Sox10<M2J>, A Point Mutation Causing White Spotting

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Mutation (allele) symbol: *Sox10*^{M2J}

Mutation (allele) name: mutation 2 Jackson

Strain of Origin: B6Ei.Cg-*Nr0b1*^{tm1Lja} Tg(Sry)2Ei Chr Y^{AKR}/Ei

Current Strain name: B6Ei.Cg-*Sox10*^{M2J}/GrsrJ

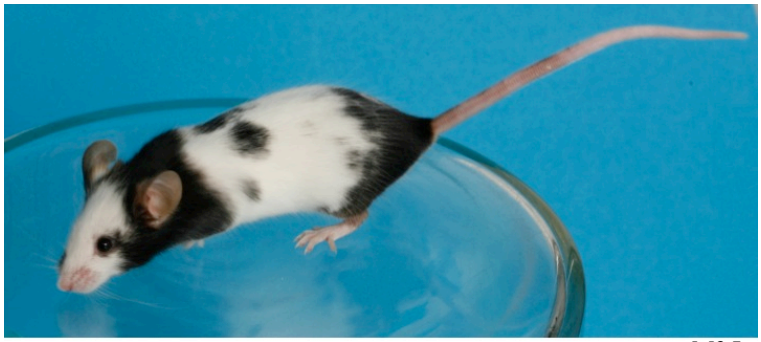
Stock #012857 (jaxmice.jax.org)

Phenotype categories: pigmentation

Abstract

A dominant mutation that causes a white spotting phenotype resembling piebald spotting was identified as a point mutation within the SRY-box containing gene 10 (*Sox10*). *Sox10*^{M2J} heterozygous mice phenotypically resemble mice carrying the *Sox10* mutation dalmation (*Sox10*^{Dal}) and the two mutations are hypothesized to code for identical proteins, with identical amino acid substitutions. Heterozygous *Sox10*^{M2J} mice do not develop megacolon, a condition associated with the dominant megacolon (*Sox10*^{Dom}) allele of *Sox10* and some of the *Sox10* targeted null mutations.

Origin and Description



Sox10^{M2J} heterozygote

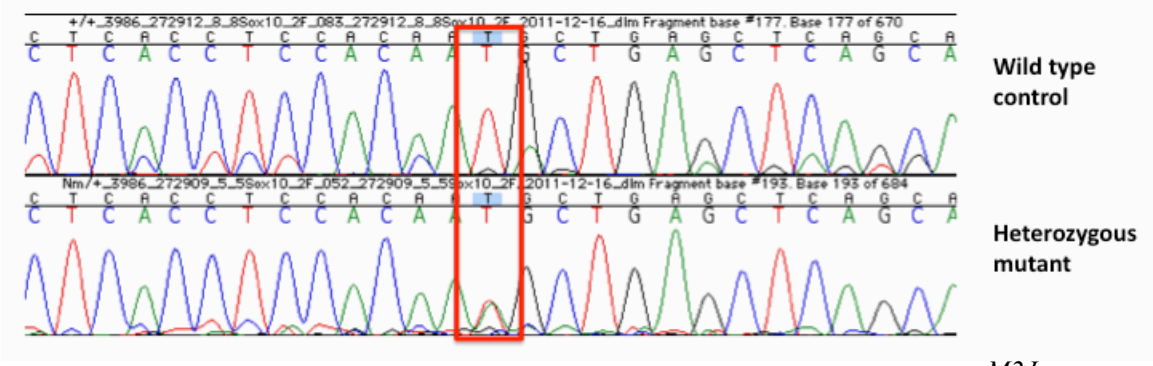
In 2007 a dominant mutation, now symbolized *Sox10*^{M2J}, was identified in a B6Ei.Cg-*Nr0b1*^{tm1Lja} Tg(Sry)2Ei Chr Y^{AKR}/Ei (Stock #006305) mouse. *Sox10*^{M2J} causes a white piebald-like spotted coat, white feet, white vibrissae in regions of the face lacking pigmentation, and variable white regions on the tail. Heterozygote *Sox10*^{M2J} mice have a normal lifespan and are fertile. (A 3 month-old mutant female developed a dilated uterus and loosely organized stroma in an ovary lacking corpora lutea. Whether these abnormalities are related to *Sox10*^{M2J} is unknown.) The *Nr0b1*^{tm1Lja} and Tg(Sry)2Ei

mutations together with the AKR Y chromosome were eliminated from the *Sox10*^{M2J} breeding colony using three rounds of backcrossing to C57BL/6Ei (Stock #000924).

