Polygenic hazard score in preclinical Alzheimer’s disease

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Outline

Polygenic hazard score (PHS)

1. Development and validation (Desikan et al., 2017; *PLoS Medicine*)

2. Cognitive and clinical decline in preclinical AD and MCI (Tan et al., 2017; *Annals of Neurology*)

3. Enrichment marker for CSF/PET amyloid & tau (Tan et al., *under review*)
AD polygenic risk

- Apolipoprotein E (APOE) ε4
- Other AD-associated SNPs (small effects)
- PHS: combining APOE & 31 AD-associated SNPs
- Polygenic risk score? Polygenic hazard score?
- When rather than if
IGAP: Identify set of AD-associated SNPs at $p < 10^{-5}$

ADGC (phase 1): Select final set of SNPs using Cox regressions with stepwise procedure

ADGC (phase 2): Validation
PHS – Development and validation

Desikan et al., 2017, PLoS Medicine
PHS – Annualized incidence rates

- Combining PHS with disease incidence in general US population (Brookmeyer, 1998)
- Instantaneous risk

Desikan et al., 2017, PLoS Medicine
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PHS in preclinical AD and MCI

• Clinical trial failures – too advanced in disease

1. Identifying CN & MCI individuals most likely to progress to AD dementia

2. Identifying CN & MCI individuals who will experience the greatest rate of cognitive and clinical decline

Tan et al., 2017, Ann Neurol
PHS – Annualized incidence rates

CN

- NACC dataset
- CN = 1081, MCI = 571
- CN: (HR = 2.36, 95% CI = 1.38 – 4.03)

- Using only GWAS between cases and controls to generate polygenic risk may be suboptimal

Tan et al., 2017, Ann Neurol
PHS – Clinical decline

- CERAD: mod – freq
  1. APOE ($p = 0.61$)
  2. PHS in e3e3 ($p < .05$)

Tan et al., 2017, *Ann Neurol*
# PHS – Cognitive decline

## CN & MCI

<table>
<thead>
<tr>
<th>Test</th>
<th>β (SE)</th>
<th>p-value</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory</td>
<td>-1.51 (0.68)</td>
<td>2.74x10^-2</td>
<td>1,224</td>
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<tr>
<td>WAIS-R Digit Symbol</td>
<td>-1.53 (0.35)</td>
<td>1.60x10^-5</td>
<td>1,143</td>
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<td>Boston Naming Test</td>
<td>-0.96 (0.24)</td>
<td>6.98x10^-5</td>
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<td>Trail-Making Test A</td>
<td>-3.25 (1.00)</td>
<td>1.05x10^-3</td>
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<tr>
<td>Trail-Making Test B</td>
<td>-4.36 (1.04)</td>
<td>2.85x10^-5</td>
<td>1,212</td>
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<tr>
<td>Digit Span (forward)</td>
<td>-1.07 (0.39)</td>
<td>5.47x10^-3</td>
<td>1,258</td>
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<tr>
<td>Digit Span (backward)</td>
<td>-0.59 (0.53)</td>
<td>0.26</td>
<td>1,258</td>
</tr>
</tbody>
</table>

- **CN individuals**
  1. WAIS-R Digit Symbol
  2. Trail-making Test B
  3. Digit Span (forward)

Tan et al., 2017, *Ann Neurol*
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PHS – Enrichment marker for amyloid and tau

- High amyloid PET screen failure rate in preclinical AD

1. Identifying CN & MCI individuals most likely to be amyloid/tau positive

2. Combination of PHS and biomarker to predict cognitive and clinical decline.
PHS - Predicting biomarker status

ADNI: CN = 347, MCI = 599

CN + MCI

Amyloid + (CSF/PET)

Total tau + (CSF)
PHS + biomarker: Cognitive and clinical decline

CN + MCI

Memory

- amyloid +
- total tau +
- high PHS and amyloid +
- high PHS and total tau +

CDR-SB

Tan et al., under review
Conclusion

Polygenic hazard score (PHS)

1. Predict biomarker positivity

2. PHS + biomarker : Best predict longitudinal cognitive and clinical decline

3. May be useful in preclinical AD and MCI trials
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