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REVIEW ARTICLE

Isolated autosomal recessive woolly hair/hypotrichosis: genetics, pathogenesis and therapies

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Abstract

Isolated autosomal recessive woolly hair/hypotrichosis (ARWH) is a rare hereditary hair disease characterized by tightly curled sparse hair at birth or in early infancy. Patients with ARWH consist of genetically heterogeneous groups. Woolly hair autosomal recessive 1 (ARWH1) (MIM #278150), woolly hair autosomal recessive 2 (ARWH2) (MIM #604379) and woolly hair autosomal recessive 3 (ARWH3) (MIM #616760) are caused by mutations in *LPAR6*, *LIPH* and *KRT25*, respectively. In addition, nonsense variants in *C3ORF52* (*611956) were identified in ARWH patients. The frequencies of the mutations in the causative genes in ARWH patients are thought to differ by ethnicity and country/geographical area. Large numbers of ARWH families with *LIPH* mutations have been described only in populations from Japan, Pakistan and the Volga–Ural region of Russia. In that region of Russia, most ARWH families have an extremely prevalent founder mutation, the deletion of exon 4, in *LIPH*. In the Pakistani population, 47.2% of ARWH families had the disease due to *LIPH* mutations and 52.8% of them carried *LPAR6* mutations. The prevalent, recurrent *LIPH* mutation c.659_660delTA (p.Ile220Argfs*29) was found in more than half of Pakistani ARWH families with *LIPH* mutations. Most Japanese ARWH families (98.7%) harbor *LIPH* mutations, including the two highly prevalent, recurrent *LIPH* mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn). In ARWH patients whose disease was due to *LIPH*, *LPAR6* or *C3ORF52* mutations, the loss of function of LIPH, LPAR6 or C3ORF52 leads to reduced LIPH-LPA-LPAR6 signaling, resulting in the decreased transactivation of EGFR signaling and the phenotype of underdeveloped hairs. Our recent prospective interventional study suggests that topical minoxidil might be a promising treatment for ARWH due to *LIPH* mutations, although sufficiently effective treatments have not been established for ARWH yet.

(280 words)

Key words: *C3ORF52, KRT25, LIPH, LPAR6, lysophosphatidic acid, minoxidil*

Conflicts of interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Introduction

Isolated autosomal recessive woolly hair/hypotrichosis (ARWH) is a rare hereditary hair disease characterized by tightly curled hair at birth or in early infancy, leading to sparse hair later in life without any other organ or tissue involvement (Fig. 1). ARWH is a genetically heterogenous disease. To date, mutations in the four genes *LIPH*, *LPAR6*, *KRT25*, and *C3ORF52* are known to underlie ARWH.[1-5] Owing to remarkable advances in molecular biological techniques, we are now able to perform causative mutation searches easily and frequently for patients with ARWH. Accordingly, our understanding of the causative genetic defects and pathogenetic mechanisms of ARWH has significantly progressed in recent years.

This review comprehensively summarizes our knowledge of the genetic background and pathogenic mechanisms of ARWH. Furthermore, I mention current treatments and novel, potential therapeutic strategies for ARWH. I include a list of abbreviations used in the present review for readers to easily understand the contents (Table 1).

The disease phenotype and differential diagnoses of isolated ARWH

Clinical features of isolated ARWH

Patients with woolly hair show tightly curled hair on the entire scalp. The affected hair shafts are irregularly bent with rough cuticles and waves at very short intervals.[6,7] Woolly hair consists of syndromic and non-syndromic forms. Isolated woolly hair is a non-syndromic form in which the scalp hair abnormality is the only phenotype and no other skin symptoms or extracutaneous organ involvement is seen. Isolated woolly hair comprises ARWH and autosomal dominant woolly hair.[8] In most patients with ARWH, the eyebrows, eyelashes, beard and pubic hair seem to be unaffected.[8] Individuals affected with ARWH have defective hair growth, with their woolly hair seldom growing longer than a few inches.[8] Most patients with ARWH suffer from moderate to severe hypotrichosis (sparse scalp hair). Patients with *LIPH* mutations (see below) show the

