

# GENETIC FACTORS OF PREDISPOSITION TO PATHOLOGICAL SCARRING AFTER SURGICAL INTERVENTIONS

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## ABSTRACT

Hypertrophic and keloid scars complicate the healing of surgical wounds; however, existing genetic data have yet to provide a reliable basis for predicting their development in individual patients. Comparing findings across studies is challenging because inherited genetic variants and the molecular alterations observed in established scars reflect different stages of the pathological process. This study aimed to critically evaluate the genetic factors involved in scarring and to assess their potential utility for preoperative risk prediction. The analysis drew upon 43 sources – including official statistics, Russian clinical guidelines, original research, and reviews – identified through a search of PubMed, Europe PMC, and the websites of scientific journals and professional organizations (covering the period 2021–2026). The data were subjected to comparative analysis, systematization, and critical qualitative assessment, with careful consideration given to scar type, the origin of the injury, sample composition, and the independent replication of reported associations. Inherited genetic variants were examined separately from alterations in gene expression, while prognostic models were evaluated based on external validation and their incremental value beyond established clinical risk factors. By synthesizing genetic associations alongside the cellular and epigenetic mechanisms of scarring, this review distinguishes between factors related to hereditary susceptibility and those reflecting the state of the affected tissue. The primary limitations identified include the heterogeneity of scar phenotypes, insufficient reproducibility of findings, and a scarcity of data concerning surgical patients: out of 26 loci discovered through an analysis of 7,837 keloid cases and 1,593,009 control subjects, only 12 have been independently validated. To assess the practical utility of genetic information, it has been proposed to compare clinical, genetic, and combined models within independent cohorts of patients who have undergone similar surgical procedures, while evaluating hypertrophic and keloid outcomes separately.

**KEYWORDS:** *pathological scarring, genetic predisposition, postoperative scars, keloid scars, hypertrophic scars, genetic polymorphism, risk prediction*

## INTRODUCTION

Genetic predisposition to pathological scarring is relevant to preoperative assessment of hypertrophic and keloid scar risk. The use of genetic information, however, requires evidence of predictive value. The scale of surgical care underscores the practical importance of this problem: according to Rosstat, 10.383 million inpatient operations and 5.874 million outpatient or day-hospital operations were performed in Russia in 2024 [1]. These figures describe surgical volume rather than the incidence of pathological scarring. The central question of this review is which inherited factors add information to clinical risk assessment and whether their use before surgery is justified.

Addressing this question requires comparison of clinical scar-prevention strategies with genetic research. Russian clinical guidelines describe the management of hypertrophic skin changes [2]; V. V. Gladko and I. V. Izmailova discuss current treatments for hypertrophic and keloid scars [3], while O. B. Borzykh and colleagues review prevention and treatment [4]. Genetic evidence includes a study by D. V. Sobolev and colleagues involving 196 patients with combat injuries [6]. The characteristics of that cohort limit generalization to elective surgical patients. A genetic association must therefore be distinguished from demonstrated ability to predict postoperative scarring.

**Materials and Methods.** The review included 43 sources comprising official statistics, Russian clinical guidelines, original genetic and molecular studies, and review articles. Publications were searched in PubMed, Europe PMC, journal websites, and professional organization websites using combinations of the terms pathological scarring, postoperative scars, genetic predisposition, keloid, hypertrophic scar, surgical scar, genome-wide association, and single-cell sequencing, including Russian-language equivalents. The search covered 2021–2026. Eligibility was assessed with regard to the presence of genetic or molecular data and the ability to identify the origin of the injury. Postoperative scars, scars of other etiologies, and experimental studies were analyzed separately; inherited variants were distinguished from gene-expression changes.

The quality of evidence was evaluated according to scar phenotype definition, sample size and composition, control-group selection, and reproducibility. For prediction models, the separation of training and validation data, external validation, and

intended use were additionally considered, distinguishing identification of an existing keloid from prediction of its development after surgery. Reporting recommendations by G. S. Collins, K. G. M. Moons, P. Dhiman, and colleagues provided a methodological reference [40]. A qualitative synthesis was performed; no original meta-analysis was conducted.

