Functional genomic profiles of normal aging process in the brain and Alzheimer's disease

Yi-Shian Peng[1] (彭奕憲), Hoong-Chien Lee[1-3] (李弘謙)

[1]Institute of Systems Biology and Bioinformatics, National Central University, Zhongli, Taiwan 32001
[2]Center for Dynamical Biomarkers and Translational Medicine, National Central University, Zhongli, Taiwan 32001
[3]Department of Physics, Chung Yuan Christian University, Zhongli, Taiwan 32001
Corresponding authors: bim962511@gmail.com (YS Peng), hclee12345@gmail.com (HC Lee)

Introduction

Aging (AG) is the natural process of becoming older [1]. Previous studies showed ageing increases a person's odds in getting AD, and neuroscientists are still studying how ageing neurons affect the AD process. The relationship between brain aging and AD is contentious. There are two competing views: one view holds AD results when brain aging surpasses a threshold; the other postulates that AD is not a consequence of AG [2].

Research Purposes

A. Extract from microarray data, separately, AG induced and AD induced changes in whole-genome gene expression, and from these results changes in biological functions and pathways.
B. Identify changes in gene expression and biological functions and pathways common to AG and AD.
C. From (a) and (b), infer possible causative relations between the two disorders.
D. Such knowledge will be useful for the early detection, diagnosis, and treatment of both disorders.

Result

Table 1. AG-DEG set (FDR<0.001) and its overlap with a set of 298 genes given in the public database on aging, "Human Ageing Genomic Resources" [3].

AG dataset		Size of DEG set in our results (FDR<0.001)	No. of genes in overlap of our result and HAGR [3]	
Old stage (> 70) vs. Young stage (< 40)	up-regulated	765	24	18.4%
	down-regulated	1472	31	

Table 2. AD-DEG sets (FDR<0.001) for five brain regions and their overlaps with the single set of 1,030 genes (504 up-regulated, 526 down-regulated) given in [4] (FDR <0.05, 2011). Average overlap is about 24%.

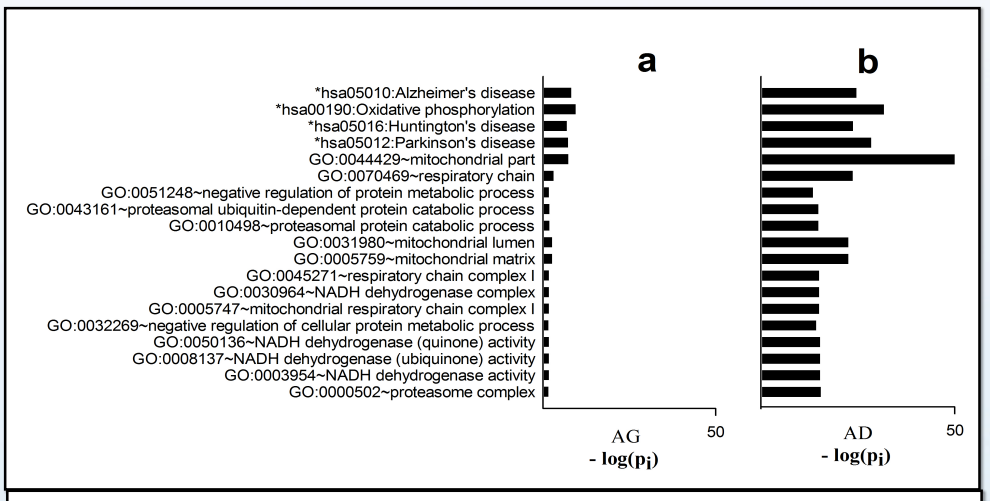
AD dataset		Size of DEG set in our results (FDR<0.01)	No. of genes in overlap of our result and [4]	
AD vs. Controls (EC)	up-regulated	2042	159	31.5%
	down-regulated	2899	168	31.9%
AD vs. Controls (HC)	up-regulated	1862	52	10.3%
	down-regulated	3146	122	23.2%
AD vs. Controls (MTG)	up-regulated	2211	174	34.5%
	down-regulated	2898	138	26.2%
AD vs. Controls (PC)	up-regulated	825	25	5.0%
	down-regulated	1910	103	19.6%
AD vs. Controls (SFG)	up-regulated	1175	102	20.2%
	down-regulated	2933	193	36.7%

Table 3. The Core Gene Sets were identified and defined in our results, include 18 AG-DEGs, and 26 AD-DEGs (AG sets for FDR < 1x 10^{-7}; AD sets for FDR < 1x 10^{-4} , and the consensus AD-DEGs in one that appears in at least four of the regional DEG sets).

Core Datasets	Up-regulated	Down-regulated
Core AG-DEGs	0	18
Core AD-DEGs	3	23

Summary

In our results, we identified several interesting and prominent functional profiles on aging(AG) and Alzheimer's disorder(AD), and defined the two core gene sets for AG and AD. Such results will advance the understanding and suggest new targets for the treatment of both disorders, and are useful for drug discovery.



