COMMUNITY GENETICS RESEARCH PROGRAM

Update for Research Participants

Dr. Laura Arbour and our team at the Community Genetics Research Program have partnered with the Gitxsan for health research over the last 13 years, on studies including the Impact of Long QT Syndrome on First Nations People of Northern BC ('Long QT study') and the Canadian Alliance Study for Healthy Hearts & Minds ('Alliance study'). With your support, the research has come a long way. We hope you find this research update helpful in sharing some results from the research, introducing new research that is underway, and discussing next steps.

1 Community Research Gathering in Hazelton – March 28, 2018

Bringing it Home: A Gathering to Share Results and Experiences of a Decade of Community-Research Partnership and Plan for Next Steps

In partnership with the Gitxsan Health Society, we have received grant funding from the Canadian Institutes of Health Research to hold a community gathering (including dinner) in Hazelton to share key results from our research studies with the community and discuss new research directions. Community members, scientists, and students who have contributed to the research over the years will present their thoughts and research findings. This will be a place to have your questions answered, provide feedback, and contribute to future research directions. All research participants, as well as other interested community members and healthcare providers are welcome to attend.

More information about this event will be available soon. **Please keep your eye open for advertisements at your local health centre, the Gitxsan Health Society website and Facebook!**

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2 The Impact of Long QT syndrome (LQTS) on First Nations People of Northern BC study

This research study began in 2004, when the Gitxsan Health Society and other concerned community members asked doctors and researchers at the University of British Columbia to study why there seemed to be a high rate of Long QT Syndrome (LQTS) in people with First Nations ancestry from Northern BC.

Since that time, Dr. Laura Arbour's research team has been working together with community members, healthcare providers in the North, and other researchers and doctors at the University of British Columbia to learn about the causes and impact of LQTS in Northern BC.

Although LQTS is rare in most populations, it is common in First Nations of Northern BC due to the presence of certain gene changes in the communities that predispose to the condition. A genetic change called the **V205M change in the *KCNQ1* gene** is the most common cause of LQTS in the Gitxsan, while a second genetic change, called the **R591H change in the *KCNQ1* gene**, is another cause of LQTS in a neighbouring Northern BC First Nation.

What is hereditary Long QT syndrome (LQTS)?

Hereditary LQTS is a heart condition that may cause an abnormal heart beat (arrhythmia) that can lead to sudden fainting, seizures, or even cardiac arrest. A parent with the condition has a 50% chance of passing it on to each child. Although LQTS poses a risk for cardiac arrest and sudden death, the majority of people with this condition live a long, healthy life. LQTS is a treatable condition. Effective treatment and prevention strategies are available to those who are diagnosed.

LQTS STUDY PROGRESS

To date, over **850 people** have enrolled in the LQTS research study, including **149 participants** who have tested positive for one of the common gene changes predisposing to LQTS.

New grant funding news: As of July 2017 we received 2 new Canadian Institutes of Health Research grants in partnership with the Gitxsan Health Society. The research priorities as we move forward include:

- Studying how LQTS presents in infants and children, and women of childbearing years
- Learning the psychological effects of a LQTS diagnosis for children and mothers
- Determining if children with a combination of the KCNQ1-V205M gene change and a second gene change (see information box on CPT1a gene change, p.4) are at higher risk for cardiac events and low blood sugar
- Finding out how many people carry the S646F change in the ANK2 gene (is it rare or common?), and how this gene change might contribute to heart disease, and possibly brain effects (seizures and aneurysms).

LQTS STUDY PROGRESS

S646F change in *ANK2* gene: In addition to the two common gene changes noted above on pg.2, a small number of participants in our study carry a less common genetic change, called the **S646F change in the *ANK2* gene.**

Less is known about how changes in the *ANK2* gene might affect the heart or other body tissues. Due to the occurrence of brain aneurysms, seizures, and structural heart disease (abnormal size or shape of the heart) in some research participants who carry the S646F gene change, **we have partnered with another scientist, Dr. Leigh Anne Swayne at the University of Victoria**, to carry out laboratory studies to see how the S646F change actually affects heart and brain cells. This involves looking at cells with the S646F gene change in the lab to see if they behave differently from cells that have normal copies of the ANK2 gene.

