

**Environmental exposures modifying clinical expression of
LRRK2-associated Parkinson's disease**

Application for planning funds

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Abstract:

The incomplete penetrance, variable age at onset and variable pathology of Parkinson's disease associated with LRRK2 mutations suggests the influence of other genetic and/or environmental factors on the clinical expression of this disorder. Environmental influences on the penetrance or expressivity of LRRK2 are not yet known and to our knowledge have not yet been studied. In order to detect potentially small but important effects of environmental exposures, a much larger sample size than any one centre is able to provide is necessary. We propose to coordinate a large, multicentre effort to evaluate multiple environmental risk factors for their influence on the expression of LRRK2-associated PD. In our pilot phase we have initiated a collaboration with 11 centers across North and South America, Europe and Asia to study environmental influences on the expression of LRRK2-associated Parkinson's disease. With these investigators we have collected information on smoking, caffeine intake and head injury from 171 subjects with PD and LRRK2 mutations in order to assess their influence on age at onset. The next phase of our project will involve a much larger group of collaborating investigators, will expand the risk factors to be investigated and will study the effect of these exposures on phenotypic

characteristics other than age at onset, such as presenting symptoms and rate of disease progression. In addition, we will investigate factors determining the presence of non-motor features associated with early PD in initially nonmanifesting LRRK2 carriers. **This grant application requests funds to plan our more extensive investigation of environmental influences on the expression of LRRK2-associated Parkinson's disease in preparation for an application to NIH in mid 2008.** This will include (i) finalizing a study steering committee, identifying additional study investigators (ii) finalizing study design and preparation of study materials and (iii) collecting and analyzing preliminary data of two types: a) data describing expected study subjects (mutation type, demographic characteristics, disease features if affected) and b) data regarding environmental exposures and their relationship to age at onset of LRRK2-associated Parkinson's disease.