A multi-omics approach to modeling disease mechanisms in frontotemporal dementia

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Ethical review	Approved WMO
Status	Pending
Health condition type	Neurological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON54408

Source
ToetsingOnline

Brief title
CTG-PoC

Condition

- Neurological disorders NEC

Synonym
frontotemporal dementia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,TKI,Roche

Intervention

Keyword: Frontotemporal dementia, iPSC, multi-omics

Outcome measures

Primary outcome

Collect iPSC derived neurons from FTD patients for further proteomics and cellomics studies. Using proteomics, a signature protein profile will be ascertained for genetic and sporadic FTD cases. With cellomics, effects of protein regulation in FTD can be investigated on the cellular functional level.

Secondary outcome

Genetic testing for known causal FTD genes in sporadic patients will help affirm the sporadic nature of FTD symptoms in these patients. In case a mutation is identified, the patient will be notified if there is a treatment available and if the patient consented to receiving this information. Neuropathological reports from the NBB on the post-mortem state of FTD brain tissue will help us to better subcategorize sporadic FTD patients, and to eliminate confounding pathology or disease.

Study description

Background summary

Frontotemporal dementia (FTD) is a neurodegenerative disease that affects behavior and personality and ultimately leads to death. There are currently no means to prevent or cure FTD. Finding a therapeutic intervention for FTD is challenging due to the pathological and genetic heterogeneity. Pathologically, frontotemporal lobar degeneration (FTLD) consists of three major subclasses: FTDL-TDP, FTLD-tau and FTLD-FUS. Genetically, up to 30% of FTD patients are hereditary, and is most often caused by mutations in the MAPT (FTLD-tau), GRN (FTLD-TDP), or C9orf72 (FTLD-TDP) genes. The remaining 70% of patients

(non-hereditary or sporadic FTD) seem to be due to a combination of unknown genetic and environmental factors. Underlying pathology in sporadic FTD patients cannot be determined based on the clinical picture and can be seen in all three pathological subclasses. We hypothesize that unravelling the diversity of molecular pathways within these subtypes, and identifying potential common denominators by integrating clinical, pathological, molecular and cellular knowledge of iPSC-derived neurons and brain tissue of well-phenotyped FTD patients will accelerate drug development for these disorders.
To understand the implications of our findings, we need to approach proteins and their pathways in vivo. An innovative way to validate our preliminary findings is to study disease mechanisms in FTD patient derived induced pluripotent stem cell (iPSC) lines. Importantly, contrary to the use of animal models, iPSC technology enables research in all subtypes of FTD.

Study objective

To overcome the heterogeneity dilemma that hampers drug development, we propose a translational within-subject approach that integrates clinical, pathological, and molecular/cellular data of induced pluripotent stem cells (iPSC) derived neurons and brain tissue of the same donor to identify molecular profiles and (novel) drug targets for personalized treatment strategies.

Our specific objectives are to:
1) Collect clinical, pathological and biochemical data of FTD patients to define the phenotype of the patients in detail
2) Identify and validate skin biomarkers for FTD
3) Reprogram fibroblasts towards iPSCs, characterize the iPSCs and generate welldefined iPSC-derived neuronal cells that can be used for FTD research
4) Identify molecular (proteomics) and cellular (cellomics/microscopy) profiles of postmortem
brain tissue and iPSC of the same FTD patients to aid in identification and validation of druggable targets for personalized therapeutic strategies.

Study design

We will collect skin biopsies of whom pathological confirmation will be available via the Netherlands Brain Bank and validate skin biomarkers. In parallel, we will prospectively collect skin biopsies from well-phenotyped sporadic patients who gave consent to future brain donation, and patients with a genetic form of FTD. We will generate well-defined iPSC-derived neurons. Using advanced -omics techniques we will define molecular profiles of the iPSC and braintissue samples of the same donor. This will enable us to identify and validate druggable targets.

Study burden and risks

The patients participating will undergo a skin biopsy of 3 mm. Risks related to the skin biopsy are occurrence of a hemorrhage, infection and a minimal chance for scarring. The patient will get offered a local anesthetic to reduce the pain associated with the biopsy. To minimize the chance for complications, a detailed history with regard to medications that can cause prolonged bleeding, increase risk of infection or delay healing will be checked. The chance for the occurrence of an infection will be minimized by following standardized biopsy protocol and execution of the biopsy will only be performed by a physician or trained and certified nurses. The biopsy location will be along relaxed skin tension to optimize healing and minimize scarring (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728909/) . The burden will be kept minimal. The study has to be performed in a population of FTD patients and is therefore group related. The outcomes of our project will eventually be beneficial to all FTD patients of all subgroups. In particular this project makes sense for the 80% of sporadic FTD cases, who have been relatively neglected in FTD fundamental research. There has been no research using iPSC in sporadic FTD so far. The research that we aim to perform will create great opportunities for the international research community as well as pharma. Since drug development takes several years after completion of this project, there will be no direct benefit for patients currently suffering from FTD. However when successful, the benefit will be clear for future FTD patients. This project is the stepping stone for the assay development and drug testing that is to the standards of clinical screening. A future advantage is that we have a large and trial-ready clinical FTD cohort available that has been deeply phenotyped using clinical, biological, neuroimaging, and genetic markers.

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

- Diagnosed with non-genetic Frontotemporal Dementia, diagnosed by a physician at the Alzheimercentrum Amsterdam (AmsterdamUMC locatie VUmc and; Registered at the Dutch Brain Bank (Nederlandse Hersenbank) to donate their brains when they decease
- Diagnosed with genetic frontotemporal dementia

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Contra-indication to perform a skin biopsy (known cause for prolonged bleeding, high risk of infection)
- No cerebral spine fluid biomaterial or biomarker results available to exclude co-existing Alzheimer pathology

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:	Pending
Start date (anticipated):	01-02-2023
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-04-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL74596.029.20