A new X-linked dominant mutation called wavy tiger

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Mutation (allele) symbol: *Wtgr*

Mutation (allele) name: wavy tiger

Gene symbol*:* *Wtgr*

Strain of origin*:* D2(B6)/Ei

Current strain name*:* D2(B6)-*Wtgr*/EiGrsrJ

Stock #003397 (jaxmice.jax.org)

Phenotypic categories: skin and hair

Origin and Description:
We report here a new dominant X-linked mutation that was discovered in a research colony by Eva Eicher at The Jackson Laboratory in 1998. The female mutants *(Wtgr/+)* are characterized by a small size, a wavy coat that appears striped, and curly whiskers.

The smaller mouse shown on the left is heterozygous for the wavy tiger mutation. The mouse on the right is an unaffected littermate control.

Because of their small size, the litters are weaned at a later age, usually around 4-5 weeks. The stock is maintained by mating a heterozygous (*Wtgr/*+) mutant female to a control (+/Y) male. Hemizygous (*Wtgr/*Y) mutant males on the D2(B6) background rarely survive to adulthood but do not reproduce. Examination of sperm reveals lack of motility of most sperm with occasional motility for short periods of time. Hemizygous mutant males (*Wtgr/*Y) are viable on the CAST/Ei and C57BL/6J hybrid backgrounds. Heterozygous mutant females (*Wtgr/*+) are fertile but have small litters. Hearing was assessed by auditory brain stem response (ABR). Female control (+/+) and heterozygous mutant (*Wtgr/*+) mice have normal hearing at three weeks of age. However, the mice develop age-related hearing loss due to the DBA background strain. The hearing of mutant and control mice is normal on a D2(B6) X B6 F1 hybrid mixed background at all ages assessed. The *Wtgr* mutation was mapped to Chromosome X between the markers *DXMit62* (89.07 Mb NCBIm36) and *DXMit16* (95.5 Mb) distal to the striated (*Str*), and bare patches (*Bpa*) gene and proximal to tabby (*Ta*). Because of the wavy coat that causes striping on the fur, we named this mutation Wavy tiger.

Genetic Analysis:

For linkage analysis, a normal CAST/Ei male was mated to a heterozygous mutant female (*Wtgr/*+). Visible heterozygous female mutants (*Wtgr/*+) from the F1 generation were then backcrossed to an unrelated D2(B6) control (+/Y) male. Spleens of affected hemizygous mutant males (*Wtgr*/Y) and unaffected control males were collected and stored at -70° C for subsequent DNA typing to map the location. DNA was extracted from thirty-nine controls (+/Y) and twenty-four hemizygous male mutants (*Wtgr*/Y) and polymerase chain reaction was carried out with MIT primer pairs (MapPairs, Research Genetics, Huntsville Ala.) Initial genetic mapping along the X chromosome using mutant (*Wtgr*/Y) and control (+/Y) males localized the mutation between 90.9 and 129.1 Mb (Ensembl m36, 2006). This region excluded the candidate gene NAD(P) dependent steroid dehydrogenase-like (*Nsdhl*), the gene responsible for *Bpa* and *Str* mutations, but includes ectodysplasin-A (*Eda*) the gene underlying the (*Ta*) mouse mutation. Further analysis utilizing the female backcross progeny refines the distal flanking marker at *DXMit16 (95.5 Mb),* thus excluding *Eda* as a candidate gene. A candidate gene within this region is ectodysplasin A2 isoform receptor (*Eda2r*) because mutations of this gene cause hypohidrotic ectodermal dysplasia (Newton, 2004).

Pathology:

A standard pathological screen[1] of one heterozygous female mutant at eleven weeks of age and two heterozygous female mutants at 4 weeks of age showed that clumps of melanocytes are present in the dermis and in the subdermal adipose tissue (Figure 1). This is never seen in normal mice. The zigzag hairs are abnormally thin, slightly wavy, and have clumps of melanin (Figures 2 and 3).

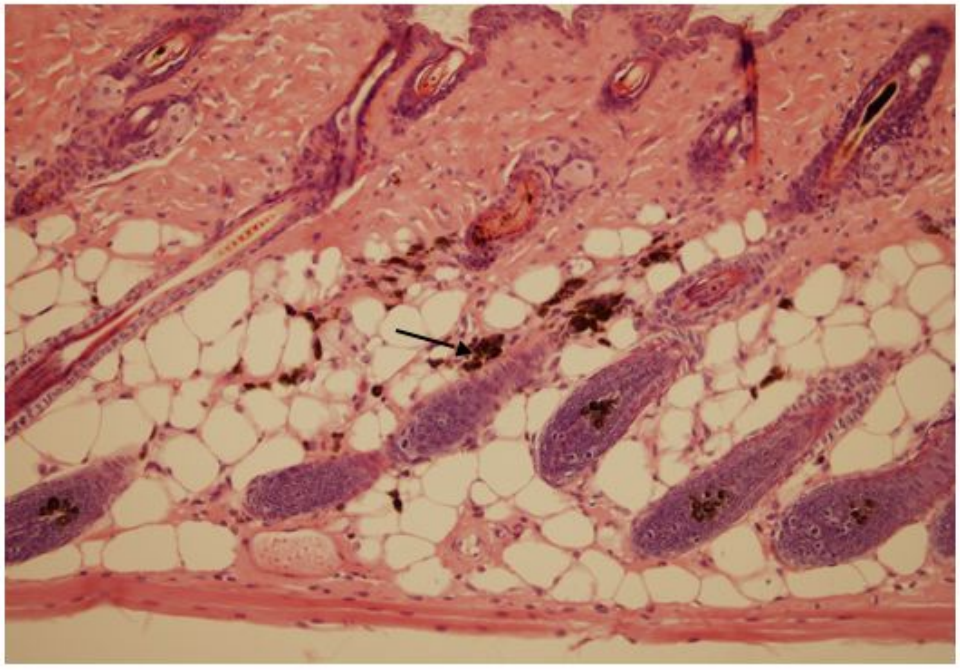

Figure 1: Histological section of the skin of a *Wtgr* mutant mouse showing clumps of melanocytes in dermis. (20x)

