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Differentially Expressed Genes in Atopic Dermatitis: Bioinformatics analysis of pooled microarray gene expression datasets in Gene Expression Omnibus

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ABSTRACT

Introduction:

Atopic dermatitis (AD) is a chronic and refractory inflammatory skin disease characterized by relapsing eczematous and pruritic skin lesions. The global prevalence of AD ranges from 1% to 20%, and its incidence rates are increasing. It affects individuals from infancy to adulthood, significantly impacting their daily lives and social activities. Despite its major health burden, the precise mechanisms underlying AD remain unknown. Understanding the specific gene expression patterns associated with AD is crucial for advancing diagnosis and targeted treatment development. Using bioinformatics methods, candidate genes and biological pathways involved in AD pathogenesis were identified based on gene expression profiles in the Gene Expression Omnibus (GEO) database.

Materials and Methods:

A comprehensive analysis of four pooled transcriptomic datasets (GSE16161, GSE32924, GSE130588, and GSE120721) obtained from the Gene Expression Omnibus (GEO) database were conducted. Differential gene expression analysis was performed using the GEO2R. The differentially expressed genes (DEGs) between lesion skin of AD patients and normal skin of individuals were analyzed using the Gene Ontology (GO) term enrichment analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway, and protein-protein interaction (PPI) network to explore the functional roles of these genes.

Results:

Among the patient-level gene expression datasets, we identified 133 shared DEGs, consisting of 48 upregulated genes and 85 downregulated genes. GO analyses revealed these DEGs to be significantly enriched in biological processes including inflammatory responses, cytokine-mediated signaling pathway, mitotic spindle organization, lymphocyte chemotaxis, and cell division. These DEGs were also enriched in the KEGG pathway, including viral protein interaction with cytokine and cytokine receptor, C-type lectin receptor signaling pathway, cytokine-cytokine receptor interaction, JAK-STAT signaling pathway, and Adipocytokine signaling pathway. PPI analysis showed that the top hub genes of atopic dermatitis are MKI67, CCNA2, HMMR, AURKA, CCNB1, NCAPG, TTK, MELK, RRM2, and NDC80.

Conclusion:
This bioinformatics study discovered some key genes and pathways related to AD, which provided potential clues and targets for AD pathogenesis research and diagnosis and treatment research. However, by comparing with other studies using the same method, we found that in addition to the already confirmed pathways such as inflammatory response, different studies have found changes in different hub genes and metabolic pathways, which prompts us to develop individualized treatments for AD that are of great significance.

Keywords: atopic dermatitis; GEO database; bioinformatics; study comparison

INTRODUCTION:

Atopic dermatitis (AD), also known as eczema, is characterized by recurrent skin rashes, dry skin, and itching. The disease usually begins in childhood and continues into adulthood. A worldwide study found that approximately 15%–20% of children and up to 10% of adults have AD, although prevalence varies by race and ethnicity. The etiology of the disease has not yet been fully elucidated, but it is generally believed that the disease is a heterogeneous disease that is a combination of genetic and environmental factors, of which genetic factors are the main ones. [1, 2]

Regarding the pathogenesis of AD, there are several models as follows. Initial studies identified the immune response as the main driver, leading to an "inside-out" model in which immune dysregulation leads to compromised skin barrier function. Subsequently, due to the discovery of abnormal skin barrier function due to genetic defects, an "outside-in" model was proposed, in which skin barrier dysfunction leads to antigen penetration, which in turn elicits an immune response. However, recent studies have found that the disease is a complex process of multiple factors interacting with skin barrier defects, skin microbes, immune dysregulation, and the pathophysiology of pruritus. [3, 4]

Although there is no definitive cure for AD, symptoms can often be managed successfully, and up to 70% of children with AD will go into clinical remission before puberty. Treatment of AD includes skin care education and practice, anti-inflammatory therapy with topical corticosteroids and/or topical calcineurin inhibitors (TCIs), and treatment of skin infections. Systemic immunosuppressants (eg, cyclosporine, azathioprine, and methotrexate) can be used in severe cases. Non Sedating second-generation antihistamines are also of some benefit. Biological agents that regulate immune pathways have developed rapidly in recent years. Drugs that have been approved by the FDA include dupilumab, which is a monoclonal antibody against co-receptor of the type 2 effector cytokines interleukin (IL)-4 and IL-13 (IL-4Rα), Tralokinumab, a monoclonal antibody against IL-13, Janus kinase (JAK) inhibitors Abrocitinib, Baricitinib, Upadacitinib, etc. [5, 6]

In order to elucidate the pathogenesis of AD, multi-level studies have been carried out. Family and twin studies have shown that the concordance rate of identical twins is 72-86%, and that of fraternal twins is 21-23%, indicating that genetic factors play a major role in the pathogenesis of AD. [7] However, to date, it is estimated that AD-associated genes have been found to account for approximately 30% of the heritable contribution to AD. Therefore, there is still a lot of work to be done in the genetics study of AD. At present, the main strategies of genetic research include broad omics research and directed gene, protein and metabolic pathway research. The broad omics research includes genome-wide association studies, whole-exome sequencing and whole-genome sequencing, epigenome, transcriptome, proteome, metabolome, lipidome, microbiome analysis. In addition, the research on environmental factors includes the analysis of exposomic data. [8, 9]

