

Alzheimer's Disease Apolipoprotein Pathology for Treatment Elucidation and Development

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on behalf of ADAPTED

Why ADAPTED?

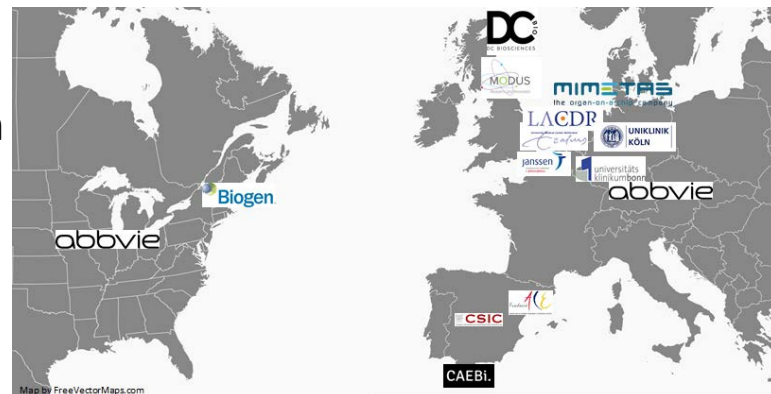
- APOE4 remains the most prominent genetic risk factor for late onset AD
- It is still not clearly understood how APOE increases AD risk, not even by which pathway
 - Relatively little study has focussed on APOE
 - Many of the APOE studies were on how APOE fits into other hypotheses
- APOE is therefore not used or addressed as treatment option

Project Objectives

1. **Increased APOE understanding:** Clarification of the role of APOE as a risk factor in the development of AD
 - *unbiased*
 - *human focus*
 - *leveraging current technologies, e.g. large data sets, -omics, iPSC*
2. Identification of promising entry points (**targets**) for the treatment of AD
3. Generation and validation of selected high value **APOE-related model systems**
4. Uncover the basic scientific evidence required to progress the development of a **stratified** approach

Total budget, duration and current status

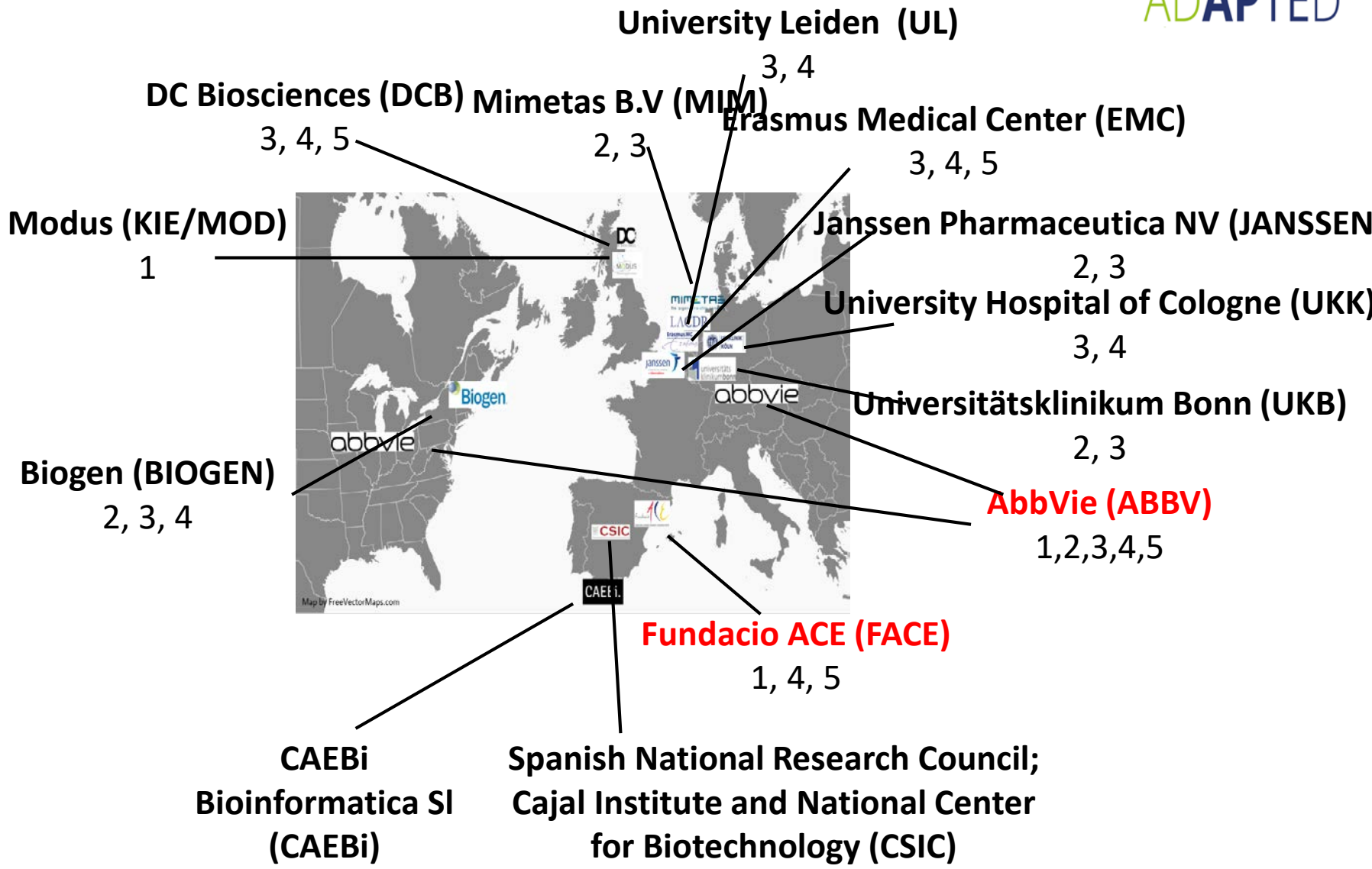
- Committed EFPIA in-kind contribution: € 3 million
- IMI-JU funding: € 3,5 million
- 3 year project: 1 Oct 2016 – 30 Sept 2019
+ 6 months extension **31 March 2020**



