alzheimer's association
AAIC 19
ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE
July 14–18, 2019 > Los Angeles, USA

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

Martin Kindermans, MSc[1], Mohammad Afshar, MD, PhD[1], Patrizia Andrea Chiesa, PhD[2,3,4], Adrien Etcheto, MSc[1], Simone Lista, PhD[2,3,4], Pablo Lemercier[2,3,4], **Frédéric Parmentier, PhD[1]**, Andrea Vergallo, MD[2,3,4], Coralie Williams, MSc[1] and Harald Hampel, Prof., MD, PhD[3]

(1) Ariana Pharma, Paris, France
(2) Institute of Memory and Alzheimer's Disease (IM2A), Department of Neurology, Pitié-Salpêtrière Hospital, AP-HO, Boulevard de l'hôpital, F-75013, Paris, France
(3) Sorbonne University, GRC n° 21, Alzheimer Precision Medicine (APM), AP-HP, Pitié-Salpêtrière Hospital, Boulevard de l'hôpital, F-75013, Paris, France
(4) Brain & Spine Institute (ICM), INSERM U 1127, CNRS UMR 7225, Boulevard de l'hôpital, F-75013, Paris, France

AAIC 2019, July 14-18
Los Angeles, CA, U.S.

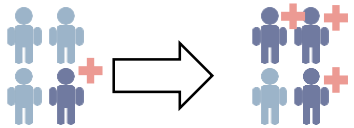
Disclosure

- **Frederic Parmentier** is an employee of Ariana Pharma

Introduction

Towards earlier detection of Alzheimer's disease

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

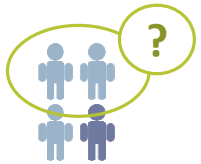


2018 2030

Source: World Alzheimer Report 2018

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



Today!

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

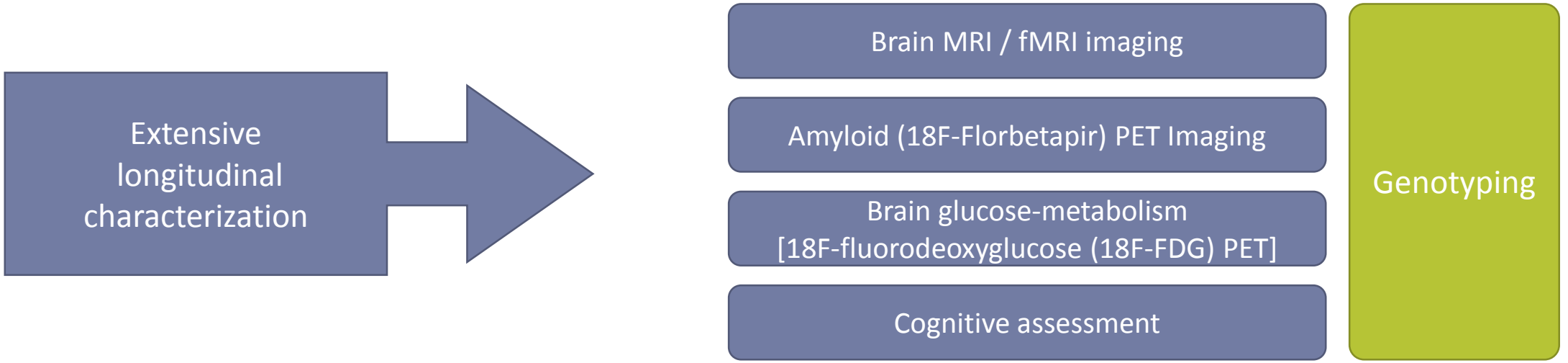
Introduction

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



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 ?

