

A computational approach to identify microRNA (miRNA) based biomarker from the regulation of disease pathology.

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Abstract

In the post genomic era, identification of a potential miRNA in a computational approach for the significance of a discovery of systemic biomarker to treat diseases is a challenging task to execute. The challenge was addressed by identifying the associate genes from Pubmed, OMIM and DisgeNet and it was followed by identifying the miRNAs and transcription factors of associate target genes from RegNetworks. In the next step, a miRNA based regulatory network was constructed on the basis of association between gene-miR-TFs. Finally, the network was analyzed on the basis of statistical studies and miRNA based compatibility to identify a potential miRNA to be utilized as a biomarker to treat diseases in future. In this article, the computational approach was used for the identification of a miRNA based systemic biomarker in Psoriasis and in future this approach can also be used for other diseases.

Keywords: Post genomic era, RegNetworks, miRNA, Biomarkers.

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Introduction

Psoriasis is a disorder mediated by immune system by making certain faulty signals in the human body. It's still a belief that psoriasis can be developed under the specified condition i.e., "when the immune system signals the body to accelerate the growth of skin cells. In case of psoriasis, the skin cells mature in 3-6 days. Instead of being in shed, the cells in skin get pile up to cause the visible lesions. It was also found that the genes that cause psoriasis can determine the reaction of a person's immune system. These genes can either cause psoriasis or other conditions which are immune-mediated like Type-I diabetes or rheumatoid arthritis. Pathophysiology of psoriasis involves the understanding of the occurrence of prominent pathologies in the major components of skin i.e., the epidermis and the dermis. There are two well established hypotheses about the process that occurs in the development of the disease. The first hypothesis considers psoriasis as a disorder with excessive growth and reproduction of skin cells. Here, the problem is viewed as a fault of the epidermis and its keratinocytes. In second hypothesis, the disease is viewed as an immune-mediated disorder. Here, the excessive reproduction of skin cells is secondary to the factors produced by the immune system [1,2].

Micro RNA is a family of non-coding RNA (ncRNA) which was discovered in 1993, it consist of 19-25 nucleotides and regulates the expression of approximately 30% of protein-coding miRNAs in humans [3]. Base pairing at the position of 2-8 nucleotides were relative to the 5' end of the small RNA to be termed as the "seed" region and it appears to be important for target recognition. Maturation of miRNAs involves multiple steps and initially two intermediate forms of miRNAs, namely primary (pri-) and precursor (pre-) miRNAs, were produced sequentially. In this process, Drosha (RNase III enzyme) and the double-stranded RNA (dsRNA) binding protein Dgcr8 cleaves the pri-miRNAs to produce a hairpin-shaped pre-miRNAs

that are recognized by Exportin5 and they are subsequently transported from the nucleus to cytoplasm. There is another RNase III enzyme called Dicer which cleaves the pre-miRNAs to release ~22-nt double-stranded RNA duplexes (namely miRNA/miRNA* duplexes) with ~2-nt 3' overhangs [4]. One strand of a RNA duplex is termed as a mature miRNA which is further loaded into an Argonaute protein in the RNA-induced silencing complex (RISC) to exert its regulatory function on the basis of its binding with the target transcripts [5].

A unique miRNA can regulate the expression of hundreds of proteins and the expression of a specific protein may be controlled by several miRNAs [6]. The sequence conservation of most miRNAs lies between the distantly related organisms to suggest the impact of a strong evolutionary pressure [7] and they have been shown to participate in many fundamental life processes like development, differentiation, organogenesis, growth control and apoptosis. Accordingly, deregulation of miRNA expression has been shown to contribute to cancer, heart diseases, infectious diseases, inflammatory diseases and other medical conditions, making them potential targets for medical diagnosis and therapy [8]. Initially, Lee had found lin-4 as a regulator of developmental timing in nematode *Caenorhabditis elegans* [9]. After several years, Reinhart had discovered lethal-7 (let-7) gene in *Caenorhabditis elegans* [10]. At present, 2500 miRNAs are in the human genome. Majority of miRNA are intragenic [11]. Micro RNAs are initially transcribed as a part of an RNA stem-loop that in turn forms part of a several hundred nucleotides long miRNA precursor miRNA (pri-miRNA) [12-15].

Materials and Methods

PubMed

PubMed is an online search engine with open access facility to refer MEDLINE for identifying references and abstracts

on topics in biomedical and life sciences. The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez system to retrieve information. Most of the records in PubMed contain links to the complete article, in PubMed Central [16-18]. Information regarding the indexed journals in MEDLINE can be found in the Catalog of NLM.

DisGeNET

DisGeNET [19] is a platform of pattern discovery, designed for addressing the queries regarding the genetic imprint of human diseases. DisGeNET is one of the largest repositories of gene-disease associations (GDAs) in humans [19]. It offers a set of tools in bioinformatics to facilitate the data analysis by different users. It is maintained by the Integrative Biomedical Informatics (IBI) Group of the (GRIB)-IMIM/UPF at the Barcelona Biomedical Research Park (PRBB), Barcelona in Catalonia.

OMIM

Online Mendelian Inheritance in Man (OMIM) is a comprehensive compendium of human genes and phenotypes [20] that are available freely and updated daily. The complete text, referenced in the overviews of OMIM contains information on all known Mendelian disorders for 15,000 genes.

RegNetwork

RegNetwork [21] is a data base that contains five types (Transcription factor-transcription factor, transcription factor-gene, transcription factor-microRNA, and microRNA-transcription factor) of transcriptional and posttranscriptional regulatory relationships for human and mouse.

Cytoscape

Cytoscape [22] software is used for network construction, visualization and analysis in bioinformatics with an open source platform for visualizing the interactions in molecular networks and integrating them with the profiles of gene expression. Additional features in cytoscape are available as plugins for network and molecular profiling.

Cytohubba

Cytohubba [23] is a cytoscape plugin for performing the analyses of gene regulation and protein-protein interaction involved in the process of cellular pathways in the process of signal transduction. Cytohubba ranks the nodes of network by topological methods like radiality, betweenness, closeness, bottleneck, eccentricity and etc.

MiRmap

miRmap [24] software addresses the challenges in post transcriptional repression of miRNAs in human genome by evolutionary, probabilistic thermodynamic and sequence-based features.

Triplex RNA

Triplex RNA [25] is a database of cooperating miRNAs with their mutual targets. In this database miRNA target prediction is based on the analysis of predicted miRNA triplex with molecular dynamics simulations and differential modeling procedures in mathematics.

DAVID

The Database for Annotation, Visualization and Integrated Discovery (DAVID) contain complete information about functional annotation of genes. The current version of DAVID [26] is 6.8 and it provides a set of comprehensive tools for functional annotation of genes.

Methodology (Computational approach of miRNA associated regulation)

1. Identify the disease associated genes from Pubmed, DisGeNET and OMIM.
2. Obtain the associated list of miRNAs and transcription factors for the disease associated genes from Reg networks.
3. Construct and analyze the network in Cytoscape.
4. Identify the miRNA based hub genes and transcription factors from cytohubba.
5. Identify the implication of miRNA in Regulatory network in miRmap and miRNA triplex.
6. Identify and analyze the gene associated pathways in DAVID.

Results

Text mining of Genes from Pubmed, DisGeNET and OMIM along with the miRNAs and transcription factors from Regnetworks resulted in the identification of interaction between 92 genes-437 miRNA-285 transcription factors and the results were given in Table 1. A regulatory network was constructed in Cytoscape and the properties of the network were analyzed in the Network Analyzer. Finally, the hub genes were identified from cytohubba and the miRNA based regulation was analyzed on the basis of seed pairing in miRmap and the experimental evidences from the previous literature.

Construction of regulatory network (Cytoscape)

The regulatory network was constructed with 92 genes, 437 miRNAs and 285 TFs. Network was initiated by the Pubmed and Database Mining of 722 regulators (i.e., 285 TFs and 437 miRNAs) to interact with the 92 target genes in such a way to form 822 nodes and 2119 edges.

