Reducing the Screening Time Required for Therapeutic Exon Skips in Duchenne Muscular Dystrophy Using ab initio Modeling

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Duchenne muscular dystrophy (DMD) is a progressive disabling neuromuscular disorder caused by recessive X-linked mutations in the dystrophin protein and affects 1 in every 3,500 live male births worldwide. Exon skipping therapy is a promising curative treatment that makes use of the repetitive nature of dystrophin and seeks to correct mutations during mRNA maturation by skipping over mutation-containing exons and connecting flanking ones. However, designing and testing one exon skip in labs takes 6-18 months and could yield to variable outcomes. The purpose of this project was to use the Robetta program's ab initio protein modeling to validate the program. The known structure of cytochrome c was used as control. The amino acid sequence was obtained from the NCBI protein databank and inserted into the program. After the model was produced, it was compared to the X-ray diffraction model of cytochrome c and 98% maximum homology was obtained, indicating that Robetta is a reliable software. The same procedures were applied when modeling exon skipped dystrophins. The stability of the corrected structures were evaluated by a measure of free energy and validated by comparing them to laboratory-created exon skipped proteins. Software modeled proteins had a maximum homology of 90%. These results offer that Ab initio modeling may be a new promising screening method to precede lab testing by reducing time and cost required for personalized gene therapy.

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