The disease process of hereditary frontotemporal dementia in the presymptomatic stage: a search for sensitive biomarkers

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Netherlands

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The disease process of hereditary frontotemporal dementia in the presymptomatic stage: a search for sensitive biomarkers

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ZonMw

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The project/programme is most relevant to:

Alzheimer's disease & other dementias

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Research Abstract

Frontotemporal dementias (FTD) constitute the second most common type of dementia before the age of 65, characterized by frontotemporal lobar degeneration. Amyotrophic lateral sclerosis (ALS) leading to progressive motor deficits and disability, is associated to FTD in 20% of the patients. Selective frontal and/or temporal atrophy on MRI characteristic for FTD has proven to be preceded by structural and functional connectivity changes in white matter tracts and between specific cortical regions on functional MRI.

Genetic factors play an important role, with mutations in three different genes (MAPT, GRN, and C9orf72) associated FTD segregating in an autosomal dominant mode of inheritance within families. These genetic factors are associated with two main neuropathological subtypes and can be distinguished: 1) neuronal and glial tau-positive neuronal inclusions associated with MAPT mutations 2) neuronal protein inclusions with TDP-43 as major constituent found both in brains with GRN mutations and C9Orf72 repeat expansions.

Therapeutic interventions in dementia are currently focusing to the earliest stages of the disease. The group of asymptomatic mutation carriers from families with hereditary FTD is the ideal study population to investigate the earliest alterations in FTD, and are also important for aforementioned interventional studies. Sensitive neuroimaging and neurochemical biomarkers as surrogate endpoints are essential in the design of such interventions. We are participating in a large European Genetic Frontotemporal Dementia Initiative (GENFI). Longitudinal studies of our existing cohort will enable us to define the temporal dynamics of these changes, and to determine their sensitivity over time for evaluating the effect of disease-specific modifying agents in future clinical trials.
Our aim is to carry out a longitudinal study of presymptomatic mutation carriers in order to track the disease process in the presymptomatic stage and evaluate the sensitivity of these biomarkers for disease-modifying treatments.

Lay Summary
Further information available at:

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