A spontaneous mutation disrupting the grainyhead-like 1 gene

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Mutation (allele) symbol: *Grhl1*^{m1J}

Mutation (allele) name: mutation 1, Jackson

Gene symbol: *Grhl1*

Strain of origin: B6Smn(C3)-*Fasl*^{gld} *Kitl*$^{Sl\text{-}23J}$/GrsrJ

Current strain name: B6.Cg-*Grhl1*^{m1J}/GrsrJ

Stock #014101 (jaxmice.jax.org)

Phenotype categories: Skin and hair

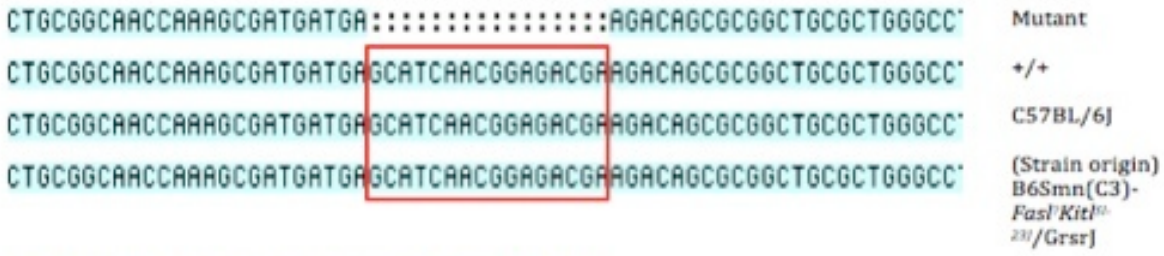
Abstract
A recessive mutation that arose spontaneously causes an abnormal growth in hair. Through phenotypic characterization, SNP genotyping, and subsequent sequence analysis it was determined that this is a mutation in *Grhl1* (grainyhead-like 1) and has been designated *Grhl1*^{m1J}.

Origin and Description
A new spontaneous recessive mutation, *Grhl1*^{m1J}, has been discovered and characterized. This mutation was identified in 2006 at The Jackson Laboratory by Richard Samples in a Mouse Mutant Resource colony of B6Smn(C3)-*Fasl*^{gld} *Kitl*$^{Sl\text{-}23J}$/GrsrJ. Mice homozygous for the *Grhl1*^{m1J} mutation have ichthyotic balding evident at 1.5 weeks of age. They are almost bald at weaning age, notably smaller than littermate controls at weaning age, and their coats remain sparse throughout adulthood (see photos on the allele detail page). Homozygotes are viable and fertile.

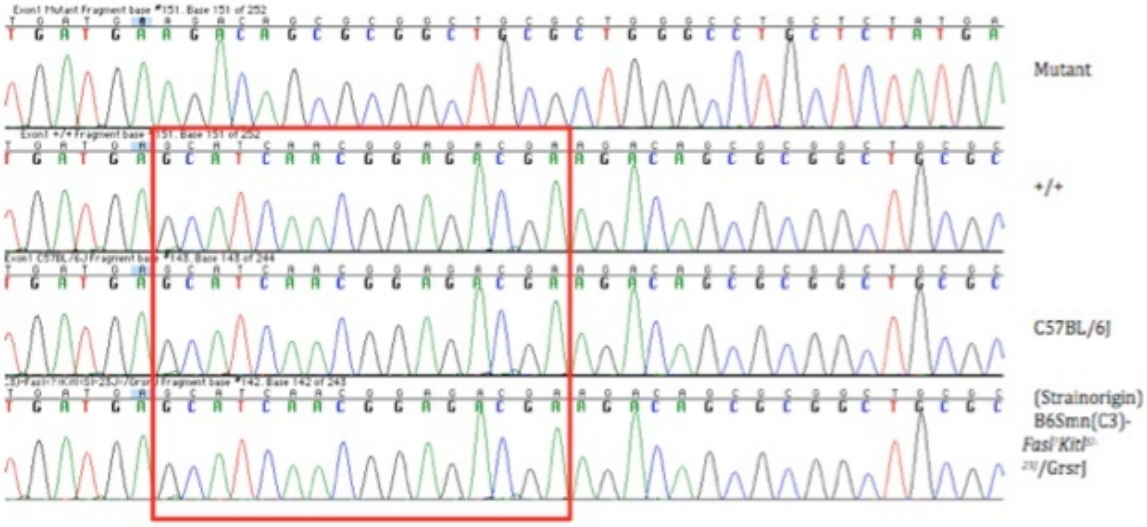
The mutant subline was backcrossed for six generations to C57BL/6J. Through this breeding scheme the *Kitl*$^{Sl\text{-}23J}$ mutation and possible *Fasl*^{gld} mutation were bred out of the mutant subline.

