In Silico Basis to Understand the Molecular Interaction of Human *NNATGene* with Therapeutic Compounds of *Anorexia Nervosa*

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ABSTRACT

Introduction*: Anorexia nervosa* (AN)– a perplexing heritable, psychiatric eating disorder condition characterized by low body weight. The prevalence of AN is found to be high in younger age adults with a raised mortality rate. Genetic studies have been insufficient in identifying the role of specific genes that predispose an individual to AN.

Objectives: The objective was to explore the role of *NNAT* (neuronatin) gene variants and its structure based molecular interactions with therapeutic compounds of AN. To investigate the role of structural missense pathogenic variants (SNPs: single nucleotide polymorphism) or change in the expression of *NNAT* with possibility of AN.

Methodology: NNAT gene protein coding sequence, SNPs were extracted and validated from public databases. Gene to gene interactions, protein localization and human tissue-specific expression analysis of *NNAT* gene showed highest tissue-specific expression in the brain. Estimates of functional impact of SNPs using transcript sequence and machine learning based approaches (*in silico* algorithms) were computed to investigate the pathogenicity and protein stability of NNAT variants. Sequence alignment, *ab initio* 3D structure-modeling of wild-type, validation and recognition of binding cavities of NNAT through *in silico* web based tools were performed. Alternate model prediction for NNAT variants through residue specific mutation approach and structural validation were also done through Chimera tool. The 3D compounds involved in the management of AN were extracted from the Drug Bank database, afterwards energy minimization and rule of drug-likeness were performed. The eligible 3D compounds were docked with identified variants, to evaluate the drugs binding molecular mechanics.

Results & Conclusion: Overall, 10 NNAT missense variants were extracted on the basis of minor allele frequency (MAF $\leq$ 0.001) and other consequence types. Further three variants were selected among ten according to the transcript sequence, which includes*rs542858994* (F26L), *rs539681368* (C30Y) and *rs542858994* (F53L). Structures for these variants' protein were generated, validated and docked with AN drugs. The functional impact analyses of selected missense SNPs of NNAT showed high risk pathogenicity and can cause changes in the physical and chemical properties of amino acids, thus affecting the function of protein. The computation of binding energies of variants of NNAT with AN compounds strengthen the hypothesis that these variants strongly interact with the AN drugs, hence reducing the level of free NNAT as well as target drugs, for neuronal functioning. Therefore, constitutionally reduced level of NNAT and binding of NNAT variants with AN drugs may serve as the basis to increases the susceptibility towards AN.

Keywords: Cephalosporin, Coagulase Negative Staphylococci, Coagulase Positive Staphylococci, MRSA.

REFERENCES

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