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Desmoglein genes are up-regulated in the *pk* mutant mouse

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Abstract

Plucked (*pk*) is an autosomal recessive mouse mutation with a hair phenotype that arose spontaneously in the DBA/2J strain. Histological studies indicate that adult *pk* mutant mice lose truncal hair because of the scarring of follicles due to an apparent obstruction of the outward movement of the hair shaft within the follicular canal. We mapped the *pk* mutant phenotype to a 1.1 cM region of chromosome 18 (between 6.6 and 7.7 cM from the centromere) using 370 backcross progeny. Within this region, among others, are genes for desmosome cadherins. Desmosome cadherins are interesting candidates because of their critical roles for cell–cell adhesion in epidermal function. Northern Blot analysis of wild-type and *pk* mutant mice indicates that expression of both desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) is up-regulated in the skin of mutant *pk* mice.

Keywords: Dsg1; Dsg3; Plucked; Hair; Skin; Genetic mapping

The mouse *plucked* (*pk*) mutation that originated spontaneously in the DBA/2J inbred strain results in an abnormal development of the skin and hair [1]. The mutation is autosomal recessive and was assigned to a large segment of chromosome 18 between *twirler* (*Tw*) (3.0 cM) and *shaker-with-syndactylism* (*sy*) (32.0 cM) mutations by breeding to various mutant stock mice [2]. The *pk* mutant mice can easily be identified by their short bristly coat, wrinkled skin, and absence of whiskers at birth (Fig. 1A). Although they live a normal life span, at about 7 days of age, the skin of *pk* mutants become thickened, folded, and darkly pigmented. The first hair becomes visible at about 11 days and is composed of very short, bristly, and irregular growths.

Earlier studies suggested that the primary lesion in the mutant is in the progression of the shaft out of the follicle because of a retained inner root sheath [1]. This obstruction may lead to follicle degeneration, inflammation, and scarring. Trigg postulated that the primary target of *pk* mutation is the sebaceous gland which is enlarged. Studies in our laboratory and others have suggested that sebaceous gland plays an important role in shaft-sheath dissociation [3–6]. As we have had a long term of interest in the dissociation of the shaft from the sheath, we initiated the study toward characterization of molecular basis for the *pk* mutant phenotype. We postulated that understanding the molecular basis of *pk* mutation may help us to better understand the pathophysiology of hair follicle in conditions such as scarring alopecia (also known as cicatricial alopecia), an idiopathic condition causing localized hair loss due to follicular scarring. As the first step toward cloning *pk* gene, a genetic mapping of *pk* locus was performed.

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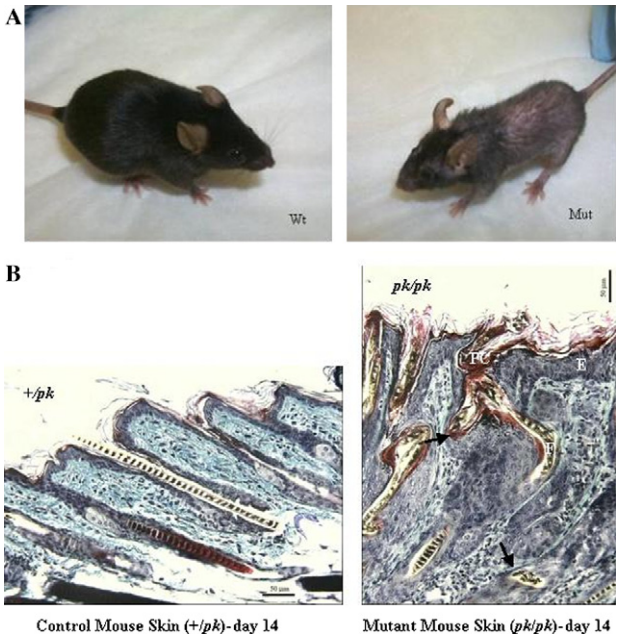

Fig. 1. Phenotype and histological characterization of *pk* mutant mice. (A) The mutant mice can be easily distinguished from their non-mutant littermate by their obvious hair phenotype, including lack of whiskers. (B) Full thickness skin sections from the *pk* mutant and heterozygote control mice (14 days postnatal) after SACPIC staining (for details see Materials and methods). Notice the disoriented follicles (F), the thickened epidermis (E), and the obstructed pilary canals (PC) of the mutant skin follicles. The mutant skin shows marked follicular distortion, retained inner root sheath, and focal perforation of shaft through the outer root sheath (arrow).

