THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

LEUCINE RICH REPEAT KINASE 2 (LRRK2)

The mutations in the *LRRK2* gene which increase the LRRK2 kinase activity are a common genetic form of Parkinson's disease (PD). The most common mutation is the G2019S mutation which increases kinase activity ~1.5 fold. The R1441C/G mutation increases kinase activity ~4-fold. There are a number of models available to study LRRK2-related mutations/function. Below you will find a list of those that are commonly used. Please note, this list is by no means comprehensive. Good review of models can be found in Seegobin et al 2020 and Xiong, Dawson, & Dawson 2017.

G2019S LRRK2 TRANSGENIC MODEL

- Description: There are many transgenic models available that use human *LRRK2* cDNA under different promoters or BAC to overexpress the mutant transgene. Each line displays different phenotypes/pathology:
  - CMV/PDGFβ Moore/Dawson Mouse line (neuron-specific)– 18% loss of nigral DA neurons at 21 months with some evidence of autophagy abnormalities. No motor deficits.
  - CMV/PDGFβ Chen Mouse line (neuron-specific)– 50% loss of nigral DA neurons at 12-16 months with motor deficits.
  - TH Dawson Mouse line (inducible, DA neuron-specific) – 20-40% nigral DA neuron loss at 15-24 months with late motor deficits in stride length and pole test but not rotarod or open field. NE neuron loss at 24 months
  - PITX3 Cai Mouse line (inducible, DA neuron-specific) – no nigral DA neuron loss or motor deficits.
  - CaMKII Cai Mouse line (inducible, neuron-specific) – no nigral DA neuron loss but increased locomotion at 12 months.
  - BAC Farrer Mouse line – no nigral DA neuron loss or motor deficits, reduced DA release.
  - BAC Li Mouse line - no nigral DA neuron loss or motor deficits, reduced DA release.
  - BAC MJFF Mouse line – no nigral DA neuron loss or motor deficits.
  - Thy1 Herzig Mouse line (neuron-specific) –no nigral DA neuron loss or motor deficits.
  - BAC Wade-Martins Rat line – no nigral DA neuron loss, reduced striatal DA release at 18 months with motor and cognitive phenotypes.
  - BAC Li Rat line – no nigral DA neuron loss but some motor phenotypes reported.
- Recommended Use: A G2019S LRRK2 transgenic mouse/rat model is suitable for studies investigating the human *LRRK2* gene. As phenotypes are driven by LRRK2 overexpression and are generally expression-level dependent, a WT LRRK2 transgenic model should be used as a control.
- Helpful Resources:
  - Commercially available lines are: Moore/Dawson CMV/PDGFβ (JAX #016575), Cai CaMKII (JAX #012441), Farrer BAC (JAX #012446), MJFF BAC (JAX #018785), Li BAC (JAX #009609), Li BAC rat (Taconic #10681), and Wade-Martins BAC rat (RRRC #776).

LRRK2 R1441C/G TRANSGENIC MODEL

- Description: There are many transgenic models available that use human *LRRK2* cDNA under different promotors or BAC to overexpress the mutant transgene. Each line displays different phenotypes/pathology:
  - CMV/PDGFβ Moore/Dawson line (neuron-specific)– conflicting reports of nigral neuron loss at late ages but motor deficits were observed at 15 months.
  - TH Weng line (inducible, DA neuron-specific) – 30% nigral DA neuron loss at 16 months with motor deficits.
  - ROSA26 DAT-Cre Moore line (DA neuron-specific) – No nigral DA neuron loss or motor deficits.
  - BAC Li line - No nigral DA neuron loss but motor deficits at 12 months
  - BAC Wade-Martins Rat line – Minor striatal dopamine deficits at 18 months with motor and cognitive phenotypes. No nigral DA neuron loss.

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

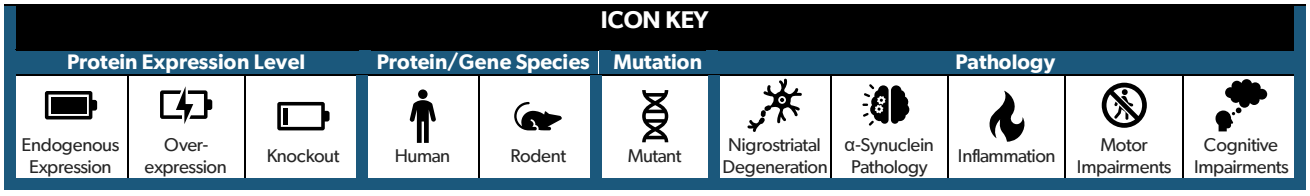
- Recommended Use: R1441C/G LRRK2 transgenic mouse/rat models are suitable for studies investigating the impact of the R1441C/G mutation on human LRRK2. As phenotypes are driven by LRRK2 overexpression and are generally expression-level dependent, a WT LRRK2 transgenic model should be used as a control.
- Helpful Resources:
  - Commercially available lines are: Moore/Dawson CMV/PDGFβ mouse (JAX #016576), Moore ROSA26 DAT-Cre mouse (JAX #022793), Li BAC mouse (JAX #009604), and Wade-Martins BAC rat (RRRC #775).

