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# Psoriasis Associated Hub Genes Revealed by Weighted Gene Co-Expression Network Analysis

**Zeinab Darvish, M.Sc.[1], Saeed Ghanbari, Ph.D.[1]*, Saeid Afshar, Ph.D.[2], Leili Tapak, Ph.D.[3], Payam Amini, Ph.D.[1]***

**1. Department of Biostatistics and Epidemiology, School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran**
**2. Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran**
**3. Department of Biostatistics, School of Public Health and Modeling of Non-communicable Disease Research Center, Hamadan University of Medical Sciences, Hamadan, Iran**

## Abstract

**Objective:** Psoriasis, an immune-mediated disorder, is a multifactorial disease with unidentified cause(s). This study aimed to discover possible biomarkers of this papulosquamous skin disease.

**Materials and Methods:** The gene chip GSE55201, resulted from an experimental study, including 44 Psoriasis patients and 30 healthy controls was downloaded from GEO and weighted gene co-expression network analysis was utilized to identify hub genes. Key modules were determined using the module eigenvalues. We used biological functions (BFs), cellular components, and molecular functions in the Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes enrichment analysis in the gene metabolic pathway were used for enrichment analysis.

**Results:** Adjacency matrix was built by using power adjacency function and the power to turn the correlation to adjacency matrix was four with a topology fit index of 0.92. Using the weighted gene co-expression network analysis, 11 modules were identified. The green-yellow module eigenvalues were significantly associated with Psoriasis (Pearson correlation=0.53, P<0.001). Candidate hub genes were determined by their higher connectivity and relationship with module eigenvalue. The genes including *SIGLEC8, IL5RA, CCR3, RNASE2, CPA3, GATA2, c-KIT*, and *PRSS33* were recorded as the hub genes.

**Conclusion:** We can conclude that *SIGLEC8, IL5RA, CCR3, RNASE2, CPA3, GATA2, c-KIT,* and *PRSS33* have an important role in the immune response regulation and they could be considered as a potential diagnostic biomarker and therapeutic target for Psoriasis.

***Keywords:*** Gene, Gene Modules, Gene Network, Psoriasis

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## Introduction

Psoriasis is an autoimmune and genetic disease with abnormally prominent areas of skin (1). This superficial skin disease has been defined as a systemic inflammatory process that affects multiple organs. This chronic skin disorder is known for its red and scaly plaques which occur most commonly on the elbows, knees, scalp, and lower back (2). Psoriasis is followed by serious adverse psychological and social consequences and its cost to patients and healthcare systems is considerable (3). It has been argued that a major proportion of countries lack information on the epidemiology of this immune mediated inflammatory skin disease. The disease is more prevalent among adults than children, but some surveys have demonstrated that it can be found in different age groups, especially from 20 to 30 years old and 50 to 60 years old among patients (4). Developed countries reported more cases suffering Psoriasis (5). Prevalence of psoriasis in Western countries is about 2-4% of the population (6).

This non-communicable disease has multiple causes that are not fully understood yet, but the most commonly known factors are infections and injuries to skin, family history, weather, some medications, stress, smoking and exposure to secondhand smoke, overweight, and alcohol consumption. Psoriasis can be mild, moderate and severe. If it is mild, topical medications such as calcineurin inhibitors and keratolytics, topical corticosteroids and vitamin D analogues can be used (7, 8). Individuals with moderate to severe psoriasis routinely receive more treatments, such as systemic medications, ultraviolet light, and rotational therapies, in which medications are changed to reduce toxicity of the systemic treatments over time (9).

