

第十屆海峽兩岸生物學啟發的理論科學問題研討會

上海应用物理研究所/揚州大學

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Functional genomic analysis of normal brain aging and Alzheimer's disease

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Outline

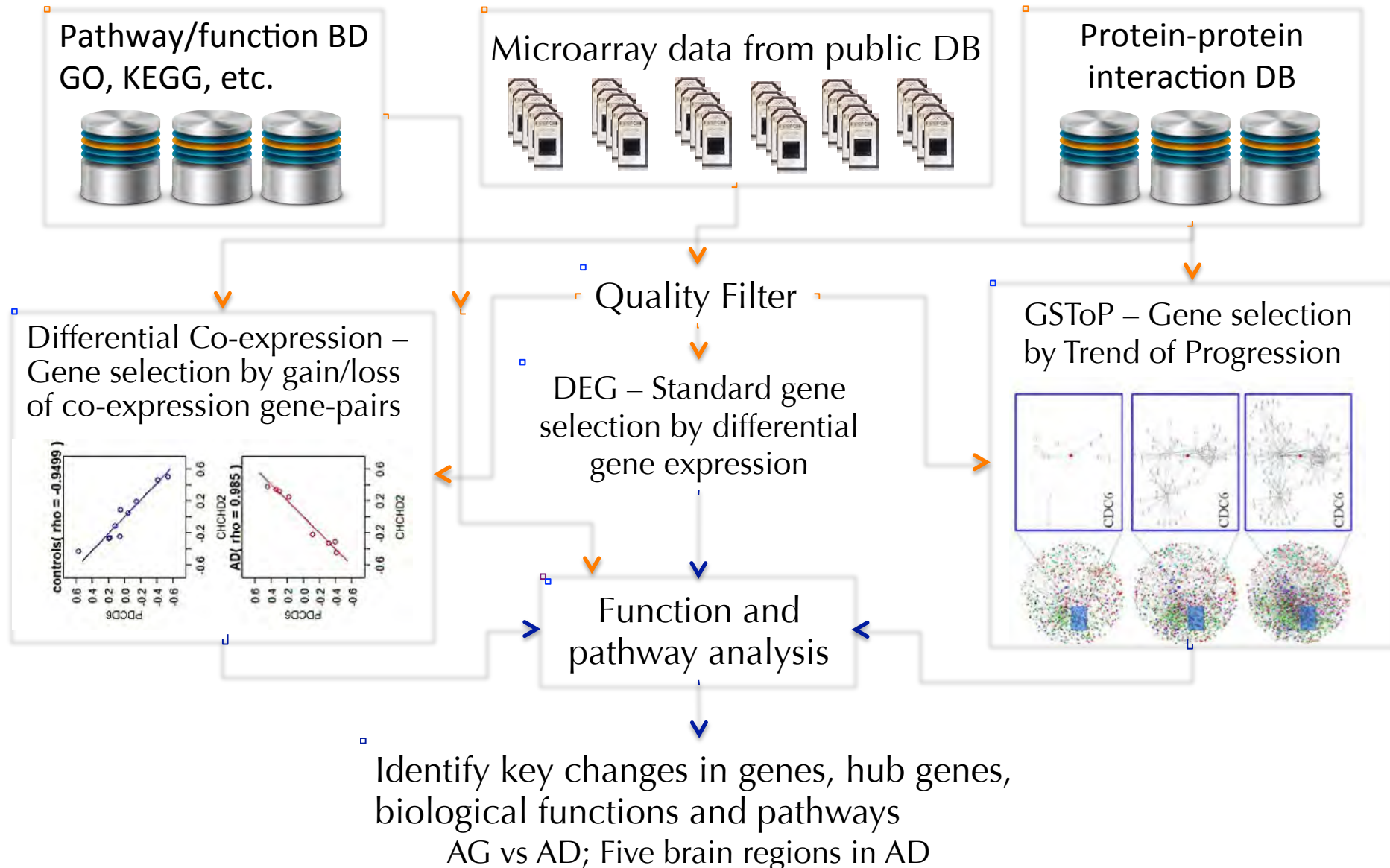
- **Aims – Understand:**
 - Functional genomic profiles of normal brain aging (AG) and the Alzheimer's disease (AD)
 - How normal AG and AD differ in functional genomics
 - How AD manifests differently in five brain regions
 - Key affected genes, functions, and pathways
- (Future) repurposed drugs to arrest/slow disorder progression

Outline (cont'd)

Material – Public data on AG and region-specific AD whole-genome microarray data on human cohorts, protein-protein interaction DB, function and pathway DBs

Methods – Whole genome analysis, functional genomics, gene selection based on trend of disease progression (network theory)

Workflow



Material

Microarray datasets AG dataset, A0; AD datasets, A1 to A5 from five brain regions.

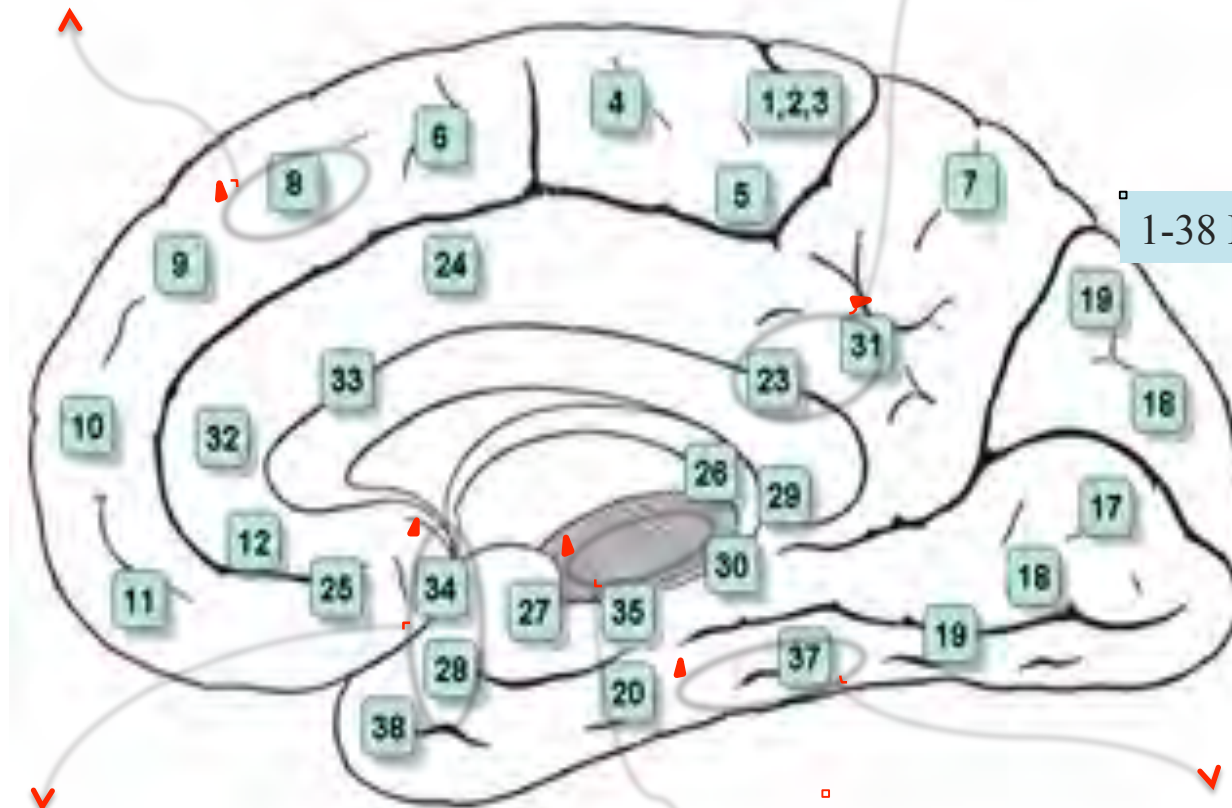
Code	Datasets	Original set size	Set size after quality control	Previous citations
A0	Old (> 70) vs Young (< 40)	20 vs. 21	10 vs. 10	[7]
A1	EC/AD vs Control	10 vs. 13	9 vs. 11	
A2	HC/AD vs Controls	10 vs. 13	8 vs. 10	[8, 9]
A3	MTG/AD vs Controls	16 vs. 12	14 vs. 11	
A4	PC/AD vs Controls	9 vs. 13	9 vs. 10	
A5	SFG/AD vs Controls	23 vs. 12	12 vs. 8	

