Molecular mechanisms of LRRK2-related neurodegeneration

https://neurodegenerationresearch.eu/survey/title-of-pimolecular-mechanisms-of-lrrk2-related-neurodegeneration/

Title of project or programme

Title of PI Molecular mechanisms of LRRK2-related neurodegeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Dr	Vincenzo	Bonifati	Erasmus University Medical Center, Genitics	Netherlands

Address of institution of lead PI

Institution	Erasmus University Medical Center, Genitics
Street Address	Dr. Molewaterplein 50
City	Rotterdam
Postcode	3015 GE

Country

- Netherlands

Source of funding information

Netherlands Organisation for Health Research and Development (ZonMw)

Total sum awarded (Euro)

600000

Start date of award

1-11-2007

Total duration of award in months

60

The project/programme is most relevant to

- Parkinson’s disease

Keywords

Research abstract in English

Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease, with a prevalence of more than 1% after the age of 65 years, and an increasing public-health problem in the aging population. Despite intensive research efforts, the molecular mechanisms of PD remain mostly unknown. The ongoing identification of primary genetic defects in patients with inherited forms of the disease is rapidly expanding the possible approaches to disentangling the

complex pathogenesis of PD. The recent identification of mutations in the Leucine-Rich Repeat Kinase 2 gene (LRRK2) in families with autosomal dominant PD represents a major step forward in this endeavour. LRRK2 mutations are a frequent genetic cause of PD; the associated clinical and pathological phenotypes are in most cases indistinguishable from classical, late-onset PD. My laboratory contributed substantially to the field, by discovering the LRRK2 G2019S and G2385R variants, today the most common known PD-causing mutation and genetic risk factor, respectively. Very little is known about the biology and pathobiology of the protein encoded by the LRRK2 gene. In this proposal, I describe a strategy to unravel the molecular mechanisms of LRRK2-related neurodegeneration and its implications for the common forms of PD.
The associated key objectives are: modelling the LRRK2-related neurodegeneration in cell models over-expressing human wild type or PD-associated LRRK2 variants; identification of interactors and substrates of the LRRK2 protein; testing the hypotheses of interaction between the LRRK2 and a-synuclein pathways, and of modification of the LRRK2-related disease by modulating the protein quality control systems (molecular chaperones, ubiquitin-proteasome system). I strongly believe that the research described in this proposal will provide crucial insights for understanding the molecular mechanisms of PD, novel and better models for this disease, and novel tools for evaluating future therapeutic strategies for interventional trials in the patients with PD and related diseases.

In which category does this research fall?

- Basic research

Lay Summary