Nedoszytko et al. summarized the genes that have been found to be associated with the pathogenesis of AD: the first group is genes related to epidermal barrier function, the second group is genes related to innate immune response, the third group is genes related to innate immune response, the fourth group is genes related to signaling proteins released by keratinocytes under stress, the fifth group is genes related to regulation of DNA methylation, and the last group is genes related to vitamin D metabolism. Of course, this grouping method cannot include all AD-related genes (Nedoszytko et al., 2020). [10]

Different levels of Omic data reflect different levels of metabolism. Of course, a complete study needs to correspond to the results of different levels in order to fully understand the

pathogenesis of AD. Through the study of Omics data, it is often found that dozens or even hundreds of genes have significant changes, and often involve changes in dozens of metabolic pathways. Are the results of studies with different samples similar, or are they very different? How does this contribute to the understanding of the pathogenesis of AD? To explore this question, we performed a transcriptomic study on AD skin tissue and compared the results with similar studies using the same GEO dataset but different groups of samples, since there are many similar studies using this method, which is convenient for comparison.

MATERIALS & METHODS:

Data Source

The original datasets, GSE16161, GSE32924, GSE120721, and GSE130588 were downloaded from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). The microarray data for GSE16161 consist of an mRNA expression profile of 9 AD samples and 9 normal samples, the GSE32924 consist of 13 AD samples and 8 normal samples, the GSE120721 consist of 5 AD samples and 6 normal samples, and the GSE130588 consist of 51 AD samples and 20 normal samples. AD samples were obtained by biopsy from lesioned skin, and control samples were obtained from normal skin biopsies of healthy volunteers.

Identification of Differentially Expressed Genes

Differentially expressed genes (DEGs) between AD and control skin biopsies were identified by GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/), where $p<0.05$ and $|logFC| >1$ was required. [11] The common upregulated and downregulated DEGs shared between these four datasets were identified by Venn diagram analysis (https://bioinformatics.psb.ugent.be/webtools/Venn/).

GO and KEGG Pathway Analyses

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyzes can be carried out with a bioinformatics database DAVID (https://david.ncifcrf.gov/). [12] The

gene list of all the common upregulated and downregulated DEGs was submitted to the DAVID database. There are 3 domains in the GO analysis. The first domain was biological process (BP), which gives information on the biological processes a gene is involved in. The second one was molecular function (MF), which describes molecular activities of a gene, and the final one was cellular component (CC), which describes the location or structure of the expression product of a gene. The KEGG pathway provides information on molecular pathways, biological processes, and other functional aspects of a gene.

Protein–Protein Interaction (PPI) Network Analysis

The gene list of all the common upregulated and downregulated DEGs was submitted to the STRING database (http://string-db.org) to establish a PPI network. [13] Cytoscape software is used to visualize this network (https://cytoscape.org/), and the CytoNCA plug-in is used to calculate the PPI node degree (https://apps.cytoscape.org/apps/cytonca). [14]

RESULTS:

Identification of DEGs in AD

The volcano plots of differential genes for the four RNA expression profiling datasets (GSE16161, GSE32924, GSE120721, and GSE130588) are shown in Fig. 1A. Venn diagram analysis obtained 85 downregulated DEGs in common, and 47 upregulated ones in common, as shown in Fig. 1B and Table 1.

Table 1. Common upregulated/downregulated DEGs identified among GSE16161, GSE32924, GSE130588, and GSE120721

Type	Gene name
Upregulated DEGs	CCNB1, CCL22, MELK, NDC80, SOCS3, CCNA2, CKS2, FAM83A, LRP8, KRT16, ADAM8, MPHOSPH9, SNHG3///SNORA73A, ITCH, AKR1B10, KIF18B, CCL17, CENPN, S100A8, POLQ, PRR11, RRM2, NFATC2IP, UHRF1, FOSL1, TNFRSF10A, ADAM19, AURKA, CCL26, AURKAIP1, NUF2, STAT1, IQGAP3, LINS1, MKI67, CFLAR, CSNK1A1, ARHGAP9, TRIM13, HMMR, JAK3, TTK, PRSS53, NCAPG, COL6A6, DCLRE1C, CTSC
Downregulated DEGs	EPB41L4B, ZEB1, MSRB3, AQP9, IL1F10, EMX2, SPTBN1, FHL1, SORBS2, IL17D, ARHGEF26, LGR5, WIF1, CRTAP, HBA2///HBA1, CITED2, OGN, LEPROT///LEPR, PALMD, ACSL1, RGS22, HBB, CPE, SERPINA5, RNASE4, HDLBP, CORO2B, MYH11, ANG, CPQ, SLITRK6, PGRMC1, KLF7, ID4, PTPN21, ALDH1A1, PSORS1C2, FOXD1, ADGRF4, GATM, FIBIN, CYP39A1, DKK2, LRFN5, HLF, RPS6KA6, PDGFD, MAP1LC3B, C5orf46, SVIP, MAP7, C1QTNF7, CNKSR2, EPHB1, CHMP4C, ANGPTL1, GREM2, SLC1A6, RAI2, MACC1, KBTBD4, PIGC, MACROD2, LOC143286, SPINK1, PTPN11, GAN, SCIN, FAM149A, FBLN1, TPM1, AGTR1, SCEL, CD34, PRSS12, BTC, PLXDC2, IL37, LOC100294033///TCAF1, ZFYVE21, RHOBTB3, SGSM2, CYP2J2, BEX5, GPLD1