Data and Analysis plan

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

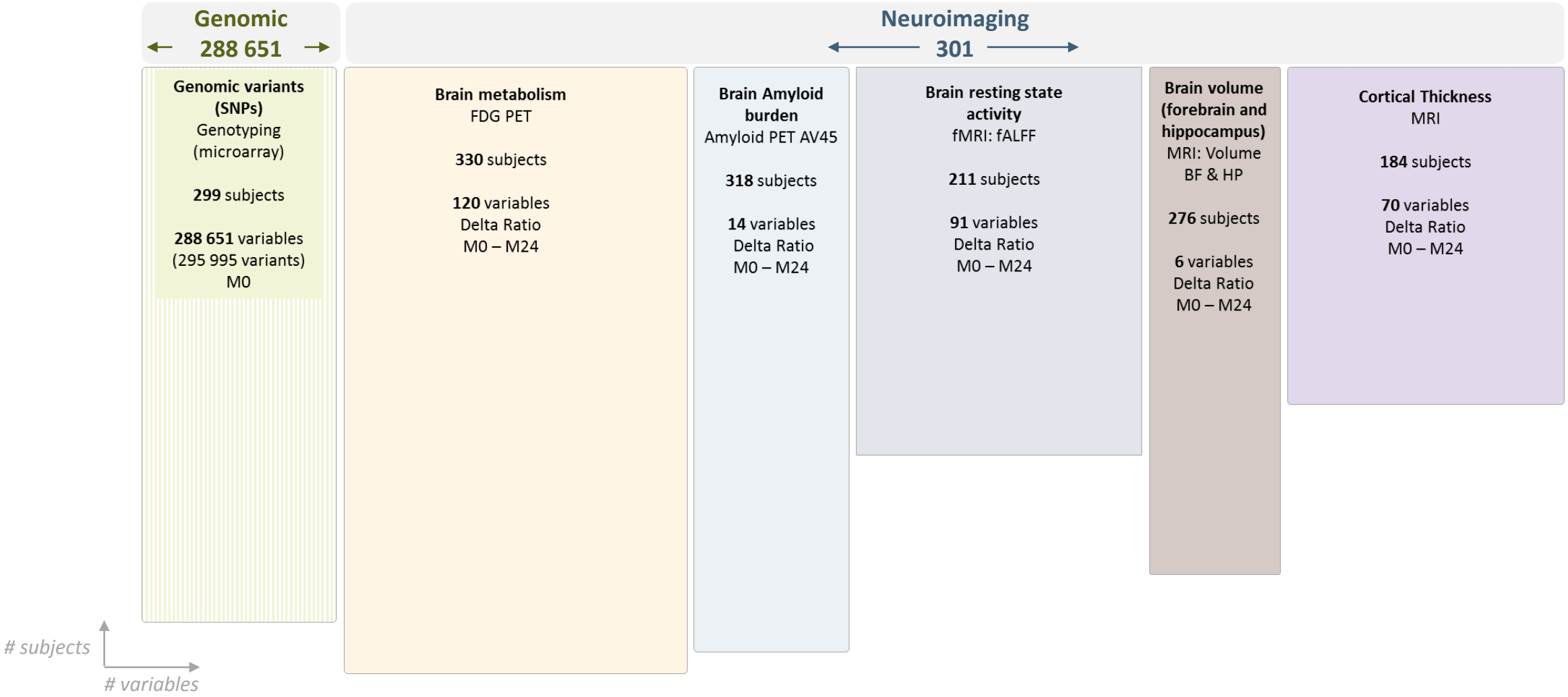
Imaging descriptors normalized using z-score, and the delta ratio of z-score between baseline (M0) and 24th month (M24) calculated.

A total of 301 delta ratio of neuroimaging variables generated

SNP: single nucleotide polymorphism

Data and Analysis plan

Database has 288 952 variables across 6 categories, dominated by Genomic and Brain metabolism.
Number of subject is 184-330, depending on variable category.



