdP causes irregular contractions of the heart and blood flow to the rest of the body, which may result in syncope and seizures. In some cases, TdP may progress to ventricular fibrillation (quivering, instead of contracting, of the heart) and sudden cardiac death.[27]

2.2.3. Genetics

A prolongation of the QT interval can be caused by acquired or genetic factors. Acquired LQTS may be due to electrolyte imbalances, chronic disease, exposure to environmental toxins, or medications.[28] Congenital LQTS is due to changes in genes (variants) that are involved in the electrical rhythm of the heart. Congenital LQTS can be classified by the clinical presentation and symptoms of the patient (phenotype) or numerically by the affected gene.[29]

Phenotypically, two forms of LQTS exist: Romano-Ward Syndrome and Jervell and Lange-Nielsen Syndrome.[29] Romano-Ward Syndrome is the more common presentation of LQTS, and follows an autosomal dominant inheritance pattern, meaning that an individual only needs one copy of the genetic variant to have LQTS. On the other hand, Jervell and Lange-Nielsen Syndrome is an autosomal recessive form of LQTS, meaning that the variant must be found in both copies of an individual's genes to express this LQTS. Jervell and Lange-Nielsen Syndrome is a rare type of LQTS, and is associated with cardiac symptoms and sensorineural deafness.[29] While classically long QT is divided into these two syndromes, in practice the divide is a range of clinically observed phenotypes[29] and some patients with congenital LQTS may not experience any features of LQTS, a phenomenon known as incomplete penetrance.[30] Additionally, among genotype-positive individuals that do show symptoms, there is a range in the severity of symptoms experienced, an observation referred to as variable expressivity.[31]

To date, variants in 17 genes have been identified in individuals with congenital LQTS.[32] About 80% of all congenital LQTS is due to variants in three canonical genes: *KCNQ1*, *KCNH2* and *SCN5A*,[33] and correspond to LQTS type 1, LQTS type 2, and LQTS type 3 respectively.[32] These genes encode proteins that form part of ion channels, which are responsible

for maintaining the electrical rhythm of the heart (table 2.1). Variants in these genes cause alterations in protein functioning, and thus disrupt ion channel functioning and heart rhythmicity.[32]

Table 2.1. Gene, protein and ion channel involvement in common forms of LQTS.

Type	Gene	Protein	Ion Channel
LQTS1	*KCNQ1*	I_{KS} potassium channel alpha subunit (K_VLQT1, K_V7.1)	slowly activating delayed rectifier potassium channel (I_{KS})
LQTS2	*KCNH2*	I_{KR} potassium channel alpha subunit (HERG, K_V11.1)	rapidly activating delayed rectifier potassium channel (I_{KR})
LQTS3	*SCN5A*	cardiac sodium channel alpha subunit (Na_V1.5)	voltage-gated sodium channel type 5 (I_{Na})

LQTS type 1, the most common form of LQTS, is due to loss-of-function variants in the *KCNQ1* gene which encodes the alpha protein subunit of the I_{KS} channel.[32] A disruption in the formation of the I_{KS} channel alters the flow of potassium ions out of cardiac cells. This slows down the time it takes for cardiac cells to reset (repolarize) to their baseline electrical potential after a heartbeat, thus prolonging the QT interval (Figure 2.4).[25]

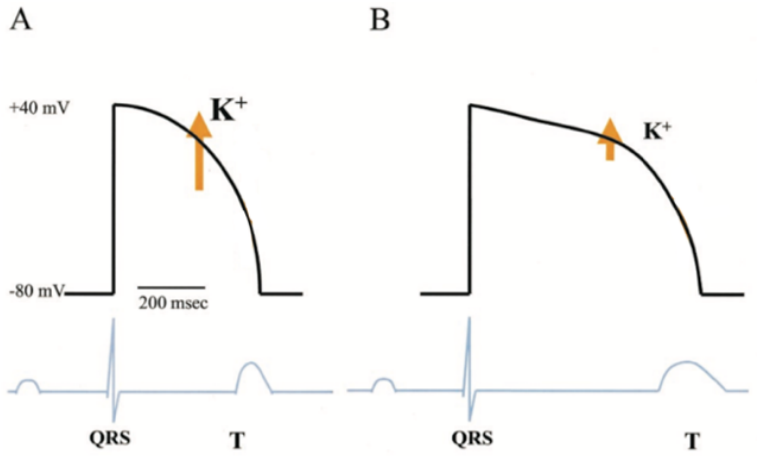


Figure 2.4. A cardiac muscle cell's electrical activity (action potential) during one heartbeat A) without and B) with LQTS type 1. In LQTS type 1, the flow of potassium out of the cell is slower and it takes longer for the cell to reset and reach its starting electrical potential. Image adapted from Tristani-Firouzi et al., 2001 with permission.[34]

2.2.4. Long QT Syndrome and Gitxsan Peoples

As previously mentioned, there is a high rate of long QT syndrome among the Gitxsan Nation. This is due to a novel autosomal dominant genetic variant, p.V205M in the *KCNQ1* gene[1] (LQTS type 1), taking the phenotypic form of Romano-Ward Syndrome.[35] This genetic variant causes a change in amino acid at position 205 of the *KCNQ1* gene. This region of the gene encodes for the S3 transmembrane helix of the pore forming protein domain Kv7.11 in the I_{KS} channel. The change in amino acid results in a disruption of I_{KS}, resulting in LQTS1.[1] Although homozygous cases are documented, there is minimal pre-lingual hearing loss, therefore even when homozygous, the phenotype is typical of Romano-Ward syndrome, rather than Jervell and Lange-Nielsen syndrome.

Since the discovery of the p.V205M variant, another genetic variant in the *KCNQ1* gene has been found in the Gitxsan population. The variant p.L353L was found to act as a modifier of

the LQTS type 1 phenotype.[36] In adult males, the p.L353L variant was observed to prolong the QT interval both alone and in combination with the p.V205M variant. In adult females, the L353L variant was observed to prolong the QT interval alone but was not found to have any interaction effect while in combination with the p.V205M variant. The size of the combined effect of the p.L353L and p.V205M variants in males was clinically significant, while the lone effect of p.L353L in either sex was not. While the pathophysiology of this variant is not yet fully understood, research suggests that it may alter the splicing of the *KCNQ1* gene, changing the expressivity of exon 8, and ultimately decreasing the function of the I_{KS} channel.[36]

2.2.5. Diagnosis and Management

The diagnosis of LQTS is most commonly based on an ECG, exercise/stress test and a detailed medical and family history of cardiac events.[37] On an ECG, a QTc reading (corrected QT interval, standardized for heart rate) of over 450ms for males and 460ms for females is considered prolonged.[38] A LQTS diagnosis is further refined into acquired or congenital LQTS. Acquired LQTS is occurs in the absence of a genetic cause for LQTS and may be a result of other conditions (such as autoimmune disease), obesity, and the use of QT prolonging drugs.[28,39] In some cases, acquired LQTS may be indicative of underlying genetic variants exacerbated by additional risk factors, and can be considered a "forme fruste" of congenital LQTS.[40] Congenital LQTS is confirmed through genetic testing.[32] however, congenital LQTS may be caused by genes not yet identified, or by variants in genes not amenable to standard next generation sequencing or targeted variant testing. Overall genetic variants are found in approximately 80% of those with a LQTS phenotype.[32] Genetic testing for LQTS is often recommended if a patient has a phenotype consistent with LQTS, or if an individual is related to a person with congenital LQTS where a

genetic variant has been confirmed, a process known as cascade testing.[32] The process of clinical genetic testing is most often guided by a genetic counselor or geneticist.[41]

The decision to test children for genetic variants known to cause disease is a complex decision.[42] Pediatric testing for adult or late childhood onset conditions is discouraged in order to respect the child's autonomy and potential wish to not know;[43] however, this does not apply to LQTS. LQTS symptoms, including sudden death, can occur at any age and treatments exist to mitigate these risks.[44] As such, pediatric testing is generally encouraged when an increased risk for LQTS is identified.[45]

There are a variety of treatments for LQTS. The most common treatment is beta-blocker therapy, an oral medication taken daily to reduce adrenergic stimulation to the heart. Adrenergic stimulation is known to trigger Tdp and lead to ventricular arrhythmia in LQTS patients.[24,37] Beta-blockers have been shown to be an extremely effective way to treat LQTS1, however, common side effects include lethargy, weight gain and depression.[46] Beta-blockers are the primary therapy recommended to all symptomatic patients, or patients with a QTc of >470ms. The prescription of beta-blockers for asymptomatic LQTS patients with a QTc ≤470ms is currently supported as a class IIa (moderate) recommendation by the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS).[47] Symptomatic patients that are non-responsive to beta-blockers, or for whom beta-blockers are not appropriate, may be recommended surgery to denervate the left sympathetic cardiac nerve in order to reduce adrenergic stimulation to the heart. Implantation of a cardiac defibrillator (ICD), a device which monitor the heart and discharge electrical shocks if an arrhythmia is detected, is a therapeutic option for high-risk patients.[37,48]

Lifestyle management is also important. Individuals must avoid medications which are known to prolong the QT interval, many of which are ubiquitous, such as common types of antibiotics and antidepressants.[49] Moreover, genotype specific recommendations are also made. For example, individuals with LQTS type 1 are recommended to avoid certain types of physical activity, such as swimming and intense exercise training.[37] The exercise guidelines for LQTS type 1 patients have recently become more lenient, allowing participation in competitive sports in some circumstances.[50]

2.2.6. An Additional LQTS Consideration – *CPT1A*

An additional consideration regarding LQTS in the Gitxsan population is the p.P479L variant in a gene called carnitine palmitoyltransferase 1A (*CPT1A*). The p.P479L variant is common among Northern Indigenous populations in Canada,[51,52] Alaska,[53] Russia[54] and Greenland[55] and is known to have up to a 25% homozygosity rate in Coastal First Nations in Northern British Columbia.[52] The *CPT1A* gene encodes a liver enzyme important in fatty acid metabolism and has been found to be associated with hypoglycemia[56–58] and sudden unexpected death in infants.[52,59] Hypoglycemia can present with symptoms similar to long QT syndrome, such as seizures, and it is important to recognize this when interpreting potential LQTS symptoms.[60]

Complicating matters further, both LQTS1[61] and beta-blocker therapy[62] have been found to be associated with hypoglycemia, and hypoglycemia has been found to prolong the QTc interval[63] and trigger arrhythmia.[64] There is a well-known association between nocturnal hypoglycemia and sudden cardiac death occurring in young healthy diabetic individuals, an observation referred to as the "dead in bed syndrome."[65] Moreover, at least four First Nations children in Northern British Columbia with LQTS1 have presented with symptomatic

hypoglycemia and a reduced level of consciousness (table 2.2). All children were either heterozygous or homozygous for the *CPT1A* p.P479L variant, carriers of a pathogenic variant in *KCNQ1*, and taking beta-blocker medication. Due to the interlinked nature of hypoglycemia and cardiac arrhythmia, the *CPT1A* p.P479L variant should be taken into account when assessing the effects of LQTS in Gitxsan children.

Table 2.2. Case presentation of four Northern BC First Nations children with symptoms of hypoglycemia and reduced levels of consciousness.

Case	Sex	*KCNQ1* Variant	*CPT1A* Variant	Age‡	Clinical Presentation	Illness (Y/N)§	Beta-blocker
1	M	p.V205M carrier	p.P479L homozygote (PP)	4 yrs	low level of consciousness: unable to rouse from sleep in morning, blood glucose 2.6 mmol/L; previous history multiple febrile seizures at ages 5 months and 4 years.	Y	nadolol
2	F	p.V205M carrier	p.P479L homozygote (PP)	4 yrs	hypoglycemic seizure: onset 5 am during sleep, blood glucose 1.6 mmol/L	N	propranolol
3	F	p.V205M carrier	p.P479L heterozygote (PL)	3.5 yrs	hypoglycemic seizure: onset 7am when asking for breakfast, blood glucose 1.6mmol/L	N	nadolol
4	M	p.R591H carrier†	p.P479L heterozygote (PL)	2.5 yrs	2 hypoglycemic episodes in morning: 1) staring at celling and hollering, confused; 2) shaking and sweating	N	nadolol*

M – male, F – female
‡ – Age at clinical presentation of hypoglycemic episode in years.
§ – Intercurrent illness at the time of hypoglycemic episode.
* – Nadolol recorded at the time of first event, unknown beta-blocker use at the time of second event.
† – p.R591H is a pathogenic variant in the *KCNQ1* gene which causes LQTS1.
An increased prevalence of p.R591H is observed in an First Nations population adjacent to the Gitxsan.[66]

2.3. Genetic Testing & Counseling

Clinical genetic testing for inherited medical conditions such as LQTS is a process most often lead by a geneticist and/or genetic counselor. In addition to testing itself, appropriate pre-

and post-test genetic counseling must be given. Genetic counseling is "the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease."[59] This may include interpreting a family's medical history to assess the chance of disease occurrence; educating a family or individual about disease inheritance, testing, prevention and management; and counseling to promote informed choices and risk adaptation.[59]

2.3.1. Pediatric Genetic Counseling

Genetic counseling in a pediatric population poses unique challenges. Both the Canadian and American medical guidelines state that genetic testing should be performed with the best interest of the child in mind.[67,68] The genetic counselor and/or geneticist must discuss with the family and weigh the potential benefits of testing, with the potentially harmful psychological and social impacts that could arise.[67] Situations where a genetic test would be appropriate include: 1) diagnostic purposes for a symptomatic child, 2) pre-symptomatic/predictive testing for adult onset diseases where childhood treatment/prevention is of benefit, and 3) pre-symptomatic/predictive testing for childhood onset diseases.[68] Testing for LQTS falls into the latter category.[45]

Beyond the actual genetic test however, the physician and/or genetic counselor must also consider the family dynamics throughout the counseling process. This includes the developmental stage of the child, support resources, the family's culture and unique interpretation of the genetic information.[42] While pre-school age children have been shown to comprehend that some diseases may be "caught," while others may "run" in families,[69] a staged approach to genetic counseling is recommended, where sessions are planned over several years to clarify information and discuss the child's maturing emotional responses to the condition.[42]

2.3.2. Cardiogenetic Healthcare in Northern British Columbia

Providing healthcare to rural, remote and Northern communities is a challenge throughout Canada. In British Columbia, these challenges include geographic remoteness, fewer available healthcare providers, low population densities and challenging weather conditions.[70] Moreover, providing specialty services, such as cardiogenetic care, poses additional challenges as physicians specializing in electrophysiology and genetics are only located in cities such as Vancouver and Victoria. As such, to receive care for a cardiogenetic condition, patients are required to travel to these larger centers for treatment or attend an outreach clinic in their community or a near-by town. These outreach clinics were previously offered through by multidisciplinary teams supported by the research program and were replaced by the British Columbia Inherited Arrhythmia Program (BCIAP) in 2013 (http://www.cardiacbc.ca/our-services/programs/bc-inherited-arrhythmia-program). Through the BCIAP, an interdisciplinary team (electrophysiologist, geneticist and genetic counselors) provide care to patients in Vancouver and Victoria. In Northern BC, two local internists trained in LQTS, along with a Northern Heart Health Nurse, a genetic counselor, and a geneticist, provide care to those in Hazelton, Terrace, and New Aiyansh, with support from electrophysiologists in Vancouver and Victoria. In addition, pediatric cardiology clinics are held annually in Northern BC (Hazelton), and all children with LQTS are followed by a visiting pediatric cardiologist or attend clinics at the BC Children's Hospital.

Noteworthy, is that the Gitxsan community receives additional support from genetic counselors through the LQTS research study. Dr. Arbour's Community Genetics Research Laboratory ensures that all participants have access to a genetic counselor by phone and are sent annual update letters through the program.

Chapter 3. Literature Review

3.1. Introduction

This thesis explores the impact of LQTS on children and youth in two ways. First, a quantitative approach is taken to explore the clinical effects of LQTS on Gitxsan children. Second, a qualitative method is used to learn about the lived-experience of long QT syndrome from one young Gitxsan adult. As such, the literature review has been divided into two respective sections to reflect this. Section 3.2 of this literature review discusses the current body of knowledge surrounding the clinical impact of LQTS1 in childhood. Section 3.3 of this literature review discusses what is known about the impact of LQTS on the well-being of Indigenous children and youth.