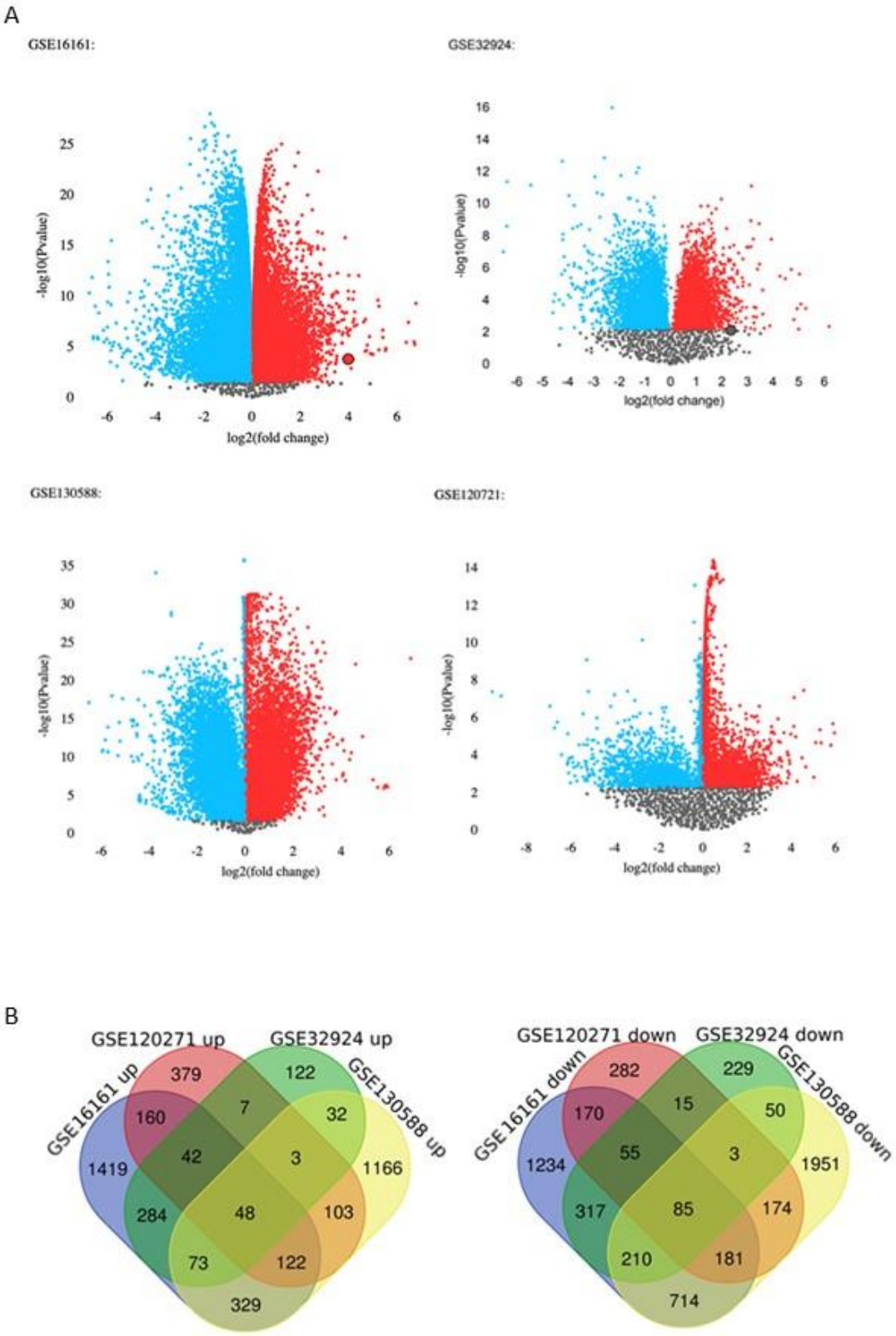

Figure 1. Differentially expressed genes (DEGs) in the 4 datasets (A) and identification of shared up and down regulated DEGs (B).

