THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

PARKIN

Mutations in the *parkin* gene cause autosomal recessive, young onset Parkinson's disease (PD). The PD-linked mutations in *parkin* lead to loss of expression/function of the Parkin protein, an E3 ubiquitin-ligase with roles in protein turnover and mitochondrial function. Preclinical models for PD focus on reducing or eliminating the activity of the Parkin protein, either through genetic knockout or loss-of-function mutations. Below you will find a list of those that are commonly used. Please note, this list is by no means comprehensive.

PARKIN KNOCKOUT (EXON 3) MOUSE

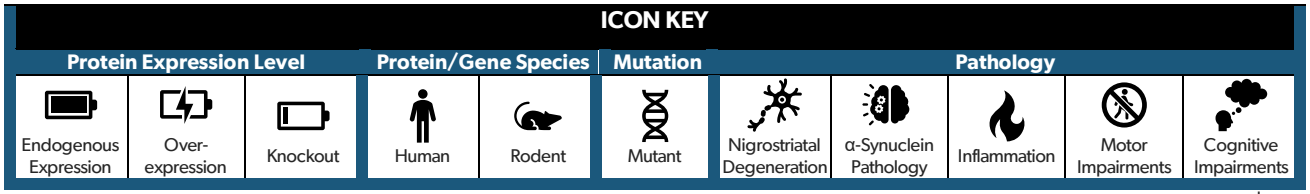
- Description: Although a number of Parkin KO mouse lines have been generated, the most commonly used model was developed by the Shen lab. Although this line does not display nigral neuron loss and striatal dopamine and dopamine metabolites do not appear altered, extracellular striatal dopamine is increased at ~9 months of age and motor phenotypes were reported (although there have been issues in replicating these behavioral phenotypes). No synuclein pathology is observed in Parkin knockout mice. Learning and memory are affected in this model.
- Recommended Use: This model is recommended for researchers that want to study the effects of Parkin loss when absence of the protein is acceptable. It is suitable for biological studies and studies intervening to replace or circumvent loss of Parkin.
- Helpful Resources:
  - Summary of line phenotypes: https://www.neurodegenerationresearch.eu/models-for-parkinsons-disease/in-vivo-mammalian-models/parkin/parkin-koex3-mouse/
  - Commercial availability – This line is available at JAX (ID 006582).

FLOXED PARKIN KNOCKOUT MOUSE

- Description: A conditional knockout model was developed by the Dawson lab in which the Parkin gene with a floxed exon 7 can be knocked out through injection of a Cre-expressing viral vector or crossing with Cre transgenic mice. This allows temporal/spatial restriction of Parkin knockout. Injection of a lentivirus expressing Cre into the ventral midbrain at 2 months of age results in nigral neuron loss in addition to decreased mitochondria size, numbers, and biogenesis 9 months post-injection. Inflammation has also been reported in this model.
- Recommended Use: This model is recommended for researchers that want to study the effects of Parkin protein loss restricted to a specific tissue/cell type (or to avoid developmental compensation from constitutive Parkin knockout).
- Helpful Resources:
  - Initial characterization of the line - https://www.pnas.org/doi/epdf/10.1073/pnas.1500624112
  - Commercial availability – This line is currently being transferred to Taconic for distribution (expected early 2024).

PARKIN KNOCKOUT (EXON 4) RAT

- Description: A rat model is available in which a deletion in exon 4 of the *Parkin* gene results in Parkin knockout in Long Evans rats. This model does not exhibit significant loss of nigral dopamine neurons or striatal dopamine neurochemistry deficits up to 8 months of age. Motor phenotypes are not observed in this line. Altered mitochondrial function and protein expression were observed in the striatal synapses in 2-3 month old rats.
- Recommended Use: This model is recommended for researchers that want to study the effects of Parkin loss when absence of the protein is acceptable. It is suitable for biology studies and studies to replace/circumvent Parkin loss.
- Helpful Resources:
  - Summary of line phenotypes - https://www.alzforum.org/research-models/parkin-ko-rat
  - Commercial availability – This line is available at Envigo (breeding license required).



PARKIN Q311X BAC MOUSE

- Description: The Q311X mutation linked to recessively inherited PD results in C-terminal 155 amino acid truncation of Parkin. The hemizygous mouse line expresses low levels of the human Parkin Q311X protein (~40% of endogenous mouse mRNA) with a FLAG epitope tag driven by the mouse dopamine transporter promoter within a 200 kb BAC vector. This results in selective expression in dopaminergic neurons and loss of neurons in the substantia nigra at age 16 months, with loss of striatal dopamine, progressive motor behavior deficits, and alpha-synuclein inclusions in remaining nigral neurons.
- Recommended Use: This model may be useful for studies looking at interventions to address the nigrostriatal degeneration and motor deficits that occur with dominant toxicity of transgene expression in dopaminergic neurons, which does not necessarily reflect the pathogenic mechanisms of PD-linked Parkin mutations.
- Helpful Resources:
  - Summary of line phenotype - https://www.alzforum.org/research-models/parkin-q311x-mouse-bac-tg
  - Characterization of the line - https://pubmed.ncbi.nlm.nih.gov/19228951/
  - Commercial availability – This line is currently available at JAX (ID 009090).

PARKIN S65A KI MOUSE

- Description: The S65A mutation results in the inability of PINK1 to activate Parkin, similar to the S65N mutation causally linked to recessive PD. The homozygous line expresses Parkin at physiological levels but shows decreased ubiquitination of Parkin substrates and phospho-ubiquitin. The model displays motor impairments in the beam task at 12-18 months of age, but not in the rotarod test or gait measures. The nigrostriatal system remains intact, with no loss of dopaminergic neurons or striatal neurochemistry deficits. Mitochondrial respiration is impaired in the striatum at 12 months of age but basal mitophagy is unaltered. Inflammation is not observed.
- Recommended Use: This model is recommended for researchers that want to study the implications of diminished activation of the Parkin E3 ubiquitin ligase or develop therapies that restore/replace this activity. The benefit of this model is that the Parkin protein is still present at physiological levels, making this model ideal for testing therapies seeking to activate Parkin through non-PINK1 mechanisms.
- Helpful Resources:
  - Characterization of the line - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6282074/
  - Commercial availability – This line is currently available at JAX (ID 029247).

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 rotarod, 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).