Clinical inventaristation and identification of (modifier) disease genes for movement disorders using next generation sequencing

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The main aims of our study are 1) to make a clinical inventory of MD cases, 2) to identify (modifier) disease genes underlying MD and 3) to link the clinical data with the genetic data in a data-base.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON42121

Source
ToetsingOnline

Brief title
Next Generation Sequencing in movement disorder

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Movement disorders (incl parkinsonism)

Synonym
dystonia and ataxia, Movement disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Prinses Beatrix Fonds en NutsOhra

Intervention

Keyword: clincal inventarisation, exome sequencing, genetics, movement disorders

Outcome measures

Primary outcome

1) Clinical inventarisation of Dutch MD patients.

2) Mapping and identification of disease genes.

3) Phenotype-genotype evaluation.

4) Molecular studies in patient-derived iPs cells.

Secondary outcome

1) To improve diagnosis and genetic counselling and contribute to the

development of better care for the MD patients and their relatives.

2) To improve our knowledge on the disease pathology by functional

characterization of novel (modifier) disease genes.

Study description

Background summary

Movement disorders (MD) are often progressive dominantly or recessively inherited disorders that affect specific areas of the brain leading to dysfynction of motor coordination, gait, and/or muscle contractions. This work

focuses mainly on the (spino-) cerebellar ataxias, dystonia and, hereditary essential tremor. These diseases are clinically and genetically heterogeneous as to date more than 30 cerebellar ataxia, 15 dystonia genes have been identified. Despite this large number of recognized disease genes, still more than 40% of the patients remain genetically undiagnosed leading to insecurity in diagnosis and prognosis for doctors and patients .

Study objective

The main aims of our study are 1) to make a clinical inventory of MD cases, 2) to identify (modifier) disease genes underlying MD and 3) to link the clinical data with the genetic data in a data-base.

Study design

Non-therapeutic study that will lead to diagnosis that can not be made in an alternative way and may open opportunities to treat these disorders. Patients with a familial or sporadic form of movement disorders, who visit the patient clinic of the Neurology Department of the UMCG, will be recruited. The number of patients that will be included depends on some variables such as 1) the heritable compontent (dominant of recessive) of the disorder 2) the family structure, 3) the number of available family members. This number will thus vary per case and can not be predicted in advance, To be able to perform the genetic analysis the familymembers will be categorized based on their disease status (affected or non-affected). This work focusses mainly on adults, however, in some recessive movement disorders the disease might predispose to clinical complaints in childhood. In these families, we are limited to the affected childhood cases and we can not do anything else than to include them in our study in order to elucidate the disease ethiology. Making an ethiological diagnosis will always be in the benefit of the patiënt (adult and child) and his or her family members by 1) possibilities to treat the disorder or 2) improves decising making in family planning.

We will make a digital clinically inventory of all collected cases with MD, and will perform genetic analysis of the patients and their relatives by genome-wide genotyping, shared haplotype analysis, and next generation sequencing such as sequencing of disease gene panels using an targeted array or exome sequencing. In special cases, a MRI will be neccessary to (re-)confirm the clinical diagnosis and/or to validate our genetic findings.

When we are unable to set a genetic diagnosis using DNA sequencing, we will also use RNA sequencing as well (in cases of whom RNA material is availbale and when the case approves) to identify the genetic cause. This layer of additional information will increase our insight in which genetic variants alter transcript levels are are thus more likely disease causing.

The DNA material of cases and their relative in whom we are unable to set a genetic diagnosis ourselves can be send to internal collaborations. These samples will be used in so-called GWAS studies or will be screened for mutations in novel disease genes. The overall aim is to enhances our genetic diagnosis of the patients and their relatives.

Additionally, patient-derived IPs cells will be generated from fibroblast of cases in whom the disease gene has been identified. These cells will be used for additional molecular and transcriptome

Study burden and risks

There are no risks associated with this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

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

Inclusion criteria

Patient: Patient with diagnosis movement disorder
Family member: Family member of a patient with a diagnosis of movement disorder

Exclusion criteria

Patient: Not a patient with diagnosis movement disorder
Family member: Not a family member of a patient with a diagnosis movement disorder
No informed consent obtained for this study
(Severe) physical illness
Not being able to understand Dutch language

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:	Recruiting
Start date (anticipated):	01-09-2014
Enrollment:	1000
Type:	Actual

Ethics review

Approved WMO Date:	11-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL48444.042.14