TACKL-PRED

TACKLing the challenges of PREsymptomatic sporadic Dementia

Alzheimer's disease and related dementias are becoming an epidemic and there is an urgent need to develop effective therapies to prevent or delay onset. However, clinical trials to date have failed to find an effective drug even though there is some evidence of adequate target engagement in many studies, but without a corresponding clinical benefit. One reason for these failures may be that multiple co-pathologies, including neurodegenerative causes together with cerebrovascular disease, underlie the more common sporadic forms of dementia. Thus drugs used in trials targeting a single neuropathological entity, such as beta-amyloid, do not cover the full spectrum of underlying pathology. To leverage large, multimodal datasets from patients representing the full spectrum of neurodegenerative dementia as well as those at risk and apply well-informed data-driven analytic approaches to identify neurodegenerative dementia spectra and biotypes that can discern between pure from mixed forms of dementia during both the presymptomatic and symptomatic stages, i.e., that represent the true complexity of the underlying pathologies, which does not rely on original clinical diagnosis. We will combine multivariate, heterogeneous, and multimodal genomic, neuroimaging, cognitive/behavioural, biomarker and demographic datasets from four Canadian dementia cohorts (Ontario Neurodegenerative Disease Research Initiative [ONDRI], Brain Eye Amyloid Memory [BEAM] study, Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study and the Sunnybrook Dementia Study [SDS]), a Czech dementia cohort (Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementias, a JPND cohort acquired at CEITEC, MU [APGEM_MU]) and a Czech prodromal Lewy body diseases cohort (proLBD), and an Italian dementia cohort (Ca' Granda Cohort [CGC]), including the full spectrum of pathologies associated with dementia (Alzheimer's disease, Parkinson's-Lewy body disease, frontotemporal dementia/ amyotrophic lateral sclerosis, cerebrovascular disease), and a longitudinal aging cohort (Rotterdam Study) to achieve this goal. Specifically, we will evaluate how genomic, age, education, sex, and cardiovascular risk factors impact neuroimaging, biomarker, and cognitive/behavioural signatures in a disease- agnostic fashion, i.e. blinded to diagnosis, and use this information to locate an individual subject along dementia spectra. Dementia biotypes will also be defined using a variety of data-driven analytic approaches developed by the expertise of our neuroinformatics team. These dementia spectra will also be applied to the aging cohorts to see how they predict development of dementia/cognitive impairment and which specific biotype, i.e., presymptomatic disease signatures. Validation will take place using an autopsy subset of the data. Understanding shared mechanisms leading to this underlying pathological complexity in late onset sporadic dementia represent a critical knowledge gap and may inform future clinical trial design and more appropriate patient selection a priori (i.e., applied precision medicine approaches).

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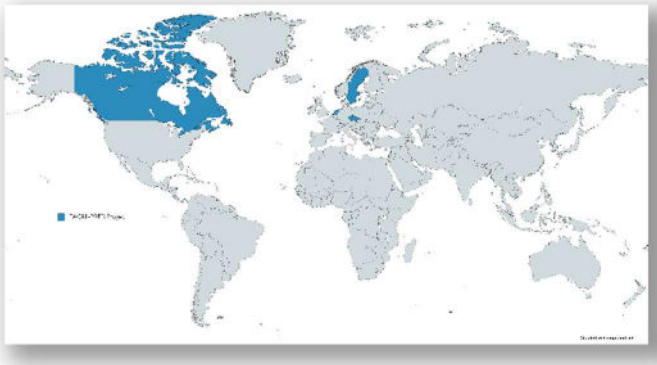

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