REVIEW

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# The *Hairless* Gene: A Putative Navigator of Hair Follicle Development

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## Abstract

The *Hairless* (*HR*) gene regulates the expression of several target genes as a transcriptional corepressor of nuclear receptors. The hair follicle (HF), a small independent organ of the skin, resides in the epidermis and undergoes regenerative cycling for normal hair formation. HF development requires many genes and signaling pathways to function properly in time and space, one of them being the *HR* gene. Various mutations of the *HR* gene have been reported to cause the hair loss phenotype in rodents and humans. In recent studies, it has been suggested that the *HR* gene is a critical player in the regulation of the hair cycle and, thus, HF development. Furthermore, the *HR* gene is associated with the Wnt signaling pathway, which regulates proliferation and differentiation of cells and plays an essential role in hair and skin development. In this review, we summarize the mutations responsible for human hair disorders and discuss the roles of the *HR* gene in HF development.

***Keywords:*** *hairless*, corepressor, hair follicle, hair cycle, hair loss

## Introduction

The hair follicle (HF) is a small independent organ of the skin that undergoes regenerative cycling for normal hair formation. HF formation during embryogenesis and regenerative cycling periods occurs through close cross-talk between epithelial and mesenchymal cells (Millar, 2002). HF cycling is composed of the growth phase (anagen), regressing phase (catagen), and resting phase (telogen) (Paus *et al*., 2004).

The HF, a complex skin appendage, is composed of many different compartments, including the sebaceous gland, which produces oil; the bulge, which is the niche for stem cells; the bulb, which has actively proliferating and differentiating cells; and the stalk, which is divided into three layers the hair shaft, inner root sheath (IRS), and outer root sheath (ORS) (Fig. 1; Blanpain *et al*., 2006). Each layer expresses layer-specific keratin proteins that contribute to HF keratinization, leading to formation of a rigid structure (Langbein *et al*., 2005; Shimomura *et al*., 2010).

The *hairless* (*Hr*) gene was first cloned in the 'hairless' ($Hr^{hr}$) mouse, whose genome contained an endogenous murine leukemia provirus in intron 6 of this gene (Stoye *et al*., 1988). Homozygous $Hr^{hr}$ mice initially grow hair until the beginning of the hair cycle, when they start to lose hair from the head and continue to lose it until reaching the caudal area (Brooke, 1926). Then, this hairless phenotype is permanent hence the name 'hairless'. A study of $Hr^{hr}$ mutant mice has revealed that the *Hr* gene is important for hair growth and the hair cycle (Panteleyev *et al*., 1998). The rat *hr* gene was isolated as a gene that is regulated by thyroid hormone (Thompson, 1996), and the human *HR* gene was identified as a gene that is responsible for congenital hair disorders (Ahmad *et al*., 1998a; Ahmad *et al*., 1998b; Cichon *et al*., 1998).

The mouse, rat, and human *Hr* genes encode an approximately 130-kDa protein (HR) that localizes to the nucleus and contains a single zinc-finger domain (Cachon-Gonzalez *et al*., 1994; Djabali *et al*., 2001). The

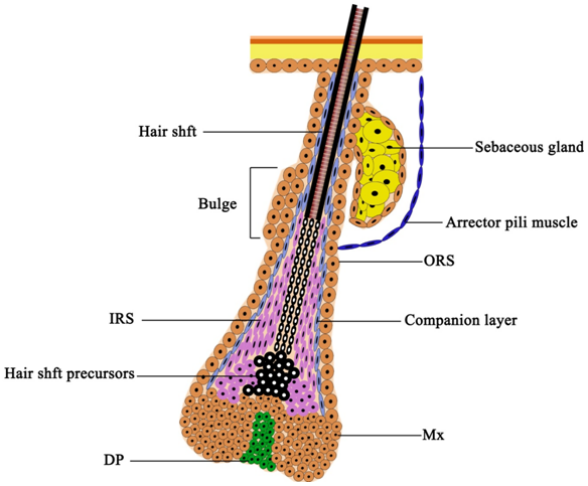


**Fig. 1.** Schematic of hair follicle (Blanpain *et al*., 2006).

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mouse *Hr* gene is expressed mainly in the brain and skin, with minor expression elsewhere (Cachon-Gonzalez *et al*., 1994; Cachon-Gonzalez *et al*., 1999).