In the diagnostic field of Psoriasis, while its molecular tissue research has not been completed, the genetic structure is confirmed. Using quantitative reverse transcription polymerase chain reaction (qRT-PCR) and microarray methods to find patterns of gene expression in a systematic screening, prominent genes, regulator of stem cell proliferation, and progression of Psoriasis are

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***Corresponding Address: Department of Biostatistics and Epidemiology, School of Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran**
**Emails: saeedghanbari6.24@gmail.com, payam.amini87@gmail.com**

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identified (4). Psoriasis lesions are significantly associated with immune cells, such as $CD3^+$ T and $CD11c^+$ dendritic cells (DCs) and cytokines produced by these cells; particularly tumor necrosis factor-a (TNFα), interferon-g (IFNg), interleukin-17 (IL-17), IL-22, IL-23, IL-12, and IL-1b are associated with the pathogenesis of Psoriasis through activation of keratinocytes and the other dermal skin cells (9).

Weighted Gene Co-expression Network Analysis (WGCNA) (10) is used to find high-correlation gene clusters (modules). They are summarized using a gene that is closely related to the surrounding genes and it is called a hub gene (11). WGCNA is a gene screening method that offers several benefits, such as taking into account the variability of gene expression across various biological conditions, and potential for identifying higher-order relationships among genes. WGCNA creates modules of highly associated genes using Pearson correlation and defines clusters based on these correlations. WGCNA constructs a network in which it is able to investigate the correlation between modules and variables. Moreover, WGCNA assists determination of hub genes related to the study process. Another strength point related to WGCNA is that by assessing correlation between the eigengenes of the most important modules (known as the first module principle component) and variables of interest, multiple tests can be managed (12).

WGCNA has been widely used to identify key genes involved in many diseases. Nevertheless few attempts have been made in analyzing Psoriasis. While the role of environmental factors including stress, mechanical trauma and streptococcal infections has been well established in triggering Psoriasis, importance of genetic components cannot be neglected due to its multifactorial nature. This study aimed to use WGCNA to evaluate system biology of transcriptome of patients with Psoriasis in comparison to healthy people.

## Materials and Methods

### Data source and preprocessing

Using publicly available dataset of Psoriasis from an experimental type of study, blood transcriptome dataset [available in GEO repository: GSE55201 dataset generated using the Affymetrix U133 Plus (microarray) with platform ID GPL570] was investigated. This dataset consisted of expression data of 30 healthy controls and 44 Psoriasis patients at baseline and 7 Psoriasis patients after two weeks of treatment (13). In this study, data of 30 healthy controls and 44 Psoriasis patients at baseline samples were used for data analysis utilizing “R” programming software (version 4.1.1) for subsequent analysis. The codes for these analyses are accessible through: https://github.com/payamamini87/WGCNA.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1400.687). Due to the public accessibility of the data on GEO, the consent to participate is not applicable.

### Weighted Gene Co-expression Network Analysis

Prior to WGCNA, we investigated and filtered genes in the data to eliminate features exhibiting little variation across samples to avoid any reduction of the results accuracy. To do so, we used the "varFilter" package in "R" programming software to use those features with value for variation greater than 0.95. We applied WGCNA using the "R" package WGCNA in "R" programming software (14). We used the goodSamplesGenes function to check data for missing values and zero-variance genes.

As the first step, a Pearson correlation matrix for each pair of genes with the elements  was constructed, based on the amount of genes co-expression. Later, the adjacency matrix was constructed using the .To do so, a power adjacency function as  was utilized to construct the adjacency matrix between each pair of genes *i* and *j* in which  are the elements of adjacency matrix and report the connection strength between gene pairs. To find the best power for the subsequent analysis of the network, the pickSoftThreshold function and 90% cut-off point for scale free topology model fit was utilized.

One of the most important goals of co-expression network analysis was to find a set of genes (modules) that were strongly linked together. One of the most famous of these measurements is topological overlap matrix (TOM). The topological overlap of two genes indicates their relative linkage. The elements of TOM are as , in which  indicates number of the genes that both genes i and j are connected with,  are the elements of adjacency matrix;  and . TOM elements vary between 0 and 1, due to the weighted nature of the network. Using the resulting elements, TOM and the corresponding dissimilarity from the adjacency matrix were built. Hierarchical clustering using the average method was applied on the dissimilarity matrix and the first principle component of each clustering module was calculated to form module eigenvalue (ME). Finally, a similarity cut-off point of 0.75 was used for eigenvalues to merge similar modules in which 30 genes in each module was proposed as the least number of genes.