EC, entorhinal cortex 嗅皮層; HC, hippocampus 海馬; MTG, medial temporal gyrus 內側顳中回; PC, posterior cingulate; SFG 後扣帶; SFG, superior frontal gyrus 額上回. All microarray data are in Affymetrix U133 plus 2.0 platform.

The five brain regions

5 - superior frontal gyrus 額上回
self-awareness, laughter

4 - posterior cingulate 後扣帶
emotion, memory, meditation



1-38 Brodmann's areas

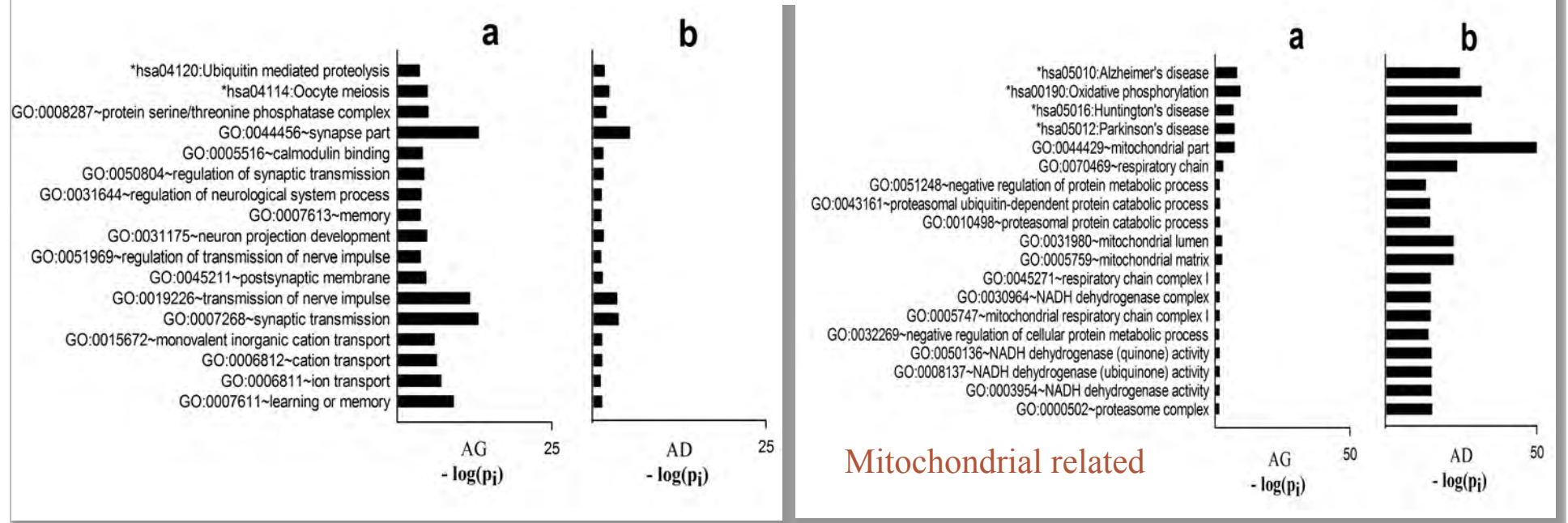
1- entorhinal cortex 嗅皮層
*declarative memory,
spatial memory*

3- medial temporal gyrus 內側顳中回
(face recognition, reading)

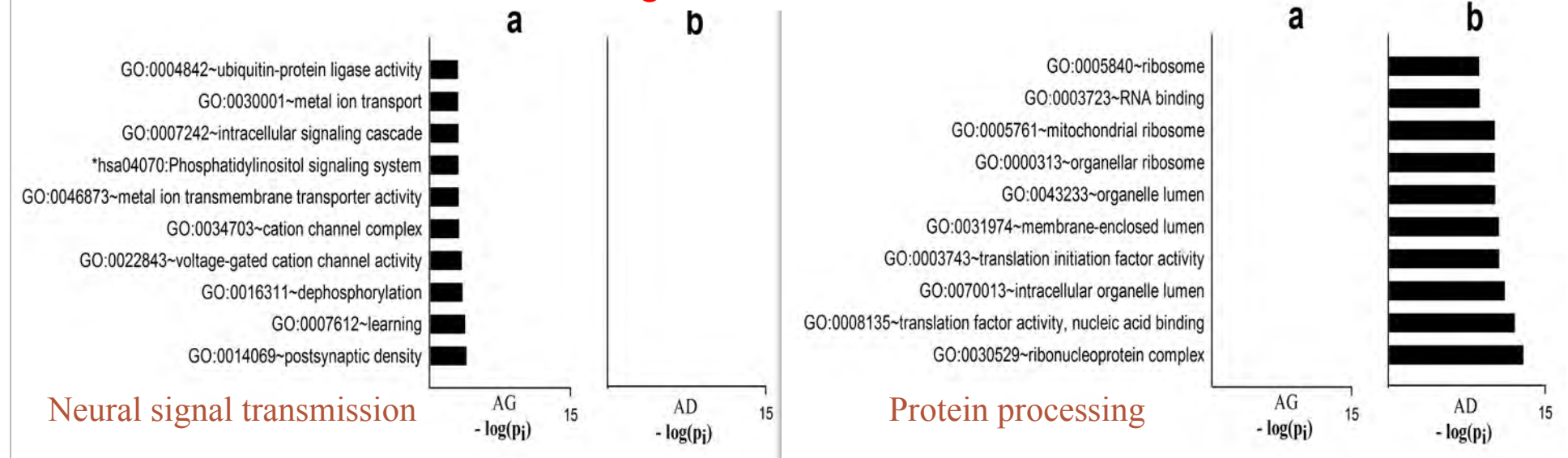
2- hippocampus 海馬
memory, spatial & navigation

Results from standard DEG analysis

Functions significant in both AG and AD



Functions significant in either AG or AD



Significant loss of functions in AG and AD

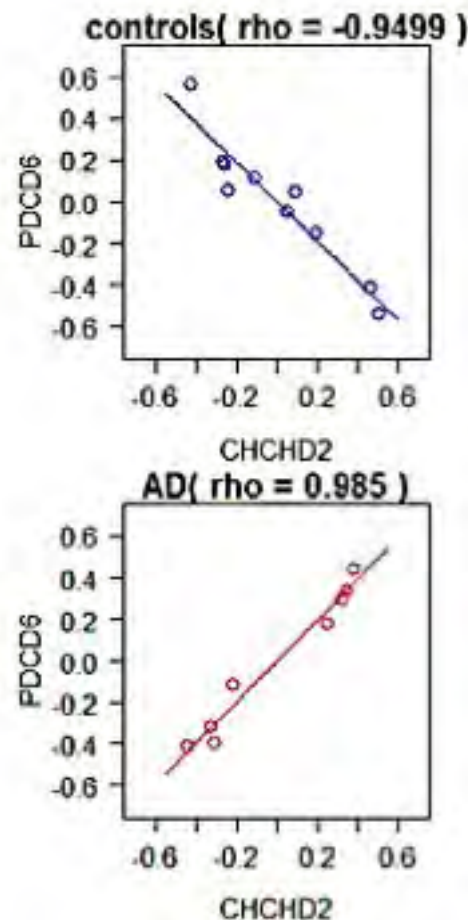
Gene selected using LIMMA. Functional categories significant in AG ($p < 0.05$) but not in AD, and vice versa. AD was represented by consensus gene set from five brain regions.