3.2. Clinical Impact of LQTS on Children

The clinical impact of LQTS is largely conceptualized by impact on the QTc, and rate of cardiac events (such as syncope, seizure, cardiac arrhythmia or cardiac arrest) in children. With the exception of a University of Victoria Honours' Thesis (Gauthier, 2013) on the same population,[71] to our knowledge, no previous literature has explored the clinical impact of LQTS in First Nations children. Gauthier, 2013 was limited by a small sample size, and as such re-analysis of the data is warranted. Initial findings by Gauthier, 2013 found that children with the p.V205M variant (n=23) do not experience a high rate of cardiac events, but do have a prolonged QTc interval.[71] Previous research has explored the clinical impact of LQTS in the broader pediatric population and is discussed below. Additionally, this literature review includes an overview of the current scientific discussion regarding beta-blocker therapy in LQTS children, and presents the current evidence suggesting a link between *CPT1A* and LQTS.

3.2.1. Pediatric LQTS and the QTc Interval

Healthcare professionals use a variety of factors to determine the risk for cardiac events for LQTS1 patients, including QTc interval length, other ECG and stress test measurements, past history of cardiac events, family history, age and sex.[37] The length of the QT interval, corrected for rate (QTc) is used as a measure of risk for individuals with LQTS, and a higher QTc reflective of an increased risk for cardiac events such as ventricular arrhythmias, syncope, seizures and sudden cardiac death. The current guidelines by the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) classify a prolonged QTc to be ≥450ms in men and ≥460ms in women.[38] Notably, a higher cut-off for women of 470ms has been proposed by some researchers.[72] The ACC/AHA/HRS do not specify specific QTc measurements for children, however, several studies have proposed >460ms to indicate a prolonged QTc for children <15 years of age,[72,73] with measurements between 440 and 460ms are suggested to be "borderline."[72]

The QTc is used as a predictor of cardiac event risk by physicians, especially when individuals are genetically diagnosed with LQTS but do not experience symptoms of the syndrome.[74] Among asymptomatic individuals with genetically diagnosed LQTS (ages 1 to 40 years old), individuals with a prolonged QTc of >440ms experience more life-threatening cardiac events than those with a QTc of ≤440ms. Additionally, each 10ms increase in QTc above 440ms was found to confer an 8% increased risk of life-threatening cardiac events.[75]

Among children, the precise QTc value reflective of increased risk for cardiac events is uncertain. A multi-national study of 3,015 children found that a QTc of >500ms was only predictive of increased life-threatening cardiac event risk in males, with prior syncope the only significant predictor of risk in females.[76] However, a smaller study of 316 LQTS type 1 and 2

children found that a QTc of >500ms conferred an increased risk of cardiac events (including syncope) compared to children with a QTc <470ms.[77] Among 2,772 adolescent individuals, a QTc of ≥530ms was found to be associated with increased risk of life threatening cardiac events.[78] Thus, while it is clear than an elevated QTc generally increases one's risk of cardiac events, the exact measurement which accurately predict an increase risk in children is still deliberated.

Adding to the complexity of QTc length in children, sex has been demonstrated to affect the QTc interval and risk of adverse cardiac events among pediatric LQTS patients. During the first 12 years of life, no sex differences in QTc length are observed, yet male children are observed to experience an increased risk of cardiac events compared to female children.[76,79,80] At the age of 13 to 18, the gender risk equalizes, and after the age of 18 females experience a longer QTc and a greater risk of cardiac events than males.[81] The sex difference is largely theorized to be due to the difference in sex hormones, as testosterone has been found to shorten the QT interval and estrogen lengthen the QT interval.[82]

In addition to age, sex, and QTc length, children who were the first in their family to be diagnosed with LQTS1, commonly referred to as probands, experience a greater risk of cardiac events than non-proband carriers.[79,80,83] Moreover, the specific genetic variant causing LQTS1 is thought to play a role in the severity of the phenotype, with more severe phenotypes due to missense mutations in the intracellular cytoplasmic (C-loop) region of the KCNQ1 gene. Beta-blocker therapy is observed to significantly reduce risk of life-threatening cardiac events in individuals with C-loop mutations, whereas the effect of beta-blockers is significantly attenuated among other KCNQ1 mutations.[84]

3.2.2. Pediatric LQTS1 and Cardiac Events

Review of the literature found six studies that reported the rate of cardiac events in pediatric patients with LQTS1.[77,79,83,85–87] The rates of cardiac arrest appear to be low (table 3.1) with the number of children who experienced cardiac arrest ranging from 1.6-0.9% within the study cohorts.[77,79,83,85–87] The rates of syncope varied from 0-27% among study cohorts.[77,79,85,86] However, the rate of 27% was observed in a study cohort exclusively composed of children not taking beta-blockers,[79] and among cohorts prescribed beta-blockers the rates of syncope were observed to be 0.0-9.3%.[77,85,86] There was heterogeneity between cohorts regarding beta-blocker compliance and how the authors reported such data to their readership.

Table 3.1. Literature review of cardiac events in LQTS1 pediatric patients.

Study	# LQT1 Pediatric Patients	Mean Follow-up (years)	Cardiac Events During Follow-up		Beta-blocker Therapy
			Syncope (%)	Cardiac Arrest (%)	
Chambers et al. 2017	82	7.2	4 (4.9)	0 (0.0)	Among the 4 children with syncope: 1 compliant, 1 unknown compliance and 2 non-compliant[85]
Vink et al. 2017	108	5	Not Specified	1 ACA‡ (0.9)	Among study cohort: 91% prescribed beta-blocker therapy[87]
Ozawa et al. 2016	271	12.5	74* (27.0)	1 CA (0.4)	Among the study cohort: 0% taking beta-blockers[79]
Koponen et al. 2015	224	12	21 (9.3)	2 ACA† (0.9)	Among the study cohort: 86% compliant, 24% non-compliant[77]
Petko et al. 2008	43	4.7	Not specified	0 (0.0)	Among the study cohort: 99% prescribed beta-blocker therapy (unspecified compliance)[83]
Villain et al. 2004	61	7.5	0 (0.0)	1 SCD § (1.6)	Individual with cardiac arrest was non-compliant[86]

ACA – aborted cardiac arrest, SCD – sudden cardiac death, CA- cardiac arrest (unspecified)
† Includes a patient with suspected Jervell and Lange-Nielsen syndrome
§ Event occurred after parents discontinued treatment with beta-blockers
‡ One near-drowning event also reported
* Included individuals 1-20 years old

3.2.3. Pediatric LQTS and Beta-Blocker Therapy

One key area of interest regarding the medical management of LQTS1 in pediatric populations is the use of beta-blocker therapy. Beta-blockers have been shown to significantly reduce the risk of cardiac events in LQTS1[46] and are the most common therapy prescribed to individuals with long QT syndrome.[81] However, they also have known side effects such as weight gain and lethargy,[46] and may contribute to hypoglycemia in children.[88] As outlined in Chapter 2, the ACC/AHA/HRS guidelines recommend that all LQTS patients with a QTc ≥470ms take beta-

blockers and state that the prescription of beta-blockers to asymptomatic molecularly diagnosed individuals with a QTc <470ms is reasonable.[47] The prescription of beta-blockers to asymptomatic individuals with a QTc <470ms is a class IIa recommendation, stating that the benefits of beta-blockers are greater than the risks. However, recent discussion has suggested that beta-blocker therapy may be unnecessary in some asymptomatic children. It has been proposed that beta-blockers may not be essential if: "1) the QTc is less than 470ms and, 2) the patients does not have a C-loop LQTS type 1 missense mutation and, 3) the patient does not partake in high risk activities, and 4) the patient is either a preschool boy or prepubertal girl."[81]

Moreover, research out of Finland has suggested that the requirement for beta-blocker therapy may be influenced by the variant itself. *KCNQ1* and *KCNH2* variants found in Finnish founder populations have been found to be associated with significantly fewer cardiac events than Finnish non-founder *KCNQ1* and *KCNH2* variants. The largest reduction in cardiac events was found in children with the *KCNH2* Finish founder variants, and the researchers concluded that beta-blocker therapy may be initiated later in childhood but before the onset of puberty to asymptomatic LQTS2 Finish founder children, provided their QTc was below 470ms, and there was no family history of cardiac arrest or sudden cardiac death.[77] Evidence suggests that the p.V205M variant in the Gitxsan First Nation is also a founder variant[1] and as such we may expect a milder phenotype than other LQTS patients. Thus, current research raises the question of whether beta-blocker therapy is required for all Gitxsan children with LQTS.

3.2.4. *CPT1A* and LQTS: The Potential Link

As introduced in the background section, there is growing evidence to suggest that the *CPT1A* variant p.P479L may impact the health of children with LQTS. While no previous studies

have looked at the cardiac phenotype of children with both of the *KCNQ1* p.V205M and *CPT1A* p.P479L variants, research has suggested that variants in both genes individually may be linked to hypoglycemia, and hypoglycemia to cardiac arrhythmia.

The I_{KS} ion channel, partly encoded by the *KCNQ1* gene, is expressed in both the heart and pancreatic islet cells. As such, it has been hypothesized that loss-of-function *KCNQ1* variants, such as the p.V205M, may lead to increased insulin production and predispose individuals to hypoglycemia.[61] Indeed, a study of 14 individuals with LQTS1 found that during oral glucose tolerance testing participants with LQTS demonstrated increased insulin release and reduced plasma glucose levels compared to controls. Six of the 14 individuals were taking beta-blocker therapy, but all individuals were free of the medication for at least 24 hours prior to the glucose test. No metabolic differences were observed between the group of LQTS individuals that took beta-blocker medication and the group that did not.[61] The same study compared 24 hour glucose-monitoring between four LQTS1 individuals (not taking beta-blocker therapy) and four control subjects. LQTS1 individuals were found to experience on average 77 minutes of hypoglycemia per day, compared to zero minutes in control subjects.[61] In addition to the p.V205M variant itself being related to hypoglycemia, a known side effect of beta-blockers is hypoglycemia,[88] and hypoglycemic loss of consciousness events secondary to beta-blockers have been documented as rare events in LQTS children.[60]

In addition, the *CPT1A* variant p.P479L has been linked to hypoglycemia in children.[56–58] Classical CPT1A deficiency is a rare autosomal disorder that increases risk of hypoglycemia, seizures, hepatic encephalopathy, and sudden unexpected infant death. It is caused by loss-of-function variants which impair the import of long-chain fatty acids across the outer mitochondrial membrane by the CPT1A enzyme.[89] Similarly, the p.P479L variant common to Northern

Indigenous populations has been observed to decrease the function of the CPT1A enzyme by 25-50%.[55,90,91] The p.P479L variant is thought to be a mild variant because the enzyme retains a higher amount of residual activity compared to classical *CPT1A* loss-of-function variants.[57] The p.P479L variant is also observed to be thermolabile, degrading at high temperatures, and is hypothesized to contribute to decompensation in homozygous children during times of fever.[57]

Although not as frequently observed as in classical CPT1A deficiency, the p.P479L variant has been found to be associated with hypoglycemia,[56–58] seizures[92] and sudden death in children.[52,59,93] Most recently, neonatal hypoglycemia among term, non-risk factor, Inuit newborns was observed to occur in 22% of p.P479L homozygotes, 19.8% in heterozygotes, compared to 4.8% of non-carriers in Nunavut.[56] In British Columbia, the p.P479L variant was also found to be relatively common among First Nations, with the highest rates of the variant found in coastal communities. Moreover, within these coastal communities, there was an overrepresentation of unexpected infant deaths among p.P479L homozygote children (OR=3.92, 95%CI=1.69-9.00).[52]

Hypoglycemia has been found to be associated with both QTc prolongation and cardiac arrhythmia. Previous research has found a strong correlation between low blood glucose values and high QTc measurements in type 1 diabetic children[63] and this correlation further supports evidence that hypoglycemia acts as a trigger for cardiac arrhythmia by lengthening the QT interval.[64] Hypoglycemia is also known to increase adrenergic stimulation on the heart, as well as lead to hypokalemia in some circumstances due to increased secretion of catecholamines. These changes are well-known triggers of cardiac arrhythmia.[64] Furthermore, the "dead in bed" syndrome, referring to an association between nocturnal hypoglycemia and sudden cardiac death occurring in young healthy diabetic individuals is important to consider.[65]

3.3. Impact of LQTS on the Well-Being of Indigenous Children

This literature review found no previous studies that explored the impact of an inherited cardiac condition on the well-being of Indigenous children. As such, this literature review explores three categories of literature which are related to this topic and contribute to the discussion of LQTS in Indigenous children: 1) long QT syndrome and pediatric genetic testing, 2) long QT syndrome and pediatric well-being, and 3) long QT syndrome and Indigenous adults' well-being.

3.3.1. Long QT Syndrome and Pediatric Genetic Testing

Genetic testing in children for LQTS is most often done before the child shows any symptoms of the condition, a process referred to as pre-symptomatic or predictive testing. To date, most research into the impact of pre-symptomatic/predictive genetic testing of children has focused on cancer predisposition or Huntington's disease, with minimal research investigating testing for inherited cardiac conditions like LQTS.[44]

The situation of testing for Huntington's disease is different than LQTS as it is an adult onset condition. More similar to LQTS are pediatric cancer syndromes such as Familial Adenomatous Polyposis (FAP) or Li Fraumeni Syndrome.[44] One study which explored the impact of predictive testing for FAP, found that children who undergo testing do not experience clinically relevant levels of anxiety or depression. However, an increase in sub-clinical anxiety was observed in tested children with mothers affected by FAP. This increase in anxiety was consistent across all children with FAP-affected mothers regardless of their own test result (e.g. children who tested negative still experienced increased levels of anxiety). One explanation for this hypothesized is that the act of genetic testing caused children to worry about their own mothers' health status and cancer risk.[94] Additionally, a study which explored the impact of predictive testing for a group of hereditary cancer predisposition syndromes found that young adults who were tested in

childhood perceived benefits from the testing. Moreover, these individuals felt that a reminder of the genetic result would have been of benefit during times of transition, such as from youth to young adulthood.[95]

Although our literature search did not find any studies specific to LQTS predictive testing, a small amount of research has investigated the impact of predictive testing of inherited cardiac conditions in general. It has been found that children diagnosed with inherited cardiac conditions were pragmatic about their positive test results.[44] Contrary to children's reactions, however, parents' were documented to have a profound reaction to their child's diagnosis,[44,96,97] with over 50% of parents exhibiting clinically relevant levels of distress at the time of diagnosis[98] and 33% of parents eighteen months later.[99]

A common theme in the LQTS literature is the moral dilemma faced by affected individuals about how and when to disclose information to children and other relatives.[44,96,100,101] Parents worried about the possibility that their child might test positive and the psychological consequences of the diagnosis.[44] This concern was complicated by the incomplete penetrance that accompanies congenital LQTS. A positive genetic test result does not guarantee the child will manifest LQTS symptoms and this uncertainty has been known to contribute to parents' hesitation surrounding LQTS genetic testing.[44] This is unlike pediatric cancer syndromes such as FAP which manifests in nearly complete penetrance by early adulthood.[102]

3.3.2. Long QT Syndrome and Pediatric Well-Being

To date, only four published studies have focused on the well-being of children with long QT syndrome. All four of these studies were quantitative in nature. Three studies measured quality of life (QOL) scores, and even though similar methodologies were used, the results of these studies

conflict. One study, which compared QOL in carrier children with genetic variants that cause LQTS, hypertrophic cardiomyopathy and familial hypercholesterolemia, to reference-group children found that there was no significant difference in QOL. Contrary to these findings, the other two studies focused on children with LQTS specifically and found that LQTS children have a significantly reduced QOL compared to healthy control children[103] and children with bicuspid aortic valve or congenital complete heart block.[104] It has been determined that there is significant variation in QOL scores in electrophysiologic disease, and as such stratification of disease type and targeted psychosocial research and interventions are recommended.[104] The fourth study compared anxiety and fear in children with LQTS to children with asthma, and found that children with LQTS reported a lower fear of death and medical procedures and a higher fear of failure and criticism compared to children with asthma. The children with LQTS also reported a higher score of internalizing problems and the authors' suggested that LQTS children may be more hesitant to report their true feelings of anxiety.[105]

Our literature search found no qualitative peer-reviewed papers which focused on children's lived experiences with LQTS. We did locate two graduate theses ("grey literature") which explored children's experiences with LQTS. One thesis interviewed children diagnosed with LQTS and found these children worry about acceptance and being treated differently, but emphasized that receiving LQTS medical care is important to them.[106] The other thesis interviewed unaffected siblings of children with LQTS and found that the majority of siblings maintained positive relationships with their family and that their lives did not greatly differ from unaffected families.[107] Both of these theses concluded that more research needs to be done regarding children and LQTS.[106,107]

While there are no peer-reviewed qualitative studies investigating LQTS in childhood, past qualitative research has investigated adult perceptions of living with the condition. Adults with LQTS expressed that their diagnosis was a significant life event[44,101] and felt that daily life adjustments to reduce risk contributed positively to their ability to cope with the syndrome.[101] In some cases a positive diagnosis brought participants relief[101] and caused them to make positive lifestyle adjustments.[108] Among individuals was shared concern of the perceived lack of knowledge healthcare providers held regarding long QT syndrome.[97,101]

3.3.3. Long QT Syndrome and Indigenous Adults' Well-Being

To our knowledge, only one qualitative study has investigated the impact of LQTS in Indigenous peoples to date.[14,109] This study interviewed Gitxsan adult women either diagnosed with LQTS themselves or impacted by the syndrome through affected family members. For these women, the initial diagnosis of LQTS was described as an overwhelming event, where gradual acceptance led to coping. A good understanding of LQTS, supportive family relationships and spiritual faith benefitted coping; whereas, a poor understanding of LQTS biology, contradictory medical advice, and disbelief regarding LQTS hindered coping ability. This study concluded that more exploration regarding LQTS and First Nation's well-being is required.[14,109]

3.4. Literature Gap

In summary, no previous peer-reviewed studies have specifically explored the clinical impact of LQTS caused by the p.V205M variant on children, nor have any previous studies focused on the well-being of Indigenous children with LQTS. Both the clinical aspect and lived-experience of LQTS are important to keep in mind when providing medical care, and as such this thesis aims to address this gap in the literature.

