Gene expression network analysis of gender differences in Alzheimer's Disease

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Objectives:

-identify male/female differences in the pathogenesis of Alzheimer's disease (AD)
-generate novel hypotheses addressing their causes and consequences

Approach Rationale:

Unbiased➔ Genome-wide

AD-relevant➔ Human Brain

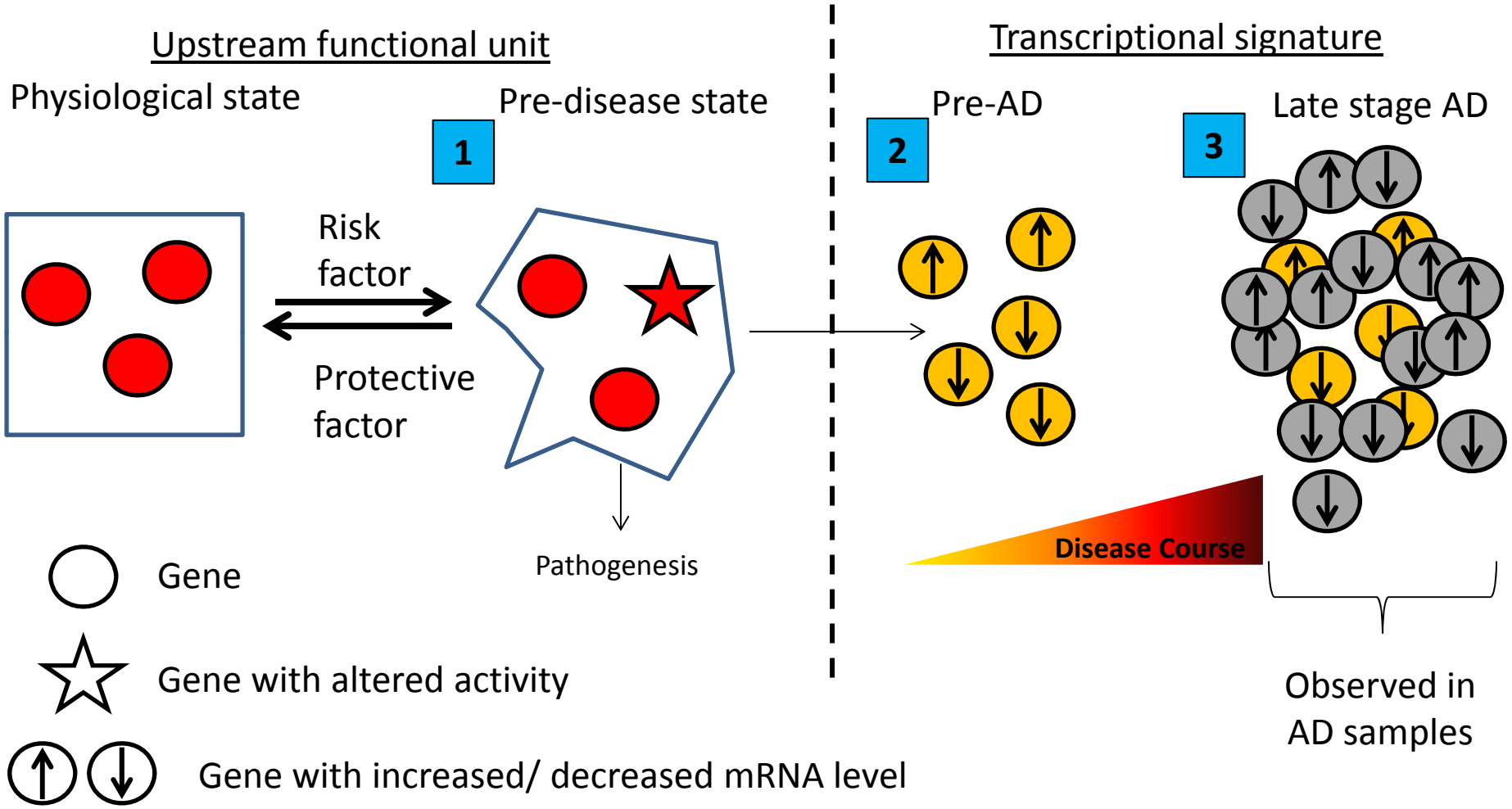
Functional ➔ Gene expression

Causal➔ Co-expression Network

➔ Differential Co-expression Analysis (DCA) of gender-related AD processes in human brain

