

Type II Diabetes and *KCNQ1* mutations in First Nations People of Northern British
Columbia

by

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B.Sc., Vancouver Island University, 2010

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of the Requirements for the Degree of

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Supervisory Committee

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Supervisor

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Abstract

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Background: A novel mutation (V205M) within the *KCNQ1* gene was previously delineated and confirmed to predispose to long QT syndrome (LQTS) in a First Nations community in Northern British Columbia (Gitxsan). LQTS is an autosomal dominant genetic disease that is named for the elongation of the ECG (electrocardiogram) Q-T interval, corrected for rate, but is reflective of delayed repolarization predisposing to LQTS. Clinically, LQTS presents as sudden loss of consciousness (fainting, seizures) and sudden death. *KCNQ1* is responsible in part for I_{Ks} the slow rectifying potassium channel in the heart, and also accounts for about 30% percent of all genetically confirmed cases of LQTS. The *KCNQ1* gene is also expressed in the pancreas, and recent Genome Wide Association Studies (GWAS) have identified variants found within the *KCNQ1* gene to be strongly associated with type 2 diabetes (T2D) in Asian and European populations. In Canada, and around the world, Indigenous populations have the higher rates of T2D. We set out to determine if the V205M mutation could influence the development of T2D in this First Nations population.

Methods: Participants were recruited from a contact data base from the original study (entitled '*The Impact of Long QT on First Nations People of Northern British Columbia*') and invited to determine if their *KCNQ1* mutation status influenced their HbA1c values, and therefore risk for diabetes. Body mass index (BMI), waist circumference (WC), exercise levels and HbA1c test values were collected from each participant. Sixty-five participants (18 mutation positive and 47 mutation negative) were included in this sub-study.

Results: Adjusting for anthropometric measurements, V205M+ participants were almost ten times more likely to attain an 'at-risk' (or 'pre-diabetic') HbA1c value (adjusted OR: 9.62; $p=0.002$; CI: 2.23-41.46). Although there was no difference in average HbA1C levels ($p=0.963$). The distribution of values was markedly different between those in the mutation positive vs mutation negative group.

Conclusion: Although it is premature to declare a true risk for diabetes in this cross-sectional study, our results suggest that HbA1C levels are influenced by the presence of the V205M mutation, and further study is indicated to determine if insulin secretion is affected in these individuals. This work has potential implications for others with LQTS who might have altered glycemic control as a result of mutations in KCNQ1. Furthermore, in this First Nations population, broader health implications might need to be considered for those with the V205M mutation.

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Dedication

I would like to dedicate this work to the people of Wrinch Memorial Hospital, thank you for all your accommodation and kindness. I would also like to dedicate this work to the Gitksan people who have endured so much pain and hardship, thank you for your friendship and openness. I would like to dedicate this work to my mentors personally and professionally.

Chapter 1

Introduction

The Hazelton area (or the *Hazeltons*) is approximately 300 kilometers North West from coastal city of Prince Rupert and about 1200 kilometers North from Vancouver. There are approximately 14,000 Gitksan people who collectively live in these traditional lands. Recent archaeological evidence has indicated that the original inhabitants of the Northern BC were the Gitksan, Nisga'a, and the Tsimshian peoples, and these people have resided on their traditional lands for at least thirteen millennia (FPHLC, 2007; Multicultural Canada, 2012). Seven communities comprise of the *Hazeltons*: Old Hazelton (Gitanmaax), Gitanyow (formerly Kitwancool), Kitsequecla (Gitsegukla), Kitwanga (Gitwangak), Glen Vowell (Sik-e-Dahk), Kispiox (Anspa'yaxw), Cedarvale (Minskinish) (Gitksan, 2012). A community-initiated research project has been in place since 2005 in the rural-remote Aboriginal communities of the *Hazeltons* in Northern British Columbia.

It has become recognized that congenital Long QT syndrome type 1 (LQTS1) is common within the Gitksan people. LQTS is an imbalance of cardiac function due to the improper or inhibited opening and closing of potassium channels that leads to delayed ventricular repolarizations, early after-depolarization's, and to the elongation of the ECG (electrocardiogram) Q-T interval. The name LQT comes from the measurement of the interval of ventricular contraction and relaxation on the

ECG . This condition may cause arrhythmia, which may lead to fainting, cardiac arrest and sudden death.

It has been elucidated that a unique mutation in *KCNQ1* (V205M) is present in the Gitksan peoples. To date, 74 mutation carriers of the V205M mutation have been recognized in the Gitksan peoples. It is important to note that this gene is also expressed in the pancreas, and variants found within the *KCNQ1* gene have been seen to confer type 2 diabetes (T2D) risk in Asian and European populations (Bleich and Warth, 2000; Jonsson et al., 2009; Unoki et al., 2008; Yasuda et al., 2008). Additionally, it has been shown that T2D has an influence the QT interval measurement on an ECG and would impact the diagnosis of LQTS1 (El-Gamal et al., 1995; Nagaya et al., 2010 and 2009; Okin et al., 2000; Vinik et al., 2003 and 2007).

T2D has become a global epidemic: it has been forecasted that by 2025 diabetes will affect 300 million people worldwide (Taylor, 2006). In Canada, Aboriginal people are three to five times more likely to develop T2D than the general population (CDA,2008) . Diabetes is present within the Gitksan peoples. Nevertheless, there are various different pathogenic processes that are involved with the development of diabetes (See ***Diabetes and HbA1c***); therefore, it is important to determine effective treatment strategies and better T2D management. Furthermore, V205M (predisposing to LQTS1) may play a role in T2D susceptibility. As a sub-study of a larger study, this project aims to determine whether the LQTS causing V205M mutation alters T2D susceptibility.

HbA1c measures glycosylated hemoglobin, which represents blood glucose concentration over a 3-month period. HbA1c is a diagnostic tool for T2D

development. Using a case-control study design we hypothesized that the presence of the V205M mutation would alter HbA1 C results possibly reflecting impaired insulin secretion affected by sub-optimal potassium pump function in the pancreatic beta cells.

Objectives:

1. To determine if the presence of the V205M mutation affects HbA1c results, and alters any risk for type II diabetes (T2D) development (diagnosed by HbA1c threshold values) within the Gitxsan community.
2. To evaluate QTc intervals (ECG records) to determine whether the V205M negative participants have a prolonged QTc in relation to diabetes status and obesity.

Literature Review

Social Dimension of Health and Risk Factors of T2D in Aboriginal People

Indigenous people of North America have undergone drastic social and cultural changes since the colonization of the Americas. Traditional diet suppression, displacement of whole communities, natural resource exploitation, and sedentary lifestyle environments are just to name a few paradigm shifts Aboriginal people of Canada (and throughout the world) have experience post-colonially (Smeja and Brassard, 2000; Browne et al., 2005; Reading, 2010). Consequently, Aboriginal people of Canada and other Indigenous peoples throughout the world have experienced disproportionate (compared to non-Aboriginal or non-Indigenous populations) disease/chronic illness risk due to disparities in social determinants of health, funding, and prioritization (Browne et al., 2005; FNC, 2011; Reading, 2010).

Aboriginal health research can be studied through different lenses. For example, a life course approach can be taken or a 'risk factor' determinant direction could be taken (Ben-Shlomo and Kuh, 2002; Reading, 2010). The identification of risk factors has improved health outcomes for various populations throughout the world (including Indigenous peoples) (Reading, 2010). Yet, 'risk factor' determination research has its limitations in particular populations: chronic disease prevalence has decreased in Western counties, but has increased in vulnerable populations like Aboriginal peoples. Furthermore, the risk-based approach will identify a need to change a lifestyle in an adult at a particular time, yet fail to foster the development of that change in the following generation, hence leaving the

following generation in similar conditions (Smeja and Brassard, 2000; Reading, 2010). On the other hand, life course based methodologies also have their own empirical limitations—i.e., adequate life course/exposure data across a human life may be problematic along with its analysis (Ben-Shlomo and Kuh, 2002). The life course approach has been defined as the study of biological, behavioural and psychosocial pathways that operate within an individual's life course. It is also the study of long-term effects of social and physical exposures during gestation, childhood, adolescence, young adulthood and later adult life (Ben-Shlomo and Kuh, 2002; Reading, 2010). This research approach enables the recognition of physiological and psychosocial factors occurring throughout an individual's life that could affect their general well-being, physical functioning and the development of chronic diseases (Ben-Shlomo and Kuh, 2002; Reading, 2010). Nevertheless, both types of research initiatives are viable and used throughout Aboriginal health research. Specific to Canadian Aboriginal populations, perspectives on well-being and health include physical, mental, emotional, and spiritual perspectives in the past, present and future (Issak and Marchessault, 2008; Reading, 2010). Therefore, research in the field of Aboriginal health research must account for both traditional and scientific perspectives to be an appropriate research initiative.

The social dimension of health concerning the development and prevalence of T2D is considered to be interlinked, complex and a priority in Aboriginal peoples of Canada (Ghosh and Gomes, 2011; Millar and Dean, 2011). Furthermore, the steady increase of T2D prevalence in Aboriginal peoples in Canada can be indicated by the drastic sociocultural changes experienced by Aboriginal people over the past

several decades (Ghosh and Gomes, 2011; Young et al., 2000). A particular hypothesis has been postulated for the reason behind continued and intergenerational continuum of chronic illness and chronic stress: Allostasis and Allostatic load (McEwen, 2000). Allostasis and Allostatic loads are burdens of stress that effect the health of an individual. Over a short period of time, the body methods of handling stress can have beneficial or damaging consequences; however, stress responses over long periods of time may indeed accelerate disease processes (McEwen, 2000).

The risk factors associated with the development and prevalence of T2D have been studied and identified; however, risk factors are inconsistent between Aboriginal communities, which demonstrates the complex nature of various different risk factors involved (Ghosh and Gomes, 2011; Reading, 2010). Risk factors for T2D development include genetic predispositions (Hegele et al., 1999), albuminuria (Wang and Hoy, 2006), increased obesity (Amed et al., 2010), diet shifts (DiMeglo and Mattes, 2000; Gittelsohn et al., 1997; Young et al., 2000), decreased physical activity (Shaibi et al., 2008) and family history (Millar and Dean, 2011; Ghosh and Gomes, 2011). Other associated risk factors include MetS prevalence, increased C-reactive protein (Wang and Hoy, 2007), sedentary lifestyles (Lui et al., 2006), and gender (Ghomes and Gomes, 2011).

The social determinants of health can be classified as distal (e.g., historic, political or economical), intermediate (e.g., community infrastructure, resources, and capacities), and proximal (e.g., health behaviours, physical and social environment) (Reading and Wein, 2009). Specific social determinants of health or

sociocultural factors include poverty, social marginalization (exacerbated by colonization) (Campbell, 2002), unemployment and household income (Millar and Dean, 2011; Reading, 2010), language and traditional beliefs regarding T2D (Onowa, 2009; Millar and Dean, 2011), and access to health care (Booth et al., 2005). Studies have found direct statistical evidence that associate altered traditional methods of food preparation and increased fat consumption with risk for diabetes in some Aboriginal communities in Canada (Gittelsohn et al., 1998). Along with risk factors, protective factors exist and are used that build resilience and at time negate risk factors all together (Onowa, 2009). Some Aboriginal health protective factors include increased connection between the land and traditional medicine (Onowa, 2009; Wilson, 2003), spirituality (Receveur et al., 1997), consumption of traditional foods (Wolsko, 2006), and language (Hallett et al., 2007; Onowa, 2009). Social determinants influence the dimensions of health outcomes and the environments that create space to facilitate such outcomes.

KCNQ1 and Long QT Syndrome

I_{ks} (Slow Delayed Rectifier K⁺ current) is an ion-channel responsible, in part, for the late repolarization phase of the cardiac action potential (AP) and regulates AP duration. They are involved in the maintenance of vascular smooth muscle tone, cell volume regulation, leukocyte activation and proliferation, and many other physiological functions (Roura-Ferrer et al., 2009). Predominantly, there are two genes which are responsible for the assembly and regulation of I_{ks}: *KCNQ1* and *KCNE1* (Charpentier et al., 2009; Harmer et al., 2007; Moss et al, 2005; Rudy, 2007).

More specifically, *KCNQ1* is the gene responsible for Iks α subunit and *KCNE1* for the β subunit (Moss et al., 2005).

The structure of Iks is made up of four identical α subunits (pore-forming unit) all with transmembrane spanning segments. The β subunit is a single transmembrane protein that is essential to the regulation, trafficking, and structure of Iks (Figure 1.1). The α subunits (voltage sensitive) are positively charged and move and open in response to a depolarizing event: a change in charge from negative (-90mV) to positive charge(+52mV) inside the cardiac cell (Charpentier et al., 2009; Moss et al., 2005; Rudy, 2007). The repolarization event is due to the late opening of the Iks channel (and the fast opening of the Ikr channels) and regulated by phosphorylation via a signaling cascade (β -adrenergic receptors) during periods of elevated sympathetic nerve activity (i.e., epinephrine and norepinephrine). Therefore, when mutations are present in *KCNQ1* and/or *KCNE1*, the regulation/phosphorylation of the Iks channel can be disrupted or disabled. As well, mutations in either *KCNQ1* or *KCNE1* may inhibit and/or delay the transport and assembly of the Iks subunits to the cell membrane from the Rough Endoplasmic Reticulum. This imbalance of function due to the improper or inhibited (due to loss of function) opening and closing of Iks leads to delayed ventricular repolarizations, early after depolarization's, and to the elongation of the Q-T interval on an ECG measurement (Harmer et al., 2007; Kass et al., 2003; Moss et al., 2005; Peroz et al., 2008).

Ventricular AP's are unique in their timing and separation. On an ECG, The P wave is generated by the excitation through the atria and is followed by the QRS

complex. The QRS complex represents ventricular activation. The ECG ends finally with a T wave, which reflects ventricular repolarization (Moss et al., 2005). The time between depolarization (DP) and repolarization (RP) is longer (about 450 milliseconds) in cardiac myocytes. The timing of the depolarization and repolarization is crucial since the depolarized myocyte cannot be re-excited until the entire cycle resets (protects the cell from premature excitation). The duration of depolarization in a cardiac myocyte is often referred to as the plateau phase (Figure 1.2) (Kass et al., 2003; Moss et al., 2005; Rudy, 2007). This plateau phase is also important because it is directly implicated in the cardiac cycle of diastolic filling and ejecting intervals. This in turn is what determines the QT interval on an Electrocardiogram (ECG). Furthermore, the majority of mutations concerning *KCNQ1* lead to the loss or limited function of the I_{Ks} and lead to the prolonged repolarization of ventricular cardiac myocytes. Presentation of an elongated QT interval ($>470\text{ms}$) on an ECG is preliminary evidence for Long QT syndrome type 1 diagnosis (Kass et al., 2003).

Long QT type 1 is an, autosomal dominant, genetic disease of which 70% is known to be caused by 12 different genes, largely influencing ion channel function in the heart. The most commonly delineated gene, *KCNQ1* accounts for 30% of all known cases. Hereditary LQTS is associated ventricular arrhythmias, torsade de pointes, and ventricular fibrillation, leading to syncope and sudden death (Khan and Gowda, 2004; Modell and Lehmann, 2006; Zhang et al., 2010). In general, the prevalence of LQTS is approximately 1:2000-5000 (Zhang et al., 2010).

Mutations within the *KCNQ1* gene are responsible for the delayed ventricular repolarization that is indicative of LQTS1 (Charpentier et al., 2009; Harmer et al., 2007; Moss et al., 2005; Rudy, 2007). However, mutations that cause LQTS have been discovered at various other loci and on many other genes. There are twelve different types of LQTS: LQTS1 to LQTS12 (Table 1.1) (Modell and Lehmann, 2006; Moss et al., 2005; Peroz et al., 2008; Zhang et al., 2010).

Non-cardiac Expression of KCNQ1

KCNQ1 has been shown to be expressed in the pancreas and the islet cells within the pancreas (Bleich and Warth, 2000; Jonsson et al., 2009; Unoki et al., 2008; Yasuda et al., 2008). Specifically, KCNQ1 expression has been reported in the human pancreas and within insulin secreting cell lines through Reverse-Transcription Polymerase Chain Reaction experiments (Unoki et al., 2008). Furthermore, KNCQ1 has been shown to be excessively expressed in diabetic mice: the diabetic mice had a higher quantity of KCNQ1 mRNA than control mice (Yasuda et al., 2008). As seen in other non-cardiac expression of KCNQ1, KCNQ1 forms a K⁺ channel, which is used in a recycling fashion of K⁺, to produce a driving force (voltage dependent) behind Ca²⁺ influx (Bleich and Warth, 2000; Holmkvist et al., 2009). The Ca²⁺ influx causes insulin secretion in beta islets cells in the pancreas. It has been hypothesized that mutations in the genes responsible for the K⁺ channels found in the pancreas play an important role in the pancreatic beta cells. Recent studies have shown, with compelling evidence, that mutations related to the control

and assembly of K⁺ channels (*KCNQ1* encoded) found in the human pancreas could be a factor in type 2 diabetes—impaired insulin secretion (Table 1.2).

Non-cardiac expression of *KCNQ1* has also been reported in the gastrointestinal tract, kidneys tubules, lungs, inner ear, placenta, liver, and pancreas (Johnson et al., 2009; Grahammer et al., 2001; Bleich and Warth, 2000). Similar to the gastrointestinal tissue, kidney tubules act in an analogous fashion in relation to *KCNQ1* expression and function. In the mid or late renal proximal tubule's epithelial cells, glucose and amino acids re-absorption is coupled to Na⁺ influx (depolarization); therefore, *KCNQ1* plays the role of repolarization to maintain the driving force behind Na⁺ re-absorption (Bleich and Warth, 2000; Embark et al., 2003; Robins, 2001; Vallon et al., 2005). However, just like the gastrointestinal tract, the affect of human *KCNQ1* mutation in renal function is unknown (Vallon et al., 2005).

Expression of *KCNQ1* and *KCNE3* in lung epithelial has been shown via northern blot experiments and using pharmacological blocking experiments (Grahammer et al., 2001; Bleich and Warth, 2000). In the lungs, secretion and absorption mechanism are essential for ciliary clearance: the transport of mucous and foreign particles out of the lungs to the pharynx. However, in the autosomal recessively inherited disease, cystic fibrosis (CF), these transportation mechanisms are hindered. CF patients often have hyperabsorption of Na⁺ and reduced Cl⁻ secretion (Grahammer et al., 2001; MacVinish et al., 1998). Therefore, it is hypothesized that *KCNQ1* may play a role of possible regulation of Cl⁻ secretion by its K⁺ channel properties. However, there has been debate whether *KCNQ1* plays a

functional role or not (Grahammer et al., 2001; MacVinish et al., 1998). While there has been evidence showing that in *KCNQ1* knockout non-CF carrying mice do not reduce Cl⁻ secretions, it has nevertheless been shown that the *KCNQ1* complex does play a role in Cl⁻ secretion and Na⁺ reabsorption in wild type mice (Grahammer et al., 2001). In spite of these findings, it is still unclear whether or not *KCNQ1* complex play an important role in human lung epithelial cells.

KCNQ1 and *KCNE1* are also found in the inner ear of humans. *KCNQ1* and *KCNE1* form a complex to form functional channels found on the marginal cells of the stria vascularis of cochlea (Benatar, 2000; Bleich and Warth, 2000, Robins, 2001). In the cochlea, the *KCNQ1/KCNE1* complex plays an important role in K⁺ recycling between the perilymph (rich in Na⁺ concentration) and the endolymph (rich in K⁺ concentration) containing spaces. When there is an excitation of the inner hair cells by an acoustic vibration, K⁺, from the scala media (endolymph containing), rushes into the hair cells. There, the K⁺ leaves the hair cells—its is speculated that *KCNQ4* channels may play a part in this process of K⁺ flow—and passes into the scala tympani (perilymph). Then the K⁺ must be shunted back into the scala media: the *KCNQ1/KCNE1* complex (found on the stria vascularis membrane) is the channel where this re-shunting of K⁺ back into the scale media occurs (Figure 1.3) (Benatar, 2000; Bleich and Warth, 2000; Robins, 2001). Mutations in the *KCNQ1/KCNE1* complex in the inner ear have been suggested to be the underlying cause for sensorineural deafness and prolonged cardiac repolarization in the rare genetic autosomal recessive disorder called Jervell-Lange Nielsen Syndrome (JLNS) (Benatar, 2000, Bleich and Warth, 2000, Robins, 2001;

Wang et al, 2002). However, whether mutations in the *KCNQ1*/*KCNE1* complex or the *KCNQ4* channel, or both, causes sensorineural deafness remains unclear and unknown (Robins, 2001).

KCNQ1 has been shown to be expressed in the pancreas and the islet cells within the pancreas. (Bleich and Warth, 2000; Jonsson et al., 2009; Unoki et al., 2008; Yasuda et al., 2008). Specifically, *KCNQ1* expression has been reported in the human pancreas and within insulin secreting cell lines through Reverse-Transcription Polymerase Chain Reaction experiments (Unoki et al., 2008). Furthermore, *KCNQ1* has been excessively expressed in diabetic mice: the diabetic mice had high quantity of *KCNQ1* mRNA than control mice (Yasuda et al., 2008). As seen in other noncardiac expression of *KCNQ1*, *KCNQ1* forms a K⁺ channel, which is used in a recycling fashion of K⁺, to produce a driving force (voltage dependent) behind Ca²⁺ influx (Bleich and Warth, 2000; Holmkvist et al., 2009). The Ca²⁺ influx causes insulin secretion in beta islets cells in the pancreas. It has been hypothesized that mutations in the genes responsible for the K⁺ channels found in the pancreas play an important role in the pancreatic beta cells. Recent studies have shown, with compelling evidence, that mutations related to the control and assembly of K⁺ channels (*KCNQ1* encoded) found in the human pancreas could be a factor in type 2 diabetes—impaired insulin secretion (Table 1.2).

KCNQ1 and T2D susceptibility

KCNQ1 is also expressed in the human pancreas (Bleich and Warth, 2000; Jonsson et al., 2009; Unoki et al., 2008; Yasuda et al., 2008). Recent genome-wide

association (GWA) studies have been conducted to elucidate possible genetic variants (and the genes themselves) in relation to T2D susceptibility or development (Table 2). Particularly, single nucleotide polymorphisms (SNP) within the *KCNQ1* gene have been identified as conferring susceptibility to T2D (Been et al., 2011; Campbell et al., 2012; Chen et al., 2010; Grallert et al., 2009; Holmkvist et al., 2009; Hu et al., 2009; Jonsson et al., 2009; Liu et al., 2009; Mussig et al., 2009; Parra et al., 2011; Qi et al., 2009; Saif-Ali et al., 2011; Tan et al., 2009; Unoki et al., 2008; Voight et al., 2010; Yasuda et al., 2008). Most SNPs were found in intron 15 in the *KCNQ1* gene on chromosome 11: cytogenetic location 11p15.5, and one was found within intron 11 within the same region (Been et al., 2011; Voight et al., 2010) (Table 2).

