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Original Article

COMPUTATIONAL APPROACH FOR IDENTIFYING THERAPEUTIC MICRO RNAs

A.HARISHCHANDER[1], D. ALEX ANAND[2*]

[1]Department of Bioinformatics, Sathyabama University, Chennai, [2]Department of Biomedical Engineering, Sathyabama University, Chennai.
Email: danielalexanand@gmail.com

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ABSTRACT

Objective: Identification of novel micro RNAs (miRNAs) in treating diseases has become a challenge in the era of post genomics and the ability to apply an accurate computational approach leads to the discovery of therapeutic miRNAs to treat diseases.

Methods: Initially we have identified the list of list of genes from $PharmG_{kB}$ and then we have identified the validated miRNA targets from miRTarBase. Finally we have found the connectivity map between the gene and validated miRNA target from miRmap and the number of binding sites were analyzed for each pair (gene-miRNA).

Results: We have applied the above mentioned approach to Psoriasis. In case of Psoriasis, 29 genes are present in pharmacogenomic database and among those 29 genes only IL6, ABCC1, VDR and ABCG2 contain validated miRNAs with strong experimental evidence in miRTarBase. Binding sites were analyzed for the obtained miRNAs and it has been found that hsa-let-7a-5p, hsa-miR-26a-5p, hsa-miR-345-5p, hsa-miR-125b-5p, hsa-let-7a-5p, hsa-miR-27b-3p and hsa-miR-328-3p contain 1 binding site. Similarly hsa-miR-365a-3p, hsa-miR-7-5p, hsa-miR-519c-3p and hsa-miR-520h contain 2 binding sites.

Conclusion: Since hsa-miR-365a-3p of IL6, hsa-miR-7-5p of ABCC1, hsa-miR-519c-3p and hsa-miR-520h of ABCG2 contain two binding sites, these miRNAs have a maximum probability to become a therapeutic target of Psoriasis in future and the above mentioned methodology can also be applied for other diseases.

Keywords: miRNAs, Post genomics, $PharmG_{kB}$, miRTarBase, Mirmap.

INTRODUCTION

Micro RNA is a small nucleotide sequence of non coding RNA molecules with a sequence length of 22-24 nucleotides found in plants, virus, animals and humans which help in the process of transcriptional and post transcriptional repression of gene expression [1]. Majority of miRNA are intragenic [2].Micro RNAs are initially transcribed as part of an RNA stem-loop that in turn forms part of a several hundred nucleotides long miRNA precursor miRNA (pri-miRNA) [3]. Mature miRNA is a part of an RNA-induced silencing complex (RISC) which contains Dicer and many associated proteins [4].Since miRNA is involved in the functioning of eukaryotic cells, dysregulation of miRNA is associated with disease and miR2Disease database was created for storing documents with known relationships between miRNA dysregulation and human diseases [5]. Micro RNAs can bind to target messenger RNA (mRNA) transcripts of protein-coding genes and negatively control their translation or cause mRNA degradation and the key factor is to identify the importance miRNA target with accuracy. A detailed review for the advances in the miRNA target identification methods and available resources has been published by Zheng et.al. [6].Several other methodologies were also proposed on the basis of tertiary structure of precursor miRNA by Hin et.al. [7], system biology by Manczinger et.al. [8], SNPs by Marcin et.al.[9],molecular dynamic simulations by Yonghua et.al.[10].

MATERIALS AND METHODS

Pharmacogenomic database

$PharmG_{kB}$ is a knowledge resource with clinical information about dosing guidelines and drug labels. This database summarizes the vital pharmacogenomic genes of various diseases. In our case we have extracted the list of Pharmacogenomic genes associated with Psoriasis and cross validated with published SNPs of Ryan et.al. [11].

miRTarBase

miRTarBase is a online repository of genes and validated microRNA-target. At present, miRTarBase contain more than fifty thousand miRNA-target interactions. In our study, we have obtained the list of miRNAs for the genes which associated with psoriasis in Pharmacogenomic database.

miRmap

miRmap is a software which allows us to examine feature correlations a using high throughput experimental data from immunopurification, transcriptomics and proteomics experiments. Overall, accessibility of target site appears to be the most predictive feature of miRmap.

RESULTS

Pharmacogenomic based Psoriasis related genes are identified from $PharmG_{kB}$ and their corresponding miRNAs are identified from miRTarBase. The complete list of pharmacogenomic related genes of Psoriasis and their corresponding miRNAs are given in Table 1.