Chapter 4. Methods

4.1. Objectives

This thesis is composed of two research objectives:

1. To explore how the *KCNQ1* genetic variants p.V205M and p.L353L, and the *CPT1A* genetic variant, p.P479L, either alone or in combination, affect the cardiac health of Indigenous children in Northern British Columbia.
2. To learn about the lived-experience of Indigenous children with diagnosed with LQTS in Northern British Columbia.

4.2. Research Questions

This thesis aims to answer five research questions:

1. How do the *KCNQ1* variants p.V205M, p.L353L, and their combined effect, affect the maximum QTc in children from birth to 18 years of age compared to controls?
2. How do the variants *KCNQ1* p.V205M, *CPT1A* p.P479L, and their combined effect, affect the maximum QTc in children from birth to 18 years of age compared to controls?
3. Do the *KCNQ1* variant p.V205M and the *CPT1A* variant p.P479L variant, either alone or in combination, impact the number of children that experience syncope and/or seizures in childhood (from birth to 18 years of age)?
4. Is it reasonable for some children with the p.V205M *KCNQ1* variant to not be prescribed beta-blockers?
5. What is the lived-experience of Indigenous children who grow up with long QT syndrome in Northern British Columbia?

4.3. Hypotheses

This thesis hypothesizes:

1. Children with the p.V205M variant will have a longer QTc interval than children without the variant.
2. Children with both the p.V205M variant and the p.L353L variant in combination will have a longer QTc interval than children with the p.V205M variant alone.
3. Children with the p.V205M variant will experience more syncope and seizures than children without the variant.
4. Children with the p.P479L variant will experience more seizures than children without the variant. The p.P479L variant will have no effect on syncope.
5. Children with the p.V205M variant and the P.P479L will experience more syncope and seizures than children with either variant alone.

4.4. Methodology

In order to address the above objectives and research questions, a mixed-methods approach was taken. A quantitative approach was taken to explore the clinical impact of LQTS and is herein referred to as "Part I" of this thesis. Additionally, a qualitative approach was taken to learn about the experiences of Indigenous youth with LQTS, referred to as "Part II." The methodologies of which are elaborated on in section 4.5 and 4.6 respectively.

Both of these methodologies were rooted in a community-based participatory research approach (CBPR). CBPR is a guiding principle for conducting ethical research within Indigenous communities and is centered around serving the community's priorities for research.[110] This thesis reflects this approach as the Gitxsan Nation identified LQTS as a priority within their community.

Dr. Arbour has partnered with the Gitxsan community for over 15 years and hosts annual community research gatherings at the local health center. This study was presented at the 2019 spring research gathering by the master's student and was met with support. Additionally, the Gitxsan Research Advisory Board was consulted in the development of this study, approved all research protocols and study amendments, and will review all results prior to publication.

Harmonized ethics approval for Part I of this thesis was obtained from University of British Columbia, University of Victoria, Island Health Authority and Northern Health Authority (REB#:H05-70330). Harmonized ethics approval for Part II of this thesis was obtained from University of Victoria, University of British Columbia, and Thompson Rivers University (REB#: H19-0703) (Appendix D). This study was funded by the Canadian Institutes of Health Research, research grant no. 152972 to Dr. Laura Arbour, and through the British Columbia Graduate Scholarship awarded through University of Victoria to Simona Bene Watts.

4.4.1. Part 1 – The Clinical Impact of LQTS1

With the goal of learning more about the clinical impact of LQTS in Gitxsan children, a retrospective review of pediatric health data previously collected by Dr. Arbour and her team was analyzed. From this pediatric health data, this study compared three measurements of cardiac health (the QTc and rates of syncope and seizures) between children of different genotypes. The highest QTc measurement for each child recorded in childhood (0-18 years of age) was compared between children with different genotypes. Moreover, the proportion of children that experienced at least episode of syncope and/or seizure in childhood was also compared between genotypes. Syncope and seizures are potential outcomes of a prolonged QTc.

Data Collection

The data for this study was collected as part of Dr. Arbour's main Long QT Study ("The Impact of Long QT Syndrome on the First Nations People of Northern British Columbia: A Community-Based Research Program"). Initiated in 2005, this study sought to determine the reason for the high prevalence of LQTS in the Gitxsan community. Any First Nations individual who has LQTS, or was related to a person with LQTS, from Northern British Columbia was invited to participate. In addition to demographic and medical information, blood or saliva was collected for DNA sequencing under the stipulation of DNA on Loan.[15] DNA genotyping for the *KCNQ1* variants p.V205M, p.L353L, p.R591H variants was performed at the Molecular Genetics Laboratory at the British Columbia Children's & Women's Hospital via clinical grade Sanger Sequencing. Research testing for the *CPT1A* p.P479L variant was performed at the Centre for Applied Genomics at The Hospital for Sick Children in Toronto. Medical information gathered from each participant included past cardiac events (syncope, seizures, cardiac arrest), electrocardiogram tracings, comorbidities and medication use. In addition to medical history, a comprehensive family history and pedigree was recorded by a qualified genetic counselor. Additional details of the main Long QT Study are outlined in Arbour et al., 2008.[1]

The de-identified genetic, medical and demographic information collected from participants who entered Dr. Arbour's main Long QT study as children were used in this thesis. Participants were considered children if they were 0-18 years old at the time of enrollment in the Long QT Study. This thesis included data collected from the start date of the main Long QT Study, 2005, to August 2019. Appropriate assent and consent for this analysis was obtained at the time of enrollment in the initial study. Data coded in encrypted Microsoft Excel files which were stored

electronically on Dr. Arbour's laboratory research drive housed through University of Victoria. All participants were de-identified and referred to by a study code.

A total of 277 children were reviewed. QTc measurements were determined from ECG tracings collected as part of the main Long QT Study. Both manual and computer QTc measurements (mQTc and cQTcs) were recorded. As manual reads are considered more accurate than computer reads,[111] manual reads were used when available. All manual reads were calculated by two pediatric cardiologists blinded to variant and clinical status. The QT interval was measured in by the tangent method[112] in lead II or V, and corrected for heart rate using Bazett's formula.[113] When no manual read was available, the Stata 16-IC program was used to determine linear interpolation of mQTc on cQTcs (ECG computer calculated QTc) for the missing values of the mQTcs. The highest QTc read (mQTc or iQTC if manual was not available) for each individual is referred to as the "peak QTc." About 60% of QTc reads were manual, allowing a robust iQTc determination.

The documentation of syncope and seizures (potential cardiac events) in childhood were coded as binary variables. For example, if a child experienced at least one seizure in childhood this was coded as "1," whereas, if no seizures were documented this was coded as "0." A cumulative category "loss of consciousness" was coded as "1" if a child experienced either a seizure and/or syncope in childhood.

Relatives to be included as a control group were determined by reviewing pedigrees created as part of the main Long QT Study. Relative status was also coded as a binary variable. All p.V205M non-carrier children related to either a first, second or third degree relative with molecularly diagnosed or obligate p.V205M carrier status were coded as "1" indicating they were a non-carrier relative of a person with the p.V205M variant.

Data Analysis

Statistical analyses were done in collaboration between Ms. Bene Watts and Dr. Anders Erickson, a statistician and research consultant for the Long QT Study. STATA 16-IC was used to perform all statistical analyses. Following preliminary descriptive analyses, linear regression (Ordinary Least Squares, OLS) was used to explore the effect of genetic variants on peak QTc. Univariate, bivariate and multivariate analyses were carried out considering the *KCNQ1* p.V205M, *KCNQ1* p.L353L, *CPT1A* p.P479L variants independently, and in combination. Sex was also included as a variable in the analysis.

Linear Regression analyses were run using the peak QTc recorded at any age during childhood (0-18 years old) and at various age categories: <1 year old, 1-4 years old, 5-9 years old, 10-14 years old, and 15-18 years old. Only mQTc reads were included in the age category regressions, as the age in childhood at which cQTc measurements were taken was not available at the time of the analysis. For each individual, the peak mQTc recorded at each age category was selected; thus, it was possible for one individual to contribute a mQTc to multiple age categories.

To ascertain whether the p.V205M and/or p.P479L variants, either alone or in combination affect the loss of consciousness events experienced in childhood Pearson's Chi-Squared and Fisher Exact tests (2-sided) were performed. These tests compared the proportion of children that experienced loss of consciousness events in childhood both with and without the *KCNQ1* p.V205M and *CPT1A* p.P479L variants, alone and in combination, and determined if they were statistically different. Additionally, binomial logistic regression analysis was used to further investigate and quantify the effect of genetic variants on loss of consciousness events. Univariate, bivariate and multivariate analyses were carried out considering the *KCNQ1* p.V205M and *CPT1A*

p.P479L variants, independently and in combination. A significance level of $p = 0.05$ was used for all analyses.

Data visualizations were created using GraphPad Prism 8. The peak QTc was selected for every child with a manual read. A histogram was created comparing the peak QTc of children with the *KCNQ1* p.V205M variant to children without the variant. Additionally, six *KCNQ1* p.V205M carrier individuals with ≥4 ECGs and mQTc measurements between the ages of 0-18 years old were graphed via scatterplot to demonstrate intrapatient QTc variability.

The histogram visualization carried out using only p.V205M non-carrier control children who were either a first, second, or third degree relative of a p.V205M positive individual. All other analyses used all control children regardless of relative status.

4.4.2. Part 2 – The Lived-Experience of LQTS1

With the goal of learning about the lived-experience of Indigenous children diagnosed with LQTS in Northern British Columbia, a young adult was interviewed from the Gitxsan community and the data analyzed as a qualitative case study.

Data Collection

Originally, this study had planned on interviewing approximately five young Gitxsan adults about their experiences of growing up with LQTS. The inclusion criteria required: 1) the participant must have been clinically diagnosed with a positive p.V205M genetic variant change (molecularly diagnosed LQTS) while under the age of 18, 2) the participant to identify as First Nations, 3) the participant to have been between the ages of 18 and 30 years old at the time of enrollment, and 4) the participant be able to understand and give informed consent.

Participants were recruited from Dr. Arbour's previously established research participant cohort. The research records from participants currently enrolled in the main Long QT Study were reviewed to determine if consent for future research recontact was given. If consent for recontact was given, and the participant fit the inclusion criteria, the participant was then mailed a letter inviting them to participate in the interview study. The letter was then followed up with a phone call invitation. Despite best efforts to recruit participants through this method, and even with the help of the local community health center to update contact information for potential participants, only one participant was recruited.

Data was collected through a semi-structured interview approach. A list of open-ended questions, drafted in collaboration with all thesis supervisors and the Gitxsan Research Advisory Board, was used as a touchstone during the interview process (Appendix C). In an effort to help guide the participant tell their story, the interview questions were centered around three timepoints: 1) the participant's first contact with LQTS, 2) childhood, and 3) present day and the future. Follow-up prompts to the interview questions were informed by the Indigenous medicine wheel and previous qualitative LQTS research conducted in Gitxsan adults by Lee-Anna Huisman.[14]

Potential participants were originally offered the choice to interview in-person at their local health center in Northern British Columbia, or via teleconference using secure Skype for Business Software hosted through University of British Columbia. However, during the data collection period of this thesis, the COVID-19 pandemic occurred and all non-essential travel and in-person gatherings were restricted in British Columbia. Adapting to these circumstances, potential participants were then only offered to interview via phone or teleconference. The participant in this study chose to participate via teleconference. The interview was an hour and a half long. The

interview was recorded using the teleconference software. The interview was then transcribed verbatim from the audio-recording into a password protected Microsoft Word document.

The participant was offered her choice of giving oral or written consent. The participant chose to give oral consent. The oral consent form was emailed to the participant approximately one week prior to the day of the interview. Oral consent was then obtained via videoconference on the day of the interview, prior to interview commencement. The oral consent originally obtained from the participant was for her interview data to be used as part of a group study, and as such, additional oral consent for her interview to be used as a single case study was obtained during a post-interview phone call. Harmonized behavioural ethics approval for this study was approved by University of British Columbia, University of Victoria and Thompson Rivers University (see Appendix D for ethics certificates).

Data Analysis

The data was originally planned to be analyzed using two methods, using both an Indigenist narrative approach,[114] as well as a qualitative method employing Interpretative Phenomenological Analysis (IPA).[115] This dual analysis approach was inspired by Margaret Kovach's work[116,117] and aimed to embody Debbie Martin's Two-Eyed Seeing philosophy.[118] Two-Eyed Seeing seeks to embrace both Indigenous and Western worldviews and methodologies to improve Indigenous health research. "Two-Eyed seeing adamantly, respectfully, and passionately asks that we bring together our different ways of knowing to motivate people, Aboriginal and non-Aboriginal alike, to use all our understandings so that we can leave the world a better place."[118]

The narrative approach was coined by Indigenous scholar Margaret Kovach,[116,117] and presents a condensed version of the interview transcript directly to the reader. This approach

allows the reader to interpret the narrative directly, rather than the researchers' interpretations.[119] Moreover, this method honours Indigenous worldview and value of holistic contextual knowledge.[117]

IPA is a qualitative approach which can be used to thematically analyze interview transcripts to identify overarching themes. It can be used for a single case study or to identify themes across multiple participants. IPA has a strong history of being used in the field of health psychology[120] and aims to "explore in detail how participants are making sense of their personal and social world."[121] IPA and phenomenological research has also been supported and used in previous Indigenous health research.[122,123] Moreover, IPA produces a succinct list of findings which can be easily used by healthcare providers to inform future healthcare practices.[124]

All potential participants were offered their choice to have their interview data used in one or both of these methods. The choice to remain anonymous or be recognized by name and/or share co-authorship was offered. The participant recruited to this study preferred her interview be used for the IPA method only, and she preferred to remain anonymous.

Interpretative Phenomenological Analysis

As only one participant was recruited and the participant preferred her transcript be analyzed using IPA methodology, an IPA case study was conducted. The participant interview lent itself well to an IPA case study as it was in-depth and detailed. IPA analysis was performed using the four steps recommended by Smith, Flowers and Larkin (2009)[124]: 1) Reading and Re-reading, 2) Initial Noting, 3) Developing Emerging Themes, 4) Searching for Connections Across Emergent Themes. Each step is discussed in turn:

Step 1: Reading and Re-reading

Multiple in-depth readings of the participant's transcript were performed. For the first reading, the audio-recording was listened to alongside the transcript to ensure tone of voice and meaningful pauses were also understood.