Throughout the GWA studies concentration has been placed in the rs223795 and rs2237892 polymorphisms: they have been seen in both Asian and European populations and over a wider ancestral range (Grallert et al., 2009; Yasuda et al., 2008; Unoki et al., 2008). Moreover, SNPs in *KCNQ1* gene have been detected (and associated with) in people with T2D in Japanese, Singaporean, Korean, Chinese (Hong Cong, Han, and Shanghai Chinese), Malay, Mexican, South American, Asian Indian, Danish, German, Swedish, and Finnish ancestries (Campbell et al., 2012; Grallert et al., 2009; Qi et al., 2009; Mussig et al., 2009; Unoki et al., 2008; Yasuda et al., 2008; Holmkvist et al., 2009)

The GWA studies have found that the risk SNPs were significantly associated with people with T2D. Furthermore, the studies have shown associations with risk polymorphisms with impaired insulin secretion and β -islet cell function (Grallert et

al., 2009; Jonsson et al., 2009; Qi et al., 2009; Mussig et al., 2009; Tan et al., 2009; Yasuda et al., 2008; Holmkvist et al., 2009; Unoki et al., 2008). Furthermore, *KCNQ1* variants have been associated with first and second phase insulin secretion (biphasic secretion) (Vilet-Ostaptchoux et al., 2012).

Glimpses of the pathogenesis of T2D in relation to these SNP's studies have been addressed. Recent studies have shown significant differences in insulin action—insulin action measures included Homeostasis Assessment Model Beta cell function-HOMA-B, Fasting Glucose and Hyperglycaemic Glucose Clamps—between their T2D cases and controls (Tan et al., 2009; Vilet-Ostaptchoux et al., 2012; Yasuda et al., 2008). These studies re-enforced the hypothesis that pathogenesis of T2D is mediated through *KCNQ1* effects on the human pancreatic β -islet cell and the secretion of insulin. Yet, other possible SNPs may increase the risk of T2D through regulation by nearby genes, consequently, more in-depth identification within that region may allow for the specific identification of the main causal SNP (Mussig et al., 2009; Tan et al., 2009; Yasuda et al., 2008).

Insulin secretion is regulated and maintained by an electrogradient within the β -islet cell (Figure 1.4). Glucose induces β -cell depolarization resulting in the firing of action potentials (APs), which are the primary electrical signal of the β -cell—this change of electrical gradient drives the influx of calcium and hence insulin secretion. The depolarization of the cell activates voltage-gated potassium channels (Kv) which regulates membrane repolarization and ends calcium influx and insulin secretion (*Please See **Non-cardiac Expression of KCNQ1***). Interplay between K⁺ATP channels, Kv channels, and voltage-gated Ca²⁺ channels allow for proper insulin

secretion (Bleich and Warth, 2000; Jacobson and Philipson et al., 2007; Holmkvist et al., 2009). Mutations in the genes coding KATP channels (KCNJ11) have been shown to be associated with T2D and gestational diabetes (Jacobson and Philipson et al., 2007; Holmkvist et al., 2009). However, association studies involving *KCNQ1* SNPs or mutations and T2D or impaired insulin secretion have not elucidated the exact protein functioning (or mal-functioning) or exact function of the *KCNQ1* coded K⁺ channels within the pancreatic β -islet cell (Ashcroft and Rorsman, 2012).

Body Mass Index (BMI) measurements have been calculated from participants in studies involving the risk SNPs and T2D. Interestingly, two SNPs (rs2237892 and rs2237895) have been associated with increased BMI in East Asian populations (Chen et al., 2012; Qi et al., 2009; Tan et al., 2009). Waist measurements and body fat content were not associated with the risk SNPs (Jonsson et al., 2009; Mussig et al., 2009; Tan et al., 2009). In addition, Yasuda et al., (2008) discussed that their inclusion criteria for their study included Japanese diabetics with BMI measurements of or less than 30 kg/m² since they wanted to represent the most common subtype of diabetic (most Japanese people have a BMI of below 30kg/m²) (Yasuda et al., 2008). Risk SNPs have been shown to be associated with elevated BMI measurements.

Body Mass Index, Age and Waist Circumference: Type 2 Diabetes

Due to recent lifestyle, diet, societal structure and environment, “epidemic” trends of increasing obesity have been reported in Aboriginal populations in Canada and throughout the world (Lear et al., 2007; Foulds et al., 2011; Hegele et al., 2005;

Reading, 2010). Specifically, obesity is a risk factor for many disease including T2D, metabolic syndrome (MetS) hypertension, hyperlipidemia, cardiovascular diseases (Arslan et al., 2010; Hegele et al., 2005; Reading, 2010; Wang and Hoy, 2004).

Obesity has traditionally been measured by calculated BMI: BMI is the measure of one's weight over one's height squared (See **Methods** chapter). BMI is typically stratified by risk category (Figure 1.6). However, obesity rates differ between Aboriginal and non-Aboriginal populations: rates of obesity in Aboriginal communities are elevated compared to non-Aboriginal (Daniel et al., 1999; Foulds et al., 2011; Hegele et al., 2005; Reading, 2010; WHO, 2011). It has strongly argued that obesity is strong indicator for a risk to develop T2D (Young et al., 2000). It will be important to measure the BMI of participants to determine obesity rates within our study population.

BMI has been shown to be a strong risk factor for T2D development (Table 3)(Daniel et al., 1999, WHO, 2011). WHO (2011) categories are as follows:

Normal Range: 18.50 - 24.99	Overweight: ≥25.00	Pre-obese: 25.00 - 29.99	Obese: ≥30.00
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BMI has also been positively correlated to lipid profiles. Caucasian, North Indian, American indigenous and European ethnicities across broad BMI categories have been studied in relation to BMI and lipid profile association. Increasing BMI has been correlated to decreased HDL-C, increased C-reactive protein, increased TG, overall negative lipid parameter, and, in most, decreased LDL-C (Hu et al., 2000; Nagila et al., 2008; Sanlier and Yabanci, 2007; Shamaï et al., 2011; Vikram et al., 2003). Therefore, based on previous studies, BMI could be lipid profile indicator.

Waist circumference (indicator of excess abdominal fat—WC) has also been seen to be a strong predictor of T2D development (Wang and Hoy, 2004; WHO, 2008). WC (and BMI) has been positively correlated with increased QTc measurements (Arslan et al., 2010). Furthermore, Wang and Hoy (2004) demonstrated that WC is indeed a better predictor of T2D and other chronic conditions; however, whether WC is a better predictor of T2D (and other conditions) remains unclear (Lear et al., 2007; WHO, 2008). Nevertheless, WC has been strongly correlated to BMI in previous studies: both have validity concerning body fat (Hu et al., 2000; Nagila et al., 2008). The Canadian guidelines for WC are as follows: a WC at or above 102 cm (40 in.) for men, and 88 cm (35 in.) for women, is associated with an increased risk of developing health problems such as diabetes, heart disease and high blood pressure (Health Canada, 2005).

KCNQ1 and Lipid Profiles

In recent years, *KCNQ1* has been found to be associated with lipid profiles and plasma lipid levels (along with T2D susceptibility). SNPs in *KCNQ1* at chromosome 11p15.5 have been found to be associated with increased triglyceride levels, decreased HDL-C, increased LDL-C, increased total cholesterol, and overall lipid parameters (Chen et al., 2012; Chen et al., 2010a; Vilet-Ostapchoux et al., 2012). Interestingly, the same SNPs found to be associated with lipid profiles are the same SNPs found to be associated with T2D susceptibility (Dehwah et al., 2010; Grallert et al., 2009; Jonsson et al., 2009; Qi et al., 2009; Mussig et al., 2009; Tan et

al., 2009; Unoki et al., 2008; Yasuda et al., 2008; Holmkvist et al., 2009). In particular, SNP's rs12720449 (Chen et al., 2012) rs2237892 and rs2283228 (Chen et al., 2010a; Chen et al., 2012; Vilet-Ostaptchoux et al., 2012). All the studies found were limited to Asian populations: Chinese, Chinese Han and Japanese (Chen et al., 2012; Chen et al., 2010a; Vilet-Ostaptchoux et al., 2012). However, the trend is the same for all *KCNQ1* association studies: *KCNQ1* SNP's that are associated with T2D susceptibility are also associated with decreased lipid profiles in Asian populations.

Diabetes and HbA1c

Diabetes mellitus is defined as a metabolic disorder characterized by hyperglycaemia (high blood glucose levels) resulting from defects in insulin secretion, insulin action and function, or both (Alberti and Zimmet, 1998; Diabetes, 2004). Diabetes mellitus may cause long-term damage, dysfunction, and failure of various organs throughout the body (i.e., heart, kidneys, eyes, blood vessels). Some characteristic symptoms include polyuria, thirst, blurry vision, and weight loss (Alberti and Zimmet, 1998; Diabetes, 2004). Deficient insulin action results from insufficient insulin secretion and/or inadequate tissue responses to insulin. There are various different pathogenic processes that are involved with the development of diabetes. For example, autoimmune destruction of the β -cells of the pancreas—i.e., mitochondrial point mutations, hepatic nuclear transcription factor mutations (*HNF1 α* ; chromosome 12), glucokinase mutations within the β -cell of the pancreas ('glucose sensor'; chromosome 7p), and *HNF4 α* (transcription factor for *HNF1 α* ;

chromosome 20q)—result in consistent insulin deficiencies and abnormalities that result in insulin-resistance (Alberti and Zimmet, 1998; Diabetes, 2004).

There are two main categories of diabetes mellitus: type 1 (T1D or insulin-dependent diabetes-IDD) is an absolute deficiency of insulin secretion where external insulin is required for survival (β -cell destruction). The other category, type 2 diabetes (T2D or non-insulin-dependent diabetes-NIDD) is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretion response (Diabetes, 2004). T2D is a common, yet complex metabolic disorder and is a poorly defined disease (Balkau et al., 2003). Gestational Diabetes Mellitus (GDM), Gestational Hyperglycaemia (GH), Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), and Diabetes in children are other types of impaired (or disabled inability) glucose metabolism or deficient insulin action or secretion.

Glucose-stimulated insulin secretion is biphasic: impaired or absent first-phase insulin secretion is an early feature of T2D, while the second phase insulin secretion deterioration is characteristic during the progression of the disease (Holmkvist et al., 2009). The biphasic secretion of insulin is triggered by electrical signaling in the β -cell from the functional interplay between K-ATP channels, K-v channels, and voltage-dependent Calcium channels (Holmkvist et al., 2009; Jacobson and Philipson, 2007). *KCNQ1* is involved with this insulin secretion and may play a key role in T2D and its development. While there are various etiological classification, diagnostics, treatments and definitions for T2D, it is clear that both

environment and genetic predispositions are factors with the development (and the risk) of the disease.

Historically and clinically, T2D has been defined through the diagnosis of the disease using Fasting Plasma Glucose (FPG) and Oral Glucose Tolerance Test (OGTT) (Table 1.3). For example, an individual with a FPG concentration of 6.1 mmol l⁻¹ (110 mg dl⁻¹) or greater (whole blood 5.6 mmol l⁻¹; 100 mg dl⁻¹), but less than 7.0 mmol l⁻¹ (126 mg dl⁻¹) (whole blood 6.1 mmol l⁻¹; 110 mg dl⁻¹) is considered to have Impaired Fasting Glycaemia (IFG). FPG values can vary between individuals and test instances, so an OGTT is performed to solidify the diagnosis (ADA, 2012; Diabetes, 2004.). Both tests require the participant to fast (and/or diet) for an extended period of time—i.e., OGTT fasting time period (prior to a 75g of anhydrous glucose) is 8-14hrs—and are therefore limited by resources, effort, and time. As a result, hemoglobin A1c (HbA1c) has been a widely used and accepted diagnostic index for mean blood glucose (ADA, 2012, 2012; Balkau et al., 2003; Benhalima et al., 2010; Chamnan et al., 2010; Currie et al., 2010; Hornsten et al., 2008; Nathan et al., 2008; Rohlfing et al., 2000; WHO, 2011).

HbA1c is a measurement of the hemoglobin that is glycosylated. It is a reliable measure of long-term glycemic exposure and has been correlated to micro and macrovascular complications of diabetes (Balkau et al., 2003; Chamnan et al., 2010; Nathan et al., 2008). HbA1c is the bond of glucose and red blood cells in the blood. The amount of the HbA1c is correlated to the amount of glucose can be found in the blood over a three-month period. HbA1c measurements can be accomplished at any time of the day, no fasting is required, only one single blood draw is necessary, and

does not require any special patient preparation: it is less of an intrusive test for the patient (Rohlfing et al., 2000; Nathan et al., 2008). Moreover, HbA1c is a specific and sensitive measurement for mean blood glucose and reflects a 3-month period of glucose accumulation (ADA, 2012; Balkau et al., 2003; Currie et al., 2010; Nathan et al., 2008). On a patient-to-patient basis, the reduction of HbA1c has been correlated to an effective treatment measure to decrease microvascular (i.e., diabetic neuropathy, diabetic nephropathy) and macrovascular complications (i.e., atherosclerosis, coronary heart disease)(Figure 1.5) (Fowler, 2008; Benhalima et al., 2010). Similar to the OGTT and FPG, HbA1c uses a threshold value in order to define, classify, and diagnose patients: the 'cut-off' point for T2D is $\geq 6.5\%$ within an HbA1c assay (percent of hemoglobin that is glycated) (ADA, 2012; Benhalima et al., 2010; CDA, 2008; Chamnan et al., 2010; Nathan et al., 2008; Rohlfing et al., 2000). HbA1c facilitates a biochemical basis for T2D diagnosis and allows for greater sensitivity, ease, and convenience.

In a recent position statement in 2012 (unchanged since 2010) from the American Diabetes Association (ADA), pre-diabetic and diabetic HbA1c were published: 5.7%-6.4% for pre-diabetic and greater than or equal to 6.5% for diabetic HbA1c values. In a study conducted by Nowicka et al., they found in a review of over 44,000 participants in 16 cohorts that participants with a HbA1c value of 5.5%-6.0% had an 9-25% increased risk of diabetes development over 5 years. Participants with HbA1c values of 6.0%-6.5% had a 25-50% increased risk of diabetes development (ADA, 2012); The ADA recommended that any elevated HbA1c test value be repeated two-times in order to confirm diabetes. For example, a

HbA1c value of 7.0% and a second HbA1c value of 6.8% can confirm diabetes (ADA, 2012). Furthermore, two different tests (e.g., HbA1c and FPG) are both at elevated risk thresholds, diabetes can be confirmed as well. The WHO has also recognized these thresholds for HbA1c values, but does not recommend those thresholds for international purposes (WHO, 2011). The Canadian Diabetes Association (CDA) does recognize a diabetic diagnostic of T2D using a HbA1c threshold similar to ADA's diabetic threshold: $\geq 6.5\%$. However, the CDA does not yet recognize HbA1c pre-diabetes values as criteria for pre-diabetes (CDA, 2008). In practice, a recent study conducted by Ralph-Campbell et al., 2009, found HbA1c values $> 6.1\%$ were associated with increased risk for undiagnosed diabetes in a Metis population: 8.1% of the sample population were classified as undiagnosed diabetic (Ralph-Campbell et al., 2009). In a recent study conducted by Chamnan et al., (2010) the incidence of T2D across baseline HbA1c levels: one-third of T2D development occurred with individuals with HbA1c baselines of 6.0-6.4%. Since the ADA has published standards, this sub-study was based on those thresholds.

Metabolic Syndrome: Lipid Profiles and T2D

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities including hyperglycemia, abdominal obesity, dyslipidemia, and hypertension. MetS is considered to be present if 2-3 (depending on the source) traits are present in an individual (Table 1.4). Most metabolic abnormalities are most often associated with obesity and insulin resistance. Furthermore, the combinations of these metabolic conditions have a synergistic effect that increases the risk for cardiovascular

disease and T2D (Hanson et al., 2002; LaGuardia et al., 2011; Lorenzo et al., 2003; Riediger and Clara, 2011; Simmons et al., 2010; Wilson et al., 2005).

MetS has become a growing global concern varying from 10-40% in different populations—specifically, based from the Canadian Health Measures Survey 2007-2009, about one in five Canadians had MetS (LaGuardia et al., 2011; Riediger and Clara, 2011). MetS development is considered to be due by environmental and genetics factors (Hegele and Pollex, 2005; Hegele, 2003). SNP's have been associated with MetS in Obji-Cree in Canada: angiotensinogen (AGT), G-protein Beta-3 subunit (GNB3), hepatic nuclear factor-1 alpha (HNF1A) and apolipoprotein (APOC3) (Hegele and Pollex, 2005; Pollex et al., 2006). MetS has been reported in Aboriginal communities in Canada (Hegele and Pollex, 2005; Pollex et al., 2006). For example, in the Oji-Cree peoples of northern Ontario, 30% of adults and 43.4% of adults ≥ 35 years of age had MetS (Pollex et al., 2006). Moreover, BMI has been positively correlated to metabolic syndrome in Obji-Cree Aboriginal people in Canada. However, BMI is not a part of metabolic syndrome diagnosis (Pollex et al., 2006).

QT/QTc Interval Association with Type 2 Diabetes (T2D) and Obesity

It has been established that both prolonged Qtc /QT intervals may be associated with obesity and T2D (El-Gamal et al., 1995; Nagaya et al., 2010 and 2009; Okin et al., 2000; Vinik et al., 2003 and 2007). During a resting ECG, the QT interval is a biomarker of the autonomic balance between parasympathetic and sympathetic activities: a longer QT interval is an indication of relative predominance

of sympathetic activity within the autonomic system (and a diagnostic indicator for LQTS). Interestingly, insulin secretion also stimulates the sympathetic nervous system, and autonomic sympathetic cardiovascular dysfunctions have been associated with the prolonged QTc intervals (Lehtinen et al., 2009; Nagaya et al., 2010; Vinik et al., 2007) Prolonged QTc intervals, sudden death and ventricular arrhythmias have been associated with diabetic patients (Nagaya et al., 2010; Rana et al., 2005; Unoki et al., 2008). Therefore, in recent years, QTc intervals were used as a diagnostic tool for some diabetic autonomic abnormalities (Nagaya et al., 2010).

In a study conducted by Nagaya et al., (2010), they demonstrated that prolonged QT (regardless of heart rate-corrected QT—QTc) predicted the risk of developing T2D within a sample of both men and women in a healthy Japanese population. Interestingly, the development of T2D was independent of age, body mass index (BMI—a scale to measure obesity), smoking, drinking, exercise and education (Nagaya et al., 2010). In a recent study conducted by Arslan et al. (2010), it was demonstrated that uncomplicated obesity does indeed prolong QT intervals and that weight gain inversely affects cardiac repolarization in uncomplicated obesity using a young (22 mean age) male sample population (Arslan et al., 2010). Reasoning behind why QT intervals are prolonged is not well understood (Kusama et al., 1992; Lehtinen et al., 2009). The diabetic patients have been shown to exhibit a variety of abnormalities in ion transport, including depression of sodium and calcium exchange processes and inhibition of ATPase activities (Kusama et al., 1992). Lehtinen et al., (2008) investigated genetic variants associated with QT intervals and reported 34% of their diabetic study population to be on QT

prolonging drugs. Nevertheless, both obesity and T2D may in part play a role in prolonged QT interval.

Genetics of T2D and Aboriginal Peoples: The Americas and Australia

Aboriginal people have experienced an increased rate of T2D prevalence and incidence as spoken beforehand in this introductory chapter. In addition to the social determinants of health, genetics factors play an important role in the development of diabetes (Busfield et al., 2002). “Genetic determinants would therefore act not as a direct determinant of the disease, but instead would determine susceptibility within the prevailing environmental context.” (Busch et al., 2001). Yet, the acknowledgement that T2D does indeed have a genetic component, the identification of susceptibility genes has proven difficult (Hegele et al., 1998). However, there has been a great deal of work within indigenous peoples concerning SNPs and their associations with T2D susceptibility (Table 1.5).

In summary, more than 55 studies have investigated the association between T2D and genetic variations. Although many of the associations in Table 1.5 have worked with the Pima Indians of Arizona, various indigenous populations have been studied. Most genetic variants are unique to the indigenous population in question; however, there are genetic variants that span over different Indigenous populations. For example, SNP’s associated with T2D found within HNF-1 α have been found in Canadian Oji-Cree, Pima Indians, Antioquian, and Indigenous Mexican peoples (Appendix 1). Furthermore, the variants do not always provide a positive T2D association. Many genes have conflicting results concerning T2D association:

the IGF2BP2 gene has a positive T2D association within Indigenous Mexicans, whereas, within the Pima Indians, the IGF2BP2 gene has a negative T2D association (Appendix 1). It is clear that further research concerning T2D association studies is needed.

Through this research, our goal is to determine whether the V205M mutation found in Northern BC confers any altered risk for T2D development. We have gathered background introductions of topics to address our objective to this sub-study. Will the V205M+ participants have significantly higher HbA1c values than the V205M- participants? How might V205M play a role in diabetes prevalence in northern BC? We aim to determine these questions and put forth good recommendations for future research and possibility future our understanding of LQTS in First Nations people of northern BC.

