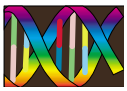
OBSERVATION

Clinical Genetics of Familial Keloids



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Background: Keloids are proliferative fibrous growths that result from an excessive tissue response to skin trauma. Most keloids occur sporadically, but some cases are familial. However, the genetics of keloid formation have only rarely been documented, and the mode of inheritance is not known.

Objective: To elucidate the clinical genetic characteristics of keloid wound-healing disorder.

Observations: We studied the clinical and genetic characteristics of 14 pedigrees with familial keloids. The ethnicity of these families is mostly African American (n=10), but also white (n=1), Japanese (n=2), and African Caribbean (n=1). The pedigrees account for 341 family members, of whom 96 displayed keloids. Of the affected family members, 36 are male and 60 are female. The age of onset varies from early childhood to late adulthood. There is variable expression of keloids within the same families: some affected members have only minor earlobe keloids, whereas others have very severe keloids affecting large areas of the body. In the described pedigrees, 7 individuals are obligate unaffected carriers, revealing nonpenetrance in about 6.8% of keloid gene carriers. Syndromes associated with keloids, namely Rubinstein-Taybi and Goeminne syndrome, were not found in these families. Additionally, linkage to the gene loci of these syndromes and X-chromosomal linkage were excluded.

Conclusions: The pattern of inheritance observed in these families is consistent with an autosomal dominant mode with incomplete clinical penetrance and variable expression. This is the most comprehensive collection of keloid families described to date, and it allows for the first time the elucidation of the clinical genetic characteristics of the familial form of this wound-healing disorder.

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KELOIDS ARE proliferative fibrous growths that result from an excessive tissue response to skin trauma. Keloids frequently persist at the site of injury, often recur after excision,[1] and always overgrow the boundaries of the original wound manifested by invasion of clinically normal skin.[2]

Most keloids occur sporadically, but some keloid cases are familial. A hereditary component in keloid etiology has been considered, mainly based on the higher occurrence in darker-skinned races. A difference in occurrence based on sex has not been demonstrated convincingly. Although some epidemiological studies have shown that more keloid patients are female,[3] this might well be explained by greater cosmetic concerns about keloids in female individuals than in male, and by the greater frequency of ear piercing in females. In fact, other studies show equal incidence of keloids in male and female subjects.[4-6]

The genetic characteristics of keloid formation have only rarely been documented. Omo-Dare[6] proposes an autosomal recessive inheritance pattern based on a collection of small pedigrees, whereas Bloom[7] suggests an autosomal dominant inheritance pattern, mainly based on an Italian family whose pedigree spanned 5 generations, to our knowledge the only reported large pedigree of a family with keloids to date. Most previous genetic keloid studies, however, are based on small families. This makes it difficult to elucidate the clinical genetic characteristics, and leads to inconclusive results. Thus, the mode of inheritance is not known.

For this study, we observed 14 pedigrees with familial keloids. All of the pedigrees presented here span at least 3 generations, some even 5 generations. This is the most comprehensive collection of keloid families described to date, and it allows for the first time the elucidation of the clinical genetic characteristics of the familial form of this wound-healing disorder.

PATIENTS AND METHODS

For this study, affected and unaffected family members were carefully examined by dermatologists or plastic surgeons with substantial clinical experience treating keloids. The diagnosis was made clinically, based on the criterion that the scar extended beyond the boundaries of the original injury. Sites of keloid formation were documented by photography. Detailed inquiry was made into the family history, and information was collected about deceased or unavailable individuals. This study was approved by all institutional review boards. All family members who were interviewed and examined signed an informed consent to participate in the study.

To investigate the mode of inheritance, pedigree charts were constructed from the obtained data. Pedigree members were classified as keloid former (affected) or nonkeloid former (unaffected). Unaffected children and adolescents were included in the pedigrees, but were not considered in the analysis of the inheritance pattern because they might clinically express keloids as they age. Unaffected family members with an affected parent and at least 1 affected child were regarded as obligate carriers.