ARWH phenotype on the scalp from early infancy. They have tightly curled hair continuously during their entire life, but the severity of hypotrichosis varies by patient and family.[8-10] The most severe cases suffer from a total loss of scalp hair.[11,12] In addition, the severity of the hypotrichosis differs among patients in a given family.[11,12] Furthermore, the severity of the hypotrichosis changes variably during the disease course. Some patients show a roughly unchanging severity with aging, whereas others exhibit variable levels of improvement or worsening of hypotrichosis with aging.[11,12]

Differential diagnoses of isolated ARWH

A number of congenital hair shaft disorders are thought to be differential diagnoses of isolated ARWH.[7,13] Syndromic hereditary hair shaft disorders and hypotrichosis are differentially diagnosed from their accompanying cutaneous and extracutaneous symptoms. The isolated hair shaft diseases that are differential diagnoses include monilethrix, pili torti, trichorrhexis nodosa, trichorrhexis invaginata, and trichothiodystrophy.[7,13] Monilethrix can be differentially diagnosed from its characteristic beaded appearance due to the periodic thinning of the hair shafts.[13] Patients with monilethrix often show perifollicular papules and erythema, which are not seen in ARWH patients. Autosomal dominant monilethrix is caused by mutations in the type II hair keratin genes *KRT81*, *KRT83* and *KRT 86*.[6] Autosomal recessive monilethrix is due to mutations in *DSG4*.[6] Patients with *DSG4* mutations show short, twisted, coarse brittle hair shafts called pili torti, which resemble steel wool.[13,14] Unlike in ARWH, the hair shafts in pili torti are bent only slightly at irregular intervals.[13] Trichorrhexis nodosa is a common hair shaft abnormality that can be diagnosed from the characteristic hair shaft appearance suggestive of two brush ends pushed toward each other due to the breakdown of the hair shafts.[13] Patients with trichorrhexis nodosa do not show woolly hair. Trichorrhexis nodosa is a symptom in some syndromes, including Menke's kinky hair syndrome.[13] Trichorrhexis invaginata also has a very characteristic structure of hair shafts called bamboo hair. In bamboo hair, the distal hair shaft invaginates into the

proximal hair shaft. Trichorrhexis invaginata is a main symptom in Netherton syndrome due to *SPINK5* mutations.[13]

A number of isolated hereditary hair loss disorders are also considered to be differential diagnoses of ARWH.[14] However, most isolated hereditary hypotrichoses do not show woolly hair and are easily excluded from the differential diagnoses of ARWH. Patients with a rare hereditary hypotrichosis called "hereditary hypotrichosis 3 and woolly hairs", which results from KRT74 mutations, show a woolly hair phenotype similar to ARWH. Unlike ARWH, hereditary hypotrichosis 3 and woolly hairs is autosomal dominant.[14]

Genetics of isolated ARWH

Causative genes of isolated ARWH

As mentioned above, patients with ARWH consist of genetically heterogenous groups (Table 2). Woolly hair autosomal recessive 1 (ARWH1) (MIM #278150) is caused by mutations in *LPAR6*, also known as *P2RY5*.[2,3] Woolly hair autosomal recessive 2 (ARWH2) (MIM #604379) is known to be caused by mutations in *LIPH*.[1] In addition, Woolly hair autosomal recessive 3 (ARWH3) (MIM #616760) is due to mutations in *KRT25*.[4] Furthermore, very recently, nonsense variants in *C3ORF52* (*611956) were identified in ARWH patients from two independent families.[5]

LIPH encodes lipase H (LIPH), also known as membrane-associated phosphatidic acid (PA)-selective phospholipase $A_1\alpha$ (mPA-$PLA_1\alpha$), which produces lysophosphatidic acid (LPA) from phosphatidic acid.[15] LPA is an extracellular lipid mediator with various biological functions. To date, 32 mutations (13 missense/nonsense, 5 splice-site, 5 small-deletion, 3 small-insertion, 3

small-indel, 2 gross-deletion and 1 gross-insertion mutation) in *LIPH* have been identified in ARWH patients in several populations (www.hgmd.cf.ac.uk) (Table 3).[9-12,16-46]

LPAR6 encodes a G protein-coupled receptor, LPA receptor 6 (LPAR6), also known as P2Y5 and P2RY5. To date, 27 mutations (15 missense/nonsense, 4 small-deletion, 4 small-insertion, 2 small-indel, 1 gross-deletion and 1 gross-insertion mutation) in *LPAR6* have been identified as underlying ARWH in patients from several populations (www.hgmd.cf.ac.uk) (Table 3).[19,20]

