Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Potential Targets Related to Skin Aging: Based on eQTL and GWAS Datasets

Hanping Shi[1,2], Xianwei Cao[1–3]

[1]School of Public Health, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China; [2]Jiangxi Provincial Key Laboratory of Disease Prevention and Public Health, Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China; [3]Department of Dermatology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China

Correspondence: Xianwei Cao, Department of Dermatology, The First Affiliated Hospital of Nanchang University, No. 17 Yongwai Street, Donghu District, Nanchang, Jiangxi, 330006, People's Republic of China, Tel +86-0791-88692748, Email ndyfyygk@163.com

Background: The aging of skin has important impact on various systems, and certain skin aging (SG) markers can not only help with early diagnosis, but also provide new ideas for pathophysiological research and treatment strategies.

Objective: To identify target genes related to SG through bioinformatics technology and provide ideas for skin anti-aging.

Methods: Differential expression genes (DEGs) related to SG were screened through transcriptome information from GEO datasets (GSE85358 and GSE670988). Based on eQTL and GWAS datasets, Mendelian Randomization (MR) analysis was applied to identify associations between gene expression and SG. Then, aging skin related important genes (AS-IGs) were obtained based on above two steps, and functional and pathway analyses were performed to explore the potential mechanisms AS-IGs in SG. Finally, the CIBERSORT evaluation was used to assess the infiltration of immune cells related to SG.

Results: Seven AS-IGs were selected through intersection from 612 DEGs and 399 eQTL genes. Then, enrichment analysis results showed there were 60 GO terms may involved in the process of SG, like fatty-acyl-CoA metabolic process, while KEGG enrichment pathways identified mainly involved in mechanisms related to fatty acid metabolism, energy generation, and inflammation regulation. The CIBERSORT evaluation showed that NK cells resting were the main infiltrating cells.

Conclusion: AS-IGs may play important roles in the process of SG in the body. These molecules involve multiple systems and mechanisms in the body, such as immune function, metabolic function, and neuroendocrine function.

Keywords: skin aging, biomarkers, eQTL, GWAS, Mendelian analysis

Introduction

With the extension of life expectancy, skin aging (SG) is no longer limited to purely cosmetic dimensions, but gradually presents functional dimensions beyond cosmetics and appearance, becoming a hot topic for discussion.[1] As the largest organ in the human body, it is also associated with multiple different systems of the organism, including the nervous, immune, circulatory, and endocrine systems. Anti-skin-aging treatment can not only improve skin appearance, but also achieve the ultimate goal of improving physical health. Understanding the promotion mechanisms of SG on systemic aging may facilitate the development of technology to alleviate systemic aging and age-related diseases through skin prevention or treatment methods.[2] Various anti-aging methods, including local treatments, energy-based dermal rejuvenation procedures, and skin fillers, all aim to achieve anti-aging effects by restoring the molecular characteristics of SG.[3] Therefore, understanding the specific molecular markers or mechanisms involved in the process of SG is of great significance for anti-aging treatment.

The role of genomic mutations in SG researches has been a focal point in recent years. As the largest organ in the human body, the skin is continuously exposed to environmental factors such as ultraviolet radiation, pollutants, and oxidative stress, which can cause genomic damage and accelerate the aging process. At the same time, cellular decline occurs under many different internal triggering factors, including DNA damage, telomere dysfunction, oncogene activation, and organelle pressure. It is also been related to processes such as tumor suppression, tissue repair,

Received: 27 November 2024
Accepted: 5 March 2025
Published: 21 March 2025

embryogenesis, and biological aging, all of which are inseparable from genetic changes and their related mechanisms in the body.[4] Understanding the genomic changes that occur during SG may provide new treatment options for degenerative skin diseases and prolonged skin and systemic health. For example, after downregulating the mTORC1 pathway with melatonin, collagen expression in "systemic" skin significantly increased.[5] However, more work needs to be done to understand the mechanisms behind these benefits and their impact on SG. The study of genetic variations in SG can not only be used to evaluate the efficacy of intervention measures, but also to further develop effective skin "rejuvenation" technologies. Developing genetic biomarker models is an important task that cannot be abandoned in today's multi omics era.

Expression quantitative trait loci (eQTL) studies measure the expression levels of all genes in the genome, providing a fair perspective on the regulation of gene expression. [6] The eQTL catalog is a resource developed by reprocessing data from dozens of studies involving over 30000 samples, [7] These studies and the resulting resources demonstrate the value of eQTL information in inferring pathogenic genes and variations at GWAS loci. [6] The combination of eQTL database and GWAS database will provide more accurate perspectives on human diseases and pathological conditions. There was an analytical framework that integrates cis eQTL or cis DNA methylation QTL with GWAS data through the MR method had successfully identified gene expression or DNA methylation loci associated with various phenotypic pleiotropy or potential causality, such as cardiovascular disease, systemic lupus erythematosus, inflammatory bowel disease, and education level, indicating that it is a promising tool for exploring genes associated with complex trait pleiotropy. [8]

Our study used Mendelian Randomization (MR) analysis to integrate and utilize data from the eQTL database and GWAS database to analyze genes that are causally associated with SG. Then, by combining the differential expressed gene analysis between SG and control group samples based on the GEO database, and integrating the results of both analyses, aging skin related important genes (SA-IGs) were obtained.

