A Novel Nonsense Mutation and Polymorphisms in the Mouse Hairless Gene

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A novel autosomal recessive mutation arose spontaneously in a breeding colony of Chinese Kunming mice. The characteristics of these mutant mice include progressive irreversible hair loss soon after birth, rhinocerotic appearance, and shorter life span. Histological evaluation of skin revealed the homogeneous enlargement of utriculi, and the formation of several rows of large cysts. Sequencing the complete cDNA of the hairless gene identified two polymorphisms and a homozygous transition for a G → A at nucleotide position 3110 (exon 12) leading to the substitution of tryptophan by a nonsense codon, designated W911X. This allele was named rhinocerotic and short-lived, with the symbol *hr*^{rhsl}. Addition of hairless gene mutation into the expanding hairless mutation database allows further development of genotype/phenotype correlations towards understanding inherited atrichia.

Key words: cysts/genetic variation/hair/skin
J Invest Dermatol 124:1200–1205, 2005

Mutations of the hairless (*hr*) gene are autosomal recessive allelic mutations that cause severe abnormalities during the first hair follicle regression (catagen), resulting in hair loss soon after birth (Panteleyev *et al*, 1998c). Histologically, the skin of all alleles of hairless mutations is characterized by a complete absence of normal hair follicles and the formation of intradermal cystic structures (Panteleyev *et al*, 1998b). Analysis of the hairless gene structure and organization reveals remarkable conservation between mice, rats, non-human primates, and humans (Ahmad *et al*, 1998; Brancaz *et al*, 2004). Hairless mutation in mice closely resembles the human diseases known as papular atrichia (MIM 209500) (Ahmad *et al*, 1999b). Currently the human homolog of the *hr* gene has been identified and linked to human Chromosome 8p21, in a region syntenic with mouse chromosome 14 (Ahmad *et al*, 1998; Cichon *et al*, 1998; Nothen *et al*, 1998), and further mutation detection in *hr* gene has elucidated the molecular causes of papular atrichia in families from around the world (Cichon *et al*, 1998; Ahmad *et al*, 1999a, b; Kurse *et al*, 1999; Djabali *et al*, 2004). Including this report, some 16 allelic mutations in the mouse *hr* gene have been reported, ranging from recessive to semidominant, and with minor to severe clinical features (Panteleyev *et al*, 1998b; Ahmad *et al*, 1999a; Cachon-Gonzalez *et al*, 1999; Brancaz *et al*, 2004; Tian *et al*, 2004). These studies have revealed an intricate relationship between a varying phenotype and a wide range of mutations spread over the entire length of the gene in mice and humans (Panteleyev *et al*, 1998b; Klein *et al*, 2002). Like mutation in *hr* gene, some mutations in the vitamin D receptor (VDR) gene result in congenital hair loss in mice and humans, suggesting that the biochemical interaction of VDR and *hr* proteins is functionally relevant (Miller *et al*, 2001; Zarach *et al*, 2004).

The *hr* gene encodes a putative single zinc finger transcription factor, and its product acts as a nuclear receptor co-repressor. On the other hand VDR is a member of the steroid binding receptor family and functions as a co-repressor for hairless gene (Miller *et al*, 2001; Hsieh *et al*, 2003). Both the VDR and *hr* genes play a role in the mammalian hair cycle, as inactivating mutations in either result in generalized atrichia (Hsieh *et al*, 2003; Zarach *et al*, 2004). Moreover, *hr* mutation is pleiotropic, including such effects as reproductive and immunological abnormalities, and elevated sensitivity to chemically induced skin carcinogenesis (Panteleyev *et al*, 1998b). But, the precise function of the corresponding protein of the hairless gene remains elusive. The novel spontaneous allelic mutations provide crucial insights in this regard, and are powerful tools for understanding variations in human clinical symptoms for inherited atrichia.

