Alzheimer's Disease Apolipoprotein Pathology for Treatment Elucidation and Development

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on behalf of ADAPTED

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115975. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations

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

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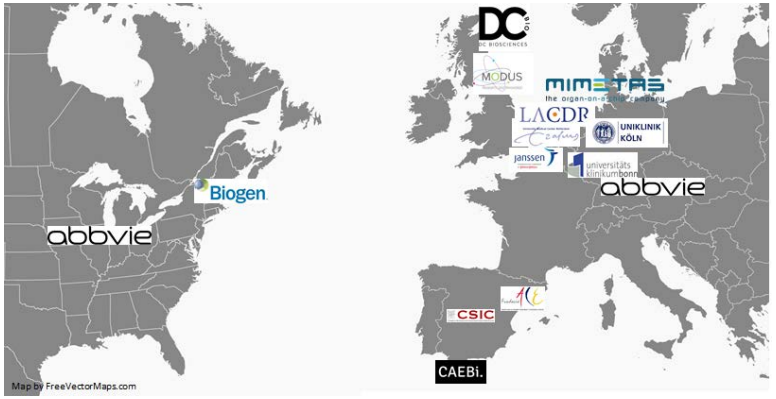
Project Specifics

Total budget, duration and current status

- Committed EFPIA in-kind contribution: € 3 million
- IMI-JU funding: € 3,5 million
- 3 year project: Oct 1, 2016 - Sept 30, 2019



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

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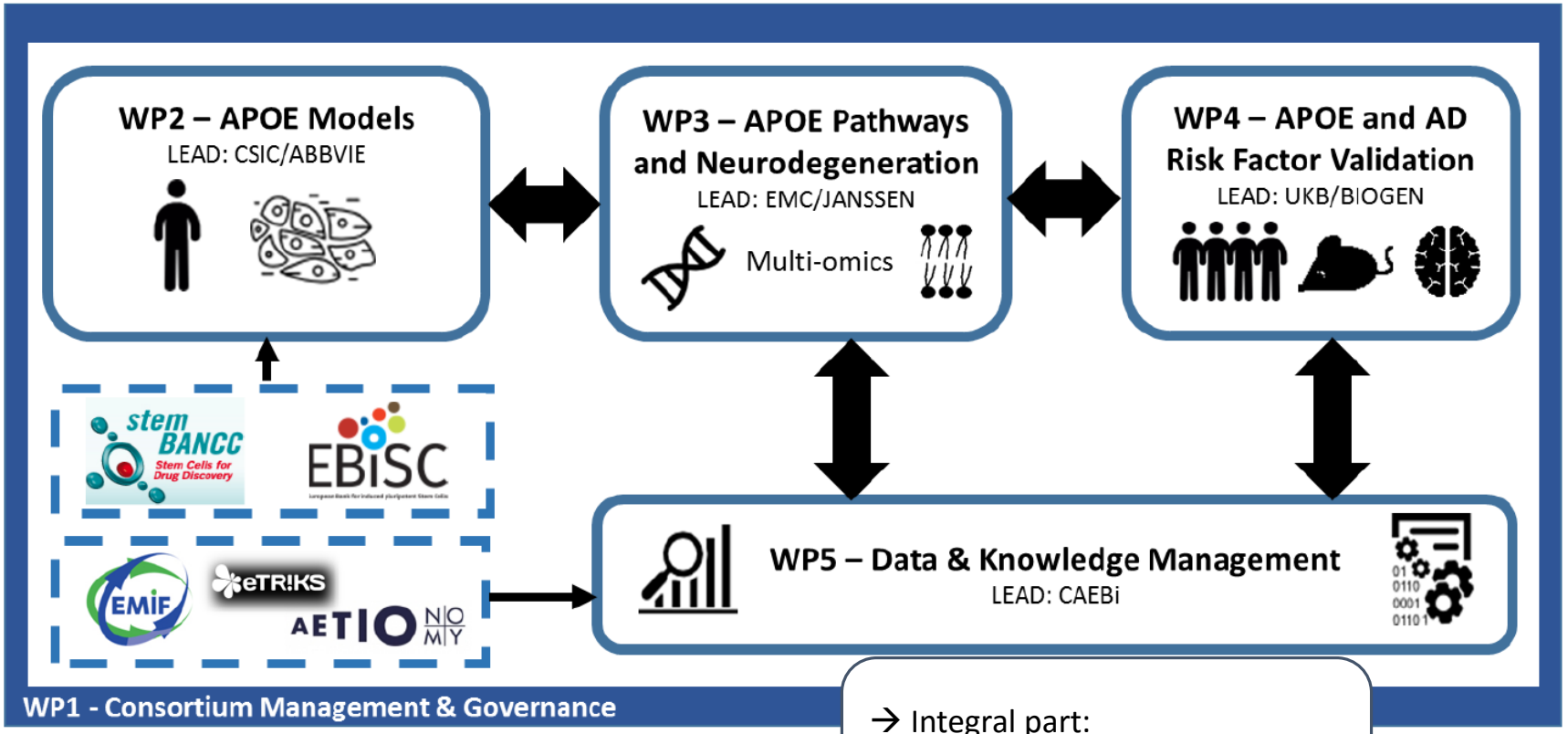
Project Structure