Function and Pathway Enrichment Analyses of the DEGs

GO term enrichment analysis of biological processes (BP) revealed that many DEGs were associated with inflammatory responses and cell proliferation, such as cytokine-mediated signaling pathway, response to hydrogen peroxide, inflammatory response, nitric oxide transport, mitotic spindle organization, lymphocyte chemotaxis, and so on. Molecular function (MF) analysis revealed that these genes were commonly associated with protein binding, organic acid binding, haptoglobin binding, heme binding, and oxygen transporter activity, etc. Cellular component (CC) analysis results revealed that these genes were commonly found in extracellular region, extracellular space, kinetochore, extracellular exosome, and haptoglobin-hemoglobin complex, etc. The top terms were selected based upon p-value rankings are shown in figure 2A and table 2. The top KEGG pathways based on p-value rankings were viral protein interaction with cytokine and cytokine receptor, C-type lectin receptor signaling pathway, cytokine-cytokine receptor interaction, JAK-STAT signaling pathway and adipocytokine signaling pathway, etc. as shown in Fig. 2B and Table 2.

Table 2. GO and KEGG pathway enrichment analyses for module genes. The top 5 terms were selected based upon p-value rankings

Category	Term	Count	P-Value
BP	GO:0019221: cytokine-mediated signaling pathway	8	5.97E-05
	GO:0042542: response to hydrogen peroxide	5	1.61E-04
	GO:0030185: nitric oxide transport	3	4.00E-04
	GO:0006954: inflammatory response	11	4.26E-04
	GO:0007052: mitotic spindle organization	5	5.15E-04
CC	GO:0005576: extracellular region	33	2.76E-06
	GO:0005615: extracellular space	26	4.15E-04
	GO:0000776: kinetochore	7	5.10E-04
	GO:0070062: extracellular exosome	27	1.04E-03
	GO:0031838: haptoglobin-hemoglobin complex	3	2.02E-03
MF	GO:0005515: protein binding	101	2.44E-04
	GO:0043177: organic acid binding	3	1.82E-03
	GO:0031720: haptoglobin binding	3	1.82E-03
	GO:0020037: heme binding	6	3.24E-03
	GO:0005344: oxygen transporter activity	3	7.27E-03
KEGG	hsa04061: Viral protein interaction with cytokine and cytokine receptor	5	9.27E-03
	hsa04625: C-type lectin receptor signaling pathway	5	1.06E-02
	hsa04060: Cytokine-cytokine receptor interaction	8	1.10E-02
	hsa04630: JAK-STAT signaling pathway	6	1.20E-02
	hsa04920: Adipocytokine signaling pathway	4	1.92E-02

