Predict to prevent frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)

https://www.neurodegenerationresearch.eu/survey/predict-to-prevent-frontotemporal-lobar-degeneration-ftld-and-amyotrophic-lateral-sclerosis-als/

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Predict to prevent frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS)

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5

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Research Abstract

The project focuses on C9orf72, the most frequent genetic form of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). FTLD is the second commonest cause of degenerative dementia in presenium after Alzheimer’s disease. Behavioural and cognitive impairments progressively lead to dementia. ALS produces progressive muscle weakness leading to the death in 2 to 4 years. Since 2006, major discoveries have linked FTLD

and ALS: 1) TDP-43 aggregates in neurons and 2) C9orf72 mutations is a major genetic cause in both disorders. Two major pathological subtypes are now defined in FTLD, FTLD-TDP and FTLD-TAU. C9orf72 mutations (associated to FTLD-TDP) are the most frequent genetic causes of FTLD (15%), FTLD-ALS (65%) and ALS (40%).

FTLD is difficult at an early stage; and no clinical, biological or imaging features can predict the underlying pathology in living patients. Therapeutic perspectives emerged against tau aggregation, progranulin deficit and C9orf72 expansion (antisense). Presymptomatic carriers of genetic FTLD would benefit, before onset of symptoms, from these therapeutic that would delay or prevent the disease. At this step, it becomes crucial to develop markers to know how many years before symptoms, does the pathological progress begin, to treat the patients at the most early stage of the disease. Markers are also needed to predict the pathology (FTLD-TDP/FTLD-tau) in patients that will be eligible for trials targeting specific pathological lesion.
The objectives of the project are to develop appropriate biomarkers of disease onset, to determine the ideal time for initiating preventive therapies in presymptomatic subjects, and of disease progression to monitor therapeutic trials. We will conduct a multimodal study (cognition, brain imaging, omics) in C9orf72 families. We will take advantage of one of the largest cohort of C9orf72 families worldwide. This project assembles a consortium of experts in multiples disciplines: clinicians, researchers in neuroimaging, genetics and transcriptomics. The clinical phase of FTLD will be studied in patients carrying C9orf72 mutation; the preclinical phase will be studied in asymptomatic first-degree relatives that carry the mutation (presymptomatic carriers). The cohort will be followed at 3-time points (M0, M18, M36). Longitudinal analyses will aim at characterizing the trajectory of decline across time.

Brain structural changes will be evaluated by 1) morphometric analysis to assess global brain atrophy, cortical thickness, sulci opening; 2) functional connectivity analysis of resting-state MR data; 3) structural connectivity analysis of diffusion-weighted MRI. Brain metabolism will be evaluated with FDG-PET. RNA sequencing in lymphocytes of patients and presymptomatic carriers will detect differential gene expression and splicing alterations. It is a relevant way to identify peripheral biomarkers, considering the role of TDP-43 in regulation of transcription and splicing.

This ambitious project will give the opportunity to capture the very early phenotypical changes, the initial steps of brain structural, metabolic changes and biological cascades leading to neuronal death. The project will have important impact on public health by improving diagnosis and care of the patients. The discovery of appropriate markers will be rapidly translated into clinical practice to reduce misdiagnosis of FTLD and ALS. Markers of disease progression will represent reliable parameters to evaluate the disease severity and progression that will be incorporated in prevention trials. Notably, the project will create an appropriately-sized cohort of presymptomatic subjects that will be available for participation to potential therapeutic trials. Finally, the identification of novel targets of TDP-43 by transcriptomics will pave the way to identification of novel biological pathways, disease mechanisms and potential therapeutic targets in FTLD/ALS.

Further information available at:

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