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Mutations in the *LIPH* gene in three Japanese families with autosomal recessive woolly hair/hypotrichosis

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To the editor

Autosomal recessive woolly hair/hypotrichosis (ARWH/H: OMIM #278150/604379/611452) is a rare hereditary hair disease characterized by tightly curled hair at birth which can lead to sparse hair later in life. The disease was recently shown to be caused by mutations in either the lipase H (*LIPH*) or the *P2RY5* gene [1–3]. The *LIPH* gene encodes a phospholipase A1 family member which produces lysophosphatidic acid (LPA) from phosphatidic acid [4]. LPA is an extracellular mediator which possesses many biological functions. The *P2RY5* gene encodes a G protein-coupled receptor, known as P2Y5, which has recently been shown to be a LPA receptor [5]. Both LIPH and P2Y5 are abundantly expressed in human hair follicles, where their expression overlaps in the inner root sheath [2, 3]. Thus, it has been postulated that LIPH and P2Y5 are components of a common signaling pathway and play a crucial role in hair growth in humans [2, 3, 5, 6]. As only a limited number of mutations in the *LIPH* and *P2RY5* genes have been reported to date [1–3, 6–10], clinical characteristics and the spectrum of mutations in the *LIPH* and *P2RY5* genes remain undefined. In this study, we identified novel pathogenic mutations in the *LIPH* gene in three Japanese families with ARWH/H.

All three families (Families 1–3) are a small pedigree of Japanese origin with unaffected parents and one affected sibling. Consanguinity between the parents in each family is unclear, but all three families are from Niigata prefecture in Japan. The proband in Family 1

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is a 4-year old boy who had tightly curled hair at birth (Fig. 1A). Since the age of 2, the hair has become thinner and stopped growing at a few inches (Fig. 1B). Both the eyebrows and eyelashes are also thin and sparse. Small light-colored follicular papules were diffusely observed on the scalp skin. A skin biopsy from the scalp skin shows an enlarged infundibulum with keratotic plugs (Fig. 1C) and miniaturized bulb portion without obvious structural anomalies (Fig. 1D). Families 2 and 3 have an affected girl of 3- and 4-year old, respectively. Both patients have shown similar clinical features to those of the patient in Family 1 (Fig. 1E, F).

Following informed consent, genomic DNA was extracted from peripheral blood sample of the family members. Using the genomic DNA as templates, all exons and exon-intron boundaries of the *P2RY5* and *LIPH* genes were amplified by PCR, and the PCR products were directly sequenced following the methods described previously [2, 3]. None of the three families carry any sequence variants in the *P2RY5* gene (data not shown). However, we did identify mutations in the *LIPH* gene in all three families. The patient in Family 1 carries two heterozygous nucleotide transitions, c.736T>A and c.742C>A, in exon 6 of the *LIPH* gene, which results in amino acid changes, p.C246S and p.H248N at the protein level, respectively (Fig. 1G). We were unable to obtain the parents' genomic DNA. Therefore, to determine whether the two mutations reside on the same allele or different alleles, we cloned the PCR product for exon 6 of the *LIPH* gene of the patient into pCR®II vector (Invitrogen), which enabled us to sequence the paternal and maternal *LIPH* genes separately. The results clearly showed that each mutation individually exists on different alleles (data not shown). Screening assays with restriction enzymes excluded the existence of both mutations in 100 unrelated healthy control individuals (200 chromosomes) of Japanese origin (data not shown), thus we concluded that the patient carries compound heterozygous mutations in the *LIPH* gene. Both patients in the other two families are homozygous for the mutation c. 736T>A (p.C246S) in the *LIPH* gene (Fig. 1G). The parents in both families are heterozygous for the mutation (data not shown). Genotyping using microsatellite markers close to the *LIPH* gene suggested the p.C246S to be a common founder mutation in the Japanese population (data not shown).

