

Abstract

Type 2 diabetes mellitus (T2DM) is one of the leading preventable chronic diseases with high rates of morbidity and mortality. It is multi-factorial, polygenic, and characterized by chronic hyperglycemia. Transcription factor 7-like 2 (TCF7L2) is a main constituent of the canonical Wnt signaling pathway and is T2DM susceptible gene. Fat mass and obesity associated (FTO) is most commonly coupled alongside obesity, an excessive fat mass suffice to elevate the possibilities as well as hazards of mortality and morbidity. Both of these genes are recognized as the susceptible factors for various non-communicable illnesses including type 2 iabetes mellitus (T2DM), leading preventable chronic disease. Pakistan is occupied with the rising trend of T2DM in the adult population, hence to advocate the previous though rare findings, this case-control study was designed. to see T2DM prevalence and its association with TCF7L2 and FTO intronic variants, respectively. The objectives of present study to do bioinformatic analyses of TCF7L2 and FTO genes, proteins and its variants furthermore, to identify the genes variants, rs12255372 and rs9939609 susceptibility with T2DM and obesity within Pakistani cohort. Out of the total enlisted case control individuals, genotyping was executed on 162 test samples by using economical technique T-ARMS PCR. The demographic and clinical data were statistically analyzed. The bioinformatic analyses showed the structural influence of SNPs on best protein coding transcripts of genes. TCF7L2 and FTO variants change the wild type amino acids proline and tyrosine to mutant type glycine and asparagine at the position of 552 and 46, correspondingly in transcripts. Glycine substitution leads to conformational change in the TCF7L2 protein and converts the protein conformation from rigid to highly flexible. However, mutated asparagine present in the highly conserved domain region and affects hydrogen bond contact with residue present in other domain subsequently, disrupts the function of FTO. The genotyping findings showed high genes minor allele frequency among diabetic cases. This study also concludes FTO variant association to body mass index as well as waist circum-ference. Moreover, TCF7L2 lethal allele showed susceptibility to T2DM in the progressive age of females and the early age of males. More genetic studies are recommended in Pakistani population essential to advocate the current and previous outcomes.