Common significant DEGs of Type 2 diabetes and Alzheimer's disease tend to be oppositely differentially expressed and have opposite changes in co-expression

Yi-Shian Peng[1*] (彭奕憲), Hung Chang[1*] (張翃), Po-Jen Chang[1] (張伯任), Chia-Wei Tang[1] (湯佳薇), Yi-Yun Peng[1](彭伊筠), Li-Ching Wu[1#] (吳立青), Shu-Lin Guo[2] (郭書麟), Hoong-Chien Lee[1,3#] (李弘謙)

[1]Department of Biomedical Sciences and Engineering, National Central University, Taoyuan, Zhongli, Taiwan 32001
[2]Department of Anesthesiology, Cathay General Hospital, Taipei, Taiwan 10630
[3]Department of Physics, Chung Yuan Christian University, Taoyuan, Zhongli, Taiwan 32023
*Contacts: YSP bim962511@gmail.com, HC _zero102x@hotmail.com
Corresponding authors

Abstract

Alzheimer's disease (AD) is a leading aging 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 typical of neurodegenerative disorders. Recent reports showed type 2 diabetes (T2D) patients have an increased risk of AD and dementia. Incidents of comorbidity between AD and T2D have recently been give the term "type-3" diabetes. The molecular relation between AD and T2D remains unclear.

Here, for the purpose of discovering any possible connection between AD and T2D, we studied public gene expression microarray data from four T2D tissues and five brain regions AD, and hospital clinical records of T2D and AD patients. For each set of microarray data (Table 1) we identified pairs of significant differentially expressed genes (DEGs) exhibiting significant differential co-expression (DCE). The up-regulated T2D_islets and down-regulated AD_hippocampus DEGs were found to have significant overlaps and among the overlapping genes were 27 common DCE pairs. Some of the pairs involve known AD or T2D target genes.

A total of 4,142,680 distinct clinical records, on 175,706 males and 266,331 females and dating from 2006 to 2009 inclusive, were obtained from Cathay General Hospital. Patient disorders were coded by International Classification of Diseases (ICD-9). Prior-comorbidities associated with AD and T2D, respectively, were constructed. There were comorbidities common to AD and T2D, but patients of these common comorbidities were found to have either AD or T2D, but not both. These results may provide insights useful for the early detection of AD and T2D, and for devising therapeutic strategies.

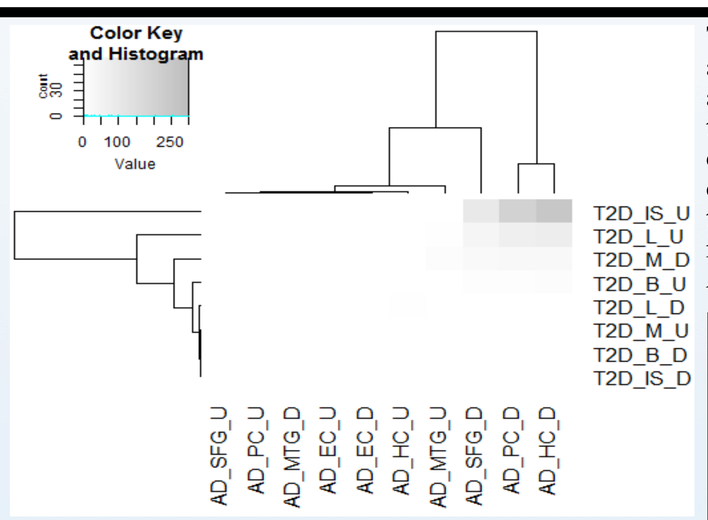

Figure 1. Two-way hierarchical clustering based on overlaps of DEGs from region-specific AD and from tissue-specific T2D DEGs were selected using LIMMA with q <0.05 for T2D and q<0.001 for AD. Color key in grey denotes -$\log_{10} p$ the overlap two DEG sets using Fisher's exact test. Abbreviations: EC, entorhinal cortex; HC: hippocampus; MTG, medial temporal gyrus; PC, posterior cingulate; SFG, superior frontal gyrus; M, muscle; IS, islets; B, blood; L, liver; U, upregulated DEGs; D, downregulated DEGs.

Table 3. Known AD and T2D target genes among the overlap of up-regulated T2D_islets and down-regulated AD_HC DEGs T2D known targets were separately selected from Online Mendelian Inheritance in Man (OMIM) and T-HOD database. The 210 AD known targets were from three public AD databases. Abbreviations: U, up-regulated DEGs; D, downregulated DEGs; APP, Amyloid precursor protein.

