BALB/cNctr-Npc1<sup>m1N</sup>/J

Stock No: 003092 | Niemann type C1 NIH

Spontaneous Mutation

Also Known As: np<n> c<sup>nih</sup>, Niemann Pick type C1 NIH

This strain provides a broadly used model for severe infantile Niemann Pick Type C1, but unlike human NPC1, no neurofibrillary tangles are found. This null allele has a slightly later onset and decreased severity on this BALB background relative to homozygotes on a C57BL/6 congenic background or homozygotes for the Npc<sup>1<sup>58<sup>tm</sup></sup></sup> allele on a C57BLKS/J background, but this model is more severe than the C57BL/6J-Npc<sup>1<sup>116<sub>tm</sub></sup></sup>/J model.

GENETIC OVERVIEW

<table>
<thead>
<tr>
<th>Genetic Background</th>
<th>Generation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>?&lt;sup&gt;+&lt;/sup&gt;F&lt;sub&gt;46&lt;/sub&gt;</td>
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<td>(2018-11-30 00:00:00)</td>
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Npc<sup>1m1N</sup>

<table>
<thead>
<tr>
<th>Allele Type</th>
<th>Gene Symbol</th>
<th>Gene Name</th>
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<tbody>
<tr>
<td>Spontaneous</td>
<td>Npc1</td>
<td>NPC intracellular cholesterol transporter 1</td>
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</table>

RESEARCH APPLICATIONS

Mouse/Human Gene Homologs
Neurobiology Research
Sensorineural Research
Reproductive Biology Research
Metabolism Research
Internal/Organ Research
Cardiovascular Research
Immunology, Inflammation and Autoimmunity Research
NPC1 is a transmembrane protein with a sterol-sensing domain that is essential for intracellular transport of unesterified cholesterol out of the endolysosomal compartment to the cytosol. It is primarily localized to late endosomes and lysosomes, but also cycles through the Golgi apparatus. Defects in this gene cause Niemann-Pick Disease Type 1C, in which failed lipid metabolism leads to accumulation of cholesterol and fatty acids in all tissues, with pronounced consequences in spleen, liver, lungs, lymph nodes, thymus, bone marrow and brain. Mice homozygous for the spontaneous Npc1<sup>m1N</sup> mutation on the BALB/cNctr background have neuronal accumulation of unesterified cholesterol and gangliosides by birth, develop axonal spheroids beginning at approximately 3 weeks of age, progressive weight loss, progressive cerebellar ataxia with onset beginning at approximately 6 weeks of age, microgliosis, and neurodegeneration that is pronounced in the thalamus and Purkinje cells. Purkinje cells show progressive, patterned degeneration from rostral to caudal beginning with zebrin II negative Purkinje cells. Cerebellar sections showed a normal number of Purkinje cells at 30 days of age, by 50 days most were gone from lobules I-III, and by 70 days they only remained in lobule X, but Bergman glia, oligodendrocytes, and granules cells remained intact in all lobules at 70 days of age (Ko et al., 2005). By 40 days of age the brains of homozygotes are significantly smaller than normal. The average reported lifespan is approximately 9-11 weeks. Loss of glia in the corpus callosum precedes the loss of Purkinje cells, and neuroinflammation in BALB/cNctr-Npc1<sup>m1N</sup>/J homozygotes involves atypical microglia (Cougnotx et al., 2018) that are present by 9 days of age and in significant numbers by 22 days of age (Reid et al., 2004). Hypomyelination of the corpus callosum, anterior commissure, and cerebral cortex is found by 10 days of age and progresses, although the optic tract, brainstem, cerebellar white matter, external capsule and optic nerves remain well myelinated. Although premyelinating oligodendrocytes are plentiful at 10 days of age, there is a significant diminution in mature oligodendrocytes at 20 days of age (Takikita et al., 2004). Hyperphosphorylation of tau was found in extracts from BALB/cNctr-Npc1<sup>m1N</sup>/J homozygous cerebrum and cerebellum, but no neurofibrillary tangles were detected (Treiber-Held et al., 2003). Hovakimyan et al. (2013) found highly disrupted olfactory epithelium, abnormal olfactory nerve morphology, increased activated microglia in the olfactory epithelium, loss of olfactory neurons and impaired olfactory response to phenylethyl alcohol, hydrogen sulfide, and carbon dioxide in homozygotes by 10 weeks of age, with less severe changes already evident by 35 days of age. Mitochondrial membrane potential and ATP level are lower than normal in tissues from homozygotes, and the mitochondria of the brain are smaller and more rounded than normal with translucent matrices and irregular cristae. Addition of ATP to culture medium allows the neurite extension and sprouting that is normally diminished in neurons from homozygotes, indicating that the deterioration of neurite outgrowth in homozygous brains stems from inadequate ATP (Yu et al., 2005).

