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Genetic susceptibility for type 2 diabetes mellitus among North American Aboriginals

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Type 2 diabetes (T2D) is a complex human disease which has become extremely prevalent among indigenous populations of Canada and the United States in recent decades. T2D is etiologically complex and refers to a group of disparate metabolic diseases, having major genetic and environmental risk factors. It is believed that a combination of genetic susceptibility and lifestyle changes among indigenous people are to blame for the recent diabetes epidemic. Hypotheses for possible thrifty genotypes and phenotypes have been proposed to explain the causes of the high incidence of T2D in North American Aboriginal populations. Non-genetic factors such as income, living conditions and crime rates also show evidence of affecting T2D risk among Aboriginal people through physiological stress mechanisms. Recent advances in genetic technology have facilitated the identification of a number of gene variants that show positive predictive and diagnostic value for T2D. One of these genes is specific to a group of Aboriginal people in Canada and its occurrence is consistent with the thrifty genotype hypothesis. Identification of susceptibility genes can provide researchers with a starting point for understanding the specific metabolic processes responsible for causing T2D in different populations. This information can be used for producing methods of therapeutic intervention in the future. In the meantime, reducing environmental risk factors for T2D through lifestyle changes remain an important means of preventing the expression of the disease phenotype in Native American and Canadian Aboriginal people.

Key words: Type 2 diabetes, Aboriginals, North America, genetic and non-genetic factors.

INTRODUCTION

Clinical description of diabetes

Diabetes is not a simple disease. It has numerous causes and manifestations, all with the common feature of chronic elevated plasma glucose levels (ADAM Medical Encyclopedia, 2011). Four categories of diabetes have been classified by the United States National Diabetes Data Group and were later accepted by the World Health Organization (WHO). They include type 1 or insulin dependent diabetes mellitus (T1D), type 2 or non-insulin dependent diabetes mellitus (T2D), gestational diabetes (GDM), and diabetes associated with rare inherited syndromes and other disease states (ADAM Medical Encyclopedia, 2011; Szathmáry, 1994). Among these forms of diabetes, T2D is exceedingly the most common, with recent estimates showing that more than 90% of the over 18 million North Americans with diabetes have T2D (Center for Disease Control and Prevention, 1997; Inzucchi and Sherwin, 2005).

Like other forms of diabetes, T2D and T1D are typically caused by a disruption in one of a number of molecular signalling pathways involved in glucose metabolism. The major metabolic defects characterising T2D are resistance of the liver, muscle and peripheral tissues to circulating insulin for glucose uptake, and β-cell insensitivity to glucose for insulin production (Szathmáry, 1994; Surwit and Schneider, 1993).

Insulin is a hormone produced by the pancreas in response to stimuli such as the absorption of ingested glucose or protein into the blood (Szathmáry, 1994). Insulin regulates carbohydrate metabolism by signalling liver and muscle tissues to take up glucose from circulating

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blood and store it as glycogen. Insulin also suppresses the release of glucagon, thus inhibiting the use of fat as an energy source (Szathmáry, 1994). For some patients with T2D, insulin secretion is greater than normal and for others it is compromised (similar to T1D). For those who experience insufficient insulin secretion from the pancreas in response to glucose stimulation, peripheral tissue insulin resistance may only be minimal (Banerji and Lebovitz, 1989). With T1D, insulin is produced by the β-cells of the pancreas at below normal rates or not at all. This reduction in insulin secretion is induced by an auto-immune process, where the body's immune system targets and destroys the insulin-producing β-cells of the pancreatic Islets of Langerhans (Surwit and Schneider, 1993; Altmüller et al., 2001).

The different forms of diabetes have similar long-term complications which are related to the damage of organs and blood vessels from chronic hyperglycaemia, as the liver over secretes glucose into the blood because of disrupted insulin signalling (Szathmáry, 1994). These complications include cardiovascular disease, end-stage renal disease, retinopathy, leading to blindness and gangrene of the extremities (Wetterhall et al., 1992; Young et al., 2000). Additionally, glucose toxicity may eventually destroy the insulin secretory capability of the pancreas and contribute to insulin resistance in other tissues, further impairing glucose metabolism (Kajimoto and Kawamori, 2002; Leahy, 1990; Diabetes and Geneics Initiative, 2007). Because diabetes is a chronic disease, the rate and severity of complications generally rises as the age of onset decreases (Lillioja and Wilton, 2009). Living with these complications means that many patients suffering from diabetes will experience pre-mature death or disability as well as a compromised quality of life (Young et al., 2000).

Genetic complexity

The multifactorial nature of diabetes is a major cause of its scientific complexity. Many different genes must function correctly for all of the cellular signalling pathways involved in glucose metabolism to work properly. Therefore, diabetes may be defined by a number of subtly different phenotypes, all created by various genetic abnormalities (Lillioja and Wilton, 2009; Busch and Hegele, 2002). T2D, which is often viewed as a single disease, is actually caused by a number of distinct meta-bolic defects which all result in similar symptomatic features.

Many characteristics of T2D make it a difficult disease to understand genetically. First of all, it is phenotypically complex. There are different clinical forms of diabetes with varying ages of onset, insulin secretion and insulin resistance. Insulin resistance is also something which can be caused independently by environmental agents (diet) or by one or more genetic mutations (phenocopies) (Altmüller et al., 2001; Hattersley et al., 2009; Haman et al., 2010).

