Quaking 2 Jackson, a remutation of the Quaking (*Qk*) gene on Chromosome 17 in the Mouse.

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Mutation (allele) symbol: *qk-2J*

Mutation (allele) name: quaking 2 Jackson

Gene symbol: $Qk^{qk\text{-}2J}$

Strain of origin: BKS.Cg-*m*+/+$Lepr^{db}$

Current strain name: B6.Cg-$Qk^{qk\text{-}2J}$/GrsrJ

Stock #005089 (jaxmice.jax.org)

Phenotype categories: neuromuscular

Abstract
We have identified a new allele of the Quaking gene (*Qk*) by a direct test for allelism. Affected progeny were produced when a quaking homozygote and a mouse heterozygous for the new mutation were mated together. The phenotype is similar to the original quaking (qk) mutation.

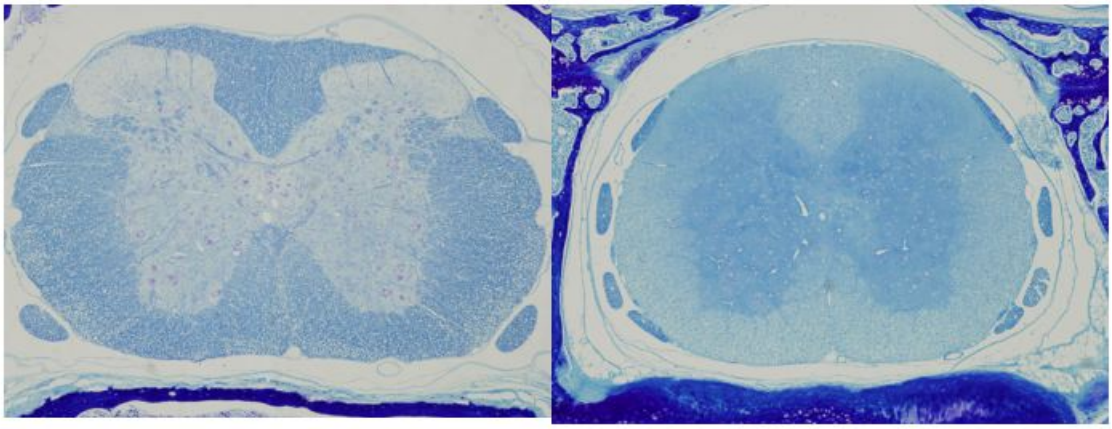
Origin and Description
The $Qk^{qk\text{-}2J}$ remutation was discovered by Fred Rumill, Jr. in 2003 in a production colony of diabetic mice of the strain BKS.Cg-*m*+/+$Lepr^{db}$ at The Jackson Laboratory. Mice homozygous for this spontaneous remutation are recognizable at about two weeks of age by their rapid tremors, which is similar to the original quaking mutation. Homozygous *qk-2J*/*qk-2J* mice from neither sex has been used for breeding, and it is not known whether or not they are able to reproduce. Homozygous mutants may live to adulthood but survival is variable. In order to determine the mode of inheritance, ovaries from a female, homozygous for this new mutation, were transplanted into C3SNSmn.CB17-$Parkdc^{scid}$/J hosts which were then mated to an unrelated C57BL/6J male. No affected offspring were observed in the F1 generation produced from this mating (0 affected/33 born). Mice from this F1 generation were then mated together to produce F2s, and in this cross both affected and unaffected animals were produced showing that the mutation is recessive.

Genetic Analysis
A direct test for allelism was set up by mating a homozygous female from the original quaking strain B6C3Fe-*a*/*a*-Qk^{qk}) to a male heterozygous for this new mutation. This mating produced two litters in which seven affected quaking progeny were produced out of fourteen progeny born, proving the new mutation to be an allele of *Qk*. Quaking is

located on Chromosome 17 at the 5.9 cM position (MGI) or NCBIm33 position 9.7 Mb.

Pathology

Routine pathological screening[1] of mutants and controls showed that 3-week-old homozygotes had holes in the striatum of the cortex and cerebellum and also in the myelin of the spinal cord. This lesion is similar to that seen in the original quaking mutation.



On left is spinal cord from a control showing normal staining of myelin and on the right is from a mutant showing pale staining myelin. (10X)

Hearing as assessed by Auditory brain stem response testing (ABR)[2] showed abnormal pattern waves and normal thresholds on all four homozygous mutants tested. The hearing pattern observed was similar to the pattern observed with the original quaking mutants. The eyes of four female and two male *qk-2J /qk-2J* mutants were examined with an ophthalmoscope and were determined to be normal. Controls tested had normal eyes.

Discussion

We have a new remutation to the Quaking gene that arose on a diabetic background segregating for the coat color "misty". This remutation exhibits a similar clinical and histopathological phenotype to the original quaking mutation and has been proven to be allelic.

Acknowledgements

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References

Mouse Genome Database (MGD) Mouse Genome Informatics Project, The Jackson Laboratory, Bar Harbor, Maine. World Wide Web (2005) (www.informatics.jax.org)

MGSC27.33c.1. Mouse Genome Sequencing Consortium (ensembl.org/Mus_musculus/)

[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.