# Autosomal dominant inheritance of central centrifugal cicatricial alopecia in black South Africans

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***Background:*** Central centrifugal cicatricial alopecia (CCCA) is the commonest type of primary scarring alopecia in women of African descent. Little is currently known about the disease genetics.

***Objective:*** We sought to investigate patterns of inheritance in CCCA and ascertain the contribution of nongenetic factors such as hair-grooming habits to the pathogenesis of the disease.

***Methods:*** Affected individuals with at least 1 available family member were recruited from 2005 through 2012 inclusive for pedigree analysis. CCCA was diagnosed on clinical and histopathological grounds.

***Results:*** Fourteen index African families with 31 immediate family members participated in the initial screening. The female to male ratio was 29:2 with an average age of 50.4 years. All patients displayed histologic features typical for CCCA. Pedigree analysis suggested an autosomal dominant mode of inheritance. Hair-grooming habits were found to markedly influence disease expression.

***Limitations:*** Small number of patients is a limitation.

***Conclusion:*** CCCA can be inherited in an autosomal dominant fashion, with partial penetrance and a strong modifying effect of hairstyling and gender. (J Am Acad Dermatol 2014;70:679-82.)

***Key words:*** African; black; familial; follicular degeneration syndrome; genetic; hair loss; lymphocytic primary scarring alopecia; scarring alopecia; South Africa.

Primary scarring alopecia is a form of hair loss in which hair follicles are destroyed and replaced by fibrous tissue.[1] Central centrifugal cicatricial alopecia (CCCA) is the most common type of primary scarring alopecia in African American women,[2-5] and characteristically manifests with irreversible hair loss involving either the vertex or mid scalp that tends to progress symmetrically in a centrifugal pattern.[6]

*Abbreviations used:*

CCCA: central centrifugal cicatricial alopecia
CHLG: central hair loss grading
DM: diabetes mellitus

Histologic features include perifollicular lymphocytic infiltrate and fibroplasia,[7] which may be

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associated with perivascular lymphocytic infiltrate and premature disintegration of the inner root sheath.[6,8]

The majority of CCCA studies have been conducted with African American participants. A survey by the North American Hair Research Society was carried out in Cleveland, OH, and showed that 28% of 326 African American females had clinical evidence of CCCA.[9]

Although the prevalence of CCCA in black South Africans is unknown, a cross-sectional study conducted among 874 African adults recruited from 2 church groups, 1 community organization, and 2 male hostels in Cape Town, South Africa, found that 1.9% of this population had CCCA, all of whom were women.[10] In a recent 7-year retrospective survey of 6664 African patients seen in a predominantly black urban dermatology practice in Durban, South Africa, hair disorders in general and CCCA more specifically accounted for 5.2% and 0.4% of all skin conditions seen, respectively.[11]

The cause of CCCA remains elusive, with interaction between a genetic predisposition and hair-grooming techniques in women of African descent having been suggested.[6,12] Although considerable effort has been invested in characterizing incriminated hairstyling techniques, much less is known regarding the genetics of the disease. Supporting a predominant role for inherited factors in the pathogenesis of CCCA, independent of hair-grooming habits, is a recent report on 2 families with natural hair and with clinical and histologic evidence of CCCA.[13]

The pathomechanisms underlying hair follicle scarring in primary scarring alopecia, and more specifically in CCCA, are not well understood. Everts et al[14] have shown altered retinoid metabolism in human and mouse models with primary cicatricial alopecia, particularly CCCA. Karnik et al,[15] in a recent study of lichen planopilaris, proposed that abnormal function of the peroxisome proliferator–activated receptor gamma could possibly trigger inflammation, with resultant abnormal lipid metabolism within the sebaceous gland, resulting in a toxic accumulation of lipids with ensuing inflammatory response. Whether this mechanism applies to CCCA as well remains to be determined.

In this article, we report 14 index families with 31 immediate family members in Durban, South Africa, all of whom had a clinical and histologic diagnosis of CCCA and provide evidence for autosomal dominant inheritance of this condition.

