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Revisiting Spontaneous Keloids: Aetiology, Genetics and Evidence for a Polygenic Pathogenesis

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ABSTRACT

Keloids are abnormal scars resulting from dysregulated wound healing extending beyond the original injury. While typically triggered by trauma, rare cases of spontaneous keloid formation challenge this paradigm and suggest potential endogenous drivers. This study synthesises all reported cases to date and explores pathogenic mechanisms underlying their diverse etiologies. Special emphasis is placed on syndromic disorders associated with spontaneous keloids, with clinical and genetic data presented to support informed diagnostic and genetic decision-making. A representative case, in which genetic testing and bioinformatic analyses uncovered potential candidate genes consistent with a polygenic model of keloid pathogenesis, is provided to illustrate the clinical relevance and complexity of this condition. The insights discussed may reframe keloid formation as not solely a reactive complication of wound healing, but rather a primary manifestation of polygenic dysregulation within wound healing cascades.

1 | Introduction

Keloids are disfiguring, debilitating scars that result from aberrant wound healing extending beyond the original injury [1]. Increasing evidence supports a genetic contribution to keloid pathogenesis, including high heritability estimates in individuals of African ancestry and the identification of multiple susceptibility loci in genomic studies, many of which reside in non-coding regulatory regions rather than protein-coding genes, supporting that keloid development reflects complex dysregulation of gene expression networks [1]. This pattern suggests a polygenic, context-dependent inheritance model involving interactions between genetic susceptibility and cutaneous triggers such as mechanical trauma [1]. Spontaneous keloids remain rare, and debate persists regarding whether they are ever truly spontaneous. The characterisation of spontaneous keloid relies on the absence of patient recollection of prior, perhaps subclinical, microtrauma or inflammatory lesion which, if historically present, would necessitate reclassification to secondary keloid formation. Despite being labelled 'spontaneous', most published cases may represent misclassified secondary keloids and describe non-progressive, few or solitary keloids with focal distribution or preceding trauma, apart from one case [2]. Notably, this case's patient exhibited severe intellectual disability and distinguishing craniofacial features, namely orbital hypertelorism, broad nasal bridge, cleft lip and high-arched palate, which are highly suggestive for Rubinstein–Taybi syndrome (RSTS) though, critically, she did not undergo genetic testing, and the

Abbreviations: BM, Bethlem myopathy; COL6, collagen type VI; FDR, false discovery rate; FLNA, filamin A; RSTS, Rubinstein–Taybi syndrome; TGF-β, transforming growth factor-β.

authors did not implicate a diagnosis [2]. With the exception of this intriguing case, truly spontaneous keloids have only been documented in association with malignancy, isotretinoin and few genetic syndromes, which are under-characterised, contributing to significant gaps in our clinical assessments. We explore potential pathogenic mechanisms underlying spontaneous keloid formation and, with an illustrative case, propose a polygenic model to explain their emergence in genetic syndromes.

2 | Case Illustration

A 68-year-old African American male presented with a 40-year history of diffuse, ulcerating keloids refractory to intralesional steroids, pulsed-dye laser therapy and radiation (Figure 1). Since there was no reported preceding trauma or inflammatory lesions, the keloids were characterised as spontaneous. The patient had a 5-year history of ascending to ubiquitous arthralgia, myalgias and muscle atrophy. Physical examination revealed large, diffuse, ulcerated and draining keloids involving the scalp, torso, groin and extremities (Figure 2). There was extreme crepitation on movement, diffuse weakness and bilateral hip contractures. Extensive autoimmune testing was negative and, without a clear explanation for the irregular presentation, genetic studies were conducted. DNA from fibroblasts cultured from an excised keloid specimen was submitted for whole genome sequencing using the HiSeq 4000 sequencing system (Illumina). Raw sequence reads were aligned to the reference human genome (Genome Reference Consortium Human Build 38) and variants were identified using Dynamic Read Analysis for GENomics hardware/software server platform with a field-programmable gate array pipeline. Analysis of the keloid fibroblast specimen revealed a cysteine to alanine missense mutation on the *collagen type VI alpha 3 chain*, suggestive of Bethlem myopathy (BM). Family history and pedigree analysis were obtained from collateral reports, though information on keloid severity and spontaneity in relatives was limited, and genetic testing was performed only in the index patient. After 4 years of multidisciplinary conservative management, the patient was transferred to a skilled nursing facility and died shortly thereafter from Covid respiratory complications.

3 | Discussion

The majority of published reports on spontaneous keloids describe non-recurrent, isolated, or focal lesions, which do not raise strong clinical suspicion for a syndromic or genetically driven process. These cases include BM (two cases with focal shoulder distribution and two cases with traumatic precursor lesions), Noonan syndrome (one case of single post-traumatic toe keloid) and Dubowitz syndrome (one case of single clavicular

FIGURE 1 | Progressive development of spontaneous facial keloids. Serial photographs demonstrating the evolution of keloid lesions on the patient's face over time.

