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Molecular Analysis of Heredity Hypotrichosis in Consanguineous Families in the District of Karak, Pakistan

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ABSTRACT

Background: *Hereditary hypotrichosis is a rare genetic disorder characterized by sparse or absent scalp and body hair. It can manifest as an isolated condition or in association with other ectodermal abnormalities and follows either an autosomal dominant or recessive inheritance pattern. Variants in several genes, including HR, DSG4, LIPH, DSC3, KRT25, and LPAR6 (P2RY5), have been implicated in recessive forms of the disease. Among these, LPAR6, which encodes a G-protein–coupled receptor involved in lysophosphatidic acid (LPA) signaling, plays a crucial role in hair follicle morphogenesis and hair shaft differentiation.* ***Objective:*** *To investigate the clinical, genetic, and molecular basis of autosomal recessive non-syndromic hereditary hypotrichosis in two consanguineous families from the Karak district of Pakistan and to identify the underlying pathogenic variant.* ***Methods:*** *Two unrelated consanguineous families with multiple members affected by hypotrichosis were recruited for this study. Detailed clinical examinations and pedigree analyses were performed to document the phenotype and inheritance pattern. Genomic DNA was extracted from affected and unaffected individuals, and linkage mapping was conducted using highly polymorphic microsatellite markers. Sanger sequencing of the LPAR6 gene was performed to identify pathogenic variants. Conservation analysis, in silico pathogenicity prediction, and three-dimensional protein modeling were used to assess the functional impact of the identified mutation.* ***Results***: *All affected individuals exhibited early-onset, sparse, woolly scalp hair that remained thin and lightly pigmented throughout life, with no additional ectodermal anomalies. Linkage analysis localized the disease locus to chromosome 13q14.2, where LPAR6 resides. Sanger sequencing revealed a homozygous missense variant, c.436G>A (p.Gly146Arg), which co-segregated with the disease phenotype in both families. Conservation analysis showed that glycine at position 146 is highly conserved across species, indicating functional importance. In silico tools predicted the variant as "probably damaging," and protein modeling suggested that substitution with arginine disrupts the transmembrane helix, impairing receptor conformation and signaling.* ***Conclusion:*** *This study confirms the pathogenic role of the c.436G>A (p.Gly146Arg) variant in LPAR6 as the cause of autosomal recessive hereditary hypotrichosis in two Pakistani families. The findings expand the known mutational landscape of LPAR6, highlight the essential role of the LPA–LPAR6 signaling pathway in hair follicle development, and underscore the importance of genetic diagnosis and counseling in populations with high consanguinity. These results provide a basis for future research into targeted therapeutic approaches for hereditary hair growth disorders.*

Keywords
Hereditary hypotrichosis, autosomal recessive, LPAR6, woolly hair, consanguinity, gene mutation, hair follicle development

INTRODUCTION

Hair growth is a highly regulated biological process that serves not only aesthetic and protective roles but also acts as a clinical marker for various genetic and systemic disorders. Among these, hereditary hair disorders encompass a broad spectrum of phenotypes ranging from mild hair thinning to complete alopecia, often manifesting in early childhood and persisting throughout life (3). These conditions can occur in isolation or as part of multisystem syndromes and are frequently associated with significant psychosocial distress for affected individuals and their families due to their visible nature (3,6). Accurate identification of the underlying genetic cause is therefore crucial, not only for diagnosis and prognosis but also for genetic counseling, family planning, and potential targeted interventions.

Hypotrichosis is a rare hereditary hair disorder characterized by sparse or absent hair on the scalp and other body regions. It exhibits considerable phenotypic heterogeneity, with variations in hair texture, pigmentation, and associated cutaneous features. The condition can be broadly categorized into isolated forms, which occur without additional systemic abnormalities, and complex types that co-exist with ectodermal defects such as anomalies of teeth, nails, or sweat glands (6). The inheritance pattern of hypotrichosis may follow either an autosomal recessive or autosomal dominant mode, depending on the specific gene involved. Autosomal recessive forms are often associated with early-onset, severe hair loss and

may result from homozygous or compound heterozygous pathogenic variants in genes essential for hair follicle development and differentiation (6,7).