Keratin 25 is a type I (acidic) keratin, and keratins 25–28, which are type I, are expressed in the hair medulla and the inner root sheath of hair follicles. The inner root sheath plays an important role in intact hair shaft formation and elongation. To date, only two missense mutations in *KRT25* have been identified in the Pakistani population[4] and in the population of the Volga–Ural region of Russia (Table 3).[21] Most ARWH patients (116 of 119 patients) in the population of that region of Russia had the prevalent founder *LIPH* mutation: the deletion of exon 4.[21] However, the other three patients with relatively mild phenotypes had the founder *KRT25* mutation c.712G>T (p.Val238Leu) in the population from the Volga–Ural region of Russia.[21]

Two homozygous nonsense variants in *C3ORF52* were reported in ARWH patients in two independent families (Table 3).[5] C3ORF52 encoded by *C3ORF52* is thought to be necessary for LPA synthesis by LIPH.[5] One variant, c.492T>A (p.Tyr164*), in *C3ORF52* was found in an unrelated family of Hispanic origin. The other variant, c.34G>T (p.Glu12*), was detected in a related family of Arab Muslim origin.

Frequencies of mutations in each causative gene and prevalent recurrent mutations causative of ARWH by ethnicity or geographic area

The frequencies of the mutations in the causative genes in ARWH patients are thought to differ depending on ethnicity and country/geographical area.

LIPH mutations in ARWH families have been reported in Russian,[1] Pakistani,[22] Jewish,[23] Arab-Muslim,[23] Italian,[23] Indian,[12] Japanese,[24] Lebanese[25] and Chinese[16] populations. However, large numbers of ARWH families with *LIPH* mutations have been described only in populations from Japan, Pakistan, and the Volga–Ural region of Russia[1] (Table 4). Most ARWH families in populations from Japan, Pakistan, and the Volga–Ural region of Russia have extremely prevalent founder mutations in *LIPH* (Table 4).[1,9-12,16-19,22,24,26-46]

In the Japanese population, the situation of *LIPH* mutations causative of ARWH is particularly unique. The two highly prevalent, recurrent *LIPH* mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn) were found to be genetic causes of ARWH in the Japanese population (Table 4).[38] Indeed, c.736T>A (p.Cys246Ser) and/or c.742C>A (p.His248Asn) were detected in all 75 previously reported Japanese ARWH families with *LIPH* mutations.[9,10,17,18,24,33-46] Our previous study revealed 1.5% and 0.5% of healthy Japanese individuals to have one of the *LIPH* mutant alleles, c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn), respectively.[38] The mutant allele frequencies of c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn) in healthy Japanese individuals were 0.79 and 0.12, respectively.[9] Thus, it can be estimated that there are approximately 10,000 Japanese patients with ARWH due to *LIPH* founder mutations.

LPAR6 mutations in ARWH families have been reported in Arab-Muslim,[2] Pakistani,[3,46] Brazilian,[47] Indian,[48] Turkish,[48] Iranian,[49] Syrian,[50] Chinese[51] and Japanese populations.[52] However, a large number of ARWH families with *LPAR6* mutations have been described only in the Pakistani population (Table 5).[3,19,20,27,30,49,53,54]

Highly prevalent founder mutations in *LIPH* and/or *LPAR6*, as seen in the population of the Volga-Ural region in Russia and the Japanese population, might exist in other ethnic populations.

From the combined data on *LIPH* and *LPAR6* mutations, among the 89 Pakistani ARWH families whose causative mutations were identified, 47.2% of the families had the disease due to *LIPH* mutations and 52.8% of the families carried *LPAR6* mutations.[3,11,19,20,22,26-32,53,54] In contrast, most of the Japanese ARWH families (75/76, 98.7%) harbored *LIPH* mutations as a cause of ARWH. Therefore, in order to define the causative mutations in Pakistani ARWH patients, we have to perform mutation searches in both *LIPH* and *LPAR6*, although we should start by searching for the two founder *LIPH* mutations in Japanese ARWH patients.