→ Integral part:
APOE stratified analysis and integration of human OMICS data

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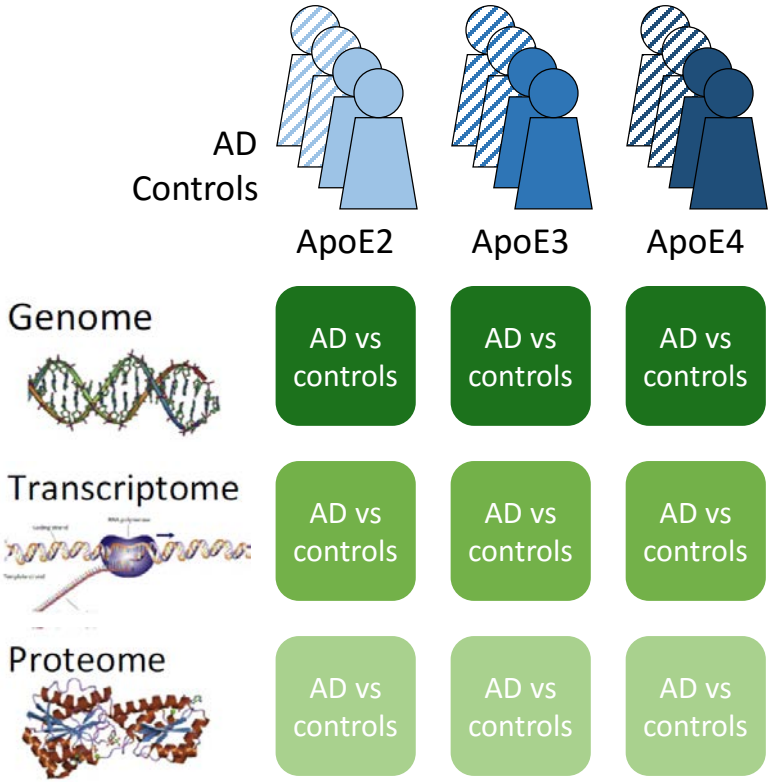
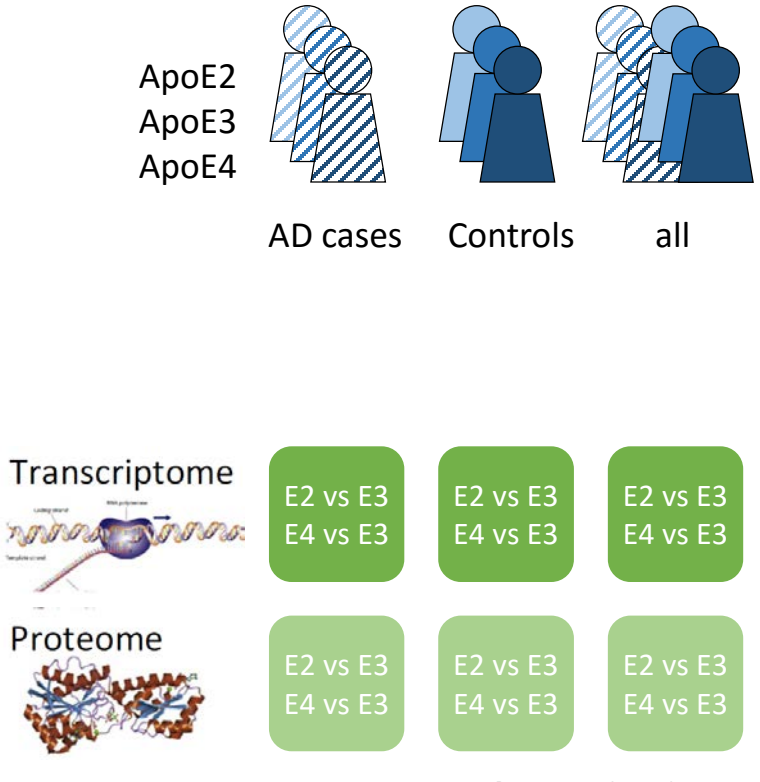
APOE stratified analysis and integration of human OMICS data