Step 2: Initial Noting

Initial stream of consciousness notes were annotated on the transcript by hand. After the first set of preliminary notes were made by hand, three sets of notes were made on the computer. Each time a set of notes was made the transcript was read in full. A table with the interview transcript in one column and notes in the other was created in Microsoft Word following the recommendation by Smith et al (2009).[124] The first set of notes recorded descriptive comments. These comments included observations on the subject and context of what the participant said in the interview. The second set of notes recorded linguistic comments and recorded insights into the specific language used by the participant. The third set of notes recorded conceptual comments, documenting broader, more interpretative insights made by the analyst. Each set of notes was recorded using a different typographical emphasis, with descriptive comments recorded in regular font, linguistic comments recorded in italics, and conceptual comments underlined.

Step 3: Development of Emergent Themes

Emergent themes were then identified from the original transcript and comprehensive set of initial notes. An emergent theme is a brief phrase or statement that encapsulates the important information in a piece of transcript and notes. As described by Smith et al. (2009) "[emergent] themes are usually expressed as phrases which speak to the psychological essence of the piece and

contain enough particularity to be grounded and enough abstraction to be conceptual."[124] The emergent themes were recorded in another column in the Microsoft Word document. A preliminary list of emergent themes were identified and then refined. At the researcher's first attempt in noting emergent themes 57 preliminary emergent themes were identified.

Noting redundancy in the 57 preliminary themes, the researcher further refined her list to nine emergent themes. This was done by printing out the list of 57 preliminary emergent themes and cutting each theme into individual small rectangles of paper. These slips of paper each listing an emergent theme were then physically sorted into categories by the researcher. This physical manipulation of the themes allowed the researcher to visualize spatially connections and patterns between preliminary emergent themes. The refined list of nine emergent themes were then checked against the original text to ensure accuracy. While traditionally this method is suggested by Smith et al (2009) to be used in the identification of superordinate only,[124] the researcher found it useful to aid in the refinement of emergent themes as well. As Smith et al (2009) emphasizes that their methodological approach to categorizing themes is not prescriptive and encourages the researcher to explore thematic grouping creatively,[124] the researcher felt incorporating this methodological step was appropriate.

Step 4: Searching for Connections Across Emergent Themes

The nine emergent themes were then sorted once again into four superordinate themes. This was done by printing out the nine emergent themes and once again manipulating the themes spatially to search for connections. The hierarchy of preliminary emergent themes, emergent themes and superordinate themes is depicted in figure 4.1.

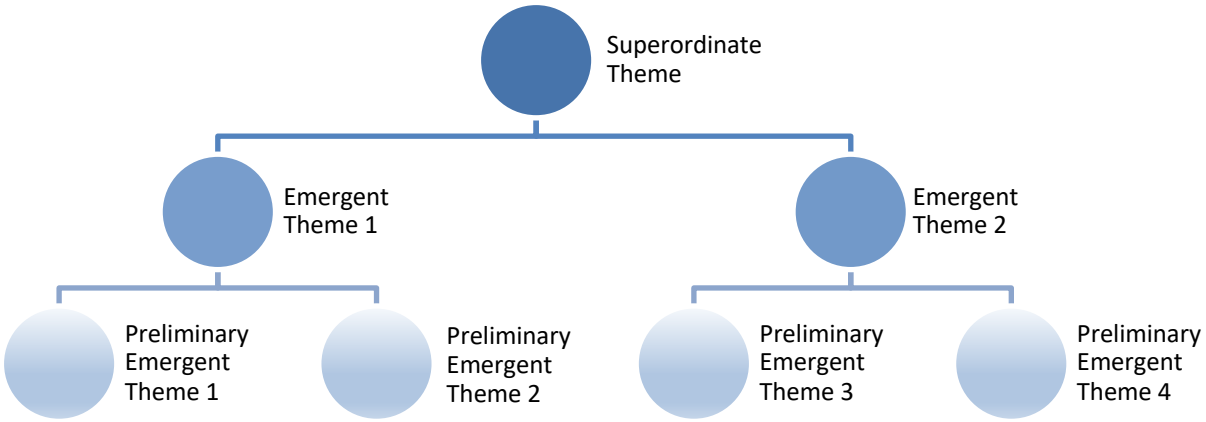


Figure 4.1. The hierarchy of preliminary emergent themes, emergent themes and superordinate themes.

Following these four steps of IPA analysis, the final list of emergent themes and superordinate themes were then written-up as a case study (see Section 5.2). The case study was de-identified by referring to the participant by a pseudonym (chosen by the participant) and replacing all reference to specific locations and family members with general statements that are still accurate but do not pose a risk to anonymity.[125] A draft of the case study was sent to the participant for member checking. A brief phone call (10 minutes) was performed to ensure that the researcher's interpretations were correct and that the results were appropriately de-identified to the participants comfort level.

4.5. Reflexivity

Throughout this thesis project, the researcher engaged in the process of reflexivity. The process was done through journaling, whereby the researcher examined her own worldview and reflected on how it may impact her role as a researcher. Reflexivity called upon the researcher to

consistency question her own beliefs, assumptions and motivations in order to better understand the lens from which she viewed the world, and how it might consciously, or subconsciously shape the research. Reflexivity also asked the researcher to examine her relationship with the participant, and how this may have shaped the results. Reflexivity is a method which not only increases the validity of qualitative research,[126] but is also an important part of performing ethical research with an Indigenous community as a non-Indigenous researcher.[127] As Kovach (2009) shares, "Reflexivity is the researcher's own self-reflection in the meaning making process."[128]

Chapter 5. Results

5.1. Part 1 – The Clinical Impact of LQTS1

5.1.1. Participants

A total of 277 participants enrolled in childhood from 2005 to 2019 were reviewed. Of these 277 individuals, 55 individuals had no relevant ECGs (the ECGs were either illegible or taken at >18 years of age), nine individuals had an unknown p.V205M variant status, and two individuals were excluded because their cQTc measurements were determined to be outliers. The remaining 211 individuals formed the QTc analysis, and their demographics are presented in table 5.1. From the 211 individuals, two additional individuals were removed from the syncope/seizure portion of this thesis because of a neurological medical history (diagnosed seizure disorder through electroencephalogram studies and brain injury) possibly confounding the events. Additionally, two individuals reported "possible" seizures and were excluded from the seizure analysis. One of these two individuals reported a syncopal event and as such was included in the LOC analysis; the second individual reported having no syncopal events and was excluded from the LOC analysis. No participants in this study were homozygous for the p.V205M variant. The mean age of participants was 14.7 years. Participants in this study were followed for a mean time of 9.2 years in the main Long QT Study.

Table 5.1. Participant demographics.

Characteristic	# of Participants	Characteristic	# of Participants
***KCNQ1* (p.V205M)**		**Sex**	
(+)	45	male	105
(-)	166	female	106
***KCNQ1* (p.L353L)**		**LOC Events**	
(+)	21	syncope	38
(-)	183	seizures	33†
unknown	7	LOC*	60†
***CPT1A* (p.P479L)**		**mQTc**	
PP	49	yes	144
PL	101	no	67
LL	50	**Number of ECGs‡**	
unknown	11	1	143
Related to p.V205M Carrier		2-5	58
yes	78§	6-10	8
no	88	11	2
n/a	45¶		

LOC – loss of consciousness, ECG – electrocardiogram**,** mQTc – manually read QTc interval
PP – homozygous wildtype for *CPT1A* p.P479L
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.479L
§ – included 1st, 2nd and 3rd degree relatives
¶ – n/a because individual was a p.V205M carrier
‡ – number of childhood ECGs recorded
* – combined syncope and seizures
† – two individuals omitted due to neurological medical history.

5.1.2. QTc Analyses

Frequency Distribution

The peak mQTc recorded in childhood (0-18 years old) was compared between children with and without the *KCNQ1* p.V205M variant. All children without the *KCNQ1* p.V205M variant (the control children) were related to either a first, second or third degree relative with p.V205M in this analysis. Children with the *KCNQ1* p.V205M variant have a higher peak QTc than children

without the variant (mean QTc = 459.5ms ± 22.5ms and 432.5ms ± 21.0ms respectively) (figure 5.1). The difference between the two means is statistically significant ($t(85)=5.597$, $p<0.0001$).

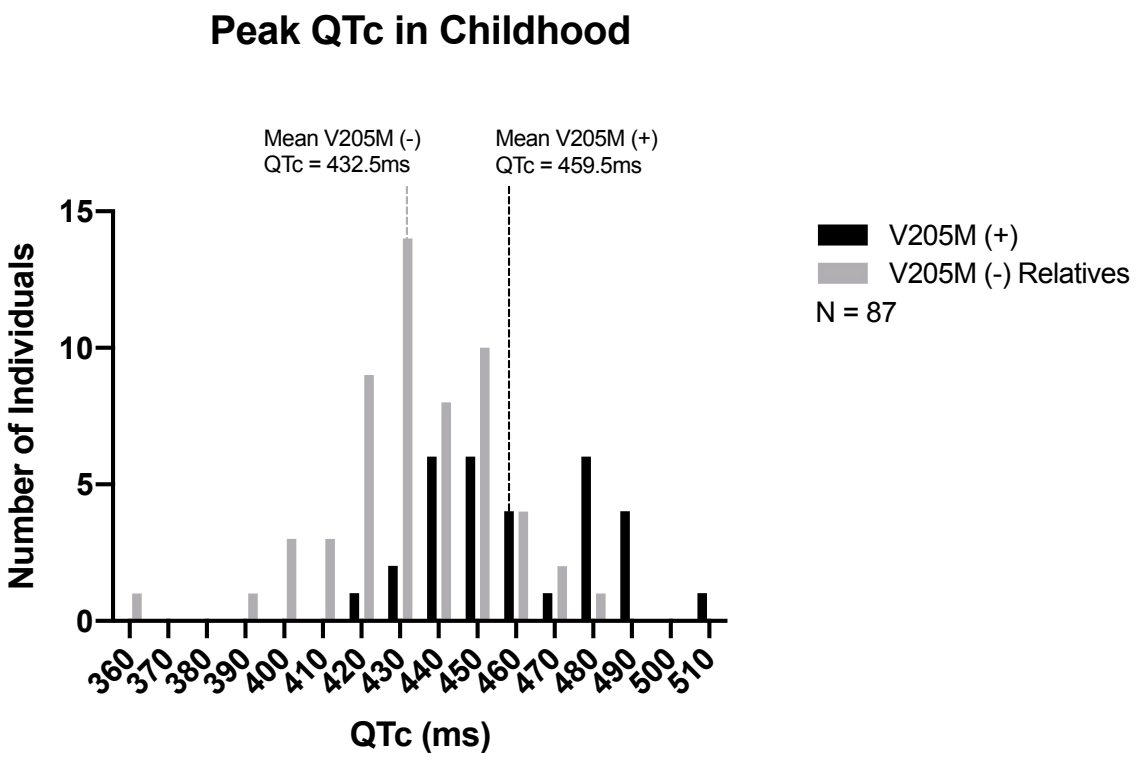


Figure 5.1. Frequency distribution of peak QTc by *KCNQ1* genotype.

The highest mQTc measured in childhood from p.V205M carrier children is depicted in black. The highest mQTc measured in childhood from non-carrier control children is depicted in grey.

Peak QTc in Childhood – KCNQ1

Linear regression analysis was run to further explore the effects of the *KCNQ1* p.V205M variant, as well as the p.L353L variant, and their combined effect on the QTc. Table 5.2 presents the variant distribution of all participants included in the regression models. Table 5.3 presents the linear regression models' predictions of the variants effect on peak QTc (mQTc or iQTc) in childhood (0-18 years of age).

For children of both sexes (table 5.1, n=204), the baseline QTc was 430.2ms, and the regression model predicted the p.V205M variant to prolong the QTc by 22.4ms ($p<0.001$). The p.L353L variant alone was predicted to increase the QTc by 6.5ms, but the effect was not statistically significant ($p=0.356$). When both the p.V205M and p.L353L variants are inherited together, the QTc was predicted to increase another 10.8ms in addition to the effect of each variant alone, however, again this affect was not statistically significant ($p=0.547$). Notably, the sample size of children with both variants was very low and only included male children (n=2). The effect of sex as a variable was non-significant but did show female children to have a slightly higher QTc than male children on average (β coefficient=3.2ms, $p=0.332$).

When linear regression models are separated by sex (5.2B and 5.2C), the models found the effect of the p.V205M variant to be stronger in females (n=100) prolonging the QTc by 25.0ms ($p<0.001$), compared to 19.7ms in males (n=104, $p=0.001$).

Table 5.2. Distribution of participant variant status by sex.

Variant Status of Participants	Males	Females	Total
p.V205M only	21	21	42
p.L353L only	11	8	19
p.V205M*p.L353L	2	0	2
unknown p.L353L	1	6	7
negative for all variants	70	71	141

Table 5.3. Linear regression analysis of variant effect on peak QTc in childhood.

Variable	Beta Coefficient†	95% CI	p Value
A) Males and females, n=204, intercept=430.2ms, adjusted R^2=0.13			
p.V205M	22.4	14.2 to 30.5	<0.001
p.L353L	6.5	-4.8 to 17.8	0.356
p.V205M*p.L353L	10.8	-24.5 to 46.1	0.547
Sex	3.2	-2.2 to 9.7	0.335
B) Males, n=104, intercept=433.6ms, adjusted R^2=0.11			
p.V205M	19.7	7.8 to 31.6	0.001
p.L353L	8.9	-6.6 to 24.3	0.259
p.V205M*p. L353L	10.8	-27.7 to 49.4	0.578
C) Females, n=100, intercept=436.2ms, adjusted R^2=0.15			
p.V205M	25.0	13.8 to 36.3	<0.001
p.L353L	3.2	-13.7 to 20.0	0.710
p.V205M*p.L353L	-	-	-

†Beta coefficients from OLS linear regression representing the baseline (intercept) and change in QTc (ms).
QTc, corrected QT.

Peak QTc in Childhood – CPT1A

Linear regression analysis was performed to look at the possible effect of the *CPT1A* variant on QTc in childhood, alone and in combination with the *KCNQ1* p.V205M variant. No significant effects of p.P479L alone, or in combination with the p.V205M variant, were observed (see Appendix A, table A1).

Peak QTc in Age Category

To explore the effect of the p.V205M variant at different periods in childhood, linear regression analyses were run at various age categories (<1yr, 1-4yrs, 5-9yrs, 10-14yrs, 15-18yrs). Each regression model used the peak QTc recorded from each child in that each age category. Only the manual reads were used for this analysis. The sample size for these age-category regression models were significantly underpowered. Preliminary findings from this analysis are presented in Appendix A (table A3), but the results should be interpreted with extreme caution due to the small sample size. Further manual reads are underway to increase the sample size in each category.

Intrapatient QTc Variability

While the above regression analyses used the peak QTc measurement from each individual, there is significant variability in QTc measurements throughout childhood. Figure 5.2 depicts QTc measurements from six p.V205M carrier children, each with four or more ECGs taken at different time points in childhood. Notable intrapatient QTc variability is observed.

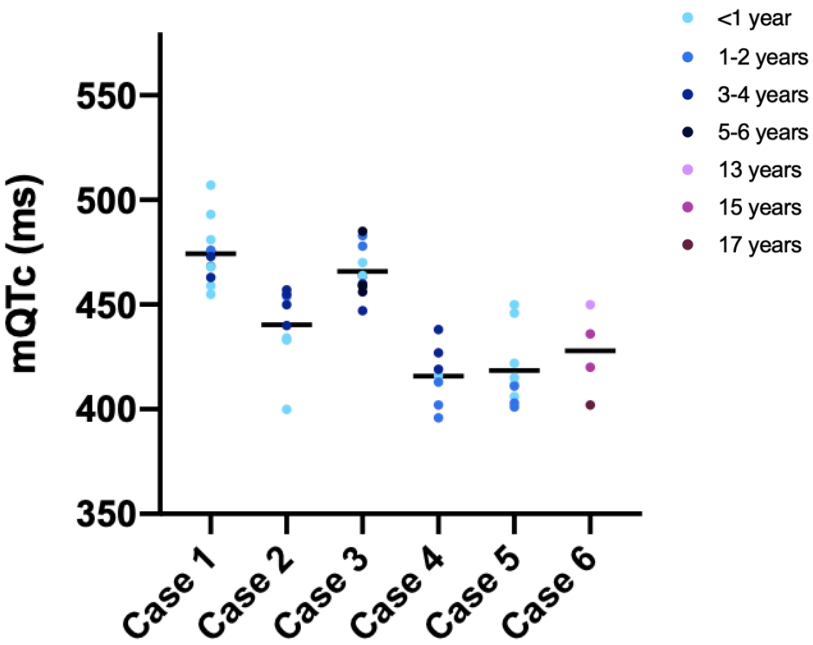


Figure 5.2. Intrapatient QTc variability in childhood.

