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A Case of Autosomal Recessive Woolly Hair/Hypotrichosis with Alternation in Severity: Deterioration and Improvement with Age

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Key Words
Woolly hair/hypotrichosis · Scanning electron microscopy · Lipase H gene

Abstract
Autosomal recessive woolly hair/hypotrichosis (ARWH/H) is a nonsyndromic hair abnormality characterized by sparse, short and curly hair (WH/H). We report the case of a 3-year-old female, with no consanguineous ancestry, who exhibited WH/H. Normal hair was observed at birth, but severe hair loss had developed within the first 6 months; however, her hair density had improved somewhat by age 3. Light microscopy showed hair shaft invaginations, and polarized light microscopy suggested complete medullary disruption of the hair. Direct sequence analysis of peripheral blood showed a homozygous missense mutation in exon 6 of the lipase H gene (*LIPH*: c.736T>A, p.Cys246Ser), and the exact same mutation was found in the heterozygous state in both parents. The initial deterioration followed by improvement with age observed in this case suggests that the clinical course of ARWH/H may vary among patients with the same mutation in *LIPH* detected in this case, indicating that additional factors may influence the effect of *LIPH* on hair development.

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Introduction

Woolly hair/hypotrichosis (WH/H) is a hair shaft disorder characterized by fine, tightly curled hair that grows slowly and reaches only a few centimeters in length. WH/H is classified as syndromic or nonsyndromic according to the presence or absence, respectively, of systemic abnormalities. Nonsyndromic WH/H is categorized as autosomal dominant (OMIM 194300) or recessive (ARWH; OMIM 278150/604379/611452) according to its inheritance pattern. Recently, lipase H *(LIPH)* and *LPAR6* were identified as the causative genes of ARWH/H [1–4]. The clinical course of ARWH/H varies, but usually sparse hair is observed at birth and worsens or improves with age. Here, we report a case of ARWH/H with a mutation in *LIPH* in which the hypotrichosis initially worsened followed by improvement in hair density over the next 3 years.

Case Report

A 3-year-old girl's parents brought her to our department complaining of hair loss and insufficient hair growth. Her delivery had been normal and her development otherwise unremarkable. She had no siblings, and both parents had apparently normal hair. Neither parent reported any family history of consanguinity. Physical examination showed fine, curly hair ranging in length from 3 to 5 cm and distributed uniformly sparsely. Her eyebrows and eyelashes were unaffected (fig. 1a, b). Her parents reported that her hair density and growth had been normal at birth (fig. 1c); however, significant hair loss had developed when she was 3 months old (fig. 1d, e) and had gradually reversed somewhat over the next 3 years. Laboratory tests, including thyroid hormone levels and autoantibody titers, showed no significant abnormality. Light microscopy showed hair shaft invaginations (fig. 1f), and polarized light microscopy revealed a damaged appearance of the hair cortex (fig. 1g). Scanning electron microscopy showed a partial defect of the medulla and fragile outer cortex of the hair shaft (fig. 1h). As the hair of both parents appeared normal, we suspected ARWH/H and performed direct sequencing of the *LIPH* gene on peripheral blood from the patient and her parents after obtaining the family's informed consent. The patient was found to be homozygous and both parents heterozygous for a missense mutation in exon 6 of *LIPH* (c.736T>A, p.Cys246Ser) (fig. 2). Our patient was diagnosed with ARWH/H resulting from a homozygous mutation in *LIPH*.

Discussion

LIPH, a causative gene of ARWH/H, encodes PA-PLA$_1\alpha$, a phospholipase A1 family member that produces lysophosphatidic acid (LPA) from phosphatidic acid [5]. Furthermore, *P2RY5*, another gene that can cause ARWH/H, encodes an orphan G-protein-coupled receptor that binds LPA as its ligand [3]. Both PA-PLA$_1\alpha$ and P2RY5 are strongly expressed in the inner sheath of the hair shaft, suggesting that they are closely involved in the development of the inner hair sheath [2]. Our polarized light and scanning electron microscopy observations indicated severe damage to the medulla of the hair shaft; this is the first report to describe the medulla of the hair in a case of ARWH/H with an *LIPH* mutation using these 2 microscopy techniques. The mutation in this case, c.736T>A, p.Cys246Ser, is considered with c.742C>A p.H248N to be a founder mutation in the Japanese population, and the frequencies of the carrier states of these gene mutations among the Japanese population

are 1.5 and 1.0%, respectively [1, 6]. There has been no report of a clear association between the genotype and phenotype in patients with *LIPH* mutations. Shimomura et al. [7] reported 2 Guyanese families with ARWH/H in which affected siblings with exactly the same mutation in *LIPH* had different severities of hypotrichosis, developmental abnormalities and other clinical features such as keratotic follicular papules on the legs in 1 sibling. Indeed, Japanese patients with the c.736T>A mutation in exon 6 of *LIPH*, as in the present case, exhibit various clinical courses; that is, the hair abnormalities may be apparent at birth or develop only after several months, or the hair volume may increase with age [6, 8]. Interestingly, our patient's hair density has fluctuated over the 3 years since her birth. This observation suggests that *LIPH* is associated with unidentified, linked genes, which may be up- or downregulated or may be modified by single nucleotide polymorphisms, resulting in inner sheath development with age. As mentioned earlier, LPA, which is synthesized from LIPH, is an extracellular mediator of many biological functions and is thought to have growth-promoting effects on hair epithelial cells that protect against catagen induction by activating mitogen-activated protein kinase/extracellular signal-regulated kinase, as reported in murine hair epithelial cells [9]. However, it remains unclear how LPA regulates other hair-linked genes or how exactly LPA contributes to the formation of the wooly and sparse hair phenotype in the human inner root sheath.