Project Participants & Organization

- Project jointly led by
 - Fundació ACE (Institut Català de Neurociències Aplicades, Barcelona (coordinator)
 - AbbVie (leader)
- 3 EFPIA participants (AbbVie, Janssen and Biogen)
- 10 Academic/non-profit research organizations/SMEs
- 6 Countries (Belgium, Germany, Netherlands, Spain, UK, USA)
- 5 Work Packages

Consortium Members



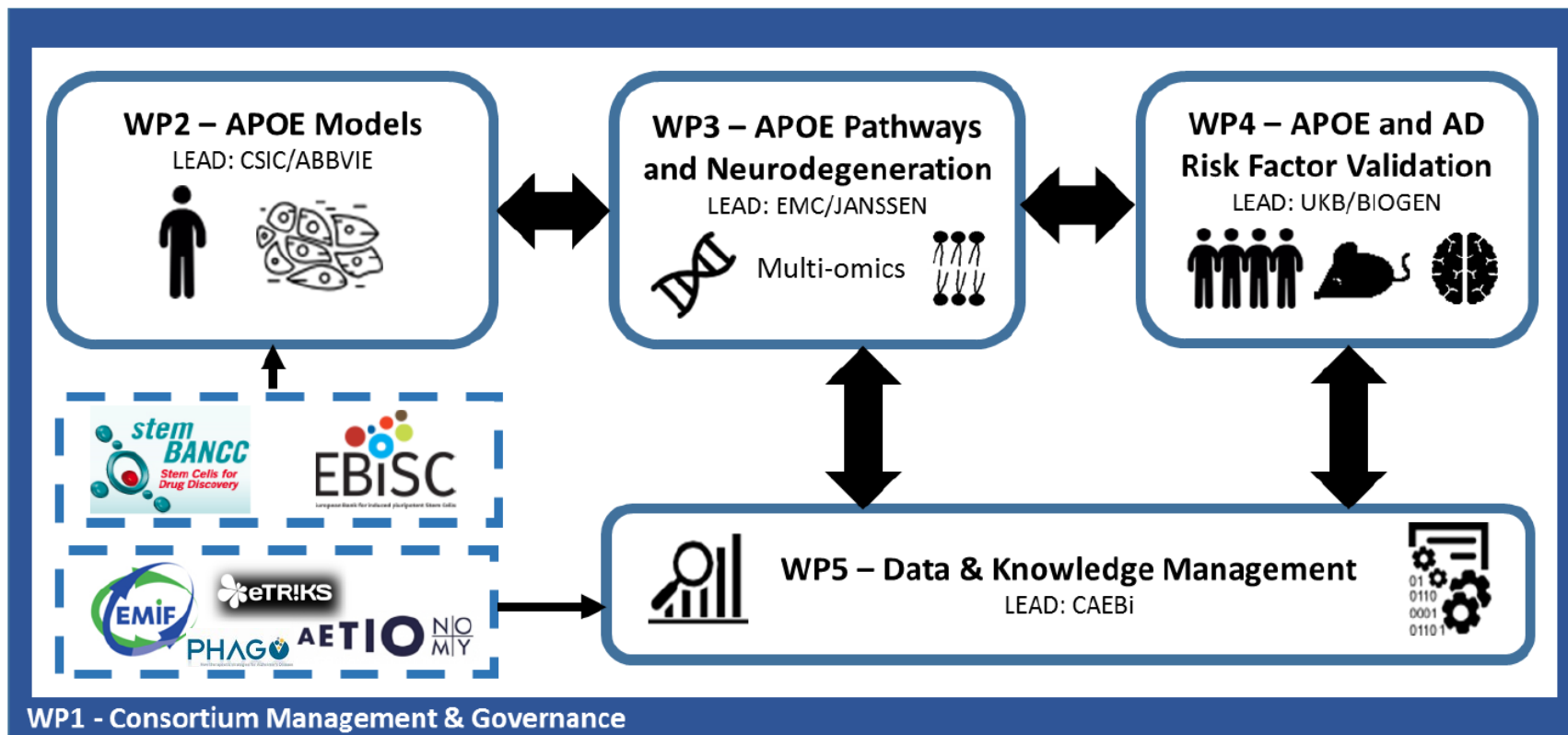



Figure 11 ADAPTED workflow diagram¹⁰⁹

- Data storage and analysis platform. 
- SOPs for experimental procedures and data analysis.
- Compilation of multi-omics data from external repositories.
- Gene-edited iPSC lines generated (isogenic, E2, E3 or E4 alleles) and differentiated into different cell types (astrocytes, neurons, macrophages, microglia).
- Plasma and CSF samples from Controls/AD/MCI individuals collected.
- Compilation of multi-omics data from ADAPTED datasets (transcriptomics, methylomics, proteomics, metabolomics).
- Hypothesis about APOE generated (validation ongoing).



innome
init

ADAPTED: External datasets

Study ID	Study Title	Source	GWAS	GWES (arrays)	GWES (RNAseq)	Proteo.	Epigen.	NGS	Metab.
EX-ACT	AMP-AD Adult Change Thought	Synapse				65			
EX-ADDN	AddNeuroMed	Synapse	529	529		433			
EX-ADGC	Alzheimer's Disease Genetics Consortium (ADGC)						506		811
EX-ADNI	Genome Wide Association Study	dbGap	6065						
EX-ADNI	ADNI	LONI	811	811		811			
EX-AGEC	AgeCoDe	UKB	2191						
EX-BANN	Banner Sun Health Research Institute's Brain and Body Donation Program	Synapse				201			
EX-BLSA	AMP-AD Baltimore Longitudinal Study on Aging	Synapse				35			
EX-DCN	DCN	UKB	600						
EX-EMERGE	Group Health/UW Aging and Dementia eMERGE Study (LOAD CIDR)	dbGap	5729						