Differences by disease status



Differences by ApoE status:



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

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Genes with suggestive genotype specific AD associations identified by GWAS

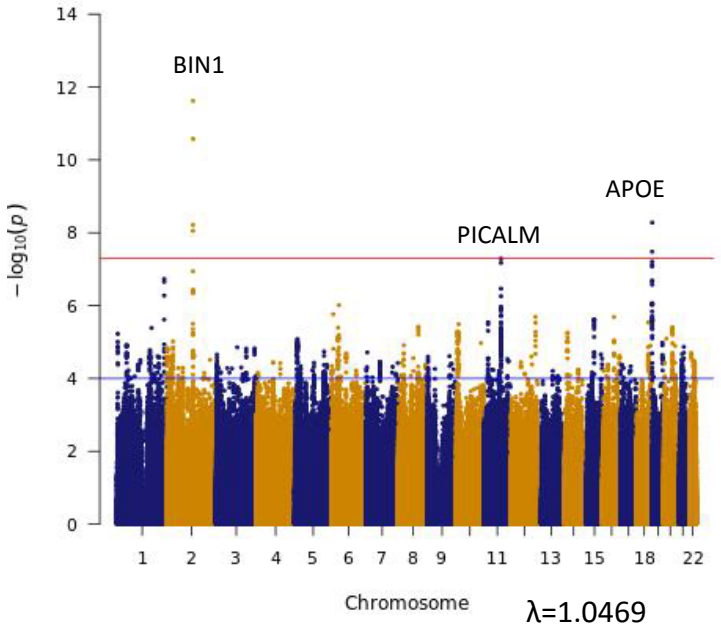
Stratified GWAS analysis on AD status:

- in two stages (stage I and stage II)
- In total 27,841 samples: ApoE2:2447, ApoE3 14,404, ApoE4: 10,990
- adjusted gender, PMI, age and race

Significant loci of combined analysis (p-value(Stage I)<0.001, p-value(Stage II)<0.05 and p-value(Stage I+II)<0.0001):