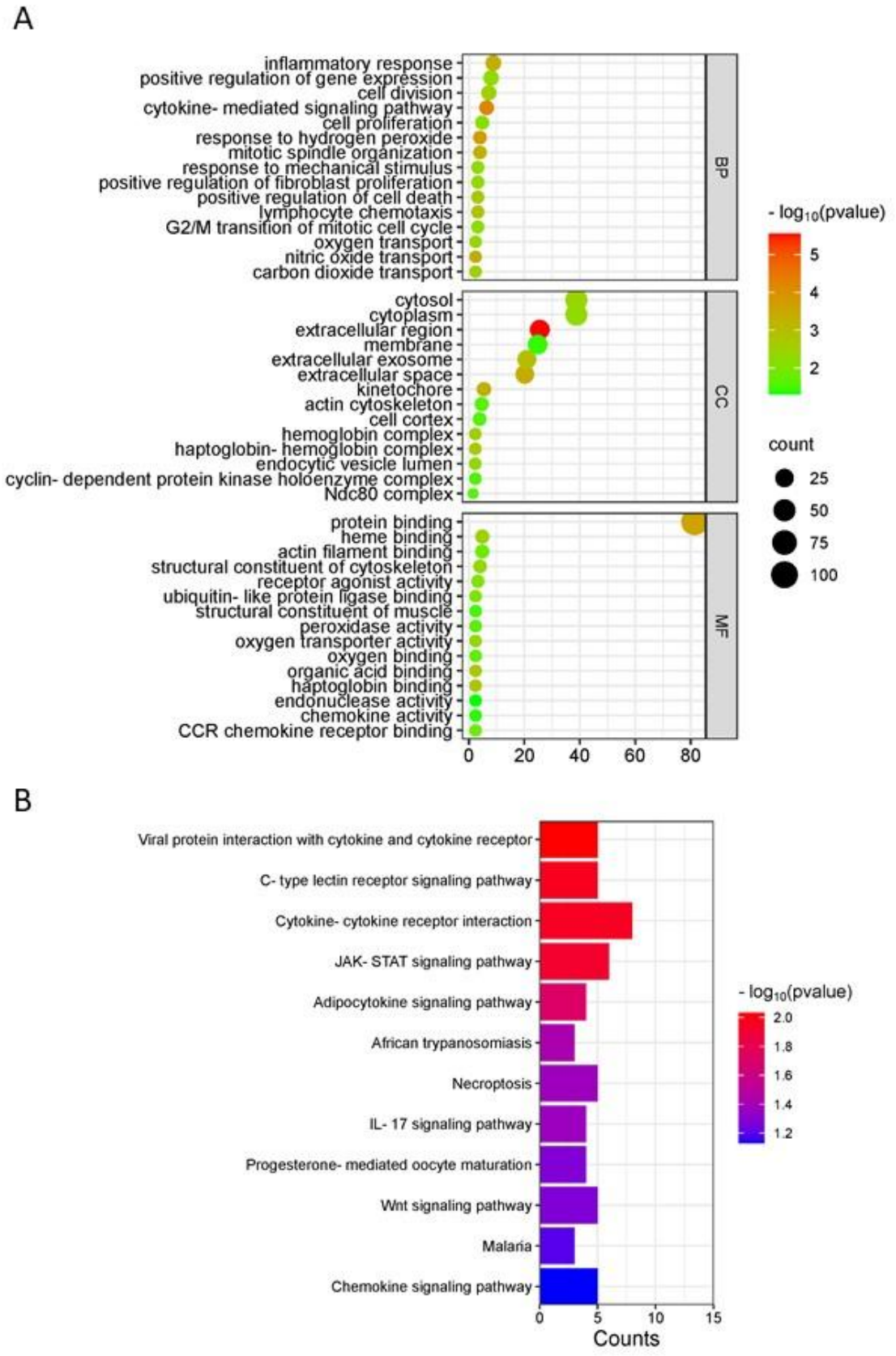

Figure 2. GO term enrichment analysis results (A) and KEGG pathway enrichment results (B).

PPI Network Construction and Hub Gene Identification

PPI Network Analysis shows that there are 84 nodes and 201 edges, as shown in Fig. 3. The 10 nodes with the highest PPI node degree are the hub genes: MKI67, CCNA2, HMMR, AURKA, CCNB1, NCAPG, TTK, MELK, RRM2 and NDC80, and these 10 genes are all up-regulated genes (Table 3 and Fig. 4).

Table 3. Top ten genes in PPI network with higher node degree

Gene	Full Name	Degree	Up or Down
MKI67	Marker Of Proliferation Ki-67	38.0	Up
CCNA2	Cyclin A2	36.0	Up
HMMR	Hyaluronan Mediated Motility Receptor	36.0	Up
AURKA	Aurora Kinase A	36.0	Up
CCNB1	Cyclin B1	34.0	Up
NCAPG	Non-SMC Condensin I Complex Subunit G	34.0	Up
TTK	TTK Protein Kinase	34.0	Up
MELK	Maternal Embryonic Leucine Zipper Kinase	34.0	Up
RRM2	Ribonucleotide Reductase Regulatory Subunit M2	34.0	Up
NDC80	NDC80 Kinetochore Complex Component	32.0	Up

