Chapter 1

INTRODUCTION
1.0 INTRODUCTION

Diabetes mellitus is characterized by abnormally high levels of glucose in the blood. Type 2 diabetes is the most common form of diabetes, which accounts for more than 90% of diabetic population. It is multifactorial in origin, with both genetic and environmental factors contributing to its development (Kahn et al., 1996). The incidence and prevalence of diabetes is rising globally and has become a major public health problem, associated with enormous personal, social, and economic burden in both developed and developing countries. It is posing a serious challenge to human health. Estimates predict that worldwide there are more 150 million people with diabetes and this number will rise to 300 million by 2025 (King et al., 1998). The prevalence of type 2 diabetes vary among the world populations with an incidence of 2.4% in population of European descent (Elbein et al., 1999), 10-15 % in American Hispanics (Hanis et al., 1996, Duggirala et al., 1999, Cox et al., 1999), 35% in Pima Indians (Hanson et al., 1998); 41.3% in Nauruans (McCarty and Zimmet, 1994). India is witnessing a depressing situation due to escalating incidence and prevalence of type 2 diabetes mellitus (T2DM) and its inevitable outcomes of diabetic neuropathy, nephropathy, retinopathy and cardiovascular diseases (Ramachandran et al., 1997). Presently, there are more than 33 million adults with type 2 diabetes in India. This number is likely to increase to 79.4 millions by the year 2030 (King et al., 1998; Wild et al., 2004). The prevalence of type 2 diabetes in Asian Indians ranges from 2.7% in rural India to 14% in urban India and up to 16-22% in the migrant Indians living in Europe or USA or Africa or Fiji (Knight et al., 1992, Dhawan et al., 1994, Simmons, 1995, Chandalia et al., 1999). This increase is of great concern because of high morbidity, mortality, and cost associated with the complications of diabetes (World Health Organization report, 1999). Several previous reports indicate that Asian Indians have high prevalence and an increased susceptibility to T2DM and premature coronary heart disease (CHD) that occurs at least a decade or two earlier than seen in Caucasians (McKeigue et al., 1991, Marita, 1998; Marita et al., 1998, Banerji et al., 1999, Snehalatha et al., 1999, Chambers et al., 2001, Mohan et al., 2001). It is believed that the higher incidence of T2DM could contribute to premature CHD in Asian Indians. However, the traditional risk factor for type 2 diabetes cannot explain their increased risk.
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Many risk factors have been identified which influence the prevalence of type 2 diabetes (Gerich, 1998). Factors of particular importance are a family history of diabetes mellitus, age, obesity, increased abdominal fat, hypertension, ethnic background and lack of physical exercise. Several biochemical parameters have also been identified as risk factors, including fasting hyperinsulinaemia, increased triglycerides, decreased HDL-cholesterol and increased LDL-Cholesterol levels (DeFronzo, 1997b).

Type 2 diabetes exhibits familial predisposition, indicating strong genetic components associated with the susceptibility to the disease. Several genes are involved in pathogenesis of type 2 diabetes. Because of its complex nature, type 2 diabetes from different regions or races show heterogeneity in both inheritance and phenotype, and makes identification of susceptibility genes of type 2 diabetes even more difficult. The identification of susceptibility genes responsible for the genetic component of type 2 diabetes could greatly assist in the elucidation of the underlying pathophysiological mechanisms leading to disease and is central to the development of more effective preventative and therapeutic strategies for this condition. Candidate gene studies have identified at least 250 genes that are mainly involved in glucose and lipid metabolism and show modest association to type 2 diabetes susceptibility in different population studies (DeFronzo, 1997a), but the conclusive role of all of these genes in the pathogenesis of type 2 diabetes is still unclear.

Identification of genes influencing individual susceptibility to type 2 diabetes offers a route to better understanding of the molecular mechanisms underlying pathogenesis, a prerequisite for the rational development of improved preventative and therapeutic methods. Finding variations in the genes that make people more susceptible to type 2 diabetes will help us to understand the genetic causes of type 2 diabetes. This is really important, as despite over 150 million people in the world having type 2 diabetes, we still do not know why people develop this condition. This genetic approach may provide new information for diagnostic treatment and prevention.

Our study on the genetics of type 2 diabetes in Asian Indians from North India has public health significance because this disease has reached epidemic proportions in this particular region (Chadha et al., 1990; McKeigue et al., 1991; Misra et al., 2001). There has been no authenticated genetic study of diabetes in this region of the world. A few
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Genetic studies of T2DM among Asian Indians have focused on Indians settled in Europe (Cassell et al., 2000), Singapore (Tai et al., 2003), or the United States (Abate et al., 2003; Guettier et al., 2005), and these studies used Indian samples with diverse socio-religious and ethnic backgrounds. Our study has a unique advantage because it is drawn from a small endogamous caste group from a relatively uniform environment. Khatri Sikh community of Northern India is one of the groups at highest risk of developing T2DM (Sanghera et al., 2006). This suggests that this community may possess unique genetic factors that predispose them to the development of type 2 diabetes.

The main aim of present study was to investigate the factors associated with the risk of type 2 diabetes in Khatri Sikh population of Northern India. This was the first systematic case-control study conducted to identify the environmental factors and genetic variations in the candidate genes of type 2 diabetes in an endogamous population of Northern India.

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