Hair Shaft Abnormalities in Localized Autosomal Recessive Hypotrichosis 2 and A Review of Other Non-syndromic Human Alopecias

Hiraku Suga[1], Yuichiro Tsunemi[1], Makoto Sugaya[1], Satoru Shinkuma[2], Masashi Akiyama[2], Hiroshi Shimizu[2] and Shinichi Sato[1]
Departments of Dermatology, [1]Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, and [2]Hokkaido University Graduate School of Medicine, Sapporo, Japan. E-mail: hiraku_s2002@yahoo.co.jp
Accepted December 16, 2010.

Localized autosomal recessive hypotrichosis (LAH) 2 is a type of non-syndromic human alopecia that is inherited as an autosomal recessive trait. We describe here a patient with LAH2 who had mutations in the *lipase H* (*LIPH*) gene. We analysed hair shaft morphology using light and scanning electron microscopy (SEM). In addition, we review the features of other non-syndromic human alopecias.

CASE REPORT

The patient was a 4-year-old boy, the firstborn of healthy and unrelated Japanese parents, born after an uneventful pregnancy. He had scant hair at birth, which grew very slowly in infancy.

Clinical examination revealed hypotrichosis of the scalp (Fig. 1a). The hairs were sparse, thin, and curly, and not easily plucked. The left eyebrow hair was sparse, but the eyelashes and other body hair were present in normal amounts. Teeth, nails, and the ability to sweat were completely normal. Clinical features of keratosis pilaris, milia, scarring, and palmoplantar keratoderma were absent. Psychomotor development was normal. The patient's younger brother also had severe hypotrichosis; since birth his hair was curly, and his eyebrow hair virtually absent (Fig. 1b). No other family members, including his parents, had similar hair abnormalities. Laboratory tests of the patient showed normal serum levels of copper and zinc, and liver and kidney function tests were all within normal ranges. Over a period of 2 years there was no improvement or exacerbation of hypotrichosis in the patient.

Light microscopy of the patient's scalp hairs revealed that approximately 10% had structural abnormalities. Abnormal hairs were composed of thick dark parts and thin light parts (Fig. 2a). SEM revealed alterations of the cuticular architecture. Cuticular cells were absent from both the thick and thin parts (Fig. 2b). Cross-sectional observation showed that thick, but not thin, sections had hair medulla (Fig. 2c, d). Light microscopy on hairs from the patient's younger brother revealed that they were composed of thin and thick parts (data not shown).

Based on the clinical features, hair microscopy and family pedigree, we suspected LAH2 or LAH3. To determine the type of LAH, we looked for gene mutations in *LIPH* and *LPAR6* (encoding lysophosphatidic acid receptor 6). Two prevalent missense mutations in *LIPH* were found (1); c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn). The mutations were carried in a compound heterozygous state. No mutations were found in *LPAR6*. The parents did not consent to genetic testing of the younger brother or themselves.

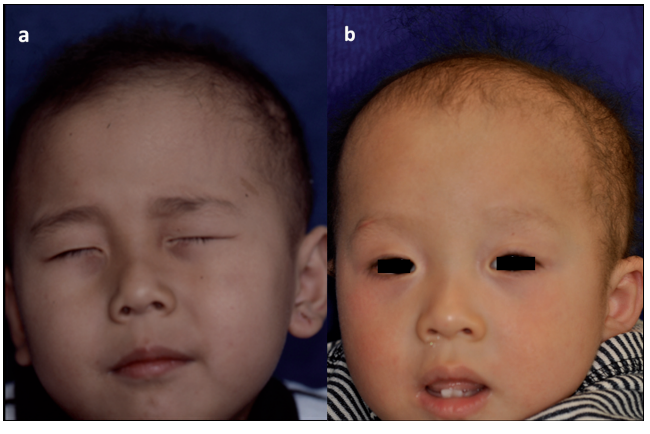

Fig. 1. (a) Clinical features of the patient at 4 years of age. (b) Clinical features of the younger brother at 1 year 4 months of age. Permission is given from the parents to publish these photos.

DISCUSSION

The different LAH subtypes map to chromosomes 18q12.1, 3q27.3 and 13q14.11–13q21.32, and are designated LAH1, LAH2 and LAH3, respectively (2–4). Mutations in *DSG4* (encoding desmoglein 4) have been found to be responsible for LAH1 (5). Kazantseva et al. (6) reported deletion mutations in *LIPH* leading to LAH2. Pasternack et al. (7) reported disruption of *LPAR6* in families affected with LAH3.