EX-EMOR	AMP-AD Emory ADRC Brain Bank (syn3218563)	Synapse							
EX-FACE	Fundacio ACE (GRACE)	FACE	8000						
EX-GERAD	Genetic Risk for Late-onset Alzheimer's Disease	Cardiff U.	13164						
EX-GNADA	Genotype-Phenotype Associations in Alzheimer's disease	dbGAaP	1588						
EX-GSE15222	Genetic control of human brain transcript expression in Alzheimer's disease.	NCBI GEO		286					
EX-GSE48350	Alzheimer's Disease Dataset	NCBI GEO		426					
EX-GSE5281	Alzheimer's disease and the normal aged brain	NCBI GEO		150					
EX-HBTR	AMP-AD Harvard Brain Tissue Resource Center	Synapse		463					
EX-MAYO	AMP-AD Mayo	Synapse	434	166	374	115			45
EX-MSBB	AMP-AD Mount Sinai	Synapse		125	233	266		277	
EX-NIA	National Institute of Aging	dbGap	4561						
EX-NXC	Neocodex-Murcia	FACE/CAEBi	1133						
EX-PXD00963	Proteomics of Alzheimer's Disease mouse models	PRIDE				16			
EX-ROSMAP	AMP-AD Religious Orders Study and Memory and Aging Project (ROS/MAP) Study	Synapse	1047	495	649		712		
EX-ROTT	The Rotterdam Study	EMC	14926	900	900		1526		
EX-TGEN	The Translational Genomics Research Institute	FACE	1411						
EX-ARIC	The Atherosclerosis Risk in Communities Study ApoE stratified results	CHARGE	8545						
EX-CHS	The Cardiovascular Health Study ApoE stratified results	CHARGE	2020						
EX-FHS	The Framingham Heart Study ApoE stratified results	CHARGE	3802						
EX-RS	The Rotterdam Study ApoE stratified results	CHARGE	5523			316			
EX-GSE67835	A survey of human brain transcriptome diversity at the single cell level	NCBI GEO			466				
EX-GSE102956	Isogenic APOE3 and APOE4 human iPSC lines (Lin et al.)	NCBI GEO			26				
TOTAL			82079	4351	2648	2258	2744	277	856