Our mapping study identified several candidate genes, including desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) in a narrowed interval. Both Dsg1 and Dsg3 have been reported to be important in skin and hair because of their roles in keratinocytes adhesion, epidermal and hair follicle differentiation, and in anchoring hair to the follicle in companion layer [7–11]. In this paper, we describe our results toward fine mapping of *pk* mutation using microsatellite markers and expression analysis of candidate genes, especially Dsg1 and Dsg3, present in the defined genetic interval of the mutation.

Materials and methods

Mice breeding and DNA isolation. All mice were purchased from The Jackson Laboratory (Bar Harbor, Maine). Male mice homozygous for pk mutation [B6.D2 (*pk*/*pk*)] were crossed with female Castaneus (*Cast*/*Ei*) mice to produce F1 heterozygotes. *Cast*/*Ei* mice were chosen as they are well known to be highly polymorphic for most genomic markers when compared to many inbred strains of mice. Backcross progenies were obtained by mating the F1 heterozygous females (*Cast*/*pk*) with *pk*/*pk* mutant males. A total of 370 backcross animals were generated and their genomic DNA was used for genotyping. Genomic DNA from euthanized mice was isolated according to vendor's instructions (Stratagene, CA).

Microsatellite markers, PCR-based genotyping, and linkage analysis. Chromosome 18 microsatellite PCR primers of the D18Mit series based on MIT genetic map (http://www.genome.wi.mit.edu) were purchased from Research Genetics (Huntsville, AL). PCR-based genotyping was performed using genomic DNA with the following conditions: (i) denaturing at 95 °C for 2 min; (ii) 38 cycles of 94 °C for 45 s, 55 °C for 45 s, and 72 °C for 1 min; and (iii) final extension at 72 °C for 7 min. The PCR products were analyzed on 3% agarose gel (Agarose-1000, Life Technologies, Maryland) and alleles were scored as maternal (*Cast* or *pk* from F1 hybrid) or paternal (*pk*). Map Manager XP Program (designed by Dr. Kenneth Manly, University at Buffalo) was used for linkage analysis.

Histology. Dorsal skin from wild-type (+/*pk*) and mutant mice (*pk*/*pk*) at 14 days old were clipped to remove hair, excised and fixed in 10% formalin containing PBS buffer. Fixed tissues were sectioned, processed, and embedded in paraffin for H&E staining, SACPIC staining [12].

RNA, Northern blots, and probes. Total RNA from mouse (7, 10, and 14 days) skin was isolated according to the manufacturer's protocol (RNA STAT-60, Tel-Test, Friendswood, TX). The RNA (15 μg/lane) was electrophoresed (1% agarose–6% formaldehyde gel) and blotted on Hybond-N membrane (Amersham). The blotted membranes were UV-crosslinked and hybridized with [α-^{32}P]CTP-labeled cDNA probe in ExpressHyb hybridization solution (Clontech) at 62 °C for at least 2 h. The membrane was washed with 2× SSC (150 mM sodium chloride, 15 mM sodium citrate, pH 7.0) containing 0.1% SDS for 30 min at 62 °C twice. After the final wash with 0.1× SSC/0.5% SDS at 62 °C for 30 min, the membranes were exposed to X-ray film with intensifying screens at −70 °C. The lanes were normalized by hybridization to a GAPDH probe (Clontech). cDNA probes were generated from mouse skin total RNA by RT-PCR using primers at coding sequence regions.

Dsg1 forward primer: 5′-AAGAAGTTGGCAGATATCAGCCTG-3′
Dsg1 reverse primer: 5′-TAGACTTGAGCCTGGCGCTATTAC-3′
Dsg3 forward primer 5′-ACAGCACAGAGAAGATGGGAC-3′
Dsg3 reverse primer: 5′-GCATTTAGGATCATTACCAGGG-3′

Results

pk mutant phenotype—histological studies on hair follicle morphogenesis

The *pk*/*pk* mice are smaller in size compared to the heterozygote littermate (Fig. 1A) though they live a normal lifespan. In order to study the evolution of the cutaneous changes, histological study of truncal skin was performed every other day for the first 25 days of life. The morphological changes correspond essentially as described previously [1]. Normal follicle precursors formed during the first week of life and the fully developed anagen follicle was longer and deeper placed than normal (data not shown). Fig. 1B shows the typical histological features of fully grown hair follicles in a two-week-old mutant and heterozygote control mice. In the lower proximal follicle the forming shaft was distorted and bulbous was compared to the control. In the mid and upper follicle there retention of the inner root sheath. The infundibular epithelial portion of the follicle was thick and irregularly folded. In some foci it appeared as if the twisted shaft had penetrated the upper follicular sheath and there was an associated

inflammatory reaction and eventually fibrosis. In adulthood the follicular pathology became much less severe. In all follicles the sebaceous glands were larger than in the controls but their histology appeared morphologically normal (data not shown).