Table I summarizes of genetic, non-syndromic human alopecias. In *hypotrichosis simplex of the scalp*, hair loss

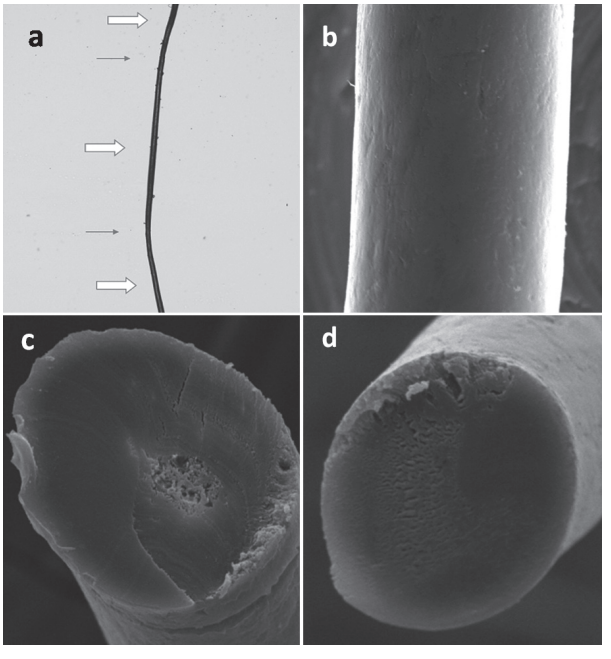

Fig. 2. (a) Light microscopy (×40). Hair was composed of thick (⇨) and thin parts (→). (b) Scanning electron microscopy (×900). Cuticular cells were absent in both thick and thin sections. (c, d) Scanning electron microscopy (cross-section, ×900). (c) Thick regions showed hair medulla, while (d) thin regions did not.

is limited to the scalp without hair shaft abnormalities. The causative gene is *CDSN* (encoding corneodesmosin) on 6p21.3 (8). The clinical presentations of *monilethrix* vary among patients. Mild cases have hair loss limited to the scalp, while severe cases show generalized alopecia. Hair shaft abnormalities are characteristic, demonstrating regularly-spaced, spindle-shaped swellings. The nodes are as thick as normal hair and the atrophic internodes represent areas where the hair is easily broken. Causative genes are *hHb1*, *hHb3* and *hHb6* (12q13) (9), which encode for basic hair keratins.

In case of *atrichia with papular lesions*, hair loss on the entire body occurs several months after birth. The gene responsible is *HR* (encoding "hairless") (10), a transcription modulating factor that influences the regression phase of the hair shaft cycle. Patients with *hypotrichosis, Marie Unna type* have hard and rough scalp hair, described as iron-wire hair. Generalized hypotrichosis is often seen. *U2HR*, an inhibitory upstream open reading frame of the human hairless gene (11), is mutated in this condition. *Hereditary hypotrichosis simplex* is characterized by hair follicle miniaturization. The defective gene is *APCDD1* (encoding adenomatosis polyposis down-regulated 1) (12). Hairs are short, thin, and easily plucked. Eyelashes and eyebrows are also affected.

As already mentioned, there are three types of *localized hereditary hypotrichosis*. LAH1 patients have hair shaft abnormalities that resemble moniliform hair (13). LAH1 can be viewed as an autosomal recessive form of monilethrix. Patients with LAH2 and LAH3 have woolly hair (14, 15), and eyelashes and eyebrows are often sparse or absent. Upper and lower limb hairs are sometimes absent too.

Our patient had hypotrichosis of the scalp with sparse left eyebrow hair and irregularly spaced segments of thick and thin hair, but not to a degree that could be labelled moniliform. The mode of inheritance was autosomal recessive and *LIPH* was found to be abnormal, thus establishing a diagnosis of LAH2. One of the mutations (c.736T>A) leads to an amino acid change (p.Cys246Ser) of a conserved cysteine residue, which forms intramolecular disulphide bonds in the lid domain in the structure model of LIPH (1). The other mutation (c.742C>A) results in alteration of one of the amino acids of the catalytic triad (Ser^{154}, Asp^{178}, and His^{248}) of LIPH (p.His248Asn) (1).

Regarding hair shaft morphology, Horev et al. (14) reported that hairs of LAH2 patients showed decreased diameter under light microscopy. This is the first report to describe hairs from an LAH2 patient by SEM. Shimomura et al. (13) observed hairs of LAH1 patients by SEM and found variable thickness of the hair shaft, resulting in nodes and internodes. Which are absent in LAH1 (our observation). Longitudinal ridges and flutes were observed at internodes, and the breaks always occurred at internodes in LAH1. These features resemble those of moniliform hair rather than LAH2. However, in the end gene analysis is probably easier to accomplish than SEM to distinguish the two types of LAH.

ACNOWLEDGEMENTS

We thank Dr Andrew Blauvelt, Department of Dermatology, Oregon Health & Science University, for many helpful comments.