Materials and Methods

Gene Expression Matrix from GEO Database

"Skin aging" was entered as the search object into the GEO database search box, the gene expression microarray datasets GSE85358 and GSE67098 were selected and downloaded. The criteria for selecting the dataset are as follows: aged skin samples with detailed gene expression information and control skin samples. The GSE85358 dataset is based on the GPL17077 platform and includes 24 aging skin tissue samples and 24 control skin tissue samples. The GSE67098dataset is based on the GPL570 platform and includes 9 aged skin tissue samples and 7 control skin tissue samples.

Differential Expressed Genes Screening Through GEO Database

All differential analyses were performed on merged dataset using the "Limma" package in R software. Compared with the control group, genes in aging-skin tissue samples were upregulated or downregulated, with P-values less than 0.05 and $|\log_2$ fold changes (FC)| greater than 0.585 considered statistically significant in the difference analysis of above two datasets. Principal Component Analysis (PCA) is a commonly used data dimensionality reduction technique that can help researchers discover multidimensional pattern datasets, reduce data complexity, and reveal potential relationship variables between data,[9] which was used to remove batch effects from different dataset from different platforms, in order to integrated the gene expression matrix data from the GSE85358 dataset and merged the GSE67098 dataset into one merged matrix.

Exposure and Outcome Data

eQTLs data was obtained from the eQTLGen Consortium (https://eqtlgen.org/), which contains 16987 genes and 31684 cis eQTLs (FDR < 0.05) from blood samples of most healthy European individuals.[10] The genetic data for SG was obtained from the latest GWAS database, with GWAS ID ukb-b-2148, which includes 423999 participants of European descent with whole genome genotypes, including 9851867 single nucleotide polymorphisms (SNPs).

Mendelian Randomization

Before MR analysis, strict quality control was carried out on the instrument variables (IVs). The selection criteria of IVs are based on following key points: SNPs ($P < 5\times10^{-8}$) significantly correlated with exposure or outcome factors as the threshold; F-statistic ≥ 10 (F-statistic = (beta/SE) ^{2}).[11] Then, based on each Genomes population panels, carefully select variants with low linkage disequilibrium (LD: $r^2<0.1$, and distance > 10000kb).[12] Finally, genes with SNPs accounting for a percentage of variance greater than the exposure percentage were filtered out by Steiger.[13] Exposure and outcome data were cross-checked and palindromic SNPs were removed prior to analysis, while the palindromic SNPs are SNPs with A/T or G/C alleles.

Functional Analysis

SA-IGs are defined as cross genes between differentially expressed genes in GEO database and causal associated genes in eQTL analysis. We used the R software package "Clusterprofiler" to perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis on SA-IGs, with a screening criterion of q value <0.05, to explore their biological functions, signaling pathway enrichment, and disease similarity.

Immunotherapy Response Prediction

The correlation between SA-IGs expression and immune cell infiltration can provide important information for understanding the mechanisms of immune cell influence in the aging microenvironment.[14,15] After the source gene expression data downloaded from the GEO database were standardize, the CIBERSOR algorithm[16] was used to analyze the infiltration of 22 immune cells in each sample, which can transform the standardized gene expression matrix into the composition of infiltrating immune cells. The results of CIBERSORT are visualized using the R package "corplot", "vioplot", "ggplot2", and "glment".

Statistical Analysis

All analyses were conducted using R (version 4.4.1). Multiple comparisons were made, and FDR correction was used to control the false positive rate.

The MR analysis was conducted using the "TwoSampleMR" R software package (version 4.3.3). The inverse variance weighted (IVW) method is a fundamental MR analysis method. When the P-value of IVW results is less than 0.05 and the direction of IVW is consistent with that of MR Egger, weighted median, simple mode, and weighted mode, then the results have statistical significance. MR results are represented by odds ratios (ORs) and corresponding 95% confidence intervals (CI).[17,18]

Cochran Q test[19] was conducted to evaluate the heterogeneity of each SNP, and scatter plots of SNPs-exposure association and SNPs-outcome association were generated to visualize the test results. "Leave one out" analysis was performed to evaluate whether each SNP will affect the results (by sequentially excluding each SNP and performing IVW on the remaining SNPs to assess the potential impact of specific variants on the estimated values).[20] Furthermore, we used MR Egger regression to test and correct for potential horizontal pleiotropy.

Results

Differential Expression Analysis Through Comprehensive Transcriptome

Prior to downstream analysis, a new gene expression matrix was obtained by combining all samples from GSE85358 and GSE67098, and the combined batch effects were evaluated using two principal component analyses (PCA). The results show that the distributions of the two datasets are fused with each other and can be used for subsequent data analysis (Figure 1A). Subsequently, based on the significance level of P-value < 0.05, we obtained 612 differential expressed genes (Figure 1B) Then, the hierarchical heatmap showed that these 67 DEGs could be clustered into two different groups, with one group consisting of 297 genes upregulated in the experimental group and 315 genes down regulated in the other group (Figure 1C).

