Search for Genetic Factors in Parkinson*s disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON37785

Source
ToetsingOnline

Brief title
Erasmus GPS
(Erasmus Genetic Parkinson Study)

Condition

- Neurological disorders congenital
- Movement disorders (incl parkinsonism)

Synonym
Parkinsonism, Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Internationaal Parkinson Fonds

Intervention

Keyword: Etiology, Genetic Association Study, Genetic Linkage, Parkinson's Disease

Outcome measures

Primary outcome

- Genetics variants causing or predisposing to Parkinson*s disease.

- Characterisation of the clinical phenotype associated to specific genetic

variants.

Secondary outcome

Frequency of known mutations in the subjects.

Study description

Background summary

The recent discovery of genetic mutations causing Mendelian forms of Parkinson*s disease (PD), such as those in the α-synuclein, parkin, DJ-1, PINK1, and the LRRK2 gene, have provided novel clues into the mechanisms of this disease. However, none of these mutations is common in the Dutch population, and the etiology of the disease remains here almost totally unknown. Recent large-scale genome-wide association studies (GWA) highlighted the role of common variants in the α-synuclein and tau gene as risk factors for the sporadic forms of this disease in the population of European ancestry. However, these variants possess very low penetrance, and while they only account for a portion of the disease heritability at the population level, they do not explain the familial aggregation of PD, present in up to 25% of cases. Taken together, these data suggest that most of the genetic determinants of PD remain to be identified in several populations including the Dutch one, and particularly, additional highly-penetrant mutations remain to be discovered in one or several PD-causing genes. The identification of further PD-causing genes is urgently needed by the research community at large, as these genes might provide further important clues for the dissection of the disease pathogenesis, and for the identification of biomarkers and of innovative therapeutic targets. In the post-GWA era, the focus on families with PD, likely harboring high-penetrance mutations is therefore gaining novel momentum. The Dutch population appears very suitable for family-based genetic studies, because large families are still frequently observed, family relationships are kept

strong, and excellent genealogical records are available to researchers.

Study objective

The aims of this study are the ascertainment, characterization, and longitudinal follow-up of a large cohort of Dutch families segregating Parkinson*s disease, including affected and unaffected first-degree relatives. The cohort will be characterized clinically and genealogically. Moreover, a bank of biological samples (DNA, RNA, plasma, serum, blood cells, fibroblasts) will be established. The cohort, together with the clinical-genealogical database and the biological bank will represent an important resource for a number of molecular genetic studies aimed at the identification of novel genetics determinants of PD.
The cohort will also be suitable for monitoring early, pre-clinical disease stages and for biomarker discovery (e.g. using serum proteomics and metabolomics, gene expression profiling, functional imaging, smell-testing, neuropsychological testing). Last, the cohort of non-manifesting at-risk relatives will constitute an ideal population for testing neuroprotective strategies, as soon as they become available.

Study design

Written informed consent is obtained from every participating subject and the project has been submitted to the Medical Ethic Committee of the Erasmus MC Rotterdam. From each subject we plan to collect detailed clinical and genealogical data and a blood sample (20 cc) for the isolation and storage of serum, plasma, genomic DNA and total RNA. An aliquot of freshly collected blood will also be stored in adequate medium for future generation of Epstein-Barr-virus transformed lymphoblastoid cell lines.
From critical individuals, such as patients from very large families or very interesting phenotypes, we will also collect skin biopsies and establish primary fibroblasts lines. These lines might be used in the future for the preparation of induced pluripotent (stem-like) cells (iPC), which in turn, can be differentiated into dopaminergic neurons for modelling the disease in vitro.
The clinical diagnosis of Parkinson*s disease will be established according to the UK Brain Bank criteria, and the disease severity assessed using the Unified Parkinson*s disease rating scale, the SCOPA-COG, FAB and the Hoehn-Yahr staging.

Study burden and risks

We expect no serious adverse events in this study. Peripheral venous blood sampling (max. 20 mL) is a routine minimally-invasive procedure which will be performed only by highly experienced and certified nurses or physicians. Further, our neurologic and neuropsychological assessments are highly structured and have been extensively tested, without any known serious adverse

events.

Adverse events may include minor bruising or local tenderness at the site of venous blood sampling. All patients will be monitored to ensure proper hemostasis.
A selection of patients and family members will be asked to give consent for a skin biopsy. This is a minimally invasive procedure that is not very painful but might produces some discomfort. Prior to the biospy, the skin is treated with a creme as a local anesthetic. Some scar tissue could form and there is a small chance to develop an infection.
During interviews and neuropsychological testing, the patient will be fully aware of his/her right to terminate the testing at any time and for any reason.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- The probands (index cases) must have a diagnosis of idiopathic Parkinson*s disease according to the established clinical criteria (familial or sporadic disease).
- The relatives of the probands are first-, second-, or third-degrees relatives of the probands; they might or might not have Parkinson*s disease.
- The unrelated controls, as well as their first degree relatives, must be free from clinical signs of Parkinson*s disease and dementia.
- All subjects (probands, relatives, controls) must be 18 years of age at recruitment.
- All subjects (probands, relatives, controls) might be male or female.
- All subjects (probands, relatives, controls) must have signed the informed consent (before entry into study). In case of a legally incapacited subject, for instance due to cognitive impairment, the legal representative will be approached to obtain informed consent.

Exclusion criteria

- Subjects who are unable to speak and be interviewed in Dutch or English (to ensure validity of the interviews).
- Patients with secondary forms of parkinsonism (such as drug-induced, toxic, vascular, tumour)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2012
Enrollment:	700

Type:	Actual

Ethics review

Approved WMO Date:	25-04-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL38860.078.11