In some cases, histological specimens from keloids of affected family members were obtained. Here, the clinical diagnosis was confirmed histologically, using standard hematoxylin-eosin staining procedures. Keloids contain large, thick collagen fibers composed of numerous fibrils closely packed together. The collagen fibers in keloids appear thicker and more irregular than in normal dermis (**Figure 1**). We collected venous blood samples, extracted genomic DNA, and performed linkage analysis as previously described.[8]

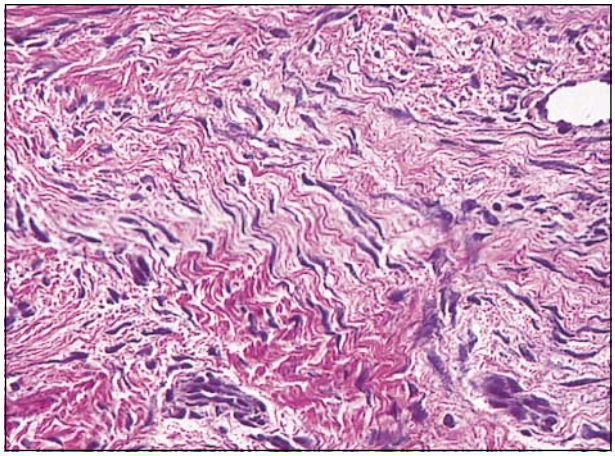

Figure 1. Collagen fibers in keloids appear thicker and more irregular than in normal dermis. Histological specimen from a keloid of a member of family 5 (hematoxylin-eosin, original magnification ×100).

RESULTS

CLINICAL GENETIC CHARACTERISTICS

We here describe 14 pedigrees with familial keloids. The ethnicity of these families is mostly African American (n=10), but also white (n=1), Japanese (n=2), and African Caribbean (n=1). The pedigrees account for 341 family members, of whom 96 display keloids. Of the affected family members, 36 are male and 60 are female. In the described pedigrees, 7 individuals are obligate unaffected carriers, revealing nonpenetrance in about 6.8% of keloid gene carriers. Seven pedigrees span 3 generations; five span 4 generations; and two, 5 generations (**Table**). Syndromes associated with keloids, namely, Rubinstein-Taybi (*Online Mendelian Inheritance in Man* [OMIM] No. 180849) and Goeminne syndrome (OMIM No. 314300), were not found in these families. Additionally, linkage to the gene loci of these syndromes and X-chromosomal linkage were excluded.

DESCRIPTION OF SELECTED PEDIGREES

Family 5

This family is of African American ethnicity and accounts for 13 affected members and 2 obligate carriers (**Figure 2**A). Most of the affected family members presented with multiple keloids, affecting commonly the chest and shoulder areas. Three affected members showed particularly large keloids at several sites, whereas the others had only punctate small keloids. For some affected individuals, minor trauma (eg, chickenpox vaccination) led to keloid formation, whereas for others only major wounds (eg, hysterectomy) resulted in keloids. This 4-generation pedigree reflects, as do the other presented pedigrees, the characteristics of an autosomal dominant mode of inheritance with reduced penetrance.

Family 8

This is an African-American 5-generation family with 3 obligate unaffected carriers. Individual II:2 is considered a carrier (Figure 2B). His son (III:11) might have inherited the keloid gene mutation from him or from his affected mother or from both. It is possible that this family shows keloids based on 2 different mutations. This may even represent locus heterogeneity within a single large pedigree. Such possibilities will have to be addressed once the first keloid gene mutation has been discovered in this family. Keloids of family member V:5 might have evolved through a de novo mutation. Otherwise III:3 and IV:12 would be unaffected carriers of the keloid allele. Most of the affected individuals in this family have multiple keloids, but only 2 of them have large chest keloids.

Family 9

This African Caribbean family spans 5 generations, with 10 affected family members, and 1 obligate carrier, again demonstrating autosomal dominant inheritance (Figure 2C). The sizes and locations of the keloids also vary within this family.

