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Mutations with Hair Shape Phenotypes Abnormalities—The Morphogenetic Waves and Related Diseases

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ABSTRACT

Hair morphology is one of the most conspicuous features of human variation. The hair follicle has attracted significant attention as a model for the investigation of diverse biological problems. Whereas, very little is known about the genes influencing the morphology and structure of the hair shaft. Curly hair is very common character of hair phenotypes of human, while most congenital curl occurs owing to genetic factors and some are closely related with genetic diseases. This review highlights current related genes reported affecting hair curliness and human diseases which are due to gene mutations.

Keywords: Waved Hair; Curly Hair; Gene Mutations; Diseases

1. Introduction

A mammal's pelage is generally one of its first noticeable attributes and is aesthetically pleasing. Moreover, the skin is an essential organ which protects the organism from invasion of pathogens and chemicals and prevents the escape of liquids and nutrients [1]. Its ectodermal appendages, such as hair, feather and tooth, are attractive models for understanding the mechanisms underlying epithelial mesenchymal interactions [2].

Hair is composed of terminally differentiated, dead keratinocytes (trichocytes), which are compacted into a fibre of amazing tensile strength, the hair shaft. Hair morphogenesis and epidermal development are orchestrated by an array of cytokines and growth factors [3]. The presence of hair is characteristic for mammals, in which it exerts a wide range of tasks, including physical protection, thermal insulation, camouflage, dispersion of sweat and sebum, sensory and tactile functions, and social interactions [4]. In human society, hair is of enormous, psychosocial importance, and many human diseases are associated with abnormalities in hair follicle morphogenesis, cycling, and structure.

A hair grows from the papilla and with the exception of that point of generation is made up of dead, cornified cells. It consists of a shaft that projects above the skin, and a root that is imbedded in the skin. Its basic components are keratin (a protein), melanin (a pigment), and trace quantities of metallic elements [5]. These elements are deposited in the hair during its growth and/or absorbed by the hair from an external environment. After a period of growth, the hair remains in the follicle in a resting stage to eventually be sloughed from the body. As the place of origin of the hair, the structural change of hair follicle could directly cause the change of hair phenotype [6,7].

The hair follicle represents an attractive experimental system because of its accessibility, dispensability, and self-renewal capacity. Owing to its complex but highly organised architecture, this mini-organ can serve as an excellent model for investigating aspects of stem cell biology, cell lineage specification, cell differentiation, patterning processes, and cell-cell interactions [8,9]. In addition, hair follicles and shafts are of significant cosmetic relevance. The follicle provides the source for hair production and, thus, eventually determining appearance by affecting the hair shaft's structure and shape. Hair features are not only affected by the follicle's capacity to give rise to a normal shaft but also by the so-called hair growth cycle which controls the periodic growth and shedding of hair.

Human hair is one of most keratinous fibres. There are various fibre shapes in human hair and it is commonly

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accepted that the curliness of hair fibres is roughly classified by their ethnic origin in the three major ethnic groups: African hair which has a strong curl shape, Caucasian hair which has a moderately waved shape, and Asian hair which is apt to have a comparatively straight shape [10]. The corresponding difference in the internal nanostructure, however, still remains unrevealed.

The structured pattern of hair is determined by their length, width, and shape. Whereas the prototype hair is straight, hair can adopt different shapes owing to bending. In principle, bending could be achieved by diverse means. Differences in cell proliferation on opposite sides of the hair follicle would inevitably give rise to hair curvature [11]. Understanding the factors that contribute to the curly morphology of human hair is important for anthropological and physiological studies. According to a recent report, hair curling in man is a consequence of different proliferation rates within the hair follicle that appear to be reflected by the shape of the follicle [12,13]. This correlation is reminiscent of the potential link between follicle and hair size.

