Quivery runt, a new spontaneous mouse mutation

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Mutation (allele) symbol: *qvyr*

Mutation (allele) name: quivery runt

Current strain name: B6(Cg)-*qvyr*/GrsrJ

Stock #012875 (jaxmice.jax.org)

Phenotype categories: neurological

Origin and Description

A new recessive mutation was identified in the progeny of an ENU mutagenized C57BL/6J male in the laboratory of Dr. Simon John at The Jackson Laboratory. This mutagenesis program involved crossing the mutagenized C57BL/6J male to C3Fe.Cg-*Rw* and then crossing the offspring to C3Fe.Cg-*Hm* +/+ *Rw* to identify mutations mapping to the rump white deletion of Chromosome 5. Mice homozygous for this new mutation are noticeable by their quivering movement and runted appearance at three weeks of age. Their symptoms progress rapidly in a short period of time, and they can die anytime after wean. Only a few have survived to 10 weeks of age. Because of the severity of the phenotype and the need to backcross away from any contaminating ENU-induced mutations, this mutation has been maintained primarily by breeding homozygous ovarian transplant hosts to C57BL/6J males then intercrossing the obligate heterozygous offspring.

Genetic Analysis

Mutant animals were outcrossed to DBA/2J mice to establish heritability. No affected mice were found in the F1 generation. Intercrossing unaffected F1 animals produced affected F2 animals, indicating a recessive mode of inheritance. A population of F2 mice was generated for linkage analysis and fine mapping. Using standard SNP protocols, linkage analysis for this mutation was completed in the Fine Mapping Laboratory at The Jackson Laboratory. This mutation mapped to Chromosome 14, between position 35928972 bp and position 71324217 bp (MGSCv37).

Pathology

Routine pathological screening[1] of five homozygotes of varying ages did not find any consistent causative lesions. One mutant at two weeks of age had foamy cells in the white marrow of the spinal cord, which may have been immature cells. One mutant at 7 weeks age showed aberrant cells in the testis. One mutant at 9 weeks of age showed scattered very small muscle fibers in muscles, particularly in the back. No lesions were identified in one mutant at five weeks age or one mutant at 10 weeks of age.

The eyes of one homozygote and one control at age 3 weeks were tested by

electroretinography (ERG) and showed normal ERG response, and ophthalmoscopic examination found no abnormalities of the eyes.

Hearing assessments by auditory brainstem response testing[2] showed severe hearing loss in some, but not all homozygotes, and there is indication that hearing loss may accompany disease progression. One homozygote at age 3.5 weeks showed severe hearing loss, two of three homozygotes at age three weeks showed severe hearing loss while the third had normal hearing, and one homozygote at 22 days of age showed mild hearing loss while three others had normal hearing. It was observed that the two deaf homozygotes at three weeks of age were weak, and also gave no response to the click box test.

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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.

[2]**ABR thresholds** in mice are determined using a semi-automated computer system (Intelligent Hearing Systems, Miami, Florida). Subdermal needle electrodes are inserted at the vertex and ventrolaterally to both ears of anesthetized mice. Specific auditory stimuli from 10-100 dB SPL are delivered binaurally through plastic tubes from high frequency transducers. ABR thresholds are obtained, in an acoustic chamber, for clicks and for 8, 16, and 32 kHz pure-tone pips.