

Systems and Computational Biology Journal

Computational Analysis of Pharmacogenomic Based Regulatory Network in Psoriasis: An Approach of Systems Biology to Initiate the Discovery of Systemic Biomarkers to Treat Psoriasis

Harishchander Anandaram*

| Department of Bioinformatics, Sathyabama University, India

Abstract

In the era of post genomics, performing a computational analysis to understand the pharmacogenomic based regulation of Psoriasis with respect to the principles of data mining and constructing a regulatory network with respect to the principles of systems biology and analyzing the network with respect to the principles of test statistic remains a challenging task to execute. The challenge was approached by identifying the associated genes of Psoriasis from PharmGkb and it was followed by identifying the associated regulators (MicroRNAs and Transcription Factors) from PharmacomiR/RegNetworks. Finally the regulatory networks were analyzed by the statistical measures.

Introduction

Psoriasis is a disorder mediated by the immune system by making certain faulty signals in the human body. It's still a belief that psoriasis can be developed under the specified conditions, i.e. "when the immune system signals the body to accelerate the growth of skin cells. Normally, skin cells get matured from the surface of the skin for every 28-30 days. In case of psoriasis, the skin cells mature in 3-6 days. Instead of being in the shed, the cells in the skin get piled 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 consider 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 the 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].

In current research, the inflammatory mechanisms are immune based and maintained by T cells in the dermis. Antigen-presenting cells in the skin like Langerhans cells were believed to migrate from the skin to the regional lymph nodes to interact with T cells. Presentation of an unidentified antigen to the T cells along with various co-stimulatory signals triggers an immune response to lead to the activation of T cells and release of cytokines. Co-stimulatory signals were initiated by the interaction of adhesion molecules on the antigen-presenting cells like Lymphocyte Function-Associated antigen (LFA)-3 and the intercellular adhesion of molecules with their respective receptors (CD2 and LFA-1) on T cells. These T cells are released into the circulation. Reactivation of T cells in the dermis and epidermis with local effects of cytokines like Tumor Necrosis Factor (TNF) to lead to the cell mediated immune responses, inflammation and epidermal hyper proliferation in persons with psoriasis. The immune based model of psoriasis was supported on the basis of the observation that the immunosuppressant medications can clear plaques in psoriasis. However, the complete role of the immune system needs refinement in understanding. It was recently reported that an animal model of psoriasis can be triggered in mice without T cells. This concept is a paradox to researchers because the reduction in the count of T-cell causes psoriasis [3] but the count of CD4-T-cell decreases with the progression of HIV in psoriasis. As an additive, HIV is characterized by a strong profile of Th2 cytokine but psoriasis vulgaris is characterized by a strong secretion pattern of Th1. It was also hypothesized that the presence of diminished CD4-T-cell can cause an over-activation in CD8-T-cells to exacerbate the cause of psoriasis in patients with HIV positive [4].

Materials and Methods

PharmGkb

The Pharmacogenomics Knowledge Base, PharmGKB is an interactive tool for researchers involved in the analysis of genetic variation to affect a drug response. PharmGKB

Article Information

DOI: 10.31021/scbj.20181101
Article Type: Research Article
Journal Type: Open Access
Volume: 1 **Issue:** 1
Manuscript ID: SCBJ-1-101
Publisher: Boffin Access Limited

Received Date: 18 October 2017

Accepted Date: 23 January 2018

Published Date: 28 January 2018

*Corresponding author:

Harishchander Anandaram

Department of Bioinformatics

Sathyabama University

Chennai, India

Tel: 91-9940066227

E-mail: harishchander.a@gmail.com

Citation: Anandaram H. Computational Analysis of Pharmacogenomic Based Regulatory Network in Psoriasis: An Approach of Systems Biology to Initiate the Discovery of Systemic Biomarkers to Treat Psoriasis. Syst Comput Biol J. 2018 Jan;1(1):101

Copyright: © 2018 Anandaram H. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 international License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

contain information about the genotype, molecular, and clinical knowledge to get integrated into a pathway and users can browse the knowledge base by drugs, diseases, genes, variants and pathways [5].

