cal abnormality may also accompany the
jb mutation.

Juvenile bare is expressed on strains C57BL/6J, ABP/Le, and MEV/1Ty and C.B-17-
Prkdcscid/Prkdcscid, but seldom expressed on C3HeB/FeJ, A/J, and CAST/Ei, and only
partially expressed on the C57BL/6J × C3HeB/FeJLe-a/a hybrid. The expression of
jb may depend upon one or more un-
linked loci that are polymorphic among in-
bred strains. Finding this manifesting loc-
cus or loci may be possible by additional
designed linkage crosses. At present the
jb mutation is maintained in a breeding col-
ony on the C57BL/6J background and in
the homozygous inbred strain, but it was
placed in the Frozen Embryo Repository
on a heterogeneous B6C3Fe-a/a back-
ground prior to the development of the
C57BL/6J-jb line.

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Shorn (shn): A New Mutation
Causing Hypotrichosis in the
Norway Rat

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P. Radaskiewicz, and T. R. King

We report the identification of an autosomal recessive
mutation in the Norway rat
that causes an almost complete absence
of normal hair. The mutation, named shorn
(gene symbol shn), is distinct from fuzzy,
hairless, and Rowett nude, and is not
closely linked with any of these markers or
with albino.

Hypotrichosis, the complete or partial abs-
ence of normal hair, has been identified
as a heritable trait in many mammalian
species including mice, rats, cats, dogs,
guinea pigs, and primates. Interest in hy-
potrichotic mutants often extends beyond
the hair and skin anomaly, since many of
the known hypotrichotic mutations gen-
erate pleiotropic effects, including athy-
mia (Festing et al. 1978; Pantelouris 1973),
immunodeficiency and autoimmune dis-
ease (Shultz 1988), defective cellular im-
munity (Morrissette et al. 1980), suscepti-
bility to viral leukemia (Meier et al. 1969),
and progressive nephrosis (Marit et al.
1995). In addition, rodent models that lack
a full coat often offer a distinct advantage
in studies involving wound healing (Bur-
gess et al. 1990), transdermal migration of
chemicals (Peck et al. 1988), percutaneous
drug absorption (Auclair et al. 1991, Brad-
ley et al. 1990; Chanez et al. 1989; Mori-
 moto et al. 1992; Rougier et al. 1987, 1990;
Twist and Zatz 1989), and skin pharmacol-
ogy (Bouclier et al. 1988; Rommain et al.

Hypotrichotic mutants may also provide
an ideal opportunity to genetically dissect
the crucial steps in the development of a
complex mammalian tissue, the skin and
hair. First, the spontaneous (or induced)
mutation of key elements in hair formation
is readily detected visually. Second, much
of the development of a hairy coat occurs
postnatally and is therefore easily acces-
sible to experimental observation. Third,
mutation (or experimental manipulation)
of single-copy genes required for the development of a normal hairy coat can be expected to render the animal hairless, but (most likely) viable.

A spontaneous hypotrichotic mutant was recently discovered in our colony of albino Norway rats. This article presents the results of (1) crosses performed to determine the trait’s mode of inheritance, (2) complementation tests with three other hypotrichotic rat mutants, and (3) preliminary genetic linkage analyses. This new mutation, designated shorn (shn), is shown to be an autosomal recessive that is distinct from the phenotypically similar rat mutations fuzzy (fz), Rowett nude (nu), and hairless (hr).

Materials and Methods

Our rat colony consisted of random-bred Sprague Dawley rats (Hsd:SD) obtained from Harlan Sprague Dawley, Inc. (Indianapolis, Indiana). After several generations of random breeding within the colony, a litter was produced that included some hypotrichotic offspring, as described in Results. In all breeding experiments described, ratios of normal and affected animals were analyzed by the chi-square test. In subsequent generations (through F3, at the conclusion of this study), mutant stock was maintained by brother-sister mating of affected, hypotrichotic rats. For complementation testing, male fuzzy rats (genotypically fz/fz) and male Rowett nude rats (nu/nu) were imported from Harlan Sprague Dawley, while hairless rats (hr/hr) were obtained from Charles River Laboratories (Wilmington, Massachusetts).

To assess the shn-carrier status of a rat, progeny tests were performed with a hypotrichotic rat, homozygous for shn. Progeny testing for the presence or absence of the nu allele was generally performed using mu/+ heterozygotes, owing to the expected poor viability of mu/nu homozygotes. Thus a test for shn was considered to be conclusive when either (1) hypotrichotic offspring were observed (confirming carrier status) or (2) no hypotrichotic offspring were observed among a minimum of 10 offspring (confirming noncarrier status due to rejection at \( P < .01 \) of the null hypothesis of fit with a 3:1 intercross ratio).