efpia

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ADAPTED datasets

ID	Description	RNA	Methylation	Proteomics	Metabolomics
IN-01-SCNA	iPSC derived neurons WS2	Finished	In progress	In progress	Finished
IN-01-SCAS	iPSC derived astrocytes WS2	In progress	In progress	Finished	Finished
IN-02-SCAS	iPSC derived astrocytes WS4	In progress	In progress	In progress	In progress
IN-01-SCMA	iPSC derived macrophages WS2	Finished	In progress	Finished	In progress
IN-02-SCMA	iPSC derived macrophages WS2 (activation assay)	Finished	In progress	In progress	In progress
IN-03-SCMA	iPSC derived macrophages WS4	In progress	In progress	In progress	In progress
IN-04-SCMA	iPSC derived macrophages WS4 (activation assay)	In progress	In progress	In progress	In progress
IN-03-ADMO	Patient derived monocytes	Finished	Finished	In progress	In progress
IN-01-SCMI	iPSC derived microglia WS2	Finished	In progress	Finished	In progress
IN-02-SCMI	iPSC derived microglia WS4	Finished	In progress	Finished	In progress
IN-07-MICE	Humanised APOE mice models	Finished	In progress	Finished	In progress
IN-01-CSF	MCI patients (CSF)	In progress	In progress	Finished	Finished
IN-01-PLAS	MCI patients (Plasma)	In progress	In progress	Finished	Finished

