Introduction

The implementation of personalized medicine in the prevention of Alzheimer’s disease (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 differences in regulatory patterns in brain regions in AD, 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.

Methods

The method of differential expression genes (DEG), gene set enrichment analysis (GSEA) and miRNA and gene-gene interaction networks (GGNs), constructed from interacting differentially co-expressed (IDCE) gene pairs, were used in this study.

Results

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 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 of DEG sets, selected using LIMMA with q<0.05 for T2D and specific T2D genomic data.

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 (HC), (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. At log_{10}(FDR) refers to the difference between the log_{10}(FDR) value of the DEG and the threshold value (log_{10}(FDR)=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 (RS2), and hsa-mir-29a (NAV1), known miRNA-targets. The up-regulated islet/T2D and down-regulated HC/AD DEGs had significant overlap. Classes of enriched pathways differed intraregionally 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 MTG; however, they were absent in HC and SFG.