**CAPSULE SUMMARY**

- Central centrifugal cicatricial alopecia is a lymphocytic cicatricial alopecia occurring commonly in women of African descent.
- Central centrifugal cicatricial alopecia is familial, and is inherited in a dominant fashion. It is triggered by certain hairstyles. Although it also occurs in black males, gender-related hair-grooming habits may explain the preponderance of female patients.
- Early detection and counseling of family members regarding hair-grooming approaches may arrest progression of alopecia.

## METHODS

### Patients

Ethical approval for the study was obtained from the Nelson R. Mandela School of Medicine Institutional Review Board (BE 180/11). All patients who presented with CCCA from 2005 through 2012 inclusive were recruited from both the private- and public-sector hospitals in Durban, South Africa. To be included in the study, patients had to fulfill published clinical criteria for CCCA diagnosis.[2,7,16] A general skin and hair examination by an experienced dermatologist familiar with ethnic hair was undertaken to exclude skin and scalp infection, traction alopecia, or acne.

We used a central hair loss grading (CHLG) score as previously described.[17] A CHLG of 0 was taken as normal hair thickness without discernible alopecia; a CHLG of 1 was given in the presence of slight alopecia and early CCCA without obvious effect on hair density; a CHLG of 2 was indicative of subtle clinical alopecia; and a CHLG of 3 to 5 corresponded to clinically obvious mild, moderate, and severe CCCA. In addition, patients needed to have a minimum of 1 affected family member available for examination of the scalp and who agreed to be subjected to a confirmatory scalp biopsy, to be included in the study. Immediate family members included the index patient's parents, siblings, and offspring. Written informed consent was obtained from all participants or their legal guardians. A detailed history of personal and family history of diabetes mellitus (DM), along with hair grooming and drug consumption, was obtained.

### Histopathology

Supportive evidence for CCCA was obtained through dermoscopic examination[18] and histopathological studies. Two dermoscope-guided 4-mm

punch scalp biopsies were performed for each individual with a clinical diagnosis of CCCA.

Scalp biopsy specimens were fixed in 10% buffered formalin and thereafter embedded in paraffin. Both horizontal and vertical sections were stained with hematoxylin-eosin for routine histopathological examination. All samples were reviewed by 1 dermatopathologist. The diagnosis of CCCA was established according to criteria previously published.[2,7,16] A numeric scoring system was devised to evaluate biopsy specimens for a diagnosis compatible with CCCA.

According to this system, 3 points were awarded for the presence of lichenoid lymphocytic folliculitis (lymphocytes surrounding follicles with exocytosis into follicular epithelium), 2 points for perifollicular lymphocytes (lymphocytes in the immediate vicinity of follicles but separated from the follicular epithelium), 1 point for perifollicular fibrosis (concentric fibrosis of variable thickness surrounding follicles), and 1 point for the presence of compound follicles (fused infundibula of follicles indicating disturbed follicular dynamics). A diagnosis of CCCA was considered likely with a score of 3 or more.

## RESULTS

### Clinical features

All patients were of African descent. There were 14 index African families with a total of 31 participating immediate family members, and the female to male ratio was 29:2. The average age was 50.4 years (range: 11-94) with 45% between age 30 and 50 years, whereas the average age of onset was 41 years (range: 11-75), with 48% being between age 30 and 50 years. All but 1 female had traction alopecia (28; 96.5%). This individual, aged 11 years, kept natural hairstyle only.

None of the participants had skin infections or a positive drug history; acne and DM were diagnosed in 1 participant each.

As defined by the inclusion criteria, all patients had 1 or 2 members of their family with a clinically and histologically confirmed diagnosis of CCCA. In 2 families, 2 generations were affected, whereas in another family, cousins were also affected. Only in 1 (2%) family were males given the diagnosis of CCCA, ie, father and son. All the affected families showed an autosomal dominant pattern of inheritance (Fig 1; available at http://www.jaad.org).