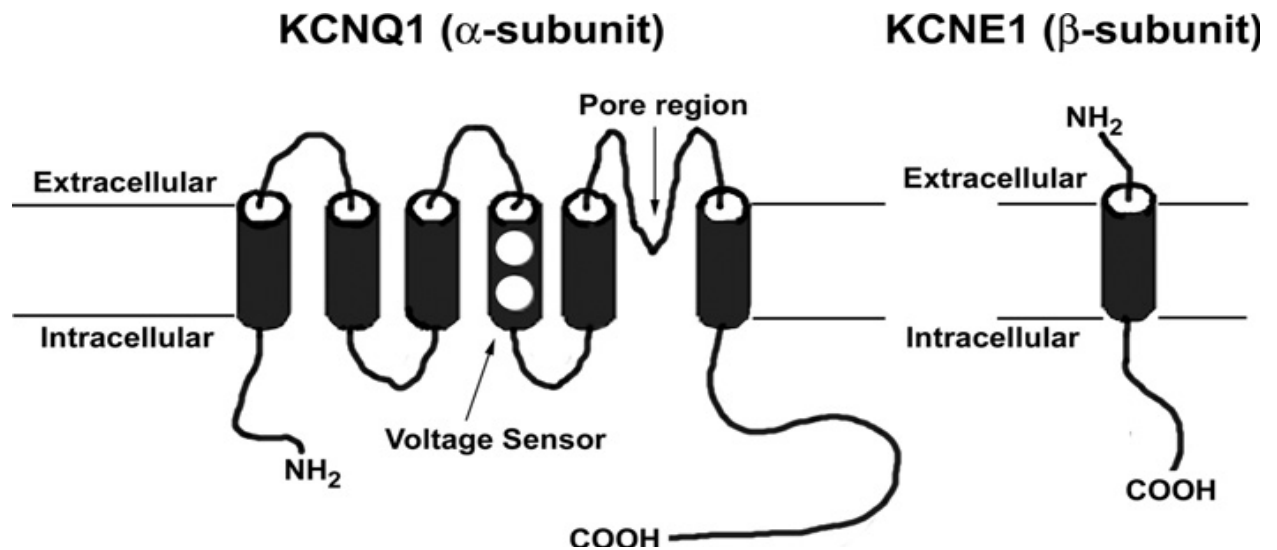


Figure 1.1: Structure of *I_{Ks}* (*KCNQ1*) channel (Harmer et al., 2007)

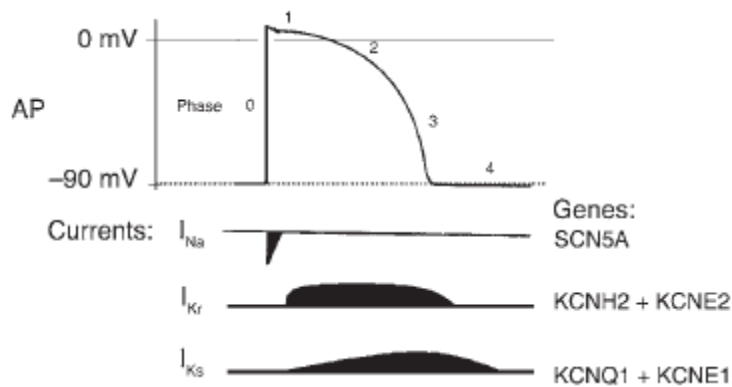


Figure 1.2: Three major cardiac ion channel currents (I_{Na} , I_{Kr} , and I_{Ks}) and respective genes responsible for generation of portions of the ventricular action potential (Moss et al., 2005)

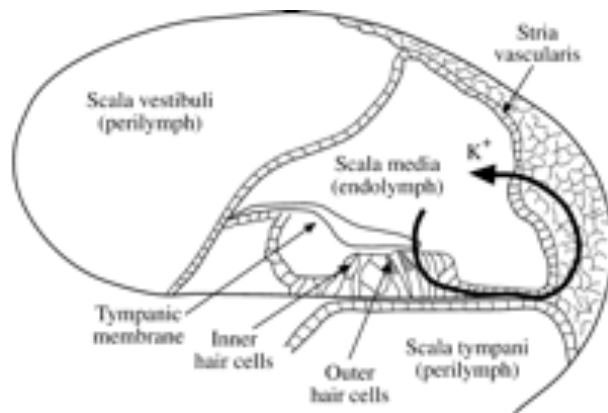


Figure 1.3: K^+ homeostasis in the cochlea. (Benetar, 2000)

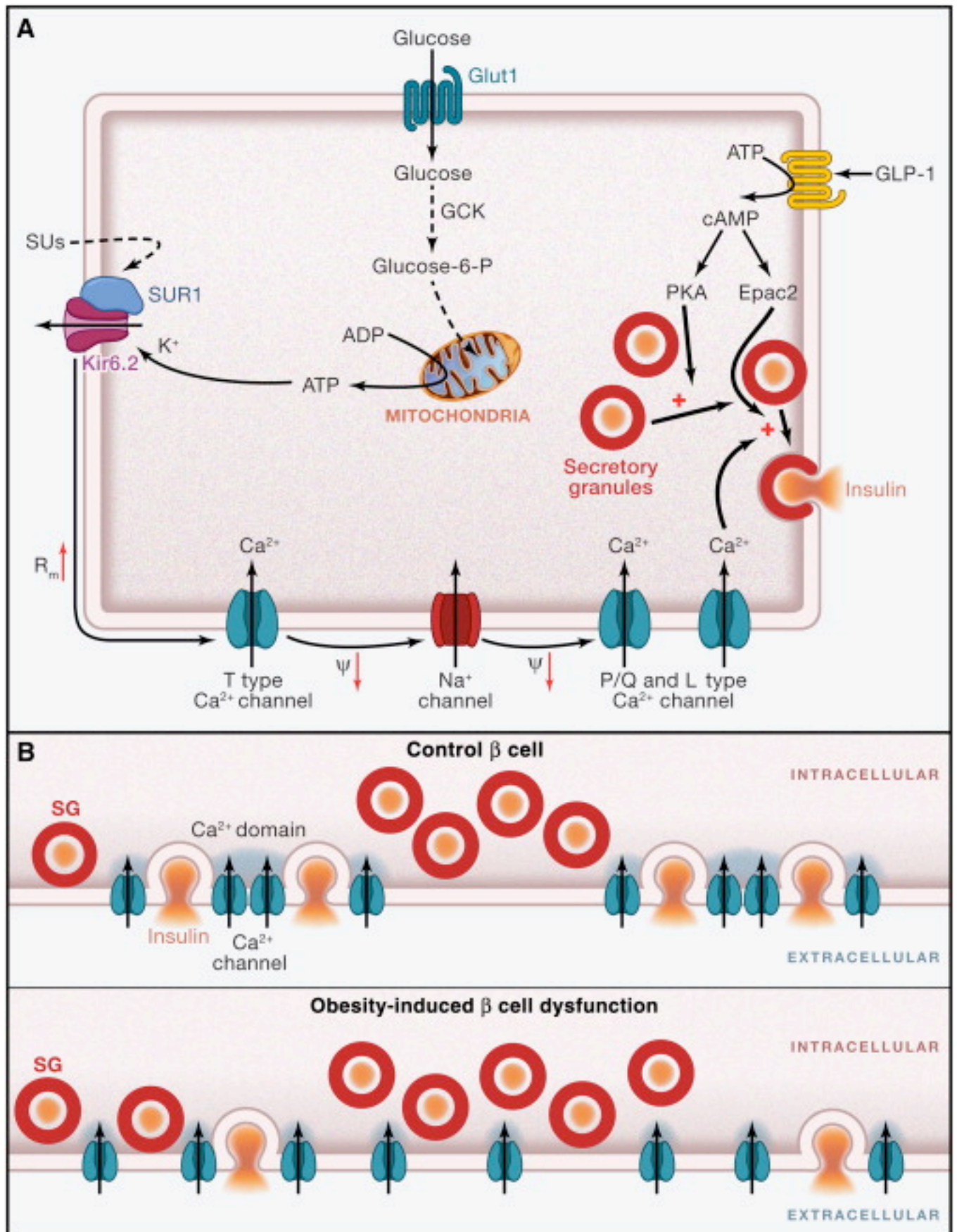


Figure 1.4: (A) Insulin secretion in human β -cells (Ashcroft and Rorsman, 2012).

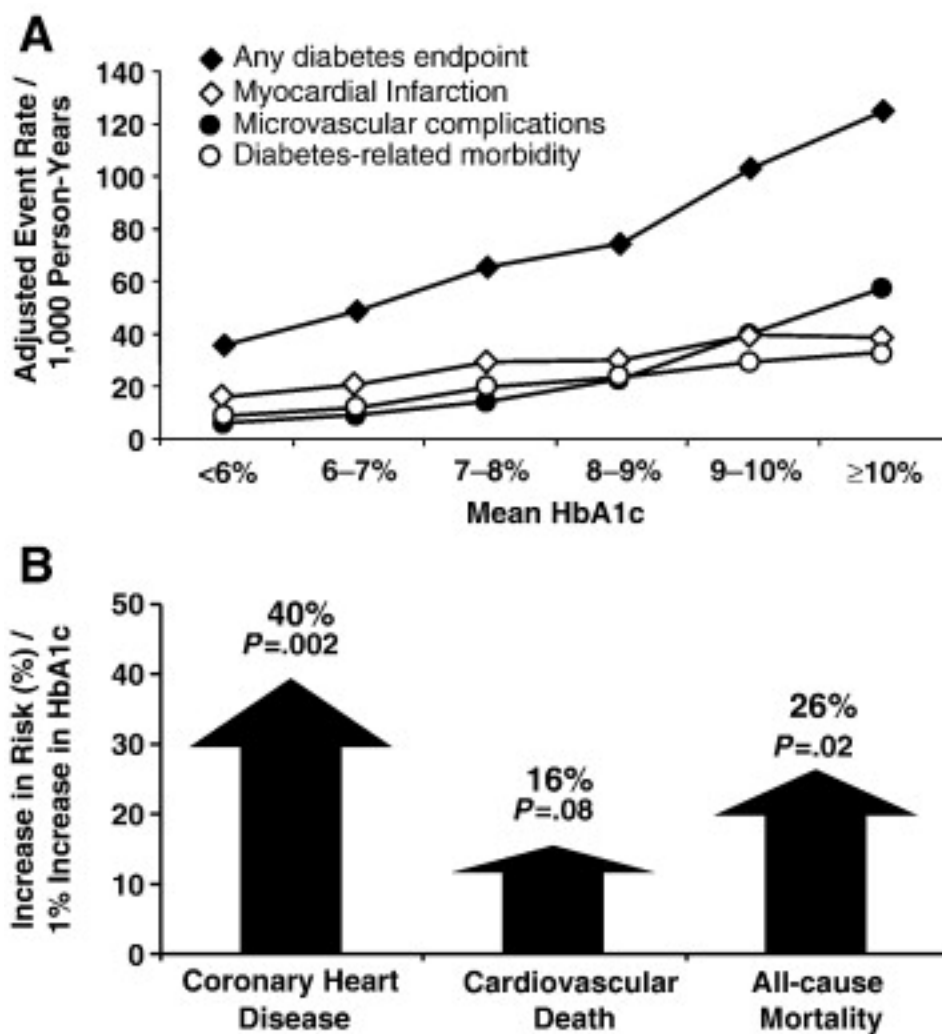


Figure 1.5: (A) Relationship between updated mean HbA1c and risk for diabetic complications in patients with newly diagnosed Type 2 diabetes. (B) Association between a 1% increase in HbA1c and risk for coronary heart disease, cardiovascular death and all-cause mortality (Benhalima et al., 2010).

Figure 22: Body Mass Index (BMI) by gender

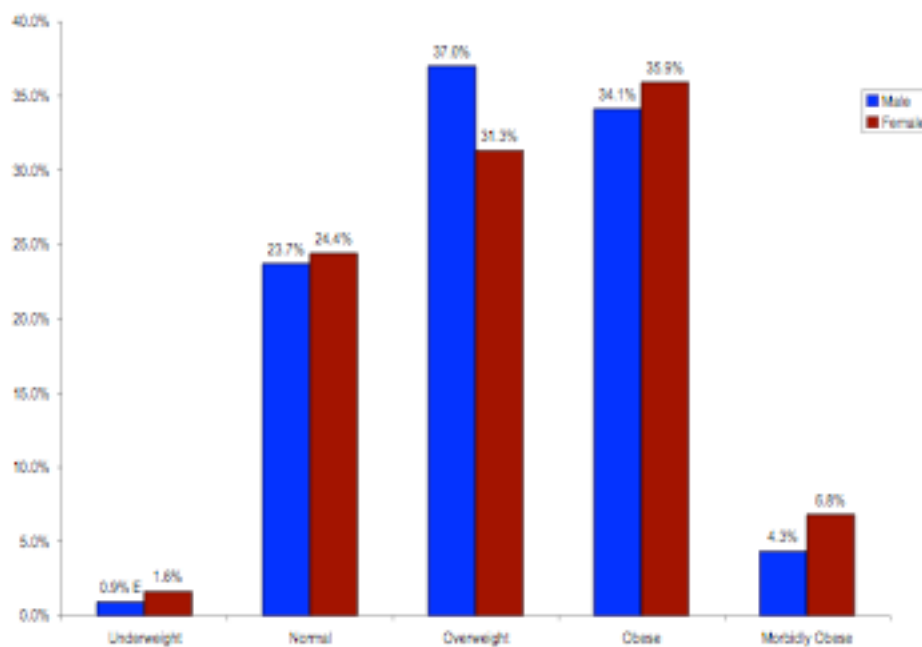


Figure 1.6: Distribution of body weight groups among adults, living in Canada (Reading, 2010; RHS, 2011).

Table 1.1: Summary of the twelve LQTS-associated genes (Zhang et a., 2010).

Table 1. Summary of 12 LQTS-associated genes

Phenotype	LQT1	LQT2	LQT3	LQT4	LQT5	LQT6	LQT7	LQT8	LQT9	LQT10	LQT11	LQT12
Gene	<i>KCNQ1</i>	<i>KCNH2</i>	<i>SCN5A</i>	<i>ANK-2</i>	<i>KCNE1</i>	<i>KCNE2</i>	<i>KCNJ2</i>	<i>CACNA1C</i>	<i>CAV3</i>	<i>SCN4B</i>	<i>AKAP9</i>	<i>SNTA1</i>
Chromosome	11p15.5	7q35- 36	3p21	4q25- 27	21q22	21q22	17q23.1 -24.2	12p13.3	3p25	11q23.3	7q21- 22	20q11.2
OMIM#	607542	152427	600163	106410	176261	603796	600681	114205	601253	608256	604001	601017
No pathogenicity	75	61	84	14	15	9	5	2	8	2	13	4
Possible pathogenicity	56	67	105	9	19	6	2	0	0	0	1	0
Pathogenicity	333	433	189	7	16	13	45	5	6	1	1	1
Unknown pathogenicity	7	29	24	30	1	0	1	0	0	3	32	4
Total unique mutations	471	590	402	60	51	28	53	7	14	6	47	9

Table 1.2: Single Nucleotide Polymorphism (SNP) found within the *KCNQ1* gene associated with T2D susceptibility/development.

KCNQ1 variant/SNP	Population	Evidence	Author
SNP rs2237892	Korean population	T2D association study	Lee et al., 2008
SNPs rs2283228, rs2237897, and rs2237895	Japanese, Singaporean and Danish populations	GWAS	Unoki et al., 2008
SNP rs2237892	Japanese, Korean, Chinese and European ancestry populations	GWAS	Yasuda et al., 2008
SNP rs2237895	German population	T2D association study	Grallert et al., 2009
SNP rs2237895	Danish population	T2D traits (insulin release) association study	Holmkvist et al., 2009
SNPs rs2074196, rs2237892, rs2237895, and rs2237897	Shanghai Chinese population	T2D association study	Hu et al., 2009
SNP rs2237895	Scandinavian (Swedish) population	T2D association study	Jonsson et al., 2009
SNPs rs2237892, rs2237895, and rs2237897	Chinese Han population	T2D association study	Lui et al., 2009
SNPs rs2237892, rs2237895, and rs2237897	German population	T2D traits (insulin secretion) association study	Mussig et al., 2009
SNPs rs2237892, rs2237895 and rs2237897	Chinese Han population	T2D association study	Qi et al., 2009
SNP rs2237892	Japanese population	T2D association study	Takeuchi et al., 2009
SNPs rs2237897, rs2237892, and rs2283228	Chinese, Malay, Asian Indians populations	T2D association study	Tan et al., 2009
SNPs rs2237892, rs2237895, rs2237897, and rs2283228	Chinese population	T2D association study- NO T2D association	Chen et al., 2010b
SNPs rs2237892,	Hubei Han Chinese	Meta-analysis	Dewah et al., 2010

rs2237895, rs2237897 and rs2074196	and East Asian populations		
SNP rs231362 (Intron 11)	European populations	GWA meta-analysis	Voight et al., 2010
SNPs rs2237895 and rs231362 (Intron 11)	Asian Indian population	T2D association study	Been et al., 2011
SNP rs2237892	Native Mexican	T2D association study	Parra et al., 2011
SNPs rs2237892, rs2283228, and rs2237895	Malaysian Chinese	T2D association study	Saif-Ali et al., 2011
SNP rs2237892	Antioquian (South America mestizo- Columbia)	T2D association study	Campbell et al., 2012
SNP rs151290, rs2237892, and rs2237895	Dutch population	T2D association study	Vliet-Ostapchouk et al., 2012

Table 1.3: Diagnosis criteria for diabetes (ADA, 2012).

A1C $\geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Table 1.4: Traits and thresholds of traits required to diagnose MetS (LaGuardia et al., 2011)

TABLE 1

Parameters	WHO (1998)	NCEP ATP3 (2001)	IDF (2005)
Required	Insulin resistance in the top 25%; glucose		Waist >94 cm (men) or 80 cm (women)
Number of abnormalities	>2	>3	>2
Glucose	>6.1 mmol/L (110 mg/dL); 2-hour glucose >7.8 mmol/L (140 mg/dL)	>5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	>5.6 mmol/L or diagnosed diabetes
HDL cholesterol	<0.9 mmol/L (35 mg/dL) (men); <1.0 mmol/L (40 mg/dL) (women)	<1.0 mmol/L men (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C	<1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C
Triglycerides	≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides	≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides
Obesity	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m ²	Waist ≥102 cm (men) or ≥88 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)
Hypertension	≥140/90 mmHg	≥130/85 mmHg or drug treatment for HTN	≥130/85 mmHg or drug treatment for HTN

TABLE 2

Measure	Categorical cut points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides or drug treatment for elevated triglycerides	≥150 mg/dL
Reduced HDL-C or drug treatment for reduced HDL-C	<40 mg/dL in men, <50 mg/dL in women
Elevated blood pressure or antihypertensive drug treatment	Systolic ≥130 mmHg and/or diastolic ≥85 mmHg
Elevated fasting glucose or drug treatment of elevated glucose	≥100 mg/dL

Adapted from [22].

Table 1.5: Candidate susceptibility genes associated with T2D involved with Indigenous peoples. Isolated to North, Central, South America and Australia (Appendix 1).

Gene	Variant (mutation or polymorphism)	Indigenous population	Evidence	Reference
HNF-1 α	1-4, G319S 5. SNP's rs3212183, rs2071197, and rs6031558 6. SNP rs1169288 7. SNP rs7305618	1-4., Canadian Oji-Cree 5. Pima Indians 6. Antioquian (South America mestizo-Columbia) 7. Mexican ancestry	1,2,4,5,6,7. Association study 3. Mutational mechanism study	1. Triggs-Raine, B. L., et al. 2002. Proc Natl Acad Sc 2. Sellers, E. A. C., et al. 2002. Diabetes Care 3. Harries, L. W., et al. 2008. Diabetes 4. Hegele, R. A., et al. 1999 5. Muller, Y. L., et al. 2005. Diabetes. 6. Campbell, D. D., et al. 2012. PLoS ONE 7. Parra, E. J., et al. 2011. Diabetologia.
PTP-1B	1. C981T 2. SNP's rs196749, rs4811074 and rs4811075	1. Canadian Oji Cree 2. Pima Indians	1. Association Study- PROTECTION from T2D 2. Association study- NO T2D association	1. Mok, A., et al. 2001. Journal of Clinical Endocrinology & Metabolism. 2. Traurig, M., et al. 2007. Diabetologia.
PPAR γ	1, 3. Pro12Ala 2. Gly482Ser	1, 2. Pima Indians 3. Canadian Oji-Cree	1,2. Association study- NO T2D association 3. Association study	1. Muller, Y. L., et al. 2003b. Diabetes. 2. Muller, Y. L., et al. 2003a. Diabetes. 3. Hegele, R. A., et al. 2000. Journal of Clinical Endocrinology & Metabolism.
11 β -HSD1	SNP1 and 5 (Not named)	Pima Indians and Tohono O'odham Indians	Association study	Nair S, et al., 2004. Diabetologia.
INSRR	Various SNPs (not	Pima Indians	Association study-	Wolford, J. K., et al.

	named)		NO T2D association	2001. Molecular and Cellular Probes.
GYS1	Mutations or mRNA alterations within GYS1	Pima Indians	Genome wide association study- NO T2D association	Majer, M., et al. 1996. Diabetologia.
TCF7L2	1. Polymorphisms IVS3C>T, IVS3T>C, IVS4G>T, and IVS4G>C 2, 4. Microsatellite (DG10S478) and 5 SNP's (rs7901695, rs7903146, rs7895340, rs1196205, and 12255372. 3. rs12255372 T allele and the DG10S478 microsatellite	1. Pima Indians 2. Pima Indians 3. Mexican (Guerrero) 4. Antioquian (South America mestizo-Columbia)	1. Association study 2. Association study - NO T2D association 3, 4. Association study	1. Tong, Y., et al. 2009. BMC Medical Genetics. 2. Guo, T., et al. 2007. Diabetes. 3. Parra, E. J., et al. 2007. Clinical Genetics 4. Campbell, D. D., et al. 2012. PLoS ONE
ACDC	SNP-12823, SNP-11365, SNP 45, SNP 276, and SNP 3286	Pima Indians	Genome wide association— NO T2D association	Vojarova de Courten, B., et al. 2005. Diabetes.
CRP	1. SNP 133552 2. CRP Serum levels	1. Pima Indians 2. Canadian Oji-Cree	1. Association study 2. Association study- NO T2D association	1. Wolford, J. K., et al. 2003. Molecular Genetics and Metabolism. 2. Ley, S. H., et al. 2010. Cardiovascular Diabetology.
PEA15	4 SNP's	Pima Indians	Association study	Wolford, J. K., et al. 2000. Gene.
IL6	174 G/C	Pima Indians	Association study	Vojarova, B., et al. 2002. Human Genetics
TNF α	1, 2. 308 G/A	1. Pima Indians 2. Aboriginal Australian	1. Association study- NO T2D association 2. Association study	1. Hamann, A., et al. 1995. Biochemical and Biophysical Research Communications 2. Dalziel, C., et al. 2002. Obesity Research.
ORP15	ORP150-2 and ORP150-	Pima Indians	Association study-	Kovas, P., et al.

