Identification of Mutations in MicroRNA Binding Sites Within Risk Genes Associated With Diseases Through a Computational Approach

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MicroRNAs (miRNAs) are non-coding RNAs that bind to the coding sequences of target messenger RNAs (mRNAs), where they regulate gene expression. Mutations of miRNA binding sites within risk genes disrupt miRNA binding, contributing to diseases such as cancer. Given the immense combination of binding sites, motif sequences, and risk genes, pinpointing critical mutations experimentally is laborious and costly. This study proposes an optimized computational approach that integrates large databases to identify significant mutations in miRNA binding sites. Our previous research identified four candidate miRNAs that regulate two lung cancer risk genes. In this study, we first used Diana-MicroT to locate miRNA binding sites in coding sequences of lung cancer genes and the COSMIC database to detect mutations within these sites. MIENTURNET network-based analysis recognized additional risk gene targets, along with their related diseases, shared by the four candidate miRNAs. We implemented the MEME Suite to detect significant motif regions among these new risk genes and subsequently found mutations within them. Finally, AlphaFold V2 was used to generate 3D protein models, visualizing the identified mutations. This approach efficiently identified four miRNAs and their two lung cancer-associated target genes, as well as 8 binding site mutations out of 24 million somatic mutations acknowledged by the databases. Additionally, we identified 10 additional risk genes among 12,440 candidates, their associated diseases, and mutations in their miRNA binding sites. Our findings provide a foundation for the experimental validation of miRNA-target interactions and binding site mutations, characterizing them as potential therapeutic targets for miRNA-based treatments.

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