Bulging disc disease (*bdd):* a new skeletal mutation on Chromosome 2

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Mutation (allele) symbol: *bdd*

Mutation (allele) name: bulging disc disease

Gene symbol: *bdd*

Strain of origin: A/A +<*us*>/+

Current strain name: STOCK-*bdd*/J

Stock #003818 (jaxmice.jax.org)

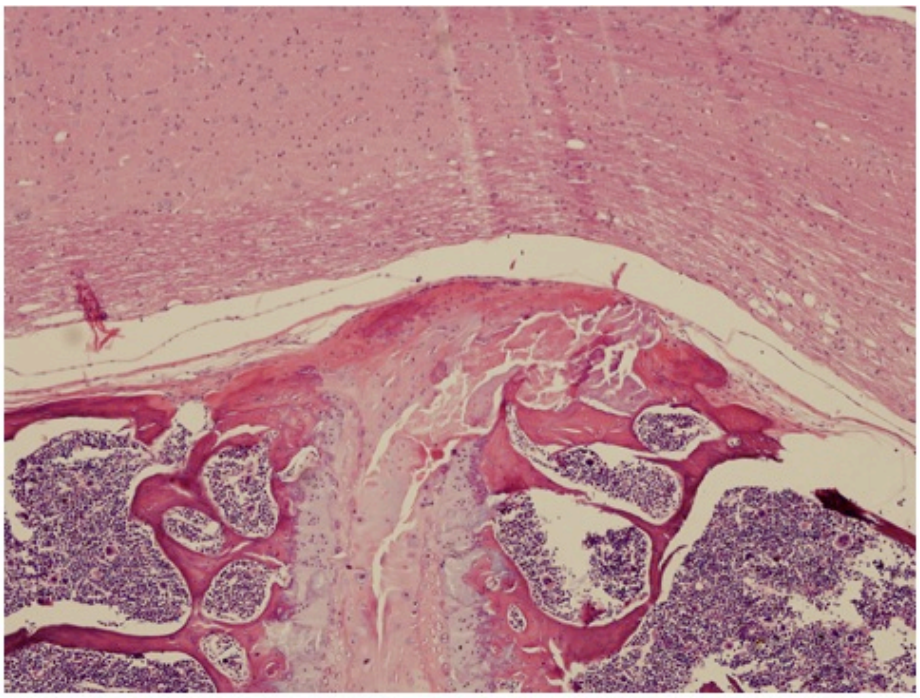
Phenotype categories: skeletal

Abstract
A new spontaneous recessive mutation has been identified and mapped to Chromosome 2. This new mutation causes affected mice to be smaller in size than their littermates, and to have "horseshoe" shaped hips. By one year of age mutant mice develop prolapsed discs in the spinal cord.

Origin and Description
The new bulging disc disease (*bdd*) mutation was found by Priscilla Lane in a production colony of A/A +<*us*>/+ mice at the Jackson Laboratory. Mice affected by the *bdd* mutation are recognized at 3 weeks of age by their small body size and when lifted by the tail, mutant mice exhibit an abnormal positioning of the rear legs. Both males and females breed and live a normal lifespan, however with age they appear to have a paralysis-like dragging of the hind limbs.

Genetic Analysis
Using our standard mapping protocols both a backcross to CAST/EiJ and an intercross to NZB/B1NJ were utilized to generate progeny for linkage analysis. Linkage was found on Chromosome 2 with *D2Mit266* showing 5 % recombination with the CAST/EiJ linkage cross and no recombination with the NZB/B1NJ cross. Based on phenotype and map location, the *Col9a3* gene was thought to be a good candidate gene. The entire protein coding sequence from start codon to stop codon was tested and no mutation was found; however, regulatory regions of the gene have not been examined.

Pathology
A pathological screen of six mutants was performed at 1 and 1.5 years of age and results indicate prolapsed discs found in longitudinal sections of the spinal cord (see slide below). No muscle loss or neurological damage was detected in the legs. X-rays of a mutant at approximately 1 year of age were normal.



Degenerative inter-vertebral disk material protrudes dorsally, displacing the overlying spinal cord

Hearing as assessed by auditory brainstem response (ABR) testing revealed a progressive hearing loss in mice homozygous for the *bdd* mutation. Five mutant mice (*bdd*/*bdd*) and three heterozygous control mice (+/*bdd*) tested at 50 days of age exhibited normal ABR thresholds; however, two mutant mice tested at 156 days of age exhibited thresholds about 30 decibels (dB) above those of heterozygous controls, and a mutant mouse tested at 248 days of age exhibited a 40 dB increase in ABR thresholds.

The eyes of 16 mutants were examined with an ophthalmoscope and ERG tested and all mice were affected in at least one eye with a bad iris, bad cornea or a bad retina.

Discussion

Although we did not detect any mutation in its protein coding sequence, *Col9a3* still remains an attractive candidate gene for *bdd*. Mutations of the human *COL9A3* gene have been shown to underlie increased susceptibility to intervertebral disc disease (Paassilta et al. 2001), a phenotype similar to that of bdd mutant mice. Human *COL9A3* mutations also have been associated with moderate progressive sensorineural hearing impairment (Asamura et al. 2005) as are *bdd* mutant mice, and mice with a knockout of another type IX collagen gene, *Col9a1*, show progressive hearing loss (Suzuki et al., 2005).

References

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