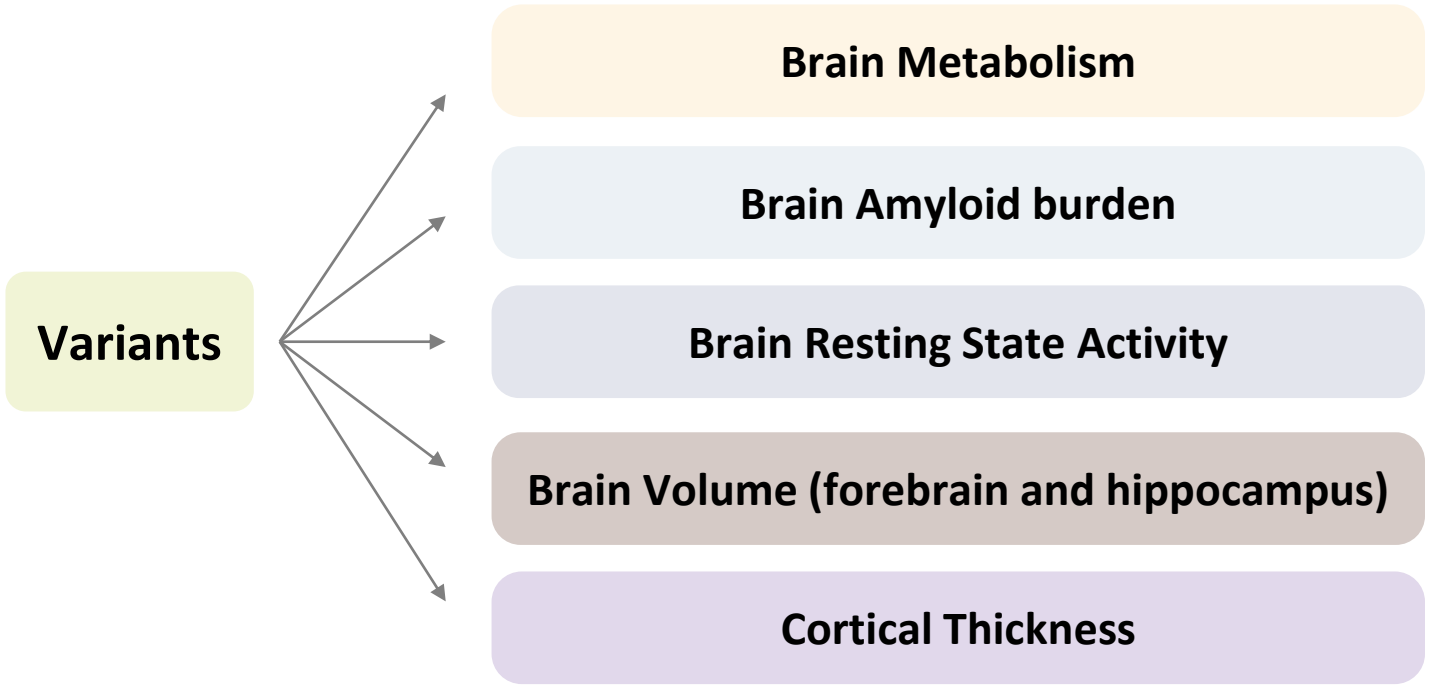
BF: basal forebrain; HP: fractional amplitude of low frequency fluctuations

Data and Analysis plan

Linking variants with neuroimaging features

Estimated number of relations that can be extracted from the data: **3×10^{11}**

A subset of 3.5×10^{8} relations link genomic variants to imaging descriptors:



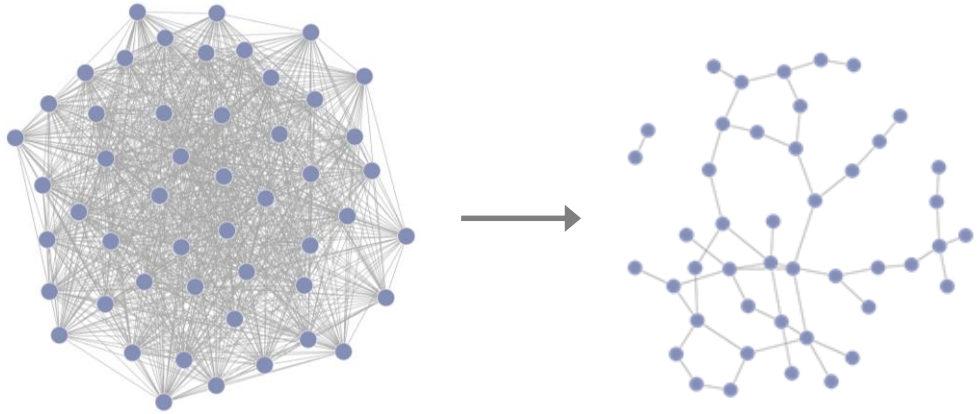
Using KEM® Artificial Intelligence
to
generate
explore
rank
these relations

