

## ABSTRACT

Type 2 diabetes (T2D) is a multifactorial disease and genetics play a crucial role in its pathogenesis. The current research was aimed to report the economic burden, risk factors and susceptible genes of T2D in Pakistani population. A total of 591 subjects were included in epidemiology study and 458 were further evaluated for genetic analysis. The selection of candidate genes was based previous studies and their role in glucose homeostasis and complications of diabetes. The selected genes with single nucleotide polymorphisms (SNPs) were *CDKLI* (rs7756992 A>G), *NPPA* (rs5064 G>A), *GNB3* (rs5443 C>T), *PPARG* (rs1801282 G>C), *IL6* (rs1800796 C>G), *IDE* (rs6583813 C>T, rs7910977 C>T), *POU2F1* (rs3767434 A>T, rs10918682 A>T, rs2146727 A>G), *WFS1* (rs734312 A>G), *PON1* (rs854560 T>A), *IL1 $\alpha$*  (rs1800587 C>T) and *IL1 $\beta$*  (rs1143634 C>T). Genotyping was performed by Nested PCR (DNA amplification) and direct sequencing. Incidences of diabetes were highest in age group of 41-60 years with 61.42% of total diabetes cases. Urban Men (10.69%) and women (21.14%) were diagnosis at early age  $\leq$  35 years as compare to rural men (2.94%) and women (4.11%) respectively. Overweight (Body Mass Index > 25) and positive family history of diabetes were strong predictors of disease onset at early age with  $P = 0.01$  and  $P = 0.003$  respectively. Retinopathy and nephropathy were three times higher in rural population than urban residents. Average annual cost per patient was 210.92US\$ (19,157 PKRs) and insulin treatment was of higher cost ( $P < 0.001$ ) in comparison to oral medication. Families were spending 12-20% of their income to manage the disease. Genetic results indicated that rs7910977 in *IDE* showed significant association with the development of T2D [ $P = 0.012$ , OR = 1.677 (95% CI = 1.112-2.438)]. The rs10918682 in *POU2F1* was associated with T2D [ $P < 0.001$ , OR = 3.606 (95% CI = 2.165- 6.005)] in Pakistani population. The rs854560 in *PON1* was associated with incidences of T2D and increased the risk of cardiovascular complications [ $P = 0.031$ , OR = 0.663 (95% CI = 0.455-0.965)] in diabetics. The rs1801282 in *PPARG* and rs1800796 from *IL6* were significantly associated with T2D [ $P = 0.004$ , OR = 2.188 (1.254, 3.815);  $P = 0.0001$ , OR = 0.394 (0.265, 0.584)]. Genotype analysis showed the association of rs5443, rs1801282 and rs1800796 with the onset of T2D ( $P < 0.05$ ) where the risk genotypes were TT, CG and GG respectively. Haplotype analysis of rs1800587-rs1143634 depicted C-C haplotype increased the susceptibility to diabetes ( $P < 0.05$ ). Haplotype G-A-A from rs2146727-10918682-rs3767434 was protective against diabetes ( $P < 0.01$ ) and G-G-A exhibited the association with T2D ( $P < 0.01$ ). Haplotype C-T from

rs6583813-rs7910977 was protective against diabetes ( $P = 0.02$ ). Linear regression analysis between demographic characteristics and genotypes showed a positive association of CC from rs1800796 with family history of diabetes ( $P < 0.05$ ). The CT genotype from rs7756992 was associated to complications of T2D ( $P < 0.05$ ).

**Conclusion:** SNPs in *KCNQ1*, *GNB3*, *PPARG*, *IL6*, *CDKLI*, *IDE*, *PON1*, *WFS1*, *POU2F1*, *ITGA2*, *IL1 $\alpha$*  and *IL1 $\beta$*  associated with T2D in Pakistanis. Diabetes is the one of major health issue in Pakistan making the socioeconomic and health problems for the nation. Further studies are needed to develop a comprehensive program for targeting susceptible communities and prevention of diabetes.