In silico Prediction and Analysis of Non Synonymous Single Nucleotide Polymorphisms (nsSNPs) in Autophagy Related Gene 5 (ATG5)

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Abstract—*Autophagy is an evolutionary conserved, homeostatic process for degradation and recycling of damaged cellular proteins and cytoplasmic organelles. ATG5, a key autophagy related protein, forms complex with ATG12 and ATG16L1 and acts as an E3-like activating enzyme in lipidation of ATG8, which plays a pivotal role in elongation of autophagosomal membrane. Polymorphisms in ATG5 have been shown to contribute to the susceptibility of various diseases in human. Moreover, altered expression levels or mutations of any of the genes of this complex may lead to defects of autophagosome formation and ultimately autophagy disruption. In this study, we have identified and analyzed functional non-synonymous single nucleotide polymorphism (nsSNPs) in ATG5 by computational methods. Three nsSNPs (rs34793250, rs77859116 & rs115576116) were predicted by the SIFT (Sorting Intolerant from Tolerant) tool among which two nsSNPs (rs34793250 & rs115576116) were observed to be functionally deleterious by PredictSNP and MutPred tools. I-MUTANT2, iPTREE-STAB, WET-STAB, DUET, CUPSTAT tools, used for protein stability analysis showed decreased stability both at sequence and structure level upon mutations. Structural analysis done by PDBsum revealed functional deviations of mutant structure from native structure upon mutation. Mutant structure modeling was performed using Pymol, SWISS PDB –VIEWER, Discovery Studio 4.1 for computing their RMS gradient and total energy; we observed increase in total energy of mutant structure as compared to native. This study suggested that the predicted nsSNPs exert structural and functional impact on ATG5 protein that may destabilize ATG12–ATG5-ATG16L1 complex leading to defects in autophagy which could aid in pathogenesis of different diseases.*