Current Understanding of the Genetic Causes of Keloid Formation

Donald A. Glass II[1]

Keloids are an exuberant response to cutaneous wound healing. Several lines of evidence suggest that keloid scarring is influenced by genetic factors. This review will discuss our current understanding of genetic influences on keloidal scarring via familial inheritance patterns; ethnic differences in prevalence; syndromes with keloid occurrence; linkage analysis, genome-wide association studies, and admixture mapping studies; transforming growth factor beta and p53 variant studies; and human leukocyte antigen polymorphisms.

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Keloids are benign proliferative scars that grow beyond the confines of the original insult to the skin, invading into adjacent normal tissue. This differentiates them from hypertrophic scars, which are raised scars that remain within the boundaries of the inciting cutaneous insult. Besides being aesthetically disfiguring, keloids can be pruritic, painful, and/or hyperesthetic. They can also limit range of motion if they extend across joints.

There are several lines of evidence that suggest that genetics has a strong influence on keloid predisposition. The first is that there are ethnic differences in the occurrence rate of keloids, with people of darker skin complexion having a higher predisposition than fairer-skinned individuals (LeFlore, 1980). Those of African descent have the highest prevalence rate; it is estimated to be 4–6% but has been reported as high at 16% in an adult population in Zaire. Those of Asian and Hispanic heritage are less predisposed, with whites having the lowest prevalence rate, as low as 0.09% in England (Bloom, 1956).

The inheritance of keloids within families also supports genetics having an influence on keloid occurrence. First, there is an increased prevalence of keloids in twins (Marneros et al., 2001; Ramakrishnan et al., 1974). Second, there are families in which multiple members are affected by keloids over several generations. In these families, the scarring predisposition tends to segregate within the family in an autosomal dominant inheritance pattern, with incomplete penetrance and variable expressivity (Clark et al., 2009; Marneros et al., 2001). However, there have been reports of autosomal recessive and even X-linked inheritance (Goeminne, 1968, Omo-Dare, 1975), suggesting that several different genes may predispose to keloid formation. Finally, compared with individuals with sporadic keloids (i.e., no family history of keloid), individuals with familial keloids tend to have keloids occurring on multiple body sites, and there are instances in which multiple family members exhibit keloids in the same distinct locations (Bayat et al., 2005a, Clark et al., 2009). This similarity in phenotypic presentation within the same family argues for some genetic predilection, in contrast to an exclusively environmental influence.

Although familial inheritance plays prominently into our understanding of genetic influence, the identification of these predisposing genes within familial keloids has been difficult to obtain. Using linkage analysis, keloid susceptibility loci have been identified in a Japanese family to chromosome band 2q23 and in an African-American family on chromosome band 7p11, both with logarithm of the odds scores greater than 3 (Marneros et al., 2004) (Table 1). The *TNFAIP6* gene at chromosome band 2q23 and the *EGFR* gene at chromosome band 7p11 were proposed to be candidate genes within these respective loci. A separate study on a Chinese family did not show linkage to chromosome band 7p11, suggesting that there may be locus heterogeneity with regard to familial keloids (Chen et al., 2006). Two possible susceptibility loci identified in Chinese Han pedigrees were on chromosome bands 10q21.21 and 18q21 (Chen et al., 2007; Yan X. et al., 2007). With the latter locus, several *SMAD* genes and the *PIAS2* gene were proposed to be candidates. Further research is needed to determine whether these genes are indeed susceptibility genes for keloid formation.

With regard to syndromes, the one most commonly associated with keloids is Rubinstein-Taybi syndrome, due to autosomal dominant mutations in *CREBBP* or *EP300*. Patients with this syndrome have broad thumbs and toes, facial dysmorphism, and an increased prevalence of keloids (up to 33%) (Siraganian et al., 1989). That *CREBBP* and *EP300* can function as either transcriptional coactivators or as histone acetyltransferases suggests that genetics, epigenetics, or both may be influencing keloid pathogenesis. The epigenetic influence is intriguing because recent evidence suggests that epigenetic alterations affect the wound-healing properties of cultured primary keloid fibroblasts (Russell et al., 2010). Other syndromes reported to have an association with keloids include Ehlers Danlos Type III, the X-linked Goeminne syndrome, and *FLNA* mutations leading to joint

[1]*Department of Dermatology, the University of Texas Southwestern Medical Center, Dallas, Texas, USA*

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Correspondence: Donald A. Glass II, Assistant Professor, Department of Dermatology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9069, USA. E-mail: donald.glass@utsouthwestern.edu

Abbreviations: HLA, human leukocyte antigen; SNP, single-nucleotide polymorphism

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Table 1. Summary of loci identified via linkage analysis[1]

Locus	LOD Score	Ethnicity	Suggested Gene of Interest within the Region	Reference
2q23	3.01	Japanese	*TNFAIP6*	Marneros et al., 2004
7p11	3.16	African American	*EGFR*	Marneros et al., 2004
7p11	<−2	Chinese	N/A	Chen et al., 2006
10q23.31	1.74	Chinese	N/A	Chen et al., 2007
15q22.31−q23	<−2	Chinese	N/A	Yan X et al., 2007
18q21.1	2.2	Chinese	*SMAD2, SMAD4, SMAD7, PIAS2*	Yan X et al., 2007

Abbreviations: LOD, logarithm of the odds; N/A, not applicable.
[1]This table includes the loci, LOD scores, ethnicities, and possible genes within the regions identified through linkage analyses of families with keloids.

contractures, keloids, large optic cup-to-disc ratio, and renal stones (Lah et al., 2016; Shih and Bayat, 2010).