Data analysis was carried out using R statistical programming language, version 4.1.3. All statistical tests were 2-sided, and a $P<0.05$ was considered statistically significant.

### Determining candidate hub genes

Heat map of the sample expression was plotted using the resulting MEs and module with the highest expression was determined as the key module. To determine association between the modules and presence of the disease, the MEs and genes expression in each module was calculated using correlation tests and intramodularConnectivity function. Therefore, a module with the highest correlation

between its MEs and psoriasis was defined as the most important module. The hub gene in this module was the gene composed of the highest correlation with psoriasis and the highest connectivity with other genes in the module. The resulting statistics in this step contributed to find the hub genes in the key modules. Moreover, the constructed network for the final module was analyzed using the cytohubba plugin. The important genes were explored by tree topological algorithms degree, maximum neighborhood component (MNC), and maximal clique centrality (MCC) (15).

### Enrichment analysis

To determine the important and key modules, functional enrichment analysis of the genes in the modules were done based on the genetic information corresponding to the DAVIA database (https://david.ncifcrf.gov/summary.jsp) (16). The outputs of the biological functions (BFs), cellular component (CC), and molecular function (MF) in the Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis in the gene metabolic pathway were recorded.

### Protein-protein interaction network analysis

The protein-protein interaction (PPI) network of green-yellow module genes was constructed using the string version 11.5 considering the minimum required interaction score of 0.7. The constructed network was analyzed through the cytoHubba plugin under cytoscape software version 3.9.

### Validation of data

We used the GSE41662 dataset to verify and validate the findings of our analysis on this data. The chosen genes were subjected to the further evaluation (17).

## Results

### Construction of the network

Based on the scale free topology model fit index and mean connectivity, a power of four was selected. An quantity of 2703 genes were allocated in 11 co-expression modules (number of genes) by the WGCNA and named as brown (923), blue (549), green (380), yellow (245), black (148), pink (121), magenta (80), purple (78), green-yellow (74), tan (61), and salmon (44) (Fig.1).

### Finding target modules

Genes in the green-yellow (correlation=0.53, P=0.01) and magenta (correlation=0.51, P=0.01) modules were more associated with the disease rather than the others. Based on the results, further analysis was carried out using the green-yellow module based on its highest correlation with psoriasis. The yellow modules yellow and pink were up-regulated in the presence of psoriasis; so that higher expression of the genes in these modules was associated with higher probability of psoriasis. Other modules and especially the green-yellow module (the most important module) has a negative association with psoriasis; so that, higher expression of the genes in this module (and other modules with negative association with psoriasis) associated with lower probability of psoriasis.

### Evaluation of the key genes in green-yellow module

Pearson correlation test was used to assess association between genes and MEs of modules in this study. Moreover, the adjacency matrix was calculated to investigate connectivity of genes based on the sum of correlation coefficients between each gene and the other genes. Furthermore, Table 1 presents the top 10 genes with the highest correlation with the green-yellow module eigengenes (MEs), as well as their connectivity with neighboring genes. This was performed to demonstrate level of association between genes within the module. Based on the two statistics, *GATA2, RNASE2, CPA3, SIGLEC8, CCR3*, and *IL5RA* are the genes with relative correlation above 0.90.