Curliness has commonly been assessed using words such as straight, wavy, curly and frizzy, a variety of attributes of subjective nature with no clear definition and limits [14]. Curly hair is very common character of hair phenotypes of human, which is caused by many reasons. Most congenital curl occurs as the result of genetic factors and some are closely related with genetic diseases. Genetic analyses of common diseases in humans have revealed that gene mutations are involved in diseases. Genome sequencing projects of various mammalian species followed by comparative genome analyses have revealed that a large number of genes are shared among species. Thus, it is thought that mutations found in model animals and animals carrying such mutations are of large significance in studying hair growth regulation and the relationship with some hereditary diseases.

2. The Curly Hair-Specific Genes

Several genetic alterations with different follicular localizations of the primary aberration give rise to curly or wavy hair and curly pelage is an easily recognized transspecies coat anomaly, moreover, several detailed studies in various mammalian species. In mice, Caracul (Ca) mice, a dominant mutation mapped to mouse chromosome 15 and missense point to a single amino acid exchange at the beginning of the a-helical rod domain of Krt71, a few amino acids apart from four identified Ca alleles possess curly hair and vibrissae after birth [15]. two novel krt 71^{rco12} and ^{rco13} mutant mice, displaying a wavy pelage and curly vibrissae, have been identified as missense point mutations in the first exon of the krt 71gene [16]. In rat, the autosomal dominant Rex (Re) mutation in the Krt71 gene, on chromosome 7, causes wavy body hair in Re/+ and body hair loss in Re/Re rats after the first molt. The homozygote exhibits more waved pelage and smaller body size and histological analysis of 1-month-old mice revealed bent hair follicles and fragile hair shafts, vibrissae of the homozygote are more strongly curled than those in the heterozygote [17,18].

Recently, genome-wide single-nucleotide polymorphism (SNP) association studies led to candidate gene screening for the curly/wavy coat of the portuguese water dog. A SNP in keratin-71 (KRT71) was shown to cause a nonsynonymous mutation in exon 2, having been recently identified in curly hair in dogs [19]. In cat, a complex sequence alteration of the KRT 71 gene, also causing a splice variation, was identified in the Devon Rex breed with curly coats [20]. In cattle, an autosomal recessive form has been described in Hereford cattle, an 8-bp deletion mutation occurring in exon 1 causes an early truncated KRT71 protein resulting in a curly-hair coat [21]. More gene mutations affecting the morphogenetic waves are showed in the **Table 1**.

3. Hair Curliness-Related Inherited Diseases

3.1. Pseudofolliculitis Barbae (PFB)

Pseudofolliculitis barbae, a common human hair disorder, showing a chronic, irritating, and potentially disfiguring condition that develops as a result of attempts to eliminate hair from the beard area, usually by shaving [56]. The disease is, however, not gender-specific, nor restricted to the face, but can occur in any hairy skin region upon regular shaving or other means of hair removal [57]. Compared to Caucasian males, black males are distinctly more susceptible to developing PFB due to their genetic predisposition for strongly curved hairs and the study showed that incidence rate of the disorder can affect up to 1 out of every 5 Caucasian individuals while it occurs much more commonly in black persons [58]. The mutation analysis of K75 and the IRS keratins in a three-generation Caucasian family whose male members suffered from relatively severe PFB symptoms revealed that affected males exhibited a heterozygous point mutation in the KRT75 gene. The mutation was also present in a female member of the family, however, this individual did not shave nor remove hairs by other means, and she was free of symptoms. Clinical features include the appearance of inflammatory papules and pustules. Molecular analysis in a family study and a large-scale investigation of randomly sampled PFB-affected and -unaffected individuals showed that an unusual single-nucleotide polymorphism, which gives rise to a disruptive Ala12Thr substitution in the 1A a-helical segment of the companion layer-specific keratin K6hf of the hair follicle, is partially responsible for the phenotypic expression and represents an additional genetic risk factor for PFB [59].

Table 1. Genes mutations causing the morphogenetic waves.

