

Abstract :

Aim: Maturity-onset diabetes of the young (MODY) is a genetically and clinically heterogeneous group of autosomal dominantly inherited nonketotic diabetes. MODY2 or (GCK-MODY) subtype is caused by heterozygous mutations in the GCK gene coding for glucokinase. In our current study, we aim to confirm a clinically suspected GCK-MODY phenotype at molecular level and subsequently, to estimate co-segregation of the detected mutation with hyperglycemia among Algerian related subjects. Lastly, assessment of mutation effect was performed using a combination of computational tools. **Methods:** Sixteen related subjects were implicated in this study (proband and 15 relatives). Blood samples were used for biochemical, immunological and genetic assays. The proband was screened for mutation in the GCK gene using PCR-sequencing technique. Mutation screening among proband's relatives was performed by PCR-Restriction fragment length polymorphism (PCR-RFLP) technique. Computational analysis was performed with a combination of predictive tools to assess effect of the detected mutation on glucokinase structure/function and stability. **Results:** Genetic analysis results revealed the presence of c.253A>T (p.R85W) GCK mutation at heterozygous state in 11 subjects, while it was absent in 5 others. Biochemical analysis showed that all subjects carrying the p.R85W mutation were affected with diabetes or impaired fasting glucose (fasting glucose 6.94 ± 0.63 mmol/l, HbA1c $6.92 \pm 0.77\%$), whereas the five non-carriers were normoglycemic (fasting glucose 5.01 ± 0.26 mmol/l, HbA1c $5.36 \pm 0.17\%$). All computational tools predict the detected mutation to be 'damaging' or 'probably damaging' with high scores. **Conclusion:** The p.R85W GCK mutation segregates with diabetes or IFG in a large pedigree. Clinical features of Algerian GCK-MODY patients are similar to those of other populations; in case of double diabetes the co-occurring diabetes overcomes the GCK-MODY phenotype. In silico predictions results are consistent with metabolic study.