Table 1: Micro RNAs and mRNA related to pharmacogenomics of Psoriasis

Genes (Pharmacogenomic Database)	Validated miRNAs (miRTarBase)	Number of mRNA binding sites (miRmap)
IL6	hsa-let-7a-5p	1
	hsa-miR-26a-5p	1
	hsa-miR-365a-3p	2
ABCC1	hsa-miR-345-5p	1
	hsa-miR-7-5p	2
VDR	hsa-miR-125b-5p	1
	hsa-let-7a-5p	1
	hsa-miR-27b-3p	1
ABCG2	hsa-miR-328-3p	1
	hsa-miR-519c-3p	2
	hsa-miR-520h	2

Futher the number of mRNA binding sites of the corresponding miRNAs of Psoriasis related genes are obtained by the gene-miRNA pair mapping and the details about the number of binding sites and their corresponding maps are given from Fig.1-Fig.11 respectively.

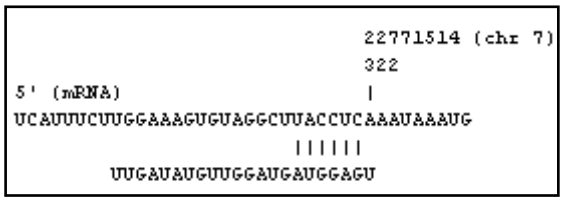

Fig. 1: Binding of hsa-let-7a-5p with the mRNA of IL6

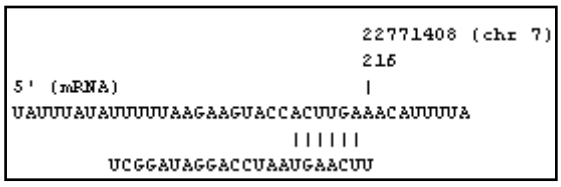

Fig. 2: Binding of hsa-miR-26a-5p with the mRNA of IL6

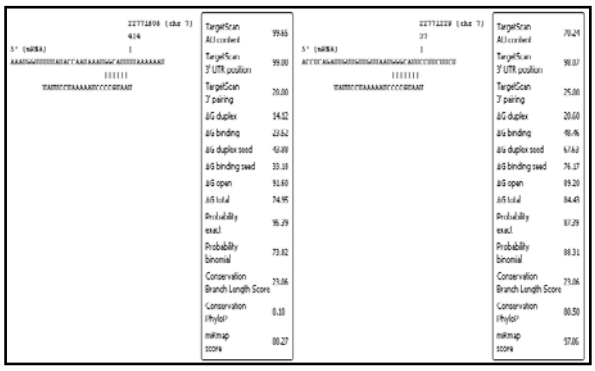

Fig. 3: Binding of hsa-miR-365a-3p with 2 mRNAs of IL6

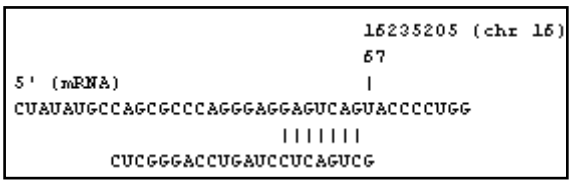

Fig. 4: Binding of hsa-miR-345-5p with the mRNA of ABCC1

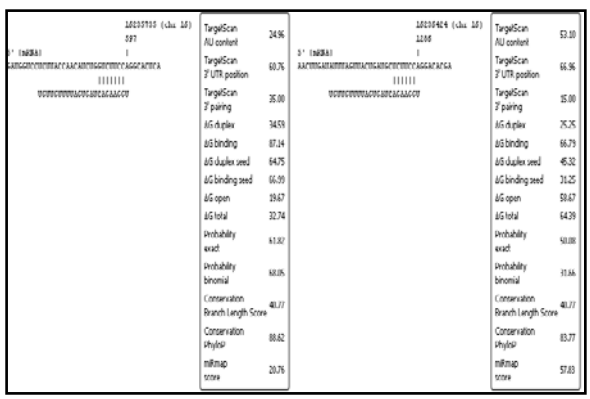

Fig. 5: Binding of hsa-miR-7-5p with 2 mRNAs of ABCC1

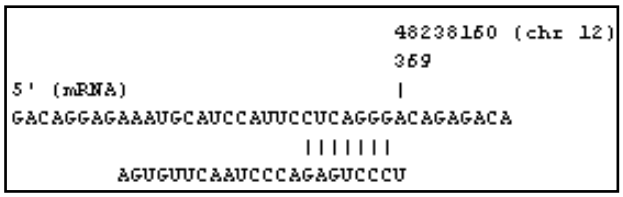

Fig. 6: Binding of hsa-miR-125b-5p with the mRNA of VDR

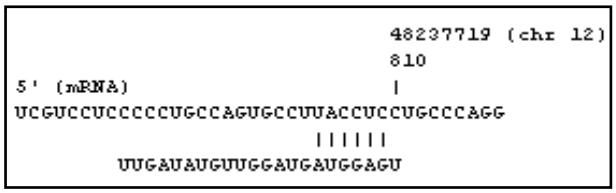

Fig. 7: Binding of hsa-let-7a-5p with the mRNA of VDR

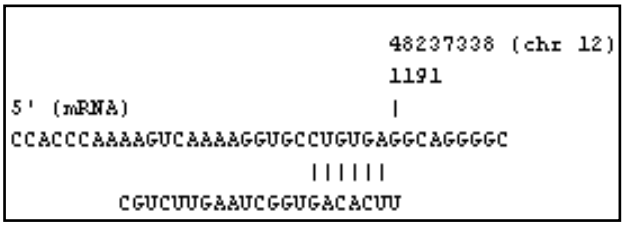

Fig. 8: Binding of hsa-miR-27b-3p with the mRNA of VDR

Fig. 9: Binding of hsa-miR-328-3p with the mRNA of ABCG2

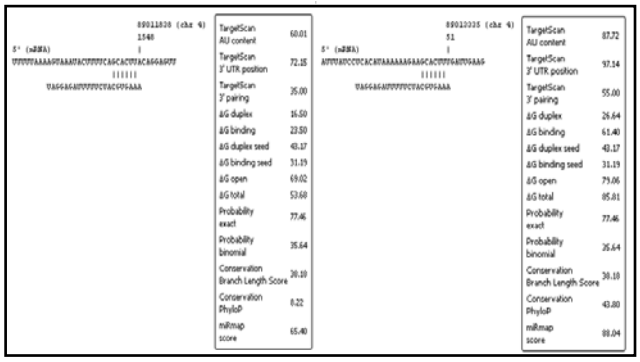

Fig. 10: Binding of hsa-miR-519c-3p with the mRNA of ABCG2

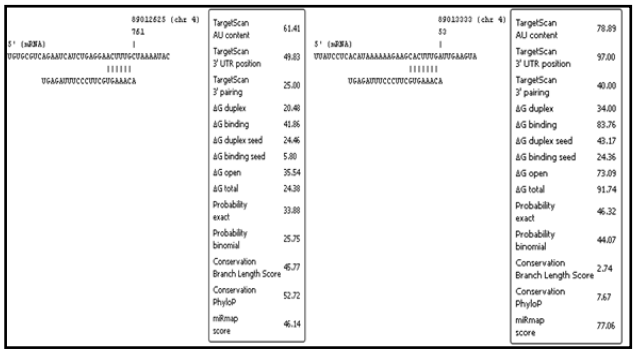

Fig. 11: Binding of hsa-miR-520h with the mRNA of ABCG2

