Polygenic Risk for Alzheimer's Disease Predicts MMSE Decline in APOE4 carriers and noncarriers

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Can a polygenic risk score (PRS) aid in the prediction of cognitive decline associated with dementia?

Introduction A limiting factor in the optimal balance of clinical trial arms for Alzheimer's disease (AD) is the significant heterogeneity in the progression of cognitive impairment associated with AD. Polygenic risk scores (PRS) may increase accuracy to predict cognitive decline in individuals at risk for AD.

Methods A PRS was calculated using genome-wide association study (GWAS) summary statistics for clinical AD diagnosis (Jansen et al, 2019; N=455,258). PRS derived from this GWAS study were computed for participants drawn from two aging studies, the National Alzheimer's Coordinating Center (NACC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). All non-APOE SNPs (<1Mb) that were significant at the p=0.5 level in the parent GWAS study were included in the respective PRS calculation. Logistic regression models assessed the association between PRS and Mini Mental State Exam (MMSE) decline covarying for age, sex, education, APOE-ε4, and baseline MMSE score. Age and sex interactions with PRS were also assessed.

Results Participants in the training and test set showed similar baseline ages, years of education and baseline MMSE scores in the whole sample and after stratification by APOE4 carrier status. The test cohort had a lower percentage of females compared to the training set (training, 52% female; testing, 43% female). The PRS model was a significant predictor of MMSE decline (p=8x10-5), as well as in APOE4 carrier and noncarrier populations (carriers p<0.001; noncarriers p=0.02). The PRS model showed the highest classification accuracy in APOE4 noncarriers in both the training and test sets (81 and 80%, respectively). Compared to a base model for MMSE decline, which included age, sex, and education as predictors, the PRS model increased the area under the receiver-operator curve by 2% in the test cohort (base model, AUC=0.83; PRS model, AUC=0.85). The sample was narrowed to participants with a baseline MMSE of 30-25 to represent early phase of disease, and in the overall test sample the PRS model showed a 3% increase in area under the receiver-operator curve compared to the base model described above which did not consider genetics (base model, AUC=0.77; PRS model, AUC=0.80). There were no age or sex interactions with the PRS on MMSE decline.

Conclusion The proposed PRS model explains heterogeneity in cognitive decline above and beyond the APOE4 allele, as APOE and it's surrounding region were excluded from the computation of the PRS. PRS models appear to have predictive power in the early stages of cognitive decline (baseline MMSE 30-25). Utilization of additional genomic factors beyond APOE in PRS models could

enhance clinical trial recruitment and stratification strategies for trial analyses, such that APOE4 carriers are selected for probable cognitive decline, in addition to APOE3 carriers that are also high on polygenic risk.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

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