From a population standpoint, two genome-wide association studies have identified four single-nucleotide polymorphisms (SNPs) across three loci that are associated with keloid formation. These three loci are found on chromosome bands 1q41, 3q22.3−23, and 15q21.3 (Nakashima et al., 2010, Zhu et al., 2013) (Table 2). Of the SNPs, only one of them is found within a gene: rs8032158 is found within the intron of the *NEDD4* gene (Nakashima et al., 2010). NEDD4 is an E3 ubiquitin ligase enzyme that targets proteins for ubiquitination, and NEDD4 is an essential protein for animal development and survival via the insulin-like growth factor−1 signaling pathway (Cao et al., 2008). In contrast to Asian ancestry, admixture mapping performed on an African American cohort identified SNPs within the *MYO1E* gene, which is near *NEDD4* on chromosome bands 15q21.2−22.3, as being associated with keloid occurrence (Velez Edwards et al., 2014) (see Table 3). When this region was excluded from their analysis, the researchers also found an association on chromosome band 11q13 with the *MYO7A* gene. These two myosin genes suggest that alterations in the cytoskeleton affect keloid pathogenesis, potentially via enhanced invasive or migratory properties. In all of these instances, the manner in which these SNPs and putative genes influence keloid susceptibility remains to be elucidated.

Transforming growth factor beta (TGF-β) plays a critical role in many fibrotic diseases including keloids. Keloid fibroblasts have increased levels of TGF-β1 and TGF-β2, decreased TGF-β3 levels, and an increase in the ratio of the TGF-β1/TGF-β2 receptors compared with normal fibroblasts (Bock et al., 2005). However, studies to date have not identified any mutations or polymorphisms that are associated with keloids in any of the aforementioned *TGFB* genes, nor in the downstream signaling molecules *SMAD3, SMAD6,* and *SMAD7* (Bayat et al., 2002, 2003, 2004, 2005b; Brown et al., 2008a). This suggests that there are either upstream genes affecting *TGFB* genes and/or long-range enhancers/repressor variants of the components of the TGF-β pathway that thereby regulate the expression of the *TGFB* genes in keloids.

Because the tumor suppressor p53 plays a critical role in cell proliferation and apoptosis, its potential dysregulation in keloid pathogenesis has been studied. However, the role of the TP53 gene, and in particular the codon 72 polymorphism, remains unclear. One study found TP53 gene mutations in seven out of seven keloid tissue biopsy samples but none in normal tissue or buccal swabs obtained from the same patients (Saed et al., 1998). Although some studies have shown an association between the TP53 codon 72 polymorphism and keloids (Zhuo et al., 2005a; Zhuo et al., 2005b), others have not made similar observations (Yan L. et al., 2007).

Inflammation plays an important role in wound healing, implicating the immune system, and its potential dysregulation, in keloid pathogenesis. Two major studies have addressed human leukocyte antigen (HLA) polymorphisms in the setting of keloids. One, looking at *HLA-DRB1* alleles in a Northern European white cohort, found a positive association with keloids and *HLA-DRB1*15* (Brown et al., 2008b). The other, which analyzed *HLA-DQA1* and *HLA-DQB1* in Chinese Hans, found a positive association of *HLA-DQA1*0104, DQB1*0501,* and *DQB1*0503* and a negative

Table 2. SNPs associated with keloids from GWAS[1]

					Japanese[2]			Chinese Han[3]		
SNP	Chr	Gene	Normal Allele	Risk Allele	*P*	OR	95% CI	*P*	OR	95% CI
rs873549	1q41	none	T	C	5.89×10^{-23}	1.77	1.58−1.99	3.03×10^{-33}	2.05	1.82−2.31
rs1442440	1q41	none	A	G	—	—	—	9.85×10^{-18}	0.56	0.49−0.64
rs1511412	3q23	*LOC389151 FOXL2*	G	A	2.13×10^{-13}	1.87	1.58−2.21	0.01596	1.9	1.12−3.24
rs940187	3q23	none	C	T	1.80×10^{-13}	1.98	1.65−2.39	0.01291	1.48	1.08−2.02
rs8032158	15q21.3	*NEDD4*	T	C	5.96×10^{-13}	1.51	1.35−1.69	—	—	—
rs2271289	15q21.3	*NEDD4*	C	T	—	—	—	1.02×10^{-11}	0.66	0.58−0.74

Abbreviations: A, adenine; C, cytosine; Chr, chromosome band; CI, confidence interval; G, guanine; GWAS, genome-wide association study; OR, odds ratio; *P*, p-value; SNP, single-nucleotide polymorphism; T, thymine.
[1]This table lists the SNPs with the highest association from keloid genome-wide association studies performed in Japanese and Chinese Han populations.
[2]From Nakashima et al., 2010.
[3]From Zhu et al., 2013.