Gene-environment interaction adds to the etiologic complexity by reducing the experimental association be-tween the disease phenotype and susceptibility genes (Hauser and Boehnke, 1998; Weeks and Lathrop, 1995). Additionally, genes may have incomplete penetrance, meaning that individuals who are genetically predisposed may fail to express the disease phenotype altogether (Altmüller et al., 2001; Hauser and Boehnke, 1998). Epigenetic effects, parental-origin-specific effects, and epistasis can also hide the connection between genes and their phenotype, making it more difficult for re-searchers to detect variants associated with the disease (Altmüller et al., 2001; Ahlqvist et al., 2010).

Finally, T2D frequently has a late age of onset and a high population frequency, making it challenging to study using traditional genetic analysis methods (Hauser and Boehnke, 1998). In spite of all these convoluting factors, researchers have succeeded in identifying a number of gene mutations that are associated with different forms of diabetes and increase susceptibility to the disease (Altmüller et al., 2001; Hattersley et al., 2009; Perry and Frayling, 2008).

EXPERIMENTAL METHODS

The method traditionally used by researchers for locating genes implicated in human diseases is positional cloning (Altmüller et al., 2001). Positional cloning begins with the identification of a chromosomal region which is transmitted in families along with the disease phenotype. This is achieved by evaluating family units having affected members (for example, affected sibling pairs) with evenly spaced markers positioned across the genome. These markers are then compared to identify the chromosomal regions that consistently segregate with the disease (Hegele, 2001). Positional cloning is used to identify sequence variants from coding or controlling DNA segments associated with the disease phenotype (Altmüller et al., 2001). This method has helped to find the genes responsible for diseases that have simple Mendelian inheritance, such as cystic fibrosis (Zielenski and Tsui, 1995). However, the large amount of data generated from whole genome scans is difficult to synthesize and interpret for complex human diseases like diabetes.

Positional cloning studies have identified T2D susceptibility loci scattered all throughout the human genome. Unfortunately, only a few of these results could be reproduced in later experiments (Altmüller et al., 2001; Perry and Freyling, 2008). The difficulty in replicating experimental results indicates limitations in the linkage analysis techniques for multi-genetic diseases with multiple co-located independent susceptibility genes (Altmüller et al., 2001). Individual positional cloning studies have lacked the power to consistently identify specific gene loci associated with T2D, and this is likely related to the disease's genetic heterogeneity.

With the completion of the Human Genome Project in 2003, genome-wide association (GWA) studies have be-come the most popular and successful method used to identify genes and mutations associated with T2D (Perry and Freyling, 2008). Most GWA studies are non-hypothesis-driven and use brute force methods to analyze hundreds of thousands of single nucleotide poly-morphisms (SNP's) across the entire genome to find association with the disease phenotype (Perry and Frayling, 2008; National Human Genome Research Institute, 2011). The use of new technologies like DNA chips allow thousands of DNA samples

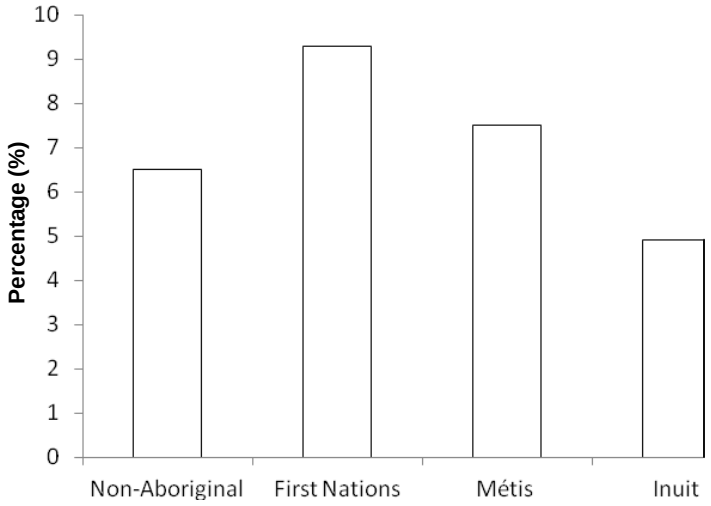

Figure 1. Percentage of Canadian individuals diagnosed with diabetes, organized by Aboriginal identity group, off- reserve population aged 20 and older.
Sources: Aboriginal Peoples Survey (2006), Canadian Community Health Survey (2007), cycle 4.1. (Garner et al., 2010).

INCIDENCE OF DIABETES AMONG ABORIGINALS AND NATIVE AMERICANS

Prevalence of diabetes in Canada and the United States

In 2006, it was estimated that approximately 2 million Canadians, equalling 6.2% of the total population, were living with diagnosed diabetes (Public Health Agency of Canada, 2009). At the same time, about 18 million people in the United States were living with diabetes, with one-third of these cases undiagnosed and 90 to 95% being T2D (Centers for Disease Control and Prevention, 2006). It is expected that one-third of American children born in the year 2000 will develop diabetes in their lifetime (Centers for Disease Control and Prevention, 2006).