Results

Origin, Inheritance, and Description

In 1993 three hypotrichotic rats were discovered among a litter of standard (SD: Hsd) albino laboratory rats in our random-bred colony. This variant litter consisted of three hypotrichotic females, four unaffected (hairy) females, and one hairy male offspring. In order to maintain a possible new mutation and to determine its mode of inheritance, the hairy male was crossed with all of his sisters. The ratio of normal to affected among 41 progeny produced by crossing the hairy male with his three affected sisters (Table 1, cross 1) conformed well with the 1:1 ratio expected from a testcross \((P > .4)\), suggesting that these females were homozygous and the male was heterozygous for an autosomal recessive mutation. Mating of the hairy male with three of his hairy sisters produced litters including some hypotrichotic progeny (Table 1, cross 2), suggesting that these three females were also carriers of the recessive mutation. Indeed, the observed ratio of normal to affected among these 42 offspring is in good agreement \((P > .35)\) with the 3:1 ratio expected for an intercross of heterozygotes. The last hairy sister, presumably homozygous for the wild-type allele, produced only hairy offspring in crosses with her carrier brother (Table 1, cross 3). As expected for autosomal recessive inheritance, matings between affected, hypotrichotic rats produced only affected offspring (Table 1, cross 4; and stock-maintenance crosses to date). Good agreement with expected ratios in all these crosses further suggests that the trait is fully penetrant and that viability is at least not strongly impacted in homozygotes.

This recessive mutation has been provisionally designated shorn (shn). Homozygotes are generally smaller than unaffected littermates and display only a very sparse, patchy coat throughout their life span. A 4-week-old mutant displaying the typical shorn phenotype is shown in Figure 1. By 6 weeks, a sparse, short coat of hair develops on the body but not on the face; by 8 weeks the body is again almost hairless and short sparse hair decorates the face in a mask pattern. Adults often retain a sparse mask of short hair on the face and patchy, ragged hair on the rump and belly. Shorn mutants are distinguishable even as newborns by their short, kinky vibrissae. While the anatomy and physiology of the shorn rat has not yet been investigated in any detail, it is notable that these mutants appear to be euthyemic.

Complementation Testing

To determine if shn is allelic with other mutations known to generate recessive hypotrichosis, three commercially available mutants; homozygous for fuzzy (fz), Palm and Ferguson (1976), hairless (hr, Meier et al. 1969), or Rowett nude (nu; Festing et al. 1978) were obtained and crossed with shn/shn homozygotes. The hybrid progeny of all three crosses \((N > 20\) for each cross) were phenotypically normal (data not shown), indicating that shn is a mutation in a gene distinct from those identified by fz, hr, and nu. However, several other recessive mutations that generate a similar hypotrichotic phenotype have been reported in the rat (reviewed by Robinson 1979; and Ferguson et al. 1979; Hanada et al. 1988; Hedrich 1990), and shn might be allelic with any of these.

Linkage Analysis

To restrict the number of hypotrichotic mutants that would need to be tested for complementation with shn/shn rats, we have performed crosses to assess linkage between shn and some of the other visible markers currently maintained in our colony. We reasoned that complementation testing would only be necessary between shn and similar mutations that could be

Table 1. Segregation data for hypotrichosis suggests an autosomal recessive mode of inheritance

<table>
<thead>
<tr>
<th>Cross</th>
<th>Parents</th>
<th>Total progeny (no.)</th>
<th>Phenotype</th>
<th>Expected ratio (hairy : affected)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Affected × Carrier</td>
<td>41</td>
<td>18 23</td>
<td>1:1</td>
<td>0.610</td>
<td>.50 &gt; ( P &gt; .40 )</td>
</tr>
<tr>
<td>2</td>
<td>Carrier × Carrier</td>
<td>42</td>
<td>29 13</td>
<td>3:1</td>
<td>0.794</td>
<td>.40 &gt; ( P &gt; .35 )</td>
</tr>
<tr>
<td>3</td>
<td>Normal × Carrier</td>
<td>14</td>
<td>14 0</td>
<td>1:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Affected × Affected</td>
<td>20</td>
<td>0 20</td>
<td>0:1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on autosomal recessive inheritance.*
Figure 1. Photographs of rats segregating shn. (A) An shn/shn rat (foreground) with an shn/+ littermate control at 4 weeks of age. (B) A closer view of the same mutant rat. Note the short, kinky vibrissae and dried red porphyrin pigments (chromodacryorrhea) around the eyelids, especially at the medial canthus.

syntetic with shn. These linkage analyses consisted of testcrossing animals dihybrid for shn and one other visible marker. In such crosses, markers fz, hr, and albino (c) were all seen to assort independently of shn (Table 2, crosses 5–7).