Our preliminary research findings were recently published* and our research is ongoing. So far, our results show evidence that the ANK2 gene change predisposes to various heart rhythm problems, including LQTS. If a connection to structural heart disease or brain aneurysms/seizures is also confirmed, this will have an important impact on healthcare and screening for affected individuals in the community.

*Swayne LA, et al. Novel variant in the ANK2 membrane-binding domain is associated with Ankyrin-B Syndrome and structural heart disease in a First Nations population with a high rate of Long QT syndrome. Circ Cardiovasc Genet. 2017;10(1):e001537 circgenetics.ahajournals.org/content/10/1/e001537

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ADDITIONAL GENETIC TESTING FOR LQTS STUDY PARTICIPANTS

One of the ongoing research priorities is to understand why some people who carry a gene change for Long QT syndrome (LQTS) are more severely affected than others.

For example, some people who carry a common *KCNQ1* gene change for LQTS may never develop any symptoms, while others have serious heart events such as fainting, seizures, or cardiac arrest. We do not yet fully understand the reasons for these differences, although we have made good progress. With our new funding we continue to explore this question by carrying out additional testing to look at other gene changes that may influence how mild or severe the disease is. Learning whether having a combination of certain gene changes puts some people at higher risk for cardiac events is important for improving healthcare and prevention, and predicting who might be at greater risk.

Although the majority of participants have some remaining genetic material (DNA) available for this ongoing testing from their original sample collected at the time they joined the study, we may be re-contacting some participants to offer additional DNA collection as we go forward.

The additional testing being done includes looking for these specific gene changes:

P497L variant in the *CPT1a* gene: See information box on *CPT1a* gene variant. Usually it is not a serious concern to carry the *CPT1a* variant. However, we are exploring whether those who carry both a *KCNQ1* gene change predisposing to LQTS and the common *CPT1a* gene variant may be at increased risk for: 1) **serious low blood sugar events**, such as hypoglycemic seizures, and 2) **more severe LQTS symptoms** due to the effect low blood sugar can have on heart rhythm.

To investigate this question, we plan to test all LQTS participants for the *CPT1a* variant; however, because low blood sugar can be more serious in children we will focus on this age group. If we see evidence of a higher risk for children who carry both gene changes, this will have important implications for healthcare and prevention. **Please be reassured that all children diagnosed with a *KCNQ1* gene change can already access *CPT1a* variant testing outside of this research study, as part of their medical care. Clinical *CPT1a* testing is currently being suggested for all children who carry a *KCNQ1* gene change.**

S646F change in the *ANK2* gene: As discussed above on p.2, this change in the *ANK2* gene has been found in a small number of study participants who have LQTS. Some of the individuals who carry this gene change also have brain aneurysms or abnormal heart structure. Testing all LQTS study participants will help us learn how many people in the community carry this gene change (is it rare or common in the community?), and what health effects are associated with the gene change. Given the evidence that the *ANK2* gene change likely predisposes to heart rhythm problems, including LQTS, **we will re-contact those participants who are found to carry the *ANK2* gene change to to inform them of their result and offer medical follow-up.**

Other minor gene changes: There are other minor changes in genes that might influence how a person presents with LQTS. We will continue to explore the possibility of testing for other LQTS-related gene changes as we move forward.

What is the common CPT1a gene variant?

A gene change called the **P479L variant in the Carnitine Palmitoyltransferase 1a (CPT1a) gene** is common in some B.C. First Nations communities. It is more frequent in the Northern regions of B.C and Vancouver Island. It is not clear how common it is in the Gitxsan Territory.

In general, **those who carry the CPT1a genetic variant are healthy** and will grow and develop normally.
However, it may increase the chance of having **low blood sugar** (hypoglycemia). Babies and young children are most at risk for low blood sugar events, especially during times of illness or when not feeding well.
With our research, we are exploring whether children who carry **both** a *KCNQ1* gene change predisposing to LQTS and the *CPT1a* gene variant have an increased risk for serious low blood sugar events, such as hypoglycemic seizures. We are also studying whether those who have both LQTS and the *CPT1a* gene variant may have more severe LQTS symptoms, since low blood sugar can affect heart rhythm.

