Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Autosomal Recessive Woolly Hair Caused by *LIPH* Mutations: A Case Series of Six Chinese Patients

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Background: Autosomal recessive woolly hair (ARWH) is a rare genetic disorder characterized by tightly curled, sparse hair with variable degrees of hypopigmentation and slow growth. Pathogenic variants in the *LIPH* gene are a major cause, but information on Chinese patients remains limited.

Methods: Six unrelated patients with congenital woolly hair were analyzed. Clinical features were assessed by examination, trichoscopy, and scalp biopsy. Whole-exome sequencing (WES) and Sanger confirmation were performed, and variants were classified according to ACMG guidelines.

Results: All patients presented with sparse, curly hair since early childhood. WES identified biallelic *LIPH* variants in all cases. Three patients were homozygous for c.742C>A (p.H248N), one was homozygous for c.454G>A (p.G152R), and two were compound heterozygotes. Patients carrying the c.454G>A (p.G152R) variant tended to show milder hair loss compared with those with c.742C>A (p.H248N), suggesting a potential genotype–phenotype relationship.

Conclusion: This study broadens the understanding of *LIPH*-related ARWH in the Chinese population. The c.454G>A (p.G152R) variant may represent a recurrent allele among Chinese patients with ARWH.

Keywords: *LIPH* gene, autosomal recessive woolly hair, hypotrichosis, genotype-phenotype correlation, Chinese population

Introduction

Autosomal recessive woolly hair/hypotrichosis (ARWH) is a rare congenital alopecia characterized by sparse, tightly curled hair with varying degrees of hypopigmentation and slow hair growth.[1] ARWH has been associated with mutation of several genes, including *LIPH* (OMIM #607365), *LPAR6* (OMIM #609239), *KRT25* (OMIM #616760), *C3orf52* (OMIM #611956), and *ADAM17* (OMIM #603639).[1–5] The *LIPH* gene encodes lipase H (PA-PLA1α), a key enzyme in the synthesis of lysophosphatidic acid (LPA).[6] LPA activates the LPAR6 receptor, which regulates hair follicle development through multiple signaling pathways and ultimately modulates the expression of growth factors and their receptors, such as transforming growth factor α (TGF-α) and epidermal growth factor receptor (EGFR).[7] Pathogenic variants in *LIPH* impair the enzymatic activity of lipase, resulting in decreased LPA levels in hair follicles and disruption of hair growth via the *LIPH*/LPA/LPAR6 signaling axis.[6]

Although ARWH has been described in Asian populations, reports in Chinese patients are limited. Studying a Chinese cohort may reveal population-specific or recurrent variants and broaden the phenotypic spectrum. Defining genotype–phenotype correlations is clinically relevant for diagnosis, counseling, and prognosis. This study details the clinical features and genetic mutations of six ARWH patients, providing novel insights into the genetic basis of this condition.

Methods

Genetic Analysis

This study retrospectively reviewed six patients from six unrelated families presenting to our department between 2021 and 2024. Written informed consent for publication of the clinical details and images was obtained from all patients, as well as from the

Received: 3 June 2025
Accepted: 25 October 2025
Published: 27 November 2025

parents of the 7-year-old patient. The study was conducted in accordance with the Declaration of Helsinki. Peripheral blood samples were collected from all six patients, and genomic DNA was extracted for subsequent analysis. Whole-exome sequencing (WES) was performed by Novogene Bioinformatics Technology Co., Ltd. (Beijing, China). Briefly, 0.4 μg of genomic DNA was fragmented to an average size of 180–280bp using a Covaris LE220R-plus (Covaris, USA). DNA fragments were end-repaired, phosphorylated, A-tailed, and ligated with paired-end adapters, followed by PCR amplification. Libraries were captured using the Agilent SureSelect Human All Exon V6 kit (Agilent, USA, Catalog #5190-8864), purified with AMPure XP (Beckman Coulter, USA), assessed for size distribution (Agilent 5400 system), and quantified by real-time PCR (Life Technologies, USA). Qualified libraries were sequenced on Illumina platforms (PE150 strategy).

Sequencing reads were aligned to the human reference genome, and variants were called and filtered. Candidate variants were validated by Sanger sequencing in selected families and compared against the 1000 Genomes, gnomAD, and ExAC databases. Variant interpretation followed the American College of Medical Genetics and Genomics (ACMG) guidelines.