	Functional categories	Genes common to functional categories
AG	- voltage-gated cation channel activity - cation channel complex - metal ion transmembrane transporter activity - metal ion transport	CACNA1G, CACNA2D1, CACNB2, CACNB4, CACNG3, KCNA6, KCNB1, KCND2, KCNF1, KCNJ3, KCNJ4, KCNJ6, KCNK1, KCNQ5, KCNV1, KCTD16, SCN2A, SCN2B, SCN8A
	Neural signal transmission related	
AD	- ribonucleoprotein complex - organellar ribosome - mitochondrial ribosome - ribosome	MRPL12, MRPL16, MRPL27, MRPL3, MRPL32, MRPL34, MRPL35, MRPL36, MRPL39, MRPL40, MRPL47, MRPL52, MRPL55, MRPL9, MRPS11, MRPS15, MRPS18A, MRPS21, MRPS22, MRPS25, MRPS28, MRPS33, MRPS35, MRPS9
	Mitochondrial and protein processing related	

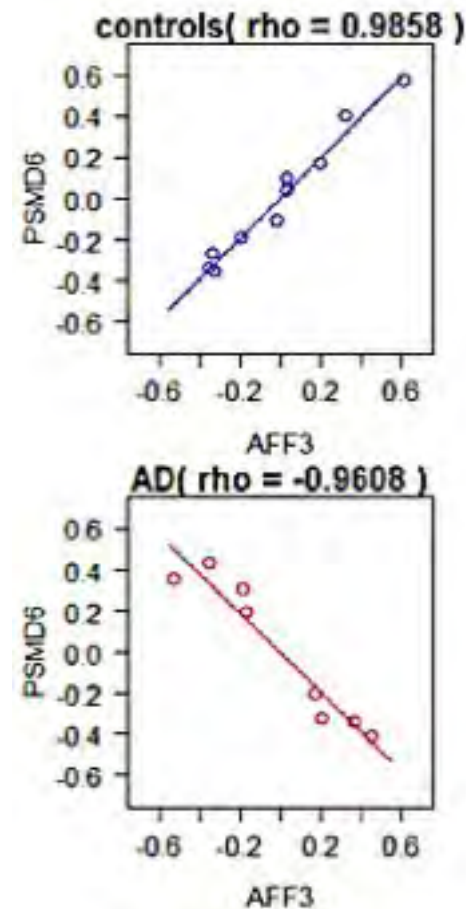
Method – Differentially co-expressed gene pairs (DCE)

Consider co-expression of a gene pair in control and test data, respectively. Pair may have gain of correlation (GOC) or loss of correlation (LOC)

GOC in control vs AD
PDCD6-CHCHD2



LOC in control vs AD
PSMD6-AFF3



Results from DCE analysis

Top hub genes

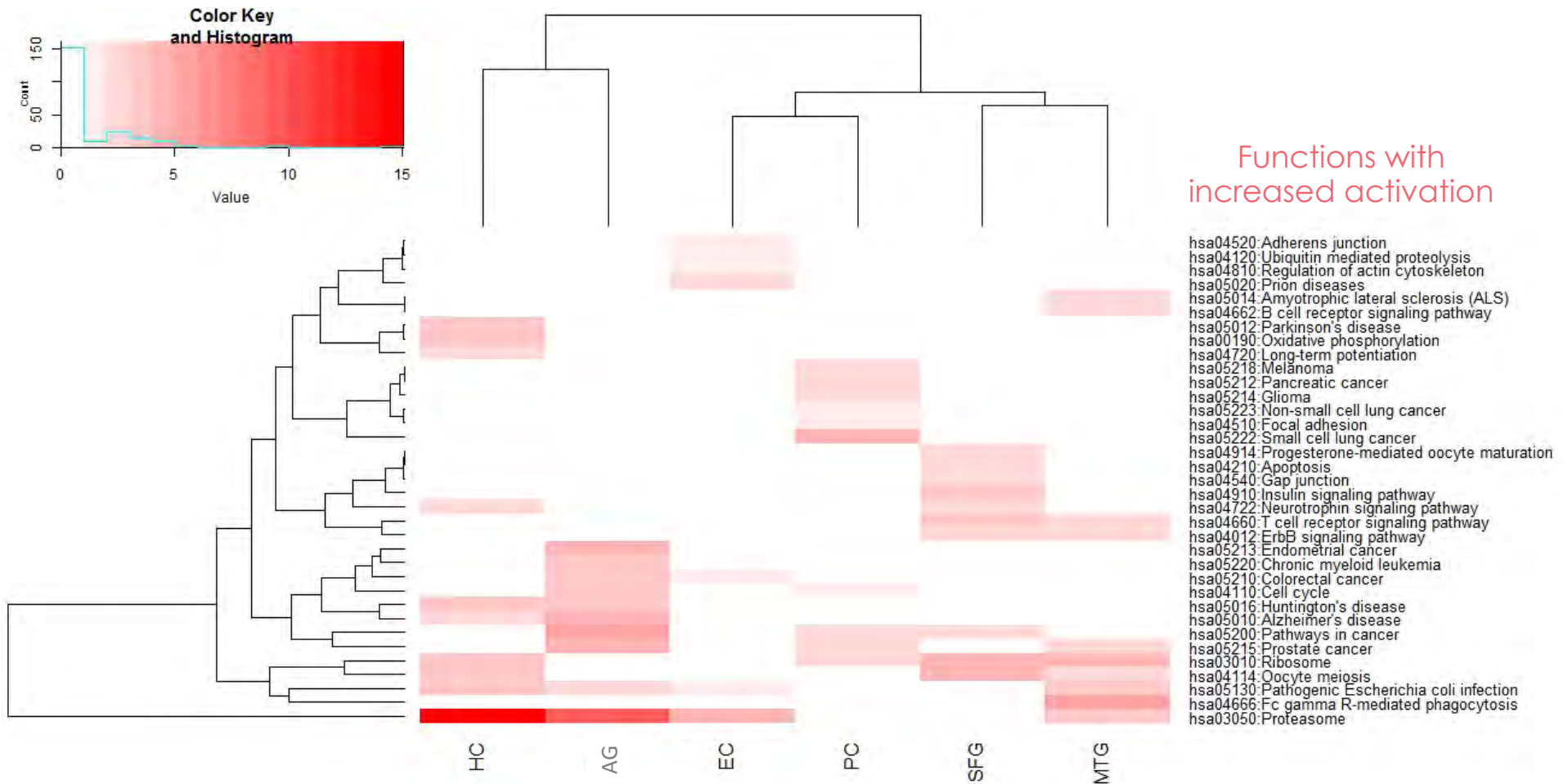
Gene with number of parings (degrees) >5 and top 5 highest

Dataset	Hub genes
AG	PSMD4, PSMA3, PSMC2, SSX2IP, PSMC5, PSMD2 *PSMD6, PSMA7, *PSMC6
EC/AD	YWHAZ , PHF20, IGHG1 , TUBB , PLA2G4F, TUBA4A CLTC, YWHAG , SETX, ACTG1 , STXBP1, *PSMC6, CCT8
HC/AD	YWHAZ , PSMA2, ACTB, *PSMD6, TUBB , ACTG1 , RPL7 RPL17, CCT7, PSMD8
MTG/AD	TUBB , NSF, HSPA8, YWHAG , YWHAZ , TUBA4A , TCP1 PPP3CA
PC/AD	GAPDH, EEF2
SFG/AD	IGHG1

Red, common to three or more AD brain regions. **Blue**, common to two AD brain regions. Asterisk *, common to AG and one of five AD brain regions.