Cohorts	T2D_islets (U) vs. AD_HC (D)	
Gene in overlap	Number	1,660
Known AD target genes	Number	46
	Example	*APP, PSEN1
Known T2D target genes in OMIM	Number	1
	Example	IRS2
Known T2D target genes in T-HOD	Number	62
	Example	*APP, GSK3B, GAPDH, MAPK1
Common known AD and T2D target genes	Size	5
	*= intersection genes	

Results

Table 1. Microarray datasets used in the present study AD datasets are from five brain regions, and T2D datasets include four different tissues. All cohorts were from human samples. Abbreviations: EC, entorhinal cortex; HC, hippocampus; MTG, medial temporal gyrus; PC, posterior cingulate; SFG, superior frontal gyrus; islets, pancreatic islets; muscle, skeletal muscle; PCA, principal components analysis.

Name	Original dataset		Dataset used in study		Datasets ID
	size	PCA score	size	PCA score	
AD-EC	10 vs. 13	0.71	9 vs. 11	0.91	GSE5281
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	
T2D- islets	6 vs.7	0.85	4 vs.4	1.00	GSE25724
T2D- liver	10 vs. 7	0.00 (failed)	5 vs.5	0.70	GSE23343
T2D- blood	8 vs.8	0.75	5 vs.5	1.00	GSE15932
T2D-muscle	10.s.15	0.00 (failed)	6 vs. 11	0.77	GSE25462

Table 2. Forty-nine Q2 <0 comorbidities common to AD and T2D all had non-overlapping cohorts The two disorders AD and T2D had 49 common early onset (Q2 <0) comorbidities with confidence scores greater than one. In all common comorbidities the AD-comorbidity and T2D-comorbidity cohorts were disjoint, i.e., they did not have shared patients. The table lists the top-15common comorbidities ranked by confidence score for T2D. Q2 <0 means in the A-occurred-before-B time-distribution of patients common to disorders A and B only those in the second quartile are counted.

ICD-9	Disease Name (No. patients in disease networks)	AD cohort		T2D cohort	
		No. of comorbidities pairings with AD cohorts	Confidence Scores	No. of comorbidities pairings with T2D cohorts	Confidence Scores
25040	Diabetes with renal manifestations (2,159)	4	12.76	49	34.22
29410	Dementia in conditions classified elsewhere without behavioral disturbance (104)	3	198.62	2	29.00
585	Chronic Renal Failure (4,303)	2	3.20	52	18.22
25000	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled (20,133)	17	5.81	229	17.15
4148	Other Specified Forms Of Chronic Ischemic Heart Disease (4,298)	3	4.81	30	10.52
4149	Chronic ischemic heart disease (5,172)	6	7.99	36	10.50
41400	Coronary atherosclerosis of unspecified type of vessel (4,163)	3	4.96	28	10.14
43310	Occlusion and stenosis of carotid artery without mention of cerebral infarction (923)	1	7.46	5	8.17
40290	Unspecified hypertensive heart disease without heart failure (6,465)	2	2.13	33	7.70
2720	Pure hypercholesterolemia (1,836)	1	3.75	9	7.39
4019	Unspecified essential hypertension (38,956)	20	3.54	177	6.85
37210	Chronic conjunctivitis (5,579)	3	3.70	25	6.76
42731	Atrial fibrillation (2,028)	1	3.40	9	6.69
4379	Unspecified cerebrovascular disease (6,204)	17	18.9	27	6.56
2724	Other and unspecified hyperlipidemia (17,857)	9	3.47	77	6.50