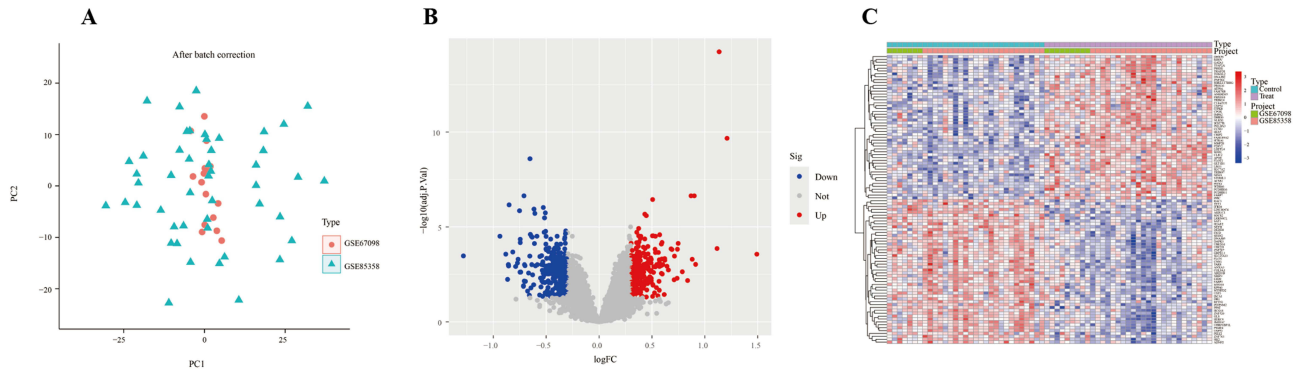

Figure 1 The GSE85358 and GSE67098 datasets were merged for differential expression analysis. (**A**) Two dimensional principal component analysis of the merged GSE85358 and GSE67098 datasets; Red, GSE67098; Blue, GSE85358. (**B**) Volcano chart, displaying the data set and the differential expression analysis results between the control group and the experimental group. (**C**) A heatmap of differential expressed genes expressed between the control group and the experimental group.

MR Analysis Between eQTL and SG

As Supplementary Tables 1 and 2 showed the SNPs considered in the regional target analysis of eQTL and ficial aging expectively. According to the above screening threshold, the F-statistic of all SNPs obtained is greater than 10, reducing potential weak tool bias. After removing palindromic SNPs, a total of 26152 SNPs of eQTL and 17232 SNPs of ficial aging were used as IVs expectively. Next, we used these SNPs as IVs to replace eQTL for "exposure", SG for "outcome" to conduct MR analysis. IVW was used as our main method, and MR Egger, weighted median, simple mode, and weighted mode served as auxiliary judgment methods. The IVW results showed that were 399 eQTL genes significantly correlated with ficial aging (Supplementary Table 3).

SA-IGs Selection and Casual Relations with SG

The intersection genes of differentially expressed genes and eQTL genes correlated with ficial aging were identified as SA-IGs (USP53, IFRD1, IGF2BP2, CDV3, SCRN1, ACSBG1, RIN1). USP53, IFRD1, IGF2BP2, CDV3 and SCRN1 are downregulated genes (Figures 2A and 3), ACSBG1 and RIN1 are upregulated genes (Figures 2B and 3). Furthermore, we explored the casual relations between these 7 SA-IGs and SG based on MR analysis. Through MR

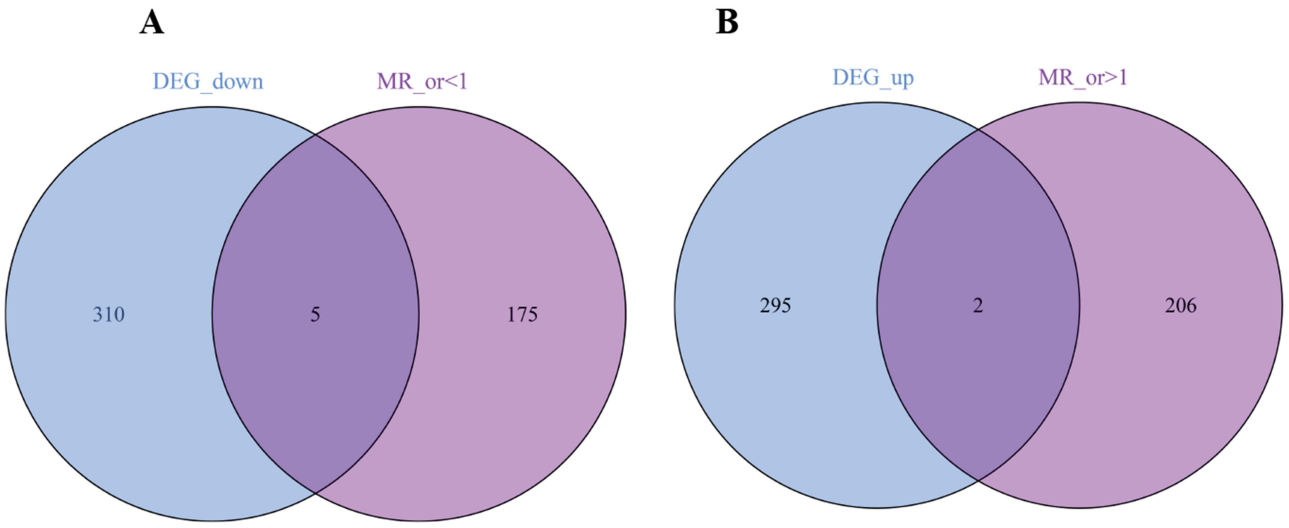

Figure 2 Intersection of potential casual eQTL genes and DEGs from merged GEO datasets. (**A**) Down-regulated genes. (**B**) Up-regulated genes.