	9		NO T2D association	2002. Diabetes
MGEA5	SNP1 and SNP 2	Pima Indians	Association study- NO T2D association	Farook, V. S., et al. 2002. Mol. Genetics and Metabolism
ATF6	Three variants: amino acid substitutions	Pima Indians	Association study	Thameem, F., et al. 2006. Diabetes.
CHRM3	rs3738435	Pima Indians	Association study	Guo, Y., et al. 2006. Diabetes
ACAD10	rs601663 and rs659964	Pima Indians	Association study	Bian, L., et al. 2010. Diabetologia.
ASK1	SNP's rs35898099, rs1570056, and rs7775356	Pima Indians	Association study	Bian, L., et al. 2010. Diabetes.
Ca (v)2.3	SNP +8130G/A and rs3753737	Pima Indians	Association study	Muller, Y. L., et al. 2007. Diabetes
PBX1	SNP16	Pima Indians	Association study- NO T2D Association	Thameem, F., et al. 2001. Biochimica et Biophysica Acta
KCNJ9	Val366Ala	Pima Indians	Association study	Wolford, J. K., et al. 2001. Molecular Genetics and Metabolism.
KCNJ10	SNP1—Not named	Pima Indians	Association study	Forook, V. S., et al. 2002. Diabetes
LMNA	3408C/T	Pima Indians	Association study- NO T2D association	Wolford, J. K., et al. 2001. Diabetologia.
DRD2	polymorphisms Ser311Cys and TaqIA	Pima Indians	Association study- NO T2D association	Jenkinson, C. P., et al. 2000. International Journal of Obesity
PTGS2	2 out of 5 SNP are significantly associated with T2D—Not named	Pima Indians	Association study	Konheim, Y. L., et al. 2003. Human Genetics.
IRS1	SNP Ala804	Pima Indians	Association study	Kovacs, P., et al. 2003a. Diabetes
DIO2	Thr92Ala, rs225011 and rs225015	Pima Indians	Association study	Nair, S., et al. 2012. Thyroid.
ABCA1	SNP R230C	1. Pima Indians 2. Mexican-Mestizo	1, 2: Association study	1. Acuña-Alonzo, V., et al. 2010. Human Molecular Genetics. 2. Villarreal-Molina, M. T., et al. 2008. Diabetes

PCLO	rs976714, rs10954696, rs10487656, and rs6950504	Pima Indians	Association study	Ma, L., et al. 2008. Diabetes
MGST3	SNP's 13, 3, 11,20, and 23	Pima Indians	Association study- NO T2D association	Thameem, F., et al. 2003. Human Genetics
ARHGEF1 1	Variant R1467H	Pima Indians	Association study	Ma, L., et al. 2007. Diabetes.
KLF11	Variant Q62R	Pima Indians	Association study- NO T2D association	Ma, L., et al. 2008. J Clin Endocrinol Metab
HLA- DRB1	SNP rs9268852	Pima Indians	Association study- PROTECTIVE for T2D	Williams, R. C., et al. 2011. Diabetologia
SIRT1	SNPs rs10509291 and rs7896005	Pima Indians	Association study	Dong, Y., et al. 2011. Mol Gen and Metabolism.
FOXC2	SNPs C-512T and G-350T	Pima Indians	Association study- NO T2D association	Kovacs, P., et al. 2003b. Diabetes
FTO	SNPs rs8050136, rs9939609, and rs7193144	Pima Indians	Association study- NO T2D association	Rong, R., et al. 2009. Diabetes
CDKAL1	1. SNPs rs7754840, rs10946398, rs4712523, and rs7756992 2. SNP rs9465871 3. SNP rs7305618	1. Pima Indians 2. Antioquian (South America mestizo-Columbia) 3. Mexican ancestry	1. Association study- NO T2D association 2,3. Association study	1.Rong, R., et al. 2009. Diabetes 2. Campbell, D. D., et al. 2012. PLoS ONE 3. Parra, E. J., et al. 2011. Diabetologia
SLC30A8	1,2. SNP rs13266634	1. Pima Indians 2. Indigenous Mexican	1,2. Association study- NO T2D association	1. Rong, R., et al. 2009. Diabetes. 2. Gutiérrez-Vidal, R., et al. 2011. Genetic Testing and Biomarkers
HHEX	1. SNP's rs1111875 and rs10509646 2. SNP rs1111875 and rs7923837	1. Pima Indians 2. Indigenous Mexican	1,2. Association study- NO T2D association	1. Rong, R., et al. 2009. Diabetes 2. Vidal, R. G., et al. 2011. Genetic Testing and Molecular Biomarkers
IGF2BP2	1. SNP's rs4402960, rs1470579, rs6777038	1. Pima Indians 2. Mexican	1. Association study- NO T2D	1. Rong, R., et al. 2009. Diabetes

	and rs16960234 2. SNP rs7305618	ancestry	association 2. Association study	2. Parra, E. J., et al. 2011. Diabetologia
LOC387761	1, 2. SNPs rs7480010 and rs9300039	1. Pima Indians 2. Indigenous Mexican	1. Association study- NO T2D association 2. Association study	1. Rong, R., et al. 2009. Diabetes 2. Vidal, R. G., et al. 2011. Genetic Testing and Biomarkers
EXT2	1. SNP's rs3740878 and rs1113132 2. SNP's rs3740878, rs11037909, and rs1113132	1. Pima Indians 2. Indigenous Mexican	1,2. Association study- NO T2D association	1. Rong, R., et al. 2009. Diabetes 2. Vidal, R. G., et al. 2011. Genetic Testing and Molecular Biomarkers
CDKN2B	1. SNP rs10811661 2. SNP rs1333051	1. Pima Indians 2. Mexican ancestry	1. Association study- NO T2D association 2. Association study	1. Rong, R., et al. 2009. Diabetes 2. Parra, E. J., et al. 2011. Diabetologia.
MBL2	rs11003125 and rs1800450	Pima Indians	Association study	Muller, Y. L., et al. 2010. Diabetes
PCK1	SNP C232G	Canadian Oji-Cree and Inuit	Association study	Cao, H., et al. 2004. Journal of Clinical Endocrinology & Metabolism
KCNQ1	1, 2. SNP rs2237892	1. Antioquian (South America mestizo-Columbia) 2. Mexican ancestry	1,2. Association study	1. Campbell, D. D., et al. 2012. PLoS ONE 2. Parra, E. J., et al. 2011. Diabetologia
RBMS1	SNP rs6718526	Antioquian (South America mestizo-Columbia)	Association study	Campbell, D. D., et al. 2012. PLoS ONE
ZNF239	SNP rs9326506	Antioquian (South America mestizo-Columbia)	Association study	Campbell, D. D., et al. 2012. PLoS ONE
FABP2	1-4: Ala54Thr polymorphism	1,2. Indigenous Chilean 3. Pima Indians 4. Keewatin	1,3,4: Association study 2. Association study- NO T2D	1. Albala, C., et al. 2007. Diabetes Research and Clinical Practice

		Inuit	association	2 Pérez-Bravo, F., et al. 2006. Acta Diabetologica 3. Baier, L. J., et al. 1995. The Journal of Clinical Investigation 4. Hegele, R. A., et al. 1997. Journal of Molecular Medicine
ADRB3	1,2. Trp64Arg	1. Pima Indians 2. Canadian Oji-Cree	1. Association study 2. Association study- NO T2D association	1. Walston, J., et al. 1995. New England Journal of Medicine. 2. Hegele, R. A., et al. 1998. Diabetes Care
CAPN10	1. G4852G 2. G→A polymorphism (UCSNP-43)	1. Canadian Oji-Cree 2. Pima Indians	1, 2: Association study- NO T2D association	1. Hegele, R. A., et al. 2001. Diabetes Care 2. Baier, L. J., et al. 2000. The Journal of Clinical Investigation
PC-1	K121Q	Canadian Oji-Cree	Association study- NO T2D association	Hegele, R. A., et al. 2001. Diabetes Care
PPPIR3	5 bp DNA polymorphism within the 3'-untranslated region	Canadian Oji-Cree	Association study- NO T2D association	Hegele, R. A., et al. 1998. Journal of Clinical Endocrinology & Metabolism
PON2	G148 variant	Canadian Oji-Cree	Association study- NO T2D association	Hegele, R. A., et al. 1997. Journal of Clinical Endocrinology & Metabolism
NAT2	SNP C282T	Canadian Oji-Cree	Association study- NO T2D association	Hegele, R. A., et al. 2000. Pharmacogenetics.

Chapter II: Methodology and Results

Setting

This sub-study was conducted at the Wrinch Memorial Hospital (WMH). WMH operates out of Hazelton/Gitanmaax in the North West of British Columbia. This health care facility services the surrounding area of five Gitxsan villages (Gitwangak, Gitsegukla, Gitanmaax, Glen Vowell, Kispiox) and two provincial municipalities (Hazelton, New Hazelton) (FPHLC, 2007).

Recruitment

Volunteer participants were recruited from the on-going/original research project entitled '*The Impact of Long QT on First Nations People of Northern British Columbia*'. The original research project has current ethical approval from the University of British Columbia and Northern Health Authority (Arbour et al., 2008). Prior to data collection, we received a letter of support from the Gitxsan Health Society for this sub-study to be conducted. We obtained ethics approval for this sub-study from the University of British Columbia, the University of Victoria, and the Northern Health Authority. Only participants who indicated on their preexisting consent form from the original research project that they wished to be '*contacted for future LQTS research*' were contacted.

A letter of introduction and invitation to partake in the sub-study was sent to each potential participant with background and contact information (Appendix 2). A waiting period of approximately two weeks was allowed for the letters to be

received and read. Three rounds of phone calls were made to all potential participants concerning the invitation letter that was sent to them, more background information on the sub-study, and an invitation to set up a face-to-face appointment to meet with Mr. Polanco (lead researcher) at WMH. A research assistant living in Hazelton helped contact participants whose contact information from the original study was incorrect or missing.

Demographics

Our sample volunteer population for this sub-study included 70 full-Gitksan participants: 5 volunteer participants were not included due to refusal of the HbA1c test or being pregnant at the time of sub-study. The consent was explained to each participant and every participant signed a consent form (Appendix 3). Every participant also signed a Release of Information (ROI) for all preexisting and/or current diabetes records (Appendix 4). Data from 65 participants were used for the results for this sub-study: 48 females (age ranges 25 to 84 years) and 17 males (ages range 21 to 82 years). 70% (34 out of 48) females were V205M negative and 30% (14 out of 48) were V205M positive. 72% (14 out of 17) males were V205M negative and 18% (3 out of 17) males were V205M positive. All mutation statuses were already established from the original study (Arbour et al., 2008).

Participants:

Each participant signed a consent form outlining exact protocols, expectations and procedures. Each participant also signed a Release of Information

(ROI) respective to his or her local health station. Exclusion criteria included participants under the age of 18 years old and pregnant women: pregnant women have decreased HbA1c values during early pregnancy and during their third trimester (Nielsen et al., 2004).

Waist circumference measurements were assessed according to the Canadian Physical Activity Fitness and Lifestyle Approach standardized protocols (Foulds, H., et al. 2011; CPAFLA, 2010). Weight and height was measured using a calibrated beam balance and stadiometer (Daniel, M., et al. 1999). Participants were asked to remove shoes and any extra clothing before recording weight and height. BMI was calculated using (Patenaude, J., et al. 2005):

$$\text{BMI (kg/m}^2\text{)} = \frac{\text{Weight (kg)}}{\text{Height (m}^2\text{)}}$$

A questionnaire was administered to each participant following anthropometric measurements (Appendix 5). The questionnaire addressed questions of contact information, medical history, knowledge of previous/existing diabetes diagnosis and/or management of diabetes (if any), exercise level (high: 30 min, 3 days/week; moderate: < 30 min, 3 days/week; low: never/almost never) any other chronic conditions and comments.

After measurements, a blood requisition form was completed for a HbA1c blood draw. Blood was drawn at the WMH for HbA1c analysis. The HbA1c analysis was carried out at the University Hospital of Northern British Columbia (UHNBC) in Prince George, British Columbia and the results were sent to Dr. Laura Arbour's research lab at the University of Victoria. At UHNBC, HbA1c was analyzed using a

ROCHE Integra 800. The Integra 800 uses the Tina-quant method of analyzing HbA1c blood samples. The Tina-quant method is a turbidimetric immunoassay (BIOLABO, 2010). This immunoassay uses the principles of turbidity to measure the amount of glycated hemoglobin corresponding to an antigen-antibody reaction in a given blood sample (BIOLABO, 2010; Price et al., 1987). This method of determining HbA1c percentages (via immunoassay) has been shown to be precise, comparable and accurate (Fleming et al., 2007; Ralph-Campbell et al., 2009). We defined HbA1c values as follows (ADA, 2012):

Low risk HbA1c Category	At Risk HbA1c Category	Diabetic HbA1c Category
<5.7%	5.7%-6.4%	>=6.5%

Ranges of HbA1c values between 5.0% to 6.0% have been previously shown to confer an increased risk of diabetes with 5-year incidence rates between 9% to 25% (Zhang et al., 2010). However, the American Diabetes Association has recently published defined 'pre-diabetic' or 'increased risk for diabetes' categories: 5.7% - 6.4%. 'Pre-diabetic' status refers to an elevated blood glucose level whereby a diabetic diagnostic has not yet been determined (ADA, 2012).

Data Security

All of the study data and the master list of participants' names and study identifiers was locked within the Medical Sciences building in the Community Genetics Program (Rm 234) at the University of Victoria (UVIC) under a double

password protected database only accessible inside Rm 234. The Gitxsan Health Society will revise any publications prior to publication. All biological samples from the original study were collected under the stipulation of *DNA on Loan* (Arbour et al., 2008; Arbour and Cook, 2006). However, this sub-study had all biological samples (blood for HbA1c tests) destroyed after HbA1c test was completed.

Data analysis

A case-control model was used to determine *KCNQ1* mutation influence on HbA1c values. Student t-tests and 95% Confidence Intervals (CI) were used to detect a significant difference between the mutation negative HbA1c group (control) and the mutation positive HbA1c group (cases) ($p < 0.05$). Linear regression analyses were used to determine mutation status influence on HbA1c while controlling for BMI and age. Linear regression analyses were also used to determine BMI's effect on HbA1c while controlling for age and mutation status. Correlation analyses were completed on BMI and waist circumference values.

Analyses were undertaken using MS EXCEL 2011 (t-tests, descriptive statistics, CI) and STATA© (linear regressions, correlation statistics) (Statcorp, 2009).

Results

Sixty five participants comprised the study population. 17 participants were V205M mutation positive (V205M+) and 48 were V205M mutation negative (V205M-) (Table 2.2).

The mean HbA1c values for all participants was 5.84% (SD=0.96). Twenty-nine participants had 'low risk' HbA1c values (>5.69%), 31 at a 'at risk' level (5.7-6.4%), and 5 at a 'diabetic' level ($\geq 6.5\%$) (Figure 2.1) (ADA, 2012). Stratifying by mutation status, crude average HbA1c values between both groups (+/-) were not significantly different ($p=0.963$) (Figure 2.3). However, crude HbA1c levels odds ratio calculations, when stratified according to HbA1c risk categories, revealed that participants who were V205M positive (V205M+) were almost five times more likely to attain an 'at risk' HbA1c value (Figure 2.2 and Table 2.1)(OR=5.60; $p=0.009$; CI: 1.29-16.3). After adjusting for BMI, age, QTc, and exercise levels using a logistic regression model shown those who were V205M+ were almost ten times more likely to attain an 'at risk' HbA1c value (adjusted OR: 9.62; $p=0.002$; CI: 2.23-41.5). In other words, individuals V205M positive were at a ten times greater risk to have a HbA1c result that fell into the 'at risk' HbA1c level, previously established to confer a 25-50% increased risk to develop a diabetic HbA1c value (Figure 2.4).

Using a linear regression (LR) model (using HbA1c as the dependent variable throughout) and adjusting for age, BMI had an overall significant linear effect on HbA1c values: where one unit increase of BMI increased HbA1c values by 0.03 ($p=0.019$; CI: 0.0053 to 0.057). However, there was not a linear trend for those who were V205M positive, that is, BMI did not increase HbA1c significantly ($p=0.39$; CI: -0.013 to 0.032). For those who were V205M negative, as with the combined total results, BMI increased HbA1c values significantly, if mutation negative, one unit increase of BMI increased HbA1c values by 0.036 ($p=0.023$; CI: 0.0052 to 0.066). In

general, BMI is a risk factor for elevated HbA1c values. However, if mutation positive BMI does not seem to increase risk for elevated HbA1c values.

When considering Waist Circumference (WC) in the LR model of effects on HbA1c, BMI had the greater effect, and WC correlated highly with BMI, therefore, BMI was selected as the variable for statistical analysis (BMI and WC correlation = 0.88). Independently, WC did not influence the HbA1c ($p=0.103$; CI: -.002 to .0211).

Odds ratio calculations were used to analyze the effects of mutation status on exercise levels: mutation status did not influence exercise levels. Adjusting for age, exercise levels between mutation carrier groups were not significant ($p=0.222$; CI: 0.138 to 1.62). Furthermore, exercise levels did not affect QTc or HbA1c values ($p=0.676$; CI: -11.88 to 18.20 and $p=0.923$; CI: -.478 to .434). Both moderate and low exercise categories were used as the comparison groups throughout the analysis due to their majority rates and their ability to demonstrate differences between exercise levels: all exercise levels were insignificant throughout.

Before adjusting for BMI, age, and exercise levels, mutation status was not significantly correlated with increased QTc measurements ($p=0.068$). However, after adjusting for all variables in this sub-study, mutation status was shown to have a significant effect on QTc measurements. Using a LR model (holding QTc as the dependent variable) and adjusting for age, sex, BMI, WC and exercise levels V205M+ participants had significantly higher QTc measurements than V205M- participants: a 16.8ms increase between mutation negative and positive mutation carriers ($p=0.031$; CI: 1.54 to 32.1). V205M+ individuals are more at risk of having an

increased QTc level, as established in the original study (Arbour et al., 2008). , HbA1c had no significant effect on QTc measurements (p=0.146).

Using a LR model and adjusting for BMI, QTc and exercise levels, age was not a risk factor for increasing HbA1c values (p=0.211; CI: -.282 to 1.16). Age was an insignificant variable for HbA1c. BMI (or exercise levels) did not influence QTc measurements. Using QTc as the dependent variable in a LR model and adjusting for BMI and exercise levels, QTc measurements in both mutation negative (BMI: p=0.410; CI: -.628 to 1.51 – Exercise: p=0.495; CI: -12.6 to 25.7) and positive participants (BMI: p= 0.187; CI: 0.665 to 3.09) were not altered significantly.

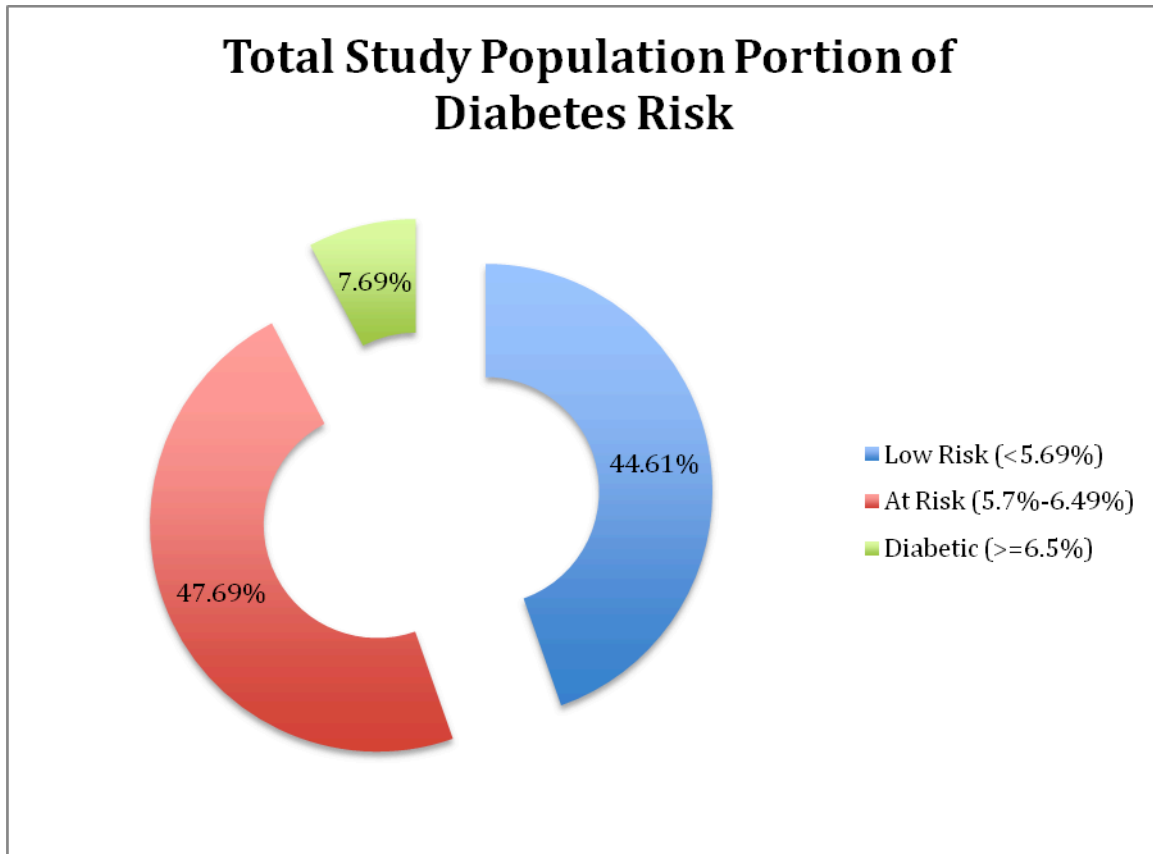
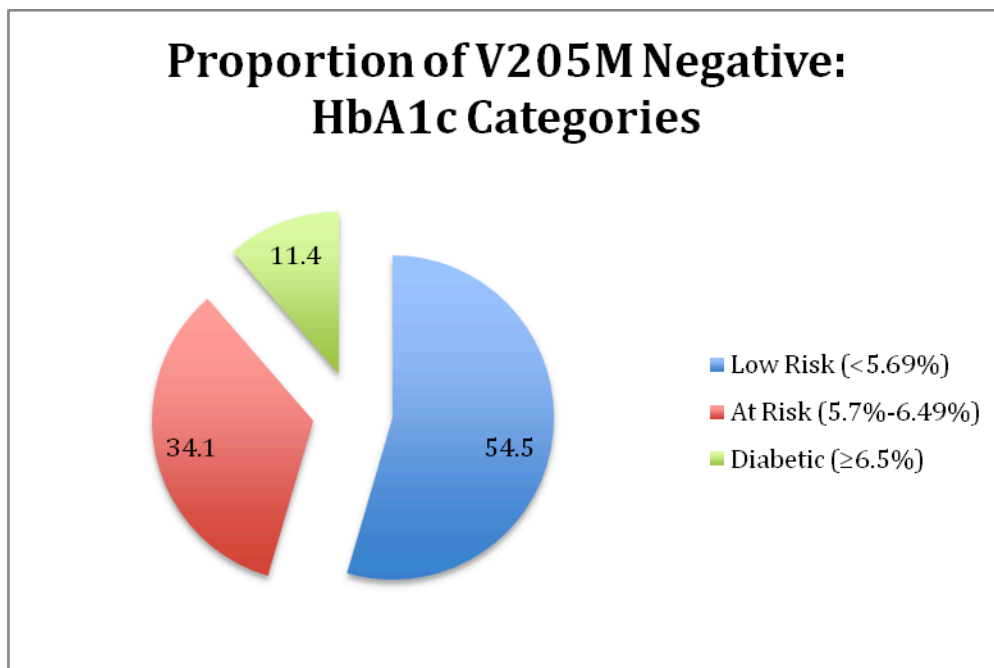


Figure 2.1: Portion of HbA1c values classified by diabetes risk thresholds (n=62, low risk=28, at risk=29, diabetic=5).



