INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 14, No. 4, p. 123-134, 2019

REVIEW PAPER OPEN ACCESS

Review on genes involved in hereditary hypotrichosis

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Key words: Hair loss, Hypotrichosis, Alopecia, Woolly hair.

http://dx.doi.org/10.12692/ijb/14.4.123-134 Article published on April 15, 2019

Abstract

In human, hair loss disorders are the heterogeneous group of genetic disorders. The characteristics of the genetic hair disorders are thin to complete loss of hair, but rarely on scalp has firmly twisted curled woolly hair been reported. Pattern of the hair loss is also in autosomal recessive or autosomal dominant form. The genes which are responsible for autosomal recessive heredity hypotrichosis are *LIPH* gene mapped on chromosome number 3q27.2 and Lysophosphatidic acid receptor 6, also known as *LPAR6* gene which is located on chromosome number 13q14.2, Desmoglein-4 (*DSG4*) gene on chromosome number 18q12.1, Desmocollin-3 (*DSC3*) gene on chromosome number 18q12.1 and Hairless (*HR*) gene on chromosome number 8p21.3. There are also some autosomal dominant genes which are responsible for heredity hypotrichosis. In this review, several genes and different mutations of the hair disorders are discussed.

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Introduction

In this review, five major genes involved in hypotrichosis are described. Which are mostly reported in Pakistani populations. Genetic disorder is a condition, caused by one or more abnormalities in the genome. Genetic disorders are mostly rare. The causative agents for genetic disorders are chromosomal abnormalities or environmental factors. Hereditary genetic disorders are those which passed down from the parent's gene. Genetic disorders are mainly of two types that are autosomal recessive as well as autosomal dominant. In the case of autosomal dominant from the affected individual must have one mutated copy of the gene while in autosomal recessive form the affected individual have two mutated copies of the gene.

In humans hair loss is a genetic disorder which is caused as a result of different factors. These causes might be generally genetic or largely depend on external factors (Pasternack *et al.*, 2008). Hair loss is one of the most familiar diseases along with all patients discuss with a dermatologist and is generally related with severe mental disorders, signs of depression and distress (Chartier, 2002; Shrivastava, 2009; Schmitt *et al.*, 2012). It can be short-term or permanent.

One type of hereditary hair loss is known as Alopecia that takes place consequently any type of alteration/disturbancein the genetic composition of the proteins/genes associated with the hair morphogenesis/development (Hardy, 1992; Rosenquist and Martin, 1996). Alopecia is a situation in which confluent; disperse pattern or irregular hair loss happen from various parts of the body, generally from the scalp (Norwood, 1975). The etiology of alopecia is not completely clear but several causes are described in current time and one of the strongest cause is connected through autoimmune disorders. In Alopecia patient's anxiety disorders, depression and high frequency of mood change are generally seen (Madani and Shapiro, 2000; Sawaya and Shapiro, 2000). Alopecia's found in human as result of a correlation with problem in ectodermal and additional structures (syndromic) or an isolated anomaly (non-syndromic). Alopecia areata (AA) is an inflammatory scalp, non-scarring autoimmune, or body hair loss situation (Wasserman *et al.*, 2007). In humans, the second major familiar reason of the hair loss is alopecia areata, along with a 2% of lifespan possibility (Gilhar and Kalish, 2006). Alopecia areata is a type of autoimmune disease specific to tissue but its mechanism at molecular level remains unknown. Various factors, such as stress and viral infections may be caused this process (Garcia *et al.*, 1999). It can be connected by further autoimmune disorders, such as thyroid disease (Tosti *et al.*, 2009). The comorbidity of psychiatric disorders, mostly general anxiety disorder, phobic states and depression, is high (Ruiz *et al.*, 2003; Khalaf *et al.,* 2004). Treatments for alopecia areata consist of biologic response modifiers and immunomodulating agents (Shapiro and Price, 1998).

