The Epidemiology of Keloids

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Take-Home Messages

- Despite the fact that keloids are common throughout the world, their epidemiology has not been adequately investigated.
- The demographic distribution of keloids, mainly on the geographical regions and ethnic racies.
- Genetic risk factors can shape keloid rates, in particular certain diseases appear to amplify or suppress keloid formations.
- Environmental factors also contribute to keloid development and progression and therefore shape keloid rates, such as local mechanical stimuli.

4.1 Background

Keloids are pathological scars that are characterized histologically by an overwhelming aggregation of fibroblasts and collagen type I within the inflammatory reticular dermis [1]. Their clinical characteristics include continuous growth and invasion into the neighboring healthy skin beyond the original wound boundary via an erythematous and pruritic leading edge. They also show a strong tendency to recur when they are surgically excised in the absence of adjuvant therapies. Despite the fact that keloids are common throughout the world, their epidemiology has not been adequately investigated.

In this chapter, we will summarize the limited epidemiological data on keloids that exists to date. Most of these data are from English language papers that are listed in PubMed. Below, we will describe what is known about (1) the demographic distribution of keloids, mainly on the geographical regions and ethnic races; (2) the internal genetic factors that shape keloid rates; and (3) the external environmental factors that influence keloid epidemiology. The aim of the chapter is to facilitate a greater understanding of the complexity and diversity of keloids from an epidemiological perspective, thereby potentiating further and deeper explorations into individualized strategies that prevent and treat keloids.

4.2 Demographic Risk Factors That Shape Keloid Rates

The studies on the demographic distribution of keloids in the world are sparse and occasionally contradictory. However, keloid rates can be affected by geography and ethnicity.

In terms of geographical distribution, it has long been cited that the incidence of keloids ranges widely from 0.09% in England to 16% in Zaire [2, 3]. While these reviews did not indicate how these incidences were determined, they are somewhat supported by the few large-scale studies on geographical incidence that have been performed. One of these was a review of the 5735 patients who underwent surgery in the 33 surgical facilities in Zambia between 1993 and 2008: the study showed that of the 5774 surgical diagnoses, 514 are related to keloids. Thus, keloids accounted for nearly 9% of all those surgical cases in Zambia during the study period [4]. Moreover in Kenya, the keloid prevalence is 8.5% among people with normally pigmented skins [5]. By contrast, the keloid incidence in Japan is around 0.1% [6] (Table 4.1). Considering that the keloid incidence data is limited and scattered, which can hardly be comparable in a strictly defined background covering key factors such as statistical period/cycle, population size/composition, and diagnostic criteria on scar type/severity, it is still difficult to depict an accurate keloid distribution map at this time. And the average keloid incidence can only be estimated as 5–10% in African, 0–0.1% in Asian, and <0.1% in other countries, as seen in Fig. 4.1.

Table 4.1 The incidences of keloid reported in different countries

Country	Keloid incidence (%)	Reference
England	0.09%	[2, 3]
Japan	0.10%	[6]
Kenya	8.50%	[5]
Zambia	9%	[4]
Zaire	16%	[2, 3]

It is suspected that this large geographical variation in keloid rate may reflect racial differences in skin pigmentation (Fig. 4.2). However, the data on keloid prevalence in various races is conflicting. First, Louw states that both Blacks and Asians are more susceptible to keloid formation than Caucasians [3]. Indeed, the Black/Caucasian ratio was reported varying from 14:1 to 2:1 [7]. However, the above reports may suggest that Asians could have similarly low incidences of keloid as Caucasians (0.1% in Japan versus 0.09% in England) [2, 3, 6]. Two studies also suggest that at least one specific type of keloid, acne keloidalis nuchae (AKN), is much more common in Blacks than in Asians. Na et al. showed that of 254,785 patients who attended the dermatology department of a Korean hospital in 2005–2017, 17 had AKN (0.007%) [8]. By contrast, another study showed that of 13,422 new patients who visited a large university hospital in Benin in 1993–2002, 0.7% (90 cases) had AKN, and the prevalence was reported as 0.37% (90