### Pathological Scarring as a Heterogeneous Clinical Outcome

Hypertrophic and keloid scars should be analyzed separately. Hypertrophic scars remain within the boundaries of the original injury, whereas keloids extend into surrounding skin, as reflected in Russian guidelines [2, 41]. Their molecular profiles also differ. A. S. Walter, M. Stocks, E. Akova, and colleagues examined 18 scar specimens obtained during hand and plastic surgery and identified transcriptional differences between keloids and normal and hypertrophic scars [7]. Pooling these outcomes can obscure phenotype-specific associations.

X. Cheng, Z. Gao, S. Shan, and colleagues used a different comparison: keloid and nonaggressive scar tissue were studied against a shared genetic background [8]. Keloids showed an enrichment of fibroblasts with pronounced mechanosensitive and migratory properties. This design assesses the local microenvironment, but the limited material does not establish that the cell population is universal. At the population level, inherited susceptibility is investigated by relating genomic variants to defined scar outcomes.

### Evidence of Hereditary Predisposition

C. A. Greene, G. Hampton, J. Jaworski, and colleagues reported different estimates of keloid heritability attributable to the single-nucleotide variants studied: 6% in participants of European ancestry, 21% in East Asian ancestry, and 34% in African ancestry [9]. These estimates describe population-level trait variation, not an individual's probability of developing a keloid. Differences between populations may reflect disease definitions, sample structure, and variant representation as well as ancestry.

Familial and association evidence reviewed by S. Liu, H. Yang, J. Song, and colleagues [11] and A. J. Cohen, N. Nikbakht, and J. Uitto [12] implicates immune and regulatory mechanisms in keloid development. In a review of 50 studies, A. J. James, R. A. Torres-Guzman, S. C. Chaker, and colleagues identified associations involving human leukocyte antigen genes, NEDD4, and the vitamin D receptor [10]. HLA-DRB1\*15 was associated with keloids in three ethnic groups, whereas findings for several class I alleles differed across populations [10]. Studies directly relating genotype to healing of a surgical wound are therefore particularly important.

### Candidate Genes and Genetic Variants Associated with Postoperative Scarring

D. V. Sobolev, M. S. Kishenya, A. V. Visyagin, and E. V. Anchikova investigated rs1800471 in TGFB1, which encodes transforming growth factor beta 1, among 196 postoperative patients [6]. For the GG genotype, the odds ratio for pathological scarring was 2.34 (95% confidence interval, 1.20–4.59). Scars were assessed at 3, 6, 9, and 12 months, covering several stages of scar maturation.

The clinical context limits the applicability of this finding: the study concerned postoperative complications after combat trauma, and the groups differed in healing duration [6]. Extrapolation to elective surgery requires confirmation in patients with comparable injuries and treatment conditions. Table 1 places this result alongside population-level associations and functional evidence.

Table 1 – Inherited Variants and Molecular Factors in Pathological Scarring

| Factor                   | Main finding                                                               | Material or outcome                                     | Limitation                                       |
|--------------------------|----------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------|
| TGFB1, rs1800471         | GG genotype: OR 2.34; 95% CI 1.20–4.59 [6]                                 | Postoperative pathological scarring after combat injury | Replication in other surgical cohorts required   |
| NEDD4, rs11632096        | G allele: OR 1.21; CI 1.17–1.26 [9]                                        | Keloid formation in multi-ancestry analysis             | Applicability to specific operations unknown     |
| PHLDA3, rs35383942       | T allele: OR 1.50; CI 1.39–1.61 [9]                                        | Keloid formation                                        | Association does not establish causation         |
| ITGA11 locus, rs34647667 | T allele: OR 1.39; CI 1.32–1.45 [9]                                        | Keloid formation                                        | Functional and clinical interpretation required  |
| CTHRC1, SPP1             | Macrophage–fibroblast interaction associated with collagen deposition [18] | Keloid tissue and functional studies                    | Not evidence of an inherited risk variant        |
| FTO, COL1A1              | Regulation of mRNA stability and collagen production [21]                  | Molecular and cellular studies                          | Does not establish preoperative predictive value |

The first four associations in Table 1 concern susceptibility, whereas CTHRC1/SPP1 and FTO/COL1A1 data describe fibrotic mechanisms. Effect estimates cannot be compared directly because populations and outcomes differ. Cellular studies help clarify how a profibrotic response is maintained.