- ApoE2: 1 locus
- ApoE3: 10 loci
- ApoE4: 6 loci

Manhattan plot of ApoE3 GWAS (stage I and II)
Filtered for maf >0.5



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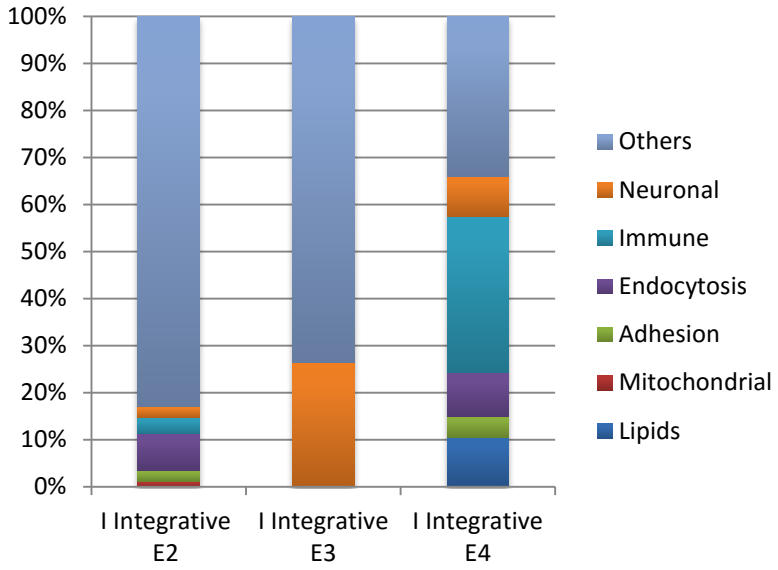
Integrative scoring enables aggregating genomics and transcriptomics results

Integrative analysis - Scoring

- robust rank aggregation (RRA) used to integrate ranked gene lists from the GWAS metaanalysis, the brain and blood expression analysis
- genes were given a final rank according to the calculated RRA scores sorted in ascending order

Pathway analysis:

- performed on top 200 genes scored by RRA with WebGestalt
- Immune pathways were enriched in top genes from ApoE2 and ApoE4 stratum



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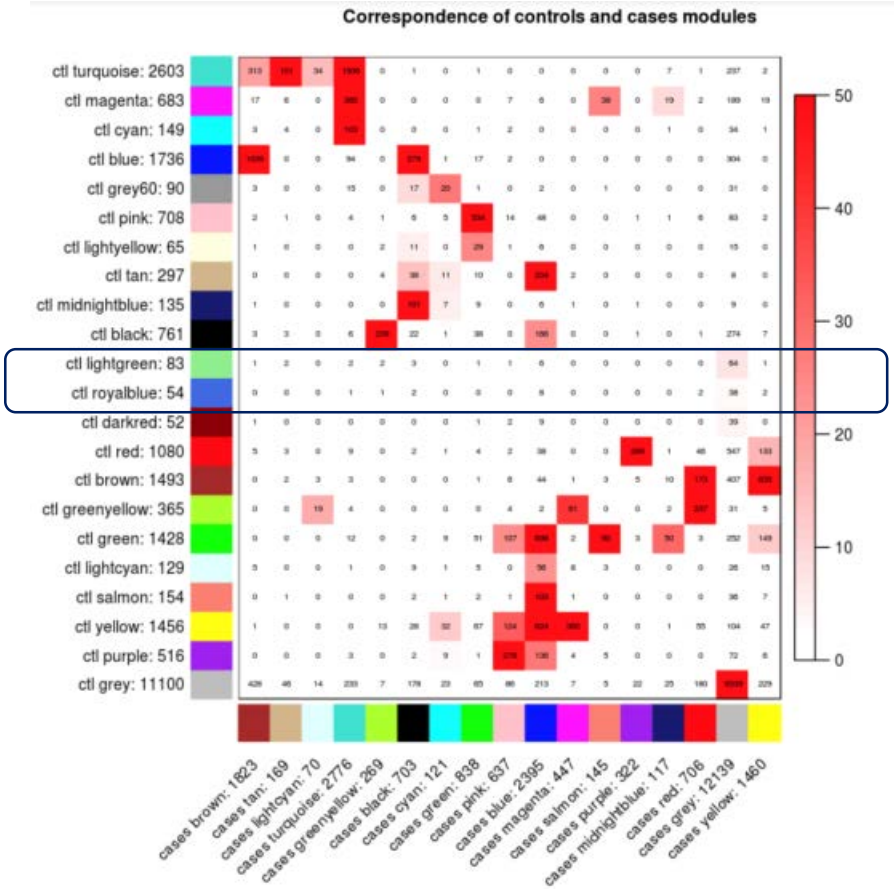
Network analysis to investigate genotype specific processes



