Supplementary Material (ESI) for Molecular BioSystems
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Supplementary materials for “Detecting and analyzing differentially activated pathways in brain regions of Alzheimer's disease patients”

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S1. More on the algorithm

Our algorithm was implemented in six brain regions to detect the region-specific active pathways individually. The common and difference of these active pathways were then identified and analyzed. The following Figure S1.1 is an example showing that different starting edges result in different active pathways. In these candidate active pathways identified by starting from different local optima edges, we regard the one with the most significant *p*-value as the output active pathway. Our method takes a greedy manner and extends the high-scored edges in sequence. After all the edges are chosen, the minimum p-value can be calculated. Then we get a candidate active pathway from one local optima edge. O(eloge) will be needed for ranking the edges. O(e^2) will be needed for the growing process and O(e) will be needed for choosing the most significant candidate pathway. The complexity of our algorithm is O(e^2), where e is the number of edges in the protein-protein interactions.

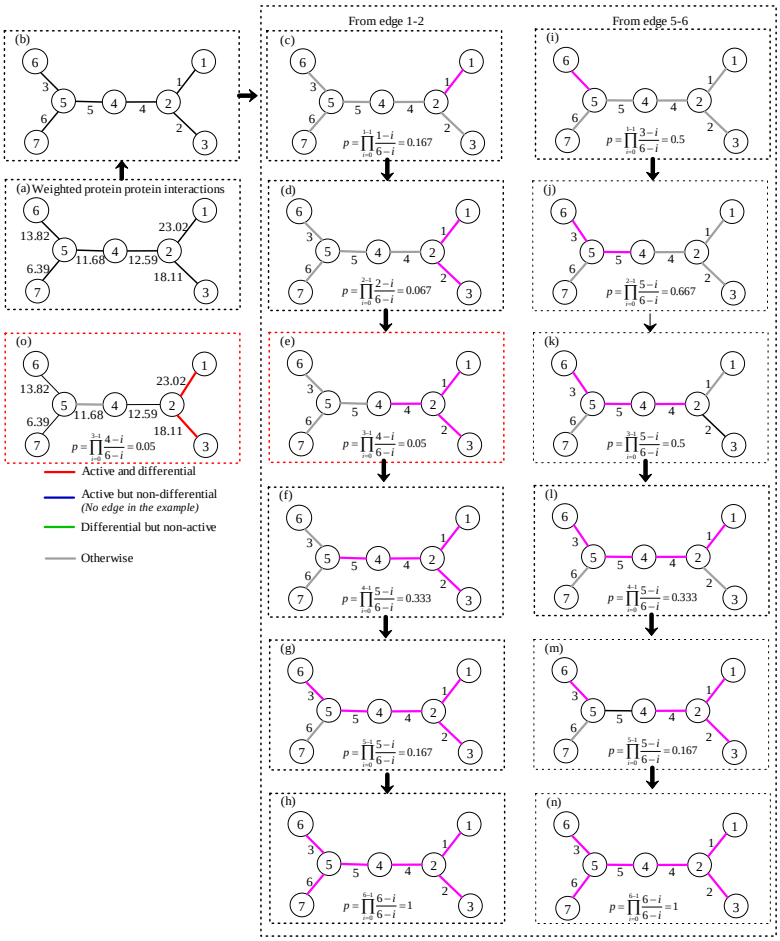


Figure S1.1: An example shows that different starting local optima edges result in different active pathways.

S2. Active pathways in other five brain regions

We identified the active pathways in six diseased brain regions. We presented the pathway of EC in the main text. The pathways of other five regions, i.e. HIP, MTG, PC, SFG and VCX, are listed in the following figures.

S2.1 HIP

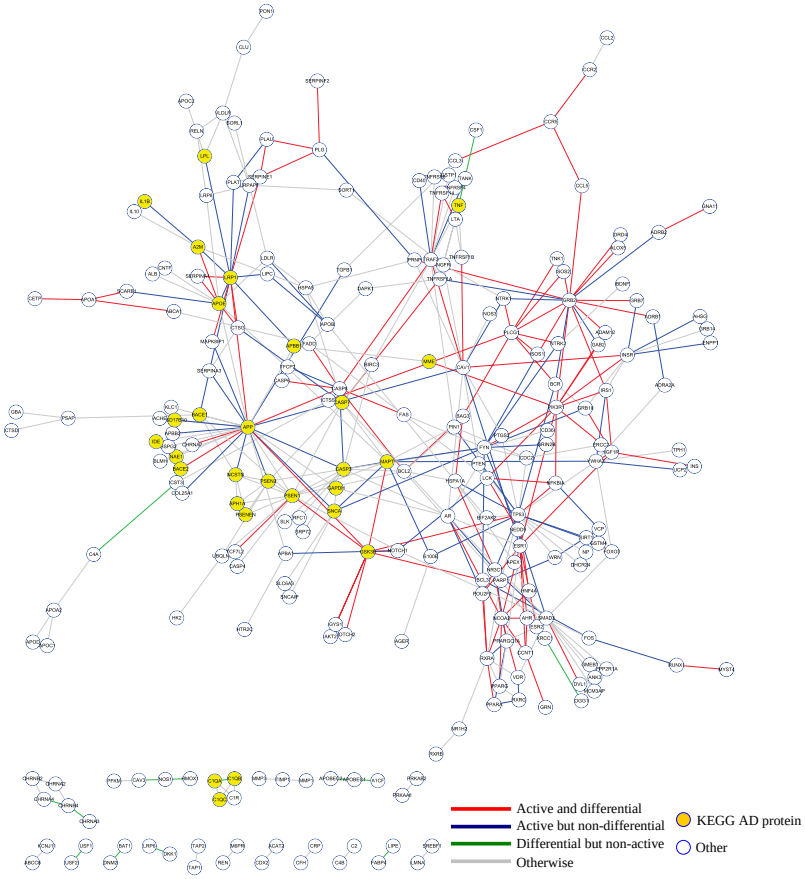


Figure S2.1.1: Identified active pathway of HIP in the ensemble AD protein-protein interaction network (p-value < 1.55e-85). The interactions are classified into four types. The connected active pathway is contained in those red and blue edges. Red edges are those active pathway edges which are also differentially co-expressed. Blue ones are those involved in the identified active pathway while they are not significant in differential co-expression. Green ones are those differentially co-expressed interactions, but they are not involved in the identified active pathway. The others are represented as grey.

The identified pathway underlying KEGG AD proteins

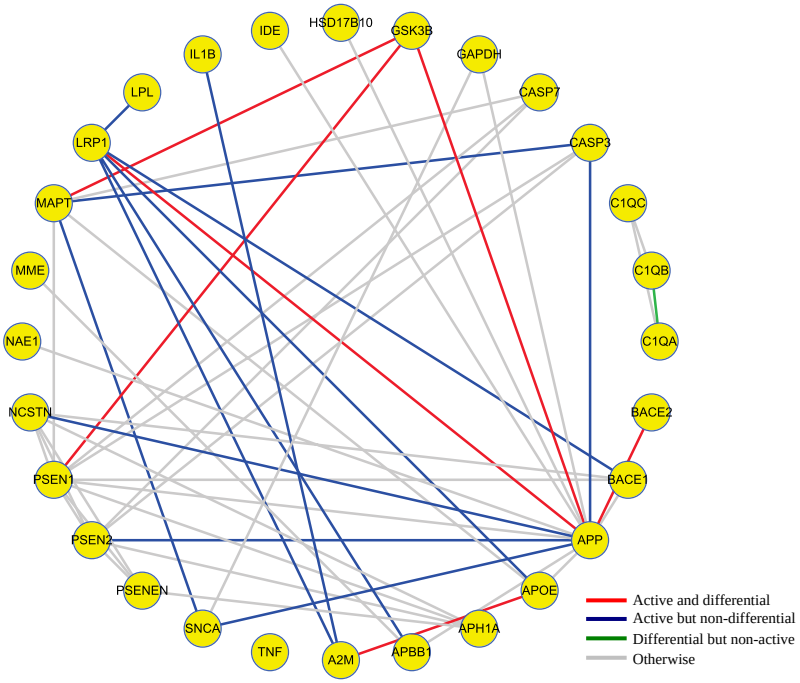


Figure S2.1.2: The active pathway underlying KEGG AD proteins in HIP. Part of the identified HIP active pathway contains the red and blue edges. The meaning of edge color is the same as that in Figure S2.1.1.

S2.2 MTG

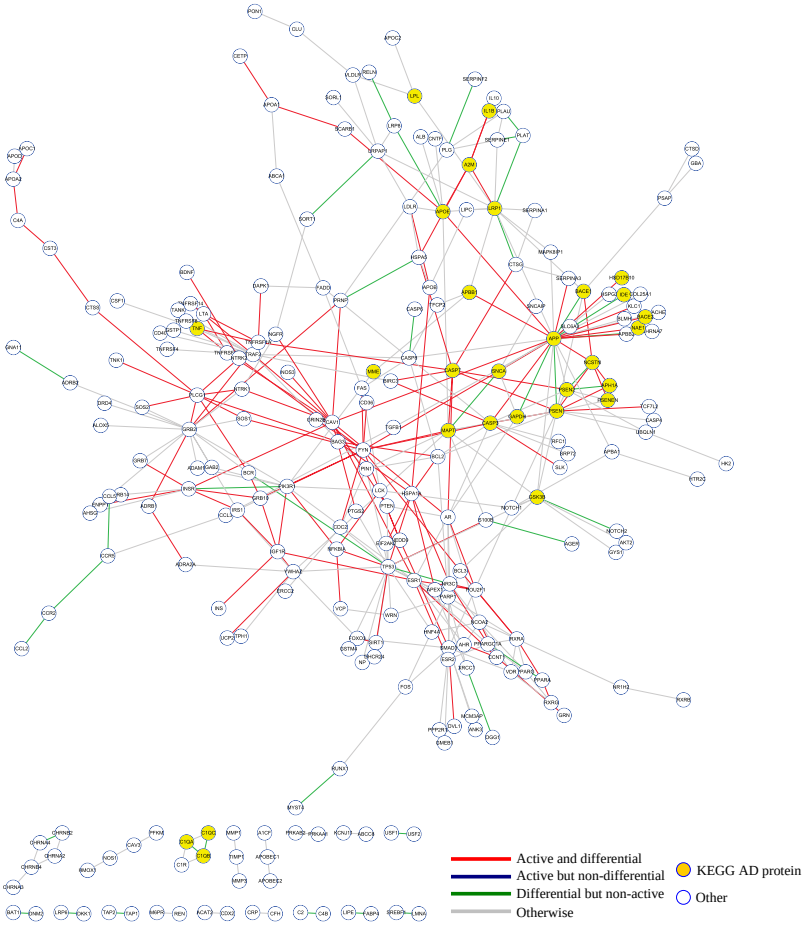


Figure S2.2.1: Identified active pathway of MTG in the ensemble AD protein-protein interaction network (p-value < 3.47e-90). The meaning of edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

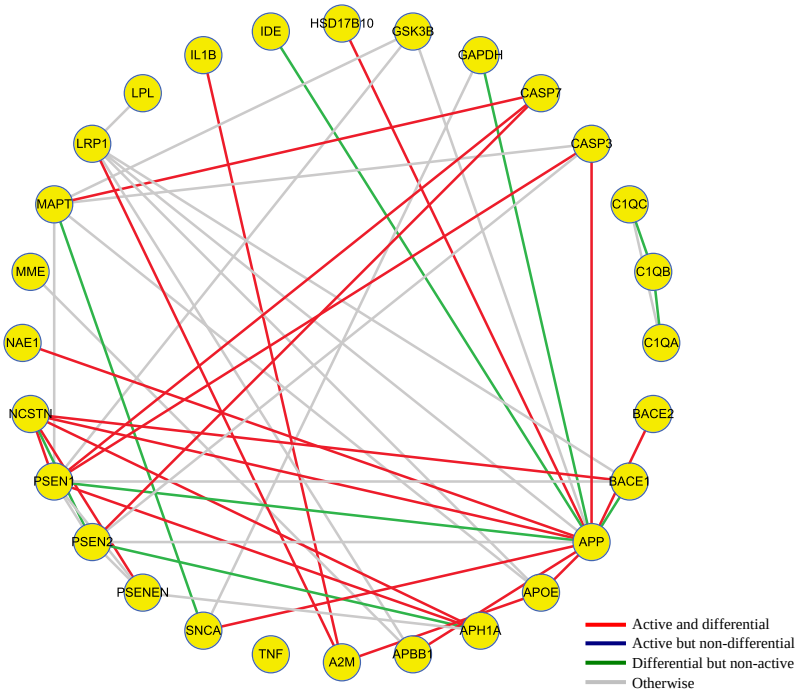


Figure S2.2.2: The active pathway underlying KEGG AD proteins in MTG. Part of the identified MTG active pathway contains red and blue edges. The meaning of edge color is the same as that in Figure S2.1.1.

S2.3 PC

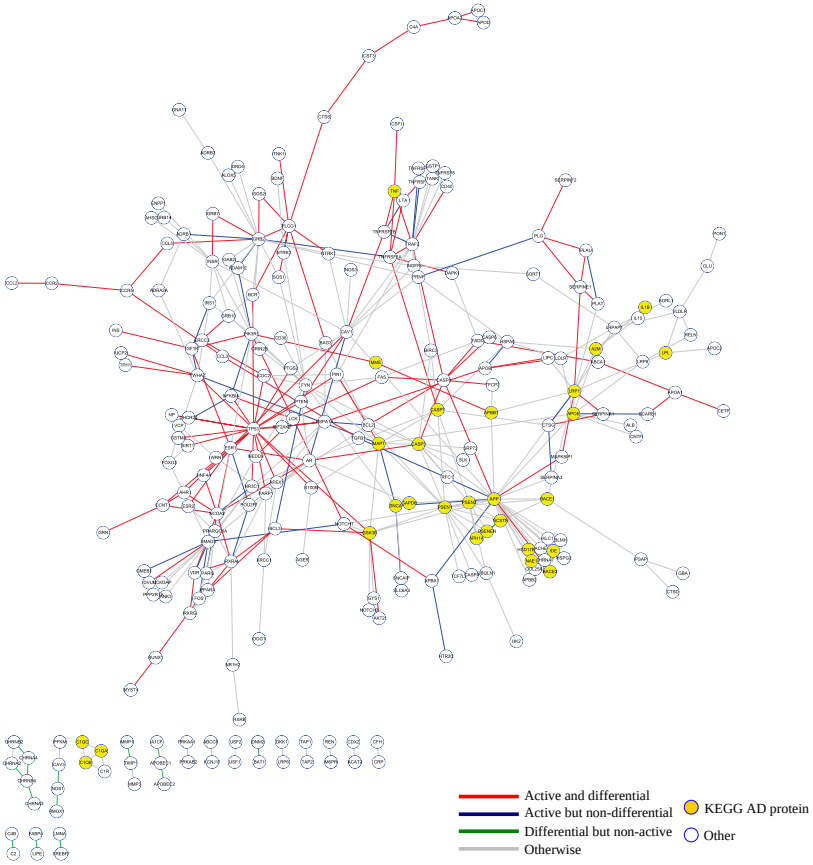


Figure S2.3.1: Identified active pathway of PC in the ensemble AD protein-protein interaction network (p-value < 1.16e-85). The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

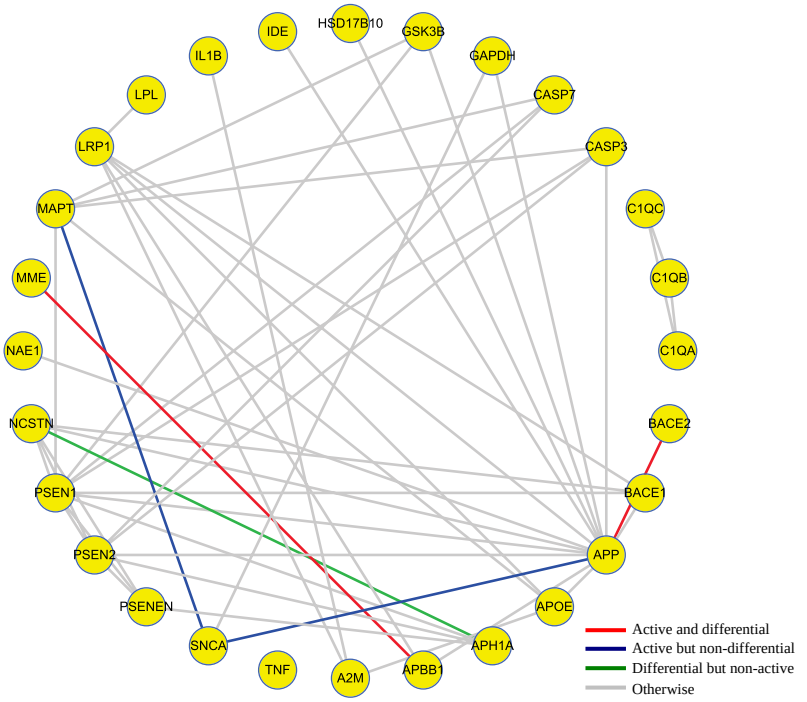


Figure S2.3.2: The active pathway underlying KEGG AD proteins in PC. Part of the identified PC active pathway contains red and blue edges. The meaning of the edge color is the same as that in Figure S2.1.1.

S2.4 SFG

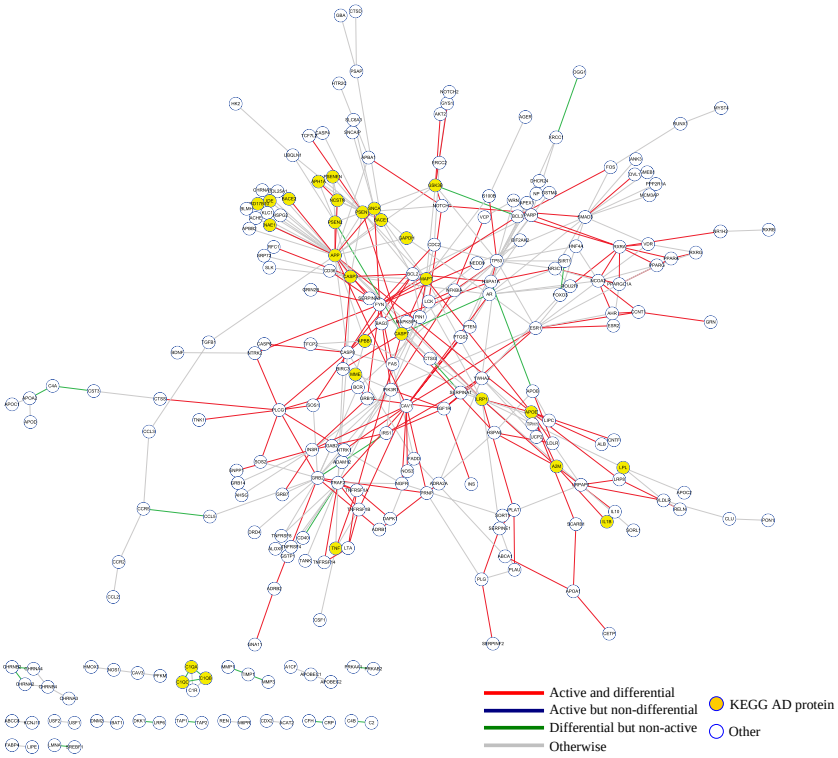


Figure S2.4.1: Identified active pathway of SFG in the ensemble AD protein-protein interaction network (-p-value < 4.17e-87). The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

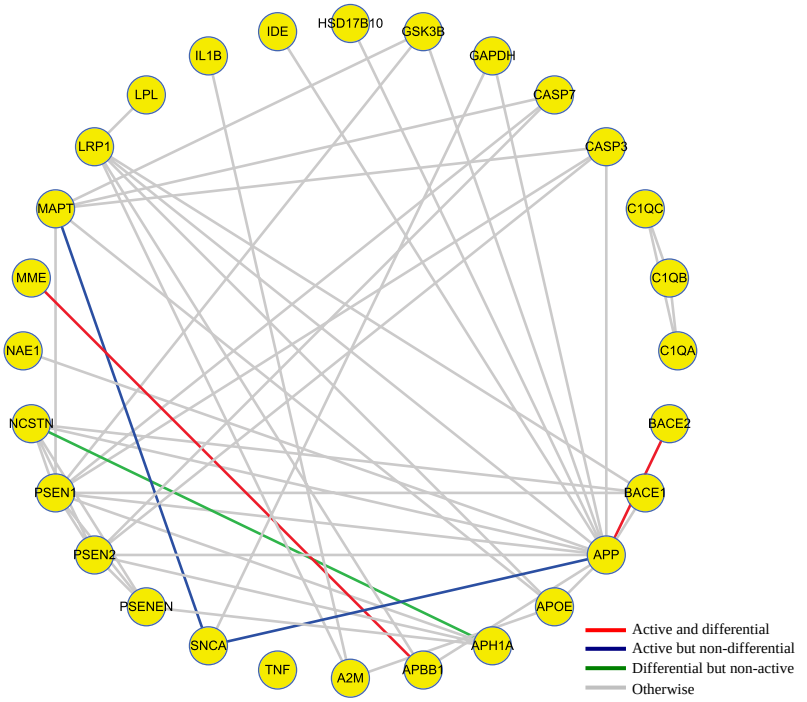


Figure S2.4.2: The active pathway underlying KEGG AD proteins in SFG. Part of the identified SFG active pathway contains red and blue edges. The meaning of the edge color is the same as that in Figure S2.1.1.