Another heredity hair shaft abnormality is known as woolly hair which is described by tightly curled hair (Whiting, 1987). Woolly hair arises with or without additional syndrome or physical findings (Chien *et al.*, 2006). Woolly hair is very curly which stops growing at a minute inches (0.5cm) and do not grow extremely well. In 1907, the case of woolly hair was first explained by Gossage in a European family (Gossage, 1907). The hair texture resembles sheep's hair whereas the hair color most often shows no unusual characteristics (Schokking, 1934). The classification of WH was descripted by Hutchinson *et al* in 1974 (Hutchinson *et al.*, 1974), and classified the WH in three sub-types: the localized or isolated type, the familial recessive and the inherited dominant. Successively the generalized type was different in non syndromic and syndromic and the last one in autosomal recessive and autosomal dominant (Matsuno *et al.,* 2013; Ramot and Zlotogorski, 2015). Heritably hypotrichosis is an autosomal recessive, autosomal dominant X-linked inheritance. Up to now, seven autosomal recessive and the same numbers of autosomal dominant isolated types have been recognized (Basit *et al.,* 2015). Autosomal recessive hypotrichosis is one of the hereditary hair loss defects

which are described by short, thin, diffuse hair on scalp, spare to complete deficiency of axillary, eye-lashes/brows, pubic hair and body hair are inborn in recessive means of heritance.

Till now, in autosomal recessive hypotrichosis there are five genes have been recognized. These consist of: desmoglein-4 (*DGS4*, MIM 607892) for LAH1 (Kljuic *et al.*, 2003), Lipase-H (*LIPH*, MIM 607365) for LAH2 (Kazantseva *et al.*, 2006), purigenic G coupled receptor protein (*P2RY5*/*LPAR6*, MIM 609239) for LAH3 (Pasternack *et al.*, 2008; Azeem *et al.,* 2008; Tariq *et al.*, 2009), desmocollins-3 (*DSC3*, MIM 600271) with recurrent skin vesicles for autosomal recessive hypotrichosis (Ayub *et al.*, 2009) and Hairless gene (*HR*, MIM 602302) (Ahmad *et al.*, 1998; Cichon *et al.*, 1998) with atrichia with popular lesions are autosomal recessive hypotrichosis. Currently, two novel autosomal recessive hypotrichosis loci have been mapped onto chromosome number 10q11.23-22.3 as well as 7p21.3-p22.3 (Naz *et al.*, 2010; Basit *et al.*, 2010). The affected members of these families which are mapped on these chromosomal regions illustrated same clinical characteristics, similar to different autosomal recessive hair loss disorders.

Most lately, Shimomura and Pasternack *et al* described the interruption of *P2RY5* (MIM 609239) which is G protein-coupled receptor gene, along with autosomal recessive hypotrichosis simplex and autosomal recessive woolly hair, in six Pakistani and three Saudi Arabian families (Shimomura *et al.,* 2008; Pasternack *et al.*, 2008).

The rare disorder illustrated mainly by sparse scalp hair or tightly twisted curled hair is known as autosomal dominant woolly hair/hypotrichosis.

Autosomal dominant hair loss disorders result from mutations in the inhibitory upstream open reading frame (*U2HR*) of the *HR* (Wen *et al.*, 2009), small nuclear ribbonucleoprotein polypeptide E (Pasternack *et al.*, 2013), at chromosome 1p13.3, epidermal growth factor receptor pathway substrate 8- like 3 (Tocchetti *et al.,* 2003), adenomatosis polyposis down regulated (Shimomura *et al.,* 2010a) and in the genes for keratin-74 (*KRT74*) (Shimomura *et al.*, 2010b) and corneodesmosin (*CDSN*) (Levy *et al.,*2003).

The current review was written in order to make available the hypotrichosis data from a single source, instead of scattered.

Genetic basis of the hair loss

Several genes responsible for autosomal recessive hypotrichosis have been reported (Table 1).

Table 1. Major genes involved in hereditary hypotrichosis.