Methodology

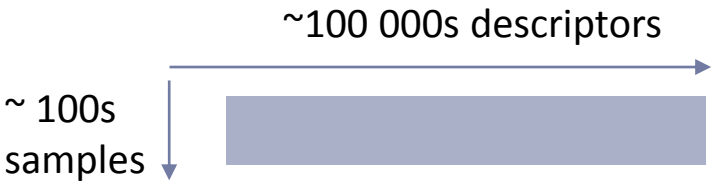
Combining and analyzing genomic and imaging data using the Artificial Intelligence platform KEM®

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



From data to knowledge



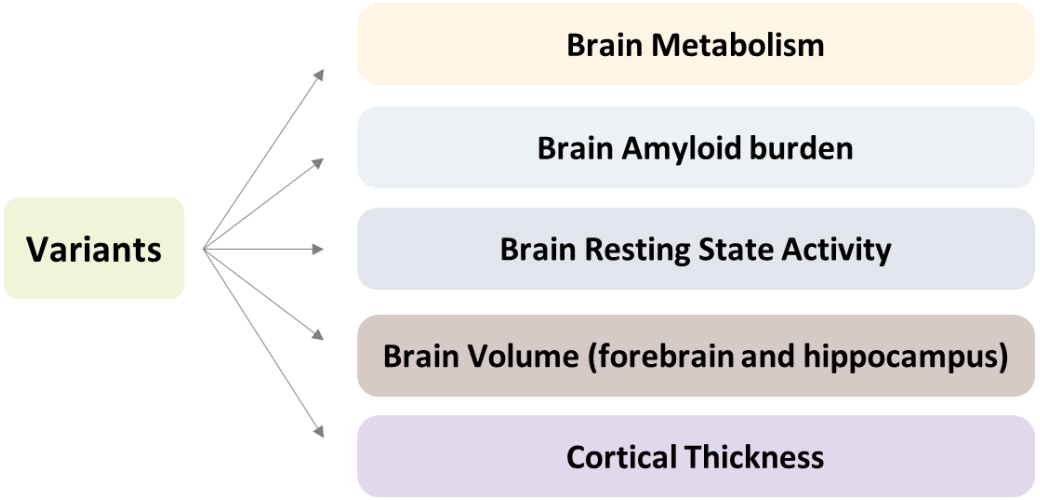
Unsupervised and explainable Machine Learning - Artificial Intelligence Platform Supporting Observational studies and Clinical Trial Design KEM® using **Formal Concept Analysis (FCA)**

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 | Right



- 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%

OR: 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[1]
Ensembl BioMart
https://www.ensembl.org/info/data/biomart/

1,785 rules

Multiple testing corrected $p < 0.05$

1 rules

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

Any disease can be included.

Single relation linking clinicaly relevant gene and imaging EP

[1]: ClinVar, Richards *et al*, Genet Med. 2015.

Results

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

snp	Gene	Outcome	Evolution	Experiment	Brain Region	Hemisphere	n	Conf.	Lift	p
cl204843	COG6	Frontal Med Orb DeltaRatio	Decreased	fALFF	medOFC	Left	22	0.79	2.39	3.34E-02

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

Source: www.ncbi.nlm.nih.gov
Variation Viewer www.ncbi.nlm.nih.gov/variation/view/

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

JCB Journal of Cell Biology
Rockefeller University Press
This article at JCB.org Editors Contact Instructions for Authors

J Cell Biol. 2002 Apr 29; 157(3): 405–415.
doi: 10.1083/jcb.200202016
PMCID: PMC2173297
PMID: 11980916

Characterization of a mammalian Golgi-localized protein complex, COG, that is required for normal Golgi morphology and function

Daniel Ungar,[1] Toshihiko Oka,[2] Elizabeth E. Brittle,[1] Eliza Vasile,[2,3] Vladimir V. Lupashin,[4] Jon E. Chatterton,[2] John E. Heuser,[5] Monty Krieger,[2] and M. Gerard Waters[1]