Several genes have been implicated in the molecular etiology of hypotrichosis, each contributing to different aspects of hair follicle morphogenesis. Recessive forms have been linked to mutations in genes such as HR (hairless) (2), DSG4 (desmoglein 4) (9), LIPH (lipase-H) (7), P2RY5/LPAR6 (G-protein-coupled receptor) (12), DSC3 (desmocollin-3) (5), and KRT25 (keratin 25) (4). These genes encode proteins involved in structural integrity, signaling, and lipid-mediated pathways critical for hair shaft formation and follicular maintenance. In contrast, autosomal dominant variants are often associated with milder phenotypes and involve genes such as CDSN (corneodesmosin) (10), APCDD1 (adenomatosis polyposis coli downregulated 1) (14), KRT74 (keratin 74) (16), and upstream regulatory elements of HR (18). Collectively, these findings highlight the genetic complexity and heterogeneity of hereditary hypotrichosis.

Among the known genes, LPAR6 (also known as P2RY5) has emerged as a critical regulator of hair follicle biology. This gene encodes a G-protein-coupled receptor that mediates lysophosphatidic acid (LPA) signaling, a pathway essential for hair growth and differentiation (12,15). Pathogenic variants in LPAR6 disrupt this signaling cascade, resulting in impaired follicular development and characteristic clinical manifestations such as sparse, woolly, or depigmented scalp hair (15). Previous studies have identified several disease-causing mutations in LPAR6 across diverse ethnic populations, with certain variants showing a higher prevalence in consanguineous families from South Asia and the Middle East (8,15,17). These observations underscore the importance of investigating population-specific genetic variants to better understand disease mechanisms and improve diagnostic precision.

The present study investigates two consanguineous families from the Karak district of Khyber Pakhtunkhwa, Pakistan, exhibiting an autosomal recessive form of non-syndromic hereditary hypotrichosis. Through molecular analysis, we aimed to identify the underlying genetic variant, establish genotype–phenotype correlations, and contribute to the growing body of knowledge on LPAR6-associated hypotrichosis. These findings provide further insight into the molecular mechanisms of hair development and may support future strategies for genetic counseling and targeted therapies in affected populations.

MATERIAL AND METHODS

This study was conducted following approval from the Advanced Studies and Research Board (ASRB) of Kohat University of Science and Technology (KUST), Pakistan. Written informed consent was obtained from all participants or their legal guardians prior to enrollment, including permission for the use of clinical photographs and genetic data for research and publication purposes. Two consanguineous families residing in the Karak district of Khyber Pakhtunkhwa, Pakistan, were recruited based on clinical suspicion of autosomal recessive non-syndromic hereditary hypotrichosis. Detailed pedigree charts were constructed after interviewing family members across four generations to trace inheritance patterns and assess consanguinity.

Comprehensive clinical examinations were performed on affected and unaffected individuals to evaluate hair density, distribution, and texture. Additional features such as the condition of teeth, nails, skin, and sweat glands were also examined to rule out syndromic associations. Blood samples (5 mL) were collected from affected individuals, their siblings, and parents using EDTA-containing vacutainers. Genomic DNA was extracted using the standard phenol–chloroform method as described by Sambrook et al. (13). DNA quantity and purity were assessed by spectrophotometry and agarose gel electrophoresis before proceeding to molecular analysis.

For genetic mapping, linkage analysis was performed using highly polymorphic short tandem repeat (STR) microsatellite markers spanning the chromosomal region 13q14.2, where the LPAR6 gene is located. The genetic positions and sequences of the markers were obtained from publicly available human genome linkage maps (11). PCR amplification was carried out for all selected markers, and genotyping was performed to determine allele segregation patterns. The presence of linkage to the LPAR6 locus was inferred from the co-segregation of specific haplotypes with the disease phenotype across multiple family members. Once linkage was established, the LPAR6 gene was prioritized for sequencing analysis.