Family 13

In this small family, 2 women are identical twins, and both display keloids. We collected 3 further pedigrees (not shown), each having a set of identical twins. All twins

Characteristics of 14 Keloid Families With a Total of 341 Members, of Whom 96 Are Affected and 7 Are Unaffected Carriers*

Family	No. of Generations	No. Affected	Unaffected Carrier	Affected, M:F	Ethnicity	Total No.	Family Members, M:F
1	3	6	1	3:3	African American	32	(15:17)
2	3	3	0	1:2	Japanese	9	(4:5)
3	4	3	0	0:3	Japanese	15	(6:9)
4	3	3	0	1:2	White	15	(8:7)
5	4	13	2	5:8	African American	78	(41:37)
6	3	3	0	2:1	African American	11	(6:5)
7	4	7	0	0:7	African American	10	(3:7)
8	5	10	3	5:5	African American	66	(32:34)
9	5	10	1	3:7	African Caribbean	37	(19:18)
10	3	6	0	4:2	African American	10	(7:3)
11	4	5	0	2:3	African American	11	(6:5)
12	3	6	0	3:3	African American	10	(5:5)
13	3	5	0	1:4	African American	7	(3:4)
14	4	16	0	6:10	African American	30	(11:19)
Total	. . .	**96**	**7**	**36:60**	. . .	**341**	**(166:175)**

*Ellipses indicate not applicable.

developed keloids, in support of a dominant genetic component for keloid formation.

COMMENT

EPIDEMIOLOGY

If a trait is common in a population, there is a high chance that it may be brought into the pedigree independently by 2 or more people. Thus, the classic pedigree patterns are best seen with rare traits. Keloids are common as a sporadic condition, but not as a familial disorder. There are no completely satisfactory epidemiological data about the occurrence of familial keloids.

In a study of 1000 patients with keloids in South India,[4] 19 families had multiple affected members. In another study of 247 keloid patients, only 8 (3.2%) had a family history of keloids.[3] Jacobson[9] reported familial occurrence in 21 keloid cases (3.4%) in a study of 625 individuals; however, patients were not always specifically asked about inheritance of keloid formation. Interestingly, he noted a pair of twins who were vaccinated for smallpox and developed keloids at the same time.

The epidemiology of keloids in general is variable. The reported incidence of keloids in the general population ranges from a high of 16% among the adults in Zaire to a low of 0.09% in England.[7] It is widely accepted that darker-skinned populations have a higher incidence of keloid formation than lighter-skinned populations, but the reported incidence ratio between the 2 groups ranges from 2:1 to 19:1.[10] Most of the families in this study were of African American ethnicity, supporting a higher incidence of keloid formation in darker-skinned than in lighter-skinned populations. This might, however, be a result of different ethnicity rather than different skin color, since some of the lighter-skinned members of these African American families developed more severe keloids than their darker-skinned relatives. The varying epidemiological data might be explained in part by the many factors influencing keloid formation, such as ethnicity, age, anatomic location, and type of trauma.

FAMILIAL KELOIDS IN RARE SYNDROMES

Familial keloids have been reported as a clinical feature in rare syndromes, namely, Rubinstein-Taybi syndrome (OMIM No. 180849) and Goeminne syndrome (OMIM No. 314300). Rubinstein-Taybi syndrome is caused by mutations in the gene encoding the transcriptional coactivator CREB-binding protein (*CBP*) on 16p13.3. Affected individuals display mainly broad thumbs and toes, a characteristic facies, and mental retardation. Several reports indicate an increased frequency of keloids in individuals with Rubinstein-Taybi syndrome.[11-16] Goeminne[17] described an X-linked trait in affected individuals presenting with torticollis, keloids, cryptorchidism, and renal dysplasia. The gene locus has been assigned to Xq28.[18] Clinical examination excluded these syndromes for members of the families described here. We further investigated if the gene loci for these syndromes coincided with a potential gene locus for the keloid pedigrees. Extensive linkage analysis using microsatellite markers localized on 16p13 showed no significant linkage of these pedigrees to the Rubinstein-Taybi syndrome locus (data not shown). Genotyping with X-chromosomal markers at a 10-cM (centimorgan) spacing excluded significant linkage of the keloid pedigrees to the X-chromosome as well, and hence to the Goeminne locus on Xq28 (data not shown). Thus, the familial keloids described here do not occur as part of one of these syndromes. This indicates that gene mutations can predispose specifically to keloids without causing further clinical features.

