MUTATIONS OF Ntrk2, Megf8 and Islr2 IN MOUSE MODELS

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Technology description

Invention novelty: This tangible material includes a mutant strain of mice produced by inducing chemical mutations of Ntrk2, Megf8 and Islr2 mutations in mouse models.

Value Proposition

023046 B6.129S6(Cg)-Ntrk $^{2tm2.1Ddg}$ /J

025417 STOCK Megf8 $^{tm1.2Ddg}$ /J

025418 C3;B6-Megf8 ^{m687Ddg} /J

025615 STOCK Islr2 $^{tm2.1Ddg}$ /J

027214 B6.129S6(Cg)-Ntrk2 $^{tm3.1(cre/ERT2)Ddg}$ /J

Technical Details

Johns Hopkins researchers have developed various strains of mice by chemically induced mutations of Ntrk2, Megf8, and Islr2 in mouse models. They are as follows:

023046 B6.129S6(Cg)-Ntrk $^{2tm2.1Ddg}$ /J

Ntrk2 (neurotrophic tyrosine kinase, receptor, type 2; also called TrkB) is a receptor for neurotrophin 4 (now called neurotrophin 5, Ntf5) and brain derived neurotrophic factor (Bdnf).

A tau-enhanced EGFP cassette was inserted into the first coding exon of Ntrk2 in this targeted mutant strain. Approximately 7% of adult thoracic dorsal route ganglion neurons express EGFP. These neurons have medium-diameter somata and exhibit properties Aδ-low-threshold mechanoreceptors (LTMRs): mechanical sensitivity, rapidly adapting responses to supra threshold stimuli, intermediate conduction velocities, and narrow uninflected somal spikes. The neurons form longitudinal lanceolate endings associated with zigzag and awl/auchene hair follicles. Homozygotes are neonatal lethal, consistent with it being a null allele.

025417 STOCK Megf8 $^{tm1.2Ddg/}$ J

Megf8 (multiple EGF-like-domains 8) is widely expressed during early embryonic development with strong expression in the somites, limb buds, primordial gut, developing eye, and pharyngeal arches. Throughout embryogenesis and into the postnatal period, MEGF8 is present in the sensory neurons of the dorsal root ganglion and trigeminal ganglion, as well as the central nervous system including the developing neuroepithelium, postnatal hippocampus, layer 4/5 of the cortex and the olfactory bulb. Megf8 has been identified as a novel modifier of BMP4 (bone morphogenetic protein 4) signaling in

trigeminal ganglion (TG) neurons. TG axon growth is robustly inhibited by BMP4, and this inhibition is dependent on MEGF8 expression.
The last exon of Megf8 is flanked by loxP sites in this conditional mutant strain. Cre excision of the floxed region creates a knockout of the gene. Loss of MEGF8 disrupts axon guidance in the peripheral nervous system and leads to defects in development of the limb, heart, and left-right patterning.
025418 C3;B6-Megf8 ^{m687Ddg} /J
This mutant strain carries a chemically-induced loss-of-function L1775P (leucine to proline) mutation of the mouse Megf8 gene. Heterozygotes are viable and fertile with no overt phenotype, but homozygotes die by embryonic day 16.5 (E16.5). The mutation leads to pre-axial polydactyly, skeletal defects, disruption of left-right patterning, and severe heart defects. Homozygous embryos exhibit severe defasciculation of the ophthalmic branch of the trigeminal nerve, have a split sternum and show delayed ossification of the rib cage. Complete left-right inversion of heart looping is also seen.
025615 STOCK Islr2 $^{tm2.1Ddg}$ /J
Islr2 (immunoglobulin superfamily containing leucine-rich repeat 2; also called Linx) is expressed in the peripheral nervous system, prethalamus, lateral ganglionic eminence-derived corridor, corticofugal axons and elsewhere. It binds to thalamocortical projections and promotes their outgrowth guiding them in the ventral forebrain and mediating reciprocal interactions between ascending thalamocortical and descending corticofugal axons in the internal capsule (IC) region.
A portion of exon 3 of the mouse Islr2 gene is flanked by loxP sites in this conditional mutant strain. Cre-mediated excision of the floxed region results in a knockout allele. Mice deficient in this transmembrane protein exhibit a complete absence of the internal capsule (IC).
027214 B6.129S6(Cg)-Ntrk2 $^{tm3.1(cre/ERT2)Ddg}$ /J
These TrkBCreER mutant mice express Cre-ERT2 (Cre recombinase fused to a mutant form of the human estrogen receptor ligand binding domain) from the mouse Ntrk2 promoter. Endogenous NTRK2 expression is knocked out. Treatment with synthetic estrogen receptor 4-hydroxytamoxifen (OHT) enables the Cre fusion protein to access the nuclear compartment for directed excision of floxed sequences bred into this strain.
No overt phenotype is observed in TrkB ^{CreER} heterozygotes. Homozygotes are not viable. Expression of Cre is consistent with that of Ntrk2 expression.
When progeny from a cross with Rosa26 $^{LSL-tdTomato}$ mice (see Jax Stock No. 007909) are treated with a single injection of OHT during embryonic development, excision of a floxed Stop enables constitutive tdTomato labeling of medium diameter, Ntrk2-expressing dorsal root ganglion neurons of adult mice.
Data Availability: Animal data
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