Polygenic risk score predicts mild cognitive impairment and Alzheimer's disease significantly better than *APOE* in ADNI dataset

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Background

Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting millions of people worldwide. The pathological process begins decades before the AD onset and so early identification of adults at elevated risk for AD is crucial.
Mild cognitive impairment (MCI) is an intermediate phenotype that in some individuals progresses to AD, and may indicate the first manifestation of AD[1]. Amyloid-beta plays a key role in the pathogenesis of AD and it is often used as a biomarker even though it has been shown that it has low specificity for predicting development of AD[2]. Polygenic Risk score (PRS) approach has shown great potential in identifying individual risk for AD[3] and MCI[4]. The aim of this study is to systematically examine the prediction accuracy of AD PRS differentiating between AD/MCI/controls/amyloid deposition in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset in different scenarios(http://adni.loni.usc.edu).

ADNI dataset

ADNI is a longitudinal study that assesses clinical, imaging and genetic data during aging in MCI, AD and cognitively normal individuals.
Analysis was performed on 770 individuals with available whole genome sequenced information (MCI- 344, AD- 174 and 224-cognitively normal individuals), respectively. The latest available diagnosis and PET scan was used for diagnosis and amyloid deposition classification, see Table 1.

Methods

PRS was performed using latest IGAP summary statistics[5] as discovery dataset and ADNI as the test dataset. Standard quality controls check has been performed in ADNI and remaining SNPs have been matched with IGAP, leaving 5,771,686 SNPs in the analysis.
To separate *APOE* effect from PRS score, *APOE* region was excluded from the simulations and ε2 and ε4 effects were calculated directly from the genotypes using logistic regression and AD phenotype in ADNI dataset. Predictions of AD vs controls, MCI vs controls, amyloid deposition and AD(converters) vs MCI(not converters) were made in different scenarios using models of *APOE* (ε2 and ε4) alone, PRS without *APOE* and full PRS model (*APOE* and PRS together). Note that sex and age were used for all analysis as predictors. We present results for p-values threshold of 0.5.

Table 1. Amyloid deposition and phenotypes in ADNI dataset

Amyloid status	N samples	MCI positive (%)	AD positive (%)	Controls (%)
Amyloid positive	357	162 (47 %)	120 (69%)	65 (29%)
Amyloid negative	304	148 (43 %)	18 (10%)	128 (57%)
NA	89	34 (10 %)	36 (21 %)	31 (14 %)
All samples	770	344	174	224

Results

PRS and *APOE* predictions in ADNI dataset of AD vs controls, MCI vs controls, and their extremes can be seen in Table 2. We also observed that for amyloid deposition a good accuracy can be achieved by *APOE* risk alleles alone (AUC_{APOE}=0.76) and AD PRS does not improve significantly this prediction.

Table 2. PRS and APOE predictions in ADNI dataset

	Model: *APOE*(ε2+ε4) +sex+age			*Model: APOE(ε2+ε4)+PRS(p<0.5)+sex +age*			Anova (*APOE, APOE+* PRS)	PRS extremes ±1.5 standard deviation	
	B^1	P	AUC	B^{1-4}	P	AUC	P	Sensitivity	AUC
AD vs controls	0.99 [0.13]	1.06e-18	0.757	0.93[0.13] 0.86[0.13] -0.63[0.24] 0.04[0.02]	1.9e-29	0.82	2.1e-13	0.88	0.94
MCI vs controls	0.3 [0.1]	9.6e-5	0.62	0.26[0.1] 0.66[0.1] -0.47[0.18] -0.005[0.01]	1.1e-12	0.68	1.8e-10	0.83	0.9

B^1=beta *APOE*(ε2+ε4), B^2=beta(PRS), B^3=beta(sex), B^4=beta(age)

Results of using different scenarios to predict phenotypes with the *APOE* and full PRS model can be seen in Figure 1 and 2.

Figure 1. APOE and full PRS predictions in sample that were first clinically diagnosed with MCI.

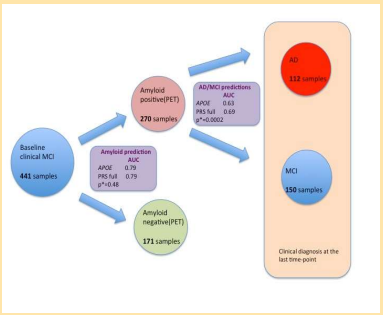
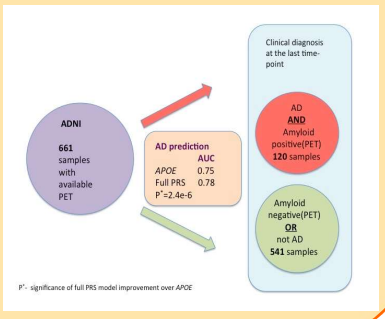


Figure 2. APOE and full PRS predictions for AD amyloid positive individuals.



Discussion

The highest prediction accuracy was achieved using all predictors (full model), for both AD and MCI status, the area under the curve AUC=82% for AD and AUC=68% for MCI. The prediction accuracy of the full model was 6% higher when compared to the model based upon *APOE* risk alleles only in both cases. Accuracy of predictions of PRS extreme individuals (±1.5 standard deviation) reaches AUC of 90% and above. PRS improves predictions above *APOE* when comparing individuals with AD vs MCI, both amyloid positive. These findings could potentially facilitate AD clinical trials.

Founding funders:

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