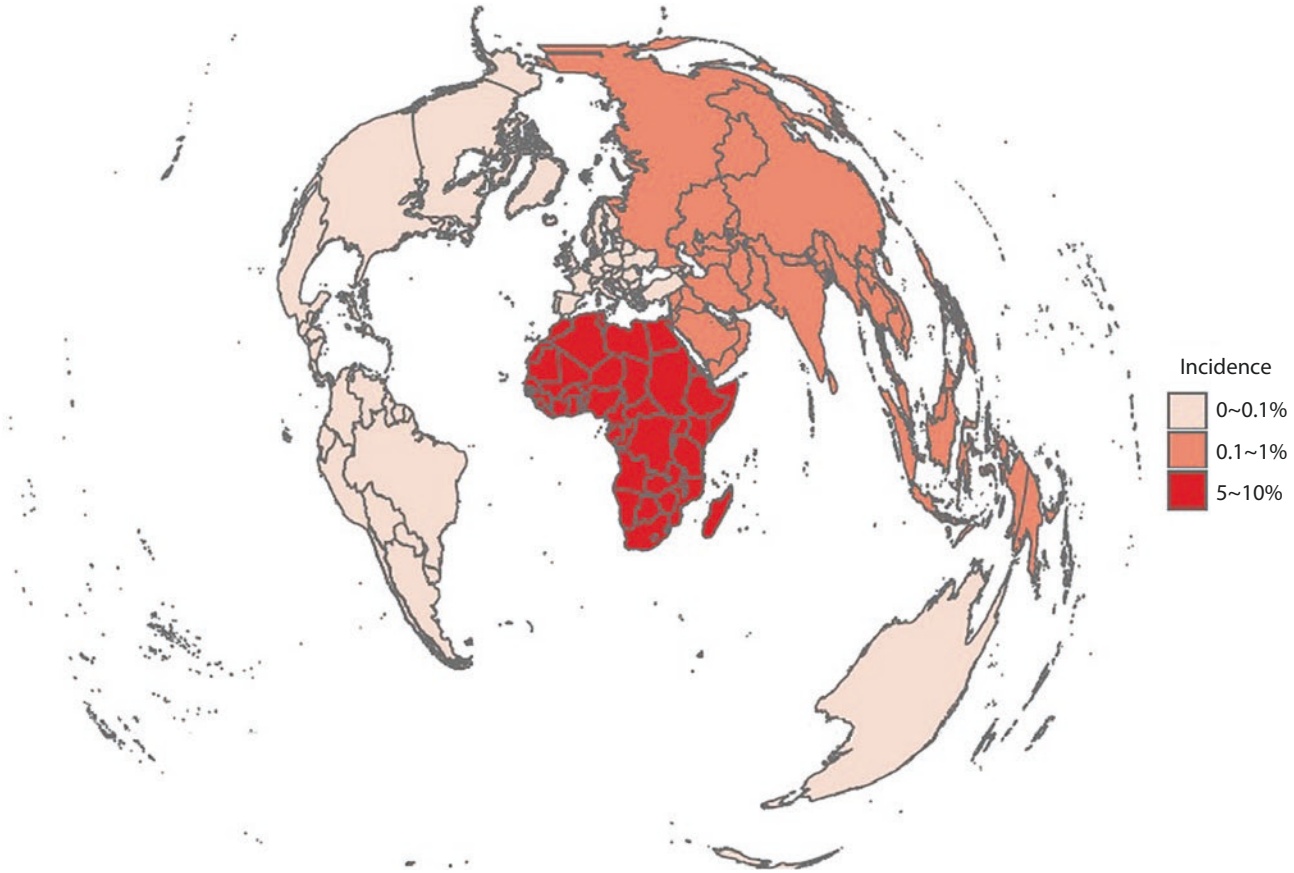

Fig. 4.1 Heatmap of keloid epidemiology in the world. The average keloid incidence can only be estimated as 5–10% in African, 0–0.1% in Asian, and <0.1% in other countries

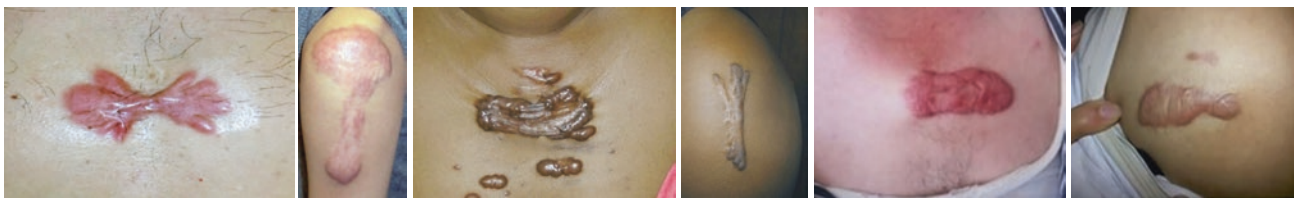

Fig. 4.2 Chest and shoulder keloids in different racial groups of Asians, Africans, and Caucasians. 4.2.1 The images are from Huang et al. with permission (Huang et al. [11]). 4. 2.2 The images are from Bayat et al. with permission (Bayat et al. [12]). 4. 2.3 The images are from Shaheen et al. with permission (Shaheen et al. [13]. © All rights reserved)

