

Identification and Validation of the Potential Key Biomarkers for Atopic Dermatitis Mitochondrion by Learning Algorithms

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Purpose: Atopic dermatitis (AD) is a common inflammatory skin condition characterized by erythema and pruritus. Its precise pathogenesis remains unclear, though factors such as genetic predisposition, autoantigen response, allergen exposure, infections, and skin barrier dysfunction are involved. Research suggests a correlation between AD and mitochondrial dysfunction, as well as oxidative stress in skin tissues.

Methods: Skin sample datasets related to AD (GSE36842, GSE120721, GSE16161, and GSE121212) were retrieved from the GEO database. Differential gene analysis identified differentially expressed genes (DEGs) in AD. Three potential biomarkers—COX17, ACOX2, and ADH1B—were identified using LASSO and Support Vector Machine (SVM) algorithms. These biomarkers were validated through ROC curve analysis, nomogram modeling, calibration curves, and real-time PCR. Immune infiltration analysis assessed correlations of the biomarkers. Additionally, single-cell analysis of the GSE153760 dataset identified nine cell clusters and confirmed expression patterns of the three hub genes.

Results: Differential analysis identified 150 upregulated and 367 downregulated genes. Enrichment analysis revealed significant pathways related to mitochondrial function, oxidative stress, and energy metabolism in skin samples from AD patients. Area under the curve (AUC) values for biomarkers COX17, ACOX2, and ADH1B were 1.000, 0.928, and 0.895, respectively, indicating strong predictive capacity. qPCR results showed COX17 was highly expressed in AD lesions, while ACOX2 and ADH1B were higher in normal skin, consistent with previous findings. Correlation analysis indicated ACOX2 and ADH1B were positively correlated with resting mast cells but negatively with activated T cells and NK cells, while COX17 showed a positive correlation with activated T cells and a negative correlation with resting mast cells.

Conclusion: This study suggests that the hub genes COX17, ACOX2, and ADH1B may serve as potential biomarkers in the pathogenesis of AD. These findings could provide insights for the treatment and prognosis of AD and related inflammatory skin conditions.

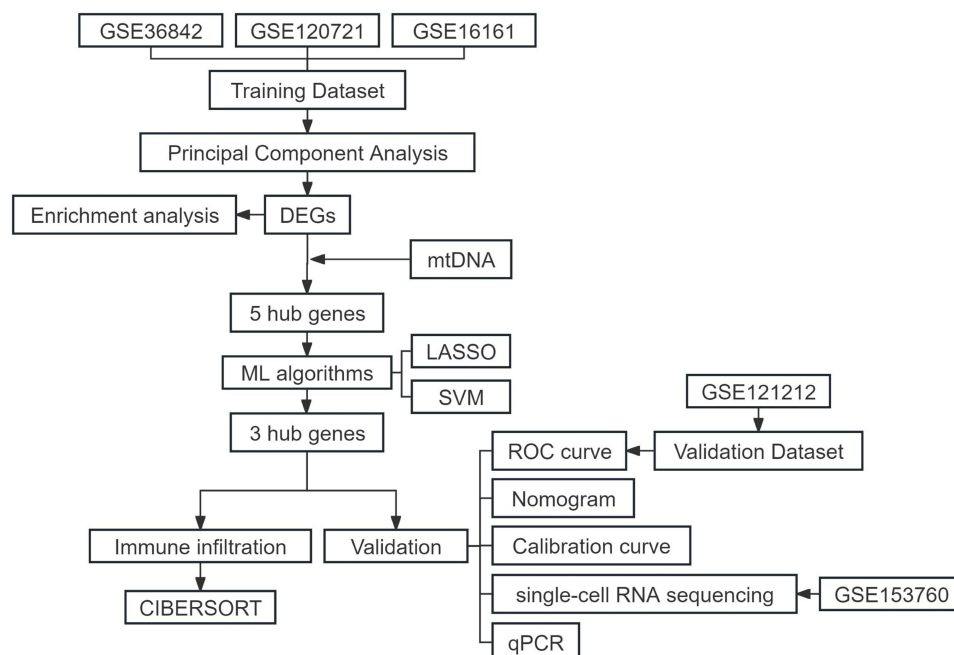
Keywords: atopic dermatitis, mitochondria, learning algorithm, biomarkers, oxidative stress, immune infiltration

Introduction

Atopic dermatitis (AD), also known as atopic eczema or neurodermatitis, is one of the most common inflammatory skin diseases.¹ It is characterized by intense itching and red rashes. AD primarily affects infants and children but can persist in certain forms throughout adulthood. The exact cause of AD remains unclear, but it is thought to result from an interaction between genetic and environmental factors.² According to the Global Burden of Disease Study, the prevalence of AD is 15% to 20% in children and up to 10% in adults, making it the 15th most common non-fatal disease and the highest-burden skin condition globally.³

In recent years, research on AD has advanced significantly. For instance, studies on the pathogenesis of AD in both adults and children showed that while they share core characteristics, there are notable differences, such as the higher

Graphical Abstract



prevalence of seborrheic dermatitis-like symptoms in children.⁴ Additionally, novel therapies targeting immune cells and mitochondrial reactive oxygen species (ROS) have been developed, such as imidazole propionate (IMP).⁵ Despite these advancements, current treatment and prognostic approaches still fail to fully meet patient needs, particularly for moderate to severe AD, where effective and safe targeted therapies remain an unmet challenge. Thus, there is an urgent need for novel, effective, and safe treatment regimens and drug development approaches. This study aimed to identify potential biomarkers related to the pathogenesis of AD by mining and analyzing public databases, providing new design insights and basis for future treatment regimens.

The study of immune infiltration indicates that the pathogenesis of atopic dermatitis (AD) is associated with potential genetic links between certain immune cells. For instance, mast cells play a crucial regulatory role in pathological processes such as vascular tone regulation, neuroinflammatory responses, and sensory conduction,^{6,7} and they mediate the development of AD.^{8–12} Dysregulation of natural killer (NK) cells also contributes to the progression of AD.¹³ Furthermore, research has shown a negative correlation between NK cell cytotoxicity and the severity of AD.¹⁴ CD4+ memory-activated T cells exhibit significant research potential in anti-infective responses and can also mediate the development of AD.^{15–19} Naive T cells are key components of the immune system that can activate and differentiate in inflammatory environments, participating in tissue repair.²⁰ Studies have demonstrated that abnormal expression of naive T cells can influence the development of AD.^{21–23}