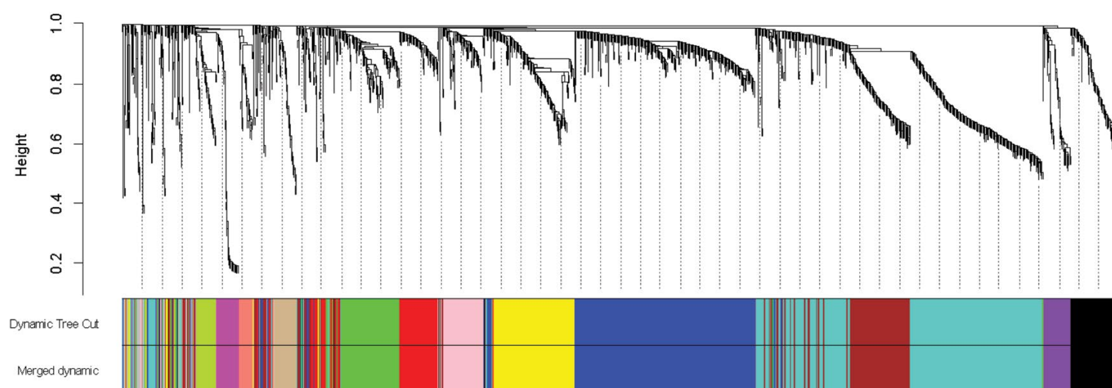


**Fig.1:** Module hierarchical clustering tree to detect clusters (horizontal axes) of genes based on the distance between the genes (vertical axes). Dynamic tree cut shows module divided based on clustering output; merged dynamic indicates module divided according to similarity of the module. Based on the figure, merging is not necessary.

**Table 1:** Connectivity, relative connectivity, and correlation between the green-yellow module eigengenes and gene expression for the first 10 most important genes

| Gene | Connectivity | Relative connectivity | Intra modular correlation (correlation between MEs and gene expression) | |
|---|---|---|---|---|
| | | | Correlation | P value |
| *GATA2* | 22.805 | 0.996 | 0.904 | <0.001 |
| *RNASE2* | 22.720 | 0.992 | 0.913 | <0.001 |
| *CPA3* | 22.038 | 0.962 | 0.906 | <0.001 |
| *SIGLEC8* | 22.115 | 0.966 | 0.986 | <0.001 |
| *CCR3* | 22.897 | 1.000 | 0.944 | <0.001 |
| *IL5RA* | 22.527 | 0.984 | 0.905 | <0.001 |
| *OLIG2* | 20.427 | 0.892 | 0.974 | <0.001 |
| *SLC29A1* | 19.823 | 0.866 | 0.901 | <0.001 |
| *KIT* | 19.952 | 0.871 | 0.891 | <0.001 |
| *PRSS33* | 19.772 | 0.864 | 0.899 | <0.001 |
| *IL5RA1* | 19.396 | 0.847 | 0.855 | <0.001 |

### Enrichment analysis for key candidate genes in green-yellow module

The enrichment analysis was carried out for the hub genes in the green-yellow module by GO analysis including the CC, MF, biological process (BP) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The results are shown in Table S1 (See Supplementary Online Information at www.celljournal.org), using P value and false discovery rate.

### Biological process

Module hub genes were significantly enriched in 15 GO BP terms including nitrobenzene metabolic process, xenobiotic catabolic process, glutathione derivative biosynthetic process, digestive tract development, inflammatory response, chemotaxis, cellular detoxification of nitrogen compound, regulation of activated T cell proliferation, glutathione metabolic process, somatic stem cell population maintenance, proteolysis, negative regulation of cell proliferation, phosphatidylinositol phosphorylation, G-protein coupled purinergic nucleotide receptor signaling pathway, and positive regulation of angiogenesis. The BP found GSTM1, GSTM2, and GSTM4 enriched genes in nitrobenzene metabolic process and somatic stem cell population maintenance and regulation of activated T cell proliferation, xenobiotic catabolic process, and glutathione derivative biosynthetic process, GATA2 in digestive tract development and positive regulation of angiogenesis, ALOX15 in inflammatory response, RNASE2 in chemotaxis, IDO1 in glutathione metabolic process, CPA3 in proteolysis, H2AC8 in negative regulation of cell proliferation, FGFR2 in phosphatidylinositol phosphorylation, and P2RY14 in G-protein coupled purinergic nucleotide receptor signaling pathway.

