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GENE INVOLVED IN HUMAN GENETIC HAIR LOSS DISORDER

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Abstract

The hereditary hair disorder diagnosis is very essential to detect the reason of abnormalities. Hair disorders are of many types can be inherited in isolated and non-isolated form. These disorders are very rare. The family's history and Phenotypic inspection of hair and other ectodermal structures such as sweat glands, nails and inquiry of all provide important evidences to begin the correct diagnosis. Many causal genes for hereditary hair diseases have been identified due to significant developments in molecular genetics. These genes are located on different human chromosomes, Alopecia is a group of inherited abnormalities associated with hair loss that can occur in dominant or recessive forms. i.e The HR, LIPH, LPAR6, DSG4 and DSC3 genes are involved in autosomal recessive forms of hair loss. These genes shows different mutations in different human population. Mutations in the APCDD1, CDSN, KRT74, genes, as well as the U2HR, 5, EPS8L3, SNRPE, and RPL21 genes, have been linked to autosomal dominant hair loss disorders. Corneodesmosomes, they are found in various cornified squamous epithelia as well as the human epidermis is a protein, encoded by CDSN gene. In human populations, this gene is highly polymorphic. Variations have been linked to skin illnesses such psoriasis, hypotrichosis, and peeling skin syndrome. An abundantly generated membrane-bound glycoprotein in human hair follicles is called APCDD1. It works ahead of -catenin and inhibits Wnt signalling in a cell-autonomous manner. KRT74 is the epithelial (soft) keratin 74 that is particular to the inner root sheath (IRS).. More than likely, KRT74 haploinsufficiency is the primary cause of woolly hair. The goal of this review was to look into the mutations and functions of the muted genes that encode different types of proteins and are responsible for autosomal recessive and dominant alopecia.

Keywords: *Alopecia, Hereditary, Hair loss, HR, LIPH, LPAR6, DSG4, DSC3, APCDD1, CDSN, KRT74, U2HR, 5, EPS8L3, SNRPE, RPL21MI*

INTRODUCTION

Hereditary hair loss is among the most prevalent reason of hair loss, affecting a big number of men and women, and many people notice that it grows worse as they get older. Both adults and children can develop severe alopecia due to genetic hair problems, which can sometimes manifest as a multisystem disease. Hair loss, whether total or partial, is frequently seen in conjunction with other abnormalities as part of a wide range of disorders (1) or as a stand-alone anomaly. The following is a list of main defects linked to complete or partial hair loss, either singularly or in various combinations, as examined by (1) mental retardation, nail dystrophy, Dwarfism, microcephaly, epilepsy, hyperkeratosis, total or partial anodontia, cataracts, retinitis pigmentosa, impaired sweating, and other conditions are among the most common. Therefore, identifying these genetic anomalies is essential not only for starting the right treatment, but also for finding further ectodermal problems and getting the right genetic counselling. The children and parents who are affected by such situations typically have psychological effects (2).

EPIDEMIOLOGICAL DATA

Alopecia, or hair loss, is a prevalent complaint in dermatology offices and can be brought on by a number of diseases, each with its own identification. Despite the fact that androgenetic alopecia is the most common kind of hair loss in adults,, there are other types of hair loss (3). The prevalence of particular kind of baldness may be influenced by environmental and cultural variables. The clinical presentation, age, and sex hair loss in locations other than the scalp, itching or scales, afflicted site, and the course of the condition are all factors to consider are all essential considerations in the classification of hair disease. A hair problem

could be caused by a dietary deficiency, such as a lack of iron or zinc. As a result, a paediatrician or dermatologist's hair examination is an important aspect of the physical examination (4).

AUTOSOMAL RECESSIVE FORMS OF ISOLATED HAIR LOSS

The associated genes have been identified in all but three of the at least seven autosomal recessive variations of isolated hair loss syndromes that have been identified to different human chromosomes. Hair loss syndromes that are autosomal recessive have been linked to gene mutations, including HR, LIPH, LPAR6, DSG4 and DSC3 genes. Genetic analysis is a strong tool for determining a gene's and biological function of proteins which are encoded by them. Many genes that encode proteins with well-defined biochemical roles have had loss-of-function mutations as a result of the advancement of technology that makes it possible to change the mouse genome. A number of spontaneous mutations in mice, including the mammalian hairless (hr) gene, fall into this category. Hereditary alopecia affecting the scalp, trunk, and extremities is known as autosomal recessive hypotrichosis. The majority of people affected have sparse to non-existent brows and eyelashes. Affected men may acquire normal beard hair in some circumstances.

