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Review

Genomic and Epigenetic Landscapes of Keloid Scarring: Ancestry–Dependent Insights and Therapeutic Implications—A Narrative Review

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Abstract

Background: Keloid scarring is a fibroproliferative disorder driven by a complex interplay of genetic, epigenetic, and environmental factors, resulting in significant cosmetic and functional impairment. Despite its high prevalence in African, Asian, and Hispanic populations, the molecular mechanisms underlying ancestry-dependent susceptibility remain incompletely understood. Methods: This narrative review synthesizes current genomic, epigenetic, and multi-omic evidence related to keloid scarring. Relevant literature was identified through a targeted, structured, non-systematic search of PubMed, Scopus, Web of Science, SciELO, and Google Scholar up to August 2025, focusing on genetic susceptibility loci, epigenetic regulation, and ancestry-related differences. PRISMA-ScR guidelines were used as a reporting framework to enhance transparency, without implying a formal systematic review methodology. Results: This synthesis identifies recurrent susceptibility loci at 1q41, 3q22.3, and 15q21.3 across multiple populations. Variants in NEDD4 and regulatory regions near BMP2 emerge as key modulators of profibrotic signaling pathways, including TGF-β/SMAD and NF-κB. Additionally, epigenetic reprogramming and long non-coding RNA networks, such as CACNA1G-AS1, appear to sustain fibroblast hyperactivation. A persistent limitation is the marked underrepresentation of Latin American populations in current genomic studies. Conclusions: Integrating ancestry-specific genomic variation with epigenetic markers is essential for advancing precision diagnostic and therapeutic strategies in keloid scarring. Future research should prioritize diverse, multicenter cohorts and integrative multi-omics approaches to improve risk stratification and enable targeted interventions for this disfiguring condition.

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1. Introduction

Keloid scarring acts as a persistent fibroproliferative disorder in which the body's wound-healing mechanisms fail to resolve. Unlike hypertrophic scars, keloids aggressively invade healthy tissue beyond the initial wound margins, frequently recur post-surgery, and often inflict debilitating pain and pruritus [1–3]. But the impact is not merely physical. The condition carries a heavy psychosocial burden, significantly impairing quality of life, a reality that elevates it to a clinical priority far exceeding cosmetic concerns [4,5].

At a cellular level, the pathology stems from dermal fibroblasts that remain locked in a hyperactive state, releasing dysregulated cytokine signals and churning out excessive type I and III collagen [6,7]. Deciphering genetic architecture driving these molecular errors is vital, not least because our current treatment arsenal remains largely empirical.

Central to this dysfunction is the hyperactivation of core profibrotic pathways, specifically TGF-β/SMAD and BMP signaling, alongside inflammatory cascades such as NF-κB and IL-17 [6,8,9]. This molecular convergence drives cell hyperproliferation and the relentless extracellular matrix (ECM) accumulation that characterizes invasive keloid growth [9,10]. Integrative molecular studies increasingly support the concept that keloid formation results from a complex interaction between genetic susceptibility and dysregulated wound healing pathways [11]. Intercellular communication mediated by extracellular vesicles and exosomes has also been implicated in the propagation of profibrotic signaling between fibroblasts and surrounding cells within the keloid microenvironment [12].

Recent transcriptomic studies have further highlighted complex regulatory networks linking TGF-β signaling with downstream transcriptional programs that sustain fibroblast activation in keloid tissue [13].

Although factors such as trauma, anatomical site, age, and hormonal status often trigger the onset, genetic predisposition serves as the decisive driver [6,9,14]. The epidemiological data make this starkly clear: prevalence reaches 16% in populations of African ancestry and Hispanics, and ranges between 4% and 16% in Asian groups; by comparison, rates in European populations remain vanishingly low, staying below 0.1% [4,7,8,15]. Such a profound disparity cannot be explained away by environmental factors or mechanical skin tension alone; instead, it points directly to ancestry-dependent genetic determinants.

Pathological scarring results from dysregulated wound healing processes characterized by persistent inflammatory signaling, sustained fibroblast activation, and abnormal extracellular matrix deposition. Contemporary reviews of scar biology emphasize that these processes interact to sustain a profibrotic microenvironment that ultimately drives keloid formation [16].

Familial clustering reinforces this view, typically following an autosomal dominant pattern with incomplete penetrance [17,18]. Early linkage studies identified susceptibility regions on chromosomes 2q23 and 7p11, establishing genetic heterogeneity well before the modern genomic era [19,20]. More recently, genome-wide association studies (GWAS) have pinpointed canonical loci at 1q41, 3q22.3, and 15q21.3, predominantly within Asian and African-descendant cohorts [21,22]. In addition, multi-ancestry GWAS analyses have identified further susceptibility loci associated with pathological scarring in European populations, including variants at 1q32.1 and 15q21.3, highlighting the ancestry-dependent genetic architecture underlying keloid susceptibility [23].

In parallel, epigenetic mechanisms, including DNA methylation and non-coding RNAs, appear to lock in these profibrotic programs, effectively trapping fibroblasts in a state of hyperactivity [24–27].

Recent experimental studies further support the role of epigenetic regulation in keloid fibroblast behavior, as pharmacological inhibition of chromatin-modifying complexes has been shown to significantly reduce fibroblast proliferation, migration, and invasion, underscoring the importance of epigenomic regulation in keloid pathogenesis [28].

Yet, a critical gap persists: the current molecular landscape is heavily skewed toward non-Latin American populations, leaving a significant blind spot regarding Mexico and other admixed groups [6,29,30]. Given the region's unique genetic admixture, this omission represents both a clinical challenge and a major scientific opportunity to define more precise, population-specific risk profiles.

An integrated overview of the molecular pathways, genetic susceptibility, and epigenetic regulation involved in keloid pathogenesis is summarized in Figure 1.

