International Journal of Scientific Engineering and Technology (ISSN : 2277-1581)
Volume No.3 Issue No.6, pp : 720-721 1 June 2014

An Insilico Methodology for Predicting Novel Micro RNAs with Therapeutic Significance

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Abstract : Identification of a novel method for predicting therapeutic micro RNAs (miRNAs) to treat 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 conserved miRNAs. Initially we have identified the list of genes from Pharmacocogenomic database (PharmG$_{KB}$) and then we have predicted the conserved miRNA targets from TargetScan. 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). We have applied the above mentioned approach to Psoriasis. In case of Psoriasis, 29 genes are present in PharmG$_{KB}$ and among them; PSORS1C2, IL6, ENOSF1, ABCC1, FCGR2A, FCGR3A, TYMS, VDR and ABCG2 contain conserved miRNAs on the basis of seed pairing in TargetScan. Number of mRNA (messenger RNA) binding sites were analyzed for the obtained miRNAs and it has been found that hsa-miR-370, hsa-miR-3074-5p and hsa-miR-4756-3p of FCGR3A and similarly hsa-miR-3163 and hsa-miR-4496 of ABCG2 contain more than 2 mRNA binding sites in their respective genes and hence there is a maximum probability for the utilization of the above mentioned miRNAs as a lead for miRNA based drug discovery. At present we have applied this model for Psoriasis and the above mentioned methodology can also be applied for other diseases in future.

Keywords: **miRNAs, auto immune diseases, post genomics, PharmG$_{KB}$ and 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 been associated with disease and a miR2Disease database contain documents with known relationships between miRNA dysregulation and human disease [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] and text mining with 3d modeling of miRNA target identification using pharmacogenomic and GWAS data by Harishchander et.al.[11,12].

Results and Discussion:

Pharmacogenomic based Psoriasis related genes are identified from PharmG$_{KB}$ and their corresponding miRNAs are identified from TargetScan. The complete list of genes associated with psoriasis and their corresponding miRNAs are given in Table 1.

Materials and Methods:

PharmG$_{KB}$- 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. [13]

TargetScan- TargetScan predicts biological targets of miRNAs by searching the presence of conserved sites (7mer and 8mer) in the seed region of each miRNA. In Humans, TargetScan considers the match to annotate human UTRs (Untranslated regions) and their orthologs, as defined by whole-genome alignments from UCSC browser.

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.

Table 1: Micro RNAs and mRNA associated with Pharmacogenomics of Psoriasis

Genes (PharmG$_{KB}$)	Conserved miRNAs (TargetScan)	Number of mRNA binding sites

PSORS1C2	hsa-miR-4458	2
	hsa-miR-4500	2
IL6	hsa-miR-4458	1
	hsa-miR-4500	1
ENOSF1	hsa-miR-544b	1
	hsa-miR-3690	1
	hsa-miR-3920	1
	hsa-miR-4477b	1
ABCC1	hsa-miR-133a	1
	hsa-miR-133b	1
FCGR2A	hsa-miR-3691-5p	1
	hsa-miR-3911	1
	hsa-miR-4490	1
	hsa-miR-4752	3
FCGR3A	hsa-miR-326	1
	hsa-miR-330-5p	1
	hsa-miR-370	3
	hsa-miR-3074-5p	3
	hsa-miR-3690	2
	hsa-miR-4756-3p	3
TYMS	hsa-miR-215	1
VDR	hsa-miR-125a-5p	1
	has-miR-4319	1
ABCG2	hsa-miR-3163	3
	hsa-miR-4496	3

Conclusion: Based on our analysis it has been found that **hsa-miR-370**, **hsa-miR-3074-5p** and **hsa-miR-4756-3p** of FCGR3A and similarly **hsa-miR-3163** and **hsa-miR-4496** of ABCG2 contain more than 2 mRNA binding sites and hence the above mentioned miRNAs have a maximum chance to become a therapeutic target for Psoriasis. Since other miRNAs contain only one binding site, it was not consider for selection. Further understanding of the complete mechanism involved in miRNA dynamics require 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 a probable therapeutic target for genetic diseases.

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