S2.5 VCX

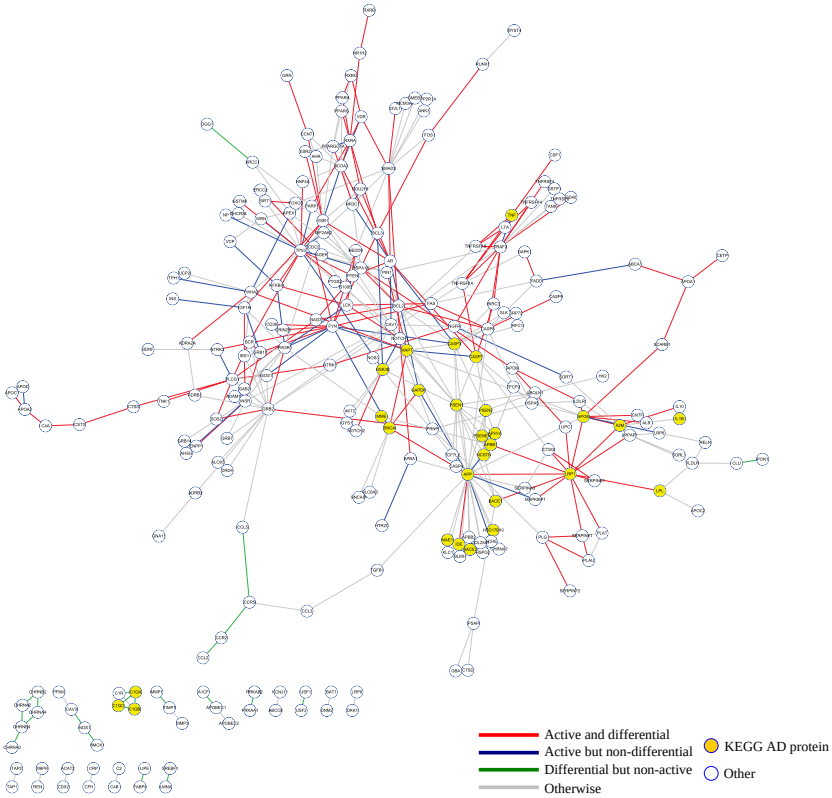


Figure S2.5.1: Identified active pathway of VCX in the ensemble AD protein-protein interaction network (p-value < 5.35e-80). The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

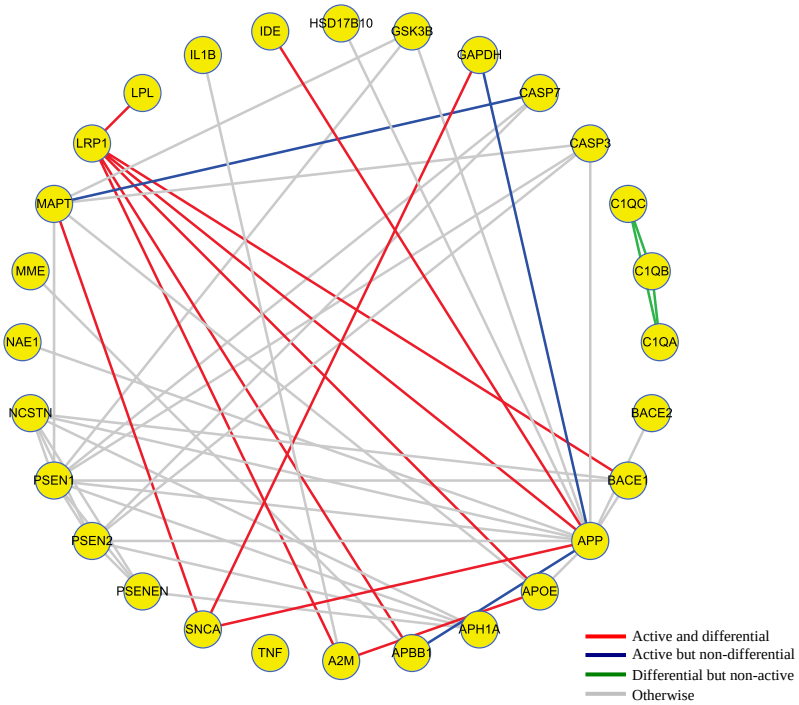


Figure S2.5.2: The active pathway underlying KEGG AD proteins in VCX. Part of the identified VCX active pathway contains red and blue edges. The meaning of the edge color is the same as that in Figure S2.1.1.

S2.6 Hierarchical clustering of six brain regions

We have compared the similarities and differences of the identified active pathways between the six brain regions. When we used the identified overlapping status of edges in these pathways shown in Table 1 as the distance matrix of the six brain regions and implemented the hierarchical clustering. The result is shown in the following Figure S2.6. We found that superior frontal gyrus (SFG) and visual cortex (VCX) have relatively larger distance than the other four regions. This fact provides evidence to support that the two brain regions, i.e. SFG and VCX, tend to have slight correlation with AD neurodegeneration, especially for the visual cortex which is very minimally affected by AD progression.

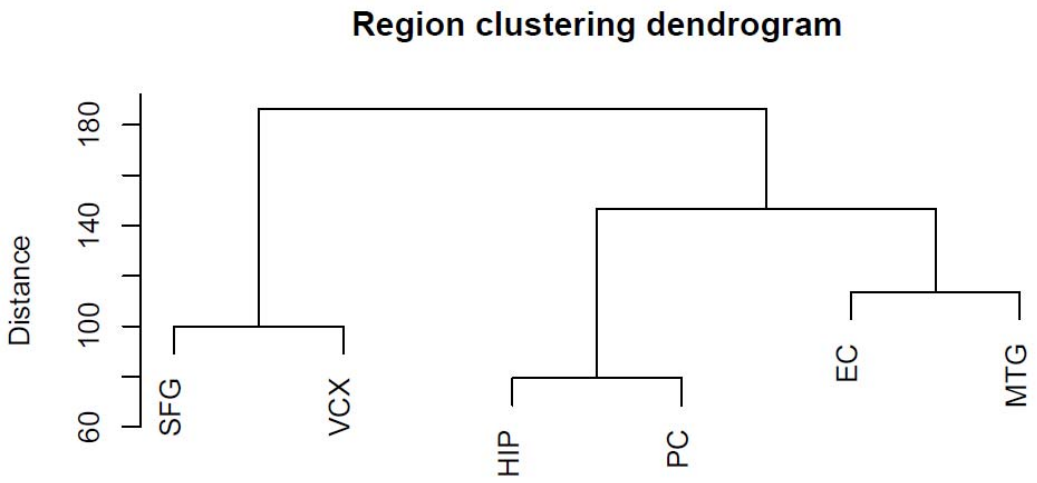


Figure S2.6: Hierarchical clustering of six brain regions by the overlapping status between these identified active pathways.

S3. Differentially co-expression edges of different thresholds

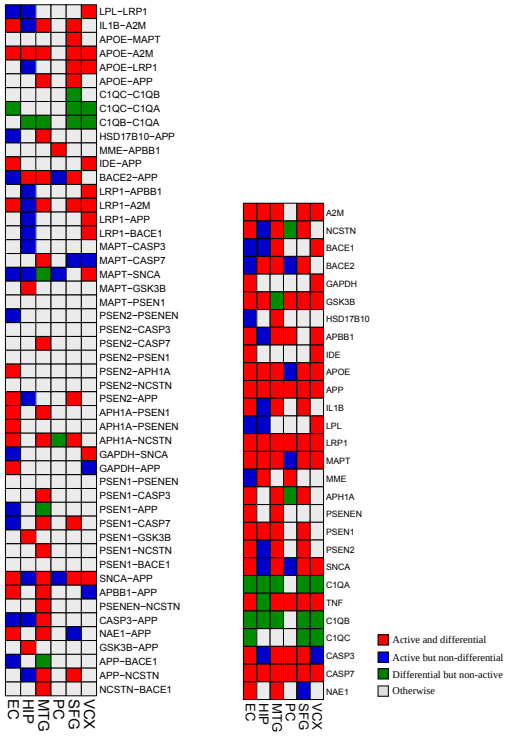
We define an edge as a differentially co-expressed edge when its score is more than 12.59 which corresponds to the critical value for p-value 0.05 in chi-square test. We also use different thresholds, i.e. 14.45 (p-value 0.025) and 16.81 (p-value 0.01), to define the differentially co-expressed edges. Table S3.1 shows the number of differentially co-expressed edges in the ensemble AD protein interaction network and that contain in the active pathways in various AD brain regions.

Table S3.1: The number of differentially co-expressed edges in the ensemble 381 protein interactions using different thresholds. The number in the bracket means the number of differentially co-expressed edges contained in the identified active pathways, e.g. when we use the 12.59 (p-value 0.05) as the threshold, we get 161 edges of differentially co-expressed, of which 148 edges are included in the identified active pathway of EC.

	EC	HIP	MTG	PC	SFG	VCX
12.59 (0.05)	161 (148)	120 (106)	172 (132)	138 (124)	167 (142)	152 (130)
14.45 (0.025)	138 (125)	103 (91)	158 (132)	111 (98)	140 (125)	125 (106)
16.81 (0.01)	111 (100)	87 (77)	139 (128)	75 (65)	106 (93)	93 (77)

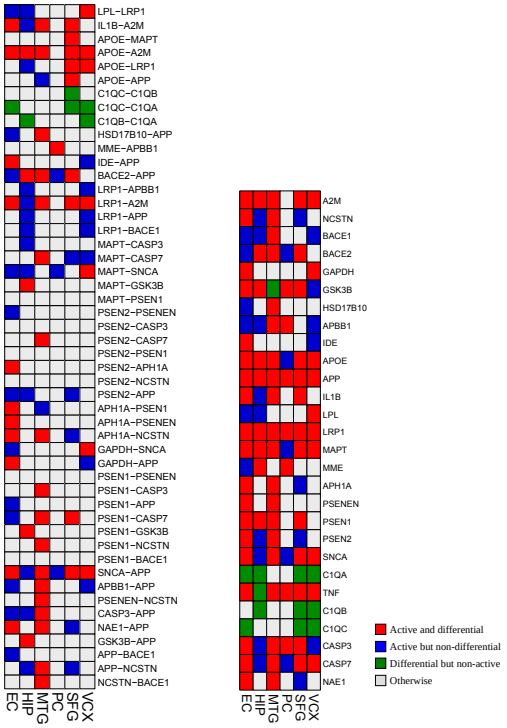
Using different thresholds to classify the differentially co-expressed edges, we also identify the pathways underlying KEGG AD proteins in six brain regions individually. The results for p-value 0.05

have been represented in the text. The rest results are presented in the following figures. Figure S3.2 is for that of p-value 0.025 and Figure S3.3 is for that of p-value 0.01.



(a) (b)

Figure S3.2: The edges and nodes of the active pathways underlying KEGG AD proteins in different brain regions. (a) is the edges and (b) is the nodes. The edges are represented in four different colors classifying their memberships in six AD brain regions. The edge is defined as a differentially co-expressed edge when its score is more than 14.45 (p-value 0.025).



(a) (b)

Figure S3.3: The edges and nodes of the active pathways underlying KEGG AD proteins in different brain regions. (a) is the edges and (b) is the nodes. The edges are represented in four different colors classifying their memberships in six brain regions. The edge is defined as a differentially co-expressed edge when its score is more than 16.81 (p-value 0.01).

S4. More on GO enrichments of active pathways

We identified the significance of GO biological processing terms in the active pathways in six brain regions individually. We show the top five enriched GO functions in these identified pathways. The lists of significant GO terms (p-value < 0.001) have been shown in Table S4.1. If we choose more specific GO terms, such as the level more than 4, the functional annotation will be more specific.

Table S4.1: Significant GO biological processes enriched in the identified active pathways in various brain regions (p-value < 0.001).

Region	GO term	Description	Level	Frequency (In pathway/AD proteins)	p-value
EC	GO:0007165	signal transduction	4	32/51	4.98E-14
	GO:0006355	regulation of transcription, DNA-dependent	8	21/30	2.48E-10
	GO:0006916	anti-apoptosis	8	17/22	2.61E-09
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	13/14	1.23E-08
	GO:0006508	Proteolysis	6	17/24	1.92E-08
	GO:0044419	interspecies interaction between organisms	3	14/19	3.02E-07
	GO:0006915	Apoptosis	6	12/16	2.56E-06
	GO:0006350	Transcription	5	11/14	4.53E-06
	GO:0006917	induction of apoptosis	8	11/14	4.53E-06
	GO:0007275	Development	3	12/18	1.39E-05
	GO:0006509	membrane protein ectodomain proteolysis	7	7/7	9.16E-05
	GO:0006629	lipid metabolism	4	12/22	0.000171244
	GO:0007267	cell-cell signaling	4	9/13	0.000221274
	GO:0007186	G-protein coupled receptor protein signaling pathway	6	9/13	0.000221274
	GO:0006468	protein amino acid phosphorylation	8	9/13	0.000221274
	GO:0007242	intracellular signaling cascade	5	7/8	0.000318214
	GO:0008285	negative regulation of cell proliferation	6	7/8	0.000318214
	GO:0030154	cell differentiation	4	8/11	0.000431494
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.000508904
	GO:0007049	cell cycle	3	6/6	0.000508904
	GO:0030308	negative regulation of cell growth	6	7/9	0.000829321
HIP	GO:0007165	signal transduction	4	32/51	4.22E-15
	GO:0006355	regulation of transcription, DNA-dependent	8	22/30	3.50E-12
	GO:0044419	interspecies interaction between organisms	3	16/19	3.68E-10
	GO:0007186	G-protein coupled receptor protein signaling pathway	6	12/13	2.90E-08
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	12/14	1.18E-07
	GO:0006955	immune response	3	13/17	2.10E-07
	GO:0007267	cell-cell signaling	4	11/13	6.77E-07

	GO:0006508	proteolysis	6	14/24	5.15E-06
	GO:0007242	intracellular signaling cascade	5	8/8	9.14E-06
	GO:0006915	apoptosis	6	11/16	1.27E-05
	GO:0006350	transcription	5	10/14	2.63E-05
	GO:0030308	negative regulation of cell growth	6	8/9	3.61E-05
	GO:0007275	development	3	11/18	5.31E-05
	GO:0008283	cell proliferation	3	7/7	5.66E-05
	GO:0006916	anti-apoptosis	8	12/22	7.87E-05
	GO:0006874	calcium ion homeostasis	10	7/8	0.000199
	GO:0007050	cell cycle arrest	7	7/8	0.000199
	GO:0006917	induction of apoptosis	8	9/14	0.000249
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.000342
	GO:0006954	inflammatory response	4	10/18	0.000375
MTG	GO:0006916	anti-apoptosis	8	17/22	2.31E-11
	GO:0044419	interspecies interaction between organisms	3	15/19	3.62E-10
	GO:0007165	signal transduction	4	24/51	7.25E-10
	GO:0006915	apoptosis	6	12/16	1.10E-07
	GO:0006355	regulation of transcription, DNA-dependent	8	16/30	1.81E-07
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	10/14	4.21E-06
	GO:0006509	membrane protein ectodomain proteolysis	7	7/7	1.59E-05
	GO:0006468	protein amino acid phosphorylation	8	9/13	2.44E-05
	GO:0007242	intracellular signaling cascade	5	7/8	5.74E-05
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.00012
	GO:0007267	cell-cell signaling	4	8/13	0.000263
	GO:0042632	cholesterol homeostasis	6	7/10	0.000351
	GO:0006629	lipid metabolism	4	10/22	0.000454
	GO:0007275	development	3	9/18	0.000494
	GO:0007220	Notch receptor processing	7	5/5	0.000868
	GO:0016485	protein processing	8	5/5	0.000868
	GO:0043085	positive regulation of enzyme activity	5	5/5	0.000868
	GO:0044419	interspecies interaction between organisms	3	18/19	2.13E-13
	GO:0007165	signal transduction	4	29/51	1.66E-12
	GO:0006355	regulation of transcription, DNA-dependent	8	22/30	1.80E-12

PC	GO:0006955	immune response	3	13/17	1.46E-07
	GO:0006468	protein amino acid phosphorylation	8	11/13	4.98E-07
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	11/14	1.53E-06
	GO:0006954	inflammatory response	4	12/18	4.39E-06
	GO:0006916	anti-apoptosis	8	13/22	8.00E-06
	GO:0007186	G-protein coupled receptor protein signaling pathway	6	10/13	8.18E-06
	GO:0007267	cell-cell signaling	4	10/13	8.18E-06
	GO:0006915	apoptosis	6	11/16	9.47E-06
	GO:0006917	induction of apoptosis	8	10/14	2.01E-05
	GO:0007275	development	3	11/18	4.00E-05
	GO:0042632	cholesterol homeostasis	6	8/10	8.56E-05
	GO:0006508	proteolysis	6	12/24	0.000159
	GO:0006350	transcription	5	9/14	0.000198
	GO:0006935	chemotaxis	6	6/6	0.000293
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.000293
	GO:0006629	lipid metabolism	4	11/22	0.000354
	GO:0016481	negative regulation of transcription	8	7/9	0.00044
	GO:0008203	cholesterol metabolism	6	8/13	0.000839
	GO:0007596	blood coagulation	4	6/7	0.000909
	GO:0006979	response to oxidative stress	4	6/7	0.000909
	GO:0042981	regulation of apoptosis	6	7/10	0.000972
	GO:0007165	signal transduction	4	30/51	1.52E-14
	GO:0006916	anti-apoptosis	8	17/22	1.16E-10
	GO:0006355	regulation of transcription, DNA-dependent	8	19/30	9.04E-10
	GO:0007275	multicellular organismal development	3	13/18	1.47E-07
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	11/14	6.84E-07
	GO:0044419	interspecies interaction between organisms	3	12/19	3.93E-06
	GO:0006917	induction of apoptosis	8	10/14	9.94E-06
	GO:0006629	lipid metabolism	4	12/22	2.58E-05
	GO:0006915	apoptosis	6	10/16	4.50E-05
	GO:0007186	G-protein coupled receptor protein signaling pathway	6	9/13	5.19E-05
	GO:0006468	protein amino acid phosphorylation	8	9/13	5.19E-05

