

University of Dundee

## LRRK2 kinase in Parkinson's disease

Alessi, Dario R; Sammler, Esther

*Published in:*  
Science

*DOI:*  
[10.1126/science.aar5683](https://doi.org/10.1126/science.aar5683)

*Publication date:*  
2018

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Alessi, D. R., & Sammler, E. (2018). LRRK2 kinase in Parkinson's disease. *Science*, 360(6384), 36-37.  
<https://doi.org/10.1126/science.aar5683>

### General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## **LRRK2 kinase in Parkinson's disease**

### [Signalling analysis uncovers roles for Rab proteins and immune responses in Parkinson's.](#)

Dario R Alessi<sup>1</sup> and Esther Sammler<sup>1,2</sup>

MRC Protein Phosphorylation and Ubiquitylation Unit, School of Life Sciences, University of Dundee, Dundee DD1 5EH. 2. Department of Neurology, School of Medicine, Dundee, Ninewells Hospital, Ninewells Drive, Dundee DD1 9SY, United Kingdom

[d.r.alessi@dundee.ac.uk](mailto:d.r.alessi@dundee.ac.uk) and [e.m.sammler@dundee.ac.uk](mailto:e.m.sammler@dundee.ac.uk)

Despite intensive research, attempts to pause or even just slow the progression of Parkinson's have thus far failed. While most cases of Parkinson's are idiopathic and with largely unknown aetiology, mutations in about 20 genes including LRRK2 (leucine-rich repeat kinase 2), cause rare, genetic Parkinsonism. In the case of LRRK2, all pathogenic mutations result in hyperactivation of the LRRK2 kinase, offering the prospect of elaborating disease-modifying treatments. Indeed, LRRK2 inhibitors have entered Phase I clinical trials. Data is also emerging for LRRK2 involvement in idiopathic Parkinson's, suggesting that inhibitors may benefit patients beyond LRRK2 mutant carriers. Recent advances point towards LRRK2 controlling autophagy and lysosome function by phosphorylating a subgroup of Rab proteins and regulating their ability to bind cognate effector proteins. LRRK2 is highly expressed in immune cells. Intriguing research indicates that in early life, increased LRRK2 activity may protect against opportunistic pathogenic infection, but later, increases the risk of developing Parkinson's, a concept known as antagonistic pleiotropy.

Autosomal dominant missense mutations within the LRRK2 gene account for 1-2% of all Parkinson's cases, and a much higher proportion in some populations (Ashkenazi Jews and North African Berbers) (1). LRRK2-associated Parkinson's closely resembles idiopathic disease in terms of late age of onset, signs and symptoms (1). The penetrance of LRRK2 mutations is incomplete and dependent on age and specific mutation. For example, the majority of carriers of the most common G2019S mutation may never develop disease (penetrance as low as 24%), while the R1441G mutation appears to be more penetrant (up to 95% in later life) (2, 3). Variations at the LRRK2 locus also mildly increase the risk for idiopathic Parkinson's (1, 3). LRRK2 is a large protein (2527 residues) that in addition to its kinase domain possesses a second enzymatic GTPase domain (ROC/COR domain) as well as other motifs (Fig). The clearly pathogenic genetic changes cluster within the GTPase (e.g R1441G) as well as kinase domains (e.g. G2019S) and stimulate protein kinase activity. The G2019S mutation results in a moderate increase in kinase activity (~2-fold). Pathogenic mutations in the GTPase domain enhance GTP binding and stimulate LRRK2 activity to a greater extent (around 4-fold), through interactions with the Rab29 protein and the Golgi apparatus (4, 5).