In this study, several mice lacking hair arose spontaneously in a closed colony of Chinese Kunming mice maintained in our lab. With age their skin become excessively wrinkled in a fashion similar to rhino mice previously reported (Panteleyev *et al*, 1998b). But, in contrast to nude mice, these hairless mice possess thymus (Zhang *et al*, 2002). The inheritance mode of this phenotype was revealed, by testcross, to have resulted from an autosomal recessive mutation (Zhang *et al*, 1997). We have designated this mouse Yuyi using the laboratory code (Laboratory Animal Center of Zhengzhou University), and established Yuyi hairless mice (YYHL) of segregated inbred strains (Zhang *et al*, 2002). To elucidate further the underlying pathogenesis of this inherited atrichia we used a molecular approach

Abbreviations: bp, base pairs; hr, hairless; VDR, vitamin D receptor; YYHL, Yuyi hairless mice

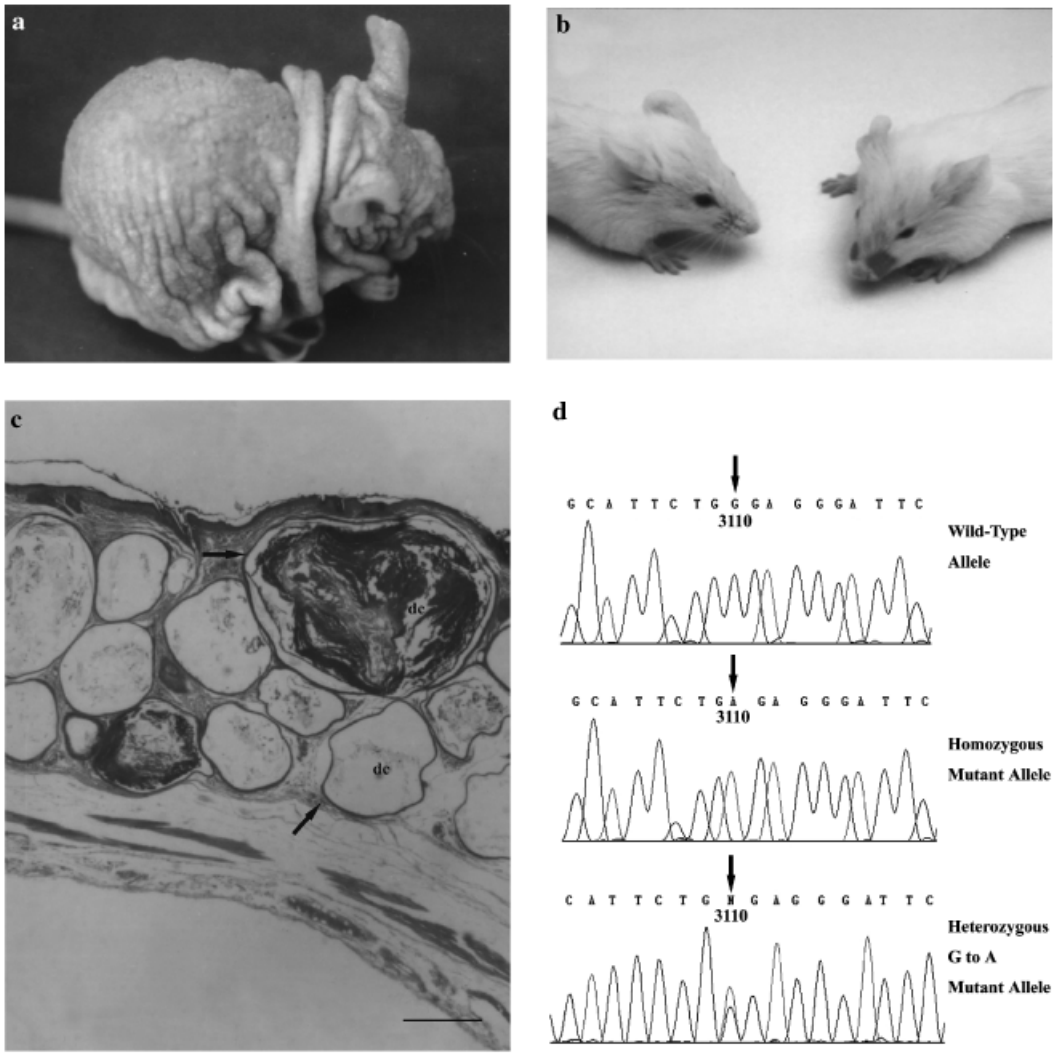

Figure 1
Phenotypic characterization and molecular analysis. (*a*) Illustration of rhinocerotic appearance of this mutant at 6 mo. Note the waxy deposition on the skin, and elongated and curved claws. (*b*) The 3 wk-old mouse (*right*) shows the characteristic hair loss on either side of the snout. The mouse (*left*) is a normal BALB/c mouse. (*c*) Histopathology in 8 mo-old hairless skin. Note the several rows of large dermal cysts (*arrow*) filled with masses of cornified material, cysts nearly obliterating the dermis and the adipose layer (hematoxylin and eosin). dc, dermal cysts. *Scale bar* = 100 μm. (*d*) Direct automated sequencing showing part of exon 12 sequence in a wild-type mouse (*upper panel*), an affected mouse (*middle panel*), and a heterozygous mouse (*lower panel*). The G to A substitution at nucleotide position 3110 is marked with an *arrow*. The mutation is predicted to result in the conversion of a tryptophan residue to a stop codon with premature termination of the hairless gene product, designated W911X.

to test the hypothesis that this mutation was allelic with the hairless gene and to screen for a potential mutation in the *hr* gene (GeneBank Accession No. Z32675). Here we report a novel nonsense mutation in the coding region of the *hr* gene designated rhinocerotic and short-lived (symbol hr^{rhsl})[1] (MGI Accession No. 2678250), and two polymorphisms in the gene.

Results