PharmacomiR

PharmacomiR [6] consists of miRNAs, genes and drugs. The output consists of miRNA based pharmacogenomic data set or a list of unique associations between miRNAs, genes and drugs.

RegNetworks

RegNetwork [7] is a database that contains five types (Transcription Factor-Transcription factor, Transcription Factor-Gene, Transcription Factor-microRNA, microRNA-Transcription Factor) of transcriptional and posttranscriptional regulatory relationships for human and mouse. RegNetwork integrates the curated regulations from various databases and the potential regulations were inferred on the basis of Transcription Factor Binding Sites (TFBSs). Transcription Factor (TF) and microRNA (miRNA) in gene regulations. Recently, more regulatory relationships in databases and literatures are available and it's valuable for studying the system of gene regulation by integrating the prior knowledge of the transcriptional regulations between TF and target genes along with the posttranscriptional regulations between miRNA and targets. The conservation of knowledge about the binding site of transcription factor (TFBS) can also be implemented to couple the potential regulation between regulators and their targets.

Cytoscape

Cytoscape [8] 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. Plugins may be developed using the Cytoscape

Method (Sequential data mining & Systems biology)

- Obtain the list of genes associated with psoriasis from PharmGkb.
- Analyze the list of associated genes with an impact on drug efficacy of Psoriasis in a larger population study.

- Obtain the list of miRNA associated with psoriasis from PharmacomiR.
- Obtain the list of transcription factors associated with psoriasis from RegNetworks.
- Construct and analyze the network in Cytoscape.

Results & Discussion

In case of indirect approach in regulatory analysis of genes associated with psoriasis; the genes are paired with the associated miRNAs and Transcription Factors (Table 1).

Further the genes, miRNAs and proteins in indirect approach were subjected to network analysis and the further details about the statistical methods were given below.

Network construction & analysis (Cytoscape)

Genes and their regulators were subjected to the analysis by various statistical methods (Degree, Edge Percolated Component, Maximum Neighborhood Component, Density of Maximum Neighborhood Component, and Maximal Clique Centrality with six centralities Bottleneck, Eccentricity, Closeness, Radiality, Betweenness and Stress) to identify their connectivity.

In case of MCC analysis in direct approach; VDR, MTHFR, GSTP1, ABCC1, TYMS and SLC19A1 were ranked from 1 to 6 respectively. Then; CYP1A2 and HLA-B were ranked 7. Finally; MAX and MYC were ranked 9. VDR polymorphism is associated with Psoriasis (Figure 1).

In case of DMNC analysis in direct approach; MTHFR, AHR, ARNT, CUX1, E2F1, EP300, hsa-miR-103, hsa-miR-107, hsa-miR-125a-3p and hsa-miR-138 were ranked 1. MTHFR polymorphism is a possible factor for reducing the clinical severity of psoriasis (Figure 2).

In case of MNC analysis in direct approach; MTHFR, AHR, ARNT, CUX1, E2F1, EP300, hsa-miR-103, hsa-miR-107, hsa-miR-125a-3p and hsa-miR-138 were ranked 1. MTHFR polymorphism is a possible factor for reducing the clinical severity of psoriasis (Figure 3).

In case of degree analysis in direct approach; VDR, MTHFR, GSTP1, ABCC1, TYMS and SLC19A1 were ranked from 1 to 6 respectively. Then; CYP1A2 and HLA-B were ranked 7. Finally; MAX and MYC were ranked 9. VDR polymorphism is associated with Psoriasis (Figure 4).