### Cellular Heterogeneity and Profibrotic Programs

X. Liu, W. Chen, Q. Zeng, and colleagues analyzed 28,064 cells and identified changes in fibroblast and vascular endothelial programs involving TWIST1, FOXO3, and SMAD3 [15]. C. Feng, M. Shan, Y. Xia, and colleagues found differences in

cellular composition and the immune microenvironment in 12 paired samples of keloid and adjacent skin [16]. Spatial transcriptomics by J. Shim, S. J. Oh, E. Yeo, and colleagues further characterized fibroblast–endothelial interactions [17]. J. Liu, Y. Huang, Y. Gong, and colleagues linked collagen production to stimulation of CTHRC1-positive fibroblasts by macrophage-derived SPP1 [18]. Thus, isolated fibroblasts alone cannot fully capture profibrotic activity.

Other cell types are also implicated. M. Direeder, T. Weiss, D. Copic, and colleagues described profibrotic properties of Schwann cells [19], and T. Gong, Y. Wang, S. Dong, and colleagues examined their interactions with extracellular-matrix-associated cells [20]. Candidate markers include TNC (J. Xie et al. [26]); VCAM1, CALCRL, and HLA-DPB1 (H. Wang et al. [27]); and BMP1 and IL1R1 (Y. Zhang et al. [28]). D. Li and colleagues characterized proinflammatory populations [29], Z. Liu and colleagues tested the function of TXNDC5 [30], and W. Zhang and colleagues proposed a keloid classification based on fibroblast differentiation [31]. These observations call for further study of gene regulation during healing.

### **Epigenetic and Post-Transcriptional Mechanisms**

S. Ren, Y. Ji, M. Wang, and colleagues demonstrated a role for the demethylase FTO in regulating COL1A1 through messenger RNA modification and stability [21]. Y. Li, W. Wang, Y. Wang, and H. Ai investigated an FTO-associated mechanism involving KLF4 and keloid fibroblast proliferation [22]. Comparing 14 keloid specimens with 14 normal skin specimens, C. X. Lin, Z. J. Chen, Q. L. Peng, and colleagues identified differences in RNA methylation and Wnt pathway activation [23]. These studies do not establish a single overall direction of methylation change; specific molecular targets and their functional effects are more appropriately compared.

Regulatory changes also involve genomic sequences. P. Prabsattru, T. Nakbua, S. Sengphairogh, and colleagues observed reduced methylation of LINE-1 and Alu repeats in 38 keloid specimens compared with 32 normal skin specimens [24]. In a reanalysis of data, Z. Zhu, S. Ni, J. Zhang, and colleagues identified altered alternative splicing– the production of distinct RNA transcripts from one gene– in individuals predisposed to keloids [25]. These changes may precede tissue injury or arise during inflammation and remodeling. Samples collected before injury and during healing are needed to establish their temporal sequence.

### **Genome-Wide Association Studies and Functional Interpretation of Loci**

Genome-wide association studies (GWAS) examine variants without prior selection of candidate genes. C. A. Greene and colleagues analyzed 7,837 keloid cases and 1,593,009 controls, identifying 26 associated loci, of which 12 were independently replicated [9]. These included NEDD4, PHLDA3, and ITGA11, with variants summarized in Table 1. An association signal does not by itself establish its mechanism. Unreplicated findings are not necessarily disproved, but their transferability remains uncertain. Surgical applications require confirmation in patients undergoing comparable procedures and follow-up.

J. Huang, X. Zhou, W. Wang, and colleagues combined genetic associations, RNA expression, and chromatin spatial organization with subsequent cell experiments to interpret loci functionally [13]. Y. Q. Zhu, N. H. Zhou, Y. W. Xu, and colleagues performed exome analysis of nine paired keloid and normal tissue samples [14]. The latter study examined somatic changes within lesions and therefore did not establish inherited susceptibility. These distinct designs require separating baseline risk variants from acquired alterations and interpreting both in relation to wound conditions.

