Computational Analysis of Micro RNA based Target Interactions Related to Genome Wide Association Studies of Psoriasis

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Identification of a micro RNA (miRNA) based biomarker with multiple gene targets is a major challenge in the era of post genomics and the ability to apply an accurate computational method leads to the initiation of discovering novel miRNAs. In order to identify a miRNA based target interaction among the genes which are associated in the disease pathology of Psoriasis, we obtained a list of Psoriasis related genes from a database for Genome Wide Association Studies (GWAS) and then we went on to identify the network of miRNAs which are significantly related to the GWAS of Psoriasis. Further, we performed an enrichment analysis for identifying a specific miRNA on the basis of statistical tests to predict the miRNA which has the potential to become a biomarker. Finally we have identified the binding of the selected miRNA with the genes which are associated with Psoriasis. At present we have applied the above mentioned protocol for Psoriasis and in future this protocol can also be applied to other diseases.

Key words: Biomarker, Pathology and Psoriasis.

Psoriasis is a chronic skin disease and there is currently no permanent cure for Psoriasis. Psoriatic skin displays an inflammatory response by scaly lesions with an aberrant change in the gene expression[1]. Recent studies have revealed the fact that miRNAs play a vital role in regulating a class of post-transcriptional genes in Psoriasis. Micro RNA belongs to the family of non coding RNAs (ncRNA) which were discovered in 1993 by Victor Amoros, it consist of 19-25 nucleotides. Micro RNAs regulate the expression of about 30% of protein-coding mRNAs in humans. Initially, Lee *et al*. had found lin-4 as a regulator of developmental timing in Caenorhabditis elegans[2]. After several years, Reinhart *et al*. had discovered lethal-7 (let-7) gene in Caenorhabditis elegans[3].

Currently there are about 2500 miRNAs in the human genome. Majority of miRNA are intragenic[4]. Micro RNAs are initially transcribed as part of an RNA stem-loop that in turn forms a part of a several hundred nucleotides long precursor (pri-miRNA)[5]. Mature miRNA is a part of an RNA-induced silencing complex (RISC) which contains Dicer and many associated proteins[6]. 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[7]. 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 vital target of miRNA with accuracy. A detailed review for the advances in the miRNA target identification methods are available from the resources published by Zheng *et al*.[8]. Several other methodologies were also proposed on the basis of

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tertiary structure of precursor miRNA by Hin *et al.*[9], systems biology by Manczinger *et al.*[10] and text mining by Harishchander *et al.*[11-14].

MATERIALS AND METHODS

Catalog of Genome Wide Association Studies

Single Nucleotide Polymorphisms (SNPs) in the genome of a diseased population was taken from literature and to summarize the vital variations in the associated genes of diseased population, we have extracted the list of genes which are associated with Psoriasis and those genes were also cross validated with the published SNPs of Psoriasis[15,16].

Enrichr

Enrichr is an interactive tool for the enrichment analysis of gene list. It predicts the

Table 1. Enrichment Analysis of miRNAs related to GWAS of Psoriasis

| Micro RNAs	P-value	Z-score	Combined Score
hsa-miR-19a & hsa-miR-19b	0.007265	-1.93	2.54
hsa-miR-34b	0.02956	-1.83	2.37
hsa-miR-138	0.04989	-1.86	2.32
hsa-let-7a,hsa-let-7b,hsa-let-7c,hsa-let-7d,hsa-let-7e,hsa-let-7f,hsa-let-7g,hsa-let-7i & hsa-miR-98	0.02222	-1.77	2.30
hsa-miR-320	0.06218	-1.74	2.17
hsa-miR-224	0.02584	-1.65	2.14
hsa-miR-101	0.06218	-1.74	2.17
hsa-miR-22	0.05187	-1.65	2.05
hsa-miR-148a,hsa-miR-148b & hsa-miR-152	0.08474	-1.63	2.01
hsa-miR-25,hsa-miR-32,hsa-miR-92,hsa-miR-363& hsa-miR-367	0.08665	-1.63	2.00
hsa-miR-26a & hsa-miR-26b	0.08191	-1.47	1.81
hsa-miR-130a,hsa-miR-130b & hsa-miR-301	0.1350	-1.62	1.78
hsa-miR-490	0.1034	-1.40	1.71
hsa-miR-504	0.1291	-1.49	1.64
hsa-miR-27a & hsa-miR-27b	0.1750	-1.57	1.63
hsa-miR-362	0.1020	-1.19	1.46
hsa-miR-507	0.1917	-1.24	1.29
hsa-miR-194	0.1623	-1.22	1.27
hsa-miR-409-3p	0.2086	-1.23	1.26
hsa-miR519e	0.1824	-1.16	1.20
hsa-miR-365	0.1609	-1.15	1.20
hsa-miR-202	0.2526	-1.21	1.19
hsa-miR-323	0.2327	-1.12	1.15
hsa-miR-205	0.2252	-1.10	1.13
hsa-miR-143	0.2150	-1.10	1.12
hsa-miR-511	0.2826	-1.09	1.00
hsa-miR-145	0.3194	-1.09	0.98
hsa-miR-448	0.2920	-1.07	0.98
hsa-miR-24	0.3149	-1.03	0.92
hsa-miR-186	0.3598	-1.05	0.85
hsa-miR-141 & hsa-miR200a	0.3980	-1.03	0.80
hsa-miR-142-5p	0.3766	-0.96	0.77
hsa-miR-128a & hsa-miR-128b	0.4274	-0.99	0.76
hsa-miR-125a & hsa-miR-125b	0.4178	-0.97	0.75
hsa-miR-29a,hsa-miR-29b &hsa-miR-29c	0.5787	-1.02	0.53
hsa-miR-9	0.5640	-0.90	0.47
hsa-miR-506	0.7079	-0.93	0.32