There appeared to be a strong correlation between the severity of CCCA as interpreted by the CHLG score, and the frequency and preference of hair-grooming methods. Fifteen (48%) participants who had CHLG greater than 2 practiced frequent braiding and weaving for hair grooming, of whom 9 (29%) gave a history of braiding or weaving chemically processed hair (relaxed or permed). Of those with CHLG 0 to 1, 11 (35%) had natural virgin hair, had never used any chemicals or traction on their hair, and maintained short hairstyles. These were either very young (<15 years) or very old (>75 years) female participants who had escaped the latest hair-grooming trends, or males who had kept natural short haircuts, as culturally accepted. With regards to symptomatology, 11 (35%) patients presented with thinning and breakage of the vertex hair as the main symptom, as observed by other authors,[4] 9 (29%) were asymptomatic and the remaining 11 (35, 5%) patients presented with either painful papules, tender scalp, dandruff, or pruritus.

### Histopathology

A total of 31 scalp biopsy specimens were submitted. Twenty biopsy specimens of late lesions were submitted for vertical sectioning and 19 for horizontal sectioning. Eleven biopsy specimens of early lesions were submitted for vertical sectioning and 10 for horizontal sectioning. Combining vertical and horizontal sections increased the diagnostic yield and the diagnosis of CCCA was made on all 31 specimens. Hair shaft granulomas caused by disruption of follicular epithelium were evident in 2 biopsy specimens, as were atrophy of follicular epithelium, concentric perifollicular fibrosis, and lymphocytes.

## DISCUSSION

We have described 14 index African families with a total of 31 immediate family members who displayed characteristic clinical and histologic features of CCCA.[2] To our knowledge, a similar cohort of patients has not been described in the literature. Each of the 14 index patients had at least 1 immediate family member who had CCCA. Family members were recruited and examined, and subjected to a confirmatory dermoscope-guided biopsy.[18] The pedigrees of the 14 families are highly suggestive of an autosomal dominant mode of inheritance (Fig 1; available at http://www.jaad.org), with partial penetrance and a strong modifying effect of hairstyling and gender. In the majority of patients, a strong family history of CCCA from the maternal side was observed. The case of paternal transmission rules out X-linked inheritance provided CCCA is genetically homogeneous. We believe that gender-related hair-grooming habits may explain the preponderance of female patients in our cohort. Indeed, most African males in South Africa keep their hair natural and very short, making it difficult to pick up the subtle areas of alopecia.

In fact, in the only family with male patients studied, the index patient had been using chemical hair relaxers and we have documented chemical hair grooming as an aggravating environmental factor. The absence of DM and skin infections in the majority of our patients casts doubt on any association of DM and skin infections in patients with CCCA, as was reported by Kyei et al.[19] Similarly, we could not find any association between CCCA and acne as previously reported.[19]

In contrast, we detected a positive correlation between use of traction-inducing hairstyles such as braids/weaving, and the severity of CCCA, more so in patients who applied traction on chemically processed hair.[6,15,19] Traction alopecia was found in most female patients (96.1%), as described by other authors suggesting that traction alopecia in CCCA may serve as an environmental trigger in patients with an inherited propensity to develop CCCA. However, the fact that 6 (19.4%) patients had natural hair, yet had clinical and histologic confirmation of CCCA, lends further support to the notion that endogenous factors play a pivotal role in the disease pathogenesis of some primary cicatricial alopecias.[20,21]

In conclusion, results of this study are strongly suggestive that CCCA can be inherited in a dominant fashion, and confirm the important contribution of hairstyling to the disease manifestations.[22] Certainly a population study to screen for early symptoms and signs of CCCA in younger African girls and women would be desirable, particularly those with affected family members.

Natural hairstyles should be encouraged in patients with CCCA and their relatives to obviate the rapid progression and severity of the hair loss, which may result in major psychological effects (unpublished data, October 2013). Public and hairstylist educational campaigns will hasten early recognition and diagnosis.