### **Interaction Between Molecular Susceptibility and Wound-Healing Conditions**

J. Kim, C. Won, S. Ham, and colleagues investigated mechanical influences on scarring: cyclic stretching on a culture platform enhanced the profibrotic response of keloid fibroblasts [32]. Multi-omic research linked fibrotic and regenerative trajectories of experimental wound healing to mechanotransduction and the regulator Trps1 [33]. S. Mascharak, M. Griffin, H. E. Talbott, and colleagues subsequently suppressed scarring in a porcine wound model [34]. These findings support consideration of mechanical loading, although experimental models must be selected for their research purpose and no single standard for hypertrophic scar modeling has been established [42]. Genotype-by-mechanical-environment interactions remain to be investigated.

Clinical context also affects interpretation. E. D. Verbovaya and colleagues reported associations of scarring with demographic and metabolic characteristics, although causal inference was limited by the retrospective design [5]. A. W. Stevenson, G. Cadby, and H. J. Wallace assessed genetic determinants of scar vascularity in 665 burn patients of European ancestry [35] and identified no individually significant variants. This result highlights the importance of phenotype definition and statistical power without excluding inherited effects. Burn injuries cannot be equated directly with surgical incisions. The reviewed literature contains mainly large population studies of keloids, with less direct evidence concerning postoperative hypertrophic scars.

### **Prospects for Genetic Risk Prediction**

Genetic analyses can help prioritize molecular targets. Y. Wang, X. Wang, Z. Yuan, and colleagues identified seven potential protein targets using Mendelian randomization and additional checks [36]. X. He and Y. Song investigated CCND2 and KLF4 [37], while H. Xu, K. Li, X. Liang, and colleagues examined DUSP1 and HOXA5 [38]. Target identification is distinct from predicting individual postoperative outcomes. Table 2 compares research approaches with the evidence required for clinical implementation; polygenic and combined models are presented as developmental directions.

Table 2 – Applicability of Research Approaches to Postoperative Scar Prediction

| Approach | Main purpose | Potential relevance | Required for clinical use |
|----------|--------------|---------------------|---------------------------|
|----------|--------------|---------------------|---------------------------|

|                         |                                                 |                                       |                                                 |
|-------------------------|-------------------------------------------------|---------------------------------------|-------------------------------------------------|
| Single-variant analysis | Test genotype–scar association                  | Identify candidate predictors         | Replication and predictive accuracy assessment  |
| GWAS                    | Identify susceptibility loci                    | Describe genetic architecture         | Validation in surgical cohorts                  |
| Transcriptomic analysis | Characterize gene activity in tissue            | Identify cellular states and targets  | Demonstrate prediction before scar formation    |
| Mendelian randomization | Assess putative causal role of molecular traits | Prioritize mechanisms and targets     | Assumption checks and independent confirmation  |
| Polygenic model         | Jointly evaluate many variants                  | Potentially quantify inherited risk   | Development, calibration, external validation   |
| Genetic–clinical model  | Integrate individual risk information           | Potential preoperative stratification | Demonstrated advantage over clinical assessment |

The six approaches in Table 2 address different questions, from discovering associations to developing predictive models. Classifying an existing keloid from tissue does not demonstrate the ability to predict its future occurrence. The reviewed literature did not provide adequate validation of polygenic or combined models for particular surgical procedures. A 2024 review by A. J. James and colleagues found no reliable genetic test for keloid risk [10]. J. Ji, X. Shi, E. Tang, and colleagues did not confirm a causal association between serum vitamin D and keloids or hypertrophic scars by Mendelian randomization [39]. This does not exclude involvement of the vitamin D receptor or local vitamin D metabolism in keloid tissue [39, 43]. A predictive model must distinguish outcomes and provide probabilities consistent with observed event rates. Its value depends on whether it improves prevention and follow-up decisions beyond clinical assessment [40].

### Limitations of the Evidence and Future Research

Comparing the 18 scar specimens studied by A. S. Walter and colleagues [7] with the nine tissue pairs analyzed by Y. Q. Zhu and colleagues [14] illustrates the heterogeneity of available evidence: molecular measurements and research objectives differed. Further limitations include injury origin, population composition, and follow-up duration. Control selection is critical: the absence of a keloid in an individual without comparable injury does not describe their response to a surgical wound. Comparing different outcomes after similar procedures is more informative. Study heterogeneity and the qualitative review design precluded quantitative pooling of associations and estimation of overall predictive accuracy.