Much research, based on studying localization and verifying consequences of manipulating the expression of wild type and mutant forms of LRRK2, reveals that it plays a major role in vesicular membranes, as well as autophagy and lysosome, function (6). Recent work suggests that this role of LRRK2 could be mediated via the ability of LRRK2 to phosphorylate a subgroup of Rab GTPases, including Rab8A (Thr72) and Rab10 (Thr73), at a highly conserved site located at the centre of the effector binding motif of these GTPases (7, 8) (Fig). Rab proteins are master regulators of membrane trafficking, orchestrating vesicle formation, vesicle movement along actin and tubulin networks, as well as membrane docking and fusion; all important aspects in autophagy and lysosome biology. Consistent with Rab proteins

comprising relevant substrates for Parkinson's, all pathogenic LRRK2 mutations tested enhance Rab phosphorylation in vivo (7,8).

There is mounting evidence that disruption of Rab biology and membrane trafficking is involved in Parkinson's. Mutations in genes encoding two Rab proteins (Rab29 and Rab39B) and at least 3 other membrane trafficking machinery components (VPS35, VPS13C, DNAJC6) are causally linked to Parkinson's (3). Mutations in the PINK1 protein kinase are associated with young-onset recessive Parkinson's, and PINK1 indirectly controls the phosphorylation of certain Rab GTPases including Rab8A, at a distinct site relative to LRRK2 (Ser111 on Rab8A) (9). Furthermore, various Rab proteins, including LRRK2 substrates Rab3A and Rab8A, can attenuate cytotoxicity linked to aggregated  $\alpha$ -synuclein, a factor that is frequently associated with Parkinson's and other neurodegenerative disorders (10). Recent work has also revealed that poorly studied proteins termed RILPL1 and RILPL2, previously implicated in regulating ciliary membrane content, specifically bind to Rab8 and Rab10 once they have been phosphorylated by LRRK2 (8). Interestingly, pathogenic LRRK2 mutations inhibit primary cilia formation induced by serum starvation (8), but it remains to be established whether this is mediated through LRRK2 phosphorylated Rab8/10 interaction with RILPL1/2 (Fig).

Inflammation plays an important role in the development of Parkinson's. LRRK2 is highly expressed in macrophages, monocytes and neutrophils suggesting it functions in the defence against intracellular pathogens. In humans, single nucleotide polymorphisms within or close to the LRRK2 gene have been linked to inflammatory conditions including ulcerative colitis, Crohn's disease and also increased susceptibility to leprosy infection (11). In mice, LRRK2 is required for mucosal immunity against the opportunistic pathogen, *Listeria monocytogenes*, and co-localizes with intracellular *S. Typhimurium* during bacterial infection in macrophages (11). The LRRK2 kinase is most closely related to the RIP kinases that are key regulators of inflammasomes. Inflammasomes are multi-protein signalling complexes assembled upon stimulation of the innate immune system by either pathogens or toxins and play a crucial role in the inflammatory response and host defence (12). Recent findings indicate that LRRK2 may participate in modulating inflammasome assembly. Mice lacking LRRK2 or treated with an LRRK2 inhibitor, exhibit impaired ability to clear *S. Typhimurium* infection (13). In contrast, knock-in mice bearing the kinase-activating G2019S LRRK2 mutation, are protected from infection (13). Moreover, in response to *S. Typhimurium* infection, LRRK2 interacts with and reportedly phosphorylates the NLRC4 protein at a critical residue (Ser533) required for the assembly of NLRC4 containing inflammasomes (13). This leads to the activation of Caspase-1, which processes and produces a variety of pro-inflammatory agents such as IL-1 $\beta$  that if sustained over a long time, could lead to neuroinflammation and increased Parkinson's susceptibility. Therefore, current understanding suggests that LRRK2 activation would promote pro-inflammatory responses offering protection against infection and survival benefit in earlier life, before Parkinson's strikes.

