THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

PTEN-INDUCED KINASE 1 (PINK1)

Mutations in the *PTEN-induced kinase 1 (PINK1)* gene cause autosomal recessive, young onset Parkinson's disease (PD). The PD-linked mutations in *PINK1* lead to loss of expression/function of the PINK1 protein, which is a kinase that localizes to mitochondria and phosphorylates ubiquitin and Parkin. PINK1 has been shown to function in mitophagy and in restraining immune responses. Preclinical models for PINK1-linked PD are based on reducing or eliminating the activity of the PINK1 protein, either through genetic knockout or knockin of loss-of-function mutations. Below are commonly used animal models of PD linked to PINK1 mutations. Please note, this list is by no means comprehensive.

PINK1 KNOCKOUT (EXONS 4-7) MOUSE

- Description: Although a number of PINK1 KO mouse lines have been generated, the most commonly used model was developed by the Shen lab. Although this line does not display nigral neuron loss and striatal dopamine and dopamine metabolites do not appear altered, evoked dopamine release and striatal synaptic plasticity are altered. Motor phenotypes were reported at 3-6 months in spontaneous locomotion and 4-6 months in vocalizations. Inflammation may be impacted in this model, as mitochondrial stress increased serum cytokines abnormally.
- Recommended Use: This model is recommended for researchers that want to study the effects of PINK1 loss when absence of the protein is acceptable. It is suitable for biological studies and studies intervening to replace or circumvent loss of PINK1, or studies looking at how loss of PINK1 can affect inflammation.
- Helpful Resources:
  - Summary of line phenotypes: https://www.alzforum.org/research-models/pink1-ko-mouse
  - Commercial availability – This line is available at JAX (ID 017946).

PINK1 KNOCKOUT (EXON 4) RAT

- Description: A rat model is available in which a deletion in exon 4 of the *PINK1* gene results in PINK1 disruption in Long Evans rats. This model displays progressive loss of nigral dopaminergic neurons, with 25% loss at 6 months and 50% loss at 8 months. However, striatal terminals appear intact at these ages. Striatal dopamine changes have been reported at 8 months of age, but there have been conflicting reports of the direction of change with some showing an increase and others showing a decrease. Mitochondrial function is impaired starting at 4 months of age. Synuclein aggregates are present in multiple brain regions of the model beginning at 4 months of age. Motor deficits are present. This includes vocalization and swallowing deficits at 2 months of age with brainstem pathology in addition to with deficits in the beam test at 5 weeks, hindlimb deficits starting at 2 months, and decreased open field mobility at 4+ months of age.
- Recommended Use: This model is recommended for researchers that want to study the effects of PINK1 loss when absence of the protein is acceptable. It is suitable for biological studies and studies intervening to replace or circumvent loss of PINK1. It is also a good model for efficacy studies given the nigral cell loss, motor deficits, and synuclein pathology resulting from PINK1 knockout.
- Helpful Resources:
  - Summary of line phenotypes - https://www.alzforum.org/research-models/pink1-ko-rat
  - Review of the model - https://www.sciencedirect.com/science/article/abs/pii/S0891584920316671
  - Commercial availability – This line is available at Envigo (breeding license required).

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	α-Synuclein Pathology	Inflammation	Motor Impairments	Cognitive Impairments

PINK1 G309D KI MOUSE

- Description: The G309D mutation is a disease-linked mutation that causes incorrect splicing and instability of PINK1, resulting in loss of protein (the homozygous line expresses a 97% reduction in PINK1 protein in the brain). While dopamine concentration is decreased in the striatum starting at 9 months of age, there is no loss of nigral dopamine neurons in this model (analyzed up to 18 months of age). Spontaneous locomotor activity is decreased at 16 months of age. By 3 months of age, mitochondrial import is affected and increases in severity with age. At 6 months of age, mitochondrial respiration, ATP production and membrane potential are also reduced. Total synuclein levels appear to be increased in the model but pS129 aSyn and Lewy body pathology are absent. There is some evidence of inflammation in the line at 18 months of age.
- Recommended Use: This model is recommended for researchers that want to use a mouse model with a disease-linked mutation in the PINK1 protein leading to functional knockout. The model is useful for studies looking at interventions to address the mitochondrial dysfunction that occurs with loss of PINK1.
- Helpful Resources:
  - Summary of line phenotype - https://www.alzforum.org/research-models/pink1-g309d-pink1-mouse-ki
  - Commercial availability – This line is currently available at JAX (ID 013050).

PARKIN/PINK1 DOUBLE KNOCKOUT RAT

- Description: A double knockout rat line was generated by crossing the Parkin knockout rat and PINK1 knockout rat models from Envigo. This double knockout rat displays striatal mitochondrial dysfunction at 3 months of age, with changes in maximal respiration and respiratory capacity. Starting at 6 months of age, the line exhibits a reduction in nigral dopamine neurons that progresses with age. Motor dysfunction is present at 6+ months of age, with deficits in rotrod, pole test, and hindlimb strength. Gait abnormalities are also present at 8 months of age.
- Recommended Use: This model is recommended for researchers that want to study the effects of PINK1/Parkin loss when absence of the protein is acceptable. As phenotypes of this line are more aggressive than the single knockout rat models, groups may be interested in this model for early mitochondrial dysfunction, nigrostriatal degeneration, and/or behavioral readouts.
- Helpful Resources:
  - Publication of phenotypes: https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.2020.34.s1.03409
  - Commercial availability – This line is available at Envigo (breeding license not required).

PINK1-ASYN COMBINATION MODELS

- To study the relationship between PINK1 and alpha-synuclein (aSyn), groups have combined different PINK1 models with synuclein models. The following are examples of such work (titles provide hyperlink to example publication):
  - PINK1 Knockout Rat + aSyn PFFs – Injection of aSyn preformed fibrils (PFFs) into the PINK1 KO rat striatum results in increased midbrain aSyn pathology at 4 weeks post-injection with accompanying loss of dopaminergic neurons in the substantia nigra (but no increase in striatal dopamine fiber denervation).
  - PINK1 G309D KI mouse x PrP Human A53T aSyn mouse – This double mutant line displays strong motor phenotypes, with decreased spontaneous movements at 3 months of age and progressive paralysis at 12+ months. Synuclein pathology is observed in the spinal cord and midbrain at 15-17 months and increased synuclein ubiquitination is observed at 18 months. This line is available at JAX (ID 017678).
  - PINK1 KO Mouse + AAV aSyn – Compared to WT mice, PINK1 KO mice have greater loss of nigral dopaminergic neurons and greater number of phosphorylated aSyn aggregates in the substantia nigra 4 weeks post-injection of AAV-aSyn.

ICON KEY

Protein Expression Level			Protein/Gene Species		Mutation	Pathology				
Endogenous Expression	Over-expression	Knockout	Human	Rodent	Mutant	Nigrostriatal Degeneration	α-Synuclein Pathology	Inflammation	Motor Impairments	Cognitive Impairments