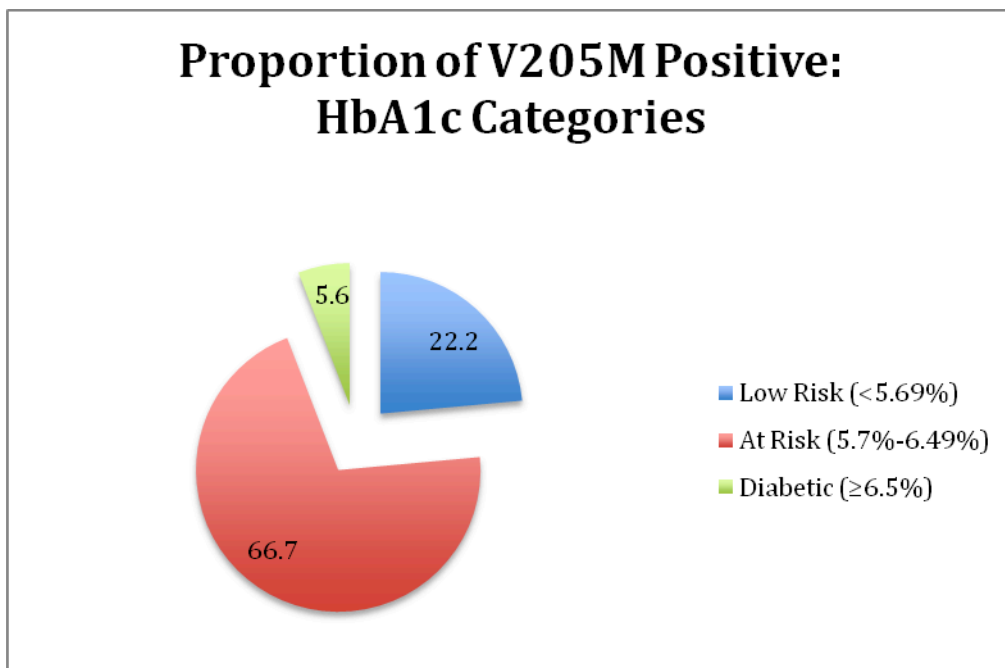


Figure 2.2: Porportions of HbA1c categories compared between mutation statuses: negative (top) and positive for the V205M mutation.

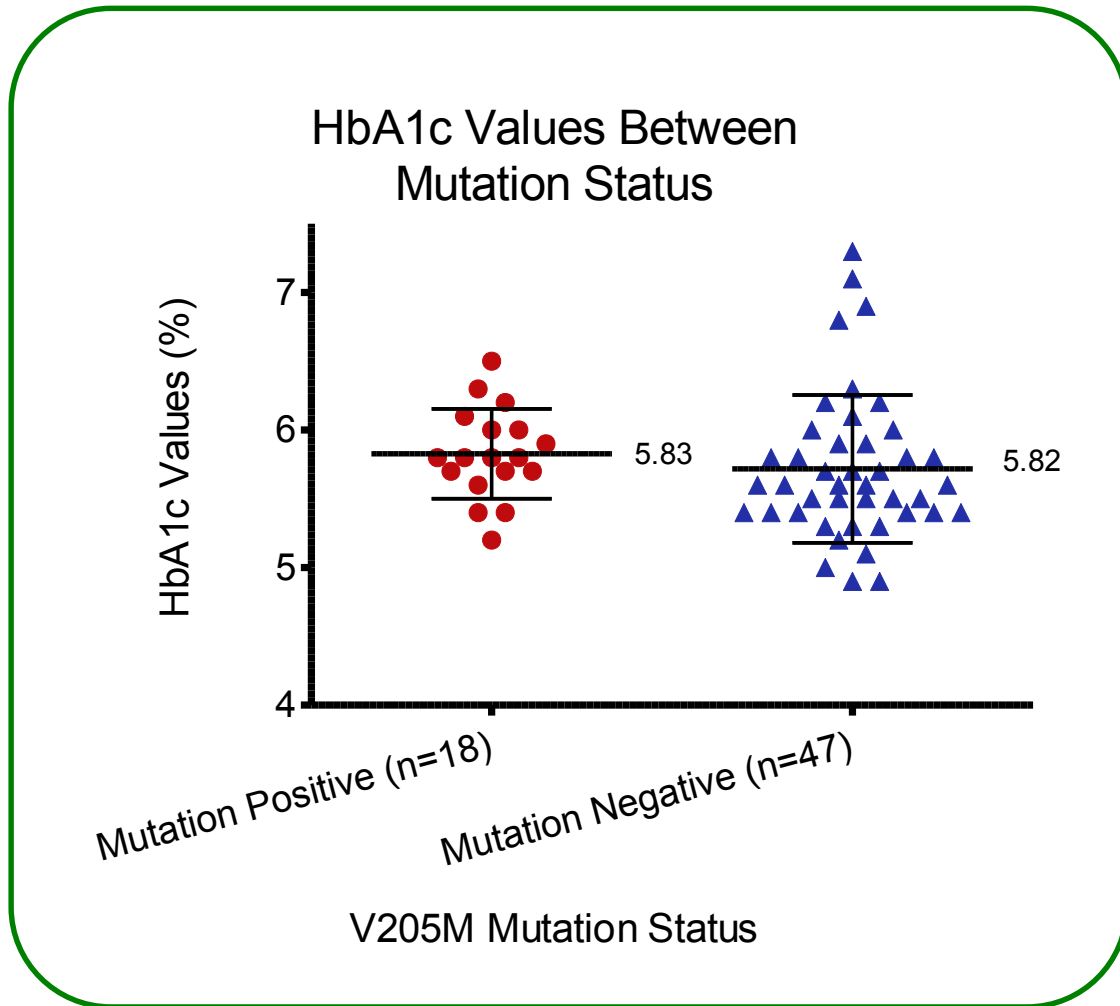


Figure 2.3: HbA1c values between V205M mutation statuses. V205M+ mean HbA1c value, 5.82. V205M- mean HbA1c value, 5.83 (p=0.963, CI: -0.47 to 0.45).

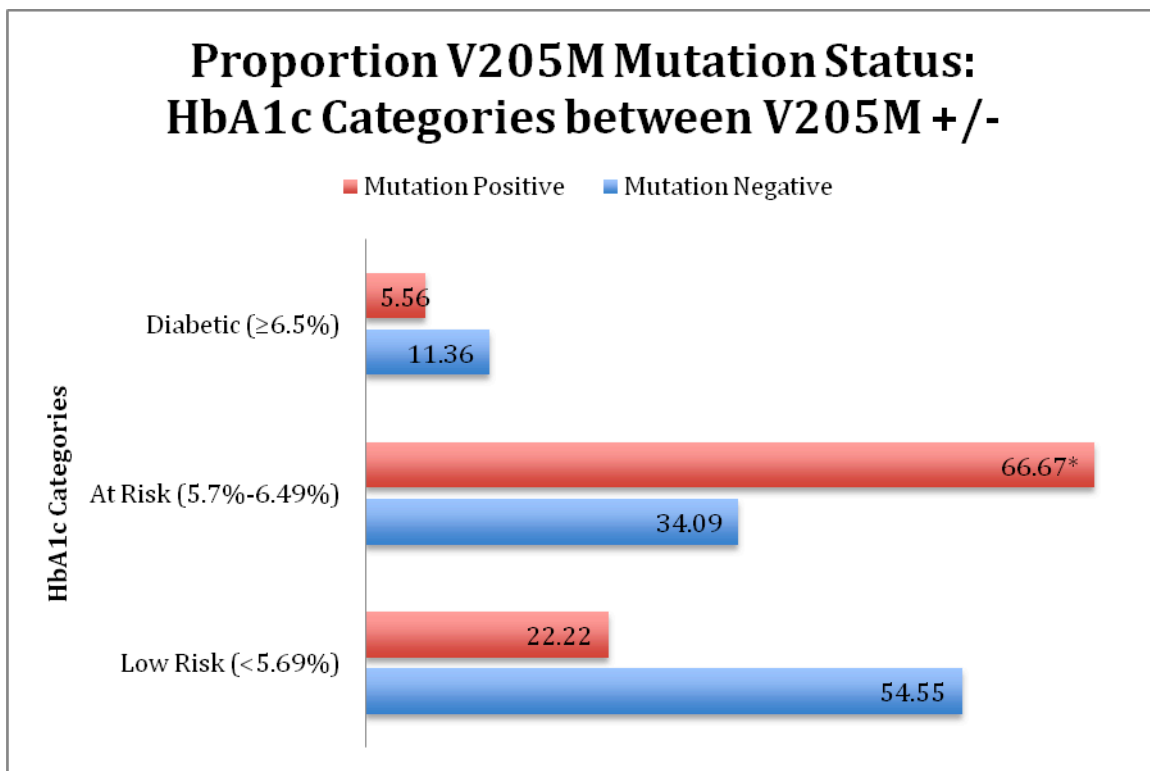


Figure 2.4: Proportion of both + and - V205M mutation statuses combined with HbA1c categories.

* Indicates statistical significance.

Table 2.1: 2X2 Contingency Tables

HbA1c Category	Mutation Negative	Mutation Positive	Total
'Low Risk' (>5.69%) and (≥6.5%)	30	5	35
'At Risk' (5.7%- 6.49%)	17	13*	30
Total	47	18	65

*Odds ratio is 5.02 (CI: 1.29 to 16.3) for 'At Risk' and Mutation Positive

HbA1c Category	Mutation Negative	Mutation Positive	Total
'Not Diabetic' (>5.69%) and (5.7%-6.49%)	42	17	59
'Diabetic' (≥6.5%)	5	1*	6
Total	47	18	65

*Odds ratio is 0.46 (CI: 0.0524 to 4.66—not significant) for 'At Risk' & Diabetic' and Mutation Positive

HbA1c Category	Mutation Negative	Mutation Positive	Total
'Not Low Risk' (≥6.5%) and (5.7%-6.49%)	22	14	36
'Low Risk' (>5.69%)	25	4*	29
Total	47	18	65

*Odds ratio is 0.24 (CI: 0.0484 to 4.346) for 'Low Risk' and Mutation Positive

Table 2.2: Unadjusted summary statistics and univariate analysis comparing mutation positive to mutation negative. ¹

Variables	Mean	V205M mutation negative	V205M mutation positive	P- value ²	Adjusted P-value
Age (years)	51.4±14.8	52.0±12.3	53.3±17.2	0.675	0.222
HbA1c (%)	5.83±0.82	5.84±0.93	5.83±0.33	0.963	0.902 (0.002)³
BMI (kg/m ²)	32.04±8.38	32.37±8.71	32.05±7.91	0.998	0.019
Waist Circumference (cm)	111.90±18.04	112.61±17.0	111.53±21.07	0.919	0.103
QTc measurements (ms)	457.5±28.0	453.7±29.6	467.6±20.6	0.068	0.031

¹ Values are reported as means (±SD)

² Differences by mutation status are derived using t-tests

³ When stratified by 'At Risk' HbA1c categories between mutation statuses.

Chapter III:

Discussion

Most Aboriginal communities in Canada retain a constant burden of chronic illness. Diabetes, obesity and other chronic conditions influence the Indigenous people who live in the communities (Reading, 2010). Our sub-study research was conducted in the Aboriginal community where, based on our results, demonstrated an elevated BMI, WC and HbA1c means. Our study population may not be reflective of the background population, but the prevalence of T2D is elevated, similar to many other First Nations communities. In 2008/2009 almost 2.4 million Canadians were living with diagnosed T2D (10% T1D and 90% T2D and others) and Aboriginal people are three – five times more likely to develop T2D (CDA, 2008; Health Canada, 2011). 17.2% of First Nations on-reserve people in Canada have T2D and 10.3% of First Nations off reserve have T2D. However, B.C. the rate of diabetes is 4.9 for the general population and 1.6% for Aboriginal people (Health Canada, 2011). According to Health Canada, socio-cultural, biological, environmental and lifestyle changes over the last half-century have contributed to the higher prevalence of T2D in First Nation, Inuit and Metis people of Canada (Health Canada, 2011; Reading, 2010). Our population might indeed reflect increased rates of obesity and WC. In the Gitksan territory of Northern BC, the V205M loss of function mutation in the *KCNQ1* gene has been shown to confer risk to LQTS (Arbour et al., 2008).

LQTS1 is an autosomal dominant, genetic disease that is caused by mutations in the *KCNQ1* gene expressed in the cell membranes of cardiac myocytes. With

known variable penetrance associated features include ventricular tachyarrhythmias, torsade de pointes, and ventricular fibrillation, leading to syncope and sudden death (Khan and Gowda, 2004; Modell and Lehmann, 2006; Zhang et al., 2010). The *KCNQ1* gene is also expressed in non-cardiac tissues throughout the body, and notably for this study in the pancreas. Consequently, recent Genome Wide Association Studies (GWAS) in various populations have identified Single Nucleotide Polymorphisms (SNPs) located in introns 15 (majority) and 11 within the *KCNQ1* gene have been found to be strongly associated with T2D whereby impaired insulin secretion was the mechanism suggested rather than insulin resistance (Mussig et al., 2009; Tan et al., 2009; Unoki et al., 2008; Yamagata et al., 2011). Significant associations with SNPs (in particular rs2237892, rs2237895, rs2237897) within *KCNQ1* and T2D have been confirmed by others (Table 1.2). The characterized SNPs associated with T2D have been found to be gain-of-function SNPs (Masato et al., 2011), however not all associated SNPs have been characterized. The molecular mechanism is still unclear as to how *KCNQ1* SNPs affect insulin secretion. However, a recent study, with induced over-expression of *KCNQ1* in MIN6 mouse β -cell lines (using a retrovirus mediated gene transfer system) resulted in impairment of insulin secretion when the mice were challenged with glucose, but uncertainty still remains to exact how *KCNQ1* is expressed or present (Masato, 2011; Yamagata et al., 2011). Nineteen other studies have supported the role of SNPs in *KCNQ1* in T2D development (Table 1.2) (Been et al., 2011; Campbell et al., 2012; Chen et al., 2010; Grallert et al., 2009; Holmkvist et al., 2009; Hu et al., 2009; Jonsson et al., 2009; Liu et al., 2009; Mussig et al., 2009;

Parra et al., 2011; Qi et al., 2009; Saif-Ali et al., 2011; Tan et al., 2009; Unoki et al., 2008; Voight et al., 2010; Yasuda et al., 2008).

This sub-study attempted to determine whether the V205M mutation does indeed alter HbA1c values to lead to T2D based on nineteen other studies associating variants within *KCNQ1* and T2D. In this stub-study, categorizing between mutation positive and negative participants, unadjusted HbA1c values between groups were not significantly different ($p=0.963$) and adjusting for age and BMI did not alter the result significantly ($p=0.902$). However, when HbA1c results were stratified according to risk as established by the American Diabetes Association (ADA), our results showed that the V205M mutation confers an almost ten times likelihood to attain an 'at risk' HbA1c value—this could be interpreted as the V205M mutation does *indeed confer risk to attain a 25%-50% greater risk to develop T2D*. Yet, our results only demonstrate a single time frame and are not following our volunteer participants over an extended period of time to determine whether they do indeed attain a diabetic HbA1c value as would be predicted by their current result

Since BMI, WC, age and exercise levels were controlled for these variables our results suggest that the V205M mutation may indeed alter glycemic homeostasis and deserves more study to determine whether there is an increase in T2D susceptibility. Interestingly, to date, only gain of function SNPs in *KCNQ1* have been suggested to contribute to T2D, presumably by reducing insulin secretion. Our results suggest that loss-of-function mutations within *KCNQ1* could also alter insulin secretion. It has been speculated that our loss-of-function mutation found within

KCNQ1 (V205M) impairs the physiological ability of I_{Ks} channels to respond at increased rates (based on in vitro mechanistic studies) thereby affecting repolarization (Arbour et al., 2008). A similar effect of the V205M mutation could be involved in the β -islet cell.

Insulin secretion is regulated and maintained by an electrogradient within the β -islet cell—for insulin secretion to occur, the β -islet cell needs to be in a state of hyperpolarization to facilitate changes in voltage. The potassium channels (K_{ATP} channels) involved with the insulin secretin pathway act to allow Ca^{2+} influx to facilitate the exocytosis of insulin granules. When glucose concentrations are low, K_{ATP} channels remain open to keep the β -cell hyperpolarized, preventing electrical activity (and the release of insulin). However, when glucose concentrations are elevated, there is increased ATP generation, which leads to the closing of the K_{ATP} channels and influx of Ca^{2+} resulting in a de-hyperpolarized gradient, with insulin secretion as a response (Ashcroft and Rorsman, 2012; Bleich and Warth, 2000; Jacobson and Philipson et al., 2007; Holmkvist et al., 2009). K^+ channels have been hypothesized to influence the β -cell repolarization via reduction of action potential duration, which would limit calcium influx and insulin secretion—mutations in the genes coding K_{ATP} channels, in addition to the *KCNQ1* gene, have been shown to be associated with T2D and gestational diabetes (Jacobson and Philipson et al., 2007; Holmkvist et al., 2009). Nevertheless, there is still debate and uncertainty whether *KCNQ1* is indeed present or expressed (or how the discovered SNPs influence the *KCNQ1* expression) within the β -cell. Moreover, T2D is a polygenic condition with possibly various different genes (Ashcroft and Rorsman, 2012; Yasuda et al., 2008).

Our results raise the possibility that our loss-of-function V205M mutation may have an effect on the ion channels in the B cell electrogradient. (Figure 3.2). In other words, our V205M mutation may play a dual role 1) cardiac repolarization cycle and 2) within the β -cell re-hyperpolarization state in relation to delayed action potential activity. Possible molecular mechanism studies of gain-of-function SNPs within the *KCNQ1* have been associated with impaired insulin secretion (Yamagata et al., 2011).

The majority of participants in this sub-study were within the 'at risk' category of HbA1c (34.1% total V205M negative); which according to the ADA suggests a 25%-50% increased risk for T2D development, which is sometimes referred to as the 'pre-diabetic' category (ADA, 2011). HbA1c as a diabetes evaluation tool has been reported to achieve a sensitivity and specificity of 88% using 6.5% as a diabetic diagnostic 'cut off' (Kumar et al., 2010). Specifically in Aboriginal peoples of Canada, prevalence for 'pre-diabetes' has been reported to be as high as 11% (Ralph-Campbell et al., 2009). In a Métis population of northern Alberta Canada, 'pre-diabetes' (using HbA1c as their diabetes evaluation tool) was reported to be 8.1% (Ralph-Campbell et al., 2009). Furthermore, in the Oji-Cree peoples of Ontario Canada, 'pre-diabetic' rates has been reported to be as high as 11% (Dannenbaum et al., 1999; Harris et al., 1997). Our results suggest that our Gitksan sample population may be at a greater risk to develop T2D within their population based on our HbA1c values and proportion of participants with an 'at risk' HbA1c value. Overall, our Gitksan population, regardless of mutation status, averaged an HbA1c value of 5.8%, which is an 'at risk' value of glycated hemoglobin

or 'pre-diabetic' status. Our results greatly exceed previous studies observing an elevated proportion of 'pre-diabetic' HbA1c values: 47.69% (31/65) were 'at-risk' or 'pre-diabetic' (Dannenbaum et al., 1999; Harris et al., 1997; Ralph-Campbell et al., 2009). Diabetes prevalence within Aboriginal communities still remains complex, and the reasoning behind why such a high rate of 'pre-diabetes' is seen within this Aboriginal community is still just as complex. Our results do show an important genetic factor (controlling for anthropometric measurements), but it is important to address all perceivable factors (i.e., obesity, high sodium/fat diet, exercise inactivity, environmental, and social determinants). Our results suggest evidence that our Gitksan sample population have an increased risk to develop T2D (based on the elevated proportion of 'at-risk/'pre-diabetic' values), which is partly accounted for by the V205M mutation.

Obesity has been considered to be the strongest predictor and risk factor for T2D, and BMI has been established as a standard predictor of diabetes status, including within Aboriginal communities in Canada (Brimblecombe et al., 2006; Daniel et al., 1999). Previous studies investigating obesity in Aboriginal communities have reported obesity rates as high as 48% (Flouds et al., 2011; Vanasse et al., 2006). Our population of Gitksan participants had an average BMI of 32.04 ± 8.38 kg/m² (55.4% of total population), which by, according to WHO and Health Canada, falls into the obese category (>30.0 kg/m²) (Health Canada, 2003; WHO, 2010). In our LR model, BMI influenced the HbA1c results. Our overall (mutation +/- combined) results demonstrated a linear association of HbA1C with BMI, where one-unit increase of BMI increased HbA1c values by 0.03 (p=0.019; CI:

0.0053 to 0.057). Yet when stratifying by mutation status, mutation positive individuals did not show this trend: HbA1c values did not increase in that group with increasing BMI. Therefore, interestingly in this group, BMI was not a risk factor for elevated HbA1c—this result is unexpected. Interestingly, in studies of the influence of SNPs within *KCNQ1* increased BMI has been associated with the same SNPs that are also associated with T2D (Chen et al., 2012; Qi et al., 2009; Tan et al., 2009). Our results suggest that the V205M mutation might, in addition to increasing the HbA1c to an ‘at risk’ category (based on our HbA1c results), might also confer a protective effect on increasing HbA1c due to a common contributor of T2D, that is obesity. Given this result, and the fact that the actual risk for diabetes (HbA1c of >6.5% / ‘diabetic’) in the V205M positive participants was less (0.46, CI: 0.0524 to 4.66—for V205M positive participants having a ‘diabetic’ HbA1c), one can speculate that the decreased secretion of insulin contributed by the altered K⁺ channel dynamics, could be a benefit when other contributors such as diet may increase the risk for diabetes due to insulin resistance.

As introduced before, insulin resistance typically is the cause of T2D. Specifically, obesity and lifestyle choices play major roles in T2D development contributing to β -cell dysfunction and increased resistance to insulin uptake (Figure 3.3) (Ashcroft and Rorsman, 2012). Our results devote our T2D development risk to limited insulin secretion due to improper functioning of possible *KCNQ1* K⁺ channels/regulation. Moreover, our results show a narrowed range of HbA1c values (only one diabetic and few low risk) for V205M mutation carriers. It can be

postulated that our V205M prevents excessive insulin secretion, which might be otherwise prompted by diet.

