The Impact of Long QT Syndrome (LQTS) on First Nations People of Northern British Columbia:

Update to the Research Participants

May 2014

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*This is the **fifth** of a series of update notices sharing the progress and results of the LQTS study with participants and their families. Please contact us if you would like copies of the previous update notices.*

Thank you for your ongoing participation in the Long QT Syndrome research study. With your support, the research has come a long way. We are also introducing a new study for the prevention of chronic diseases like other heart diseases, cancer, stroke, and dementia. Please see the information on **page 6** of this newsletter about the **Canadian Alliance Study for Healthy Hearts and Minds**.

Background Information: "The Impact of Long QT syndrome in Northern BC" study

This research study was started in 2005, 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 from UBC has been working together with community members, health care 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.

Through this research study, a genetic change called the ***V205M mutation in the KCNQ1 gene*** was found to be the most common cause of LQTS in the Gitxsan.

> The normal job of the KCNQ1 gene is to help control the **electrical current in our heart**, which causes the heart to beat in a regular rhythm. The V205M change is like a 'spelling mistake' in this gene, which results in the gene not working properly. People who carry the V205M gene change are at risk for an **abnormal heart rhythm (called *arrhythmia*),** and other features of LQTS. The V205M change in the KCNQ1 gene is inherited. Anyone who carries it has a 50% chance passing it on to each of his/her children. Therefore, it can be passed down through the generations. Hundreds of years ago, a common ancestor must have carried this gene change, and over time it became common in the community.

Since 2005, we have been inviting anyone with First Nations ancestry from Northern BC who has a diagnosis of LQTS or who has a blood relative with LQTS, to join this study.

> Joining the study involves giving a blood or saliva sample for testing of the V205M gene change (and for some other smaller genetic 'variations' that may contribute to LQTS), having an ECG (heart rhythm test) done, answering some health questions, and providing consent to gather some medical records related to the heart.

Over the last year, we have also introduced **'Community Screening'** for LQTS, which allows *anyone* with First Nations ancestry from Northern BC to join the research study and be tested for the V205M gene change, even if they have no diagnosis of LQTS, and no known family history of LQTS.

Progress to Date

- **Enrolment of Participants**

  Over 650 people are now enrolled in the study, and 113 participants have tested positive for the common V205M gene change. We always welcome new participants. As more people join the study, we will learn more about LQTS. Even for those people who test "negative" for the common gene change, participation is still very important. You can enrol in the study by contacting Julia Sundell at Wrinch Memorial Hospital, or by calling the Victoria research team on our toll-free line (please see contact information at the end of this letter).

- **Community genetic screening**

  We have now launched the "community screening" aspect of the research study. This means that **we are now offering LQTS genetic screening to anyone with First Nations ancestry from Northern BC, even those who do NOT have any personal or family history of LQTS**. This will give everyone the chance to learn if they carry one of the common gene changes known to cause LQTS in Northern BC. It will also lead to a better understanding of how many people in the community are at-risk for LQTS, and how LQTS is presenting (e.g. what range of symptoms are being seen) across the entire community.

  To date, we have held "community screening" clinics in Kispiox, Gitwangak, Gitanyow, Gitsegukla, Sik-e-Dakh, Gitanmaax, Moricetown and Hagwilget. A total of 44 people enrolled during these clinics. We will arrange more community screening clinics, as needed. **Please call Fernanda Polanco at Gitxsan Health Society (250-250-842-6876, ext. 47) if you are interested in enrolling in this study, or if you feel there is enough of a demand in your community to arrange additional screening clinics.**

- **Expanded Genetic Analysis for LQTS**

  Changes in *at least 13 different genes can cause LQTS*. As the study has progressed, we have found that there are some families who have LQTS (i.e. they have an increased QT interval on the ECG and symptoms of LQTS) but do NOT have the common V205M gene change in the KCNQ1 gene. It is possible that the LQTS in these families is caused by a *different* gene change. It is also possible that some families with the V205M gene change have *additional* genetic factors contributing to LQTS. Trying to find these other genetic factors is challenging, since so many different genes (and sometimes other factors) can be involved in LQTS.