REFERENCES

1. Shinkuma S, Akiyama M, Inoue A, Aoki J, Natsuga K, Nomura T, et al. LIPH prevalent founder mutations lead to loss of P2Y5 activation ability of PA-PLA1α in autosomal recessive hypotrichosis. Hum Mutat 2010; 31: 602–610.
2. Rafique MA, Ansar M, Jamai SM, Malik S, Sohail M, Faiyaz-Ul-Haque M, et al. A locus for hereditary hypotrichosis localized to human chromosome 18q21.1. Eur J Hum Genet 2003; 11: 623–628.
3. Aslam M, Chahrour MH, Razzaq A, Haque S, Yan K, Leal SM, et al. A novel locus for autosomal recessive form of hypotrichosis maps to chromosome 3q26.33-q27.3. J Med Genet 2004; 41: 849–852.
4. Wali A, Chishti MS, Ayub M, Yasinzai M, Kafaitullah, Ali G, et al. Localization of a novel autosomal recessive hypotrichosis locus (LAH3) to chromosome 13q14.11-q21.32. Clin Genet 2007; 72: 23–29.
5. Kljuic A, Bazzi H, Sundberg JP, Martinez-Mir A, O'Shaughnessy R, Mahoney MG, et al. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. Cell 2003; 113: 249–260.
6. Kazantseva A, Goltsov A, Zinchenko R, Grigorenko AP, Abrukova AV, Moliaka YK, et al. Human hair growth deficiency is linked to a genetic defect in the phospholipase gene LIPH. Science 2006; 314: 982–985.
7. Pasternack SM, von Kugelgen I, Aboud KA, Lee YA, Ruschendorf F, Voss K, et al. G protein-coupled receptor P2RY5 and its ligand LPA are involved in maintenance of human hair growth. Nat Genet 2008; 40: 329–334.

Table I. *Features of genetic, non-syndromic human alopecias*

Disease (ref)	Hair shaft shape	Eyelash/eyebrow	Causative gene	Mode of inheritance
Hypotrichosis simplex of scalp (8)	Normal	Normal	*CDSN*	Autosomal dominant
Monilethrix (9)	Regularly spaced, spindle-shaped swellings	Absent to normal	*hHb1, 3, 6*	Autosomal dominant
Atrichia with papular lesions (10)	Normal	Absent	*HR*	Autosomal recessive
Hypotrichosis, Marie Unna type (11)	Iron-wire	Sparse	*U2HR*	Autosomal dominant
Hereditary hypotrichosis simplex (12)	Short, thin, easily plucked	Absent to sparse	*APCDD1*	Autosomal dominant
Localized hereditary hypotrichosis (LAH1) (2, 5, 13)	Moniliform	Absent to normal	*DSG4*	Autosomal recessive
Localized hereditary hypotrichosis (LAH2) (3, 6, 14)	Curled	Absent to normal	*LIPH*	Autosomal recessive
Localized hereditary hypotrichosis (LAH3) (4, 7, 15)	Curled	Absent to normal	*LPAR6*	Autosomal recessive

8. Davalos NO, Garicia-Vargas A, Pforr J, Davalos IP, Picos-Cardenas VJ, Garcia-Cruz D, et al. A non-sense mutation in the corneodesmosin gene in a Mexican family with hypotrichosis simplex of the scalp. Br J Dermatol 2005; 153: 1216–1219.
9. Richard G, Itin P, Lin JP, Bon A, Bale SJ. Evidence for genetic heterogeneity in monilethrix. J Invest Dermatol 1996; 107: 812–814.
10. Ahmad W, Faiyaz ul Haque M, Brancolini V, Tsou HC, ul Haque S, Lam H, et al. Alopecia universalis associated with a mutation in the human hairless gene. Science 1998; 279: 720–724.
11. Wen Y, Liu Y, Xu Y, Zhao Y, Hua R, Wang K, et al. Loss-of-function mutations of an inhibitory upstream ORF in the human hairless transcript cause Marie Unna hereditary hypotrichosis. Nat Genet 2009; 41: 228–233.
12. Shimomura Y, Agalliu D, Vonica A, Luria V, Wajid M, Baumer A, et al. APCDD1 is a novel Wnt inhibitor mutated in hereditary hypotrichosis simplex. Nature 2010; 464: 1043–1047.
13. Shimomura Y, Sakamoto F, Kariya N, Matsunaga K, Ito M. Mutations in the desmoglein 4 gene are associated with monilethrix-like congenital hypotrichosis. J Invest Dermatol 2006; 126: 1281–1285.
14. Horev L, Tosti A, Rosen I, Hershko K, Vincenzi C, Nanova K, et al. Mutations in lipase H cause autosomal recessive hypotrichosis simplex with wooly hair. J Am Acad Dermatol 2009; 61: 813–818.
15. Horev L, Saad-Edin B, Ingber A, Zlotogorski A. A novel deletion mutation in P2RY5/LPA_6 gene cause autosomal recessive woolly hair with hypotrichosis. J Eur Acad Dermatol Venereol 2010; 24: 858–859.