Identification of hub genes in regulatory network in top-down approach (Cytohubba)

The genes and their regulators (Micro RNAs and transcription factors) were subjected to the analysis in cytohubba by various global based statistical methods like edge percolated component, bottleneck, eccentricity, closeness, radiality, betweenness and Stress along with local based statistical methods like maximal clique centrality, density of maximum neighborhood component, maximum neighborhood component and degree to identify their connectivity. Among the various methods of analysis in top down approach only a global based statistics of eccentricity method and the local based statistics of maximal clique centrality along with density of maximum neighborhood component and clustering coefficient methods in cytohubba resulted in obtaining a regulatory network of gene-miRNA-TFs

Table 1. Psoriasis associated genes, miRNAs and transcription factors.

S. No.	Genes (Pubmed, DisGeNET and OMIM)	miRNAs (RegNetworks)	Transcription Factor (RegNetworks)
	HPSE	hsa-miR-1258	ETS1; ETS2; ETV4; MAX; MXI1::CLEC5A; AR; ESR1 HOXA7
	CCL20	hsa-miR-21-5p; hsa-miR-144; hsa-miR-145; hsa-miR-21; hsa-miR-330-3p; hsa-miR-338-5p; hsa-miR-361-3p hsa-miR-380; hsa-miR-496; hsa-miR-518e; hsa-miR-525-5p; hsa-miR-548d-3p; hsa-miR-590-3p; hsa-miR-590-5p hsa-miR-635; hsa-miR-766; hsa-miR-802; hsa-miR-921	CTCF;MYC; PPARG::RXRA RELA; SP1
	CCL2	hsa-miR-124-3p; hsa-miR-124; hsa-miR-124a; hsa-miR-141; hsa-miR-142-5p; hsa-miR-323-3p; hsa-miR-374a; hsa-miR-374b; hsa-miR-421; hsa-miR-495; hsa-miR-545; hsa-miR-577; hsa-miR-633	JUN; NFIC; NFKB1; NFKB2; NR2F2; REL; RELA; SMAD3 SMAD4; SP1; SRF; STAT1; STAT2; STAT3; STAT4; STAT6
	EIF4E	hsa-miR-1; hsa-miR-122; hsa-miR-141; hsa-miR-145-3p; hsa-miR-146b-5p; hsa-miR-150; hsa-miR-16; hsa-miR-186; hsa-miR-195; hsa-miR-203; hsa-miR-206; hsa-miR-325; hsa-miR-34c-3p; hsa-miR-377; hsa-miR-380; hsa-miR-495; hsa-miR-498; hsa-miR-503; hsa-miR-520d-5p; hsa-miR-524-5p; hsa-miR-545; hsa-miR-582-5p; hsa-miR-586; hsa-miR-592; hsa-miR-599; hsa-miR-613; hsa-miR-654-5p; hsa-miR-656; has-miR-9; has-miR-141-3p; has-miR-145-5p; has-miR-497-5p; has-miR-768-3p	BACH1; CUX1; EMX2; FOS; FOSB; FOSL1; FOXD1; FOXF2; JUN; JUNB; JUND; MAX; MXI1::CLEC5A; MYC NFIL3; NFYA; NR3C1; PML STAT1; STAT2; STAT3; STAT4; STAT6; USF1
	PPARD	hsa-miR-138-5p; hsa-miR-29b; hsa-miR-29c; hsa-miR-93	ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BCL6; CREB1; CTCF; EGR1; EP300; GABPA; HDAC1; HDAC2; HDAC3; HDAC7; JUP; LEF1; NCOR1; NCOR2; NR0B2; NRIP1; PROX1; RELA; RXRA; RXRB; RXRG; SMAD9; SPEN TCF7; TCF7L1; TCF7L2
	TAP2	hsa-miR-330-3p; hsa-miR-370-3p; hsa-miR-384; hsa-miR-670-3p; hsa-miR-6893-3p; hsa-miR-185; hsa-miR-219-2-3p; hsa-miR-330-3p; hsa-miR-370; hsa-miR-371-5p; hsa-miR-384; hsa-miR-409-3p; hsa-miR-433; hsa-miR-522; hsa-miR-582-5p; hsa-miR-645; hsa-miR-655; hsa-miR-875-3p; hsa-miR-885-5p; hsa-miR-921	CREB1; CUX1; ESR1; MAX; MYC; NFE2L1; STAT5A
	CYLD	hsa-miR-181b-5p; hsa-miR-182-5p; hsa-miR-362-5p; hsa-miR-500a-5p hsa-miR-130a; hsa-miR-130b; hsa-miR-15a; hsa-miR-15b; hsa-miR-16 hsa-miR-181b; hsa-miR-181d; hsa-miR-182; hsa-miR-186; hsa-miR-195 hsa-miR-197; hsa-miR-19a; hsa-miR-19b; hsa-miR-301; hsa-miR-301a; hsa-miR-301b; hsa-miR-340; hsa-miR-362-5p; hsa-miR-424; hsa-miR-454 hsa-miR-497; hsa-miR-508-3p; hsa-miR-543; hsa-miR-544; hsa-miR-548a-5p; hsa-miR-548b-5p; hsa-miR-548c-5p; hsa-miR-548d-5p; hsa-miR-579; hsa-miR-590-3p; hsa-miR-656; hsa-miR-944	ATF2; EGR1; IKKKG; JUN; LHX3; NFKB1; NFYA; POU2F1; SP1; TCF3