Bidirectional Sanger sequencing was employed to amplify all coding exons and exon–intron junctions of the LPAR6 gene. PCR products were purified and sequenced using an automated sequencer. The obtained sequences were aligned and compared with the reference human genome sequence (Ensembl Genome Browser: http://www.ensembl.org/) using the BioEdit sequence alignment editor (http://www.mbio.ncsu.edu/BioEdit/bioedit.html) to identify single nucleotide variants. Variant pathogenicity was assessed based on allele frequency, conservation, and predicted functional impact. Segregation analysis was performed within families to confirm co-segregation of the identified variant with the disease phenotype.

To predict the structural and functional consequences of the identified nucleotide substitution, bioinformatic analyses were conducted. The potential deleterious effect of the amino acid change on protein structure and function was predicted using the PolyPhen-2 algorithm (http://genetics.bwh.harvard.edu/pph/) (15). Evolutionary conservation of the altered amino acid residue was evaluated by multiple sequence alignment of LPAR6 orthologs from various vertebrate species using the ClustalW tool (http://www.ebi.ac.uk/clustalw/). Additionally, three-dimensional structural modeling of the wild-type and mutant LPAR6 proteins was generated using PyMOL (Schrödinger, LLC) to visualize the spatial impact of the amino acid substitution on the transmembrane helix and receptor conformation.

All analyses were performed in accordance with established genetic research protocols and ethical guidelines. Variants were classified based on their predicted molecular impact, segregation evidence, and prior documentation in published literature. The methodological approach was designed to integrate clinical phenotyping, linkage mapping, molecular genetics, and bioinformatics analyses to elucidate the genetic basis of autosomal recessive hereditary hypotrichosis in the studied families.

RESULTS

Clinical Findings

Two unrelated consanguineous families (Family A and Family B) from the Karak district of Khyber Pakhtunkhwa, Pakistan, were recruited for this study. Pedigree analysis confirmed autosomal recessive inheritance in both families, with multiple affected individuals born to phenotypically normal carrier parents. Family A comprised four generations with two affected members (IV-1 and IV-3), while Family B included four generations

with two affected individuals (IV-6 and IV-8). In both families, consanguineous unions were consistently observed across generations, strongly supporting a recessive inheritance pattern (Figure 2).

Clinical examination revealed that affected individuals presented with sparse, woolly scalp hair from early childhood. The condition was non-progressive, with hair remaining thin, lightly pigmented, and tightly curled into adulthood. Other ectodermal structures, including teeth, nails, and skin, appeared normal, and no associated systemic abnormalities were detected. Notably, some affected individuals reported minor sweating disturbances. Body hair distribution was otherwise unremarkable. Representative clinical images of affected individuals during childhood (ages 6 and 7) and adulthood (ages 26 and 36) are shown in Figure 1.

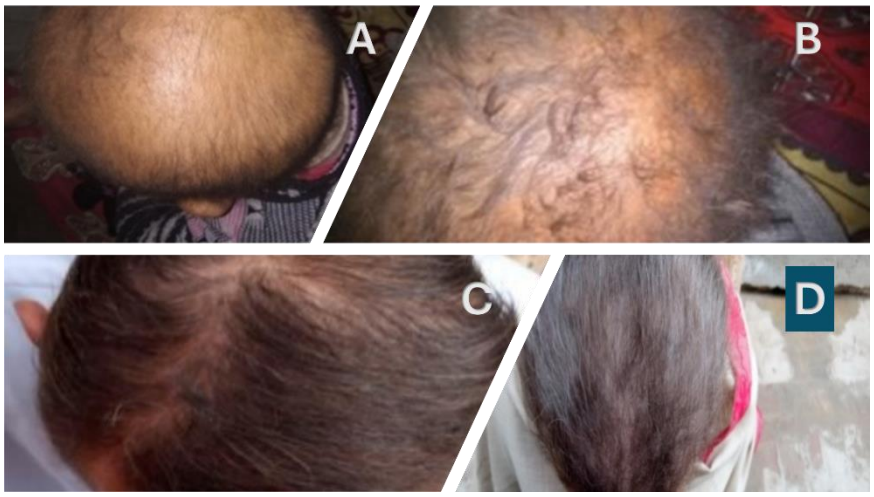

Figure 1 Clinical presentation of autosomal recessive hereditary hypotrichosis in affected and unaffected individuals from two consanguineous families. Panels A and B show pediatric patients aged 6 and 7 years, respectively, exhibiting sparse, woolly scalp hair characteristic of early-onset hypotrichosis. Panels C and D depict adult individuals aged 26 and 36 years with persistent thin, lightly pigmented, and woolly scalp hair, illustrating the chronic and non-progressive nature of the phenotype.