In this review, we will summarize the molecular characteristics of the *Hr* gene, the roles of the *Hr* gene in HF development, and the mutations that are responsible for human hair disorders.

## *HR*, a Corepressor of Nuclear Receptors

The HR acts as a transcriptional corepressor through interaction with nuclear receptors. Nuclear receptors regulate the expression of specific genes as transcription factors in developmental processes and other various physiological processes. Typically, nuclear receptors activate the transcription of target genes through binding to their ligands, such as steroid hormone, thyroid hormone, and other small molecules, including retinoic acids and vitamin D. In some cases, nuclear receptors repress transcription in the absence of their ligands (Jepsen *et al*., 2002; Mangelsdorf *et al*., 1995; Privalsky, 2004; Smith *et al*., 2004), and this repression occurs through association with its corepressors, such as nuclear receptor corepressor (N-CoR), silencing mediator for retinoic acid and thyroid hormone receptors (SMRT), and HR (Chen *et al*., 1995; Horlein *et al*., 1995; Sande., 1996; Thompson *et al*., 2006; Zhongjian *et al*., 2006). HR has been shown to interact with thyroid hormone receptor (TR), retinoic acid orphan receptor $\alpha$ (ROR$\alpha$), and vitamin D receptor (VDR) (Thompson, 1996; Hsieh *et al*., 2003; Moraitis *et al*., 2002).

### Interaction with the thyroid hormone receptor and retinoic acid orphan receptor-$\alpha$

TR is a receptor for thyroid hormone, which is an essential component of development of the central nervous system (CNS), and functions as a transcription factor that regulates the expression of target genes in response to thyroid hormone binding. The interaction between HR and TR was found in a yeast two-hybrid screen for HR-interacting proteins, and its interaction was reduced in the presence of thyroid hormone (Thompson *et al*., 1997). *In vitro* biochemical assays and *in vivo* coimmunoprecipitation experiments have demonstrated that *hr* has two independent TR-interacting domains (TR-ID)-TR-ID1 and TR-ID2 span amino acids 816-830 and 1026-1038 of the rat *hr* gene, respectively (Fig. 2). These TR-ID domains of HR contain a consensus sequence, a stretch of hydrophobic residues: I/LIXXL/VV. This essential motif is similar to those of other corepressors, such as N-CoR and SMRT (Potter *et al*., 2001; Potter *et al*., 2002; Thompson *et al*., 1997).

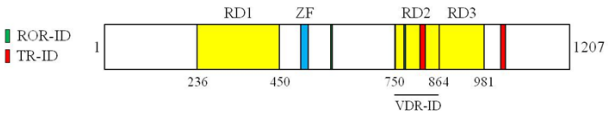


**Fig. 2.** Schematic of rat HR functional domains. Repression domains (yellow: RD1, 236-450; RD2, 750-864; RD3, 864-981); ROR-interacting domains (green: ROR-ID1, 586-590; ROR-ID2, 778-782); TR-interacting domains (red: TR-ID1, 816-830; TR-ID2, 1026-1038); VDR-interacting domains (overlaps with RD3, 750-864). ZF indicates zinc-finger domain (621-646) (Thompson, 2009).

Deletion mapping of *HR* revealed three repression domains (RD) that span amino acids 236-450 (RD1), 568-864 (RD2), and 864-981 (RD3) (Fig. 2). The repression activity usually occurs through interaction with histone deacetylases (HDACs) (Burke *et al*., 2000; Glass *et al*., 2000; Pazin *et al*., 1997). The HR protein interacts with several HDACs, including HDACs 1, 3, and 5, and the repression activity of HR is reduced on treatment with HDAC inhibitors. Furthermore, HR localizes in the nuclear matrix-associated deacetylase body, which comprises corepressors and HDAC complexes (Potter *et al*., 2001; Potter *et al*., 2002, Downes *et al*., 2000). This evidence suggests that HR may contribute to brain or CNS development through TR, acting as a transcriptional corepressor.

