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PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1188898>Available online at: <http://www.iajps.com>**Review Article****MOLECULAR BASIS OF HAIR LOSS-A MINI REVIEW****Abdul Rehman*, Sheikh Ahmed, Syed Ashraf Uddin, Muhammad Javed Khan, Mehwish Durrani, Sahrish Khan.**

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Abstract:

Molecular basis of the heredity hair loss has shown different types of mutations in different types of genes which are responsible for it among which of the major types of mutations includes Novel mutation, Recurrent Mutation and Splice Site mutation in following four genes that includes LIPH Gene on the chromosome number 3q26.3, G-protein coupled receptor (LPAR6/P2RY5) Gene the chromosome number 13q14.2, Desmoglein-4 (DSG4) gene at the chromosome number 8p21, Desmocollin (DSC3) genes, having locus on the chromosome number 18q12. These genes are mainly responsible for the Autosomal Recessive Heredity Hypotrichosis. While this point also cannot be ignored that Hypotrichosis also occurs in Autosomal Dominant form and some other types of genes are also discovered to be responsible for it that includes the KRT74 gene, which is responsible for the keratin k74 protein synthesis. Such genes are being found to be expressing themselves in the Human being's hair follicles. Sequencing analysis of the KRT74 revealed heterozygous mutation c.422T4G (p. Phe141Cys) along the gene of K71 Keratin Initiation Helix Initiation encoded by KRT71 gene.

Keywords: BASIS, Gene, Desmoglein-4 and Desmocollin**Corresponding Author:**

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INTRODUCTION:

Hair loss (Alopecia) has been a problem since prehistoric era and since that time its related with different causal agents that may include environmental as well as Genetic factors. The environmental factor includes deficiency of dietary components because of depending on same diet regularly. Other environmental factors may include exposure to different radiations and washing them with expired shampoos and detergents and careless handling of hairs.

Similarly, the genetic factor is that, some genetic materials in the form of genes are responsible for the hair loss. This genetic factor is considered as heredity hair loss because Hair loss in this case shows the features of disorder in human genetics.

From among the different types of heredity hair loss, Autosomal Recessive Heredity Hypotrichosis is a non-syndromic genetical disorder in human characterized by progressive hair loss of the scalp and rest of the body.

Woolly hair (WH) is a group of hair shaft disorders, which is characterized by fine and tightly curled hair. Chien *et al.*, 2006

Generally, the complete hair loss is considered to be related to the P2RY5 Gene protein and Autosomal Recessive Hypotrichosis is mainly associated with mutation in this P2RY5 Gene.

This disorder in the genetics has two different forms that are Autosomal Recessive and Autosomal Dominant. In the case of autosomal recessive form, the affected individuals must have both of alleles of the genes in mutated form. Nevertheless, in case of autosomal dominant form, the individuals become affected by gaining either a single mutated gene of the allele. Lonely Woolly Hair is apparent of Autosomal Dominant and Autosomal Recessive character of inheritance [1].

Heredity Hypotrichosis has been reported in both autosomal recessive form and autosomal dominant forms. In most of cases, it has been reported in the autosomal recessive forms.

Major Causal Genes involved in Autosomal Recessive Woolly Hair. (ARWH/Hypotrichosis).

Up to yet there has been reported many genes responsible for the Autosomal Recessive Woolly Hair/Hypotrichosis. The phenotypic characteristics of the Autosomal Recessive Heredity Hypotrichosis

were noted to be linked with multiple genes of the multiple loci such as

- LIPH Gene on the chromosome number 3q26.3
- (P2RY5) Gene of G-Protein coupled receptor on the chromosome number 13q14.2
- Desmoglein-4 (DSG4) gene at the chromosome number 8p21.
- Desmocollin (DSC3) genes, having locus on the chromosome number 18q12.

The LIPH gene encodes for an enzyme that is called Lipase Membrane H. It is a triglyceride membrane bound family of lipase enzyme and the reaction of 2-acyl Lysophosphatidic acid (LPA) production is mainly catalyzed by these enzymes.

P2RY5 gene is also known as Lysophosphatidic Acid Receptor 6 (LPA6) gene or LPAR6 gene. This gene encodes a protein called GPR87 and binds with a G-protein coupled receptor for the signaling of lipids binding.