Pathogenetic mechanisms of ARWH due to a defective LIPH/LPAR6 pathway

Both LIPH (PA-PLA1α) and LPAR6 are abundantly expressed in human hair follicles. Kazantseva *et al.*[1] reported that the expression of LIPH mRNA was observed in anagen hair follicles, including in the bulge, but not in the dermal papilla. Shimomura *et al.*[3] demonstrated that LPAR6 protein was predominantly expressed in the inner root sheath (IRS) of hair follicles. Thus, the expressions of LIPH and LPAR6 are thought to overlap in IRS. It has been postulated that LIPH and LPAR6 are components of a common signaling pathway that plays a crucial role in hair growth in humans.[2,55] The idea that LIPH and LPAR6 work cooperatively in hair follicle formation is reinforced by observations that individuals with mutations in *LIPH* and *LPAR6* show clinically indistinguishable phenotypes of ARWH.

LIPH is a membrane-associated phosphatidic acid-selective phospholipase A1 that produces 2-acyl LPA from phosphatidic acid.[5] In cellular membranes, LIPH hydrolyzes PA and produces 2-acyl-LPA (with an acyl chain at the sn-2 position of glycerol).[15] LPAR6 is a G-protein-coupled receptor and is a receptor of LPA.[2,3,56] Inoue *et al.*[57] postulated that LIPH hydrolyzes PA on the plasma membrane of the outer root sheath (ORS) cells and provides 2-acyl-LPA for LPAR6, which leads to hair follicle formation.

Inoue *et al*.[57] generated and analyzed LIPH-deficient (*LIPH*$^{-/-}$) mice. Their report elucidated the fact that LIPH, tumor necrosis factor-α-converting enzyme (TACE, ADAM17), transforming growth factor-α (TGF-α), and phosphorylated-epidermal growth factor receptor (EGFR, HER1) co-localize in IRS and the fact that both LIPH and LPAR6 are expressed during the anagen phase of the hair cycle. LPA species with unsaturated fatty acids, potent agonists for LPAR6, are reduced in *LIPH*$^{-/-}$ mice.[57] Activation levels of TGFα and EGFR are down-regulated in *LIPH*$^{-/-}$ mice.[57] In addition, *in vitro* studies have demonstrated that LPA is an initiator of EGFR transactivation in various cells, such as corneal epithelial cells and lung epithelial cells.[58-60] From these findings, Inoue *et al*.[57] finally proposed a system in which hair follicle development is regulated by LIPH and LPAR6. They proposed that LIPH is expressed in IRS of hair follicles and produces 2-acyl-LPA from PA on the outer leaflet of the plasma membrane by hydrolyzing the acyl chain at the sn-1 position. The 2-acyl-LPA produced by LIPH activates LPAR6 in a paracrine and/or autocrine manner, eliciting ADAM17-dependent shedding of membrane-bound TGFα (pro-TGFα). Soluble TGFα released by that shedding binds to EGFR expressed on the IRS cells of hair follicles. Activated/phosphorylated EGFR provokes the IRS development that is required for the appropriate formation of the hair shaft (Fig. 2). Actually, EGFR is well known to be expressed in the outer root sheath.[61] Regarding the IRS, Inoue et al.[57] showed the phosphorylated form of EGFR to be co-expressed with LIPH, ADAM17 and TGFα in the IRS, specifically in the IRS cuticle of the keratin 72-positive layer by immunofluorescence staining. Previous studies reported TGFα and LPAR6 to be expressed in the IRS.[3,62] From these data, Inoue et al.[57] suggested that LIPH and LPAR6 regulate hair follicle formation via the ADAM17-TGFα-EGFR pathway in the IRS. Indeed, Inoue et al.[57] confirmed that immunofluorescence staining for phosphorylated EGFR in the IRS is reduced in the hair follicles of LIPH-deficient mice.

Recently, nonsense variants in *C3ORF52* were found in ARWH patients.[5] C3ORF52 has previously been demonstrated to interact with LIPH according to data obtained from BioPlex 2.0

(Biophysical Interactions of ORFeome-derived complexes).[63,64] Based on prediction software analyses, Malki *et al.*[5] suggested that C3ORF52 and LIPH may be involved in common lipid metabolism-associated pathways. It is speculated that C3ORF52 might functionally interact with LIPH and play an important role in LPA synthesis as a co-factor for LIPH activity (Fig. 2).