In addition to the role of immune cell infiltration, mitochondrial function is also vital for skin health and is closely linked to the pathogenesis of atopic dermatitis. The skin regenerates continuously and depends on ATP for energy. Existing research has shown that mitochondria play a critical role in skin function²⁴ and are closely linked to the development of AD.²⁵ ROS, generated by mitochondrial oxidative phosphorylation (OXPHOS), can harm macromolecules and cell structures, with mitochondria being the main source of endogenous ROS.²⁶ Excessive accumulation of ROS leads to oxidative stress²⁷ and chronic skin inflammation.²⁸ Oxidative stress, a key factor in many inflammatory diseases, is linked to the progression of AD.²⁸ Other studies found that in non-lesional AD, keratinocytes show increased mitochondrial activity, ROS levels,²⁹ and expression of oxidative stress-related hub genes.³⁰

At the same time, with the advancement of computer technology, machine learning has emerged as a powerful data analysis tool, widely applied across various aspects of medical research. It can handle large volumes of case data, uncover potential biological mechanisms, identify disease patterns, and predict the efficacy of drug treatments.^{31–35} Given the highly heterogeneous phenotypes of AD, subtype identification is particularly important. Current studies have utilized machine learning techniques to analyze and classify the different phenotypes of AD.^{36–38} Additionally, machine learning has been extensively applied in the identification of biomarkers for various diseases.^{39–43} In recent years, research on AD has increased, exploring various pathogenic mechanisms, including genetic defects, epigenetics, and immune factors.⁴⁴ In summary, this study was conducted to explore the potential relationship between the pathogenesis of atopic dermatitis (AD) and the increased mitochondrial activity and oxidative stress caused by mutations in specific hub genes, utilizing Support Vector Machine (SVM) and LASSO algorithms to assist in the verification.

Materials and Methods

Study Design

Differential expression analysis was executed using multiple datasets. Enrichment pathway analysis was then conducted, and mitochondrial metabolism-related genes were overlapped with differentially expressed genes (DEGs). Machine learning (ML) methods were applied to validate and screen hub genes, followed by verification of gene expression using validation datasets and single-cell RNA sequencing data. The findings of this study contributed to understanding the mechanisms and progression of AD and propose potential biomarkers that may be useful for therapeutic and prognostic research.

Data Acquisition and Preprocessing

This study collected RNAseq data of AD from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/>), specifically datasets GSE36842, GSE120721, GSE16161, and GSE121212. GSE36842, GSE120721, and GSE16161 were normalized to eliminate batch effects. GSE121212 was used as a validation dataset, and single-cell sequencing data (GSE153760) was also downloaded for validation. All datasets used in this study are publicly available online (Table 1).

DEGs Analysis and Functional Enrichment Analysis

GSE36842, GSE120721, and GSE16161 were merged and subjected to differential expression analysis using the “limma” package, with a threshold of absolute $\log_2FC > 1$ and $P < 0.05$. Heatmaps and volcano plots were generated utilizing “ggplot2” and “pheatmap” packages to compare gene expression differences between AD and normal groups.

To further explore the biological and molecular mechanisms underlying AD, GO and KEGG enrichment pathway analyses were conducted on DEGs using the “enrichplot” and “org.Hs.eg.db” packages. Additionally, GSEA pathway analysis was performed using “ReactomePA” to uncover the potential functions and pathways of the DEGs in the disease mechanism. Results with a P -value < 0.05 were deemed statistically significant.

ML Algorithms

Two ML algorithms, LASSO and SVM, were used to identify hub genes. The “glmnet” package was employed for LASSO regression analysis, to select genes with significant predictive capability from the intersecting gene set by

Table 1 Statistics of the GEO Datasets

GEO Accession	Sequencing Method	Sample Information		Species	Platform
		AD	CTRL		
GSE36842	RNAseq	8	8	Homo sapiens	GPL570
GSE120721	RNAseq	10	6	Homo sapiens	GPL570
GSE16161	RNAseq	9	9	Homo sapiens	GPL570
GSE121212	RNAseq	21	38	Homo sapiens	GPL16791
GSE153760	ScRNAseq	8	7	Homo sapiens	GPL21290

minimizing regression coefficients through weighting. The “e1071” package was used for SVM analysis, and the common genes identified by both LASSO and SVM algorithms were deemed hub genes.

ROC Curve and Nomogram Construction

To assess the diagnostic performance of the hub genes in AD, ROC curves were plotted using the “pROC” package. A nomogram was constructed using the “rms” package, and calibration curves were drawn to evaluate the predictive accuracy for AD.

Immune Infiltration Using CIBERSORT and Correlation Analysis

To investigate the impact of hub genes on immune infiltration in AD, this study applied the CIBERSORT deconvolution algorithm to analyze the merged dataset. The relative proportions of 22 immune cell types were estimated. The results were visualized using the “ggplot2” package, and Spearman correlation analysis was conducted to assess the relationship between gene expression levels and the relative proportions of immune cells.

Single-Cell Gene Sequencing Analysis and Hub Gene Validation

To explore the association between AD samples and hub genes at the single-cell sequencing level, this study used the “Seurat” package to analyze the GSE153760 single-cell sequencing dataset. The proportion of mitochondrial genes in cells was evaluated as a basic quality control metric for single-cell data. Cell populations were identified and classified into nine clusters, and t-SNE plots were generated for subsequent analysis. The “SingleR” and “cellidex” packages were used to project the expression activity of COX17, ADH1B, and ACOX2 onto the t-SNE plot, with corresponding degree of staining applied. Bubble charts were then used to display the expression levels and the proportion of cells expressing these hub genes across different cell subpopulations, as well as in comparisons between AD and normal samples.

Establishment and Experimental Design of AD Animal Model

Atopic dermatitis (AD) mice were obtained from STATRAY (Chengdu, China). Before the experiment, the mice underwent anesthesia, shaving, and depilation. A 0.2% solution of 2,4-dinitrofluorobenzene (DNFB) was applied to the back for initial sensitization. The model group received DNFB on days 5, 8, and 14, applied to the right ear and back to induce dermatitis. Further applications were made on days 16 and 21 to enhance the response, with all DNFB dissolved in olive oil.

Six mice were divided into a normal control group and an AD model group. They were housed in specific pathogen-free (SPF) conditions at the Barrier Animal Experimental Facility of Zhejiang Chinese Medical University (temperature: $23 \pm 2^{\circ}\text{C}$; humidity: 60%-70%; 12-hour light/dark cycle), with two mice per cage and free access to food and water. All procedures complied with the NIH Guidelines for the Care and Use of Laboratory Animals (Jones-Bolin, 2012).

qPCR Analysis of Gene Expression in AD and Control Groups

Skin samples were extracted from the mouse epidermis, and GAPDH was used as the internal reference. First-strand cDNA synthesis was performed with the EntiLink™ 1st Strand cDNA Synthesis Super Mix (ELK Biotechnology, EQ031). Real-time qPCR was conducted on the QuantStudio 6 Flex System PCR instrument from Life Technologies, with three replicates per sample. The EnTurbo™ SYBR Green PCR SuperMix kit (ELK Biotechnology, EQ001) was used, and relative expression levels of target genes were calculated using the $2^{-\Delta\Delta\text{CT}}$ method. All PCR reactions were repeated three times.

