Exosome LRRK2 in Predicting Parkinson Disease Phenotypes

https://neurodegenerationresearch.eu/survey/exosome-lrrk2-in-predicting-parkinson-disease-phenotypes/

Principal Investigators

WEST, ANDREW B

Institution

UNIVERSITY OF ALABAMA AT BIRMINGHAM

Contact information of lead PI
Country

USA

Title of project or programme

Exosome LRRK2 in Predicting Parkinson Disease Phenotypes

Source of funding information

NIH (NINDS)

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€ 885,035.78

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01/06/2016

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

LRRK2 gene, exosome, disease phenotype, Parkinson Disease, mutation carrier

Research Abstract

DESCRIPTION (provided by applicant): “”Exosome LRRK2 in Predicting Parkinson Disease Phenotypes”” There is a critical need for quantitative biomarkers that predict Parkinson disease (PD) susceptibility and progression. Such biomarkers would aid the development of new

therapies that slow or halt disease. PD has a clear genetic component that contributes to disease susceptibility. One gene in particular, leucine-rich repeat kinase 2 (LRRK2), harbors pathogenic missense mutations prevalent in some populations. LRRK2 is further linked to PD susceptibility through genome-wide association studies. Pathogenic LRRK2 mutations upregulate LRRK2 kinase activity and increase levels of the auto phosphorylated residue serine S1292 (pS1292). In our previous project “”Exploratory Laboratory and Analysis Projects in PDBP”” (U18 NS082132), we focused our efforts on analyzing and measuring LRRK2 in clinical samples. We discovered that auto phosphorylated LRRK2 (pS1292-LRRK2) could be detected and quantified in exosome fractions from both cerebral-spinal fluid (CSF) and urine. We found elevated levels (~5 fold) of pS1292-LRRK2 in urinary exosomes from G2019S-LRRK2 mutation carriers with PD. In G2019S-LRRK2 mutation carriers, pS1292-LRRK2 levels successfully predicting clinical PD manifestation. We further analyzed pS1292-LRRK2 in a large cohort of cases and controls (n=160) from the University of Alabama at Birmingham Parkinson’s Disease Biomarker Program (UAB PDBP) and found that pS1292-LRRK2 levels predicted PD phenotypes in patients. Here we will determine the potential of exosome pS1292-LRRK2, purified from urine and CSF, in predicting PD susceptibility and progression in both early and mid-stage idiopathic PD cases as well as in LRRK2 mutation carriers. Project success will include the discovery of novel insights into the role of LRRK2 in the pathogenesis of PD and the development of a novel biomarker (exosome pS1292-LRRK2) that may predict PD manifestation in LRRK2 mutation carriers. The successful prediction of LRRK2 mutation carriers that will go on to develop PD would aid in future clinical trial design for LRRK2-directed therapies. Finally, we predict that the novel biomarker exosome pS1292- LRRK2 may help stratify idiopathic PD patients that will experience rapid progression of PD symptoms from those with more benign disease courses. Identification of PD cases with a poor prognosis would assist physicians in making treatment choices and clinical trial design for novel neuroprotective therapies.

Lay Summary
PUBLIC HEALTH RELEVANCE: “”Exosome LRRK2 in Predicting Parkinson Disease Phenotypes”” Parkinson disease (PD) is the second most common neurodegenerative disorder. There are a lack of biochemical markers of disease prediction and progression. Our project will explore a particular form of a protein linked to PD called LRRK2 in bio fluids collected over several years to determine the suitability as a new marker for disease prediction and prognosis.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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2016

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N/A

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