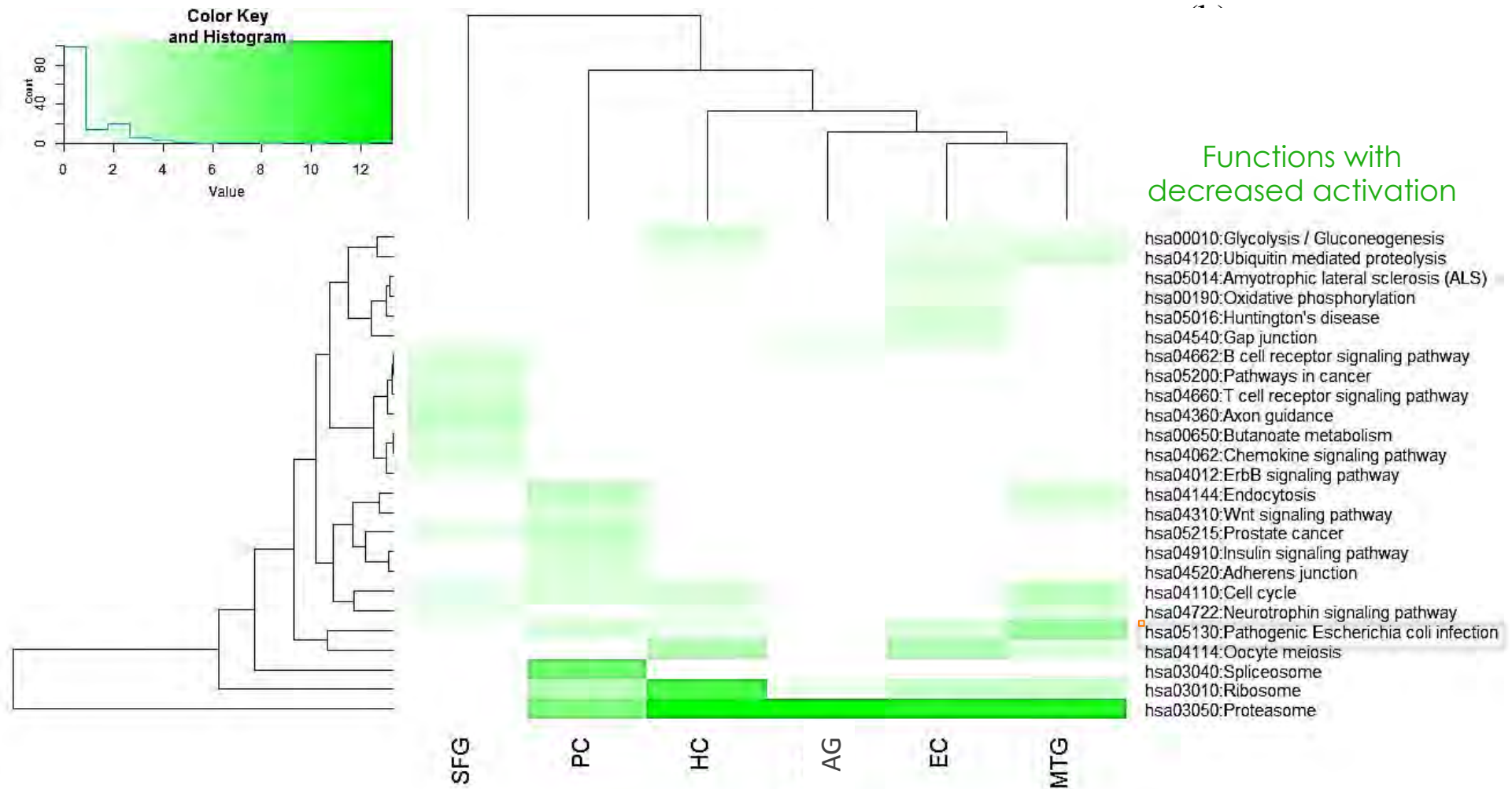
YWHAZ, Protein Kinase C Inhibitor Protein-1. Mediate signal transduction (and regulate insulin sensitivity). TUBB, Tubulin, Beta Class I. Protein coding gene, associated with brain malformation.

KEGG terms enriched (gain-of-co-expression)



EC, entorhinal cortex 嗅皮層; HC, hippocampus 海馬; MTG, medial temporal gyrus 內側顳中回; PC, posterior cingulate; SFG 後扣帶; SFG, superior frontal gyrus 額上回。

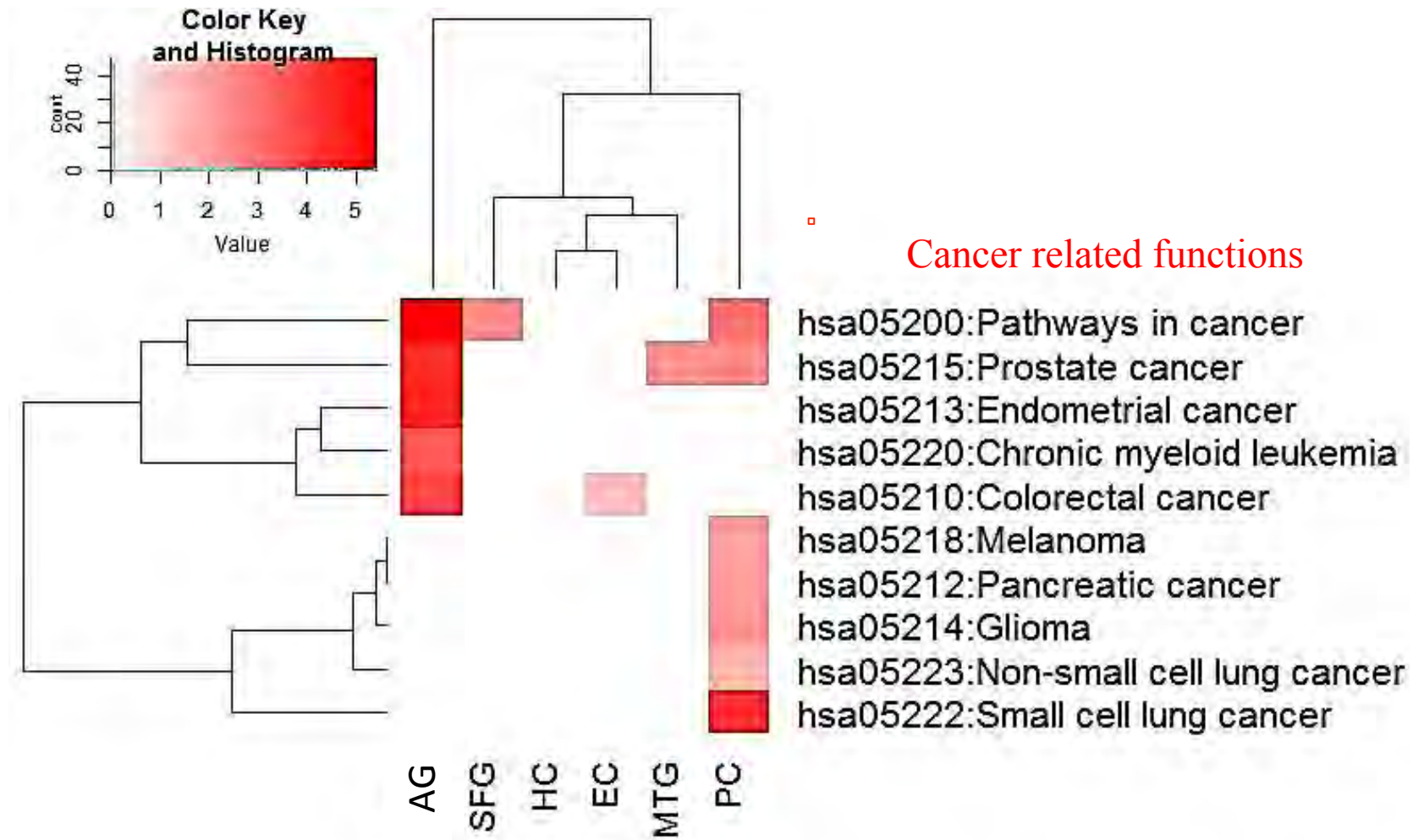
KEGG terms enriched (loss-of-co-expression)



