A New Spontaneous Mutation in Fgfr3

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Mutation (allele) symbol: *Fgfr3*^{m1J}

Mutation (allele) name: Fibroblast growth factor receptor 3, mutation 1 Jackson

Gene symbol: *Fgfr3*

Strain of origin: CByJ.A-*fsn*$^{?}$ *Atp2b2*$^{dfw\text{-}2J}$/J

Current strain name: CByJ.Cg-*Fgfr3*^{m1J}/GrsrJ

Stock #014182 (jaxmice.jax.org)

Phenotype categories: neurological

Abstract
We have identified a spontaneous mutation in the *Fgfr3* gene that causes phenotypically identifiable kyphosis, scoliosis, and crooked tails in affected mice by two weeks of age, which is identical to the phenotype of *Fgfr3* targeted mutants at that age. A mapping intercross with *Mus castaneus* originally mapped this mutation to Chromosome 5 and a subsequent direct test for allelism with *Fgfr3*^{tm1Dor} proved the two mutations to be allelic.

Fgfr3^{m1J} homozygote on the right and sibling control on the left

Origin and Description

This new mutation to *Fgfr3* was discovered by Richard Samples at The Jackson Laboratory in a Mouse Mutant Resource colony of CByJ.A-*Atp2b2*$^{dfw\text{-}2J}$/J mice, which may have had the flaky skin mutation still segregating in the background. It was first identified by its twisted body shape and crooked tail. All the mutants display kyphosis and scoliosis with a bent tail, which appears to be an extension of the spinal bending (see photo and x-ray). Palpation does not reveal any vertebral kinks in the tail. Homozygous males have not bred to date, but homozygous females do breed and successfully rear their young. This colony has been maintained primarily by progeny test and homozygotes are easily identifiable by three weeks of age. Occasionally affected mice are found dead by three weeks of age, but most live to adulthood. Heterozygous littermates are phenotypically normal and live a normal lifespan.

Genetic Analysis

Using standard mapping protocols the new mutation to *Fgfr3* was mapped to Chromosome 5 using progeny from an intercross to CAST/EiJ. No affected mice were produced in the F1s. The F1 progeny were intercrossed and 40 F2 homozygotes produced were used for mapping. This new spontaneous mutation mapped between *D5Mit386* (NCBI 37 position 28.0 Mb) and *D5Mit106* (NCBI 37 position 45.3 Mb) and was non-recombinant with *D5Mit229* (NCBI 37 position 31.9 Mb). This map position placed this locus in the same region where the *Fgfr3* gene (NCBI 37 position 34.0 Mb) is located on Chromosome 5. Two direct tests for allelism with *Fgfr3*^{tm1Dor} subsequently proved this

new mutation to be an allele of *Fgfr3*: One heterozygous female *Fgfr3*^{tm1Dor} and a male heterozygous new mutant produced two affected homozygotes out of 24 total progeny born and two heterozygous new mutant females crossed to one heterozygous *Fgfr3*^{tm1Dor} male mouse produced 14 affected progeny out of 29 total born.

Pathology

In addition to the kyphoscoliosis found in all mutants, and the occasional death by wean age, hearing and inner ear defects were detected. A routine pathological screen showed a homozygous male at eight weeks of age having absent hair cells in the ear. Hearing as assessed by auditory brainstem response testing (hearingimpairment.jax.org/abr.html) showed testing results in the deaf range on one homozygote and three of five unaffected controls at two months of age. However, these mice were screened before the deaf waddler 2 Jackson (*dfw-2J)* mutation was bred away from the strain, thus the *dfw-2J* likely affected the results. Once the *dfw-2J* mutation was removed, hearing tests on one 3-week-old and two 1-month old affected mice showed hearing loss to the point of deafness compared with normal hearing sibling controls. One 10-week old female mutant was found to have otitis, one 32-week old female mutant was found to have mild osteoarthritis in the knees and spine with emphysema, and another 32-week-old female was found to have bronchiolitis obliterans organizing pneumonia with many macrophages in the lung and a slight loss of Purkinje cells. Eye examinations of one male and one female mutant and one male and one female control from the same litter had a possible finding of a cataract from a corneal hole in both males but not the females, so no mutation-associated eye defect can be reported. Screening of additional mutants at 8, 9, 10, and 11 weeks of age found no other lesions.

Discussion

We report a spontaneous mutation that has skeletal deformities and deafness similar to those reported for *Fgfr3* targeted mutants, and a map position consistent with being an allele of *Fgfr3*. Allele tests confirmed that this is an *Fgfr3* mutant and this new mutation has been named fibroblast growth factor receptor 3, mutation 1 Jackson. *Fgfr3*^{m1J} homozygotes routinely live longer than three weeks, whereas several other targeted mutations of *Fgfr3*, including *Fgfr3*^{tm1Dor}, *Fgfr3*^{tm1Llm}, and *Fgfr3*^{tm1Led}, result in a high rate of premature lethality. This difference may be due to the predominantly BALB/cByJ background or to the molecular basis of this mutation, which may be a hypomorph instead of a null allele.

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