Pedigree and Genetic Analysis

Detailed pedigree analysis demonstrated autosomal recessive inheritance patterns in both families, with affected individuals segregating only among the offspring of consanguineous unions (Figure 2). DNA samples were obtained from a total of 14 individuals, including 4 affected and 10 unaffected family members. For Family A, genomic DNA was isolated from five members (two affected and three unaffected), while nine samples (two affected and seven unaffected) were collected from Family B.

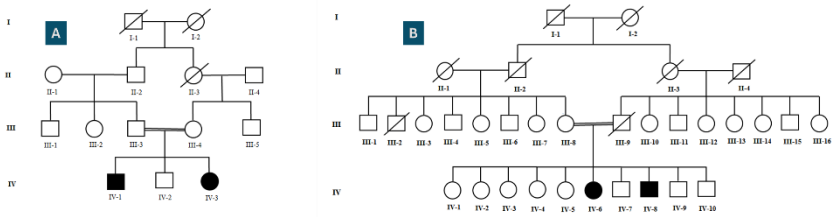

Figure 2. Pedigree analysis of two consanguineous families (A and B) affected by autosomal recessive hereditary hypotrichosis. (A) Pedigree of Family A demonstrating affected individuals (IV-1 and IV-3) born to consanguineous parents, with inheritance consistent with autosomal recessive transmission. (B) Pedigree of Family B illustrating multiple generations with consanguineous unions and affected individuals (IV-6 and IV-8). Squares represent males and circles represent females; filled symbols indicate affected individuals, open symbols indicate unaffected individuals, and diagonal slashes denote deceased family members. Asterisks mark individuals from whom DNA samples were collected for genetic analysis.

Genotyping was performed using highly polymorphic short tandem repeat (STR) markers flanking the LPAR6 locus at chromosome 13q14.2. Linkage analysis demonstrated co-segregation of the disease phenotype with markers surrounding the LPAR6 gene. The genetic markers and their relative positions are summarized in Table 1.

Table 1. microsatellite markers used for linkage analysis flanking the LPAR6 gene locus (13q14.2)

Marker ID	Chromosomal Position	Genetic Distance (cM)	Status
D13S287	13q14.11	51.7	Linked
D13S118	13q14.13	52.7	Linked
D13S164	13q14.2	52.0	Linked
D13S153	13q14.2	52.0	Linked
LPAR6	13q14.2	c.436G>A	Causative variant
D13S273	13q14.3	52.8	Linked

Sequence Variant Identification

Sanger sequencing of the coding regions and exon–intron junctions of LPAR6 revealed a homozygous missense variant c.436G>A, resulting in a glycine-to-arginine substitution (p.Gly146Arg) in affected individuals. Heterozygous carriers exhibited both wild-type and mutant alleles, while unaffected individuals were homozygous for the reference allele. The chromatograms of normal, heterozygous, and affected genotypes are presented in Figure 3.