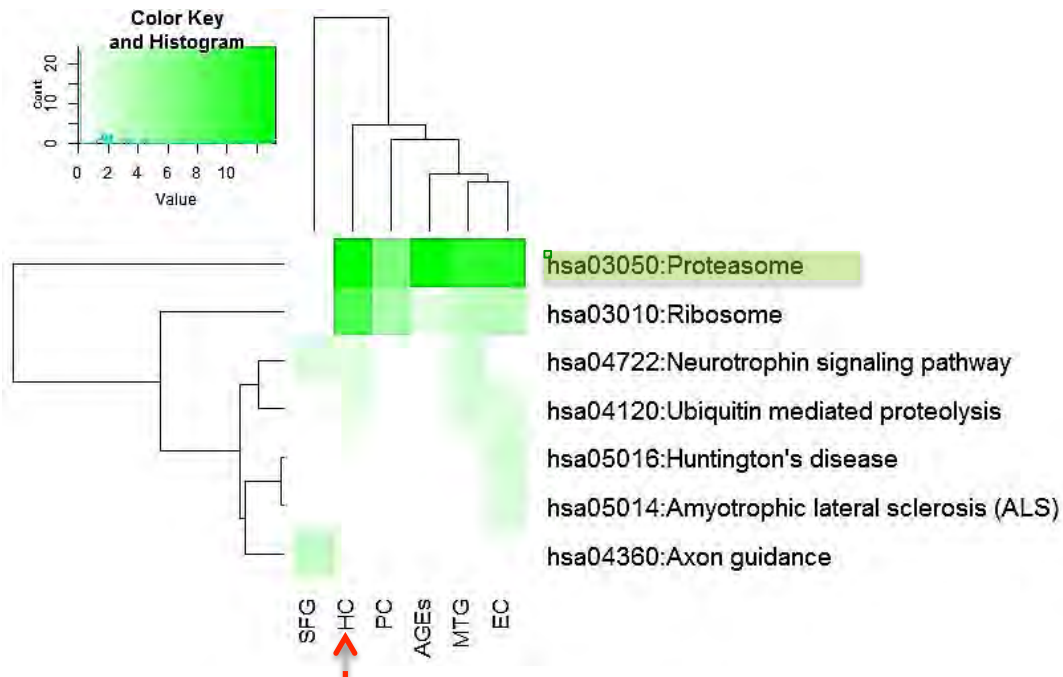
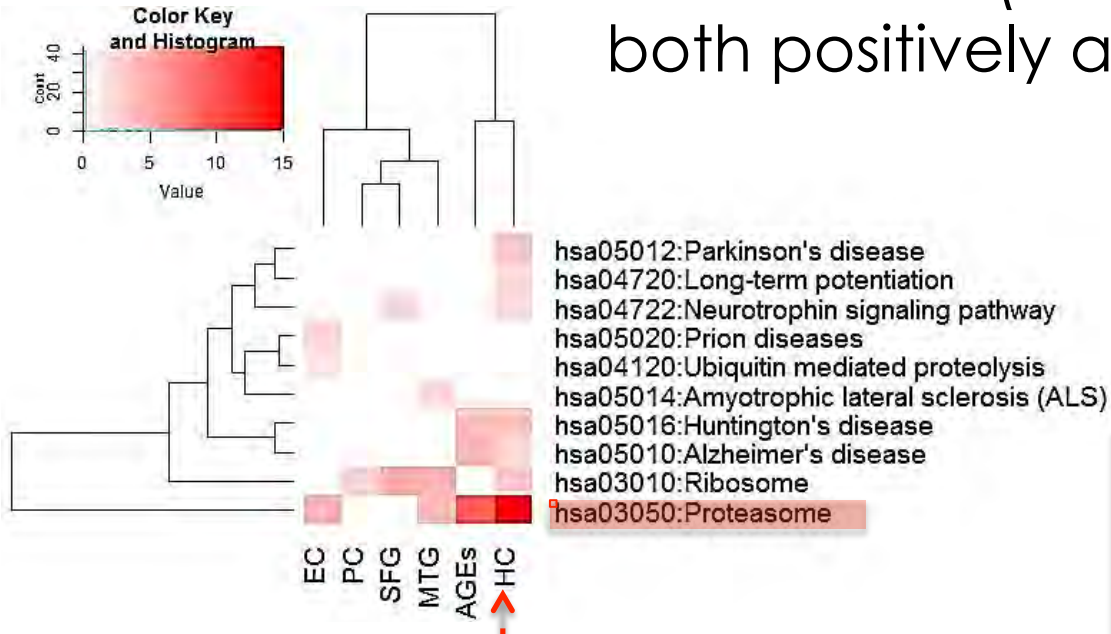
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DCE result

Functions related to cancer are highly enriched in AG but show no significance in HC/AD