Thus, in ARWH patients whose disease is due to *LIPH*, *LPAR6* or *C3ORF52* mutations, the loss of function of LIPH, LPAR6 or C3ORF52 leads to reduced LIPH-LPA-LPAR6 signaling, resulting in the decreased transactivation of EGFR signaling and the phenotype of underdeveloped hairs (Fig. 3). In fact, genetic deletions of these key molecules in the regulation system of hair follicle development, LIPH/LPAR6, LIPH,[1,57] LPAR6,[2,3] ADAM17,[65,66] TGFα,[62,67] and EGFR,[61] result in aberrant hair formation in mice and/or humans.

Treatments for isolated ARWH

Cho *et al.*[68] reported that non-ablative fractional lasers induced the growth of intact hair in three adult patients with ARWH. However, sufficiently effective treatments have not been established for ARWH.

The efficacy of topical minoxidil was suggested in ARWH patients with *LIPH* mutations.[44,46] Tanahashi *et al.*[44] reported that application of topical minoxidil at 1% or 5% for 6 months to 3 years improved hypotrichosis in four ARWH patients with *LIPH* mutations, three patients with the homozygous mutation c.736T>A (p.Cys246Ser), and one patient with compound the heterozygous mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn). Furthermore, Choi *et al.*[69] reported that two children with woolly hair whose causative mutations were not identified were treated with the daily application of a topical minoxidil (3%) and tretinoin (0.025%) gel combined with an oral vitamin D analog, alfacalcidol (0.25 □cg/day), for 5 months, and that the patients' hair thickness and density were improved. Kinoshita-Ise *et al.*[46]

described two adult ARWH patients with the homozygous *LIPH* mutation c.736T>A (p.Cys246Ser) as responding well to topical minoxidil, with increased total hair counts and hair thicknesses. We recently performed a one-year, single center, open-label, prospective interventional study.[70] Topical minoxidil at 1% was found to improve hypotrichosis in all eight ARWH patients with *LIPH* mutations enrolled in the study.[70] There were no serious adverse events; only some mild adverse events were seen: dry skin on the scalp, trichiasis, and mild hypertrichosis on the entire body.[70]

Despite more than 30 years of minoxidil use around the world, mainly for androgenic alopecia, the mechanisms of action underlying its hair growth-promoting effects remain to be fully clarified.[71] Improved blood supply to the hair follicles was suggested as a mechanism behind the hair growth effects of minoxidil.[72] In addition, minoxidil promotes the induction of anagen from telogen by vascular endothelial growth factor and fibroblast growth factor 7 via the production of adenosine.[73,74] In terms of clinical effects, minoxidil has been reported to increase the size of hairs and to alter the hair cycle (anagen phase prolongation).[46] Kinoshita-Ise *et al.*[46] reported no observably low total hair counts, but did find a remarkable miniaturization and increased telogen/anagen hair ratio in patients with ARWH with c.736T>A homozygous mutations in *LIPH*. Considering that small hair shaft diameters and high telogen/anagen ratios are main factors responsible for hypotrichosis in ARWH, it is reasonable to regard minoxidil as beneficial for ARWH patients with *LIPH* mutations.

In 2020, Peled *et al.*[75] confirmed that gentamicin induces *in vitro* read-through activity across a *CDSN* mutation that causes hypotrichosis simplex of the scalp, and they successfully treated 4 patients with hypotrichosis simplex of the scalp with topical gentamicin. Considering that topical gentamicin improves hypotrichosis via the read-through of a causative nonsense mutation, I consider that there is a possibility that topical gentamicin might be an effective treatment for ARWH cases resulting from nonsense mutations in *LIPH*, *LPAR6* or *C3ORF52*. I hope that

innovative curative treatments such as translational read-through therapies across causative mutations by enhancers of ribosomal read-through activity including gentamicin, LIPH replacement therapy and the application of LPAR6 agonists will be developed in the near future.

Conclusions

The present summary of the data on causative mutations of ARWH in various populations around the world—both of *LIPH* mutations and *LPAR6* mutations causative of ARWH—shows that predominant recurrent mutations, probably founder mutations, including certain extremely predominant founder mutations, exist among certain ethnicities and in certain geographical areas. Such information on the frequencies of causative genes and mutations would enable the smooth, prompt genetic diagnosis of ARWH. The pathogenetic mechanisms of ARWH due to mutations in *LIPH* and *LPAR6* have not been elucidated completely. I hope that information on the genetics and pathophysiology of ARWH that has been accumulated will contribute to innovations in novel therapeutic strategies for ARWH.