### Kyoto Encyclopedia of Genes and Genomes

Module hub genes were enriched in several pathways in KEGG analysis such as glutathione metabolism, drug metabolism- cytochrome P450, metabolism of xenobiotics by cytochrome P450, chemical carcinogenesis, and hematopoietic cell lineage. In the molecular function, seven terms were enriched in the selected genes including glutathione binding, glutathione transferase activity, phosphatidylinositol-4,5-bisphosphate 3-kinase, protein homodimerization activity, G-protein coupled purinergic nucleotide receptor activity, Ras guanyl-nucleotide exchange factor activity, and protein tyrosine kinase activity. KEGG identified IL5RA in hematopoietic cell lineage and the other genes such as *GSTM1*, *GSTM2*, and *GSTM4* enriched genes in glutathione metabolism, drug metabolism- cytochrome P450, metabolism of xenobiotics by cytochrome P450, and chemical carcinogenesis.

### Cellular component

In the CC, three terms were enriched including integral component of plasma membrane, integral component of membrane, and extracellular space. The CC enrichment identified SLC29A1 as the enriched gene in the integral component of plasma membrane.

### Molecular function

The MF enrichment identified GSTM1, GSTM2, and GSTM4 enriched genes in glutathione transferase activity and protein homodimerization activity, FGFR2 in phosphatidylinositol-4,5-bisphosphate 3-kinase activity, P2RY14 in G-protein coupled purinergic nucleotide receptor activity, IL5RA in Ras guanyl-nucleotide exchange factor activity and protein tyrosine kinase activity.

## Screening of the key hub genes

Venn diagram of the key candidate genes for green-yellow module based on connectivity and correlation between gene expression and green-yellow MSs is shown in Figure 2. Moreover, the Venn diagram in Figure 3 demonstrated the in common genes between the cytohubba plugin approaches tree topological algorithms degree, MNC, and MCC. Therefore, the identified hub genes were *SIGLEC8*, *IL5RA*, *CCR3*, *RNASE2*, *CPA3*, *GATA2*, *KIT*, and PRSS33. Figure 4 demonstrated the resulting network in the green-yellow module for genes with relative connectivity more than 0.60.

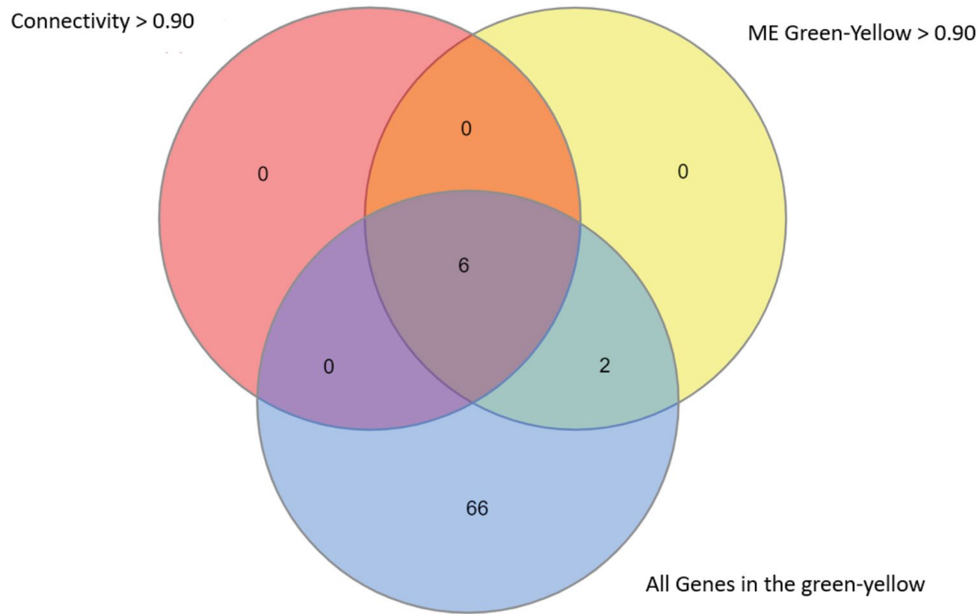


**Fig.2:** Venn diagram to identify the key candidate genes in the green-yellow module based on module eigengenes (ME) and connectivity.

