Atrichia with papular lesions is a rare form of hair loss with an autosomal recessive mode of inheritance characterized by the absence of normal hair follicles and formation of intradermal cystic structures. Mutations in the hairless (HR) gene in both mice and human have been implicated in the development of this phenotype. HR codes for a putative transcription factor containing a single zinc-finger DNA binding domain, with restricted expression in the brain and the skin. Here, we report the first case of atrichia with papular lesions in a Taiwanese family with no detectable mutation in HR.

Introduction

Atrichia with papular lesions (APL) (OMIM 209500) is a rare, autosomal recessive form of total alopecia. Normal hairs are present at birth in most APL patients, but the neonatal hairs are usually shed within the first few months of life and never replaced. Histological examination of the affected scalp skin shows the absence of mature hair follicle structures. At approximately 2 years of age, affected patients begin to develop multiple follicular papules with variations in the structure and morphology of the hair follicle remnants.

Recently, linkage of APL to chromosome 8p12, followed by a large number of mutations have been identified, thereby establishing the molecular basis of this disorder. Hairless (HR) encodes a predicted 127 kD protein containing a zinc finger domain, suggesting its functions as a transcription factor.

HR is highly expressed in the brain and the skin, where it appears to be an essential regulator of apoptosis during the remodeling of the catagen-stage hair follicle. Loss of HR activity in the mouse results in several basic integument abnormalities, including complete disintegration of the outer root sheath, failure of the upward movement of the dermal papilla required for subsequent re-initiation of the hair cycle, and the complete shedding of hair during days 14 to 21 of postnatal life. The elucidation of the genomic structure of HR suggests that it codes for a putative transcription factor with a single zinc-finger domain with high homology to the zinc-finger domains found in the GATA family of transcription factors.

Published estimates of the prevalence of APL remain very low and most cases are Arab Palestinian, Pakistani, Caucasian and Australian. To our knowledge, APL has not been documented in China or Taiwan. In this study, we reported the first Taiwanese family with APL and a mutation analysis of their HR gene.

Case report

We studied a Taiwanese family affected by APL (Figure 1). The family history was significant for parental consanguinity and consistent with autosomal recessive inheritance. Three homozygous recessive children were born to the healthy parents by pure probability. According to the proband’s mother, the elder sister was born with short hair which shed out at about 1 year of age, and the two boys were born without...
Atricia with papular lesions without HR gene mutation

The proband was a 19-year-old man, the third child of the family. Physical examination revealed a total absence of scalp and body hair (Figure 2). His scalp was covered with tiny papules (Figure 3B). He had normal nails, teeth (Figures 3C and 3D), and sweating, as well as normal development and intelligence. Scalp biopsy of the proband was performed to confirm the diagnosis. Histopathology revealed reduced pilosebaceous units with a total absence of inferior segment of terminal hair follicles and vellus hair follicles (Figure 4A). The sebaceous glands and infundibular portion of the hair follicles were well developed. Some of the infundibula showed cystic dilation filled with keratin (Figure 4B) and some were destroyed with a supplicative and granulomatous infiltrate. The sweat glands appeared normal.

Polymerase chain reaction and automatic sequencing

Genomic DNA was extracted from peripheral blood of the proband’s family members with informed consent; polymerase chain reaction (PCR) was performed with QIAamp Blood DNA Midi Kit (QIAGEN Inc., Valencia, CA, USA). DNA samples were then subjected to mutation screening by amplification of segments of HR with primers synthesized on the basis of intronic sequences from the Genbank (NT_023666) (Table 1).

For PCR amplification, approximately 200 ng of genomic DNA, 12.8 pmol/L each for the two primers, 10.0 mol/L dNTP and 1.25 U Taq polymerase (QIAGEN Inc.) were used in a total volume of 50μL. The amplification conditions were 94°C for 5 minutes, followed by 40 cycles at 94°C for 45 seconds, annealing temperature (see Table 1) for 45 seconds, 72°C for 45 seconds, and extension at 72°C for 10 minutes. PCR products were purified by QIAquick columns (QIAGEN Inc.) and sequenced with both forward and backward primers with 377 ABI automatic sequencer (Applied Biosystems, Foster City, CA, USA). Despite direct sequence all the exons of HR gene, no pathogenic mutation was identified.

Discussion

The hair follicle is a dynamic structure that generates hair through a complex multistep process requiring a series of epithelial-mesenchymal signals for the execution of an intricate program of developmental events. There are several forms of human hair loss, collectively known as alopecias. The more common forms include alopecia areata and androgenetic alopecia. Alopecia areata is typified by patchy hair loss on the scalp that can progress to affect the entire scalp (alopecia totalis) and eventually the entire body (alopecia universalis). In the present family, the two brothers were born without hair; alopecia universalis is therefore not likely. Based on the absence of lymphocytic infiltrate in the histopathology of scalp biopsy, alopecia universalis was also excluded. Androgenetic alopecia, also known as male pattern baldness, affects 50% of all males over the age of 50. In this family, the alopecia was congenital; the pathology did not favor androgenetic alopecia, either.

In contrast to alopecia areata and androgenetic alopecia, there are several forms of hereditary alopecia that do occur as single gene disorders. As reviewed by Feinstein et al.,18 alopecia may occur alone or in association with various defects such as abnormalities of the teeth and nails, microcephaly, cataracts, retinitis pigmentosa, epilepsy, mental
retardation, pyorrhea and total or partial anodontia. In the current report, the family members did not have any ectodermal or other abnormalities.

According to the APL clinical and molecular diagnostic criteria as suggested by Zlotogorski et al,\textsuperscript{19} the clinical and histological pictures of APL in the present case are similar to those of previous reports, including family history, atrichia prior to 1 year of age, associated papules, normal nails and teeth, and absence of normal hair follicle structures with infundibular cysts in histopathology. However, in this family, no HR mutation can be identified, despite direct sequencing all the exons and intron-exon boundaries. Possible explanations that might account for the negative result in our mutation analysis include that the mutation was
located in the promoter area, the intron area, or in another gene that encodes a protein which interact with HR protein. Further study is needed to confirm the above hypotheses.

References