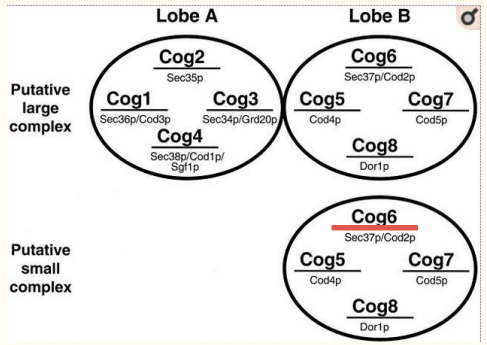


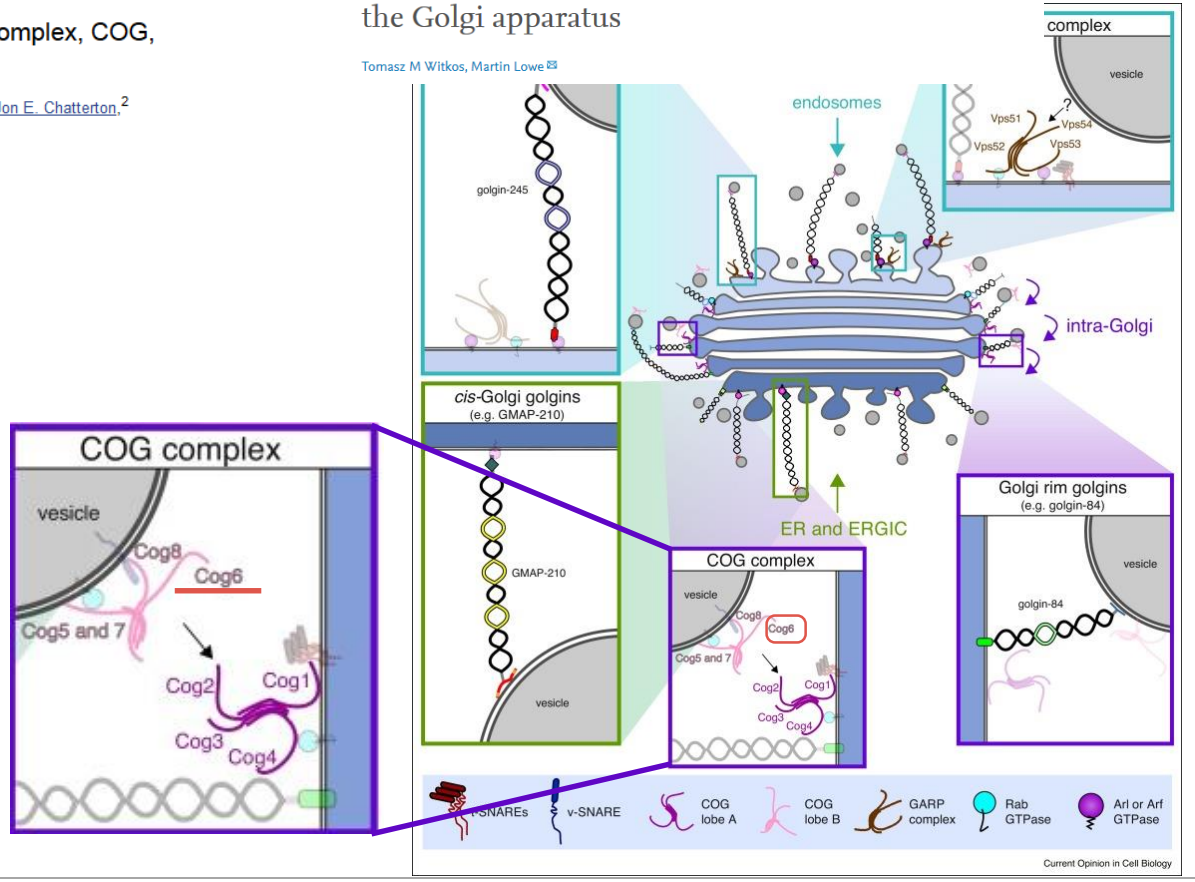
Figure 9.

