Spontaneous hepatitis: A new liver disease model exhibiting hepatitis maps to Chromosome 7

Belinda Harris, Patricia F. Ward-Bailey, David E. Bergstrom, Roderick T. Bronson, and Leah Rae Donahue

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Mutation symbol: *shep*

Mutation name: spontaneous hepatitis

Gene symbol: *Relb* (updated October, 2011)

Strain of origin: (BALB/cJ x A/J) progeny

Current strain name: A;C-*Relb*^{shep}/GrsrJ

Stock #012856 (jaxmice.jax.org)

Phenotype categories: metabolic, body size, immunologic

Abstract
We have identified a new autosomal recessive mouse mutation that results in a pale thin tail, pale liver, bloated abdomen and small body size as compared to littermate controls. Homozygotes generally die by three weeks of age. Pathology showed severe hepatitis in five homozygotes examined. Clinical chemistry assessments of homozygotes confirms classic hepatitis with decreased albumin, amylase and total protein. This new mutation has been mapped to Chromosome 7.

Origin and Description
A recessive mutation was discovered at The Jackson Laboratory in approximately 2001 by Babette Gwynn in a colony derived from a cross of BALB/cJ x A/J. Homozygotes were first recognized by their anemia and smaller overall body size. The phenotype lasts throughout the short lifespan of the mutant, which is generally not more than three weeks of age although a few have lived to 4 weeks of age. The reduced body size of homozygotes can first be detected between 10 and 14 days of age and homozygotes are approximately 65% smaller by weight compared to control littermates by 20 days of age .

A *shep* homozygote on the right
with a control littermate on the left

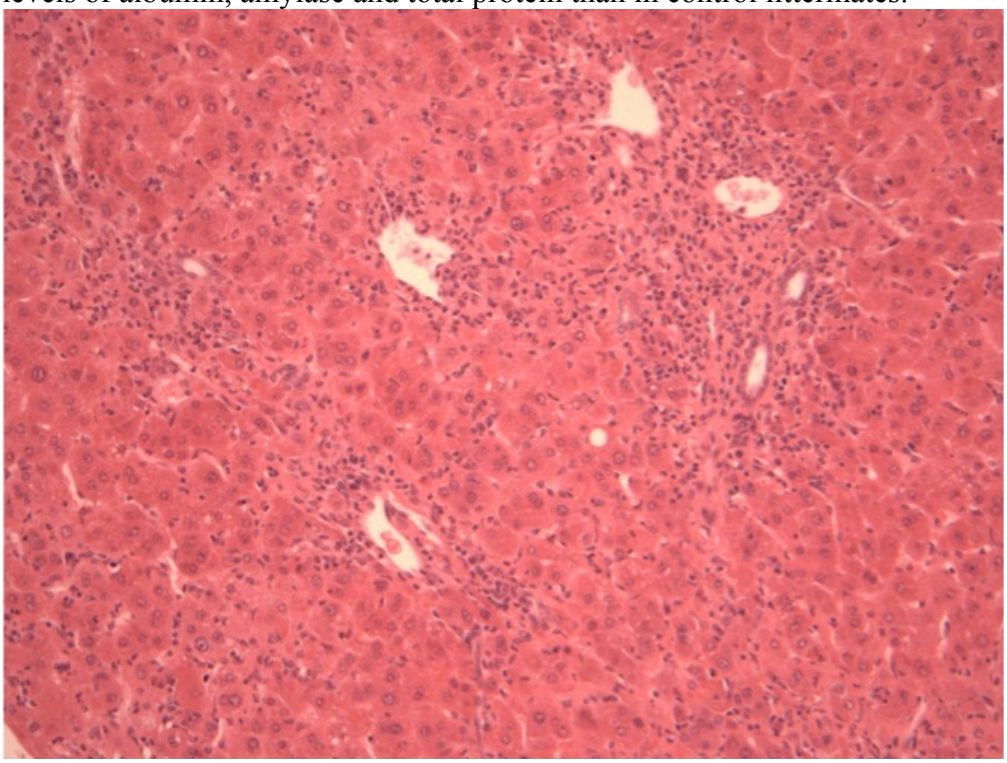
Further characterization revealed that these mutants develop spontaneous hepatitis. The mutation was assigned the mutation symbol shep for spontaneous hepatitis. Because homozygotes do not live long enough to breed, this colony is maintained by progeny testing unaffected offspring of heterozygotes to identify the next generation of heterozygotes for breeding. Fewer than the expected 25% affected progeny are generated from proven heterozygous pairs: only 56 affected mutants were identified out of 367 mice born, with 19 missing and 5 found dead before phenotypic onset. This is a yield of 15.2% affected. If the pups that were missing and found dead are added into the affected numbers, the percentage is closer to the expected 25% (80/367=21.8%)). Heterozygotes appear to live a normal lifespan and are fertile.

Genetic Analysis

Mapping was accomplished using an intercross to CAST/EiJ, which placed shep on Chromosome 7 proximal to *D7Mit267*. This intercross produced fewer than the expected 25% homozygotes in the total progeny: 27 affected mutants were identified out of 416 mice born with 2 pups missing and 4 found dead prior to characterization, which is less than 8% even assuming that the missing and found dead pups were homozygotes. This suggests *in utero* lethality. This mutation maps near *Tgfb1* but a direct allele test did not produce any affected mutants.

Pathology

Pathology and clinical chemistry on homozygotes show classic hepatitis with lower levels of albumin, amylase and total protein than in control littermates.



Severe hepatitis characterized by infiltration of mononuclear cells and fibrosis around and extending from portal areas. Hematoxylin and eosin x 20.

Low levels of albumin in homozygotes coincided with end stage liver disease, malnutrition, and cirrhosis. Lower levels of amylase coincided with hepatitis and liver disease. Lower total serum protein coincided with cirrhosis and hepatitis. There was no difference in liver enzymes alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase or in blood urea nitrogen.

Discussion

We report a spontaneous autosomal recessive mutation, *shep*, that affects the liver of homozygotes with classic hepatitis symptoms and pathology. Homozygotes do not live to adulthood, and thus do not survive to breed. This mutation maps to proximal Chromosome 7 but a direct allele test with *Tgfb1*^{tm1Doe} has failed to prove *shep* to be an allele of *Tgfb1*.

Acknowledgements

We thank Babette Gwynn for her original discovery of this mutation, Susan Grindle for clinical analysis and Coleen Kane for histological preparations.

Addendum

This mutation was identified as a GC to TG mutation at Chromosome 7:20197995-6 which causes a single amino acid change of glutamine to lysine at amino acid 334 of *Relb*. Please see Fairfield *et al*. Genome Biology 2011, Sept 14; 12(9):R86.