Machine Learning and Pharmacophore-Based Drug Discovery for Treating Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy is a neuromuscular disease that causes progressive muscular degeneration. About five to fifteen percent of Duchenne Muscular Dystrophy (DMD) cases are caused by premature termination codon (PTC) mutations in the dystrophin gene that lead to the production of a truncated, non-functional dystrophin polypeptide. PTC-suppressing compounds (PTCSC) have been developed in order to restore protein translation by allowing the incorporation of an amino acid in place of a stop codon. However, limitations still exist in terms of efficacy and toxicity. In order to identify compounds that have PTC-suppressing ability, existing PTC-suppressing compounds were selected and clustered based on structural similarity. After the flexible alignment of known PTCSC, two clusters were selected for the design of one seven-feature and one ten-feature pharmacophore model, which were used to search the NCI compounds and FDA-approved DrugBank databases. Fourteen compounds from the NCI compounds database and fifteen FDA-approved drugs from the DrugBank database were selected from the pharmacophore search. Additionally, a Multilayer perceptron model was trained and tested using machine learning in order to predict potential PTCSC and validate the pharmacophore-based results. These results suggest that the most potent compounds such as dipyridamole warrant further investigation for pharmacodynamic characterization and experimental validation.