10 YEARS OF BREAKTHROUGHS
A HEALTHIER FUTURE

ADAPTED

13

Candidate genes and pathways from ADAPTED Stage I integrative analysis

Laura Madrid[1], Antonio González-Pérez[1], Agustín Ruiz[2], María Eugenia Sáez[1]

[1] CAEBi. Centro Andaluz de Estudios Bioinformáticos. Sevilla. Spain . [2]Fundació ACE. Institut Català de Neurociències Aplicades. Barcelona. Spain

Facts & Figures

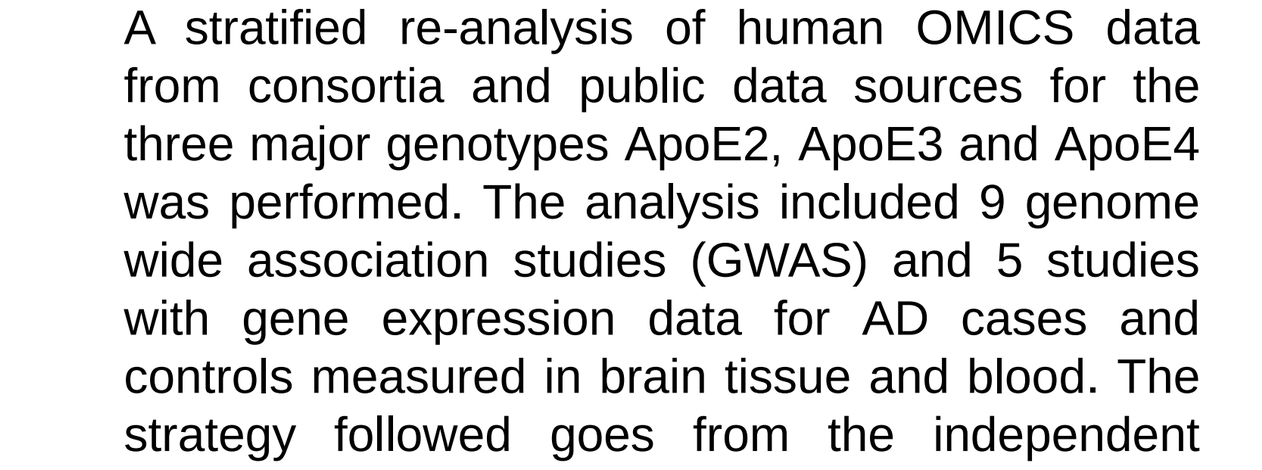
Start date:	01/10/2016
End date:	30/09/2019
Contributions	
IMI funding:	3 510 000 €
EFPIA in kind:	3 286 740 €
Other:	0 €
Total Cost:	6 796 740 €
Project website:	www.imi-adapted.eu
Social media:	adapted_project

Challenge

Apolipoprotein E (APOE) ε4 allele is the most prominent risk factor for sporadic Alzheimer's disease (AD), but the molecular bases of ApoE4 pathology are still unknown. The aim of ADAPTED project is to identify ApoE allele specific signatures using a multi-omics integrative approach on publicly available datasets divided in three strata according to ApoE genotype (ApoE2: ε2/ε2 and ε2/ε3; ApoE3: ε3/ε3; ApoE4: ε3/ε4 and ε4/ ε4).

Approach & Methodology

A stratified re-analysis of human OMICS data from consortia and public data sources for the three major genotypes ApoE2, ApoE3 and ApoE4 was performed. The analysis included 9 genome wide association studies (GWAS) and 5 studies with gene expression data for AD cases and controls measured in brain tissue and blood. The strategy followed goes from the independent analysis of the different datasets stratified by ApoE to a unified ranking list of candidate genes per strata by integrating results across the two data types (Figures 1&2). Pathway analysis was applied to the gene level results.



Results

This preliminary integrative analysis suggests a pivotal role for immune system in the brain changes of AD patients carrying the ApoE4 genotype and, to a lesser extent, of ApoE2 carriers. Endosome components showed the strongest enrichment in the ApoE2 stratum. For ApoE4 subjects, lipoprotein particles (GO CC) and blood vessel morphogenesis (GO BP) were also shown to play a role in AD pathology (Figure 4). In the ApoE3 stratum, sarcomere and axon were the most prominent CC GO categories. Endosomal and lipoprotein related categories observed in the brain study were also seen at the blood level. By contrast, blood biomarkers did not show enrichment on immune system related pathways.

