EADB

Methodological approach and first results of the MCI project of the European Alzheimer's disease DNA Biobank

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The influence pathophysiological processes underlying the clinical progression of Alzheimer's disease (AD) may change over the disease course. Amyloid pathology, for instance, develops early in the disease course but shows little change at later stages. The influence of genetic determinates of distinct pathophysiological processes might therefore also change during the development of AD. To explore the genetic underpinnings of disease progression in the prodromal stage of AD, the EADB project is conducting a genome-wide association study (GWAS) on the longitudinal cognitive decline in patients with mild cognitive impairment (MCI).

The cognitive decline of patients with MCI shows a non-linear trajectory over time and previous research has shown that ignoring this decline can seriously distort the identification of determinates of decline (Bauer & Cai, 2009). As traditional approaches to GWAS are inappropriate for the analysis of non-linear changes, we established a new methodological framework for longitudinal GWAS. We developed a fast and flexible method for the estimation of linear mixed model of change over time based on a generalized least square approximation (Rönnegard et al., 2016). This approach was combined with a partial derivative-based meta-analysis (Roshchupkin et al., 2016) that yields identical statistical power as pooled analyses of data from multiple cohorts but without the need of sharing individual participant data. Monte Carlo simulation studies confirmed that our approaches dramatically reduces the computational time for longitudinal GWAS, shows negligible bias and appropriate type I errors and provides a considerable improvement of the statistical power for the detection of rare variants.

While the analyses of the whole EADB MCI samples is underway, first GWAS of cognitive decline in 2664 MCI patients with up 12 years of follow-up identified the APOE as a risk factor for cognitive deterioration at the genome-wide significance level and revealed 10 additional signals with suggestive evidence of association. Two of those were within genes related to glutamatergic transmission.