  One of the major focuses of our research is carrying out expanded genetic testing to try to identify the *other* genetic factors that may be contributing to LQTS within the community.

  1) **We are studying a 'variation' in the Ankryn 2 (ANK2) gene, which is present in some families from Northern BC.**

  A small number of research participants have been found to carry a less common genetic change, called a **variation in the ANK2 gene**. Like the *KCNQ1* gene, the *ANK2*

gene also works in the heart to help electrical currents pass through heart cells. This flow of electricity is what causes our heart to beat. Certain changes in the ANK2 gene are known to interfere with the flow of electricity in the heart and can cause LQTS, other arrhythmias, as well as other heart problems. However, the particular ANK2 'variation' found in some of our research participants is a rarer 'spelling mistake' that has not been studied before by other scientists, so its effect on the heart is unclear. Some of our research participants who carry this gene change have LQTS, so it is quite possible that this variation is having an effect on the heart.

To understand whether S646F is contributing to LQTS in the community:

- **We are offering genetic testing for this ANK2 variant to any research participants who are related to someone who carries it**. We will then be able to compare the health of those who carry the variant to those who don't have the variant. If there is a higher rate of LQTS and/or other heart problems in the group of people with the ANK2 variant, it would provide evidence that this variant has a clinical impact on the heart.
- **We are partnering with another scientist, Dr. Leigh Anne Swayne at the University of Victoria, to carry out laboratory studies to see how this variant actually affects heart cells.** This involves looking at cells with this gene variant under special microscopes to see if they behave differently from cells that have a normal ANK2 gene. Seeing abnormal behaviour in the cells with the variant would provide evidence that this variant affects the function of heart cells.

2) **We are continuing to study the smaller L353L 'variation' in the KCNQ1 gene**

It is normal for people to have many small genetic 'variations' (differences) in their genes. Most of these variations are NOT harmful. One of our research goals is to determine if any these variations, in combination with the V205M gene change, could cause a more severe form of LQTS. As expected, a number of study participants have been found to carry one or more 'variations' in the LQTS genes, and we are looking to see if these genetic changes have any effect at all.

In particular, we are looking closely at **a variation called L353L in the KCNQ1 gene**. So far, **90 people** in our study have tested positive for the L353L variation, suggesting it is very common in the community. **At this time, our results show that the variation by itself does *not* seem to cause LQTS.**

- However, it is possible that individuals who have the L353L variation might have an increased chance of developing LQTS if they also have certain other genetic changes or if they take certain medications/drugs that are known to increase the QT interval.
- For now, to be cautious, **we are recommending that those with the L353L variation avoid the same medications/drugs that can prolong the QT interval and potentially trigger symptoms of LQTS.** For this reason we are contacting all of our main study participants who carry the L353L variation (unless they are already known to carry the V205M gene change) just to let them know that it

was found, and to encourage them to avoid the medications/drugs on the LQTS drug list. At this time, we are not making any other medical recommendations for people with the L353L variation. We are working with other scientists in the United States (at the Mayo Clinic) to understand the effect within cells in a similar way to how we are studying the ANK2 variant in the lab.

- Please note: Due to the unclear information about L353L, we have not been routinely giving L353L results to our "Community Screening" study participants, because these participants are at low risk for LQTS. **However, we welcome Community Screening participants to call Sarah McIntosh on our toll-free number if they would like to learn their L353L result.**

- **List of Medications and Drugs to Avoid**

Certain medications, over-the-counter remedies and street drugs are known to affect the heart and increase the QT interval. **These medications and drugs can be very dangerous for people who have LQTS or are at-risk for LQTS, and should be avoided!** These substances can trigger an abnormal heart rhythm and potentially cause people with LQTS to have a serious problem (e.g. fainting, or even sudden cardiac arrest). As mentioned above, **we are also suggesting that people with the L353L variation avoid these drugs.**