Clinical Evaluation

Trichoscopy was performed in selected patients to evaluate hair shaft and scalp features. Scalp biopsy specimens were obtained for histopathological evaluation of hair follicles.

Protein Structure Modeling

Wild-type and mutant protein structures were generated using SWISS-MODEL. The resulting models were visualized and compared with PyMOL.

Results

Clinical Characteristics

We collected clinical data from six patients with diffuse hair thinning and curly hair since childhood . All patients denied parental consanguinity, and none exhibited abnormalities in other organ systems.

All six patients exhibited sparse, curly hair since childhood and reported increased hair fragility with easy breakage (Figure 1a), with trichoscopy consistently showing woolly hair patterns (Figure 1b). Sparse eyebrows were observed in most patients (Patients 1# and 3#~6#). Notably, trichoscopy of Patient 4# revealed twisted, irregularly arranged eyebrow hairs with a wavy, woolly pattern (Figure 1c).

Among all six patients, Patient 1# developed progressive, mid-scalp hair thinning after the age of 18, and trichoscopy revealed markedly greater hair shaft diameter diversity at the mid-scalp compared with the occipital region, indicating coexisting female pattern hair loss. Patient 5# reported increased hair shedding over the past two years, and trichoscopy demonstrated upright regrowing hairs, suggestive of chronic telogen effluvium.

Scalp biopsy was done in Patient 2# and Patient 5# for further diagnosis (Figure 1d). Histopathological examination of Patient 2# revealed no significant inflammatory infiltrates, although some follicles showed abnormal morphology. In Patient 5#, follicular abnormalities were more pronounced, and an increased proportion of telogen follicles was observed, consistent with a diagnosis of concomitant telogen effluvium.

Genetic Findings

Sequencing revealed that all six patients carried variants in the *LIPH* gene on chromosome 3 (Table 1). Patient 1# harbored compound heterozygous variants c.742C>A (p.H248N) and c.686delAinsGTAGAACCCAACCTGGCT (p.Asp229Glyfs*37), while Patient 2# carried compound heterozygous variants c.742C>A (p.H248N) and c.454G>A (p.G152R). Patient 3# was homozygous for c.454G>A (p.G152R). Patients 4#, 5#, and 6# were homozygous for c.742C>A (p.H248N), and segregation analysis in Patient 3#, 4# and 6# confirmed parental inheritance. According to the genome aggregation database (gnomAD v2.1.1, East Asian subset), c.742C>A (p.H248N) shows an allele frequency of 0.125% (25/19952), and c.454G>A (p.G152R) has a frequency of 0.010% (5/19952), while c.686delAinsGTAGAACCCAACCTGGCT (p.Asp229Glyfs*37) was not detected in East Asian population. According to the ACMG guidelines, all variants were classified as pathogenic except c.454G>A (p.G152R), which was considered likely pathogenic.

Table 1 Clinical and Genetic Characteristics of Six Patients with *LIPH* Variants

Patient	Sex	Age at Exam	Age at Onset	Hair Features & Course	Combined Hair-Loss Disease	Family History	*LIPH* Variant(s)	ACMG Evidence	Zygosity	Sanger Validation
1#	F	37y	Childhood	Diffuse sparse, curly hair; progressive hair thinning since 18	AGA	Brother	c.742C>A (p.H248N)	PM2_Supporting, PP3, PM3_Very Strong, PP1	Compound heterozygous	Not performed
							c.686delAinsGTAGAACCCAACCTGGCT (p.Asp229Glyfs*37)	PVS1, PM2_Supporting, PM3_Supporting		
2#	F	37y	Childhood	Diffuse sparse, curly hair; stable	/	/	c.742C>A (p.H248N)	PM2_Supporting, PP3,PM3_Very Strong,PP1	Compound heterozygous	Not performed
							c.454G>A (p.G152R)	PM2_Supporting, PP3,PM3, PS3_Supporting		
3#	F	24y	Childhood	Diffuse sparse, curly hair; stable	/	/	c.454G>A (p.G152R)	PM2_Supporting, PP3_Strong, PM3_Supporting	Homozygous	Maternal & Paternal
4#	M	7y	Childhood	Diffuse sparse, curly hair; stable;	/	/	c.742C>A (p.H248N)	PM3_VeryStrong +PS3 +PM2_Supporting +PP3	Homozygous	Maternal & Paternal
5#	F	52y	Childhood	Diffuse sparse, curly hair; stable	TE	/	c.742C>A (p.H248N)	PM2_Supporting, PP3, PM3_Very Strong, PP1	Homozygous	Not performed
6#	F	21y	Childhood	Diffuse sparse, curly hair; diffuse hair shedding in last 2 years	/	/	c.742C>A (p.H248N)	PM3_VeryStrong +PS3 +PM2_Supporting +PP3	Homozygous	Maternal & Paternal

