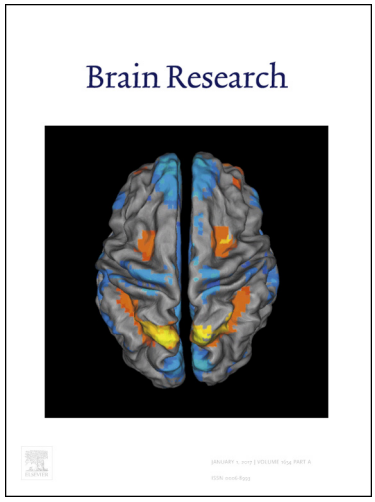

Research report

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Analysis of macroautophagy related proteins in G2019S LRRK2 Parkinson's disease brains with Lewy Body pathology

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Abstract

LRRK2, the gene encoding the multidomain kinase Leucine-Rich Repeat Kinase 2 (LRRK2), has been linked to familial and sporadic forms of Parkinson's disease (PD), as well as cancer, leprosy and Crohn's disease, establishing it as a target for discovery therapeutics. LRRK2 has been associated with a range of cellular processes, however its physiological and pathological functions remain unclear. The most prevalent LRRK2 mutations in PD have been shown to affect macroautophagy in various cellular models while a role in autophagy signalling has been recapitulated *in vivo*. Dysregulation of autophagy has been implicated in PD pathology, and this raises the possibility that differential autophagic activity is relevant to disease progression in PD patients carrying LRRK2 mutations. To examine the relevance of LRRK2 to the regulation of macroautophagy in a disease setting we examined the levels of autophagic markers in the basal ganglia of G2019S LRRK2 PD post-mortem tissue, in comparison to pathology-matched idiopathic PD (iPD), using immunoblotting (IB). Significantly lower levels of p62 and LAMP1 were observed in G2019S LRRK2 PD compared to iPD cases. Similarly, an increase in ULK1 was observed in iPD but was not reflected in G2019S LRRK2 PD cases. Furthermore, examination of p62 by immunohistochemistry (IH) recapitulated a distinct signature for G2019S PD. IH of LAMP1, LC3 and ULK1 broadly correlated with the IB results. Our data from a small but pathologically well-characterized cases highlights a divergence of G2019S PD carriers in terms of autophagic response in alpha-synuclein pathology affected brain regions compared to iPD.

Abbreviations: 5'AMP-activated protein kinase (AMPK); Leucine rich repeat kinase (LRRK2); Lysosomal ssociated membrane protein 1(LAMP1); idiopathic PD (iPD); mammalian target of rapamycin (mTOR); microtubule-associated protein1A/1B light chain 3 (LC3); Parkinson's disease (PD); Post mortem delay (PMD); substantia nigra (s.nigra); Unc like kinase 1(ULK1).