We are pleased that Mr. Peter Piddington, the local pharmacist at Wrinch Memorial Hospital, has worked with our team to **create a new, easy-to-use version of the LQTS medications/drugs list** which highlights the *most important* medications/drugs to avoid. It is available on our research website and on the Gitxsan Health Society website. We would also be happy to mail a copy to you if you contact us at Dr. Arbour's research office. We hope you will find it useful, as it is more concise and much easier to follow than the full medication/drug list available at www.qtdrugs.org. It is a good idea for those with LQTS and their at-risk family members to double-check with their doctors and/or pharmacist before taking *any* medication or drug (and this includes over-the-counter drugs bought without prescription at drug stores).

- **Type 2 Diabetes and the KCNQ1 Gene**

Background information about type 2 diabetes: Your body gets energy by taking **glucose** (a type of sugar) from foods like bread, potatoes, rice, pasta, milk and fruit. To use this glucose, your body needs insulin. **Insulin** is a hormone that helps your body control the level of glucose in your blood. Type 2 diabetes is a disease in which your pancreas (a body organ) either does not produce enough insulin, or your body does not properly use the insulin it makes. If you have **type 2 diabetes**, glucose builds up in your blood instead of being used for energy. If left untreated, this extra glucose in the blood can cause many health problems.

Fernando's diabetes sub-study:
New research has suggested that genetic changes in the same genes that cause LQTS may also affect a person's chance of developing diabetes. The KCNQ1 gene, which is responsible for most cases of LQTS in the Gitxsan, plays an important role in the pancreas and may affect the way insulin is released into the blood. **Fernando Polanco**, a UVic Master's student, has carried out a sub-study

to determine whether having the V205M change in KCNQ1 influences one's chance of developing type 2 diabetes.

Fernando presented his preliminary results at an Elder's conference in Hazelton last Spring. His preliminary results suggest that those with the V205M change may have a higher chance of having pre-diabetes. **Pre-diabetes** means having blood glucose levels that are above normal, but not high enough to be diagnosed as type 2 diabetes (i.e. 'borderline' blood glucose). Those with pre-diabetes have a higher chance of developing diabetes in the future, although many people never develop the disease. It is important to note that Fernando's preliminary results show no evidence of a higher rate of actual **diabetes** in those with the V205M change. He is currently completing his final analysis.

- **LQTS in children**

  A UVic Biology Honours student, Barbara Gauthier, worked with our team last Fall to study the effects of the V205M mutation on children who are younger than 18 years old. Although the analysis is still underway, we can be reassured that **the V205M positive children in our study have remained very healthy and very few have had LQTS-related 'events' such as fainting or seizures**. Barbara is currently analyzing the children's ECG tests, to see if there is a difference in the length of the QT intervals (as read by pediatric cardiologists, Dr. Shu Sanatani and Dr. Libby Sherwin) between the V205M positive and V205M negative children in our study. We will provide further information once this analysis is complete.

- **Childbirth and LQTS**

  Olivia Fleming, a Canadian student who is attending medical school in Ireland, worked with our team last summer and will return this summer to study whether women with the V205M gene change show risks during pregnancy and delivery. With consent, we are continuing to collect pregnancy records on all the women enrolled in our main study who have the V205M gene change and have had a baby. Our impression is that most Gitxsan women with LQTS go through childbirth without a problem, but Olivia will analyze the data more closely so we can be sure.

- **Delivery of Cardiology & Genetics Services to Northern BC**

  We have continued to work with local hospital staff and the BC Inherited Arrhythmias Program to bring a cardiologist (heart specialist) and a genetic counsellor to the North, so that those with LQTS or other heart rhythm problems have the opportunity to access specialist care near their home communities, rather than travelling a great distance. Last year, **Dr. Charles Kerr**, a cardiologist from St. Paul's Hospital in Vancouver, held clinics in Hazelton, New Aiyansh, and Terrace. Dr. Kerr just recently held the first clinic for 2014 in Hazelton, and additional clinics are planned for Terrace (June), New Aiyansh (June), and Hazelton (Fall).