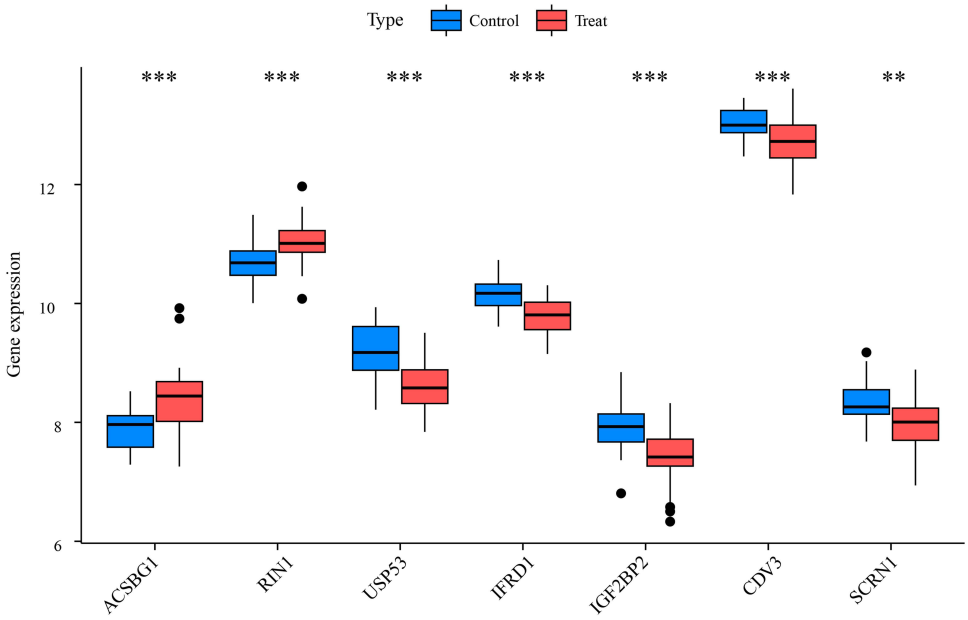

Figure 3 Differential expression of SA-IGs between the control group and the experimental group. The data are expressed as the mean + SEM, **P <0.01, ***P <0.001.

analysis, it was found that the risk of SG was increased when ACSBG1 and RIN1 expression increased (ACSBG1:OR =1.007, 95% CI: 1.002–1.012, RIN1: OR = 1.007, 95% CI: 1.001–1.014, both P < 0.005), while the risk of SG was decreased when USP53 (OR = 0.996, 95% CI: 0.992–0.999, and P = 0.020), IFRD1 (OR = 0.995, 95% CI: 0.991–1.000, and P = 0.047), IGF2BP2 (OR = 0.988, 95% CI: 0.977–0.999, and P = 0.033), CDV3 (OR = 0.993, 95% CI: 0.986–0.999, and P=0.027), and SCRN1 (OR = 0.994, 95% CI: 0.989–0.999, and P = 0.022) expression decreased (Figure 4A). In this MR analysis, the Cochran Q test results showed no heterogeneity of IVs, no significant intercept was observed in the MR Egger's test results, confirming the absence of pleiotropy bias in IVs in MR analysis. In addition, the "leave one out" method demonstrated the robustness and reliability of our research results, as no single SNP had a significant impact on the results, see. Supplementary Figures 1–7 While as Figure 4B shows the positions of 7 SA-IGs on chromosomes. ACSBG1 is located in Chromosome chr 15, RIN1 is located in chr 11, USP53 is located in Chromosome chr 4, IGF2BP2 and CDV3 both located in chr3., while IFRD1 and SCRN1 both located in chr7.

GO and KEGG Functional or Pathway Enrichment Analysis of SA-IGs

GO and KEGG functional or pathway enrichment analysis was performed on SA-IGs using the R software package. Through GO enrichment analysis, 43 biological processes (BP), 5 cellular components (CC), and 12 molecular functions (MF) based on 315 differentially expressed genes were obtained (Figure 5A and B). The GO terms indicated that the molecular composition, biosynthesis, and regulatory processes related to fatty-acyl-CoA are crucial for SG, like long-chain fatty-acyl-CoA biosynthetic process, long-chain fatty-acyl-CoA metabolic process, fatty-acyl-CoA biosynthetic process, acyl-CoA biosynthetic process, very long-chain fatty acid-CoA ligase activity and long-chain fatty acid-CoA ligase activity, etc. While nerve fibers and nerve signal transduction also played important roles in the results, as shown in the Figure 5B, negative regulation of collateral sprouting, collateral sprouting and Collateral sprouting, etc.

