Evaluation of glucocerebrosidase pathway biomarkers in Parkinson Disease

https://neurodegenerationresearch.eu/survey/evaluation-of-glucocerebrosidase-pathway-biomarkers-in-parkinson-disease/

Principal Investigators

SAUNDERS-PULLMAN, RACHEL

Institution

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

Contact information of lead PI
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USA

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Evaluation of glucocerebrosidase pathway biomarkers in Parkinson Disease

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01/04/2016

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2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

glucosylceramidase, Parkinson Disease, Idiopathic Parkinson Disease, progression marker, Biological Markers

Research Abstract

PROJECT SUMMARY Parkinson disease (PD) due to monoallelic glucocerebrosidase (GBA1)

gene mutations (GBA-PD) is at the forefront of novel approaches to the treatment of PD. Exciting potential therapeutic agents that target the pathway disrupted in this genetic form of PD are becoming available, and evidence suggests that benefits extend to non-mutation PD, as well. Trial development is at a pivotal stage. Demonstration of effects in trials of potential disease-modifying agents for PD in general has been impeded by uncertainty about disease etiology, heterogeneity of underlying mechanisms, few identified targets, few sensitive and stable outcome measures (especially for non-motor outcomes), and insufficient surrogate markers. This proposal aims to set the stage for clinical trials using GBA-PD as a model to transcend trial design hurdles. GBA1 mutations cause deficiency in the lysosomal glucocerebrosidase enzyme (GCase) and are the most common genetic factor associated with PD. This well-defined pathway allows study of a population with decreased heterogeneity of etiologic mechanism, and a known target for intervention. Evaluation of biochemical markers in this pathway in conjunction with clinical motor and non-motor features will provide outcome measures for clinical trials. Further, disruption of the GCase pathway may be an important representative mechanism for non-mutation, idiopathic PD (IPD), and has been implicated as a possible etiology in at least a subset of IPD. While we have cross- sectional preliminary data, validation and longitudinal assessment of these biomarkers are needed to optimize their utility in clinical trials. Unprecedented sharing of biospecimen and clinical data through the Parkinson's Disease Biomarker Program (PDBP) enables us to leverage our extensive GBA cohort at Mount Sinai Beth Israel (MSBI). Using extant samples from our MSBI cohort, the Harvard Biomarker Study (HBS), the Parkinson's Progression Markers Initiative (PPMI), and the PDBP, we propose to characterize focused biochemical measures of the GCase pathway, including central and peripheral biomarker assessments of enzyme, lipid and ?-synuclein levels and their relation to clinical outcomes and decline. This will not only improve the likelihood of clinical trial success, but will lead to better understanding of the pathophysiologic mechanisms of this prominent etiology of PD. Specifically, we will: (Aim 1) validate findings in the MSBI dataset, associate peripheral and CSF markers, and assess their longitudinal change; (Aim 2) analytically derive a clinical severity score to optimally relate clinical and biological markers; (Aim 3) evaluate markers in IPD to discern whether a subset of IPD shares the same etiologic mechanism; and (Aim 4) evaluate RNA expression and identify genetic modifiers in extremes of GBA. Completion of these aims addressing progression and putative pharmacodynamic markers leveraging these special cohorts will provide necessary information to foster trial development and success, and expand our knowledge of the pathophysiology of GBA-PD and IPD.

Lay Summary

PROJECT NARRATIVE/RELEVANCE TO PUBLIC HEALTH Parkinson Disease (PD) can be a devastating disorder that limits mobility and independence, and treatments to slow or prevent disease have not been successful. Therefore, the proposed study is relevant as 1) mutations in the glucocerebrosidase1 (GBA1) gene are the most common genetic factor of PD; 2) the proposed study, utilizing longitudinal data from our site, Mount Sinai Beth Israel (MSBI), the Harvard Biomarker Study (HBS), and Parkinson's Progression Markers Initiative (PPMI), would represent one of the largest clinical and biological biomarker studies focusing on GBA-PD; 3) it would allow a tremendous window of opportunity to characterize progression of markers in GBA-PD over time; and 4) it would identify markers of target engagement, serving to inform the development of PD therapies and clinical trial design in GBA-PD and idiopathic PD.

Further information available at:

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United States of America

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