SFG	GO:0007242	intracellular signaling cascade	5	7/8	0.000103
	GO:0007399	nervous system development	5	7/8	0.000103
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.000195
	GO:0007049	cell cycle	3	6/6	0.000195
	GO:0006508	proteolysis	6	11/24	0.000416
	GO:0008203	cholesterol metabolism	6	8/13	0.000498
	GO:0007267	cell-cell signaling	4	8/13	0.000498
	GO:0043066	negative regulation of apoptosis	7	6/7	0.000612
	GO:0008283	cell proliferation	3	6/7	0.000612
	GO:0042632	cholesterol homeostasis	6	7/10	0.000614
	GO:0006350	transcription	5	8/14	0.000888
VCX	GO:0006355	regulation of transcription, DNA-dependent	8	23/30	1.23E-13
	GO:0006629	lipid metabolism	4	13/22	8.72E-06
	GO:0007165	signal transduction	4	28/51	1.78E-11
	GO:0044419	interspecies interaction between organisms	3	16/19	2.58E-10
	GO:0007275	multicellular organismal development	3	15/18	1.56E-09
	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	10	13/14	3.48E-09
	GO:0030154	cell differentiation	4	10/11	8.73E-07
	GO:0006917	induction of apoptosis	8	11/14	1.65E-06
	GO:0006915	apoptosis	6	11/16	1.02E-05
	GO:0006350	transcription	5	10/14	2.15E-05
	GO:0007596	blood coagulation	4	7/7	4.93E-05
	GO:0043066	negative regulation of apoptosis	7	7/7	4.93E-05
	GO:0006916	anti-apoptosis	8	12/22	6.28E-05
	GO:0042632	cholesterol homeostasis	6	8/10	9.03E-05
	GO:0042981	regulation of apoptosis	6	8/10	9.03E-05
	GO:0006508	proteolysis	6	12/24	0.000171
	GO:0006955	immune response	3	10/17	0.000178
	GO:0008286	insulin receptor signaling pathway	8	6/6	0.000305
	GO:0006810	transport	3	8/12	0.000462
	GO:0008203	cholesterol metabolism	6	8/13	0.000882
	GO:0006468	protein amino acid phosphorylation	8	8/13	0.000882
	GO:0008283	cell proliferation	3	6/7	0.000944

S5. Active pathways identified by jActiveModules method

We use jActiveModules plugin in Cytoscape (version 2.6.1) (www.cytoscape.org) to detect the active pathway in every scored network in six brain regions individually. The algorithm uses the stimulated annealing to detect the most significant subset of nodes and all their interactions as the identified pathway. So, we use the default parameters (i.e., General parameters: Number of module 5; Overlap threshold 0.8. Searching parameters: Search depth 1; Max depth from start nodes 2) and run it for four times. In every time, there will be 5 ranked significant sets of node as the output. We select the most significant one (with maximum score) as the identified pathway in these sets of nodes in the four time runs by jActiveModules. The details of the output of jActiveModules are available at: http://www.aporc.org/doc-files/ADR/src/jactivemodules.xls

Moreover, we performed the greedy search in jActiveModules to identify the active subnetworks in six brain regions individually. The results are shown in the following figures. The details of the output of jActiveModules by greed searching are available at:
http://www.aporc.org/doc-files/ADR/src/jactivegreedymodules.xls

Table S5.1: The number of edges/nodes in the ensemble 381/243 protein interactions/proteins which are identified in the active pathway by jActiveModules. From the number of edges and nodes in the jActiveModues active pathways, we can find that there are fewer edges as well as fewer nodes are included than that are included in our active pathways (EC: 192/142; HIP: 185/131; MTG: 132/106; PC: 160/127; SFG: 142/117; VCX: 117/128). Moreover, we can find that there are also fewer edges and nodes in 50/28 KEGG AD proteins interactions/proteins involved in these jActiveModules active pathways than that in our active pathways (EC: 23/25; HIP: 18/18; MTG: 20/20; PC: 4/12; SFG: 14/17 ;VCX: 14/15).

	EC	HIP	MTG	PC	SFG	VCX
In AD protein interaction network						
Default parameters	76/52	108/73	72/51	95/71	102/71	108/71
Greedy search	135/84	116/75	104/59	92/64	152/88	142/86
Underlying KEGG AD proteins						
Default parameters	0/5	2/6	1/4	0/3	7/8	4/7
Greedy search	16/12	5/7	16/8	0/4	20/13	7/9

S5.1 EC

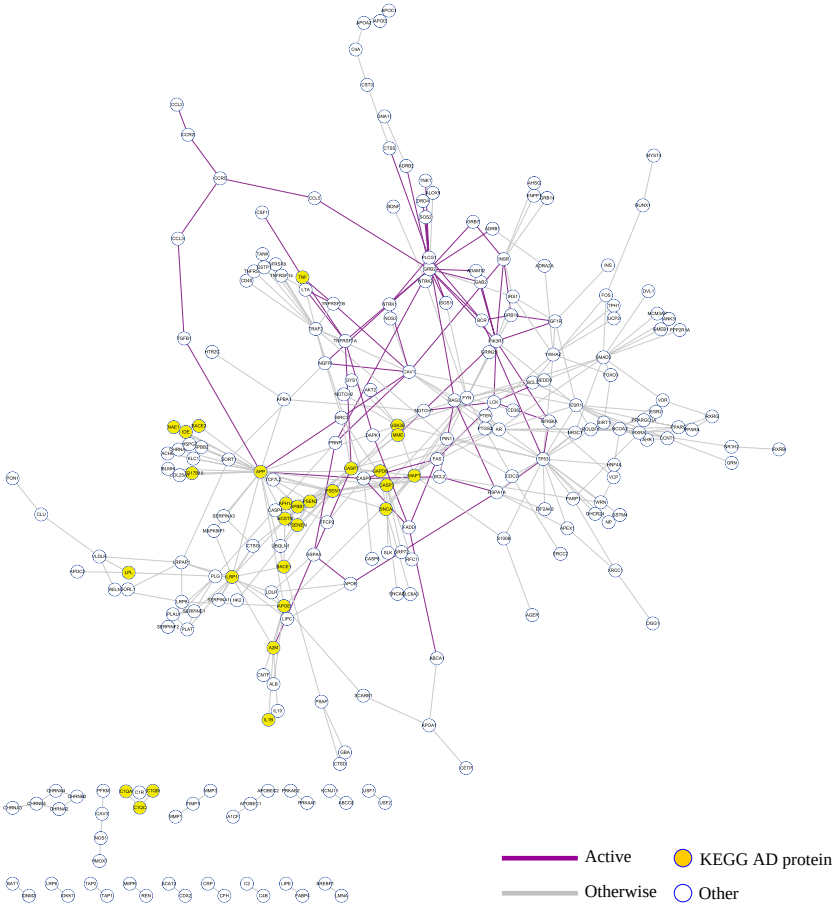


Figure S5.1.1: Identified active pathway of EC in the ensemble AD protein-protein interaction network by jActiveModules with default parameters. Active pathway is involved in the purple edges.

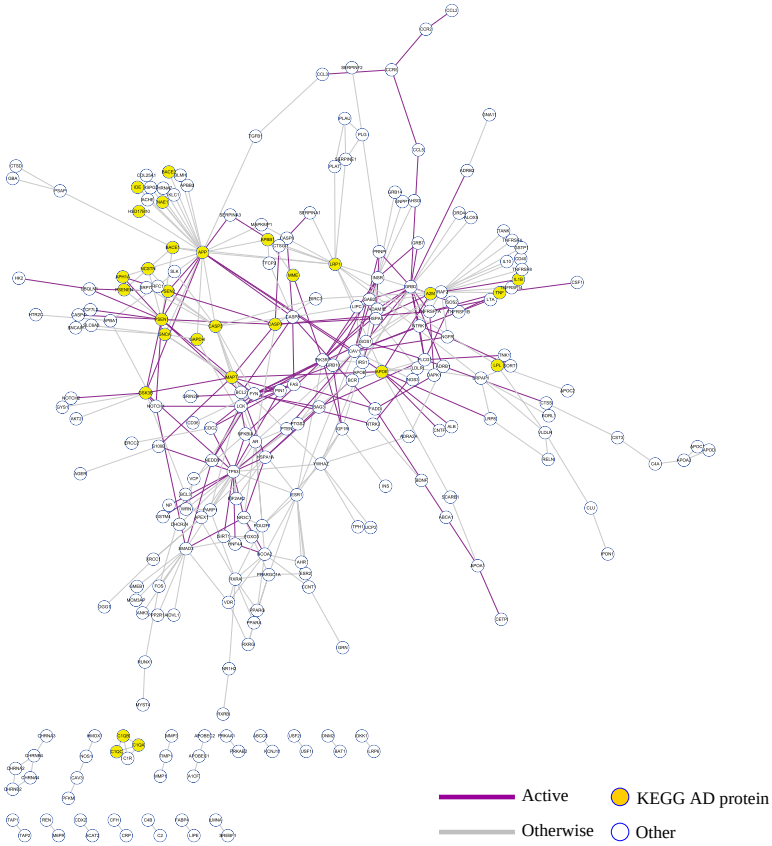


Figure S5.1.2: Identified active pathway of EC in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy. Active pathway is involved in the purple edges.

The identified pathway underlying KEGG AD proteins

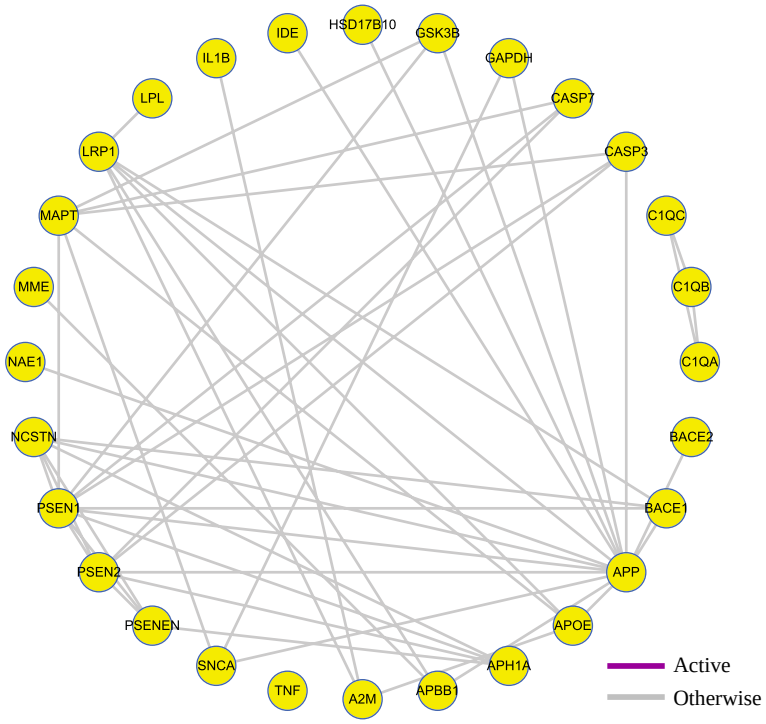


Figure S5.1.3: The active pathway underlying KEGG AD proteins in EC by jActiveModules with default parameters.

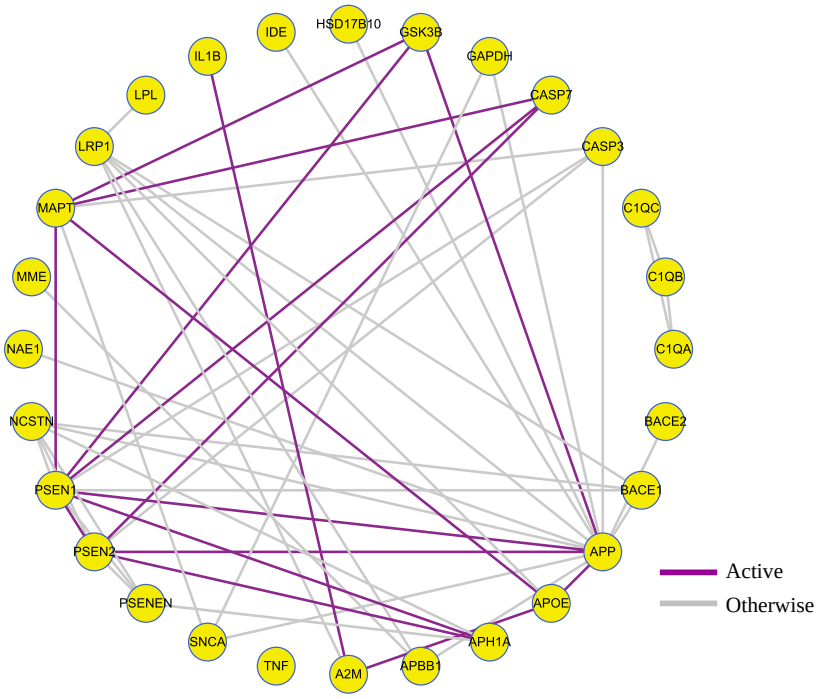


Figure S5.1.4: The active pathway underlying KEGG AD proteins in EC by jActiveModules with greedy searching strategy.

S5.2 HIP

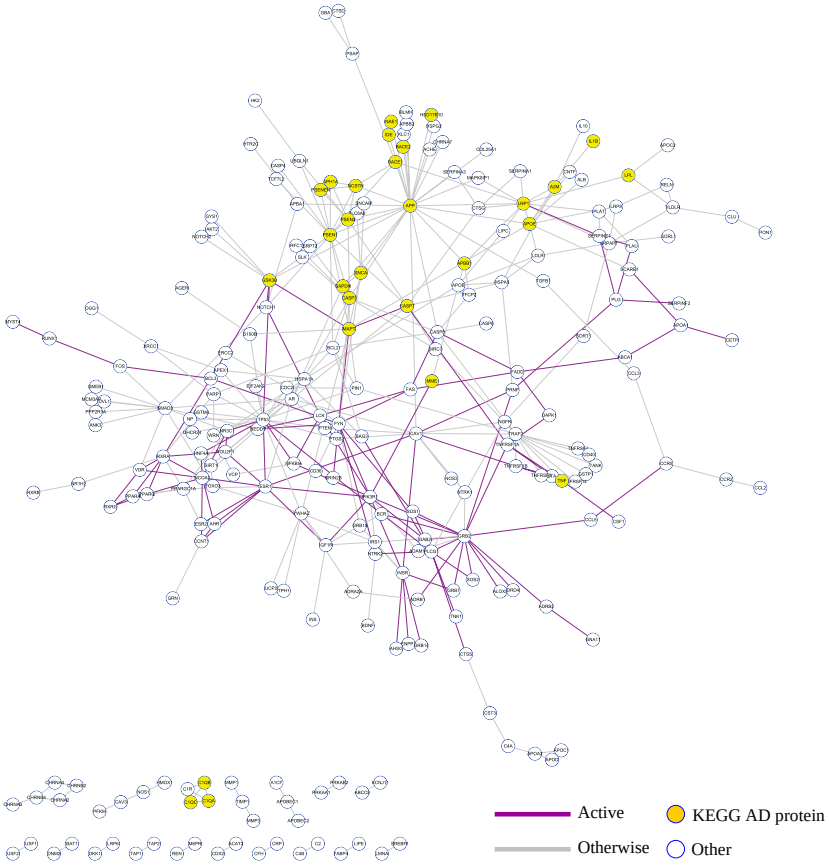


Figure S5.2.1: Identified active pathway of HIP in the ensemble AD protein-protein interaction network by jActiveModules with default parameters.

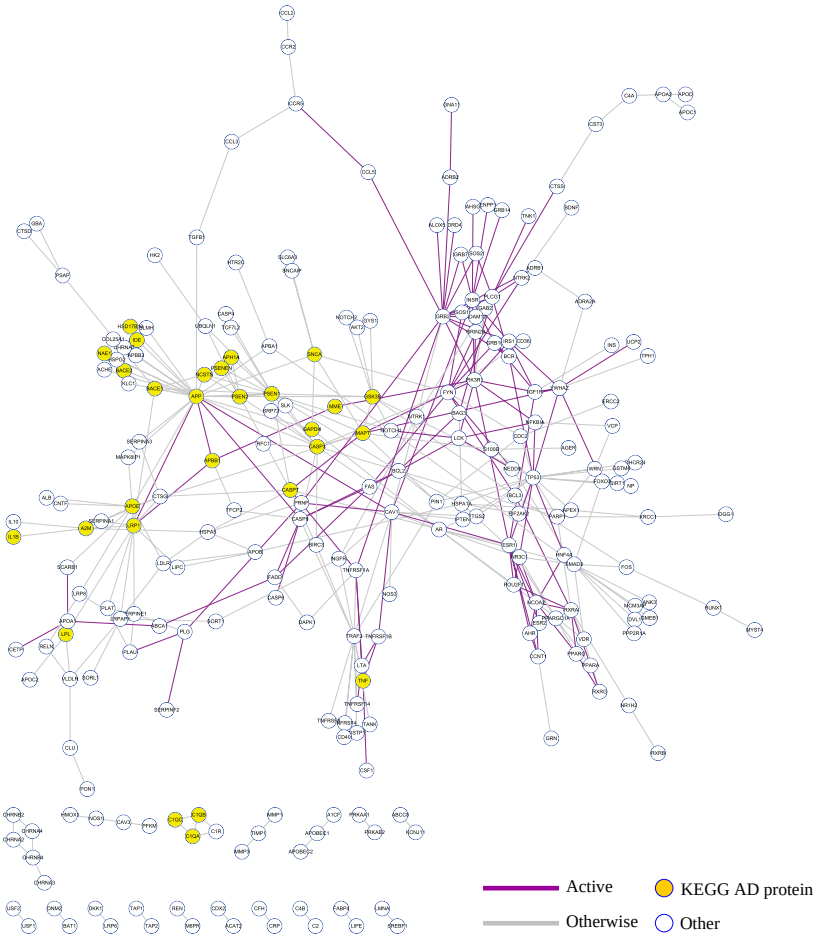


Figure S5.2.2: Identified active pathway of HIP in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy.

The identified pathway underlying KEGG AD proteins

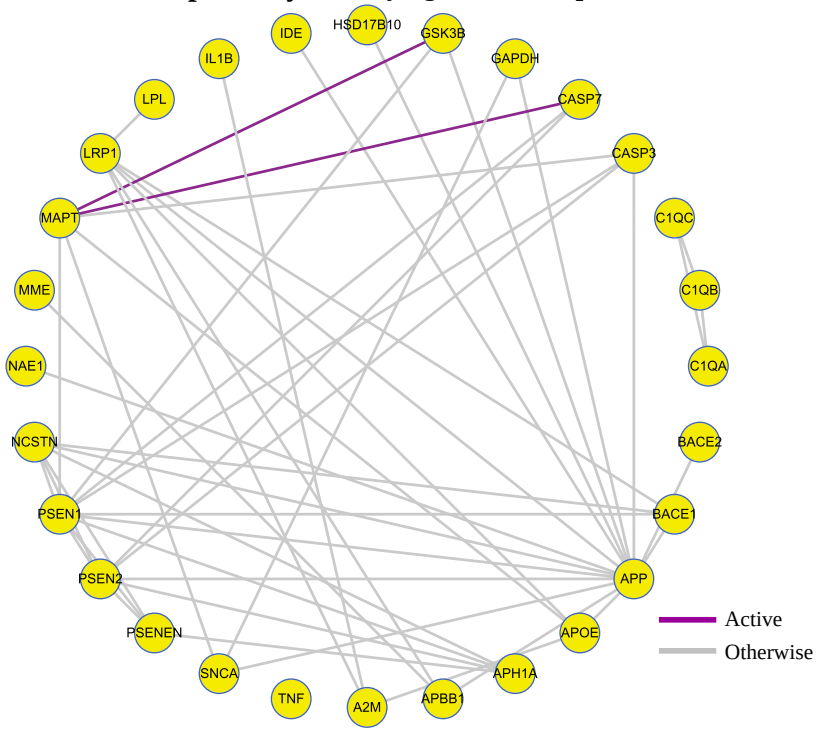


Figure S5.2.3: The active pathway underlying KEGG AD proteins in HIP by jActiveModules with default parameters.

