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Parkinson's disease (PD): Mutations in leucine-rich repeat kinase 2

David Boyer Ramsden[1], Philip Wing-Lok Ho[2], Hui-Fang Liu[2], Lingfei Li[2], Matthew Chi-Ting Leung[2], Colin Siu-Chi Lam[2], Shirley Yin-Yu Pang[2], Michelle Hiu-Wai Kung[2] and **Shu-Leong Ho[2]**
[1]University of Birmingham, UK
[2]University of Hong Kong, Hong Kong

Statement of the Problem: Mutations in leucine-rich repeat kinase 2 (LRRK2) are associated with familial and sporadic PD. How LRRK2 interacts with synaptic proteins, and its role in dopamine (DA) homeostasis, synaptic vesicle recycling and α-synuclein catabolism are unclear.

Methods: To explore the pathogenic effects of LRRK2 mutation, we generated C57BL/6N mice with homozygous LRRK2R1441G knock in (KI).

Findings: Although no abnormal phenotype was observed in mutant LRRK2R1441G mice, the KI mutation increased vulnerability to reserpine-induced striatal DA depletion and perturbed DA homeostasis resulting in presynaptic dysfunction and locomotor deficits. Subsequently, we found that mutant primary cortical and mesencephalic dopaminergic neurons were more susceptible to rotenone-induced ATP deficiency. Compared with wild-type controls, striatal synaptosomes isolated from young mutant mice exhibited significantly lower dopamine uptake after rotenone toxicity, due to reduced striatal synaptosomal mitochondria and synaptic vesicular proton pump protein (V-ATPase H) levels. Mutant mice developed greater locomotor deficits in open-field tests than wild-type mice following low oral rotenone doses given twice weekly over 50 weeks (half their lifespan). The increased locomotor deficit was associated with specific reduction in striatal mitochondrial complex-I (NDUFS4) in rotenone-treated mutant mice. Finally, we showed greater age-dependent increases of striatal oligomeric α-synuclein (toxic species) in KI mice compared to wild-type (WT). Given that a significant proportion of cellular α-synuclein is metabolized via lysosomal degradation, such accumulation of its oligomers may be a result of an age-dependent decrease in chaperone-mediated autophagy (CMA) activity associated with impaired assembly/disassembly of multimeric lamp2a translocation complexes.

Conclusion: Enhancement of CMA represents a potential treatment for PD.

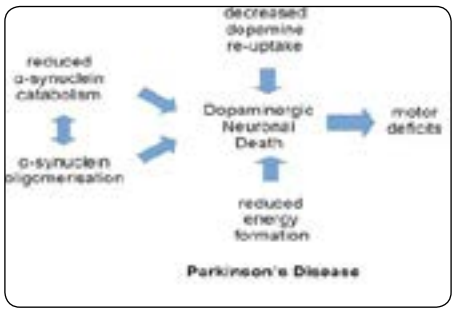

Figure 1: Effects of LRRK2 mutation

Recent Publications

1. Gilks W P, Abou-Sleiman P M, Gandhi S, Jain S, Singleton A, Lees A J, Shaw K, Bhatia K P, Bonifati V, Quinn N P, Lynch J, Healy D G, Holton J L, Revesz T and Wood N W (2005) A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet, 365:415-6.
2. Li J Q, Tan L and Yu J T (2014) The role of the LRRK2 gene in Parkinsonism. Mol Neurodegener 12(9):47.
3. Liu H F, Lu S, Ho P W, Tse H M, Pang S Y, Kung M H, Ho J W, Ramsden D B, Zhou Z J and Ho S L (2014) LRRK2 R1441G mice are more liable to dopamine depletion and locomotor inactivity. Ann Clin Transl Neurol, 1(3):199-208.

4. Liu H F, Ho P W, Leung G C, Lam C S, Pang S Y, Li L, Kung M H, Ramsden D B and Ho S L (2017) Combined LRRK2 mutation, aging and chronic low dose oral rotenone as a model of Parkinson's disease. Sci Rep, 7:40887.
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Biography

David Boyer Ramsden (Honorary Professor), S-L Ho (Professor of Neurology) and PW-L Ho (Assistant Professor) have collaborated for twenty years on the causes, effects and treatment of Parkinson's disease. He got his Ph.D degree in Biochemistry from Bradford University. Currently, he is an Honorary Professor at The Medical School, University of Birmingham. His current researches are based on endocrine disruptors, evolution N-methyltransferases in primates, Parkinsons disease and other. He had 190 publications on a range of topics and 21 chapters in various books.

d.b.ramsden@bham.ac.uk

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