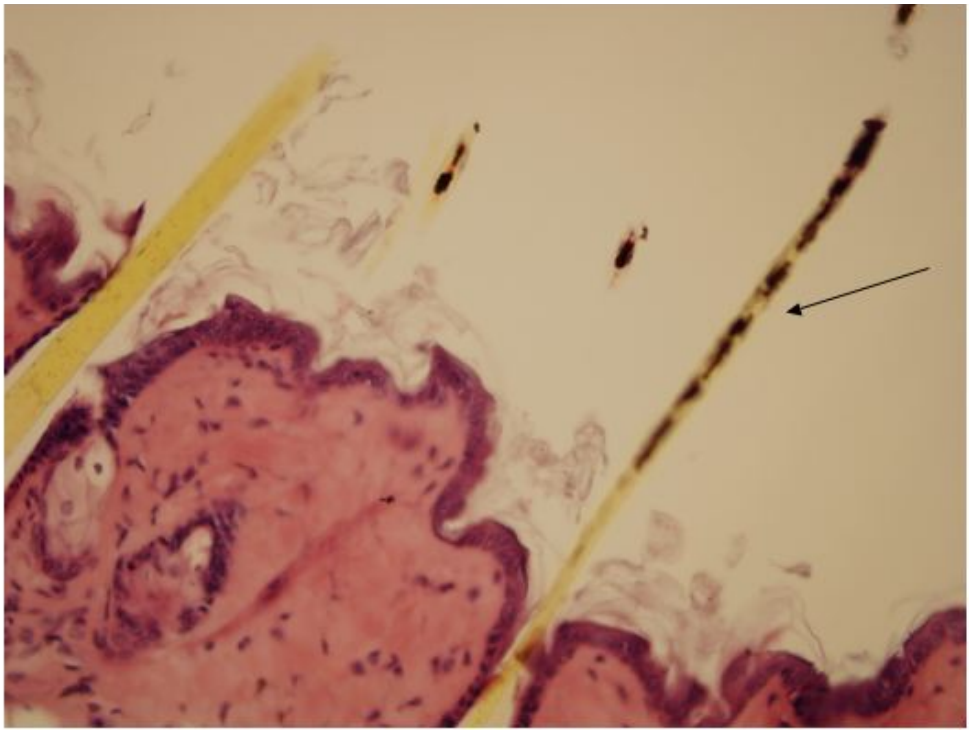

Figure 2: Histological section of hair showing abnormally clumped melanin. (20x)

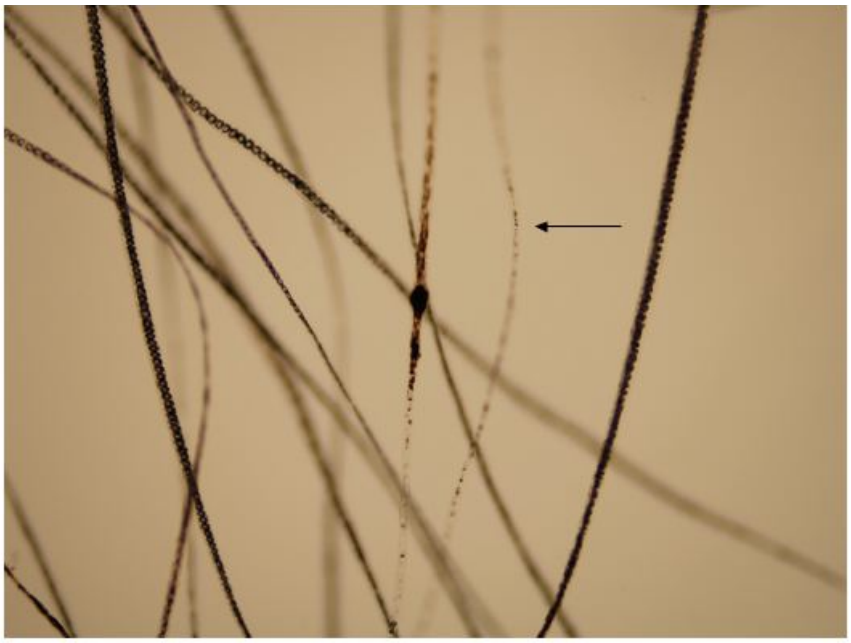

Figure 3: Hair samples taken from a *Wtgr* mutant mouse showing that the zigzag hairs are abnormally thin, slightly wavy and have clumps of melanin. (20x)

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References:

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Myodegeneration in EDA-A2 transgenic mice is prevented by XEDAR deficiency. Mol Cell Biol, 24(4): 1608-13.

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Footnotes:

[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.