The recommendations of G. S. Collins and colleagues [40] provide criteria for model evaluation. Prospective surgical cohorts should determine genotype before surgery and assess scars at prespecified intervals, recording hypertrophic and keloid outcomes separately. Incision site, type of procedure, complications, and preventive measures should be documented. Absolute risk calibration and the incremental clinical value of genetic information must be evaluated.

Applying these criteria reveals that genetic findings differ in readiness for preoperative prediction. Twelve of 26 loci identified in a large keloid GWAS were independently replicated [9], and TGFB1 rs1800471 was associated with postoperative scarring in combat-injury patients [6]. Whether either finding supports a clinically useful prediction in other surgical cohorts remains to be tested. The central methodological error is to extrapolate susceptibility to keloids to the prediction of any pathological scar despite differences in injury type, phenotype, and healing conditions. Identifying additional loci alone does not resolve individual risk prediction. What matters is the information genotype adds to known clinical characteristics.

The additional contribution of genotype should be assessed by sequentially comparing three models: a clinical model, a genetic model, and a combined model. These models should be tested in independent cohorts of patients undergoing comparable surgical procedures, with hypertrophic and keloid outcomes evaluated separately. This design will determine whether genetic information improves the accuracy of estimated probabilities and changes the selection of preventive measures [40]. If adding genotype does not improve prediction compared with the clinical model, its independent use in preoperative assessment will remain unjustified. Demonstrated improvements in prediction and clinical decision-making establish practical relevance; statistical significance of an association is not sufficient.

### CONCLUSION

Genetic research has expanded our understanding of predisposition to pathological scarring; however, its application in surgery remains limited by insufficient validation of individual risk prediction. The association of TGFB1 rs1800471 with scar changes is directly relevant to postoperative outcomes. NEDD4, PHLDA3, and ITGA11 characterize broader susceptibility. Cellular and epigenetic studies explain the maintenance of fibrosis but do not independently establish inherited risk. Clinical translation remains limited by inadequate evidence of the additional predictive value of genetic indicators in comparable surgical cohorts. Developing preoperative risk prediction requires integrating genotype, procedural characteristics, and wound-healing conditions, with independent evaluation of model accuracy and clinical utility.

### REFERENCES

1. Federal State Statistics Service. Healthcare in Russia. 2025: Statistical Collection. Moscow: Rosstat; 2025. 149 p. [In Russian]. Available from: Official Rosstat publication.
2. Russian Society of Dermatovenereologists and Cosmetologists. Hypertrophic Skin Changes: Clinical Guidelines [Internet]. [In Russian]. Available from: Clinical guidelines, ID 974\_1 [cited 2026 Oct 16].