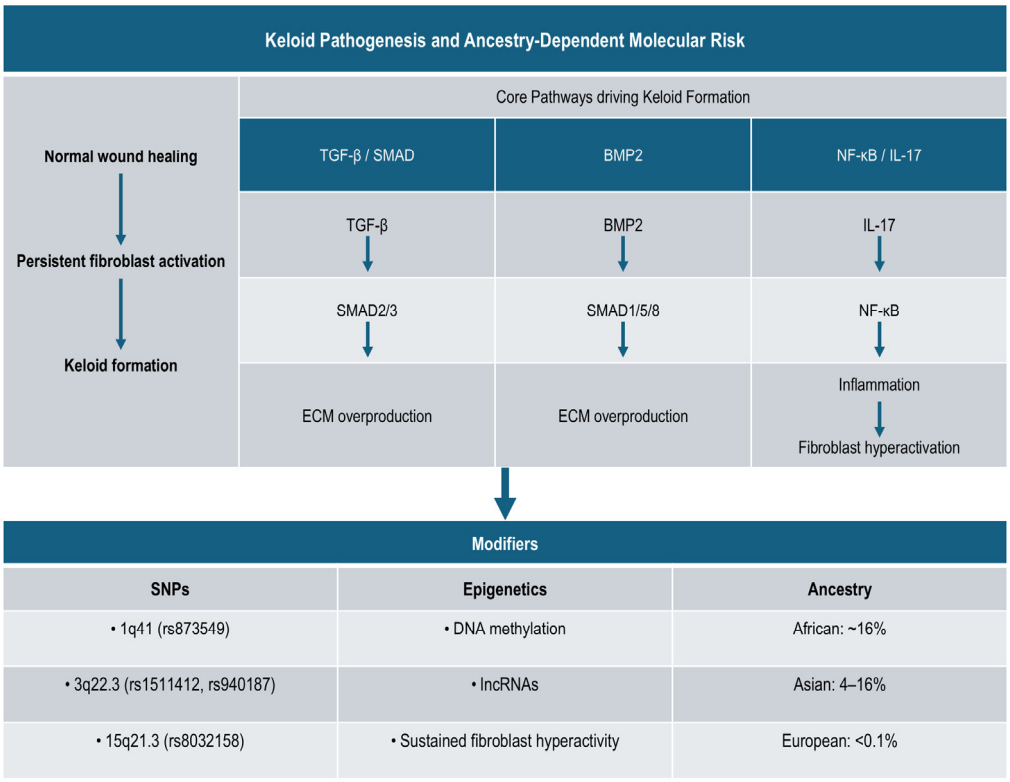

Figure 1. Integrated schematic overview of keloid pathogenesis. This diagram illustrates the interplay between dysregulated wound healing, profibrotic signaling pathways, and ancestry-dependent susceptibility. Persistent fibroblast activation, driven by altered inflammatory signaling and canonical profibrotic axes (TGF-β/SMAD, BMP2), converges to promote excessive ECM deposition and invasive scar growth. Genetic risk variants and epigenetic mechanisms modulate these pathways, shaping disease expression across different ancestral backgrounds.

In this context, this narrative review synthesizes existing genomic and epigenetic evidence regarding keloid scarring, placing specific emphasis on ancestry-dependent susceptibility. We summarize key genetic variants across diverse populations, examine the regulatory networks governing fibroblast activity, and discuss how translating these findings could refine risk stratification and pave the way for precision therapeutic strategies.

2. Materials and Methods

2.1. Study Design and Search Strategy

We designed this study as a narrative review to provide a critical, integrative synthesis of the genomic and epigenetic literature surrounding keloid scarring. To ensure transparency in the literature selection process, we adopted reporting standards from the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). Notably, this work functions as a narrative synthesis rather than a formal systematic review or meta-analysis; as such, formal registration in databases like PROSPERO was not applicable, and we did not perform quantitative risk-of-bias assessments (e.g., ROBINS-I or Newcastle-Ottawa scales).

Search operations covered major electronic databases, including PubMed, Scopus, Web of Science, SciELO, and Google Scholar, for articles published up to December 2025. To capture the full scope of the topic, we used combinations of English and Spanish keywords such as "keloid", "keloid scarring", "genetics", "SNP", "genome-wide association study", "fibroblasts", "BMP2", "epigenetics", and "Mexican population".

2.2. Eligibility Criteria

Our inclusion criteria focused on original research, specifically GWAS, candidate gene association studies, gene expression analyses, and epigenetic or functional studies, involving human subjects of any age. We also incorporated relevant systematic reviews and book chapters that offered essential context regarding epidemiology or molecular mechanisms. By contrast, we excluded isolated case reports lacking molecular analysis, animal models not validated in humans, duplicate records, and studies focused exclusively on physiological wound healing without specific relevance to keloid pathology.

3. Synthesis of Genomic and Epigenetic Evidence

3.1. Study Selection

Our initial search identified 212 records. After removing 76 duplicates, we screened 136 unique articles by title and abstract. From this pool, we excluded 65 studies that did not meet specific eligibility criteria regarding genomic or molecular relevance. This left 71 full-text publications to form the analytical corpus of this review (Figure 2). These articles, comprising original GWAS, candidate gene association studies, and functional analyses, provide the evidentiary basis for the ancestry-dependent synthesis presented below.

3.2. Genomic Basis and Epidemiological Patterns

Substantial epidemiological evidence points to a strong genetic component in keloid scarring. Prevalence rates vary drastically across populations: they reach 16% in Zaire, 8.5% in Kenya, and 9% in Zambia, yet estimates in England remain as low as 0.09% [5,14,15,19]. In East Asia, prevalence sits at approximately 0.1% in Japan but climbs notably higher in Taiwan, confirming distinct regional susceptibility [22,31]. By comparison, cohorts of European ancestry, such as those in the UK Biobank, show a considerably lower disease burden [5]. Crucially, studies in Latin America are currently limited to clinical reports with minimal genomic characterization, leaving a significant gap in regional knowledge [4,14,29].