Highly potent, selective and brain penetrant LRRK2 inhibitors have been reported. Such drugs could offer benefit not only to subjects bearing LRRK2 mutations but also other patients in whom LRRK2 activity is driving disease. Much research is taking place to develop tests to interrogate LRRK2 activity and function in patients. This includes studying LRRK2 autophosphorylation and Rab protein phosphorylation in neutrophils, monocytes and cerebrospinal fluid. Several pharmaceutical companies are in late stages of preclinical evaluation of LRRK2 inhibitors, while one has recently completed a Phase 1 clinical trial in healthy volunteers. Studies in LRRK2-deficient rodents and non-human primates treated with LRRK2 inhibitors, highlighted potential liability concerns in lung and kidney, resulting from loss of LRRK2 kinase activity that might be linked with altered autophagy and lysosomal biology (14, 15). Therefore, lung and kidney function will need to be closely monitored in

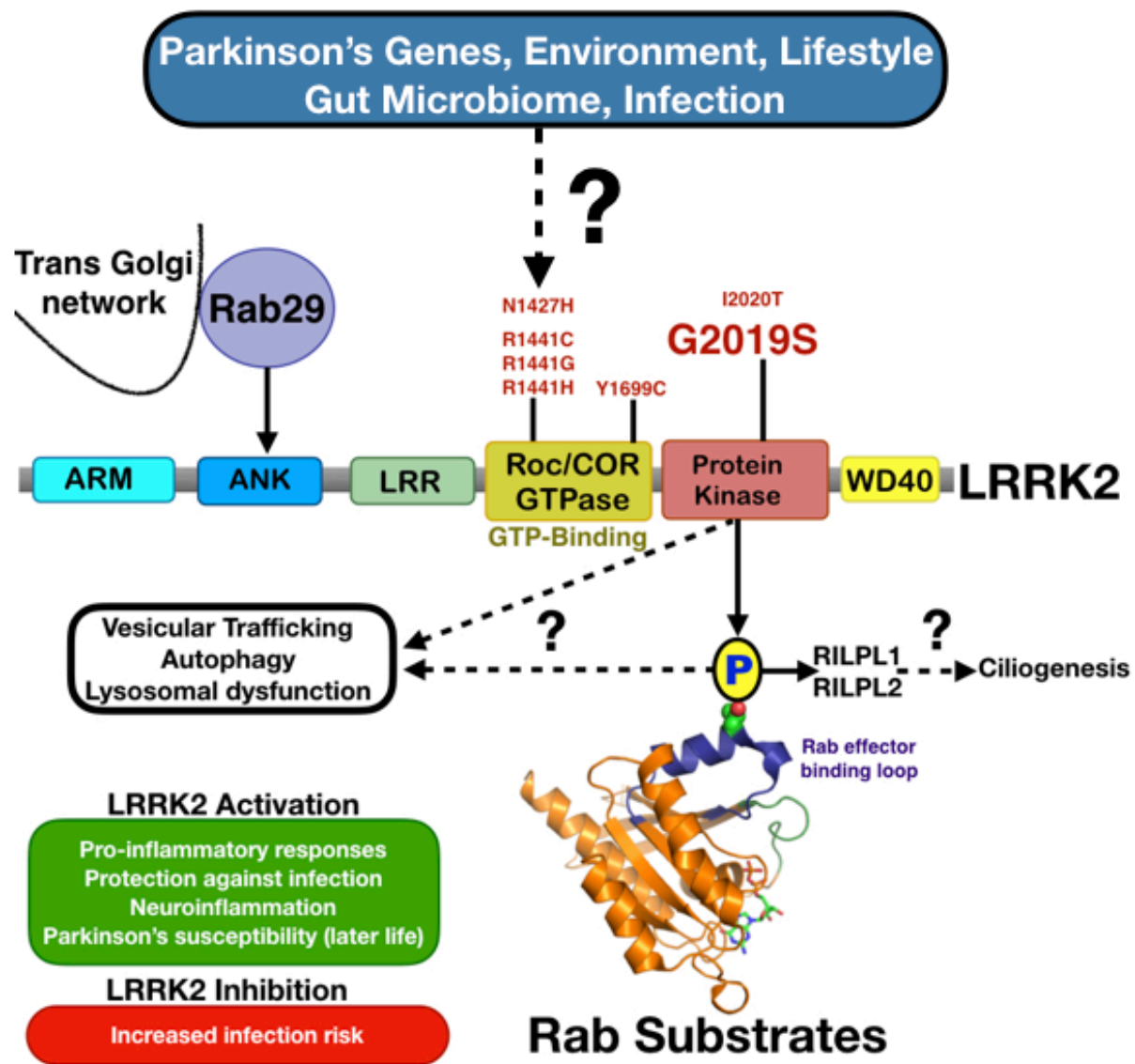
LRRK2 inhibitor clinical trials. Given challenges of translating findings in immunity from mice to human, LRRK2 inhibitor clinical trials present a unique opportunity for refining our understanding of the LRRK2-related immune function in humans. Above all, it would be important to establish whether LRRK2 inhibitor treatment significantly increases the risk for opportunistic infections.

