Chapter - 4

Conclusion
In the spectrum of diabetic disorders, type 2 diabetes is the most common form of diabetes accounting for more than 90% of world’s diabetic population. During the year 2007, an estimated 40.9 million diabetic individuals within the age group of 20-79 years were residing in India which makes it top the list of countries with highest number of diabetic individuals in the world.

Prevalence of diabetes varies from population to population implying that certain populations in the world are at higher risk of developing the disease than the others. In the developing countries, the majority of diabetes patients are in the age range of 45-64 year, whereas in the developed countries they are over 65 year of age. Younger age at the onset of diabetes had been reported in migrant Asian Indians.

The initial family studies confirmed inheritance of type 2 diabetes, nonetheless the pattern of inheritance was not clear. Until recently limited success was achieved in identification of genetic risk factors associated with the disease. The linkage studies suffered from being seriously underpowered for sensible susceptibility models, because linkage is best suited to detect variants with high penetrance. The candidate gene association approach historically has been compromised by difficulties associated with choosing credible candidate genes. The recent advances in molecular biology and genetics had helped in identification of new unconventional disease susceptibility loci for the diabetes.
Adiponectine is secreted by white adipose tissue and its role in lipid metabolism and as insulin-sensitizing hormone has made it a suitable candidate gene for type 2 diabetes. Studies in different populations of the world, including a South Indian population, have reported association of SNPs of the gene with type 2 diabetes. But most of these studies were based on initial reports on European populations.

Initially mutations in \textit{KCNJ11} were reported to be associated with neonatal and early onset diabetes but as years passed the gene emerged as one of the major susceptibility loci for type 2 diabetes. Coding a protein which maintains intracellular Ca\textsuperscript{2+} concentration, which in turn is essential for insulin secretion by pancreatic β cells, the gene was implicated in hyperinsulinemia and insulin resistance.

In addition to the pathway based disease gene identification, the arrival of genome-wide association (GWA) analysis has transformed the potential to uncover genes influencing common complex phenotypes including type 2 diabetes, and has resulted in the identification of a growing number of trait susceptibility loci such as \textit{HHEX}, \textit{ADIPOQ}, \textit{KCNQ}, and \textit{ENPP1}, among others. In type 2 diabetes, the genome scans performed so far have concentrated on the European populations and have only been designed to detect those variants represented on the commodity genotyping arrays.

The present study was planned to dissect the role of three type 2 diabetes candidate genes namely \textit{ADIPOQ}, \textit{HHEX} and \textit{KCNJ11} by sequencing their coding and conserved intronic regions in population of Mysore district, Karnataka.

The results showed that the mean BMI of diabetic cases was higher (24.2±4.1) than non-diabetic controls (22.2±4.4) and it was within the
normal range as per the WHO classification (WHO, 2000). However, according to WHO (2004) classification for the Asian populations, the mean BMI of the present diabetic cases was in increased risk category for diabetes and heart diseases. Mean waist circumference of type 2 diabetic subjects was higher than the control subjects and the same pattern was observed for waist to hip ratio.

Relatively higher percentage of type 2 diabetes subjects was found to be under hypertension medication which implies that such subjects were at high risk for secondary hypertension in the study population. Low diastolic blood pressure in the cases indicated high risk for cardiovascular disease.

In the present study, more than half of the observed variants in ADIPOQ gene were novel. In contrast to a previous report by Codner et al. (2005) who observed KCNJ11 SNP g. 602T>G in a case of early onset of diabetes, in the present work this SNP was observed in three type 2 diabetic subjects, with a mean age of onset of the disease as 47.25 yr. This indicates population specific functionality of variants of the gene. As in a previous report by Minton et al. (2007), this study also did not find any variants in the exon regions of HHEX gene.

Although minor allele frequencies of SNPs rs5219 and rs5215 in KCNJ11 gene were higher in the cases than controls, the difference was found to be statistically non-significant. Similarly, none of the SNPs in ADIPOQ gene were significantly associated with type 2 diabetes. The two SNPs near HHEX gene viz., rs1111875 and rs5015480 showed nominal association with the disease.
**ADIPOQ** SNP rs1501299 showed nominal association with 2 h plasma glucose level under additive and dominant genetic models, suggesting its possible role in insulin resistance. Haplotype GT of SNPs rs182052 and rs62292784 of *ADIPOQ* gene showed relatively high frequency in the cases (0.09) than controls (0.04) and difference was nominally significant, indicating the gene’s possible role in type 2 diabetes.

In conclusion, the present study identified as many as 16 novel variants in *ADIPOQ* gene. This work could not replicate the association of *KCNJ11* SNPs with type 2 diabetes in the present population. No SNPs were observed in the *HHEX* exons, albeit rs1111875 and rs5015480 which are located near the gene showed nominal association with the disease. *ADIPOQ* SNP rs1501299 showed nominal association with 2 h plasma glucose level and a haplotype of the gene showed nominal association with type 2 diabetes. To fully appreciate the role of different candidate genes in type 2 diabetes, further investigations are desirable to corroborate the results of the present study in other populations of India.