Your Genetics Are Driving Advances in Alzheimer’s Disease

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Genetics of AD

Autosomal dominant inherited (monogenic) forms
early onset (30-60 yrs of age); < 1%
• amyloid precursor protein (APP)
• presenilin 1 (PS1)
• presenilin 2 (PS2)

Sporadic forms (genetic components variable)
late onset (60 + yrs of age)
• apolipoprotein E (APOE) (e4 isoform)
• many other potential genes
  - genome-wide association studies (GWAS)
  - multigenic risk
APOE (and the others)

Kunkle et al., *Nature Genetics* 2019

Genetics of Alzheimer’s Disease

McCarthy et al., *Nat Rev Genetics*, 2008
Short-Read Sequencing vs. Long-Read Sequencing

Stanford ADRC Sequencing

- Short-read sequencing on most everyone
- Long-read sequencing on most everyone
- One early, important finding...
Protective Variant on TMEM106B in Frontotemporal Dementia and AD

Table 1  TMEM106B risk association studies in GRN vs C9orf72 mutation carriers

<table>
<thead>
<tr>
<th>Mutation group</th>
<th>References</th>
<th>Group 1 (N)</th>
<th>Group 2 (N)</th>
<th>Model</th>
<th>SNP</th>
<th>Minor allele</th>
<th>p-value</th>
<th>Odds Ratio</th>
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</thead>
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<tr>
<td>GRN</td>
<td>Van Deerlin et al. [76]</td>
<td>CON (2589)</td>
<td>GRN (89)</td>
<td>Alleric</td>
<td>rs1990922</td>
<td>C</td>
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<td>Fischer et al. [19]</td>
<td>CON (822)</td>
<td>GRN (78)</td>
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<td>Nicholson et al. [52]</td>
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<td>Lattante et al. [38]</td>
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<td>Lattante et al. [38]</td>
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<td>9.54 x 10^{-8}</td>
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</tbody>
</table>

TMEM106B Alu Deletion

A

B

Chemparathy*, Le Guen* et al., Submitted
Conclusions

• Long-read sequencing is turning up new large genetic variants that affect risk of Alzheimer’s disease
• Stanford ADRC is leading the charge in finding large genetic variants (THANKS TO YOU)
• Lots more findings to come
• Tune in next year