Genes (PharmGkb)	miRNAs (PharmacomiR)	Transcription Factor (RegNetworks)
MTHFR	hsa-miR-103; hsa-miR-107; hsa-miR-125a-3p; hsa-miR-138; hsa-miR-16; hsa-miR-195; hsa-miR-214; hsa-miR-22; hsa-miR-220b; hsa-miR-24; hsa-miR-424; hsa-miR-486-3p; hsa-miR-497; hsa-miR-516a-5p; hsa-miR-565; hsa-miR-642; hsa-miR-646	AHR; ARNT; CUX1; E2F1; EP300; JUN; MAX; MXI1::CLEC5A; MYC; REST; SP1; SREBF1; SREBF2; TFAP2A; USF1 XBP1; YY1
CYP1A2	Nil	CUX1; NFIC; NKX6-1; TAL1; TCF4; USF1; USF2; YY1
SLC19A1	Nil	ATF1; CREB1; E2F1; ETS1; MAX; MXI1::CLEC5A; MYC; TFAP2A; TP53; USF1; USF2
HLA-B	Nil	ATF7IP; NFKB1; NFKB2; NFYA; RELA; RELB; STAT1; STAT2; STAT5A
TYMS	hsa-let-7b; hsa-miR-338-5p	E2F4; GABPA; MYC; TP53; USF1; USF2
VDR	hsa-miR-124; hsa-miR-125b; hsa-miR-506; hsa-miR-544	BACH2; CREBBP; CTCF FOS; FOSB; FOSL1; GTF2B; HMGN3; HNF4A; HR; JUN; JUNB; JUND; KDM5A; LMO2; MAX; MED1; NCOA1; NCOA2; NCOA6; NR0B2 NR1H2; NRIP1; RXRA; RXRB; RXRG; SMAD3; SNW1; STAT1; TRIM24
GSTP1	Nil	AR; CREB1; FOS; FOSB; FOSL1; FOXA2; JUN; JUNB; JUND; MAX; MYC; NFKB1; RARA; RARB; RARG; RELA; SRF
ABCC1	hsa-miR-134; hsa-miR-326; hsa-miR-330-5p; hsa-miR-345; hsa-miR-7; hsa-miR-133a-3p.2; hsa-miR-133b	CEBPA; ETS1; MAX; MYC; SP1; TP53

Table 1: Associated genes, miRNAs and Transcription Factors of Psoriasis

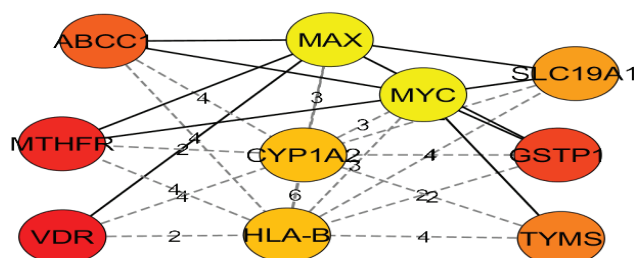


Figure 1: MCC Analysis of genes and regulators in Direct Approach (Cytohubba)

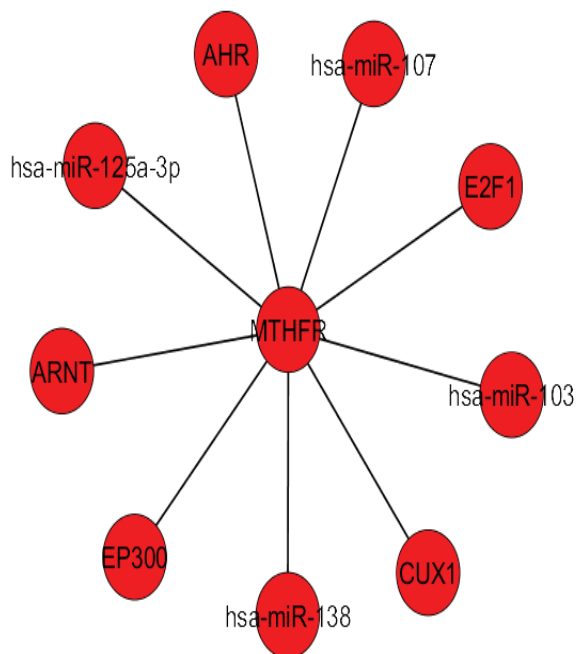


Figure 2: DMNC Analysis of genes and regulators in Direct Approach (Cytohubba)