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Figure legends

Figure 1 Clinical features of patients with ARWH

(a) An adult male patient with severe hypotrichosis. (b) A boy with moderate hypotrichosis. Both patients had the compound heterozygous *LIPH* mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn). ARWH patients uniformly show tightly curled hair, although the severity of the hypotrichosis varies depending on the case and course.

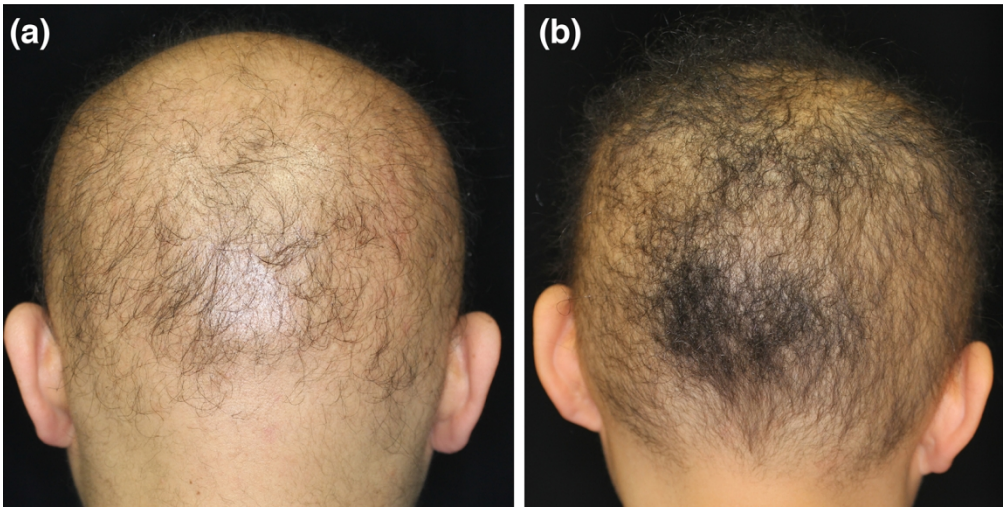
Figure 2 Schematic of the LIPH-LPA-LPAR6 signaling pathway in the development of IRS and the formation of intact hair shafts

In IRS, after interacting with C3ORF52, LIPH hydrolyzes PA and produces 2-acyl-LPA. 2-acyl-LPA binds to LPAR6 as a ligand in a paracrine and/or autocrine manner. The activated LPAR6 provokes the ADAM17-dependent shedding of membrane-bound pro-TGFα and upregulates soluble TGFα release. TGFα binds to EGFR and drives the development of IRS, which is required for the formation of intact hair shafts.

Figure 3 Schematic of the disease pathomechanisms in ARWH due to the loss of function of LIPH, LPAR6 or C3ORF52

LIPH mutations result in loss of function or the deficiency of LIPH, leading to the defective conversion of PA to 2-acyl-LPA and following defective activation of the LIPH-LPA-LPAR6 signaling pathway (left). *LPAR6* mutations cause deficient enzyme activity of LPAR6, resulting in the defective activation of ADAM17 and the loss of LIPH-LPA-LPAR6 signaling (center). *C3ORF52* mutations lead to the defective conversion of PA to 2-acyl-LPA by LIPH, resulting in the loss of activation of the LIPH-LPA-LPAR6 signaling pathway (right). The defective LIPH-LPA-LPAR6 signaling leads to the aberrant development of the IRS and the malformation of the hair shaft.

Molecules and arrows in faint gray indicate deficiency or loss of activity. X marks indicate loss-of-function or deficiency of the molecules by disease causative mutations.