Within Canada, the highest prevalence's of diabetes are found in the south, where a large portion of the Euro-Canadian population resides, making latitude a significant predictor of disease risk. In fact, age-standardized diabetes rates for Aboriginal populations in the Northwest Territories, the Yukon Territory, and British Columbia were lower than the national average (Szathmáry, 1994), with the Inuit being the only large group of Canadian Aboriginal people having diabetes prevalence rates lower than the rest of the country (Public Health Agency of Canada, 2003). The prevalence of diabetes among different Canadian groups is shown in Figure 1 (Garner et al., 2010).

Rising rates of diabetes among North American indigenous peoples

Not all North American indigenous people have shown higher morbidity for diabetes than European- or African-derived citizenry, however, this disease was rarely observed among Aboriginal populations prior to 1940 and its incidence has been clearly increasing since the 1960's (West, 1974; Young, 1993). This trend is evident among indigenous populations living in other parts of the world as well, including Micronesians and Polynesians (Zimmet et al., 1990), Australian Aborigines (O`Dea, 1991), and the people of Papua New Guinnea (Martin et al., 1980).

In the 1970's, a global health survey identified the emerging epidemic of T2D in North American Aboriginals (Young et al., 2000). This epidemic is simultaneous with rapidly rising rates of diabetes among the North American population in general (Figure 2), however, the disease is especially prevalent among a number of Canadian First Nations and Native American populations. Statistics from the First Nations Regional Longitudinal Health Survey (2002, 2003) have shown that Aboriginal women and men living on a reservation had about 4 times greater risk of death due to diabetes than other Canadian adults (Reading and Wien, 2005). Furthermore, diabetes rates in selected Aboriginal populations, including Algonquin reserves in north-eastern Quebec (Delisle and Ekoe, 1993) and Oji-Cree of Sandy Lake, in north-western Ontario (Harris et al., 1997) have reached up to 25% in all adults and 80% in targeted age groups.

Incredibly, the Oji-Cree people of northern Ontario have actually been recorded to show approximately 40% prevalence of T2D (Hattersley et al., 2009). This was over six times higher than the prevalence of T2D in the general Canadian population and was found to be the third highest prevalence recorded for any population in the world (Harris et al., 1997). Even more remarkably, diabetes was virtually non-existent as a medical diagnosis

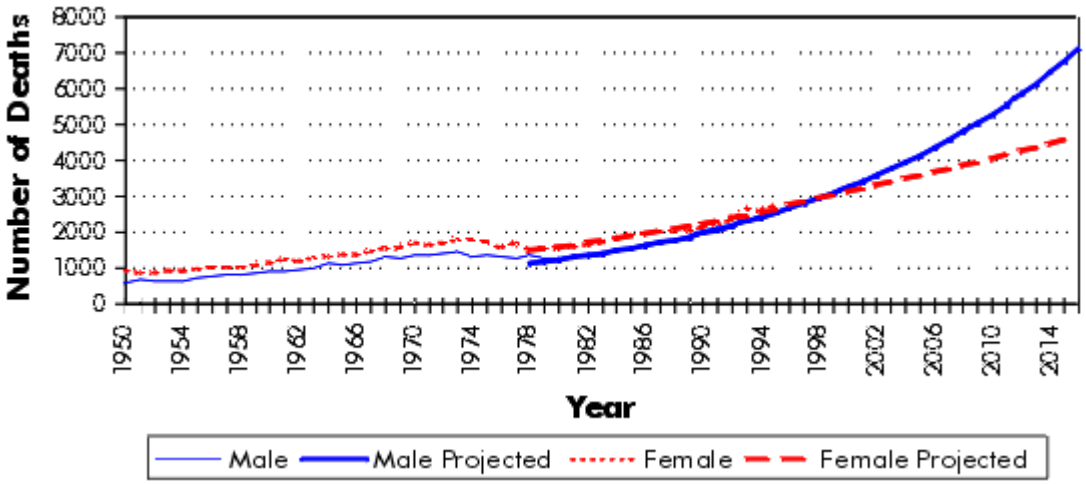

Figure 2. Number of Canadian diabetes deaths (1950 to 1995) and projections to year 2016, by gender. Projections based on deaths from 1978 to 1995. Source: LCDC (1998) - using Statistics Canada Mortality Data (Public Health Agency of Canada, 1999).

among this group; 70 years ago (Harris et al., 1997;

Young et al., 1990). The highest known rates of T2D in the world are found in the American population of Pima. Indians of the Gila River community in Arizona have, with an almost 20-fold increased incidence of T2D, compared to a typical American population (Knowler et al, 1978). The surprising prevalence of T2D among these indigenous populations suggests that these people carry some sort of endogenous susceptibility to the disease.

HYPOTHESES FOR DIABETES RISK IN INDIGENOUS POPULATIONS

Thrifty genotype hypothesis

The high morbidity of T2D among many Aboriginal populations appears to indicate a genetic predisposition to diabetes (Hegele, 2001). Because of the short time period involved and the size of the population affected (geographically and numerically), the genetic factors of this predisposition cannot reasonably be explained by recent mutations in the genomes of Aboriginal people. These gene variants must have been selected for (or at least, not selected against) a long time ago, when the gene-environment interaction resulted in an advantageous or neutral phenotype. One hypothesis which attempts to explain this situation is the thrifty genotype hypothesis.