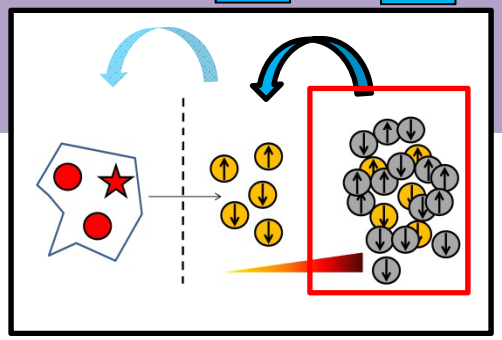
Conceptual framework

Underlying mechanisms altered by AD risk factors : Bottom-up approach



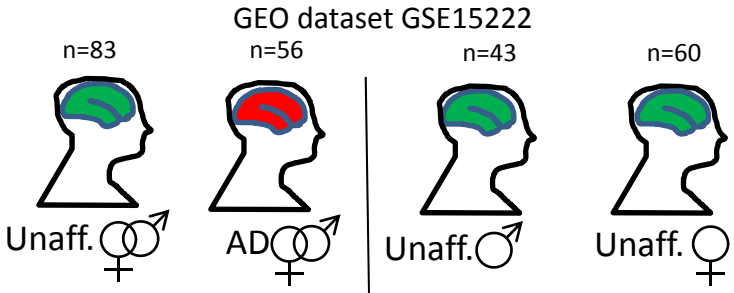
➔ Objective of the bioinformatic analysis: "Rewind" in silico the chain of events, from the signature observed in **3** to the gene whose function is altered in **1**

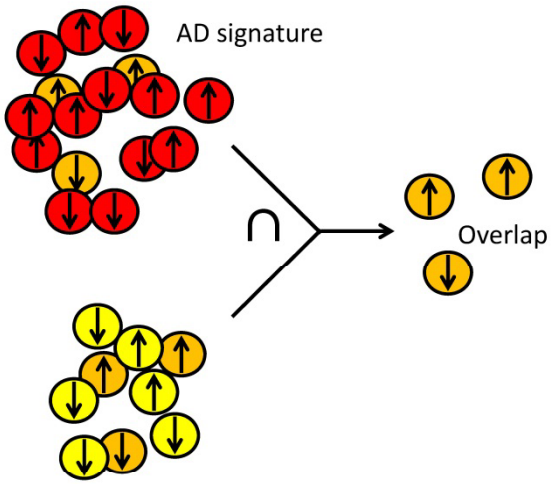
from **3** to **2**



Implementation – Step 1

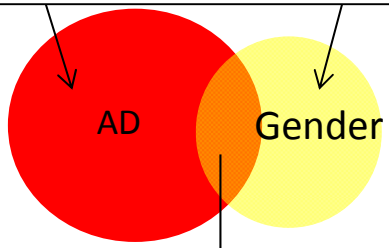
Identifying pre-AD transcriptional signature



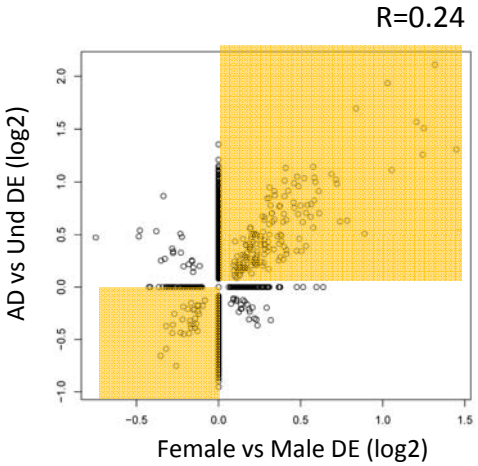


Intersecting AD and gender transcriptomic signature to extract a pre-AD gender signature