Abbreviations: M, male; F, female; Y, years; AGA, androgenetic alopecia; TE, telogen effluvium; PVS, pathogenic very strong; PS, pathogenic strong; PM, pathogenic moderate; PP, pathogenic supporting.

https://doi.org/10.2147/CCID.S544350

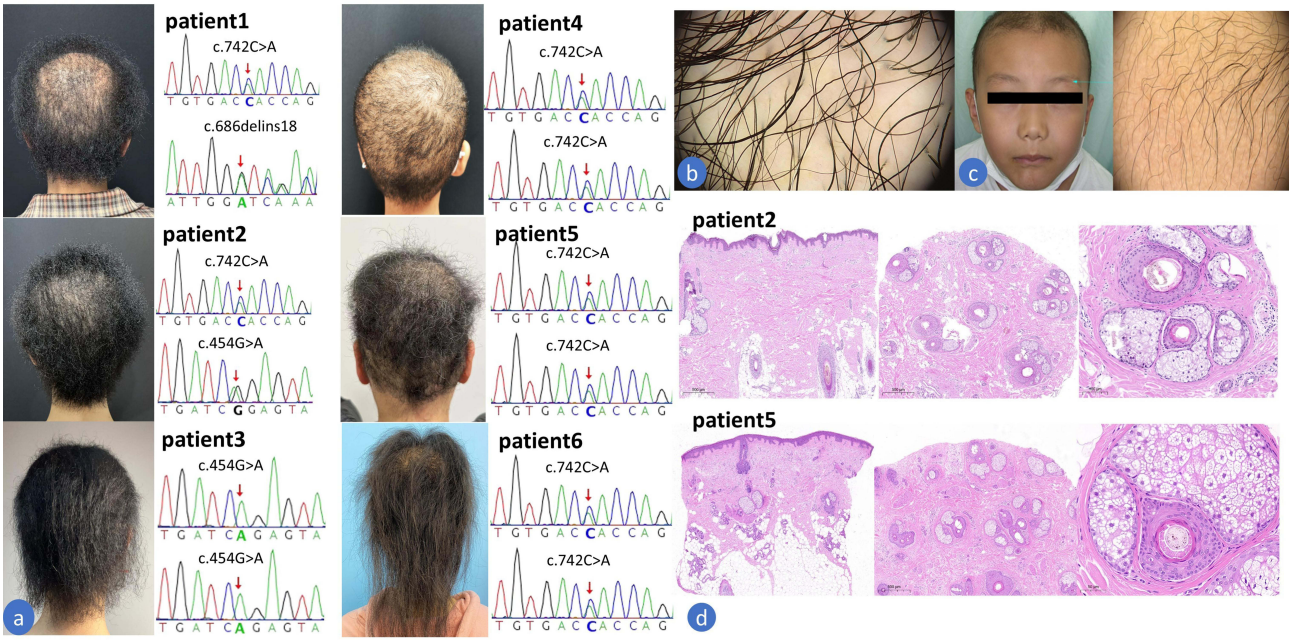

Figure 1 Clinical, Trichoscopic, Histopathological, and Genetic Characteristics of Patients with *LIPH*-Related Woolly Hair (**a**) Clinical presentation and whole-exome sequencing results of six patients with woolly hair; (**b**) Trichoscopy of Patient 2# reveals numerous fine, soft hairs exhibiting a curly pattern, resembling a wavy hair texture; (**c**) Trichoscopy of Patient 4# shows the eyebrows with a curved, irregular arrangement; (**d**) Histopathological findings of Patients 2# and 5#. Longitudinal sections showed no inflammatory cell infiltrates, while horizontal sections at the isthmus level demonstrated reduced follicle counts with some follicles showing abnormal morphology and triangular-shaped outer root sheaths. In Patient 5 #, an increased proportion of telogen follicles was noted, consistent with chronic telogen effluvium.