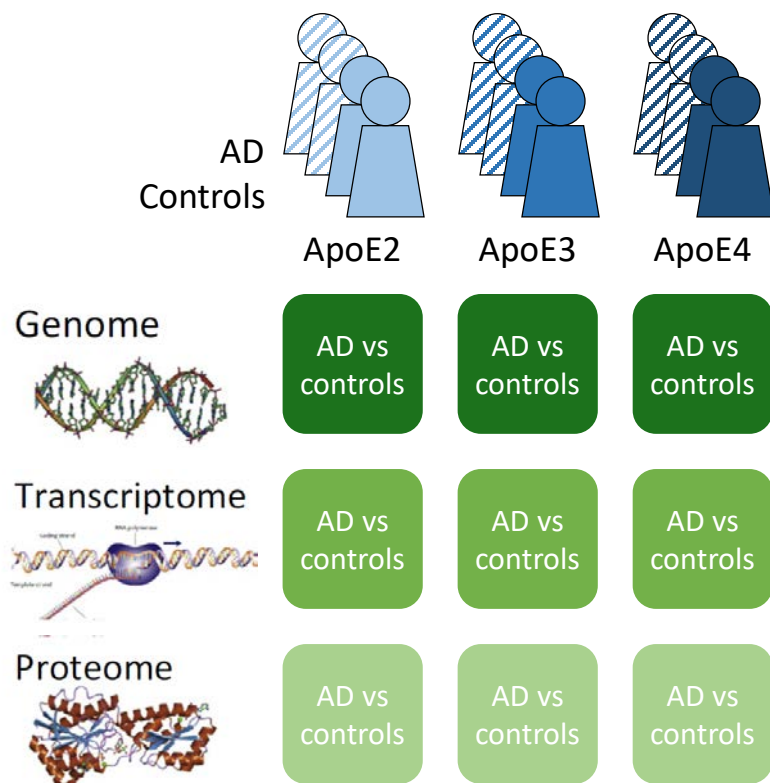


In progress

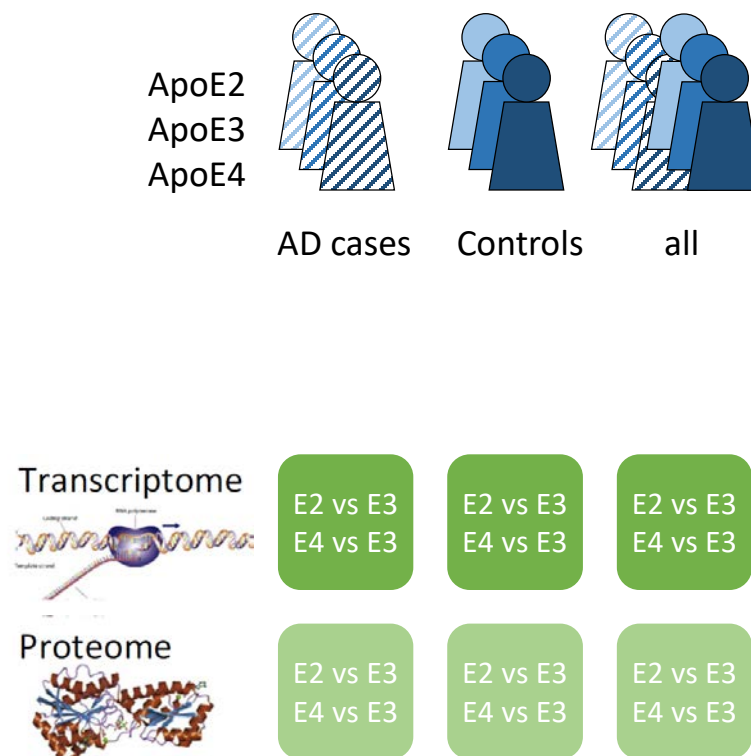


Finished

Differences by disease status



Differences by ApoE status:

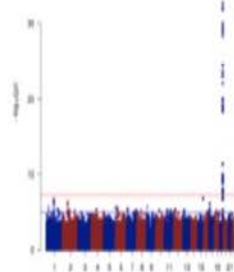


[Yugi et al (2016), Trends in Biotechnology]

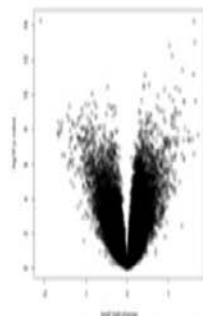


Data Cleaning/QC

Association analysis



GWAS Analysis
per dataset



GWES Analysis
per dataset

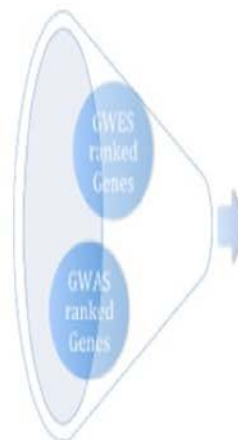
Meta-analysis

RANK	P_VALUE	GENE
1	4.34E-05	RGS16
2	4.81E-05	RGS8
3	5.67E-05	OSBP16
4	7.45E-05	RNASEL
5	9.10E-05	TOMM70A
6	0.0001105	AKAP6
7	0.00011168	GPRIN3
8	0.00012734	RNF152
9	0.00013014	GLUL

- Meta Analysis GWAS
- Meta Brain GWES
- Meta Blood GWES

RRA integrative analysis

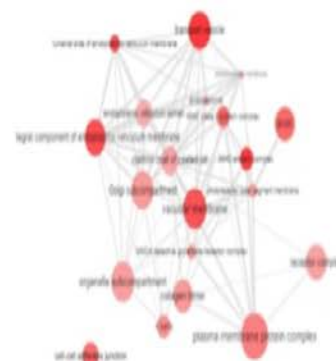
(Kolde et al., 2012)