	IGF1	hsa-miR-27a-3p; hsa-miR-29a-3p; hsa-miR-190a-5p; hsa-miR-199a-3p; hsa-let-7i-5p; hsa-miR-299-3p; hsa-miR-190b; hsa-let-7e-5p; hsa-miR-483-3p; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-1; hsa-miR-105; hsa-miR-128; hsa-miR-129-5p; hsa-miR-1297; hsa-miR-130a; hsa-miR-130b; hsa-miR-149; hsa-miR-152; hsa-miR-154; hsa-miR-186; hsa-miR-18a; hsa-miR-18b; hsa-miR-190; hsa-miR-192; hsa-miR-19a; hsa-miR-19b; hsa-miR-206; hsa-miR-215; hsa-miR-221; hsa-miR-222; hsa-miR-23a; hsa-miR-23b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-301a; hsa-miR-301b; hsa-miR-340; hsa-miR-361-5p; hsa-miR-362-5p; hsa-miR-377; hsa-miR-410; hsa-miR-425; hsa-miR-450b-5p; hsa-miR-454; hsa-miR-486-5p; hsa-miR-488; hsa-miR-489; hsa-miR-495; hsa-miR-502-5p; hsa-miR-503; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-556-3p; hsa-miR-561; hsa-miR-576-5p; hsa-miR-590-3p; hsa-miR-592; hsa-miR-599; hsa-miR-607; hsa-miR-613; hsa-miR-626; hsa-miR-632; hsa-miR-634; hsa-miR-656; hsa-miR-758; hsa-miR-942; hsa-miR-98	CEBPA; CTCF; ESR1; FOXD1; FOXF2; JUN; MYB; POU3F2; RFX1; STAT1; STAT2; STAT3; STAT5A; STAT5B; TGIF1
	BCL2	hsa-miR-34b-5p; hsa-miR-21-5p; hsa-miR-153-3p; hsa-miR-204-5p; hsa-let-7a-5p; hsa-miR-15a-5p; hsa-miR-15b-5p; hsa-miR-16-5p; hsa-miR-34a-5p; hsa-miR-20a-5p; hsa-miR-17-5p; hsa-miR-29a-3p; hsa-miR-29b-3p; hsa-miR-29c-3p; hsa-miR-34b-3p; hsa-miR-181a-5p; hsa-miR-181b-5p; hsa-miR-181c-5p; hsa-miR-181d-5p; hsa-miR-33b-5p; hsa-miR-34c-5p; hsa-miR-192-5p; hsa-miR-195-5p; hsa-miR-630; hsa-miR-451a; hsa-miR-125b-5p; hsa-miR-365a-3p; hsa-miR-449a; hsa-miR-200b-3p; hsa-miR-200c-3p; hsa-miR-429; hsa-miR-7-5p; hsa-miR-136-5p; hsa-miR-24-2-5p; hsa-miR-148a-3p; hsa-miR-24-2-5p; hsa-miR-182-5p; hsa-miR-143-3p; hsa-miR-205-5p; hsa-miR-126-3p; hsa-miR-18a-5p; hsa-miR-497-5p; hsa-miR-1915-3p; hsa-miR-206; hsa-miR-448; hsa-miR-708-5p; hsa-miR-184; hsa-miR-30b-5p; hsa-miR-135a-5p; hsa-miR-224-5p; hsa-miR-503-5p; hsa-miR-494-3p; hsa-miR-211-5p	
	AREG	hsa-miR-34a-5p; hsa-miR-200a-3p; hsa-miR-129-5p; hsa-miR-135a; hsa-miR-135b; hsa-miR-345; hsa-miR-34a; hsa-miR-34c-5p; hsa-miR-449a; hsa-miR-449b; hsa-miR-499-5p; hsa-miR-517a; hsa-miR-517c; hsa-miR-548a-5p; hsa-miR-548c-5p; hsa-miR-556-5p; hsa-miR-559; hsa-miR-561; hsa-miR-577; hsa-miR-583; hsa-miR-584; hsa-miR-590-3p; hsa-miR-640 hsa-miR-944	AR; BRCA1; CREB1; E2F1; EGR1; HOXB13; IRF1; NFKB1 PAX2; RARA; RELA; SMAD3 SMAD4; SP1; STAT5A; WT1
	VNN3	hsa-miR-138-5p; hsa-miR-455-5p; hsa-miR-135a; hsa-miR-135b; hsa-miR-199a-3p; hsa-miR-345; hsa-miR-371-5p; hsa-miR-421; hsa-miR-455-3p; hsa-miR-455-5p; hsa-miR-505 hsa-miR-514; hsa-miR-744	CTCF; FOXA2; NFKB1;NFKB2 REL; RELA; STAT5B
	MMP9	hsa-miR-451a; hsa-miR-491-5p; hsa-miR-338-3p; hsa-miR-9-5p; hsa-miR-211-5p; hsa-let-7e-5p; hsa-miR-133b; hsa-miR-29b-3p; hsa-miR-191; hsa-miR-204; hsa-miR-339-5p; hsa-miR-451; hsa-miR-483-3p; hsa-miR-494 hsa-miR-515-5p; hsa-miR-520a-5p; hsa-miR-525-5p	AR; BACH1; BACH2; ERG; ETS1; ETS2; ETV4; FLI1; FOS; FOSB; FOSL1; JUN; JUNB; JUND; MYC; NFE2; NFE2L1; NFKB1; NFKB2; PPARA; PPARG; RELA; RELB; SMAD3; SP1; SPI1
	HBEGF	hsa-miR-194-5p; hsa-miR-132-3p; hsa-let-7d; hsa-let-7g; hsa-let-7i; hsa-miR-132; hsa-miR-135a; hsa-miR-135b; hsa-miR-182; hsa-miR-183; hsa-miR-194; hsa-miR-212; hsa-miR-27a; hsa-miR-27b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-31; hsa-miR-376c; hsa-miR-379; hsa-miR-623; hsa-miR-662; hsa-miR-96	CTCF; ETS2; MAX; TBP; ZBTB16
	TGFA	hsa-miR-152-3p; hsa-miR-376c-3p; hsa-miR-101; hsa-miR-130a; hsa-miR-130b; hsa-miR-137; hsa-miR-148a; hsa-miR-148b; hsa-miR-152; hsa-miR-205; hsa-miR-23a; hsa-miR-23b; hsa-miR-301	CTCF; EPAS1; ESR1; FOXA1; FOXA2; HIF1A; NFKB1; NFKB2; NKD2; PGR; TFAP2A; TP53
	LHFP	hsa-miR-133a-3p.2; hsa-miR-133b; hsa-miR-101; hsa-miR-133a; hsa-miR-133b; hsa-miR-141; hsa-miR-147; hsa-miR-153; hsa-miR-200a; hsa-miR-200b; hsa-miR-200c; hsa-miR-218; hsa-miR-26a; hsa-miR-297; hsa-miR-300; hsa-miR-337-3p; hsa-miR-340; hsa-miR-381; hsa-miR-429; hsa-miR-448; hsa-miR-491-3p; hsa-miR-500; hsa-miR-501-5p; hsa-miR-607; hsa-miR-618; hsa-miR-632; hsa-miR-9	AHR; ARNT; CTCF; PATZ1

	EGFR	hsa-miR-7-5p; hsa-miR-145-5p; hsa-miR-128-3p; hsa-miR-146a-5p; hsa-miR-21-5p; hsa-miR-128b; hsa-miR-133a-3p; hsa-miR-133b; hsa-miR-27a-3p; hsa-let-7a-5p; hsa-miR-574-3p; hsa-miR-219a-5p; hsa-miR-302b-3p; hsa-miR-125a-5p; hsa-miR-218-5p; hsa-miR-21; hsa-miR-1; hsa-miR-128; hsa-miR-141; hsa-miR-146a; hsa-miR-16; hsa-miR-21; hsa-miR-27a; hsa-miR-27b; hsa-miR-548c-3p; hsa-miR-7	AR; CEBPB; CTNNB1; E2F1; EGR1; ELF3; ESR1; ESR1; ESR2; HOXC10; HTT; MEF2A; MYB; NFKB2; PPARG; REL; RELA; SMURF2; SP1; STAT1; STAT3; STAT5A; STAT5B; TFAP2A; TP53; WT1; WWP1; XRCC6
	SGCG	hsa-miR-137	Nil
	SDC4	hsa-miR-18a-5p; hsa-miR-1; hsa-miR-124; hsa-miR-194; hsa-miR-224; hsa-miR-506; hsa-miR-548d-3p; hsa-miR-637; hsa-miR-941	EBF1; MAX; NFKB1; REL; RELA; SP1; STAT5A; STAT5B; mTFAP2A; TFAP2C; TGFB11
	IGF1R	hsa-miR-122-5p; hsa-miR-133b; hsa-miR-145-5p; hsa-miR-7-5p; hsa-miR-138-5p; hsa-miR-194-5p; hsa-miR-99a-5p; hsa-miR-223-3p; hsa-miR-100-5p; hsa-miR-497-5p; hsa-miR-152-3p; hsa-miR-139-5p; hsa-miR-376a-3p; hsa-miR-376c-3p; hsa-miR-383-5p; hsa-miR-181b-5p; hsa-miR-335-5p; hsa-miR-320a; hsa-let-7e-5p; hsa-miR-125b-2-3p; hsa-let-7c-5p; hsa-miR-16-5p; hsa-miR-630; hsa-let-7b-5p; hsa-miR-143-3p; hsa-miR-133a-3p; hsa-miR-140-5p; hsa-miR-150-3p; hsa-miR-375; hsa-miR-503-5p; hsa-miR-378a-3p; hsa-miR-185-5p; hsa-miR-206; hsa-miR-21-5p; hsa-miR-26b-5p; hsa-miR-486-5p; 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-100; hsa-miR-106a; hsa-miR-122; hsa-miR-133b; hsa-miR-138; hsa-miR-139-5p; hsa-miR-140-5p; hsa-miR-141; hsa-miR-143; hsa-miR-145; hsa-miR-153; hsa-miR-15a; hsa-miR-15b; hsa-miR-16; hsa-miR-182; hsa-miR-186; hsa-miR-194; hsa-miR-195; hsa-miR-200a; hsa-miR-202; hsa-miR-203; hsa-miR-214; hsa-miR-22; hsa-miR-223; hsa-miR-300; hsa-miR-302b; hsa-miR-302c; hsa-miR-302d; hsa-miR-30a; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e; hsa-miR-320; hsa-miR-328; hsa-miR-329; hsa-miR-330-3p; hsa-miR-340; hsa-miR-361-3p; hsa-miR-362-3p; hsa-miR-372; hsa-miR-373; hsa-miR-376c; hsa-miR-377; hsa-miR-378; hsa-miR-379; hsa-miR-381; hsa-miR-409-5p; hsa-miR-422a; hsa-miR-424; hsa-miR-448; hsa-miR-455-5p; hsa-miR-489; hsa-miR-493; hsa-miR-494; hsa-miR-495; hsa-miR-497; hsa-miR-503; hsa-miR-505; hsa-miR-507; hsa-miR-509-3-5p; hsa-miR-509-5p; hsa-miR-520a-3p; hsa-miR-520b; hsa-miR-520c-3p; hsa-miR-520d-3p; hsa-miR-520d-5p; hsa-miR-520e; hsa-miR-524-5p; hsa-miR-539; hsa-miR-548c-3p; hsa-miR-548d-3p; hsa-miR-557; hsa-miR-570; hsa-miR-577; hsa-miR-583; hsa-miR-625; hsa-miR-626; hsa-miR-646; hsa-miR-650; hsa-miR-653; hsa-miR-671-3p; hsa-miR-7; hsa-miR-769-5p; hsa-miR-892b; hsa-miR-944; hsa-miR-96; hsa-miR-98; hsa-miR-99a	BACH1; BACH2; BRCA1; CTNNB1; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; EGR1; ESR1; FOXO1; FOXO3; FOXO3B; FOXO4; MAX; MXI1::CLEC5A; MYB; MYC; MZF1; PAX5; REL REL; SMURF2; SP1; SREBF1; SREBF2; STAT3; TFAP2A; TP53 USF1; WT1; WWP1
	LEP	hsa-miR-9-5p; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-331-3p hsa-miR-369-5p; hsa-miR-520g hsa-miR-520h; hsa-miR-575; hsa-miR-875-5p; hsa-miR-9	ARNT; CEBPA; CEBPB CEBPD; FOXO1; HIF1A HLF; MIF; TBP
	KLK13	hsa-miR-330-3p; hsa-miR-455-5p; hsa-miR-542-3p; hsa-miR-591; hsa-miR-620; hsa-miR-654-5p	CREB1; EGR1; KLF12; MZF1; PPARG
	HMOX1	hsa-miR-196a-5p; hsa-miR-122-5p; hsa-miR-24-3p; hsa-miR-16; hsa-miR-196a-3p; hsa-miR-873	BACH2; CREB1; ERG; ETS1; FLI1; HIF1A; HNF4A; MAX; MXI1::CLEC5A; MYC; NFE2; NFIC; NFKB1; PPARG::RXRA; RXRA; SMAD7; SP1; SPI1; STAT3; TFAP2A; USF1; USF2
	IFI6	hsa-miR-1225-3p; hsa-miR-558; hsa-miR-624; hsa-miR-920	TFAP2C; USF1