Paraffin Sectioning and H&E Staining

Paraffin sections were deparaffinized, stained with hematoxylin for nuclei, differentiated with 1% hydrochloric acid, blued in ammonia water, and then counterstained with eosin. The sections were then dehydrated, cleared, and mounted with neutral resin to complete paraffin section staining. Frozen sections were taken from a -20°C environment and stained by fixing in 4% paraformaldehyde, washing with pure water, rewarming, and other steps. Finally, cells were stained by fixing with 4% paraformaldehyde, stained with celestine blue solution, and after appropriate treatment, the slides were mounted either by dehydration and clearing in alcohol and xylene followed by mounting with neutral resin or directly with glycerin jelly without dehydration. Images were captured with an upright bright-field microscope (Olympus).

Statistical Methods

Bioinformatics statistical analysis and visualization were performed using R (v4.4.0). Spearman's test was used to analyze the correlation between two variables. A $P < 0.05$ was deemed statistically significant. Results were expressed as mean \pm standard deviation (SD). Based on the significance level: $P < 0.0001$ was marked as ****; $P < 0.001$ was marked as ***; $P < 0.01$ was marked as **; $P < 0.05$ was marked as *.

Results

DEGs in AD

First, the three datasets were merged for analysis (Figure 1A). The combat method was then applied to remove batch effects (Figure 1B), and the data were normalized (Figure 1C). The results of the two-dimensional principal component analysis (PCA) showed a clear distinction between AD and normal samples (Figure 1D). Differential expression analysis was conducted using the criteria of an absolute $\log_2FC > 1$ and P -value < 0.05 , yielding 517 DEGs. Of these, 150 were upregulated and 367 were downregulated (Figure 1E and F).

Functional Enrichment Analysis of DEGs

To explore the potential biological processes in AD, enrichment pathway analysis was performed on the DEGs. Gene ontology (GO) analysis showed that the genes were mainly enriched in pathways related to organelle fission, mitochondrial fission, superoxide metabolic regulation, growth factor signaling pathway regulation, and superoxide anion generation regulation (Figure 2A). Kyoto encyclopedia of genes and genomes (KEGG) analysis indicated that key pathways in AD included signaling molecules and interactions, immune system pathways, signal transduction, xenobiotic biodegradation and metabolism, cardiovascular diseases, and cofactor and vitamin metabolism (Figure 2B). Additionally, gene set enrichment analysis (GSEA) (Figure 2C) revealed that the DEGs were mainly enriched in pathways related to mitochondrial activity, including mitochondrial translation, FOXO-mediated oxidative stress response, neuron growth, biooxidation, inflammatory cell recruitment, and Toll-like receptor signaling pathways. These findings suggested that mitochondrial metabolic activity may play a crucial role in the pathophysiology of AD. As a result, a Venn diagram was plotted to compare the 517 DEGs with mitochondrial energy metabolism-related genes, ultimately identifying 5 mitochondrial energy metabolism-related hub genes (Figure 2D).

Hub Gene Screening Through ML Algorithms

In this study, hub genes were identified using the LASSO algorithm (Figure 3A and B) and the SVM algorithm (Figure 3C). Ultimately, three hub genes were identified, namely: COX17, ADH1B, and ACOX2 (Figure 3D). COX17 was highly expressed in AD samples compared to normal samples, while ACOX2 and ADH1B were expressed at lower levels in diseased samples. In addition, external dataset GSE121212 confirmed these findings (Figure 3E and F). Receiver operating characteristic (ROC) curve results showed that the AUC was 0.895 for ADH1B, 1.000 for COX17, and 0.928 for ACOX2, indicating that the three hub genes could effectively distinguish between normal and AD samples (Figure 3G). Furthermore, to demonstrate the rigor of the study, an independent validation was conducted using the external dataset GSE121212 (Figure 3H). The AUC values were 0.628, 0.873, and 0.768 for COX17, ADH1B, and ACOX2, respectively, indicating certain diagnostic potential of these genes. Subsequently, based on the fitted results, a corresponding nomogram model was generated (Figure 3I) to assess the diagnostic probability of AD, and a calibration curve was drawn. The results of the calibration curve showed that the predictive model had strong predictive capability, relatively small error, and favorable consistency between the predicted results and the actual observations (Figure 3J).

Immune Infiltration Analysis

In this study, CIBERSORT was used to calculate the relative proportions of immune cells in the samples (Figure 4A), and the differences in immune cell content between AD and normal samples were compared. The results showed that the

