

Genetic heterogeneity in Alzheimer's disease derived from five brain regions suggest new counteractions



*Yi-Shian Peng¹, Hung Chang¹, Chia-Wei Tang¹, Yi-Yun Peng¹, Ya-Hsin Tien¹, Hsueh-Chuan Liu¹,

Kun-Wei Lin¹, Li-Ching Wu¹, Shu-Lin Guo^{2,3}, #Hoong-Chien Lee^{1,4}

¹National Central University, Department of Biomedical Sciences and Engineering, Zhongli District, Taoyuan, Taiwan R.O.C.

²Cathay General Hospital, Department of Anesthesiology, Taipei, Taiwan R.O.C.

³Tri-Service General Hospital and National Defense Medical Center, Department of Anesthesiology, Taipei, Taiwan R.O.C.

⁴Chung Yuan Christian University, Department of Physics, Zhongli District, Taoyuan, Taiwan R.O.C.

*Contact: YSP <https://sites.google.com/site/yishianpeng/> # Corresponding author, hlee12345@gmail.com



Introduction

Alzheimer's disease (AD) is a leading neurodegenerative disorder and one of the most challenging health problems of the 21st century. It is characterized by the progressive impairment of cognition and other mental functions. The implementation of personalized medicine in the prevention of AD depends on understanding subtypes of AD. Recent reports suggest that the diagnosis of the clinical onset of AD may be brain-region specific. Here, in order to clarify possible regional differences in functional abnormalities in AD affected brain, we studied public gene expression microarray data from five brain regions – entorhinal cortex (EC), hippocampus (HC), medial temporal gyrus (MTG), posterior cingulate (PC), and superior frontal gyrus (SFG) – of AD patients and controls (Table 1). Methods of differential expression genes (DEG), gene set enrichment analysis (GSEA) [1], miRNA analysis, and gene-gene interaction networks (GGNs), constructed from interacting differentially co-expressed (IDCE) gene pairs, were used in this study.

Table 1. Microarray datasets used in the present study AD datasets are from five brain regions, entorhinal cortex (EC), hippocampus (HC), medial temporal gyrus (MTG), posterior cingulate (PC), and superior frontal gyrus (SFG), and T2D datasets from four tissues, pancreatic islets, blood, liver, and skeletal muscle. PCA refers to principal components analysis.

Name	Original dataset		Dataset used in study		Reference
	size	PCA score	size	PCA score	
AD-EC	10 vs. 13	0.71	9 vs. 11	0.91	[2]
AD-HC	10 vs. 13	0.88	8 vs. 10	1.00	
AD-MTG	16 vs. 12	0.97	14 vs. 11	1.00	
AD-PC	9 vs. 13	0.91	9 vs. 10	0.95	
AD-SFG	23 vs. 12	0.00 (failed)	12 vs. 8	1.00	[3]
T2D- islets	6 vs. 7	0.85	4 vs. 4	1.00	
T2D- liver	10 vs. 7	0.00 (failed)	5 vs. 5	0.70	[4]
T2D- blood	8 vs. 8	0.75	5 vs. 5	1.00	[5]
T2D-muscle	10 vs. 15	0.00 (failed)	6 vs. 11	0.77	[6]
T2D-Glomeruli	9 vs. 13	0.91	-	-	[7]

Results

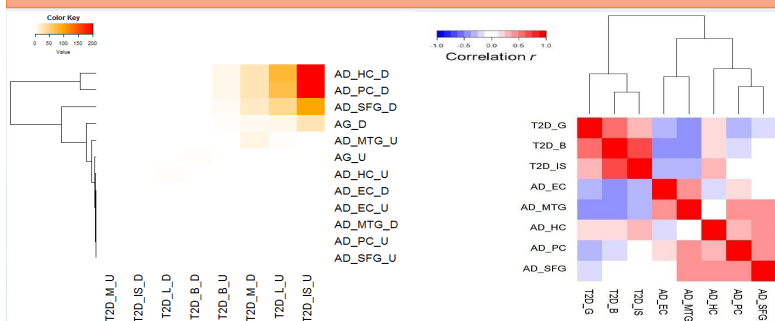


Figure 1. Association between region-specific AD and tissue-specific T2D genomic data Left panel, AD vs. T2D overlap matrix of DEG sets, selected using LIMMA with $q < 0.05$ for T2D and $q < 0.001$ for AD. Right panel, matrix of GSEA enrichment scores (correlation r). Both results indicate high islets/T2D-AD, especially HC, association. Abbreviations: EC, entorhinal cortex; HC, hippocampus; MTG, medial temporal gyrus; PC, posterior cingulate; SFG, superior frontal gyrus; M, muscle; IS, islets; B, blood; L, liver; G, Glomeruli (kidney); U, upregulated DEG; D, downregulated DEG.