Studies concerning Inuit peoples have observed increased levels of obesity, but historically low prevalence's of insulin resistance, MetS and T2D (Hegele et al., 2005; Lemas et al., 2011). A recent study conducted with the Yup'ik Eskimo of Alaska revealed that a particular variant (P479L) found within the carnitine palmitoyltransferase 1A (CPT1A) gene was found to confer a selective advantage that was both cardio-protective (through increased HDL-cholesterol) and decreased adiposity (Leman et al., 2011). CPT1A is key hepatic lipid oxidation enzyme involved with fatty acid oxidation and its contribution to obesity and metabolic outcomes. Lemas et al., (2011) proposed a 'healthy obesity' measurement concerning their population. 'Healthy obese' individuals have markedly increased body fat yet this excess of fat does not translate to insulin resistance. Their results argue that the P479L variant is associated with this 'healthy obese' phenotype: being P479L is selective for decreased adiposity and elevated HDL-cholesterol (Lemas et al., 2011). Our results could be interpreted as having similar results as the Inuit study conducted by Lemas et al., (2011). Our V205M mutation predisposes risk for T2D (one characteristic of MetS presence) and protects against increasing BMI as HbA1c values increase. Our V205M positive participants have elevated WC and BMI, yet there is protection against rising HbA1c values. Our results suggest an increased risk for T2D development, but do not suggest a high rate of T2D itself. The V205M may have conferred some advantage due its ability to keep HbA1c levels from being effected by increasing BMI. The V205M mutation may be both harmful for LQTS risk

and T2D development risk, but may be beneficial for increasing HbA1c due to higher BMI. These results of protection and predisposition reflect studies seen with Inuit people of Canada and Alaska (Hegele and Pollex, 2005; Lemas et al., 2011). We suggest that our Gitksan population genetically mirrors that of the Inuit people due to this pleiotropic effect. However, both populations do not share the same environment. Our results only demonstrate a 25-50% increased risk to develop T2D; therefore, we do not know whether these individuals will indeed develop frank T2D in the future.

It has been argued that some of the reasoning behind why the Inuit people of North America have been classified as 'healthy obese' is that their diet is rich in n-3 polyunsaturated fatty acids (n-3 PUFA), and compared to the general population peoples in Inuit communities have an intake 20 times greater than the general public (Johnson et al., 2009; Lemas et al., 2011). Also, the increased distance from westernized culture (or focus on traditional ways of life) has also been shown to be behind decreased rates of T2D and MetS (Hegele, 1999; Hegele and Pollex, 2005). This sub-study did not record any diet measurements and therefore cannot speak to our sample Gitksan population and its association with dietary habits or westernization.

Increasing age has been reported to increase the risk for T2D development in various Aboriginal peoples (Brimblecombe et al., 2006; Ghosh and Gomes, 2011; Hegele et al., 2000a; Liu et al., 2006). Conversely, a study exploring HbA1c levels in American Indian/Alaskan native adults, HbA1c was seen to decrease as age increased (Gilliland et al., 2002). Furthermore, in study exploring HbA1c levels

within eight New Mexico tribes, individuals aged ≥ 65 had significantly lower HbA1c levels than individuals < 55 years old (Carter et al., 2000). In this sub-study, age was not a statically significant factor concerning mutation status, HbA1c, QTc, BMI and exercise levels: age did not increase HbA1c values, influence QTc length, increase BMI, or effect exercise level variations. This result could solidify the genetic predisposition concerning V205M influence on increasing T2D development risk.

We assessed WC to determine if it influenced HbA1c levels, and the QTc measurement based on previous studies demonstrating significant effects of increasing BMI (and increased T2D development risk) due to elevated WC measurements (Arslan et al., 2010). Our study observed no significant WC effect on any measurements, i.e., WC did not predict elevated HbA1c or elevated QTc. However, our study did reveal that the Gitksan population does indeed have an elevated WC average (111.90 ± 18.04). According to Health Canada, our elevated WC average would put our population at an increased risk for the development of health problems such as diabetes, heart disease and high blood pressure (Health Canada, 2005). It is important to recognize that our population is a greater risk for health concerns according to Health Canada; however, considering that WC did not bear any effect in our population, WC does not seem to predict elevated QTc or HbA1c.

Interestingly, and similar to WC, exercise levels did not influence any anthropometric measurement, HbA1c values or QTc measurements. Exercise levels did not increase QTc or the HbA1c levels. The majority of participants reported a moderate or low physical activity level. However, this sub-study was conducted from September 2011 to March 2012, which are the months of the year where snow

and less physical activity is more common. Exercise levels were also self-reported and may not have properly reflected actual levels. Nevertheless, according to Statistic Canada research initiative concerned with physical activity among First Nations people of Canada, Aboriginal off-reserve peoples and Métis people have been reported to be more likely to be physically active than non-Aboriginal populations, yet chronic conditions within First Nations people is still higher than non-Aboriginal people of Canada (Findlay, 2011). Socioeconomic status and other socio-demographics differences between these two populations have been suggested to be the catalyst for the observed disparity (Findlay, 2011; Hanna, 2009; Reading, 2010). Our results (high proportion of elevated BMI, WC and HbA1c) for self-reported physical activity may be biased due to socio-demographics (no data collected) and to QT patient exercise regimes. Participants with prolonged QT intervals may have altered their physical activity regime due to their sensitive sympathetic nervous triggers. LQTS treatment includes avoidance of QT prolonging drugs, use of implanted cardioverter-defibrillators and/or the use of β -blockers (Jackson et al., 2011). The latter treatment option addresses the avoidance of the cardiac events due the increased sympathetic system activation and its effect on prolonging the QT interval. Theoretically, avoidance of stressful situation or avoidance of heavy physical exertion may have been prescribed to the LQTS patient involved with this sub-study, hence, our majority of low and moderate physical activity levels regardless of mutation status. Nevertheless, this sub-study reveals a lack of association between physical activity (at all levels of exercise) and QTc, HbA1c or mutation status.

Allostatic load implications may have affected (or helped sustain an increased level) the elevated anthropometric measurements: overall obese BMI, overall elevated WC, overall 'at risk' HbA1c values. The genome can be considered as a conduit where environment plays a large role on the observed phenotypes involved with health and disease (Franks, 2011). A relationship does indeed exist between stress and allostatic loads. For example, stress (and its constituents) has been reported to activate early gene expression to activate downstream genes that affect the function and structure of cells (Mansi et al., 1998). Allostatic load implications are most important on stress regulation and the hormones associated with that regulation (McEwen, 2000). Glucocorticoids (GC) have been identified as a key regulator/mediator of stress responses (i.e., GC are up-regulated in a stressful environments) and have implicated in many important metabolic pathways including gluconeogenesis, immune system regulation (specifically with immune system suppression) and transcription suppression/up-regulation. Furthermore, GC (cortisol) has been reported to increase insulin resistance, hypertension, and many other adverse health outcomes (Figure 3.1) (Kotelevtsev et al., 1997). GC is expressed throughout the body and GC activation is mediated via the glucocorticoid receptor (GR). 11β -Hydroxysteroid dehydrogenase type 1 (11β -HSD1) converts inactive cortisone to cortisol (converts 11-keto steroids into active glucocorticoids) whereby increases the GC's local action and concentration (McEwen, 2000; Seckl et al., 2004; Tomlinson and Stewart, 2007).

Recent mice model research concerning 11β -HSD1 has discovered 11β -HSD1 knock-out mice to be resistant to stress-induced obesity and improved glucose

tolerance (Kotelevtsev et al., 1997; Tomlinson and Stewart, 2007). Concurrently, GC have been observed to increase appetite, locomotor activity and food seeking behavior (Tomlinson and Stewart, 2007). To combined research principals together, the stress-mediating steroid hormone GC is up-regulated in cases of stress, which in turn causes adverse health outcomes; GC is converted by the 11β -HSD1 enzyme, and enhanced or increased transcription has been reported to be associated with obesity, T2D and MetS; the allostatic load principle stipulates that short-term homeostasis of stress can, over a long period of time, accelerate disease progression. Throughout this sub-study detrimental environmental issues were being established in the Gitksan territory threatening their natural and physical environment, disrupting traditional procedures and creating even greater divides within the Gitksan people. During the time each participant went through the interview process, individuals were encouraged to talk and feel comfortable. In combination with the continual intergenerational residential school healing and post and neo colonization of European contact, a stressful environment surrounded our population. This stressful environment may have contributed to increase GC expression, up-regulated 11β -HSD1 action, which may also have led to the elevated measures in this sub-study. However, this sub-study did not measure GC levels; therefore, GC contributing to up-regulation of 11β -HSD1 action is only speculation.

There were limitations to this sub-study. Our sample population was underpowered. The predicted power calculated a power of $n= 38$ in each mutation positive and mutation negative. Nevertheless, our statistics reported strong significance and did not included confounding variables. Our sample population was

not a random sample. Our participants were recruited based on their involvement with the original and already well-established research study. Our sample population may be biased due to their involvement and knowledge of LQTS: knowing about LQTS may have affected participant's diet, lifestyles, exercise regime, and frequency of clinic visits. Nevertheless, the high prevalence of LQTS is a well known fact within the Gitksan population and the Gitksan Health Society also promotes our study results to all their contacts and participants. The generalizability of this sub-study to other Aboriginal communities may be limited. The original study conferred specific knowledge to the community at large, each Aboriginal community may be completely different with traditions, life styles and procedures, and our sample was underpowered. Yet, our population was representative of the larger community and of findings do suggest strong implications worth of recognition and action. In the original study and within this sub-study, our researchers have also been aware of the difficulty to not saturate the community with research and to acknowledge the research capacity. We believe that this sub-study did meet its maximum ascertainment without community and individual research fatigue.

Our sub-study was indeed a different type of genetic research project: our results were unknown and there was no assumptions made about the origins of the *KCNQ1* as a 'thrifty gene.' The thrifty gene postulates the reason why some ethnic groups tend towards obesity and diabetes on an evolutionary premise (Neel, 1962). This sub-study does not attempt to answer any question of evolutionary need for the *KCNQ1*: our sub-study attempts to answer objectives based on previous

knowledge concerning possible insulin secretion limitation mechanisms and previous genetic *KCNQ1* studies concerning T2D.

The implications of this sub-study are important and may suggest new perspectives and allow for future research to be created. Due to the risk associated with T2D development with mutation positive individuals, a recommendation (in partnership with the Gitksan Health Society) could be in the form of extended care concerning V205M. This study suggests that if an individual is V205M+ then he/she is almost ten times as likely to develop T2D based on a 'at risk' HbA1c value; however, since we are not follow our participants through time (i.e., a longitudinal study) our results are only interpretation of our results. Yet, if an individual does indeed test positive for V205M, then a follow up with a HbA1c could be suggested. If the V205M mutation confers risk in our sample population, our results suggest that other loss-of-function mutations might also confer risk. Another recommendation could in the form of specific future research. Other studies concerning *KCNQ1* and its association with T2D measured insulin secretion using HOMA as their diagnostic test (Yamagata et al., 2011; Unoki et al., 2008). Using HOMA as another measurement coupled with HbA1c may be a way to address whether insulin secretion specifically is being altered.

In summary, our sub-study suggests evidence that a variation within the *KCNQ1* gene does confer an 'at risk' HbA1c value susceptibility, but no T2D development. It will be important to begin to explore how the V205M mutation exactly has altered HbA1c values, to determine the role of pathogenicity of SNPs/mutations found in *KCNQ1*.

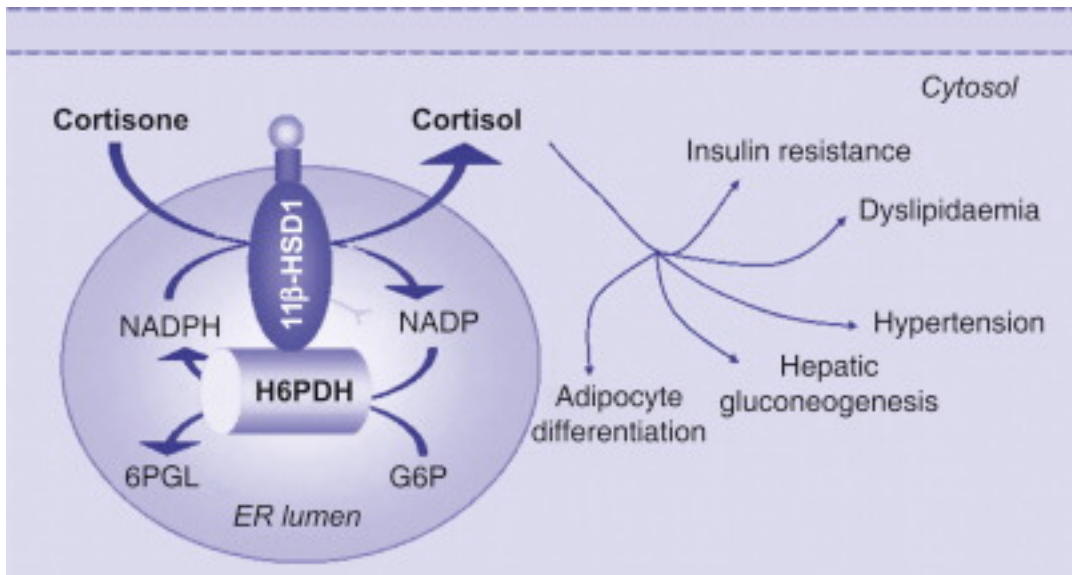


Figure 3.1: 11 β -HSD1 generates active glucocorticoid, cortisol, utilizing the cofactor NADPH. Enhanced activity and expression of 11 β -HSD1 has been implicated in many features of obesity, metabolic syndrome and type-2 diabetes (Tomlinson and Stewart, 2007).

Beta Cell:
In a hyperpolarized state--
V205M proposed action

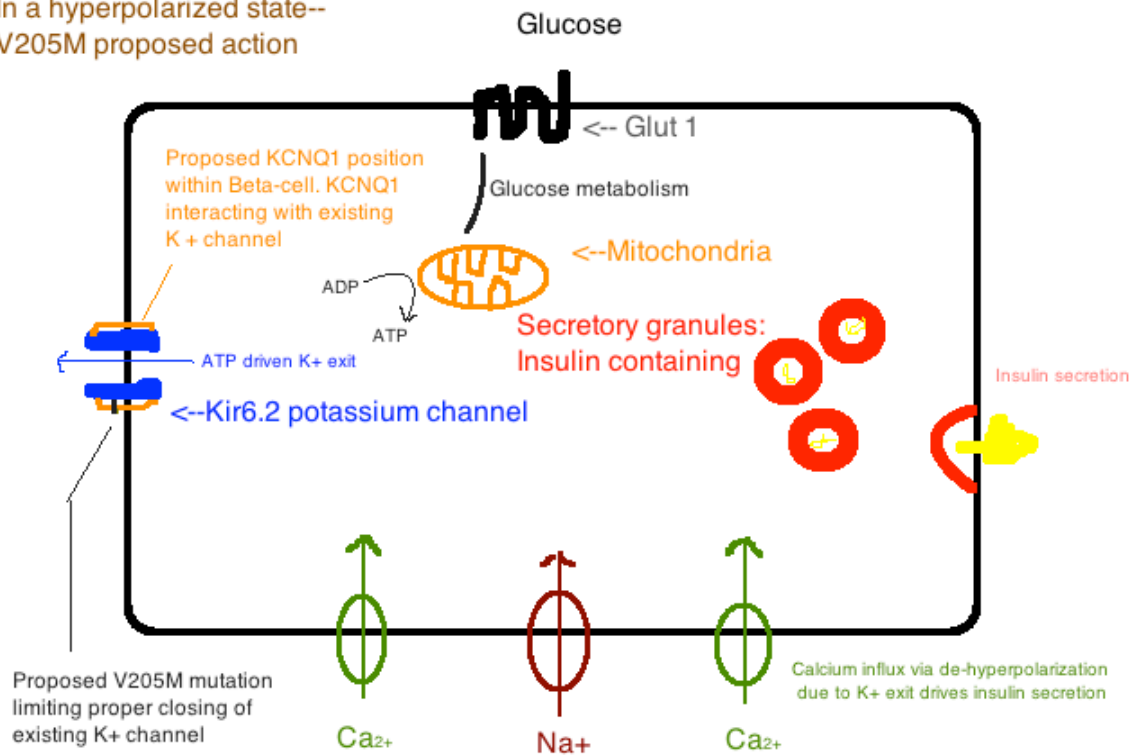


Figure 3.2: Proposed KCNQ1 and V205M action in the pancreatic beta-cell.

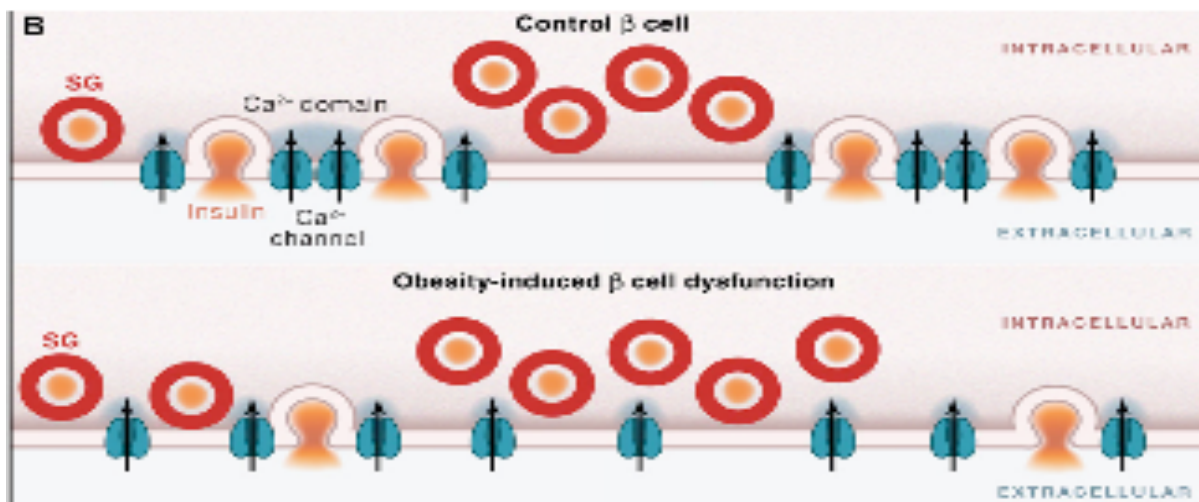


Figure 3.3: Obesity-induced β -cell dysfunction. Ca²⁺ channels cluster when exposed long-term to elevated levels of free fatty acids (FFA) (bottom graph) compared to control β -cell (above graph) (Ashcroft and Rorsman, 2012).

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Appendix

Appendix 1

HNF-1 α

Hepatic nuclear factor-1 α (HNF-1 α) is one of the transcription factors involved in the transcription of hepatic genes including albumin, α -1-antitrypsin, apolipoproteins, and several clotting factors (α - and β -fibrinogen). HNF-1 α regulates genes involved in glucose and fatty acid metabolism, as well as insulin secretion, and is therefore critical for maintaining lipid and glucose homeostasis. It is also expressed in pancreatic β -cells and has been significantly associated with T2D in various indigenous populations: Oji-Cree of Sandy Lake Ontario, Canada (specifically the G319S variant and extensive research with Oji-Cree concerning HNF-1 α), Pima Indians of Arizona, indigenous Mexican, and Antioquian (South America mestizo-Columbia) (Canada: Hegele et al., 1999a; 1999b; Ley, S. H., 2010; Sellers et al., 2002; Triggs-Raine et al., 2002 / U.S.: Muller et al., 2005 / South America: Campbell et al. 2012 / Mexico: Parra et al., 2011). It has been hypothesized that the G319S variant causes T2D susceptibility due to the combination of abnormal splicing and reduced activity of the G319S protein. The G319S variant results in the production of two abnormal transcripts and an alteration in the relative balance of normal splicing products (Harries et al., 2008).

PTP-1B

Protein tyrosine phosphatases play an important role in the regulation of insulin signal transduction, and a number of protein tyrosine phosphatases have

been reported to regulate insulin receptor (IR) signaling both under normal conditions and in the insulin-resistant state. PTP1B has been shown to serve as a negative regulator of IR and IR substrate (IRS)-1 phosphorylation. Several studies, with Caucasian, Danish, and American-Hispanic have demonstrated PTP1B SNP's associated with insulin-resistant states and/or fasting glucose levels (Rondinone et al., 2002; Traurig et al., 2007). However, other studies with French, Chinese, and Swedish populations have seen the opposite non-significant result (Florez et al., 2005; Traurig et al., 2007) Yet, both in the Canadian Oji-Cree and in the Pima Indian populations, non-significant associations to T2D have been studied (Mok et al., 2002; Traurig et al., 2007). Interestingly, Oji-Cree participant with a particular PTP-1B 981T/981C genotype were approximately 40% less likely to have IGT or diabetes; therefore, it was hypothesized that these very preliminary findings suggest that genomic variation in PTP-1B is associated with a reduced risk of diabetes and are consistent with the idea that this protein is important in metabolism (Mok et al., 2002).

PPAR γ

Peroxisome proliferator-activated receptor γ coactivator-1 (PCG-1) is a transcriptional co-activator of peroxisome proliferator-activated receptor γ and α (PPAR γ and PPAR α). PPAR γ plays an important role in glucose and lipid metabolism, insulin sensitivity, insulin-sensitizing drugs, and adipogenesis (Andrulionytè, et al., 2004; Hegele et al., 2000; Muller et al., 2003a & 2003b). Variants in PPAR γ have been found to be associated with T2D (specifically Gly482Ser variant) in Danish and UK populations. However, in the Pima Indians, the

Gly482Ser variant was not seen to be associated with T2D (Muller et al., 2003a and 2003b). Nevertheless, other variants (specifically Pro12Ala) within the PPAR γ have been associated with T2D in Indigenous populations: the early T2D susceptibility in the Oji-Cree people of Sandy Lake Canada and only metabolic predictors of T2D in the Pima Indians of Arizona (Hegele et al., 2000; Muller et al., 2003b). It has been hypothesized that since early metabolic predictors of T2D have been associated with T2D, promoter sequences upstream from the PPAR gene contribute to functional consequences on PPAR and may contribute to T2D phenotypes (Muller et al., 2003b).