Genetic Analysis
This new mutation was shown to have recessive inheritance by mating a homozygote to an unrelated CAST/EiJ mouse. The F1 hybrids were all unaffected. These unaffected F1 hybrids were intercrossed, and affected F2 mice were generated for linkage analysis. Using standard SNP protocols, linkage analysis for this mutation was completed in the Fine Mapping Laboratory at The Jackson Laboratory. This mutation maps to Chromosome 12, between NCBI 37 position 003567042 bp and NCBI 37 position 074494300 bp.

Based on similar skin and hair phenotype and location within the mapped critical interval, *Grhl1* was considered a plausible candidate gene. Sequence analysis revealed a mutation in exon 1. A PCR product from genomic DNA was used to sequence the *Grhl1*^{m1J} mutation. Primers were generated that were predicted to produce from controls a 303 base pair product flanking exon 1 of the *Grhl1* wildtype allele; primer exon 1 Left is AGCTTCTAAGCTGTCTGGCTG and primer exon 1 Right is GAATCAGGTGCGTCTGAGC. Sequence analysis of mutant DNA identified a sixteen base pair deletion, which alters the reading frame in the chromatogram. Thus, *Grhl1*^{m1J} is a deletion in exon 1.



A. The 16 nucleotides enclosed in the red box above for wild-type controls are deleted from the mutant sequence.



B. Comparison of DNA sequence chromatograms of the homozygous *Grhl1*^{m1J} mutant (Top) and the three controls (+/+, C57BL/6J and strain of origin) sequence. The boxed red region corresponds to the boxed red region shown in A.

Pathology

A routine pathological screen[1] of two *Grhl1*^{m1J} homozygous mice at 30 weeks of age, prior to the removal of the *Kitl*$^{Sl\text{-}23J}$ and *Fasl*^{gld} mutations from this line, showed large tumors under their forelimbs in the armpit area. Further analysis of the two homozygotes revealed one having no additional lesions and the other having lymphoid hyperplasia in

various organs. These pathological results are possibly due to the *Fasl*^{gld} phenotype in the of strain origin.

Hearing as assessed by auditory brainstem response testing (ABR) of one mutant at 5 months of age was normal.

The eyes of two mutants at age 27 weeks of age, prior to the removal of the *Kitl*$^{Sl\text{-}23J}$ and *Fasl*^{gld} mutations, were tested by electroretinograph (ERG). One mutant had poor rod function, but otherwise these two homozygotes were clinically normal.

Acknowledgements
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References
J:133318 Wilanowski T et al., "Perturbed desmosomal cadherin expression in grainy head-like 1-null mice." EMBO J 2008 Mar 19;27(6):886-97

[1]**Standard Histology Protocol used in the Mouse Mutant Resource**
For fixation of tissues, mice were deeply anesthetized with tribromoethanol (avertin) until they no longer displayed a withdrawal reflex in the hind limbs and then perfused intracardially with Bouin's fixative following a flush of the vasculature with saline solution. After soaking in Bouin's for one week to demineralize bones, tissues were dissected. Six segments of spine with axial muscles and spinal cord in situ, representing cervical, thoracic and lumbar spinal segments, were dissected. The brain was removed and sliced into 6 cross sectional pieces at the levels of olfactory lobes, frontal cortex, striatum, thalamus, midbrain, rostral and caudal medulla with cerebellum. Midsagittal slices of hind leg through the knees were prepared. Slices of basal skull through the pituitary and inner ears were taken. Both eyes, salivary glands and submandibular lymph node, trachea plus thyroid and sometimes parathyroid were removed and cassetted. A longitudinal slice of skin from the back was removed. The thymus, slices of lung, and a longitudinal slice of heart were cassetted. Similarly slices of liver through gall bladder, kidney with adrenal attached, pancreas and spleen were prepared. The stomach was sliced longitudinally to include both squamous and glandular portions. Loops of small intestine from 3 levels and slices of large intestine and cecum were removed, as were slices of urinary bladder. The whole uterus, with ovaries attached, was taken. In males testes were sliced longitudinally. The accessory male organs including seminal vesicles, coagulating gland and prostate were removed en block. Altogether in most cases all tissue fit into a total of 10 cassettes. The cassettes were processed in an automatic tissue processor to dehydrate tissues which were then embedded in paraffin. Six micron sections were cut and stained with hematoxylin and eosin (H&E). Sections of brain and spinal cord in vertebral bones also were stained with luxol fast blue (LFB) for myelin and cresylecht violet (CV) for cellular detail.