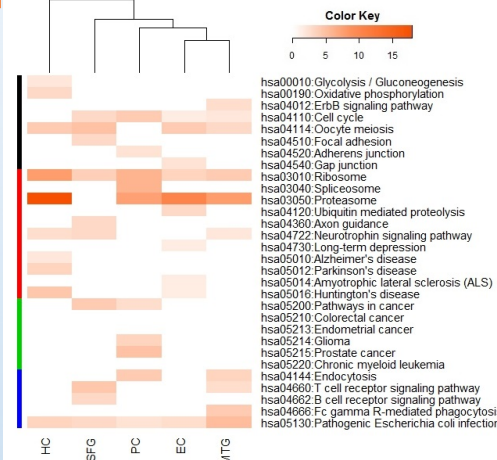


Figure 2. Enriched KEGG terms in the five regions of AD affected brain The 30 selected enriched KEGG terms are from four categories: cell proliferation, black (color bar to the right); neurodegeneration, red; carcinoma, green; inflammation, dark blue. Numerals in color refer to $-\log_{10} p$ values; proteasome was the most highly enriched term in four of five AD regions.

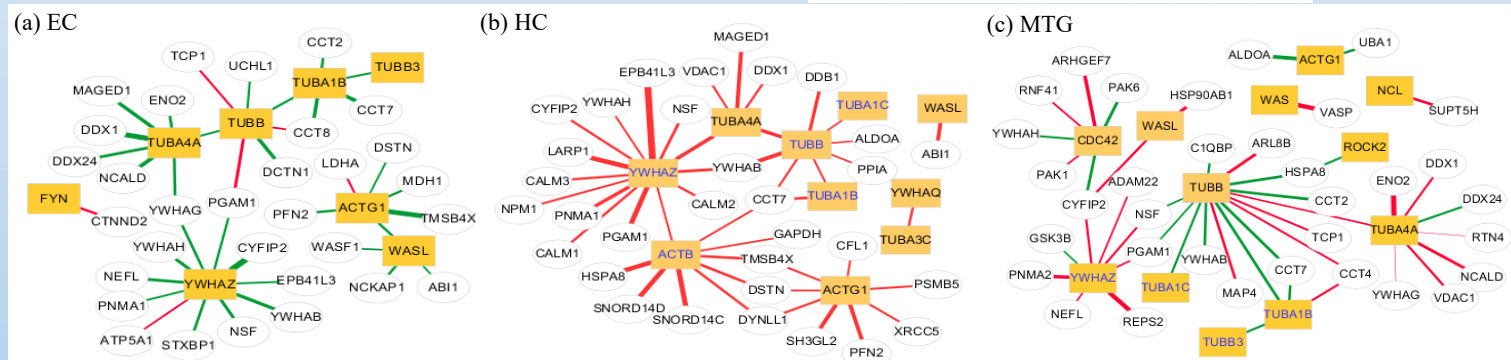


Figure 3. Heterogeneity in regional AD sub-GGNs related the KEGG *Escherichia coli* infection pathway (hsa05130) The sub-GGNs are for the (a) entorhinal cortex (EC), (b) hippocampus (HC), and (c) medial temporal gyrus (MTG) regions. In each sub-network, rectangle boxes are hits in the *E. coli* infection pathway. Hits given in blue letters are also DEGs, all of which were down-regulated (t -score < 0). Links indicate interactions between proteins encoded by linked genes; red/green indicate gain/loss of co-expression pairing. Thickness of link is proportional to the linear regression of the linked pair.

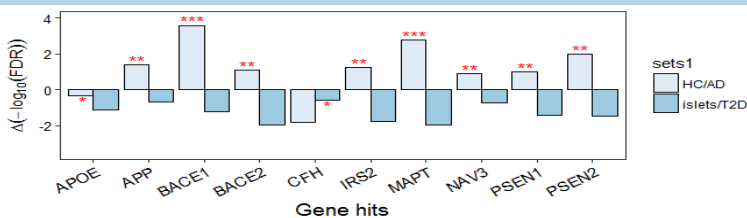


Figure 4. Difference in HC/AD versus islets/T2D expressions of biomarkers $\Delta(-\log_{10}(\text{FDR}))$ refers to the difference between the $-\log_{10}(\text{FDR})$ value of the DEG and the threshold value ($-\log_{10}(\text{FDR}_0) = 2$), where FDR is the false discovery rate. Symbols: *, FDR < 0.05 ; **, FDR < 0.01 ; ***, FDR < 0.001 . *APP*, *MAPT*, *PSEN1*, *PSEN2* and *BACE1*, are known AD targets, and the other three, *hsa-mir-29a* (*CFH*), *hsa-mir-195* (*IRS2*), and *hsa-mir-29a* (*NAV3*), known miRNA-targets.

Summary

Among the DEGs of five region-specific AD and four tissue-specific microarray gene expression datasets, the up-regulated islet/T2D and down-regulated HC/AD DEGs had significant overlap, and this was corroborated in GSEA analysis. Classes of enriched pathways differed intra-regionally in AD. For instance, cancer pathways were seen to be highly enriched in PC and SFG, but were absent in HC, EC and MTG. Some pathways, including proteasome and *E. coli* infection, were enriched in at least four regions. Details of enrichment tended to be region specific. There were also common features, e.g., *TUBB*, *YWHAZ* and *TUBA4A* were hub genes in the *E. coli* infection sub-GGNs for HC, EC and MTG. The five known AD target genes, *APP*, *MAPT*, *PSEN1*, *PSEN2* and *BACE1*, were significant in HC/AD, but not in islets/T2D, as was, surprisingly, the known T2D target *IRS2*. Our results highlighted the heterogeneity of AD in the five brain regions, and indicated a possible AD-T2D connection. These may be useful in devising strategies for the early detection of AD as well as T2D.

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*Disclosure: none of the results have conflict of interest.