Gene	Name	Symbol	Synonyms	Chr	Characteristic	Reference
Adam 17	a disintegrin and metallopeptidase domain 17; mutation 1, Bruce Beutler	$Adam17^{tm1Btlr}$	Waved X	12	Wavy coat	[22]
Adam 17	a disintegrin and metallopeptidase domain 17; waved with open eyelids	$Adam17^{woe}$	$Adam17^{delta252-281}$, $Adam17^{deltaexon7}$, $Adam17^{T265M}$, wa3	12	Wavy fur	[23, 24]
Areg	amphiregulin; targeted mutation 1, David C Lee	$Areg^{tm1Dle}$	AR-	5	Wavy hair and curly vibrissae due to HF orientation and alignment problems.	[25]
Egf	epidermal growth factor; targeted mutation 1, David C Lee	Egf^{tm1Dle}		3		
cub	curly bare	cub		11	The mice with a single dominant allele show wavy hair.	[26]
Dicer1	dicer 1, ribonuclease type III; targeted mutation 1, Sarah E Millar	$Dicer1^{tm1Smr}$	$Dicer^{flEx22-23}$ $Dicer^{flox}$	12	External hair becomes wavy between P12 and P14 in doxycycline-treated mice	[27]
Drosha	drosha, ribonuclease type III; targeted mutation 1, Dan R Littman	$Drosha^{tm1Litt}$	$Drosha^{F}$, $Drosha^{flEx9}$, $Drosha^{lox}$	15		
Egfr	epidermal growth factor receptor ; dark skin 5	$Egfr^{Dsk5}$		11	Slight wave to the coat becomes less apparent with age	[28]
Egfr	epidermal growth factor receptor; targeted mutation 1, David W Threadgill	$Egfr^{tm1Dwt}$	$Egfr^{fl}$	11	$Egfr^{f/f}$, K14-Cre mice at 3 months of age display wavy coat	[29]
Egfr	epidermal growth factor receptor; velvet	$Egfr^{Vel}$		11	The first coat is wavy	[30]
Egfr	epidermal growth factor receptor; waved 2	$Egfr^{wa2}$	wa2, wa-2, waved2	11	Aggregation chimeras between $Egfr^{wa2}$/$Egfr^{wa2}$ and +/+ embryos result in a patchy distribution of waved and normal hair	[31]
Egfr	epidermal growth factor receptor; waved 5	$Egfr^{Wa5}$	GENA 239	11	The first coat is described as wavy and subsequent coats are scruffy in appearance.	[32]
Ets2	E26 avian leukemia oncogene 2, 3' domain; targeted mutation 1, Robert G Oshima	$Ets2^{tm1Rgo}$	$Ets2^{db}$ $ets2^{db1}$	16	Wavy hair, curly vibrissae, abnormal HF shape and arrangement.	[33]
Ets2	E26 avian leukemia oncogene 2, 3' domain; targeted mutation 5.1, Robert G Oshima	$Ets2^{tm5.1Rgo}$	$Ets2^{fl}$ $Ets2^{LoxP}$	16	$Ets2^{fl/fl}$ adult has a waved hair phenotype	[34]
Foxe1	forkhead box E1; targeted mutation 1, Roberto Di Lauro	$Foxe1^{tm1Rdl}$	Titf2-	4	On grafted skin, the hair coat appears kinky.	[35]
Hag	hague	Hag		15	Curly hair is more obvious in young mice [less than 2 months of age]	[36]
Krt25	keratin 25; rex	$Krt25^{Re}$	Re	11	Beginning at 1 month of age pelage is wavy compared to wild-type mice but this waviness becomes weaker as mice age	[37]
Krt71	keratin 71; caracul Rinshoken	$Krt71^{Ca-Rin}$		15	Hair is wavy and points in all directions. After 4 weeks, the wavy hair is less apparant but mice maintain a plush-like appearance	[15]
Krt71	keratin 71; caracul	$Krt71^{Ca}$	Ca	15	Curved vibrissae and wavy hair until about 4 weeks of age.	[38]
Krt71	keratin 71; Martin Hrabe de Angelis reduced coat 12	$Krt71^{Mhdarco12}$	$Krt71^{Rco12}$, rco12, reduced coat 12	15	Curly hair is visible by P10 and becomes less pronounced by 3 months of age	[39]
Krt71	keratin 71; Martin Hrabe de Angelis reduced coat 13	$Krt71^{Mhdarco13}$	$Krt71^{Rco13}$, rco13, reduced coat 13			
Krt71	keratin 71; RIKEN Genomic Sciences Center (GSC), 689	$Krt71^{Rgsc689}$	Krt2-6g1^{Rgsc}, M100689	15	Curl of coat was prominent at early stage (before 6 weeks) but unremarkable after 8 weeks	[15]

