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Single-gene Etiologies of Keloid and Hypertrophic Scars: A Systematic Review of Mutational Landscape in 296 Patients

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 March 2025 and was last updated on 10 March 2025.

INTRODUCTION

Review question / Objective To identify and systematically review single-gene etiologies associated with keloid and hypertrophic scars using the PICOS framework, focusing on the mutational landscape, genetic pathways involved, inheritance patterns, and clinical phenotypes of affected patients.

Rationale Keloids and hypertrophic scars (KHS) are challenging fibroproliferative disorders linked to genetic predispositions. Despite advances, genetic testing in clinical practice remains limited. Understanding the genetic underpinnings can enhance clinical management, diagnosis, and personalized treatments. This review aims to elucidate single-gene causes to inform clinical approaches.

Condition being studied Keloid and hypertrophic scars (KHS) are fibroproliferative skin disorders resulting from abnormal wound healing processes, characterized by excessive extracellular matrix accumulation. They often cause cosmetic and functional impairments, frequently exhibiting familial clustering.

METHODS

Search strategy Electronic databases searched include MEDLINE, Scopus, Web of Science, and Google Scholar. Keywords used: Keloid, Hypertrophic Scar, Single-gene susceptibility, monogenic mutation, mendelian inheritance, extracellular matrix.
8. Patient, Participant, or Population: Patients diagnosed with monogenic forms of keloids or hypertrophic scars, irrespective of age, ethnicity, gender, or geographical location.

Participant or population Patients diagnosed with monogenic forms of keloids or hypertrophic scars,

irrespective of age, ethnicity, gender, or geographical location.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included Case reports, case series, cross-sectional studies, clinical trials, cohort studies, and case-control studies.

Eligibility criteria Included articles clearly linking KHS to single-gene etiologies. Excluded were studies lacking specific causal gene identification, non-monogenic etiologies, insufficient phenotype details, and acquired cases.

Information sources Electronic databases (MEDLINE, Scopus, Web of Science, Google Scholar), citation tracking, manual searches of references, and author contacts for additional information.

Main outcome(s) Identification and comprehensive characterization of single-gene mutations causing KHS, including detailed gene names, mutation types (e.g., missense, nonsense, frameshift), specific inheritance patterns (autosomal dominant, recessive, X-linked), clinical manifestations (including severity, associated syndromic features), and molecular pathways involved (e.g., extracellular matrix remodeling, inflammation, signaling pathways).

Additional outcome(s) Detailed analysis of anatomical distribution of scars (limbs, trunk, face, etc.), triggers initiating scar formation (injuries, surgeries, spontaneous, piercings, acne), prevalence differences among ethnic groups, and detailed statistical analysis of age at onset.

Data management Endnote and Excel software were systematically utilized for record management, identification and removal of duplicates, comprehensive data extraction, and meticulous tracking of study details. Regular consensus meetings among authors ensured accuracy and resolved discrepancies.

Quality assessment / Risk of bias analysis The quality of included studies was rigorously evaluated using the Joanna Briggs Institute criteria tailored specifically for case reports, case series, and cross-sectional studies. Each study was systematically classified into "good," "fair," or "poor" quality categories based on clearly defined parameters.

Strategy of data synthesis Narrative synthesis was performed with a detailed presentation of identified gene mutations, clearly articulated affected molecular pathways, comprehensive clinical phenotype descriptions, and detailed inheritance patterns. Additionally, descriptive statistical analyses were employed to characterize patient demographics and clinical features systematically.

Subgroup analysis Subgroup analyses were conducted based on inheritance patterns (autosomal dominant, autosomal recessive, X-linked), mutation types (missense, nonsense, frameshift, deletions), and specific molecular pathways involved (e.g., TGF-β, NF-κB, inflammasome pathways), allowing detailed insights into the genetic and clinical heterogeneity of KHS.

Sensitivity analysis Sensitivity analyses assessed the robustness of findings through variations in study quality (good vs. fair vs. poor), strictness of inclusion criteria applied (broader vs. narrower genetic evidence), and strength of evidence categorization (strong, moderate, weak genetic evidence).

Language restriction English language only.

Country(ies) involved Iran; United States.

Keywords Keloid; Hypertrophic Scar; Monogenic Mutation; Genetic Susceptibility; Fibroproliferative Disorders; Mendelian inheritance; Extracellular matrix.

Dissemination plans Findings will be published in peer-reviewed journals, presented at scientific conferences, and made accessible through online databases to encourage clinical adoption.

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