	SFXN1	hsa-miR-30a-5p; hsa-miR-30b-5p; hsa-miR-30c-5p; hsa-miR-30d-5p; hsa-miR-30e-5p; hsa-miR-1; hsa-miR-128a hsa-miR-134; hsa-miR-30a; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e	HNF4A; MAX; MYC
	IL23R	hsa-miR-383-5p.2; hsa-miR-216a; hsa-miR-297; hsa-miR-331-5p; hsa-miR-454; hsa-miR-509-3p; hsa-miR-583; hsa-miR-875-3p; hsa-miR-876-3p; hsa-miR-936	FOS; JUN; RORA; STAT3
	PTPN22	hsa-miR-181a-5p; hsa-miR-133a; hsa-miR-133b; hsa-miR-325; hsa-miR-630	CDC5L; IRF1; MEF2A TP53
	LOR	hsa-miR-196a-5p; hsa-miR-196b-5p; 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-135a; hsa-miR-135b; hsa-miR-196a; hsa-miR-196b; hsa-miR-28-3p; hsa-miR-296-3p; hsa-miR-331-3p; hsa-miR-450b-5p; hsa-miR-490-5p; hsa-miR-570; hsa-miR-583; hsa-miR-641; hsa-miR-766; hsa-miR-873; hsa-miR-875-3p; hsa-miR-922; hsa-miR-98	ATF1; CREB1; FOS; FOSB; JUN; JUNB; JUND; SP3
	S100A9	hsa-miR-196a-5p	AR; CTCF; MYB; RARA RARB; RARG; SPI1; TBP TFAP2A; TP53
	S100A8	hsa-miR-24-3p; hsa-miR-135a; hsa-miR-135b; hsa-miR-202; hsa-miR-326 hsa-miR-330-5p; hsa-miR-544	AR; FOS; FOSB; JUN; JUNB; JUND; PDCD11; RARA; RARB; RARG TBP; TP53
	IL10	hsa-miR-106a-5p; hsa-let-7c-5p; 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-106a; hsa-miR-10b; hsa-miR-142-3p; hsa-miR-186; hsa-miR-198; hsa-miR-202; hsa-miR-337-5p; hsa-miR-543; hsa-miR-588; hsa-miR-597; hsa-miR-630; hsa-miR-671-5p; hsa-miR-769-5p; hsa-miR-888; hsa-miR-98	ATF1; CEBPA; CEBPB; CREB1; E2F1; ESR1; ETS1; MEF2A; NFKB1 POU3F2; PPARG; SP1; STAT3; TBP
	IL24	hsa-miR-203a-3p; hsa-miR-205-5p; hsa-miR-132; hsa-miR-140-3p; hsa-miR-141; hsa-miR-183; hsa-miR-186; hsa-miR-200a; hsa-miR-200b; hsa-miR-200c; hsa-miR-203; hsa-miR-205 hsa-miR-27a; hsa-miR-27b; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-300; hsa-miR-324-3p; hsa-miR-338-5p; hsa-miR-380; hsa-miR-381; hsa-miR-425; hsa-miR-429; hsa-miR-452; hsa-miR-495; hsa-miR-506; hsa-miR-518a-3p; hsa-miR-518b; hsa-miR-518c; hsa-miR-518f; hsa-miR-520a-5p; hsa-miR-525-5p; hsa-miR-573; hsa-miR-582-5p; hsa-miR-600; hsa-miR-601; hsa-miR-602; hsa-miR-616; hsa-miR-628-5p; hsa-miR-767-5p hsa-miR-891b; hsa-miR-943	CEBPB; JUN; TFAP2A TFAP2C
	ADAM17	hsa-miR-26a-5p; hsa-miR-122-5p; hsa-miR-145-5p; hsa-miR-152-3p	CTCF; EGR1; FHL2; GABPA; HNF4A; NOTCH2; NOTCH3; NOTCH4;PPARG::RXRA; SP1; TFAP2A; TFAP2C; YY1
	IL36RN	hsa-miR-216a-5p; hsa-miR-122; hsa-miR-338; hsa-miR-338-3p; hsa-miR-507; hsa-miR-197; hsa-miR-338-3p	MCM6; SKIL; SSBP2 SSBP4
	IL1RN	hsa-miR-125a-5p; hsa-miR-125b-3p; hsa-miR-371-3p; hsa-miR-515-5p	BACH1; BACH2; EBF1; FOXA2; HNF4A; NFKB1; NR3C1; PAX5; RXRA; RXRB::RARB; SPI1; STAT5A