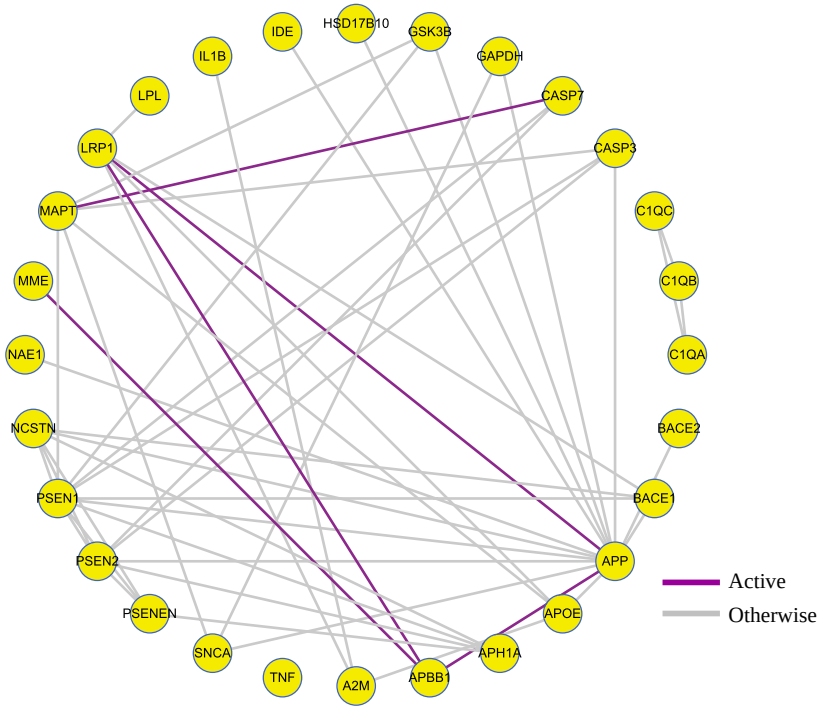


Figure S5.2.4: The active pathway underlying KEGG AD proteins in HIP by jActiveModules with greedy searching strategy.

S5.3 MTG

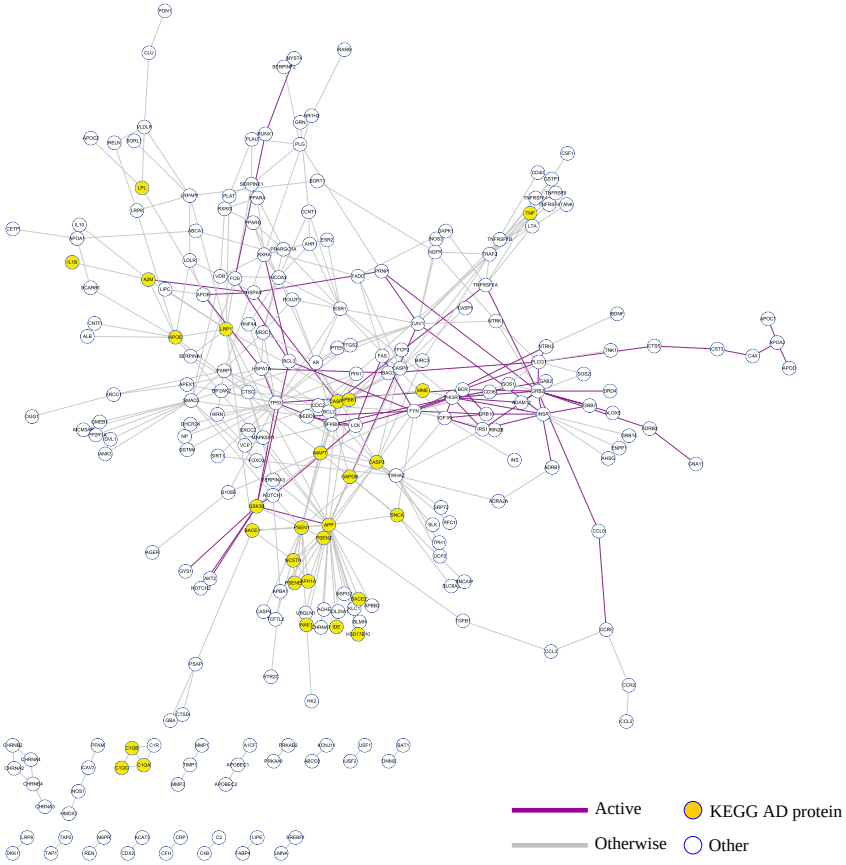


Figure S5.3.1: Identified active pathway of MTG in the ensemble AD protein-protein interaction network by jActiveModules with default parameters.

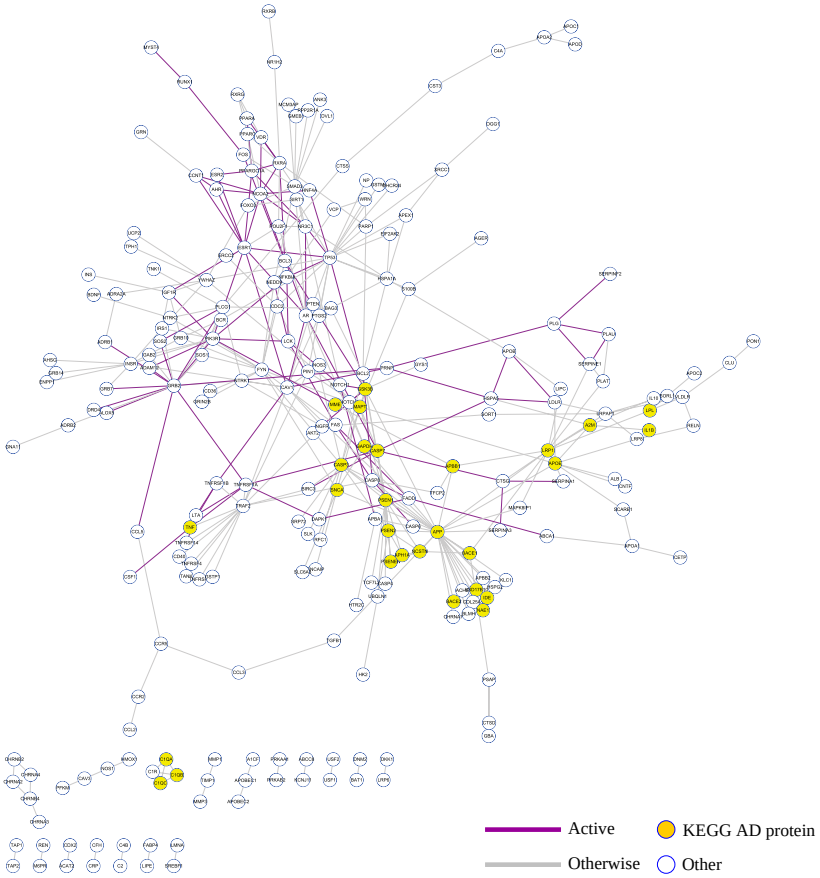


Figure S5.3.2: Identified active pathway of MTG in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy.

The identified pathway underlying KEGG AD proteins

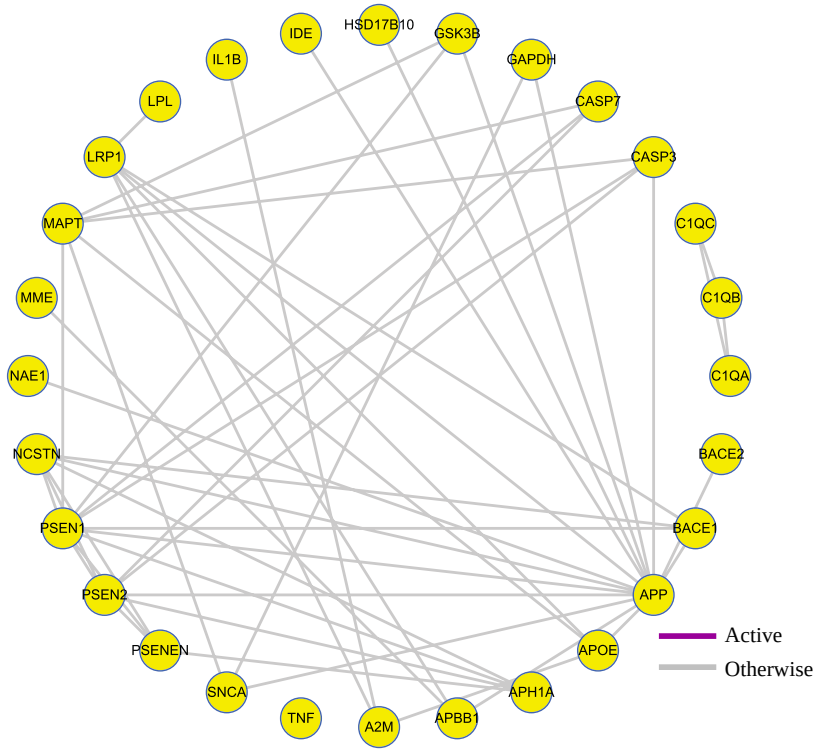


Figure S5.3.3: The active pathway underlying KEGG AD proteins in MTG by jActiveModules with default parameters.

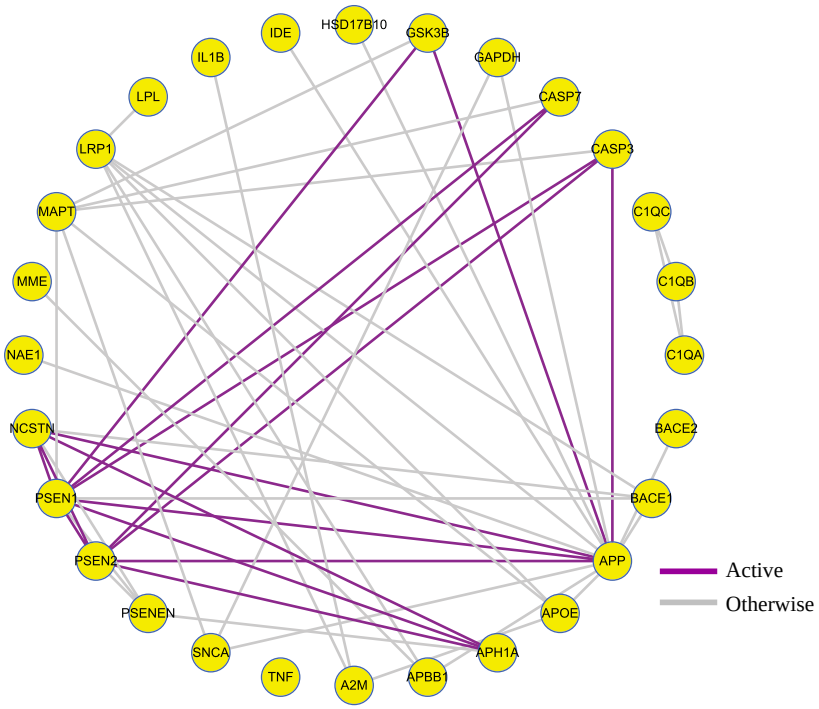


Figure S5.3.4: The active pathway underlying KEGG AD proteins in MTG by jActiveModules with greedy searching strategy.

S5.4 PC

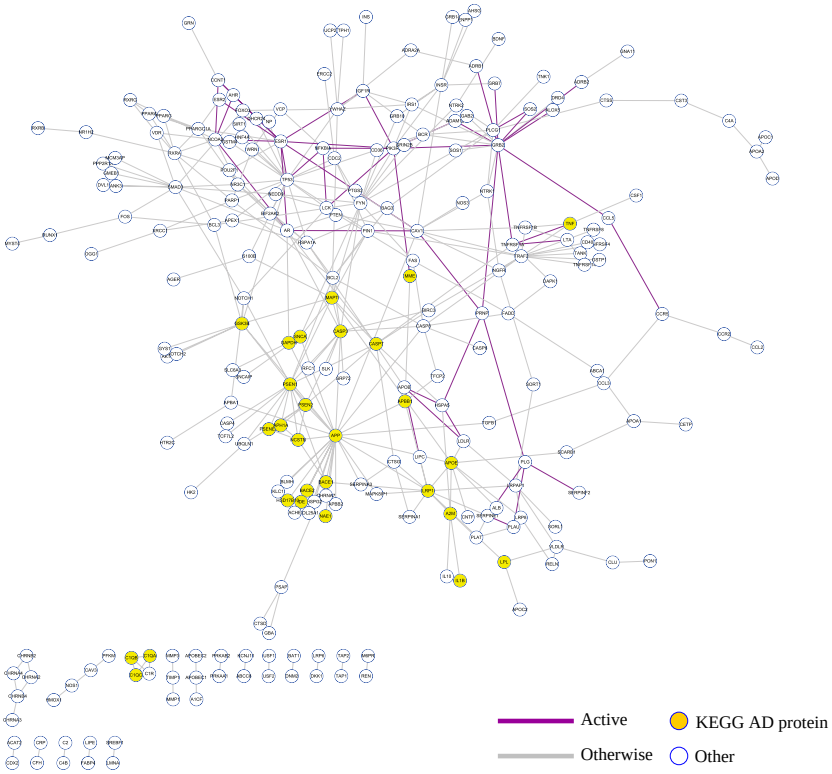


Figure S5.4.1: Identified active pathway of PC in the ensemble AD protein-protein interaction network by jActiveModules with default parameters.

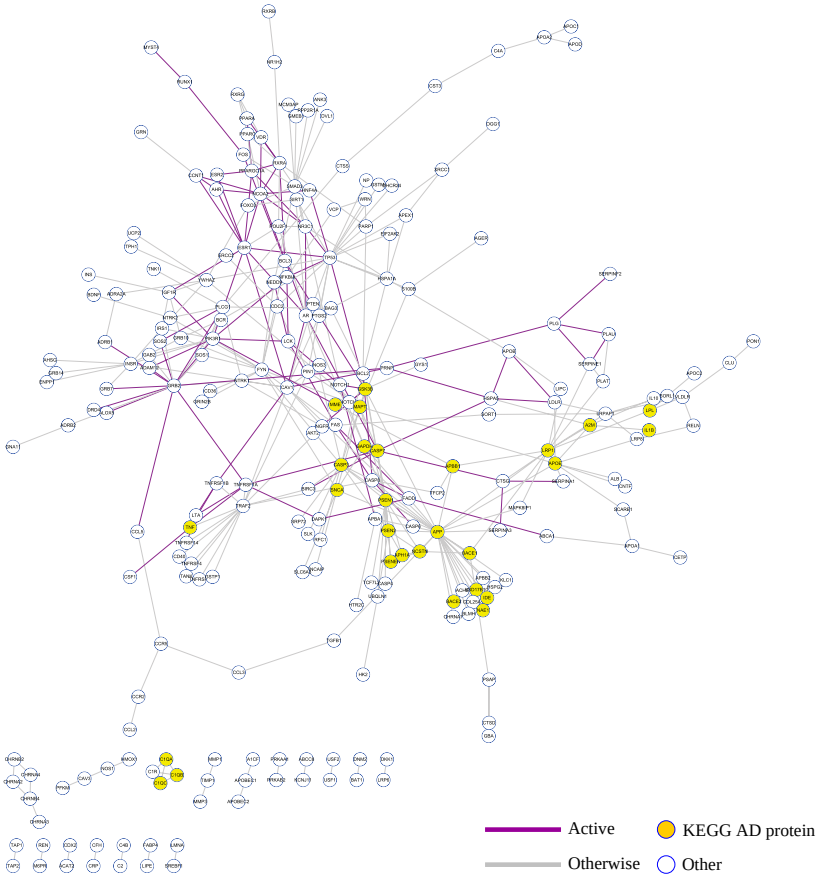


Figure S5.4.2: Identified active pathway of PC in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy.

The identified pathway underlying KEGG AD proteins

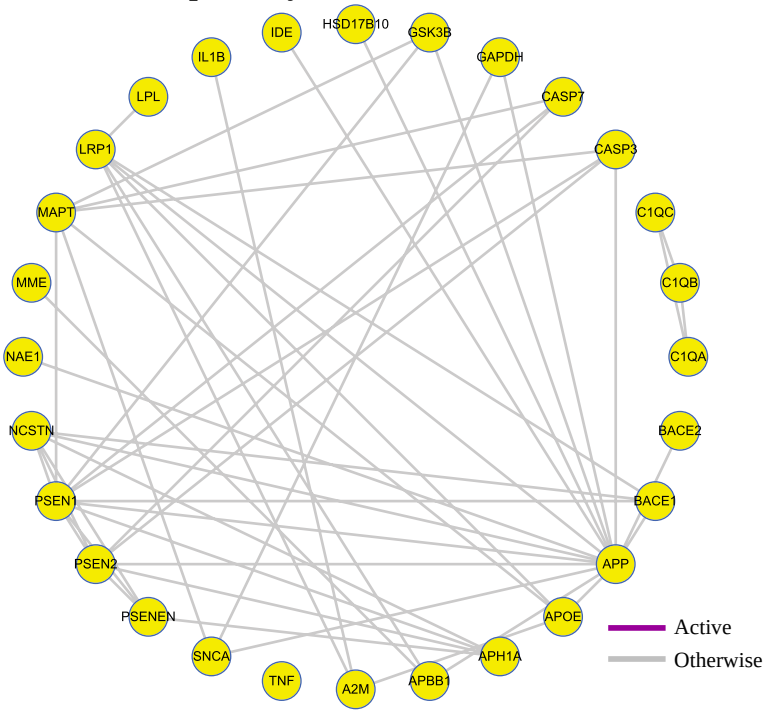


Figure S5.4.3: The active pathway underlying KEGG AD proteins in PC by jActiveModules with default parameters.

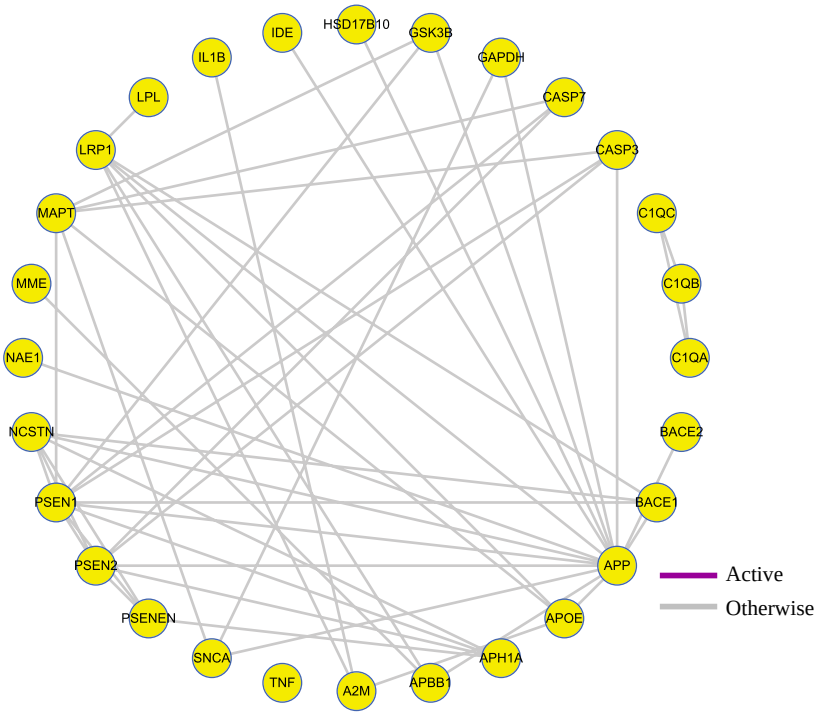


Figure S5.4.4: The active pathway underlying KEGG AD proteins in PC by jActiveModules with greedy searching strategy.