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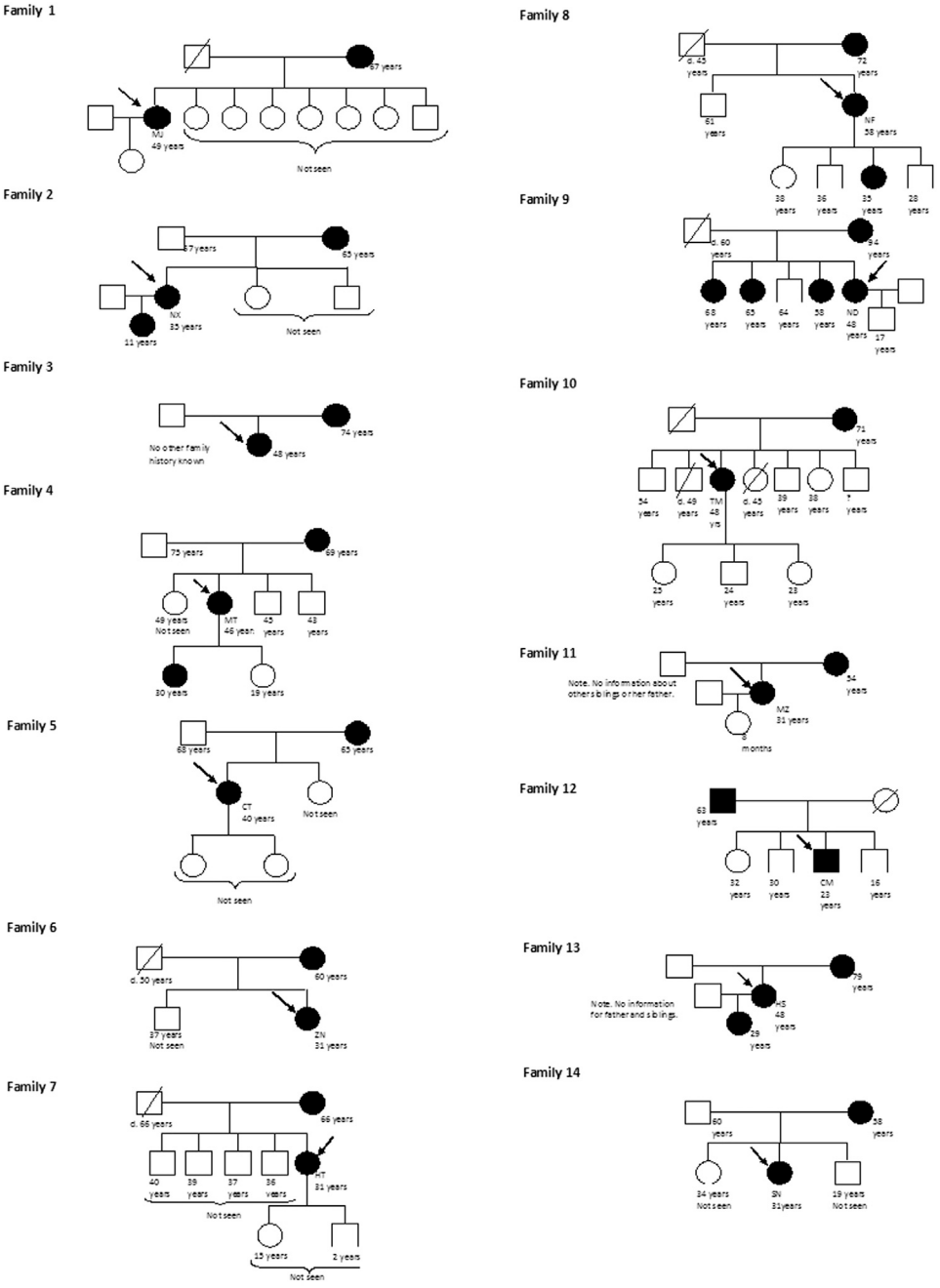


**Fig 1.** Pedigrees depicting autosomal dominant inheritance of central centrifugal cicatricial alopecia in all 14 affected families.