HR GENE

The hair follicle (HF) is known as dynamic structure that produces hair by intricately controlled remodelling cycles and growth. However, little is understood about the nature, chronology, and interactions between the chemical signals that cause the HF to cycle through the states of rest (telogen), growth (anagen), and regression (catagen) (5). One vitally useful regulatory molecule for modulating the hair cycle is the hairless (hr) gene, according to several lines of evidence. Papular atrichia is a disorder caused by hairless gene autosomal recessive mutation in humans (6). HF malformations demonstrate that the product of HR gene promotes to normal skin physiology in a functionally significant way, specifically when HF cycling begins as a cell enters the first catagen (5). This was subsequently validated by the discovery of the human equivalent of the hr gene, in which a recessively inherited mutation causes papular atrichia (total loss of body hair) (7). On chromosome 8p21, which is about 14 kb long and has about 19 exons, the human hairless gene is found. It took 75 years for the hr gene mutation to be first identified in a mouse. An endogenous retrovirus generated the original mutation, and By identifying the site of the retroviral insertion, the mouse hr gene was cloned (8). Later, it was determined that the mammalian ortholog was connected to genetic hair defects. There are several mouse and human alleles known, and they all exhibit the same pattern: normal development of hair at first, but no hair growth after shedding. The phenotypic varies, but it can include full hair follicle loss, papular rash, and severe skin wrinkles (9). In humans, congenital atrichia is an unusual, recessively inherited form of baldness that affects both men and women and is characterised by the complete absence of hair follicles. Missense, nonsense, and deletion mutations in the hr. Gene are connected to congenital atrichia. A mutation in the human hairless gene has recently been linked to the development of congenital atrichia (10). HR produces a 130-kilodalton protein that has a significant impact on hair follicles, the epidermis, and the brain (11, 12). This gene is important in the cellular transition of the hair cycle; if it is not present, hair follicles degenerate and never rebuilds (13). A missense variation in the zinc-finger area of the hairless hr gene has been found in a sizable inbred family of Irish travellers who have congenital atrichia (7). Two consanguineous families from Basti Mochi Wala and Mouza Gulab Shah in Punjab's Muzaffargarh District were studied for the deletion c.429delc in exon 2 of the HR gene (Pakistan) (14). Exon 9 of the mammalian hairless gene contains the first deletion mutation (2147del C) in Five Palestinian families of Arab heritage, which causes a frameshift and a downstream premature stop codon.The discovery of a 22-bp loss in exon 3 of the hairless gene in huge Arab Palestinian Israeli villager's consanguineous family from a nearby village was reported (15).

LIPH GENE

LIPH is a member of the phospholipase A1 family with three catalytic residues: 154S, 178D, and 248H. At its N-terminus, it also features a ß9 loop and a lid domain, both of which are important for substrate recognition. The cysteine residue at position 246 is thought to be crucial for disulfide bond

formation. As a result, the p.C246S mutation is expected to have a significant impact on the structure of the *LIPH* protein. Similarly, the mutation p.H248N occurs in one of the *LIPH* protein's three catalytic residues, causing the enzyme to operate abnormally. Furthermore, both 246C and 248H are highly conserved among *LIPH* from various species as well as other members of the human lipase family (16). The lipase enzymes are encoded by the *LIPH* gene. These enzymes are responsible for the breakdown of phosphatidic acid and the production of LPA (lysophosphatidic acid) and free fatty acids. *LPA* acts as a ligand and has a number of receptors, one of which is LPA6, which is responsible for the maturation and regulation of the number of cells in hair follicles. Hair development is dependent on the appropriate function and division of these cells, hence their management is critical.