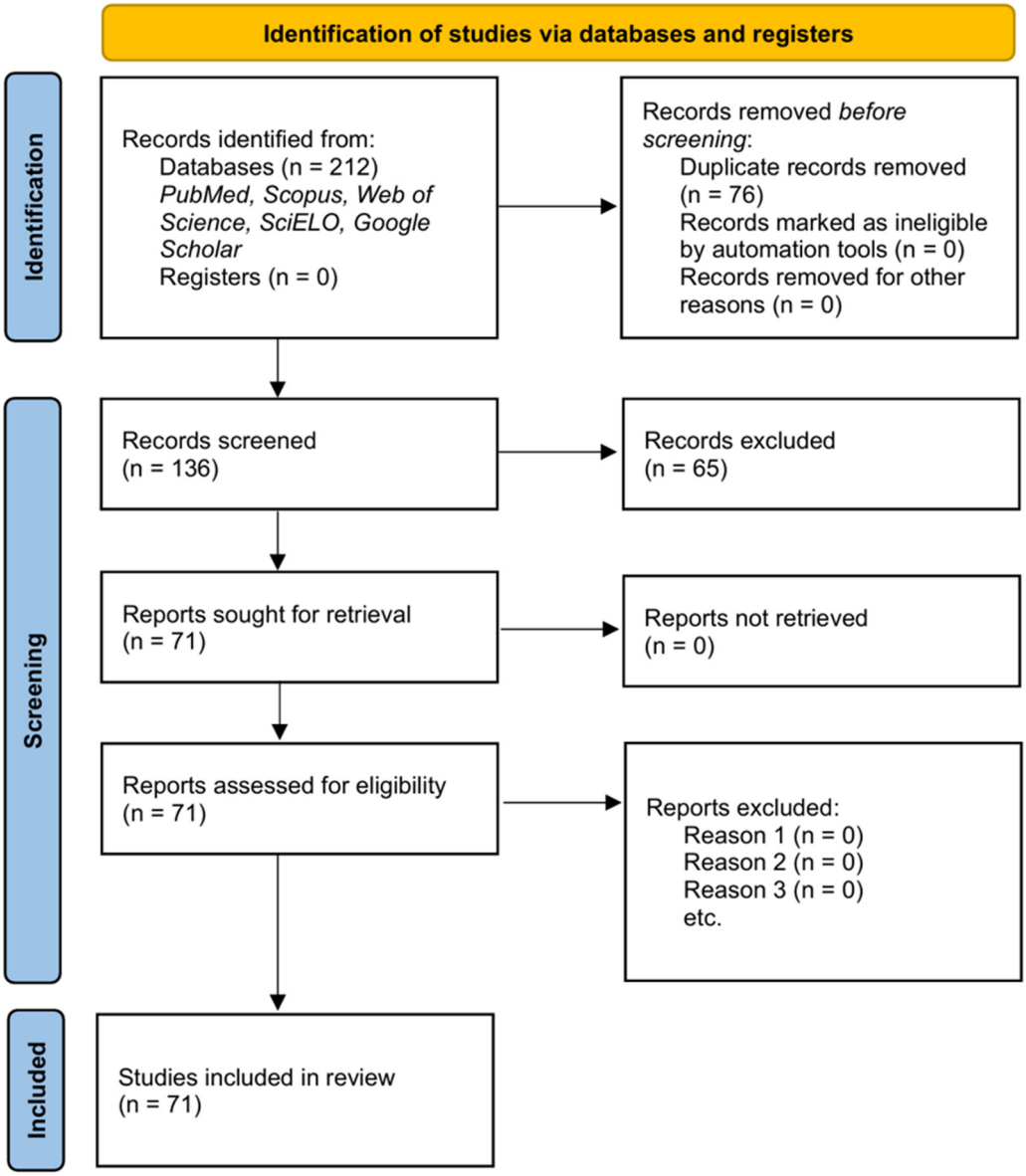

Figure 2. PRISMA 2020 flow diagram detailing the study selection process. The flowchart outlines the identification, screening, and eligibility assessment phases conducted to select the final articles included in this review.

Familial clustering further supports a hereditary basis. Although autosomal dominant inheritance with incomplete penetrance is the most widely accepted model [17,18,32,33], genetic heterogeneity was apparent even before the genomic era. Additionally, rare syndromic associations have historically reinforced this genetic predisposition [30,34]. Pioneering linkage studies by Marneros et al. [20] identified loci on 2q23 (*TNFAIP6*) and 7p11 (*EGFR*) in Japanese and African American families. These foundational findings paved the way for GWAS, which later confirmed three canonical susceptibility loci: 1q41, 3q22.3, and 15q21.3 (Figure 3).