Differential expression analysis

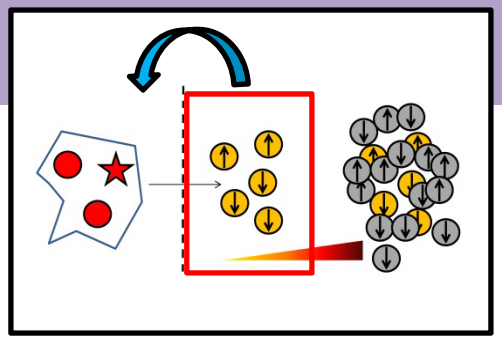


AD/Gender transcriptional signature



➔Significant similarity between female transcriptomic signature in the elderly brain and AD brain

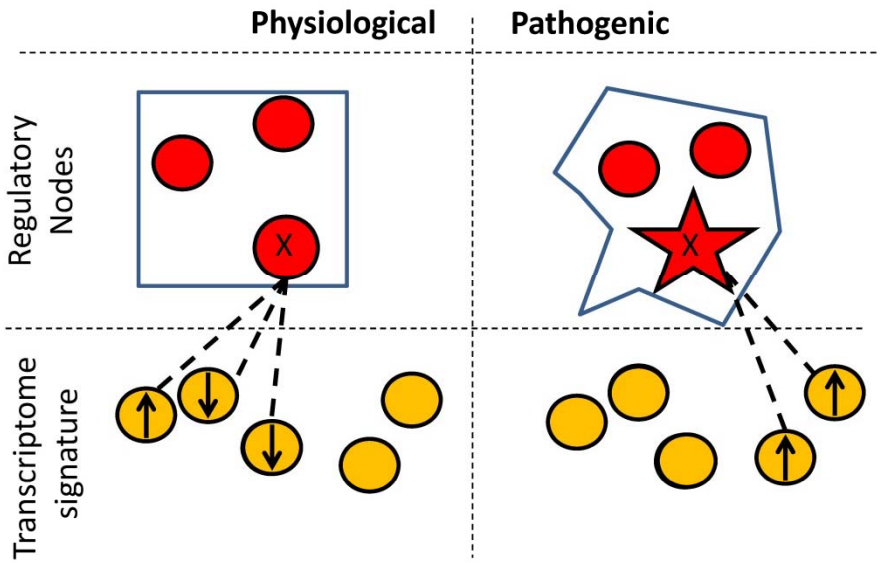
from 2 to 1



Implementation – Step 2

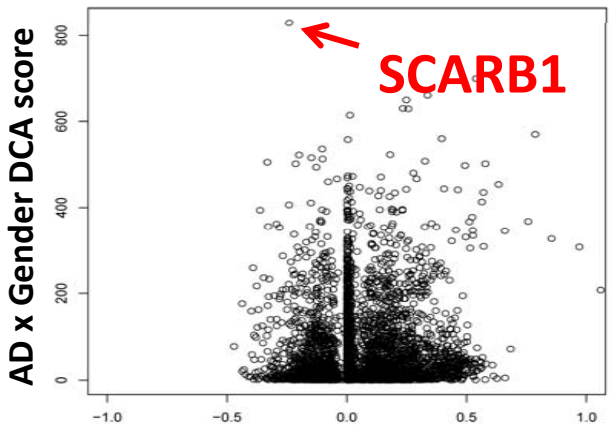
Identifying causal effector candidates

Genes identified by Differential Co-expression Analysis:
Key effectors = genes cumulatively most differentially wired to the most differentially expressed genes



Identifying altered activity by differential co-expression

- ➔ Identify genes whose activity is the most altered **without requirement for a change in their mRNA levels.**
- ➔ Identify the genes from the upstream functional unit whose activity is altered **by gender and by AD**.