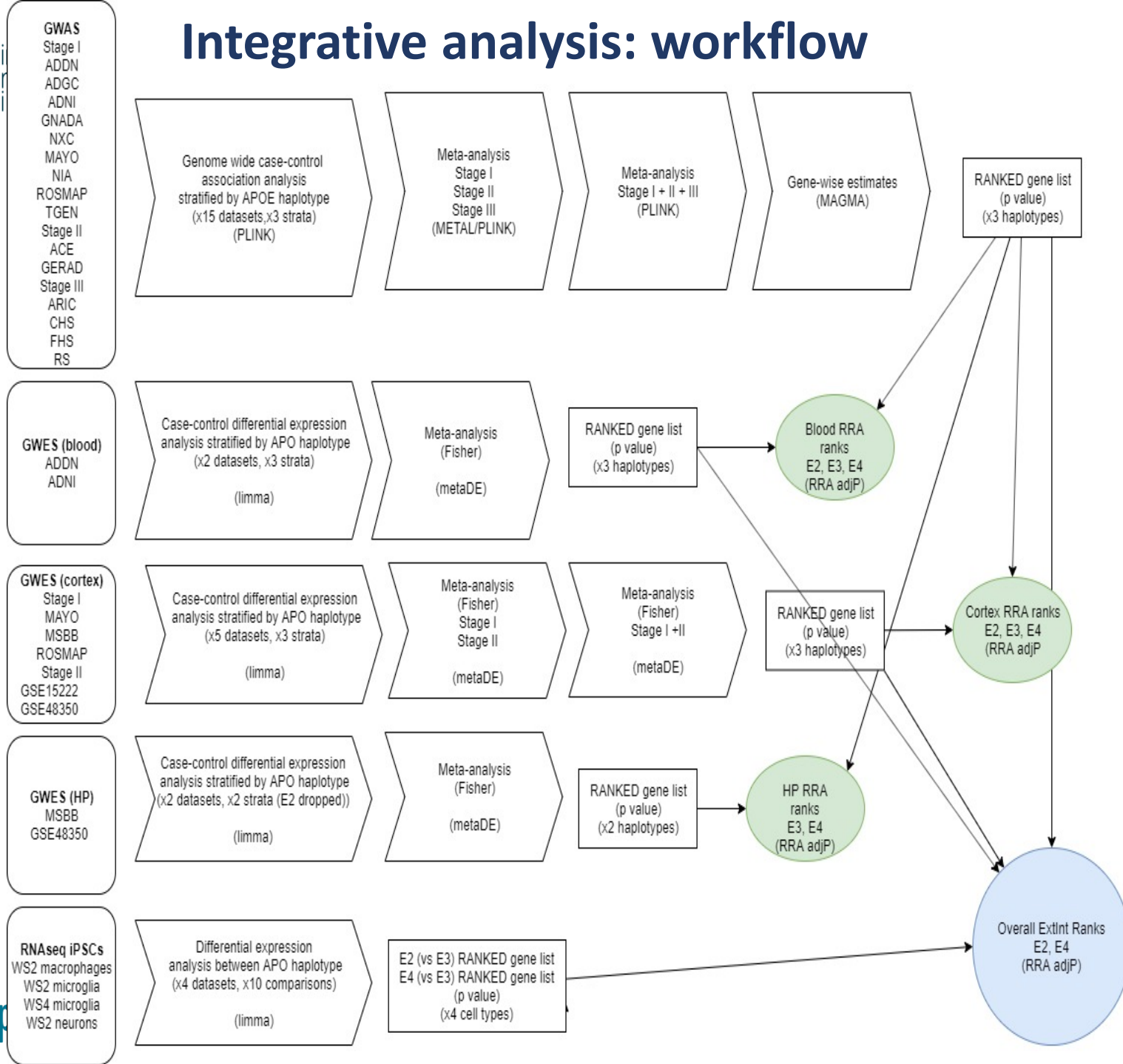
Integrative Analysis
x2 Brain & Blood

rank	Name	Score
1	GPRIN3	5.4E-05
2	SLC44A1	2.5E-04
3	AKAP6	4.3E-04
4	C1orf195	4.9E-04
5	HLA-DRA	5.0E-04
6	RGS16	6.5E-04
7	ANO6	6.7E-04
8	SMARCA4	6.7E-04
9	OSMR	7.1E-04
10	CD44	7.5E-04

