Published in final edited form as:

Mov Disord. 2018 January ; 33(1): 72. doi:10.1002/mds.27267.

LRRK KO mouse model: linking pathological hallmarks of inherited and sporadic Parkinson's disease

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Autosomal dominant mutations in *LRRK2* underlie the most common cause of familial Parkinson's disease (PD) and have also been associated with sporadic cases [1][2]. However, *LRRK2* mutation knockin and *LRRK2* knockout animal models do not show dopaminergic neurodegeneration or α -synuclein aggregation in the brain, two of the main pathological hallmarks in PD.

To address whether *LRRK1*, the homologue of *LRRK2*, explains the lack of face validity in *LRRK2* animal models by a compensatory mechanism, Giaime et al. generated *LRRK1/LRRK2* double knockout (LRRK DKO) mice[3]. In contrast with *LRRK1/LRRK2* single KO mice, LRRK DKO mice exhibit drastically decreased body weight and unexplained mortality with cataracts at 16 months of age.

From the perspective of PD, the first exciting findings came from neuronal counts in brain areas affected in PD. LRRK DKO mice show a small but significant loss (~22%) of dopaminergic neurons in the substantia nigra pars compacta (SNpc) at 15 months but not younger ages. Loss of both dopaminergic and medium spiny neurons was observed in the striatum at 15 months, whereas the number of neurons in the cerebral cortex and cerebellum remained unaltered. The levels of dopamine and its metabolite DOPAC were also significantly reduced in the striatum. Together, these data suggest a specific, age-dependent neurodegeneration. Interestingly, this neurodegeneration is accompanied by increased apoptotic markers in the SNpc and striatum of LRRK DKO mice.

In addition, the striatum and SNpc of LRRK DKO but not *LRRK1/LRRK2* single KO mice showed increased immunostaining for α -synuclein and western blot analysis revealed increases in monomeric and high-molecular weight α -synuclein in the striatum.

Finally, the autophagic marker p62 was increased in the multiple brain areas. Further electron microscopic structural analysis revealed the presence of autophagic structures in the

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Financial disclosure and conflict of interest:
Nothing to report

SNpc and striatum of LRRK DKO mice. Remarkably, this increase in autophagic structures was observed at 10 months and therefore preceded neurodegeneration, indicating autophagy may contribute early to neurodegeneration.

The LRRK DKO is an exciting model but it has a few limitations. First of all, motor impairments in LRRK DKO mice were not reported and the young mortality of LRRK DKO mice at 16 months may limit investigation of the effects of aging on brain pathophysiology. The precise underlying mechanism of age-dependent dopaminergic neurodegeneration by *LRRK1/LRRK2* deficiency is unknown. In addition, pathogenic *LRRK2* mutations are thought to be gain-of-function mutations, thus, while a knockout model may be enlightening within the context of understanding LRRK biology, the direct relevance of such a model to disease should be interpreted with this opposite mode of action in mind.

References

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