Mutant phenotype YYHL grew a normal first pelage when younger than 12 d. Subsequently, they began to lose the hair around the eyes, and the shedding then progressed in the direction of the tail. Total depilation was normally completed within 2 wk with the exception of the vibrissae. Young hairless mice had a delicate pink skin. As affected mice aged, the skin became progressively thick, loose, and redundant, forming rhinoceros-like folds. A waxy deposition on the skin that peels off in large flakes developed in aging mutant mice (Fig 1*a*). Toenails also became excessively long and curved, especially the toes of the hind limbs. Heterozygous mice had normal hair and were indistinguishable from genotypically normal individuals. Yuyi hairless female and male mice were fertile, but most females displayed abnormalities in their maternal behavior; they did not nurse their young well, and usually ate their young after 1–2 d of postnatal life. Heterozygous mice had a normal reproductive capability. The thymus of mutant mice underwent accelerated atrophy with age. The homozygotes had reduced life span and usually expired at the age of 6–10 mo. Autopsy on deceased mice revealed only the remnants of the thymus and a marked enlargement of the spleen and liver. But there were no other macroscopic abnormalities in other internal organs, compared with haired littermates. When successive backcrossing onto BALB/c strain was performed to two rounds, a few heterozygous offspring appeared with the dominant characteristic of shedding of hair on either side of their snouts (Fig 1*b*).

Histopathology Histological sections of skin from the backs of mice were observed and revealed obvious histopathological defects when compared with the wild-type mouse of the same age. YYHL showed the disintegration of hair follicles and formation of utriculi and dermal cystic structures in the dermis and both the follicular and epidermal hyperkeratosis. The utriculi were hypertrophic, excessively large, and filled with masses of cornified material.

[1]This allele nomenclature has been approved by MGI.

Table I. PCR primers for the amplification of exons 1–19 of *hr* gene

Primer name	cDNA region	Primers (forward/reverse)	Annealing temperature (°C)	Products (bp)
BP	1–336	GGGGCCGCCGAATCACG/CCCCATGGCCGGACAGAGG	59	884
CP	230–1229	CTGAGCAGAAAGCGGGAGAACG/CAGGCCTGGGGGACAAGAAG	56	1000
DP	1103–1795	AGGCCCCTCACTTCACCA/AGCCTAATCCTGCCATCTCG	59	693
AP	1737–2615	AAGGCGGAGGCAGAGCAACAAGAG/TGACCGGCCAGCACCATCC	61	879
EP	2501–3206	AACTCCCCCAACTCCACAACCT/CACCCTGCTAGCGTCCTTATCC	55	706
FP	2961–4016	GGCCAGCCCGTGTTAGTGTCAG/AAGTTCCCCAGTACCATTCATTCC	56	1056
GP	3864–4017	GTGCTGGAACGCGATTGAAAA/CAGGGCCAGGACGAGGAACA	52	272

bp, base pairs; *hr*, hairless.