NONPENETRANCE

Nonpenetrance commonly occurs with dominant conditions. We regarded unaffected family members with an affected parent and at least 1 affected child as obligate carriers. However, affected children of unaffected parents could

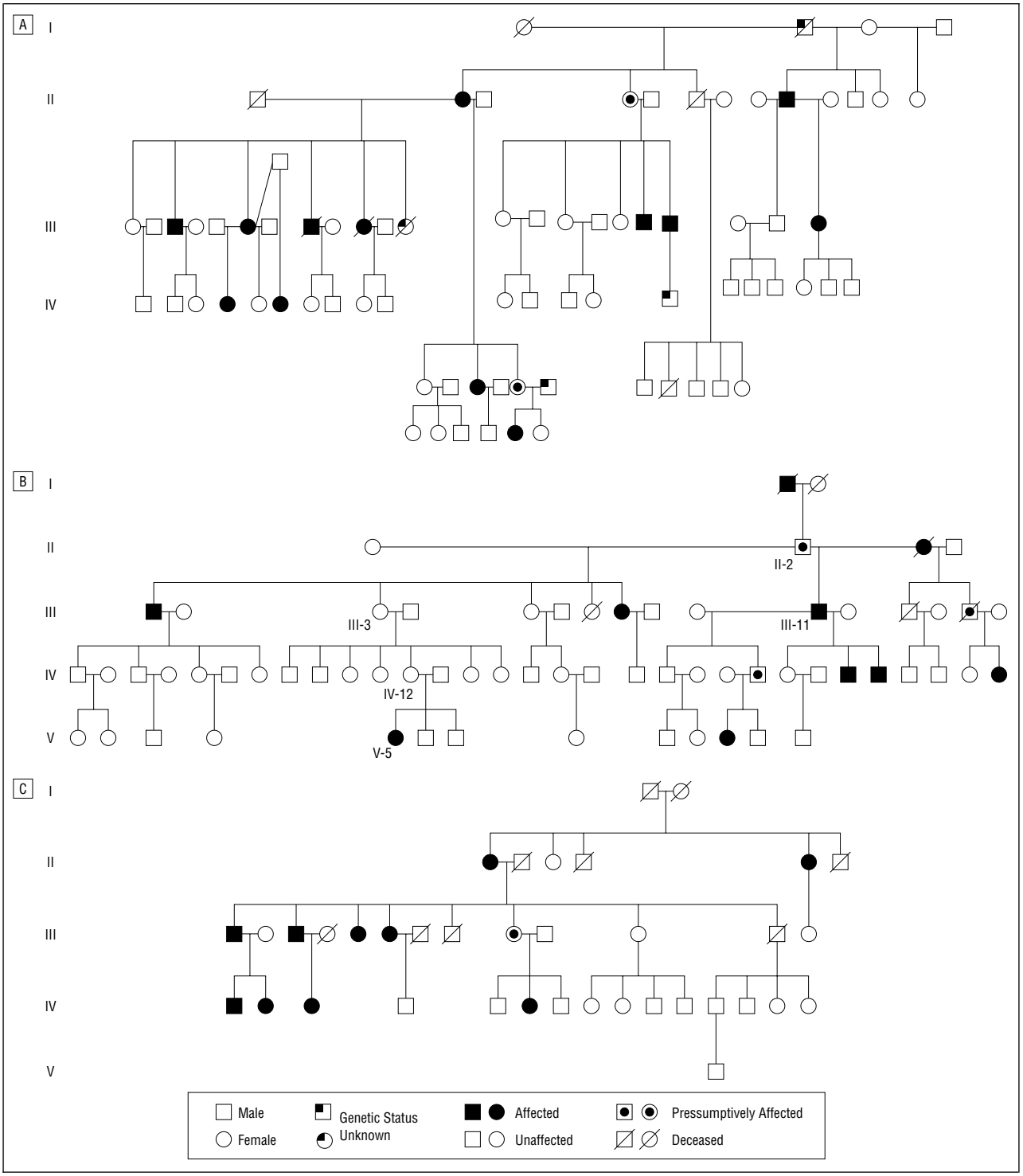

Figure 2. These selected pedigrees of keloid families 5 (A), 8 (B), and 9 (C) demonstrate an autosomal dominant mode of inheritance with incomplete clinical penetrance.

in our families represent de novo mutations, especially since sporadic keloids seem to occur with a high incidence in the African American population. In 2 instances the fathers of affected children from unaffected mothers (marked as obligate carriers) were not available for examination. In these cases, we cannot entirely exclude the possibility that a keloid-causing mutation had been passed on by the fathers. We describe 7 of the family members as obligate unaffected carriers, and 96 as affected individuals, demonstrating that nonpenetrance accounts for about 6.8% of keloid gene carriers in these families.