The results of KEGG pathway enrichment analysis (Figure 5C) show that these biological processes and signaling pathways are mainly related to fatty acid metabolism, energy generation, and inflammation regulation, which are crucial in the process of SG.[21–24]

https://doi.org/10.2147/CCID.S508946

A

exposure	nsnp	method	pval	OR(95% CI)
ACSBG1	6	Weighted median	0.001	1.010 (1.004 to 1.016)
	6	Inverse variance weighted	0.003	1.007 (1.002 to 1.012)
CDV3	3	Weighted median	0.043	0.993 (0.986 to 1.000)
	3	Inverse variance weighted	0.027	0.993 (0.986 to 0.999)
IFRD1	7	Weighted median	0.086	0.996 (0.992 to 1.001)
	7	Inverse variance weighted	0.047	0.995 (0.991 to 1.000)
IGF2BP2	4	Weighted median	0.005	0.986 (0.976 to 0.996)
	4	Inverse variance weighted	0.033	0.988 (0.977 to 0.999)
RIN1	5	Weighted median	0.021	1.007 (1.001 to 1.012)
	5	Inverse variance weighted	0.029	1.007 (1.001 to 1.014)
SCRN1	7	Weighted median	0.005	0.993 (0.989 to 0.998)
	7	Inverse variance weighted	0.022	0.994 (0.989 to 0.999)
USP53	3	Weighted median	0.016	0.995 (0.992 to 0.999)
	3	Inverse variance weighted	0.020	0.996 (0.992 to 0.999)

B

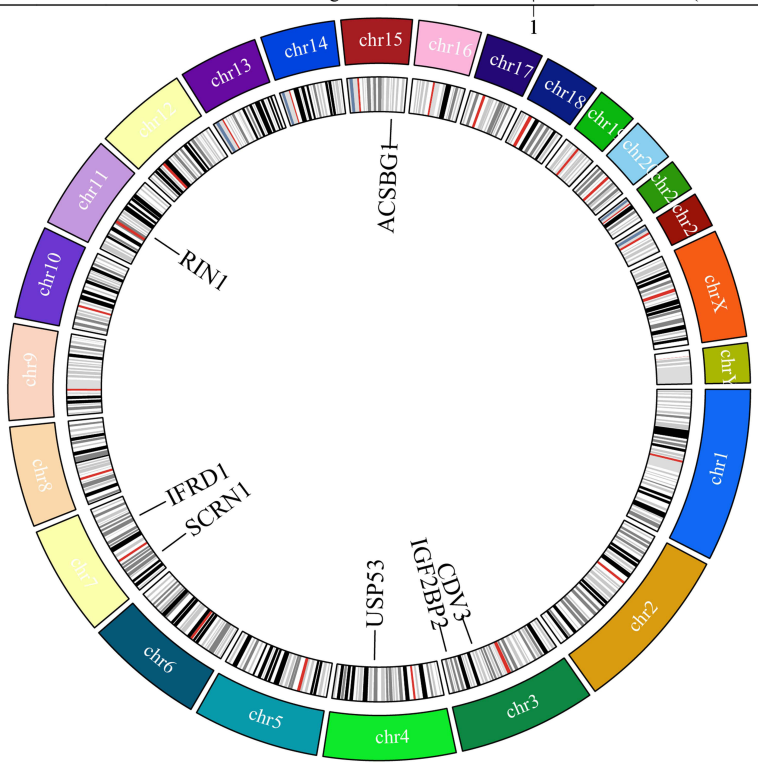

Figure 4 Association Between skin aging and SA-IGs Estimated by the MR. (**A**) Forest plot of SA-IGs for each 1 SD increase of aging risk. (**B**) chromosome mapping of 7 SA-IGs. (OR=odds ratio).

Immunotherapy Response Prediction of SA-IGs

As the largest immune barrier in the human body, the physiological and pathological processes of the skin cannot be separated from the role of immune function. The immune components of the skin will change with the changes of Langerhans cells, antigen-specific immunity, and regulatory cell populations.[25] Therefore, we analyzed the infiltration of 22 immune cells in each sample based on the CIBERSORT algorithm, and proposed further insights into SG from the perspective of immune function. The results showed that NK cells may be the main immune cells associated with SA-IGs. NK cells resting is apparently decreased in SG group compared with control group (Figure 6A and B). In addition, the correlation between the expression of 7 SA-IGs and the proportion of differentially infiltrating immune cell types was further explored. As shown in Figure 6C, ACSBG1, RIN1, USP53, IFRD1, IGF2BP2, CDV3 and SCRN1 were significantly positively correlated with NK cells monocytes, neutrophils, dendritic cells activated and mast cells activated, and significantly negatively correlated with M0 macrophages, M1 macrophages, dendritic cells resting and mast cells resting.