Disease	Genetic Locus	Gene	Gene OMIM number	Phenotype	Refrences
LAH1	*18q12.1*	*DSG4*	607892	Scalp with sparse hair and follicular papules, with no eyebrows, eyelashes and with normal Pubic as well axillary hair.	(Kljuic *et al.*, 2003)
LAH2	*3q27.2*	*LIPH*	607365	Scalp with fragile, Sparse, short and thin hair or light colored tightly curled wooly hair. Sparse to normal eyebrows, eyelashes and body hair.	(Kazantseva *et al.*, 2006; Levy *et al.,* 2008)
LAH3	*13q14.2*	*LPAR6*	609239	Wooly, firmly curled slow growing scalp hair and sparse to normal eyelashes, eyebrows, occipital region with popular lesions.	(Pasternack *et al.,* 2008; Azeem *et al.*, 2008; Tariq *et al.*, 2009)
Hypotrichosis with recurrent skin vesicles	*18q12.1*	*DSC3*	600271	Sparse hair on scalp, lack of eyebrows, eyelashes along with body hair, vesicles on scalp and skin.	(Ayub *et al.*, 2009)
Atrichia with papular lesions	*8p21.3*	*HR*	602302	Complete absence of hair on scalp as well as body, lack of eyelashes, eyebrows, normal nails, teeth and glands.	(Ahmad *et al.*, 1998; Cichon *et al.*, 1998)

LIPH Gene

LIPH gene (MIM 607365) has been located on chromosome number 3q27.2. *LIPH* gene has been expressed into numerous tissues containing liver, kidneys, heart, pancreas, lungs, male and female gonads, prostate, small and large intestine (Sonoda *et al.,* 2002).

In hair shaft and hair follicle strong appearance of the gene has been illustrated (Kazantseva *et al.*, 2006). *LIPH* gene contains 10 exons which are encoded by a 451 amino acid protein of lipase H to makes LPA (Sonoda *et al.,* 2002). *LIPH* belongs from triglyceride lipase family which produces oleoyl-L-a-LPA from phosphatidic acid which is used as a ligand for *LPAR* receptors to initiate the signaling pathway for maintenance and regulation of hair growth cycle (Pasternack *et al.,* 2008).

In Lipase-H (*LIPH*, MIM 607365) mutations are fundamental reason for two clinically overlying hair loss disorders that is woolly hairs (ARWH)/autosomal recessive hypotrichosis, (LAH2), located on chromosome 3q27 (Kazantseva *et al.,* 2006; Shimomura *et al.,* 2008).

Till date, 27 distinct types of mutations reported into *LIPH* gene in which mostly are small deletion and missense mutation. Kazantseva *et al* described first deletion mutation of exon 4 of 985 bp also reported flanking intronic succession of the *LIPH* gene in the affected individuals from Volga-Ural region of Russia.

Ali *et al* reported five base pair of the deletion mutation (c.346350delATATA) in this gene of exon 2 most important into frame shift as well mutation in downstream premature of the termination codon which is second mutation (Ali *et al.,* 2007).

Recently, Jelani *et al* reported third deletion mutation of the two base pairs (c.659-660delTA), which is placed on exon 5 in *LIPH* genes in a family belonging from Pakistan province from populations of Pashto speaking in North Western Frontier (Jelani *et al.,* 2008).

