awag: A New Mouse Mutation with a Late Onset Abnormal Gait Maps to Mouse Chromosome 2

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Mutation (allele) symbol: *awag*

Mutation (allele) name: Ages With Abnormal Gait

Gene symbol: *awag*

Strain of origin: C57BL/6J-*Tyr*$^{c\text{-}2J}$/J

Current strain name: C57BL/6J-*Tyr*$^{c\text{-}2J}$-*awag*/GrsrJ

Stock #005349 (jaxmice.jax.org)

Phenotype categories: neuromuscular

Abstract
A new spontaneous mouse mutation named "ages with abnormal gait" (*awag*) has been identified. The mutant mice look like normal control littermates until they are about 2 months of age when a distinct tremor is observed when they walk. This mutation was mapped using an intercross with CAST/Ei and was found to be on Chromosome 2.

Origin and Description
A new spontaneous mouse mutation named "ages with abnormal gait " was discovered in 1998 by Jay Wellington in a production colony of C57BL/6J-*Tyr*$^{c\text{-}2J}$/J mice at The Jackson Laboratory. Mutants have a distinct tremor when walking that first appears around 2 months of age. When lifted by the tail the mutant mice do not splay their hind legs out as normal mice do, instead they hold their legs in a bowlegged umbrella like way and arch their backs. Mutant mice of both sexes breed and live a normal life span. The mutant strain is maintained by mating heterozygous siblings or by mating female homozygotes with untested male littermate controls.

Genetic Analysis
Using our standard mapping procedures, an intercross between the strains C57BL/6J-*Tyrc-2J-awag*/J and CAST/Ei was set up and generated 30 affected F2 progeny of which 21 were used for linkage analysis. The mutation maps between *D2Mit7* at Ensembl psition 38.1 mb (1/36 recombinants) and *D2Mit72* at Ensembl position 49.2 Mb (2/36 recombinants) and is non-recombinant with *D2Mit320* at Ensembl psition 39.1, *D2Mit237* at Ensembl position 40.9 mb, and *D2Mit322* at Ensembl position42.8. To prevent errors of misclassification, only mice with the most obvious mutant phenotype were included in the linkage analysis.

Pathology

Hearing as assessed by auditory-evoked brainstem response in mutant animals showed variable results. Two mutants at 3 months of age had hearing loss. Two other *awag* mutants tested at 6 months had normal to almost normal hearing. All controls had normal hearing. The eyes of both mutant and control mice were examined with an ophthalmoscope and all animals tested had corneal holes and cataracts. These observations of the eyes are characteristic of the background strain and not the result of this new mutation. Comprehensive histopathologic examination[1] of 7 mutant mice ranging in age from 3-18 months showed no significant lesions in somatic organs. Three had mild hydrocephalus, assumed to be a strain background occurrence.

Discussion

We report on a new spontaneous mouse mutation on Chromosome 2 that causes an abnormal gait in homozygotes. This new mutant differs from many of the neuromuscular mutants such as tottering, staggerer, waddles, wobbler, abnormal wobbly gait, shiverer, etc. (MGI), in that the *awag* phenotype is not observed until mutants are about 2 months of age, and also *awag* mutants live a normal life span.

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References

MGD 2004, Mouse Genome Database, Mouse Genome Informatics Project, The Jackson Laboratory, Bar Harbor, ME. (informatics.jax.org)

Ensembl, Mouse Genome Assembly NCBI m33

[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.