Continued

Liph	lipase, member H; targeted mutation 1, Junken Aoki	Liph^{tm1Aoki}	PA-PLA1alpha^{-}	16	Wavy hair cuticle	[40]
Notch1	notch 1; targeted mutation 2, Raphael Kopan	Notch1^{tm2Rko}	fN1, N1^{f}, NICD1^{fl}, Notch1^{flox}, Notch1^{tm1Shn}	2	Regions of wavy hair that have a twisted, knotted morphology	[41]
Ppp1r13l	protein phosphatase 1, regulatory (inhibitor) subunit 13 like; waved 3	Ppp1r13l^{wa3}		7	Curly hairs. Thinner hair shafts. At P8, abnormal shape and orientation of HFs.	[42]
Ppp1r13l	protein phosphatase 1, regulatory [inhibitor] subunit 13 like; waved with open eyelids 2	Ppp1r13l^{woe2}		7	Beginning around P14 and remaining throughout life	[25]
Sgk3	serum/glucocorticoid regulated kinase 3; fuzzy Iasi congenital atrichia	Sgk3$^{fz\text{-}ica}$		1	Sparse hair,curly vibrissae, abnormal hair shaft morphology, abnormal hair cycle	[43]
Sgk3	serum/glucocorticoid regulated kinase 3; fuzzy Mark D Fleming	Sgk3$^{fz\text{-}Mdf}$		1		[44]
Sgk3	serum/glucocorticoid regulated kinase 3; targeted mutation 1, David Pearce	Sgk3^{tm1Dpea}	Sgk3-	1	Early hair follicle development is normal, however by P4 the follicles have failed to enlarge and migrate deep into the subcutis	[45]
Stk11	serine/threonine kinase 11; targeted mutation 1.1, Ronald DePinho	Stk11$^{tm1.1Rdp}$	Lkb1^{lox}	10	Adult hair is wavy	[46]
Tg[EGFR]0Jlj	transgene insertion 0, Jose Luis Jorcano	Tg[EGFR]0Jlj	K5-HERCD-533, T0		Dominant negative. Short and waved hairs and curly whiskers. Degeneration and destruction of HFs in 3 to 4 weeks old mouse.	[47]
Tg[Notch1]1Anc	transgene insertion 1, Angela M Christiano	Tg[Notch1]1Anc			Wavy hairs and short, curly vibrissae. Defect in differentiation of the inner root sheath. Persistence of inner root sheath remnants in later stage of the hair cycle.	[48]
Tg[Notch1]A5Rko	transgene insertion A5, Raphael Kopan	Tg[Notch1]A5Rko	MHKA-Notch^{deltaE}		Decreased curvature of zigzag hairs	[49]
Tgfα	transforming growth factor alpha; targeted mutation 1, Ashley R Dunn	Tgfα^{tm1Ard}	Tgfαlpha -	6	Attenuated slightly with age	[50]
Tgfα	transforming growth factor alpha; targeted mutation 1, University of North Carolina	Tgfα^{tm1Unc}	TGFalpha-, Tgfa^{tm1Dcl}	6	Between 2 - 4 weeks of age the coat develops a wavy appearance.	[51]
Tgfα	transforming growth factor alpha; waved 1	Tgfα^{wa1}	wa-1, waved	6	Wavy hair is obvious at 10 days of age, extreme waviness of the first coat is lost in later hair generations but the coat never looks normal	[52]
Tgm3	transglutaminase 3, E polypeptide; targeted mutation 1, Susan John	Tgm3^{tm1Sjo}		2	Wavy hair is most obvious in the first four weeks of life	[53]
Trpv3	transient receptor potential cation channel, subfamily V, member 3; targeted mutation 1.2, David E Clapham	Trpv3$^{tm1.2Clph}$	V3 KO	11	HFs were gently curved and pointed in different directions with variable angles.	[54]
wal	waved alopecia	wal		14	At 2 weeks of age the hair is curly	[55]

