Modulatory Role of TMPRSS6 (transmembrane serine protease 6) rs855791T>C Polymorphism on Iron Homeostasis: an *in-silico* Protein-protein Docking Model

H. L. T. C. Abeywickrama [1], L. Samaranayake[2], T. Thoradeniya[3], G. H.Galhena[1*]

[1]Department of Zoology and Environment Sciences, Faculty of Science, University of Colombo

[2]Department of Chemistry and Chemical Biology, Northeastern University

[3]Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Colombo

*gayani@zoology.cmb.ac.lk

The molecular mechanisms of iron deficiency (ID), the most common global nutritional problem, are not yet fully understood. Regulatory messenger molecules like TMPRSS6 (transmembrane serine protease 6) play a vital role in systemic iron homeostasis. When iron levels are low TMPRSS6 cleaves membrane bound hemojuvelin (HJV) causing a negative regulation of BMP-SMAD (Bone morphogenetic proteins-sons of mothers against decapentaplegic) signaling to inhibit hepcidin, the master regulator of iron, and restore iron balance. Our previous study on TMPRSS6 gene among pregnant women, has shown rs855791T>C polymorphism in *TMPRSS6* gene to be associated with ID in the presence of T allele. rs855791T>C is a missense variant in the catalytic domain of TMPRSS6 protein and causes valine (V; by T allele) to alanine (A; by C allele) change at 736 position. Functional studies have demonstrated that, 736A variant inhibits hepcidin more than 736V variant. This may explain the high risk of ID in the presence of latter in our previous study, although the exact mechanism is not yet clarified. We attempted predicting possible molecular mechanisms of rs855791T>C polymorphism and ID using an *in-silico* protein–protein docking model. YASARA workplace was used to build the homology models of HJV and TMPRSS6 proteins. Amino acid changes corresponding to rs855791 SNP were introduced to TMPRSS6 protein using Schrödinger Maestro v 9.0 to obtain the two protein variants. The predicted protein models were validated with Ramachandran plots using RAMPAGE online server. Two protein-protein docking web servers, PatchDock and FireDock were used to predict the protein complexes made by HJV with the two TMPRSS6 protein variants. This was followed by a local docking carried out using Rosetta web server. Interface energy was calculated for these complexes through ROSIE. The complex made of TMPRSS6-736V and HJV generated an interface energy of -4.689 kJ/mol while the complex made of TMPRSS6-736A and HJV generated an interface energy of -7.934 kJ/mol. These results suggest that the TMPRSS6-736A: HJV complex to be thermodynamically more stable than the TMPRSS6-736V: HJV complex. This may explain the observed high risk of ID in the presence of 736V variant, favouring hepcidin action, in pregnant women studied, which warrant further exploration.

Keywords: Iron deficiency, Protein docking, Interface energy