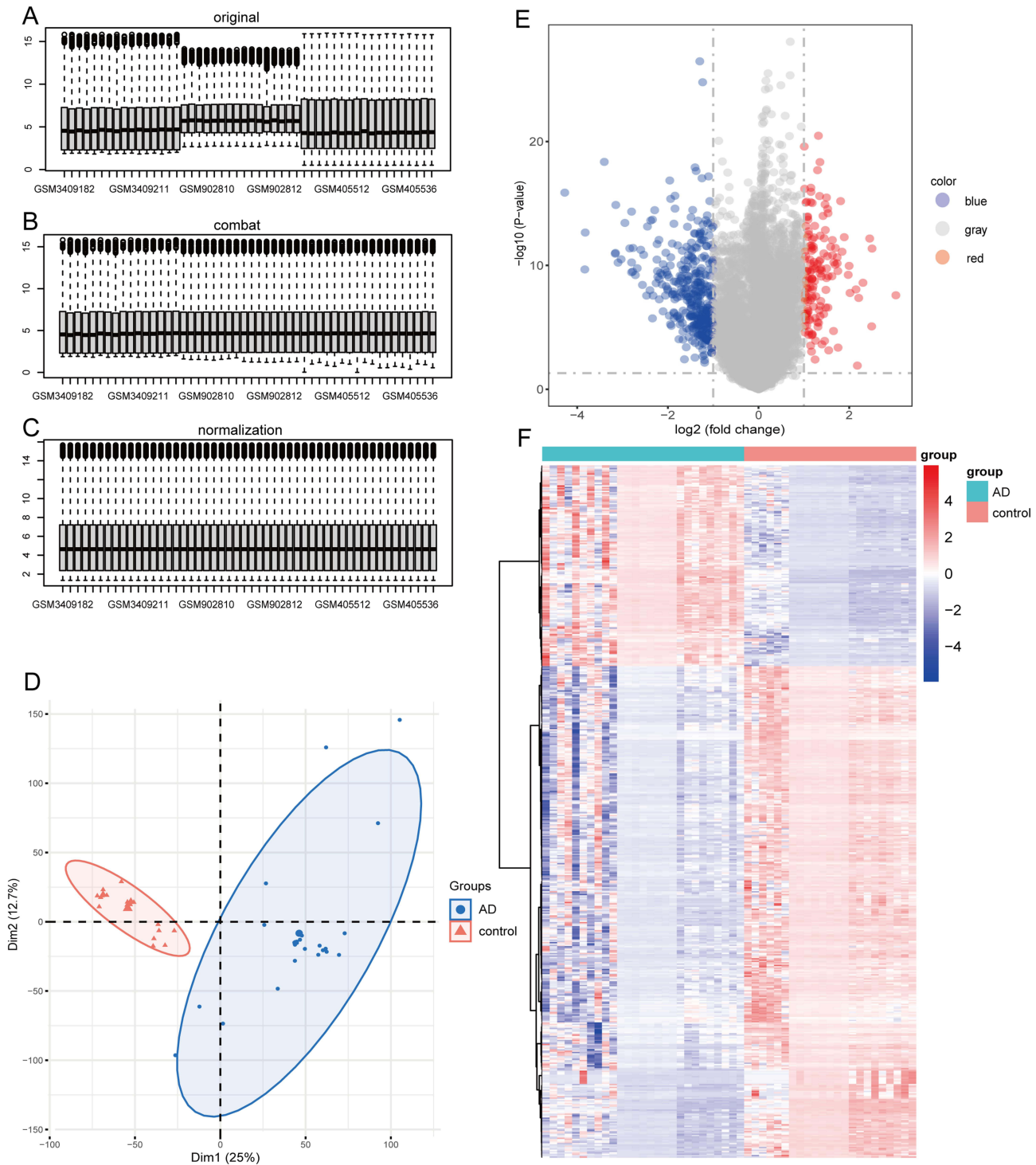


Figure 1 Processing and differential analysis of the merged GSE386842, GSE120721, and GSE16161 datasets. **(A)** Boxplot of the three RNAseq datasets; **(B)** Merged dataset after batch effect removal; **(C)** Normalized merged dataset; **(D)** Two-dimensional PCA of the merged dataset; **(E)** Volcano plot of DEGs between AD and normal samples; **(F)** Heatmap of DEGs.

relative proportions of immune cells, such as mast cells, NK cells, CD4+ memory-activated T cells, and naive T cells, were increased in AD samples (Figure 4B). In addition, this study analyzed the correlation between the expression of the three hub genes and the relative proportions of various immune cells (Figure 4C–E). Results indicated that COX17 was

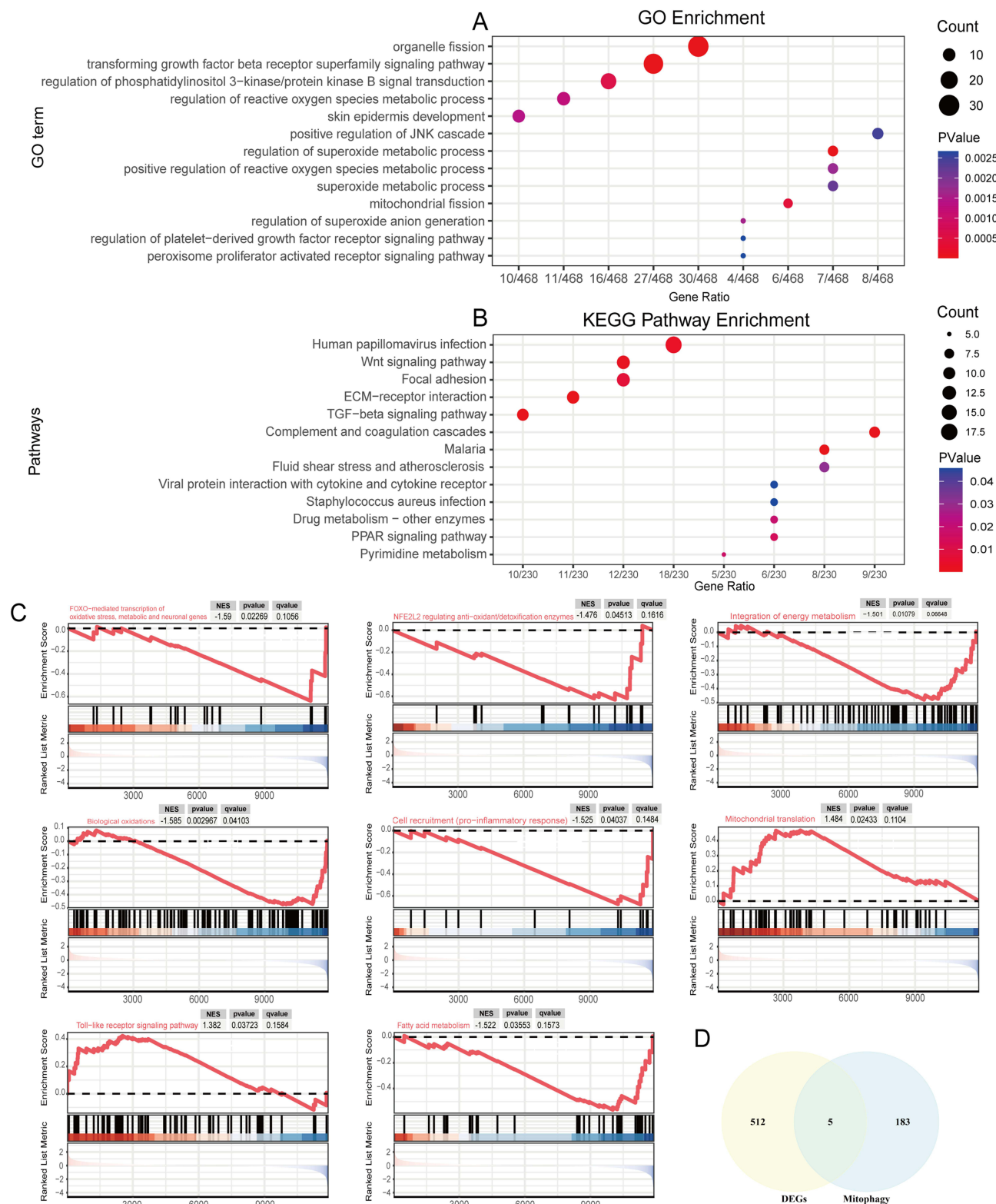


Figure 2 Intersection of mitochondrial genes in GO and KEGG enrichment pathways. **(A)** Bubble chart of GO enrichment analysis pathways; **(B)** Bubble chart of KEGG enrichment analysis pathways; **(C)** GSEA pathway by GO and KEGG; **(D)** Venn diagram showing the overlap between DEGs and mitochondrial-related genes.

