Effect of Pathway-specific Polygenic Risk Scores for Alzheimer's Disease on Rate of Change in Cognitive Function and AD-related Biomarkers among Asymptomatic Individuals

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Abstract

Brain aging and genetic scores for late-onset Alzheimer's disease (LOAD) have been associated with cognitive decline and biomarker variations during the preclinical stages of dementia. Although an overall polygenic risk score (PRS) may be more powerful in the prediction of overall cognitive status and LOAD risk, a pathway-specific polygenic risk score (p-PRS) is more appropriate in predicting a specific biomarker or cognition component underlying LOAD pathology. However, the roles of LOAD-related genetic factors implicated in the normal brain aging process under various pathways of LOAD pathology are still not clear. In this study, we leveraged 10 years of longitudinal data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) and explored changing patterns in cognition and biomarkers at various age points along six pathways (APP metabolism, cholesterol metabolism, endocytosis, tau pathology, immune response, and axon development) among initially cognitively normal individuals. PRS and p-PRSs with and without apolipoprotein E (*APOE*), the strongest genetic risk factor for LOAD, have been constructed separately based on the significant genes associated with LOAD in the recent IGAP genome-wide association study meta-analysis and compared to *APOE* alone. We used a linear mixed-effects model to assess the association between PRS/p-PRSs and overall/sub-cognitive dimensions among 1,175 individuals. We also applied the model to the outcomes of cerebrospinal fluid (CSF) biomarkers for beta-amyloid 42 (Aβ42), Aβ42/40 ratio, total-tau, and phosphorylated tau based on predetermined hypotheses among 197 individuals. Additional analyses include a sex-stratified analysis and replication performed in an independent sample. We found that the adverse effect of the overall and p-PRSs, including *APOE*, on cognitive function appears ~10 years earlier than the PRS/p-PRSs when *APOE* is excluded. Pathway-specific PRSs have similar prediction performance as the overall PRS in cognitive outcomes, even though the p-PRSs can predict the memory-related cognitive decline earlier than the overall PRS when *APOE* is excluded. Females are more susceptible to the adverse effect of PRS/p-PRSs on cognitive decline than males between

the ages of 65 and 75, but the risk difference diminishes with age. Regarding CSF biomarkers, for the pathways hypothesized to be affected by *APOE*, only the association between PRS/p-PRSs and Aβ deposition show similar changing patterns as cognitive outcomes, and p-PRSs are more predictive than the overall PRS when *APOE* is excluded. The inclusion of *APOE* does not affect the prediction performance of PRS/p-PRSs on tau, but the adverse effect of PRS/p-PRSs on tau deteriorated with aging.