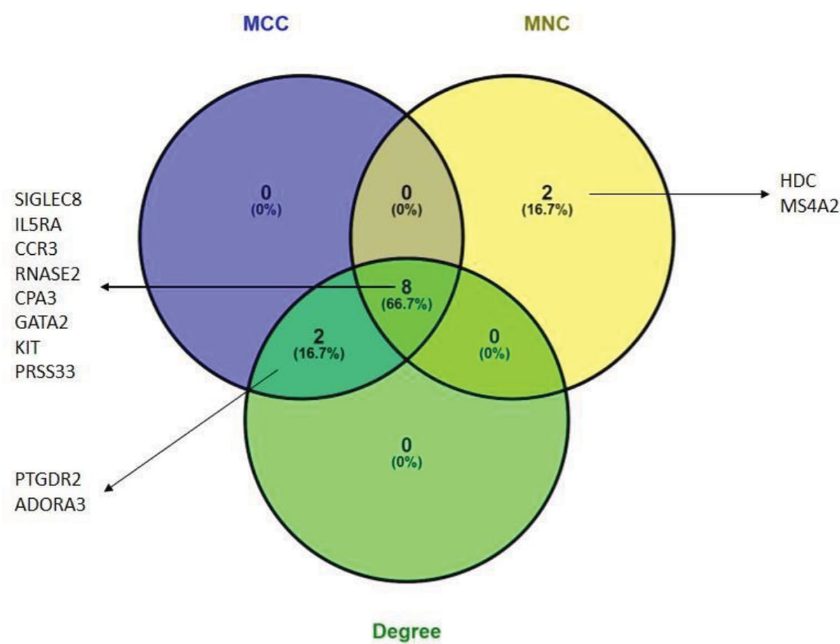


**Fig.3:** Venn diagram of hub genes in green-yellow module based on maximal clique centrality (MCC), maximum neighborhood component (MNC), and node connect degree (degree).

**Fig.4:** The resulting network in the green-yellow module for genes with relative connectivity more than 0.60.

**Validation data receiver operating characteristic curve analysis**

The results of receiver operating characteristic curve (ROC) curve analysis in the validation data (GSE41662) outputted the area under curve (95% confidence interval) of 0.52 (0.35-0.68) for *IL5RA*, 0.84 (072-0.95) for *CCR3*, 0.54 (0.37-0.71) for *RNASE2*, 0.57 (0.40-0.73) for *CPA3*, 0.84 (0.72-0.95) for *GATA2*, 0.92 (085-0.99) for *c-KIT*, and 0.71 (0.56-0.86) for *PRSS33*.

## Discussion

In this study, we used WGCNA to determine 11 co-expression network modules. We successfully found the specific module related to psoriasis based on the MEs. WGCNA uses soft thresholds, which demonstrated the efficiency of biological networks more successfully than hard thresholds (12). Finally, through the PPI network analysis for green yellow module sialic acid-binding Ig-like lectin 8 (*SIGLEC8*), interleukin 5 receptor alpha *(IL5RA*), chemokine receptor 3 *(CCR3*), ribonuclease A family member 2 (*RNASE2*), carboxypeptidase A3 (*CPA3)*, GATA binding protein 2 (*GATA2*), *c-KIT*, and serine protease 33 (*PRSS33*) were identified as the key core gene for psoriasis. WGCNA determined the hub genes by correlation between the genes and module eigenvalues; so that the genes with higher correlations were the potential candidates. In addition to the correlation between gene and MEs, gene connectivity was the other result of WGCNA contributing to finding the hub genes and it was calculated by summation of correlation coefficients of a gene with the others. Using WGCNA, a small number of modules and hub genes reflected a large number of genes and it was possible to assess association between the resulting genes and external traits. Expression of the hub genes including *SIGLEC8*, *IL5RA*, *CCR3*, *RNASE2*, *CPA3*, *GATA2*, *c-KIT*, and *PRSS33* is highly associated with psoriasis and based on the association between the green-yellow MEs and psoriasis, higher expression of these genes caused lower probability of psoriasis.