The HR protein interacts with another nuclear receptor, ROR$\alpha$, which plays an important role in cerebellar development, lipid metabolism, and neoplasia (Gigue're., 1999; Moraitis *et al*., 2003). HR binds to ROR$\alpha$ using two interaction motifs, containing an LXXLL consensus sequence, and represses transcriptional activation by ROR$\alpha$ (Moraitis *et al*., 2002). Cotransfection analysis revealed that HR represses transcriptional activation by all ROR isoforms-$\alpha$, $\beta$, and $\gamma$. Interestingly, the repression activity of ROR$\alpha$ by HR is dependent on two LXXLL motifs, as mutations in these motifs abolished repression activity by HR, while these mutations did not affect the repression activity of TR by HR (Moraitis *et al*., 2002).

### Interaction with the vitamin D receptor

Although HR interacts with TR and ROR$\alpha$, this is not enough to explain the skin phenotype in HR mutants, because there is no evidence that defects in these receptors cause a phenotype that is as striking as the complete hair loss that is observed in HR mutants (Alonso *et al*, 2003). On the other hand, mutants with a deletion in the VDR manifest a hair loss phenotype,

which resembles that of *HR* mutant in mice and humans (Li *et al*., 1997; Yoshizawa *et al*., 1997).

The VDR not only mediates signals of 1, 25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$) but also acts as a transcription factor, even in the absence of vitamin D. Targeted gene deletion studies revealed that VDR is associated with multiple biological processes, especially the progression of the normal hair cycle in mammalian skin (Yoshizawa *et al*., 1997; Li *et al*., 1997; Malloy *et al*., 1999; Hirst *et al*., 1985; Hughes *et al*., 1988; Rut *et al*., 1994).

VDR regulates gene expression by forming a heterodimer with RXR and binding to a vitamin D-responsive element in target genes. As a partner of the heterodimer of VDR, RXR$\alpha$ is relevant for hair cycling, since conditional inactivation of RXR$\alpha$ in mice caused alopecia, as in VDR-null mice (Li *et al*., 2000). GST pull-down assays revealed that *HR* interacts with VDR protein *in vitro*, and this interaction is unaffected by the $1,25(OH)_2D_3$ ligand. Coimmunoprecipitation experiments also showed an interaction between HR and VDR in mammalian cells (Hsieh *et al*., 2003). The interaction domain of HR for VDR overlaps with the interaction domains for TR and ROR$\alpha$ (Fig. 2), and the minimal amino acid region was mapped to 750-864 (RD2) of HR (Hsieh *et al*., 2003). The transcriptional repression of VDR by HR occurs both in the presence and absence of its ligand, vitamin D, which is different from that of TR, in that HR mediates repression only by unliganded TR (Potter *et al*., 2001; Hsieh *et al*., 2003). In humans, HR interacts with VDR and represses the reporter activity of its target genes, such as involucrin, transglutaminase, PLC-$\gamma$1, and 24-hydroxylase, in human keratinocytes (Zhongjjan *et al*., 2006). *In situ* hybridization assay revealed that *HR* and VDR mRNA colocalize in a subset of cells in murine HFs, including the matrix and ORS (Hsieh *et al*., 2003). Immunostaining showed that both nuclear proteins are colocalized in a subset of HF cells in human skin (Zhongjjan *et al*., 2006). These results support the biochemically defined evidence of an interaction between *HR* and VDR *in vivo* in mouse and human skin.

## Regulation of Hair Cycle and Hair Follicle Structure

### Mutant mice of *hairless* gene

Mouse models of various *Hr* mutations, such as $Hr^{hr}$, $Hr^{rh}$, and $Hr^{m1Enu}$, have been actively studied to understand the pathophysiology of human hair loss disorders (Cachon *et al*., 1994; Ahmad *et al*., 1998c; Panteleyev *et al*., 1998; Nam *et al*., 2006). Homozygous mutant mice with autosomal recessive mutations in *Hr* display a distinct phenotype with strikingly similar patterns of hair loss. These mutant mice grow hair normally in the postnatal stages; however, they shed hair progressively from the eyelids to the hind limbs and subsequently develop alopecia by the third week of postnatal life. Additionally, targeted disruption of *Hr* also causes a hair loss phenotype, which is restored by the expression of HR in keratinocytes (Beaudoin *et al*., 2005; Thompson *et al*., 2006). In $Hr^{hr}$ mice, apoptotic cell death in HFs is observed in the transition stages from the catagen to anagen, suggesting that *HR* may play a role in regulating the HF growth cycle (Panteleyev *et al*., 1999).

