ABSTRACT

Type 2 diabetes is a genetically heterogeneous disorder, phenotypically and pathogenetically, polygenic in nature. Among the Asian countries, India is becoming highly prone to the development of type 2 diabetes. Moreover, India is regarded as the “diabetic capital of the world.” According to the World Health Organization projections, India is expected to hold around 79 million people afflicted with diabetes by the year 2030, and it will be the first of the top 10 countries in the world estimated to have the highest numbers of people with diabetes. The higher prevalence of type 2 diabetes in Indians and in particular, South Indian population is attributed to central obesity, higher adiposity and familial history. It has been reported that the genetic basis of type 2 diabetes in South Indian population also differs considerably from that of the western population.

The pathogenesis of type 2 diabetes involves a complex interplay of a triad of processes, which includes, an increase in insulin resistance resulting in decreased glucose uptake into adipocytes and muscles, a progressive decline in insulin producing pancreatic β–cells, and increased hepatic glucose production. The knowledge of mechanism and sequence with which these abnormalities develop and contribute to the deterioration in glucose tolerance remains unclear, and none of these factors constitutes a single and inevitable cause. The rise in prevalence of type 2 diabetes has led to an intense search for the genetic risk factors of this disease through genome wide association studies across various populations. However, studies in India are limited and also many of the polymorphisms identified to be associated with type 2 diabetes in the western population has an altered effect in an Indian scenario.

In the present investigation, the candidate genes were selected based on previous studies and on their role in biological pathways relevant for determination of body composition and glucose homeostasis. The genetic variation in a number of loci, as assessed by single nucleotide polymorphisms (SNPs), affects the risk of type 2 diabetes. The major goal is to find out the DNA polymorphisms of MTNR1B, G6PC2, GCKR PPARG, IGF2BP2, CDKAL1, GCK, SLC30A8, CDKN2A/B, TCF7L2, HHEX, CDC123-CAMK1D and TCF2 genes, which play a vital role in the process of glucose-stimulated insulin secretion, fasting plasma glucose concentrations and impact on β-cell function and to identify the underlying biochemical factors in type 2 diabetes concerning fasting blood glucose, lipid profile, Adipokines and pro-inflammatory cytokines.
In this study, 687 participants were recruited, in which 341 were nondiabetic controls and 346 type 2 diabetes cases from Mysore district belonging to various communities at high risk for type 2 diabetes and related phenotypes. Standard clinical phenotyping was carried out by classical methods. Anthropometric measurements like height, weight, waist and hip circumference were performed. Blood pressure (systolic and diastolic) of each subject was measured, and blood sample was collected after 12 hours of fasting. Postprandial plasma glucose was measured after 2 hours of administering 75-grams of glucose. The following SNPs (related gene in brackets), already known to be risk loci of type 2 diabetes, were genotyped by TaqMan® SNP Genotyping Assay. They are as follows: rs10830962, rs10830963, rs3847554, rs2166706, rs1387153 (MTNR1B), rs563694, rs560887, rs1402837 (G6PC2), rs1799884, rs730497 (GCK), rs780094, rs1260326 (GCKR), rs1801282 (PPARG), rs4402960 (IGF2BP2), rs10946398 (CDKAL1), rs13266634 (SLC30A8), rs10811661 (CDKN2A/B), rs7903146 (TCF7L2), rs1111875 (HHEX), rs12779790 (CDC123-CAMK1D) and rs757210 (TCF2).

In the present study, nine SNPs were found to be associated with type 2 diabetes. Out of which, two SNPs (rs563694 and rs10811661) are present in the 3’UTR of G6PC2 and CDKN2A/B gene respectively. Two SNP’s (rs4402960 and rs757210) are present in the Intron 2-3 of IGF2BP2 and TCF2 genes respectively. An SNP (rs7903146) is present in the Intron 4-5 of TCF7L2 and at the last one, SNP (rs2166706) is present in the 5’UTR of MTNR1b gene. Further, the genotype-phenotype analysis revealed the association of SNPs rs3847554, rs4402960, rs7903146 with fasting and postprandial glucose. The SNP, rs7903146 is associated with HbA1c and rs4402960 associated with HomaIR and triglycerides. The SNP rs1111875 is located at HHEX gene is consistently associated with cholesterol, HDL and LDL, and the SNP rs12779790 is located at CDC123-CAMK1D gene on chromosome 10 associated with cholesterol and triglycerides. The SNPs rs560887, rs780094, rs1402837, rs1260326, rs1801282, rs10946398, rs1799884, rs730497, rs13266634, rs10830962, rs10830963 and rs1387153 were not associated with type 2 diabetes in the present study population.

These data show that several genetic variants and the levels of biomarkers play a significant role in determining the pathophysiological phenotype of patients with type 2 diabetes, with most of the influence exerted on fasting glucose and β-cell function. Thus, assessment of type 2 diabetes risk genotype may turn being useful for diagnostic, prognostic and therapeutic purposes in type 2 diabetes patients.