Genetic mapping of pk locus

As a first step toward positional cloning of the gene for the *pk* mutation, we constructed a high-resolution genetic map of *pk* using microsatellite markers and DNA derived from 370 backcross mice progeny. From the genotyping data of DNA from these mice, we identified 51 recombinants in a 5.4 cM region after haplotype construction (Fig. 2). Our initial mapping data narrowed the mutation to a 10 cM interval (data not shown), and subsequent typing with additional markers in the desired interval further refined the *pk* containing interval to 1.1 cM with flanking markers D18Mit198 and D18Mit132 at 6.6 and 7.7 cM from centromere of chromosome 18, respectively, as shown in Fig. 2. Four recombinants were detected between these two markers with two recombinants (r1, r2) between D18Mit198 and *pk*, and two (r3, r4) between D18Mit132 and *pk*. The linkage analysis established the order of markers from centromere to telomere—D18Mit92, D18Mit198, *pk*, D18Mit132, D18Mit22, and D18Mit135. The distance between these markers and their corresponding cytogenetic position in humans is shown in Fig. 3. The phenotype of mice with recombinant haplotypes was confirmed by histological examination in addition to visual inspection.

Desmoglein expression is up-regulated in pk mutant mice skin

The 1.1 cM *pk* critical region contains important desmosomal cadherin genes for desmoglein 1 (Dsg1),

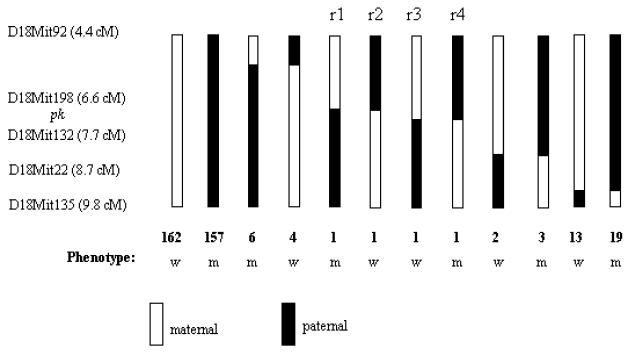

Fig. 2. Linkage analysis of the *pk* locus using microsatellite markers. The haplotype data generated from genotype data of 370 backcross mice are shown. The *pk* alleles (paternal) and the CAST allele (maternal) are denoted by black and white portion, respectively. The number below the column represents the mice with the specific haplotype out of the 370 animals. The phenotype of the mice is denoted by w (wild-type) and m (mutant).

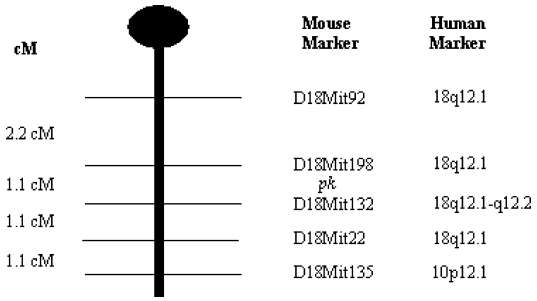

Fig. 3. Genetic map of the *pk* locus region of mouse chromosome 18. The order and genetic distances of microsatellite markers in relation to pk mutation are shown based on the linkage analysis of DNA from 370 backcross mice. Corresponding human cytogenetic position of markers is also indicated.

desmoglein 3 (Dsg3) among others. As mentioned earlier in the text (Introduction), since desmogleins are important molecules for cell–cell adhesion function and play important roles in epidermal and hair follicle differentiation, we examined if the expression of these genes is altered in the mutant skin. Dsg gene expression could be affected as a consequence of direct action of the mutant gene product or indirectly through an intermediary gene product that is under *pk* gene control. We examined the mRNA expression levels of Dsg1 and Dsg3 by Northern blot analysis using total RNAs extracted from 7-, 10-, and 14-day-old wild-type and *pk* mutant mice skin. To exclude the possibility of differential loading and/or transfer of RNA to membrane, we used increasing amount of RNA from wild-type mice and multiple mutant RNA samples in Northern blot analysis. In addition, after stripping the first probe, the blots were reprobed with an endogenous glyceraldehydes-3-phosphodehydrogenase (G3PDH) control probe.