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Disclosure Statement

The authors have nothing to declare.

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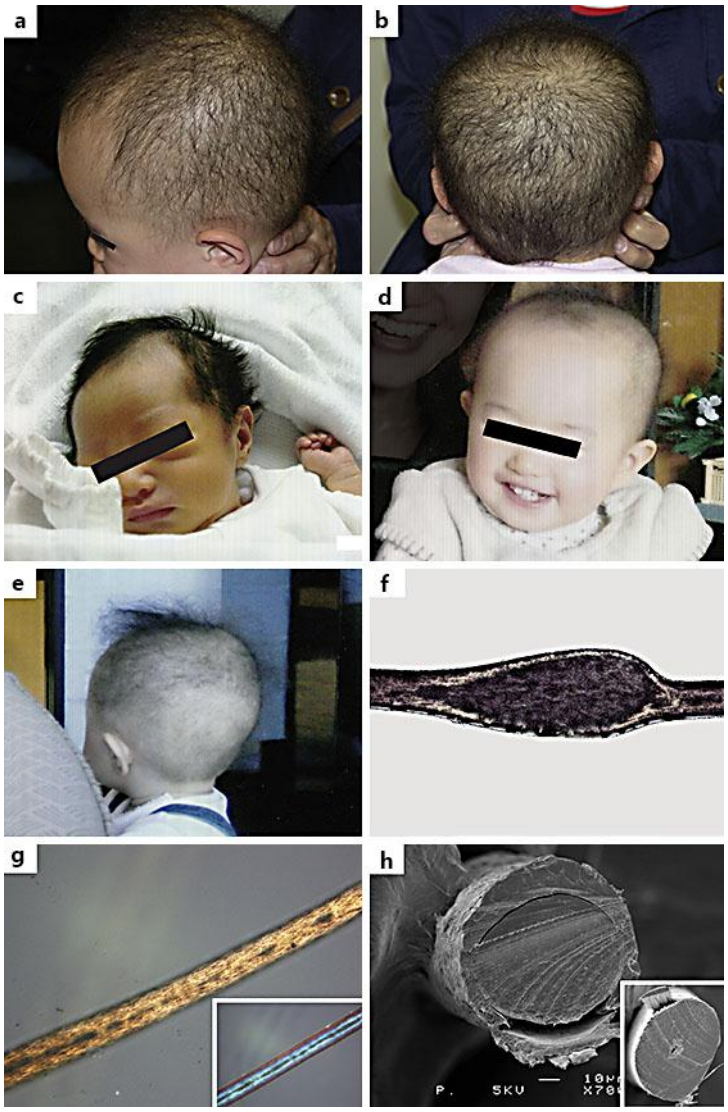

Fig. 1. **a**, **b** Clinical features of the patient's hair at the age of 3 years. **c** Normal appearance of the hair 4 days after birth. **d**, **e** Severe hair loss observed at the age of 6 months. **f** Light microscopic feature of hair shaft invagination. **g** The hair shaft observed by polarized light microscopy. The **inset** shows age-matched normal hair. **h** Scanning electron micrograph of the cross-section of the hair showing signs of fragility in the outer cortex and reduction of the medulla. The **inset** shows age-matched normal hair.

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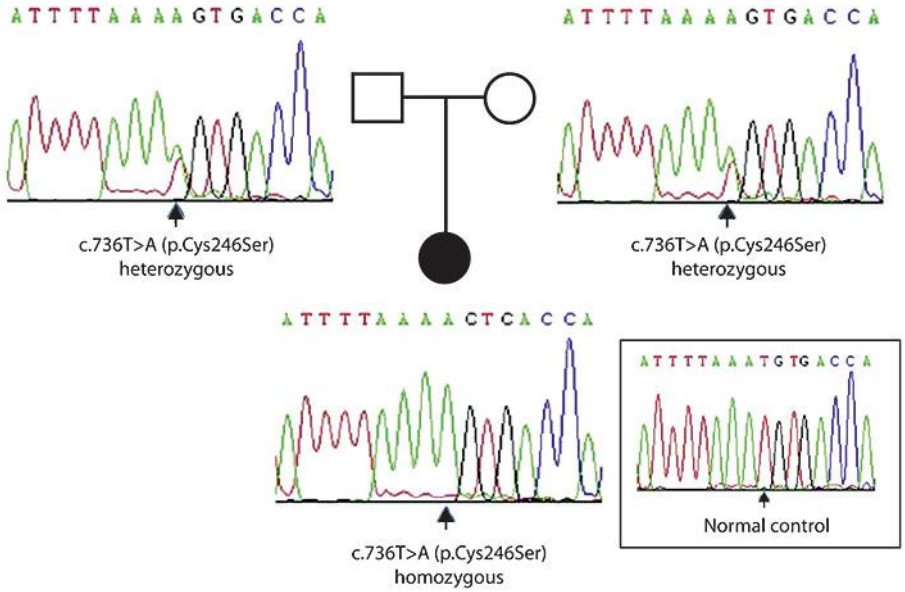

Fig. 2. Direct sequence analysis of *LIPH* in the patient and her parents. The patient harbors a homozygous missense mutation in exon 6 of *LIPH* (c.736T>A, p.Cys246Ser), and both parents harbor exactly the same mutation in a heterozygous state.