Depiction of manual QTc measurements recorded in childhood for six children (cases 1-6). Manual QTc measurements are depicted by coloured circles, with the mean mQTc measurement depicted by a black bar. The colour of the circle indicates the age at which the QTc was measured. Significant variability in mQTc measurements throughout childhood are observed in each child.

5.1.3. Syncope/Seizure Analyses

Proportionality Tests

The proportion of loss of consciousness events (syncope and/or seizures) experienced by children with and without the *KCNQ1* p.V205M and *CPT1A* p.P479L variants, alone and in combination, were analyzed using Pearson's Chi-Squared and Fisher's Exact tests. Pearson's Chi-Squared test was used, unless the sample size of any category was less than five, thus violating a statistical assumption of the Chi-Squared test.[129] In this case, a Fisher's Exact Test was performed.

The proportion of children that experienced syncope/seizures in childhood (0-18 years old) is depicted in table 5.4.

Table 5.4. Number of participants that experienced loss of consciousness events (syncope or seizures) by variant status and sex.

		LOC§†		**Seizures‡**		**Syncope**	
		Yes (%)	**No**	**Yes (%)**	**No**	**Yes (%)**	**No**
p.P479L	PP	9 (18.4)	40	3 (6.1)	46	6 (12.2)	43
	PL	26 (26.2)	73	17 (17.2)	82	15 (15.0)	85
	LL	21 (42.9)	28	11 (22.9)	37	15 (30.6)	34
p.V205M	(-)	45 (27.4)	119	24 (14.7)	139	31 (18.8)	134
	(+)	15 (34.1)	29	9 (20.5)	35	7 (15.9)	37
PP*p.V205M	(-)	5 (12.8)	34	1 (2.6)	38	4 (10.3)	35
	(+)	4 (40.0)	6	2 (20.0)	8	2 (20.0)	8
PL*p.V205M	(-)	22 (26.8)	60	15 (18.3)	67	12 (14.5)	71
	(+)	4 (23.5)	13	2 (11.8)	15	3 (20.0)	12
LL*p.V205M	(-)	16 (43.2)	21	7 (19.4)	29	14 (37.8)	23
	(+)	5 (41.7)	7	4 (33.3)	8	1 (8.3)	11
Sex¶	M	23 (23.0)	76	16 (16.3)	82	14 (14.0)	86
	F	33 (33.7)	65	15 (15.3)	83	22 (22.5)	76

Note: Two individuals were omitted from syncope/seizure analysis due to neurological medical history (genotypes: p.V205M(+)*PP and p.V205M(-)*PL.)
(%) = percent of individuals with genotype that experienced cardiac event
¶ – sex of individuals with known p.V205M and p.P479L variant status
§ – combined syncope and seizure events
PP – homozygous wildtype for CPT1A p.P479L
PL – heterozygous for CPT1A p.P479L
LL – homozygous for CPT1 p.P479L
† – one individual omitted because LOC reported as "possible"
‡ – two individuals omitted because seizure reported as "possible"

The proportion of children that experienced at least one LOC event (syncope and/or seizures) in childhood was found to be significantly different between *CPT1A* p.P479L genotypes (PP, PL, LL) [$\chi^2(2)=7.7$, $p=0.021$]. Similarly, the proportion of children with p.P479L variants that experienced syncopal events [$\chi^2(2)=6.93$, $p=0.031$] was also significantly different. The proportion of children with p.P479L variants that experienced seizures trended towards statistical significance

[$\chi^2(2)=5.41$, p=0.067]. No other statistically significant differences were found (see Appendix A, tables A4-A6 for full results).

Loss of Consciousness

Logistic regression analysis was performed to analyze the effects of the genetic variants, *KCNQ1* p.V205M and *CPT1A* p.P479L, alone and in combination, on syncope/seizures in childhood.

Table 5 presents the results from logistic regression analysis of the *KCNQ1* variant p.V205M, the *CPT1A* p.P479L, and their combined effect, on all loss of consciousness events (syncope and/or seizures) experienced in childhood. The univariate p.V205M logistic regression model shows no association between the p.V205M variant and the odds of experiencing at least one loss of consciousness event in childhood (OR=1.4; p=0.388) (table 5.5A). However, the univariate *CPT1A* regression model predicts that the odds of experiencing LOC at least once in childhood is 3.3 times higher in children who are homozygous for the p.P479L variant compared to homozygous wildtype individuals and the effect is statistically significant (p=0.010) (table 5.5B). Given our small numbers, there is no statistical evidence that heterozygous individuals (PL) compared to homozygous wildtype individuals (PP) are more likely to present with syncope or seizures to suggest a dosage effect (OR=1.6; p=0.290). When both p.V205M and p.P479L variants are modelled together, the predicted odds ratios remain relatively constant (table 5.5C), supporting the findings of the previous two univariate models. Regression analysis was also performed testing for interaction effects between the p.V205M and p.P479L genotypes, however, no evidence of interaction was apparent (p.V205M*PL OR=0.2, 95%CI=0.0-1.4; p.V205M*LL OR=0.2, 95%CI=0.0-1.6) (see Appendix A, table A7).

Table 5.5. Logistic regression analysis of loss of consciousness events in childhood.

Variant	OR	95% CI	p Value
(A) p.V205M model, n=208			
p.V205M	1.4	0.7 to 2.8	0.388
(B) p.P479L model, n=197			
PL	1.6	0.7 to 3.7	0.290
LL	3.3	1.3 to 8.3	0.010
(C) p.V205M and p.P479L model, n=197			
p.V205M	1.3	0.6 to 2.8	0.531
PL	1.6	0.7 to 3.7	0.281
LL	3.3	1.3 to 8.3	0.011

Note: one individual with LOC recorded as "possible" excluded from analysis.
PP – homozygous wildtype for *CPT1A* p.P479L, baseline *CPT1A* measurement in regression model
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.P479L

Seizures

Logistic regression analysis of the *KCNQ1* variant p.V205M, the *CPT1A* p.P479L, and their combined effect on seizures was analyzed (table 5.6). There was no statistical evidence of the p.V205M variant increasing the odds of children experiencing at least one seizure in childhood (OR=1.5, p=0.359) (table 5.6A). However, the odds of experiencing at least one seizure in childhood is 4.6 times higher in children with the homozygous p.P479L genotype compared to homozygous wildtype children (p=0.027). Additionally, the odds of experiencing at least one seizure in childhood is 3.2 times higher in children that are heterozygous for the p.P479L genotype, with the p value trending towards statistical significance at p=0.076 (table 5.6B). When both p.V205M and p.P479L are modeled together similar ORs are predicted (table 5.6C). Similar to the previous LOC analysis, logistic regression analysis was also performed testing for interaction effects between the p.V205M and p.P479L genotypes. No evidence of interaction was found

(p.V205M*PL OR=0.1, 95%CI=0.0-1.2; p.V205M*LL OR=0.2, 95%CI=0.0-4.0) (see Appendix A, table A7).

Table 5.6. Logistic regression analysis of seizures in childhood.

Variable	OR	95% CI	p Value
(A) p.V205M model, n=207			
p.V205M	1.5	0.6 to 3.5	0.359
(B) p.P479L model, n=196			
PL	3.2	0.9 to 11.4	0.076
LL	4.6	1.2 to 17.5	0.027
(C) p.P479L and pV205M model, n=196			
p.V205M	1.4	0.6 to 3.7	0.395
PL	3.2	0.9 to 11.7	0.073
LL	4.5	1.2 to 17.3	0.029

Note: two individuals with seizures recorded as "possible" excluded from analysis
PP – homozygous wildtype for *CPT1A* p.P479L, baseline *CPT1A* measurement in regression model
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.P479L

Syncope

Logistic regression analysis of the *KCNQ1* variant p.V205M, the *CPT1A* p.P479L, and their combined effect on syncope was carried out (table 5.7). The p.V205M variant was not found to have any effect on the odds of experiencing syncope in childhood. In the p.V205M univariate model (table 5.7A), the OR was 0.8 (95%CI=0.3-2.0, p=0.660), and in the p.V205M and p.P479L bivariate model (table 5.7C), the OR was 0.7 (95%CI=0.3-1.9, p=0.500). In contrast, when the p.P479L variant was modeled alone (table 5.7B), the odds of experiencing syncope in childhood was predicted to be 3.2 times higher in children with the homozygous p.P479L genotype compared to homozygous wildtype children (p=0.031). The OR for heterozygous p.P479L children was 1.3 and not statistically significant p=0.650. When both p.V205M and p.P479L are modeled together

similar ORs are predicted (table 5.7C). No evidence of interaction was found between the p.V205M and p.P479L genotypes (p.V205M*PL OR=0.6, 95%CI=0.1-5.9; p.V205M*LL OR=0.1, 95%CI=0.0-1.2) (see Appendix A, table A7).

Table 5.7. Logistic regression analysis of syncope in childhood.

Variant	OR	95% CI	p Value
(A) p.V205M model, n=209			
p.V205M	0.8	0.3 to 2.0	0.660
(B) p.P479L model, n=198			
PL	1.3	0.5 to 3.5	0.650
LL	3.2	1.1 to 9.0	0.031
(C) p.P479L and p.V205M model, n=198			
p.V205M	0.7	0.3 to 1.9	0.500
PL	1.3	0.5 to 3.5	0.665
LL	3.2	1.1 to 9.1	0.029

PP – homozygous wildtype for *CPT1A* p.P479L, baseline *CPT1A* measurement in regression model
PL – heterozygous for *CPT1A* p.P479L
LL– homozygous for *CPT1A* p.P479L

5.2. Part 2 – The Lived Experience of LQTS1: A Case Study

5.2.1. Sarah's Story

Sarah is a young adult who was diagnosed with long QT syndrome as a teenager. She was tested for the syndrome because others in her family were found to have the condition. She was raised in Northern British Columbia.

Four superordinate themes arose from Sarah's story with long QT syndrome: 1) Daily Life with Long QT Syndrome, 2) Interactions with Medical Professionals, 3) Finding Reassurance, and 4) The In-Between Age. Each superordinate theme is composed of two to three themes, with a total of nine emergent themes (table 5.8). Each superordinate theme is discussed in turn.

Table 5.8. Case study superordinate themes and emergent themes.

Superordinate Themes and Emergent Themes
1. Daily Life with Long QT Syndrome *"I almost forget"* Beta-blockers: "*A daily reminder and a daily stress"*
2. Interactions with Medical Professionals Long QT syndrome is overlooked: "*It was put on me"* Consistency in follow-up appointments Relationships and reciprocity
3. Finding Reassurance Family Awareness of self
4. The In-Between Age A difficult age to be diagnosed Long QT syndrome and Indigenous identity

5.2.2. Daily Life with Long QT Syndrome

"I almost forget"

Long QT syndrome did not have a large role in Sarah's daily life. She had never experienced any of the symptoms of the condition and many of the recommendations for managing long QT syndrome already fit well into Sarah's life. For example, Sarah did not commonly take medications, so it was easy for her to avoid QT prolonging drugs. Moreover, she felt it was relatively easy to monitor her exercise levels. All this led to Sarah almost forgetting about the syndrome:

> *"I kinda forgot about it for the most part, just 'cuz, I'm not taking beta-blockers and the only time it really is, something I have to be aware of, is when it comes to a list of medications that they recommend that you don't take. So, just like checking that list before taking certain medications. […] it doesn't like, have the biggest impact on my life… like I almost forget I have it for the most part."*

While long QT syndrome was almost forgotten in Sarah's daily life, exposure to potential cardiac triggers served as reminders. For example, Sarah would recall her long QT syndrome when being prescribed a new medication or participating in vigorous exercise. Sarah was also reminded of her long QT syndrome on social media. She mentions that viewing posts where others shared that they had experienced long QT syndrome cardiac events acted as a strong reminder. When Sarah is reminded of her long QT syndrome, she becomes more concerned with her health and reminds those closest in her life about her condition:

"I mean like sometimes when I see long QT posts it's usually because somebody, like, had their heart stop, and then like, whenever I see that like on social media, I'm kinda just like, 'hey uhm – to my [partner] – like, you know CPR right?' like that kind of stuff, just double checking that like the people around me know, I have to remind them every once and a while, just because like it isn't something that gets brought up all the time."

Beta-blockers: *"A daily reminder and a daily stress"*

Sarah largely attributed the minor impact of long QT syndrome in her life to her decision not to take beta-blockers. While long QT syndrome is not currently brought up in her daily life, Sarah viewed that taking beta-blockers would have significantly changed this:

"I honestly, just mean it comes down to me…forgetting about it [long QT syndrome], or not being reminded of it? It is in the back of my mind, but it's not something where like I'm always thinking about it, or always con.. con..? conscious about it. Whereas, if I was taking a medication every day, I'd have to be like, 'oh okay I need to take my beta-blocker,' like, 'okay what time is it? I need to make sure I take my beta-blocker.' Like, 'oh we're going on vacation, need to make sure I bring them,' whereas like the only time I get reminded of it currently, is if like somebody brings it up, or if I have to do like a stress test or something like that, or if I'm being prescribed a new prescription…"

Moreover, Sarah shares that she did not think taking beta-blockers would have been something attainable for her in her childhood:

"Yeah, I don't know, with beta-blockers it's just like that extra responsibility… and I feel like for kids that would be a harder responsibility, so while I was younger, just like

reliably taking beta-blockers every day wasn't something that was like achievable for me, and my preference, and how I felt about them."

Sarah is aware that she would most likely need to take beta-blockers in the future, but to her, the potential benefit from beta-blockers did not outweigh the negative impacts at this time. Sarah has a personal conceptualization of her own risk level and this informed her decision regarding beta-blockers:

"I feel like taking beta-blockers would be a daily reminder and like a daily stress… and I know that, like one day, when I chose to have kids, I'm probably gonna have to take beta-blockers, like it's not like I'm never taking beta-blockers, it's like one day in the future I can wait until then. Until it becomes a higher risk and stuff like that."

Sarah's conceptualization of risk was also informed by her family's experiences:

"Uhm… around the decision on not taking beta-blockers, I think my decision would have changed if my [family members] had some experience with long QT actually impacting in their life, but just because the people around me that I know, I haven't really, like, had anybody really experience any of the problem of long QT yet, just like that kinda security of, yeah we have long QT, but our ECGs are normal, our stress tests are normal, and like, there's nothing really prevalent for us with like our long QT so, just because it's like uhh.. something that is like [not] super concerning."

Additionally, the increased risk of stopping beta-blocker medication once started was very significant to Sarah, and this informed her decision to wait as long as possible until starting the medication:

> *"[…] we know that once you go on beta-blockers you're taking them like every day, probably for the rest of your life, just 'cuz like weaning off beta-blockers puts you at higher risk of like, having some sort of long QT issue. And, for like right now, like my [family member] got diagnosed for it, which is why we ended up getting tested for it, and just like, we don't, we don't notice anything significant with it. And, like every time we get like an ECG or a stress-test done it's never like any concern, so I guess [we are] like taking more of the risk than taking beta-blockers every day which is a choice that we decided to do."*

Lastly, Sarah emphasized the importance of autonomy in medical care for long QT syndrome. Due to the fact that it is a life-long condition, it was especially important to Sarah that affected individuals have positive experiences regarding the syndrome early in their youth. She demonstrated that the choice surrounding beta-blocker therapy was an important example of this:

> *"It's definitely good to be proactive with your health especially when you know that it's like something constantly there – that it's like a diagnosis that isn't going away any time soon. So, I think it would be really important just for like young kids to like, have positive experience with it so, that it doesn't end up being something that's negative for the rest of their life. So, it's not like 'okay I have to take beta-blockers' or 'I have to do this,' so that [instead] it's something that they chose to do, where it's more positive."*

5.2.3. Interactions with Medical Professionals

Interactions with medical professionals were found to be a significant component of Sarah's lived-experience with long QT syndrome.