With advancing age the cysts became larger and more numerous. In 8 mo old animals, cysts filled with keratinized laminae nearly obliterated the dermis and adipose layer (Fig 1*c*). The excessive skin mass growth is because of excessive dilatation of utriculi and the enlargement of dermal cysts.

Identification of a nonsense mutation and polymorphisms Sequencing (Table I) of the entire *hr* cDNA on both strands between mutant homozygous (hr^{rhsl}/hr^{rhsl}) (GenBank Accession No. AY547390), heterozygous, and normal Kunming control mice (GenBank Accession No. AY547391) revealed that all affected mice were homozygous for an A → G substitution at cDNA position 3110 (numbered according to Genbank No. Z32675) (Fig 1*d*), converting a tryptophan to a nonsense mutation of stop codon (W911X). The wild-type (+/+) Kunming mice possess G at nucleotide position 3110, which is the third position of the tryptophan code (TGG). The $+/hr^{rhsl}$ mice possess this mutation in the heterozygous state (G/A) (Fig 1*d*). The mutation is just in the overlap region amplified by two sets of primers EP and FP. Using five homozygous BALB/c hairless mice and sequencing from genomic DNA performed with MP primers gave the same result, confirming the mutation. Furthermore, no evidence for the mutant allele was found by direct sequencing of DNA samples from 20 normal, unrelated kunming mice; it was not a polymorphism. To reflect the characteristics of this new mutation at the *hr* locus, we have designated this allele hr^{rhsl} (MGI Accession No. 2678250) according to the rhinocerotic and short-lived

Table II. Pathogenic mutations and polymorphisms in the mouse *hr* gene

Allele	Location	Mutation[a]	Effect	Reference
Mutations				
hr^{hr}	Intron 6	Pmv43 insertion	Mis-splicing	Cachon-Gonzalez *et al* (1999)
hr^{rh}	Exon 6	2166C>T	R597X	Cachon-Gonzalez *et al* (1999)
hr^{rhsl}	Exon 12	3110G>A	W911X	This report
$hr^{rh\text{-}J}$	Exon 5	1977–1979del	E534del	Tian *et al* (2004)
$hr^{rh\text{-}7J}$	Exon 3	1253G>A	W292X	Cachon-Gonzalez *et al* (1999)
$hr^{rh\text{-}8J}$	Exon 4	1910–1911 GA>TT	Q511H, K512X	Ahmad *et al* (1999a)
$hr^{rh\text{-}bmh}$	Exon 19	3918 del 296 bp	Deletion at the 3′ end of hairless gene	Brancaz *et al* (2004)
hr^{rhChr}	Exon 4	1776C>T	R467X	Ahmad *et al* (1999a)
hr^{rhY}	Exon 16	3520ins 13 bp	Frameshift, premature stop codon at aa 1137	Panteleyev *et al* (1998a)
hr^{rhKIZ}	Exon 11	2817C>T	R814X	Tian *et al* (2004)
$hr^{Tg5053Mm}$	Intron 5–Exon 8	Transgene insertion	Deletion of most of the 3′ end of hairless gene	Cachon-Gonzalez *et al* (1999)
hr^{tm1Cct}	Exon 8–10	Homologous recombination	Loss of function (*hr*(−/−))	Zarach *et al* (2004)

Location	Variation[b]	Effect	Allele frequency	Reference
Polymorphisms				
Exon 4	1905T>A	S510T	0.75/0.25	This report
Exon 5	1978–1980del	E534del	0.725/0.275	This report

[a,b]Nucleotide numbers refer to cDNA sequence of the mouse *hr* gene (Genbank accession no. Z32675).
bp, base pairs; *hr*, hairless.