DISCUSSION

In our analysis we have found that there are 29 genes in pharmacogenomic database which is associated with Psoriasis. Further, the corresponding miRNAs of Psoriasis related genes were obtained from miRTarBase and we have found that only IL6, ABCC1, VDR and ABCG2 contain validated miRNAs with strong experimental evidences like Western blot, RNA (Ribonucleic acid) assays and RT-PCR (Real Time-Polymerase Chain Reaction).Finally binding site analysis were performed for the miRNAs in miRTarBase with the mRNAs of IL6, ABCC1, VDR and ABCG2 and it has been found that it has been found that hsa-let-7a-5p, hsa-miR-26a-5p, hsa-miR-345-5p, hsa-miR-125b-5p, hsa-let-7a-5p, hsa-miR-27b-3p and hsa-miR-328-3p contain 1 binding site. Similarly hsa-miR-365a-3p, hsa-miR-7-5p, hsa-miR-519c-3p and hsa-miR-520h contain 2 binding sites.

CONCLUSION

Based on our analysis it has been found that hsa-miR-365a-3p of IL6, hsa-miR-7-5p of ABCC1 and hsa-miR-519c-3p, hsa-miR-520h of ABCG2 contain two binding sites and on the basis of probability these miRNAs have a maximum chance to become a therapeutic target of Psoriasis. There were several other methodologies for analyzing the target dynamics of miRNA in the process of multiple mRNA selection on the basis of seed pairing, in order to understand the complete mechanism of miRNA dynamics simulation methods like monte-carlo and constrained dynamics but those methodologies are beyond the scope of our investigation. In future our methodology can also be utilized for identifying novel miRNAs which could be probable therapeutic target for other autoimmune diseases.

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