The P2RY5 gene was just decrypted that it the most important regulator in the growth of Human Hair follicles. This gene is encoding 344 Amino Acids and in addition, this gene has four extracellular Latent domains, Cytoplasmic domains are also four along with seven expected transmembrane hydrophobic regions [2].

Same as the DSG4 gene encodes for a protein that is called Desmoglein-4 protein. And that of DSC3 gene encodes for a binding protein that is known as Desmocollin-3 protein.

DSC3 gene is composed up of 52 kb pairs and comprises 16 exons, along with DSC1 and DSC2 (two further desmocollins), is expressed in the epidermis, DSC3 is a transmembrane constituent of the desmosomes, as similar to other cadherin, and includes of a numeral of domains, as well as a signal sequence, a propeptide, an extracellular domain, a transmembrane domain, and a c-terminal cytoplasmic domain [3].

Despite these genes, some other genes are also identified but in rare cases. Such as

Also another change in the DNA sequence of KRT74 Gene was identified, that is liable for the synthesis of keratin k74 protein and is being reported, showing the Autosomal Dominant Woolly Hair (ADWH). These genes are principally present in the inner root sheet of the hair follicles of the human beings. All these investigations were done in a study on a Family

belong to Japan affected by autosomal dominant Woolly Hair (ADWH) and the causative gene was discovered, having heterozygous mutation c.422T4G (p. Phe141Cys) beside the Helix Initiation Motif of the keratin k71 encoded by the gene (KRT71) only in those members of the said family that were affected.

It's clear from the of different configuration of Hairs that any alter in the keratin gene mainly determines the heterogeneity of their phenotypes, along with the cortex of hair channels, the inner root sheath and cuticle of skin. Naeem et al. 2006

Change in the K71 and K74 keratins were nominated in the pedigree of Autosomal Dominant Woolly Hair (ADWH). Also elaborated the polymorphism in KRT75 in the origin and development of pseudofolliculitis barbae Fujimoto et al. 2012

Ever latest, biallelic change was also identified in the KRT25 and was matched with the Autosomal Recessive Woolly Hair. Ansar et al. 2015, Zemov et al. 2016

Another modified monoallelic pathogenic woman belonging to a Chinese family was born with thin, lenient, and curly scalp hairs. and affected by Autosomal Dominant Woolly Hair Hypotrichosis. hairs of this proband were less dense and growing of hair was slow as compared to normal people. she no else apparent aberrations. New patients exhibited related appearance. After the extraction of genomic DNA of the following four affected members (III-1, III-3, IV-3, and V-3) and six Normal members (III-2, IV-1, IV-2, IV-4, V-1, and V-2). They were subjected to direct sequencing of the exomes of two normal and three affected members of the family firstly, Sequence variations were clarified of dbSNP146, the 1000 Genomes Project, ExAC, and internal database. Assuming Autosomal Dominant transmission. After it was also established by Sanger sequencing and determined that *KRT25* (c.1127T>G, p.Leu376Arg) was heterozygous missense mutation which was completely distributed in the disease form of the said family. 200 ethnically normal controls were also matched but found no mutation in them at all [4].

Here another gene named as DSP gene is reported as the causal gene for the heredity hair loss(Alopecia). It's also claimed that it is the first familial case in which a family. It was also reported that the said family had cardiac problems and along this their peripheral blood samples were collected and genomic DNA was isolated. After direct sequencing analysis reached a result of novel homozygous missense mutation c.1493CT (p.Pro498Leu) of DSP Gene of

the said family. This result made it clear that non syndromic hair loss is genetical in this family. These indications of the study that Heredity Hair loss is genetically in the heterogeneous and suggests that this remote form of is allelic to the cardio cutaneous syndrome [5].

Autosomal Recessive Heredity Hypotrichosis appears in such a case if the individuals he or she gets both genes of the allele mutated. The loss of hair of the affected individuals starts in the early childhood and continues up to the puberty. Those individuals that are affected by autosomal recessive heredity Hypotrichosis have also sparse woolly hair characters that are curly and can be break easily and having no elasticity.

Major of these genetic disorders are reported from the worldwide showing the main reason and that is cousin marriages and this genetic disorder is less reported from those parts of the world where cousin marriages are discouraged.