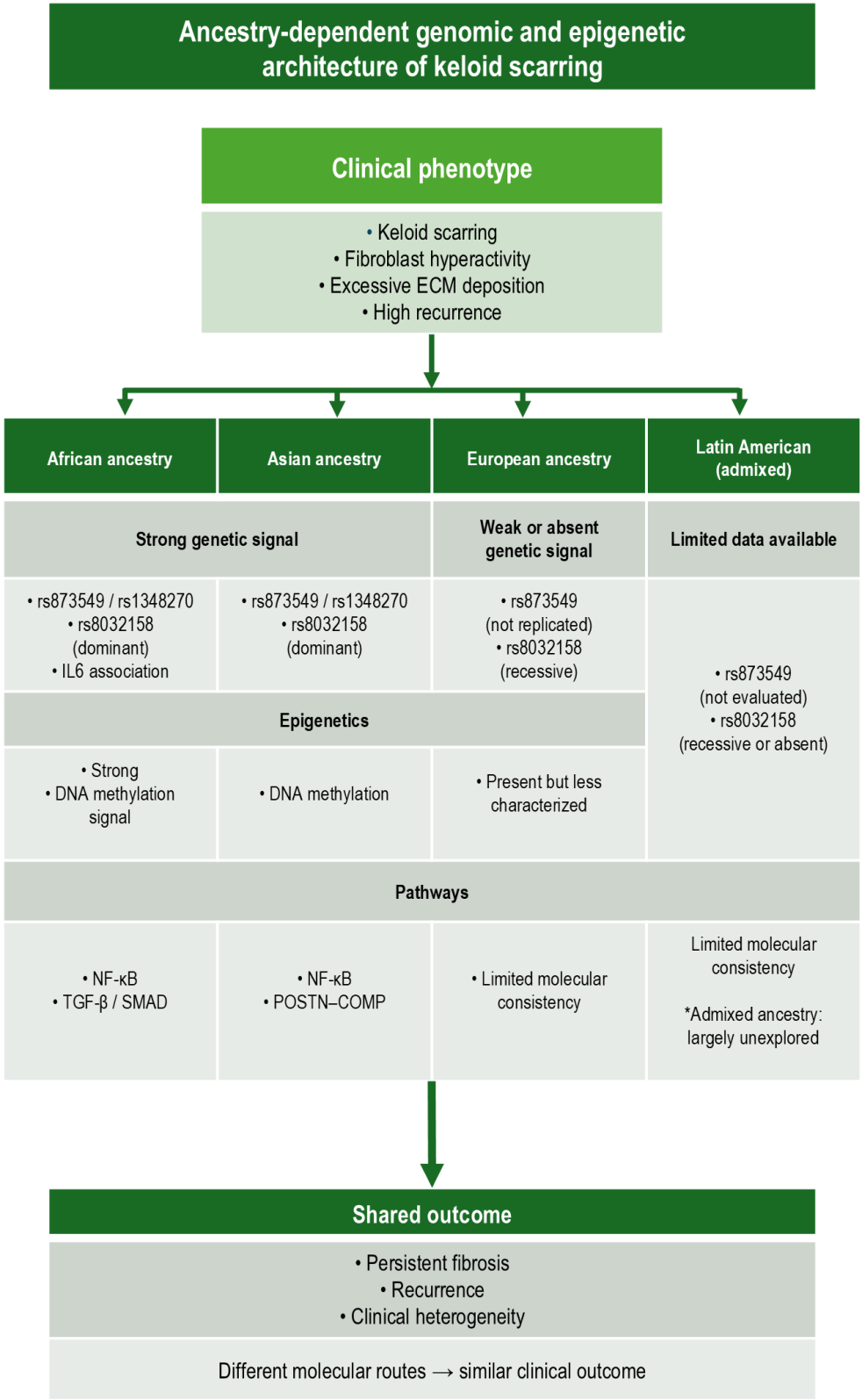

Figure 3. Ancestry-dependent genomic and epigenetic architecture of keloid scarring. This comparative schematic illustrates how similar clinical phenotypes arise from distinct molecular mechanisms across populations. While African and Asian ancestries exhibit strong, replicated genetic signals at canonical loci, European cohorts show weaker genetic associations, often requiring alternative inheritance models. Epigenetic dysregulation appears consistently involved across all groups but may be differentially regulated.

3.3. Key Susceptibility Loci and Variants

Identifying specific Single-Nucleotide Polymorphisms (SNPs) has clarified the mechanisms driving keloid pathogenesis. A comprehensive summary of these variants appears in Table 1.

Table 1. Genetic variants: SNPs associated with keloid scarring. Organized by chromosomal locus, gene/region involved, possible affected molecular pathway, studied population and reference. Includes findings from linkage studies, GWAS, meta-analyses, and differential transcriptomic studies.

Study	SNP	Locus	Gene/Region Involved	Possible Affected Molecular Pathway	Population Studied
Nakashima, 2010 [21]; Zhu, 2013 [22]	rs873549	1q41	Intergenic (*DEIK–BMP2–POSTN/COMP*) [a]	Enhancer in dermal fibroblasts; proliferation and ECM synthesis	Japanese, Han Chinese
Deng, 2023 [35]	rs1348270	1q41	Enhancer in LD with rs873549	↓DEIK → ↑BMP2 → ↑POSTN/COMP	Han Chinese
Zhu, 2013 [22]; Lv, 2020 [36]	rs1442440	1q41	Near *BMP2/POSTN* (LD with rs873549)	Epigenetic regulation of ECM and fibroblast proliferation	Han Chinese
Greene, 2025 [37]	rs10863683	1q	*LINC01705*	Intergenic regulator; multi-ancestry replication	European, African, East Asian, Latin American
Greene, 2025 [37]	rs35383942	1q	*PHLDA3*	Apoptosis; fibroblast expression	European, East Asian
Lu, 2015 [38]; Lu, 2018 [39]	rs1511412	3q22.3	*FOXL2* [b]	Differentiation/apoptosis; TGF-β/SMAD interaction; clinical severity	Japanese, Han Chinese
Nakashima, 2010 [21]; Lu, 2018 [39]	rs940187	3q22.3	Non-coding region (TF/lncRNA)	Gene regulation, ECM; clinical severity	Japanese, Han Chinese
Greene, 2025 [37]	rs6906384	6q25.1	*TAB2*	Modulates TLR/IL-1 → NF-κB	Global
Nakashima, 2010 [21]; Zhu, 2013 [22]; Farag, 2020 [40]	rs8032158	15q21.3	*NEDD4* (intron) [c]	SMAD4 ubiquitination; TGF-β/SMAD; NF-κB/STAT3	Japanese, Han Chinese, Egyptian
Yang, 2017 [41]	rs2303579/ rs2303580/ rs10518830	15q21.3	*NEDD4* (haplotype)	Missense variants and haplotypes of risk/protection	Han Chinese
Zhu, 2013 [22]; Lv, 2020 [36]	rs2271289	15q21.3	*FUT8* (intron) [c]	ECM protein glycosylation	Han Chinese
Greene, 2025 [37]	rs34647667	15q	*ITGA11*	Integrins/fibrosis	African ≫ European
Liu, 2021 [42]; Liu, 2022 [8]	rs1137101/ rs1938496/ rs7555955	1p31.3	*LEPR*	Leptin signalling and dermal inflammation	Han Chinese
Teng, 2015 [43]; Tang, 2023 [44]	rs183178644	6p25.3	*HUS1B* [d]	DNA repair, abnormal cell proliferation	Han Chinese
Greene, 2025 [37]	rs2242026	7p14.1	*EPDR1*	Dermal ECM; skin expression	Global
Greene, 2025 [37]	rs2919386	8p12	*NRG1*	Epithelial–mesenchymal signalling	Global

Table 1. *Cont.*

Study	SNP	Locus	Gene/Region Involved	Possible Affected Molecular Pathway	Population Studied
Greene, 2025 [37]	rs6476838	9p24.2	*GLIS3*	Transcription factor; inflammation	Global
Teng, 2015 [43]; Tang, 2023 [44]	rs181924090	11p15.5	*SIRT3* [(d)]	Epigenetic regulation, oxidative stress, mitochondrial metabolism; fibroblast senescence	Han Chinese
Greene, 2025 [37]	rs76024540	11p15	*SLC22A18*	Imprinting; wound healing	African
Greene, 2025 [37]	rs686722	11p15.5	*LSP1*	Cell migration, cytoskeleton	Global
Teng, 2015 [43]; Tang, 2023 [44]	rs151091483	17p13.1	*MYH8* [(d)]	Fibroblast migration and contractility	Han Chinese
Zhong, 2024 [45]	TNFAIP6	2q23 (functional)	Hyaluronan-binding protein	↓ in keloids; AUC ~1.0; ECM and inflammation role	Post-burn cohorts (China)
Santos-Cortez, 2017 [46]	ASAH1	8q23.3–p21.3	Acid ceramidase	Sphingolipid metabolism	Yoruba (Nigeria)
Han, 2014 [47]	ADAM33	20q13	Metalloproteinase	ECM remodelling	Han Chinese
Marneros, 2004 [20]	EGFR	7p11	EGFR (candidate, linkage) [(e)]	Fibroblast proliferation	African American family
Brown, 2008 [48]; Ashcroft, 2011 [49]	HLA-DRB1*15, DQA1/DQB1	6p21.3	HLA class II	Adaptive immune response; ancestry-dependent effect	Caucasian (+), Afro-Caribbean (–)
Velez-Edwards, 2014 [50]	MYO1E/MYO7A	—	Actin motor proteins	Fibroblast adhesion/migration	African American
Zhong, 2024 [45]	IGFBP6	—	Diagnostic biomarker	↓ in keloids vs hypertrophic scars; AUC ~0.75	China
Liang, 2015 [26]	lncRNAs (e.g., *CACNA1G-AS1*)	—	Differential lncRNAs	ECM–receptor interaction, Ca^{2+} signalling, focal adhesion	Han Chinese