Long QT syndrome is overlooked*: "It was put on me"*

A resounding sentiment expressed by Sarah was that long QT syndrome felt overlooked by medical professionals. Sarah had moved away from her hometown where she was initially diagnosed and expressed a feeling of disconnect between her initial diagnosis and the follow-up care provided to her. She felt that responsibility of pursuing proper follow-up care was placed on her as the patient:

> *"So, it's just like, one of those things, where like, yeah okay I was diagnosed with it, but then it's like, I was told that I should be on beta-blockers, and I was told that I should get like a stress test, so I have like my family that reminds me like 'Hey you need to go get a stress test done,' and be proactive with my own health, but it's almost like it, it was put on me."*

Sarah elaborates that she is not confident that her family doctor would consider her long QT syndrome, and further emphasizes that she felt that the responsibility to ensure she received proper care was put on her:

> *"Because like, my doctor, my family physician here, wouldn't probably think like, stress tests, or ECGs or, hey like there's beta-blockers that you can go on for long QT. Like, I've never had, I don't think my family doctor has ever mentioned it, so… it's one of those things that I have to like constantly tell people like 'oh that's a medication, let me just*

check that it won't affect my long QT' or like 'oh it's been so many years, I should probably get like an ECG.'"

This feeling of being overlooked was not specific to her interactions with her family doctor however, and Sarah explains that her long QT syndrome also felt overlooked by her cardiologist during her last check-up appointment:

"I just think for the most part, it gets overlooked by people, especially like that's the feeling I got when I went to go do my last stress test. Like, I just went to do the stress test, I didn't choose to go to that cardiologist, my doctor gave me a referral to go there, and then the way that the physician's attitudes and opinion towards it, towards me, was just extremely negative."

Consistency in follow-up appointments

Sarah felt it was important to be proactive with her own health, however at times she felt it difficult to motivate herself to attend long QT syndrome medical appointments. She felt that all of her past interactions with medical professionals regarding her long QT syndrome had been largely negative and this impacted her desire to seek out future care. Sarah shares:

"[…] when I do think to all the experiences I've had, I don't think I can think of anything being like a more neutral experience, they were definitely all negative for me."

Part of these negative experiences was Sarah's strong aversion towards stress tests. While Sarah felt that there is something inherently awful about stress tests, she also explains that having to seek out testing and bringing up long QT syndrome is unattractive to her:

> *"[Stress tests] probably just like negatively impacts my emotional health, and mental health a little – just like, like, I really dread, I really dread, going to them [stress tests]. Just, 'cuz like the medical side of it, and having to talk to doctors about it, because uhm going to my family doctor, just bringing up that I had long QT was not something that they look into."*

While at the surface Sarah struggled to find a reason for her dislike of stress tests, as she examined her experiences further, the lack of consistency in stress test procedures was found to significantly contribute to her dislike for the procedure:

> *"Making sure you see the same doctor consistently, or knowing what to expect, 'cuz I've done ECGs and stress tests in a few different settings and they all, like use different protocols like for a stress test. […] something that might help was like consistency if you're seeing the same doctor you might know what to expect."*

She then emphasized the importance of consistency even further in all long QT syndrome medical care, especially for children diagnosed with long QT syndrome:

> *"I feel like the relationship doesn't have to be strong, but just like, the familiarity being there. Like, I could imagine being younger, and always going to different physicians about the same thing, and like, having to do that, and like get ECGS from like a young age. I feel like just consistency, or like familiarity, would be probably the best for kids. Like, if I was younger, and I had to bounce between physicians and cardiologists, it would just be the most uncomfortable experience ever. And so, just having like, not*

necessarily a community, but just like, being supported by familiar people, or like going to like people that are like familiar – you take more comfort in it."

Relationships and reciprocity

Building off of her desire for consistency, Sarah also expressed a desire for a different approach towards people with long QT syndrome in general:

"Maybe just like, better support making it a more positive experience around it […] just maybe, a different kind of support, or support with a different attitude or approach to people who have it."

She described a preference for healthcare with a more consistent and collaborative angle, emphasizing an ongoing relationship between the physician and patient:

"I think it would be more positive if like you were consistently followed by certain physicians or doctors or people who actually had a positive response to it, knowing that like, oh okay, we're going to keep up with it – kinda where it doesn't feel like it's a waste of their time and a waste of my time. Just like, having a more positive association with anything associated with it."

The concept of reciprocity within the physician-patient relationship was emphasized by Sarah in the way she regards the concept of time. Both Sarah and the physician were contributing their time to the relationship, and thus mutual attention and respect was required in the meeting. The opposite was experienced by Sarah and highlighted the importance of reciprocity in healthcare:

"[The physician's] whole attitude was really negative, with like me even being there, [the physician] was just kinda like, this is something that's not affecting you right now, Uhm, I can refer you to someone who might be more 'interested' in this kind of stuff, and like, kind of had like the attitude like, this is just a big waste of my time, maybe just go to somebody who's gonna take out a study on this…"

5.2.4. Finding Reassurance

Sarah was well-adjusted to her diagnosis and was able to hold in mind the seriousness of the condition, while not fixating on the condition in her daily life. Reassurance regarding her long QT syndrome was found to arise from Sarah's family and also from within Sarah herself.

Family

Sarah spoke about how family played an integral role supporting her life with long QT syndrome. Sarah's parents played a key role in both motivating Sarah to be tested during adolescence, and to continually stay on-top of her condition as a young adult (for example, reminding her to attend check-up appointments with the cardiologist). Sarah shares how being part of a close supportive family was of benefit:

"I think just having a good relationship with my family. Like, I could imagine what it would have been like [to be diagnosed with long QT syndrome] if me and my family weren't as close and didn't have the positive relationships that we do. Like, I think what they did well was just like we are a close family that supported each other."

Additionally, Sarah's sibling, who is also diagnosed with long QT syndrome, provided Sarah with someone whom she could relate to. Both attending appointments together as youth, and now being able to discuss and compare long QT experiences as young adults was felt to be of particular value:

> "*Uhm, it's definitely nice that [my sibling] can like relate to me, because, I do go complain about a stress test and [they can] be like 'oh I didn't have to do it last time I went.' So, it is nice that we go, and we do get checkups around the same time, and for the first few ones in my home town we went together to get checkups […] And like it's nice that I do have somebody that I can go with, or like, even talk to it about. Because like with my friends, or even with my [partner], I just say like, 'oh I just had this really bad experience with a stress test' but [they have] never done a stress test, […] Whereas [my sibling] can be like 'Ooh, last time I had to do that too, or last time mine was fine' kind of thing like that.*"

Other members in participant's family had the condition as well. None of her family members had experienced adverse effects of long QT syndrome, such as syncope or cardiac arrest, and this provided Sarah with reassurance:

> *"[…] noticing that [older individuals in my family] both had it for like, many, like several years before they found out that they had it without it impacting their lives – 'cuz like, lots of people who do have it can go their whole life without having any issue with it, so just like knowing that like, my family have both like have it, and didn't show any issues with it, is like nice, like, it is serious, but it doesn't always affect you, kind of thing.*"

Awareness of self

Sarah also found reassurance from within. After her long QT syndrome diagnosis, Sarah describes increasing awareness of how her body was feeling. She is mindful of the connection between her body's physiological and emotional state, and demonstrates that an awareness of this connection can be used to help modulate her stress levels regarding long QT syndrome:

> "*Long QT probably just made me worry more about doing exercises or just being a bit more aware of like, how I am feeling, if I'm feeling light headed or need to stop and take a break, so that, my stress levels can go down, so I don't want to worry when my heart rates too fast and stuff like that.*"

This awareness allowed her to continue exercising, finding reassurance by listening to her own body:

> *"So like it didn't really impact sports or exercising at all – other than just being a bit more aware, of my heart rate and things."*

5.2.5. The In-Between Age

A difficult age to be diagnosed

Sarah explains that being diagnosed as a teenager was a difficult age to receive a diagnosis of long QT syndrome. She explains that while she was not symptomatic, she still found that it impacted her social interactions with friends and family:

> *"It was just originally that really bad impression of […] being diagnosed, especially at the age that I did. Like if it was younger, and it was maybe something that followed me*

and was just like something that was always there, but it was something that like, I was [a teenager], and then it's like 'oh here, like we recommend you take all this stuff,' and obviously like I'm a teenager, and for the most part it like, didn't impact me, but like it impacts like the way that my family encouraged me to take the beta-blocker, it impacts the way that I like, have to mention to my friends like 'hey, like I do have long QT so it's not recommended that I exercise (and stuff like that) by myself.'"

An additional challenge of being diagnosed as an adolescence was that it is a significant period of transition. Sarah explained that her regard towards long QT syndrome has changed over time, and she felt like she only had the opportunity to inquire about her condition at the initial diagnosis:

"[…] maybe just like some sort of, easier place to go to contact and reach out with questions and stuff like that, because I feel like I never really got that opportunity, except when I was like diagnosed, and when I was [a teenager], I didn't care. It was the least of my concerns, I was like, I have it, but it's not going to affect me, I could take beta-blockers, but I probably don't need to, and the most annoying part of this whole thing is the stress test. And that was just kind of my attitude for so many years, but obviously as I'm getting older, it's become less of something, and you kind of mature with age, and just being a bit more aware of it."

Long QT syndrome and Indigenous identity

Sarah explains that the age between adolescence and young adulthood was also a period of growth surrounding her own identification with her Indigenous ancestry. Initially, as an adolescent, she explains that she never strongly identified with being Indigenous:

> *"So growing up in my home town, definitely like being Indigenous was never something that I shared, I didn't necessarily look Indigenous so, not identifying with it was something that I was more like, happy to do. So uhm, when I did get diagnosed with long QT syndrome, it kinda had the association of being like Indigenous, and just like, growing up with all these negative stereotypes and the way that the community kind of looks down upon them… almost… just like the way that the Indigenous community was up there, uhm, definitely was probably stemmed from like a lack of knowledge and a lack of history."*

She felt that having long QT syndrome was strongly associated with being Indigenous, and this was an additional reason why she was displeased with her long QT syndrome diagnosis:

> *"It's just always been associated with being Indigenous, 'cuz that's kind of like what you hear when you find out when you're diagnosed with it, and it comes from my [parent's] and my [grandparent's] side of the family, it does get passed on through the gene."*

> *"[…] my diagnosis was not something I was too thrilled about, uhm, probably was just like how strongly it related to being Indigenous."*

However, as Sarah grew older, she become more accepting of her partial Indigenous ancestry and, in turn, her long QT syndrome:

> *"Uhm, just learning about it in my first few years of university it definitely made me be a bit more... accepting, and definitely more understanding of the Indigenous culture and health… and I feel like it did improve my like attitudes towards being diagnosed with*

long QT. Just because… I dunno… it just it didn't have so much of that negative association that was there originally."

Chapter 6. Discussion

6.1. Part 1 – The Clinical Impact of LQTS1

6.1.1. LQTS1 and the QTc Interval

The *KCNQ1* p.V205M variant was found to significantly prolong the peak QTc in childhood, but sample size was too small to determine if there were any specific age categories where carriers were at an elevated risk (based on their QTc length) compared to other age groups. It appears that the p.V205M variant has a slightly stronger effect among female children, compared to male children, and this finding is similar to previous findings in adults.[35]

The average peak QTc of p.V205M carrier children is less than the previously reported peak QTc in adults, however the peak QTc among non-carrier children is comparable to non-carrier adults. Previous findings in adults reported the average peak QTc among p.V205M carriers to be 476ms (±35ms) compared to 437ms (±28ms) in non-carrier relative controls.[35] Our findings in children determined the average peak QTc among carrier children to be 459.5ms (±22.6ms), with the average peak QTc among non-carrier controls 432.5ms (±22.1ms). The average peak QTc of p.V205M carrier children is at the upper limit of what is considered a borderline QTc (440-460ms) for children <15 years old.[72,73] In comparison, the measurement for Gitxsan adults (78% female) is above the threshold of 470ms for a prolonged QTc for women.[35,72] This suggests that the corrected QT interval of children may be less affected by the p.V205M variant compared to adults. It is possible there was a higher proportion of probands among the previous adult study contributing to a longer QTc among adults.

Regression analysis predicted the p.V205M variant to significantly prolong the peak QTc by 22.4ms ($p<0.001$) but did not find the p.L353L variant to statistically significantly prolong the

QTc either alone or in combination with the p.V205M variant. It should be noted however, that the sample size of children with the p.L353L variant alone (n=19) and p.L353L and p.V205M in combination (n=2) were small and this may have underpowered the effects of the p.L353L variant. The previous study documenting the effects of the p.L353L variant in Gitxsan adults found the p.L353L variant to have a stronger effect among males than females.[36] A similar trend is observed in Gitxsan children, with the p.L353L variant predicted to prolong the QTc by 8.9ms (p=0.259) among male children, compared to only 3.2ms (p=0.710) in female children, but the effect is not statistically significant in either sex. Among adults, an interaction effect between the p.L353L and p.V205M variants was only observed to occur in males.[36] The sample size is too small (n=2) and only included the male gender to make any statements about a potential p.V205M and p.L353L interaction in children in this study. More research is needed to further determine the potential effect of the p.L353L variant in children.

The *CPT1A* p.P479L variant, either alone or in combination with the *KCNQ1* p.V205M variant, was not found to prolong the peak QTc in children. It is possible that the QTc measurements were observed when all p.P479L carrier-children were well-fed and as such no QTc prolongation was observed. Our theory hypothesizes that the effects of this variant on the QTc are only observed in a hypoglycemic state. More research is needed to further examine if there is a link between *CPT1A* and QTc prolongation. A future study with 24-hour glucose monitoring and Holter ECG recordings is planned.

6.1.2. LQTS1 and Syncope/Seizures

While the p.V205M variant was found to significantly prolong the QTc and could contribute to syncope and seizure episodes in this pediatric population, our research found that the *CPT1A* p.P479L variant had a stronger association with loss of consciousness events.

The proportion of loss of consciousness events (combined syncope and seizures) was found to be statistically significantly different between the children with the *CPT1A* p.P479L genotypes (PP, PL, LL). No statistically significant difference was observed between *KCNQ1* p.V205M carriers and non-carriers. Furthermore, there was no interaction between the p.P479L and the p.V205M. Of importance, our findings predicted that children homozygous for *CPT1A* p.P479L are 3.3 times more likely to experience at least one loss of consciousness event in childhood compared to non-carriers (p=0.011), while there was no association between loss of consciousness events and the p.V205M variant. This suggests that the *CPT1A* p.P479L variant has a greater association with loss of consciousness events in Gitxsan children than the *KCNQ1* p.V205M variant. Additionally, although not significant, *CPT1A* p.P479L heterozygote children were predicted to be 1.6 times more likely to experience a loss of consciousness event (p=0.281). A larger sample size could clarify whether there is a dosage effect.

In further support of *CPT1A* having an effect on LOC events, we observed that participants who were homozygous wildtype for *CPT1A* experience rates of syncope and seizures comparable to that of the general population, while p.P479L homozygotes experienced an elevated rate of events. Syncope is known to affect approximately 15% of children,[130] and our study estimates that syncope is experienced by 12.2% of *CPT1A* wildtype (PP) individuals, 15.0% of heterozygous (PL) individuals and 30.6% of homozygous (LL) individuals. With regard to seizures, febrile seizures (the most commonly type of seizure in children) is known to affect 2-5% of the

population,[131] with epilepsy affecting <1% of children.[132] Our study estimates that 6.1% of *CPT1A* homozygote wildtype individuals experience seizures, while 17.2% heterozygotes and 22.9% homozygotes experience seizures.

It is interesting that the *CPT1A* p.P479L homozygous variant was found to not only have a statistically significant effect on seizures, but also syncope in childhood; the OR for seizures among homozygotes and heterozygotes was 4.5 (p=0.029) and 3.2 (p=0.073) respectively, while the OR for syncope was 3.2 (p=0.029) and 1.3 (p=0.665) respectively. The *KCNQ1* p.V205M was not found to statistically increase the odds of seizures (OR=1.4; p=0.395) and there was no association with syncope (OR=0.7, 95%CI=0.3-1.9, p=0.500). To our knowledge, the *CPT1A* p.P479L has not previously been associated with an increase in syncope, however, hypoglycemia is known to be a rare cause of syncope in children.[60] It is possible the association between the p.P479L variant and syncopal events is due to a misreporting of loss of consciousness events from study participants. It is likely that some participants mistook a seizure for a syncopal event.