17 Pakistani families affected with Autosomal Recessive Heredity Hypotrichosis were examined. All male members in all 17 families had normal hair in the beard and moustache area. From among these families, affected individuals of the following eight families (B, C, F, G, K, L, O, Q) had the symptoms of delicate and sparse hairs of scalp. Their axillary hair, pubic hair, eyebrow and eyelash were absent. Other six families (A, D, H, I, J, M) affected individuals had woolly hairs of scalp and no hairs on the rest of body and also sparse to absent the eyelash and eyebrows. While the rest of the remaining three families (E, N, P) affected individuals had clear symptoms of Hypotrichosis. After the extraction of the genomic DNA, and were subjected to the sequence analysis and identified four recurrent mutations (p.Phe24HisfsX28, p.Asp63Val, p.Gly146Arg, p.Ile188Phe) in LPAR6 and two recurrent mutations (p.Trp108Arg, p.Ile220ArgfsX29) in LIPH gene [6].

Another two members of a same family were subjected to the medical checkup in Japan, their ages were 8 and 11 years respectively and had the symptoms of woolly and sparse hair which were firmly coiled and thin, also their hair grew up to very few inches and also very slow, while eyelash, nail and teethes were normal, with slightly condensed eyebrow. Among these two individuals, younger proband had much severe indications then his brother. Their peripheral blood samples were collected and genomic DNA was isolated, after that a missense mutation (c.736T > A, p.Cys246Ser) was

detected in the affected individuals in homozygous form by direct sequencing, the same was found in their parents in the heterozygous form. In Japan, very rare cases are being reported as following, so that this indicates that only 1 in 10,000 affected individuals are present in Japan [7].

Other 10 affected families having the symptoms of the Autosomal Recessive Hypotrichosis from Pakistan were studied and several recurrent and Novel mutation were detected both in P2RY5/LPAR6 gene as well as LIPH gene. Among these three different recurrent and two novel mutations were detected in P2RY5 gene that includes a recurrent mutation c.69insCATGfsX29 in family A and B, another recurrent mutation, p.I188F in family C, D, E, and another recurrent mutation c.188A>T (p.D63V) in F family. Along these the novel mutation c.409T>C, c.410-426del17 was in G family and another Novel mutation p.Y245C was in H family in the LPAR6 / P2RY5 gene. None of these mutations were found in 100 control Pakistani individuals.

In addition, two more recurrent mutations designated c.659_660delTA in family I and another recurrent mutation was in the form of deletion of exon number 7 and 8 in the LIPH gene. Also none of these types of mutations were found in the 100 control Pakistani individuals. the mutations c.69insCATG and p.I188F were thought to be the founder mutations in the Pakistani community as confirmed by the Haplotype analysis [8].

Another Japanese proband was found to affected with Autosomal Recessive Woolly Hair on the basis of his clinical features. After isolation of the genomic DNA from the peripheral blood sample, and putted forwarded for the search of mutations in the LIPH genes. After direct sequencing of the patients DNA, two different heterozygous mutations were found, among which one was recurrent c.736T>A missense mutation (p.Cys246Ser) in exon 6 and a nucleotide substitution c.982+5G>T in intron 7 of the LIPH gene. To search for mutation c.982+5G>T, other 100 control individuals from different ethnics were matched with the help of restriction enzyme type DraIII, but didn't find any individual in carrier form, declaring that c.982+5G>T would be a pathogenic form. Also c.736T>A (p.Cys246Ser) mutation was already a founder mutation population of Japan. And near to the intersection of intron 7 and exon 7 the mutation c.982+5G>T occurred, and could easily cause to abolish the splice donor site, so that, the in vitro transcription assay confirmed a different splicing event from c.982+5G>T mutated allele and

lead to frame shift mutation and premature termination codon [9].

Another novel nonsense mutation in LIPH gene is claimed to be present in the Lebanese population. This nonsense Novel mutation designated c.179C>G in the LIPH gene. Also variation was matched with 100 control individuals in the Lebanese population and couldn't find any carrier for it. This mutation was found to be present at the exon 2 of the LIPH gene and is thought to be leading to the nonsense mediated RNA decay. And when the mRNA continues to express, will be in nonfunctional due to lacking of the lipase enzyme catalytic site. This was confirmed in the silico structure prediction and shortened forms of wild type by the help PHYRE2 protein fold recognition server [10].

