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Genetic Susceptibility to Alopecia

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The hair unit is composed of specialized compartments that are coordinately responsible for synthesis of the hair fiber. The principal signaling center of the hair follicle resides in the dermal papilla, which consists of a specialized fibroblast population that is responsible for regeneration and cycling of the follicle. The dermal papilla interacts with the overlying epithelial cells, known as the hair matrix, to generate the hair shaft.[1] The size of the dermal papilla niche is dynamic and actively regulated, and a reduction in the number of cells that make up the dermal papilla is believed to contribute to the loss or thinning of hair. The hair shaft itself contains a complex configuration of structural proteins, including many different hair keratins with associated proteins, which are responsible for the proper formation and growth of the hair shaft.

Distinct differences have been documented in the hair morphology in human populations of different ancestries, which are believed to be genetically determined.[2] The hair of persons of African ancestry has a flattened cross-sectional appearance, and the hair is usually coiled. The hair of persons of European ancestry has an oval cross section, and the hair of persons of Asian ancestry has a rounder, more circular perimeter, resulting in straighter hair.

Considering the complexity of hair biology, it is perhaps not unexpected that hair growth is affected in several disorders, ranging from extremely rare (usually single-gene disorders) to very common (mainly polygenic). The more common, polygenic conditions have been attributed to a number of distinct pathomechanisms. Age-associated thinning and loss of hair can be explained in part by hormonally influenced miniaturization of the follicle, which is often associated with androgenetic alopecia or pattern hair loss. Immune factors, such as lymphocyte-mediated destruction of the lower part of the follicle, are a hallmark feature of autoimmune forms of hair loss, such as alopecia areata (patchy hair loss). Genetic factors also play a role, as is the case in rare, mendelian forms of hair loss and hair fragility syndromes. For example, hair-shaft abnormalities, known as trichorrhexis invaginata (also called bamboo hair), are associated with a keratinization phenotype of dry and scaly skin in the Netherton syndrome, caused by mutations in the gene *SPINK5*, which encodes a serine protease inhibitor.

Finally, there are other forms of alopecia for which the cause has not yet been described. These include the group of primary cicatricial alopecias, including lichen planopilaris, frontal fibrosing alopecia, and until now, central centrifugal cicatricial alopecia (CCCA). In these disorders, hair loss is associated with rapid, progressive, and permanent destruction of follicles, followed by replacement with fibrotic connective tissue, which leads to irreversible hair loss.[3]

CCCA is a common and progressive form of scarring alopecia, in which histopathological

examination of the skin reveals the presence of lymphocytes early on in the proximity of hair follicles, eventually resulting in the destruction of the follicle and deposition of extracellular matrix.[4] CCCA is seen predominantly in women of African ancestry, with a reported prevalence of 2.7% among women in South Africa and 5.6% among women of African descent in North America.[5] This condition, which is also sometimes described as hot comb alopecia because it is often associated with traction-inducing hairstyling practices and use of hair chemicals, has a late onset, usually in the fourth decade of life.[6] The disorder sometimes runs in families in a perceived autosomal dominant pattern, although styling preferences within households may also contribute to the clustering of cases within families. The majority of cases of CCCA appear to be sporadic.

Malki et al., an international group of investigators, now report in the *Journal*[7] the results of a study of the genetics of CCCA, including molecular analyses of a series of 58 patients with CCCA. First, the exomes of a discovery set comprising 16 women with CCCA who were of African ancestry and living in the United States and South Africa, were sequenced; analyses of the sequence data yielded four mutations in *PADI3* in 5 women (each woman was heterozygous for the mutation). Characterization of mutant proteins led the authors to conclude that some of these mutations cause the encoded protein, peptidyl arginine deiminase 3 (PADI3), to misfold and form intracellular aggregates. PADI3 catalyzes the post-translational modification of proteins by converting arginine into citrulline — a modification that changes the charge of PADI3 and therefore results in physicochemical differences in the substrate proteins, such as trichohyalin, that can be modified by PADI3 (Fig. 1). Trichohyalin is critical to the formation and shaping of the hair shaft.

Further analyses showed that genes that are critical to hair formation (and that have been previously shown, when variant, to be associated with hair loss) are expressed at different levels in the scalp skin of women with CCCA than in unaffected women. This pattern of dysregulation may also mark a point in the progression of the disease — a point emphasized by recent findings that fibroproliferative genes, such as those for collagen types I and III, and various matrix metalloproteinases, are overexpressed in the fibrotic stage of the disease.[9]

In the second phase of their work, the authors provided replication of the findings in a cohort of 42 patients with CCCA and identified mutations (including two novel mutations) in *PADI3* in 9 of them. In total, six distinct mutations were found in 14 of 58 patients (24%) with CCCA. It is unclear whether the remaining three quarters of the patients have a type of CCCA that is phenotypically indistinguishable from those with *PADI3*. Given the complex physiology of CCCA and the results reported by Malki et al., it is unlikely that *PADI3* variants are solely responsible for the disease. Variants in other genes probably contribute to pathogenesis.

It is interesting to note that another hair disorder, uncombable hair syndrome, has also been shown in some cases to involve mutations in *PADI3*, whereas in others the gene *TCHH*, which encodes trichohyalin, is mutated.[8] The uncombable hair syndrome is a rare disorder involving hair-shaft abnormality, which is characterized by a frizzy appearance of difficult-to-manage hair (Fig. 1).[10] The manifestation of this disorder differs entirely from that of CCCA and is not associated with alopecia or scarring. The uncombable hair syndrome occurs in children, usually resolves with age, and shows no association with ancestral origin. Mutations in *PADI3* in children with the uncombable hair syndrome occur in either a homozygous or a compound heterozygous pattern, which suggests an autosomal recessive inheritance pattern,[8] in contrast to CCCA, in which the mutations were heterozygous. The mutations in *PADI3* in these two conditions are distinct, which suggests different pathogenic consequences of specific *PADI3* variants on hair development. The observation that the heterozygous parents of children with uncombable hair syndrome are apparently unaffected supports this hypothesis.

What are the implications of these findings for clinical management? The observations by Malki et al. suggest that *PADI3* mutations predispose persons to CCCA, which is then clinically manifested when hairstyling practices damage the hair. Thus, in the familial setting, such practices should be discouraged in both symptomatic and asymptomatic family members. Although

Figure 1. Central Centrifugal Cicatricial Alopecia (CCCA) and Uncombable Hair Syndrome.

The integrity of the gene *PADI3*, which encodes peptidyl arginine deiminase (PADI3), permits normal hair-follicle function (Panel A). The study by Malki et al.[7] implicates variants in *PADI3* regarding susceptibility to CCCA (Panel B), which has been reported to be associated with hot comb treatment. Previous work has shown that homozygous variants in *PADI3* cause uncombable hair syndrome (Panel C).[8] Photos courtesy of Amy McMichael, M.D., Wake Forest Baptist Medical Center, Winston-Salem, North Carolina.

PADI3 mutations would appear to predispose women to CCCA, the screening of asymptomatic women for pathogenic mutations in *PADI3* would be premature. Perhaps, once the association is tested in larger groups of women and the effect on risk is better understood[7] and there is a comprehensive genomic landscape of CCCA (i.e., other risk variants and genes are identified and their effect on risk delineated), genotyping of asymptomatic women would be warranted. The presence of variants in *PADI3* in both CCCA and uncombable hair syndrome suggests that this

gene has a pleiotropic effect on the determination of hair texture, and the finding holds implications for future development of therapy, such as the restoration of PADI3 activity.

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