	CTLA4	hsa-miR-155-5p; hsa-miR-101; hsa-miR-105; hsa-miR-155; hsa-miR-205 hsa-miR-380; hsa-miR-384; hsa-miR-429; hsa-miR-432; hsa-miR-449b; hsa-miR-451; hsa-miR-496; hsa-miR-516a-3p; hsa-miR-517a; hsa-miR-651 hsa-miR-656	BPTF; STAT5A; STAT5B
	SGPP2	hsa-miR-101-3p.1; has-miR-24	EBF1; NFKB1; NFKB2; RELA; RELB; TCF3; ZEB1
	IRF2	hsa-miR-20a-5p; hsa-miR-153; hsa-miR-18a; hsa-miR-18b; hsa-miR-214 hsa-miR-220c; hsa-miR-221; hsa-miR-222; hsa-miR-23a; hsa-miR-23b; hsa-miR-26a; hsa-miR-26b; hsa-miR-302a hsa-miR-302b; hsa-miR-302c; hsa-miR-302d; hsa-miR-340; hsa-miR-342-5p; hsa-miR-372; hsa-miR-373; hsa-miR-455-5p; hsa-miR-495; hsa-miR-512-3p; hsa-miR-520a-3p; hsa-miR-520b; hsa-miR-520c-3p; hsa-miR-520d-3p; hsa-miR-520e; hsa-miR-520f; hsa-miR-549; hsa-miR-553 hsa-miR-556-5p; hsa-miR-568; hsa-miR-571; hsa-miR-574-5p; hsa-miR-648; hsa-miR-934	EP300; HMGN1; IRF2BP1; IRF7; IRF8; KAT2B; MAX; MX1::CLEC5A; MYC; NFKB1; NFKB2; RELA; RELB; STAT1
	IL4	hsa-miR-340-5p; hsa-miR-410-3p; hsa-miR-29a	CEBPA; CEBPB; CEBPG; ETV4; GATA1; NFKB1; POU2F1; POU2F2; RELA; STAT1; STAT2; TFAP2A TP53
	IL12B	hsa-miR-23a-3p; hsa-miR-23b-3p; hsa-miR-23c; hsa-miR-130a-5p; hsa-miR-183; hsa-miR-219-5p; hsa-miR-220c hsa-miR-494; hsa-miR-545; hsa-miR-632; hsa-miR-95	CEBPA; CEBPB; ETS1; ETS2; FOS; IRF5; JUN; NFKB1; REL; RELA; SP1 SP3; SPI1
	CDKAL1	hsa-miR-370-5p; hsa-miR-873-5p.1; hsa-let-7b; hsa-let-7c; hsa-let-7d; hsa-let-7e; hsa-miR-145; hsa-miR-25; hsa-miR-301a; hsa-miR-301b; hsa-miR-451; hsa-miR-454; hsa-miR-495; hsa-miR-517b; hsa-miR-519a; hsa-miR-576-3p; hsa-miR-613; hsa-miR-616; hsa-miR-620; hsa-miR-650; hsa-miR-665; hsa-miR-766; hsa-miR-767-5p; hsa-miR-770-5p; hsa-miR-92a; hsa-miR-92b; hsa-miR-944	CUX1; POU3F2
	TNF	hsa-miR-19a-3p; hsa-miR-203a-3p; hsa-miR-187-3p; hsa-miR-130a-3p; hsa-miR-143-3p; hsa-miR-130a; hsa-miR-130b; hsa-miR-149; hsa-miR-187 hsa-miR-19a; hsa-miR-296-3p; hsa-miR-409-5p; hsa-miR-454; hsa-miR-516a-5p; hsa-miR-516b; hsa-miR-519b-3p; hsa-miR-542-3p; hsa-miR-581; hsa-miR-592; hsa-miR-599; hsa-miR-654-3p; hsa-miR-770-5p; hsa-miR-875-3p; hsa-miR-875-5p; hsa-miR-939; hsa-miR-17; hsa-miR-9; hsa-miR-31	AHR; ARNT; ATF1; ATF2; CEBPB; CEBPD; CREB1; EBF1; EGR1; EGR4; ELK1; ETS1; ETV4; FOS; IKKBK; IRF5 JUN; NFAT5; NFATC1; NFATC2; NFATC3; NFATC4; NFE2L1; NFKB1; NFKB2; POU2F1; RELA; SMAD6; SMAD7; SP1; SP3; SPI1; STAT1; STAT2; STAT3; STAT4; STAT5A; STAT5B; STAT6; TBP; TFAP2A; TP53
	TNXB	hsa-miR-30a-5p; hsa-miR-30b-5p; hsa-miR-30c-5p; hsa-miR-30d-5p; hsa-miR-30e-5p; hsa-miR-137; hsa-miR-146b-3p; hsa-miR-149; hsa-miR-152; hsa-miR-30a; hsa-miR-30a-5p; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e; hsa-miR-372; hsa-miR-483-3p; hsa-miR-486-5p; hsa-miR-504; hsa-miR-512-3p; hsa-miR-638; hsa-miR-875-5p; hsa-miR-892b; hsa-miR-942	ARNT; CTCF; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; FOS; FOSB; FOSL1; HNF4A; JUN; JUNB; JUND; MAX; MEIS1; MYC; NFKB1; NR2F1; NR3C1; PAX2; PAX5; PPARG; RFX1; SREBF1; SREBF2; TFAP2A; TFAP2C; TGIF1; USF1; XBP1; YY1
	TRAF3IP2	hsa-miR-3064-5p; hsa-miR-6504-5p; hsa-miR-147; hsa-miR-191; hsa-miR-30b; hsa-miR-30c; hsa-miR-342-5p; hsa-miR-512-3p; hsa-miR-548d-3p; hsa-miR-609; hsa-miR-637; hsa-miR-665; hsa-miR-765; hsa-miR-887; hsa-miR-935	CUX1; FOXD3; FOXF2; FOXO4; IKKBK; IKKBK; MAX; MX1::CLEC5A; NKX2-2; NKX3-1; NR3C1; POU2F1; POU2F2; POU3F1; POU3F2; POU3F3; POU5F1; SRY; TCF3; USF1; ZEB1
	CCR6	hsa-miR-518a-3p; hsa-miR-150-5p	CTCF
	IL6	hsa-let-7a-5p; hsa-miR-203a-3p; hsa-miR-142-3p; hsa-miR-26a-5p; hsa-miR-365a-3p; hsa-miR-107; hsa-let-7c-5p; hsa-miR-149-5p; hsa-miR-223-3p	AR; ATF1; CEBPA; CEBPB; CEBPD; CREB1; CTCF; EGR1; FOS; IRF1; IRF5; JUN; MYC; NFE2; NFIC; NFKB1; NFKB2; PBX1; PPARG; RARA; REL; RELA; RREB1; STAT3; STAT5A; TP53 USF1; ZBTB16