Several studies have been conducted to reveal the key genes associated to psoriasis in different frameworks and determine multiple aims. Choudhary et al. (18) aimed

to identify potential therapeutic targets and affecting pathways for better insight of the disease pathogenesis using the information of lesional and non-lesional psoriasis skin cases. For their work, they used GSE13355 and GSE14905 in GEO and a total of 1013 genes were assessed. They found that in the lesional group, *IL1B* and *STAT3* altered genetic signature. Gao et al. (19) discovered novel hub genes and pathways associated with the pathogenesis of psoriasis using four gene expression profiles in the gene expression omnibus (GEO) database.

They used GO enrichment analysis, Kyoto encyclopedia of genes and genomes pathway analysis and PPI network analysis to identify the hub genes. They concluded that genes including *ISG15*, *MX1*, *OAS2*, *OASL*, and *OAS3* were overexpressed in TNF-α stimulated HaCaT cell lines. Integrated bioinformatic analysis of differentially expressed genes and signaling pathways in plaque psoriasis was performed by Zhang et al. (20) using the gene expression profiles of 175 pairs of lesional and corresponding non-lesional skin cases from five data sets in the GEO database. Based on their results, 17 hub genes including *CSK2, CDC45, MCM10, SPC25, NDC80, NUF2, AURKA, CENPE, RRM2, DLGP5, HMMR, TTK, IFIT1, RSAD2, IFI6, IFI27* and *ISG20* were found. Xing et al. (21) investigated the biomarkers of psoriasis using a combined multiomics study. They used GSE13355, GSE14905, and GSE73894 datasets from GEO and applied different machine learning approaches such as the least absolute shrinkage and selection operator, random forest, and support vector machine. They reported that GJB2 might be a potential biomarker of psoriasis. Su et al. (22) identified the hub genes and immune infiltration in psoriasis using bioinformatics approaches and datasets from GEO datasets. They suggested that some pathways and genes such as naive B cells, $CD8^+$ T cells, and activated memory $CD4^+$ T cells might reveal more details about psoriasis. In another study by Yue et al. (23) the novel hub genes related to psoriasis were investigated using a bioinformatics approach. To do so, they used GSE166388, GSE50790 and GSE42632 datasets and found that *TOP2A, CDKN3, MCM10, PBK, HMMR, CEP55, ASPM, KIAA0101, ESC02*, and IL-1β were highly associated with the disease. Nickles et al. (24) used WGCNA to identify common hub genes between cutaneous sarcoidosis and discoid lupus erythematosus using data from two cohorts. The most important module was determined based on the correlation MEs with immune and leukocyte activation. Among cutaneous sarcoidosis and discoid lupus erythematosus, seven hub genes including *TLR1, ITGAL, TNFRSF1B, CD86, SPI1, BTK,* and *IL10RA* were extracted.