When Northern blot signals of RNA from mutant mice and their corresponding heterozygote littermates are compared with their G3PDH controls, it is quite apparent that expression of both Dsg1 and Dsg3 is up-regulated consistently in all mutant *pk* mice skin samples analyzed when compared to their heterozygote (wild-type phenotype) littermate skin samples (Fig. 4). Normalized densitometry signal intensity ratio analysis of each band of test samples and the G3PDH control bands in the Northern blot indicated a 2- to 3-fold up-regulation for Dsg1 mRNA expression in 7- to 14-day-old mutant mice skin samples compared to non-mutant control samples. Dsg3 is up-regulated 2- to 3-fold in mutant mice at 7 and 10 days old, and 6-fold in mutant mice at 14 days old (Fig. 4B). Since mutant mice display only skin phenotype, we examined expression of Dsg1 and Dsg3 in multiple tissue Northern blots containing 12 different mouse tissues (purchased from OriGene, Rockville, Maryland). The data indicate that Dsg1 and Dsg3 are predominantly expressed in skin with a weak expression in stomach (data not shown). Based on the

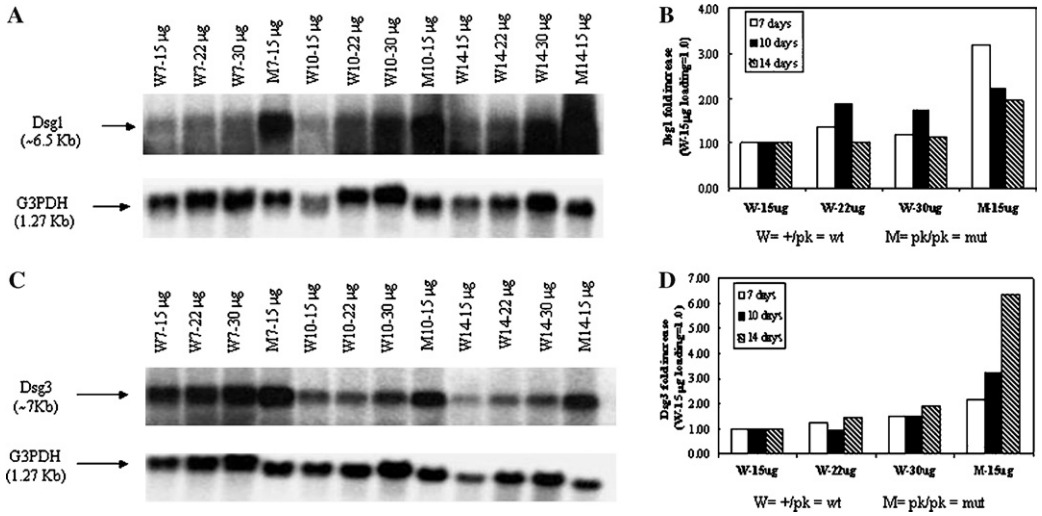

Fig. 4. Northern blot analysis of candidate genes Dsg1 and Dsg3 in mutant *pk* and their heterozygote littermate. Total RNA was extracted from wild-type and *pk* mutant mice and Northern blot analysis was performed using Dsg1 (A) and Dsg3 (C) specific probes. W, +/pk wild-type; M, pk/pk mutant. The numbers after the letter are the age of mice and the μg RNA amount used for the Northern blot analysis. The intensity of each band was determined using a LumiAnalyst, and fold increase was calculated according to the normalized ratios of Dsg1 (B) and Dsg3 (D) band density to the G3PDH band density which serves as control.

MIT mouse chromosome integrated linkage and physical map and NCBI mouse genome resources, the 1.1 cM region also includes three other candidate genes in addition to Dsg1 and Dsg3: desmocollin 2 (Dsc2), transthyretin (Ttr), and ras-associated protein (Rab18). We examined the expression of these genes in the same way as for Dsg1 and Dsg3. But the expression levels of each gene were similar in wild-type and *pk* mutant mice skin. No significant differences were observed (data not shown).