Genetic Analysis

The mode of inheritance of the new mutation was established by mating a mutant female to a normal CAST/EiJ male. Both normal and affected F1 progeny were recovered, indicating that the mutation is inherited as a dominant or semi-dominant. To ascertain whether homozygous mutant mice are viable, six matings were established between heterozygotes. Of the 98 mutant progeny (39 females, 59 males) recovered out of a total of 137 progeny, none displayed a phenotype that differed from their heterozygous parents. Although we did not verify homozygotes by genotyping, because we had not yet identified the molecular lesion, the 71.5% mutant progeny is closer to 75% than the 66.6% expected if homozygotes were non-viable, suggesting that homozygous mutants are viable and their phenotype is similar to the heterozygote.

To determine the chromosomal location of the mutation heterozygous mutant F1 females (produced by mating C57BL/6JEiJ mutant females to CAST/EiJ males) were mated to C57BL/6JEiJ males. DNA was isolated from affected offspring and a linkage assignment was determined using standard SNP mapping procedures. The mutation was mapped to a 20.8 MB Chromosome 15 segment located between *D15Mit29* (74.0 Mb) and *D15Mit76* (94.8 Mb). Whole exome sequencing[1] was used to identify candidate coding mutations in the mapped region. A single nucleotide variant (SNV) was found on Chromosome 15 in the SRY-box containing gene 10 (*Sox10*). Primers were generated that produce a 695 base pair product spanning the predicted mutation: *Sox10* forward (GGTCAAGAAGGAACAGCAGG) and *Sox10* reverse (CTCTCTCCCAAAGTTTCCCC). Sanger sequence analysis of genomic DNA samples from 4 normal and 4 heterozygous mice confirmed the presence of a single nucleotide transition from T to A at position 78,993,754 (NCBI build 37), which is in exon 2 of *Sox10*. This missense mutation results in the replacement of asparagine with lysine at residue 131 of the 466 amino acid protein (N131K). Interestingly, the ENU-induced mutation dalmatian (*Sox10*^{Dal}) is a T to G transversion at this exact position, resulting in this same expected amino acid change.



Comparison of sequence chromatograms from a wild-type control and *Sox10*^{M2J} heterozygous sample

Pathology

The *Sox10* dominant megacolon (*Dom*) allele as well as some targeted *Sox10* null alleles (e.g. Sox $Sox10^{tm2(rTA)Weg}$ heterozygotes and $Sox10^{tm4Weg}$ homozygotes) cause megacolon due to a deficiency in myenteric ganglion cells enervating the colon, resulting in death in a proportion of heterozygotes. Although neither $Sox10^{Dal}$ or $Sox10^{M2J}$ heterozygotes were examined for megacolon, no heterozygotes for either allele have a reduced lifespan, suggesting that megacolon is missing or a rare event in these mutant mice. We propose that the amino acid change caused by these two mutations is sufficient to cause a reduction in neural crest cell predecessors of pigment cells but not the nerves that enervate the colon. A routine pathological screening identified no significant gut lesions in the 12 week-old mutant examined. In addition, hearing, using auditory brainstem response testing (ABR), and vision, using ophthalmoscopy, were examined on an additional 12 week-old mutant and hearing and eye sight were normal. (A sibling control was used in all three tests.)

Acknowledgements

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[1]The exome sequencing data referred to in this website were analyzed using tools and workflows provided by Genome Quest including processes for mapping (HS3), SNP calling and annotation of variants. Our analysis focused on novel variants, which were not positioned in repetitive sequence, had expected allele ratios (>0.95 for homozygous variants and >0.2 for heterozygous variants), and displayed sufficient locus coverage (at least 5X for homozygous variants and 10X for heterozygous variants) for effective mutation discovery. High priority was given to protein coding or splice variants within mapped regions, as well as unique variants that were not found in other exome data sets or in the Sanger Mouse Genomes Database. Following these analyses, re-sequencing of additional mutant and unaffected samples was performed to validate and determine the most likely causative mutation.