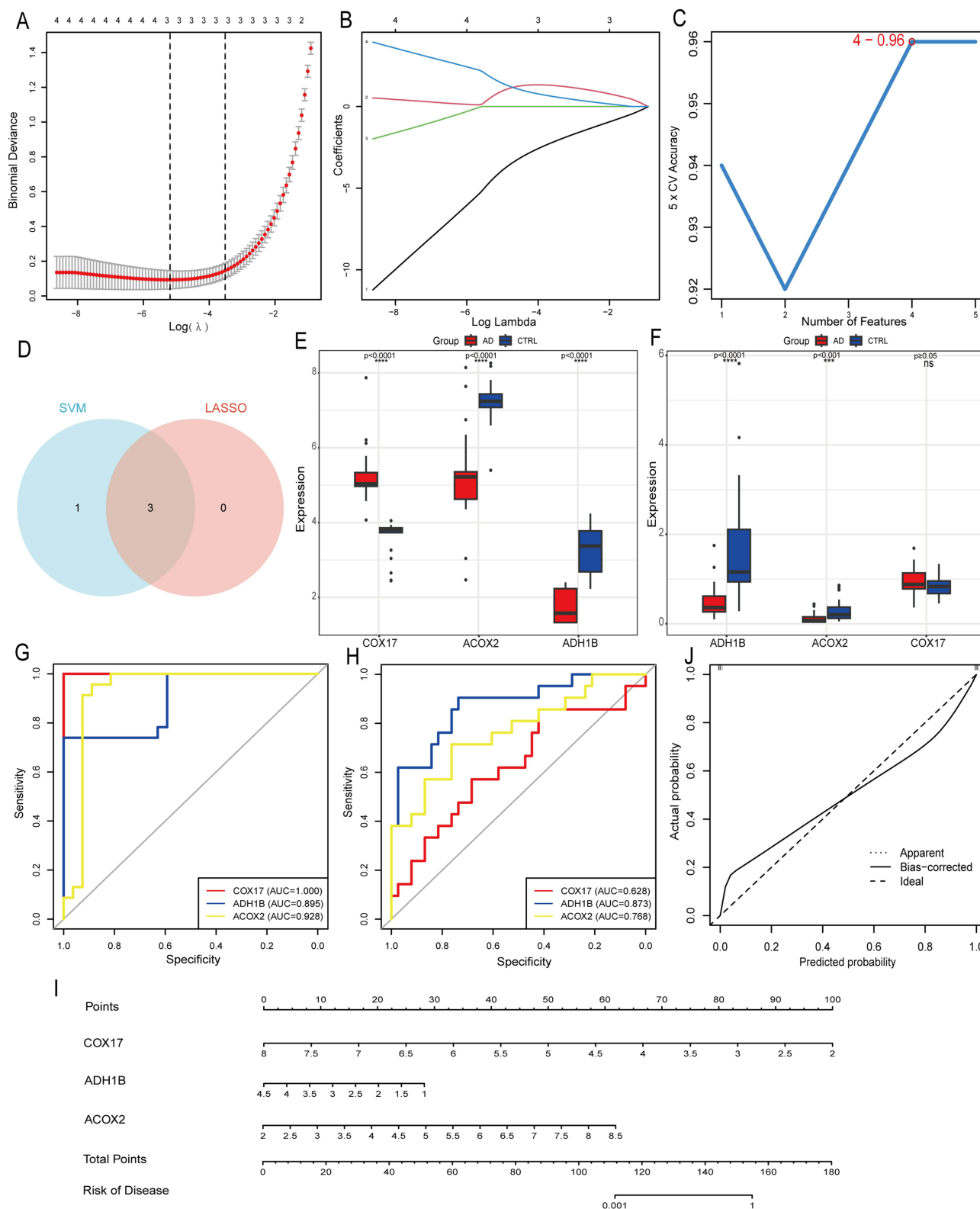


Figure 3 Gene screen by ML and its validation. **(A)** Binomial deviance presented by the LASSO algorithm; **(B)** Coefficients presented by the LASSO algorithm; **(C)** Accuracy of the SVM algorithm; **(D)** Venn diagram showing the overlapping genes between LASSO and SVM; **(E)** Expression of hub genes in AD and normal samples in the merged dataset; **(F)** Expression of hub genes in AD and normal samples in the GSE121212 validation dataset; **(G)** ROC curves of hub genes in the merged dataset; **(H)** ROC curves of hub genes in the GSE121212 validation dataset; **(I)** Nomogram model for the three genes; **(J)** Calibration curve.