Mutant mice with a loss of function in *Hr* display the hair loss phenotype, which suggests that null or a lack of functional HR causes the hair loss phenotype. Recently, it was shown that dysregulation of HR expression also causes the hair loss phenotype. The 'hairpoor' ($Hr^{Hp}$) and Naked ($Hr^{N}$) mice display a different hair loss phenotype from those reported in mice with a loss-of-function mutation in HR (Baek *et al*., 2009). The $Hr^{Hp}$/+ mouse has short and sparse hair at early ages but gradually lose hair and become almost bald at age 40 weeks, while homozygote ($Hr^{Hp}/Hr^{Hp}$) mice are born *Hairless* and stay naked (Baek *et al*., 2009). We found that this $Hr^{Hp}$ mouse harbors a mutation in the 5' untranslated region (UTR) of the *Hr* gene, and it causes overexpression of HR protein (Baek *et al*., 2009; Kim *et al*., 2010). This evidence has revealed that both loss- and gain-of-function mutations in *Hr* cause the hair loss phenotype, which suggests that expressional regulation of *Hr* is critical for maintenance of the hair cycle or development of HF.

### Regulation of hair follicle structure

Keratins are critical components of the HF. The hair shaft is highly keratinized tissue, and its major components are hair keratins (Langbein *et al*., 2005). The keratins are divided into two types-type I and type II-and their heterodimerization forms intermediate filaments that provide resilience to hair. Keratin is produced by keratinocytes, which multiply and differentiate. While some keratinocytes become epithelial cells of the ORS and IRS, some become elongated to form the hair shaft (Coulombe *et al*., 2002; Moll *et al*., 2008). Epithelial keratins are widely expressed in the ORS and IRS of the HF (Langbein *et al*., 2003; Langbein *et al*., 2001).

Keratin expression is regulated by several signaling pathways and transcription factors, such as Lef1 (a key transcription factor in Wnt signaling), Msx2, Foxn1, and Hoxc13 (DasGupta *et al*., 1999; Merrill *et al*., 2001; Ma *et al*., 2003; Schlake *et al*., 2000; Tkatchenko *et al*., 2001). Recently, we found that HR regulates the ex-

pression of keratins that reside in the IRS. The IRS forms its structure by obligate heterodimerization of specified keratins. Type I IRS keratin genes (ie, *Krt25*, *Krt27*, and *Krt28*) and the type II IRS keratin gene *Krt71* have been identified as specifically expressed in the IRS and are known to support the structures of the IRS cuticle, Huxley's layer, and Henle's layer (Runkel *et al*., 2006; Tanaka *et al*., 2007). We observed that the expression of *Krt25*, *Krt27*, *Krt28*, *Krt71*, and *Tchh* is consistently affected by HR, both *in vivo* and *in vitro* (in submission). These results suggest that *HR* affects the formation of the HF through regulation of keratin expression in the IRS.

## Association with the Wnt Signaling Pathway

Wnt/$\beta$-catenin signaling plays a crucial role not only in HF morphogenesis but also in the regeneration of the HF through regulation of anagen initiation in the adult hair cycle (Ahmad *et al*., 1998c; Huelsken *et al*., 2001; Beaudoin *et al*., 2005; Stenn *et al*., 2001). The $\beta$-catenin protein, a key molecule of the Wnt signaling pathway, is activated and translocated into the nucleus when a Wnt protein binds to its receptor, Frizzled. In the nucleus, $\beta$-catenin forms a complex with Lef1/Tcf transcription factors and regulates target gene expression (Huelsken *et al*., 2001). Inactivation of Wnt signaling occurs through its inhibitors, and keratinocyte cells, including the *Dickkopf* (*Dkk*) family, *Sclerostin domain-containing protein 1* (*Sostdc1*), *Wnt inhibitory factor 1* (*Wif1*), and the *Secreted frizzled-related protein* (*Sfrp*) family (Kawano *et al*., 2003).