cases out of 26,522 patients overall) [9]. The latter study is supported by several other studies that show that AKN is common in Blacks. For example, as high as 4.7% of Black boys in the last year of high school in South Africa can develop AKN [10]. Moreover, the postulated relationship between high skin pigmentation and greater susceptibility to keloid formation is not borne out by two studies. One is a cross-sectional study on randomly selected villages in Kenya and people with albinism who were recruited via an albino association in Kenya and dermatology training center clinics and special schools in Tanzania. Of the 1416 African people who were recruited, 1185 had normally pigmented skin, and 231 had albinism. And 954 among the 1416 people have scars on their body. For them, the total prevalence of keloid was 8.3%. The subjects with normal pigmentation did not differ significantly from the subjects with albinism in terms of keloid prevalence (8.5% versus 7.8%; $P = 0.599$) [5]. The second study described the 175 keloid patients who visited the General Hospital in Kuala Lumpur in West Malaysia in 1959–1967. West Malaysia has a multiracial population. An analysis of

the ethnicities of the keloid patient cohort showed that keloid was more common in the relatively fair-skinned Chinese: while 56% of the keloid patients were Chinese, this ethnicity accounted for only 47.47% of the population. By contrast, 22.86% and 17.14% of the keloid patients were darker-skinned Indians and Malays, respectively; these ethnicities accounted for 19.52% and 29.58% of the population, respectively [7].

4.3 Genetic Risk Factors That Shape Keloid Rates

The effect of ethnicity on keloidogenesis suggests that keloid formation is somewhat underpinned by genetic variation. This is borne out by multiple genetic studies that show that keloidogenesis associates with certain gene mutations or polymorphism [14]. Keloids also show a familial tendency [15]. Here, we will discuss less well-known genetic associations with keloids, namely, certain diseases that appear to amplify or, conversely, suppress keloid rates.

The diseases that associate with an increased risk of keloid include the Rubinstein-Taybi syndrome (RSTS), the Ehlers-Danlos syndrome, the Lowe syndrome, and the novel X-linked syndrome, and others (Table 4.2). RSTS is also called broad thumb-hallux syndrome. It is characterized by broad thumbs and toes, facial abnormalities, and short stature [16]. The etiological mutation lies in gene encoding the cyclic AMP response element-binding protein (CBP) on chromosome 16p13.3 [17] and E1A-binding protein (EP300) gene which encodes p300 protein (a cAMP response element-binding protein homologue) [18]. Keloid is reported to occur in 24% (15/62) of RSTS patients, either spontaneously or secondary to minor trauma [19]. The Ehlers-Danlos syndrome type IV (the vascular subtype) is an inherited disorder of connective tissue that is characterized by acrogeria, translucent skin, propensity to bruising, and significant arterial, digestive, and uterine complications [20]. The causative mutation is in COL3A1 gene, which encodes the pro-α1(III) chain of collagen type III [21]. Several case reports show that this syndrome can paradoxically associate with extensive keloid formation [22]. The Lowe syndrome (also called the oculocerebrorenal syndrome of Lowe [OCRL]) affects the eyes, nervous system, and kidneys [23]. It is caused by a mutation in the OCRL gene that reduces the amount of the OCRL-1 protein [24]. The formation of corneal keloids in patients with Lowe syndrome is relatively common. It is generally provoked by corneal contact lens use or after intraocular lens implantation [25]. Novel X-linked syndrome is characterized by symptoms of cardiac valvular disease, spontaneous keloid scarring, and reduced joint mobility. The causal mutation is filamin A (FLNA) substitution G1576R [26]. Other syndromes that may associate with spontaneous keloid formation include the Dubowitz syndrome [27], the Noonan syndrome [28], and the Goeminne syndrome [29], which are inherited in autosomal recessive, autosomal dominant, and sex-linked incomplete dominant ways, respectively, though the actual gene mutation remained unclear.

The diseases that associate with protection from severe pathological scarring are Hansen's disease and von Recklinghausen's disease. Hansen's disease (also known as leprosy) is a chronic disease that arises after infection with *Mycobacterium leprae* and *Mycobacterium lepromatosis*. It is characterized by granulomas of the nerves, respiratory tract, skin, and eyes and the gradual destruction of the intraepidermal innervation. Extensive scarring is extremely rare in patients with Hansen's disease [30, 31]. von Recklinghausen's disease is also known as neurofibromatosis type I (NF-I). It is characterized by the growth of tumors on the nerves. A study of 30 Nigerian patients with neurofibromatosis who underwent surgery showed that none of them developed keloid or hypertrophic scars after surgery, even though their wound healing was poor and some of their wounds were closed under tension [32]. Similarly, a worldwide multicenter study on 57 patients with von Recklinghausen's disease showed that none of the patients developed hypertrophic scar or keloid after surgery: in general, their wounds healed remarkably well. The main complications were the development of hematoma and wide white scar in six patients. By contrast, two of the 35 patients with a solitary neurofibroma who were included in the study developed hypertrophic scars after surgery [33].