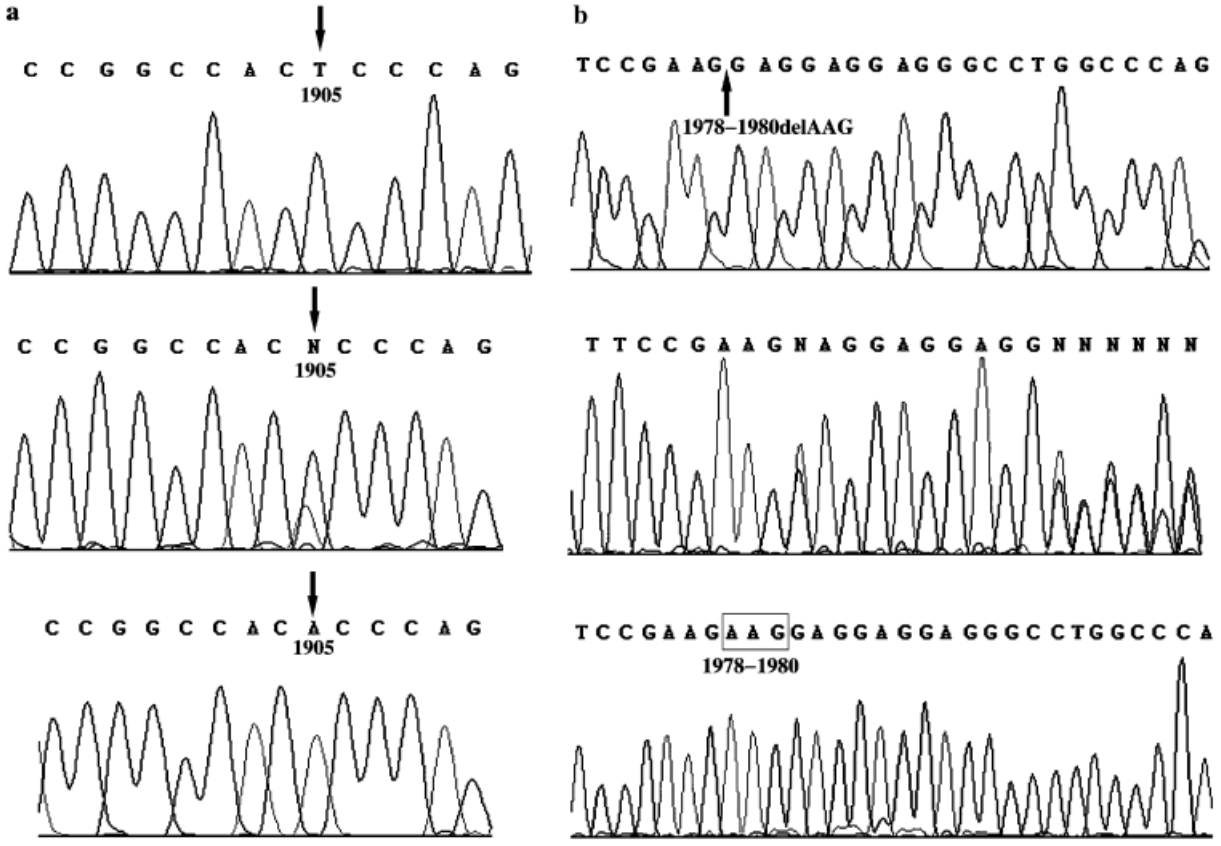

Figure 2
Direct sequencing of PCR products amplified from hairless (*hr*) gene (GenBank accession number AY547391). Arrows indicate the positions of polymorphic nucleotide changes. (*a*) Wild-type (*top*), heterozygous (*middle*), homozygous (*bottom*) for the variant. Automated sequencing reveals a T to A transition at nucleotide position 1905 that converts a serine residue (ICC) to a threonine codon (ACC). (*b*) Sequencing analysis of exon 5 reveals a deletion of nucleotide position 1978–1980 leading to a deletion of a glutamic acid at 534 of the hairless protein (E534del). DNA sequences from heterozygote shows overlapping sequence traces (*middle panel*).

phenotype of this mutation in accordance to existing guidelines for nomenclature.

During the search for pathogenetic mutation, two additional sequence variants in exons 4 and 5 were discovered (Table II). One of them, 1905 T → A, substituted a serine in position 510 by a threonine (S510T) (Fig 2*a*). The occurrence of the T → A transition was tested in 20 normal Kunming mice and revealed that the mutated allele 1905A (Thr510) has a frequency of 25%. Four mice were homozygous for the T → A transition, and two mice were heterozygous. Another, 1978–1980 del 3 base pairs (bp), resulted in a deletion of a glutamic acid at position 534 of the hairless protein (E534del) (Fig 2*b*). Of the 20 normal Kunming mice screened for this sequence variation in exon 5, 13 mice were homozygous for the AAG allele, four were homozygous for the AAG deletion allele, and three were heterozygous for AAG/AAGdel. The allele frequencies are therefore 0.725 for the AAG and 0.275 for the AAG deletion. All of them had normal hair development. Thus, these mutations represent two common polymorphisms.