LIPH is a phospholipase A1 family member which contains three catalytic residues, 154S, 178D, and 248H [4]. It also has a β9 loop and a lid domain at its N-terminus, both of which play a crucial role in substrate recognition [4]. The cysteine residue at position 246 is considered to be critical for formation of a disulfide bond [4]. Therefore, the mutation p.C246S is predicted to severely affect the conformation of the LIPH protein. Likewise, the mutation p.H248N occurs in one of the three catalytic residues of the LIPH protein, thus will markedly disrupt the protein function. In addition, both 246C and 248H are highly conserved among LIPH of different species and other human lipase members (Fig. 1H). Taken together, we conclude that the amino acid changes p.C246S and p.H248N are a novel pathogenic mutation underlying ARWH/H.

In this study, we have detected *LIPH* mutations in the Japanese population for the first time, which further underscores the world-wide distribution of *LIPH* mutations (Table 1). To date, we have not found any clear genotype-phenotype correlation in the *LIPH* mutations. Indeed, we have previously shown that an identical mutation can show wide variations in phenotype

between WH and hypotrichosis even within a single family [3]. Our findings not only expand the spectrum of the *LIPH* mutations, but also provide better understanding of the crucial role of the LIPH/LPA/P2Y5 signaling in hair growth in humans. Since the LIPH/LPA/P2Y5 signaling may represent a new target for small molecule therapy for hair growth in the future, we suggest that patients with ARWH/H are screened for mutations in the *P2RY5*/*LIPH* genes in the event future therapies become available.

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Abbreviations

ARWH/H autosomal recessive woolly hair/hypotrichosis

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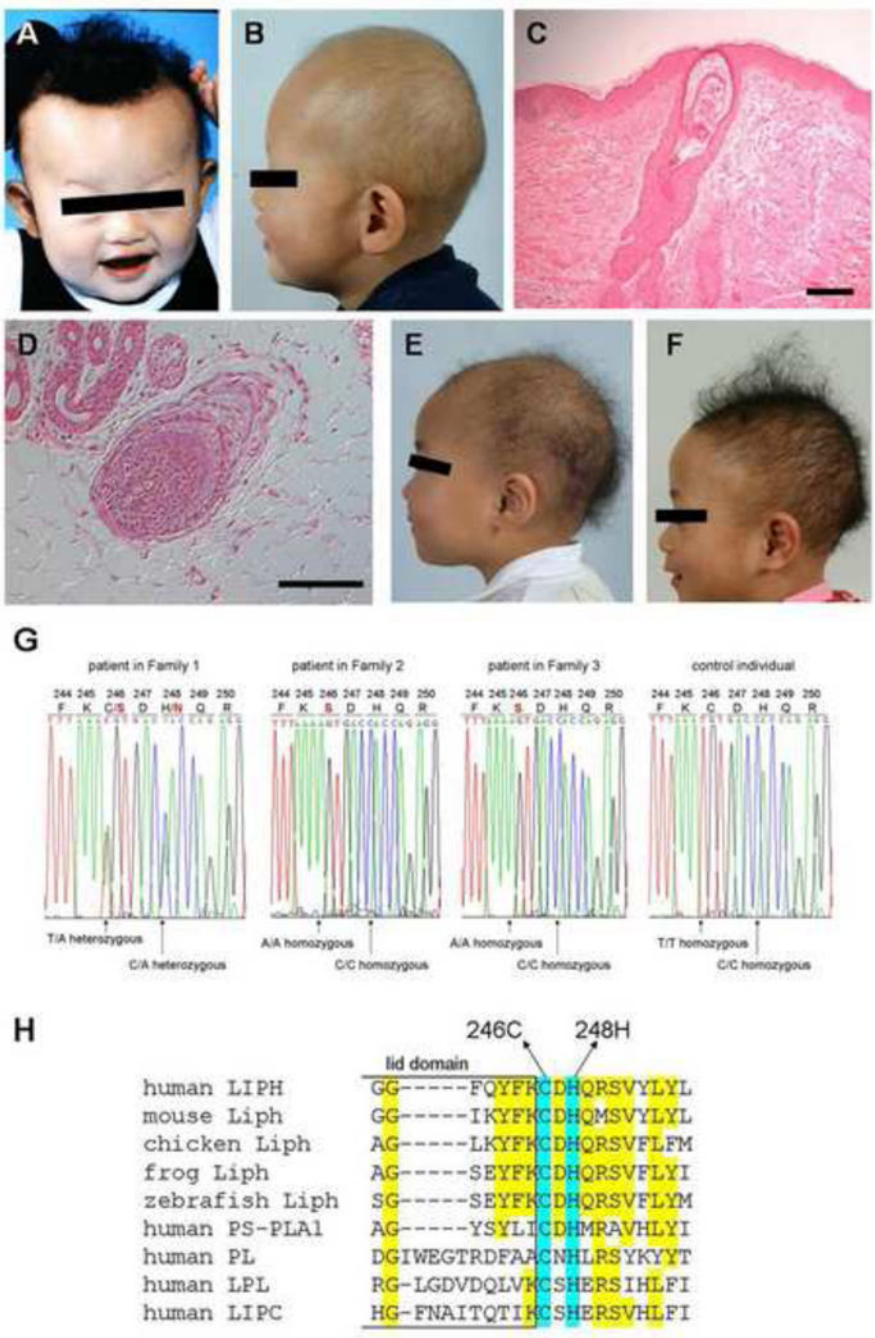