The thrifty genotype hypothesis was first proposed in 1962 by population geneticist James V. Neel (1999). The theory behind the thrifty genotype is that populations native to North America had to genetically adapt to "feast and famine" conditions. These conditions would have resulted in the selection of alleles enabling the rapid Hyphen not necessary of insulin in response to rising glucose levels, thus facilitating fast storage of glucose as triglycerides (Neel, 1999). With modern conditions of relatively constant nutrient abundance and a high glycemic load diet, this physiological response became maladaptive, resulting in hyperinsulemia, insulin resistance, hyperglycemia, obesity and diabetes (Young et al., 2000). The thrifty genotype hypothesis is a fairly well accepted expla-nation for the observed differences in diabetes prevalence's between Aboriginal and non-Aboriginal people, and it has been cited frequently in literature (Young et al., 2000; Hegele, 2001; Hales and Barker, 1992; Norman et al., 1997; Poudrier, 2007). However, this theory has been criticized for a number of reasons.

A major point of contention rests in the assumption that carbohydrate food sources comprised a large enough portion of the traditional Aboriginal diet to justify a genetic adaptation. The hypothesis that the initial populating of the Americas occurred through migrations from north-eastern Asia, across Beringia and into north-western North America is well established in the scientific community (Stinson, 1992; Wendorf, 1989). This migration required the cold climate of the last ice age and meant that early Paleo-Indians, who would later populate the rest of the Americas, had to adapt to arctic and subarctic environments (Wendorf, 1989). Therefore, high plasma glucose levels would not have been a likely event during the early periods of migration to the Americas because the diet of these Paleo-Indians would have resembled the traditional diets of modern Inuit people. These diets are high in fat (83 to 88% of total calories) and protein (11 to 15% of total calories) but low in carbohydrates (0 to 2% of total calories) (Westman et al., 2007).

This first criticism would suggest that if the selection of "thrifty genes" occurred, it did not likely happen early in the populating of the Americas and was more likely to

develop when people began living in more moderate environments and were able to use agriculture for food production. These people would have had higher carbohydrate diets and were also more likely to experience the "feast and famine" conditions believed to be the stimulus for thrifty gene selection. However, it is important to note that these carbohydrates would have had a very low overall glycemic load compared to modern Western diets (Stinson, 1992). This means that the foods consumed did not create large elevations in plasma glucose levels and the resulting insulin spikes that are common with modern diets. Thus, if the hypothesis is true, we would expect to see more genes associated with diabetes and higher rates of T2D among Aboriginal populations living in moderate climates, where there were greater selective pressures for "thrifty genes", compared to populations living in contemporary arctic and subarctic regions. The differences in morbidity supporting this hypothesis have been observed in literature (as seen in Figure 1) (Public Health Agency of Canada, 2003), however, there are not yet any published studies comparing the prevalence of diabetes susceptibility genes between Inuit and southern Aboriginal populations.

Critics have also disputed the thrifty genotype hypothesis based on the fact that the survival advantage conferred by rapid insulin secretion, to avoid energy loss through glycosuria, would require insulin sensitivity in peripheral tissues to be maintained. This necessity would make the progression to T2D through the expression of "thrifty genes" unlikely and would require a different ultimate explanation for the recent increased susceptibility of indigenous populations to T2D (Reaven, 1998).

Due to the thrifty genotype hypothesis' apparent shortcomings, a number of modified and alternate explanations exist for the selection of genes which increase the risk of T2D when expressed in contemporary environmental conditions. One example, suggested by Szathmáry (1990), does not presuppose a diet which included excess carbohydrates. This theory better explains genetic adaptations to eating habits of early Aboriginal people living in arctic and subarctic regions, which would increase risk of T2D today. The hypothesis proposes that carbohydrate restriction and high levels of physical activity may have selected for individuals expressing high rates of gluconeogenesis and fatty acid metabolism. These traits can result in elevated resting plasma glucose levels when combined with modern high-carbohydrate diets and increase susceptibility to diabetes (Szathmáry, 1994).

If the genetic mutations increasing diabetes risk occurred this early on, both Inuit and First Nations people should be considered genetically at risk for T2D. The observed differences in prevalence rates between these groups would have to be explained by environmental factors like diet and physical activity levels, with Inuit people maintaining a more traditional diet and greater levels of physical activity, thus not expressing the disease phenotype as highly (Hegele et al., 2000a).

Thrifty phenotype hypothesis

First published in 1992 by Hales and Barker, the thrifty phenotype hypothesis attempts to describe the etiology of T2D without relying in genetic susceptibility. It suggests that inadequate fetal and early post-natal nutrition triggers physiological mechanisms of nutritional thrift. This results in greatly increased susceptibility to T2D later in life because of impaired development of the pancreatic endocrine tissues (Hales and Barker, 1992; Poudrier, 2007). The hypothesis asserts that proper nutrition at these early stages of development is critical for the growth of adequate supplies of pancreatic β-cells and their proper functioning. Reduced β-cell numbers have been observed as a result of protein insufficiency *in utero*, causing insulin deficiency and T2D by mid-adulthood (Hales and Barker, 1992). Like the thrifty genotype hypothesis, the thrifty phenotype hypothesis is supported by the observation of an inverse relationship between rates of Aboriginal diabetes in Canada and latitude (Young et al., 1990), because in locations with lower prevalence of T2D, average protein intake exceeds Euro-Canadian norms (Szathmáry et al., 1987).