S5.5 SFG

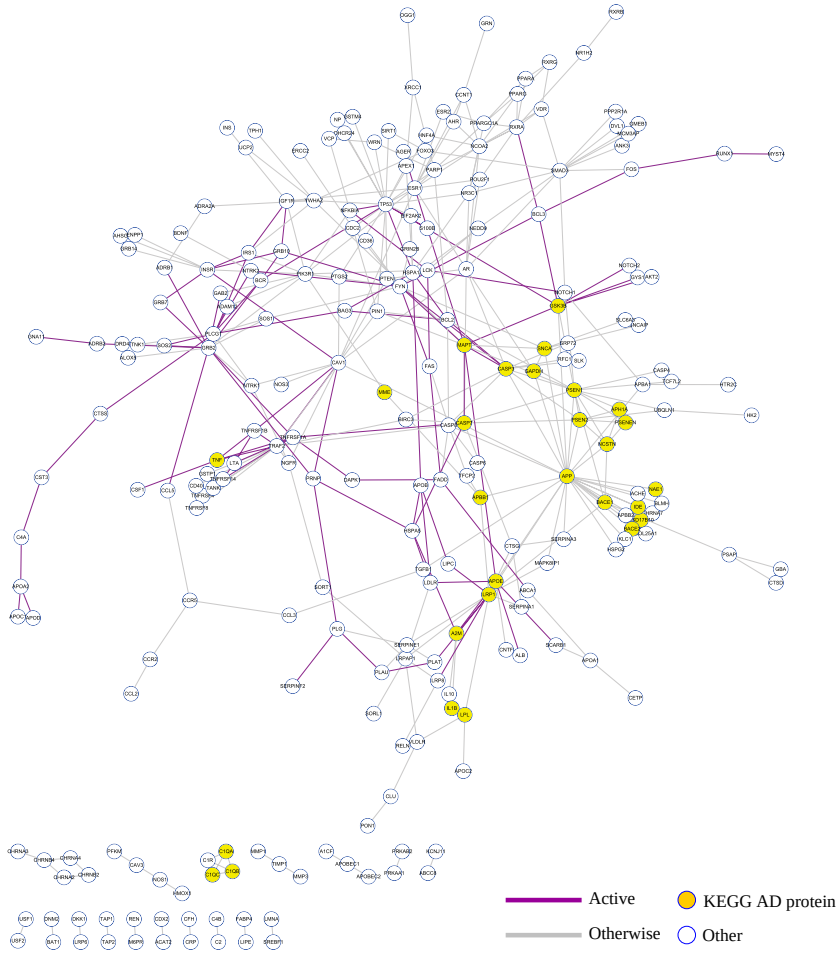


Figure S5.5.1: Identified active pathway of SFG in the ensemble AD protein-protein interaction network by jActiveModules with default parameters.

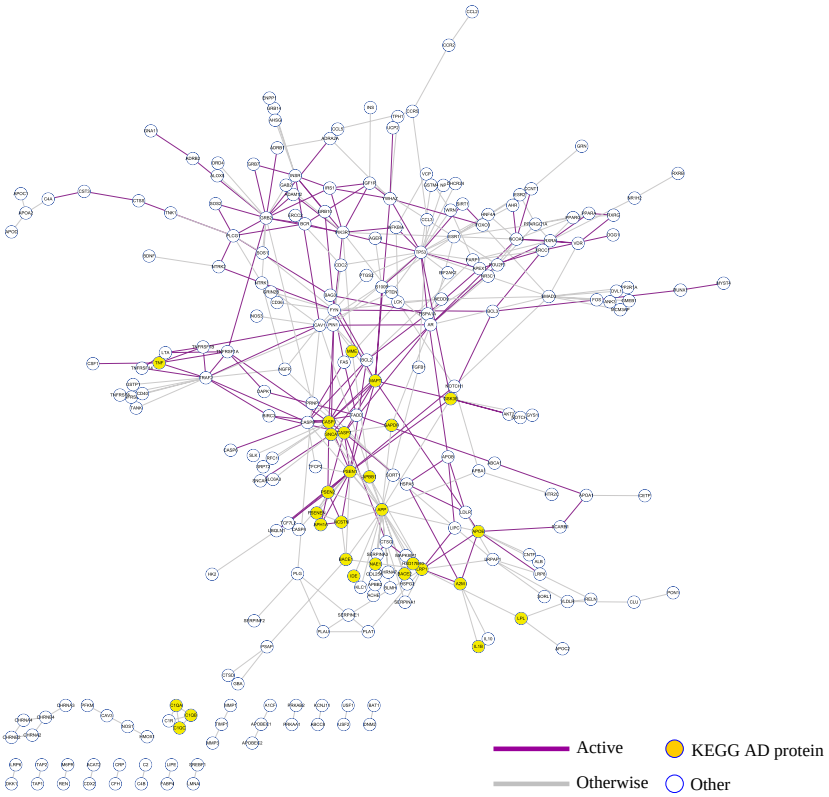


Figure S5.5.2: Identified active pathway of SFG in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy.

The identified pathway underlying KEGG AD proteins

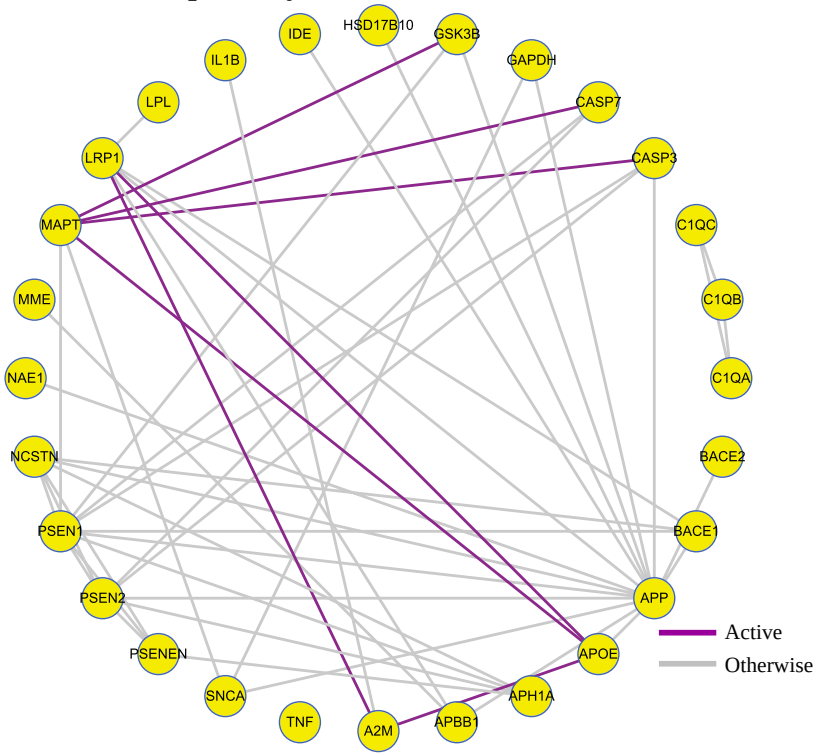


Figure S5.5.3: The active pathway underlying KEGG AD proteins in SFG by jActiveModules with default parameters.

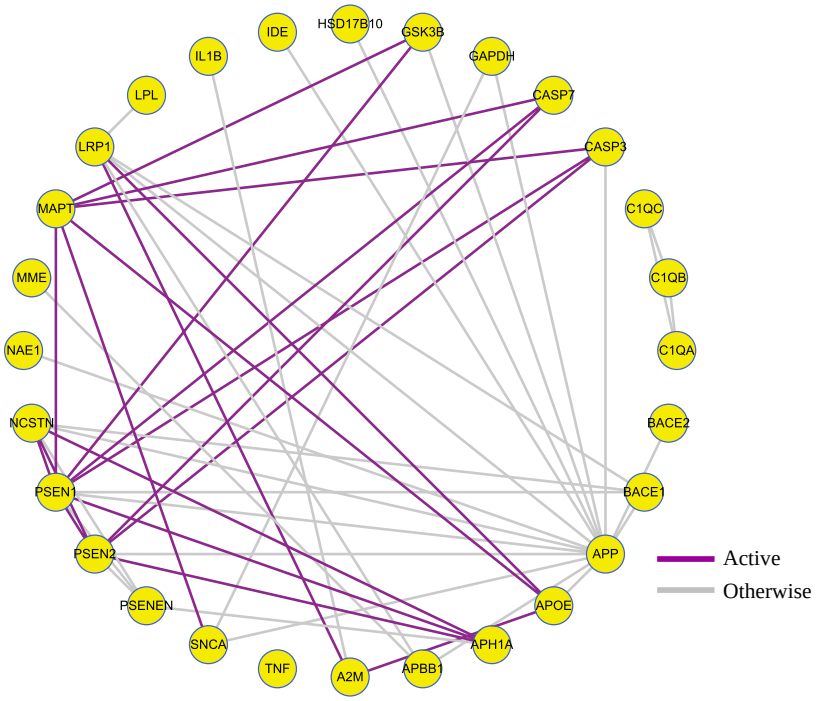


Figure S5.5.4: The active pathway underlying KEGG AD proteins in SFG by jActiveModules with greedy searching strategy.

S5.6 VCX

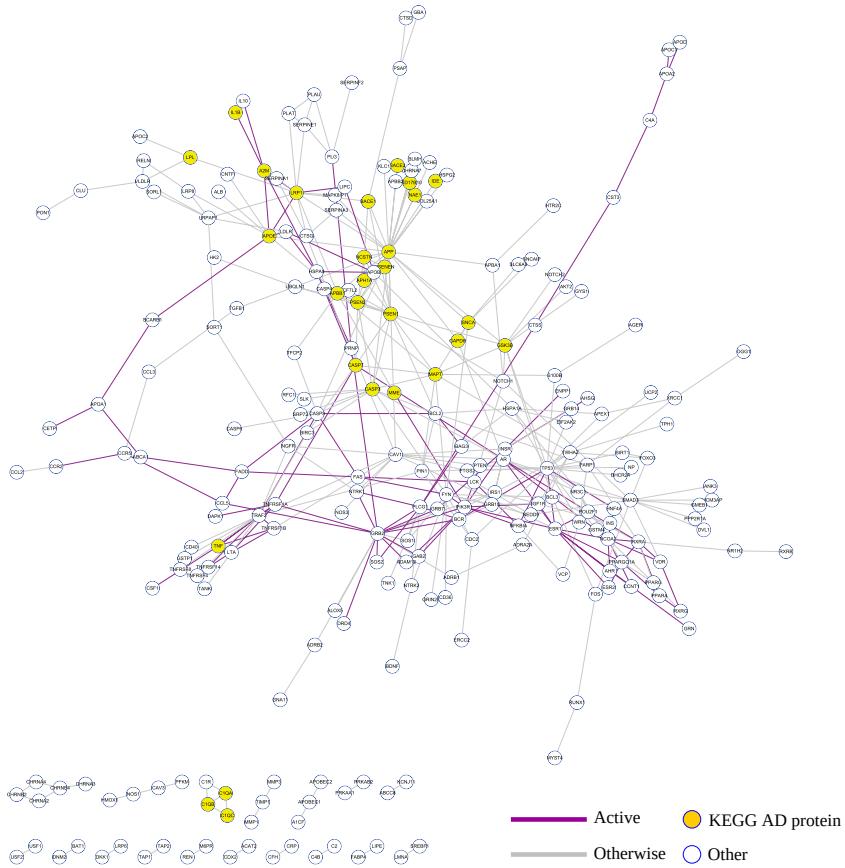


Figure S5.6.1: Identified active pathway of VCX in the ensemble AD protein-protein interaction network by jActiveModules with default parameters.

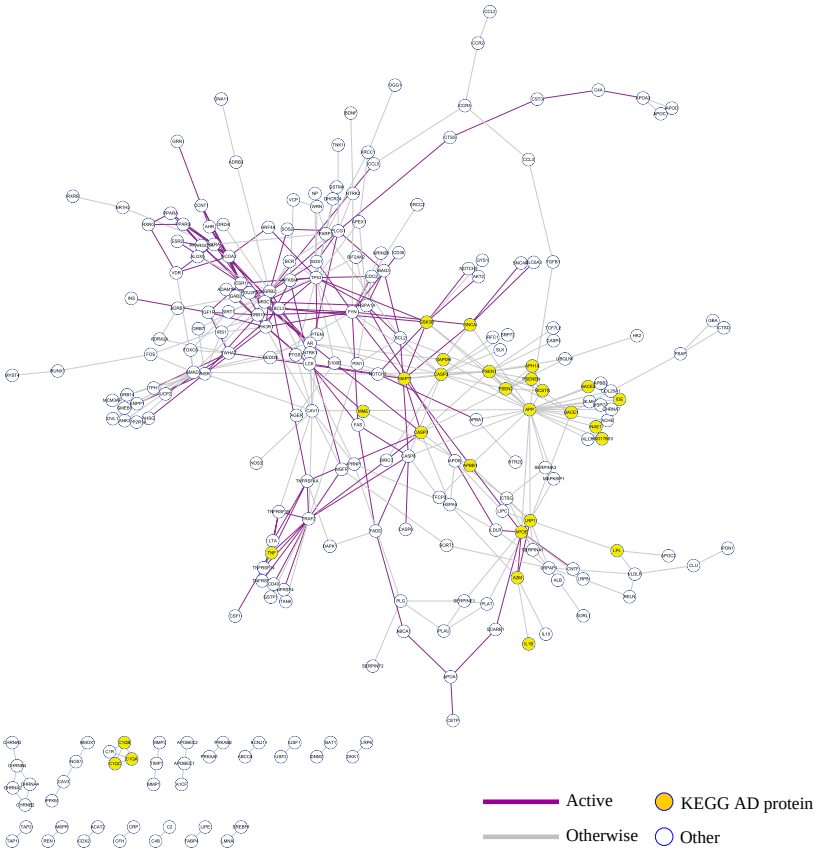


Figure S5.6.2: Identified active pathway of VCX in the ensemble AD protein-protein interaction network by jActiveModules with greedy searching strategy.

The identified pathway underlying KEGG AD proteins

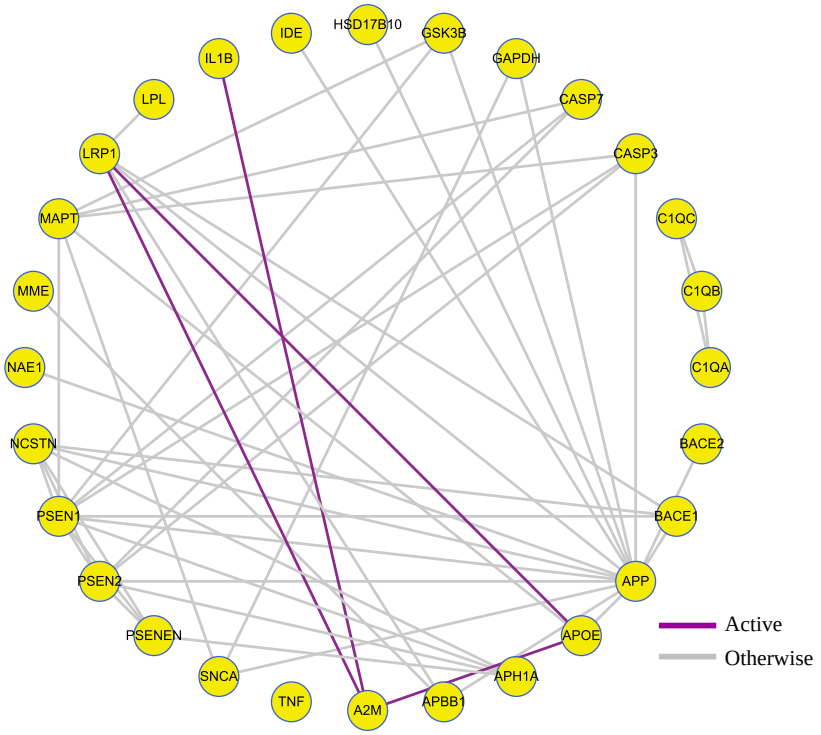


Figure S5.6.3: The active pathway underlying KEGG AD proteins in VCX by jActiveModules with default parameters.

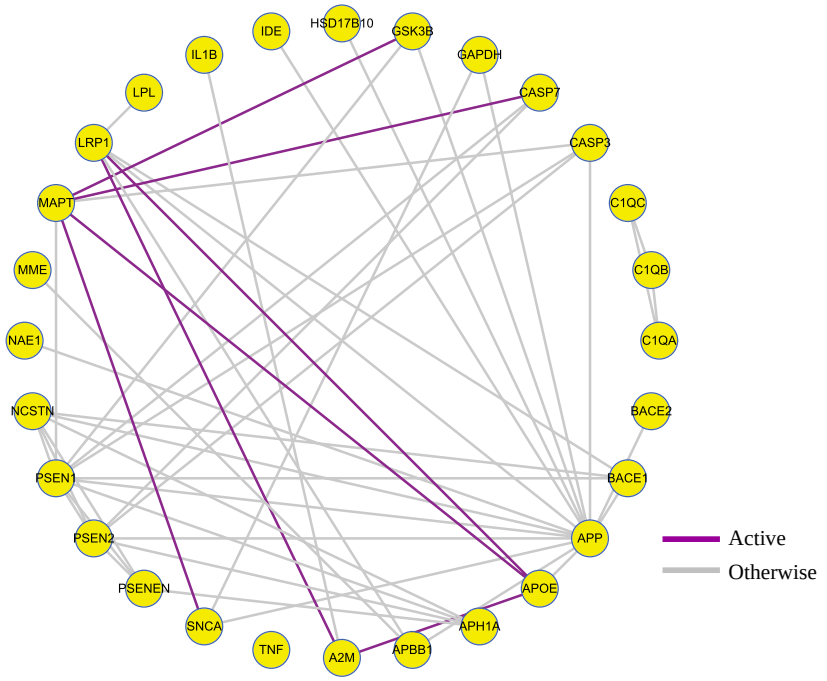


Figure S5.6.4: The active pathway underlying KEGG AD proteins in VCX by jActiveModules with greedy searching strategy.

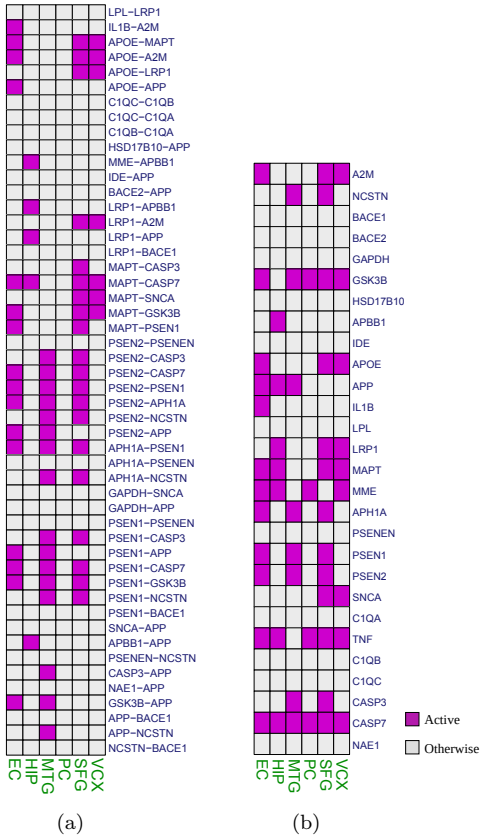


Figure S5.6.5: The active pathways underlying KEGG AD proteins detected by jActiveModules with greedy searching strategy in six AD brain regions.

