

Genotypic and Allelic Distribution of Polymorphic Variants of Gene SLC47A1 Leu125Phe (rs77474263) and Gly64Asp (rs77630697) and Their Association to the Clinical Response to Metformin in Adult Pakistani T2DM Patients

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Abstract : Background: Inter-individual variation in response to metformin, which has been considered as a first line therapy for T2DM treatment is considerable. In the current study, it was aimed to investigate the impact of two genetic variants Leu125Phe (rs77474263) and Gly64Asp (rs77630697) in gene *SLC47A1* on the clinical efficacy of metformin in T2DM Pakistani patients. Methods: The study included 800 T2DM patients (400 metformin responders and 400 metformin non-responders) along with 400 ethnically matched healthy individuals. The genotypes were determined by allele-specific polymerase chain reaction. *In-silico* analysis was done to confirm the effect of the two SNPs on the structure of genes. Association was statistically determined using SPSS software. Results: Minor allele frequency for rs77474263 and rs77630697 was 0.13 and 0.12. For *SLC47A1* rs77474263 the homozygotes of one mutant allele 'T' (CT) of rs77474263 variant were fewer in metformin responders than metformin non-responders (29.2% vs. 35.5 %). Likewise, the efficacy was further reduced (7.2% vs. 4.0 %) in homozygotes of two copies of 'T' allele (TT). Remarkably, T2DM cases with two copies of allele 'C' (CC) had 2.11 times more probability to respond towards metformin monotherapy. For *SLC47A1* rs77630697 the homozygotes of one mutant allele 'A' (GA) of rs77630697 variant were fewer in metformin responders than metformin non-responders (33.5% vs. 43.0 %). Likewise, the efficacy was further reduced (8.5% vs. 4.5%) in homozygotes of two copies of 'A' allele (AA). Remarkably, T2DM cases with two copies of allele 'G' (GG) had 2.41 times more probability to respond towards metformin monotherapy. *In-silico* analysis revealed that these two variants affect the structure and stability of their corresponding proteins. Conclusion: The present data suggest that *SLC47A1* Leu125Phe (rs77474263) and Gly64Asp (rs77630697) polymorphisms were associated with the therapeutic response of metformin in T2DM patients of Pakistan.

Keywords : diabetes, T2DM, SLC47A1, Pakistan, polymorphism

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