Discussion

In this study, we report the identification of a novel nonsense mutation W911X in the *hr* gene by automated sequencing of cDNA, genomic DNA and confirm that the hr^{rhsl} mutation is a disease-causing mutation that is responsible for the typical cutaneous phenotype of hairless mice. This result validates the hypothesis that the hr^{rhsl} hairless mutation is allelic with the *hr* gene. To date, 12 pathogenic *hr* mutations among 16 reported mutations (including this report) have been identified around the world (Table II), demonstrating the heterogeneity of the hairless phenotype. These mutations reflect a wide spectrum of possible types of mutations, including a proviral pmv43 insertion in intron 6 (Cachon-Gonzalez *et al*, 1999), as well as a series of nonsense and deletion mutations in exons of the *hr* gene (Panteleyev *et al*, 1998b; Ahmad *et al*, 1999a; Cachon-Gonzalez *et al*, 1999; Brancaz *et al*, 2004; Tian *et al*, 2004).

Furthermore, we have identified two new polymorphisms in the mouse *hr* gene, S510T and E534del. It was reported that $hr^{rh\text{-}J}$ mutation with the rhinocerotic and hairless phenotypes resulted from three base deletions at 1977–1979 position, leading to deletion of glutamic acid at 534 (Cachon-Gonzalez *et al*, 1999; Tian *et al*, 2004; Zarach *et al*, 2004). But the phenotype of Kunming mice with three base deletions at 1978–1980 position leading to the same deletion of glutamic acid at 534 is normal, indicating that this deletion is insignificant. The question is why does the same amino acid deletion may induce different results? One possibility is that the mutation of three base deletions at 1977–1979 position is in fact non-pathogenic sequence alteration. Another possibility is that the background modifiers, such

as the VDR (Miller *et al*, 2001) and retinoid X receptor-α genes (Klein *et al*, 2002), play an important role. But, the most likely explanation for the discrepant findings is that the previous reports have not yet detected the true mutation in their mice.

The nonsense mutation may lead to nonsense mediated mRNA decay (Maquat, 1996). Thus, the introduction of the hr^{rhsl} nonsense mutation has been predicted to have led to an absence of functional hairless protein (Cui *et al*, 1995).

The YYHL share several common symptoms with other alleles of this locus, including hairless (hr^{hr}/hr^{hr}) and rhino (hr^{rh}/hr^{rh}) (Panteleyev *et al*, 1998b). These include the patterns of hair loss, gross appearance, genetic features, reproductive defects, immune function impairment (Kang *et al*, 2002), and histological evidence including the disintegration of hair follicles and the formation of cystic structures in the dermis. In addition, the homozygous YYHL have a reduced life span and enhanced skin abnormalities markedly similar to rhino Yurlovo (hr^{rhY}/hr^{rhY}) (Panteleyev *et al*, 1998a). But, that the Yuyi hairless homozygous females are able to give birth normally and are different from the homozygous hr^{rhY}/hr^{rhY} females that are not fecund at all. Interestingly, when successive backcrossing onto BALB/c strain was performed to two rounds, a few heterozygous offspring appeared with the dominant characteristic of shedding of hair on either side of their snouts (Fig 1*b*). Such phenotypic diversity in different alleles of hairless gene may be because of the effects of modifier genes on different backgrounds (Panteleyev *et al*, 1998a). The clinical and histopathological features of YYHL are similar to those observed in humans with papular atrichia (Ahmad *et al*, 1999b; Kurse *et al*, 1999). Thus, the identification of hr^{rhsl} nonsense mutation emphasizes the importance of the *hr* gene in follicle development, and expands our understanding of the spectrum of mutations underlying hairlessness in mice. YYHL thereby provide a potential model for further studies of the hairless gene function, and may facilitate insights into the pathophysiology of inherited atrichia in humans associated with the disruption of *hr* gene activity (Panteleyev *et al*, 1998a, b).