Non-neuronal tissues are also severely affected resulting in hepatosplenomegaly, micronodularity and increased mass of the lungs, and reproductive defects. Histology of the lung of homozygotes on a BALB/c background at 70 days of age found thickened intra-alveolar septae, enlarged lamellar bodies in type II pneumocytes, accumulation of surfactant with increased phospholipid and cholesterol content, and clusters of large foamy alveolar macrophages and vacuolar-filled leukocytes (Roszell et al., 2013). Npc1<sup>m1N</sup> homozygous females are infertile, with underdeveloped ovarian follicles, but transplanting ovaries from homozygotes to wild-type hosts permits ovulation and formation of corpora lutea (Gevry et al., 2004). On this BALB background homozygous males are also infertile and fail to fertilize even zona-free eggs in IVF (Fan et al., 2006), although males on a mixed BALB x 129 background are reportedly fertile (Erickson et al., 2002). Npc1<sup>m1N</sup>+/+ heterozygotes on this BALB/cNctr background have also been found to display elevated cholesterol levels and decreased ATP in the cerebral and cerebellum, loss of 25-30% of Purkinje cells, and hyperphosphorylation of tau all in very old mice, 104-106 weeks of age, but not at 24 or 40 weeks of age (Yu et al., 2005). This model of the Niemann-Pick Type C1 lysosomal storage disease is an early onset model that is more severe than the Npc1<sup>m164</sup> model but less severe than when this Npc1<sup>m1N</sup> allele is backcrossed to congenicity onto the C57BL/6 background. Metabolomic profiles from liver extracts of homozygotes at 49 days of age showed a more significant increase in accumulation of ceramides,
sphingomyelins, sphingoid bases, gangliosides, free cholesterol, and oxysterols on the congenic C57BL/6J background relative to homozygotes on a BALB/c background. The impact of genetic background was less severe in brain metabolite profiles in which congenic C57BL/6J homozygotes accumulate more ceramide, lactosylceramide, and 3B,5a,6B-cholestan-triol compared with homozygotes on the BALB/c background (Praggastis et al., 2015). Axonal spheroids are highly concentrated in the fimbria on the C57BL/6J congenic background (Walkley and Suzuki, 2004). The Npc1m1N allele is a null allele; Western blot of liver extracts from homozygotes at 30 and 75 days of age failed to detect NPC1 protein, whereas small amounts of NPC1 were identified in Npc1nmtm164 homozygotes at each timepoint assessed between 30 and 120 days of age (Maue et al., 2011). Purkinje cell loss at 6 weeks of age in Npc1m1N homozygotes was reported to be equivalent to the loss found at 9 weeks of age in Npc1nmtm164 homozygotes (Maue et al., 2011) and the demyelination phenotype is less severe in Npc1nmtm164 homozygotes. Npc1nmtm164 homozygotes have bred before becoming debilitated, but Npc1m1N must be maintained from heterozygous breeders. The C57BLKS/J-Npc1nmtm164/J model displays a faster, more severe Purkinje cell loss than do these Npc1m1N homozygotes on the BALB/c background, but survive approximately 15 days longer than this model (Sarna et al., 2003).

Development

Control Suggestions

Genetics

Npc1m1N

Disease/Phenotype

Disease Terms

Research Areas By Genotype

Mammalian Phenotype Terms by Genotype

References

Technical Support

CONTACT TECHNICAL SUPPORT

Genotyping Protocols
Separated PCR: Npc1m1N
Separated MCA: Npc1
High Resolution Melting: Npc1m1N Alternate1
Genotyping resources and troubleshooting

Dietary Information
LabDiet® 5k52 formulation (6% fat)

Breeding Considerations
When maintaining a live colony, heterozygous mice may be intercrossed or bred to wildtype siblings. Homozygotes are sterile.
Additional Breeding and Husbandry Support
Mating System
++ sibling x Heterozygote

Appearance
albino, ataxic, tremors
Related Genotype: a/a Tyrp1^b/Tyrp1^b Tyr^c/Tyr^c Npc1^m1N/Npc1^m1N

albino, unaffected
Related Genotype: a/a Tyrp1^b/Tyrp1^b Tyr^c/Tyr^c Npc1^m1N/+ or +/+ 

Citation
When using the Niemann Pick Type C1 NIH mouse strain in a publication, please cite the originating article(s) and include JAX stock #003092 in your Materials and Methods section.
Facility Barrier Level Descriptions
FGB29 (Standard)

Pricing & Availability

3–6 week lead time for most orders depending on quantity and age range requested

Repository Live

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<th>International</th>
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<td>Pricing effective for USA, Canada and Mexico shipping destinations</td>
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### Live Mouse

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<th>GENOTYPE</th>
<th>PRICE</th>
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<td>Approx 4-8 weeks</td>
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<td></td>
<td>Male</td>
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### Breeder Pair

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Related Products and Services

| Frozen Mouse Embryo | $2,595.00 per straw or vial |

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Email: TechTran@jax.org

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- By Gene
- By Collection

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