Footnotes: [(a)] Genes located within the 1q41 locus include DEIK (downregulated and associated with profibrotic pathways), BMP2 (implicated in dermal remodeling and extracellular matrix production), and POSTN/COMP, which encode extracellular matrix proteins consistently overexpressed in keloid fibroblasts. [(b)] Although FOXL2 has not yet undergone direct functional validation in dermal fibroblasts, extrapolated evidence from other tissues suggests potential interaction with the TGF-β/SMAD signalling axis. [(c)] At the 15q21.3 locus, both NEDD4 and FUT8 harbour susceptibility SNPs, indicating convergence of multiple molecular mechanisms, particularly ubiquitination and glycosylation, within the same genomic region. [(d)] Gene expression profiles reported by Teng et al. (2015) [43] corroborate the involvement of SIRT3, HUS1B, and MYH8 in oxidative stress, cellular proliferation, and DNA repair, providing indirect functional support for these transcriptomic findings of Tang et al. (2023) [44]. [(e)] Susceptibility loci at 2q23 and 7p11, originally identified through linkage studies [19], lack defined rsID variants but highlighted EGFR and nearby regulatory regions as candidate loci prior to the GWAS era, reflecting the population-specific genetic architecture underlying keloid formation.

3.3.1. Locus 1q41 (The DEIK-BMP2 Axis)

Nakashima et al. (2010) first pinpointed rs873549 in a Japanese GWAS [21]. This finding was soon replicated in Han Chinese cohorts, where it showed a strong association with clinical severity [22]. This polymorphism resides in strong linkage disequilibrium (LD) with rs1348270, a variant that functionally disrupts an enhancer element. As a result, *DEIK* expression drops while *BMP2*, a key driver of fibroblast proliferation and ECM synthesis, becomes overexpressed [35,36]. Complementing this, rs1442440 (located near *BMP2/POSTN*) has been linked to epigenetic modifications that further promote collagen

synthesis [22,25]. Expanding the landscape, a recent multi-ancestry meta-analysis identified novel signals in *LINC01705* and *PHLDA3* within this locus [37].

3.3.2. Locus 3q22.3 (FOXL2)

The variants rs1511412 and rs940187 map to the *FOXL2* region. While the association appears robust in Japanese populations [18], signals in Han Chinese cohorts have proven weaker after stringent statistical correction, suggesting ancestry-dependent effect sizes [22]. A meta-analysis confirmed that rs1511412 correlates with both susceptibility and clinical severity in Asian populations [38,39]. *FOXL2* encodes a transcriptional regulator involved in cell differentiation and apoptosis, and it may interact indirectly with the TGF-β/SMAD pathway [38,39].

3.3.3. Locus 15q21.3 (NEDD4)

The SNP rs8032158 in *NEDD4* shows consistent replication across Japanese, Chinese, and Egyptian populations [21,22,40,41]. Functionally, *NEDD4* encodes an E3 ubiquitin ligase that regulates SMAD4 stability; the risk allele appears to impede SMAD4 degradation, amplifying TGF-β signaling [51]. Interestingly, in European cohorts, this association reached significance only under a recessive model [52], reflecting clear genetic heterogeneity. Within the same region, rs2271289 in *FUT8* has been associated with susceptibility in Han Chinese groups [22,36]. Adding to this, multi-ancestry data have validated additional variants in *ITGA11* and *CORO2B*, consolidating 15q21.3 as a global risk region [37].

3.3.4. Emerging Variants

Recent integrative genomic studies have broadened the field. Transcriptomic analyses identified candidates such as *SIRT3* (rs181924090) in oxidative stress regulation and *MYH8* (rs151091483) in fibroblast contractility [43,44]. In metabolic pathways, variants in the leptin receptor (*LEPR*) have been linked to increased risk in Han Chinese populations [8,42]. Ancestry-specific associations include *ASAH1* in Yoruba families (Nigeria) [46], *MYO1E/MYO7A* in African Americans [50], and *ADAM33* in Han Chinese [47]. Finally, *HLA-DRB1*15* shows a positive association in Caucasians but no signal in Afro-Caribbean populations [48,49].

3.3.5. Integrated Perspective

Taken together, genomic, epigenetic, and immunogenetic studies delineate a complex model of susceptibility to keloid scarring. Common variants such as rs873549, rs8032158, and rs1511412, alongside less frequent polymorphisms and rare mutations, converge with epigenetic mechanisms and microenvironmental factors to explain clinical heterogeneity and interpopulation variability. The strongest evidence corresponds to 1q41 and 15q21.3 (supported by multi-population replication and functional validation), whereas 3q22.3 and emerging genes contribute ancestry-dependent nuances. The multi-ancestry meta-analysis [37] identified more than twenty additional loci and reinforced the convergence of pathways such as TGF-β/SMAD and NF-κB/STAT3, linking them to inflammation, cell migration, and dermal remodelling. To date, none of these findings have been replicated in Mexican or Latin American populations, underscoring the urgent need for regional genomic studies that provide representative molecular profiles (See Table 1).

3.4. Functional Convergence and Epigenetic Regulation

Genomic variants rarely act in isolation; instead, they converge on core signaling pathways that define the fibroinflammatory phenotype of keloids (Table 2).

Table 2. Molecular pathways involved in keloid scarring: main function and effect. This table summarizes the core signaling axes and molecular mechanisms dysregulated in keloid tissue, detailing the specific function of key proteins and their downstream effects on fibroblast activation and extracellular matrix deposition. Abbreviations: ECM, extracellular matrix; TGF-β, transforming growth factor beta; SMAD, mothers against decapentaplegic homolog; BMP2, bone morphogenetic protein 2; lncRNA, long non-coding RNA.

