APGeM
Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementia

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Aims, research questions and working hypothesis
AD is heterogeneous with multiple pathologies developing on a continuum. Sporadic AD onset and progression occurs on a heterogeneous genetic background acting in concert with acquired risk- and protective factors. The consortium has strived to add to the biomarker toolbox encompassing genetics, neuropsychology, CSF biomarkers of inflammation and synapse degeneration, biomarkers of cerebrovascular disease, as well as transfer of mechanistic CSF biomarkers to a blood-based platform. **Aim 1**) Identify pre-morbid candidate genetic markers. **Aim 2**) Validate the candidate genetic markers in established case cohorts. Polygenic pre-morbid markers will subsequently be used in combination with dementia phenotypes, based on imaging, neurochemistry/proteomics and neuropsychology to improve diagnosis and validate identified markers (aim1) in a clinical setting. **Aim 3)** Develop clinical and laboratory prediction tools and test their usefulness in longitudinal studies.

Overall strategy of the workplan and means/methods
AD genetic architecture studies were employed to inform imaging- and proteomic studies targeting mechanistically identified phenotypic biomarkers, to be validated as predictors in longitudinal clinical cohort studies.

What are the outcomes of the project? (Milestones, key results obtained and publications)
Consortium partners have been instrumental in developing precise AD pre-dementia disease diagnostic tools, including novel genetic markers with mechanistic associations to inflammation, synapse degeneration and vascular disease (first milestone). Novel imaging methods capture more of the variation in incipient AD brain pathology. By using an extended MRI diffusion weighted imaging model, we have captured early, subtle signs of pathology.
By applying new methods guided by cell- and mouse-model experiments, we have captured more of the CSF and blood phenotypic variations of dementia, for mechanistic stratification at earlier stages of dementia disease.

Significance and impact on the field of the work carried out by the consortiumWhat are the next steps and future challenges now?
Important steps are taken, but the next challenges are to employ identified genetic and proteomic markers to predict disease onset (using polygenic hazard ratios), identify and stratify incipient cases by mechanistic subgroup (employing phenotype-genotype matching, improved imaging and fluid biomarkers) and test mechanistically targeted intervention strategies. Validation of mechanistic blood-based markers is ongoing.