11 β -HSD1

11 β -Hydroxysteroid dehydrogenase Type 1 (11 β -HSD1) modulates tissue specific glucocorticoid concentrations: the conversion of inactive cortisone to active cortisol (Nair et al., 2004; Tomlinson et al., 2008). 11 β -HSD1 is expressed in various tissues: liver, adipose tissue, pancreas, gonads, muscle, and brain (Nair et al., 2004). Most studies concerning 11 β -HSD1 have focused on the enzymatic function and/or mRNA levels leading to obesity and T2D. However, a study concerning the Pima Indians of Arizona demonstrated 2 SNP's associated with T2D in the 11 β -HSD1 gene (Nair et al., 2004). Nair et al., (2004) suggested that 11 β -HSD1 is likely to have a complex role in determining adiposity and insulin action due to limited or dysfunctional enzymatic control.

INSRR

INSRR is member of the transmembrane tyrosine kinase receptors--others include the insulin receptor (IR) and the insulin like-growth factor receptor (IGF-1R). It has

been shown that defects in INSRR could contribute to T2D susceptibility in Pima Indians (and Caucasians) in whole genome wide scans (Hanson et al., 1998; Wolford et al., 2001). However, INSRR was shown to have no detectable SNP's contributing to diabetes in Pima Indians (Wolford et al., 2001).

GYS1

The glycogen synthase locus (*GYS1*) is located on chromosome 19q13.3 and has been shown to encode skeletal muscle glycogen synthase, which is the rate limiting enzyme in insulin-mediated non-oxidative glucose disposal.

Polymorphisms within *GYS1* have been associated with T2D in Finnish and Japanese populations (Mayer et al., 1996). Since glycogen synthase is a key enzyme of glucose metabolism, it has been hypothesized that mutations within *GYS1* may contribute to insulin resistance (Kuroyama et al., 1994). Yet, a single Indigenous genetic study (with the Pima Indians of Arizona) found that *GYS1* SNP's were not associated with T2D (Mayer et al., 1996).

TCF7L2

Transcription factor 7-like 2 (*TCF7L2*) encodes proteins that have been implicated in blood glucose homeostasis. *TCF7L2* has been shown to be associated with T2D in various non-Indigenous ethnicities. A Microsatellite (DG10S478) and 5 SNP's found in the *TCF7L2* gene have been found to be associated with T2D in Icelandic, Danish, and American populations (Guo et al., 2007). Most studies concerning Indigenous populations have also found variant associations with T2D (South America: Campbell et al., 2012; Mexico: Parra et al., 2007; Pima Indians: Tong

et al., 2009). However, the Pima Indians have some dichotomy whether TCF7L2 is indeed associated with T2D or not (Guo et al., 2007; Hanson et al., 2007). The mechanism by which TCF7L2 increases diabetes risk remains unknown, but it has been speculated that it could be through regulation of the hormone glucagon-like peptide (GLP-1), which has a primary role in glucose homeostasis (Hanson et al., 2007).

ACDC

ACDC encodes adiponectin which is an adipose tissue derived protein with important metabolic effects: decreased plasma adiponectin levels have been associated with obesity, insulin resistance, and type 2 diabetes (Vozarova de Courten et al., 2005). SNP's found within the ACDC gene have been found to be associated with T2D in Japanese, German, and Caucasian populations (Stumvoll et al., 2002; Vozarova de Courten et al., 2005). In Indigenous populations, decreased plasma levels of adiponectin have been shown to predict the development of insulin resistance and type 2 diabetes in Pima Indians (Lindsay et al., 2002). However, Vozarova de Courten et al., (2005) found ACDC variants to not be associated with T2D, insulin sensitivity or insulin secretion. There is divide between non-Indigenous and Indigenous populations in relation to linkage or T2D susceptibility.

CRP

The pentraxin C-reactive protein (CRP) is mainly produced in the liver and is upregulated by tumour necrosis factor α , interleukin (IL)-1b and IL-6 in response to infection or injury. CRP is marker of an immune system activation and a biomarker

for inflammation. Elevated CRP serum levels has been associated with T2D in both non-Indigenous and Indigenous populations: Caucasians (European and American Europeans), African Americans, and Aboriginal people of Australia and North America (Chan et al., 2011; Shemesh et al., 2007; Wolford et al., 2003). As for a genetic T2D susceptibility variant within the CRP gene in an Indigenous population only the Pima Indians have successfully evaluated a possible SNP that may contribute to T2D susceptibility (Wolford et al., 2003). CRP has been shown to have a heritable component, which would genetically predispose individuals increased CRP levels. It has also been hypothesized that the SNP found to be associated with T2D in the Pima Indian population was found in the promoter region of CRP close to the transcription start site, which could alter function to regulate CRP mRNA expression (Wolford et al., 2003).

PEA15

The phosphoprotein enriched in astrocytes 15 (PEA15) gene encodes a protein kinase C (PKC) substrate is widely expressed, and overexpression has been shown to contribute to impairment of glucose uptake (Valentino et al., 2006; Wolford et al., 2000). PEA15 has been located within chromosome 1q linked with type 2 diabetes in Pima Indians and Caucasians; however, to date, no genetic associations have successfully seen any T2D susceptibility with variants/SNPs within the PEA15 gene in both non-Indigenous and Indigenous populations (Valentino et al., 2007; Wolford et al., 2000).

IL6

Interleukin-6 (IL6) is a cytokine secreted by both immune cells and adipose tissue, and is involved with hepatic acute phase response. Elevated IL6 levels have been associated with obesity and T2DM in both non-Indigenous and Indigenous populations (Vozarova et al., 2003). A study conducted with the Pima Indians have associated a promoter polymorphism to T2D (Vozarova et al., 2003). However, very few studies have investigated T2D associated variants in the IL6 gene (Chan et al., 2011).

TNF α

Tumor necrosis factor-alpha (TNF α) is an inflammatory cytokine produced mainly by monocytes and macrophages. It has also been postulated that TNF α plays a role in insulin sensitivity via down regulation of genes required for normal insulin action or increased free fatty acid (FFA) levels through lipolysis stimulus (Moller, 2000). Elevated TNF α levels have been shown to play a role in insulin resistance in non-Indigenous and Indigenous populations (Chan et al., 2011; Romeo et al., 2001; Zinman et al., 1999). In Aboriginal Australians, TNF α has indeed shown a variant association with T2D, whereas, variants within the Pima Indians have shown the opposite results: no T2D association (Dalziel et al., 2002; Hamann et al., 1995; Romeo et al., 2001). Yet in Chinese, Caucasians and African American no variants have been found to be associated with T2D (Romeo et al., 2001).

ORP15

The human oxygen-regulated protein-150 kDa (ORP15) gene encodes the oxygen-regulated protein, which plays a role in protein conformation (specifically chaperoned protein folding in β cells). ORP15 products play roles in cellular responses to environmental stresses: heat shock proteins, glucose-regulated proteins (GRPs), and oxygen-regulated proteins (ORPs)(Kovas et al., 2002). In the Pima Indians of Arizona, variants were found to be associated with insulin resistance, but lacking T2D associations (Kovas et al., 2002). No other populations were found to be studying ORP15 as a susceptibility gene for T2D.

MGEA5

MGEA5 gene products β -O-linked N-acetylglucosaminidase (O-GlcNAcase), which expressed widely including beta-cells in pancreatic islets. O-GlcNAcase catalyzes the removal of N-acetylglucosamine from glycosylated proteins (which frees sugar moieties). Other studies have shown that high levels of O-GlcNAcase are associated with elevated levels of extracellular glucose and glucosamine (Farook et al., 2002; Meigs et al., 2002; Lehman et al., 2005). A study working with Mexican American found that SNP's found within the MGEA5 were associated with T2D; however, in the Indigenous population of the Pima Indians, no SNP's were found to be associated with T2D (Lehman et al., 2005; Farook et al., 2002).

ATF6

ATF6 is important for protective cell response to accumulation of unfolded and mis-folded proteins in endoplasmic reticulum and disturbances of this process can contribute to beta-cell apoptosis (Meex et al., 2007; Thameem et al., 2006). In an non-Indigenous population of Dutch Caucasians, variants found within the ATF6 were found to be associated with T2D. Moreover, a study conducted with the Pima Indians showed similar results: T2D associations with SNP (Meex et al., 2007; Thameem et al., 2006). Meex et al., (2007) found that the variants found to be associated with T2D were in close proximity to an AATAAA-poly-adenylation sequence, which protects the mRNA molecules from exonucleases and is important to transcription termination. This proximity may have led to transcription termination errors (Meex et al., 2007).

CHRM3

The muscarinic acetylcholine receptor subtype M3 (CHRM3) is a receptor belonging to a larger family of G protein-coupled receptors. CHRM3 functions by binding to acetylcholine for various cellular responses (i.e., potassium channel mediation). CHRM3 is expressed in islet beta-cells and has a role in stimulating insulin secretion (Guo et al., 2006). The only paper done in an Indigenous population demonstrated that a SNP in the CHRM3 gene was associated with early onset T2D (Guo et al., 2006). The SNP found was in upstream from a potential

binding site for the HNF1- α —HNF1- α has been associated with T2D in various populations (Guo et al., 2006).

ACAD10

A dehydrogenase 10 (ACAD10) protein product catalyzes mitochondrial fatty acyl-CoA derivatives in mitochondrial beta-oxidation. Disorders in mitochondrial fatty acid oxidation have been seen to promote insulin resistance in liver and skeletal muscle (Bian et al., 2010a). A single Indigenous study has shown that two SNPs were associated with T2D in Pima Indians (Bian et al., 2010a). Bian et al., (2010a) hypothesized that their study participants were more at risk to develop T2D were due to enlarged adipocytes or limited lipid oxidation.

ASK1

Apoptosis signal regulating kinase 1 (ASK1-- also known as mitogen-activated protein kinase kinase kinase 5 (MAP3K5)) is involved with cellular stress responses and has been shown to affect insulin action in skeletal muscles (Bian et al., 2010b). A single Indigenous study demonstrated T2D association with 3 SNPs found within the ASK1 gene (Bian et al., 2010b). ASK1 has been shown to be associated with GLUT4 (a cell-receptor involved with glucose control); therefore, Bian et al., (2010b) hypothesized that ASK1 variants may have down regulated ASK1 expression and simultaneously down regulating GLUT4, which would have decreased glucose uptake by skeletal muscle.

Ca(v)2.3

Voltage-gated Ca²⁺ channels (Ca(v)2.3, also known as CACNA1E) mediate Ca²⁺ entry into cells in response to membrane depolarization. Specifically, these channels are expressed in neuronal and pancreatic beta cells, and play important roles in the release of insulin (Muller et al., 2007; Trombetta et al., 2012). SNPs in the Ca(v)2.3 gene in the Pima Indians population have been associated with T2D, and other studies with non-Indigenous populations have found variants within the Ca(v)2.3 to be associated with reduced beta-cell function (Muller et al., 2007; Trombetta et al., 2012). Muller et al., (2007) has hypothesized that their variant decreased Ca(v)2.3 levels, which would down regulate insulin action.

PBX1

PBX1 encodes for protein (a transcriptional regulator) that modulates expression of other genes; for example, pancreas duodenum factor 1(PDX1), which is required for pancreatic development in mammals, expression of somatostatin, and insulin genes (Thameem et al., 2001). In the single Indigenous study, 16 SNP's were found to not be significantly associated with T2D (Thameem et al., 2001). In other non-Indigenous studies (European Caucasians) concerning PBX1 associations with T2D found similar results (Duesing et al., 2008).

KCNJ9/ KCNJ10

The KCNJ9 and KCNJ10 genes encode for members of the inwardly rectifying potassium (K⁺) channel family (Kir) located on chromosome 1. This family of proteins plays an inhibitor role potassium transport throughout the nervous system, heart, and pancreas (Wolford et al., 2001). A single Indigenous population has seen a SNP association with T2D with KCNJ9 (Wolford et al., 2001). Similar to KCNJ9, KCNJ10 had similar results (Forook et al., 2002). However, the functional consequences are not known for both genes concerning exact pathogenicity of T2D.

LMNA

The LMNA gene encodes lamins A and C, which make up the nuclear lamina envelope. The proteins of LMNA heterodimerize to make the laminar latticework of the nuclear membrane (Wolford et al., 2001). LMNA has been associated with obesity in the Oji-Cree of Canada (Hegele et al., 2000) and increased adipocyte size in the Pima Indians of Arizona (Weyer et al., 2001). However, in a single Indigenous population study SNP were not associated with T2D in the LMNA gene (Wolford et al., 2001).

DRD2

The dopamine D2 receptor (DRD2) product is a G-coupled receptor expressed in the CNS which inhibits adenylyl cyclase, thereby down-regulating cAMP. DRD2 is also involved with appetite regulation (Jenkinson et al., 2000). Non-Indigenous studies have seen T2D (or obesity) in American Hispanics and American

Caucasians (Comings et al., 1993; Jenkinson et al., 2000). However, a study conducted with the Pima Indians has demonstrated that SNP's within the DRD2 were not associated with T2D (Jenkinson et al., 2000).

PTGS2

Prostaglandin-endoperoxide synthase-2 (PTGS2) gene products involved with inflammation. PTGS2 is also known as cyclooxygenase-2 gene (COX2—key enzyme in eicosanoid metabolism in the inflammation response). Chronic inflammation has been associated with T2D in the Pima Indians and other non-Indigenous studies (Konheim et al., 2003; Vozarova et al., 2002). Konheim et al., (2003) found a T2D association with 2 SNPs found within the PTGS2 gene. Yet, the functional significance of the SNP is not known (Konheim et al., 2003).

IRS1

The insulin receptor substrate-1 (IRS1) is a critical element in insulin-signaling pathways, and mutations in the IRS1 gene have been seen to predispose T2D in various non-Indigenous populations. For example European, North American, and Scandinavian (Burguete-Garcia et al., 2010; Florez et al., 2007). A study with the Pima Indians demonstrated that a SNP found in IRS1 was associated with T2D (Kovacs et al., 2003). Nevertheless, there has been some debate and unclear conclusions whether polymorphisms in IRS1 are indeed associated with T2D (Morini et al., 2009).

DIO2

Thyroid hormones play an important role in glucose metabolism rate and energy balance. The deiodinase gene (DIO2) encodes a deiodinase that converts the thyroid prohormone, thyroxine (T4), to the active triiodothyronine (T3) (Nair et al., 2012). DIO2 has been positively correlated with T2D determinants in studies within Danish, Caucasian, and Brazilian populations (Dora et al., 2010; Nair et al., 2012). However, only until recently has an indigenous population been studied concerning DIO2 as a T2D susceptibility gene. Three SNPs within the DIO2 have been subtly correlated with T2D in the Pima Indians of Arizona; however, the association was weak and may not be a major determinant for T2D (Nair et al., 2012).

ABCA1

ATP-binding cassette transporter A1 (ABCA1) plays a key role in cholesterol efflux: transfer from peripheral cells to lipid-poor apolipoprotein A1 (ApoA1). In pancreatic beta-cells, it is regulated by a transcriptional regulatory network including several proteins involved in lipid and glucose metabolism (Acuña-Alonzo et al., 2010; Villarreal-Molina et al., 2008). Studies with the Oji-Cree of Canada have demonstrated an association with HDL-C (Villarreal-Molina et al., 2008). Both the Pima Indians and Mexican Mestizos have unique variants found within the ABCA1 gene that are associated with T2D not found in any other population and is isolated

to the Americas (Campbell et al., 2012; Acuña-Alonzo et al., 2010). It has been hypothesized that dysfunctional ABCA1 (due to variants) could cause cholesterol accumulation in beta cells in animal models; therefore, beneficial reductions in plasma lipids concentrations may limit beta cell damage and could partially mask elevated plasma glucose levels (Acuña-Alonzo et al., 2010).

PCLO

PCLO encodes a presynaptic cytomatrix protein that functions as a Ca²⁺ sensor in beta-cells that may be involved in insulin secretion and/or insulin action (Ma et al., 2008a). PCLO has been associated with T2D in Scandinavian and other European populations (Zeggini et al., 2008). The only Indigenous population study found a nominal association of variants with PCLO and T2D. Ma et al., (2008a) have hypothesized that the variants may have played a role in limiting insulin secretion.

MGST3

the microsomal glutathione S-transferase 3 (EC.2.5.1.18) enzyme is involved with cellular defense against free radicals and is encoded by MGST3. Elevated glucose in the blood stream may induce generation of oxygen-free radicals by impairing the insulin responsiveness and leading to insulin resistance (Thameem et al., 2003). Yet, in a study working with the Pima Indians, variants found within the MGST3 were not associated with T2D (Thameem et al., 2003).

ARHGEF11

Rho guanine nucleotide exchange factor 11 (ARHGEF11) (also known as PDZ-RhoGEF and KIAA0380) encodes proteins that have putative roles in the insulin signaling cascade, furthermore, it encodes the Rho guanine nucleotide exchange factor which interacts with GTPases such as Rho, that functions as molecular switches to the insulin signaling pathway (Ma et al., 2007). ARHGEF11 variants have had mixed associations with T2D in Chinese and Caucasian populations (Liu et al., 2011). Yet, a study with the Pima Indians have demonstrated a nominal T2D association and variants found in the ARHGEF11 gene (Ma et al., 2007). Ma et al., (2007) have hypothesized that ARHGEF11 may alter insulin-mediated glucose pathways such as glycogen production in the muscles and liver.

KLF11

Kruppel-like factor 11 (KLF11) is a transcription factor for the zinc finger domain family that has been shown to regulate expression of the insulin gene. Variants in the KLF11 gene have been reported to be associated with T2D in French and Northern European population (Neve et al., 2005). However, no association with a variant in KLF11 was found to be associated with T2D in Pima Indians (Ma et al., 2008b).

HLA-DRB1

Major histocompatibility complex, class II, DR beta 1 (HLA-DRB1) plays a central role in the immune system by presenting peptides derived from extracellular proteins. Gene polymorphisms with HLA-DRB1 have studied in non-Indigenous populations like European, Middle Eastern and Chinese (Al-Daghri et al., 2012; Williams et al., 2011; Yang et al., 2007). Interestingly, a protective effect has been seen in the Pima Indians of Arizona: a SNP was associated with increased expression of HLA-DRB1 mRNA and reduced risk for T2D (Williams et al., 2011) The mode of protection is probably caused by increased insulin secretion due to enhanced self-tolerance, thereby protecting against the autoimmune-mediated reduction of insulin secretion.

SIRT1

Sirtuin 1 (SIRT1) is member of a highly conserved region NAD⁺ dependent protein deacetylases (SIRT1-7) which are found in the nucleus, cytoplasm and mitochondria; SIRT1 has been shown to regulate proteins in glucose and lipid metabolism, up regulation of insulin secretion in pancreatic beta cells, and insulin sensitivity in skeletal muscle (Dong et al., 2011). Variants within SIRT1 have been associated with other non-Indigenous populations: Mexican Americans and European ancestries (e.g., Belgian and English) (Dong et al., 2011; Peeters et al., 2008). Dong et al., (2011) have recently found SNP's within the Pima Indians to be nominally associated with T2D. Using mouse models, Dong et al., (2007)

hypothesizes that due to the dysfunctional SIRT1 caused by SNP may decrease glucose-stimulated insulin secretion.

FOXC2

Human winged helix/forkhead transcription factor gene (FOXC2) belongs to the forkhead family of transcription factors. In mice, the role of FOXC2 was found to be involved as a key regulator of adipocyte metabolism (Kovas et al., 2003). The only study working with an Indigenous population demonstrated a lack of association with SNPs found within the FOXC2 to be associated with T2D (Kovas et al., 2003).

FTO

In the last year, many studies have been published concerning T2D susceptibility genes and among many, the fat mass and obesity associated gene (FTO) has been associated in many non-Indigenous populations (Hertel et al., 2011; Rong et al., 2009). Furthermore, non-Caucasian and multi-ethnic populations have been studied investigating a FTO variant positively associated with MetS and obesity: Oji-Cree of Canada, Inuit people of Greenland, South Asian and Chinese ancestries (Al-Attar et al., 2008). Specifically with genetic research concerning T2D susceptibility in Indigenous populations with FTO variants, Rong et al., (2009) (among eight other genes) showed a nominal T2D association but after adjusting for BMI no statistical significance was observed between variants and T2D in the Pima Indians of Arizona.

CDKAL1

CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1) has a protein product that is a member of the methylthiotransferase family—the function is not exactly known. While CDKAL1 has been studied in non-Indigenous populations (Omori et al., 2008), it has also been associated in non-Indigenous populations: Pima Indians, Indigenous Mexican and Antioquian (South America mestizo-Columbia) (Campbell et al., 2012; Parra et al., 2011; Rong et al., 2009). No variants within the CDKAL1 gene have been associated with T2D in the Pima Indians (Rong et al., 2009). However, both Indigenous Mexican and Antioquian (South America mestizo-Columbia) have indeed seen variants within the CDKAL1 gene associated with T2D (Campbell et al., 2012; Parra et al., 2011). It has been speculated that decreased beta-cell function is involved with T2D association observed in European populations (Pascoe et al., 2007).

HHEX

The hematopoietically expressed homeobox gene (HHEX) encodes a member of the homeobox family of transcription factors, which are involved in developmental processes. Whether variants within the HHEX gene are associated with T2D is still unclear throughout literature and between ethnicities. In recent meta-analysis of variants within the HHEX gene and associations with T2D, they found all genetic studies concerning Caucasians and Asian populations did indeed confer risk to T2D (Cai et al., 2011; Omori et al., 2008). Within these non-Indigenous studies, it has been speculated that decreased beta-cell function may be the determinant to T2D

associations (Pascoe et al., 2007). However, in Indigenous populations, only the Pima Indians and Indigenous Mexicans (Teenek, Mazahua, Purepecha peoples) have been studied; both studies show no T2D susceptibility with variants/SNP's within the HHEX (Rong et al., 2009; Vidal et al., 2011).

LOC387761

LOC387761 is a predicted (hypothetical) gene located on chromosome 11p. A study working with a German population has demonstrated that LOC387761 is not associated with decreased beta-cell function and therefore not associated with T2D (Staiger et al., 2007). Furthermore, in Indigenous populations, a study working with the Pima Indians found a similar result as the German study (Rong et al., 2009). Yet, in a study working with Mexican indigenous groups (Teenek, Mazahua, Purepecha, and Yaqui) they found a SNP within the LOC387761 gene conferring T2D risk; they also postulate that this T2D association could contribute to a failure in insulin secretion, thereby increasing the susceptibility to T2D (Vidal et al., 2011). There is still lack of clarity whether LOC387761 confers T2D susceptibility in Indigenous populations.