SPECIFIC SUSCEPTIBILITY LOCI DETECTED IN ABORIGINAL PEOPLES AND NATIVE AMERICANS

Monogenetic forms of diabetes and the candidate gene approach

Due to the existence of multiple etiologic factors for T2D, the sensitivity and negative predictive value of gene mutations with identified association to diabetes are often low (Hegele, 2001). However, genetic studies have been very successful at identifying the causes of monogenic forms of diabetes (Altmüller et al., 2001). These types of diabetes are the result of inheritance or spontaneous occurrence of a mutation or mutations in a single gene; they are distinct from type 1 and type 2 diabetes and are very rare (Hattersley et al., 2009; Perry and Freyling, 2008).

Neonatal diabetes and diabetes diagnosed within the first six months of life appear to be commonly produced by single gene mutations, with different genes being associated to different subgroups of diabetes. For example, transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM) are often associated with an abnormality in imprinting of *ZAC* and *HYMAI* genes on chromosome 6q, and mutations in the *KCNJII* gene, respectively. In their publication, Hattersley et al. (2009) listed other genes which cause these monogenic forms of diabetes; with the most common mutation resulting in maturity-onset diabetes of the young (MODY) being in the HNF-1α gene (MODY3).

The HNF-1α gene is located at chromosome 12q24 and is expressed predominantly in the liver and kidneys (Winter et al., 1999). Specific mutations in this gene result in the non-insulin dependent diabetes mellitus type I, which is inherited as a monogenic autosomal dominant trait (National Center for Biotechnology Information, 2011). Genes identified in monogenic forms of diabetes, such as HNF1-α, are useful for candidate gene methods of searching for mutations associated with T2D. This is because of the known importance of their products in normal insulin secretion and sensitivity (Perry and Freyling, 2008).

The Oji-Cree of sandy lake, Ontario

Hegele et al. (1990) studied the Oji-Cree of sandy lake in Northern Ontario using positional cloning and the candidate gene approach to identify susceptibility loci for T2D. Candidate genes were chosen based on the known role of their products in carbohydrate and insulin metabolism. HNF-1α was studied as a candidate gene and a novel missense mutation (HNF-1α G319S variant) was found. The diabetes phenotype associated with this mutation did not resemble MODY (maturity-onset diabetes of the young), and was instead characterized by obesity and insulin resistance (Hegele, 2001). This indicates that the insulin secretion defect in HNF-1α S319 carriers is less severe than the HNF-1α mutations of MODY3 and the defective function of HNF-1α S319 is therefore, not uncovered until obesity-related insulin resistance begins to develop (Busch and Hegele, 2002).

Both HNF-1α S319/G319 heterozygotes and HNF-1α S319/S319 homozygotes showed significant odds ratios for having T2D when compared to the normal HNF-1α G319/G319 genotype (1.97 and 4.00, respectively; with 95% confidence interval) (Hegele et al., 1990). It was found that the HNF-1α S319 allele was associated with about 40% of the cases of T2D in Sandy Lake and about 20% of additional cases were accompanied by the PPARG A12 allele, which was also strongly associated with T2D (Hegele et al., 2000b). The absence of the HNF-1α G319S SNP (single nucleotide polymorphism) in other human populations suggests that his mutation is specific to the Oji-Cree. The HNF-1α G319S mutation is one of the most specific genetic tests for T2D ever described in any population (Hegele et al., 2000a). It showed consistent statistical association with T2D (97% specificity for Oji-Cree patients of age 50 or more). It had the ability to act as a predictive test for disease susceptibility (95% positive predictive value for Oji-Cree patients' age 50 or more) and was predictive of the clinical severity of diabetes (Hegele et al., 2000a). Further studies of the sandy lake First Nation, involving larger population sizes, have confirmed the greatly increased risk of T2D for carriers of HNF-1α S319 (Ley et al., 2011). More recently, genome-wide significance has been confirmed for HNF1A variant association with T2D through large-scale association analysis (Voight et al., 2010).

Another interesting discovery in this in the Oji-Cree was the functional R230C variant of the ABCA1 gene. First described in the population for its association with low plasma HDL-C cholesterol level, it is also a factor that can be associated with the development of T2D (Wang et al., 2000; Fagot-Campagna et al., 1997). Its role in T2D risk requires further analysis; however, it is a common variant exclusive to Native American and descent populations. Its presence in both North and South American Aboriginal populations and its potential positive effect on intracellular cholesterol and energy storage make this allele a possible candidate for Neel's hypothesis, probably arising early on founder populations of Beringia (Hegele et al., 1990).

