Combining Omics and Imaging Data from SMC individuals, Artificial Intelligence Technology Identifies Genomic Biomarkers for Early Detection of Alzheimer’s Disease.

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Introduction

Towards earlier detection of Alzheimer’s disease

Number of AD cases will triple, healthcare cost will double by 2030

Early detection and management of some, if not all, future AD cases is critical

Focusing on profiles at risk for AD, but not yet affected, will help us

The combination of DNA analysis and Artificial Intelligence is needed to analyze extensively characterized cohorts

We need a cohort of subjects, not having AD, MCI, or other neurological/psychiatric disorder, but at risk, with extensive DNA information

AD: Alzheimer’s disease; MCI: mild cognitive impairment

Introduction

Study performed in a large-scale, university-based, monocentric cohort

Cognitively and physically normal Caucasian individuals with SMC
SMC defined as positive response to both questions:
• Are you complaining about your memory?
• Is it a regular complaint which lasts more than 6 months?

Preclinical Cohort of subjects with subjective memory complaints SMC

- 318 subjects
- 70–85 years
- Subjective memory complaints
- Unimpaired cognition and memory

PET: positron emission tomography; MRI: magnetic resonance imaging; AD: Alzheimer’s disease
Objective

Identify relations that link genomic information with neuroimaging evolution

- Genome influencing in the evolution of brain structure and activity?
- Genomic description of the aging brain to identify profiles that are more at risk for neurodegeneration?
Genotyping: 486,137 variants (SNP) measured

Variants that are carried by only one subject are excluded.

Remaining variants are clustered: 2 variants shared by exactly the same subjects will be grouped together.

295,995 variants -> 288,651 clusters

Neuro Imaging: brain metabolism, volume, resting state activity, brain amyloid burden, and cortical thickness

Imaging descriptors normalized using z-score, and the delta ratio of z-score between baseline (M0) and 24\textsuperscript{th} month (M24) calculated.

A total of 301 delta ratio of neuroimaging variables generated
Database has 288,952 variables across 6 categories, dominated by Genomic and Brain metabolism. Number of subject is 184-330, depending on variable category.

**Data and Analysis plan**

- **Genomic**
  - Genomic variants (SNPs)
  - Genotyping (microarray)
  - 288,651 variables (295,995 variants)
  - 299 subjects

- **Brain metabolism**
  - FDG PET
  - 330 subjects
  - 120 variables Delta Ratio M0 – M24

- **Brain Amyloid burden**
  - Amyloid PET AV45
  - 318 subjects
  - 14 variables Delta Ratio M0 – M24

- **Brain resting state activity**
  - fMRI: fALFF
  - 211 subjects
  - 91 variables Delta Ratio M0 – M24

- **Brain volume (forebrain and hippocampus)**
  - MRI: Volume BF & HP
  - 276 subjects
  - 6 variables Delta Ratio M0 – M24

- **Cortical Thickness**
  - MRI
  - 184 subjects
  - 70 variables Delta Ratio M0 – M24

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BF: basal forebrain; HP: fractional amplitude of low frequency fluctuations
Data and Analysis plan

Linking variants with neuroimaging features

Estimated number of relations that can be extracted from the data: $3 \times 10^{11}$

A subset of $3.5 \times 10^8$ relations link genomic variants to imaging descriptors:

Using KEM® Artificial Intelligence to generate, explore, rank these relations.
Methodology

Combining and analyzing genomic and imaging data using the Artificial Intelligence platform KEM®

Systematic unbiased generation of all possible causal associations in a multi-parametric dataset

- >100 million relations extracted and characterized from study data
- Identification & ranking of variants relating to neuroimaging descriptors derived from a small number of samples, avoiding overfitting

Unsupervised and explainable Machine Learning - Artificial Intelligence Platform Supporting Observational studies and Clinical Trial Design KEM® using Formal Concept Analysis (FCA)

Comprehensively analyzes complex datasets by measuring all logical relations within a dataset, exploring all combinations of parameters and endpoints

Identifies most relevant and powerful causal relations, revealing hidden relationships