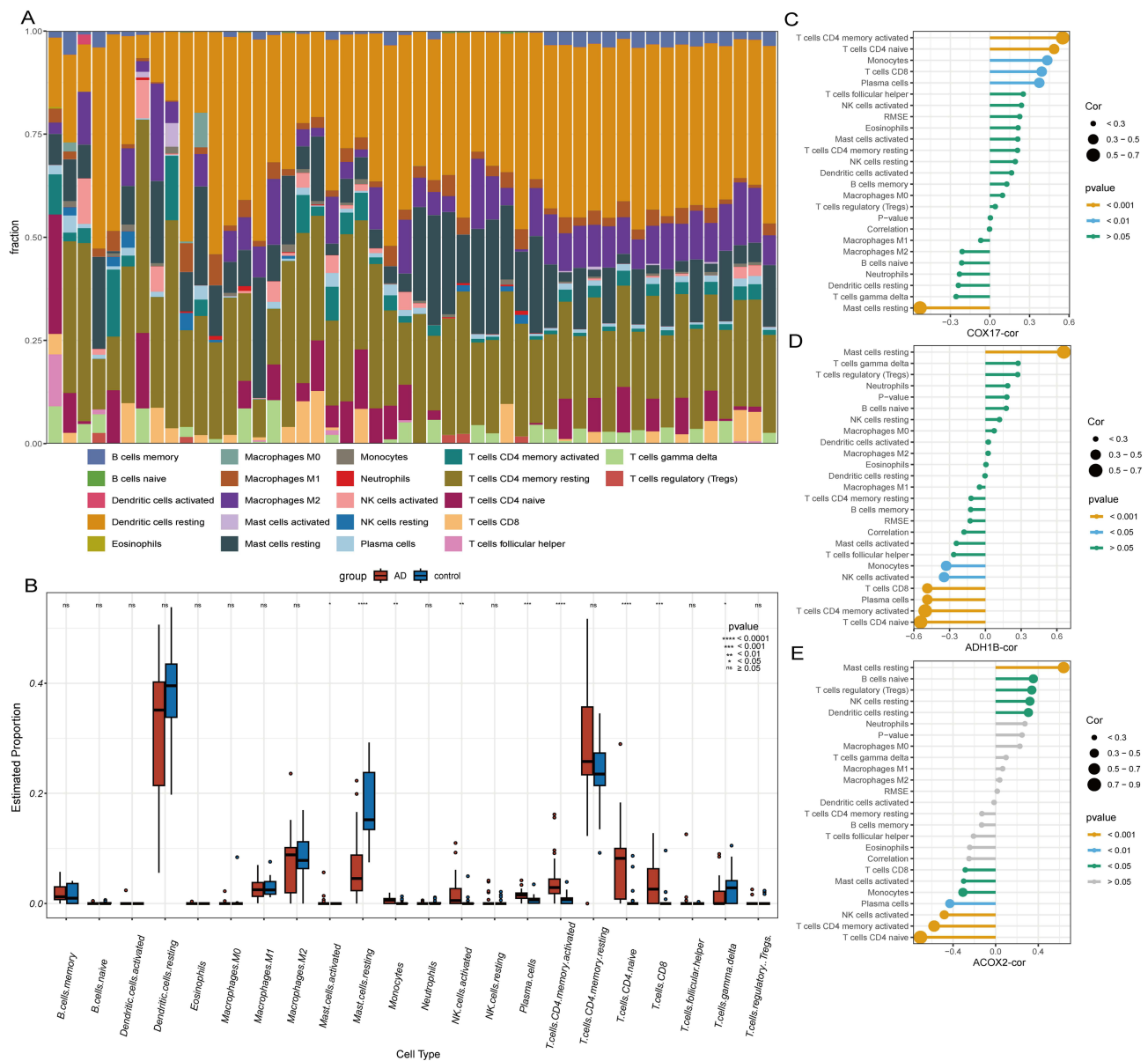


Figure 4 Immune infiltration analysis of AD and normal samples. **(A)** Results of CIBERSORT; **(B)** Box plot comparison of CIBERSORT results; **(C)** Correlation analysis of COX17; **(D)** Correlation analysis of ADH1B; **(E)** Correlation analysis of ACOX2.

negatively correlated with the resting state of mast cells, while ADH1B and ACOX2 showed positive correlations. Furthermore, COX17 was positively correlated with the activation state of CD4 memory T cells and CD4 naive T cells, while ADH1B and ACOX2 exhibited a negative correlation. Overall, the results of this study suggested that the ADH1B and ACOX2 genes may be positively associated with anti-inflammatory effects, while the expression of the COX17 gene may be negatively associated with pro-inflammatory effects.

Validation of Hub Genes at the Single-Cell RNA Sequencing Level

This study utilized scRNA sequencing data from 15 human skin samples (GSE153760) to validate the expression patterns of three hub genes: COX17, ADH1B, and ACOX2. Through data dimensionality reduction and annotation, nine major cell subpopulations were identified (Figure 5A). The expression levels of the three hub genes across different cell subpopulations were also displayed. The results showed that ADH1B was highly expressed in the fibroblast population (Figure 5B), ACOX2 showed generally low expression (Figure 5C), and COX17 exhibited higher overall expression

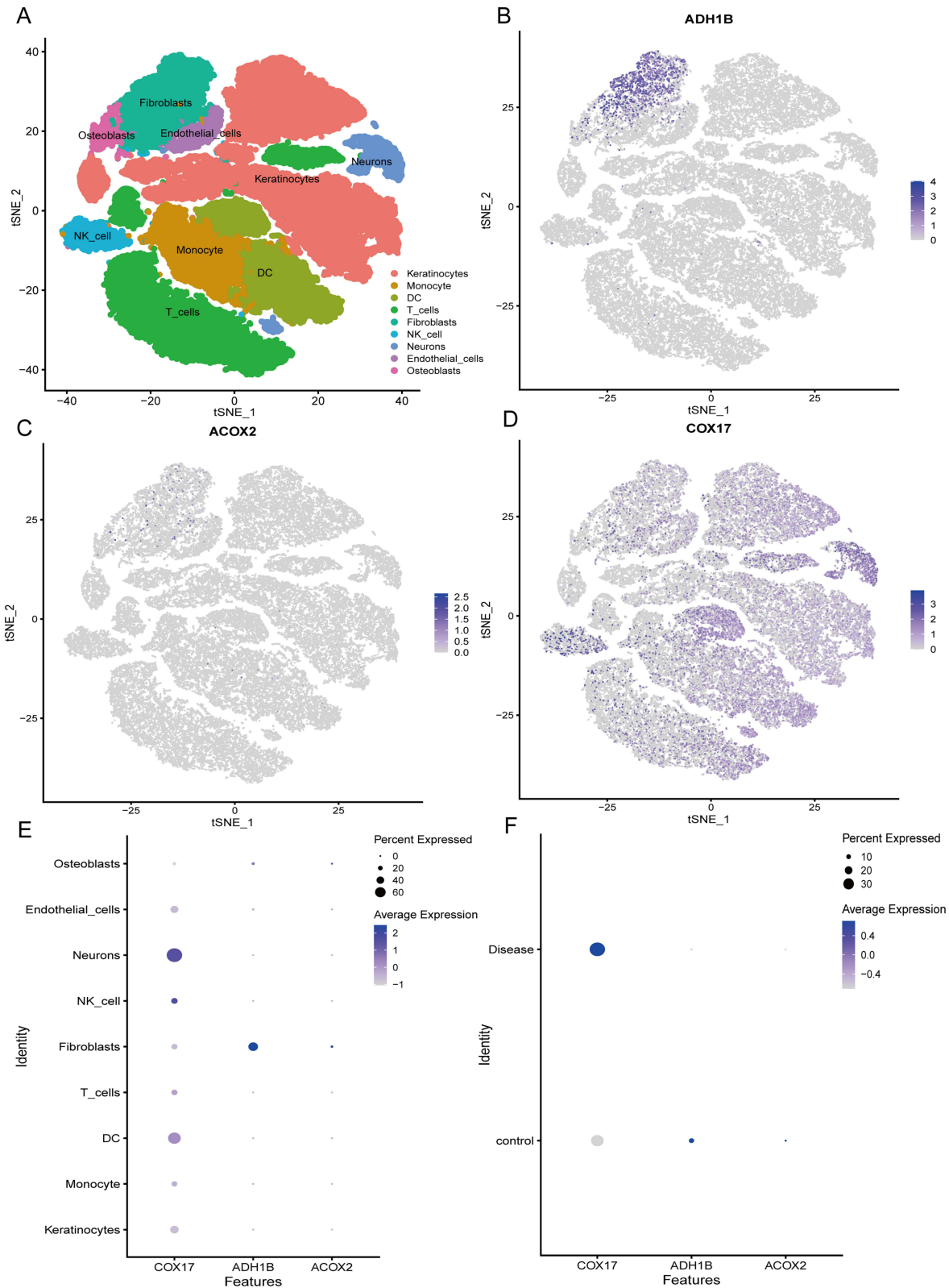


Figure 5 Expression of hub genes at the single-cell scRNA sequencing level and in cell populations. **(A)** Overall t-SNE projection of the nine stained cell clusters in the pooled samples; **(B)** Expression of ADH1B projected onto the t-SNE plot; **(C)** Expression of ACOX2 projected onto the t-SNE plot; **(D)** Expression of COX17 projected onto the t-SNE plot; **(E)** Bubble chart showing the expression of hub genes across different cell subpopulations; **(F)** Bubble chart showing the expression of hub genes in AD and normal samples.