Another small proband (Boy) in the age of four belonging to Japan had regularly progressed hair loss and had short, firmly wiry hair on the scalp. Although His sister and parents were normal and didn't showed any of the above symptoms. Based on these symptoms of the Autosomal Recessive Woolly Hair. The blood sample was collected for the studies of the genetics with the proper permission of the concerns, after isolation of the genomic DNA, direct sequencing analysis was performed and reached to the identification of a heterozygous missense mutation designed c.736T>A (p.Cys246Ser). Also it was recommended that this heterozygous missense mutation to the phenotypes of hair and its severity. And a compound heterozygous mutation c.736T>A (p.Cys246Ser) and c.417+1G>C was found in the LIPH gene and were identified to be the causal agents of mild types of Woolly Hair Hypotrichosis. And prior to this present study's findings, another two splice site mutation c.629-1G>C (Ivs4-1G>C) and c.982+5G>T in LIPH gene were reported and claimed that it could be the only third splice site mutation in LIPH gene [11].

Another five families from the different ethnic groups of Japan were brought for their genetic study and had the clear indications of the autosomal Recessive Heredity Hypotrichosis. Also after the extraction of the genomic DNA from their peripheral blood samples and then a search was accomplished for the mutation analysis in the LIPH gene, P2RY5 gene, and DSG4 gene. Amazingly two predominant missense mutations c.736T4A (p.Cys246Ser) and c.742C4A (p.His248Asn) were detected in the LIPH gene in all of the above families. In addition, this mutation c.736T4A (p.Cys246Ser) was identified in all above five families and mutation c.742C4A (p.His248Asn) was identified in four of the above

five families. Among all of the family members, the affected members of the family C were homozygous for c.736T4A mutation. Moreover, the parents whose genomic DNA was available for the sequencing were found to be carriers of the same mutations in the Heterozygous form. heterozygous. It was also claimed on the basis of these results that mutations in LIPH gene are the founder mutations of Autosomal Recessive Heredity Hypotrichosis in the population of Japan [12].

Three members of the same family from Arab origin of Palestine had the symptoms of Autosomal Recessive Woolly hair, while the parents and three other members of the same family had normal Hair and no feature of the Autosomal Recessive Woolly Hair. These three affected individuals had very dark and full hairs on the scalp at their birth and after few weeks subsequently, the hairs started shedding and were regularly substituted by thin and lightly colored curly hair. Besides these, the affected members had no other dermatological and skeletal aberrations and also the echocardiogram report had normal results. After the extraction of genomic DNA, direct Sequencing analysis was performed and a homozygous deletion of four nucleotides mutation (c.669_672delCAA; p. Asn223LysfsX7) was detected in the LPA6 gene of one affected individual., the said mutation was also present in the homozygous form in other two affected sisters, from among other normal family members, their parents and one unaffected sister had the same mutation in the heterozygous form. This mutation was also searched in the 100 control individuals of the same population and was not detected. Horev, L et al. 2010 Also another study was established to determine 11 families belonging to Pakistan and also consanguineous in relations. All the affected members of these families had clear symptoms of Autosomal Recessive Woolly Hair and other related structures of sparse hairs and also their hairs were depigmented. After the isolation of the peripheral blood genomic DNA. Identification of the mutation resulted five different types of homozygous mutations in the LIPH gene of the above 11 families. Among the followings, these mutations designated 624delT, 659–660delTA, 683delT, and Ex7_8del were in frame shift and premature termination codon. After the genotypic analysis of these families by the help of the microsatellite markers of locus of the LIPH gene on the chromosomes number 3q27. Family 7 to 11 had mutation Ex7_8del and was identified to be related to the disease haplotype in between LIPH to MSI regions and this region mainly contains the LIPH gene and specifies a founder chromosome for Ex7_8del mutation. Likewise, the

mutation 659–660delTA was homozygous of same haplotype of the all analyzed markers of the family 5 and family 6. But only the affected members of family 4 was found to be of different haplotype from two other families on the mutation 659–660delTA, so that from the above results its suggested that a founder mutation 659–660delTA exists and up to many generations these recombination events have occurred [13].

