

# Hereditary Alopecia in Pakistani families

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Hereditary alopecia is a heterogeneous group of inherited hair loss disorders with different clinical features, modes of inheritance, and genetic bases. It is characterized by diffuse or localized thinning or absence of hair beginning at birth or early childhood. The loss of hair affects the scalp, eyebrows, eyelashes, body hair, axillary and pubic hair.

Total or partial absence of hair may occur either in isolation or with associated ectodermal abnormalities as a part of syndrome of a very diverse nature. On the bases of such associations, several different syndromes featuring congenital alopecia can be distinguished. The major defects reported to be associated with total or partial absence of hair, either single or in various combinations include mental retardation, dwarfism, epilepsy, nail dystrophy, total or partial anodontia, hyperkeratosis, impaired sweating, cataracts, retinitis pigmentation etc.<sup>1</sup> In familial cases, inheritance is usually autosomal recessive, but families with autosomal dominant or X-linked recessive inheritance have also been reported. Patients with recessive form tend to have a more severe phenotype, often with complete absence of hair development, affecting scalp and body hair.

There are many forms of inherited alopecia, which vary in age of onset, severity, and associated ectodermal abnormalities. The identification of hereditary alopecia genes is an essential step in understanding the molecular

mechanism of hair loss.

Hair-follicle morphogenesis is a multistep process that requires a series of epithelial-mesenchymal interactions to execute the programme of developmental events. Hair follicles vary considerably in size and shape, depending on their location, but they all have the same basic structure. Hair follicle cycles go through periods of growth (anagen), involution (catagen), and rest (telogen) before regenerating at the onset of a new anagen growth phase. A powerful approach to advance our understanding of the pathophysiology of hair loss is to identify the genes underlying isolated and syndromic forms of hair loss. This provides an opportunity to identify factors which are directly involved in hair growth.

To date only three mutations (all deletions) in LIPH gene have been reported. The first mutation deletion of 985 bp of exon 4 and the flanking intronic sequences of LIPH gene was reported by Kazantseva et al. (2006) in large number of affected individuals of two populations from the Volga-Ural region of Russia.<sup>2</sup> The second mutation was reported by Ali et al. (2007) a five base pair deletion mutation (c.346-350delATATA) in exon 2 of the gene leading to frameshift and downstream premature termination codon.<sup>3</sup> The third deletion mutation of two base-pairs (c.659-660delTA), located in exon 5 of the LIPH gene, was identified recently in two families originating from Pashto speaking population in North Western Frontier Province of Pakistan.<sup>4</sup>

LIPH has been shown to exert stimulatory effect on proliferation and migration of cells via a G-protein couple receptor P2Y5 encoded by a gene P2RY5. Recently, Azeem et al. (2008) have shown that mutations in P2RY5 gene result in autosomal recessive hypotrichosis simplex and autosomal recessive woolly hair in Pakistani family.<sup>5</sup>

Taken together, the mutational and functional studies of LIPH and P2RY5 genes, suggested an integrated model in which LPA (lysophospholipid mediator), Lipase H and P2Y5 are involved in regulation of hair growth.

Congenital atrichia (MIM 209500) is a rare form of irreversible autosomal recessive disorder. Clinical features of affected individuals with this form of alopecia include: shedding of normal scalp hair several months after birth with failure to regrow; appearance of skin papules within the first year of life; sparse eyebrows and eyelashes; lack of secondary axillary, pubic, or body hair; and normal nails, teeth, and

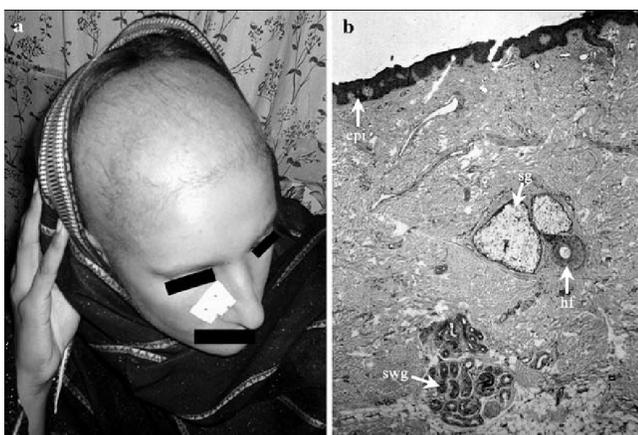


Figure-a: Clinical presentation of autosomal recessive form of Alopecia in Pakistani family. Phenotypic appearance of an affected individual of the Punjabi family showing sparse hairs on scalp, sparse eyebrows and eyelashes.