Because of its LPA production and regulation in hair growth, research suggests that mpa-PLA1a / *LIPH* contributes to inherited hairloss problems. Problems in the phospholipase gene, or *LIPH*, are the root cause of human hair development defects, according to research (17). According to Kazantesva, *LIPH* is a novel gene for hair growth problems that has been identified in 350,000 people from two Russian groups (17). According to studies, *LIPH* gene which is found on 3q27 chromosome has a deletion anomaly in those who are homozygous for it (16, 17). The AH trait has been traced to chromosome 3q27 in a four-generation Pakistani family (18). A unique five base pair deletion mutation (346 350delatata) was discovered in the putative gene *LIPH's* exon 2, as a result frame-shift and a downstream premature stop codon are caused (19) discovered two big consanguineous families of Pakistan having hypotrichosis that was autosomal recessive. The 3q27 chromosome's *LAH2* gene was linked to family. The *LIPH* gene was screened and unique deletion variant (659-660delta) of exon 5 was discovered.

LPAR6 GENE

The LPAR6 gene is made up of a single exon that is encased within the RBI gene's intron. *LPAR6* has a 344-amino-acid putative ORF. It encodes the P2Y5 protein, Due to the fact that they both have seven hydrophobic transmembrane domains and share a sequence, the P2Y family of G protein coupled receptors (gpcrs) (20). When expressed, P2Y5 in the epidermis's excellentasal layer and the inner root sheaths of hair follicles's Henley's and Huxley's layers, which increases with differentiation (21). LAH3, HYPT8 or WH phenotypes are caused by *LPAR6* gene mutations, according to two studies (22). The *LPAR6* gene, which controls LAH3 and on chromosome 13q14.11-q21.32, there is a gene called *HYPT8* (23). 23 abnormalities have so far been found in various families, 11 of which were identified in 41 Pakistani consanguineous (24). The missense mutation Gly146Arg is the most frequent mutation generating *HYPT8* in 12 distinct families. The bioinformatic analysis proved that the missense mutation weakens the P2RY5 protein's overall structure, confirming that *LPAR6* frequently plays a role in autosomal recessive woolly hair/hypotrichosis (25).

The phenotypes of people who have LAH3 include tightly coiled and brittle hair that grows slowly (26). Hair is regrown with delicate and curled hair after routine shaving (27). Affected members have regular to sparse eyelashes, eyebrows, pubic and axillary hairs (24, 27). In impacted members, a skin sample reveals smaller and smaller hair follicles (28).

DSG4 GENE

The hair shaft layer, the topmost inner root sheath of the human hair follicle's internal epithelial layers, is where this gene is located and underneath the cuticle of the hair (29) Desmosomes are formed at these sites because of this. *DSG4* is a 16-exon gene that encodes a desmosomal cadherin superfamily component. Desmosomes has a fuction in cell-to-cell adhesion and are essential for hair follicular growth and development (30). This is accomplished through interactions between their extracellular areas that are either homophilic or heterophilic.

The *DSG4* gene was found to be the most effective gene for LAH1 hypotrichosis, which is a type of localized autosomal recessive hypotrichosis (31). On chromosome 18q21.1, the *DSG4* gene can be located (32) Ex5 8del is a marker for four exons that trigger in frame deletion mutation in the EC2 region and parts of the EC1 and EC3 regions. P.pro267arg, p.Lys30Argfsx54, and p.Ala129Ser are three further homozygous

aberrations that have been discovered to be the cause of *LAH1* (33). Coarse, short, and brittle hair is a trait of LAH1 induced by the DSG4 gene. On the other hand, inherent hair may or may not exist on the scalp (32, 33), which can be recover after one week of birth by regular shaving. Affected individuals have a sparse to complete loss of brow and eyelashes, despite having adequate pubic and axillary hair (48). Affected men have normal bread, but their legs and arms are hairless (34). Affected people's hair shafts have an uneven enlargement (33, 34).