3 The Canadian Alliance Study for Healthy Hearts & Minds ('Alliance study')

Since 2014, Dr. Laura Arbour has been the local Principal Investigator of the Northern BC Aboriginal study group for the 'Alliance study', centred in the Hazeltons.

The Northern BC study group is one of 10 First Nations communities across Canada participating in this study. A total of approximately 10,000 Canadians (including 2,000 Aboriginal participants) are participating in this National study, which aims to learn about the **early risk factors for cardiovascular disease (e.g. blocked arteries, heart attacks), cancer, and brain disorders (e.g. stroke and dementia), with the hope of improving early detection and prevention of these diseases.** As part of this study, participants were invited to answer in-depth **questionnaires** about their health and well-being, **receive their own personal 'heart health risk' assessment** (which may help point out risk factors and steps for prevention of future disease), have **blood drawn** to screen for diabetes and cholesterol levels, and have a **Magnetic Resonance Imaging (MRI) scan of their brain, heart and abdomen** to research early risk factors for chronic disease. Some participants also chose to have a non-identifying blood sample stored (called '**biobanking**') for future research into chronic disease.

ALLIANCE STUDY PROGRESS

- Alliance study recruitment ended in October 2015. A total of **224** First Nations participants from Northern BC joined this study.
- Questionnaires and MRI scans for the study have been completed. MRI scans were offered to all study participants by way of a mobile MRI trailer that came to the Hazeltons on two occasions in 2014 and 2015. A total of **99** participants completed MRI scans.
- We have contacted (or attempted to contact) all participants who received a Heart Health Risk Score Report to offer them an explanation of their own personal risk for future heart disease based on their research questionnaires, physical measurements, and bloodwork. If you participated but did not receive a report by phone or mail, please give us a call.
- Blood sample collection for diabetes (HbA1c) and cholesterol (apolipoprotein A & B) screening and optional biobanking is ongoing. Over half of the Alliance participants have had blood drawn so far.

We are pleased to announce that Keith Wale, who completed his medical laboratory assistant training at Camosun College in Victoria, is completing blood draws for the study over the next several weeks. You may have already received a call or e-mail from our team about this.

If you are an Alliance study participant who has not already had a blood sample drawn, please call Keith Wale at the Sik-e-Dakh Health Centre (250-842-6876) as soon as possible to book an appointment.

ALLIANCE STUDY PROGRESS

- **Community-Level Audit:** Two audits, looking at community-level health factors such as food security, availability and affordability of fresh produce and healthy foods, access to tobacco and alcohol, and walkability/transport options in the community, were completed for the Hazeltons in June and December 2017. These audits will allow comparison of these factors between all the Alliance study sites across Canada.

Preliminary results from the study

Full results from the Alliance study are not yet available, but we have received some preliminary data regarding the health and well-being of study participants in Northern BC. Based on the data so far, the Northern BC study group appears to have a **lower rate of diabetes** and a **higher rate of physical activity** compared to the overall group of Aboriginal participants and non-Aboriginal participants across Canada. Once all enrollments across Canada are complete, there will be more information coming that may help the community with establishing health promotion strategies.

Please attend the Community Research Gathering planned for March 28 to hear more!

DEBBIE SULLIVAN

Northern Heart Health Nurse

We are happy to announce that Debbie Sullivan, a registered nurse who is well known in the community, was hired by the BC Inherited Arrhythmia Program and Gitxsan Health Society into the "Heart Health nurse" position in 2017. Debbie's office is at the Kispiox health centre. She is available to provide information and support, either by phone or in person, to families with LQTS or other heart conditions. She has been a great help in providing ongoing care for many of our research families. Please feel free to call Debbie at 250-842-6236 if you have questions about LQTS or your medical care, or if you would like further support.

Questions?

HAZLETON CONTACTS

- **Debbie Sullivan** (Northern BC Heart Health Nurse): (250) 842-6236, Kispiox Health Centre
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