A Remutation to *Atp7a*$^{Mo\text{-}pew}$ named Pewter 3 Jackson

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Mutation (allele) symbol: *Atp7a*$^{Mo\text{-}pew3J}$

Mutation (allele) name: pewter 3 Jackson

Gene symbol: *Atp7a*$^{Mo\text{-}pew3J}$

Strain of origin: CB6F1/J

Current strain name: C;B6- *Atp7a*$^{Mo\text{-}pew3J}$/GrsrJ

Stock #005042 (available only as DNA from The Jackson Laboratory DNA Resource)

Phenotype categories: neurological, coat color

Abstract
A remutation to the X linked gene *Atp7a* has been identified. The coat color of this remutation is variable depending on the background coat color genes that are segregating in the CB6F1/J background. When homozygous for non-agouti, hemizygous males are pewter; however when homozygous for brown, hemizygous males are more brownish yellow than pewter. Heterozygous females (*Mo-pew3J*/+) are variably striped brown and black when homozygous for either non-agouti or brown. When homozygous for *Mo-pew3J ,* females display the same coat color phenotype as males. More than half of the affected males die between 2 and 6 weeks of age as do homozygous females.

Origin and Description
This semidominant remutation arose in a breeding colony of CB6F1/J at The Jackson Laboratory on March 13, 2000 and was discovered by Damon E. Bell. This is an X linked remutation that causes more than half of the affected males to die and to cause those that survive to have a light grey (see Photo) or brownish yellow coat color (see Photo) depending on the segregating coat color genes from the CB6F1/J background on which the mutation arose. Since the mutant strain is maintained by sibling matings, the agouti, non-agouti, brown, and albino color alleles are present. Homozygous females have the same coat color and life span as hemizygous males. Heterozygous females are striped with the amount of striping highly variable (see photo on MGI allele detail page). Hemizygous males and homozygous females can be recognized at 8-10 days of age by their coat color. The majority of these mice appear sickly between 10 days and 5 weeks of age. Heterozygous females can be identified when the coat first starts to grow in, but if the striping is sparse it takes 3-4 weeks to identify them accurately.

Genetic Analysis
The pewter 3 Jackson mutation maps between *DXMit176* (30 cM) and *DXMit51* (58 cM) and is non-recombinant with *DXMit65* (48.5 cM). The chromosomal position of *Atp7a*$^{Mo\text{-}pew}$ is at 44cM on Chr X (MGD).

Pathology

A routine pathology screen[1] of 4 littermates at 2 weeks of age showed necrosis of cerebral cortex, hippocampus, thalamus and outer nuclear layer of retina. Mice surviving to 1 month of age had dystrophic axons (see slide) and microgliacytes in deep cerebellar nuclei and loss of Purkinjie cells.

Discussion

Based on the coat color phenotype of this remutation, it's histological similarities in the brain to mice with other *Atp7a* mutations (MGD), and it's chromosomal position, it was determined that this mutant is a remutation to *Atp7a* $^{Mo\text{-}pew}$. The histological phenotype seen in these mutants is similar to that seen in the mutant toxic milk (*Atb7b*^{tx}) where defects are due to copper deficiencies. The *Atp7a* gene encodes the alpha polypeptide of Cu^{2+}-ATPase and the mottled series alleles are associated with sequence alterations in this gene (MGD). We, however, have not tested for copper deficiencies in this new allele.

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References

Manley KF (1993) A MacIntosh program for storage and analysis of experimental mapping data. Mamm Genome 4,303-313

Mouse Genome Database (MGD) Mouse Genome Informatics Project, The Jackson Laboratory, Bar Harbor, Maine.

[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.