### Transcriptional regulation of Wnt signaling inhibitors

The fact that induction of HR protein using transgenic systems rescues the *Hairless* phenotype of HR-null mice reveals that HR functions in progenitor keratinocytes and induces the hair cycle, thus allowing HF regeneration (Beaudoin *et al*., 2005). This suggests that HR may regulate the Wnt signaling pathway, since this signaling directly regulates HF regeneration (Zarach *et al*., 2004; Beaudoin *et al*., 2005; Lo Celso *et al*., 2004). Gene expression profiling of *Hr* knockout and *Hr*-rescued transgenic mice have revealed that the Wnt-responsive gene *Axin2* is regulated by HR, which suggests that HR can promote the Wnt signaling pathway. In addition, the HR overexpression mouse $Hr^{Hp}$ shows increased expression of *Myc* and *Ccnd1*, target genes of Wnt signaling (Kim *et al*., 2010). As expected, the Wnt inhibitors *Wise* and *Soggy* are upregulated in *Hr* knockout mice and downregulated in HR-rescued transgenic skin, showing an inverse relationship with HR expression *in vivo* (Beaudoin *et al*., 2005; Thompson *et al*., 2006). Furthermore, *Sfrp2* mRNA expression is downregulated in $Hr^{Hp}$ mouse skin (Kim *et al*., 2010). A promoter analysis has suggested that the regulation of Wnt inhibitor expression is regulated by HR specifically, because there is no such regulation that is detected by another corepressor, SMRT (Beaudoin *et al*., 2005; Thompson *et al*., 2006). These findings suggest that HR can modulate more than one regulator in the Wnt signaling pathway, and it appears to be crucial that the timing and level of HR protein expression are tightly regulated for normal HF development. Regulation of Wnt signaling by HR is one component of the complex interactions of signaling pathways in HF cycling. HR may regulate the expression of genes that modulate other signaling pathways, such as Shh, BMP, and TGF-$\beta$, which regulate HF morphogenesis and cycling.

## Genetic Hair Disorders with *HR* Mutation

### Atrichia with papular lesions and Alopecia universalis congenita

Atrichia with popular lesions (APL; MIM 209500) is a rare autosomal recessive disorder. Patients are born with natal hair, which falls out in the first few months of life and never replenishes. In addition to the complete absence of any hair, including scalp hair, eyebrows, eyelashes, and pubic hair, they also develop papular eruptions on the scalp, cheeks, elbows, arms, knees, and thighs. Histological examination of a patient's skin has revealed the absence of HFs (Ahmad *et al*., 1998a; Henn *et al*., 2002; Sprecher *et al*., 1999).

A similar hair disorder as APL, alopecia universalis congenita (ALUNC; MIM 203655) also manifests as a lack of body hair without papular lesions and has been found to be caused by mutations in the *HR* gene. A skin biopsy of one patient revealed that there were few HFs present, without hair in them (Ahmad *et al*., 1998b). Multiple kinds of mutations of the human *HR* gene with a loss of function have been reported (Table 1).

As a model for APL, we and others have reported hairless mutant mice that have a similar phenotype as APL. Histological analyses have revealed that they show an absence of HFs and the formation of abnormal structures, such as utricles and dermal cysts, in the skin (Ahmad *et al*., 1998c; Panteleyev *et al*., 1998; Nam *et al*., 2006; Zarach *et al*., 2004; Sundberg, 1994). APL is also caused by recessive mutations in the *VDR* gene, as found in a vitamin D-dependent rickets type 2A