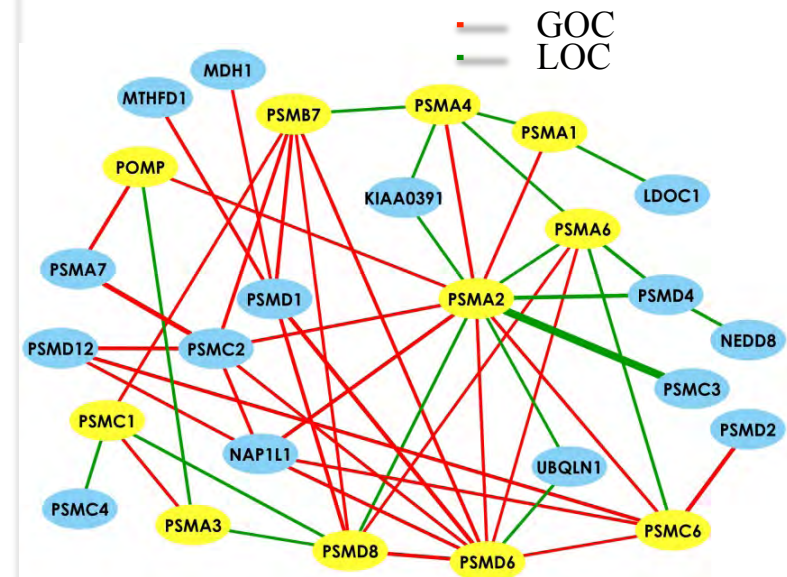
DCE result



Proteasome (PSM) related functions are both positively and negatively enriched

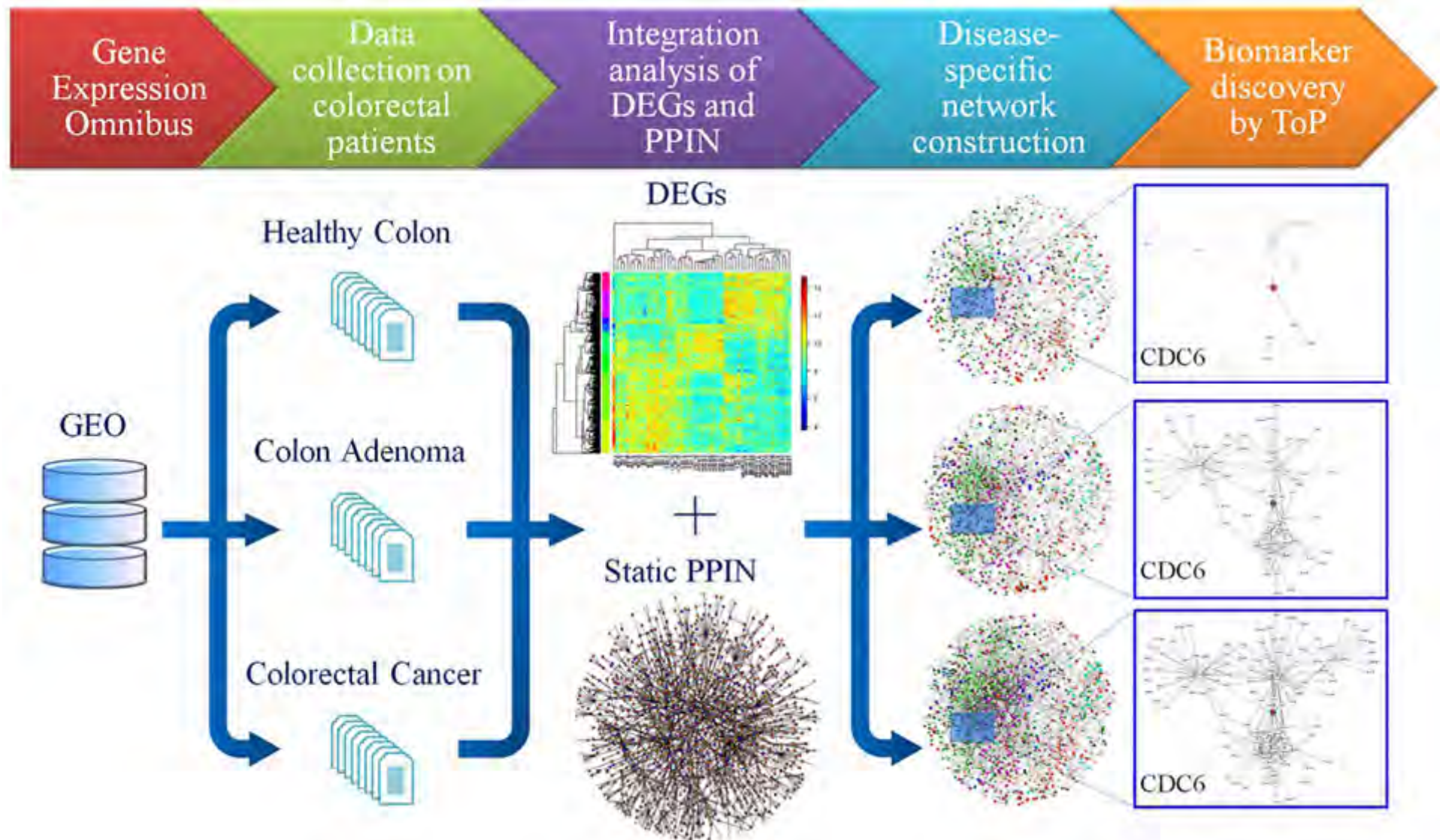
The main function of the **proteasome** 蛋白酶体 is to degrade unneeded or damaged proteins