Figure 1. Clinical features of Japanese patients with ARWH/H and identification of mutations in the *LIPH* gene

(A, B) Clinical features of the patient in Family 1 at the age of 10 months (A) and 4 years old (B). (C, D) Skin biopsy from scalp skin of this patient shows eratotic plugs (C) and HF miniaturization (D). Haematoxylin and eosin stainings. Scale bars: 100 μm (C, D). (E, F) Clinical features of the patients in Family 2 (E) and Family 3 (F). Note that all three patients originally had tightly curled hair at birth, but have developed hypotrichosis with aging. (G) Identification of novel mutations in the *LIPH* gene. The patient in Family 1 is compound heterozygous for the mutations, c.736T>A (p.C246S) and c.742C>A (p.H248N), in exon 6

of the *LIPH* gene, while both patients in Families 2 and 3 are homozygous for the mutation c.736T>A (p.C246S). (H) Multiple amino acid sequence alignment of LIPH among different species and other human lipase members. Amino acid residues that are conserved among more than 6 members are shown in yellow. 246C and 248H are colored in blue and indicated by arrows.

Table 1

LIPH mutations reported to date.

origin	mutation	consequence	references
Pakistan	c.2T>C (homo)	p.M1T	[8]
	c.322T>C (homo)	p.W108R	[3] [8]
	c.280_369dup/ c.659_660delTA*	in-frame duplication of 30 amino acids/FS&PTC	[9]
	c.346_350delATATA (homo)	FS & PTC	[7]
	c.624delT (homo)	FS & PTC	[3]
	c.659_660delTA (homo)	FS & PTC	[3]
	c.683delT (homo)	FS & PTC	[3]
	Ex7_8del (homo)	FS & PTC	[3]
Guyana	Ex7_8del/c.1303_1309dupGAAAACG*	FS & PTC/FS & PTC	[10]
	c.659_660delTA (homo)	FS & PTC	[10]
Russia	Ex4del (homo)	In-frame deletion of 34 amino acids	[1]
Austria	c.403_409dup/c.280_369dup*	FS & PTC/ in-frame duplication of 30 amino acids	[6]
Japan	c.736T>A/c.742C>A*	p.C246S/p.H248N	This study
	c.736T>A (homo)	p.C246S	This study

FS, frameshift; PTC, premature termination codon; homo, homozygous mutation;

*compound heterozygous mutations.