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GENETICS OF HUMAN HEREDITARY HAIR LOSS DISORDER

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Abstract

Human hair loss is a range of clinically and genetically diverse disorder. The loss of hair involved the scalp, eyebrows, eyelashes and body hair, manifesting itself and progressing to almost complete baldness. Hair on the scalp and other regions of the body is sparse to non-existent. The disease can be inherited in two ways autosomal recessive or autosomal dominant. There are several types of genetic hair loss, both isolated (non-syndromic) and syndromic. Significant advances in molecular genetics have led to identifying many causative genes for genetic hair disorders, The OMIM nomenclature was used to identify various types of hair loss illnesses. We have appraised the clinical and genetic features of isolated hereditary hair loss syndromes exhibiting with hypotrichosis and/or WHs in this study.

Keywords: *Autosomal recessive and dominant hypotrichosis, Hair follicle, Hereditary hypotrichosis, Mutation, Woolly hair*

INTRODUCTION

Hereditary hair loss disorder is a genomic ailment that causes sparse scalp hair, eyebrows, eyelashes, and body hair. A shorter growing phase (anagen), a brief transitory phase (catagen), and an instant resting phase (telogen). At the end of the resting period, the hair started falling out (exogen), and a new hair grows in the follicle, making a new the cycle (1). Every day whether the, up to 40 hairs (0–78 in men) reach the point of their resting time interval and fall out. Actual clinical hair loss (telogen includes the necessary) appears to occur when more than 100 hairs fallout per day (2). When the growing phase is constantly interrupted, an unusual loss of anagen hairs (anagen excludes) starts to develop, and significant alterations in this hair growth stage can cause hair cycle irregularities. Isolated, syndromic, and non-syndromic hair loss disorders are mostly as classified, people with syndromic elements of hair development abnormalities that initiates at birth or early childhood and last throughout life in both males and females with the condition (3). Hair cycle abnormalities such as sparse to non-existent hair on the scalp and rest of the body, sparse to absent eyebrows/eyelashes, can occur without the presence of other disorders such as cardiac, endocrinal gene, or ophthalmic. In non-syndromic variants, hair abnormalities are the only presenting symptom (4).

The number of isolated hair loss diseases that have been mapped on various human chromosomes and the corresponding genes have been located in all but three cases is the same for autosomal dominant and autosomal recessive kinds. Autosomal dominant hair loss illnesses have been linked to mutations in the adenomatosis polyposis downregulated 1 gene. Corneodesmosin (CDSN, MIM 602593), keratin-74 (APCDD1, MIM 607479) (1) (KRT74, MIM 608248) (3), Hairless (HR) gene (U2HR, MIM 146550), SNRPE (MIM 128260) and RPL21 (MIM 603636) genes are small nuclear ribonucleoprotein polypeptide E (SNRPE) and ribosomal protein L21 (RPL21) genes. Mutations in the genes hairless (HR, MIM 225060), desmoglein-4 (DSG4, MIM 607892), lipase-H (LIPH, MIM 607365), and lysophosphatidic acid receptor 6 (LPAR6/P2RY5, MIM 609239) have been associated to autosomal recessive hair loss illnesses.

AUTOSOMAL RECESSIVE TYPES OF HEREDITARY LOSS DISORDER

The autosomal recessive hypotrichosis disorder affects hair development. From childhood, people with this condition have had thin hair on their scalps. This type of hair is usually abrasive, desiccated, and

curvy (often described as woolly hair). Scalp hair is correspondingly more likely to be lighter than usual, as well as more sensitive and susceptible to damage (5). Those who are severely impacted exhibit hair that infrequently raises and over a few inches. On the brows, eyelashes, and other parts of the body, hair may be scarce. Hair difficulties can continue to develop or worsen over time, leading to alopecia (total hair loss) on the scalp and a decrease in body hair. The overall occurrence of autosomal recessive hypotrichosis is unknown, but in Japan one in every 10,000 people is thought to be affected by the disease. Three localized autosomal recessive hypotrichosis types with clinical similarity are given the same nomenclature. For traits localized to chromosomes 18q12.1, 3q27.2, and 12q14.11-q21.32, they were designated as LAH1, LAH2, and LAH3.