Support Resources:

We are happy to announce that **Fernanda Polanco, a registered nurse, was hired by the BC Inherited Arrhythmias Program and Gitxsan Health Society into a new "Heart Health nurse" position in April 2013.** She has also been collaborating with our research team to help run the "Community Screening" clinics. Fernanda's office is at Sik-e-Dakh health centre, and she currently works 4 days per week (Tues-Fri). 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 Fernanda at **250-842-6876, ext 47** if you have questions about LQTS or your medical care, or if you feel you would like further support.

Introducing a New Study: "The Canadian Alliance Study for Healthy Hearts and Minds"

We would like to take this opportunity to let you know about another research study coming to the Hazeltons, and to invite you to participate. Although this study is not focused on LQTS, we felt we should let everyone know about it, since it is about other health conditions that are of equal concern to the community. **This "Alliance" study is being done to learn about the early risk factors for Cardiovascular disease (blocked arteries, heart attacks, etc), cancer, and brain disorders (such as stroke and dementia), in the hopes of improving prevention and early detection of these diseases.** This is a large, National study which hopes to recruit 10,000 Canadians **between the ages of 35-69 years old**, including approximately 2,000 First Nations people. Dr. Laura Arbour was approached by the National study coordinators in Ontario to help **invite 200 First Nations people from the Hazeltons into the study.** After reviewing this study with the Gitxsan Health Society and hearing general community support for the study, Dr. Arbour obtained the appropriate ethics approvals to bring this study to the Hazeltons, and has hired a research coordinator (Chloe Curtis from Terrace) to begin advertising and recruitment. Enrollment is open to all First Nations people in the Hazeltons. For those participating in the LQTS study, it may provide the opportunity to understand whether LQTS affects other chronic diseases and how chronic diseases affect LQTS.

Some of the benefits of joining this study include **receiving your own personal 'heart health risk' assessment** (which may help point out risk factors and steps for prevention of future disease), and **having an MRI scan of your brain, heart, and abdomen** (which may identify previously unknown, important health conditions in some people). **Please see the enclosed invitation letter with more details about this study, and contact Chloe Curtis (local research coordinator at 250-842-6876) or Dr. Arbour's research team (toll-free: 1-888-853-8924) if you have any questions, or would like to join the study.** A trailer with the MRI machine will be arriving in Hazelton in mid-June to perform the study MRIs, so we are hoping to recruit most people over the next two months.

If you have any questions or would like further information, please contact the research team:

In Hazelton:
Fernanda Polanco (Heart Health Nurse): (250) 842-6876, ext 47
Julia Sundell (Research Assistant): (250) 842-5217; e-mail: skeenaplace@gmail.com
Gwen Weget-Simms (Research Assistant): (250) 842-6295

In Victoria: toll-free: 1-888-853-8924
Sarah McIntosh (Genetic Counsellor/Research Coordinator); e-mail: sarahmc@uvic.ca
Dr. Laura Arbour (Clinical Geneticist, Principal Investigator of study); e-mail: larbour@uvic.ca

In Vancouver:
Rosemarie Rupps (Genetic Counsellor/Research Assistant): email: rrupps@cw.bc.ca

Dr. Laura Arbour's research website: http://www.uvic.ca/medsci/faculty/arbour.php

Your ongoing participation and support for this research study is much appreciated.

Sincerely,

Dr. Laura Arbour and the entire LQTS research team.

Please contact us if you would like a copy of the first three update notices, which were circulated in January 2009, March 2010, March 2011, and April 2012.
This update will be posted on the Gitxsan Health Society Website: www.gitxsanhealth.com/links/long-qt-syndrome-info/