Successfully utilized in oncology and multiple other disease areas
Methodology

46 millions rules extracted over 288 952 descriptors

- Left: 288 651 clusters of variants (295 995 variants)
- Right: 301 brain imaging descriptors
- Support ≥5
- Confidence ≥0.5%
- Lift ≥1.2
- 46,799,084 rules generated
Results

2 steps of filtering select single relation

46,799,084 rules

Top 0.1%

Lift | Support | Pvalue | Confidence

348,830 rules

Left: exclude absence of variant
Right: exclude Unchanged Brain regions

239,027 rules

71,575 variants

Selecting Genes with documented clinical significance

239,027 rules

71,575 variants

528 variants within 473 genes with clinical significance
Ensembl BioMart
https://www.ensembl.org/info/data/biomart/

Examples of clinical significances:
- benign
- likely benign
- risk factor
- uncertain significance

Any disease can be included.

1,785 rules

Multiple testing corrected p < 0.05

1 rules

1 homozygous variant in **COG6** gene linked to **decrease in resting state activity** in the **Orbito Frontal Cortex**.

<table>
<thead>
<tr>
<th>snp</th>
<th>Gene</th>
<th>Outcome</th>
<th>Evolution</th>
<th>Experiment</th>
<th>Brain Region</th>
<th>Hemisphere</th>
<th>n</th>
<th>Conf.</th>
<th>Lift</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>cl204843</td>
<td>COG6</td>
<td>Frontal Med Orb DeltaRatio</td>
<td>Decreased</td>
<td>fALFF</td>
<td>medOFC</td>
<td>Left</td>
<td>22</td>
<td>0.79</td>
<td>2.39</td>
<td>3.34E-02</td>
</tr>
</tbody>
</table>

Multiple testing corrected

This variant is also linked to decrease in connectivity in the inferior temporal gyrus, although not significantly.
Results

identified variant in COG6 identified in the 3’ UTR: effect is mediated through regulation of COG6 expression


UTR: Untranslated region
Results

COG6 is required for normal function of the Golgi apparatus, as a component of the conserved oligomeric Golgi complex (COG) required for vesicle transport.
COG6: the Golgi apparatus is a critical cell component in neurodegenerative diseases

<table>
<thead>
<tr>
<th>Title</th>
<th>1st author</th>
<th>Journal</th>
<th>Year</th>
<th>URL</th>
</tr>
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<tbody>
<tr>
<td>Tau secretion is correlated to an increase of Golgi dynamics</td>
<td>Mohamed N</td>
<td>PLoS One</td>
<td>2017</td>
<td><a href="https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178288">https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178288</a></td>
</tr>
<tr>
<td>Morphometric alterations of Golgi apparatus in Alzheimer’s disease are related to tau hyperphosphorylation.</td>
<td>Antón-Fernández A</td>
<td>Neurobiology of Disease</td>
<td>2017</td>
<td><a href="https://www.sciencemag.org/content/356/6344/723.full">https://www.sciencemag.org/content/356/6344/723.full</a></td>
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<tr>
<td>Increased neuronal activity fragments the Golgi complex</td>
<td>Thayer DA</td>
<td>PNAS</td>
<td>2013</td>
<td><a href="https://www.pnas.org/content/110/19/7611.full">https://www.pnas.org/content/110/19/7611.full</a></td>
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Conclusions & Take Home Messages

• An homozygous variant in **COG6**, a protein involved in Golgi apparatus function, and putatively expressed in the Hippocampus as well as other brain region, identified to be significantly (after multiple testing correction) linked to a decrease of resting state activity of the left Orbitofrontal cortex.

  • Identified variant in COG6 located in the 3’ UTR : its effect is mediated through regulation of COG6 expression
  • COG6 is required for normal function of the Golgi apparatus, as component of the conserved oligomeric Golgi complex (COG) required for vesicle transport.
  • The Golgi apparatus is a critical cell component in neurodegenerative diseases

• **Unsupervised and explainable Artificial Intelligence** tools uncover pertinent hypotheses from complex datasets with limited number of fully characterized patients.
Thank you

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