While alleles of shn and rnu appeared to assort independently among the four genotypic types ($\chi^2 = 7.74; P > .05$), dihybrids transmitted $65\%$ parental type (shn, +; or +, rnu) gametes and only $35\%$ recombinant type (shn, rnu; or +, +) gametes (Table 2, cross 8). This binomial distribution differs significantly from the 1:1 ratio of parental to recombinant gametes expected for independently assorting genes ($\chi^2 = 4.26; P = .04$). Thus while these two genes do not appear closely linked, these data suggest that shn may be located on rat Chr 10, about $35\%$ ($\pm 7\%$) recombination from rnu (at 1 SE).

Discussion

We have described a spontaneous autosomal recessive mutation—shorn (shn)—that produces lifelong hypotrichosis and short, kinky vibrissae. Complementation and linkage analyses show that shn is distinct from and is not tightly linked with the hypotrichotic mutations rnu, fz, or hr. Thus shn is not the result of a genetic contamination of our stock or a remutation in any of these genes.

In addition, our data may suggest a linkage assignment for shn on rat Chr 10, based on two-point cross analysis with the rnu locus. Because no other hypotrichosis-generating mutations—excepting rnu (Zha et al. 1995)—have been mapped in this region (Jacob et al. 1995; Levan et al. 1986), such an assignment would suggest that shn is independent of previously described hypotrichotic rat mutations. Furthermore, no recessive hypotrichotic mutations (other than nude, nu) have been localized on mouse Chr 11, the major genomic region homologous to rat Chr 10 (Levan et al. 1991). (The only named loci on mouse Chr 11 that affect coat morphology are bald-arthritis (Bda), alopecia (A0), bareskin (Bsk), and rex (Re) (MLC/MGD 1997). Since these loci are all identified by dominant mutations, it seems unlikely that any would be a homologue of shn.) Thus it remains possible that the shn mutation identifies a new gene essential for the normal development or maintenance of a hairy mammalian coat.

Deeper understanding of the shn gene's normal role in development will require further phenotypic and genotypic characterization. Importantly, a detailed phenotypic characterization may reveal pleiotropic effects of the shn mutation and could help to implicate particular cell types, products, or a particular time or process involved in the development of the mutant phenotype.

A crucial first step in the genotypic characterization of the shn mutation will be the production of a high-density genetic map for the region surrounding shn. Such a map, while advancing the genomics of the rat, would facilitate identification of probes, candidates, and possible homologues for the shn gene [see the paradigm established by Segre et al. (1995) for the nude locus]. Ultimately the identification of the wild-type shn gene will allow molecular access to one more component essential to the normal development of mammalian skin and hair. With the gene in hand, and systems available for the manipulation and transfer of engineered genes in both whole animals and in tissue culture (see Li and Hoffman 1995), the stage will be set for a meaningful inquiry into shn's normal role in the development of mammalian integument.
Table 2. Dihybrid testcross data for shn and four recessive visible markers

<table>
<thead>
<tr>
<th>Cross</th>
<th>Dihybrid genotype</th>
<th>No. test-</th>
<th>No. progeny inheriting genotype shown from the dihybrid parent*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>cross</td>
<td>progeny type for both markers</td>
</tr>
<tr>
<td>5&quot;</td>
<td>shn/-, f2/+</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>6&quot;</td>
<td>shn/-, hr/1</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>7&quot;</td>
<td>shn/-, c+</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>8&quot;</td>
<td>shn/-, rnu/+</td>
<td>46</td>
<td>11</td>
</tr>
</tbody>
</table>

* m refers to the recessive mutant allele in question, either f2, hr, c, or rnu. In all cases the expected ratio of progeny is 1:1:1:1, based on independent assortment. Parental allele combinations are shn, + and +, m; recombinant types are shn, m and +, +.

To assess linkage between shn and f2 (or hr), a dihybrid rat was first testcrossed with a fuzzy (or hairless) homozygote and the progeny were scored for the inheritance of f2 (or hr) from the dihybrid parent, according to coat morphology. Next each testcross offspring was progenytested with shn/shn homozygote to determine if shn had been transmitted by the dihybrid (see Materials and Methods).

To assess linkage between shn and c, a dihybrid rat was testcrossed with an shn/shn, c/c double mutant. Offspring were scored for the inheritance of alleles from the dihybrid parent.

To assess linkage between shn and rnu, a dihybrid rat was first testcrossed with an shn homozygote and the progeny were scored for the inheritance of shn from the dihybrid parent, according to coat morphology. Of the 53 rats so tested, 24 were hypotrichotic and 29 had a normal coat. Next each testcross offspring was progenytested with an rnu/rnu homozygote to determine if rnu had been transmitted by the dihybrid (see Materials and Methods).

Seven of the 24 hypotrichotic rats failed to produce sufficient progeny to complete their test.

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