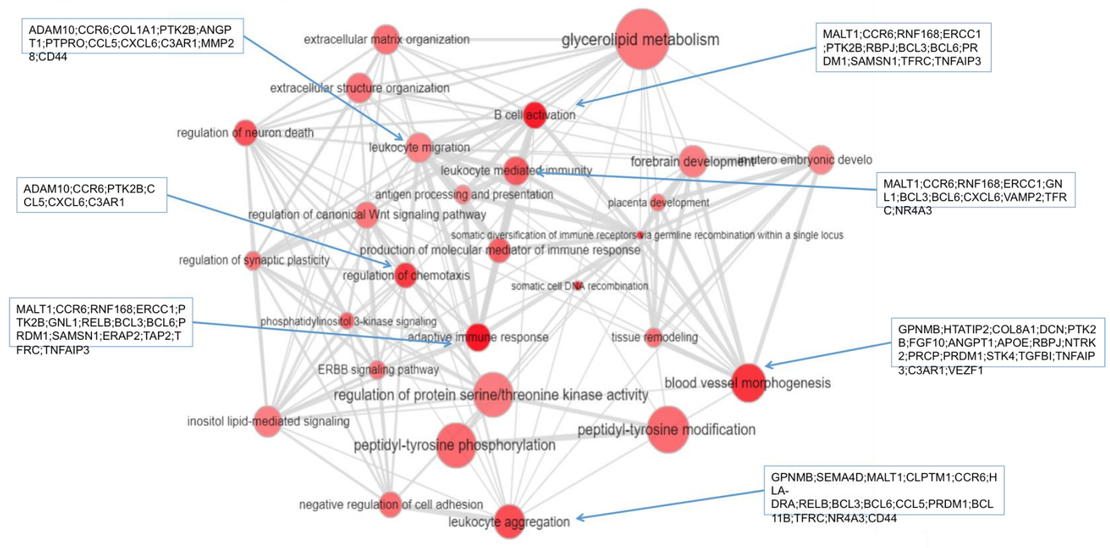
Figure 2: ApoE2, E3 and E4 list of candidate genes

Rank	Name	Score
1	GPRIN3	5.41E-05
2	SLC44A1	2.50E-04
3	AKAP6	4.33E-04
4	C1orf195	4.87E-04
5	HLA-DRA	4.99E-04
6	RGS16	6.49E-04
7	ANO6	6.68E-04
8	SMARCA4	6.73E-04
9	OSMR	7.05E-04
10	CD44	7.48E-04

Rank	Name	Score
1	RBPMS	3.13E-05
2	SNRPN	1.64E-04
3	SFMBT2	1.70E-04
3	VEZF1	1.70E-04
5	PTK2B	1.88E-04
6	RSF1	2.72E-04
7	ITIH5	3.40E-04
7	ADCYAP1	3.40E-04
9	SPTBN1	3.78E-04
10	ADRA1D	5.11E-04

Rank	Name	Score
1	AP2B1	9.00E-05
2	SHC3	1.12E-04
3	MMP28	1.40E-04
4	CCDC50	1.55E-04
5	BCL3	1.96E-04
5	SLC44A1	1.96E-04
7	AGPAT4	3.39E-04
8	TOMM40	3.92E-04
8	HLA-DRA	3.92E-04
10	IMPAD1	5.00E-04

Figure 3: Integrative results GO BP enrichment ApoE4



Value of IMI collaboration

IMI has made it possible the collaboration between private and public entities allowing the joint effort of professionals from very different disciplines that has maximized the value of the project and would no have taken place otherwise.

Impact & take home message

These results revealed promising candidate genes and pathways that might help to elucidate the mechanisms by which APOE affects the AD risk. Additional OMICS data representing complementary biological layers will soon be available to the ADAPTED consortium and further contribute to the interpretation of these results.

This work has received support from the EU/EFPIA/European Federation of Pharmaceutical Industries and Associations, Innovative Medicines Initiative 2 Joint Undertaking (Horizon 2020 grant no 115975).