AGE OF ONSET OF DISEASE

The penetrance for keloid formation is age related. There are different hypotheses for this delayed onset. Some fo-

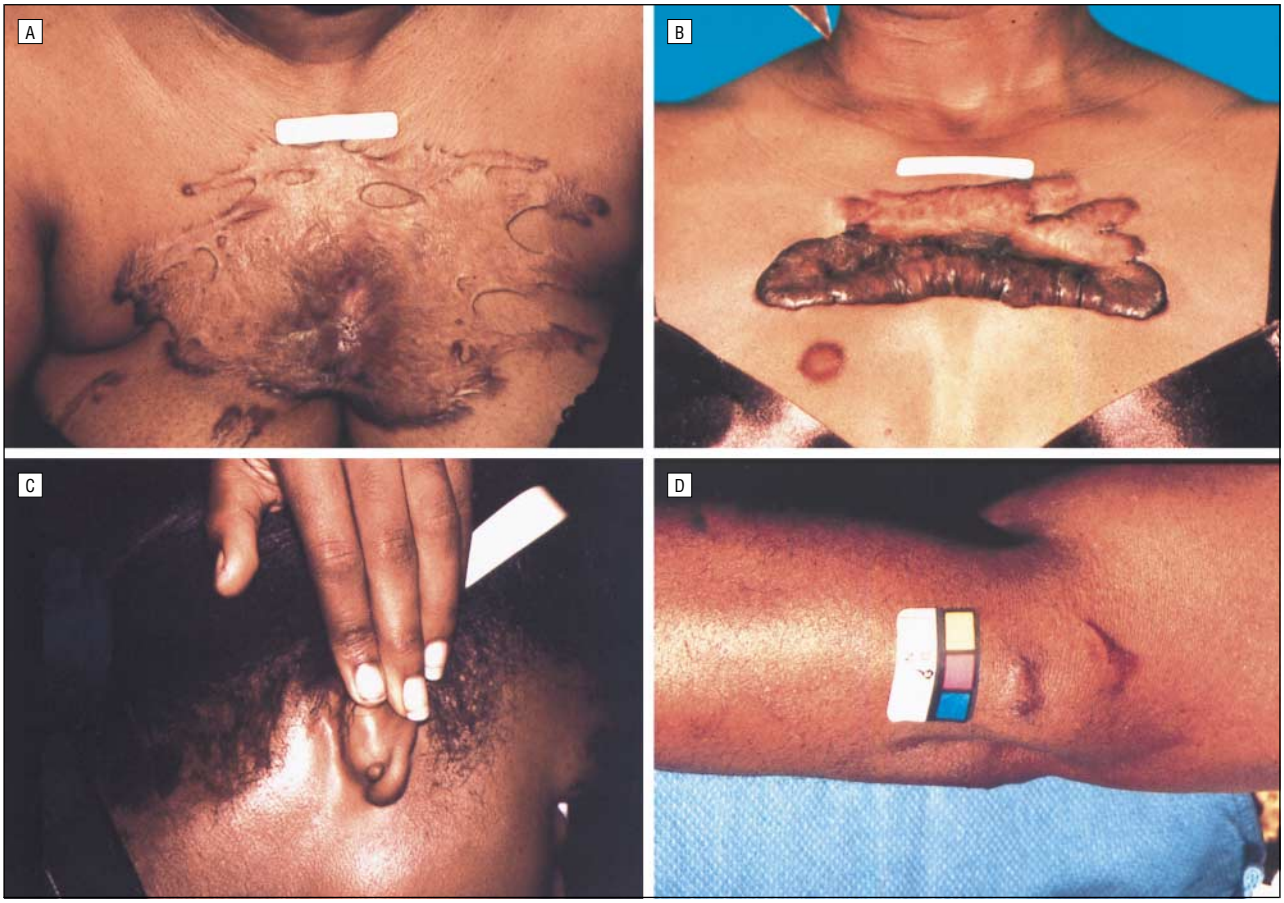

Figure 3. The clinical severity of keloid formation differs within a family. We frequently found variation in severity ranging from mild keloids to severe keloids affecting large areas of the body. A, Large chest keloid on a member of family 5; B, large upper chest keloid on a member of family 8; C, small earlobe keloid on a member of family 5; and D, small arm keloids on a member of family 8.

