Title: Unraveling the potential effects of non-synonymous single nucleotide polymorphisms (nsSNPs) on the Protein structure and function of the human *SLC30A8* gene on type 2 diabetes and colorectal cancer: An *In silico* approach

Author Names: Md Moin Uddin, Md Tanvir Hossain , Md Arju Hossain , Asif Ahsan , Kamrul Hasan Shamim , Md Arif Hossen , Md Shahinur Rahman , Md Habibur Rahman , Kawsar Ahmed , Francis M Bui , Fahad Ahmed Al-Zahran

Abstract: Background and aims: The single nucleotide polymorphisms (SNPs) in *SLC30A8* gene have been recognized as contributing to type 2 diabetes (T2D) susceptibility and colorectal cancer. This study aims to predict the structural stability, and functional impacts on variations in non-synonymous SNPs (nsSNPs) in the human *SLC30A8* gene using various computational techniques.

Materials and methods: Several *in silico* tools, including SIFT, Predict-SNP, SNPs&GO, MAPP, SNAP2, PhD-SNP, PANTHER, PolyPhen-1,PolyPhen-2, I-Mutant 2.0, and MUpro, have been used in our study.

Results: After data analysis, out of 336 missenses, the eight nsSNPs, namely R138Q, I141N, W136G, I349N, L303R, E140A, W306C, and L308Q, were discovered by ConSurf to be in highly conserved regions, which could affect the stability of their proteins. Project HOPE determines any significant molecular effects on the structure and function of eight mutated proteins and the three-dimensional (3D) structures of these proteins. The two pharmacologically significant compounds, Luzonoid B and Roseoside demonstrate strong binding affinity to the mutant proteins, and they are more efficient in inhibiting them than the typical *SLC30A8* protein using Autodock Vina and Chimera. Increased binding affinity to mutant *SLC30A8* proteins has been determined not to influence drug resistance. Ultimately, the Kaplan-Meier plotter study revealed that alterations in *SLC30A8* gene expression notably affect the survival rates of patients with various cancer types.

Conclusion: Finally, the study found eight highly deleterious missense nsSNPs in the *SLC30A8* gene that can be helpful for further proteomic and genomic studies for T2D and colorectal cancer diagnosis. These findings also pave the way for personalized treatments using biomarkers and more effective healthcare strategies.

Keywords: And colorectal cancer; Missense; Non-synonymous; Polymorphism; SLC30A8; T2D.

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