The Pima Indians of Gila river, Arizona

Similar to the Oji-Cree of sandy lake, the Pima Indians of the Gila River community show very high rates of T2D (almost 20-fold increased incidence of T2D compared to a typical American population and the highest reported prevalence of T2D of any population in the world). This has attracted the attention of researchers determined to identify gene variants associated with T2D. A productive long-term relationship between researchers and the Pima Indians has allowed for over 25 years of study into the causes of T2D in this population (Knowler et al., 1978). A number of different gene SNPs sequenced in Pima Indians of Arizona, as well as replicated variants from Caucasian genome-wide association (Caucasian GWA) studies, have been evaluated for association with T2D among this group and some other Native American populations (Nair et al., 2012; Rong et al., 2009; Guo et al., 2007; Bian et al., 2010; Muller et al., 2010; Dong et al., 2011). Most of the associations have been modest, with a few being statistically significant. However, variants of these genes have not yet been described as major risk factors for T2D in this population. So far, no gene variants known to this author have been identified in the Pima Indians that have had similar strength of association to T2D as the HNF-1α G319S variant in the Oji-Cree. The major gene or genes responsible for the extremely high incidence of T2D in this community remain unknown.

Confirmed type 2 diabetes genes

There are currently over 35 independent loci identified through linkage analysis and GWA studies that show significant genome-wide associations with T2D (Voight et al., 2010). This is up from only 18 confirmed genes associated with T2D in 2008 (Perry and Freyling, 2008) and at least one of these variants, G319S of HNF1α, was specific

to a North American Aboriginal population (Hegele et al., 1999). In spite of the numerous discoveries made through GWA studies, currently known variants account for only 10 to 15% of the estimated overall heritability of T2D (Garg, 2011). This is less surprising, considering the small effect sizes of most of the variants identified so far, ORs ranging from 1.1 to 1.3 (Ahlqvist et al., 2010).

Of the genes identified for association with T2D, TCF7L2 has the strongest effect, with a pooled OR of 1.46 for the rs7903146 polymorphism (Cauchi et al., 2007; Cruz et al., 2010). Evidence from meta-analysis has suggested that variants of the TCFL2 gene are involved in about 1/5 of all T2D cases (Tong et al., 2009). Variants at this loci have consistently shown strong association with T2D in many populations (Grant et al., 2006; Mayans et al., 2007; Marzi et al., 2007; Humphries et al., 2006; Vliet-Ostaptchouk et al., 2007; Cauchi et al., 2006; Damcott et al., 2006; Scott et al., 2006; Zhang et al., 2006; Groves et al., 2006; Florez et al., 2006; Chandak et al., 2007; Horikoshi et al., 2007; Hayashi et al., 2007) but TCF7L2 was not found to have a significant association with T2D risk when studied in Pima Indians (Gou et al., 2007). Because most of the previously identified variants are only responsible for small effects in Caucasian populations, the sample sizes from Aboriginal groups must be fairly large in order to provide sufficient power for detecting or excluding their association with statistical significance (Mayans et al., 2007). Perhaps the variants found from GWA studies of Caucasians are responsible for modest increases in T2D susceptibility in North American Aboriginals. But, due to the smaller size of sample populations, the statistical power of these studies has been mostly insufficient to confirm gene association with confidence (Rong et al., 2009).

Additionally, some of the polymorphisms robustly associated with T2D have shown substantial allele frequency differences between population groups (Hayashi et al., 2007; Parra et al., 2007). Loci identified in large GWA studies of Caucasian populations may not have single-nucleotide polymorphisms (SNPs), important to disease risk in Aboriginal groups. This is because low frequency variants which cannot be detected in Caucasian populations may be major factors in disease risk for other populations with different allele frequencies. Thus, genes responsible for T2D risk in Caucasians, which are often used to search for potential SNPs associated with T2D in other populations, may not necessarily be major factors in disease risk for Aboriginals.

The molecular mechanisms responsible for the increased susceptibility associated with many of the confirmed variants remain obscure (Voight et al., 2010). However, a large amount of the known genetic risk for T2D appears to be related to beta cell dysfunction. This is because majority of the identified gene variants associated with increased T2D risk seem to affect insulin secretion (as opposed to other risk factors like insulin resistance or excess hepatic glucose production) (Ahlqvist et al., 2010; Voight et al., 2010; Rong et al., 2009).

CLINICAL BENEFITS OF GENETIC RESEARCH FOR DIABETES IN INDIGENOUS POPULATIONS

According to Statistics Canada, over 1 million people identified themselves as Aboriginal, Métis, or Inuit in the 2006 Census of Population. In the United States, over 5 million identified themselves as American Indian or Alaska Native in the 2010 census (Norris et al., 2012). Between 1996 and 2006, the Canadian Aboriginal population grew at a rate of 45%, much faster than the non-Aboriginal population, which grew at a rate of only 8%. The Aboriginal diabetes epidemic affects a very large number of North Americans and this number is expected to increase. The median age of the Canadian Aboriginal population (27 years) is also lower than that of the rest of the Canadian population (40 years), indicating rises in the proportion of Canadians with diabetes, as these individuals age (Statistics Canada, 2010).

Diagnosed diabetes is known to shorten life expectancy by about 9 years and increase the number of visits to physicians and specialists by about two times compared to individuals without diabetes. Diabetes also dramatically increases the number of hospitalizations for limb amputations, cardiovascular disease and other major complications (Public Health Agency of Canada, 2008). The incidence of coronary heart disease, a condition commonly caused by diabetes, of Northern Ontario Aboriginals has tripled in the two decades between 1980 and 2000; it is now four times more prevalent than in the general population of Ontario (Shah et al., 2000). Finding new ways to prevent and treat T2D (and its complications) will help to decrease the overall burden of this disease on health care systems and is certainly in the interest of medical science.