Co-Expression network analysis:

- performed for the largest gene expression data set (ROS/MAP study) for cases and controls

→ Most co-expression modules are preserved in case and controls

→ few modules show poor evidence of preservation between co-expression in controls and cases

→ are enriched for immune related pathways

→ include genes that are differentially expressed between cases with ApoE2 and cases with ApoE4

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Looking for therapeutic entry points for Alzheimer's disease: lessons learned from agnostic trans-co-regulatory network analyses of APOE, TREM2, PLCG2 and ABI3 loci.

Table 1: Top ten pathways associated to AD risk genes agnostic trans-coregulatory networks

geneset	Top 10 *APOE* co-regulated pathways	Enrichment	FDR p-value
GO:0072376	protein activation cascade	20,09	4,34E-07
GO:0006959	humoral immune response	10,89	9,41E-06
GO:0050727	regulation of inflammatory response	5,99	1,53E-03
GO:1901342	regulation of vasculature development	6,05	7,26E-03
GO:0052547	regulation of peptidase activity	4,66	7,26E-03
GO:0010035	response to inorganic substance	4,19	7,26E-03
GO:0002253	activation of immune response	4,08	7,95E-03
GO:0002526	acute inflammatory response	8,06	9,44E-03
GO:0007568	aging	5,18	1,29E-02
GO:1901565	organonitrogen compound catabolic process	4,42	1,46E-02

geneset	TOP 10 *TREM2* co-regulated pathways	Enrichment	FDR p-value
GO:0002683	negative regulation of immune system process	8,29	1,17E-05
GO:0002253	activation of immune response	6,56	2,17E-05
GO:0050865	regulation of cell activation	6,17	9,76E-05
GO:0006638	neutral lipid metabolic process	12,37	1,63E-03
GO:0006898	receptor-mediated endocytosis	7,29	1,91E-03
GO:0002764	immune response-regulating signaling pathway	5,31	1,93E-03
GO:0072376	protein activation cascade	15,20	2,04E-03
GO:0006909	phagocytosis	7,99	2,34E-03
GO:0050727	regulation of inflammatory response	6,53	2,34E-03
GO:0034341	response to interferon-gamma	9,42	3,07E-03

geneset	TOP 10 *PLCG2* co-regulated pathways	Enrichment	FDR p-value
GO:0001819	positive regulation of cytokine production	5,80	0
GO:0002250	adaptive immune response	7,54	0
GO:0002253	activation of immune response	6,76	0
GO:0002263	cell activation involved in immune response	7,34	0
GO:0002274	myeloid leukocyte activation	8,70	0
GO:0002443	leukocyte mediated immunity	7,11	0
GO:0002521	leukocyte differentiation	6,28	0
GO:0002683	negative regulation of immune system process	4,63	0
GO:0002697	regulation of immune effector process	6,11	0
GO:0002764	immune response-regulating signaling pathway	6,95	0

geneset	TOP 10 *ABI3* co-regulated pathways	Enrichment	FDR p-value
GO:0007159	leukocyte cell-cell adhesion	14,85	8,36E-04
GO:0022407	regulation of cell-cell adhesion	15,51	3,52E-03
GO:0070661	leukocyte proliferation	17,62	1,40E-02
GO:0031589	cell-substrate adhesion	15,57	1,69E-02
GO:0007015	actin filament organization	14,38	1,84E-02
GO:0050900	leukocyte migration	12,75	2,45E-02
GO:0050865	regulation of cell activation	9,94	5,42E-02
GO:0006909	phagocytosis	16,56	6,43E-02
GO:0048872	homeostasis of number of cells	15,61	6,79E-02
GO:0033627	cell adhesion mediated by integrin	43,55	7,05E-02