G2019S/R1441C/G KNOCKIN MOUSE

- Description: A number of G2019S or R1441C/G KI mouse models have been developed. In general, the lines do not display nigral neuron loss or alpha-synuclein pathology. Striatal synaptic dysfunction and motor deficits have been reported to various extents depending on the lines:
  - Eli Lilly G2019S KI Mouse –No nigrostriatal degeneration or motor deficits. Elevation of striatal excitatory transmission.
  - Melrose G2019S KI Mouse – Decreased extracellular dopamine at 12 months, dystrophic mitochondria at 15 months, and increased phospho-tau at 18 months.
  - Herzig G2019S KI Mouse – No nigrostriatal degeneration but increased motor activity reported.
  - Shen R1441C KI Mouse – No nigrostriatal degeneration or motor deficits.
  - Liu R1441G KI Mouse – No nigrostriatal degeneration or motor phenotypes.
  - Giesert R1441C KI Mouse – No nigrostriatal degeneration, synuclein pathology, or tau pathology. Motor and olfactory deficits at 24+ months.
- Recommended Use: LRRK2 mutation knockin mouse models are recommended for researchers interested in the endogenous, physiological function of the mutant LRRK2 protein as these models do not suffer from the overexpression/interspecies artifacts of transgenic lines.
- Helpful Resources:
  - Multiple KI mouse models are commercially available: Eli Lilly G2019S Mouse (Taconic #13940), Melrose G2019S Mouse (JAX #030961), and Shen R1441C Mouse (JAX #009346 and 009347).

LESS COMMON MODELS

- *LRRK2* Knockout Mouse/Rat: This model harbors homozygous knockout of the *LRRK2* gene in either mouse or rat. While not relevant to mutations found in Parkinson's disease patients, *LRRK2* knockout models are used to study the function of endogenous LRRK2 or mimic the potential consequences of loss of LRRK2 kinase activity (relevant to kinase inhibitor studies). Mice and rats with *LRRK2* knockout do not display nigrostriatal degeneration (unless both LRRK1 and LRRK2 are knocked out), do not have robust motor deficits (observed in Farrer line but not Cai line), and do not have consistent synuclein pathology (reported in Shen line only). Pathological changes are observed in the lung and kidney.
  - Numerous LRRK2 knockout lines are commercially available Farrer line (JAX #012444), Shen line (JAX #016209 and #016210), Cai line (JAX #012453), MJFF line (JAX #016121); MJFF rat line (at Envigo)
- WT LRRK2 Transgenic Mouse/Rat: This model involves overexpression of wildtype human LRRK2 through cDNA or BAC transgenic mechanisms. WT LRRK2 transgenic mouse/rat lines do not display nigrostriatal degeneration or motor impairments. These lines are used as controls for G2019S LRRK2 or R1441C/G LRRK2 transgenic models.
  - Numerous WT LRRK2 transgenic lines are commercially available: Cai CaMKII (JAX #012449), Farrer BAC (JAX #012445), MJFF BAC (JAX #013725), Yue BAC (JAX #012466), Li BAC (JAX #009610), Wade-Martins BAC Rat (RRRC #00778).
- Viral Vector-Based Overexpression Models: Some researchers have chosen to use viral vectors to overexpress WT/mutant LRRK2 in a spatially and temporally controlled manner. Injection of a LRRK2-expressing herpes simplex



virus (HSV) or adenovirus (Ad) into the striatum allows retrograde transport of the virus to the nigral cell bodies, resulting in LRRK2 overexpression in the nigrostriatal system without injection-related injury to the nigra. The model generally results in nigrostriatal degeneration with pathogenic LRRK2 mutations.
  - MJFF HdAd5 LRRK2 viral vectors (WT, G2019S, G2385R) are available at the University of Iowa (datasheet here).

DUAL HIT MODELS

- LRRK2 Mutation + aSyn Models: As LRRK2 transgenic/KI models fail to develop alpha-synuclein pathology, some groups have developed combination models on which an alpha-synuclein pathological hit is layered into a transgenic/KI LRRK2 mutant line. Example of such models are as follows:
  - LRRK2 G2019S KI Mouse + AAV2/9 A53T haSyn – Nigrostriatal degeneration, motor deficits, and aSyn pathology occurred and were increased by the G2019S mutation in aged mice.
  - Li LRRK2 G2019S BAC Rat + aSyn PFFs – LRRK2 mutation increased pS129 aSyn pathology without leading to nigrostriatal degeneration at 1 month post-injection.
  - MJFF LRRK2 G2019S BAC Mouse + aSyn PFFs - LRRK2 mutation increased pS129 aSyn pathology and led to greater nigrostriatal degeneration, striatal inflammation, and motor deficits at 6 months post-injection.
  - PrP LRRK2 G2019S Mouse + MPTP (subtoxic 2.5mg/kg dose) – LRRK2 mutation increased nigrostriatal degeneration, astrogliosis, and motor deficits.
  - Herzig LRRK2 G2019S KI mouse + MPTP subacute - LRRK2 mutation increased nigrostriatal degeneration
  - CMV/PDGFβ Moore/Dawson Mouse line + acute MPTP - LRRK2 mutation increased nigrostriatal degeneration
  - AAV2/6 C-terminal G2019S LRRK2 Truncation + AAV2/6 A53T aSyn – Combination of viral vectors produced nigrostriatal degeneration, aSyn pathology, and motor deficits at 15 weeks post-injection.
- LRRK2 Mutation + Pathogen Models: Due to the role of LRRK2 in the immune system and the associations between LRRK2 and infections, some have developed systems in which LRRK2 models are exposed to a variety of bacterial pathogens to study the role of LRRK2 in infection. Some examples are as follows:
  - Herzig G2019S LRRK2 KI Mice + Salmonella – Mutation decreased salmonella infection, increases ROS production, and improves survival times from sepsis.
  - Herzig G2019S LRRK2 KI Mice + Reovirus – Mutation decreased viral load, improved leukocyte recruitment to the brain, increased total aSyn levels resulting from infection, and decreased survival times from encephalitis.
  - MJFF LRRK2 KO Mice + Tuberculosis – LRRK2 KO increases lung neutrophil inflammation at 21 days post-infection but does not affect other readouts of inflammation or decrease survival time.