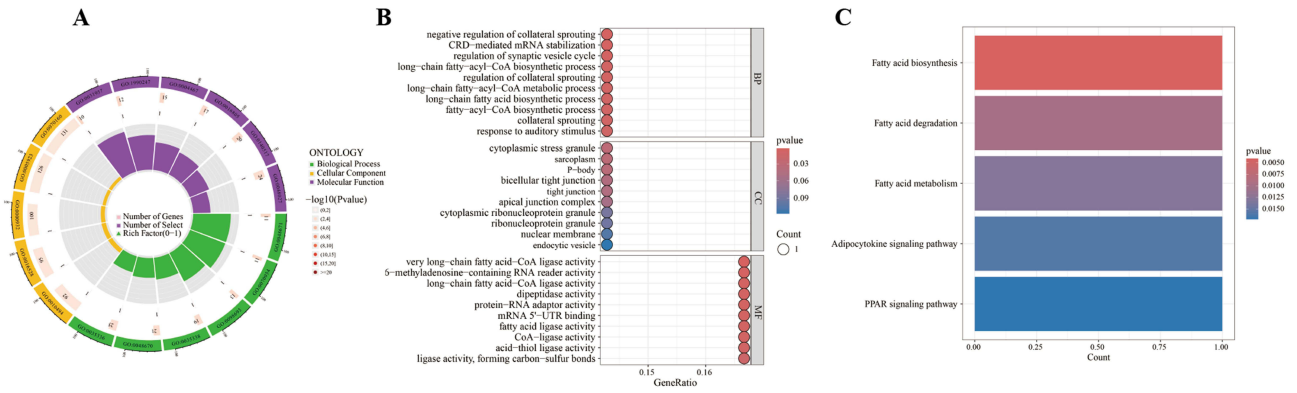

Figure 5 GO and KEGG enrichment analysis of SA-IGs. (**A** and **B**) GO terms of SA-IG; **(C)** KEGG pathways of SA-IGs.

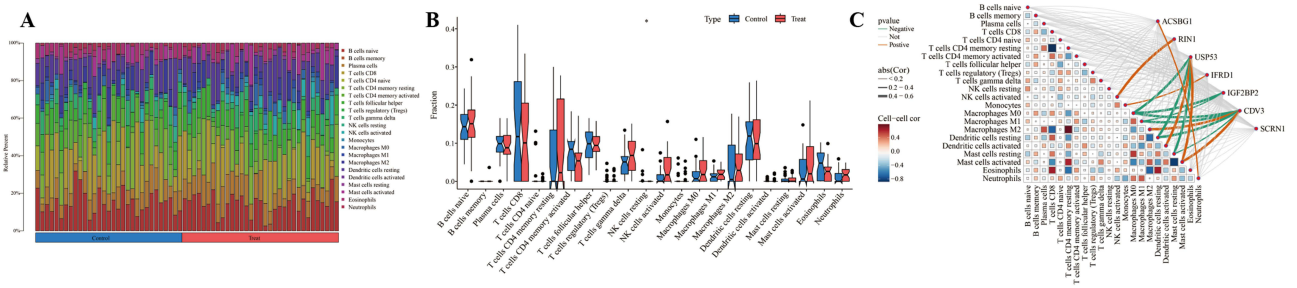

Figure 6 Immune infiltration. (**A**) The proportions of immune cells in each sample. (**B**) The infiltration degree of each type of immune cell between the control group and experimental group. (**C**) Correlation analysis between 7 SA-IGs and various types of infiltrating immune cells. The data are expressed as the mean + SEM, *P <0.05.

Discussion

The process of biological aging is very complex and is believed to be driven by the interaction of multiple dysregulated cells and biochemical processes, almost every biological process is affected by aging, and countless biomarkers have been proposed to attempt measuring it.[26] In the past decade, omics revolution has made it possible for the field to address the full molecular complexity of aging biology.[27,28] High throughput genomics, proteomics, and metabolomics methods can characterize and quantify thousands of epigenetic markers, transcripts, proteins, and metabolites, and were used to reveal the potential mechanism of aging at the molecular level.[29,30] However, the availability of large-scale omics data poses new challenges for the analysis and interpretation of molecular mechanisms.

Applying MR analysis to GWAS and eQTL research data to identify associations between gene expression and complex traits is an effective and emerging method.[31] In our study, we screened SA-IGs by integrating eQTL and GWAS data. Enrichment analysis of GO and KEGG pathways showed that SA-IGs are closely related to functions such as fatty acid metabolism, protein metabolism, RNA regulation, energy generation, and inflammation regulation in skin cells. Based on the currently retrieved evidence, fatty acid metabolism is an important process in the skin niche and for skin tissue repair function, which is closely related to SG.[32] That is same for the metabolism of other substances such as energy metabolism and protein metabolism.[33]

At present, research on biomarkers related to skin cell aging mainly includes changes in cell ultrastructure (particle size, lysosome mass, etc)., changes in cell cycle-dependent kinase inhibitors (CDKIs), changes in apoptosis-related proteins (PI3K, p21CIP/WAF-1, etc), and expression of aging related secretory phenotypes.[34] However, our research mainly focuses on the relationship between genomic changes and SG, and attempts to find possible therapeutic targets for SG-related diseases. Through literature research, we have found that our research results, SA-IGs, are a newly discovered biomarker model.

Although there is currently limited research on the relationship between SA-IGs and SG, the biological role of SA-IGs is not simple. Of these SA-IGs, ACSBG1 can regulate mitochondrial metabolic pathways and have a significant

https://doi.org/10.2147/CCID.S508946

impact on the immune system of the body;[35] RIN1 has close interactions with cells, such as cell adhesion;[36] SCRN1 and USP53 are both related to nerve fibers and nerve signal transduction;[37,38] IFRD1, IGF2BP2, and CDV3 are widely involved in substance metabolism.[39–41] So, it is required further exploration and validation on the SA-IGs, which will introduce a direction for SG research.

Conclusion

This study is mainly based on Mendelian analysis using eQTL and GWAS databases. Due to limitations from data sources, the results of this study may have certain regional biases. In the future, multi-center research can be considered to enhance the generalization of results, and multi-omics analyses or more advanced machine learning methods can be combined to improve predictive ability or interpretability of results. The research results are influenced by certain experimental conditions, so further experimental verification is needed to verify their applicability in different backgrounds. Although this study has certain limitations, it still provides useful references for skin aging research, and we look forward to further optimizing research methods in the future to improve the robustness of the results.