LPAR6 Gene

This gene is known as Lysophosphatidic acid receptor 6 (*LPAR6*) (MIM No. 609239), at the LAH3 locus on chromosome 13q14.2, most of the hair-related disorders are caused by *LPAR6* gene (Shimomura *et al.,* 2008). *LPAR6* and *LIPH* codes for proteins concerned in the production of essential constituent of cell membranes Oleoyl-Lalpha-Lysophodphatidic acid (LPA) and "2-acyl-lysophosphatidic acid" which provides like ligand used for the P2Y5 a G-protein-coupled receptor (GPCR) (Jelani *et al.,* 2008). *P2RY5* (a Homo sapiens protein) which has a molecular weight 39.392 Kda and length of 344 residues and accounted to be implicated in the management of the hair growth and differentiation pathway (Pasternack *et al.,* 2008). An unusual type of inherited alopecia is autosomal recessive woolly hair and hypotrichosis (ARWH) cause by mutation into *LPAR6*, which is illustrated with sparse hair on the scalp, as well as it can occasionally influence body hair (Khan, 2016). *LPAR6* coded protein is also comprises of a RNA recognition motif (RRM) and LA motif (LAM) and are concerned in translation, maturation of tRNAs and regulation (Bousquet and Deragon, 2009; Stavraka and Blagden, 2015).

In *LPAR6* gene number of mutations has already been recognized, including frame shift, deletion, insertion, nonsense and missense mutation (Shinkuma *et al.,* 2010). Lately, Shimomura *et al* recognized homozygous mutation C278Y in *P2RY5* along with a severe hypotrichosis in Brazilian family (Petukhova *et al.,* 2008). Recurrent or novel (if any) mutation in *LPAR6* gene would enhance the spectrum of the identified mutations; emphasizing the role of GPCR collectively with *LIPH* in variable hair growth cycle (Kazantseva *et al.,* 2006).

DSG4 Gene

DSG4 gene is termed as well Desmoglein 4 (MIM 607892), also mapped into chromosome 18q12.1. The *DSG4* gene contains 16 exons in human also spans genomic DNA almost 37 kb. *DSG4* is part of the cadherin family of desmosomal which makes desmosome components which are intracellular

junctions associated with cell to cell adhesion, signaling, differentiation and involved into different tissues development similarly epidermis of the hair follicles and skin that have ability to maintain mechanical stress (Delva *et al.,* 2009). The *DSG4* gene is considerably shown into the hair follicle shaft cortex of keratinizing region and in the hair shaft cuticle as well as the upper inner root sheath (IRS) cuticle (Bazzi *et al.,* 2006). Mutation in desmoglein-4 (*DSG4*, MIM 607892) gene caused phenotypes of autosomal recessive hypotrichosis (Ayub *et al.*, 2009). Hypotrichosis restricted to the scalp, chest and extremities, sparse eyelashes/brows as well as normal facial, pubic, axillary and beard hairs are the affected cases of LAH1 (John *et al.,* 2006; Schaffer *et al.,* 2006). Autosomal recessive monilethrix (MIM 252200) is reported as a similar disorder to LAH resulted from mutations in *DGS4*. Shafts of fragile hair which shows beaded hair are the characteristics of this disorder (Zlotogorski *et al.,* 2006).

Until now, 13 mutations in *DSG4* gene have been reported including four missense, five deletions, two insertions, one splice site, one nonsense and one deletion insertion. Two mutations were reported in the families from Pakistan, containing a large deletion (Ex5_8del) (Wajid *et al.,* 2007).

DSC3 Gene

The *DSC3* gene is known as Desmocollin-3 (MIM 600271), is mapped onto chromosome number 18q12.1 and this act as a binding protein which is determined by *DSC3* gene (Buxton *et al.,* 1993; Amagai *et al.,* 1995). In human, at long arm of chromosome 18 (18q12.1) four *DSG4* and three *DSC3* genes are located nearby to each other (Kljuic *et al.,* 2003; Whittock and Bower, 2003). The transmembrane constituent of the desmosomes is *DSC3* also has a number of domains along with a propeptide (amino acids 28–135), signal sequence (amino acids 1–27), a c-terminal cytoplasmic domain (amino acids 712–896), a transmembrane domain (amino acids 691–711) and an extracellular domain (136–690 amino acids). *DSC3* genes with 52 kb contains 16 exons, the expression of two further desmocollins (*DSC1-DSC2*) takes place into the epidermis. The expression of *Dsc1*/*DSC1*, in the mouse and humans is constrained to the epidermis topmost portion (Nuber *et al.,* 1996), in the basal layer of the epidermis *Dsc2*/*DSC2* is weekly expressed (Theis *et al.,* 2003), in basal and first super basal layers of the epidermis *Dsc3*/*DSC3* is expressed (Chidgey *et al.,* 1997). The affected individuals having fragile and sparse hair on scalp along with absent eyelashes and eyebrows but having normal teeth, nails, hearing and sweat glands. The scalp and other body skin of the affected individuals showed filled vesicles with watery, thin fluid (Ayub *et al.,* 2009). Like other cadherins, mutation in the *DSC3* gene with recurrent skin vesicles (MIM 613102) and hypotrichosis have been reported by Ayub *et al* in Pakastani family and non-sense mutation also identified in a family which belongs from Kandahar city of Afghanistan.