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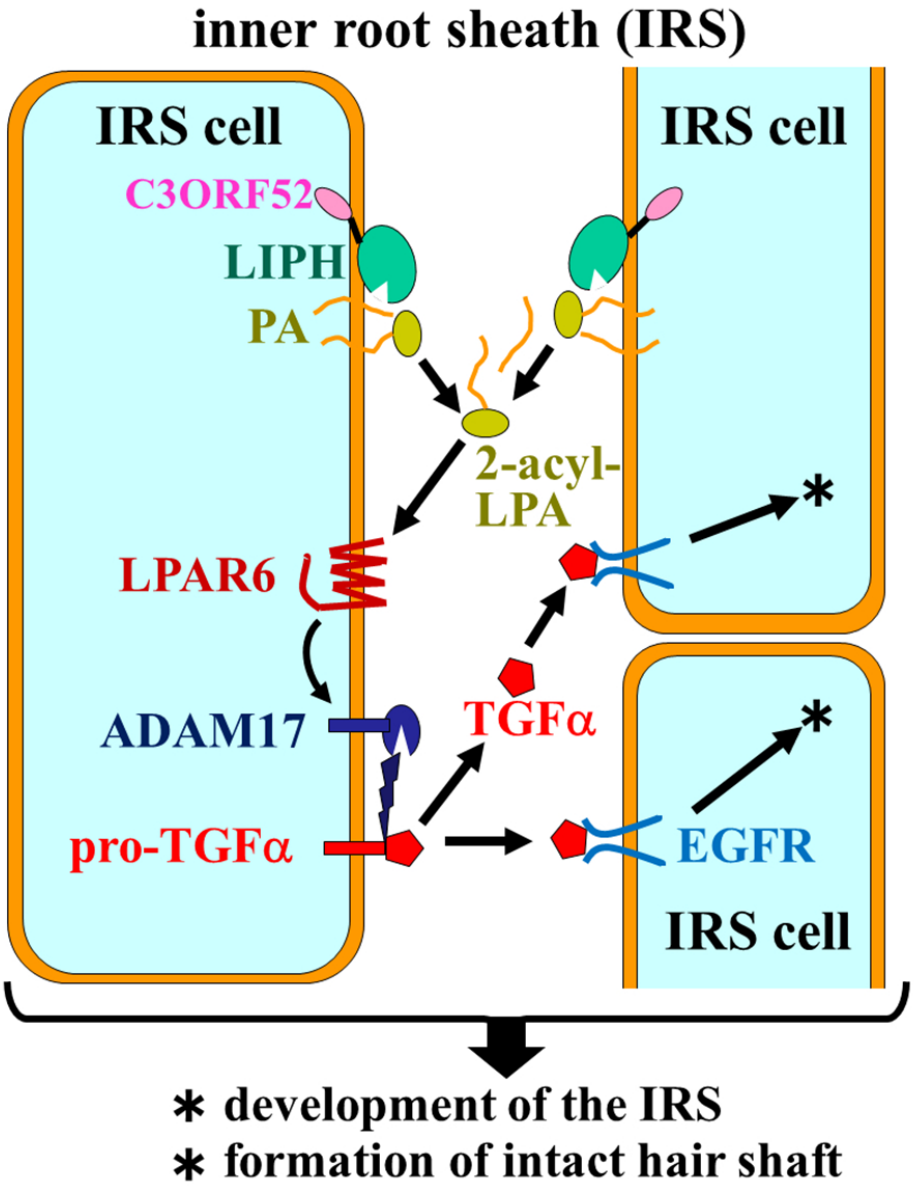

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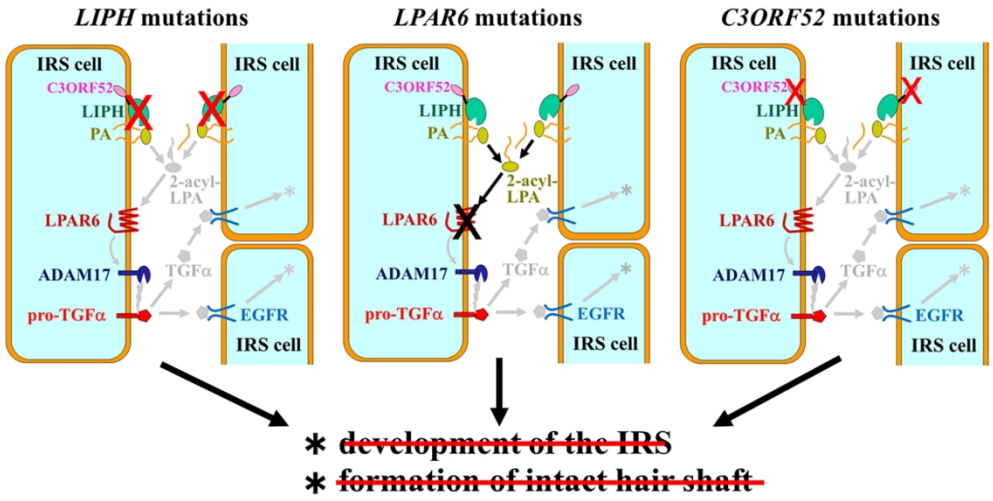

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Molecules and arrows in faint gray indicate deficiency or loss of activity. X marks indicate loss-of-function or deficiency of the molecules by disease causative mutations.