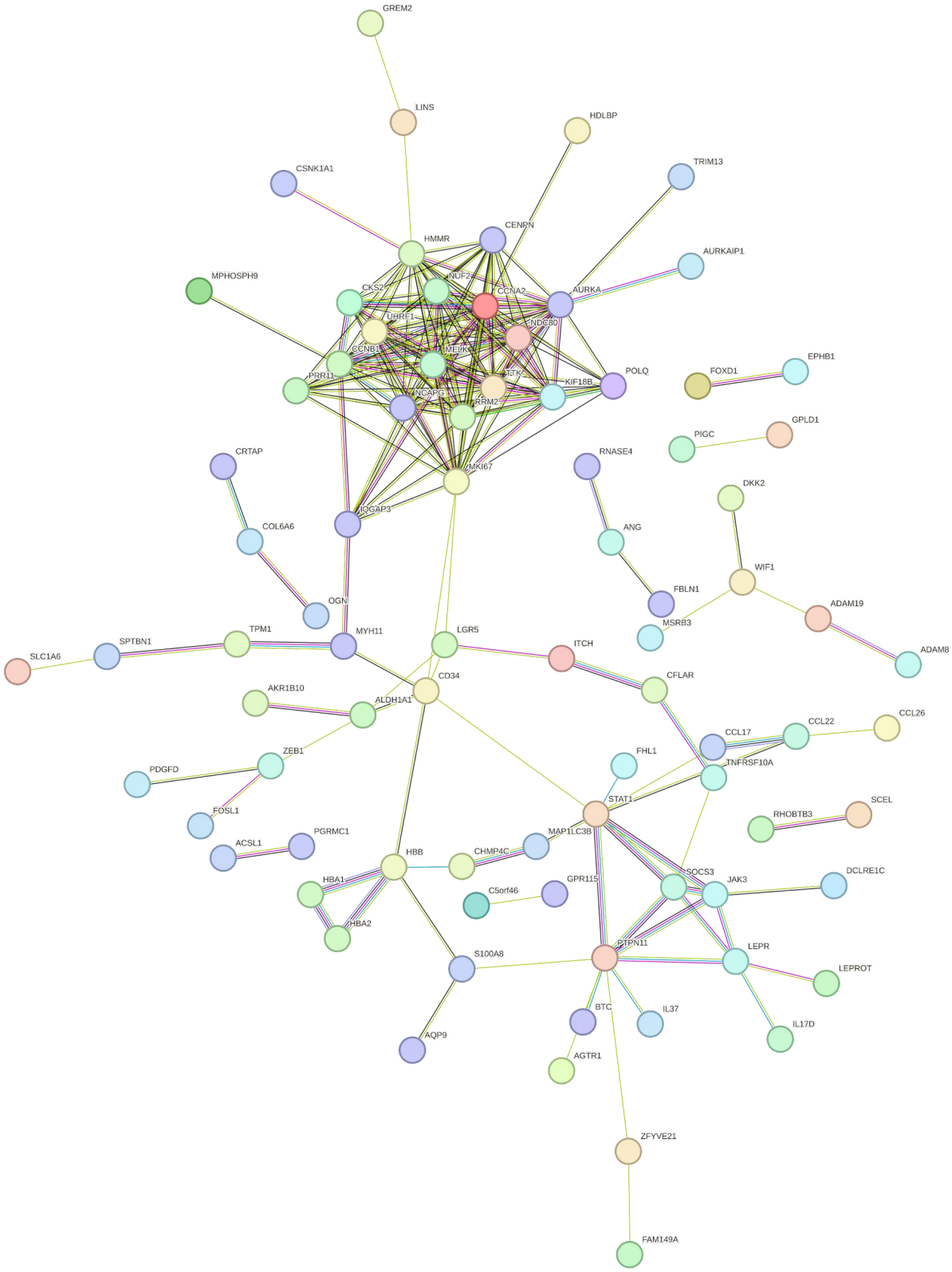

Figure 3. Protein-protein interaction network of differentially expressed genes.

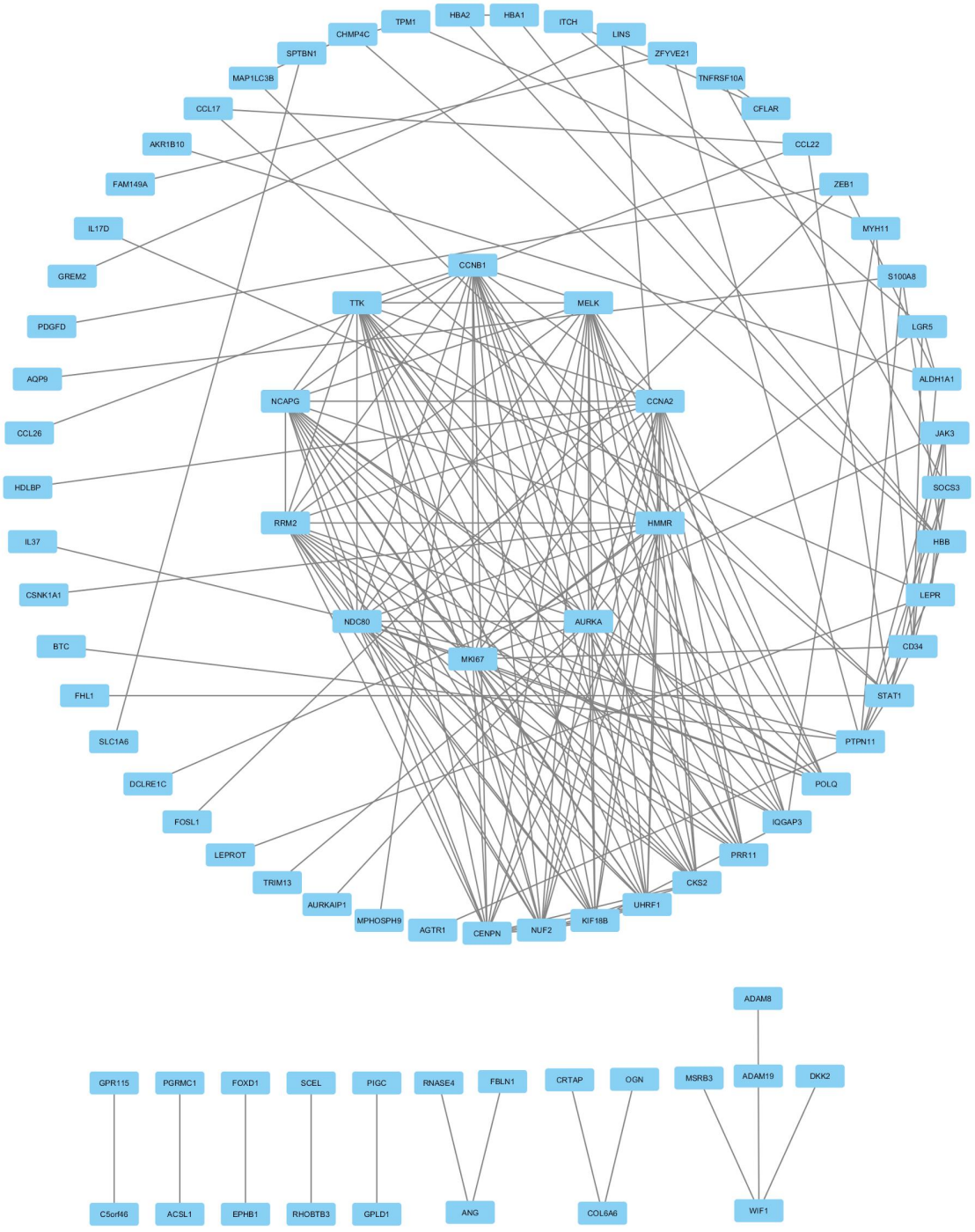

Figure 4. Top ten genes in PPI network with higher node degree.