In another study, 13 families belonging to different ethnic groups of Pakistan with features of heredity Hypotrichosis were analyzed for the studies of DNA sequencing of the P2RY5 Gene. After the linkage analysis, these all families were identified to be linked to microsatellite marker to LAH3 locus on the chromosome 13q14.11–q21.32. after this, the sequencing of P2RY5 gene revealed different of novel missense and recurrent mutations that includes Two novel missense mutation (p.N248Y; p.L277P) in first three families, and five recurrent mutations (p.24insHfsX52; p.N58–L59delinsCfsX88; p.D63V; p.G146R; p.I188F) in rest of 10 families [14].

Also two families A and B Pakistani consanguineous had different symptoms of Autosomal Recessive Heredity Hypotrichosis. While the complete hair loss had occurred in the affected individuals of the family A and that of affected individuals of family B had scalp hair just like monilethrix. After the isolation of genomic DNA, sequencing analysis of DSG4 gene was performed and reached the findings of novel mutation that is novel Deletion mutation (c.85-1_191del) in both of the above Families. And also this deletion mutation was thought out to be 2nd largest mutation in the DSG4 gene and that covers the figure of sign [15].

Before it, it was clear enough that DSG4 gene is strong contributing gene in Autosomal Recessive Heredity Hypotrichosis but this study had just turned the table that this DSG4 gene has also enough contribution as causal agent of monilethrix in many cases. Individuals affected by monilethrix have the clinical features of diffuse keratitic follicular papules and at the mid of their papules they have broken hairs. In the present study a Japanese proband was subjected to the study of genetics. His peripheral blood sample was collected and genomic DNA was collected. Sequencing of the DSG4 gene revealed a compound novel heterozygous mutation c.624delG (p.M208IfsX4) and c.2468G>A (p.W823X). It was also predicted that both of the above mutations are recessive mutations as this mutation heterozygously show normal hair in the parents. On the basis of this study describe a broad spectrum of DSG4 gene and

also shows different characters of DSG4 gene in human hair phenotype [12].

Another for the first time in Chinese population, a female proband was analyzed to LAH had such hairs that were not visible to see by the naked eyes and also even couldn't be seen in the scanning electron microscope examinations. After the extraction of genomic DNA, the sequencing analysis revealed a novel homozygous missense mutation A1103T (Asp323Gly) in the DSG4 gene of the patient. As a result of this mutation, the genotypic spectrum of LAH is being more expanded. The hairs of this patient established a connection between LAH and Monilethrix once again from 2006 and helps to make aware of researchers for different methods of diagnosis of Autosomal Recessive Heredity Hypotrichosis [1].

Another large family from Afghanistan had four affected members with clear symptoms of the Autosomal Recessive Heredity Hypotrichosis was inspected. These affected individuals had normal hairs at the time of birth and after a ceremonial shaving within two or three weeks, their hair became fragile and hair fall had started. The affected individuals had also vesicles on the skin and scalp. These individuals had also mostly lacking of typical eyebrows, eyelashes, auxiliary and rest of the body hairs. The peripheral blood was taken and pedigree was drawn after the proper discussion of the elders of the family's members. The genomic DNA was isolated and sequence analysis identified a homozygous nonsense mutation 2129 (c.2129T>G) in the DSC3 gene. In this mutation, a changed has occurred at nucleotide position 2129 (c.2129T>G) at the 14th number exon, and resulted in the transfer of Leucine amino acid to a premature stop codon. It's being claimed that this mutation is discovered for the first time and this mutation in the DSC3 gene has resulted in the formation of skin vesicles and also hair loss [5].

CONCLUSION:

To conclude that Heredity Hair loss is one of the major health problem in the world and from every corner of the world, it is reported in many different ways such as Autosomal Dominant form and Autosomal Recessive Form. But most of the cases it is not reported in Autosomal dominant forms. And the major genes that are responsible for the heredity hair loss includes LIPH gene, P2RY5 gene, DSG4 gene and DSC3 gene. These all genes are being reported in ARWH /Hypotrichosis forms. From among the followings, changes in the DNA sequence of the LIPH Genes are mostly reported. While other

three types of genes have also full contributions in the Heredity Hair loss.

Conflict of Interest:

The author has no conflict of interest or financial interest in this work.

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