	LYNX1	hsa-miR-491-5p; hsa-miR-214; hsa-miR-324-3p; hsa-miR-324-5p; hsa-miR-330-5p; hsa-miR-370; hsa-miR-423-5p; hsa-miR-432; hsa-miR-511; hsa-miR-516a-5p; hsa-miR-526b; hsa-miR-608; hsa-miR-612; hsa-miR-637; hsa-miR-940; hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i; hsa-miR-137; hsa-miR-144; hsa-miR-149; hsa-miR-153; hsa-miR-217; hsa-miR-338-5p; hsa-miR-365; hsa-miR-371-5p; hsa-miR-376a; hsa-miR-376b; hsa-miR-383; hsa-miR-548b-5p; hsa-miR-568; hsa-miR-574-3p; hsa-miR-587; hsa-miR-589; hsa-miR-655; hsa-miR-760; hsa-miR-98; hsa-miR-301b; hsa-miR-148a hsa-miR-152; hsa-miR-519c; hsa-miR-301a	CTCF
	TNFSF8	hsa-miR-24-3p; hsa-miR-146b-3p; hsa-miR-200b; hsa-miR-429; hsa-miR-525-3p; hsa-miR-626; hsa-miR-768-5p; hsa-miR-885-5p	NIL
	TNFRSF1A	hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-22; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-558	DAXX; EP300; IKBKB; IKBKG; JUN; STAT1
	VDR	hsa-miR-125b-5p; hsa-let-7a-5p; hsa-miR-27b-3p; hsa-miR-124; hsa-miR-125b; hsa-miR-506; hsa-miR-544	BACH2; CREBBP; CTCF FOS; FOSB; FOSL1; GTF2B; HMG3; HNF4A; HR; JUN; JUNB; JUND; KDM5A; LMO2; MAX; MED1; NCOA1; NCOA2; NCOA6; NR0B2; NR1H2; NRIP1; RXRA; RXRB; RXRG; SMAD3; SNW1; STAT1; TRIM24
	NOD2	hsa-miR-122-5p; hsa-miR-122-3p; hsa-miR-495; hsa-miR-671-5p	MAX; MXI1::CLEC5A NFKB1; REL; SPI1; USF1
	STAT3	hsa-miR-20b-5p; hsa-miR-337-3p; hsa-miR-21-5p; hsa-miR-92a-3p; hsa-miR-20a-5p; hsa-miR-124-3p; hsa-miR-130b-3p; hsa-miR-106a-5p; hsa-miR-106b-5p; hsa-miR-874-3p; hsa-miR-4516; hsa-miR-17-5p; hsa-miR-181a-5p; hsa-miR-1234-3p; hsa-miR-106a; hsa-miR-106b; hsa-miR-124; hsa-miR-125b; hsa-miR-130a; hsa-miR-17; hsa-miR-17-5p; hsa-miR-20a; hsa-miR-20b; hsa-miR-21; hsa-miR-372; hsa-miR-410; hsa-miR-495; hsa-miR-506; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-519d; hsa-miR-665 hsa-miR-93	AR; ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BHLHE40; BRCA1; CEBPB; CREB1 CREBBP; DAXX; EIF2AK2; EP300; FOXM1; GATA1; GATA2; GTF2I; HDAC1; HDAC2; HDAC3; HES1; HIF1A; HNF1A; IRF9; JUN; KAT5; KHDRBS1; MAX; MXI1::CLEC5A; MYC; MYOD1; NCOA1; NFKB1; NMI; NR3C1; PIAS1; PIAS2; PIAS3; PIAS4; PML; POU3F1; PTMA; RARA; RELA; STAT1; STAT4; STAT5A STAT5B; TFAP2A; TP53 USF1; ZNF148; ZNF467
	SLC9A3R1	hsa-miR-24-3p; hsa-miR-146b-3p; hsa-miR-149; hsa-miR-200b; hsa-miR-200c; hsa-miR-24; hsa-miR-339-5p; hsa-miR-367; hsa-miR-532-5p; hsa-miR-548c-3p; hsa-miR-608; hsa-miR-632; hsa-miR-659; hsa-miR-663; hsa-miR-874	CTCF; CTNBN1; E2F1; E2F2; E2F3; E2F4; E2F5; E2F6; E2F7; PPARG; SP1
	SOCS3	hsa-miR-203a-3p; hsa-let-7f-5p; hsa-miR-19a-3p; hsa-miR-221-3p; hsa-miR-155-5p; hsa-miR-19a; hsa-miR-19b; hsa-miR-203; hsa-miR-218; hsa-miR-221; hsa-miR-30a; hsa-miR-30b	AHR; ARNT; E2F1; ESR1 NFKB1; RELA; REST; STAT1; STAT2; STAT3
		hsa-miR-30e; hsa-miR-340; hsa-miR-561; hsa-miR-665; hsa-miR-765	STAT4; STAT5A; STAT5B; STAT6; TCEB1; TCEB2; YY1
	BSG	hsa-miR-22-3p	EGR1; EGR2; MAX; MXI1::CLEC5A; MYC; TFAP2A; TFAP2C; USF1

	JUNB	hsa-miR-663a; hsa-miR-101; hsa-miR-199a-5p; hsa-miR-199b-3p; hsa-miR-30d; hsa-miR-30e; hsa-miR-328; hsa-miR-495; hsa-miR-526b; hsa-miR-566; hsa-miR-615-5p; hsa-miR-656; hsa-miR-663; hsa-miR-675; hsa-miR-744; hsa-miR-886-5p; hsa-miR-936	ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; BATF; BCL6; BRCA1; CREB1; E2F1; ESR1; ETS2; FOS; FOSB; FOSL1; FOSL2; FOXO4; JDP2; MAX; MXI1::CLEC5A, MYC MZP1; NFE2L1; NFKB1 SMAD3; SMAD4; SRF TBP; TFAP2A; TFAP2C TFAP4; USF1
	TGFB1	hsa-miR-24-3p; hsa-miR-29b-3p; hsa-miR-144-3p; hsa-miR-633; hsa-miR-663a; hsa-miR-211-5p; hsa-miR-17-5p; hsa-miR-19b-3p; hsa-miR-93-5p; hsa-miR-324-3p; hsa-miR-122-5p; hsa-miR-130a-3p; hsa-miR-21; hsa-miR-24	AR; CEBPA; CEBPB; CREB1; CTCF; DAXX; EGR1; EPAS1; FOS; GATA1; HIF1A; JUN; LMO2; MYC; MZF1; PAX5; PPARA; RARA; SMAD2; SMAD3; SMAD4; SP1; SP3; TP53; USF1; USF2; WT1; YY1
	RNF114	hsa-miR-3064-5p; hsa-miR-6504-5p	EGR1; hsa-miR-124; hsa-miR-218; hsa-miR-492; hsa-miR-506; MAX; SP1; USF1
	RPTOR	hsa-miR-99a; hsa-miR-100; hsa-miR-155-5p	CEBPA; DDIT3; RFX1; TLX2
	TGM1	hsa-miR-130a; hsa-miR-130b; hsa-miR-142-3p; hsa-miR-148a; hsa-miR-148b; hsa-miR-149; hsa-miR-152; hsa-miR-301a; hsa-miR-301b; hsa-miR-345; hsa-miR-34a; hsa-miR-34c-5p; hsa-miR-361-3p; hsa-miR-378; hsa-miR-422a; hsa-miR-449a; hsa-miR-449b; hsa-miR-454; hsa-miR-502-5p; hsa-miR-508-5p; hsa-miR-558; hsa-miR-564; hsa-miR-617; hsa-miR-648; hsa-miR-920; hsa-miR-939	AR; ESR1; HOXA7; RARA; RARB; RARG; TGIF1; TP53
	FABP5	hsa-miR-144; hsa-miR-198; hsa-miR-203; hsa-miR-525-5p; hsa-miR-553; hsa-miR-562; hsa-miR-576-5p; hsa-miR-603; hsa-miR-616; hsa-miR-620	CTCF; E2F1; MAX; MYC
	TPPP	hsa-miR-1; hsa-miR-206	Nil
	WDR72	hsa-miR-186; hsa-miR-576-5p; hsa-miR-599	Nil
	HMGCS2	hsa-miR-490-5p	AR; CEBPA; NFIC; PPARA; RXRA; RXRB; RXRG; TFAP2A
	TNNI2	Nil	CTCF; CUX1; ELK1; POU2F1; RORA; SPI1; TFAP2A; TFAP2C
	CNTNAP3B	Nil	HLF; STAT5A
	ANKRD18A	hsa-miR-203; hsa-miR-518a-5p; hsa-miR-520g; hsa-miR-520h; hsa-miR-671-5p	Nil
	ANKRD33B	Nil	EBF1; NFKB1; NFKB2; RELA; RELB; SPI1; TFAP2A; TFAP2C; USF1