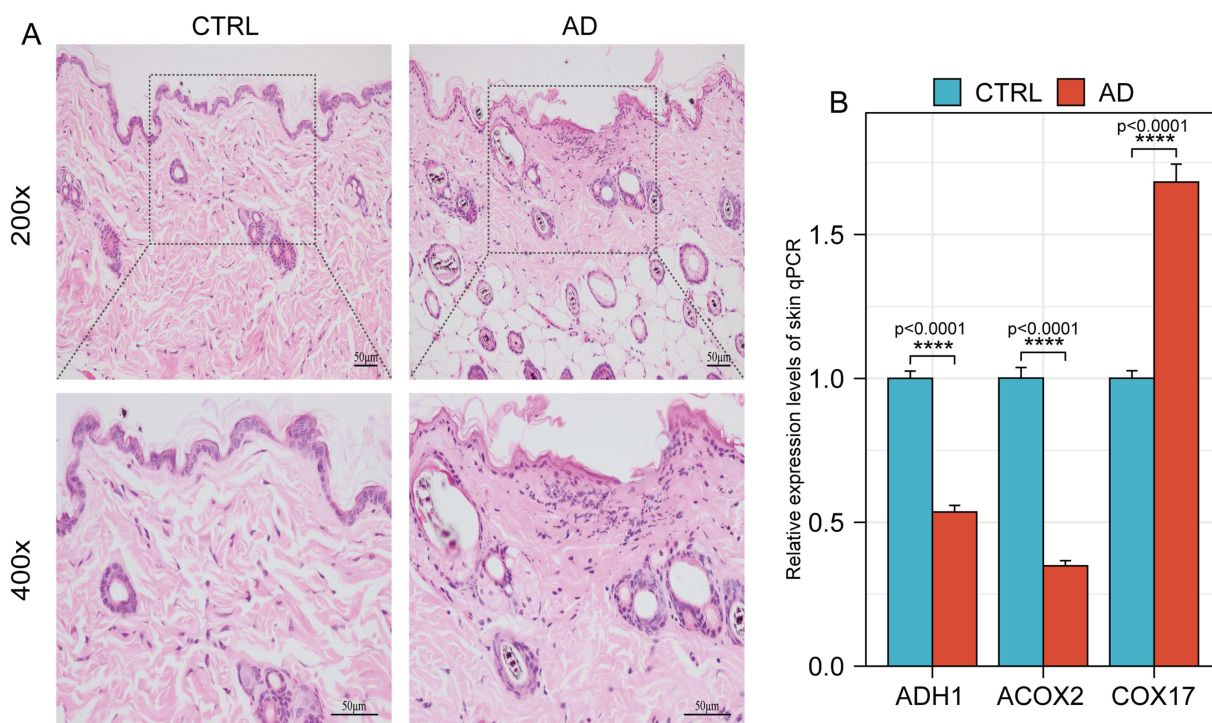


Figure 6 Staining of mouse skin tissue sections and qPCR validation. (A) Skin tissue from normal mice compared to skin tissue from mice with AD; (B) Expression of ADH1, ACOX2, and COX17 genes in AD samples and normal samples as determined by qPCR.

across different cell populations compared to ADH1B and ACOX2 (Figure 5D). To facilitate comparison, this study visualized the expression profiles of the three genes across cell populations, presenting bubble charts that depict both the proportion and expression levels of the three hub genes in different cell subpopulations (Figure 5E). Additionally, bubble charts were created to show the expression patterns of the three hub genes in AD and normal samples (Figure 5F). It was found that COX17 had the highest expression and expression level in AD samples, while ADH1B and ACOX2 showed slightly higher expression in normal samples, consistent with the results of previous analyses.

Validation of Tissue Section Staining and qPCR

Comparison between hematoxylin and eosin (H&E) stained sections of AD and normal epidermal tissues from mice (Figure 6A) revealed that mice with AD exhibited epidermal thickening, extensive inflammatory cell infiltration in the dermis and subcutaneous tissue, parakeratosis, and vascular dilation—characteristics consistent with chronic inflammation. These findings validated the effectiveness of the mouse model for AD. Additionally, qPCR results of skin samples from AD model mice and normal control mice (Figure 6B) showed that the ACOX2 and ADH1 genes exhibited higher expression in normal samples, while COX17 displayed higher expression in AD samples. These results are consistent with previous expression findings in merged datasets, external validation sets, and single-cell datasets. Since the ADH1B gene is specific to humans and does not exhibit such diversity in mice,⁴⁵ previous studies have used the ADH1 gene in mice as a substitute for ADH1B in humans, which achieved satisfactory validation results. Thus, this study also employed the ADH1 gene as a substitute for ADH1B in the qPCR validation experiments of mice.

Discussion

In the past decade, understanding of AD has deepened significantly, with mitochondrial metabolic activity playing a crucial role in the disease's pathophysiology. For instance, excessive mitochondrial production of hydrogen peroxide can trigger AD,³⁰ and abnormal mitochondrial expression is associated with NRF2 activation, which contributes to the condition.⁴⁶ Additionally, mitochondrial β -oxidation supports the energy needs of T cell populations involved in AD.⁴⁷ In this study, datasets GSE36842, GSE120721, and GSE16161 were merged and subjected to differential analysis.

Subsequently, five hub genes were analyzed using LASSO and SVM, confirming three hub genes related to mitochondrial energy metabolism: COX17, ADH1B, and ACOX2. ROC analysis showed that these hub genes have diagnostic value. Both the validation set and qPCR experimental results confirmed that they exhibited consistent expression trends. This suggested that these genes may serve as biomarkers for diagnosing or treating AD, potentially offering new insights into the disease's pathogenesis.

