IHCC/DAC AD PRS

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Development of transethnic AD PRS

- Score based on summary stats from stage I of Jun et al., transethnic GWAS
  - **2 stage design Stage 1 ADGC European Ancestry, African-Americans, Japanese, and Israeli-Arabs (26,320 EAs, 4983 AAs, 1845 JPN, and 115 IAs)**
  - **Stage 2 International Genomics Alzheimer's Project (EA)**

- Supplemented with Bellenguez et al., stage I data excluding UKB proxy-ADD
  European Alzheimer's Disease BioBank (EADB) consortium (&UKBB) 20,464 cases and 22k controls.
  Phase I EADB 39,106 AD cases & 46,828 UKBB proxy-ADD (n= 85,934 cases)
  Phase II ADGC, Finngen, CHARGE 25,392 cases
  75 independent loci, 33 previously reported, 42 novel

- Multi-allelic variants, indels and rare SNPs with MAF < 3% were excluded from analysis
- Remaining variants from the combined summary stats were LD pruned using an R^2 threshold of 0.3 resulting in a final list of 74 variants
- Validation was carried out in the eMERGE consortium Phase I-III dataset

Development of PRS in early onset dementia

- Like other published AD PRS studies the APOE region has been omitted from the score and will be incorporated as a covariate in the full model

- **APOE risk varies by ancestry**
  - The effect of APOE genotype on AD risk is highly variable across populations
  - The ε4 frequency is lower in Asians and associated with higher AD risk among Japanese (JPN) compared with EAs.
  - Effect of ε4 on AD risk is lower in African-Americans (AAs) among whom the ε4 frequency is about 50% higher than in EAs
- Other covariates include age, sex and the first 3 principal components for genetic ancestry correction.

PRS Implementation / metrics

- As all groups may not have accurate age at onset data we are requesting odds ratios (rather than hazard ratios)
  - 1) Sites will return odds ratio per standard deviation of the PRS distribution with 95% CI
  - 2) We estimate a model discrimination (AUC) with CI of A) the PRS alone B) the PRS and APOE status C) The non-genetic predictors alone D) the full model
  - 3) Tail discrimination: We're proposing to set the cutoff for the high risk group at the 97.5% of the PRS. Provide the ORs and 95% CI (and the P-value for the OR) for the high risk group vs everybody else. i.e the subjects in the top 2.5% of the PRS vs the bottom 97.5%.
  - 4) Provide the sensitivity / specificity as well as negative (NPV) and positive (PPV) predictive values at the proposed cutoff (split by ancestry if appropriate for your cohort)
- For the NPV/PPV please use prevalence adjusted metrics, i.e. PPV = (Sn * Pr) / [(Sn * Pr) + ((1 – Sp) * (1 – Pr))] and NPV = (Sp * (1 – Pr)) / [(Sp * (1 – Pr)) + ((1 – Sn) * Pr)] where Sn = sensitivity, Sp = specificity, and Pr = population based prevalence reflective of your study population.

Site	Genetic ancestry	Phenotypic outcome	# case:control	Age range (if restricted)
Dementia Endpoints				
NCGG	Japanese (East Asian)	AD, MCI	Case:1000 Normal Cognitive:1000	77(32-100)
East London Genes and Health cohort	British-Pakistani/British-Bangladeshi (South asian)	All-cause dementia (from secondary/primary care records); MCI/cognitive decline cases excluded	104 cases; 614 controls	Cases >40 years; healthy controls >70 years old
Korean Biobank Project	Korean (East Asian)	Phenotype 1: Cortical amyloid positivity (by Flutemetamol PET imaging) (Control: Cortical amyloid negativity)	191:337 (total 528)	
		Phenotype 2: Clinical Dementia Rating (CDR) global Score 1 or over (Control: CDR global 0.5 or less)	157:539 (total 696)	
Intermediate phenotypes / biomarkers				
AWI-Gen	African (Different ethnolinguistic and geographic groups)	NA		
ELSA	Brazilian (Admixed)	Neuro-cognitive endophenotypes	2844	
INTERVAL (UK Blood Donors)	European (White British)	Stroop Test (attention and reaction times), Trail Making Test (executive function), Pairs Test (Episodic Memory), Reasoning Tests (intelligence), >3K proteins on the SomaLogic proteomics platform	~9k Cognitive measure; 1140 proteomics	

Sites with AD phenotype endpoints

NCGG, East London, Korea Biobank

Phenotype 1: Cortical amyloid positivity (by Flutemetamol PET imaging) (Control: Cortical amyloid negativity)
Phenotype 2: Clinical Dementia Rating (CDR) global Score 1 or over (Control: CDR global 0.5 or less)