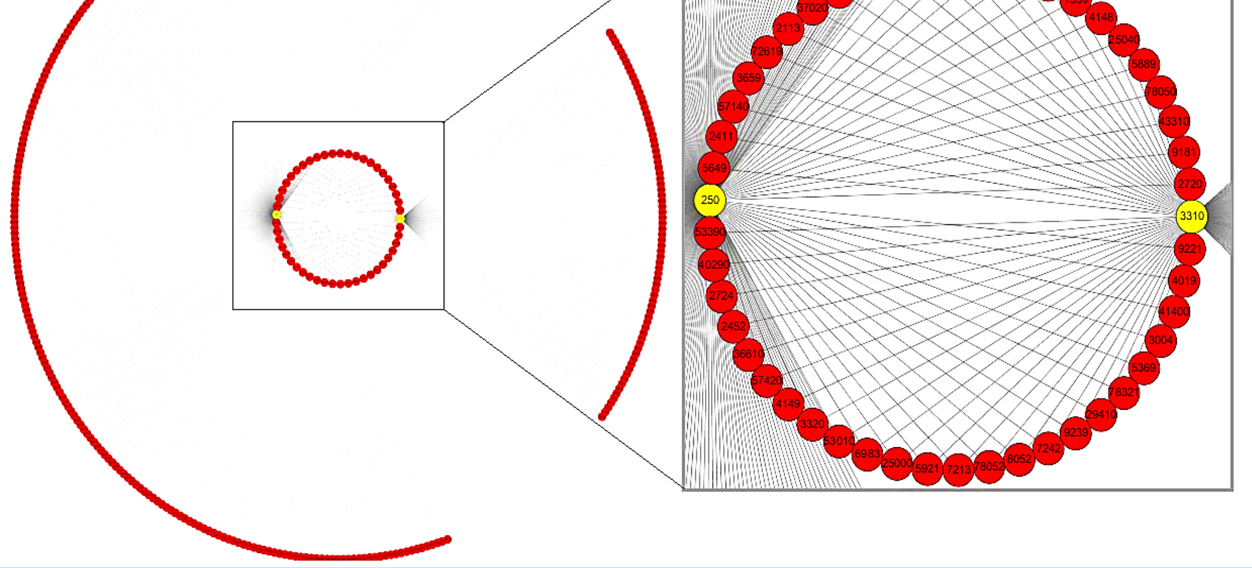

Figure 2. AD and T2D Q2 < 0 comorbidity networks Q2 < 0 disorders comorbid with AD (ICD-3310; right yellow circle) and with T2D (ICD-250; left yellow circle) are shown as red dots. Q2 < 0 means AD or T2D is earlier than its comorbidity. Red circles in the inner circle are 49 disorders comorbid with both AD and T2D (see Table 2); those in the outer circle are the 74 and 245 disorders comorbid with AD and T2D, respectively. Numerals in yellow and red circles are ICD-9 codes for disorders.

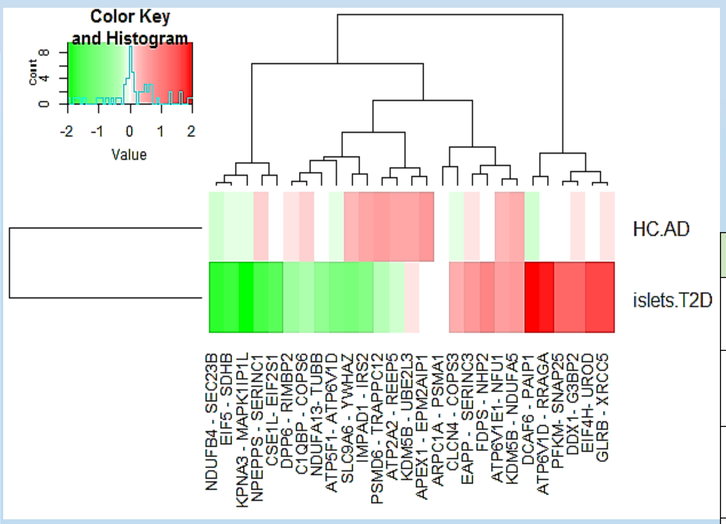

Figure 3. Two-way hierarchical clustering of 27 common differentially co-expressed (DCE) pairs among the overlap of up-regulated T2D_islet and down-regulated AD_HC DEGs Genes in each DCE pair (in the x-axis) must be DEGs of both T2D_islet and AD_HC. Color key denotes the difference in the Pearson correlations in expressions of the pair, in disease related and control cohorts, respectively. Symbols: red, gain of co-expression (GOC); green, loss of co-expression (LOC)

Table 4. Composition of 27 common differentially co-expressed (DCE) pairs in the overlap of up-regulated T2D_islet and down-regulated AD_HC DEGs Abbreviations: GOC, gain of co-expression; LOC, loss of co-expression. Asterisk indicates the gene in the DCE pair that is a known AD or T2D target.

Cohorts	islets/T2D (U) vs. HC/AD (D)	
Number of DCE pairs in two cohorts		27
Number of GOC/ LOC in two cohorts		AD: 20 / 7 T2D: 13 / 14
Number of same co-expression/ Number of opposite co-expression		14 / 13
Known AD target genes	No. of gene pairs	2
	Example	*TUBB - NDUFA13
Known T2D target genes (in OMIM)	No. of gene pairs	1
	Example	*IRS2 - IMPAD1

Summary

Among the DEGs of five region-specific AD and four tissue-specific microarray gene expression datasets, only the up-regulated T2D_islet and down-regulated AD_HC DEGs had significant overlap. Of the 1,660 common DEGs (in the overlap), 46 and 63 were known AD and T2D target genes, respectively. Twenty-seven pair of genes in the overlap were DCE pairs in both T2D_islet and AD_HC. Of these, 14 had the same DCEs (GOC-GOC or LOC-LOC) in T2D and AD, and 13 had opposite DCEs (GOC-LOC of LOC-GOC). The two disorders had 49 common Q2 <0 comorbidities, in all of which cohorts of the T2D-comorbidity and AD-comorbidity did not have common patients. Our results provide new insights on possible connection between AD and T2D, are may find use in the early detection of the two disorders, and for devising therapeutic strategies.

*Disclosure: This work has no conflict of interest.