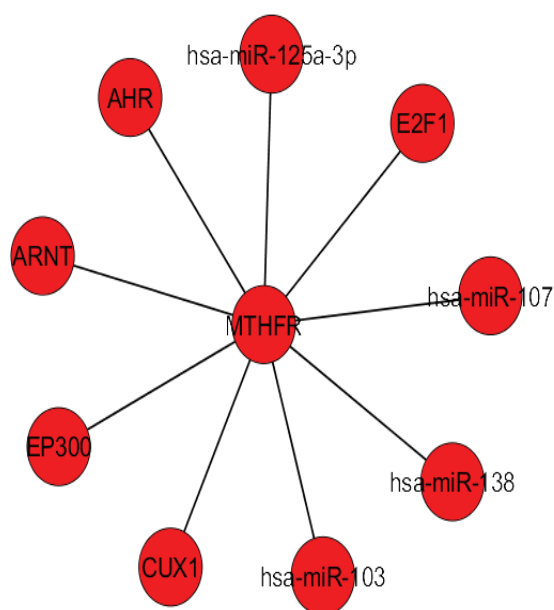


Figure 3: MNC Analysis of genes and regulators in Direct Approach (Cytohubba)

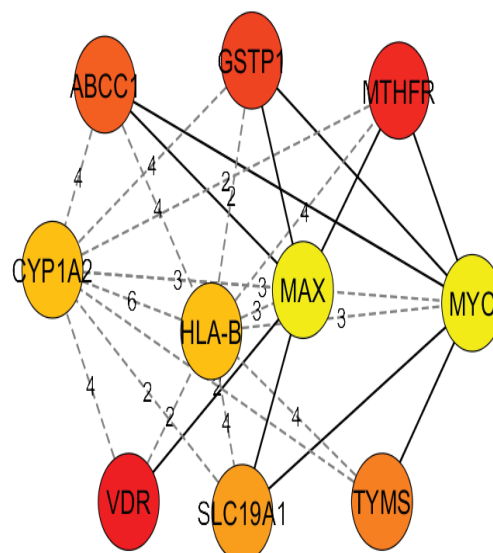


Figure 4: Degree Analysis of genes and regulators in Direct Approach (Cytohubba)

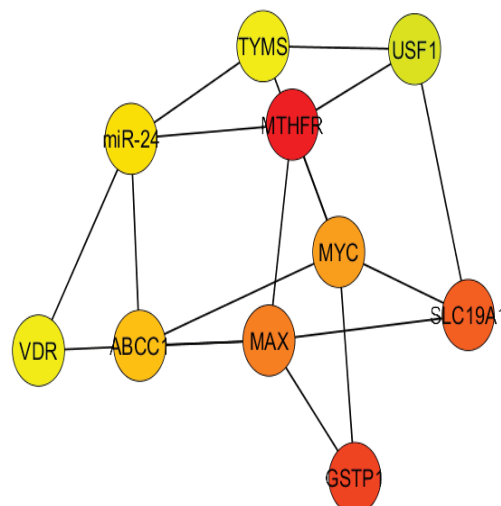


Figure 5: EPC Analysis of genes and regulators in Direct Approach (Cytohubba)

In case of EPC analysis in direct approach; MTHFR, VDR, SLC19A1, GSTP1, MAX, MYC, ABCC1, hsa-miR-24, TYMS and USF1 were ranked from 1 to 10 respectively. MTHFR polymorphism is a possible factor for reducing the clinical severity of psoriasis (Figure 5).

In case of Bottleneck Analysis in direct approach; VDR, hsa-miR-24 and MTHFR were ranked from 1 to 3. Then, MYC and GSTP1 were ranked 4. Further; ABCC1, TYMS and STAT1 were ranked from 6 to 8. Finally, YY1 and HLA-B were ranked 9. VDR polymorphism is associated with Psoriasis (Figure 6).

In case of Eccentricity Analysis in direct approach; JUN, MAX, MYC, CREB1 and hsa-miR-24 were ranked

Then; MTHFR, SLC19A1, TYMS, VDR and GSTP1 were ranked 6. JUN is associated with psoriasis because it's involved in the epidermal signaling (Figure 7).

In case of Closeness Analysis in direct approach; VDR, MTHFR, MAX, hsa-miR-24 and JUN were ranked from 1 to 5 respectively. Then, MYC and GSTP1 were ranked 6. ABCC1, TYMS and SLC19A1 were ranked from 8 to 10 respectively. VDR polymorphism is associated with Psoriasis (Figure 8).

In case of Radiality Analysis in direct approach; MAX, hsa-miR-24, VDR, MTHFR, JUN, MYC, GSTP1, TYMS, SLC19A1 and ABCC1 were ranked from 1 to 10 respectively (Figure 9).