S5.7 Figure comparison

To compare the difference of active pathways identified by our method and jAactiveModules, we also combined Figure 4 and Figure 5 in a side-by-side way in the main paper in the following Figure S5.7.

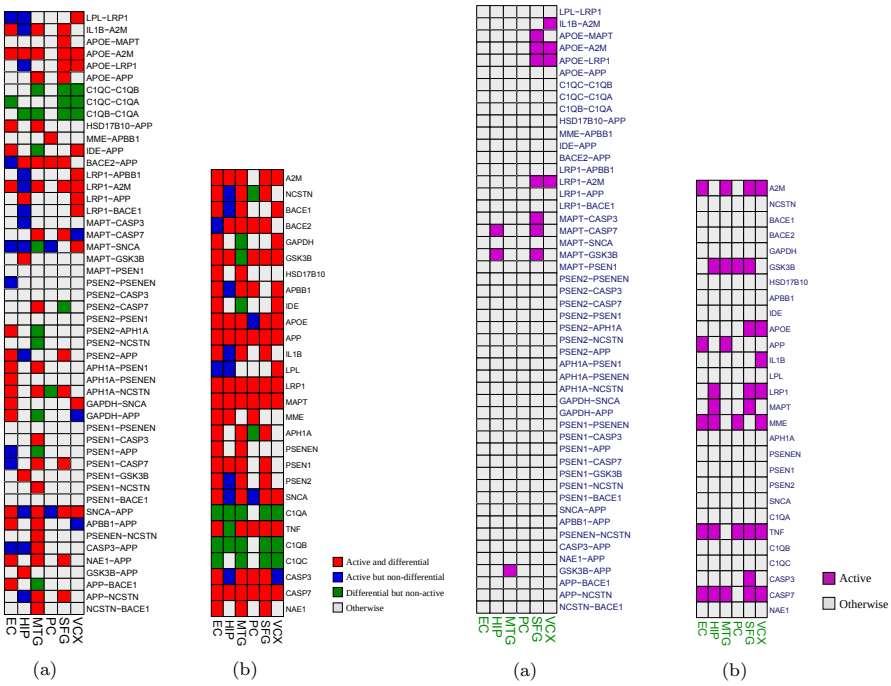


Figure 4 Figure 5

Figure S5.7: The combination of Figure 4 and Figure 5.

S6. Active pathways identified by the score of correlation

When we score the edge by the correlation between the two corresponding genes of an interaction, the active pathways identified by our method are shown in the following figures. We also classify the edges of the ensemble interactions into four types. The differentially co-expressed edges are those edges whose correlation is significance (p-value <0.05).

S6.1 EC

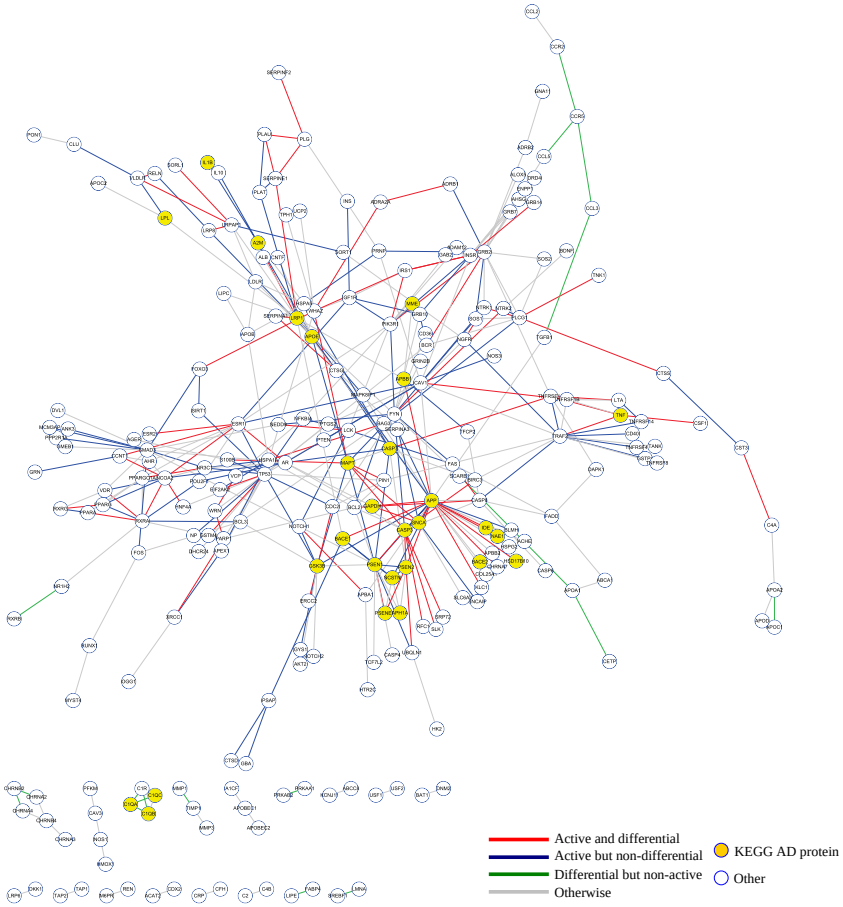


Figure S6.1.1: Identified active pathway of EC in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

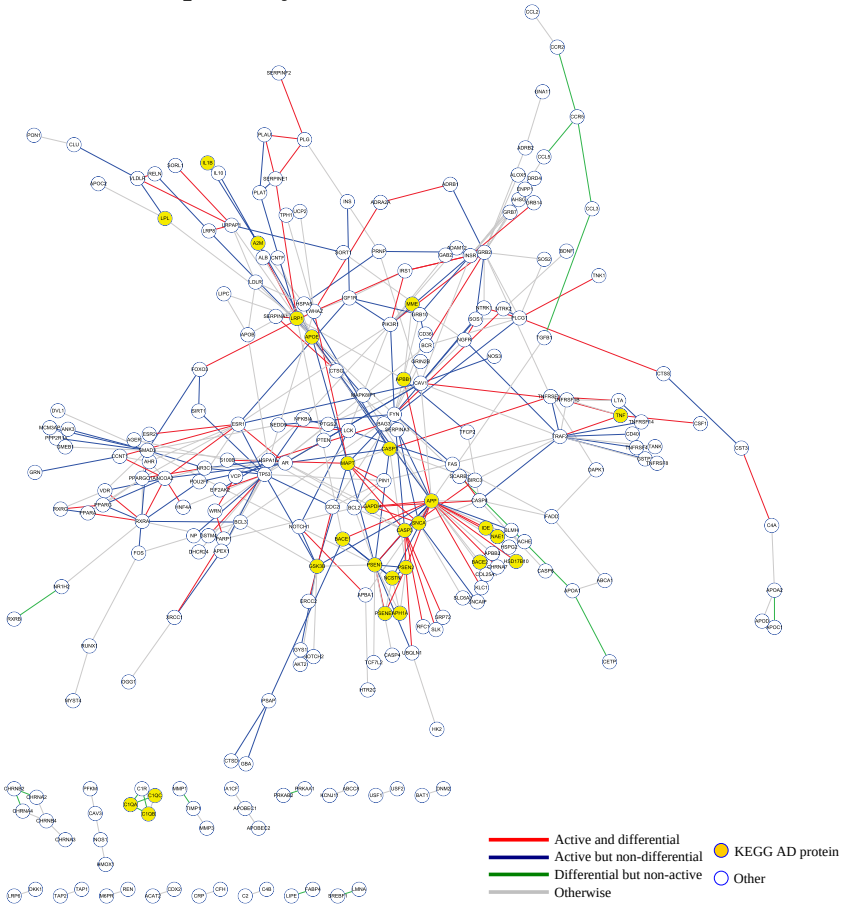


Figure S6.1.2: The active pathway underlying KEGG AD proteins in EC by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

S6.2 HIP

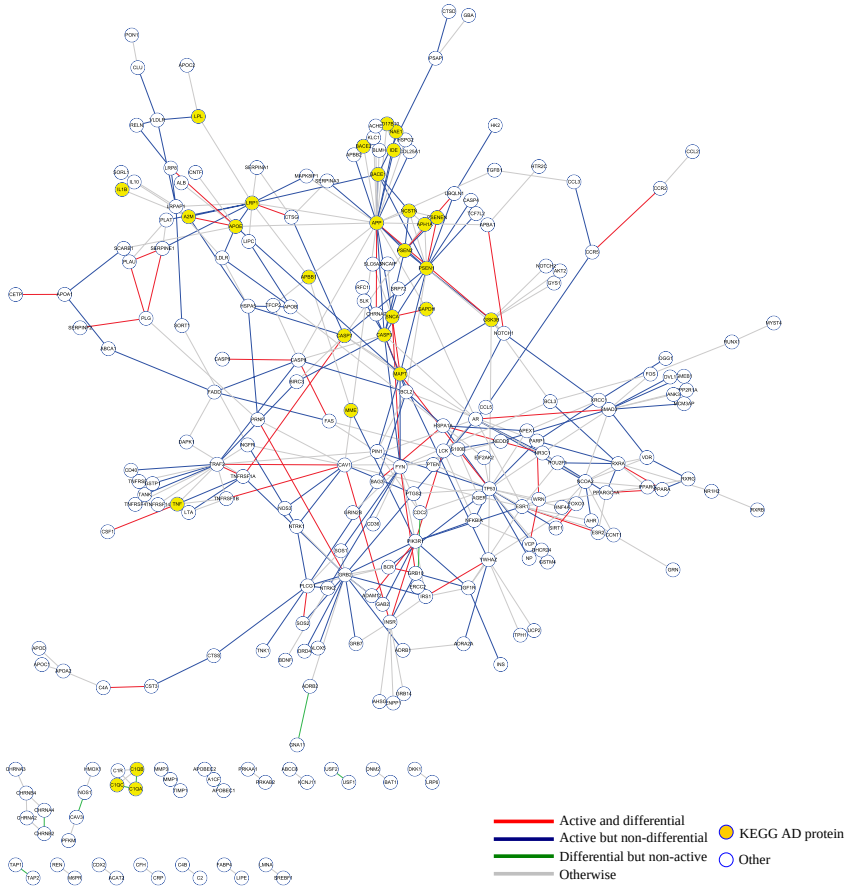


Figure S6.2.1: Identified active pathway of HIP in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

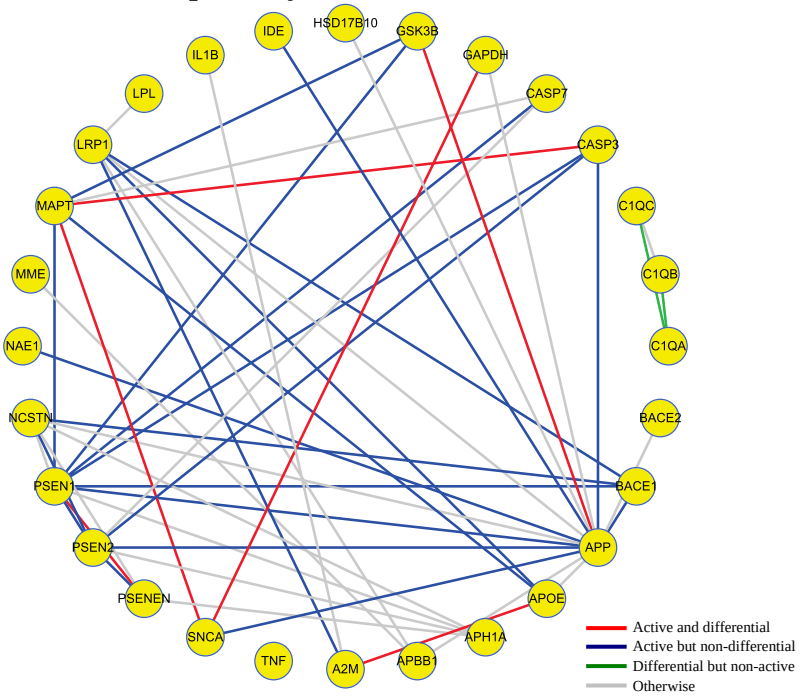


Figure S6.2.2: The active pathway underlying KEGG AD proteins in HIP by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

S6.3 MTG

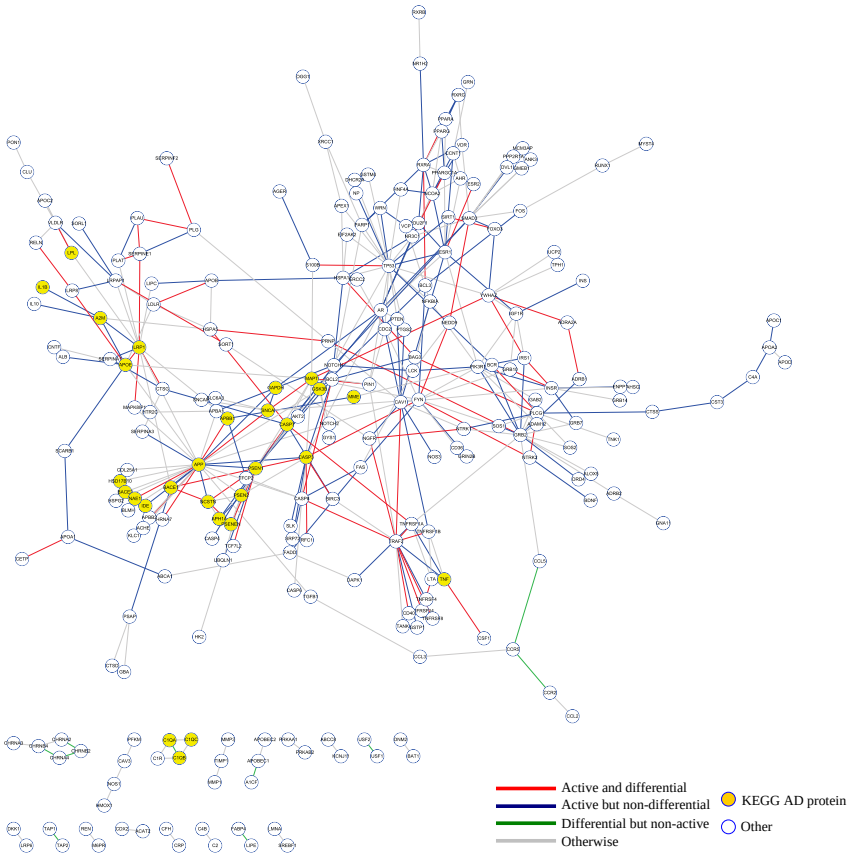


Figure S6.3.1: Identified active pathway of MTG in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

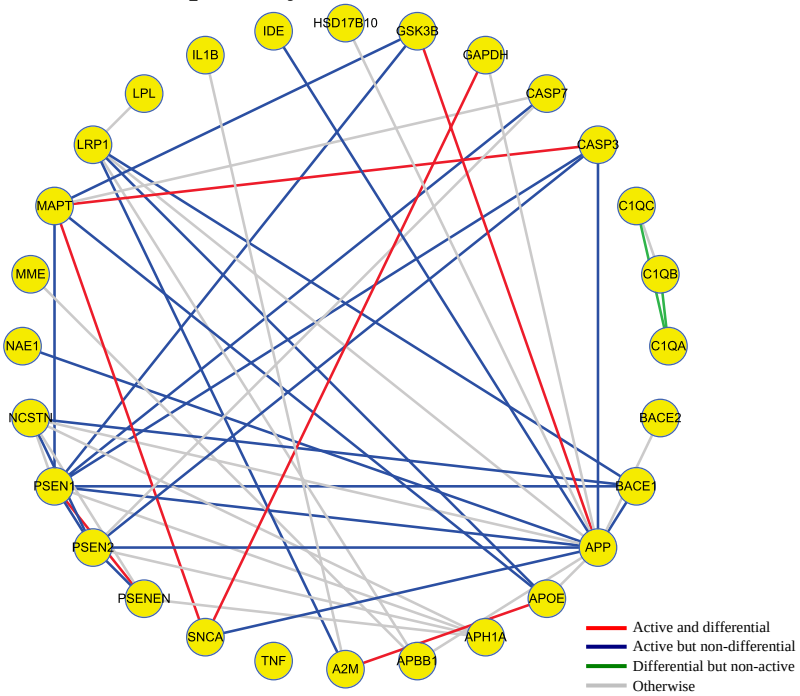


Figure S6.3.2: The active pathway underlying KEGG AD proteins in MTG by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

S6.4 PC

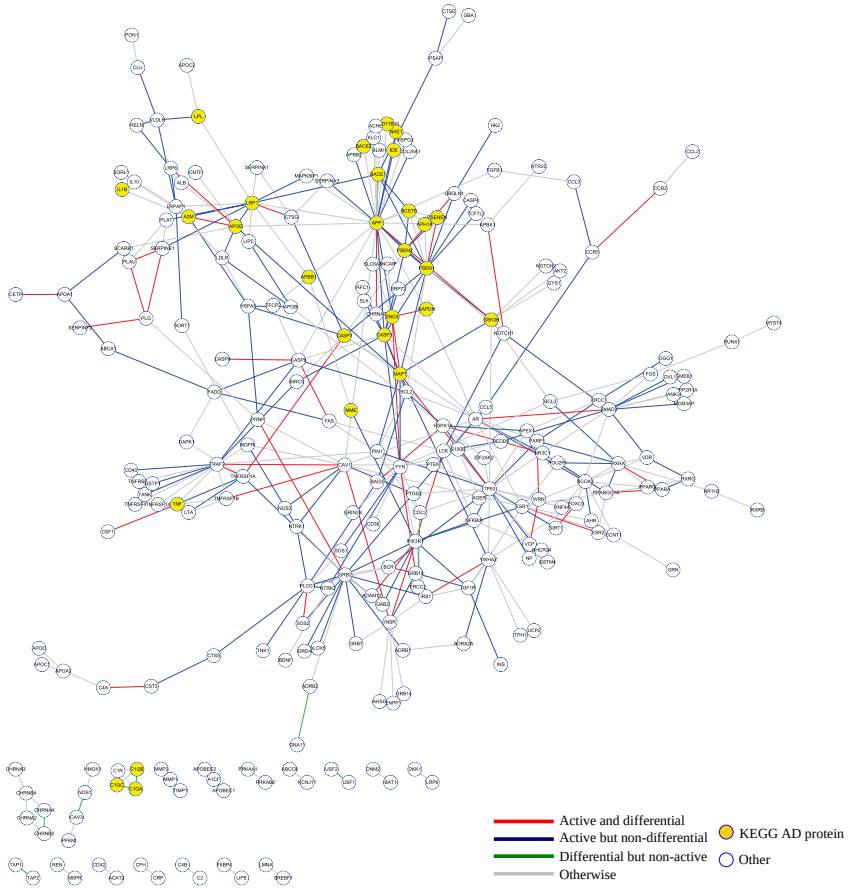


Figure S6.4.1: Identified active pathway of PC in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