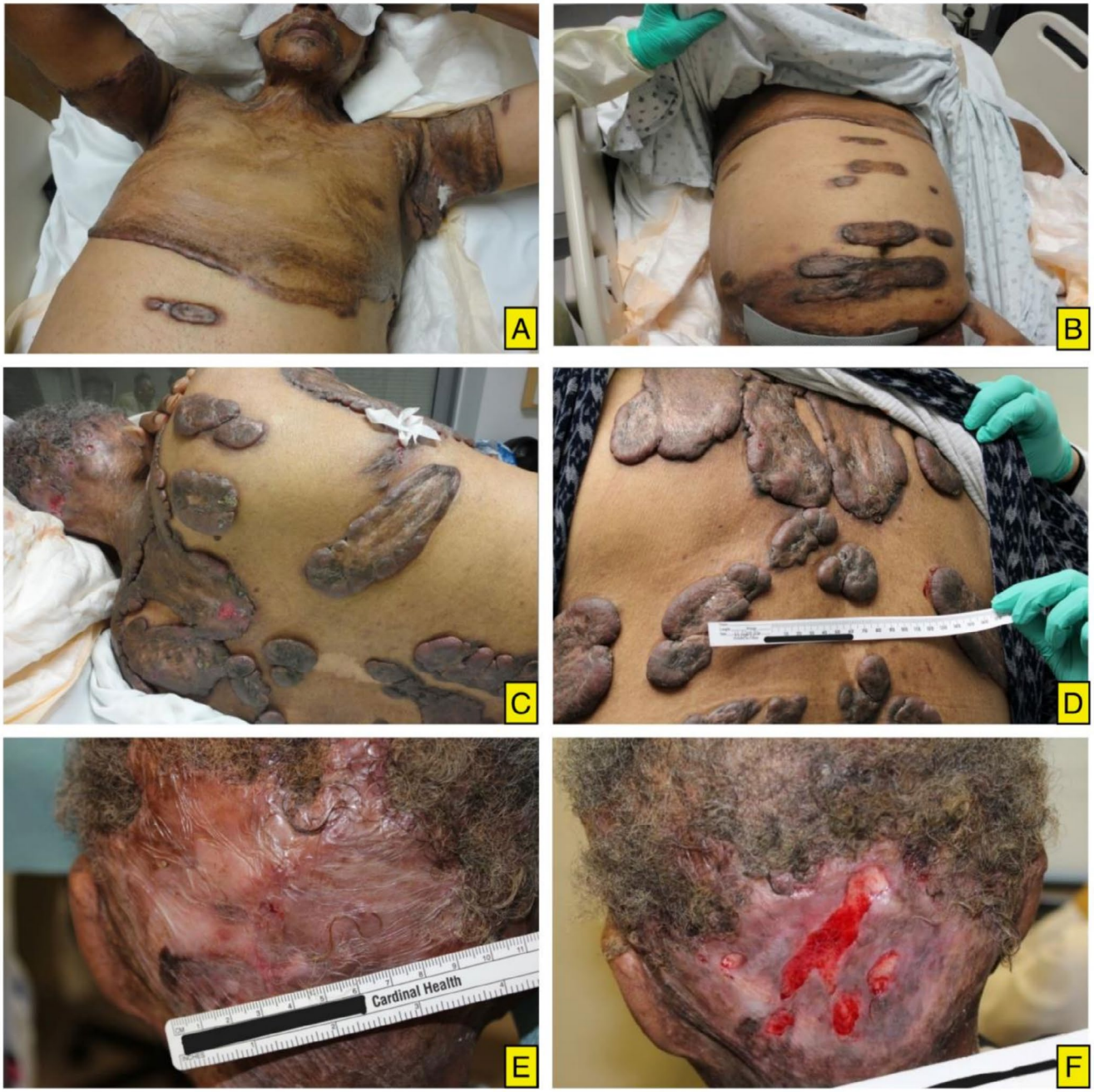

FIGURE 2 | Clinical photographs showing diffuse keloid involvement of the chest and abdomen (A, B), back (C, D) and occipital scalp, with images obtained at different time points (E, F).

keloid) [3–6]. With the addition of our BM case, true spontaneous keloids are likely underreported, with only 8 other reports in the literature, including isotretinoin-induced, paraneoplastic and rare genetic syndrome etiologies as summarised in Table S1.

Isotretinoin-associated spontaneous keloids may be related to retinoid-induced collagenase suppression and disruption of the pilosebaceous unit, which impairs re-epithelialization and inflammatory regulation [7]. In one case, coexisting Behçet's disease may have contributed to keloid formation as elevated Interleukin-6 levels in active Behçet's have been shown to promote keratinocyte and fibroblast proliferation, with keloid fibroblasts expressing both interleukin-6 and interleukin-6 receptor alpha, suggesting a possible self-reinforcing autocrine loop [7]. In RSTS, keloids are thought to result from pathogenic variants of the implicated genes, CREB binding protein or E1A binding protein p300, which function as coactivators in the transforming growth factor-β (TGF-β) signalling pathway where their dysfunction may cause an exaggerated fibrotic response [8]. TGF-β signalling may also be involved in Polyfibromatosis syndrome and X-linked cardiac valvular dysplasia where specific polymorphisms can lead to TGF-β upregulation and filamin A (FLNA) and TGF-β interactions have been suggested [9, 10]. Among these syndromes, BM offers a valuable model for studying spontaneous keloid formation, combining the causative *collagen type VI* (*COL6*) mutation with its more clearly defined role

in wound healing dysregulation. Specifically, *COL6* is upregulated at proliferating keloid margins and involved in dysregulated fibronectin deposition and *collagen type I* fibrillogenesis [11]. As illustrated in our case, genetic testing can be valuable for diagnosis in patients with spontaneous keloids. Such genetic syndromes, given the phenotypic variability or subtle manifestations, may critically go unrecognised by clinicians; Table S2 outlines key non-keloid syndromic manifestations and the available relevant genetic considerations to help guide genetic testing decisions.