In conclusion, LRRK2 lies at the nexus of an emerging signalling network of high relevance for understanding and developing treatments for Parkinson's. It will be essential to define in clearer detail the upstream and downstream components of this pathway. Understanding the interplay between LRRK2 mediated immune defence mechanisms and Parkinson's will also undoubtedly reveal fascinating biology. Reports of monozygotic LRRK2 mutation-carrying twins discordant for Parkinson's and the incomplete penetrance of LRRK2 mutations highlight the importance of environment (e.g. exposure to toxins, herbicides, pesticides, and fungicides), lifestyle (e.g. smoking, exercise, diet), gut microbiome and infection in the development of LRRK2-dependent Parkinson's. It is possible that these factors synergise with genetic mutations. In the future, aligning mechanistic insight into disease pathways with genetics and clinical phenotyping could define the roles that LRRK2 signalling plays in idiopathic Parkinson's. This will help justify the use of LRRK2 inhibitor therapy in more patients. However, for now the most exciting question will be whether LRRK2 inhibitors have disease-modifying effects in Parkinson's patients with LRRK2 mutations.

## References

1. C. Paisan-Ruiz, P. A. Lewis, *J Parkinsons Dis.* **3**, 85 (2013).
2. A. J. Lee *et al.*, *Mov. Disord.* **32**, 1432 (2017).
3. A. Domingo, C. Klein, *Handb. Clin. Neurol.* **147**, 211 (2018).
4. E. Purlyte *et al.*, *EMBO J.* **31**, 1 (2018).
5. Z. Liu *et al.*, *Hum Mol Genet.* **27**, 385 (2018).
6. D. A. Roosen, M. R. Cookson, *Mol. Neurodegener.* **11**, 73 (2016).
7. M. Steger *et al.*, *Elife* **5**, e12813 (2016).
8. M. Steger *et al.*, *Elife* **6**, e31012 (2017).
9. Y. C. Lai *et al.*, *EMBO J* **34**, 2840 (2015).
10. A. A. Cooper *et al.*, *Science* **313**, 324 (2006).
11. N. L. Dzamko, *Adv Neurobiol* **14**, 123 (2017).
12. M. Lamkanfi, V. M. Dixit, *Nature* **548**, 534 (2017).
13. W. Liu *et al.*, *J Exp Med* **214**, 3051 (2017).
14. M. A. Baptista *et al.*, *PLoS One* **8**, e80705 (2013).
15. R. N. Fuji *et al.*, *Sci Transl Med* **7**, 273ra215 (2015).

**Figure: LRRK2 Signalling Pathway.** Domain structure of LRRK2 and location of most well characterized pathogenic mutations that enhance LRRK2 activity. G2019S mutation is by far the most common. LRRK2 phosphorylates a subgroup of up to 14 Rab proteins (Rab3A, Rab3B, Rab3C, Rab3D, Rab5A, Rab5B, Rab5C, Rab8A, Rab8B, Rab10, Rab12, Rab29, Rab35 and Rab43) at the equivalent site within the centre of the effector binding loop. The possible downstream consequences of Rab protein phosphorylation are summarized. The predicted impacts of activating (green box) and inhibiting (red box) LRRK2 in the immune system are also indicated.



**Figure**