DESMOCOLLIN-3 (DSC3)

Desmosomes are important participants in the epidermis and heart muscles, where they aid in intercellular binding and tissue integrity. Desmogleins and desmocollins are two transmembrane cadherins that are key components of desmosomes. Disruption of these desmosomal proteins in mice models and human disorders has demonstrated their importance in epithelial integrity (36). The 52 kilobyte *DSC3* gene expresses in the epidermis with two extra desmocollins and contains 16 exons (*DSC1* and *DSC2*). In both mice and humans, Dsc1/DSC1 expression is restricted to the epidermis' top layer (37). Only minimal Dsc2/DSC2 expression is seen in the basal layer of the epidermis (38) and the basal and early suprabasal layers of the epidermis are where *DSC3* is most expressed (39). *DSC3*, like other cadherins, is a transmembrane component of desmosomes that consists of a signal sequence (amino acids 1-27), a propeptide (amino acids 28–135, 136–690, 691–711 and a c-terminal cytoplasmic domain) (712–896 amino acids). Five cadherin domains make up the additional division of the extracellular domain (amino acids 136–243, 244–355, 356–471, 472–579 and 580–690). The first four sub domains each have roughly 110 amino acid repetitions; four cystein residues are present in the fifth sub domain. A self-folding sequence, each cadherin repeat contains motifs from the conserved DRE, DXNDNAPXF, and DXD sequences (40). At the domain-domain interface, the many cadherin domains produce calcium-dependent rod-like structures, with a calcium-binding site. Each cadherin repetition requires specific residues to be attached by calcium ions in order to maintain proper folding and give the extracellular domain rigidity, both of which are necessary for cadherin adhesive activity. Plakophilin, Plakoglobin and Desmoplakin proteins found in desmosomal plaques, interact with intermediate filaments of cytoskeleton elements by binding to intracellular cadherin repeat sections (41). Cadherins play a role in cell fate, signalling, migration, differentiation and cell-cell interaction are also mediated by proliferation. *DSC3* has been shown to play a role in the desmosomes' typical behavior, the anchoring of the telogen hair shaft and preservation of interfollicular epidermis structural integrity in mice (42). According to Chen *et al.*, 2008, pattern of hair loss indicated a problem with telogen follicle anchorage (42). Two epithelial cell layers that enclose the lower part of the hair shaft are what hold hair to the skin, according to those researchers. It is believed that the absence of this protein causes a loss of cell adhesion and hair loss because *DSC3* is present in significant concentrations in both of these cell layers.

AUTOSOMAL DOMINANT FORMS OF ISOLATED HAIR LOSS

Mutations in the *APCDD1, CDSN, KRT74* genes, as well as the *U2HR, 5, EPS8L3, SNRPE*, and *RPL21* genes have been linked to autosomal dominant hair loss disorders.

On different human chromosomes, seven autosomal dominant variants of isolated hair loss diseases have been identified. The human hair follicle is a complicated mini-organ that develops from intricate morphogenetic processes (43).

By identifying various pathways in hair formation, molecular research of using consanguineous families as a source of information has proven to be effective in order to uncover these connections (44) described the first case of alopecia resulting from a variation in the hairless (HR) gene on chromosome 8p21.1, which caused atrichia and papular lesions in the affected individuals. Disruption of *DSC3* and *DSG4* on chromosome 18q12 caused hypotrichosis (patch hair loss) and monilethrix hair loss, along with a vesicular appearance on the skin (29). Multiple genes/loci were found to be involved with overlapping hypotrichosis symptoms, including lipase-H (LIPH) on chromosome 3q27 (17). On chromosome 13q14, there

is a G-protein coupled receptor (LPAR6/P2RY5), and on chromosome 10q11.23-22.237, there are loci with unknown genes (45).

CDSN (CORNEODESMOSIN)

Corneodesmosomes, which are seen in a protein, found in the human epidermis and other cornified squamous epithelia, encoded by this gene. During corneocyte maturation, the encoded protein goes through a series of cleavages. In human populations, this gene is highly polymorphic and variations have been linked to skin illnesses such psoriasis, hypotrichosis, and peeling skin syndrome. The gene is found in major histocompatibility complex (MHC) class I area on chromosome 6.

