Search for Genetic Factors in Parkinson's Disease - II

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The objectives of this study are: 1. to identify new genetic variants causing or predisposing to PD; 2. to characterize the clinical phenotype in PD associated to specific genetic variants; 3. to investigate the molecular mechanisms of PD in...

Ethical review	Approved WMO
Status	Pending
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON51549

Source
ToetsingOnline

Brief title
GPS2
(The ErasmusMC Genetics of Parkinson Study - II)

Condition

- 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: Stichting Parkinson Nederland; Alzheimer Nederland

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.

- Investigation of molecular mechanisms of PD in patients with specific genetic

variants.

Secondary outcome

NA

Study description

Background summary

The recent discovery of genetic mutations causing Mendelian forms of Parkinson's disease (PD), such as those in the a-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 several loci 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.
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 objectives of this study are:
1. to identify new genetic variants causing or predisposing to PD;
2. to characterize the clinical phenotype in PD associated to specific genetic variants;
3. to investigate the molecular mechanisms of PD in patients with specific genetic variants

Study design

The study involves the following steps:
1. recruitment of families segregating the disease of interest (PD), sporadic PD cases of early-onset, and unrelated controls;
2. detailed characterization of the clinical phenotype;
3. analysis of known PD-causing genes;
4. genetic linkage analysis and next generation sequencing (whole exome, whole genome sequencing) to identify new disease-causing genes;
5. screening of the entire series of cases (familial and sporadic PD) to characterize the phenotype associated to newly identified genes;
6. investigating the molecular mechanisms of disease using in-vitro neuronal and glial cell models obtained from the differentiation of induced pluripotent stem cells (iPS) from patient derived cells with specific genetic mutations and unrelated controls

Study burden and risks

Participating in this study only brings negligible risks and we expect no serious adverse events. 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 biopsy, 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
Adolescents (16-17 years)
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.
- Due to possible shared etio-pathogenetic pathways, relatives of PD probands
- 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 16 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 incapacitated 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, tumor)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2023
Enrollment:	700
Type:	Anticipated

Ethics review

Approved WMO Date:	20-02-2023
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	NL82474.078.22