According to the results of Enrichr, it has been identified that hsa-miR-19a and hsa-miR-19b has the least p value of 0.007204 and hence we consider this miRNA for binding analysis to identify its compatibility towards a biomarker.

Table 2. Binding of hsa-miR-19a-3p and hsa-miR-19b-3p with the associated genes of Psoriasis

Genes (*GWAS*)	Number of binding sites (*miRmap*)
CAST	3
TSC1	3
SPATA2	3
ERAP1	2
TNIP1	2
ERBB3	1
SDC4	1

Table 3. Binding of hsa-miR-19a-5p, hsa-miR-19b-1-5p and hsa-miR-19b-2-5p with the associated genes of Psoriasis

Genes (*GWAS*)	Number of binding sites(*miRmap*)
IL23R	2
CAST	1
TNIP1	1
TSC1	1
TRAF3IP2	1
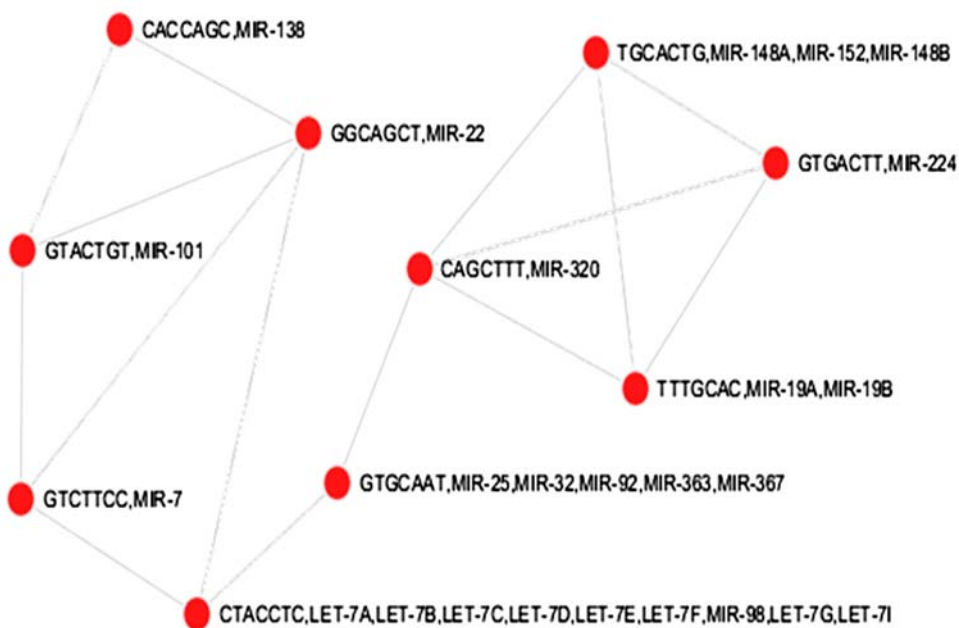
Fig. 1. Network of miRNAs associated with Psoriasis related genes in *GWAS*

miRNA regulated association with the gene list on the basis of standard deviation between the differentially expressed genes and their collective functions in mammals[17].

Mirmap

MiRmap software identifies the number of miRNA binding sites in a gene (mRNA).This software allows us to examine the feature correlation which is based on the experimental data resulted from high throughput techniques of immunopurification, transcriptomics and proteomics[18]. Overall, accessibility of target site appears to be the most predictive feature of miRmap.

RESULTS AND DISCUSSION

We have identified the list of Psoriasis related genes from GWAS catalogue and identified the network of miRNAs associated with Psoriasis, which is illustrated in Fig.1 and enrichment analysis was performed for miRNA selection, which is given in Table 1. Finally, binding analysis was performed for the selected miRNA to identify its significance as a biomarker and the results are given in Table 2 and Table 3.

Based on the binding analysis of miRmap, it has been identified that hsa-miR-19a-3p and hsa-

miR-19a-5p have a greater potential to become a biomarker for Psoriasis because it binds the mRNA of 7 genes (CAST, TSC1, SPATA2, ERAP1, TNIP1, ERBB3 and SDC4) which are associated with the Psoriasis. Whereas hsa-miR-19b-5p binds only with the mRNAs of 5 genes (CAST, TNIP1, IL23R, TSC1 and TRAF3IP2) which are associated with Psoriasis. In future, the regulatory mechanisms of hsa-miR-19a-3p and hsa-miR-19a-5p will be addressed to identify its impact on the signaling pathways of Psoriasis.

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