Opinion

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Nucleotide Variations in microRNA-Binding Sites: The Need of Novel Tools for the Nucleic Acid Alignment

Jill Zhong[1], Holly Clifton[2] and Alexander Kofman*[2]

[1]*Department of Computer Sciences, Troy University, AL, USA*

[2]*Department of Biological & Environmental Sciences, Troy University, AL, USA*

***Corresponding author:** Alexander Kofman, Department of Biological & Environmental Sciences, 210-D MSCX (McCall Hall), Troy University, AL 36082, U.S.A

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ABSTRACT

It has been proposed that naturally-occurring variations in microRNAs and their target sites on messenger RNAs may be linked with various human pathologies, including cancer. The growing number of reports clearly indicates the need of the development of complementary sequence alignment algorithms, where the interaction of two complementary RNAs (specifically microRNA and its target mRNA) can be assessed in the context of the multiple single nucleotide polymorphisms.

Keywords: MicroRNA; Nucleotide; Variations; Polymorphisms; Alignment; Algorithm

Abbreviations: mRNA: Messenger RNA; SNP: Single Nucleotide Polymorphism

Introduction

During the last fifteen years, the attention of biologists and medical scientists has been attracted to microRNAs, the small regulatory molecules of about 22 nucleotides long. The suppressive effect of microRNAs on gene expression is well-known and generally attributed to microRNA-mediated degradation of its target messenger RNA (mRNA, the molecule produced by the gene), messenger RNA translational repression, or both. To accomplish this, microRNA aligns with its mRNA target upon the principles of complementarity between the microRNA and mRNA nucleotides [1] (Figure 1). It has been suggested that naturally-occurring variations in microRNAs and their target genes may be associated with various human pathologies including cancer [2,3]. Even substitutions of only one nucleotide, the so-called Single Nucleotide Polymorphisms (SNPs) can either destroy or create microRNA-binding sites, thus, altering microRNA ability to target oncogenes and rendering tumor-suppressor genes susceptible to microRNA-mediated inhibition. By now, all human microRNA-binding sites for all microRNAs and their target mRNAs have been predicted with the help of the various software applications and compiled into the databases.

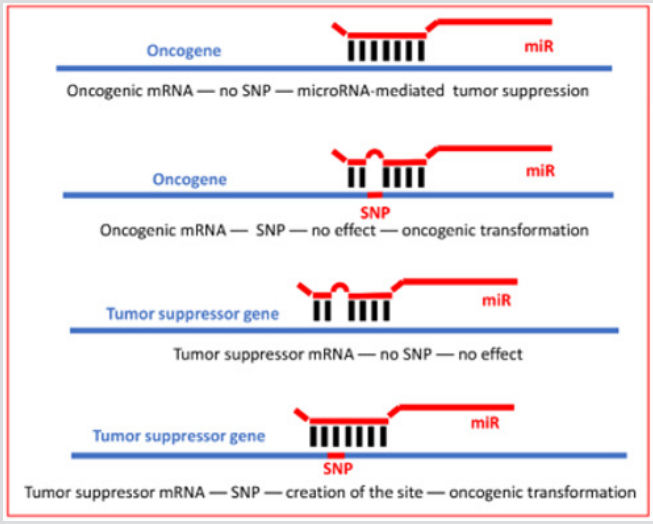

Figure 1: Destruction and creation of microRNA-binding sites by SNP; implications for oncogenesis

However, the computer-assisted prediction of microRNA-binding sites relied exclusively on one or few reference genomic sequences and did not take into consideration the significant variations within human genomes. In meantime, SNPs are reported to occur at a rate of about 1 per 300-1000 bases in the individual human genome [4] and with the frequency of 1% and higher in a population [5,6]. The number of SNP in the human genome was estimated to be around $1.5x10^6$ per individual [7]. However, the advances of NextGen Sequencing technologies revealed that some previously believed to be rare mutations exceeded the frequency threshold set at 1% 6. Previously, we demonstrated that even the only "seed" regions of microRNA-binding sites can harbor as many as 4 SNPs, and their coincidence may result in hyper-functional or completely disabled microRNA-binding sites with the following significant phenotypic variations and predisposition to cancers [8].

Conclusion

The existing data do not take into consideration the significant variability of microRNA-binding sites due to abundancy of SNPs. In addition, there is no possibility to predict the creation of the new microRNA-binding sites upon the variations of single nucleotides in the regions, where microRNA-binding sites are absent. Finally, there are no software tools to quickly assess the probability of hyper-functional or completely disabled microRNA-binding sites based on the known frequencies of SNPs. Altogether, these problems warrant the development of algorithms that allow biomedical researchers to align the individual microRNA and mRNA sequences based on their Watson-Crick complementarity in order to predict how SNPs may weaken or enhance the known microRNA-binding sites, or to create microRNA-binding sites de novo.

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