3. Gladko VV, Izmaylova IV. Review of modern methods of treating hypertrophic and keloid scars. *Bulletin of the Medical Institute of Continuing Education*. 2024;4(1):23–30. [In Russian]. doi:10.36107/2782-1714\_2024-4-1-23-30.
4. Borzykh OB, Karpova EI, Petrova MM, Shnayder NA, Danilova SV. Hypertrophic scars: modern concepts of prevention and treatment. *Vestnik Dermatologii i Venerologii*. 2025;101(6):46–59. [In Russian]. doi:10.25208/vdv16939.
5. Cho MY, Lee SG, Kim JE, Lee YS, Chang HS, Roh MR. Analysis of Risk Factors to Predict Occurrence and Prognosis of Postsurgical Hypertrophic Scar Development: A Review of 4238 Cases. *Yonsei Medical Journal*. 2023;64(11):687–691. doi:10.3349/ymj.2023.0003.
6. Sobolev DV, Kishenya MS, Visyagin AV, Anchikova EV. Molecular biological analysis of clinical and pathogenetic features of the formation of postoperative complications in combat trauma. *Molecular Medicine*. 2023;21(6):41–47. [In Russian]. doi:10.29296/24999490-2023-06-06.
7. Walter AS, Stocks M, Akova E, Gauglitz G, Hartmann D, Aszodi A, Böcker W, Saller MM, Volkmer E. Keloids are transcriptionally distinct from normal and hypertrophic scars. *European Journal of Dermatology*. 2023;33(6):604–611. doi:10.1684/ejd.2023.4582.
8. Cheng X, Gao Z, Shan S, Shen H, Zheng H, Jin L, Li Q, Zhou J. Single cell transcriptomics reveals the cellular heterogeneity of keloids and the mechanism of their aggressiveness. *Communications Biology*. 2024;7(1):1647. doi:10.1038/s42003-024-07311-1.
9. Greene CA, Hampton G, Jaworski J, Shuey MM, Khan A, Luo Y, Jarvik GP, Namjou-Khales B, Edwards TL, Velez Edwards DR, Hellwege JN. Multi-ancestry meta-analysis of keloids uncovers novel susceptibility loci in diverse populations. *Nature Communications*. 2025;16(1):7770. doi:10.1038/s41467-025-62945-x.
10. James AJ, Torres-Guzman RA, Chaker SC, Sigel ME, Perdakis G, Supp DM, Dale Slater EL. Global insights into keloid formation: An international systematic review of regional genetic risk factors and commonalities. *Wound Repair and Regeneration*. 2024;32(5):746–757. doi:10.1111/wrr.13203.
11. Liu S, Yang H, Song J, Zhang Y, Abualhssain ATH, Yang B. Keloid: Genetic susceptibility and contributions of genetics and epigenetics to its pathogenesis. *Experimental Dermatology*. 2022;31(11):1665–1675. doi:10.1111/exd.14671.
12. Cohen AJ, Nikbakht N, Uitto J. Keloid Disorder: Genetic Basis, Gene Expression Profiles, and Immunological Modulation of the Fibrotic Processes in the Skin. *Cold Spring Harbor Perspectives in Biology*. 2023;15(7):a041245. doi:10.1101/cshperspect.a041245.
13. Huang J, Zhou X, Wang W, Zhou G, Zhang W, Gao Z, Wu X, Liu W. Combined analyses of RNA-sequence and Hi-C along with GWAS loci—A novel approach to dissect keloid disorder genetic mechanism. *PLOS Genetics*. 2022;18(6):e1010168. doi:10.1371/journal.pgen.1010168.
