ABSTRACT

Maturity-onset diabetes of the young (MODY) is a monogenic disease, mainly characterized by β-cell destruction, impaired insulin biosynthesis, hyperglycemia, and dominant autosomal mode of inheritance. It is mainly caused by gene mutations. GCK gene is an essential gene for insuline biosynthesis. Therefore, any deregulation or mutation of this gene can result in MODY. Thus, nucleotide heterogeneity in this gene may be useful in identifying the probability of occurance MODY. The purpose of the current study is to determine the impact of single nucleotide polymorphisms in the human GCK gene on various protein properties such as extinction coefficient, aliphatic index, instability index, isoelectric point, half-life, transmembrane topology, sub-cellular localization 3D configuration and ontology. For this reason, we first retrieved the coding sequence of the normal GCK gene transcript ENST00000671824.1 GCK-210 and its 49 selected (Missense, frameshift & stop gained) SNPs by using the ENSEMBL database. We introduced them to the normal GCK gene coding sequence and designed 49 cases. The coding sequences of the normal GCK gene and all 49 cases were transcribed into an amino-acid sequence using the Translate tool-Expasy. Then change in the function of protein caused by SNPs was determined by changes in sub-cellular localization, Ontology, 3D configuration and physical properties using CELLO2GO, PHYRE2 and ProParam-Expasy tools. Pathogenicity analysis was also performed by using SIFT and PolyPhen tools. It was discovered that out of the forty-nine SNPs evaluated in the current study, eight variations were reported in cases 3 (rs193922259), 11 (rs1554335752), 15 (rs193922295), 16 (rs1064796410), 19 (rs1470521850), 24 (rs104894006), 28 (rs144723656), and 32 (rs1562715426) changed the physicochemical properties, 3D configuration and sub-cellular localization of mutated proteins considerably. Among thirty three SNPs, thirty were deleterious according to SIFT analysis. According to PolyPhen tool sixteen were probabily damaging, thirteen were possibly damaging and one was benign. Therefore, these genetic variations can potentially be used as biomarkers in human to assess the likelihood of having MODY.

Keywords: MODY, monogenic disease, hyperglycemia ,Translation, GCK, single nucleotide polymorphisms.