	ERBB4	<p>hsa-miR-101; hsa-miR-106a; hsa-miR-125a-5p; hsa-miR-125b; hsa-miR-130a; hsa-miR-130b; hsa-miR-135a; hsa-miR-135b; hsa-miR-137; hsa-miR-144; hsa-miR-145; hsa-miR-146a; hsa-miR-146b-5p; hsa-miR-17; hsa-miR-184; hsa-miR-186; hsa-miR-199a-3p; hsa-miR-199b-3p; hsa-miR-19a; hsa-miR-19b; hsa-miR-200b; hsa-miR-200c; hsa-miR-205; hsa-miR-219-1-3p; hsa-miR-22; hsa-miR-221; hsa-miR-222; hsa-miR-23a; hsa-miR-23b</p> <p>hsa-miR-26a; hsa-miR-26b; hsa-miR-300; hsa-miR-301; hsa-miR-301a; hsa-miR-301b; hsa-miR-302d; hsa-miR-323-3p; hsa-miR-330-3p; hsa-miR-335</p> <p>hsa-miR-339-5p; hsa-miR-340; hsa-miR-342-3p; hsa-miR-342-5p; hsa-miR-372; hsa-miR-377; hsa-miR-378</p> <p>hsa-miR-383; hsa-miR-410; hsa-miR-422a; hsa-miR-429; hsa-miR-432; hsa-miR-433; hsa-miR-454; hsa-miR-495; hsa-miR-507; hsa-miR-508-3p; hsa-miR-518a-5p; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-519d; hsa-miR-520g; hsa-miR-520h; hsa-miR-527; hsa-miR-539; hsa-miR-548c-3p; hsa-miR-548d-3p; hsa-miR-571; hsa-miR-576-5p; hsa-miR-578; hsa-miR-579; hsa-miR-583; hsa-miR-584; hsa-miR-590-3p; hsa-miR-606; hsa-miR-653; hsa-miR-7; hsa-miR-876-5p; hsa-miR-93; hsa-miR-940; hsa-miR-944; hsa-miR-96</p>	CEBPB; EP300; MEF2A; MEIS1; SMURF2; STAT5A; STAT5B; WWP1
	TMEM132B	<p>hsa-miR-10a; hsa-miR-10b; hsa-miR-137; hsa-miR-143; hsa-miR-148b; hsa-miR-152; hsa-miR-199a-5p; hsa-miR-19a; hsa-miR-19b; hsa-miR-218; hsa-miR-221; hsa-miR-222; hsa-miR-224; hsa-miR-297; hsa-miR-298; hsa-miR-338-3p; hsa-miR-377; hsa-miR-433; hsa-miR-548c-3p; hsa-miR-590-3p; hsa-miR-653; hsa-miR-766</p>	Nil
	CNTNAP3	hsa-miR-22; hsa-miR-26a; hsa-miR-26b; hsa-miR-9	HLF; STAT5A
	CNKSR2	<p>hsa-miR-144; hsa-miR-199b-5p; hsa-miR-21; hsa-miR-25; hsa-miR-28-3p; hsa-miR-29b; hsa-miR-30c; hsa-miR-32; hsa-miR-363; hsa-miR-374a; hsa-miR-374b; hsa-miR-450b-5p; hsa-miR-491-3p; hsa-miR-516b; hsa-miR-542-3p; hsa-miR-554; hsa-miR-627; hsa-miR-643; hsa-miR-942; hsa-miR-944</p>	BACH2; NFE2
	RAB3B	hsa-miR-194	SMAD1; SMAD4; TLX2
	FREM2	<p>hsa-miR-142-3p; hsa-miR-142-5p; hsa-miR-147; hsa-miR-150; hsa-miR-200b; hsa-miR-200c; hsa-miR-24; hsa-miR-299-5p; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-30b; hsa-miR-32; hsa-miR-363; hsa-miR-367;</p> <p>hsa-miR-412; hsa-miR-429; hsa-miR-494; hsa-miR-509-3p; hsa-miR-544;</p> <p>hsa-miR-548c-3p; hsa-miR-556-3p; hsa-miR-568; hsa-miR-580; hsa-miR-590-3p; hsa-miR-607; hsa-miR-628-3p</p> <p>hsa-miR-633; hsa-miR-802; hsa-miR-885-5p; hsa-miR-9</p>	CTCF; EGR3; SP1; TBP; ZEB1
	ACADL	hsa-miR-142-3p; hsa-miR-299-3p; hsa-miR-518a-5p; hsa-miR-641	PPARD; RXRA; RXRB RXRG
	CYP4A11	hsa-miR-150	AR; HNF4A; PPARA; PPARG; PPARG; RXRA; RXRB; RXRG
	BTBD16	hsa-miR-204; hsa-miR-211; hsa-miR-337-3p; hsa-miR-491-3p; hsa-miR-548c-3p; hsa-miR-599; hsa-miR-605; hsa-miR-625; hsa-miR-875-3p	CTCF; ELK1; TFAP2C; TLX2
	WFDC3	hsa-miR-185; hsa-miR-28-5p; hsa-miR-29a; hsa-miR-29b; hsa-miR-29c; hsa-miR-329; hsa-miR-331-3p; hsa-miR-361-3p; hsa-miR-362-3p; hsa-miR-455-3p; hsa-miR-619; hsa-miR-657; hsa-miR-765; hsa-miR-875-3p; hsa-miR-923	ATF1; ATF2; ATF3; ATF4; ATF5; ATF6; ATF7; CTCF; E2F1; ELK1; GABPA; JUN; NR3C1; RFX1; SP1; SP1

	ACTC1	hsa-miR-142-5p; hsa-miR-185; hsa-miR-195; hsa-miR-200b; hsa-miR-200c; hsa-miR-25; hsa-miR-30a; hsa-miR-30a-5p; hsa-miR-30b; hsa-miR-30c; hsa-miR-30d; hsa-miR-30e; hsa-miR-32; hsa-miR-324-3p; hsa-miR-340; hsa-miR-363; hsa-miR-367; hsa-miR-369-3p; hsa-miR-429; hsa-miR-495; hsa-miR-508-5p; hsa-miR-608; hsa-miR-7; hsa-miR-768-5p; hsa-miR-876-3p; hsa-miR-92a; hsa-miR-92b	BACH1; CUX1; IRF1; MEF2A; SRF; TFAP2A; TFAP2C; TGIF1; ZEB1
	LHCGR	hsa-miR-148b; hsa-miR-545	NFIC; SP1; TFAP2A
	FADS2	hsa-let-7b	AR; CEBPA; CTCF; CUX1; DDIT3; HNF4A; MYC; PPARA; RXRA; RXRB; RXRG
	GRIN2A	hsa-miR-101; hsa-miR-125a-5p; hsa-miR-125b; hsa-miR-137; hsa-miR-139-5p; hsa-miR-194; hsa-miR-19a; hsa-miR-19b; hsa-miR-206; hsa-miR-216b; hsa-miR-220b; hsa-miR-299-5p; hsa-miR-325; hsa-miR-329; hsa-miR-330-5p; hsa-miR-331-5p; hsa-miR-362-3p; hsa-miR-376a; hsa-miR-376b; hsa-miR-451; hsa-miR-454; hsa-miR-510; hsa-miR-519d; hsa-miR-520h; hsa-miR-525-5p; hsa-miR-574-3p; hsa-miR-576-5p; hsa-miR-577; hsa-miR-584; hsa-miR-593; hsa-miR-598; hsa-miR-603; hsa-miR-628-5p; hsa-miR-630; hsa-miR-656; hsa-miR-765 hsa-miR-767-5p; hsa-miR-9; hsa-miR-939	AHR; ARNT; CTCF; PAX5; REST; USF1
	SYT17	hsa-miR-22; hsa-miR-297; hsa-miR-380; hsa-miR-574-5p; hsa-miR-633	CTCF; MYC; PAX5; RREB1; TSC22D4
	RORC	hsa-let-7a; hsa-let-7b; hsa-let-7c; hsa-let-7e; hsa-let-7f; hsa-let-7g; hsa-let-7i hsa-miR-106b; hsa-miR-202; hsa-miR-205; hsa-miR-20a; hsa-miR-298; hsa-miR-485-5p; hsa-miR-519a; hsa-miR-519b-3p; hsa-miR-519c-3p; hsa-miR-593; hsa-miR-605; hsa-miR-608; hsa-miR-766; hsa-miR-93; hsa-miR-98	ARNT; ARNTL; CEBPA; CHD4; CLOCK; CTCF; FOXO4; LMO2; MAX; MXI1::CLEC5A; NCOA6 NKX2-2; NPAS2; PPARG SREBF1; SREBF2; TAL1 TCF3; USF1; ZEB1
	CA1	hsa-miR-944	TBP
	CHRM3	hsa-miR-30c; hsa-miR-629	TFAP2A
	FPGT-TNNI3K	Nil	AHR; ARNT; E2F1; E2F2 E2F3; E2F4; E2F5; E2F6 E2F7; EGR1; YY1
	AGR3	hsa-miR-32; hsa-miR-367; hsa-miR-448; hsa-miR-455-5p; hsa-miR-507; hsa-miR-548a-3p; hsa-miR-548c-3p; hsa-miR-557; hsa-miR-573; hsa-miR-656; hsa-miR-876-5p	Nil
	SOHLH1	hsa-miR-132; hsa-miR-220c; hsa-miR-484; hsa-miR-504; hsa-miR-516a-3p; hsa-miR-520a-5p; hsa-miR-525-5p; hsa-miR-600	CTCF; USF1
	CYP1A2	Nil	CUX1; NFIC; NKX6-1; TAL1; TCF4; USF1; USF2 YY1
	CYP2W1	hsa-miR-423-3p; hsa-miR-608; hsa-miR-637	ZIC2
	BTC	hsa-miR-490-3p	CTCF; FOXC1; TFAP2A USF1
	DDC	Nil	AR; HNF1A; RORA

in top-down approach. The details of regulatory network were given in Figures 1 and 2.