Discussion

Our goal in this study was to define the genetic interval for the mutation responsible for the plucked (*pk*) phenotype using microsatellite markers as a first step toward isolation of the gene whose mutation leads to the phenotype. Since a genetic defect may affect the expression of neighboring genes, we were also interested in the expression of candidate genes in the *pk* genomic interval and how the *pk* gene defect affects histopathology of hair follicle. It was hypothesized that the defect in the *pk*/*pk* follicle is due to the retention of the inner root sheath although it has not been clear what causes that retention [1]. Previous studies suggest that the sebaceous gland plays a role in hair sheath-shaft dissociation [3,5,6]. In the *pk* mutant mouse with the sebaceous gland hypertrophy, it is conceivable that the defect in dissociation of inner root sheath from the hair shaft could lead to resistance to the outward movement of the hair shaft that may explain long, acutely bent follicles and trichomalacic changes of the distal shaft as well as retention of the inner root sheath in the emerging hair shafts in the *pk* mutant mouse (Fig. 1). Interestingly, scarring alopecia has been described in a sebaceous gland mutant mouse, *asebia*, with a deletion in Scd-1 gene [6,13]. Another mutation, *defolliculated*, affects sebaceous glands and also leads to elimination of pelage hair follicles [14].

Our molecular mapping studies localized *pk* mutation to a 1.1 cM interval that contains several interesting candidate genes (Fig. 2). The molecular analyses indicate that the transcripts for Dsg1 and Dsg3, candidate genes of the region, are up-regulated in *pk* mutant skin in contrast to non-mutant skin (Fig. 4).

Desmogleins are important calcium-binding transmembrane glycoproteins of cadherin superfamily and, along with desmocollins, constitute important molecular components of desmosomes. Desmosomes form important adhesive intercellular structures to help maintain an intact skin and retain hair shaft within the follicle [7,8,15–18]. Recent studies suggest that the molecular constituents of desmosomes are not only important in cell adhesion, but also in the transduction of intracellular signals that regulate cell behavior and tumorogenesis [19,20]. Thus, their dual function may provide the means to couple changes in cellular morphology and gene expression during tissue and organ morphogenesis. It is known that autoimmune skin blistering diseases can occur when desmosomal adhesion is compromised by antibodies to desmosomal cadherins [9]. Inherited mutations in desmoglein genes can adversely affect the skin and hair as demonstrated by mutations of human Dsg1 gene in striate palmoplantar keratoderma type I and that of *Dsg3* in balding phenotype of mouse [8,10,21]. Interestingly, it is known that ectopic

expression of Dsg1 compensates for genetic loss of Dsg3 (Dsg3 knockout mice) affecting keratinocyte adhesion [22]. Recently, importance of desmoglein-4 expression in skin was established by identifying mutations in families with inherited hypotrichosis, as well as in the lanceolate hair mouse [18]. Dsg1 is known to be expressed in epidermal suprabasal cells, the inner root sheath, and the innermost layers of the outer root sheath of hair follicles. In contrast, although Dsg3 expresses throughout all layers of the follicle outer root sheath, its expression is maximum in the basal layer of the follicle infundibulum.

In vitro cell culture studies suggest that high-level expression of Dsg1, but not Dsg3, disrupted desmosomes [22]. Whether enhanced expression of Dsg1 and Dsg3 is in anyway responsible for the follicular defect of *pk* mutant is unknown at this stage but it is an attractive possibility. Various possibilities exist that could explain the increased expression of desmoglein genes in recessive *pk* mouse with a single gene defect. First, a mutation in a gene such as a transcription factor that regulates expression of both these genes can explain the phenomenon. Locus control regions (LCR) that control expression of several genes have been demonstrated in β-globin and other mammalian genes [23]. Considering the fact that desmosomal cadherins are clustered in mouse and humans, [24,25], a second possibility of a mutation in a locus analogous to LCR on chromosome 18 could cause enhanced expression of desmoglein genes in *pk* mutant mice. Another possibility of enhanced expression of Dsg1 and Dsg3 is due secondarily to the follicular rupture, perifollicular chronic inflammation, and dermal scarring found in our histological analysis. That the sebaceous glands are hypertrophic and the infundibular and epidermal epithelia are thickened could also explain the increased desmoglein expression in the mutant skin. Nevertheless whatever the exact molecular mechanism may be, which needs more in-depth studies, it is interesting to note that another cadherin component of desmosome, desmocollin-2, did not show altered gene expression between *pk* mutant and non-mutant skin.

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