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Abstracts

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MIRNA BINDING SITES IN THE MRNA OF HUMAN TITIN GENE

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Motivation and Aim: Titin, the human muscle protein, is the largest in the nature (the longest isoform IC contains 35991 amino acid residues) and plays an important role in providing the elasticity and structural integrity of sarcomeres. Interruption of its synthesis leads to the development of a number of serious cardiovascular diseases such as heart failure, cardiomyopathy, ischemic heart disease, and myocardial infarction. Titin gene expression is controlled by miRNAs (microRNAs) that bind with the mRNAs of the gene and block their translation. Therefore, it is important to determine which miRNAs most strongly regulate the synthesis of human titin and what exons of the gene contain the binding sites because different exons of the gene are expressed in different types of muscle tissue at different stages of the human body development.
Methods and Algorithms: The binding of 2563 human microRNAs with mRNA of human titin IC isoform, including all 363 exons of the human titin gene was determined using program miRTarget. The human miRNA sequences were taken from miRBase site (*www.mirbase.org/*), and the mRNA sequence of the titin gene was taken from Genbank (*www.ncbi.nlm.nih.gov/genbank*). The degree of binding ($\Delta G/\Delta G_{.}$, %) was estimated according to the value of the $\Delta G/\Delta G_{.}$ ratio, where ΔG was equal to the free energy of miRNA-mRNA binding and $\Delta G_{.}$ was equal to the energy of miRNA binding with its perfect complementary nucleotide sequence.
Results: As a result of this research, 15 miRNA binding sites with scores not less than 90% were found and marked in exons of titin mRNA. miR-6861-5p has the largest number of binding sites. This miRNA bound with the mRNA of titin at positions 37324, 38077, and 38830 nt at the boundaries of exons 178-179, 187-188, and 196-197, respectively. Other miRNAs had only one binding site each. miR-494-5p bound with titin mRNA at position 1301 nt in the seventh exon. miR-578 bound with titin mRNA in the eleventh exon at position 1960 nt. The 58th exon contained overlapping binding sites of two miRNAs (miR-374b-3p and miR-374c-3p) in positions 17239 nt and 17241 nt, respectively. Exon 59 was a target for miR-3714, which interacted with the mRNA at position 17450 nt. Exon 75 was the target of miR-34a-3p, which interacted with the mRNA at position 22116 nt. The 85th exon of the titin gene was the target for miR-1278, which interacted with titin mRNA at the position of 24928 nt. The 89th exon had a binding site for miR-544b at position 26044 nt. The 326th exon contained binding sites for miR-4738-3p and miR-136-3p. miR-4738-3p interacted with titin mRNA at position 74955 nt and miR-136-3p bound with mRNA of titin at position 71469 nt. Exon 339 also contained binding sites for miR-4693-5p and miR-4495, which bound with the mRNA for titin at positions 92464 nt and 93909 nt, respectively.
Conclusion: The results of the computer analysis provide a theoretical basis for further experiments to validate the miRNA binding sites found in the mRNA of titin and to determine the miRNA concentrations in the blood and other cells and tissues of humans and mice. These results could then be used for diagnosis and treatment of human cardiovascular diseases.