A major challenge for understanding spontaneous keloid formation in these genetic syndromes is significant genotype and molecular discordance with clinical manifestations. In RSTS, known mutations are detected in only about 50% of cases and may be due to somatic mosaicism; studies have also demonstrated identical mutations can produce both mild and severe phenotypes [12]. While some RSTS data suggests larger deletions correlate with earlier onset, they do not appear to predict phenotypic severity and the potential roles of intronic, non-coding regulatory region variants and dominant negative effects remain largely speculative [12]. In BM, phenotypic severity correlates with low *COL6* secretion, yet some BM patients exhibit low *COL6* activity without *COL6* mutations, while others have *COL6* mutations without altered *COL6* activity and, in X-linked cardiac valvular dysplasia, the 'causative' FLNA mutation may not cause any extracardiac syndromic manifestations at all [13, 14]. Given this backdrop of incomplete penetrance, variable expressivity and potential mosaicism in these syndromes, the central question remains: what drives spontaneous keloid formation in affected individuals? Despite a single-gene phenomenon being sufficient to produce syndromic features, it is likely that additional mutations may act as modifiers and shape expression of the spontaneous keloid feature—an existing model which has not yet been adapted for this context [15].

Providing preliminary support for a polygenic model and not discounting epigenetic factors, the genetic studies of our BM patient revealed 12 additional mutations linked to keloid pathogenesis and summarised in Table S3. Identification of these mutations was also helpful for excluding the possibility of a non-*COL6* confounding genetic predisposition to keloid formation. This was particularly relevant in our case where multiple relatives, similar to one of the RSTS cases, reported keloids (Figure S1) in the absence of overt BM symptomatology. Lack of clinical evaluation and confirmatory genetic testing precluded definitive exclusion of subclinical or variably penetrant BM phenotypes in these relatives. Additionally, none of the non-*COL6* identified mutations are known pathogenic drivers of keloid formation or linked to syndromic presentations, though it is possible that the patient had a genetic predisposition which has not yet been reported in the literature. Bioinformatic assessment of *COL6* and these genes suggested 94 strong interactions (molecular interaction score > 0.7), moderate node connectivity (2.31) and a local clustering coefficient of 0.467, with significant enrichment ($p = 4.88e{-}08$) and low false discovery rate (FDR = 0.00025), providing exploratory support for strong functional relatedness (Figure S2). While these findings are consistent with a polygenic model of susceptibility, the network-based genomic analysis presented is associative and exploratory in nature. Interpretation of these results should therefore be undertaken in the context of important study limitations, including the absence of functional validation and matched unaffected tissue to determine variant origin.

4 | Conclusion

Spontaneous keloid formation is a rare phenomenon with suspected paraneoplastic, drug-induced and genetic syndrome etiologies. This report synthesises all published cases to date, proposes pathogenic mechanisms and highlights key features of associated syndromes to facilitate early clinical recognition and inform genetic evaluation. With an illustrative case, we discuss the role and limitations of genetic testing and novelly implicate BM with diffuse spontaneous keloid formation. Leveraging the case's genetic and bioinformatic studies, we provide support for a polygenic model of spontaneous keloid formation which has not yet been adapted in this context due to previously disparate, under-characterised reports and lack of potential candidate keloid-related genes. It remains to be seen if endogenous genetic or molecular signalling alone, without trauma, can influence the fibrotic cascade to produce keloids; this may reframe our understanding of keloids being a purely reactive wound healing dysregulation phenomenon. We recommend genetic testing be considered in advanced diagnostic workups for patients with spontaneous, widespread patterned keloids, or systemic features concerning for connective tissue or neurologic disease to identify syndromic causes and guide multidisciplinary care.

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Ethics Statement

This study was conducted in accordance with institutional and national ethical standards.

Consent

A written informed consent was obtained and documented by the investigators.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.19463823, reference number 10.5281/zenodo.19463823.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Pedigree of patient's family history of keloid formation. **Figure S2:** Protein–protein interaction network of gene variants identified by genetic testing in the proband with Bethlem myopathy, highlighting pathways implicated in keloid pathogenesis. **Table S1:** Summary of reported cases of spontaneous keloids and suspected etiologies. **Table S2:** Non-keloid features, genetic considerations and inheritance patterns of syndromes associated with spontaneous keloids. **Table S3:** Genetic mutations identified in a Bethlem myopathy patient and their literature-reported associations with keloid pathogenesis.