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

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Conflict of Interest Disclosure

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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

Introduction

Preclinical Cohort of subjects with subjective memory complaints SMC

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?

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

Amyloid (18F-Florbetapir) PET Imaging
Brain MRI / fMRI imaging
Brain glucose-metabolism [18F-fluorodeoxyglucose (18F-FDG) PET]
Cognitive assessment

PET: positron emission tomography; MRI: magnetic resonance imaging; AD: Alzheimer’s disease
Can we identify genomic variants that are simultaneously linked to multiple types of endpoints?
AI needed to address the data analytics challenge of “wide matrices” and very large number of hypothesis

- Systematic omic Analysis of longitudinal cohorts
- Identification of biomarkers of response from clinical studies

Hypothesis free AI needed
Which AI? Going beyond the hype...
Association rules: finding strong relations missed by statistics

Many things!  N= 1000

N= 1000  P=1%

N= 10  P=90%
Principles of KEM® Galois Lattices or Formal Concept Analysis

Association rules and interestingness measures are key drivers of the approach

KEM®
- Unsupervised data mining tool based on Galois Lattices (Formal Concept Analysis)

Association rules
- Comprehensively analyze complex datasets
- Reveal hidden relationships
- Derive new hypotheses

Interestingness measures
- Measures all logical relations within a dataset
- Identifies the most relevant and powerful relations
- Decides if and how to use relations to answer a given question
Positioning of KEM® and other data analysis techniques: avoiding over-fitting, data driven (rather than hypothesis) and interpretable

KEM® vs. other data analysis techniques:

1. **Unsupervised** (hypothesis-free) rather than supervised (e.g. optimizing a discrimination objective) to avoid over-fitting;
2. **Interpretable** (white box) rather than black box;
3. **Datamining** rather than statistical (frequentist).

RESEARCH REPORT

In brief

- Many artificial intelligence applications today are effectively “black boxes” lacking the ability to “explain” the reasoning behind their decisions.

- As AI expands into areas with large impact on people, such as health care, it will be critical to subject the technology to greater human scrutiny.

- Explainable AI won’t replace human workers; rather, it will complement and support people, so they can make better, faster, more accurate decisions.
Data and Analysis plan

Cognitive and memory tests
Evolution of 8 tests monitored across 6 time points
(Follow-up: 3 years)

For each test, the **delta** of the scores between baseline (M0) and each available time point (M6, M12, M18, M24, M30, and M36) was calculated

A total of 54 delta of scores of cognitive/memory tests was generated

Genotyping: 486,137 variants (SNP) measured, 295,995 present in at least 2 individuals retained for analysis

Remaining variants are then clustered together: 2 genetic variants shared exactly by the same subjects are grouped together

**FAB**: Frontal Assessment Battery; **FCSRT**: Free and Cued Selective Reminding Test; **MBT**: Memory Binding Test; **MMSE**: Mini-Mental State Examination; **TMT**: Trail Making Test

<table>
<thead>
<tr>
<th>Variant status in subject’s genome</th>
<th>Value in data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>1</td>
</tr>
<tr>
<td>Homozygous</td>
<td>2</td>
</tr>
</tbody>
</table>

**295,995 variants -> 288,651 clusters**
Data and Analysis plan

Neuro Imaging: brain metabolism, volume, connectivity, brain amyloid burden, and cortical thickness

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

\textit{A total of 301 delta ratio of neuroimaging variables were generated}

Blood based markers: A\text{}\textbeta\text{} 40, A\text{}\textbeta\text{} 42, A\text{}\textbeta\text{} ratio, Bace1, NFL, Tau, YKL-40 at 2 time points

Blood based markers values were normalized using z-score, and the delta ratio of z-score between baseline (M0) and each available time point (M12/M18 and M24) were calculated.

FMRI: functional magnetic resonance imaging; fALFF: fractional amplitude of low frequency fluctuations; SNP: single nucleotide polymorphism
The number of relations that can be extracted from the data can be estimated to be $6.6 \times 10^{11}$. Within these, $7.4 \times 10^8$ are the relations linking genetic variants to the following End Points:

- Free and Cued Selective Reminding Test
- Trail Making Test
- Digit Span Memory Test
- Frontal Assessment Battery
- Rey Complex Figure Test
- Verbal Fluency
- Memory Binding Test
- Mini-Mental State Examination
- Brain Metabolism
- Brain Amyloid burden
- Brain Connectivity
- Brain Volume
- Cortical Thickness
- Aβ 40
- Aβ 42
- Aβ ratio
- BACE1
- NFL
- Tau
- YKL-40

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

1,078 genes (1,158 variants) were selected
Expressed in brain
& Clinically relevant
& Linked to an observed variation on, at least, one imaging biomarker

301 brain imaging descriptors,
54 cognitive scores,
14 blood based biomarkers

Variants (1158)

Digit Span
Frontal Assessment Battery
Free and Cued Selective Reminding Test
Rey Complex Figure
Fluency
Memory Binding Test
Mini Mental State Examination
Trail Making Test

Brain Metabolism
Brain Amyloid burden
Brain Connectivity
Brain Volume
Cortical Thickness

Aβ 40
Aβ 42
Aβ ratio
Bace1
NFL
Tau
YKL-40

Variant in rule must hit all 3 categories of endpoints

19 genetic variants involved in 26 relations
Results

Cognitive function is maintained, while imaging biomarkers show negative evolution

- Cognitive function, as assessed by MMSE, FAB, Digit Span Memory Test, Rey Complex Figure Test, and MBT is maintained

- While cortical thickness, forebrain and hippocampus volume are decreasing and global amyloid burden is increasing

MMSE = Mini-Mental State Examination
FAB = Frontal Assessment Battery
DSMT = Digit Span Memory Test
MBT = Memory Binding Test
Conclusion & Take Home Message

• An complex dataset, consisting of genomic, neuroimaging, cognitive tests and blood based markers, collected in a cohort of subject at risk, was successfully integrated and analyzed
• variants identified as linked simultaneously to multiple categories of endpoints: neuroimaging, cognitive tests and blood based markers

• 19 genetic variants in 253 subjects suggest that compensatory mechanisms at the cell or tissue level brain to maintain cognitive function, despite structural modifications and accumulation of amyloid plaques

• Artificial Intelligence and Association Rules are powerful tools to uncover pertinent hypotheses from dataset extensively characterized using molecular and imaging descriptors

• More detailed analysis of omic features linked to imaging data will be presented by Dr F. Parmentier) Thursday at 11:45 515 AB - O5-07-04

• Application to Exploring Gut Microbiota as a Source of Potential Biomarkers (ANAVEX®2-73 Alzheimer’s Disease Clinical Study) Wednesday 8:45 AM Concourse Hall 152 -  O4-02-04
Thank you

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