Research into the molecular basis of this complex human disease has allowed for the identification of genes associated with a number of clinical subgroups of diabetes and has helped to explain some of the phenotypic heterogeneity of the disease for variables such as age of onset and severity (as in the case of monogenic forms of MODY) (Lillioja and Wilton, 2009; Busch and Hegele, 2002; Hattersley et al., 2009; Hegele, 2001; Hegele et al., 1999). With the few T2D susceptibility loci currently identified, geneticists and molecular biologists can now begin to determine the mechanisms by which these genes influence disease risk. Improving our understanding of T2D pathogenesis will also improve our methods of treating or possibly curing its different forms.

Genetic tests remain fairly expensive and their clinical use should presently be limited to individuals who show characteristics of strong genetic etiology for their disease. For example, this includes patients who have familial diabetes with an affected parent or diabetes diagnosed within the first 6 months of life (Hatterskey et al., 2009).

When genetic testing becomes more available, identifying individuals who are at risk of developing T2D can give healthcare providers an idea of the probability of disease onset years before its clinical appearance in a patient, and allow for the selection of treatments most likely to be effective for that particular form of the disease (Poudrier, 2007). This kind of personalized medicine through genetic diagnosis is already possible for specific groups of people like the Oji-Cree, however, the identification of these genes in individual patients does not yet offer much improvement in strategies for treating T2D (Diabetes Genetics Initiative, 2007).

Until these diagnoses become economically feasible, all Aboriginal people should consider taking precautions to the development of T2D (or steps to reduce the severity of existing T2D). This includes, for example, weight reduction (with reduces insulin resistance) and consuming a more traditional diet or maintaining a high level of physical activity (as suggested by the thrifty genotype hypothesis) (Surwit and Schneider, 1993; Hegele et al., 1999). In Australian Aborigines, these preventative measures had the effect of normalizing plasma glucose and insulin levels in individuals with T2D (O`Dea, 1991). These lifestyle changes, therefore, have had documented benefits in other indigenous populations suffering from high rates of T2D and are some of the best methods presently available for reducing diabetes risk.

ENVIRONMENTAL FACTORS INFLUENCING DIABETES IN INDIGENOUS PEOPLES AND SOCIAL ISSUES INVOLVED WITH RESEARCH

Lifestyle and stress

Of the environmental component influencing T2D, the most is lifestyle (Szathmáry, 1994). Lifestyle includes the variable nutrition governed by access to food and cultural eating behaviours, as well as differing levels of activity or energy expenditure between groups of people. Changes in the typical lifestyle of Aboriginal people, from one which was characterized by high levels of physical activity to one which is much more sedentary, have been evident in the past few decades (Hegele, 2001). Studies of Pima Indians have shown elevated rates of T2D in individuals reporting low levels of leisure-time physical activity in their past, a common characteristic among diabetics (Kriska et al., 1993). Many other Aboriginal populations have also demonstrated reduced physical activity in recent years (Young et al., 2000; Hegele, 2001; Norman et al., 1997). It is highly likely that the lifestyle changes among Aboriginal peoples in the past few decades have favoured the emergence of T2D in genetically susceptible individuals and have played a large part in the current disease epidemic (Szathmáry, 1994).

Diet and exercise may not be the only environmental factors which can increase the risk of diabetes; stress may contribute significantly to the pathophysiology of T1D and T2D as well. Stress hormones such as cortisol generally have a hyperglycemic effect, elevating blood plasma glucose through hepatic glucose production, while at the same time reducing glucose utilization by the tissues and increasing lipolysis (Surwit and Schneider, 1993). These mechanisms have clear adaptive benefits in energy mobilization for healthy individuals experiencing stress; however, they become problematic when glucose metabolism is compromised, as in the case of diabetics (Surwit and Schneider, 1993). Sustained elevation of cortisol (an adrenal stress hormone) has also been implicated in the development of abdominal obesity and hyperinsulinemia (Bjorntorp, 1991). Abdominal obesity, also known as central or upper body obesity, is predictive of T2D (Hales and Barker, 1992). Few or no studies have been conducted to identify the relationship between stress and T2D in North American Aboriginal populations; however, it has been hypothesized that individuals exposed to chronic stress may be predisposed to both central obesity and diabetes (Bjorntorp, 1991).

Socioeconomic factors

Recent studies have cast doubt on the thrifty genotype hypothesis's explanation for T2D risk in indigenous people of the Americas (Campbell et al., 2012). Evidence is beginning to support the possibility that differences in T2D prevalence between ethnic groups may be better accounted for by environmental factors than population differences in risk allele frequencies at T2D susceptibility loci (De Ferranti, 2004). A study by Iwasaki et al. (2004) examining sources or stress for Aboriginal peoples suffering from diabetes in Manitoba, Canada identified a large number of individuals as living in marginal economic conditions. From interviews conducted in two Anishnaabe communities of Ontario, Canada, one participant stated: "I think the worst part of it, why people are overeating and not looking after themselves is lack of employment, lack of services, and lack of housing." (Sunday et al., 2001)