Discussion

In our study, Patient 3#, who was homozygous for the c.454G>A (p.G152R) variant, showed relatively preserved hair density, although the patient still reported fragile hair prone to breakage. Furthermore, Patient 2#, with compound heterozygous variants of c.742C>A (p.H248N) and c.454G>A (p.G152R), also showed less severe hair loss compared to patients with the homozygous c.742C>A (p.H248N) variant (Patients 4# and 6#).

Previous bioinformatics analyses demonstrated that the glycine at position 152 is highly conserved across species, and both SIFT and PolyPhen-2 predict the G152R substitution as deleterious or probably damaging, respectively.[8] The c.454G>A (p.G152R) variant has previously been functionally validated and implicated in disease pathogenesis.[8] Homology modeling showed that Ser154, Asp178, and His248 form the catalytic triad of PA-PLA1α (Figure 2).[8] The G152R substitution is positioned

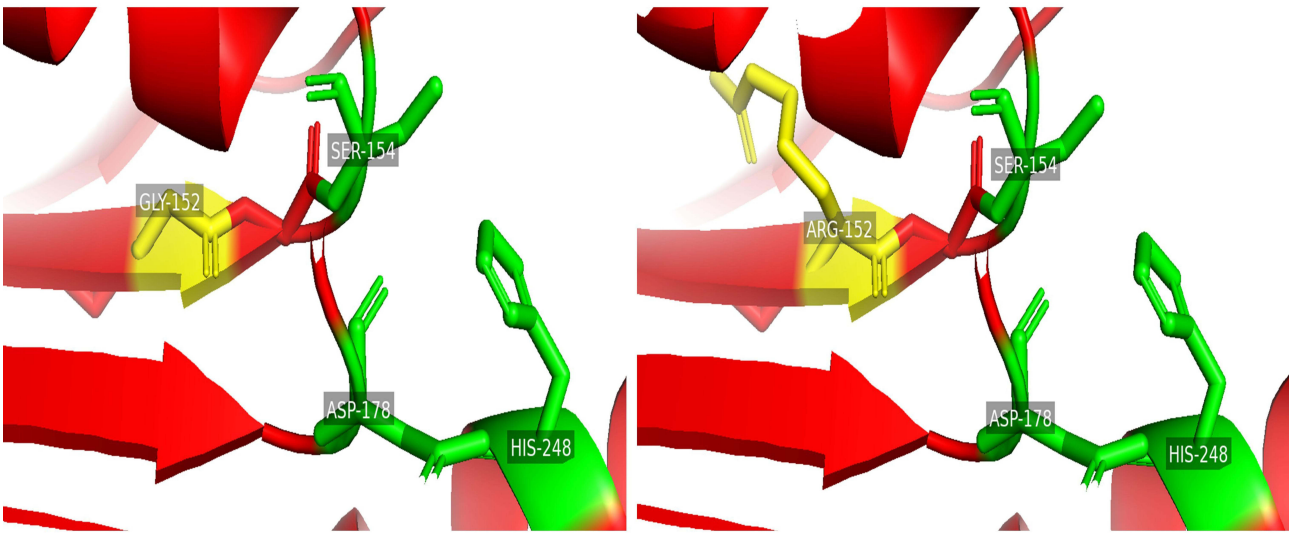

Figure 2 Structural modeling of the PA-PLA1α p.G152R variant. Homology modeling illustrates that Ser154, Asp178, and His248 form the catalytic triad, and the G152R substitution lies near the catalytic site, potentially affecting enzymatic activity.

adjacent to the catalytic serine and is predicted to disturb the geometry of the active site. Previous functional studies demonstrated that this variant causes secretion defects and loss of enzymatic activity, supporting the structural prediction.[8] In our cohort, the affected patient exhibited mildly reduced hair density but presented with hair shaft fragility. This observation raises the possibility that the variant may primarily affect hair shaft integrity, while exerting a comparatively smaller impact on follicular density. Nevertheless, further studies are required to substantiate this hypothesis.