Gene/Pathway	Involved Axis	Main Function	Effect in Keloids
TGFBR2	TGF-β/SMAD	SMAD-activating receptor promoting collagen synthesis	Excessive fibrotic activation
NEDD4	TGF-β/SMAD	Ubiquitination of SMAD4	Amplifies profibrotic signalling
DEIK (1q41)	BMP2 pathway	Repressor of BMP2 and fibrosis regulator	↓DEIK → ↑BMP2 → fibrosis
BMP2	BMP2 (TGF-β superfamily)	Growth factor promoting fibrosis and ECM deposition	Overexpressed in keloid fibroblasts
POSTN	ECM	Collagen adhesion and remodelling	Overexpression linked to stiffness and keloid volume
COMP	ECM	ECM organisation	↑ ECM accumulation
SDC1	ECM/signalling	Transmembrane proteoglycan	↑ Fibroblast proliferation and ECM synthesis
ATF3	TGF-β/SMAD	Stress-induced transcription factor	↑ Collagen production, proliferation, and apoptosis
lncRNAs	Epigenetic regulation	Long-range transcriptional regulation	Imbalance in lncRNAs (CAS1, DEIK-lncRNA) → fibroblast proliferation and profibrotic activation

3.4.1. Pathway Convergence

The primary loci (1q41, 15q21.3) and emerging candidates (*EGFR*, *TNFAIP6*) consistently dysregulate the TGF-β/SMAD and NF-κB/inflammatory axes. For instance, *BMP2* overexpression (driven by 1q41) and SMAD4 stabilization (driven by *NEDD4*) work synergistically to promote excessive collagen deposition. Emerging biomarkers like *TNFAIP6* and *EGFR* further integrate fibrosis with chronic inflammation, engaging TNF-α and IL-17 pathways [44,45,53]. Secondary modulators such as Syndecan-1 (*SDC1*) and *ATF3* amplify these routes by potentiating MAPK cascades [10,54].

3.4.2. Epigenetic Modulation

Beyond DNA sequence variations, epigenetic mechanisms sustain the "keloid memory." Global hypomethylation has been observed in profibrotic gene promoters. The rs1348270 variant (1q41) exerts its effect via long-range chromatin looping (Figure 4). This aligns with epigenetic patterns in other inflammatory contexts, where regulators like *HDAC6* and miR-9 modulate dermal immune responses [55]. In addition, over 2500 lncRNAs are differentially expressed in keloids; notably, *CACNA1G-AS1* plays a prominent role in regulating intracellular calcium and fibroblast hyperactivation [56].

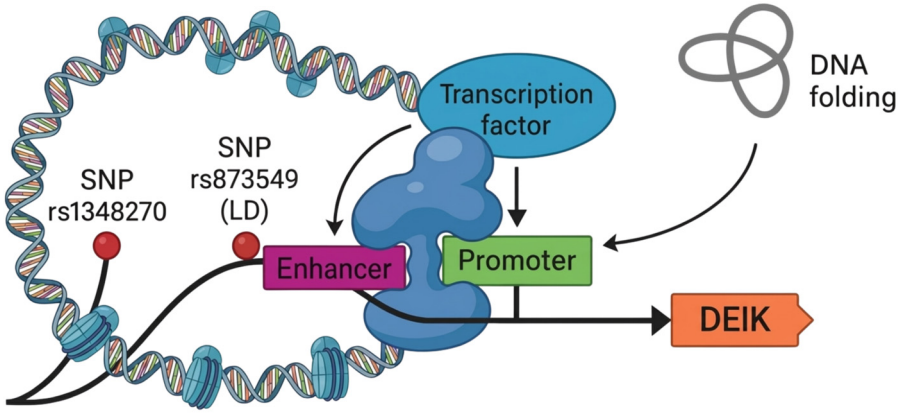

Figure 4. Mechanism of *DEIK* modulation by distal variants. The SNPs rs1348270 and rs873549 (located in linkage disequilibrium at 1q41) constitute a distal enhancer element. Through 3D chromatin folding, this enhancer interacts physically with the *DEIK* promoter to regulate its transcription. This illustrates precisely how non-coding genetic variants can modulate gene expression in dermal fibroblasts by altering long-range chromatin architecture.

3.5. Susceptibility and Inheritance Models

Population-based evidence supports complex hereditary architecture. Autosomal dominant patterns with incomplete penetrance are commonly described in African and Asian families [17,18]. Rare high-penetrance mutations, such as *ASAH1* p.Leu401Pro, can drive the phenotype in specific pedigrees [46]. By contrast, common variants like rs8032158 (*NEDD4*) may follow dominant models in Asia but recessive patterns in Europe [52]. Similarly, *IL6* variants show associations in Egyptian populations that are absent in Polish cohorts [40,57].

Taken together, these findings indicate that keloid scarring is a polygenic disorder shaped by ancestry-specific architecture, where common low-effect variants and rare mutations interact within a broader multifactorial background (Table 3).

Table 3. Main SNPs associated with keloid scarring according to population and inheritance models. This table synthesizes the hereditary architecture of keloid susceptibility, contrasting the clinical relevance of key variants across diverse ancestries and detailing the specific inheritance patterns, ranging from autosomal dominant to recessive or additive models, observed in different ethnic cohorts.

Variant/Gene	Inheritance Model	Population(s)	Key Implication
rs873549/rs1348270 (1q41)	Autosomal dominant/additive	Japanese, Han Chinese	Strongly replicated susceptibility locus regulating the DEIK–BMP2 signaling axis
rs8032158 (NEDD4)	Autosomal dominant/additive (Asian); autosomal recessive (European)	Japanese, Han Chinese, Egyptian, European	Ancestry-dependent genetic effect with differential modulation of the TGF-β/SMAD pathway
IL6–572G>C (rs1800796)	Population-specific association	Egyptian (associated), Polish (not associated)	Illustrates ethnic heterogeneity in inflammatory genetic risk
ASAH1 (p.Leu401Pro)	Autosomal dominant, high penetrance	Yoruba (Nigeria)	Rare monogenic driver acting within a broader polygenic susceptibility background
HLA-DRB1*15	Risk allele (non-Mendelian)	Caucasian (associated), Afro-Caribbean (not associated)	Ancestry-dependent immunogenetic contribution to keloid susceptibility
Global polygenic model	Multifactorial, additive	African, Asian, European	Combined effect of multiple low-effect common variants with epigenetic modulation

4. Discussion

The extensive genetic and epigenetic heterogeneity observed across diverse populations reinforces the concept of keloid scarring as a complex polygenic condition, shaped by the dynamic interplay between ancestral background and environmental triggers. Foundational epidemiological research established a clear ethnic–geographical gradient early on, with prevalence rates ranging from a negligible 0.09% in England to 16% in Zaire [14,58]. These disparities locate the highest susceptibility within African populations, followed by intermediate rates in Asian groups, while European cohorts show the lowest incidence [3,26,59].