In summary, our analytical method provides an additional research avenue for the discovery of SG biomarkers, and the research results offer a new perspective for skin anti-aging research.

Data Sharing Statement

The datasets generated for this study can be found at https://www.ncbi.nlm.nih.gov/geo/, and https://gwas.mrcieu.ac.uk/.

The patients involved in the database have obtained ethical approval. Users can download relevant data for free to conduct research and publish related articles. Our research is based on open-source data, so there are no ethical issues or other conflicts of interest.

Ethics Approval and Consent to Participate

In accordance with the "Ethical Review Measures for Life Science and Medical Research Involving Humans" (issued on February 18, 2023, by the People's Republic of China), this study complies with Article 32, Items 1 and 2, and falls under the category of research that does not require ethical review. The relevant provisions are as follows:

Article 32, Item 1: Research that does not involve human samples, data, or personal privacy, and where there is no direct intervention or collection of sensitive information from individuals, does not require ethical approval.

Article 32, Item 2: Research conducted using publicly available anonymized data or de-identified biological samples, and where no new interventions are made on participants, does not require ethical approval.

Therefore, this study does not require ethical review approval.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The National Natural Science Foundation of China, 82460621.

Disclosure

The authors declare that they have no competing interests for this work.

References

1. Draelos Z, Bogdanowicz P, Saurat JH. Top weapons in skin aging and actives to target the consequences of skin cell senescence. *J Eur Acad Dermatol Venereol*. 2024;38(Suppl 4):15–22. doi:10.1111/jdv.19648

