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Genetic link between Alzheimer’s disease and regional sulci morphology

Introduction

- Alzheimer’s disease (AD) is a heritable and polygenic. The largest genome-wide association study on AD by the International Genomics of Alzheimer’s Project (iGAP) reported 22 common variation risk loci. These 22 common variation risk loci explains only fraction of the heritable component of AD.
- Genomic studies on intermediate quantitative measurements (Endophenotype) such measures of brain MRI and cognitive impairments could: 1) help identify additional AD risk loci explaining missing heritability; 2) help decipher the biological pathways leading to AD.
- Recent GWAS on hippocampal volume showed ~15% of genetic correlation with AD, suggesting genetic risk factors for other MRI measurements might also have role in AD pathophysiology.
- Sulci measurements representing regional brain atrophy are strong candidates for neurodegenerative diseases such as AD.
- The Polygenic risk score profile created by aggregating effects of large number of common genetic variations enhances the risk prediction with AD. This AD-state independent genetic risk profiles of AD is a robust instrument to identify quantitative measurements sharing genetic roots with AD.
- Objective: To test associations between variation in polygenic risk score of AD and individual sulci measurements (openings and thicknesses) adjusting for age, sex, intracranial volume and population stratification.

Abstract

MRI-markers for cortical atrophy assessment such as sulci opening and thickness can be used as quantitative endophenotypes of dementia. Here we report the first study testing associations between genetically predicted Alzheimer’s disease (AD) risk and sulci morphology measurements in older persons of European origin. The study population to derive the polygenic risk score (PRS) comprised 6,489 participants from the French population-based 3C cohort, with 1000 genomes imputed genome-wide genotype data, and of whom 810 had a diagnosis of prevalent or incident dementia cases. Using genome-wide association study summary data on 17,008 AD cases and 37,154 controls from the International Genomics Alzheimer Project (iGAP) consortium we created the polygenic risk score (PRS) profile of the 6,489 3C participants. The parameters for the PRS analysis were optimized so that the highest predictive power was achieved for AD diagnosis in 3C (R²=0.482). The association of the PRS with sulci opening and thickness was then tested in a subset of 2,218 3C participants with brain MRI and sulci measurements. A total of 222 sulci measurements were available after quality control. Using linear regression we identified significant association of the AD PRS profiles for nine sulci opening and one sulci thickness parameters after multiple testing corrections using the permutation approach. In conclusion, we report genetic link between Alzheimer’s disease and 10 sulci morphology measurements in older community persons.

Materials and Methods

- Alzheimer disease GWAS summary data from the iGAP consortium: 17,008 cases and 37,154 controls.
- 3C population-based cohort study with 1000 imputed genotypes and information on AD status (N=6,489, 810 dementia cases).
- 3C brain MRI sub-samples with sulci measurements in 3C-Bordeaux (N=663) and 3C-Dijon (N=1,554).

Methods:
- Imaging: Sulci measurements using the MORPHOLOGIST software.
- Polygenic risk score analysis using PRSice v1.26 software.
- Permutation approach to derive the significance threshold for association accounting for multiple testing.
- Linear regression using R (in house scripting).
- Inverse variance weighted meta-analysis using R (in house scripting).

Results

- The model fit Nagelkerke’s R2 for prediction of possible and probable AD in 3C cohort is as high as 0.482 achieved using full genome-wide data.
- We identified significant association (permutation derived significant threshold for 222 correlated traits) of 10 sulci measurements with AD common variation genetic risk (Table 1).

Table 1: Association of AD polygenic risk score with sulci measurements

<table>
<thead>
<tr>
<th>Sulci measurement</th>
<th>3C-Bordeaux (N=546)</th>
<th>3C-Dijon (N=1377)</th>
<th>Meta-analysis (N=1923)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Sulcus opening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left paracentral sulcus</td>
<td>1603.8</td>
<td>727.2</td>
<td>2.9×10⁻10</td>
</tr>
<tr>
<td>Left thalamic/rostrobasal</td>
<td>711.2</td>
<td>230.4</td>
<td>4.9×10⁻10</td>
</tr>
<tr>
<td>Left posterior lateral fissure</td>
<td>425.3</td>
<td>250.8</td>
<td>9.3×10⁻20</td>
</tr>
<tr>
<td>Left lateral perisylvian fissure</td>
<td>964.2</td>
<td>393.0</td>
<td>1.5×10⁻11</td>
</tr>
<tr>
<td>Left inferior frontal sulcus</td>
<td>116.9</td>
<td>263.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Right intermediate frontal sulcus</td>
<td>100.0</td>
<td>251.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Left callosal marginal sinus</td>
<td>394.8</td>
<td>360.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Left intermediate frontal sulcus</td>
<td>153.8</td>
<td>236.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Left superior temporal sulcus</td>
<td>398.2</td>
<td>2415.0</td>
<td>3.9×10⁻10</td>
</tr>
<tr>
<td>Sulcus thickness1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior sylvian-lateral sulcus cortical thickness</td>
<td>-533.4</td>
<td>195.5</td>
<td>8.8×10⁻10</td>
</tr>
</tbody>
</table>

1. Thickness of the cortical mantle in the sulcus

Conclusion

- This is the first study reporting genetic link between polygenic risk of Alzheimer's disease and regional sulci measurements.
- We identified significant association of 10 sulci measurements.
- We sought replication of these findings in an independent study.
- The functional explorations are also ongoing.
- These findings provides guidance for multi cohort meta-analysis of GWAS for regional sulci measurements as a tool to improve our understanding of brain aging and AD pathophysiology.

References


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