While these epidemiological patterns remain consistent across studies, the underlying molecular drivers appear to diverge by ancestry, suggesting that similar clinical phenotypes can arise from distinct genetic and epigenetic architectures [21,22,37] (Table 4). Recent evidence from Taiwan has consolidated the susceptibility profile of East Asian populations [25]; by contrast, a profound gap persists in Latin America, where research focuses largely on clinical assessments rather than genomic characterization [4,14,29].

Table 4. Ancestry-dependent genomic and epigenetic architecture of keloid scarring. This comparative synthesis illustrates how similar clinical phenotypes arise from divergent molecular mechanisms across populations. It contrasts the robust involvement of BMP and TGF-β signaling pathways in African and Asian ancestries with the weaker genetic signals observed in European cohorts. ↑ indicates increased pathway activity or overexpression; ± indicates limited, variable, or inconsistent evidence across studies; * Latin American populations are genetically admixed and remain underrepresented in genomic and epigenomic studies of keloid scarring.

Pathway/Molecular Mechanism	African Ancestry	Asian Ancestry	European Ancestry	Latin American (Admixed) *
BMP Signaling & ECM (Locus 1q41)	Replicated association	Strong replicated association	No consistent association	± Limited data
Functional Impact (1q41 Axis)	↑ ECM-related pathways	↑ ECM overproduction	Not demonstrated	Unknown
TGF-β/SMAD Signaling (Locus 15q21.3)	Dominant/additive models	Dominant models	Recessive or weak effect	± Not evaluated
Inflammatory Signaling (IL-6 Variants)	Positive association (Egyptian cohorts)	± Variable evidence	No association	Not studied
Epigenetic Regulation	Strong (DNA methylation)	Strong	Present	± Largely unexplored
Dominant Pathogenic Mechanism	Inflammatory–fibrotic balance	Fibroblast hyperactivation	Limited molecular signal	Admixture-dependent
Clinical Phenotype	High susceptibility, recurrence	High susceptibility, recurrence	Lower prevalence	Unknown risk stratification

From a hereditary perspective, familial studies have predominantly identified autosomal dominant inheritance patterns with variable expressivity, particularly among African American and Asian pedigrees [17,18]. Yet early linkage scans identifying loci at 2q23 and 7p11 highlighted the condition's inherent heterogeneity even before the era of GWAS [19,20]. These early findings anticipated the population-specific effects later confirmed by GWAS, emphasizing that no single genetic model fully explains keloid susceptibility across all ancestries.

The shift to GWAS marked a turning point, identifying canonical susceptibility loci at 1q41, 3q22.3, and 15q21.3 [21,22]. The functional relevance of these regions is becoming clearer. At 1q41, variants such as rs873549 and rs1348270 appear to regulate enhancer–

promoter interactions involving *DEIK*, *BMP2*, and *POSTN*, driving the characteristic overexpression of ECM proteins [35,36]. This locus shows consistent replication in Asian populations, supporting a shared pathogenic mechanism centered on fibroblast-driven ECM dysregulation.

Similarly, at 15q21.3, the rs8032158 variant in *NEDD4* has been validated across Japanese, Chinese, and Egyptian populations [21,22,40], with evidence suggesting the *NEDD4-TV3* isoform promotes fibroblast activation via NF-κB and STAT3 signaling [51]. European cohorts, however, often require alternative genetic models or yield weaker associations, such as the recessive effect observed for rs8032158 or the lack of signal for *IL6*, highlighting the critical role of ancestry in modulating genetic risk [52,57]. Rare high-penetrance variants like *ASAH1* p.Leu401Pro further exemplify this heterogeneity, confirming that monogenic drivers can coexist within a broader polygenic architecture [46].

Genetic predisposition offers a plausible explanation for familial clustering [60], while recent studies highlight that pathways such as JAK/STAT and PI3K/AKT contribute to fibroblast hyperactivity beyond the TGF-β axis [61]. Epigenetic regulation adds another layer to keloid pathophysiology. The documentation of over 100,000 differentially methylated sites and the role of lncRNAs like *CACNA1G-AS1* illustrate sustained reprogramming that governs fibroblast hyperactivity [24,26,36]. These mechanisms may partially account for the persistence and recurrence of keloids, as well as for tissue- and ancestry-specific phenotypic variability, even in the absence of high-penetrance mutations.

Recent multi-ancestry meta-analyses identifying 26 associated loci represent a milestone toward including underrepresented groups, such as admixed Latin American populations via the All of Us cohort [37]. Complementing these advances, recent reviews have systematized the landscape of molecular biomarkers and epigenetic alterations [27,62,63], reinforcing the need for an integrative perspective. Collectively, these findings support a model where genetic susceptibility establishes a permissive background subsequently reinforced by epigenetic dysregulation.

Over the past decade, rapid advances in both molecular research and clinical management have significantly expanded our understanding of keloid pathogenesis and therapeutic strategies, highlighting the need for more integrated and individualized treatment approaches [64]. Clinically, the high recurrence rates associated with conventional therapies, often exceeding 50%, emphasize the need for precision management [63–66]. The convergence of ancestry-dependent genetic risk, epigenetic persistence, and immune modulation suggests that uniform therapeutic approaches may be insufficient across populations. Current evidence points to the integration of genomic, epigenetic, and immunological markers into clinical algorithms as essential for effective risk stratification [67]. For instance, therapies such as non-thermal plasma show promise in differentially modulating keloid fibroblasts [53], suggesting that genotype- or pathway-informed strategies could improve outcomes.

The literature supports a heterogeneous model where common variants, rare mutations, and epigenetic mechanisms converge. Crucially, ancestry emerges as a central modifier influencing genetic risk, epigenetic regulation, and disease expression. Addressing the underrepresentation of Latin American populations remains a priority; future multicenter studies must incorporate regional diversity to enable ancestry-informed strategies. Figure 5 illustrates the translational implications of these findings, linking genomic and epigenetic alterations to potential therapeutic targets.