Implication of miRNAs in regulatory network

The implication of miRNAs in the regulatory network was analyzed on the basis of compatibility with respect to gene-miRNA seed pairing and gene-miRNA-miRNA triplex with respect to nature of binding and the details were given in Table 2. In case of miRNAs implication in top-down approach hsa-miR-186-5p is highly compatible on the basis of seed pairing and triplex formation.

Pathway analysis

The obtained genes from Pubmed/DisGeNET/OMIM were subjected to pathway analysis in DAVID on the basis of P-value and Benjamini statistic and the result is given in Table 3. In case of pathway analysis, the genes associated with psoriasis follows the hierarchy of cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, TNF signaling pathway and HIF-1 signaling pathway.

Discussion and Conclusion

Combinatorial analysis of miRNA based regulatory network indicate the fact that has-miR-186-5p is involved in the repression of transcription factors EGR1, SP1 and NFKB1 and activation of gene STAT2 and the probable miRNA based regulatory networks are:

- (i) **Gene:** STAT2, miRNA: hsa-miR-186-5p and TF: EGR1;
- (ii) **Gene:** STAT2, miRNA: hsa-miR-186-5p and TF: SP1 and
- (iii) **Gene:** STAT2, miRNA: has-miR-186-5p and TF: NFKB1.

In case of regulatory analysis, STAT2 is involved in the pathogenesis of psoriasis by promoting the production of CCL5 and CXCL11 in keratinocytes [13]. The miRNA, hsa-miR-186 was differentially expressed in the lesional skin of psoriatic patients [14]. Egr-1 is regulator for the upregulation of IL-17A-induced psoriasis in psoriasis [15]. The miRNA, hsa-miR-186-5p was identified as a potential regulator in the subunits of NF-

Table 2. Implication of miRNA in regulatory network.

S. No.	Genes	Micro RNAs	Binding Score in % (miRmap)	Paired miRNA (Triplex RNA)	Binding Energy in Kcal/mol. (Triplex RNA)	Nature of Binding (Triplex RNA)
1	HPSE	hsa-miR-1258	Nil	Nil	Nil	Nil
2	TGM1	hsa-miR-1258	Nil	Nil	Nil	Nil
		hsa-miR-186	Nil	Nil	Nil	Nil
		hsa-miR-122	Nil	Nil	Nil	Nil
3	CCL2	hsa-miR-186	Nil	Nil	Nil	Nil
		hsa-miR-122	Nil	Nil	Nil	Nil
4	CCL20	hsa-miR-186	44.69	Nil	Nil	Nil
		hsa-miR-122	Nil	Nil	Nil	Nil
5	EIF4E	hsa-miR-186	38.84	hsa-miR-495	-19.06	miRNA self-complementarity
		hsa-miR-122	Nil	Nil	Nil	Nil
6	STAT2	hsa-miR-186-5p	47.13	Nil	Nil	Nil
		hsa-miR-122	Nil	Nil	Nil	Nil

Table 3. Annotation of Kegg pathways in associated genes.

S. No.	Pathway	P value	Benjamini
1.	Cytokine-cytokine receptor interaction	8.60E-16	1.20E-13
2.	Jak-STAT signaling pathway	2.40E-11	1.10E-09
3.	TNF signaling pathway	1.00E-07	2.70E-06
4.	HIF-1 signaling pathway	1.10E-04	1.10E-03
5.	FoxO signaling pathway	5.00E-04	3.60E-03
6.	Osteoclast differentiation	5.00E-04	3.60E-03
7.	Chemokine signaling pathway	2.00E-03	1.20E-02
8.	Adipocytokine signaling pathway	2.10E-03	1.20E-02
9.	Pathways in cancer	2.50E-03	1.30E-02
10.	Allograft rejection	2.80E-03	1.40E-02
11.	NOD-like receptor signaling pathway	6.50E-03	2.80E-02
12.	mTOR signaling pathway	9.80E-03	4.00E-02
13.	PI3K-Akt signaling pathway	1.20E-02	4.30E-02
14.	RIG-I-like receptor signaling pathway	1.50E-02	5.00E-02
15.	ErbB signaling pathway	2.70E-02	8.20E-02
16.	NF-kappa B signaling pathway	3.10E-02	9.00E-02
17.	T cell receptor signaling pathway	4.70E-02	1.30E-01
18.	Sphingolipid signaling pathway	5.40E-02	1.40E-01
19.	Autoimmune thyroid disease	5.60E-02	1.50E-01
20.	AMPK signaling pathway	6.00E-02	1.50E-01
21.	Rap1 signaling pathway	7.30E-02	1.80E-01

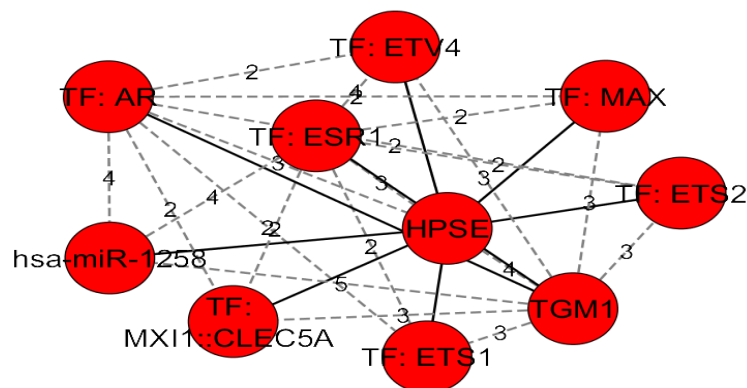


Figure 1. Regulatory network of HPSE and TGM1 (DMNC, MNC and clustering coefficient methods).

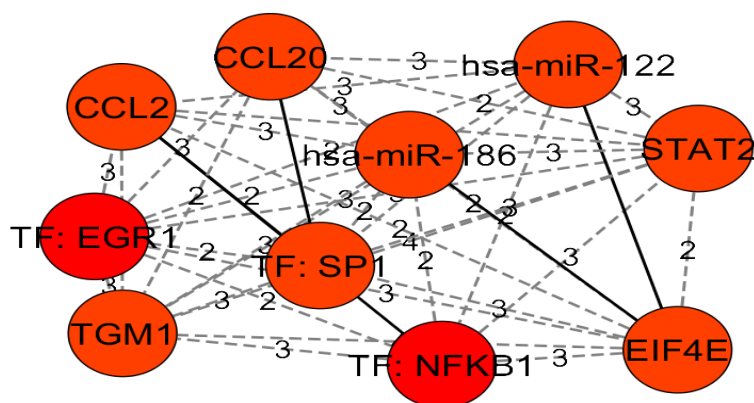


Figure 2. Regulatory network of CCL2, CCL20, TGM1, EIF4E and STAT2 (Eccentricity method).

κB [16]. SP1 promotes angiogenesis on VEGFR-2 receptors to decrease the VEGF production in psoriasis [17]. A genetic variant of NFKB1 is associated with the clinical features of *Psoriasis vulgaris* [17].

In future the complete regulation of hsa-miR-186-5p will be analyzed for the genes and proteins associated with the cytokine-chemokine receptor interactions involved in the disease pathology in Psoriasis. In this article the significance of hsa-miR-186-5p was analyzed for the associated genes of psoriasis and in the mere future the significance of miRNA will be analyzed with respect to the associated genes of other diseases.

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