LOCALIZED AUTOSOMAL RECESSIVE HYPOTRICHOSIS (LAH1)

The desmoglein-4 (DSG4; 607892) gene on chromosome 18q12 has a homozygosity or heterodimer mutation (6). Despite having normal hair at birth, affected people's hair abnormalities occur throughout that the first few months of life. Only the back of the head and the collar of neck usually implicated in moderate cases of monilethrix (55). Hair on the entire scalp, pubic hair, underarm hair, eyebrows, eyelashes, and hair on the extremities sometimes become irritated in more severe cases. Monilethrix is a skin and nail condition caused by monilethrix. DSG4 is a desmosome component that is essential for follicles cell proliferation and differentiation in humans (7, 8). It's prevalent in the hair follicle's inner epithelial layers, primarily the medial prefrontal cortex, generally lower short hair epidermis, and consistently higher IRS (7, 8). Either the DSG4 gene has a very unique expression pattern in human hair follicles. DSG4 is a 16-exons gene that produces a 1040-amino-acid protein. Five extracellular domains (584 amino acids), a transmembrane domain (21 amino acids), a cytoplasmic domain (388 amino acids), four subunit amino acids (EC1 108 amino acids, EC2 112 amino acids, EC3 116 amino acids, EC4 112 amino acids), and two desmoglein repeat several times top level domains (23 and 31 amino acids) (9, 10). There have only been ten identified mutations in the DSG4 gene, including a deletion, two missense mutations, one nonsense mutation, and six compound heterozygous mutations. LAH1, which is produced by three more homozygous mutations responsible for the monilethrix phenotype (7, 11, 12), is caused by three more hereditary hypotrichosis mutations.

LOCALIZED AUTOSOMAL RECESSIVE HYPOTRICHOSIS (LAH2)

LAH2 (MIM# 604379) is a woolly hair autosomal recessive hypotrichosis with scarce to non-present eyebrows, eyelashes, and body hair. The patients influenced usual to spare eyebrows, eyelashes, alar hair, and body hair while male had normal beard hair. Accompanying evaluation of the homozygosity for an atypical shortening mutation as well as three known mutations in the LIPH gene was reported in segregating autosomal recessive hypotrichosis (13, 14). Membrane-associated Phosphatidic acid-selective phospholipase A1 (Mpa-PLA1) hydrolyzes phosphotidic acid to produce 2-acyl lysophosphotidic acid (LPA), a lipid mediator with a wide spectrum of biological properties (15). The N-terminus sequence of the 55-kDa Mpa-PLA1 (LIPH) protein is followed by a catalytic domain (16). The inner root shealth (IRS) of hair follicles expresses cellular distribution (17). Therefore distant, the LIPH gene has seen 12 homozygous mutations, including three missenses, a small and large insertion, four inconsequential deletions and an immense deletion, deletion/insertion, a splice-site mutation, and two compound heterozygous mutations (13, 18, 19, 20-26).

LOCALIZED AUTOSOMAL RECESSIVE HYPOTRICHOSIS (LAH3)

LAH3 is encoded by the lysophosphotidic acid receptor 6 (MIM, 609239) gene, which is found on chromosomes 13q14.11-q21.32. LAH3's hairs are tightly coiled woolly, breakable, and leisurely. Hair re-grow inconspicuously after shaving, sheds more recurrently, and ultimately replaced with tinny, curly light-accentuated hair (27, 28). Eyelashes and brows those are normal to sparse, as well as axillary and pubic hairs. Popular lesions are also non-existing (29), predominant but inadequate in the occipital area. The LPA produced by Mpa-PLA1α acts as a ligand for P2R5, one of the G-protein coupled receptors, encoded by the P2RY5/LPAR6 gene (30). P2RY5 expression in the basal layers of the epidermis, of hair follicles' inner root

shealths (IRS). The P2RY5 gene codes for a 344-amino-acid protein (31). This protein has four extracellular domains E1 (1-19 amino acids), E2 (80-92 amino acids), E3 (155-181 amino acids), E4 (254-272 amino acids), four cytoplasmic domains (C1 47-55 amino acids, C2 113 amino acids, C3 210-227 amino acids, C4 293-344 amino acids), and seven aquaphobic transmembrane sections (E1 1-19 amino acids, E2 80-92 amino acids, E3 (TM1 20-46 amino acids, TM2 56-79 amino acids, TM3 93-112 amino acids, TM4 134-154 amino acids, TM5 182-209 amino acids, TM6 228-253 amino acids, TM7 amino acids) (http://au.expasy.org/uniprot/P43657). There are 17 known hypotrichosis mutations in the P2RY5 gene, including ten missense, four small insertion, three slight deletion, and a multifaceted deletion mutation (32, 33) are known causing hypotrichosis.