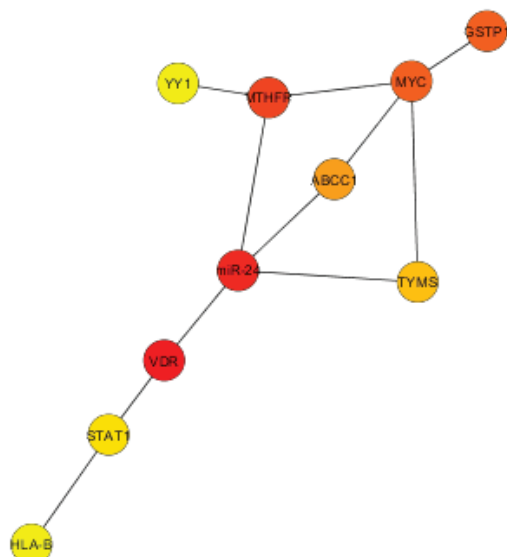


Figure 6: Bottleneck Analysis of genes and regulators in Direct Approach (Cytohubba)

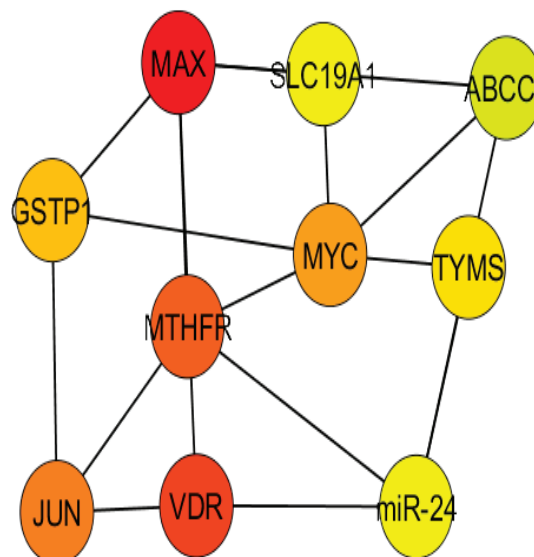


Figure 9: Radiality Analysis of genes and regulators in Direct Approach (Cytohubba)

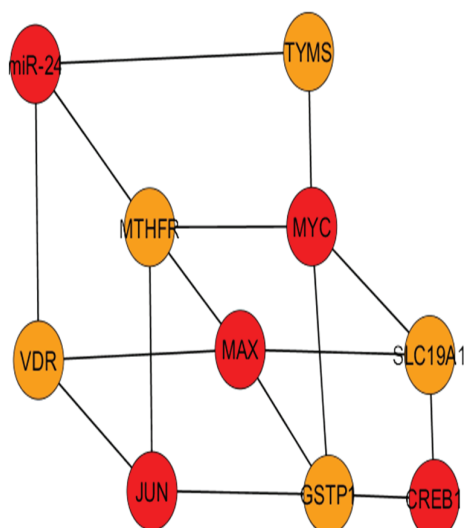


Figure 7: Eccentricity Analysis of genes and regulators in Direct Approach (Cytohubba)

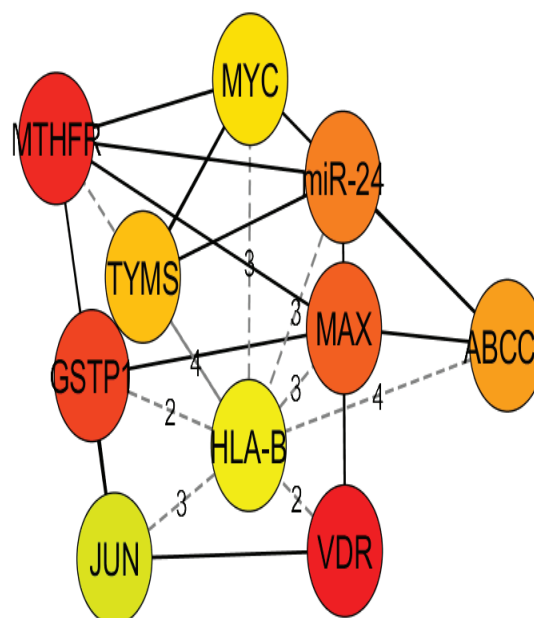


Figure 10: Betweenness Analysis of genes and regulators in Direct Approach (Cytohubba)