The elevated rate of loss of consciousness events among children with the p.P479L variant may be explained by the p.P479L variant predisposing children to hypoglycemia. As discussed in the literature review, an association with hypoglycemia and the p.P479L variant has been shown, and loss of consciousness events (most commonly seizures) are a symptom of hypoglycemia. While multiple papers have presented a link between the p.P479L variant and hypoglycemia,[56–58] to our knowledge, there is only one previous report documenting an association of loss of consciousness events with the variant. This previous study found that p.P479L homozygotes were more likely to experience non-febrile seizures compared to heterozygote and wildtype children.[92] As such, we believe this study to be the second study to report seizures as a clinical outcome for children with the p.P479L variant, and the first to report an association with syncope.

While loss of consciousness events are a logical consequence of hypoglycemia,[133] the question arises whether there is an additional factor within this study population that is exacerbating hypoglycemic symptoms leading to the elevated rate of loss of consciousness events. For example, as discussed in the literature review, there is evidence to suggest that the p.V205M variant may contribute to hypoglycemia because of hyperinsulinemia. However, no interaction effect between the p.P479L and p.V205M genotypes was observed in our regression analyses, suggesting that children with the p.P479L variant were not more severely affected if they also had the p.V205M variant. It is possible the analyses were underpowered as the sample size of p.P479L homozygotes that were carriers of the p.V205M variant was small (n=12) and as such, a potential interaction effect cannot be ruled out, however an interaction effect does not appear to be the driving force between the loss of consciousness events and p.P479L variant observed in this population.

The majority of loss of consciousness events among children within the Gitxsan community are more strongly associated with the p.P479L variant, than the p.V205M variant or any combination of both variants.

6.2. Part 2 – The Lived Experience of LQTS1

The goal of this case study was to learn more about the experience of growing up with long QT syndrome from one young adult in Northern British Columbia. While there is little prior research surrounding children's perceptions of LQTS, Sarah's story does share some similarities to prior findings. Previous graduate work found that children with LQTS worry about being treated differently by others due to their diagnosis.[106] Sarah expressed a similar sentiment, suggesting that being diagnosed as a teenager was difficult as it impacted her relationships with family and friends.

However, Sarah suggested that being diagnosed at an earlier age in childhood, rather than as a teenager may have made adjusting to her long QT syndrome easier. To our knowledge, no qualitative studies have specifically explored the perceptions of teenagers diagnosed with LQTS and more research is needed to see if this is a belief shared by others.

Sarah's story also highlighted similar findings to previous qualitative research exploring adults' perceptions of long QT syndrome. Sarah expressed a strong view that long QT syndrome is overlooked by medical professionals and that she lacked confidence in her family physician's awareness and management of the disease. A similar concern regarding healthcare providers' lack of LQTS knowledge has been documented among adults with LQTS (both within the Gitxsan community[14,109] and wider population.[97,101])

With regard to the LQTS diagnosis itself, Sarah's perception of her diagnosis was different than the previously documented perceptions of individuals diagnosed with LQTS. Past research found that adults experienced their diagnosis as a significant event, which they gradually adjusted to over time.[44,101] While Sarah did express that she was upset at her diagnosis, she shares that she had other concerns to focus on as a teenager, and that as she is growing older, she is becoming more aware of her LQTS. Additionally, she explained that her LQTS diagnosis impacted her identity as an Indigenous person. Sarah viewed LQTS to be a condition strongly associated with First Nations peoples, and as such her LQTS diagnosis served as a reminder of her Indigenous ancestry. She explained that when she was younger, she was not keen to identify as an Indigenous person, but that as she grows older, she is becoming more accepting of her Indigenous ancestry, and in turn, her long QT syndrome. Concern for discrimination arising from targeted genetic testing within specific racial/cultural groups has been previously documented, such as testing for Tay Sachs disease in the U.S. Ashkenazi Jewish population.[134] However, little is known regarding

how diagnosis with a genetic disease may impact an individual's personal identity with an Indigenous culture. More research is needed to investigate this concept.

With regard to coping with the condition, Sarah shared that being affected with long QT syndrome did not have much of an impact on her because she is asymptomatic. Similar to previous insights shared by Gitxsan adults,[14,109] Sarah felt that having supportive family relationships helped her cope with the knowledge of the condition. While Sarah did not outright identify that understanding the biological basis of LQTS benefitted her ability to cope like previous research with Gitxsan adults,[14,109] it was clear during the interview process that Sarah had a firm scientific understanding of the condition and this appeared to help her think logically about her condition. Previous research with Gitxsan adults identified spirituality to be an important factor that helped participants cope with the condition. While Sarah did not dismiss the concept of spirituality in her life, she did not view it as an important aspect in her ability to cope with LQTS.

Two novel themes arose from Sarah's story regarding the clinical care provided to children with LQTS. Sarah's desire for consistency in follow-up appointments and her perception towards beta-blockers had not previously been documented in the LQTS literature, to our knowledge. Sarah's desire for consistency regarding her LQTS encompassed both her routine stress tests, but also her interactions with physicians (including both general practitioners and cardiologists.) This notion is similar to the medical concept of continuity of care, whereby the care provided to an individual is coherent, connected and consistent with the patient's needs over time.[135] The patients' experience of continuity of care is described as: "the perception that providers know what has happened before, that different providers agree on a management plan, and that a provider who knows them will care for them in the future."[135] Continuity of care is a common goal within

healthcare and has been observed in the pediatric setting to improve health outcomes, especially in children with chronic conditions.[136]

Sarah's regard towards beta-blockers has not been reported to date in the LQTS literature. Although Sarah did not dismiss the possibility of taking beta-blockers in the future if her risk for cardiac events increased, she currently viewed them as an unwanted responsibility and reminder of her LQTS. Moreover, she expressed that reliably taking beta-blockers as a teenager would have been unattainable for her. While one study describes a child feeling uncomfortable having to take his medication around friends,[106] past literature shares that individuals with LQTS generally felt that taking their beta-blockers were important.[14,106,109,137] It is likely that the context of Sarah's diagnosis is different than participants in previous research. Sarah was diagnosed through cascade testing and did not experience symptoms herself. Sarah stressed the importance of having autonomy in her medical decisions, including the decision to take beta-blockers, and explained that being given options regarding her medical care was an important part of creating positive and collaborative experiences with her healthcare providers. She emphasized that LQTS was a condition she was going to have to manage for her whole life and as such maintaining positive relationships with healthcare providers was important.

Supporting a minor's decision regarding their medical care is a complex issue and may not always be appropriate, however, involving children and youth in their medical decisions is generally encouraged. As outlined by the Canadian Pediatric Society, "decision-making for children and adolescents should be interdisciplinary and collaborative, and should actively involve the family and, when appropriate, the child or adolescent."[138] Research suggests that promoting health-care autonomy in children with chronic illnesses where appropriate has been found to improve self-care habits and health outcomes in adolescence.[139] Moreover, it is important to keep

in mind that how an adolescent perceives their condition and treatment, may impact their care. Adolescents' mental health and perceptions towards a treatment have been documented as barriers to medication compliance among teenagers with chronic disease.[140]

6.3. The Intertwining – Management of the Asymptomatic Child

At the intersection between the quantitative and qualitative results in this thesis emerges an important space to consider the management of an asymptomatic child with the p.V205M variant.

Part 1 of this thesis found that children with the p.V205M variant experienced a statistically significant prolonged peak QTc compared to non-carrier children. However, the average peak QTc for children with the p.V205M variant fell within the "borderline" classification of QTc measurements[111] and was less than the peak average QTc in p.V205M adult heterozygotes.[35] There was no association of the p.V205M and experiencing at least one loss of consciousness event in childhood (OR=1.4, p=0.388).

Taken together, our findings suggest that children with the p.V205M may experience a mild form of LQTS1 compared to children with other variants. Similar findings have been found in Finland, where children with *KCNQ1* and *KCNH2* variants discovered in Finnish founder populations have been associated with significantly fewer cardiac events than children with Finnish non-founder *KCNQ1* and *KCNH2* variants.[77] Within a founder population, more cascade screening is performed and as such individuals with a milder phenotype are more likely to be detected. Our founder population is showing similar characteristics to the Finnish reports.

Given the findings from our study, it is logical that the management of children with the p.V205M variant be reassessed and, in particular, the requirement of beta-blocker therapy for

asymptomatic children. As outlined in Chapter 3, the AHA/ACC/HRS guidelines recommend beta-blockers to all LQTS patients with a QTc ≥470ms. Furthermore, the guidelines state that it is reasonable for asymptomatic molecularly diagnosed individuals with a QTc <470ms to take beta-blockers (class IIa recommendation). The guidelines state that the benefits of beta-blockers are greater than the risks for asymptomatic individuals with a QTc <470ms.[47] However, recent discussion has suggested that beta-blockers may be unnecessary for some asymptomatic children.[77,81] Waddell-Smith et al. (2015) proposed that beta-blockers may not be essential if: "1) the QTc is less than 470ms and, 2) the patients does not have a C-loop LQTS type 1 missense mutation and, 3) the patient does not partake in high risk activities, and 4) the patient is either a preschool boy or prepubertal girl."[81] Additionally, due to the mild phenotype observed in children with Finnish founder variants, Finnish pediatric cardiologists allow children with *KCNH2* founder variants to start beta-blockers later in childhood but before the onset of puberty, provided their QTc is below 470ms, and there is no family history of cardiac arrest.[77]

It is logical that a similar approach may be taken regarding the requirements for beta-blocker therapy for p.V205M children. We posit that beta-blockers ***may*** not be required for p.V205M heterozygous children if they are asymptomatic, consistently measure a QTc <470ms, do not participate in high risk activities, and have no family history of cardiac arrest. However, more research must be completed to determine if there is a particular age period in childhood where children experience an increased risk of events before any changes to the medical guidelines of children with p.V205M carriers are made. In accordance with the management guidelines given to all individuals with LQTS, children with a p.V205M variant should avoid QTc prolonging drugs, replenish electrolytes in periods of dehydration, monitor potential LQTS symptoms, and receive

intermittent ECG tests.[37,47] As demonstrated in figure 5.2, intrapatient variability in QTc measurements can occur throughout childhood and as such routine ECG tests are recommended.[47]

When considering the requirement of beta-blockers in the pediatric LQTS population, healthcare providers are tasked with the difficult job of evaluating the clinical evidence surrounding LQTS treatment, conveying this information to the patient and/or family, and weighing the patient's preference regarding treatment, where appropriate. In some circumstances, the evidence supporting beta-blocker therapy as a life-saving medication is firmly established and the role of conveying the vital importance of beta-blocker therapy to the patient is paramount. An example of such circumstance may be if a pediatric patient has a QTc of ≥470ms, a situation where the AHA/ACC/HRS guidelines strongly recommend beta-blocker therapy (class I recommendation).[47] However, in circumstances where the evidence in support of beta-blocker therapy is less clear (e.g. asymptomatic pediatric p.V205M carriers with a QTc <470ms), our findings suggests that there may be room to incorporate a greater focus on the patient's autonomy regarding medical decisions. Our case study with Sarah is an example of such a circumstance.

Sarah was diagnosed through cascade screening and is an asymptomatic individual with QTc measurements <470ms. While Sarah did not feel LQTS impacted her daily life, she expressed strong feelings towards beta-blocker therapy. Sarah attributed a large part of her ability to cope with LQTS to the fact that she was not often reminded of her condition and perceived beta-blockers to be "*a daily reminder and like a daily stress…*" (superordinate theme 1, quote 3). While not all asymptomatic patients will share the same regard to beta-blockers, we feel that it may be important to be aware that taking a daily medication may have a significant impact on some LQTS patients' well-being. Sarah shares:

"Yeah, I don't know, with beta-blockers it's just like that extra responsibility… and I feel like for kids that would be a harder responsibility, so while I was younger, just like reliably taking beta-blockers every day wasn't something that was like achievable for me, and my preference, and how I felt about them." (superordinate theme 1, quote 4)

Our case study suggests that some patients may benefit from being given increased autonomy in their medical care, where appropriate. Sarah viewed that being given options regarding her LQTS medical care would make managing her LQTS a more positive experience. She expressed that maintaining a positive regard to LQTS management is important because it is a life-long condition:

"It's definitely good to be proactive with your health especially when you know that it's like something constantly there – that it's like a diagnosis that isn't going away any time soon. So, I think it would be really important just for like young kids to like, have positive experience with it so, that it doesn't end up being something that's negative for the rest of their life. So, it's not like 'okay I have to take beta-blockers' or 'I have to do this,' so that [instead] it's something that they chose to do, where it's more positive." (superordinate theme 1, quote 8)

Given our findings in part 1, we suggest that it may be appropriate to widen the options regarding beta-blocker therapy to asymptomatic children with LQTS in some circumstances. As previously mentioned, more research into the effect of the p.V205M variant on specific age categories is needed before this concept comes to formal fruition, however, it is an important evolving concept that could impact the lives of children with LQTS in Northern BC.

Lastly, one additional consideration regarding the prescription of beta-blockers to treat LQTS1 in this population is the prevalence of the *CPT1A* p.P479L variant. Our research demonstrates that the p.P479L variant has significant effects on loss of consciousness events in childhood. It is possible that loss of consciousness events due to the *CPT1A* p.P479L variant may be misinterpreted as cardiac in nature, thus care should be taken by medical professionals to take a comprehensive history of each loss of consciousness event. Moreover, beta-blocker induced hypoglycemia has been observed in LQTS children[62] and previous research has found hypoglycemic syncope to be a rare side-effect which risks being misinterpreted as a arrhythmic event.[60] Increased vigilance is warranted when prescribing interpreting loss of consciousness events and prescribing beta-blockers to *CPT1A* p.P479L heterozygote and homozygote children with LQTS. The potential effect of the p.V205M predisposing individuals to hypoglycemia cannot be ruled out and more research is needed to explore a potential interaction effect between the p.V205M and p.P479L variants.

Chapter 7. Conclusion

This thesis found that the *KCNQ1* p.V205M variant significantly prolongs the peak QTc among Gitxsan children, but that the variant did not have a statistically significant association with loss of consciousness events. Conversely, the *CPT1A* p.P479L variant demonstrated a statistically significant association with both syncope and seizures and is thought to have a greater influence on the loss of consciousness events observed in this population. This thesis is the second study to observe a clinical outcome associated with the p.P479L variant.

With regard to LQTS, our findings suggest that current pediatric management strategies, including beta-blocker therapy, may need to be reassessed. Additionally, the holistic well-being of each child must be considered when providing medical care to children and youth with LQTS.

7.1. Limitations & Future Directions

This thesis is limited by several factors. In regard to the quantitative research, the sample size of individuals with multiple variants of interest were low (e.g. carriers for both the p.L353L and p.V205M variants, or homozygotes for p.P479L who also carried the p.V205M variant). Because of this, potential interaction effects between variants may not have been observed. More research with a larger sample size of these individuals would be beneficial.

Along similar lines, the sample size of QTc reads recorded at specific ages in childhood was too small to run a valid regression analysis of the impact of the p.V205M variant at different age categories. This will be an important next step in determining the impact of the p.V205M in children and refining the pediatric guidelines regarding beta-blocker therapy.

Additionally, the loss of consciousness events analyzed in this study were self-reported by participants and there is the potential of misreporting syncope and seizure events. Participants in the main Long QT Study enrolled for numerous reasons. While some participants were enrolled through cascade screening, other families may have enrolled in this study because they experienced symptoms similar to long QT syndrome. Because of this, it is possible that individuals in this study self-selected for increased rate of loss of consciousness events due to non-related LQTS reasons.

In regard to the quantitative portion of this thesis, the interview portion of this study was impacted by the COVID-19 global pandemic. Originally, a cross-case analysis of interviews from multiple participants was planned, but in-person gatherings were restricted due to the pandemic and participant interest in the study was reduced. While the individual case study presents an important perspective of living with long QT syndrome, it is unknown if similar experiences are shared by other young adults within the Gitxsan community. The inherent limitations to qualitative research were also present in this case study, such as the interview and interpretation of the results being impacted by the individual researcher conducting the study.[141] These limitations were minimized as much as possible through the process of reflexivity and expert review of the interview guide, interview process and analysis by Dr. McCormick. More research to learn about the perspectives of youth with long QT syndrome would be valuable.

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Appendix A

Table A1. Linear regression analysis of the *CPT1A* p.P479L effect on QTc in childhood (0-18yrs).