Numerous studies have reported a high prevalence of *LIPH* mutation in populations from Japan,[9] the Volga-Ural region of Russia,[1] and Pakistan.[10–12] To date, no comprehensive population-based studies on the carrier frequency of *LIPH* mutation have been conducted in China. Based on present reported cases (Table 2), approximately 49% of ARWH patients in China harbor the c.742C>A (p.H248N) variant, while 12% carry the c.736T>A (p.C246S) variant, and 15% carry the c.454G>A (p.G152R) variant.[8,13,14] In the current study, among the six patients analyzed, the c.454G>A (p.G152R) variant was found in 25% of all alleles. This finding suggests that the c.454G>A (p.G152R) variant may represent a mutation with a potentially broader affected population in China, although this assumption requires further confirmation. By comparison, population-based studies in Japan have already established two founder variants, c.736T>A (p.C246S) and c.742C>A (p.H248N), which are known to be prevalent in the general population.

Table 2 Reported Variants in Autosomal Recessive Woolly Hair Patients in China

Variant	Zygosity	References
c.742C>A (p.H248N)	Homozygous	Liu et al 2014[13]
c.614A>G (p.H205R) **c.742C>A (p.H248N))**	Compound heterozygous	Chang et al 2017[8]
c.736T>A (p.C246S) **c.742C>A (p.H248N)**	Compound heterozygous	Chang et al 2017[8]
c.454G>A (p.G152R) **c.742C>A (p.H248N)**	Compound heterozygous	Chang et al 2017[8]
c.686delinsGTAGAACCCAACCTGGCT (p.Asp229fs37X) **c.736T>A (p.C246S)**	Compound heterozygous	Lv et al 2020[14]
c.736T>A (p.C246S) **c.742C>A (p.H248N)**	Compound heterozygous	Qu et al 2022[15]
c.530T>G (p.L177R) **c.736T>A (p.C246S)**	Compound heterozygous	Huang et al 2024[16]
c.742C>A (p.H248N)	Homozygous	Chen et al 2020[17]
c.742C>A (p.H248N)	Homozygous	Pan et al 2019[18]
c.742C>A (p.H248N)	Homozygous	Huang et al 2022[19]
c.742C>A (p.H248N) **c.982+12A>G**	Compound heterozygous	Zhao et al 2024[20]
c.629–1_629delinsTT **c.686delAinsCTAGAACCCAACCTGGCT**	Compound heterozygous	Zhao et al 2024[20]
c.454G>A (p.G152R) **c.736T>A (p.C246S)**	Compound heterozygous	Li et al 2022[21]
c.973C>T (p.P325S) **c.614A>G (p.H205R)** **c.454G>A (p.G152R)**	Compound heterozygous	Yu et al 2019[22]

(*Continued*)

https://doi.org/10.2147/CCID.S544350

Table 2 (Continued).

Variant	Zygosity	References
c.742C>A (p.H248N) **c.686delAinsGTAGAACCCAACCTGGCT (p.Asp229Glyfs*37)**	Compound heterozygous	This article
c.742C>A (p.H248N) **c.454G>A (p.G152R)**	Compound heterozygous	This article
c.454G>A (p.G152R)	Homozygous	This article
c.742C>A (p.H248N)	Homozygous	This article
c.742C>A (p.H248N)	Homozygous	This article
c.742C>A (p.H248N)	Homozygous	This article

Limitation

For Patients 1#, 2#, and 5#, Sanger sequencing of the parents was not performed due to personal reasons. In addition, Patient 1# had previously been diagnosed with female pattern hair loss, while Patient 5# was also diagnosed with chronic telogen effluvium during the clinical visit. While these conditions added complexity to the differential assessment, they are unlikely to confound the diagnosis of congenital woolly hair.

Conclusion

In conclusion, our study expands the spectrum of *LIPH* mutation associated with woolly hair in the Chinese population and further underscores the critical role of *LIPH* in regulating human hair growth and texture.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During manuscript preparation, the authors used ChatGPT for language polishing. All content was reviewed and verified by the authors, who take full responsibility for the manuscript.

Consent

Informed written consent for publication of clinical features and photographs was obtained from all patients, including the legal guardians of the 7-year-old child. Institutional approval was not required for publication of case reports.

Funding

This work was supported by the National Natural Science Foundation of China (82203951 to Chen); National Natural Science Foundation of China (82173447 to Wei).

Disclosure

The authors declare that there are no financial, personal, or institutional relationships that could have influenced the conduct or reporting of the work presented in this manuscript. All authors report no conflicts of interest related to this work.

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