DISCUSSION:

We already know that genetic factors play a key role in the pathogenesis of AD, however, we do not know the mode by which these genetic factors interact to lead to the development of

the disease. A large amount of data has been accumulated for the transcriptome research of skin biopsy tissue of AD patients and health controls, such as NCBI GEO (https://www.ncbi.nlm.nih.gov/geo/) and EBI (https://www.ebi.ac.uk/biostudies/arrayexpress) that are open databases. Studies based on such databases have found that a large number of gene expressions and signaling pathways have been altered. [9] Did these similar studies based on different case groups get the same or different results? We compared the top signaling pathways and hub genes derived from these studies similar to ours with our findings, as shown in Table 4. [15, 16, 17, 18, 19, 20, 21,]

Table 4. The summary of bioinformatics studies of microarray gene expression datasets in Gene Expression Omnibus for atopic dermatitis

Studies	Samples	GO analysis	KEGG analysis	Hub genes
2022 Chen [15]	GSE5667 dataset included 12 lesional skin biopsies from patients with AD and 10 skin biopsies from healthy controls GSE120721 dataset included 5 lesional skin biopsies from patients with AD and 6 skin biopsies from healthy controls GSE121212 dataset included 21 lesional skin biopsies from patients with AD and 37 skin biopsies from healthy controls	BP: **immune system process, immune response**, **defense response**, **leukocyte activation**, **response to biotic stimulus** CC: **extracellular region, secretory granule, plasma membrane part, cytoplasmic vesicle, intracellular vesicle** MF: 2'-5'-oligoadenylate synthetase activity, Toll-like receptor binding, RAGE receptor binding, enzyme inhibitor activity, **chemokine receptor binding**	influenza A, amoebiasis, primary immunodeficiency, **cytokine-cytokine receptor interaction**, **IL-17 signaling pathway**	PTPRC, CTLA4, CD274, CD1C, IL7R, GZMB, CCL5, CD83, **CCL22**
2021 Yu [16]	GSE6012 dataset included 10 lesional skin biopsies from patients with		**Cytokine-cytokine receptor interaction**	SPRR2C, DEFB4A, CRY2, KRT19, **WIF1,**

	AD and 10 skin biopsies from healthy controls			
2021 Peng [17]	GSE63741 dataset included 10 lesional skin biopsies from patients with AD and 10 skin biopsies from healthy controls GSE124700 dataset included 10 lesional skin biopsies from patients with AD and 10 skin biopsies from healthy controls	BP: **epidermis development, granulocyte chemotaxis, lymphocyte chemotaxis, monocyte chemotaxis** CC: collagen-containing extracellular matrix, **extracellular matrix** MF: **cytokine activity, cytokine receptor binding, chemokine receptor binding**	**IL-17 signaling pathway**, **cytokine-cytokine receptor interaction**, **chemokine signaling pathway**	**HBB**, LCE3D, S100A7, **S100A8**, S100A9
2020 Yin [18]	GSE75890 dataset included 9 lesional skin biopsies from patients with AD and 8 skin biopsies from healthy controls	BP: **immune response, inflammatory response**, peptide cross-linking, **oxidation-reduction process, positive regulation of cell division**, calcium-independent cell-cell adhesion via plasma membrane cell-adhesion molecules CC: **extracellular exosome**, keratin filament, **extracellular region**, bicellular tight junction, **proteinaceous extracellular matrix, and extracellular space** MF: **motif chemokine receptor chemokine receptor binding**, receptor for advanced glycation endproducts receptor binding, **chemokine activity**, interleukin (IL)-1 receptor binding, **cytokine activity**	hematopoietic cell lineage, pertussis, p53 signaling pathway, staphylococcus aureus infection, cell cycle, tight junction	**CCNB1**, CCNB2, **CCNA2**, CXCL10, CXCL9
2018	GSE31408	BP: **immune responses,**	extracellular matrix	**CKS2**,

Li [19]	dataset included 20 lesional skin biopsies from patients with AD and 2 skin biopsies from healthy controls GSE32924 dataset included 13 lesional skin biopsies from patients with AD and 8 skin biopsies from healthy controls	**skin development, epidermal cell differentiation** CC: chromosomal region, **extracellular space** MF: **receptor binding, cell adhesion, molecular binding**	receptor interactions, **chemokine signaling pathways,** leukocyte trans-endothelial migration	**KIF18B**, KIF14, DEPDC1, HELLS, GTSE1, **NCAPG**, FANCI, KIF4A, KIF20A, DLGAP5, NEK2
2016 Ding [20]	GSE32924 dataset included 13 lesional skin biopsies from patients with AD and 8 skin biopsies from healthy controls	BP: **immune response, cell cycle, cell differentiation**	arachidonic acid metabolism, cell adhesion molecules, NOD-like receptor signaling pathway, **cytokine–cytokine receptor interaction**.	STRA13, PUSL1, PSENEN, NAP1L2, AADAC, CD320, DLX5, KLK5, CHIC2, C1orf159
2014 Zhang [21]	GSE6012 dataset included 10 lesional skin biopsies from patients with AD and 10 skin biopsies from healthy controls	BP: **epidermis development**	**chemokine signaling pathway**	LOR, KRT17, **KRT16**, SPRR2D, SPRR1A, SPRR1B, IVL

Bold text means that the term, pathway, or gene is also significant in our study.

