

Abstract

The global prevalence of type 2 diabetes (T2D) is increasing at an exponential rate. Insulin resistance and pancreatic beta cell dysfunction are the two primary causative factors. Ultimately, blood glucose levels are elevated as a result of insufficient insulin production or the potential to prevent insulin signaling. It's a polygenic disease with complex etiological factors as a combination of genetic and environmental factors, is causative to its occurrence and interrelates with one another. It is familial and heritable, with a range of 30 to 70%. Numerous genes are defined as contributing to the pathogenicity. This study was designed to evaluate the heritability of insulin resistance genes (*VDR*, *IGF-1*, *IRS-1*, *PPAR γ* , and *FTO*) to exposed their variations and expressions linkage with T2D in susceptible families of Pakistan. A total of thirty-seven families with positive family history of T2D were traced from different localities. Seven families were excluded because of lack of clinical assessment data and self-reporting. The selected thirty diabetic families were consisting of total 206 members, among which 125 were affected and 81 were unaffected (non-diabetic). Blood samples of the selected families were collected and followed by DNA extraction. Sequencing and PCR-RFLP techniques were used to identify the genotyping and RT-qPCR for expression. Phenotypic and genotypic pedigrees of the families were developed by the progeny online tool. Association of SNPs were determined by TDT (Transmission Disequilibrium Test) and DFAM (Family Based Association) analysis implemented on Plink software. The study found that gender (male/female) frequencies were 0.54 in Probands, 0.85 in FDRs (First degree Relatives), and 0.50 in SDR (Second degree Relatives). Mean age (57.70) and age of diagnosis 37.77 years was detected in affected. Disease duration was observed 7.6, 6 and 3.5 years in Probands, FDRs and SDRs respectively. Mean BMI in Probands, FDR and SDR was reported (28.79), (27.82) and (26.70) correspondingly. Probands had the high blood pressure percentage at 60%, FDR at 47% and SDR at 48%. Age has a positive correlation with diagnosis, other complications, TGI level, and random fasting glucose. BMI also has a positive correlation with status, HDL, fasting glucose, and physical activity. Other complications indicated positive correlations with HDL, random glucose, and physical activity. We found a significant association between rs731236 C/T (OR=1.522) and rs2228570 C/T (OR=1.327) at $p < 0.05$ whereas, for rs1544410 G/A (OR=0.9706) and rs7975232 T/G (OR=0.7368) there was no significant association with T2D in families ($p > 0.05$). The *IGF-1* gene variant

rs6214 shown no association, but rs5742632 demonstrated a high susceptibility to T2D. The IRS-1 gene had a substantial correlation with both rs2943641 and rs1801278. The PPAR γ gene rs3856806 was highly associated, but rs1801282 showed no significant association. The FTO genetic variation rs9939609 exhibited a significant relationship with T2D, but no association was observed for rs17817449. A significant association among two of four SNPs (rs731236, rs7975232, rs2228570, and rs1544410) were inspected significantly associated. Other genetic variants, such as rs5742632 (IGF-1), rs2943641 (IRS-1), rs1801278 (IRS-1), rs3856806 (PPAR γ), and rs9939609 (FTO), were significantly susceptible in families, while others revealed no significant association. The genetic variants (rs731236 (VDR), rs2228570 (VDR), rs5742632 (IGF-1), rs2943641 (IRS-1), rs1801278 (IRS-1), and rs9939609 (FTO) exposed a high susceptibility either within or between families of T2D. Exposed no significant link between or within T2D families the genetic variations rs7975232 (VDR), rs1544410 (VDR), rs6214 (IGF-1), rs1801282 (PPAR γ), rs3856806 (PPAR γ), and rs17817449 (FTO). Expression of VDR (* $p < 0.05$), IGF-1(* $p < 0.05$), IRS-1 (* $p < 0.05$), PPAR γ (** $p < 0.05$) and FTO (** $p < 0.05$) was detected higher in patients as compared to controls. It was concluded that associated and heritable genetic markers can be used for prognosis of T2D. More study is also needed to validate these family links and grasp the complicated interaction between environmental and hereditary elements in T2D risk.