Differences between DCA scoring (Y axis) and differential expression (X axis) results

Result:
SCARB1 as an effector of gender-dependent AD risk

SCARB1 / SR-BI:
Cell surface receptor, central player of cholesterol metabolism
Receptor for high density lipoprotein cholesterol (HDL), mediates cholesterol transfer to and from HDL.

Genetic variants associated to HDL-cholesterol levels and atherosclerosis

➔ Similar to APOE !!!

Gender-specificity:
-SCARB1 affects lipid metabolism and cholesterol efflux in **a gender-specific** fashion
-effects on myocardial infarct and atherosclerosis of genetic variants at the SCARB1 locus appear also **gender-dependent**

Confirmation:
-re-analysis of AD GWAS datasets ➔ interaction between a SCARB1 genetic variant and gender in modulating AD age of onset
(NIAGADS NG00022, NG00023 and NG00024 with n=1360 ,180 and 857 AD patients)

Druggability:
SCARB1 inhibitors: ML278, ML279 and ML312 (NIH), BLT-1 and ITX-5061 (Clinical Phase II)

Further Implementation of the Solution

Overall approach:

Complexity of the problem & modest size effect

➔**large-scale human whole organism studies** rather than animal or cell culture

➔Further human genomics approaches

1) Validation of SCARB1 variant genetic effect

2) Identification of AD-related biomarkers associated to gender and SCARB1

3) Exploration of SCARB1-related pathways by human genetics

4) Molecular dissection of the effect of gender and genetic variant on SCARB1 gene

5) Drugs reverting the AD-causing gender effects?

Further Implementation of the Solution

1) Confirmation of SCARB1 variants genetic effect in function of gender:

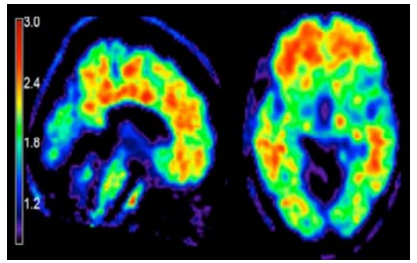
-AD GWAS cohorts for AD risk and age at onset.
-on MCI, cognitive reserve, cognitive decline.
-ADNI whole-genome sequencing data for rarer coding variants

Data sources: NIAGADS NG00017, NG00022-24, NG00026, NG00028-30, ADNI cohort, NIA-LOAD, Tgen, GenADA (More than 7000 AD patients)

➔Milestone to confirm the role of SCARB1

2)Identification of AD-related biomarkers associated to gender and SCARB1

- Biochemical: CSF Aβ, pTau or their ratio
-Imaging: Florbetapir or Pitt-stop PET imaging, cortical atrophy, frontal horn enlargement



Data sources: ADNI, PPMI

➔For proximal clinical read-out in a SCARB1 targeting clinical trial

3) Exploration of SCARB1-related pathway

-Gender-specific effects of genetic variants in other cholesterol metabolism genes (CETP, APOA1, APOE)

-3-way interaction between APOE4 genotype, gender and SCARB1

Data sources: NIAGADS datasets, ADNI cohort

➔Better stratification might reveal SCARB1 effect. And identify interacting partners/pathways.

Further Implementation of the Solution

4) Molecular dissection of the effect of gender and genetic variant on SCARB1 gene

-effect of SCARB1 genetic variants on SCARB1 mRNA levels, SCARB1 splicing.

Data sources: GEO, GSE15222 , GSE15745, GSE46706, GSE44772
dbGap phs000424.v3.p1, NIAGADS NG00025, Allen Brain Atlas

➔Understand the function of the SNP on SCARB1 function

5)Re-positioning drugs that could reverse the effect of gender on AD:

Based on SCARB1 biological knowledge

-Effect of statin or other cholesterol-modifying drug treatment on AD risk in function of gender and SCARB1 genotype

Data sources: Framingham cohort (**phs000007.v20.p8**), Baltimore Longitudinal Study of Aging, WHI (**phs000200.v8.p2**).

➔Better stratification might reveal an AD-protective effect of statins in specific segments of the population (such as women with a given SCARB1 genotype).