Table 1. List of abbreviations, full names and synonyms of molecules, structures and disorders mentioned in this review

abbreviation	full name	synonym
ADAM17	a disintegrin and metalloprotease domain 17	tumor necrosis factor-α-converting enzyme (TACE)
ARWH	(isolated) autosomal recessive woolly hair/hypotrichosis	woolly hair autosomal recessive
C3ORF52	TPA-induced transmembrane protein (encoded by chromosome 3 open reading frame 52)	-
EGFR	epidermal growth factor receptor	HER1
IRS	inner root sheath	-
LIPH	lipase H	membrane-associated phosphatidic acid-selective phospholipase $A_1\alpha$ (mPA-$PLA_1\alpha$)
LPA	lysophosphatidic acid	-
LPAR6	lysophosphatidic acid receptor 6	P2Y5, P2RY5
ORS	outer root sheath	-
PA	phosphatidic acid	-
TGF-α	transforming growth factor-α	-

Table 2. Genotypes of isolated autosomal recessive wooly hair, hypotrichosis (ARWH) and the causative genes/molecules

genotype (OMIM No.)	causative gene	causative molecule	function of causative molecule
ARWH2 (#604379)	*LIPH*	lipase H (LIPH) (membrane-associated phosphatidic acid selective phospholipase $A_1\alpha$; mPA-$PLA_1\alpha$)	LIPH produces 2-acyl-LPA from phosphatidic acid in hair follicles.
ARWH1 (#278150)	*LPAR6*	LPA receptor 6 (LPAR6) (P2Y5, P2RY5)	LPAR6 activated by 2-acyl-LPA mediates TACE-dependent TGFα release in the inner root sheath of hair follicles.
ARWH3 (#616760)	*KRT25*	keratin 25	Keratin 25 forms keratin intermediate filaments in the hair medulla and the inner root sheath of hair follicles.
- (*611956)	*C3ORF52*	C3ORF52 (protein product from *C3ORF52*)	C3ORF52 interacts with LIPH and is necessary for LPA production by LIPH.

Table 3. Summary of reported gene mutations causative of isolated ARWH

genotype (OMIM No.)	type of reported causative mutation	No. of reported mutations
ARWH2 (#604379)	*LIPH* mutations, total	32
	missense/nonsense	13
	splice-site	5
	small-deletion	5
	small-insertion	3
	small-indel	3
	gross-deletion	2
	gross-insertion	1
ARWH1 (#278150)	*LPAR6* mutations, total	27
	missense/nonsense	15
	small-deletion	4
	small-insertion	4
	small-indel	2
	gross-deletion	1
	gross-insertion	1
ARWH3 (#616760)	*KRT25* mutations, total	2
	missense	2
- (*611956)	*C3ORF52* mutations, total	2
	nonsense	2

Table 4. Prevalent recurrent *LIPH* mutations causative of ARWH by ethnicity and geographic area

ethnicity or geographic area	No. of reported families	prevalent recurrent mutation	No. of reported families
Japanese	75	c.736T>A (p.Cys246Ser)	72
		c.742C>A (p.His248Asn)	24
Volga–Ural region of Russia	50	deletion of exon 4	50
Pakistani	42	c.659_660delTA (p.Ile220Argfs*29)	22
		5290 bp genomic DNA deletion including exons 7 and 8 of *LIPH*	6

Table 5. Prevalent recurrent *LPAR6* mutations causative of ARWH in the Pakistani population

ethnicity or geographic area	No. of reported families	prevalent recurrent mutation	No. of reported families
Pakistani	47	c.436G>A (p.Gly146Arg)	10
		c.562A>T (p.Ile188Phe)	10
		c.68_69dupGCAT (p.Phe24Hisfs*29),	9
		c.188A>T (p.Asp63Val),	7