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LONGITUDINAL MODELLING FOR SINGLE NUCLEOTIDE POLYMORPHISM ASSOCIATIONS WITH ALZHEIMER'S DISEASE

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Background

Robust associations between genetic traits and neurodegenerative pathologies have been established thanks to the advent of GWAS. Meta-analysis incorporating tens of thousands of subjects allowed to discover hundreds of genetic loci associated with the diagnosis of diseases such as Alzheimer's Disease.

Our aim is to identify associations between SNPs and longitudinal features of the disease progression, such as speed of progression, feature-specific dynamic patterns, etc. A finer understanding of the link between SNPs and disease progression could help design new polygenic risk scores, targeting not the diagnosis, but rather for instance progression speed, hence allowing for higher-powered clinical trials for instance.

Method

We developed and validated a new statistical model that extracts interpretable progression parameters for patients from a longitudinal cohort. Our model is able to link time-independent covariates — such as SNP arrays — to dynamic aspects of the disease such as progression speed for each monitored biomarker, disease onset-time or progression patterns.

We applied our method to observational cohorts from the Alzheimer's Disease Neuroimaging Initiative (ADNI) effort. We modelled a multivariate progression profile that included both the evolution of cognitive neuropsychological assessments and the dynamics of imaging biomarkers (brain volumes, tau and Aβ loads). We pre-selected the SNPs that we included in our analysis from a published reference AD GWAS.

Results

Our results suggest that multiple profiles of SNP coexist even among the top-associated SNPs of GWAS (some are linked mainly with onset-time, while others show a strong association with the disease dynamics for either all or a particular subset of features).

Conclusion

We proposed a model to link individual SNP to dynamic aspects of the disease, and examined some SNPs associated with AD diagnosis, which suggested new kinds of associations based on disease dynamics.

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