cus on the influence of hormones on keloid formation. Such hypotheses are based on the observation that keloids occur commonly between ages 10 and 30 years, at which time plasma levels of growth hormone and insulinlike growth factor 1 (IGF-1) are also high. The involvement of the activated IGF-1/IGF-1 receptor axis in the pathogenesis of the invasive activity of fibroblasts has previously been suggested,[19,20] and increased androgen binding in keloids has been demonstrated.[21,22]

Another hypothesis suggests that further mutations, in addition to the inherited predisposition, are required for the formation of keloids. Somatic mutations in the tumor suppressor p53, for instance, have been identified in sporadic keloids.[23] This implies that the inherited predisposition for keloids might also contribute to the formation of malignancies. Thus, we investigated if the families described in this study showed an increased frequency of malignancies, and if there was a pattern in their occurrence in keloid vs nonkeloid formers. Interestingly, malignancies were diagnosed only rarely. Some families had no cases of malignancies at all, even for their oldest members with keloids. In conclusion, no association between keloids and malignancies was found in these families.

Additional mutations and the influence of hormones might contribute to a delayed onset of keloid formation, but do not provide satisfactory explanations for keloid formation in early childhood. Thus, the reason for the delayed onset is not known.

Our pedigrees include a number of unaffected adolescents and children. Because they may express keloids later in life, they are not informative for determining the mode of inheritance. This makes it difficult to demonstrate that about 50% of children of one affected and one unaffected parent are indeed keloid gene carriers, as one would expect for an autosomal dominant condition. However, such a ratio can be calculated for the generation of the parents in the families presented here.

In the families, the age of onset varies from early childhood to adulthood. No familial pattern for the age of onset was observed.

VARIABLE EXPRESSION

Variable expression is frequently seen in dominant conditions. The reasons may be similar to those of nonpenetrance: other genes or environmental factors can have some influence on the progression of symptoms.

The clinical severity of keloid formation differs between families, as well as within a family. We frequently found the variation in severity to range from small earlobe keloids to severe keloids affecting large areas of the body (**Figure 3**). Some individuals within a single family developed keloids on a single site, whereas oth-

ers presented with multiple keloids affecting mainly the chest and shoulder region. Interestingly, individuals with very large keloids were seen only in the African American families.

It has previously been reported that some keloids form in response to very minor trauma, whereas others result from major wounds, often accompanied by inflammation. In this study, we made detailed inquiries into the cause of keloid formation in affected family members. Often only minor trauma or a "pimple" was noted to result in a keloid. Sometimes the patients did not know the cause of the keloid, which indicates a very minor causative trauma not even noticed by the individual. However, most of the keloids were described as being posttraumatic or surgical. A number of family members indicated that not all injuries resulted in keloids, but frequently led to regular scars. Notably, the degree of trauma leading to keloid formation differed within affected members of the same family. In conclusion, no distinct familial pattern for the cause of keloid formation was observed.

MODE OF INHERITANCE

The pattern of inheritance observed in these families is consistent with an autosomal dominant mode with incomplete clinical penetrance and variable expression. The trait affects and is transmitted by either sex. A child of an affected and unaffected parent has a 50% chance of being affected (assuming that the affected person is heterozygous). All these features can be observed in these pedigrees, most certainly in the large pedigrees of families 5, 8, and 9 (Figure 2). This suggests that single gene mutations can predispose specifically to keloids.

The high incidence of keloids in different populations, variable onset of disease, variable expression, and variable responses to different treatments suggest that more than 1 gene might be involved in keloid pathogenesis. These genes might be part of the same or of different pathways involved in proliferation or apoptosis. Possible locus heterogeneity represents an additional challenge to any efforts to identify keloid gene mutations, but the number of pedigrees described here and the size of some of them should make it possible to map several loci for keloids.

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