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

NCGG, East London, Korea Biobank

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

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**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Unadjusted Model</th>
<th>PC adjusted</th>
<th>PCs + ApoE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Beta (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>Common mental disorders score</td>
<td>5.5e-09</td>
<td>13.3 (2.2)</td>
<td>1.2e-06</td>
</tr>
</tbody>
</table>

**INTERVAL (UK Blood Donors)**

Assayed 3K proteins on the SomaLogic proteomics platform

PRS + APOE SNPs

Correlation with blood APOE protein levels

<table>
<thead>
<tr>
<th></th>
<th>APOE.2937.10.2</th>
<th>APOE.5312.49.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2</td>
<td>6.55E-03</td>
<td>0.00475</td>
</tr>
<tr>
<td>P</td>
<td>0.0057</td>
<td>0.0194</td>
</tr>
<tr>
<td>BETA</td>
<td>16.9</td>
<td>15.03</td>
</tr>
<tr>
<td>SE</td>
<td>6.11</td>
<td>6.42</td>
</tr>
</tbody>
</table>

AWI-Gen

10603 participants
Genotyped on H3A chip
Imputed using Sanger AFR panel
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

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• ELSA
  • Alexandre Pereira

• INTERVAL (UK Blood Donors)
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