Schematic representation of the putative bilobed subunit organization of the mammalian (large type) and yeast (small type) COG complexes.

ELSEVIER
Current Opinion in Cell Biology
Volume 47, August 2017, Pages 16-23

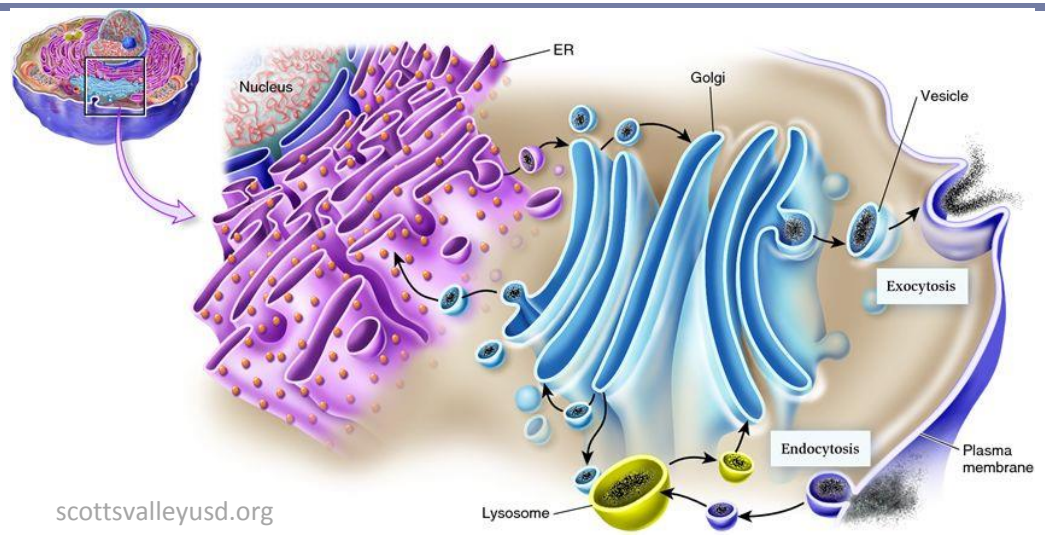
Recognition and tethering of transport vesicles at the Golgi apparatus

Tomasz M Witkos, Martin Lowe



Results

COG6: the Golgi apparatus is a critical cell component in neurodegenerative diseases



Title	1st author	Journal	Year	URL
Alterations of Golgi organization in Alzheimer's disease: A cause or a consequence?	Ayala I	Tissue Cell	2017	https://www.ncbi.nlm.nih.gov/pubmed/27894594
Tau secretion is correlated to an increase of Golgi dynamics	Mohamed N	PLoS One	2017	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0178288
Morphometric alterations of Golgi apparatus in Alzheimer's disease are related to tau hyperphosphorylation.	Antón-Fernández A	Neurobiology of Disease	2017	https://www.ncbi.nlm.nih.gov/pubmed/27793637
Editorial: Golgi Pathology in Neurodegenerative Diseases	Rabouille C	Frontiers in Neuroscience	2016	https://www.frontiersin.org/articles/10.3389/fnins.2015.00489/full
Alteration of Golgi Structure by Stress: A Link to Neurodegeneration?	Alvarez-Miranda E	Frontiers in Neuroscience	2015	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4641911/
Increased neuronal activity fragments the Golgi complex	Thayer DA	PNAS	2013	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3557034/
Golgi apparatus and neurodegenerative diseases	Fan J	International Journal of Developmental Neuroscience	2008	https://www.sciencedirect.com/science/article/abs/pii/S0736574808000889?via%3Dihub

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

Sorbonne University
Department of Neurology
Institute of Memory and Alzheimer's Disease (IM2A)
Brain & Spine Institute (ICM)
Pitié-Salpêtrière Hospital, Paris, France

Professor Harald Hampel Team

Alzheimer Precision Medicine Initiative
https://www.apmiscience.com

Ariana Pharma, Paris, France
Mohammad Afshar
Frédéric Parmentier
Martin Kindermans
Adrien Etcheto
Coralie Williams

http://www.arianapharma.com