Cornification is the process of changing keratinocytes into anucleated, flattened corneocytes at the end of epidermal development (46). In the upper epidermal layer, modified desmosomes called corneodesmosomes produce specialised keratinocyte intercellular connections that are crucial for cornoecyte cohesion (46). Corneocyte building generates stratum corneum, a cornified layer of the epidermis, structural barrier that protects the environment (47). Dsg 1, corneodesmosin and desmocollinare the transmembrane corneodesmosomal proteins (*CDSN*) (48). A 52–56 kda basic glycoprotein found only in the inner hair follicle root sheath and cornified epithelia of humans is called CDSN, or the S gene. It is located 160 kb telomeric of HLA-C (6p21.3) and encodes a basic glycoprotein with a 52–56 kda molecular weight (49). A 529-amino-acid protein called CDSN has a high serine and glycine content of 27.5 and 16%, respectively. This property is shared by a number of other epidermal proteins (50). Desmosomes modified by corneodesmosin (*CDSN*), *DSG1* and *DSC1* are found in the epidermis (corneodesmosomes). *CDSN* is expressed in the IRS starting at a later stage of keratinization and continuing until the IRS is destroyed (51), implying that IRS terminal difference involves *CDSN*. Heterozygous nonsense mutations in the *CDSN* gene are the source of hereditary hypotrichosis simplex that only affects the scalp. Histological analysis of the HF in patients revealed disruption of the IRS and aggregates of aberrant *CDSN* around the HF and papillary dermis, demonstrating the dominant-negative function of the mutant *CDSN* protein.

APCDD1 (ADENOMATOSIS POLYPOSIS DOWN-REGULATED 1)

Degenerative HF miniaturisation characterises hereditary hypotrichosis simplex is an autosomal dominant disorder characterised by the transition from thick vellus hair to fine terminal hair (52). In human HF, there is a mutation in the gene *APCDD1*, which is strongly expressed in both the dermal and epidermal compartments. Human hair follicles produce a lot of *APCDD1*1,a membrane-bound glycoprotein that can interact in vitro with WNT3A and LRP5, two essential elements of Wnt signalling. Upstream of -catenin, *APCDD1* inhibits Wnt signalling in a cell-autonomous way, according to functional investigations. Furthermore, *APCDD1* axis specification in Xenopus laevis embryos creates of neurons from progenitors during the development of the chick nervous system by inhibiting the activation of Wnt reporters and target genes. *APCDD1's* signal peptide contains the mutation Leu9Arg, which disrupts translation from the plasma membrane to the endoplasmic reticulum. *APCDD1* (L9R) is thought to act as a dominant-negative inhibitor of the wild-type protein's stability and membrane localization. These findings describe a new Wnt signalling pathway inhibitor that plays an important function in growing human hair. *APCDD1* is expressed in a wide variety of cell types. *APCDD1* may have an impact on a number of biological processes that are influenced by Wnt signalling (53). In families with androgenic alopecia, *APCDD1* has been linked to linkage intervals (54) as well as alopecia areata (55).

KRT74 (KERATIN-74) GENE

Keratin-74 (KRT74) is the epithelial (soft) keratin 74 that is particular to the inner root sheath (IRS) (53). The 529-amino-acid K74 protein is encoded by nine exons in the *KRT74* gene. Similar to other keratins, the K74 protein includes three domains: an N-terminal head domain (1-139 amino acids), a middle helical rod domain (140-149 amino acids) and a C-terminal tail domain (450-529 amino acids). Three alternative cryptic splice sites can be created by a splice site mutation that has been discovered. The coding sequence of exon 9 has a cryptic splice site (accaccccagctctgcgggt) 38 nucleotides downstream; this can lead to the tail

domain of the K74 protein losing 13 amino acids. Two more cryptic splice sites, accccaaaggtgtctgcca and aagttcccaggccctgagtt can be created at 257 and 282 nucleotides downstream in the 3′-untranslated region (3′-UTR) of the *KRT74* gene. The deletion of the K74 protein's tail domain as well as the entirety of exon 9 can occur in any of two cryptic places. By exploiting any of the three sites, nonsense-mediated mrna degradation causes the synthesis of a truncated protein or the absence of a functional protein (NMRD) (56). *KRT74* haploinsufficiency is most likely the root cause of woolly hair in the family (53) stated that K74 is expressed primarily in the Huxley layer, which is critical for preserving the structure of the hair follicle.

