There are many LRRK2 mutations that are associated with autosomal dominant inherited Parkinson’s disease (PD) with age-related penetrance and variable expressivity. Of the known mutations, pathogenicity has been most clearly confirmed by segregation of the mutation with PD for R1441C/G mutations in the ras of complex proteins (ROC) domain, Y1699C in the C-terminal of ROC (COR) domain and G2019S and I2020T in the kinase domain. There are also single amino acids variants that show association with disease, including G2385R in the WD40 domain. What links these different mutations in different domains of a complex protein to the pathogenic process that leads to PD is currently unclear. In this talk I will discuss cellular data that underpins different models that we currently have.

Of the known mutations, only G2019S increases kinase activity substantially (2-3fold) while others, including the risk factor G2385R, produce a significant decrement in activity. Other mutations decrease GTPase activity. There are several models that might rationalize these different observations, but one that I currently favor is that all mutants shift the interaction of one or more protein-interaction partners of LRRK2 such that the protein complex has persistent function. This may be reflected in the different cellular phenotypes that have been described for different LRRK2 mutations, including effects on neurons but also other cell types that will be outlined in this talk.