**Table 1.** HR mutations responsible for genetic human hair disorders

| Disease | Mutation | References |
|---|---|---|
| APL | 3434delC* | Sprecher *et al*., 1999 |
| | N970S | Kruse *et al*., 1999 |
| | V1056M | Zlotogorski *et al*., 2002 |
| | Q1176X | Henn *et al*., 2002 |
| | R33X | Zlotogorski *et al*., 2002 |
| | Q478X | Indelman *et al*., 2003 |
| | E583V | Paradisi *et al*., 2003 |
| | C622G | |
| | R154X | Ashoor *et al*., 2005 |
| | Q515X | |
| | 431delC* | John *et al*., 2005 |
| | 2021delG* | |
| | G202InsCTTCCCCCAGG* | Wali *et al*., 2006 |
| | Q260X | Michailidis *et al*., 2007 |
| | W699X | |
| | Q323X | Kim *et al*., 2007 |
| | Q502X | |
| | 1839-1841delATG* | Balighi *et al*., 2009 |
| ALUNC | T1022A | Ahmad *et al*., 1998a |
| | V1136D | Cichon *et al*., 1998 |
| | D1012N | Klein *et al*., 2002 |
| | 2661dupG* | Betz *et al*., 2007 |
| MUHH | A-321G* | Wen *et al*., 2009 |
| | A-321T* | |
| | T-320A* | |
| | G-319A* | |
| | C-315T* | |
| | C-302A* | |
| | T-251A* | |
| | C-248G* | |
| | G-245A* | |
| | G-239C* | |
| | T-218C* | |
| | A-217G* | |
| | T-320C* | Kim *et al*., 2010 |
| | | Wen *et al*., 2009 |

*indicates nucleotide sequences.

(VDDR2A; OMIM 277440) patient (Miller *et al*., 2001). This suggests that there is a functional relationship between HR and VDR in controlling postnatal cycling of the HF, as mentioned above.

### Marie Unna hereditary hypotrichosis

Autosomal dominant Marie Unna hereditary hypotrichosis (MUHH; MIM 146550) is characterized by abnormal hair density in the scalp, eyebrows, eyelashes, and body. Affected individuals are born with sparse hair that is characteristically coarse, wiry, and twisted in early childhood and progress to complete baldness (Argenziano *et al*., 1999; Unna., 1925; Ludwig., 1953). Although genetic heterogeneity has been reported in Dutch, Belgian, British, French, German, and Chinese families, the majority of MUHH pedigrees has been linked to chromosome 8p21, near the *HR* gene (Sreekumar *et al*., 2000; van Steensel *et al*., 1999; Lefevre *et al*., 2000; Cichon *et al*., 2000; Yan *et al*., 2004; He *et al*., 2004). In addition to the characteristic sparse hair phenotype at birth, MUHH is different from other *HR* defect-associated disorders, in that it is inherited in a dominant manner, whereas the other disorders are inherited in a recessive mode. Recently, 13 distinct mutations were identified in patients with MUHH. Interestingly, all of these mutations were present in the 5' UTR of *HR* (Wen *et al*., 2009), in contrast to mutations present in the coding sequences of *HR* that result in a loss of function. We and others have shown that all of these mutations upregulate HR expression at the translational level using a reporter system (Wen *et al*., 2009; Kim *et al*., 2010). In fact, in an animal model, the $Hr^{Hp}$ mouse, which has a mutation located at the same position of the *HR* gene as in MUHH, the expression of HR was found to be greatly increased compared with that of wild-type mice (Kim *et al*., 2010).

## Conclusion

The study of HR has suggested that HR functions in HF development and cycling. As a transcription factor, HR regulates the expression of many genes that are components of the HF or key molecules of the signaling pathway for hair cycling and HF maintenance. There may be many more genes that remain to be discovered as targets of HR in the skin. Identification of them will greatly facilitate the elucidation of the biological functions of HR in developmental processes and the molecular mechanisms of HF cycling. The HF is a very dynamic organ, with continuous regeneration throughout an organism's life, and the presence and behaviors of its stem cells are only recently slowly being uncovered. Since HR associates with Wnt signaling, which is an essential pathway for stem cell function, and is expressed in ORS cells, which are the same lineage as bulge cells, the elucidation of HR function in HF stem cells will be required. Further study of HR function in HF cycling as well as in stem cell biology will provide a better understanding of HF development and may help us understand the development of other HR-expressing tissues, such as brain.

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