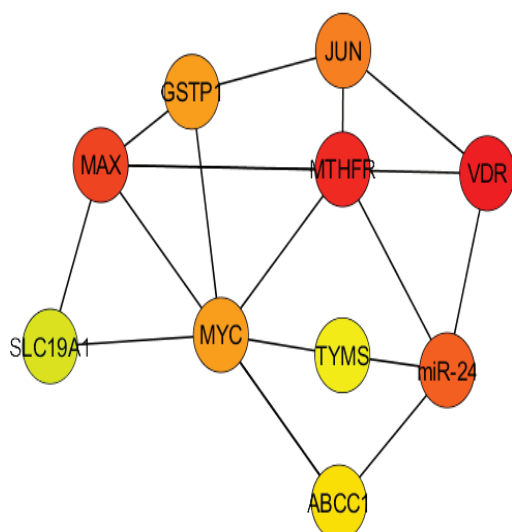


Figure 8: Closeness Analysis of genes and regulators in Direct Approach (Cytohubba)

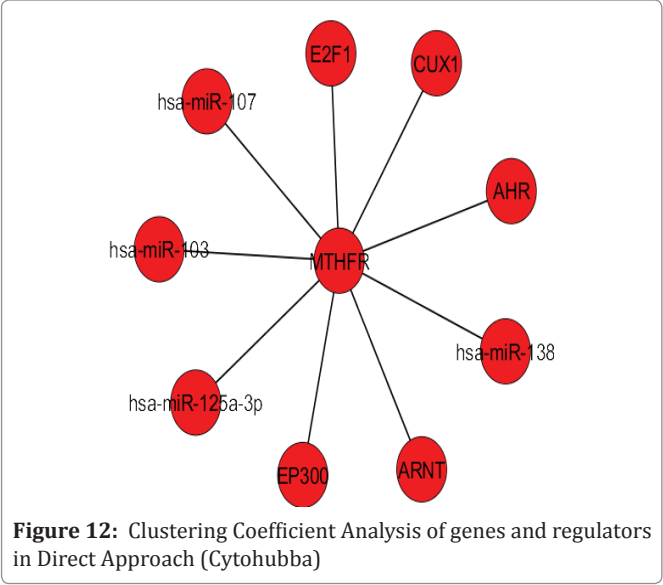
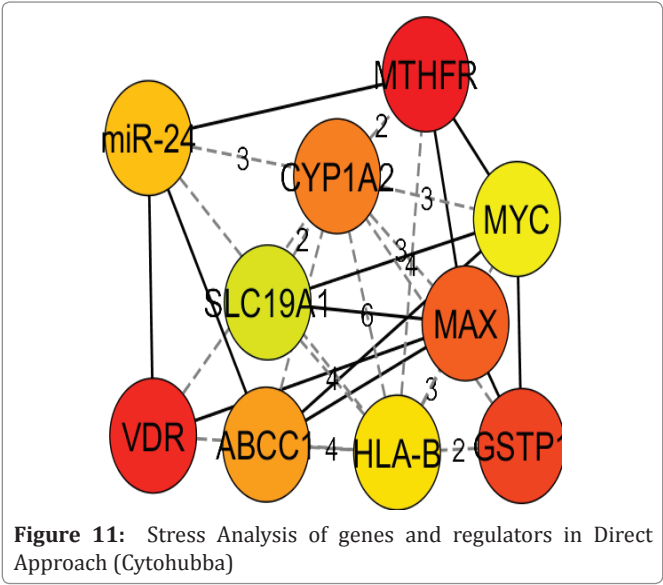
In case of Betweenness Analysis in direct approach; VDR, MTHFR, GSTP1, MAX, hsa-miR-24, ABCC1, TYMS, MYC, HLA-B and JUN were ranked from 1 to 10 respectively. VDR polymorphism is associated with Psoriasis (Figure 10).