Changes in PSM-related PPI network in HC



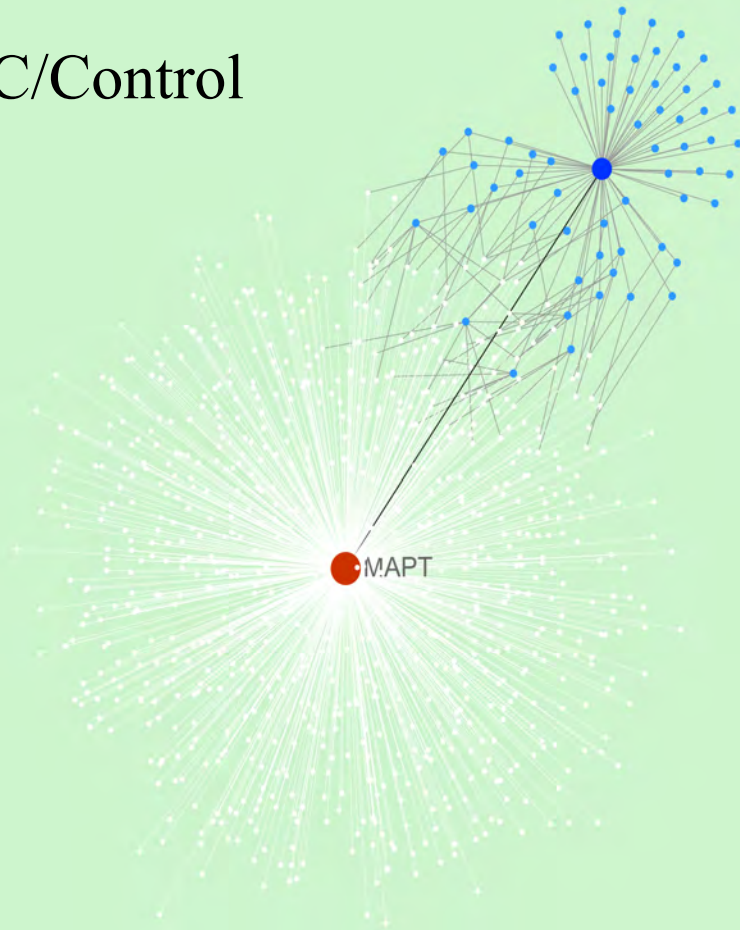
PSMDx and PSMCx are regulatory genes

GSToP – Gene Selection by Trend of Progression

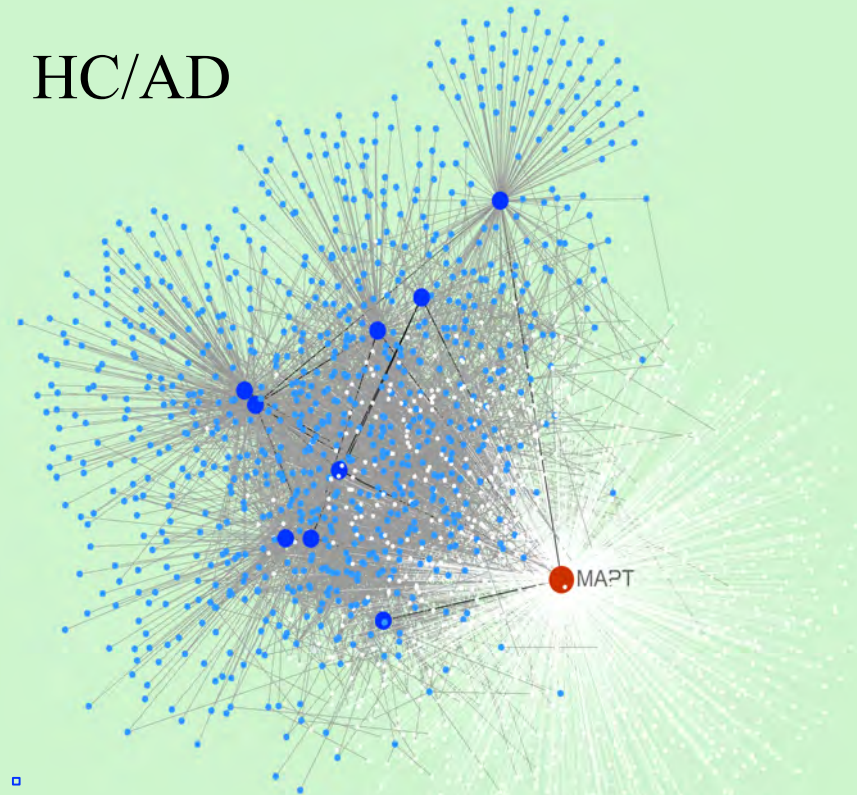


MAPT (Tau protein) gains activity with AD progression

HC/Control



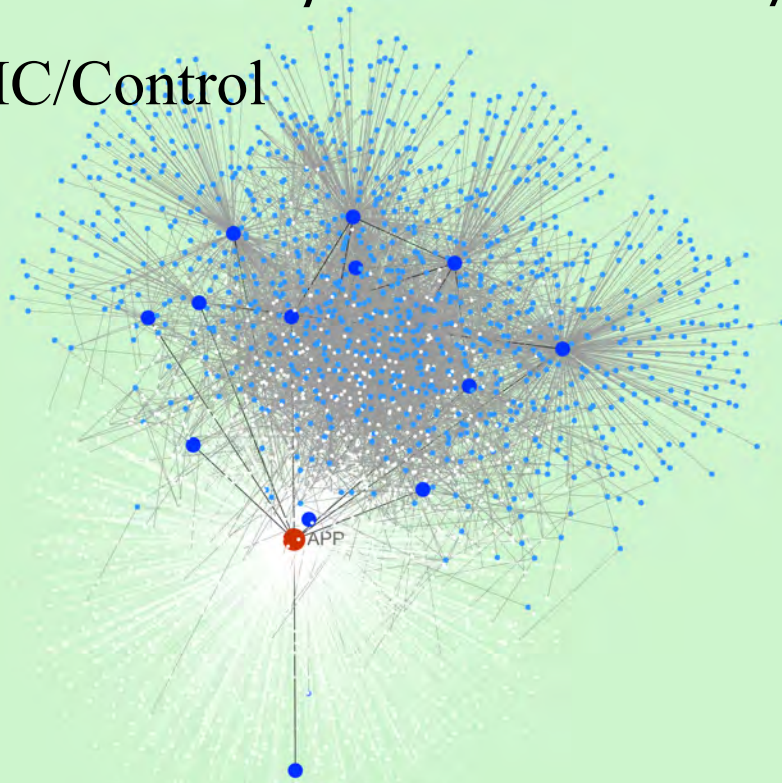
HC/AD



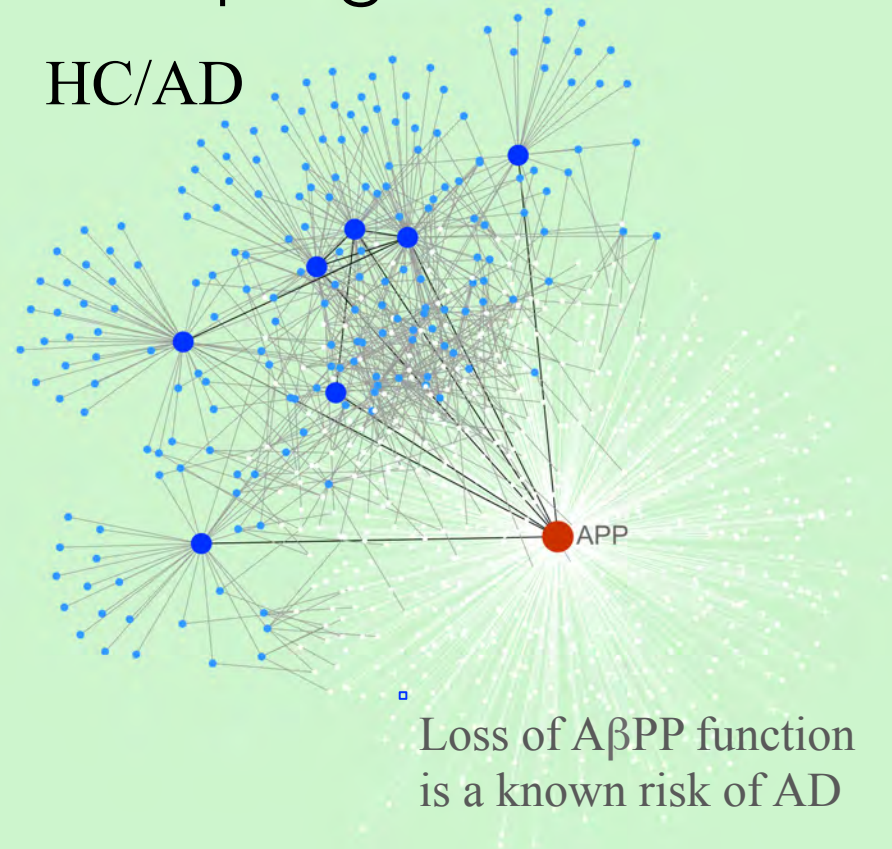
Over-expression of tau protein can result in the self-assembly of axonal tangles

A β PP (amyloid beta precursor protein β 澱粉樣前體蛋白) loses activity with AD progression