IGF2BP2

The insulin-like growth factor 2 mRNA binding protein 2 gene's (IGF2BP2) product binds to the 5'-UTR of the insulin-like growth factor 2 (IGF2) mRNAs in its mediation of human growth hormone. Studies working with Indigenous populations have seen a dichotomy of results. Parre et al., (2011) have seen a T2D association

with SNPs in IGF2BP2 in Indigenous Mexicans; however, Rong et al., (2009) has seen the opposite effect. Conversely, Li et al., (2009) have seen an association between IGF2BP2 and body fat, and its effect on insulin resistance that may contribute to diabetes in a Mexican American population. Various other non-Indigenous studies have seen similar dichotomy in results (Omori et al., 2008).

EXT2

The exostosin 2 gene (EXT2) produces a protein that modifies newly produced enzymes and other proteins. Specifically, EXT2 is involved with the modification heparan sulfate (i.e., angiogenesis and blood clotting). Similar to HHEX, all Indigenous studies have seen a lack of T2D association in SNPs found within the EXT2 gene (Rong et al., 2009; Vidal et al., 2011). Moreover, non-Indigenous studies have found lack of T2D associations as well (Omori et al., 2008).

CDKN2B

The cyclin-dependent kinase inhibitor 2B gene (CDKN2B) encodes cyclin-dependent kinase inhibitor, which prevents the activation of the CDK kinases, thereby regulating cell growth proteins. Similar to LOC387761, CDKN2B has a dichotomous characteristic with Indigenous populations and genetic T2D associations. In Pima Indians, a SNP found within CDKN2B has no T2D association (Rong et al., 2009); however, in Indigenous Mexicans, a SNP found within CDKN2B has T2D association (Parra et al., 2011). In non-Indigenous populations (Caucasian and Asian), SNPs within CDKN2B does seem to confer T2D susceptibility (Omori et al., 2009).

MBL2

Moannose-Binding Lectin (MBL2) is involved with the innate immune response. It attaches to certain carbohydrates on microorganisms to activate the complement pathway and begin opsonophagocytosis. It has been shown to be involved with MBL deficiency studies concerning T1D, insulin resistance, rheumatoid arthritis, and obesity in non-Indigenous populations (Muller et al., 2010). Moreover, a Chinese study showed a positive T2D association with SNPs found within the MBL2 gene (Zhang et al., 2011). The Pima Indians have also had a similar results with SNPs found within MBL2 (Muller et al., 2010). In a Native population study, elevated HbA1c levels were associated with high serum MBL2 levels (Best et al., 2009). Yet, the pathogenicity of MBL2 and the underlying physiologic mechanisms for T2D susceptibility are unknown (Muller et al., 2010).

PCK1

The phosphoenolpyruvate carboxykinase gene (PCK1) encodes phosphoenolpyruvate carboxykinase, which is a key enzyme in hepatic gluconeogenesis: PCK1 converts oxaloacetate into phosphoenolpyruvate and carbon dioxide. Variants in PCK1 with an association with T2D has been studied in two Aboriginal populations of Canada: Oji-Cree of Canada (Hegele et al., 2005), and the Canadian Inuit (Cao et al., 2004). PCK1 has also been studied in other non-Indigenous populations as well (Cao et al., 2004; Wegner et al., 2006). The

pathogenicity or mechanism for T2D in humans is not well understood (Cao et al., 2004).

KCNQ1

The *KCNQ1* gene encodes the I_{Ks} (Slow Delayed Rectifier K⁺ current) which is an ion-channel responsible, in part, for the late repolarization phase of the cardiac AP and regulates AP duration. Parra et al., (2011) has demonstrated that SNPs within the *KCNQ1* gene are associated with T2D risk in an Indigenous Mexican population. In addition, Campbell et al., (2012) have seen similar results with an Antioquian (South America mestizo-Columbia) population. SNPs *KCNQ1* has also been reported to be associated with T2D in various non-Indigenous populations (*please refer to **KCNQ1 and T2D susceptibility***) Furthermore, the SNP found within the Indigenous Mexican population (rs2237892) is the same SNP found in one of the original Japanese studies (Parra et al., 2011; Yasuda et al., 2008). The exact mechanism for T2D susceptibility is unknown.

RBMS1 and ZNF239

RNA-binding motif, single-stranded-interacting protein 1 (RBMS1) encodes proteins which bind single stranded DNA/RNA, which are involved in DNA replication and gene transcription. Zinc finger protein 239 (ZNF239--also known as MOK2) also encodes a group of DNA/RNA binding proteins involved with the repression of transcription with nuclear components (Dreuillet et al., 2008). SNPs in both genes have been nominally associated with T2D in an Antioquian (South America mestizo-

Columbia) population (Campbell et al., 2012). No mechanism has been explained for the associations between both SNPs and T2D susceptibility.

FABP2

The fatty acid binding protein 2 (FABP2) is an intracellular protein expressed in the villus tips of the small intestine, involved in the absorption and transport of dietary long chain fatty acids (Albala et al., 2007). Various studies have been conducted in both non-Indigenous and Indigenous populations with most studies looking at one common SNP (Ala54Thr polymorphism) found throughout all population. In the former, studies have found the common SNP within the FABP2 to be associated with T2D in Japanese, Mexican Americans, European and various Caucasian populations (Georgopoulos et al., 2002; Galluzzi et al., 2001). Yet, contradictory results have been seen as well in non-Indigenous populations (Albala et al., 2007). A positive association between SNPs in the FABP2 gene and T2D in Indigenous populations: Indigenous Chilean (Abala et al., 2007) and Pima Indians (1995). However, Pérez-Bravo et al., (2006) have seen a negative association between SNPs in the FABP2 and T2D in the same Indigenous Chilean population. Interestingly, Hegele et al., (1997) found the common SNP to be associated with lower 2-h glucose concentrations in Keewatin Inuit. There still seems to be ambiguity between populations and positive vs. negative associations with T2D and genetic variants within FABP2. It has been hypothesized that dysfunctional insulin action and increased triglyceridemia may be playing a role in the mechanism of the SNP within FABP2 (Galluzzi et al., 2001).

ADRB3

β 3-adrenergic receptor (*ADRB3*) encodes a receptor that is expressed in visceral adipose tissue, that plays a role in the regulation of lipolysis, and in the regulation of energy balance (Hegele et al., 1998). Similar to *FABP2*, *ADRB3* has a common SNP (Trp64Arg polymorphism) found in most studies concerning its association to T2D. Many studies have investigated *ADRB3* variant and its T2D association in many non-Indigenous populations, yet inconsistencies are still found (Hegele et al., 1998; Elbein et al., 1996; Silver et al., 1996; Walston et al., 1995). In the Pima Indians, a positive association between the common SNP and T2D was observed (Walston et al., 1995). Yet, in the Oji-Cree people, a negative association between the common SNP and T2D was observed (Hegele et al., 1998). An Aboriginal people in Micronesia was studied as well with negative associations (Silver et al., 1996). The inconsistencies observed in the non-Indigenous populations in also seen in the Indigenous populations. It has been postulated that since *ADRB3* has an important role in lipolysis that the Trp64Arg may accelerate the onset of T2D by altering the balance of energy metabolism in visceral adipose tissue (Walston et al., 1995).

CAPN10

The calpain 10 gene (*CAPN10*) encodes calcium-dependent cysteine proteases. In review study of 26 association studies, Song et al., (2004) observed ambiguity between populations, studies and results concerning variants in the *CAPN10* gene associated with T2D. *CAPN10* has been studied in various populations: American,

European and Asian. Song et al., (2004) concluded that many factors may have played roles in the heterogeneity between association studies: inadequate statistical power, potential gene-gene or gene-environment interactions, publication bias. In the Pima Indians and Canadian Oji-Cree populations, no T2D association was observed with SNPs within the CAPN10 gene (Baier et al., 2000; Hegele et al., 2001).

PC-1

The PC-1 gene (PC-1, also known as ectonucleotide pyrophosphatase phosphodiesterase 1 [ENPP1]) encodes the membrane glycoprotein PC-1, which is a transmembrane glycoprotein and an insulin receptor inhibitor (Tanyolaç et al., 2009). The PC-1 gene variants investigating T2D (or T2D indicators) association in various non-Indigenous populations have observed inconsistent results (González-Sánchez et al., 2003; Grarup et al., 2006; Tanyolaç et al., 2009). Yet, in the Oji-Cree (the only Indigenous population studies concerning PC-1) observed a negative T2D association with variants in PC-1 and T2D (Hegele et al., 2001).

PPPIR3

The PPPIR3 region encodes the skeletal muscle regulatory G subunit of the glycogen-associated form of protein phosphatase 1 (PPPIR3), which may play a key role in muscle glycogen metabolism (Hegele et al., 1998). In the Oji-Cree people of Canada, a PPPIR3 polymorphism has been associated with variation of plasma glucose after a postprandial glucose test, but no T2D association (Hegele et al., 1998). Other non-Indigenous populations have been studied as well, a study

working with a Chinese population, has also seen a similar negative association with T2D result with the same PPPIR3 3'-UTR polymorphism in PPPIR3 (Chen et al., 2004-Abstract only).

PON2

The paraoxonase 2 gene (PON2) encodes a protein expressed intracellular and has a antioxidative properties. PON2 reduces intracellular oxidative stress and prevents the cell-mediated oxidation of LDL-C (Rajković et al., 2011). Similar to PPPIR3, PON2 has been associated with elevated plasma glucose in participants with T2D thereby worsening glycemia, yet no actual T2D association was observed with variants found within the PON2 gene (Hegele et al., 1997, 1998).

NAT2

The N-acetyltransferase 2 gene (NAT2) encodes drug-metabolizing enzyme. Like many other possible T2D candidate genes, the results whether SNPs in NAT2 gene confers T2D is unclear (Semiz et al., 2011). In a recent European study, Semiz et al., (2011) demonstrated a positive association between 2 SNPs within NAT2 that conferred T2D development risk. Yet, in the Oji-Cree people of Canada the opposite result was observed (Hegele et al., 1999). Although some research has been done in both non-Indigenous and Indigenous population, the mechanism of pathogenicity of NAT2 SNPs has not yet been identified (Semiz et al., 2011).

Appendix 2



LQT/Diabetes Study Invitation

Dear participant,

I am writing this letter to tell you about an important study to determine if the same gene change that causes LQTS in the Gitksan also increases the chance of diabetes.

This study is open to all those (with and without the gene change) who are in the LQTS study.

This part of the study is called ***Type II Diabetes and KCNQ1 mutations in First Nations People of Northern British***. Newly published studies have suggested gene changes in KCNQ1, the same gene that causes LQTS increases the chance of diabetes. We are asking whether the gene changes that cause Long QT syndrome in the Gitksan may also increase someone's chances of developing type 2 diabetes. Comparisons of blood sugar levels, and body measurements will be made between those with the known gene changes and those without.

Enclosed with this letter is a flyer that gives more details about this part of the study.

I'd like to introduce Fernando Polanco. He is a new Masters student with our group and will be in Hazelton conducting this study. He grew up in Terrace, so is happy to be returning to the region to help with this study where he will reside at the Wrinch Memorial Hospital residence.



A follow-up phone call will be made by Fernando to talk to you more about this part of the study. In the mean time, if you want to learn more about diabetes or if you are interested in participating please contact **Kirsten Bartels** (Genetic Counsellor, Research Assistant) at our toll-free number: **1-888-853-8924** or **Betty Thomsen** (Diabetes Nurse Educator) at the Wrinch Memorial Hospital 250-842-4619.

It is your choice whether you want to be involved in this part of the study or not. If you are not interested, please let Fernando know when he calls, or feel free to contact Kirsten Bartels at the toll-free number listed above.

Thank you for your participation as we try to understand how the gene for LQTS affects the heart and health in general.

Sincerely,

Dr. Laura Arbour
Clinical Geneticist/Researcher
Department of Medical Genetics

Appendix 3



ALL SUBJECTS INFORMATION AND CONSENT FORM *[Consent form for competent adults (18 years & older)]*

Type II Diabetes and KCNQ1 mutations in First Nations People of Northern British Columbia

**A sub-study from the original,
The Impact of Long QT on First Nations People of Northern British Columbia**

Principal Investigator: Dr. Laura Arbour (Department of Medical Genetics, University of British Columbia), Medical Sciences Building, Rm 104, 3800 Finnerty Rd, University of Victoria, Victoria, BC, V8P 5C2

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Funding: The Canadian Institute for Health Research

INTRODUCTION:

You are invited to participate in this study as a participant in the Impact of LQT study.

All participants are invited to participate in this sub-study whether they have gene changes or not.

Your participation in this study is strictly voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. Please take the time to review this information, think about it, and talk about it with others before you decide whether you want to participate.

If you wish to participate, you will be asked to sign this form. If you decide to take part in this study, you are still free to withdraw at any time without giving any reason for your decision.

If you do *not* wish to participate, you do not have to provide any reason for your decision and your refusal to participate will not alter your/your child's medical care or the care of your relatives.

BACKGROUND:

We have found that specific changes in the “Long QT 1” or “KCNQ1” gene that predispose to a heart condition called Long QT Syndrome (LQTS) in several Gitksan families. LQTS is a hereditary condition caused by a gene change that sometimes causes the heart to beat irregularly. Symptoms of Long QT syndrome may include fainting, palpitations (heartbeat sensations that feel like your heart is pounding or racing), chest pain, and/or seizures. New research has suggested that some of the same gene changes that cause LQTS may also increase someone's chances of developing diabetes. This sub-study aims to determine whether changes in the KCNQ1 gene found in the Gitksan also increase a person's risk to developing type 2 diabetes (T2D).

To explain this further: your body gets energy by making glucose from foods like bread, potatoes, rice, pasta, milk and fruit. To use this glucose, your body needs insulin which is produced in the pancreas. Insulin is a hormone that helps your body control the level of glucose (sugar) in your blood. T2D is a condition in which the pancreas does not produce enough insulin, or the body does not properly use the insulin it makes. For those with type 2 diabetes, glucose builds up in the blood instead of being used for energy. The same gene which we know causes LQTS in the Gitksan is important in the pancreas and the way insulin is released. We don't know if gene changes in the KCNQ1 gene also have any effect on blood glucose.

Additionally, in Long QT syndrome, a segment of the heart beat (called the “QT interval”, noted on an electrocardiogram, or ECG test) is longer than usual, putting those with the condition at risk for fainting and sudden death. ECGs are done to measure the QT segment. We have also come to learn that diabetes can influence the QT interval and therefore another objective of this sub-study is to compare QT intervals between those who have diabetes and those who do not. QT intervals will be used from previous ECG measurements collected as part of the Impact of LQT study.

It is important that those with gene changes and those without gene changes participate in this sub-study to be sure that accurate comparison of results be made.

WHO CAN PARTICIPATE IN THE STUDY?

We are inviting all participants in the baseline study “The Impact of LQT study”.

WHAT IS THE PURPOSE OF THE STUDY?

This sub-study will explore whether certain gene changes in the KCNQ1 gene increases a person’s risk to developing T2D by comparing blood sugar levels between those with KCNQ1 gene changes and those without.

Another aim of this sub-study is to compare QT intervals between those who have diabetes and those who do not. QT intervals will be used from previous ECG measurements collected as part of the Impact of LQT study.

WHAT DOES THE STUDY INVOLVE?

Your involvement in this study will take about **2 hours**.

If you agree to voluntarily participate in this research, your participation will include:

1. An interview concerning diabetes status, exercise level, and other health related information (about 15 minutes).
2. A blood sample will be taken locally for diabetes evaluation. The blood sample will be analyzed at the Prince George Regional Hospital (PGRH) and an HbA1c test (diabetes evaluation test) will be done on each blood sample. Each blood sample will be destroyed after every test. (Travel and wait time with blood drawing about 1 hour).
3. Weight, height and waist circumference will be measured (about 10 minutes).
4. Medical records related to diabetes status will be reviewed based on the interview information. For pertinent records we may ask for a ‘release of information’ to review your medical history and medications. If you have diabetes, we will request records documenting your diagnosis. All information reviewed will be kept confidential and will not be released to third parties.

No audio-tapes/and-written notes, observations/ will be taken.

WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

- 1) The possible risks of a blood test include pain, swelling, bruising and/or infection at the needle site. There is also a risk of lightheadedness or fainting.
- 2) HbA1c is used as a diagnostic measure, which reveals an increase in measured blood glucose. All results will be explained through the team genetic counselor under the supervision of Dr. Laura Arbour. If a participant does not know they have an increased glucose level or has not yet been diagnosed with T2D, the knowledge of an increased HbA1c may come as a surprise and cause concern. The United Church Health Services-Wrinch Memorial Hospital (2510 Highway 62, Hazelton BC, V0J 1Y0—phone number: 250-842-5234) has agreed to provide a contact for participants who do not have a family physician and want one, who want to follow up on possible treatment options, or for more information.
- 3) Since all Canadians have a right to health care, medical coverage will not be affected by the knowledge of having T2D. All participation is voluntary and you can withdraw from the sub-study at any time.

WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING?

- 1) Nobody knows if you will benefit directly from this sub-study. Benefit from this sub-study cannot be guaranteed.
- 2) In general, the HbA1c test may reveal an increased risk for diabetes (based on an increased HbA1c level) that was not known before our sub-study. This information may be beneficial to the participant regardless of whether or not they carry a KCNQ1 gene change.
- 3) This sub-study may lead to increased awareness of diabetes symptoms for people in the future who learn they carry the gene changes in the KCNQ1 gene that put them at increased risk for T2D.
- 4) Health care providers will potentially be better informed as to how many people of Gitxsan ancestry are at an increased risk for T2D so that proper health services can be put in place.
- 5) Health care providers will potentially gain a better understanding of a possible relationship between T2D and Long QT syndrome in the Gitxsan community.

If the information learned from this sub-study is important for your health, with your permission we will release it to your doctor and nurses at the health centres. This would help inform your doctor about your diabetes status and organize follow-up, intervention and treatment if appropriate.

WILL MY PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be protected. No information that discloses your identity will be released or published without your specific consent. However, research records and medical records identifying you may be inspected in the presence of the Investigator or her designate by representatives of Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

The data collected from this study will also be used for the completion of Fernando Polanco's Master thesis. Thesis data will be available on the internet after completion (intended completion date is Sept 2012). However, no information that discloses your identity will be released or published without your specific consent and no records that identify you by name or initials will be allowed to leave the investigators' offices.

If any information is presented or published for other health care professionals, we will not include information that could reveal the identity of study participants. Non-identifying codes will be used instead of names. However, after discussion with community research advisors, it was agreed upon that your community 'the Gitksan community from Hazelton' can be named. Any publications will be reviewed by the Community Research Advisory Committee and the Gitksan Health Society before being finalized.

It is expected that this study will take about 2 years to complete. Every year, the progress to date will be summarized and distributed to you and your doctor(s) with our annual update sent to all LQTS participants. A copy of the report will also go to the Gitksan Health Society. No individual information about genetic predisposition will be included in the report to the Gitksan Health Society. We will also summarize the results and send a final report to all participants of the sub-study. Any publications that come from this sub-study will be sent to all participants.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, please contact Dr. Laura Arbour or one of her associates on their toll-free line: **1-888-853-8924**.

If you have any concerns about your treatment or rights as a research subject you may contact the Research Subject Information Line at the University of British Columbia by e-mail at RSIL@ors.ubc.ca or by phone at (604) 822-8598

OR the Human Research Ethics Office at the University of Victoria (250-472-4545 or ethics@uvic.ca).

CONSENT TO PARTICIPATE:

This consent form is *not* a contract and you are *not* waiving any of your legal rights as a result of signing this form.

- 🍏 I have read and understood this consent form.
- 🍏 I have had enough time to consider the information provided and to ask for advice if necessary.
- 🍏 I have had the opportunity to ask questions and have had all my questions answered.
- 🍏 I understand that my participation in this study is entirely voluntary and I am free to refuse to participate or to withdraw from this study at any time without changing in any way the quality of medical care that I receive.
- 🍏 I understand that if I withdraw from the study, the information collected up until that time will be used in the analysis of the study, unless otherwise stipulated by me.
- 🍏 I understand that there is no guarantee that this study will provide direct benefits to me.
- 🍏 I understand the possible harms/side effects of participating in this study.
- 🍏 I understand that all of the collected information and my DNA sample will only be used for the purposes of this study.
- 🍏 I understand that all of the personal information collected will be kept confidential. However, I can give permission for the study results to be shared with my doctor.
- 🍏 I have been told that I will receive a dated and signed copy of this form.

I freely consent to participate in this study as discussed with me and described above.

Study Subject's Printed Name Date	Signature	
Witness' Printed Name Date	Signature	
Printed Name of Investigator/ Date Designated Representative	Signature	

Attn: Kirsten Bartels / Dr. Laura Arbour
Medical Sciences Building, Room 104
3800 Finnerty Road
University of Victoria, Victoria BC V8P 5C2
Phone: 1-888-853-8924 Fax: (250) 472-4283

AUTHORIZATION TO RELEASE HEALTHCARE INFORMATION

Patient's Name: _____

Date of Birth: _____

Previous Name: _____

I authorize:

(names of all doctors' offices, clinics, or hospitals holding medical records)

to release the following information to Dr. Laura Arbour at the University of Victoria (see above fax # and address) for the purpose of participating in the research study entitled, "*Type II Diabetes and KCNQ1 mutations in First Nations People of Northern British Columbia*":

All records pertaining to diabetes including glucose tolerance tests, routine blood sugar, HbA1C, medical records pertaining to diagnosis and management

Other: _____

I consent to the use of this information by Dr. Arbour for the purposes of this research study only:

Participant's signature: _____ Date: _____

Representative's Name & Signature, *if needed* (e.g. guardian for minors/ incompetent patients, or executor of estate for deceased patients):

Date:

Relationship to Participant (e.g. parent, guardian, executor of estate):

Interview Questionnaire

Date of Interview: _____ Interviewer: _____

Height: _____ Weight: _____ Waist circumference: _____

2) Do you have Long QT syndrome? Yes No I don't know

3) How did you find out that you have Long QT syndrome? When was it diagnosed?
What happened to diagnose it in you?

4) Do you have Diabetes? Yes No **If Yes...**
 Which Type of Diabetes? Type 1 *or* Type 2 (late onset) I don't know
 How is it managed? Insulin Tablets Diet/Lifestyle
 How old were you when it was diagnosed? _____

5) Which activities do you participate in? (e.g. swimming, walking, running, skiing, soccer, basketball, yoga).

How often during the week are you physically active (with a cardiovascular activity)?

≥ 30 min, 3 days/week < 30 min, 3 days/week Never/almost never

6) Do you have any other major health problems? Any chronic conditions? (Please list) I.e., Lupus, cardiovascular disease

7) What information would you like to know about Long QT syndrome or diabetes?

8) Do you want to know your personal results at the end of the study? Yes No

9) Can we call you if we need more information? Yes No

Comments: _____