ARTICHIA WITH POPULAR LESIONS (APL)

APL (MIM, 209500) is a congenital hair loss condition that is accompanied by pervasive popular lesions throughout the whole of the body (34, 35). APL is an autosomal recessive gene that affects both women and men equally. Hair has grown actually regularly at birth, but it starts to fall out after a few months. Affected role with this condition have no hair on their heads, eyebrows/lashes, or body hair. Follicular granulomas, which are common chronic conditions, can emerge in children at the age as two years old. Mutations in the HR (MIM 225060) gene on chromosome 8p21.2 have been found in affected individuals from numerous racial families all over the world. (36-41).

Only HR protein is a nuclear receptor co-receptor found in the hair follicle's outer root sheath (ORS). It improves the hair cycle by moderating gene expression in hair follicle regeneration, promoting transcription factors, and lowering inhibitors of this pathway's expression (42-44). HR protein is a co-repressor of binding proteins abundant in the inner root sheath of hair follicles (45). In humans, HR gene appears to be involved in the cellular transition to the first adult hair cycle, and its absence causes hair to stagnate completely, resulting in permanent hair loss. (46-48). It also helps the hair follicle cycle by modulating gene expression. Controlling gene expression in hair follicles also enhances hair cycling. Exons 5 (566-570 amino acids) and 10 (758-762 amino acids) of the HR gene encode two thyroid hormone receptor interactions protein (TRIP) motifs, consecutively, but exon 6 (600-625 amino acids) contain unique zinc-finger structure (49). More than 40 mutations in the human HR gene including deletions, non-sense, missense, insertions, and splice site and compound mutations have been discovered so far.

HYPOTRICHOSIS WITH RECURRENT SKIN VESICLES

Hypotrichosis and recurring cutaneous vesicles are caused by the Desmocollin-3 (DSC3, MIM 600271) gene on chromosome 18q12. Pain-induced sweltering, dental glazed, and nail abnormalities are also present in some individuals (50, 51). In an Afghani family the first mutation in the desmocollin DSC3 gene were found, which causes autosomal recessive hypotrichosis and recurrent cutaneous vesicles. Exon 14 of either the gene has a homozygous nonsense genetic mutation. The patients exhibited revealing eye brows/lashes, delayed or small hair follicles, and minimal hair on their scalps. On the arms, the recurring vesicles were more evident (51)

HYPOTRICHOSIS WITH JUVENILE MACULAR DYSTROPHY (HJMD)

HJMD (MIM: 601553) is a rare genetic hair loss illness that causes retinal degeneration and vision impairment in children. Both males and females are affected in the same way by autosomal recessive inheritance. The condition causes thin, inflexible hair on the scalp from infancy, and vision problems appear, subsequently retinal impartiality within the age of fifties. CDH3, (MIM 114021) belongs to P-Cadherin family of proteins comprehending 16 exons, on chromosome 16q22.1, which has the five cytoplasmic motifs as (EC1-EC5), As with typical cadherins, they have a transmembrane region and a short intracellular tail (Yagi et al., 2000). Ca++ interaction is thought to influence the orientation connecting specific E-cadherin modules as well as the form of the extracellular region, which is necessary for specific cell-cell interactions (52). HJMD has been linked to 13 mutations and four splicing locations (53, 54).

ALOPECIA WITH MENTAL RETARDATION (AMPR)

AMPR (MIM 203650, 610422) is a mild to severe autosomal recessive hypotrichosis (55). So far, three alopecia-mental retardation syndromes (AMPR1, AMPR2, AMPR3) have been localized to chromosomes 3q26.33-q27.3, 3q26-q26.31, but the causal gene has not been discovered.

TYPES OF AUTOSOMAL DOMINANT HEREDITARY HAIR LOSS DISORDERS

Autosomal dominant woolly hair/hypotrichosis is an uncommon condition characterized by slight scalp hair or tightly spiral curled hair.