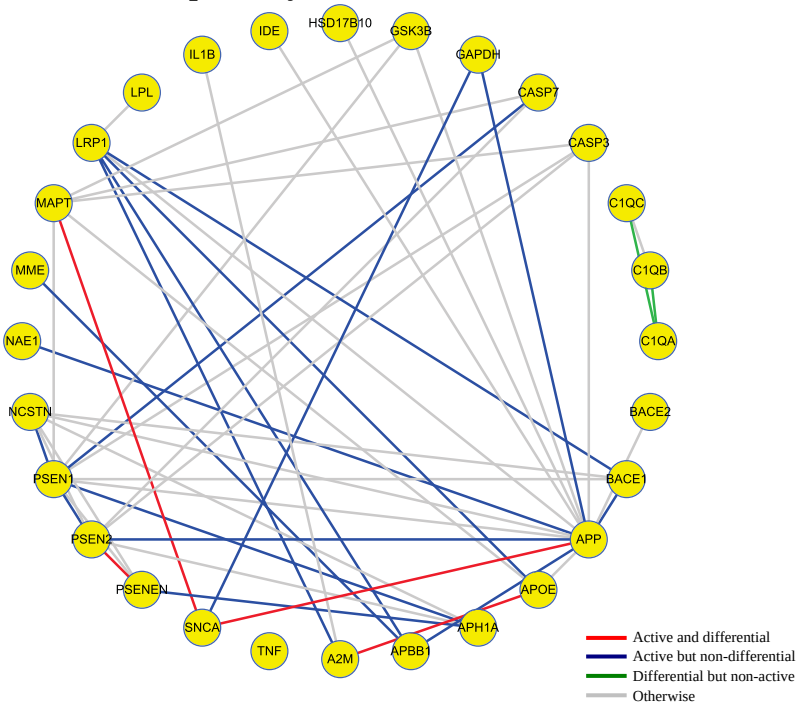


Figure S6.4.2: The active pathway underlying KEGG AD proteins in PC by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

S6.5 SFG

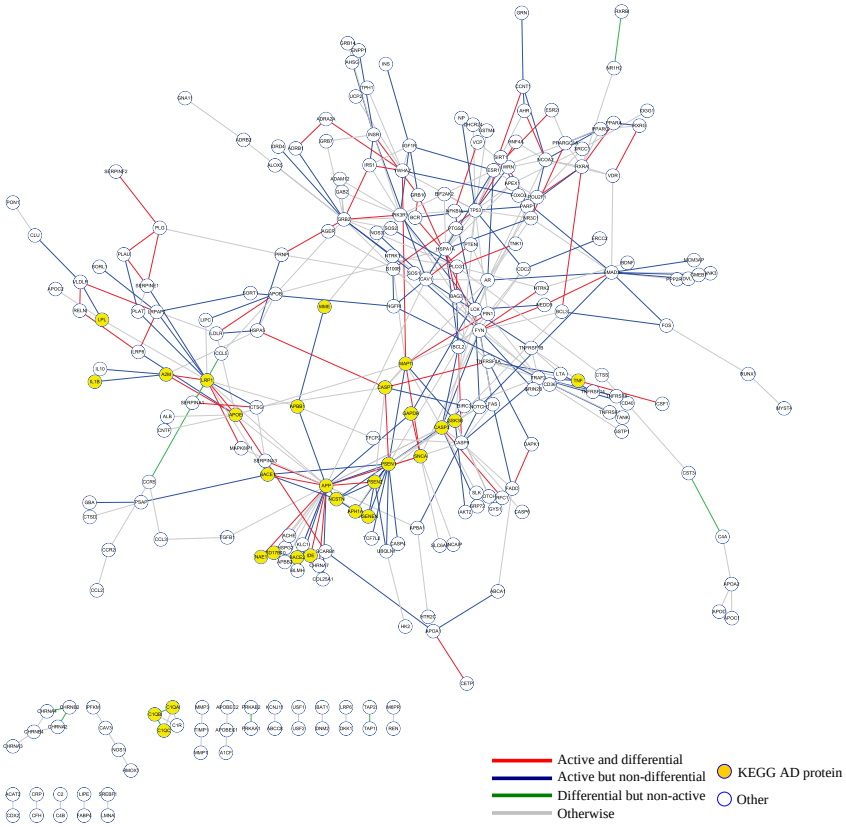


Figure S6.5.1: Identified active pathway of SFG in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins:

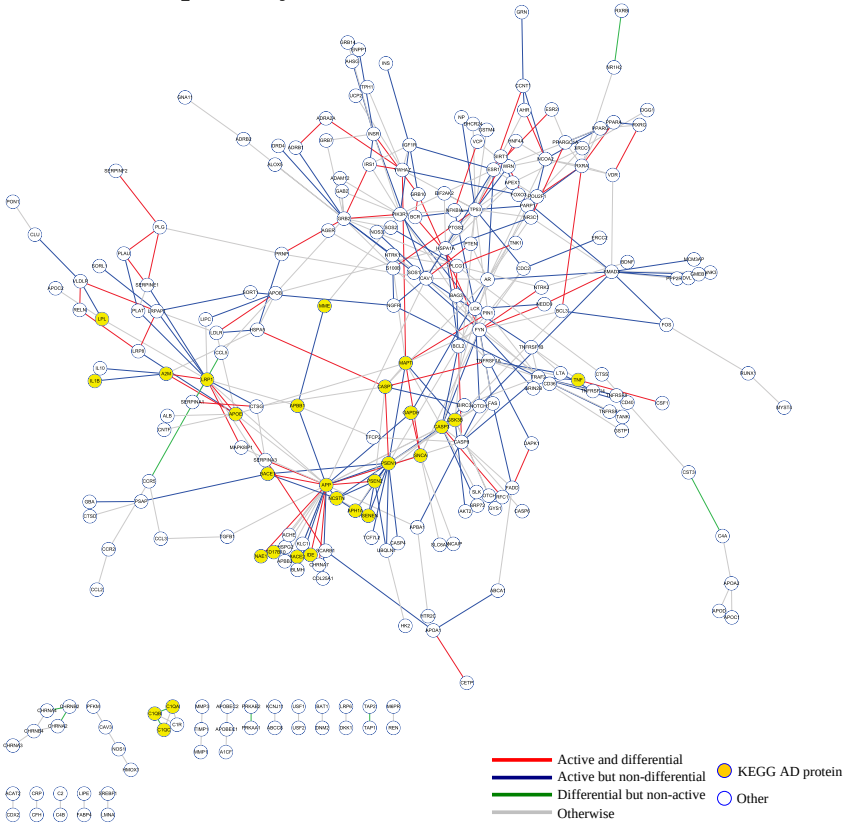


Figure S6.5.2: The active pathway underlying KEGG AD proteins in SFG by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

S6.6 VCX

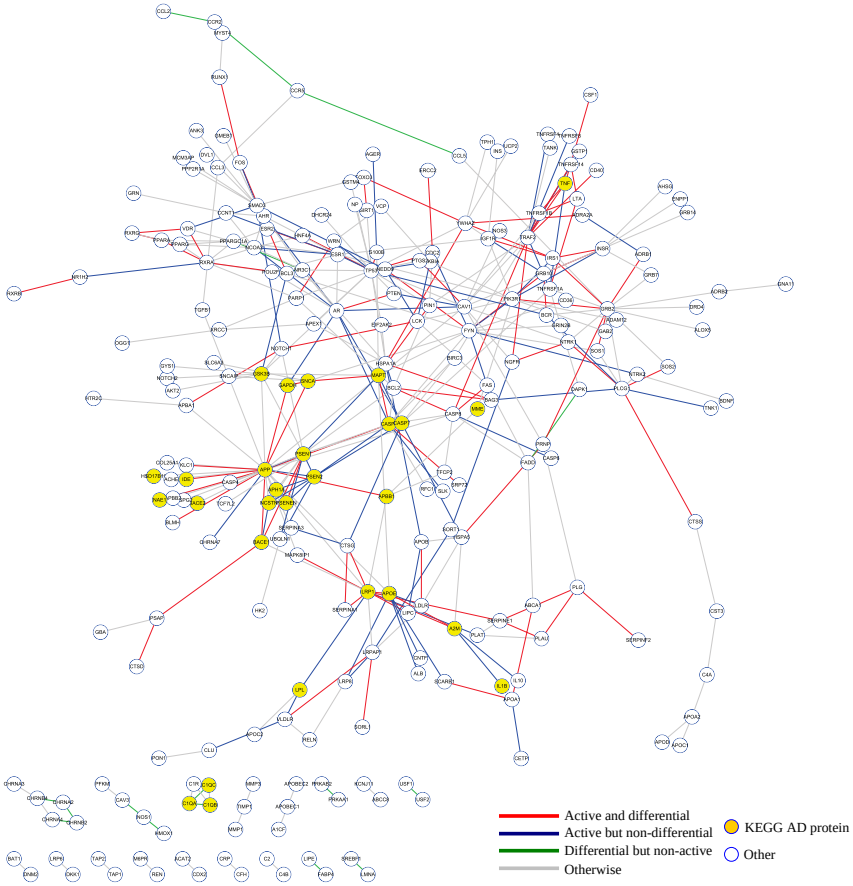


Figure S6.6.1: Identified active pathway of VCX in the ensemble AD protein-protein interaction network by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

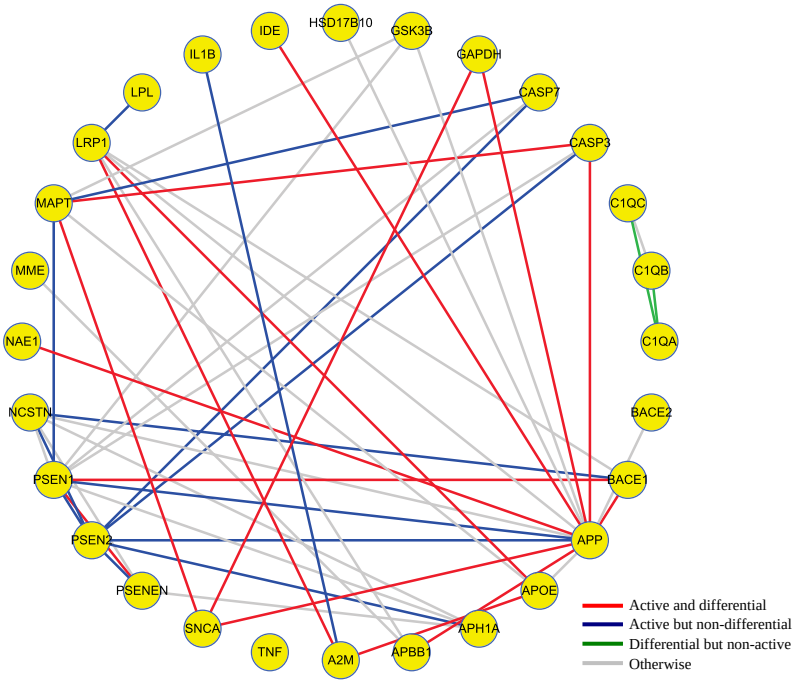


Figure S6.6.2: The active pathway underlying KEGG AD proteins in VCX by correlation scoring scheme. The meaning of the edge color is the same as that in Figure S2.1.1.

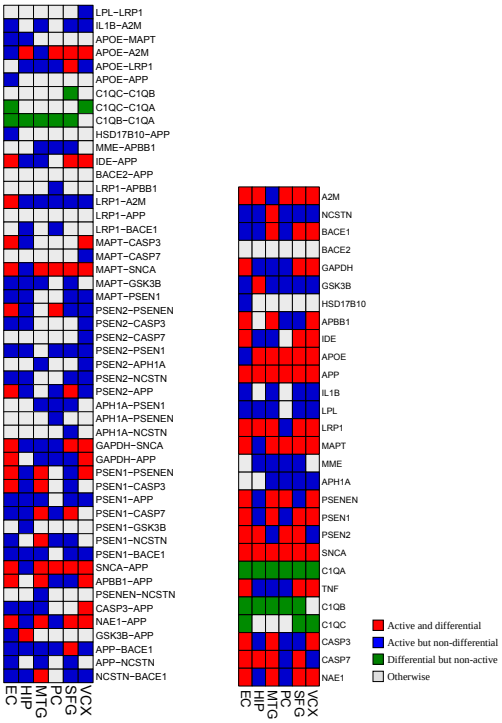
S6.7 Differentially co-expressed edges defined by correlation significance

We also use various thresholds of correlation significance to define the differentially co-expressed edges in the correlation scoring scheme. The number of differentially co-expressed edges is listed in Table S6.7.1. By comparison with Table S3.1, we can find we will identify more differentially co-expressed edges in six AD brain regions when we combine differential expression information with co-expression by Fisher's method.

Table S6.7.1. Number of differentially co-expressed edges defined by various thresholds of correlation significance in six AD brain regions. The number in the bracket is the number of differentially co-expressed edges which are included in the identified pathway in six AD brain regions.

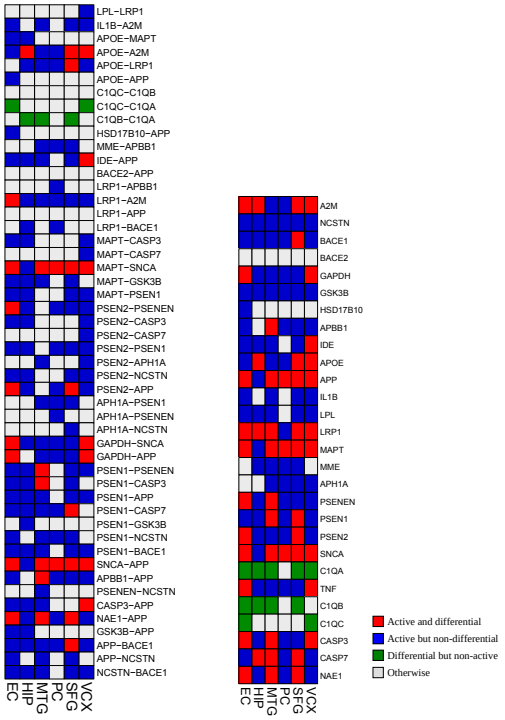
	EC	HIP	MTG	PC	SFG	VCX
0.05	100 (82)	56 (46)	77 (67)	38 (33)	72 (63)	107 (90)
0.025	75 (63)	35 (29)	53 (46)	25 (23)	48 (40)	79 (66)
0.01	49 (40)	17 (14)	34 (28)	10 (10)	34 (29)	58 (45)

We also represent the active pathways underlying KEGG AD proteins in six brain regions in Figure S6.7.1 and Figure S6.7.2 to show their similarities and differences. By comparison with Figure S3.2 and Figure S3.3, we identified fewer 'active and differential' edges (type 1) in six brain regions when use the correlation scoring scheme. We can identify more differentially co-expressed edges by using the Fisher's method to combine the gene expression and co-expression. The results for that of p-value 0.05 have been presented in the text. The following two figures are for that of p-value 0.025 and that of p-value 0.01, respectively.



(a) (b)

Figure S6.7.1: The edges and nodes of identified active pathways underlying KEGG AD proteins in six AD brain regions by the correlation scoring scheme. (a) is for the edges and (b) is for the nodes. The ensemble interactions are represented in four different colors by their memberships in different AD brain regions. The differentially co-expressed edges are those correlation scores with p-value smaller than 0.025.



(a) (b)

Figure S6.7.2: The edges and nodes of identified active pathways underlying KEGG AD proteins in six brain regions by the correlation scoring scheme. (a) is for the edges and (b) is for the nodes. The ensemble interactions are represented in four different colors by their memberships in different AD brain regions. The differentially co-expressed edges are those correlation scores with p-value smaller than 0.01.

S7. Active pathways from disease to control

We also identify the activated pathways from the disease to the control case, part of which can be considered as the depressed pathways from the control to the disease state. We use the depressed information of two genes from the control to the disease (p-values of Welch's lower-tailed t-test) and the correlation between them in the control state (p-value of association test) to score the interaction between the two corresponding proteins in normal brain regions. Similarly, we combine the differential expression p-values and co-expression p-value by Fisher's method. The results of identified pathways in six brain regions are shown in the following figures.

S7.1 EC

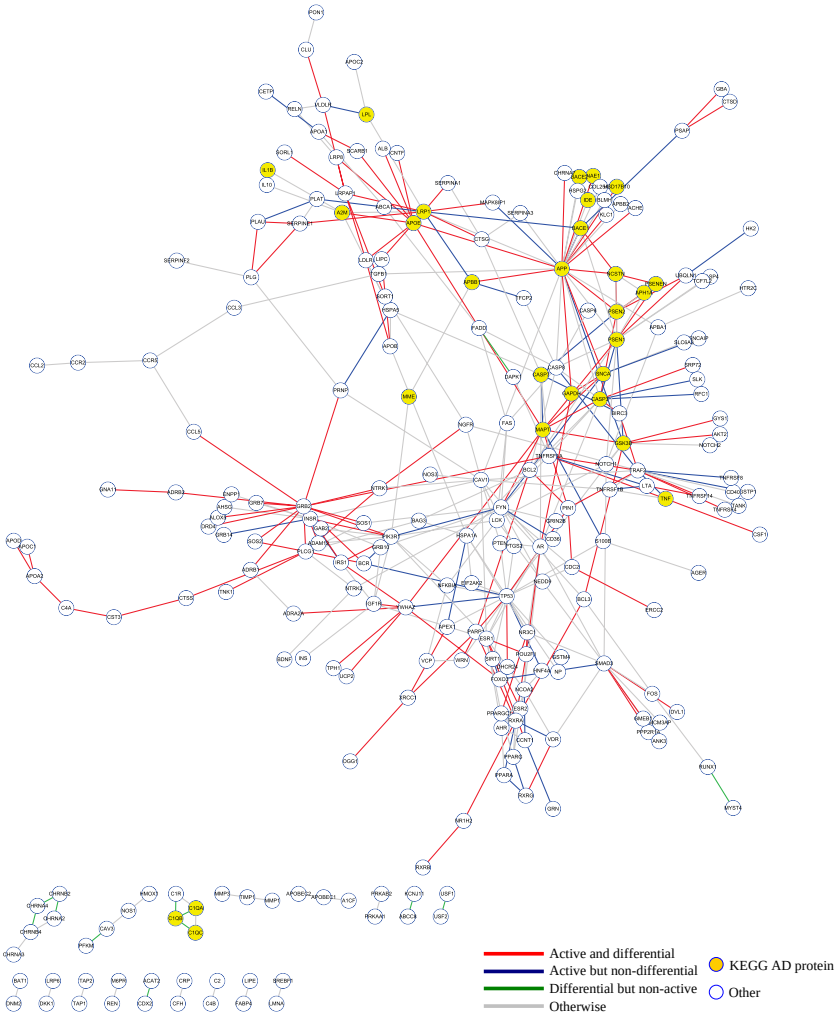


Figure S7.1.1: Identified active pathway of EC in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

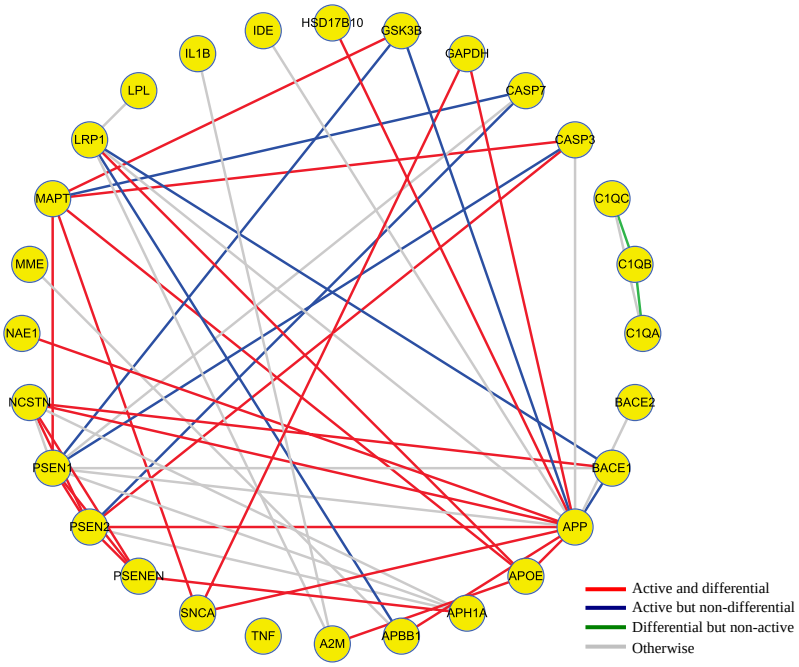


Figure S7.1.2: The active pathway underlying KEGG AD proteins in EC from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1..