In conclusion, we report and name a novel spontaneous hairless mutation in the mouse, and clarify that the molecular basis for rhinocerotic and short-lived (hr^{rhsl}) phenotype is the nonsense mutation at nucleotide position 3110 within the *hr* gene. The functional consequences of this mutation are essentially similar to those of the previously described mutation. Furthermore, we have identified two new polymorphisms in mouse hairless gene. These data once again illustrate phenotypic and genetic heterogeneity and expand our understanding of the molecular basis of the hairless phenotype.

Materials and Methods

Animals and biopsies All animals were from the Laboratory Animal Center of Zhengzhou University, and were housed in community cages under conventional conditions (12 h light periods, water and mouse chow *ad libitum*). Moreover, the mutant allele was backcrossed onto BALB/c mice, by performing successive rounds of cross–intercross, and obtaining BALB/c hairless mice. For preliminary morphological comparison, the age-matched hairless and haired mice on different months were scarified by cervical dislocation. The skin samples were harvested from the upper back and immediately frozen in liquid nitrogen for histology and nucleic acid isolation. All mice were cared for according to the Guide for the Care and Use of Laboratory Animals, and the study was approved by the Medical Ethical Committee of Zhejiang University.

Histological analysis Skin samples were fixed by immersion in neutral buffered 10% formaldehyde. The biopsies were sectioned perpendicularly to the skin surface and embedded in paraffin. Sections of 3 μm thickness of harvested skin were stained with hematoxylin and eosin for routine histology, and examined microscopically.

Mutant detection and confirmation On the basis of the similar characteristic feature and genotype of mutant hairless mice with previously reported cases of mice harboring *hr* gene mutations (Panteleyev *et al*, 1998b), we initiated a screening for a mutation in the *hr* gene from these mutant hairless mice, in contrast with normal Kunming mice. A set of primers (Table I) were designed based on the available murine *hr* gene sequence (GenBank Accession No. Z32675) and 14 Chromosome sequences (gi.20878405) to amplify 1–19 exons. Genomic DNA was extracted from the tail by standard procedures. Total RNA was extracted from mouse skin samples following the manufacturer's protocol (Qiagen, Valencia, California). Exons 1 and 19 were amplified using genomic DNA as a template. The PCR conditions were as follows: 4 min at 94°C, followed by 35 cycles of 45 s at 94°C, 1 min at appropriate annealing temperature (Table I), 1 min at 72°C, and a final extension step of 10 min at 72°C. Other exons were analyzed with mRNA selective PCR kit (TaKaRa, Otsu, Japan). The selective PCR conditions were 50°C for 25 min, 85°C for 2 min, then 30 cycles of 85°C for 1 min, the appropriate annealing temperature (Table I) for 1 min and 72°C for 1 min, with a final extension step of 10 min at 72°C. The PCR products were electrophoresed in a 1% agarose gel in 1 × TAE buffer, and eluted from the agarose gel with gel extraction kit (TaKaRa), then sequenced directly on both strands using Big Dye Terminator V3.1 cycle sequencing kit (PE Applied Biosystems, Foster City, California) on ABI Prism377 automated DNA sequencer (PE Applied Biosystems).

To confirm the mutation the above procedures were repeated using five homozygous BALB/c hairless mice carrying this mutant gene. A 252 bp PCR fragment encompassing exon 12 was amplified from genomic DNA using MP primers (forward primer 5′-GCTCCCCAACAATTCTTTTCTC-3′ and reverse primer 5′-TCCCAGCTCCCTCTATCCTATG-3′). For verification of the polymorphisms, PCR was carried out on genomic DNA from 20 normal Kunming mice with PP primers (forward primer 5′-CCCCGAGA TGGCAGGATTAGG-3′ and reverse primer 5′-GCAGCAGGCGGCA GAGTCG), and PCR products were directly sequenced.

We thank Dr Charlie Manolis and Dr Robin Fitzgerald for their help with manuscript revision. We are most grateful to Dr Y. M. Xi, C. Wood, Dr Y. C. Xu, Dr X. C. Ma, and Dr Q. H. Wan for advice and revision of the manuscript, and to Dr Cathy Lutz of mouse genome informatics, the Jackson Laboratory for kind help in the mutant and allele nomenclature. This work was supported by a Special Grant from the State Forestry Administration of China (No. 2003442).

DOI: 10.1111/j.0022-202X.2005.23744.x

Manuscript received October 28, 2004; revised January 20, 2005; accepted for publication February 4, 2005

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