Cohort	Odds ratio per SD	Estimate of model discrimination (AUC) with CI of PRS score only	Estimate of model discrimination (AUC) with CI for genetic predictors ie PRS and APOE counts	Estimate of model discrimination (AUC) with CI of the non-genetic covariates only	Estimate of model discrimination (AUC) with CI of the full model (i.e. with genomic predictor and non-genetic covariates)
Korea pheno1	1.1857 (0.9917,1.4177)	0.5482 (0.4968,0.5997)	0.6770 (0.6282,0.7259)	0.6266 (0.5762,0.6770)	0.7505 (0.7053,0.7957)
Korea pheno2	1.0403 (0.8709,1.2426)	0.5074 (0.4559,0.5589)	0.6122 (0.5604,0.6640)	0.5451 (0.4931,0.5970)	0.6372 (0.5858,0.6886)
EastLondon	1.11 (95% CIs: 0.94-1.33)	0.53 (95% CIs: 0.47-0.59)	0.54 (95% CIs: 0.48-0.60)	0.68 (95% CIs: 0.61-0.75)	0.69 (0.62-0.76)
Japan	1.120	0.545 (0.5198-0.5702)	0.6071 (0.5824-0.6318)	0.61575 (0.5907-0.6408)	0.6254 (0.6005-0.6503)

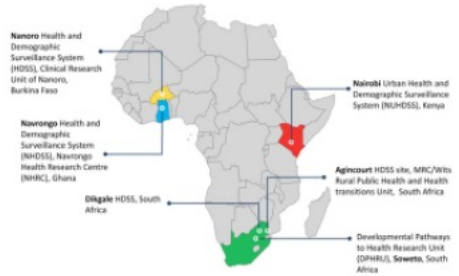
Random effects restricted maximum likelihood (REML) meta-analysis of AUC and variance 0.674 (0.643-0.706)

Neuro-cognitive endophenotypes / Proteomics

ELSA Brazil 2844 admixed individuals w/neurocognitive assessments

Trait	Unadjusted Model		PC adjusted		PCs + ApoE	
	P value	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)
Common mental disorders score	5.5e-09	13.3 (2.2)	1.2e-06	11 (2)	1.2e-06	11.2 (2.3)

AWI-Gen
10603 participants
Genotyped on H3A chip
Imputed using Sanger AFR panel



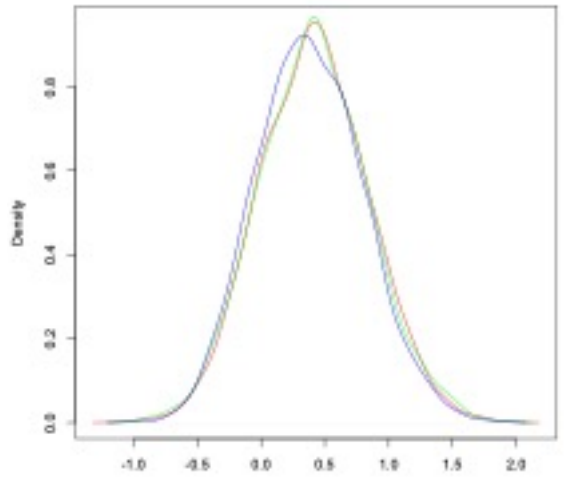
INTERVAL (UK Blood Donors)

Assayed 3K proteins on the SomaLogic proteomics platform

PRS + APOE SNPs

Correlation with blood APOE protein levels

	APOE.2937.10.2	APOE.5312.49.3
R2	6.55E-03	0.00475
P	0.0057	0.0194
BETA	16.9	15.03
SE	6.11	6.42



Conclusions and Further work

- Developed a transethnic AD PRS based on 74 variants
- Effect estimates derived from studies including individuals of European Ancestry, African-Americans, Japanese, and Israeli-Arabs
- Performance of score evaluated across dementia, neurocognitive and proteomic endpoints in diverse ancestries
- Performance varied by endpoint over ancestry
- Positive association with neurocognitive endpoint in ELSA and circulation APOE levels in INTERVAL study
- **Future work includes:**
- Evaluation of score in a large European ancestry cohort from UKB
- Evaluate inclusion of ancestry dependent APOE estimates

Acknowledgments

- **CHOP**
  - Hakon Hakonarson
  - John Connolly
- **NCGG**
  - Kouichi Ozaki
- **East London Genes and Health cohort**
  - Charlie Marshall
- **Korean Biobank Project**
  - Jae Pil
- **AWI-Gen**
  - Michele Ramsay
  - Ananyo Choudhury
- **ELSA**
  - Alexandre Pereira
- **INTERVAL (UK Blood Donors)**
  - **Adam Butterworth**