By comparison, we found that the following terms or similar terms in the Biological Process part of GO analysis were also found to have significant changes in our research: immune system process, immune response, defense response, response to biotic stimulus, leukocyte activation, granulocyte chemotaxis, lymphocyte chemotaxis, monocyte chemotaxis, oxidation-reduction process, cell cycle, positive regulation of cell division, cell differentiation, epidermis development, skin development. The terms that were not found to have significant changes in this study were peptide cross-linking, calcium-independent cell-cell adhesion via

plasma membrane cell-adhesion molecules. In the Cellular Component part of GO analysis also found in our study were extracellular region, extracellular matrix, extracellular exosome, secretory granule, proteinaceous extracellular matrix, plasma membrane part, cytoplasmic vesicle, intracellular vesicle. The terms that were not found to have significant changes in this study were collagen-containing extracellular matrix, keratin filament, bicellular tight junction, chromosomal region. In the Molecular Function part of GO analysis also found in our study were chemokine receptor binding, cytokine activity, chemokine activity, cytokine receptor binding, chemokine receptor binding, motif chemokine receptor chemokine receptor binding, receptor binding, cell adhesion, molecular binding. The terms that were not found to have significant changes in this study were 2'-5'-oligoadenylate synthetase activity, Toll-like receptor binding, RAGE receptor binding, enzyme inhibitor activity, receptor for advanced glycation endproducts receptor binding, interleukin (IL)-1 receptor binding.

For KEGG analysis, the significantly altered pathways obtained in these studies were also found in our study, including cytokine-cytokine receptor interaction, IL-17 signaling pathway, and chemokine signaling pathway. Pathways not significantly changed in our study include influenza A, amoebiasis, primary immunodeficiency, hematopoietic cell lineage, pertussis, p53 signaling pathway, staphylococcus aureus infection, cell cycle, tight junction, extracellular matrix receptor interactions, leukocyte transendothelial migration, arachidonic acid metabolism, cell adhesion molecules, NOD-like receptor signaling pathway.

For the hub genes obtained from these studies, the expression levels of which were also significantly changed in our study include CCL22, WIF1, HBB, S100A8, CCNB1, CCNA2, CKS2, KIF18B, NCAPG, KRT16. No significant changes were found in our study including PTPRC, CTLA4, CD274, CD1C, IL7R, GZMB, CCL5, CD83, SPRR2C, DEFB4A, CRY2, KRT19, LCE3D, S100A7, S100A9, CCNB2, CXCL10, CXCL9, KIF14, DEPDC1, HELLS, GTSE1, FANCI, KIF4A, KIF20A, DLGAP5, NEK2, STRA13, PUSL1, PSENEN, NAP1L2, AADAC, CD320, DLX5, KLK5, CHIC2, C1orf159, LOR, KRT17, SPRR2D, SPRR1A, SPRR1B, IVL.

From the above comparison, we can see that all studies can draw on the pathogenesis of AD that have been confirmed, such as inflammatory response, immune response, cytokine-cytokine receptor interaction, and cell proliferation. However, in different studies, due to different samples, changes in different pathways were indeed obtained, such as bicellular tight

junction, NOD-like receptor signaling pathway, RAGE receptor binding, etc. that only can be found in some studies. Especially for hub genes derived in other studies with the same methodology as ours, only a few genes also had significant expression differences in our study. From this result, we can conclude that although different AD patients have common pathological changes such as inflammatory response, immune system activation, and epithelial cell proliferation, the genes and metabolic pathways involved in different patients are quite different. This requires that in addition to drugs targeting those common pathways, it is equally important to develop drugs targeting specific changes in different patients when developing AD therapeutic drugs. In addition, genome, epigenome, transcriptome, proteome, metabolome, lipidome, microbiome and other methods will gradually be used in clinical diagnosis. In fact, this is the concept of precision medicine. [5, 9]

CONCLUSIONS:

This bioinformatics study discovered some key genes and pathways related to AD, which provided potential clues and targets for AD pathogenesis research, diagnosis and treatment research. However, by comparing with other studies using the same method, we found that in addition to the well known pathways such as inflammatory response, immune system activation, epithelial cell proliferation, etc., the hub genes discovered by different studies varied greatly. Of course, the findings of this study need to be further confirmed, but it suggests that in the development of drugs for AD treatment, in addition to drugs targeting those common pathways, it is equally important to develop individualized drugs targeting the differences in gene expression and metabolic pathways in different patients.

Disclosures

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Authors contribution:

conceptualization: Bin Li, Wenqiang Chen;
methodology: Wenqiang Chen;

formal analysis: Danna Jia, Bin Li;
*investigation:*Danna Jia, Bin Li;
writing - rough preparation: Danna Jia;
writing - review and editing: Bin Li;
visualization: Danna Jia, Wenqiang Chen.

All authors have read and agreed with the final, published version of the manuscript.
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