3.2. Tricho-Dento-Osseous (TDO)

Tricho-dento-osseous syndrome is a rare human genetic disorder first distinguished by Lichtenstein *et al*., in 1972 [60]. It is a highly penetrant autosomal dominant trait characterized by curly kinky hair in infancy, enamel hypoplasia, taurodontism, thickening of cortical bones and variable expression of craniofacial morphology [61]. Diagnostic criteria are based on the generalized enamel defects, severe taurodontism especially of the mandibular first permanent molars, an autosomal dominant mode of inheritance, and at least one of the other features (*i.e*., nail defects, bone sclerosis, and curly, kinky or wavy hair present at a young age that may straighten out later). Kinky or tightly curled hair at birth may be a characteristic and distinguishing feature in many families and aid in diagnosing TDO from hypomaturation-type amelogenesis imperfecta [62,63]. TDO syndrome is considered the ectodermal dysplasia with a high penetrance even if the individual signs and symptoms can be present in variable intensities. Genetic studies have shown a mutation in the DLX3 gene on chromosome 17q21 and a 4 bp deletion in the DLX3 gene associated with TDO, which has also been identified [64]. Some families have been reported to have wavy hair or curly hair at birth that straightened out a few years later [65-67]. Seow [68] reported that the hair defects may vary among affected members of the same family. Mayer *et al*. [62] reported that an 8-year-old girl with TDO syndrome had uncombable hair, enamel hypoplasia and enlarged pulp chambers of the molar teeth. Electron microscopic examination of the curly hair showed a flattened hair shaft with longitudinal grooves.

3.3. Oculo-Dento-Digital Dysplasia (ODDD)

Oculo-dento-digital dysplasia is a rare autosomal dominant congenital disorder caused by mutations in conserved domains of the gap junction alpha 1 gene (GJA1 or Connexin 43 (CX43)) located on chromosome 6q21-q23.2 with two exons separated by an 11-kb intron [69]. Abnormalities observed in ODDD affect the eye, dentition, and digits of the hands and feet [70]. Patients present with a characteristic facial appearance, narrow nose, and hypoplastic alae nasi. Neurological problems are known to occur as well as conductive hearing loss, cardiac defects, and anomalies of the skin, hair, and nails. Curly/kinky hair with features of early trichorrhexis nodosa was identified in a 13 years old girl with ODDD [71], this in accord with the observation by Kjaer *et al*., who found curly hair in seven out of nine affected subjects harboring a mutation in the Cx43 gene in a Danish family over five generations [72].

3.4. Woolly Hair (WH)

Woolly hair is a group of hair shaft disorders, which refers to an abnormal variant of fine, tightly curled hair that often exhibits decreased pigmentation. Hutchinson *et al*. [73] classified woolly hair into 3 variants: woolly hair nevus, autosomal dominant hereditary woolly hair, and autosomal recessive familial woolly hair. Since then, WH has also been observed in association with several genetic conditions, such as Naxos disease and Carvajal syndrome, both of which are characterized by cardiomyopathy, palmoplantar keratoderma, and WH, and are caused by mutations in the plakoglobin [74] and desmoplakin [75] genes, respectively. Furthermore, most notably is Noonan syndrome and cardiofaciocutaneous (CFC) syndrome. Andy J. Chien described a family with woolly hair and ulerythema ophryogenes spanning four generations, which have been associated with Noonan syndrome and CFC, and he found that this family did not exhibit any of the other findings characteristic of either Noonan syndrome or CFC, similar to a previously described pedigree with hereditary woolly hair [76]. In addition to these syndromes, WH without associated findings (non-syndromic WH) has also been described [77].

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