Ruiz et al. AAIC 2018. Alzheimers Dementia. July 2018. Volume 14, Issue 7, P1117–P1118
Kleineidam et al. (manuscript in preparation)

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Looking for therapeutic entry points for Alzheimer's disease: lessons learned from agnostic trans-co-regulatory network analyses of APOE, TREM2, PLCG2 and ABI3 loci.

Figure 1: Venn diagram. Shared co-regulated networks of genes observed in four AD risk loci. *APOE-PLCG2* (n=43) and *APOE-PLCG2-TREM2* (n=21) gene sets were selected for additional enrichment analyses.

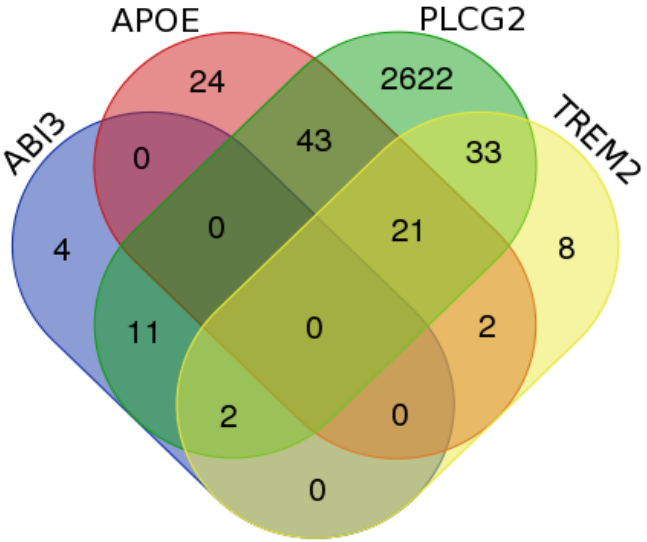
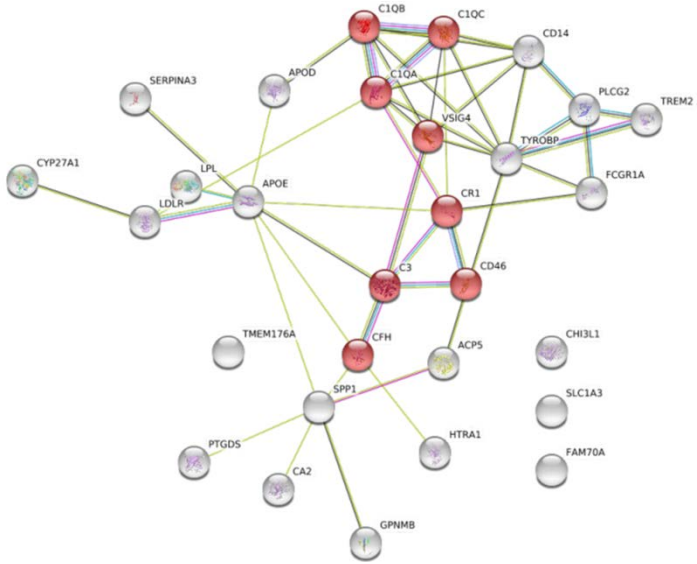


Figure 2: STRING results only using common genes observed in *APOE*, *PLCG2* and *TREM2* agnostic coregulatory networks. FDR p-value=0. Top Pathway predicted was complement activation (FDR p-value=1.09E-11, proteins in red)



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Thanks for your attention

Questions?

Ideas?

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