COX17 is an essential protein for the assembly of cytochrome c oxidase in mitochondria, which supplies copper ions to the Cu site of the oxidase complex.⁴⁸ Copper plays a crucial role in aerobic organisms.⁴⁹ Additionally, copper ions play a crucial role in the skin,⁵⁰ as they not only stimulate fibroblast proliferation but also possess antibacterial properties and promote wound healing.^{51,52} Research on the therapeutic applications of copper ions has made some progress. For instance, the use of a Cu/Zn-MOF designed with dual-site biomimetic properties can inhibit the development of specific dermatitis by suppressing Fcγ receptor-mediated phagocytosis.⁵³ Studies have shown that mitochondrial copper accumulation can trigger oxidative stress,⁵⁴ leading to mitochondrial dysfunction, which ultimately induces apoptosis and autophagy.⁵⁵ Moreover, the accumulation of copper ions is also associated with toxicity,⁵⁶ as it can lead to oxidative stress. Additionally, it may contribute to protein denaturation and a reduction in enzymatic activity.^{57,58} Copper accumulation in mitochondria can block complex IV activity and induce mitochondrial dysfunction. Knockdown of COX17 exacerbates mitochondrial copper accumulation, leading to mitochondrial dysfunction and ultimately causing cell apoptosis. In contrast, COX17 overexpression can expel copper from mitochondria, eliminate reactive oxygen species, and protect mitochondrial function. Therefore, COX17 plays a critical role in maintaining mitochondrial copper homeostasis and restoring mitochondrial activity.⁵⁹ These findings suggested that COX17 expression was negatively correlated with disease risk, consistent with the results of this study (Figure 3I). Research has shown that nerve fibers in lesional tissues of patients with AD undergo conformational changes,⁶⁰ and the number of mitochondria in neurons within these lesional tissues is increased.⁶¹ Additionally, dysfunctional peripheral and central neuronal structures can lead to neuroinflammation, hypersensitivity, and abnormal neuronal growth and development.⁶² Studies have shown that in mouse models of AD, neuroinflammation can be mediated via Cav3.2 T-type calcium channels,⁶³ indicating a connection between AD and neuroinflammation. Building on previous research, fibroblasts may serve as a critical link between the ADH1B and COX17 genes. Neuroinflammation in neurons is characterized by reverse electron transport and changes in mitochondrial complex I activity, leading to oxidative stress.⁶⁴ These findings suggested a link between neuronal mitochondria and neuroinflammation. Meanwhile, overexpression of COX17 has been shown to eliminate reactive oxygen species and restore normal mitochondrial functions. Findings of this study showed that, COX17 exhibited the highest expression levels in neurons from AD samples, and its expression was also elevated in other immune cells, such as NK cells, obviously higher than in normal samples (Figure 3E, 3F, 5F and 6B). Therefore, this study suggested that AD may lead to neuroinflammation, and neurons, might upregulate COX17 expression to suppress neuroinflammation, through certain self-protective mechanisms.

ADH1B is a primate-specific enzyme that is highly expressed, particularly in adipose tissue and the liver, and is unique within the ADH1 family. Previous studies have shown that the ADH1B gene is a key biomarker for psoriasis,⁶⁵ with a higher probability of variation in the psoriasis population.⁶⁶ Additionally, psoriasis and AD share common features in terms of genetic traits, immune pathways, and pathological changes,^{67,68} suggesting that the ADH1B gene may have a similar role in AD. The results from single-cell RNA sequencing, immune infiltration analysis, and expression analysis in this study all indicated that ADH1B was predominantly expressed in normal samples, particularly in fibroblasts, while its expression is significantly reduced in AD samples (Figure 5E and F, Figure 6B). These findings suggested that AD may be associated with changes in fibroblast activity mediated by ADH1B. Previous research has identified fibroblasts as potential drivers of AD with the ability to recruit immune and inflammatory cells.⁶⁹ Fibroblasts in AD patients also showed a significantly higher rate of abnormal genetic alterations,⁷⁰ similar to the higher mutation rate of ADH1B in psoriasis. Although current research has not definitively identified whether these genetic alterations include ADH1B, related studies have provided indirect evidence linking ADH1B to fibroblasts. In colon cancer tissues, the ADH1B has been confirmed to be associated with inflammatory responses, particularly through the regulation of the IL-6 signaling pathway.⁷¹ IL-6 is a pro-inflammatory factor known to promote inflammation, oxidative stress, and fibrosis.⁷² Moreover, studies have demonstrated that the

overexpression of the IL-6 pathway can lead to the pathogenesis of atopic dermatitis.^{73,74} It has been implicated in the development of AD.⁷⁵ Therefore, this study proposed that reduced expression of ADH1B in fibroblasts within AD may lead to elevated levels of IL-6, contributing to the disease. The nomogram analysis in this study further supported this conclusion, which showed that ADH1B expression was negatively correlated with the disease risk index (Figure 3I).

ACOX2 is a peroxisomal enzyme confirmed to be involved in mitochondrial metabolism, lipid metabolism, and inflammatory responses.⁷⁶ ACOX2 encodes branched-chain acyl-CoA oxidase, a key enzyme in the β -oxidation of branched-chain and long-chain fatty acids,^{77, 78} which produces reactive oxygen species (ROS) as byproduct.⁷⁹ Additionally, bioinformatics studies indicate that ACOX2 may influence fatty acid oxidation and ROS production through various mechanisms.⁸⁰ In addition, the expression of ACOX2 is associated with mitochondrial function and contributes to skin wound healing.⁸¹ Dysregulation of ACOX2 expression may lead to the development of skin lesions, such as squamous cell carcinoma.⁸² In summary, changes in ACOX2 expression are linked to the pathogenesis of skin diseases. This study hypothesized that ACOX2 expression is negatively correlated with AD. Based on the results, ACOX2 showed relatively high expression in normal samples (Figures 5F and 6B), with similar findings observed in single-cell and validation sets. Immune analysis results indicated that ACOX2 was positively correlated with anti-inflammatory effects (Figure 4C).

Conclusion

In conclusion, the results of this study have clarified that mitochondrial metabolic dysfunction is a key pathological process in AD, which may be mediated by COX17, ADH1B, and ACOX2. In AD samples, abnormal changes in hub genes may affect mitochondrial activity in the skin and potentially trigger oxidative stress responses, ultimately contributing to the onset and progression of AD. The results of this study contribute to an enhanced understanding of the pathogenesis and progression of AD and provide potential biomarkers for future research on its treatment and prognosis. If circumstances permit, we plan to conduct further experiments on related mechanistic pathways based on the findings of this study to enrich the depth of our research.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Ethical Approval

This study involved animal experiments, which were reviewed and approved by the Ethics Review Committee of the Model Biological Center of STATRAY.

According to the item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, we used legally obtained public data or data generated through observation without interfering with public behavior for research. The laboratory adheres to the “Guidelines for Ethical Review of Laboratory Animals—Animal Welfare Principles” (GB/T 42011-2022) issued by the National Standardization Management Committee.

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Disclosure

The authors declare that there are no conflicts of interest associated with the study.

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