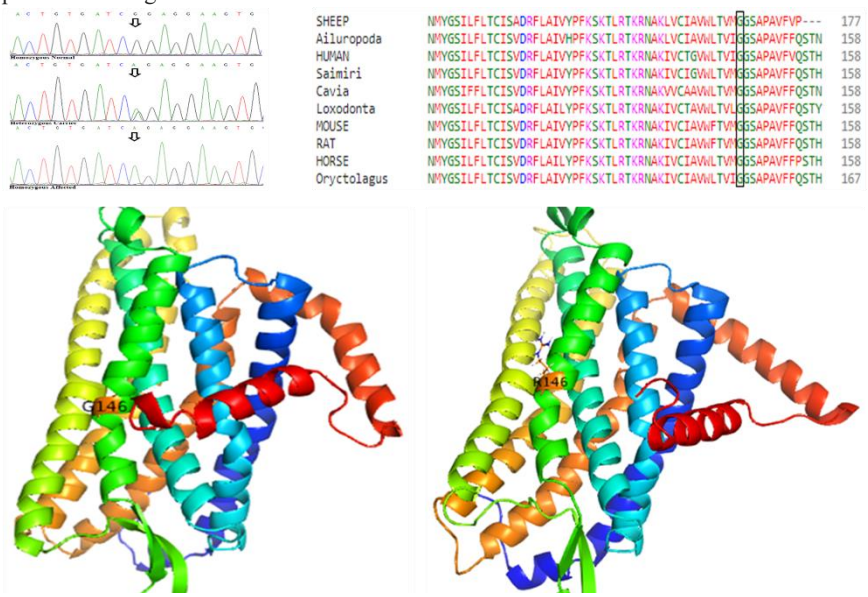

Figure 3. Molecular characterization of the LPAR6 gene variant associated with autosomal recessive hereditary hypotrichosis. (Top left) Sanger sequencing chromatograms showing the nucleotide substitution c.436G>A in three genotypes: homozygous wild-type (normal), heterozygous carrier, and homozygous mutant (affected). Arrows indicate the mutation site. (Top right) Multiple sequence alignment of the LPAR6 protein across several species demonstrates strong evolutionary conservation of the glycine residue at position 146, underscoring its functional importance. (Bottom left) Three-dimensional model of the wild-type LPAR6 protein showing glycine at position 146 located within the transmembrane helix. (Bottom right) Mutant protein structure illustrating the substitution of glycine with arginine (p.Gly146Arg), which is predicted to disrupt helix stability and impair receptor function.

The identified variant was absent from public population databases and co-segregated with the disease phenotype in all affected members, consistent with pathogenicity. Evolutionary conservation analysis demonstrated that the glycine residue at position 146 is highly conserved across multiple vertebrate species, indicating its structural and functional significance (Figure 3).

In Silico Functional Prediction and Structural Impact

In silico pathogenicity prediction tools (PolyPhen-2 and SIFT) classified the p.Gly146Arg substitution as “probably damaging” with a high confidence score (PolyPhen-2: 0.996; SIFT: 0.02). Multiple sequence alignment revealed that the glycine residue is evolutionarily conserved, suggesting a critical structural role in the transmembrane domain of the LPAR6 receptor.

Three-dimensional modeling of the wild-type and mutant LPAR6 proteins further supported these findings. In the wild-type protein, glycine at position 146 is localized within a transmembrane helix, contributing to the structural stability of the receptor. Substitution with arginine introduces a larger, charged residue that disrupts helix packing and may compromise receptor conformation and ligand-binding efficiency (Figure 3). These molecular effects likely contribute to impaired lysophosphatidic acid signaling, ultimately leading to defective hair follicle development and the hypotrichosis phenotype.

DISCUSSION

This study reports the molecular characterization of autosomal recessive non-syndromic hereditary hypotrichosis in two consanguineous families from the Karak district of Khyber Pakhtunkhwa, Pakistan. Clinical evaluation revealed a consistent phenotype across both families, characterized by sparse, woolly, and lightly pigmented scalp hair that presented in early childhood and persisted into adulthood without significant progression. No abnormalities were observed in teeth, nails, skin, or other ectodermal structures, and systemic involvement was absent. Minor sweating disturbances were reported in some affected individuals, but these were not clinically significant. These findings align with previously described phenotypic features of LAH3-type hypotrichosis, a well-documented autosomal recessive condition linked to mutations in the LPAR6 gene (12).

Genetic analysis confirmed linkage to chromosome 13q14.2, where LPAR6 is located, and Sanger sequencing identified a homozygous missense variant (c.436G>A, p.Gly146Arg) that co-segregated with the disease phenotype in all affected members. This variant results in the substitution of a conserved glycine residue with arginine at position 146, a change predicted to significantly alter protein structure and function. The LPAR6 gene, also known as P2RY5, encodes a G-protein–coupled receptor expressed predominantly in the inner root sheath of the hair follicle, particularly in Henle’s and Huxley’s layers, where it plays a critical role in hair shaft formation and follicular differentiation (15). Mutations affecting the structure or signaling capacity of this receptor disrupt normal hair development and lead to the hypotrichosis phenotype observed in our study.