HC/Control

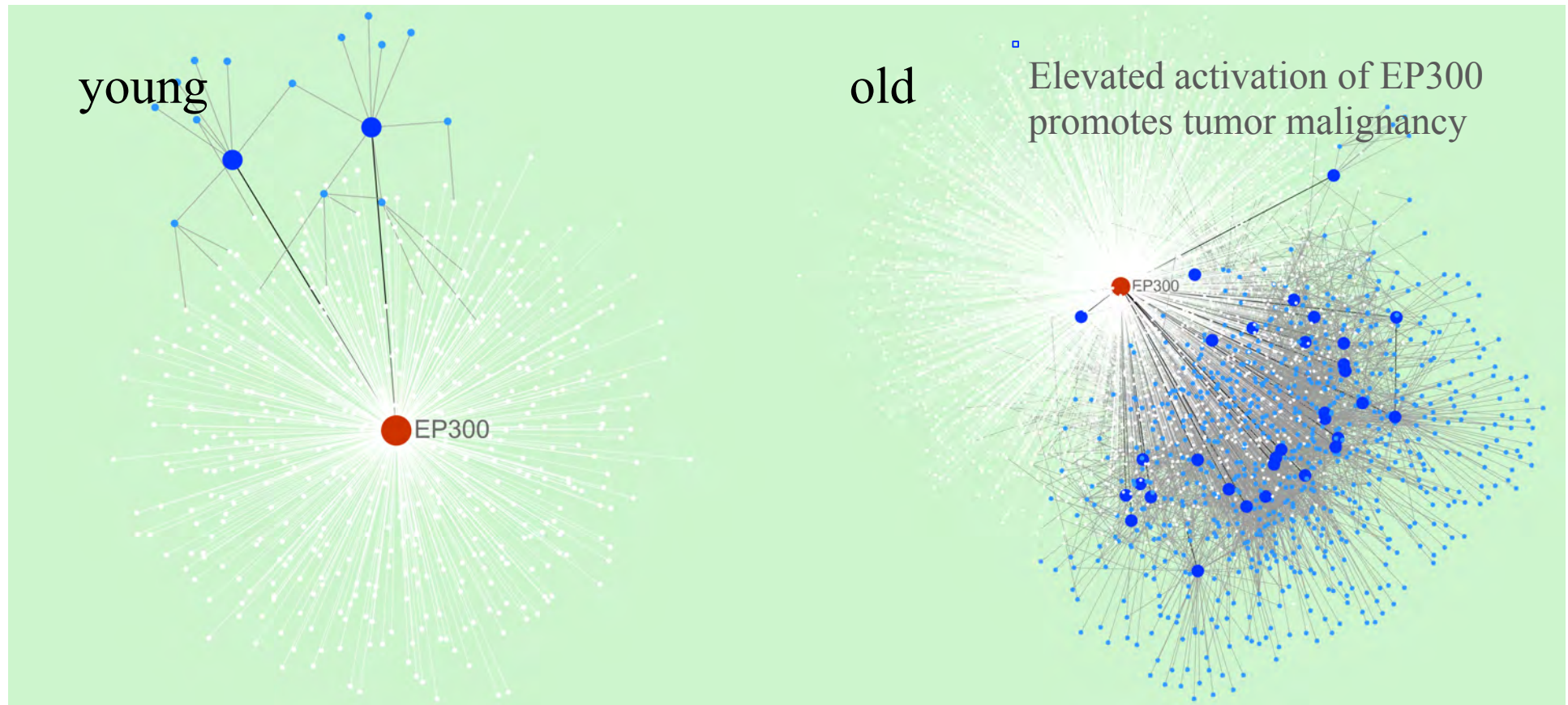


HC/AD

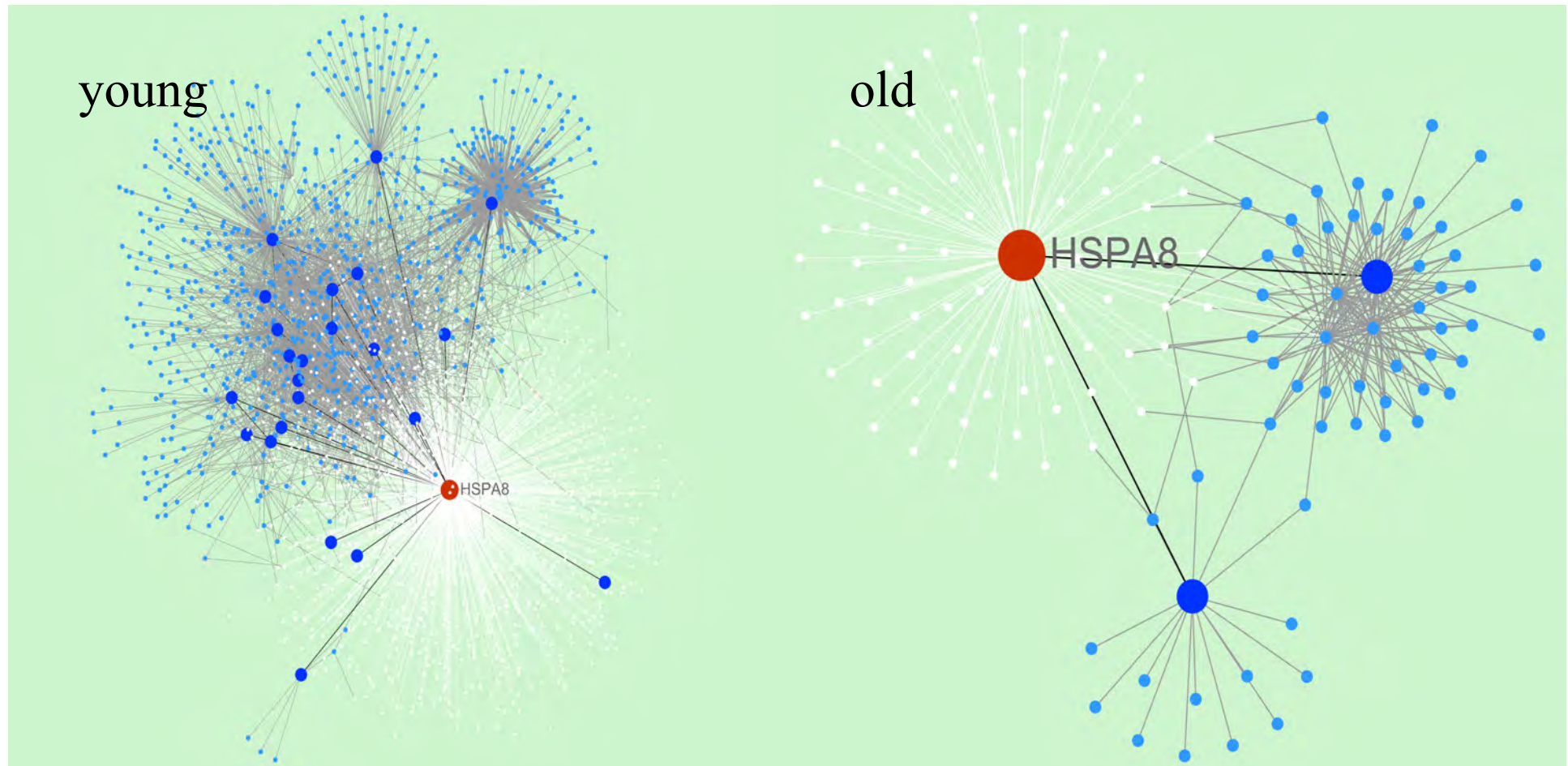


Loss of A β PP function
is a known risk of AD

EP300 (Histone acetyltransferase 組蛋白乙酰轉移 p300) gains activity with age



HSPA8 (heat shock 70kDa protein 8) loses activity with age



Many pathways dealing with bacteria and virus infection are compromised

- Epstein-Barr virus 單核細胞增多病毒 infection (AG, MTG, HC, PC, SFG)
- Legionellosis 軍團病 (MTG)
- Bacterial invasion of epithelial cells (SFG)
- Pathogenic Escherichia coli 大腸桿菌 infection (SFG)
- Salmonella 沙門氏菌 infection (SFG)
- Herpes simplex 單純皰疹 infection (AG)

Summary

- The three methods of selecting differentially behaving genes provide a complementary and consistent picture
- AD and AG have many common (molecular) abnormalities. In most cases, especially mitochondria related, the disorder in AD is more severe.
- Where AG & AD differ, AG exhibits neural transmission dysfunction; and AD, mitochondrial dysfunction and protein, including axon, deformation

Summary (cont'd)

- AG, but not AD, has significant elevated risk in cancers
- Many pathways dealing with bacteria and virus infection are compromised
- Identified most genes known to relate to AG/AD, plus many previously unreported hub genes
- We welcome collaboration on validation experiments (mouse model)

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