Enrichment analysis



Enrichment
x2 Brain & Blood



Three stages:

● Stage I (publicly available data)

- GWAS data (2 stages, 27,841 individuals)
- GWES blood (1 stage, 734 individuals)
- GWES cortex (1 stage, 980 individuals)

● Stage II (publicly available data)

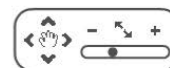
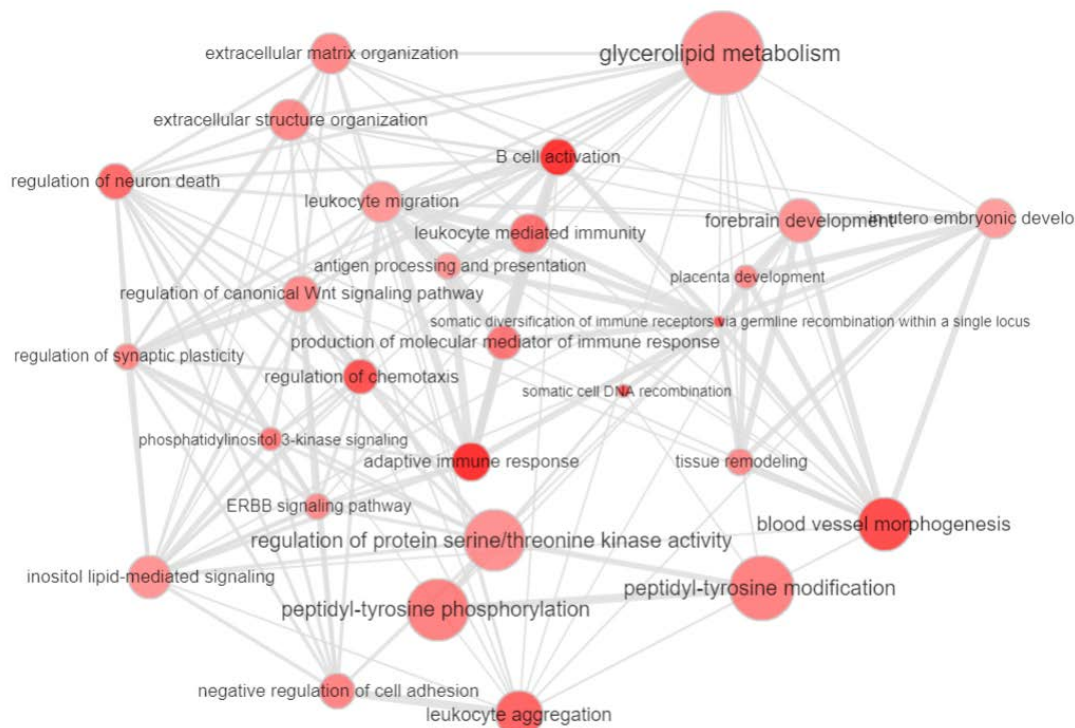
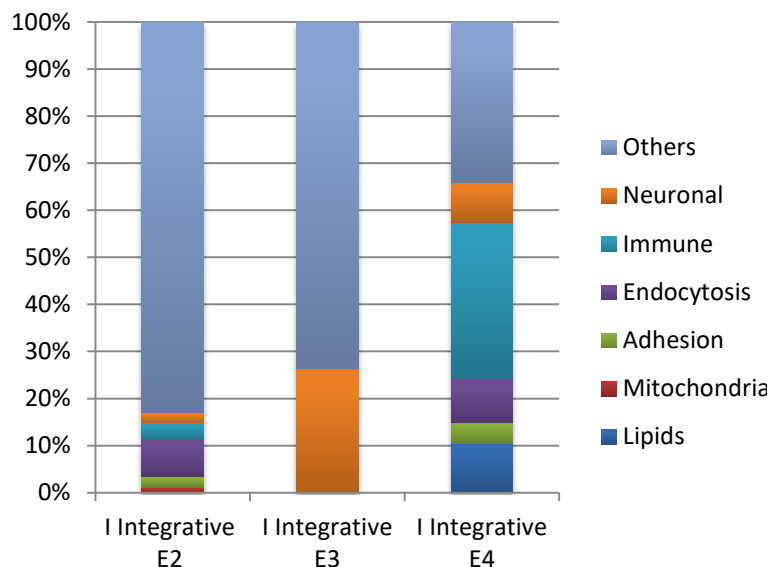
- GWAS data (3 stages, 47,731 individuals)
- GWES blood (1 stage, 734 individuals)
- GWES cortex (2 stages, 1,503 individuals)
- GWES hippocampus (1 stage, 101 individuals)

