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Long-term pharmacological inhibition of mutant leucine-rich repeat kinase 2 (LRRK2) hyperactivity reduced alpha-synuclein Serine-129 phosphorylation and oligomer levels in mouse brains

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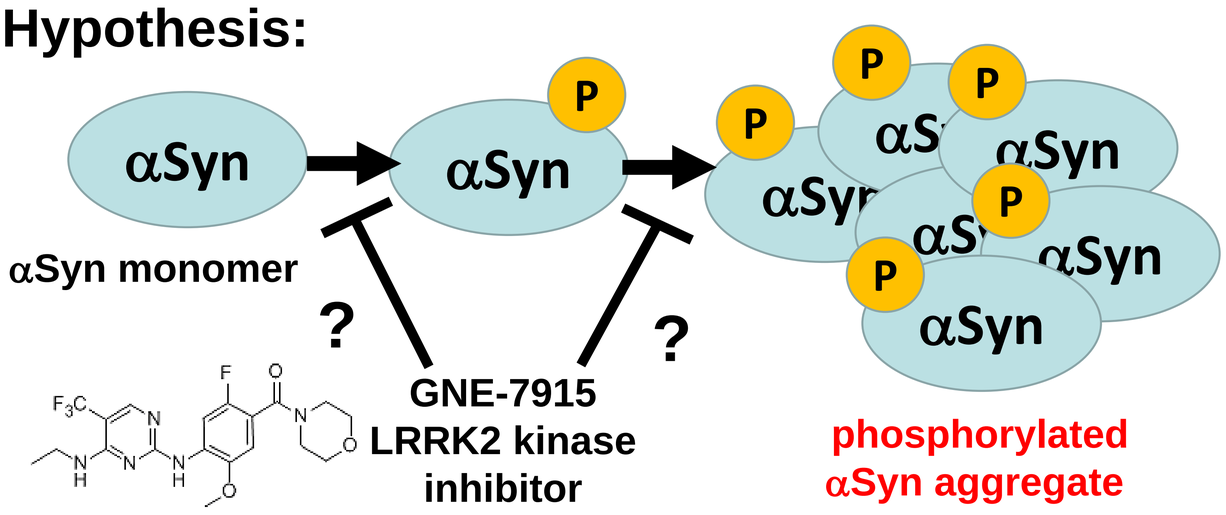
Background

Leucine-rich repeat kinase 2 (LRRK2) mutations which confer genetic risk for Parkinson's disease (PD) shows aberrant hyper-kinase activity. Alpha-synuclein aggregation in form of Lewy body deposits is a pathological hallmark of PD. We previously showed that aged LRRK2^{R1441G} knock-in mutant mice developed more alpha-synuclein aggregates in the brain than the age-matched wild-type controls. The majority of alpha-synuclein in Lewy bodies are phosphorylated at serine-129 (pSer129), and Ser129 phosphorylation is associated with increased alpha-synuclein aggregation. So far, the potential interplay between Ser129 phosphorylation and mutant LRRK2 hyper-kinase activity in PD remains unexplored. Thus, we aim to determine whether long-term administration of a brain-penetrable LRRK2 kinase inhibitor, GNE-7915, can reduce Ser129 phosphorylation and thereby reduce the formation of toxic alpha-synuclein oligomers in the brain of aged LRRK2^{R1441G} knock-in mutant mice.

Hypothesis:



Method:

s.c. injection of GNE-7915 (100mg/kg) or Vehicle

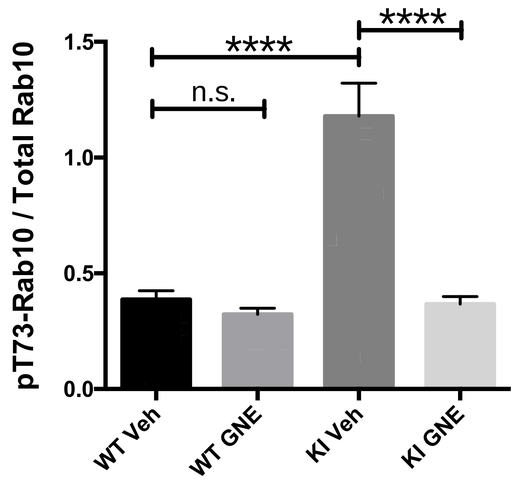
14-months old

Wildtype LRRK2^{R1441G}

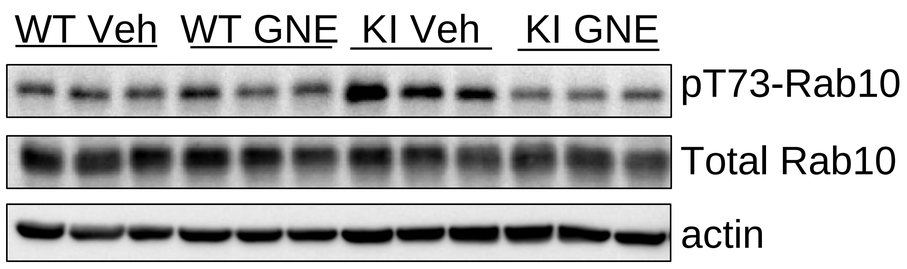
18-weeks

Tissues harvested for analysis: Western blotting & ELISA

Long-term GNE-7915 injection reduced T73-Rab10 phosphorylation level in lung

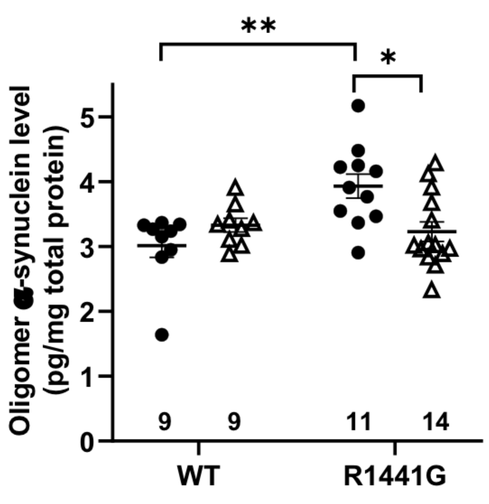


T73-Rab10 phosphorylation is a LRRK2 kinase substrate which was used to confirm the GNE-7915 mediated inhibition of LRRK2 kinase activity

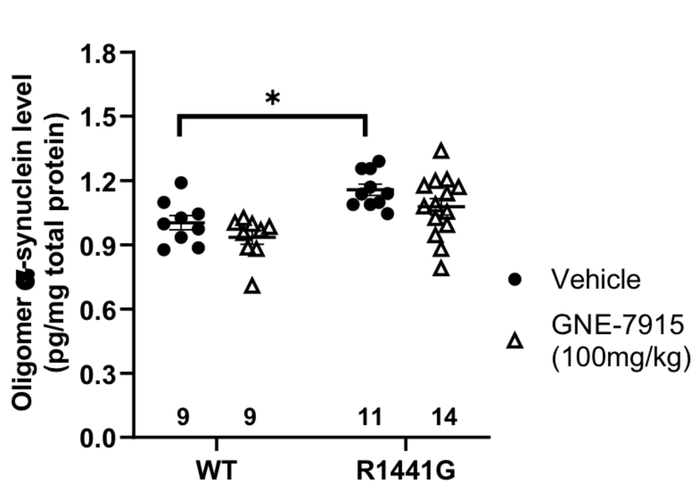


Long-term GNE-7915 injection reduced α-synuclein oligomer levels in brain

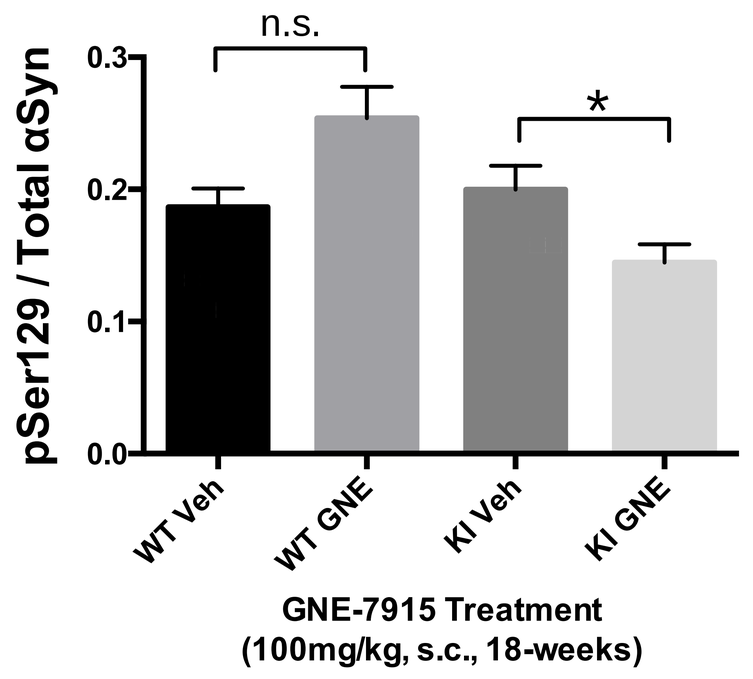
α-synuclein oligomer levels in *Striatum*



α-synuclein oligomer levels in *Cortex*



Long-term GNE-7915 injection reduced pSer129 α-synuclein in Cortex of LRRK2^{R1441G} knock-in mice



Conclusion

18-week subcutaneous injection of GNE-7915 reduced both pSer129 and oligomer levels in brains of LRRK2^{R1441G} mutant mice. These results highlight a potential therapeutic link between LRRK2 kinase inhibition and pSer129 in synucleinopathies of PD.

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