Previous research has demonstrated that sequence variations in several genes—including LIPH, LPAR6/P2RY5, and KRT25—underlie autosomal recessive forms of woolly hair and hypotrichosis (15,17,19). Among these, the LPA–P2RY5 signaling axis is particularly important: oleoyl-L-α-lysophosphatidic acid (LPA), produced by the enzyme LIPH, binds to and activates LPAR6, initiating downstream signaling essential for hair growth and differentiation (12). Disruption of this pathway due to mutations in either LIPH or LPAR6 leads to similar clinical presentations,

highlighting their interdependent roles in follicular biology. Our findings further support this mechanism, as the p.Gly146Arg substitution likely impairs receptor conformation and signaling, resulting in defective hair follicle function.

Several previous studies have reported LPAR6 mutations in diverse populations, including consanguineous families from Pakistan, the Middle East, and Europe, underscoring the gene's significance in hair biology and its role in autosomal recessive hypotrichosis (1,8,15). For instance, a study in a Saudi Arabian family described two affected individuals with woolly scalp hair but otherwise normal hair growth on other body regions, consistent with the phenotype observed in our cohort (1). Similarly, Shimomura et al. (15) reported multiple affected members in large Pakistani families with sparse and twisted scalp hair but no additional ectodermal anomalies. Khan et al. (8) also identified LPAR6 mutations as the cause of hereditary woolly hair/hypotrichosis in five unrelated Pakistani families, further establishing this gene as a major contributor to the condition. According to the Human Gene Mutation Database (HGMD), at least 27 pathogenic variants have been reported in LPAR6, highlighting the genetic heterogeneity associated with this locus.

The identification of the c.436G>A (p.Gly146Arg) variant in our study reinforces its pathogenic significance and expands the mutational spectrum of LPAR6. The evolutionary conservation of glycine at position 146 across multiple species suggests that this residue is essential for receptor structure and function, and its substitution likely destabilizes the transmembrane helix, disrupting ligand–receptor interactions. These molecular findings correlate well with the clinical phenotype, providing strong evidence for a genotype–phenotype relationship. Moreover, the recurrence of this variant in Pakistani families suggests a possible founder effect, warranting further population-based genetic studies to determine carrier frequency and penetrance in regional populations.

In summary, our findings provide additional evidence that mutations in LPAR6 are a major cause of autosomal recessive non-syndromic hereditary hypotrichosis. The identification of the p.Gly146Arg variant in two consanguineous Pakistani families contributes to the growing understanding of hair follicle biology and underscores the importance of genetic testing and counseling in populations with high rates of consanguinity. These results not only enhance our knowledge of the molecular mechanisms underlying hypotrichosis but also provide a foundation for future research aimed at developing targeted therapeutic strategies for affected individuals.

CONCLUSION

This study provides comprehensive clinical, genetic, and molecular evidence confirming the pathogenic role of the c.436G>A (p.Gly146Arg) variant in the LPAR6 gene as the underlying cause of autosomal recessive non-syndromic hereditary hypotrichosis in two consanguineous families from Pakistan. The consistent clinical phenotype—characterized by sparse, woolly scalp hair with no associated ectodermal abnormalities—together with strong linkage analysis, segregation data, and structural modeling supports a clear genotype–phenotype correlation. The evolutionary conservation of glycine at position 146 and the predicted structural disruption caused by its substitution further highlight the critical role of LPAR6 in hair follicle development and differentiation.

These findings expand the known mutational spectrum of LPAR6, underscore the importance of the LPA–LPAR6 signaling pathway in human hair growth, and emphasize the value of genetic testing and counseling in populations with high rates of consanguinity. Moreover, this study provides a foundation for future research aimed at understanding the molecular mechanisms of hair follicle biology and developing potential targeted therapies for hereditary hypotrichosis.

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