14. Zhu YQ, Zhou NH, Xu YW, Liu K, Li W, Shi LY, Hu YX, Xie YF, Lan J, Yu ZY. Genome-wide analysis of Chinese keloid patients identifies novel causative genes. *Annals of Translational Medicine*. 2022;10(16):883. doi:10.21037/atm-22-1303.
15. Liu X, Chen W, Zeng Q, Ma B, Li Z, Meng T, Chen J, Yu N, Zhou Z, Long X. Single-Cell RNA-Sequencing Reveals Lineage-Specific Regulatory Changes of Fibroblasts and Vascular Endothelial Cells in Keloids. *Journal of Investigative Dermatology*. 2022;142(1):124–135.e11. doi:10.1016/j.jid.2021.06.010.
16. Feng C, Shan M, Xia Y, Zheng Z, He K, Wei Y, Song K, Meng T, Liu H, Hao Y, Liang Z, Wang Y, Huang Y. Single-cell RNA sequencing reveals distinct immunology profiles in human keloid. *Frontiers in Immunology*. 2022;13:940645. doi:10.3389/fimmu.2022.940645.
17. Shim J, Oh SJ, Yeo E, Park JH, Bae JH, Kim SH, Lee D, Lee JH. Integrated Analysis of Single-Cell and Spatial Transcriptomics in Keloids: Highlights on Fibrovascular Interactions in Keloid Pathogenesis. *Journal of Investigative Dermatology*. 2022;142(8):2128–2139.e11. doi:10.1016/j.jid.2022.01.017.
18. Liu J, Huang Y, Gong Y, Liu Q, Lin J, Liu J, Liu M, Huang J, Pu W, Ma Y, Zhang Y, Li H, Shi X, Zhang Y, Wang J, Zhu Y, Wang Q, Wei K, Wang J, Sha Y, Wang J, Wu W. CTHRC1+ fibroblasts are stimulated by macrophage-secreted SPP1 to induce excessive collagen deposition in keloids. *Clinical and Translational Medicine*. 2022;12(12):e1115. doi:10.1002/ctm2.1115.
19. Direder M, Weiss T, Copic D, Vorstandlechner V, Laggner M, Pfisterer K, Mildner CS, Klas K, Bormann D, Haslik W, Radtke C, Farlik M, Shaw L, Golabi B, Tschachler E, Hoetzenecker K, Ankersmit HJ, Mildner M. Schwann cells contribute to keloid formation. *Matrix Biology*. 2022;108:55–76. doi:10.1016/j.matbio.2022.03.001.
20. Gong T, Wang Y, Dong S, Ma X, Du D, Zou C, Zheng Q, Wen Z. Single-cell RNA-seq reveals the communications between extracellular matrix-related components and Schwann cells contributing to the earlobe keloid formation. *Frontiers in Medicine*. 2022;9:1000324. doi:10.3389/fmed.2022.1000324.
21. Ren S, Ji Y, Wang M, et al. The m6A demethylase FTO promotes keloid formation by up-regulating COL1A1. *Annals of Translational Medicine*. 2023;11(1):15. doi:10.21037/atm-22-6021.
22. Li Y, Wang W, Wang Y, Ai H. FTO-mediated m6A demethylation of KLF4 promotes the proliferation and collagen deposition of keloid fibroblasts. *Toxicology Research*. 2025;14(2):tfaf058. doi:10.1093/toxres/tfaf058.
23. Lin CX, Chen ZJ, Peng QL, et al. The m6A-methylated mRNA pattern and the activation of the Wnt signaling pathway under the hyper-m6A-modifying condition in the keloid. *Frontiers in Cell and Developmental Biology*. 2022;10:947337. doi:10.3389/fcell.2022.947337.