The glycoproteins of desmosomes are the Desmoglein and Desmocollins that are the familiar forms of intercellular junctions of mediating cell-cell adhesion in epithelial cells of vertebrate (Grunwald, 1993). Since constituents of super family of cadherin, both desmoglein along with desmocollin genes having same structural and functional domains, which includes cytoskeleton interactions, calcium binding, membrane integration, for adhesion recognition sites and modifications of post-translational, similar to proteolysis, glycosylation and phosphorylations (Grunwald, 1993). During embryonic development they also functioning like dynamic mediators of morphogenesis and also as modulated in response to signals similar to cell differentiation, concentration of calcium, motility and potentially involved in disorder phenotypes (Silos *et al.,* 1996).

HR Gene

Atrichia with papular lesions (APL; MIM 209500) is a rare form of inherited autosomal recessive disorder characterized by permanent complete hair loss on scalp and all body parts. (Damste and Prakken, 1954; Loewenthal and Prakken, 1961; Zlotogorski *et al.,* 2002a). Patients exhibit normal hairs at birth but lost

after few months which could not regrow, as a result showing complete loss of hair from scalp, eyelashes, eyebrows as well other parts of the body but have normal nails, glands and teeth (Nothen *et al.,* 1998; Ahmad, 1999; Kruse *et al.,* 1999). Affected members of the APL having an additional characteristic of multiple diffused keratinous follicular papules as well grouped cystic particularly on the scalp, face and other body parts (Zlotogorski *et al.,* 2002b). Hairless gene (*HR*) is located on chromosome 8p21.3, which causes APL. In hairless gene (*HR*, MIM 602302) a disease causing mutation was reported by Ahmad *et al* (Ahmad *et al.,* 1998). Hairless (*HR*) gene spans more than 14 kb also arranged into 19 exons.

The product of hairless gene is 130 kDa that is a putative transcription co-repressor for several nuclear receptors, which are very expressed in epidermis, HF and brain (Cachon *et al.,* 1994; Thompson, 1996; Potter *et al.,* 2001).

Up to now, from various ethnicities about the world 51 mutations in the *HR* gene have been accounted including nonsense, insertion, compound heterozygous, missense, deletion and splice site mutations (Betz *et al.,* 2007; Kim *et al* 2007; Yip *et al.,* 2008).

Conclusion

Hereditary hair loss is a genetic disorder described by woolly to sparse hair or on scalp complete loss of hair or other body parts. Hair loss disorders are in the form of hypotrychosis and hypertrychosis.

There is difficulty in genotyping of hereditary hair loss disorders due to the wide range of inherited heterogeneity. Advances into technology and in gene profiling led to a significant understanding of genes involved in hair growth cycle. Till to date, on different human chromosomes, seven autosomal recessive as well as autosomal dominant types of hair loss disorder have been plotted. Numerous genes along with their mutations which are involved in the development of the hair loss diseases have been discovered.

Acknowledgement

We would like to thank university of Balochistan, Quetta and higher education commission (HEC), Islamabad, Pakistan who funded the work through grant No.20-2407/HEC/R & D/NRPU/14.

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