Variant	Beta Coefficient	95% CI	p Value
A) p.P479L, n=201, intercept=438.6ms, adjusted R^2=0.01			
PL	-2.16	-10.7 to 6.4	0.619
LL	7.4	-2.5 to 17.3	0.141
Sex	1.4	-5.5 to 8.4	0.682
B) p.P479L and p.V205M, n=200, intercept=433.4ms, R^2=0.14			
p.V205M	22.9	14.7 to 31.1	<0.001
PL	-1.5	-9.5 to 6.6	0.721
LL	6.1	-3.1 to 15.4	0.192
Sex	2.5	-4.0 to 9.1	0.446
C) p.P479L*p.V205M, n=200, intercept=433.5ms, R^2=0.13			
p.V205M	22.5	6.1 to 38.8	0.007
PL	-2.0	-10.1 to 6.9	0.654
LL	7.1	-3.5 to 17.6	0.190
p.V205M*PL	3.4	-17.1 to 23.8	0.745
p.V205M*LL	-3.4	-25.5 to 18.7	0.763
Sex	2.6	-4.0 to 9.1	0.441

PP – homozygous wildtype for *CPT1A* p.P479L, baseline *CPT1A* measurement in regression model
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.P479L

Table A2. Distribution of *KCNQ1* p.V205M and *CPT1A* p.P479L genotypes among participants.

Variant Status	Sample Size
p.V205M (+)*PP	10
p.V205M (+)*PL	17
p.V205M (+)*LL	12
p.V205M (-)*PP	39
p.V205M (-)*PL	83
p.V205M (-)*LL	37
p.P479L status unknown	11

PP – homozygous wildtype for *CPT1A* p.P479L
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.P479L

Table A3. Linear regression analysis of the *KCNQ1* p.V205M effect of QTc by age categories in childhood.

Variable	Beta Coefficient†	95% CI	p Value
A) <1yr old, n=20, intercept=407.6ms, adjusted R^2=0.25			
p.V205M	16.6	-2.3 to 35.5	0.082
Sex	20.8	1.4 to 40.2	0.037
B) 1-4yrs old, n=47, intercept=435.8ms, adjusted R^2=0.25			
p.V205M	27.4	11.8 to 43.0	0.001
Sex	-6.3	-20.9 to 8.3	0.389
C) 5-9yrs old, n=51, intercept=442.9ms, adjusted R^2=0.10			
p.V205M	20.8	4.8 to 36.9	0.012
Sex	-3.4	-16.2 to 9.4	0.597
D) 10-14yrs old, n=60, intercept=416.7ms, adjusted R^2=0.07			
p.V205M	18.8	0.78 to 36.9	0.041
Sex	10.5	-3.5 to 24.5	0.14
E) 15-18yrs old, n=16, intercept=408.1ms, adjusted R^2=0.04			
p.V205M	18.4	-7.0 to 43.8	0.142
Sex	8.2	-14.0 to 30.4	0.439

†Beta coefficients from OLS linear regression representing the baseline (intercept) and change in QTc (ms). QTc, corrected QT.

Table A4. Proportionality tests for loss of consciousness events in childhood by genotype.

	p.P479L	**p.V205M**	**PP* p.V205M**	**PL* p.V205M**	**LL* p.V205M**
N†	197	208	49	99	49
Pearson's Chi-Squared Test:					
χ^2 value	7.7	0.75	-	-	0.01
DF	2	1	-	-	1
p value	0.021	0.387	-	-	0.924
Fisher's Exact Test:					
p value	0.024	0.454	0.07	1.00	1.00

Chi-square values omitted if N<5 in any category, omission denoted by dash
† – one individual with LOC recorded as "possible" excluded from analysis
PP – homozygous wildtype for *CPT1A* p.P497L
PL – heterozygous for *CPT1A* p.P497L
LL – homozygous for *CPT1A* p.P497L

Table A5. Proportionality tests for seizures in childhood by genotype.

	p.P479L	**p.V205M**	**PP* p.V205M**	**PL* p.V205M**	**LL* p.V205M**
N†	196	207	49	99	48
Pearson's Chi-Squared Test:					
χ^2 value	5.41	0.85	-	-	-
DF	2	1	-	-	-
p value	0.067	0.357	-	-	-
Fisher's Exact Test:					
p value	0.055	0.359	0.102	0.729	0.430

Chi-square values omitted if N<5 in any category, omission denoted by dash
† – two individuals with seizures recorded as "possible" excluded from analysis
PP – homozygous wildtype for *CPT1A* p.P497L
PL – heterozygous for *CPT1A* p.P497L
LL – homozygous for *CPT1*A p.P497L

Table A6. Proportionality tests for syncope in childhood by genotype.

	p.P479L	**p.V205M**	**PP* p.V205M**	**PL* p.V205M**	**LL* p.V205M**
N	198	209	49	100	49
Pearson's Chi-Squared Test:					
χ^2 value	6.93	0.19	-	-	-
DF	2	1	-	-	-
p value	0.031	0.660	-	-	-
Fisher's Exact Test:					
p value	0.041	0.826	0.588	0.716	0.075

Chi-square values omitted if N<5 in any category, omission denoted by dash
PP – homozygous wildtype for *CPT1A* p.P497L
PL – heterozygous for *CPT1A* p.P497L
LL – homozygous for *CPT1A* p.P497L

Table A7. Logistic regression analysis of the *KCNQ1* p.V205M and *CPT1A* p.P479L variants on loss of consciousness events in childhood, including interaction variables.

Variant	OR	95% CI	p Value
Loss of Consciousness:			
(A) p.V205M*p.P479L interaction model, n=197†			
p.V205M	4.5	1.0 to 21.9	0.060
PL	2.5	0.9 to 7.0	0.091
LL	5.2	1.7 to 16.2	0.005
p.V205M*PL	0.2	0.0 to 1.4	0.097
p.V205M*LL	0.2	0.0 to 1.6	0.133
Seizures:			
(B) p.P479L*p.V205M interaction model, n=196††			
p.V205M	9.5	0.8 to 117.9	0.080
PL	8.5	1.1 to 67.0	0.042
LL	9.2	1.1 to 78.8	0.043
p.V205M*PL	0.1	0.0 to 1.2	0.068
p.V205M*LL	0.2	0.0 to 4.0	0.305
Syncope:			
(C) p.P479L*p.V205M interaction model, n=198			
p.V205M	2.2	0.3 to 14.1	0.410
PL	1.5	0.4 to 4.9	0.523
LL	5.3	1.5 to 18.2	0.008
p.V205M*PL	0.6	0.1 to 5.9	0.645
p.V205M*LL	0.1	0.0 to 1.2	0.065

† – one individual with LOC recorded as "possible" excluded from analysis
†† – two individuals with seizures recorded as "possible" excluded from analysis
PP – homozygous wildtype for *CPT1A* p.P479L, baseline *CPT1A* measurement in regression model
PL – heterozygous for *CPT1A* p.P479L
LL – homozygous for *CPT1A* p.P479L

Appendix B

Table B1. Table of superordinate themes, emergent themes and preliminary emergent themes.

Superordinate Theme	Emergent Theme	Preliminary Emergent Theme
1. Daily Life with Long QT Syndrome		
	"I almost forget"	almost forget about LQT not commonly brought up no symptoms continual tests reminders (to self) reminding others a constant minor stressor acutely stressing with risk factor ubiquity of medications to avoid trusting others to act if cardiac event– 'not something ever feel at ease with
	Beta-blockers: "*a daily reminder and a daily stress"*	choice no beta-blockers importance of choice risk and portion of life beta-blocker permanency reassess at different time point life-long Illness beta-blocker choice and culture/spirituality: reliance & faith beta-blockers – "a daily reminder and a daily stress"
2. Interactions with Medical Professionals		
	Long QT Syndrome is overlooked: *"It was put on me"*	overlook LQT cardiologist dismiss LQT always negative experience "it was put on me"
	Consistency in follow-up appointments	hatred stress tests/check-ups stress tests - emotional and mental health impact the search as to why… (excessive?) artificial and awkward the medical side of it - difficult to bring up inconsistency desire for consistency

		Increased consideration for LQT by local medical professionals
	Relationships and reciprocity	desire for a different kind of support; a different attitude/approach seeking an introduction to cardiologist lack of reciprocity in care physician's attitude important poor first adult experience 'it's not that walk-in/walk out process'
3. Finding Reassurance		
	Family	family inheritance of LQT reason tested family family support family unit family adjusted getting the 'worst genes' sister and participant unit someone who can relate having LQT is different than being affected by LQT / Holding both concepts in mind: 'LQT is serious, but, doesn't always affect you'
	Awareness of Self	balance of health issues mindful of triggers awareness of self
4. The In-Between Age		
	A difficult age to be diagnosed	opportunity to reach out attitude shift as mature impacted interactions family and friends impacts those closest to you adolescence difficult age dx
	Long QT Syndrome and Indigenous Identity	happy to not identify as indigenous never have been connected with Indigenous community LQT strongly related to being Indigenous
Total: 4 superordinate themes	*Total: 9 emergent themes*	*Total: 57 preliminary emergent themes (7 emergent themes became themes through subsumption)*

Appendix C.

Interview Guide.

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APPENDIX: INTERVIEW GUIDE
The Experiences of First Nations Youth Living with Long QT Syndrome

Current Demographics
Participant ID#:
Age:
Married:
Children:
Education:
Occupation:
LQTS therapy (ICD, B-blockers?):

Childhood Demographics
Age at diagnosis:
Initial diagnosis type:
Date enrolled in study:
Reason for testing:
Caregivers:
Siblings:
LQTS therapy (ICD, B-blockers?):

Timepoint 1: Initial Contact with LQTS

1. When did you first learn about long QT syndrome?

2. Do others in your life (family, friends or community members) have long QT syndrome?

Prompts
- *How do you feel about others in your life having the condition?*

3. Please tell me about your experience of finding out you had long QT syndrome.

Prompts
- *How did you feel when you found out you had long QT syndrome?*

If participant expressed that learning about their LQTS was a negative experience:
- *Did anything help you feel better about having the condition?*
- *Did anything make you feel worse about having the condition?*
- *Is there anything that you didn't have access to, but that you think would have made learning about your diagnosis easier (e.g. anything that you wished that you had)?*

Timepoint 2: Childhood

4. Please tell me about a time in your childhood when long QT syndrome had an impact on you (e.g. when long QT syndrome affected your daily life in some way)?

Prompts:
- How did you feel about that?
- Did anything help you feel better about the situation?
- Did anything make you feel worse about the situation?

Additional prompts (based off of Medicine Wheel):
Intellectual well-being:
- *Did long QT syndrome ever impact your experience at school? How so?*
- *Did long QT syndrome ever impact your experience at work? How so?*

Physical well-being:
- *Did long QT syndrome ever impact your physical well-being (e.g. playing sports, participating in outdoor activities, hanging out with friends)?*

Emotional well-being:
- *Did having long QT syndrome impact your emotional well-being/mental health? How so?*
- *Did long QT syndrome ever affect your personal relationships (e.g. Family? Friends?) How so?*
- *How did your family respond to your long QT syndrome?*
- *How did your friends or peers respond to your long QT syndrome?*
- *How did your community respond to your long QT syndrome?*

Spirituality well-being:
- *Did your culture/spirituality influence your response to LQTS growing up? How so?*

5. It's my understanding that when an individual with long QT syndrome turns eighteen, they transition from meeting with their childhood cardiologist (Dr. Sanatani) to an adult cardiologist. What was this transition like for you?

Timepoint 3: Today & the Future

6. How do you feel today about your long QT syndrome?

7. What advice do you have for future children diagnosed with long QT syndrome in your community?

8. What is your opinion of the support provided by healthcare professionals for you and others with long QT syndrome in your community?

Prompts:
-How could they have better supported you growing up?

9. Is there anything else you wish to tell me about your experience with long QT syndrome?

Post-Interview Debrief Questions

1. How are you feeling right now?
2. How did it feel to talk about your experiences with long QT syndrome?

If showing signs of distress,

1. Is there somebody you can check in with about how you are feeling?
2. Remind participant of list of community support services available to them, and perhaps highlight specific contacts the interviewer thinks might be helpful (e.g. Gitxsan Health Society Counsellor).

Appendix D.

Harmonized ethics approval for qualitative portion of thesis obtained by master's student. (Note: Ethics approval for the quantitative portion of this thesis was obtained as a larger application by Dr. Arbour (UBC REB#:H05-70330), certificate not depicted.)

University of Victoria

Certificate of Ethical Approval for Harmonized Minimal Risk Behavioural Study

University of Victoria
Human Research Ethics Board
Michael Williams Building, R. B202 PO Box 1700
STN CSC
Victoria, BC V8W 2Y2
Tel: 250-472-4545

Also reviewed and approved by:

- **Thompson Rivers University Research Ethics Board**
- **Children's and Women's Research Ethics Board**

Principal Investigator:	Primary Appointment:	Board of Record REB Number:	UBC REB Number:
Laura Arbour	UBC/Medicine, Faculty of/Medical Genetics; University of Victoria, Affiliate Professor	BC19-0419 **Board of Record:** University of Victoria	H19-01703

Study Title:
The Experiences of First Nations Youth Living with Long QT Syndrome

Study Approved: November 19, 2019 **Expiry Date: November 19, 2020**

Research Team Members:	Rod McCormick, TRU faculty member Simona M. Bene Watts, University of Victoria, Graduate student Maria del Carmen Rodriguez de France, University of Victoria, Faculty member
Sponsoring Agencies:	- Canadian Institutes of Health Research (CIHR) - "Long QT syndrome in Northern British Columbia: Gene-gene interaction, life course differences, and implications for safe management" - University of Victoria - "BC Graduate Scholarship awarded by University of Victoria's Interdisciplinary Studies Department."

Documents included in this approval:

Document Name	Version	Date
Protocol:		
Research Proposal	1	September 17, 2019
Consent Forms:		
Oral Consent Script	2	November 13, 2019
Oral Consent Documentation	1	September 17, 2019
Written Consent Form	2	November 13, 2019
Questionnaire, Questionnaire Cover Letter, Tests:		
Interview Guide	1	September 17, 2019
Letter of Initial Contact:		
Recruitment Letter	2	November 13, 2019
Recruitment Script	2	November 13,

			2019
	Other Documents:		
	Support Person Confidentiality Agreement	1	September 17, 2019
	Transcriptionist Confidentiality Agreement	2	November 13, 2019
	List of Community Support Services	1	November 13, 2019

This ethics approval applies to research ethics issues only and does not include provision for any administrative approvals required from individual institutions before research activities can commence.

The Board of Record (as noted above) has reviewed and approved this study in accordance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2, 2014).

The "Board of Record" is the Research Ethics Board delegated by the participating REBs involved in a harmonized study to facilitate the ethics review and approval process.

The application for ethical review and the document(s) listed above have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

This study has been approved either by the Board of Record's full REB or by an authorized delegated reviewer.

CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

University of British Columbia – Children's & Women's Health Centre of BC
Research Ethics Board
(UBC C&W REB)

UBC C & W Research Ethics Board
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Email: cwreb@bcchr.ubc.ca
Website: www.phsa.ca/researchethics
RISe: www.rise.ubc.ca

C&W Institutional Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	NUMBER
Laura Arbour	UBC/Medicine, Faculty of/Medical Genetics	H19-01703

CO-INVESTIGATORS:
Rod McCormick
Simona M. Bene Watts
Maria del Carmen Rodriguez de France

C&W DEPARTMENTS, PATIENT BASED PROGRAMS AND ADMINISTRATIVE JURISDICTIONS IMPACTED BY THIS STUDY:

None

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR) – "Long QT syndrome in Northern British Columbia: Gene-gene interaction, life course differences, and implications for safe management"

University of Victoria – "BC Graduate Scholarship awarded by University of Victoria's Interdisciplinary Studies Department"

TITLE
The Experiences of First Nations Youth Living with Long QT Syndrome

APPROVAL DATE:	Please note:
November 21, 2019	This certificate issued will be valid for the duration of the study; until it is closed in RISe, or if there are changes to the hospital programs required.

CERTIFICATION:

Ethical approval has been granted for the above-referenced research project. I am pleased to inform you that all necessary hospital program/resource approvals and institutional agreements/contracts are in place and that you have permission to begin (or in the case of renewal, continue) your research.

_____

Dr. Wyeth Wasserman
Executive Director, Research Institute, BC Children's Hospital
Associate Dean for Research, Faculty of Medicine
This Certificate of Approval is valid for the above term provided there is no change in the program requirement