Figure-b: Scalp skin biopsy from an affected individual of Pakistani family with Alopecia disease revealed complete absence of normal hair follicle structures. The remnants of the hair follicle infundibulum undergo hyperkeratinization. epi epidermis, sg sebaceous glands, swg sweat glands, hf hair follicle.

sweating. To date, families with congenital atrichia have been reported from 17 backgrounds, including Pakistani, Japanese, Polish, German, Israeli, Palestinian, Mexican, Italian, Korean and Mediterranean populations.

Congenital atrichia has been linked to 8p21, where several mutations of the hairless gene (HR, MIM 602302) have been reported as the underlying cause of congenital atrichia. To date, more than 38 different pathogenic mutations in affected individuals of various ethnic origins have been reported for the human HR gene.<sup>6</sup>

Marie unna hereditary hypotrichosis (MUHH; OMIM 146550) is a rare autosomal dominant disorder. Light microscopic examination from hair of the scalp could show thick, irregular, and twisted hair. The MUHH locus mapped to the same region of chromosome 8 as the human hairless gene (HR) which had been shown to carry recessive mutations responsible for congenital atrichia with papules.<sup>6</sup>

To date, three clinically similar forms of autosomal recessive hypotrichosis have been reported. Localized autosomal recessive hypotrichosis (LAH; MIM 607903) has been mapped to the region of the desmosomal cadherin gene cluster on chromosome 18q12.1, which contains the genes for desmogleins (DSG1, DSG2, DSG3, and DSG4) and desmocollins (DSC1, DSC2, and DSC3). A large, intragenic deletion of exons 5-8 (EX5\_8del) in desmoglein 4 gene (DSG4; MIM 607892) was found to be the underlying defect in two unrelated LAH families of Pakistani origin.<sup>7</sup> The same deletion mutation was subsequently detected in six additional Pakistani kindreds,<sup>8</sup> suggesting that it represents an ancestral mutation that has been widely dispersed. Recently, Wajid et al. (2007) identified a single nucleotide deletion 87delG with in exon 3 of the DSG4 gene.<sup>9</sup>

A second autosomal recessive hypotrichosis locus (AH / LAH2; MIM 604379) was mapped on chromosome 3q27. The AH locus overlaps with an alopecia mental retardation syndrome (APMR1) locus.<sup>1</sup> Interestingly, another alopecia with mental retardation syndrome (APMR2) locus was mapped proximal to AH and APMR1 loci.<sup>10</sup>

Recently, Wali et al. (2007a) ascertained two consanguineous Pakistani families from Bahawal-nagar demonstrating autosomal recessive form of hereditary hypotrichosis.<sup>11</sup> The affected individuals in these two Pakistani families exhibited typical features of the hereditary hypotrichosis. Genome wide scan using polymorphic microsatellite markers led to the identification of a third locus (LAH3; MIM 611452) on chromosome 13q14.11-q21.32 of Pakistani family.

Alopecia with mental retardation syndrome (APMR,

MIM 203650) is a rare autosomal recessive form of alopecia which show hair loss on the scalp, absence of eyebrows, eyelashes, axillary and pubic hair, and mild to severe mental retardation (1;10;12). John et al. (2006a) have mapped the APMR1 locus to human chromosome 3q26.33-q27.3 in a Pakistani family with severe mental retardation (IQ from 25-30).<sup>1</sup> The second locus for alopecia and mental retardation (APMR2) was mapped to chromosome 3q26.2-q26.31 in a Pakistani family with total alopecia and mild to moderate mental retardation (IQ from 53-61).<sup>10</sup> Recently, Wali et al. (2007b) reported the mapping of a third locus for alopecia and mental retardation syndrome (APMR3) in a large Pakistani family at chromosome 18q11.2-q12.2.<sup>12</sup>

Exclusion of several alopecia genes from linkage in Pakistani families predicts the involvement of novel gene in generating alopecia like phenotype. Therefore, identification of these genes may provide the new insights into epidermal differentiation and its effect on hair growth control mechanism.

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