In case of Stress Analysis in direct approach; MTHFR, VDR, GSTP1, MAX, CYP1A2, ABCC1, hsa-miR-24, HLA-B, MYC and SLC19A1 were ranked from 1 to 10. MTHFR polymorphism is a possible factor for reducing the clinical severity of psoriasis (Figure 11).

In case of Clustering coefficient Analysis in direct approach; MTHFR, AHR, ARNT, CUX1, E2F1, EP300 hsa-miR-103, hsa-miR-107, hsa-miR-125a-3p and hsa-miR-138 were ranked from 1 to 10. MTHFR polymorphism is a possible factor for reducing the clinical severity of psoriasis (Figure 12) (Table 2).

Conclusion

Overall network analysis of pharmacogenomic based regulatory network in psoriasis resulted in identifying 25 potential regulators



Rank	Methods for Analysis of Shortest Path of Reg					
	MCC	DMNC	MNC	Degree	EPC	Bottle Neck
1	VDR	MTHFR	MTHFR	VDR	MTHFR	VDR
		AHR	AHR			
		ARNT				
		CUX1				
		E2F1	ARNT			
		EP300	CUX1			
		hsa-miR-103	E2F1			
		hsa-miR-107	EP300			
		hsa-miR-125a-3p	hsa-miR-103			
		hsa-miR-138	hsa-miR-107			
hsa-miR-125a-3p						
hsa-miR-138						
2	MTHFR	Nil	Nil	MTHFR	VDR	hsa-miR-24
3	GSTP1	Nil	Nil	GSTP1	SLC19A1	MTHFR
4	ABCC1	Nil	Nil	ABCC1	GSTP1	MYC
						GSTP1
5	TYMS	Nil	Nil	TYMS	MAX	Nil
6	SLC19A1	Nil	Nil	SLC19A1	MYC	ABCC1
7	CYP1A2	Nil	Nil	CYP1A2	ABCC1	TYMS
	HLA-B			HLA-B		
8	Nil	Nil	Nil	Nil	hsa-miR-24	STAT1
9	MAX	Nil	Nil	MAX	TYMS	YY1
	MYC			MYC		HLA-B

Table 2: Network Analysis (Direct Approach)

of Psoriasis [20 Transcription Factors (VDR, MTHFR, GSTP1, ABCC1, TYMS, SLC19A1, CYP1A2, HLA-B, MAX, MYC, AHR, ARNT, CUX1, E2F1 and EP300) and 5 miRNAs (hsa-miR-103, hsa-miR-107, hsa-miR-125a-3p, hsa-miR-138 and hsa-miR-24)]. In a biological context, these potential regulators of psoriasis have a maximum probability to become a potential biomarker for Psoriasis and there was an identical pattern in the comparative-network analysis to illustrate the fact that there is a maximum probability for these potential regulators to be considered to treat psoriasis in future.

References

1. Yaqoob P. Fatty acids as gatekeepers of immune cell regulation. Trends Immunol. 2003 Dec;249(12):639-645.

2. Ortonne JP. Aetiology and pathogenesis of psoriasis. Br J Dermatol. 1996 Oct;135(49):1-5.

3. Pitzalis C, Cauli A, Pipitone N, Smith C, Barker J, et. al. Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. In Arthritis Rheum. 1996 Jan;39(1):137-145.

4. Ortonne JP, Lebwohl M, Em Griffiths C. Alefacept-induced decreases in circulating blood lymphocyte counts correlate with clinical response in patients with chronic plaque psoriasis. In Eur J Dermatol. 2003 Mar-Apr;13(2):117-123.

5. Thorn CF, Klein TE, Altman RB. PharmGKB: The Pharmacogenomics Knowledge Base Methods Mol Biol. 2013;1015:311-320.

6. Rukov JL, Wilentzik R, Jaffe I, Vinther J, Shomron N. PharmacomiR: linking microRNAs and drug effects. Brief Bioinform. 2014 Jul;15(4):648-659.

7. Liu, ZP, Wu C, Miao H, Wu H. RegNetwork: an integrated database of transcriptional and post-transcriptional regulatory networks in human and mouse. Database (Oxford). 2015.

8. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, et al. "Cytoscape: a software environment for integrated models of biomolecular interaction networks". Genome Res. 2003 Nov;13(11):2498-2504.