2. Franco AC, Aveleira C, Cavadas C. Skin senescence: mechanisms and impact on whole-body aging. *Trends Mol Med*. 2022;28(2):97–109. doi:10.1016/j.molmed.2021.12.003
3. Shin J-W, Kwon S-H, Choi J-Y, et al. Molecular mechanisms of dermal aging and antiaging approaches. *Int J mol Sci*. 2019;20(9):2126. doi:10.3390/ijms20092126
4. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol*. 2021;22:75–95.1471-0080 (Electronic)
5. Samra T, Gomez-Gomez T, Linowiecka K, et al. Melatonin exerts prominent, differential epidermal and dermal anti-aging properties in aged human eyelid skin ex vivo. *Int J Mol Sci*. 2023;24:15963.1422-0067 (Electronic) doi:10.3390/ijms242115963
6. Zhang J, Zhao H. Eqtl studies: from bulk tissues to single cells. *J Genet Genome*. 2023;50(12):925–933. doi:10.1016/j.jgg.2023.05.003
7. Kerimov N, Hayhurst JD, Peikova K. A compendium of uniformly processed human gene expression and splicing quantitative trait loci. *Nature Genet*. 2021;53(9):1290–1299. doi:10.1038/s41588-021-00924-w
8. Yang H, Liu D, Zhao C. Mendelian randomization integrating gwas and eqtl data revealed genes pleiotropically associated with major depressive disorder. *Transl Psychiatry*. 2021;11(1):225. doi:10.1038/s41398-021-01348-0
9. Wu M-J, Gao Y-L, Liu J-X, Zheng C-H, Wang J. Integrative hypergraph regularization principal component analysis for sample clustering and co-expression genes network analysis on multi-omics data. *IEEE J Biomed Health Inform*. 2020;24(6):1823–1834. doi:10.1109/JBHI.2019.2948456
10. Võsa U, Claringbould A, Westra H-J. Large-scale cis- and trans-eqtl analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. *Nature Genet*. 2021;53(9):1300–1310. doi:10.1038/s41588-021-00913-z
11. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol*. 2011;40(3):755–764. doi:10.1093/ije/dyr036
12. 1000 Genomes Project Consortium. An integrated map of genetic variation from 1092 human genomes. *Nature*. 2012;491(7422):56–65. doi:10.1038/nature11632
13. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Human Molecular Genetics*. 2014;23(R1):R89–R98. doi:10.1093/hmg/ddu328
14. El-Arabey AA, Abdalla M, Abd-Allah AR. SnapShot: TP53 status and macrophages infiltration in TCGA-analyzed tumors. *Int Immunopharmacol*. 2020;86:106758. doi:10.1016/j.intimp.2020.106758
15. Kaur A, Ecker BL, Douglass SM. Remodeling of the collagen matrix in aging skin promotes melanoma metastasis and affects immune cell motility. *Cancer Discovery*. 2019;9(1):64–81. doi:10.1158/2159-8290.CD-18-0193
16. Newman AM, Liu CL, Green MR. Robust enumeration of cell subsets from tissue expression profiles. *Nature Methods*. 2015;12(5):453–457. doi:10.1038/nmeth.3337
17. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology*. 2017;28(1):30–42. doi:10.1097/EDE.0000000000000559
18. Fujii R, Nakatochi M, Del Greco MF. Coffee intake, plasma caffeine levels, and kidney function: two-sample Mendelian randomization among East Asian and European ancestries. *Kidney Int Rep*. 2024;9(4):1083–1092. doi:10.1016/j.ekir.2024.01.024
19. Cohen JF, Chalumeau M, Cohen R, Korevaar DA, Khoshnood B, Bossuyt PMM. Cochran's q test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. *J Clin Epidemiol*. 2015;68(3):299–306. doi:10.1016/j.jclinepi.2014.09.005
20. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the mr-egger method. *Eur j epidemiol*. 2017;32(5):377–389. doi:10.1007/s10654-017-0255-x
21. Gruber F, Marchetti-Deschmann M, Kremslehner C, Schosserer M. The skin epilipidome in stress, aging, and inflammation. *Front Endocrinol*. 2020;11:607076. doi:10.3389/fendo.2020.607076
22. Huang TH, Wang PW, Yang SC, Chou WL, Fang JY. Cosmetic and therapeutic applications of fish oil's fatty acids on the skin. *Mar Drugs*. 2018;16 (8):256.
23. Sreedhar A, Aguilera-Aguirre L, Singh KK. Mitochondria in skin health, aging, and disease. *Cell Death Dis*. 2020;11(6):444. doi:10.1038/s41419-020-2649-z
24. Szántó M, Gupte R, Kraus WL, Pacher P, Bai P. PARPs in lipid metabolism and related diseases. *Prog lipid res*. 2021;84:101117. doi:10.1016/j.plipres.2021.101117
25. Chambers ES, Vukmanovic-Stejic M. Skin barrier immunity and ageing. *Immunology*. 2020;160(2):116–125. doi:10.1111/imm.13152
26. Rutledge J, Oh H, Wyss-Coray T. Measuring biological age using omics data. *Nat Rev Genet*. 2022;23(12):715–727. doi:10.1038/s41576-022-00511-7
27. Tobin DJ. Introduction to skin aging. *Journal of Tissue Viability*. 2017;26(1):37–46. doi:10.1016/j.jtv.2016.03.002
28. Nie C, Li Y, Li R. Distinct biological ages of organs and systems identified from a multi-omics study. *Cell Rep*. 2022;38(10):110459. doi:10.1016/j.celrep.2022.110459
29. Haga M, Iida K, Okada M. Positive and negative feedback regulation of the tgf-β1 explains two equilibrium states in skin aging. *IScience*. 2024;27 (5):109708. doi:10.1016/j.isci.2024.109708
30. Wang Y, Liu L, Song Y, Yu X, Deng H. Unveiling e2f4, tead1 and ap-1 as regulatory transcription factors of the replicative senescence program by multi-omics analysis. *Protein and Cell*. 2022;13(10):742–759. doi:10.1007/s13238-021-00894-z
31. Zhu Z, Zhang F, Hu H. Integration of summary data from gwas and eqtl studies predicts complex trait gene targets. *Nature Genet*. 2016;48 (5):481–487. doi:10.1038/ng.3538
32. Shook BA, Wasko RR, Mano O, et al. Dermal adipocyte lipolysis and myofibroblast conversion are required for efficient skin repair. *Cell Stem Cell*. 2020;26(6).
33. He X, Gao X, Xie W. Research progress in skin aging, metabolism, and related products. *Int J mol Sci*. 2023;24(21):15930. doi:10.3390/ijms242115930
34. Csekes E, Račková L. Skin aging, cellular senescence and natural polyphenols. *Int J Mol Sci*. 2021;22(23):12641. 1422-0067 (Electronic). doi:10.3390/ijms222312641
35. Kanno T, Nakajima T, Kawashima Y. Acsbg1-dependent mitochondrial fitness is a metabolic checkpoint for tissue treg cell homeostasis. *Cell Rep*. 2021;37(6):109921. doi:10.1016/j.celrep.2021.109921

36. Hu H, Bliss JM, Wang Y, Colicelli J. Rin1 is an abl tyrosine kinase activator and a regulator of epithelial-cell adhesion and migration. *Curr Biol*. 2005;15(9):815–823. doi:10.1016/j.cub.2005.03.049
37. Weiner S, Sauer M, Brinkmalm G. Scrn1: a cerebrospinal fluid biomarker correlating with tau in Alzheimer's disease. *Alzheimer's Dementia*. 2023;19(10):4609–4618. doi:10.1002/alz.13042
38. Xia G, Guo Y, Zhang J, Han M, Meng X, Lv J. An overview of the deubiquitinase usp53: a promising diagnostic marker and therapeutic target. *Curr Protein Pept Sci*. 2024;25(9):708–718. doi:10.2174/0113892037292440240518194922
39. Liu T, Liu Y, Yan T. Intermittent fasting, exercise, and dietary modification induce unique transcriptomic signatures of multiple tissues governing metabolic homeostasis during weight loss and rebound weight gain. *J Nutr Biochem*. 2024;130:109649. doi:10.1016/j.jnutbio.2024.109649
40. Wang J, Chen L, Qiang P. The role of igf2bp2, an m6a reader gene, in human metabolic diseases and cancers. *Can Cell Inter*. 2021;21(1):99. doi:10.1186/s12935-021-01799-x
41. Park G, Horie T, Kanayama T. The transcriptional modulator Ifrd1 controls PGC −1α expression under short-term adrenergic stimulation in brown adipocytes. *FEBS J*. 2017;284(5):784–795. doi:10.1111/febs.14019