HYPOTRICHOSIS SIMPLEX

Hypotrichosis simplex is an autosomal dominant condition characterized by thin hair growth with no other abnormalities moreover, eyelashes, eyebrows, and other body hairs appear normal. Hypotrichosis simplex is categorized into two kinds: the scalp-limited specific form and the generalised form, which usually affects all body hair (56). Heterozygous grouping variations in APCDD1 (adenomatosis polyposis coli downregulated 1; MIM 607479) (57), CDSN (corneodesmosin; MIM 602593) (58), SNRPE (little atomic ribonucleoprotein polypeptide E; MIM 128260) (59) and RPL21 (ribosomal protein L21; MIM 603636) (60) have been portrayed in pathogeneses of autosomal dominant hypotrichosis simplex, only one missense variation in APCDD1, one missense variation in RPL21, two missense variations in SNRPE and fifteen prearrangement variations in CDSN have been accounted for, till date.

MARIE UNNA HEREDITARY HYPOTRICHOSIS

Marie Unna hereditary hypotrichosis (MUHH) is kind of an autosomal dominant syndrome, which distinguished from hypotrichosis simplex by the existence of twisty of hair dystrophy. MUHH is considered by the patients are typically born with absence of hair on scalp and sparse to absent eye-brows/lashes. Thin, curled hair begins to grow in early childhood, but hair loss progresses and can lead to full baldness around adolescence (61, 62). Hair on the face, axillae, pubic area, and legs and torso is either being virtually nonexistent or patchy. Hair texture was biopsied and exhibited flattened and irregularly twisted hair with longitudinal different elevations (63, 64). Mutation in U2HR (MIM, 602302) gene, positioned at the 5′ untranslated section of human HR gene at chromosome 8p21.2. The hairless gene contains 18 coding exons encoding 1189 amino acids U2HR (upstream open perusing edge of the HR; MIM 146550) (61-63). About 20 different U2HR mutations have been identified.

Table I. List of hereditary hair loss disorders with symptoms

No.	Disease	Gene	Chromosome	OMIM	Symptoms
1.	Atrichia with popular lesions (APL)	HR	8p21	225060	Hair loss on scalp, rest of the body, and sparse to indefinite eyebrows/eyelashes.
2.	Localized autosomal recessive hypotrichosis (LAH3)	DSG4	18q21.1	607903	Sparse scalp hairs, absence of eyebrows and eyelashes, normal axillary and pubic hairs, follicular papules on scalp.
3.	Localized autosomal recessive hypotrichosis (LAH3)	LIPH	3q27.1-3q21.2	604379	Sparse, thin, fragile and short scalp hair. Wooly, tightly curled, light colored scalp hair. Normal to sparse eyebrows, eyelashes, axillary and body hair.
4.	Localized autosomal recessive hypotrichosis (LAH3)	P2RY5	13q14.11-q21.32	611452	Tightly curly, wooly, flimsy and sluggish cumulative hair, usual to sparse eyebrows and eyelashes, popular lesions on the occipital region

5.	Hypotrichosis and recurrent vesicles on skin	DSC3	18q21.1	613102	Sparse scalp hair, absence of eyebrows, eyelashes, axillary and body hair, skin vesicles of <1 cm in diameter on scalp and skin
6.	Hypotrichosis with juvenile macular dystrophy	CDH3	16q22.1	601553	Sparse fragile hair on scalp by birth and vision abnormalities.
7.	Alopecia with mental retardation (APMR1, APMR2, APMR3)	None	3q26.33-q27.3, 3q26.2-q26.31, 18q11.2-q12.2	610422, 203650	Exhibit complete hair loss from the scalp, absent eye-brows/lashes and body hair.
8.	Hypotrichosis simplex	RPL21, APCCD1, CDSN, SNRPE	13q12.2 18q11.22 6p21.3 1q32.1	603636, 146520, 605389	Sparse, short and thin hair on scalp and body. Eyebrows, eyelashes and beard hair are normal
9.	Marie unna hereditary hypotrichosis	U2HR	8p21.2	602302	Slow growing sparse and fragile hair

CONCLUSION

Inherited hair loss syndromes include a wide variety of clinical and genetic variability, making genotyping patients for confirmation of diagnosis and/or genetic counselling problematic. The study shows that DSG4, LIPH, P2RY5, DSC3, CDSN, U2HR, CDH3, are the most common muted genes responsible for autosomal recessive or autosomal dominant hair loss impairment. This review also accentuated the function and importance of those proteins which are encoded by muted genes. The discovery of hair loss-related genes, as well as a greater understanding of the many signaling pathways involved in hair development, may lead to the discovery of novel therapeutic targets.

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