24. Prabsattu P, Nakhua T, Sengphairogh S, et al. Methylation of LINE-1 and Alu repetitive sequence in keloid. *Scientific Reports*. 2025;15(1):31994. doi:10.1038/s41598-025-17646-2.
25. Zhu Z, Ni S, Zhang J, et al. Genome-wide analysis of dysregulated RNA-binding proteins and alternative splicing genes in keloid. *Frontiers in Genetics*. 2023;14:1118999. doi:10.3389/fgene.2023.1118999.
26. Xie J, Chen L, Cao Y, et al. Single-Cell Sequencing Analysis and Weighted Co-Expression Network Analysis Based on Public Databases Identified That TNC Is a Novel Biomarker for Keloid. *Frontiers in Immunology*. 2021;12:783907. doi:10.3389/fimmu.2021.783907.
27. Wang H, Zhou Z, Xie J, Qi S, Tang J. Integration of single-cell and bulk transcriptomics reveals immune-related signatures in keloid. *Journal of Cosmetic Dermatology*. 2023;22(6):1893–1905. doi:10.1111/jocd.15649.
28. Zhang Y, Fang C, Zhang L, et al. Identification and validation of immune-related biomarkers and polarization types of macrophages in keloid based on bulk RNA-seq and single-cell RNA-seq analysis. *Burns*. 2025;51(3):107413. doi:10.1016/j.burns.2025.107413.
29. Li D, Li Z, Liu S, Chen X, Che X, Deng G, Chen J, Li H, Wang R, Chen X, Su W, Su J. Single-cell RNA sequencing highlights the role of proinflammatory fibroblasts, vascular endothelial cells, and immune cells in the keloid immune microenvironment. *International Journal of Dermatology*. 2025;64(5):890–900. doi:10.1111/ijd.17516.
30. Liu Z, Xian L, Li J, Zheng S, Xie H. Single-cell RNA sequencing analysis reveals the role of TXNDC5 in keloid formation. *CytoJournal*. 2024;21:40. doi:10.25259/cytojournal\_58\_2024.
31. Zhang W, Lu J, Tong X, Xie S, Xian S, Liu Y, Yan J, Qian W, Sun H, Zhu Y, Jiang L, Guo X, Ding X, Li Y, Bai C, Huang R, Xia Z, Ji S. Uncovering a fibroblast differentiation-based keloid classification by integration of single-cell and bulk RNA sequencing. *Communications Biology*. 2025;8(1):1387. doi:10.1038/s42003-025-08741-1.
32. Kim J, Won C, Ham S, Han H, Shin S, Jang J, Lee S, Kwon C, Cho S, Park H, Lee D, Lee WJ, Lee T, Lee JH. Increased Susceptibility to Mechanical Stretch Drives the Persistence of Keloid Fibroblasts: An Investigation Using a Stretchable PDMS Platform. *Biomedicines*. 2024;12(10):2169. doi:10.3390/biomedicines12102169.
33. Mascharak S, Talbott HE, Januszyk M, Griffin M, Chen K, Davitt MF, Demeter J, Henn D, Bonham CA, Foster DS, Mooney N, Cheng R, Jackson PK, Wan DC, Gurtner GC, Longaker MT. Multi-omic analysis reveals divergent molecular events in scarring and regenerative wound healing. *Cell Stem Cell*. 2022;29(2):315–327.e6. doi:10.1016/j.stem.2021.12.011.
34. Mascharak S, Griffin M, Talbott HE, Guo JL, Parker J, Morgan AG, Valencia C, Kuhnert MM, Li DJ, Liang NE, Kratochil RM, Daccache JA, Sidhu I, Davitt MF, Guardino N, Lu JM, Abbas DB, DeLeon NMD, Lavin CV, Adem S, Khan A, Chen K, Henn D, Spielman A, Cotterell A, Akas D, Downer MD, Tevlin R, Lorenz HP, Gurtner GC, Januszyk M, Naik S, Wan DC, Longaker MT. Inhibiting mechanotransduction prevents scarring and yields regeneration in a large animal model. *Science Translational Medicine*. 2025;17(786):eadt6387. doi:10.1126/scitranslmed.adt6387.
35. Stevenson AW, Cadby G, Wallace HJ, Melton PE, Martin LJ, Wood FM, Fear MW. Genetic influence on scar vascularity after burn injury in individuals of European ancestry: A prospective cohort study. *Burns*. 2024;50(7):1871–1884. doi:10.1016/j.burns.2024.05.004.
36. Wang Y, Wang X, Yuan Z, Liu F, Luo X, Yang J. Identifying Potential Drug Targets for Keloid: A Mendelian Randomization Study. *Journal of Investigative Dermatology*. 2025;145(1):77–84.e6. doi:10.1016/j.jid.2024.04.023.
37. He X, Song Y. Identifying core genes in keloid and investigating immune infiltration and pan-cancer associations using eQTL and machine learning. *Bioinformatics Advances*. 2025;5(1):vbaf076. doi:10.1093/bioadv/vbaf076.
38. Xu H, Li K, Liang X, Wang Z, Yang B. Multi-omics analysis to explore the molecular mechanisms related to keloid. *Burns*. 2025;51(3):107396. doi:10.1016/j.burns.2025.107396.
39. Ji J, Shi X, Tang E, Zheng J, Liang L. Serum Vitamin D Levels and Its Relationship With Keloid, Acne or Hypertrophic Scar: A Two-Sample Mendelian Randomization Study. *Journal of Cosmetic Dermatology*. 2025;24(8):e70398. doi:10.1111/jocd.70398.
40. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B, Ghassemi M, Liu X, Reitsma JB, van Smeden M, Boulesteix AL, Camaradou JC, Celi LA, Denaxas S, Denniston AK, Glocker B, Golub RM, Harvey H, Heinze G, Hoffman MM, Kengne AP, Lam E, Lee N, Loder EW, Maier-Hein L, Mateen BA, McCradden MD, Oakden-Rayner L, Ordish J, Parnell R, Rose S, Singh K, Wynants L, Logullo P. TRIPOD+AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ*. 2024;385:e078378. doi:10.1136/bmj-2023-078378.
41. Jeschke MG, Wood FM, Middelkoop E, Bayat A, Teot L, Ogawa R, Gauglitz GG. Scars. *Nature Reviews Disease Primers*. 2023;9(1):64. doi:10.1038/s41572-023-00474-x.
42. Rössler S, Nischwitz SP, Luze H, Holzer-Geissler CJ, Zrim R, Kamolz LP. In Vivo Models for Hypertrophic Scars—A Systematic Review. *Medicina*. 2022;58(6):736. doi:10.3390/medicina58060736.
43. Hahn JM, Combs KA, Powell HM, Supp DM. A role for vitamin D and the vitamin D receptor in keloid disorder. *Wound Repair and Regeneration*. 2023;31(5):563–575. doi:10.1111/wrr.13109.

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