● Stage III (publicly available data + iPSCs data)

- Results in accordance with Stage I and Stage II preliminary results
- 117 genes preselected
- Refinement ongoing for selecting candidates to be validated in human subjects

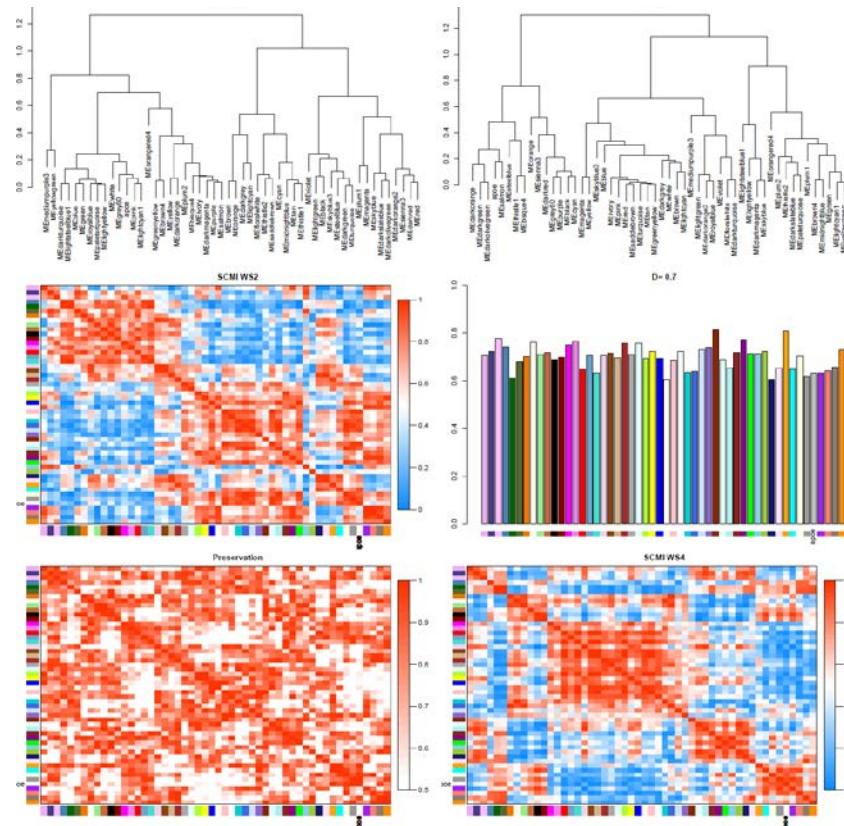
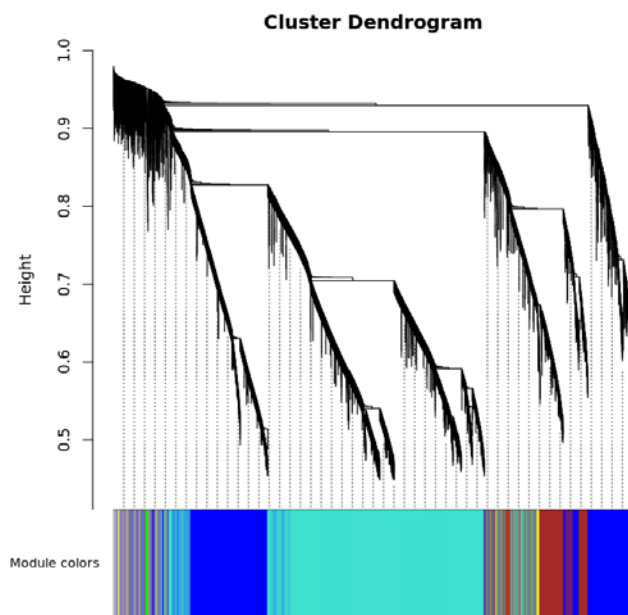
● Stage IV (before final 2019)

Collaborations are welcome!!



Additional data available

- Sex stratified GWAS analysis
- Co-expression networks:
 - Human cortex data
 - iPSC-derived cell models





Thank you!!!