This suspicion is supported by Statistics Canada surveys which show Aboriginal people of core working age (25 to 54 years) having 16% lower employment rates than non-Aboriginals (this difference is about twice as large for Aboriginal people living on reservations). In the same age group, the median total annual income of the Aboriginal population was $22,000, which was much lower than the non-Aboriginal population median income of $33,000, with only $14,000 for First Nations people living on a reserve (Statistics Canada, 2010). In 2006, 29% of First Nations people and 45% of individuals on a reserve lived in a home in need of major repairs. A much lower proportion (7%) of non-Aboriginal people were identified as living in homes in need of major repairs (Statistics Canada, 2010). Surveys have also shown that Aboriginal children are more likely to live in large families and live solely with their grandparents. First Nations and

Inuit people are less than half as likely as non-Aboriginals to have a university degree but are more than twice as likely to have less than a high school education. Furthermore, Aboriginal adults are remarkably overrepresented in the Canadian prison population (comprising only 3.1% of the adult population; however, representing 25% of adults admitted to provincial/territorial prisons and 18% of adults admitted to federal prisons in 2007 to 2008) (Statistics Canada, 2010). Finally, a 2004 survey identified Aboriginal people as over three times more likely than their non-Aboriginal counterparts to have been violently victimized in the past year (Statistics Canada, 2010).

All of these statistics point to more stressful living conditions for Aboriginal people and thus an environment of increased risk for T2D. The difference in diabetes prevalence among the Aboriginal and non-Aboriginal populations may be much less surprising when viewed in light of these dramatic differences in their lifestyles and living conditions. Socioeconomic status (SES) has been demonstrated to strongly predict disease risk, with low SES being associated with significantly higher disease risk (Florez et al., 2009). Highly significant correlation between Native ancestry and socioeconomic status (SES) (lower SES correlated with greater Native American ancestry) has been demonstrated in other countries as well, and may help to explain the concurrent significant correlation between Native ancestry and increased rates of T2D (Campbell et al., 2012; Waters et al., 2010). These environmental factors suggest that the actual genetic component of susceptibility to diabetes may be less than originally expected.

When considering variables in epidemiological studies, a great deal of attention is often given to race with the exclusion of other complex and important variables associated with chronic disease. Some of these variables include social class, level of marginalization in society, poverty, lifestyle, and living conditions (Poudrier, 2007). Considering environmental factors in the design of gene studies for T2D may help to increase the power for finding real genetic determinants of the disease by accounting for other major sources of variation associated with the disease onset. It should be noted that racial and geographical grouping of populations should not therefore be discarded; these are some of the few methods available to researchers for separating genetic risk factors among populations in a visible way.

Social issues of searching for type 2 diabetes genes in Aboriginal or Native American populations

There are definite considerations to be made concerning the implications of including race as a genetic risk factor in health discourse. For a group of people who have historically been viewed by the dominant Western society as inferior, searching for biological evidence which may support this idea should be done with care. Researchers must also be cautious not to allow the search for diabetes susceptibility genes to divert attention from important known environmental risk factors facing Aboriginal people in this multi-factorial disease. Finally, researchers must be aware of the terminology they use (for example, First Nations, Métis or Inuit) when describing Aboriginal populations and should avoid over generalizing their conclusions. The indigenous people of North America are both genetically and culturally diverse and this needs to be kept in mind when searching for T2D susceptibility genes.

Conclusions

Understanding the etiology of T2D in North American Aboriginal people has been a challenge for researchers. In spite of great efforts to identify susceptibility loci associated with T2D and other complex human diseases, the specific genetic causes remain to be clearly defined (Altmüller et al., 2001). Only a fraction of the genetic variability associated with T2D can be explained with currently identified susceptibility genes and it is clear that there are still many genes associated with this disease that remain to be found (Lillioja and Wilton, 2009; Perry and Freyling, 2008). Future genetic discoveries will likely hinge on improvements in genetic technologies and studies involving larger populations to find statistically significant results (Altmüller et al., 2001). Further meta-analysis of past GWA studies and the analysis of additional forms of genomic variation (other than SNP's), such as copy number variants (a form of structural variant which is not detected in GWA studies but has known roles in other human diseases) may also help to identify T2D disease loci in the future (Perry and Freyling, 2008).

Modern large-scale GWA studies provide the opportunity to identify completely unexpected genes that are associated with T2D and an understanding of these genes and the function of their products will broaden our awareness of the chemical pathways associated with T2D (Perry and Freyling, 2008). There is great potential for improvement of our knowledge of the pathophysiology of complex human diseases such as T2D through genetic research.

More specific studies of Aboriginal populations will be important for identifying possible "thrifty genes" that are responsible for the current epidemic in T2D among these people. It is unlikely that the identification of a single gene variant will solve this mystery. As was demonstrated by the discovery of the HNF-1α GS319S variant specific to the Oji-Cree, the Aboriginal population should not be viewed as racially or genetically homogeneous (Poudrier, 2007; Hegele et al., 1999). This means it is unlikely that the same T2D risk alleles will be identified in all Aboriginal groups. Any mutations responsible for increased risk of T2D will probably only be present in specific population groups, and identifying these groups

requires a historical understanding of Aboriginal people with reference to their genetic background and how populations moved or merged as a result of European colonization.

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