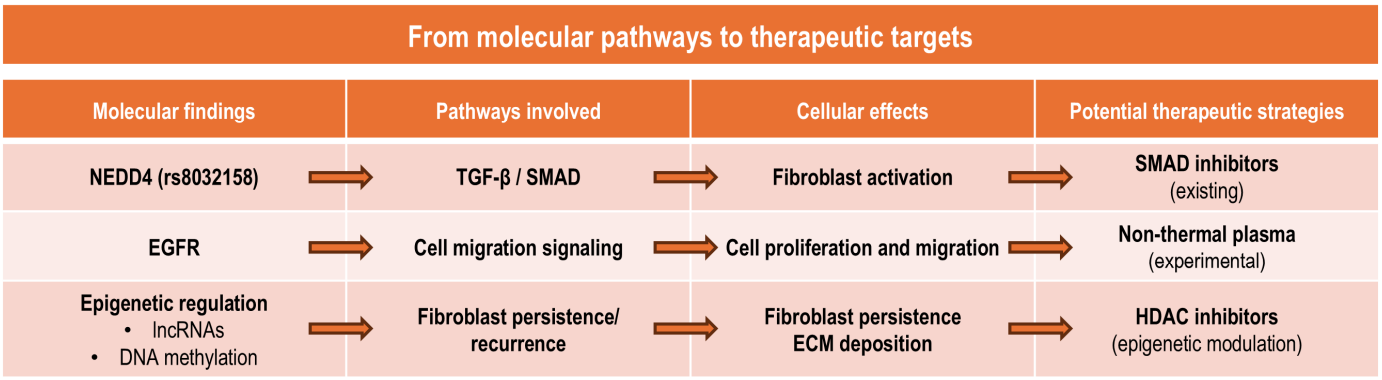

Figure 5. Translating molecular findings into therapeutic targets. Overview of how specific genomic and epigenetic alterations converge on actionable signaling pathways. Genetic variants and epigenetic regulators (DNA methylation, lncRNAs) drive fibroblast activation and persistence. These molecular nodes serve as potential targets for precision interventions, ranging from existing SMAD inhibitors to experimental approaches like non-thermal plasma and epigenetic modulators.

From a translational perspective, emerging therapeutic strategies are increasingly targeting molecular pathways involved in fibrosis, including TGF-β signaling, mechanotransduction pathways, and immune-mediated fibroblast activation, reflecting a shift toward mechanism-based interventions for pathological scarring [68]. Looking beyond current insights, emerging technologies promise to refine our understanding of keloid pathogenesis.

Approaches such as single-cell RNA sequencing and spatial transcriptomics may help disentangle fibroblast heterogeneity and define ancestry-specific cellular states. [69]. Recent multi-omics single-cell analyses have further revealed substantial cellular heterogeneity within keloid tissue, identifying fibroblast subpopulations with distinct profibrotic transcriptional programs [70].

Integrative multi-omics strategies could enable more precise mapping of regulatory networks underlying fibroblast hyperactivation. In parallel, functional genomics tools, including CRISPR-based perturbation models, may further facilitate the validation of candidate susceptibility loci. Applying these technologies to underrepresented and admixed populations will be essential to translate molecular findings into clinically relevant strategies. Ultimately, novel molecular targets derived from genomic and transcriptomic studies are currently being explored as potential therapeutic approaches for preventing pathological scar formation [71].

Limitations

Although this narrative review provides an integrative overview of genomic and epigenetic mechanisms underlying keloid scarring, we must acknowledge several limitations. First, genomic evidence remains uneven across populations, with a marked underrepresentation of Latin American and other admixed cohorts, which limits the generalizability of current findings. Second, while we focused on genomic, epigenetic, and regulatory mechanisms, detailed clinical trial data and non-genetic risk factors fell outside our primary scope. Finally, emerging areas such as microbiome, fibrosis interactions, mechanical signaling, and advanced spatial multi-omics remain underexplored in this context due to limited evidence. Recognizing these gaps underscores the need for future integrative research and defines the boundaries of this narrative synthesis.

5. Conclusions

The evidence synthesized here establishes keloid scarring as a complex, multifactorial disorder defined by a polygenic architecture and modulated by ancestry-dependent

epigenetic mechanisms. Instead of being driven by single causative factors, pathogenesis stems from the cumulative burden of common low-effect variants, rare high-penetrance mutations, and sustained transcriptional reprogramming. These factors converge on key profibrotic axes, most notably TGF-β/SMAD and NF-κB. Together, these genomic and epigenetic layers provide a coherent framework linking molecular dysregulation to the disease's characteristic persistence, recurrence, and clinical heterogeneity.

Validating canonical loci alongside emerging epigenetic regulators confirms that genetic susceptibility is inherently dynamic and population-specific. Crucially, genetic associations do not replicate uniformly across populations, highlighting ancestry as a major modifier of disease susceptibility. Variants conferring high risk in African and Asian populations frequently exhibit weaker or absent effects in European cohorts. By contrast, epigenetic alterations, including DNA methylation changes and non-coding RNA regulation, offer a mechanistic explanation for phenotypic persistence and interindividual variability that inherited sequence variation alone cannot explain. Taken together, these findings show that keloid scarring cannot be adequately understood through single-population genetic models.

From a clinical perspective, these molecular insights hold direct translational relevance. The persistently high recurrence rates associated with conventional therapies expose the limitations of uniform management strategies and reinforce the need for precision-oriented approaches. Incorporating genomic, epigenetic, and immunological markers into clinical frameworks may enable improved risk stratification, prognostic assessment, and the identification of patient subgroups who are more likely to benefit from targeted or pathway-informed interventions.

Yet, despite substantial advances, a critical imbalance remains. Current genomic and epigenomic evidence leans heavily toward Asian, African, and European populations, leaving Latin American and other admixed groups markedly underrepresented. This skew limits the generalizability of existing findings and constrains the equitable translation of genomic discoveries into clinical practice. At the same time, the unique genetic admixture characterizing Mexico and Latin America presents a valuable scientific opportunity to identify ancestry-specific modifiers that might remain undetectable in more homogeneous cohorts.

Future research must therefore prioritize the inclusion of multi-ethnic and admixed populations through multicenter study designs, alongside integrative multi-omics approaches that combine genomic, epigenomic, transcriptomic, and functional data. Such strategies are essential to refine the molecular classification of keloid scarring, clarify ancestry-specific disease mechanisms, and ultimately advance personalized preventive and therapeutic strategies applicable across diverse populations.

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Abbreviations

The following abbreviations are used in this manuscript:

GWAS	Genome-Wide Association Studies
SNP	Single-Nucleotide Polymorphism
ECM	Extracellular Matrix
TGF-β	Transforming Growth Factor Beta
SMAD	Mothers Against Decapentaplegic Homolog
NF-κB	Nuclear Factor Kappa B
BMP2	Bone Morphogenetic Protein 2
EGFR	Epidermal Growth Factor Receptor
lncRNA	Long Non-Coding RNA
HLA	Human Leukocyte Antigen
NEDD4	Neuronal Precursor Cell Expressed Developmentally Down-Regulated 4
TNFAIP	Tumor Necrosis Factor Alpha-Induced Protein 6
MAPK	Mitogen-Activated Protein Kinase
JAK/ST	Janus Kinase/Signal Transducer and Activator of Transcription
LEPR	Leptin Receptor

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