Brachypodism 4 Jackson: a new spontaneous mutation

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Mutation (allele) symbol: *Gdf5*$^{bp-4J}$

Mutation (allele) name: brachypodism 4 Jackson

Gene symbol: *Gdf5*

Strain of origin: B6.129S-*Casp6*^{tm1Flv}/J

Current strain name: B6.Cg-*Gdf5*$^{bp-4J}$/GrsrJ

Stock: 014183 (jaxmice.jax.org)

Phenotype categories: skeletal

Origin and Description

A spontaneous mutation was identified in the strain B6.129S6-*Casp6*^{tm1Flv}/J that causes the digits and all four limbs to be shortened in length. Although these mutants have short limbs, the body length appears normal. Both female and male mutants have bred, but many male mutants have been non-productive so this mutation causes reduced fertility on an individual basis in males. There is no indication of a shortened lifespan. Due to the lack of reliability of mutant males, the preferred breeding scheme for colony maintenance is mutant female bred to non-mutant sibling male. The *Casp6*^{tm1Flv} mutation was bred out of this mutant subline by backcrossing a mutant female to C57BL/6J, intercrossing the offspring, genotyping, and selecting the *Casp6* wild-type as breeders to continue the line. The removal of the targeted mutation did not alter the phenotype of this mutation.

Genetic Analysis

To determine the mode of heritability a mutant was outcrossed to C3HeB/FeJ and no mutants were found in the F1 population. When these unaffected F1 hybrids were intercrossed they produced 24 mutant and 2 born dead out of 84 offspring, proving this mutation to be recessive and fully penetrant on this background. Using this C3HeB/FeJ outcross in a modification of our standard mapping protocol, this mutation was mapped to Chromosome 2 with *D2Mit48* having no recombinations out of 21 mutants assessed. This mapped the mutation to the brachypodism locus. Because the map location and phenotype strongly indicated a mutation in *Gdf5* a complementation test was done by crossing with mice carrying either *Gdf5*$^{bp-J}$ or *Gdf5*$^{bp-H}$, which were obtained from reanimating the cryopreserved bankstock STOCK T(2;11)30H x AEJ-a *Gdf5*$^{bp-H}$/J or A/J-a *Gdf5*$^{bp-J}$/J (stock #000596). This cross produced 15 affected progeny out of 33 total born proving that this new mutation is an allele of *Gdf5*.

Pathology
A routine pathological screen of one 18-week old mutant male and one female heterozygous control showed the female control exhibiting mild hydrocephalus and the male homozygote having no pathological lesions. Auditory brainstem response (ABR) testing of one homozygote and one heterozygote at four months of age showed both having elevated thresholds at 32kHz, but two homozygotes and two heterozygous controls at 60 days of age showed normal hearing by ABR. Thus, no hearing loss phenotype is attributable to this mutation. Eye examinations of one heterozygote and one homozygote at 4 months of age were normal. Of dozens of heterozygotes assessed only one showed any abnormality of the digits. In this mouse the second digit on one of the hind feet was turned slightly out to the side.

Summary
We report finding a spontaneous mutation that causes shortened limbs and digits. Failed complementation with other brachypodism alleles proved this to be an allele of *Gdf5*. This brachypodism 4 Jackson allele provides a model for Hunter-Thompson type acromesomelic dysplasia and Grebe type chondrodysplasia.

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