4.4 Environmental Risk Factors That Shape Keloid Rates

Environmental factors also contribute to keloid development and progression and therefore shape keloid rates. One such factor is local mechanical stimulus. An interesting feature of keloids is that they show a distinct site specificity. When we analyzed 1500 keloids in 483 Japanese patients (the keloids generated from artificially created wounds, namely, those created by surgery and piercing, were excluded), we found they tended to occur on the anterior chest region (48.9%), scapular regions (26.9%), lower jaw/neck region (12.1%), upper arm (4.8%), dorsal regions (2.5%), lower abdomen (1.9%), femoral regions (1.7%), knee (0.5%) and upper abdomen (0.5%) [34]. All of these regions are characterized by high skin tension/friction. That skin tension promotes keloid development is also shown by the fact

Table 4.2 The syndromes associated with keloidogenesis

Syndrome	Other names	Characteristic features	Keloid lesions	Genes or inheritance concerned	Reference
Rubinstein-Taybi syndrome (RSTS)	Broad thumb-hallux syndrome	Broad thumbs and toes, facial abnormalities, short stature	24%	CBP on chromosome 16p13.3; EP300	[16–19]
Ehlers-Danlos syndrome type IV (vascular type)		Acrogeria, translucent skin, propensity to bruising, and significant arterial, digestive, and uterine complications	Extensive keloid formation	COL3A1 gene that encodes the pro-α1(III) chain of collagen type III	[20–22]
Lowe syndrome	Oculocerebrorenal syndrome of Lowe (OCRL)	Affects the eyes, nervous system, and kidneys	Corneal keloids	OCRL gene that reduces the amount of the OCRL-1 protein	[23–25]
Novel X-linked syndrome		Cardiac valvular disease, spontaneous keloid scarring, and reduced joint mobility	Spontaneous keloid scarring	A G1576R mutation in filamin A (FLNA)	[26]
Dubowitz syndrome		Intrauterine growth retardation, low neonatal weight, short stature, characteristic facies, atopic dermatitis, and mental retardation	Spontaneous keloidal lesions	Autosomal recessive transmission	[27]
Noonan syndrome		Craniofacial appearance, congenital cardiac defects, orthopedic abnormalities, psychomotor and growth retardation, and some skin changes including keloidal tissue formation	Keloidal tissue formation	Autosomal dominant inheritance	[28]
Goeminne syndrome		Congenital muscular torticollis, multiple keloids, cryptorchidism, and renal dysplasia	Multiple spontaneous keloids	Sex-linked incomplete dominant inheritance	[29]

that the keloids on certain regions grow into specific shapes. Thus, anterior chest keloids form symmetrical butterfly shapes that reflect the predominant stretching directions of the chest skin that are caused by the upper arm movements. By contrast, keloids on the scapula form dumbbell shapes that run down the long axis of the arm and are caused by the skin stretching caused by the hanging upper arm. Moreover, earlobe keloids often grow into balls that reflect the circular nocturnal friction on the earlobe from the head moving on the pillow [34]. This role of mechanical tension in keloid growth is further supported by the recent case of a patient in our center whose symmetrically distributed butterfly keloid on the chest was accidentally split in half at the midline. The patient was right-handed. In the subsequent 2 years, the right half butterfly of the keloid continued to progress as usual. By contrast, the left half butterfly grew much less strongly and indeed exhibited signs of amelioration [11].

4.5 Conclusion

Regardless of whether keloids occur spontaneously or after trauma, these lesions are clearly the result of both internal genetic and external environmental factors. These factors underlie the association between keloids and various demographic risk factors, namely, geographical region and ethnicity. However, our understanding of these demographic factors is limited by the paucity of and inconsistencies in the epidemiological research on keloids. To identify the respective contributions of genetic and environment factors to keloid formation, it will be necessary to conduct large-scale investigations with specific study designs, such as studies on twin cohorts or cross-sectional studies on the members of families that show a predilection toward keloidogenesis. Such explorations will help to orient further keloid research, thereby aiding the development of effective therapeutic approaches.

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