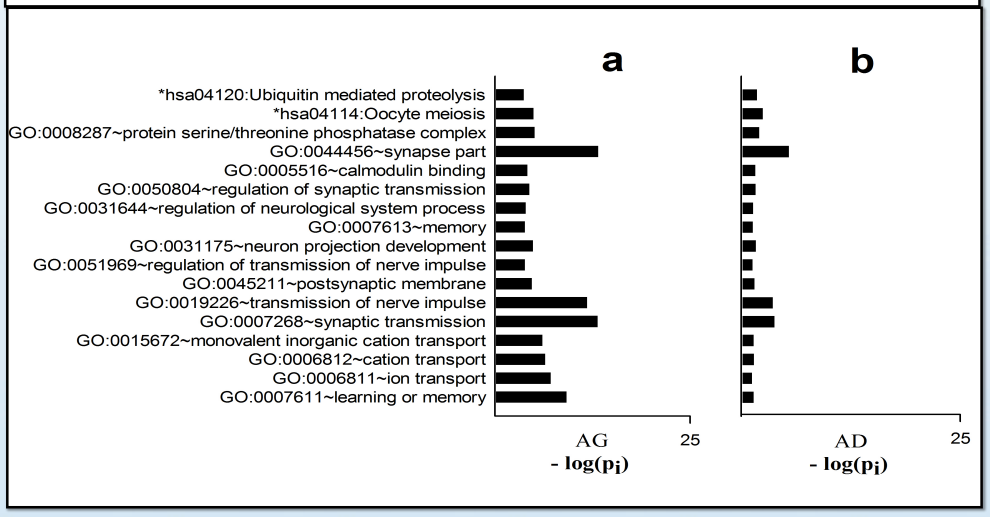


Fig 1. From our results we infer that changes common to AG and AD are predominantly related to loss of function(down-regulated). In most cases, loss of function is much more severe in AD than AD, log pAD < (log pAG)/128 (**upper**); In a much smaller number of cases the reverse is true, log pAG < (log pAD)/5 (**bottom**).

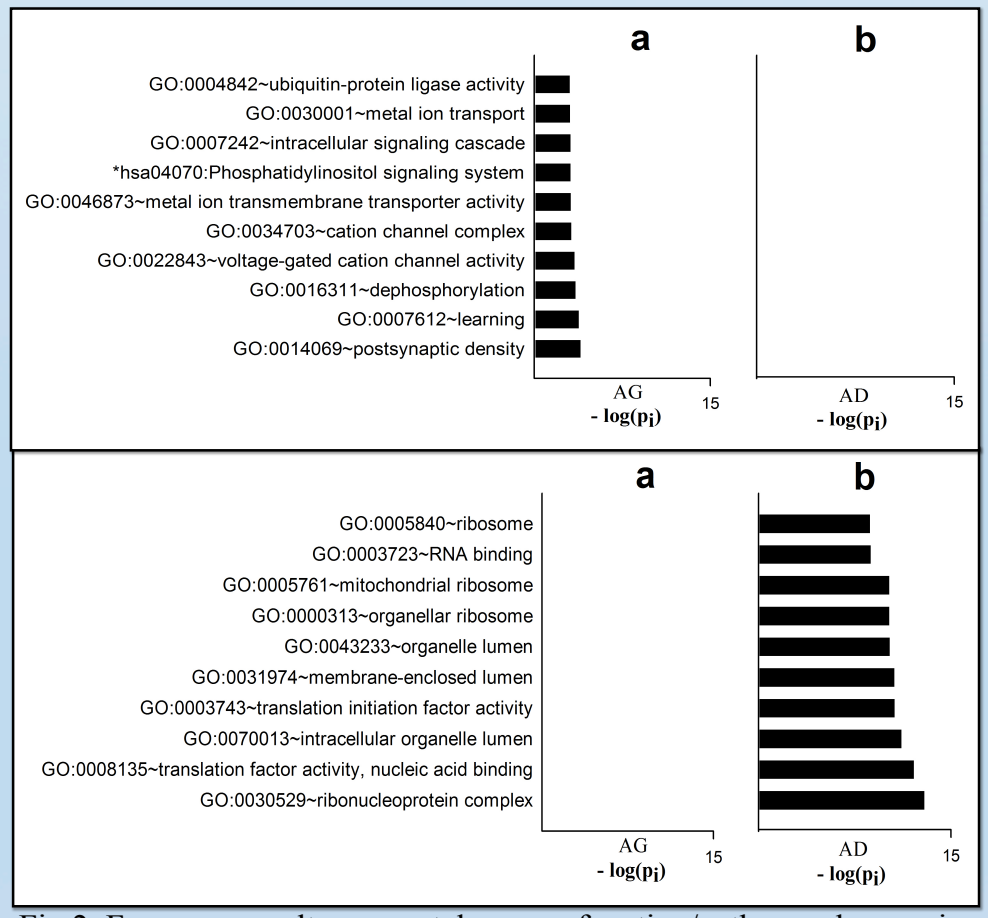


Fig 2. From our results, separately, some function/pathway changes in AG and AD were identified. Several channel-related functions lost in AG, but not in AD (**upper**); however, some ribosomal complex lost in AD, but not in AG (**bottom**).

[1] C López-Otín, *et al.* The Hallmarks of Aging. *Cell*, 2013.
[2] Russell H. Swerdlow. Brain aging, Alzheimer's disease, and mitochondria. *Biochimica et Biophysica Acta, 2012*
[3] Tacutu, R., *et al.* "Human Ageing Genomic Resources: Integrated databases and tools for the biology and genetics of ageing." *Nucleic Acids Research*, 2013
[4] Avramopoulos D, *et al.* (2011) "Gene expression reveals overlap between normal aging and Alzheimer's disease genes." *Neurobiol Aging*, 2011