The inhibitory transmembrane receptor protein encoded *by SIGLEC8*, which was expressed in mast cells and eosinophils, can be used as a therapeutic target of inflammatory and allergic disease (25, 26). The protein encoded by *IL5RA*, as a subunit of the interleukin-5 receptor, had a role in immune regulation (27, 28). *CCR3* as a member of the G protein-coupled receptors family bound to several chemokines leading to migration of eosinophil, basophils, mast cells, Th2- cells, macrophage, and neutrophils. This subsequently regulated the inflammation beginning. It has been argued that expression of chemokine receptors can be recognized as a potential biomarker for T cell differentiation and CCR3 was a candidate for immunotherapy among Lesional skin of patients with atopic dermatitis (28-30). *RNASE2* encoded the cytotoxic protein with antiviral activity. This protein had an essential role in the autoimmunity control (31). Studies showed that *RNASE2*, 3, 5, and 7 played important roles in regulating allergies or immune complications of skin. Moreover, RNASE2 was a significant predictor of neurological problems due to its neurotoxicity. In a study by Sun et al., role of human ribonuclease (RNASE) was assessed. They indicated that RNASE2 was a considerable biomarker of atopic dermatitis and psoriasis (32). Bing et al. (33), in their study, identified that *RNASE2* was one of the biomarkers of the systemic lupus erythematosus (SLE), as an autoimmune disease.

Akula et al. (34) have discussed the complex evolution of the CPA3 gene in detail. The protein encoded with *CPA3* was predominantly expressed in mast cells and it had an essential role in immunity regulation. The study conducted by Aleksiejczuk et al. (35) showed that angiotensin converted inactivity and CPA3 in skin was higher expressed, among the psoriasis cases. Additionally, activity of tissue among cases with lesional skin was almost twice of non-lesional group. The protein encoded with *GATA2* is a zinc-finger transcription factor that has an essential role in development of hematopoietic cells (36). Sahoo et al. (37), in a study on germline predisposition in myeloid neoplasms, revealed that psoriasis as well as the other autoimmune disorders were more common among the individuals with a mutation in *GATA* gene. Moreover, Amarnani et al. (38), in their study, indicated that GATA2 had a role in the regulation of immunity. The protein encoded with *PRSS33* is one of the S1 trypsin-like serine-protease family members, predominantly expressed in eosinophils and less extended in basophils (39, 40).

In the current study, we used GO and PPI networks on the same dataset to check the outputs from the WGCNA. The resultant genes in the WGCNA were also confirmed by the gene enrichment analysis. WGCNA was based on systems biology and it was proposed to build a network of genes and detect clusters. The main advantage of WGCNA in comparison to the other approaches was handling the multiple testing problem inherent in microarray data analysis by considering association of modules (clusters) and an outcome of the interest. However, different studies have used different tools to determine psoriasis related hub genes such as Pearson's correlation analysis to test the correlation between genes expression (19), differentially expressed genes and several bioinformatics methods (22).

There are limitations and strength to the present study. One of the main limitations was the limited number of GSE data sets related to psoriasis, in addition to mainly having small sample sizes. These datasets are of different

platforms, so that they cannot be merged. This study evaluates the system biology of patients' transcriptomics using a network analysis approach. However, the impact of genetic mutation on psoriasis is not well known. Further studies are required to assess effect of genetic mutation besides to the impact of personal and/or environmental variables. Moreover, this study investigated psoriasis through a system biology and transcriptomics point of view and the polymorphism of psoriasis has not been assessed regarding the nature of recorded data in GSE55201. Further studies using a huge number of samples and a polymorphism perspective might reveal impact of genetic mutations in psoriasis.

## Conclusion

Taken together, SIGLEC*8, IL5RA, CCR3, RNASE2, CPA3, GATA2*, *c-KIT*, and *PRSS33* had an important role in the regulation of immune response and they could be considered as a potential diagnostic biomarkers and therapeutic targets for psoriasis**.** Additionally, more precise studies are proposed to understand role of these genes in pathogenesis of the psoriasis.

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### Authors' Contributions

Z.D., S.Gh., P.A, S.A.; Contributed to conception and study design. Z.D., P.A., L.T.; Validated and investigated the process. Z.D., L.T., P.A., S.Gh.; Performed data curation and data analyses. All authors performed editing and approving the final version of this manuscript for submission, and participated in the finalization of the manuscript.

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