Table I. Phenotypic variation in the genes that cause hereditary hair loss

Ser.	Phenotype	OMIM Number	Gene	Location of Gene	Protein	Disorder	References
1	The scalp, axillae, eyebrows, eyelashes and body are usually devoid of hair	(209500)	HR	Chr 8p21	Protein hairless	Atrichia with common lesions	(57)
	There is no hair on the body or on the scalp.	(203655)				Alopecia Universalis Congenita	(3)
2	irregular growth and a tightly curled structure of hair	(604379)	LIPH	Chr 3q27	Lipase H	Hypotrichosis 7	(58)
	Hair loss on the scalp and body varies in severity, ranging from minor baldness to full baldness.	(278150)				Hypotrichosis Simplex	(59)
3	Hair follicles and shafts are excessively thin and atrophic, with less hair than typical.	(278150)	LPAR6	Chr13q14.11-q21.32	P2Y5	Hypotrichosis 8	(60)
4	The majority of people affected have sparse to non-existent brows and eyelashes. Affected men may acquire normal beard hair in some circumstances.	(607903)	DSG4	Chr 18q21.1	Desmoglein 4	Hypotrichosis 6	(61)
5	Hairs were present t the time of birth. hairs grew back after ritual shaving, although The occasional recurrence of hair loss regions persisted. Vesicle formation on different places of the scalp and body	(613102)	DSC3	Chr 18q21.1	Desmocollin-3	Hereditary hypotrichosis with recurrent skin vesicles	(36)

	that burst and leak watery fluid on a regular basis.						
6	fast hair loss along with psoriasis-like epidermal abnormalities	(146520)	CDSN	Chr 6p21.33	Corneodesmosin	Hypotrichosis 2	(62)
7	Affected people have normal hair at birth, but weakening of the hair shaft and hair loss begin in early infancy and worsen as they become older.	(605389)	APCDD1	Chr 18p11.22	adenomatosis polyposis down-regulated 1	Hypotrichosis 1	(63)
8	Hair follicles and shafts are abnormally thin and atrophic, and there is less hair than normal.	(615885)	RPL21	13q12.2	RIBOSOMAL PROTEIN L21	Hypotrichosis 12	(64)
9	Axillary hair is missing, eyelashes are sparse or absent, and eyebrows are sparse or absent. body hair is missing	(615059)	SNRPE	1q32.1	Small Nuclear Ribonucleoprotein Polypeptide E	Hypotrichosis 11	(22)
10	At birth, there is little or no scalp hair, wirey and uneven scalp hair in childhood, and sparse or no forehead and parietal hair in adolescence.	(612841)	EPS8L3	1p13.3	Eps8-Like Protein 3	Hypotrichosis 5	(65)
11	At birth, there is no hair on the scalp, brows, or eyelashes, or there is a scarcity of them.	(146550)	U2HR, 5	8p21.3	Hr Upstream Open Reading Frame	Hypotrichosis 4	(66)
12	Early childhood hair is normal, but hair loss limited to the scalp begins in the middle of the first decade and progresses to almost full baldness by the third decade. Hair on the body, beard, brows,	(613981)	KRT74	12q13.13	KERATIN 74	Hypotrichosis 3	(67)

axillary hair, teeth, and nails regularly	grows

CONCLUSION

Different genes responsible for human genetic hair loss disorder have been described in this review. The most prevalent genes responsible for autosomal recessive hair loss, reviewed in the study, are *HR, LIPH, DSG4, LPAR6* and *DSC3;* while the genes responsible for autosomal dominant hair loss are *APCDD1, CDSN, KRT74, U2HR, 5, EPS8L3, SNRPE,* and *RPL21.* The function and significance of proteins encoded by muted genes were also highlighted in this study. It was also reported that human genetic hair loss disorder is brought on by changes in *HR, LIPH, DSG4, LPAR6, DSC3, APCDD1, CDSN, KRT74, U2HR, 5, EPS8L3, SNRPE,* and *RPL21* genes, in the majority of consanguineous families from various ethnic groups. As a result, genetic counselling may be beneficial in the research of human genetic hair loss disorder, and detailed clinical disclosure regarding the impact of mutations in specific genes is critical in realizing the full potential.

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