Hypodactyly like, a mutation causing fused and missing digits, is likely an allele of the *Hoxa13* gene.

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Mutation (allele) symbol: *Hdlk*

Mutation (allele) name: Hypodactyly like

Gene symbol: *Hdlk*

Strain of origin: STOCK Tg(CAG-EGFP)D4Nagy/J

Current strain name: STOCK *Hdlk*/GrsrJ

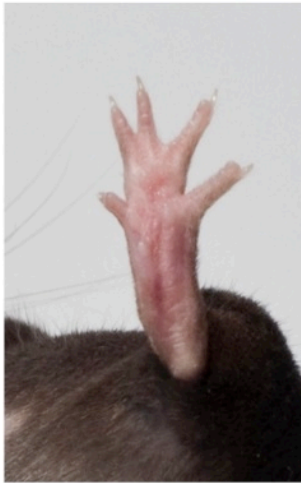
Stock #012596 (jaxmice.jax.org)

Phenotype categories: limbs/digits/renal/urinary system

Abstract
A new spontaneous semi-dominant mutation has been discovered and characterized at The Jackson Laboratory. Mice affected by the new hypodactyly like mutation have a degree of toe fusion that is similar to the phenotype of $Hoxa13^{Hd}$ mice. Standard PCR analysis determined that, based on map location, this new mutation is likely an allele of the homeobox A13 gene ($Hoxa13^{Hd}$).

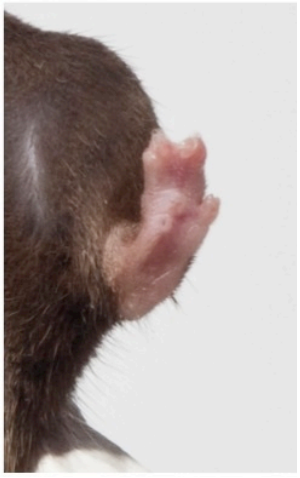
Origin and Description
The new hypodactyly like mutation arose spontaneously in a production colony of STOCK Tg(CAG-EGFP)D4Nagy/J mice at The Jackson Laboratory and was discovered by Cheryl MacLean.

Mice heterozygous for the hypodactyly like mutation have a fused digit on the hind feet and heterozygous mice have a missing terminal phalanx of the first or first and second digits of the hind feet.



The hind foot of a mouse heterozygous for the hypodactyly like mutation

This phenotype shows variable penetrance for shortening or absence of the first and second phalanx. The forefeet are normal. Heterozygous mice are fertile and live a normal life span. Homozygous mutant mice exhibit loss of the most anterior phalanx of forefeet and hind feet. Homozygous mice live to maturity but are sterile.



The hind foot of a mouse homozygous for the hypodactyly mutation

Genetic Analysis

Using the standard mapping procedures of The Mouse Mutant Resource, mice heterozygous for the hypodactyly like mutation were mated to CAST/EiJ mice. The affected F1 progeny produced from this cross were then backcrossed to CAST/EiJ mice. The resulting N2 progeny included 41 affected mice of which 21 were utilized for linkage analysis.

The hypodactyly like mutation maps to Chromosome 6, distal to *D6Mit119* (NCBI 37 position 50.8 Mb) and proximal to *D6Mit316* (NCBI 37 position 55.5 Mb) and is non-recombinant with *D6Mit118* (NCBI 36 position 52.0 Mb). The original *Hoxa13*^{Hd} mutation is located at (NCBI 37 position 55.2 Mb). Based on map location and phenotype similarities *Hoxa13* is a likely candidate gene.

Pathology

A routine pathological examination[1] of one heterozygote at 64 weeks of age showed normal somatic organs. Two mice homozygous for the hypodactyly like mutation at 27 weeks of age were examined. One homozygous mutant showed both kidneys to be cystic and completely fluid filled. Also in this mutant the right side of the uterus was enlarged and fluid filled. The urinary bladder was very small and thick walled (thicker than a normal empty bladder). The other homozygous mutant had a cystic kidney on the right side but the kidney on the left side was normal. The passage through the pelvic cavity seemed very small and constricted on both homozygous mutants.

Both mutants displayed severe hydronephrosis, pyelonephritis, and cystitis, and, in addition, an infection of the bladder, going up into the kidney causing the one kidney to dilate, probably because of paralysis of the bladder.

Hearing as assessed by auditory brainstem response testing (ABR) of two heterozygous mutants at 3 months of age and a homozygous mutant at 2 months of age showed

elevated thresholds at 32kHz, but they had normal thresholds at the other frequencies tested. The hearing loss noted is similar to that of by the strain background and is likely not caused by the *Hdlk* mutation.

The eyes of one heterozygous mouse at age 64 weeks were tested by an electroretinograph (ERG) and found to be normal.

Acknowledgements
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[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.