S7.2 HIP

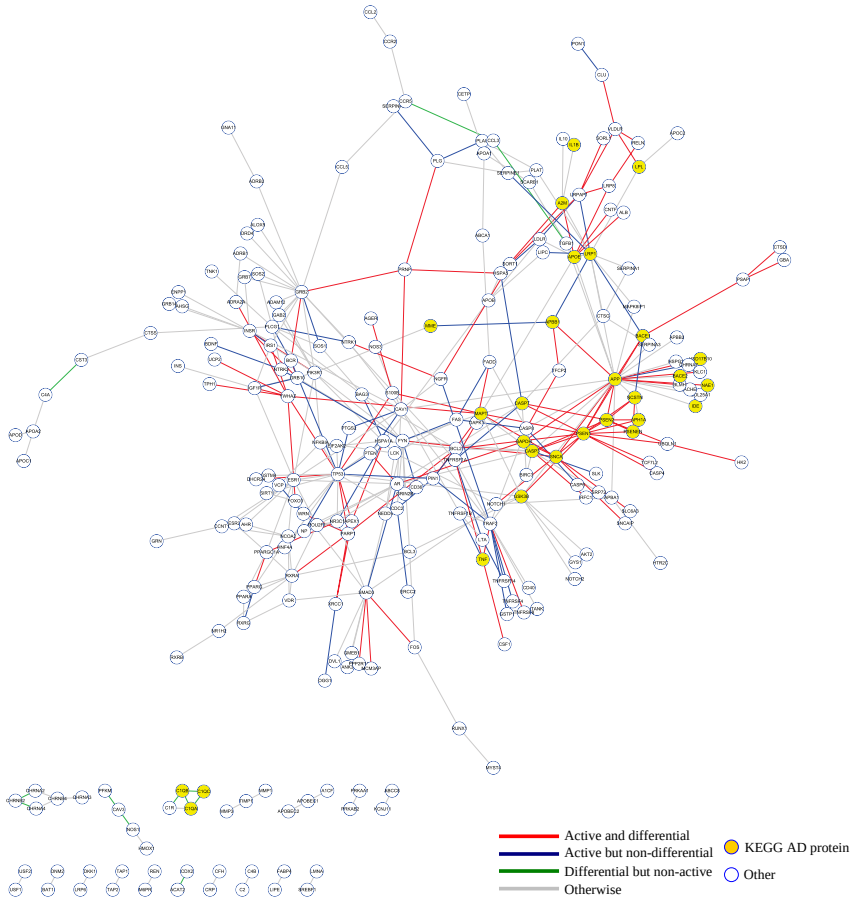


Figure S7.2.1: Identified active pathway of HIP in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1..

The identified pathway underlying KEGG AD proteins

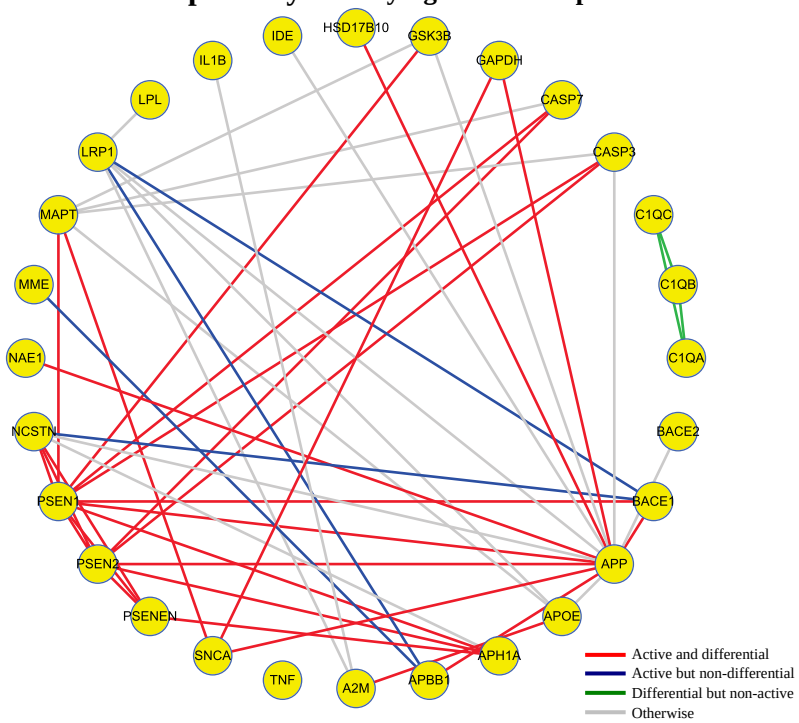


Figure S7.2.2: The active pathway underlying KEGG AD proteins in HIP from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

S7.3 MTG

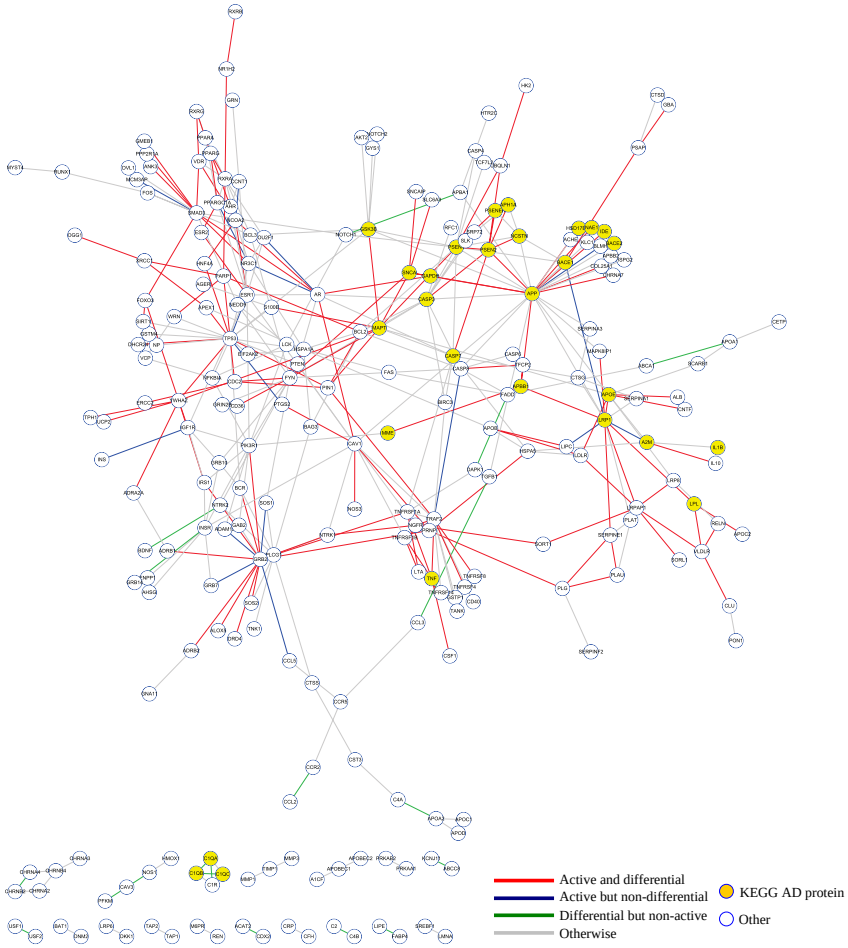


Figure S7.3.1: Identified active pathway of MTG in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1..

The identified pathway underlying KEGG AD proteins

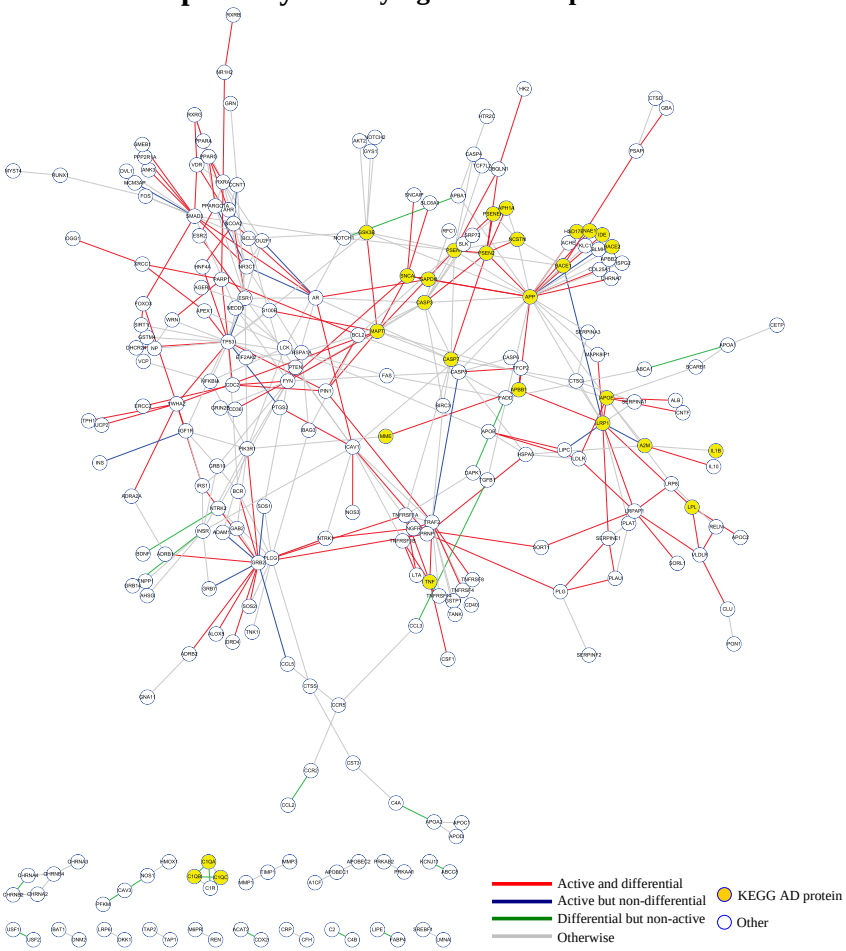


Figure S7.3.2: The active pathway underlying KEGG AD proteins in MTG from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

S7.4 PC

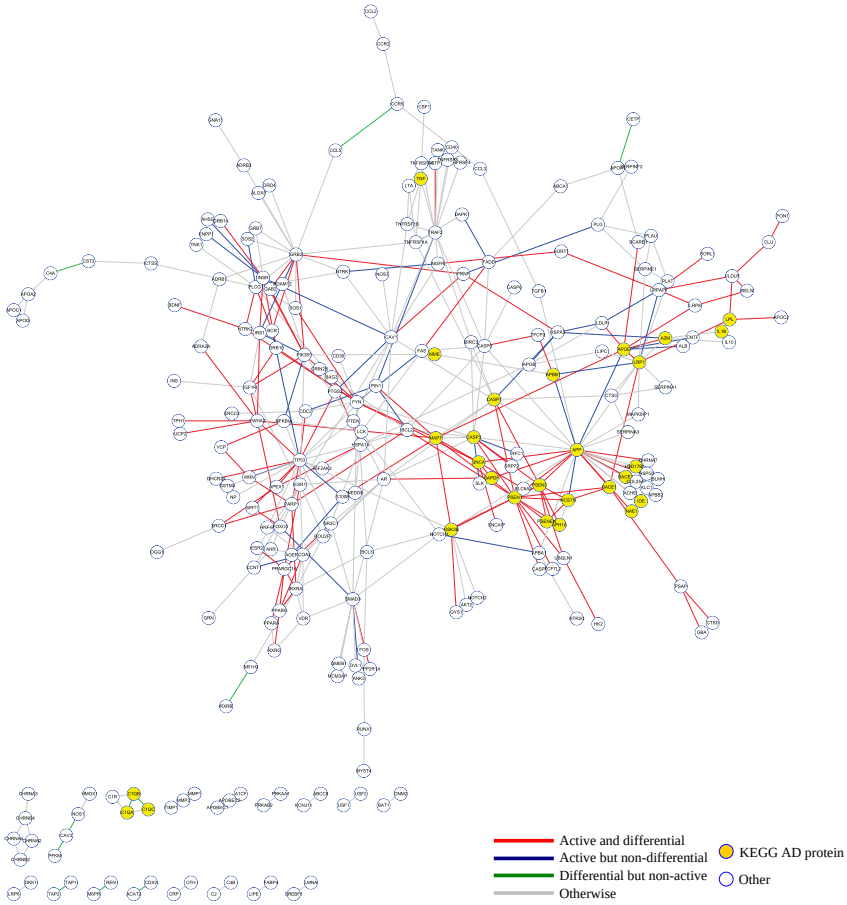


Figure S7.4.1: Identified active pathway of PC in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

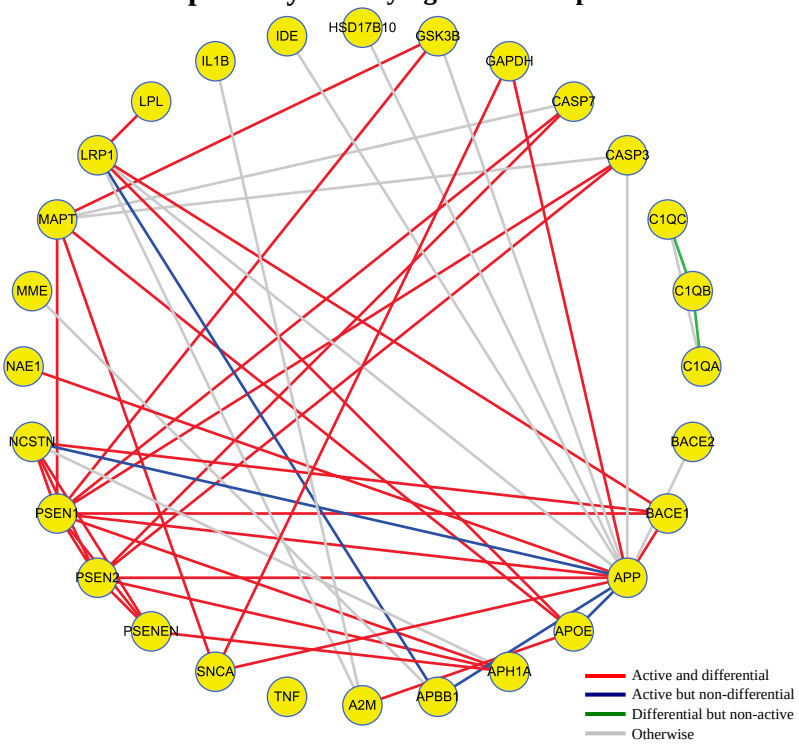


Figure S7.4.2: The active pathway underlying KEGG AD proteins in PC from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

S7.5 SFG

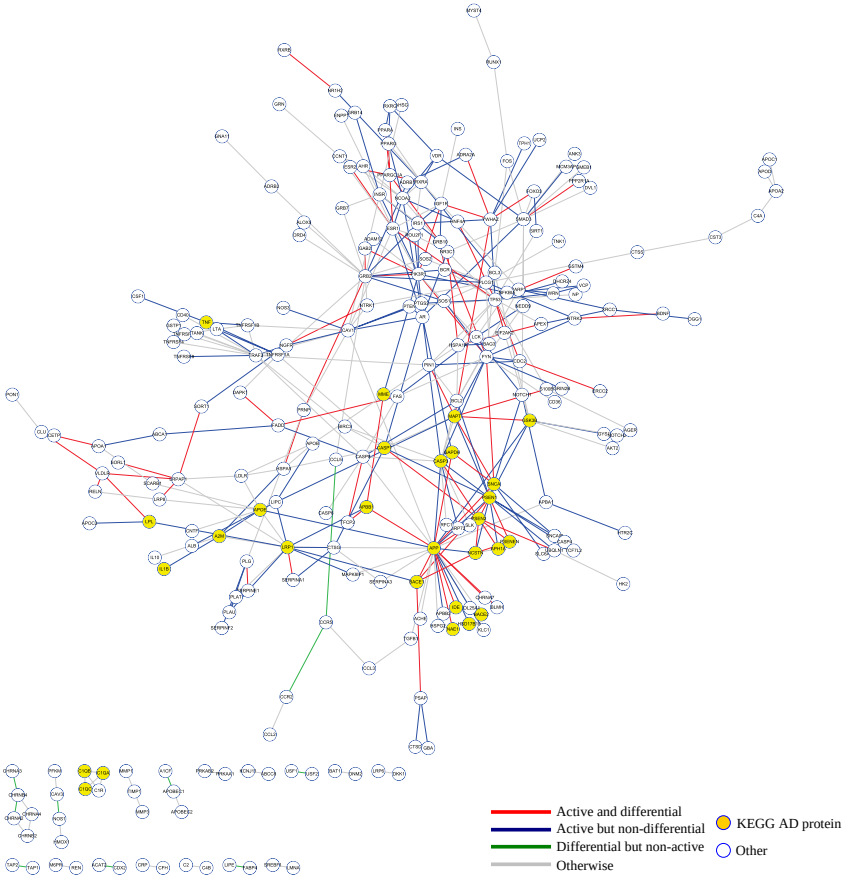


Figure S7.5.1: Identified active pathway of SFG in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

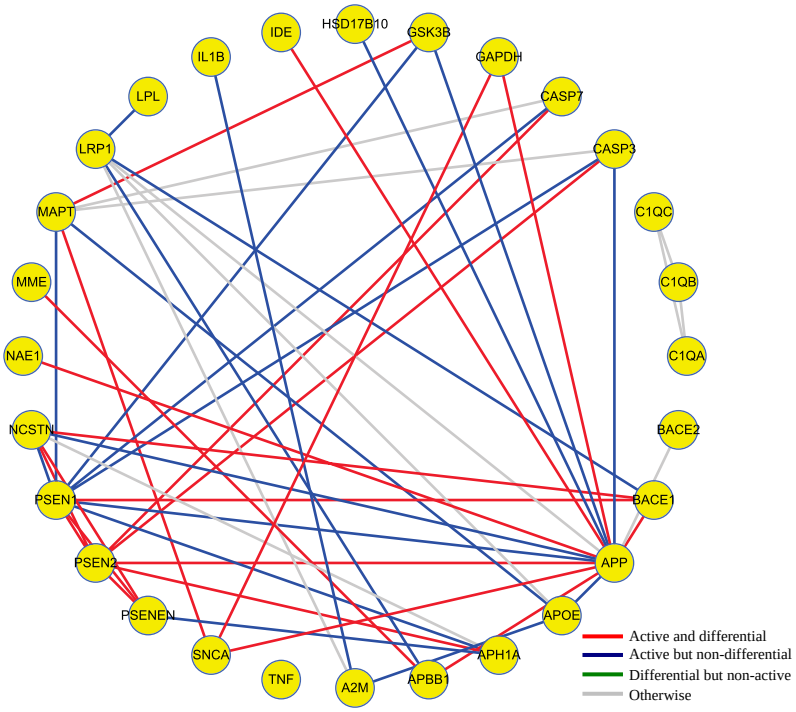


Figure S7.5.2: The active pathway underlying KEGG AD proteins in SFG from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

S7.6 VCX

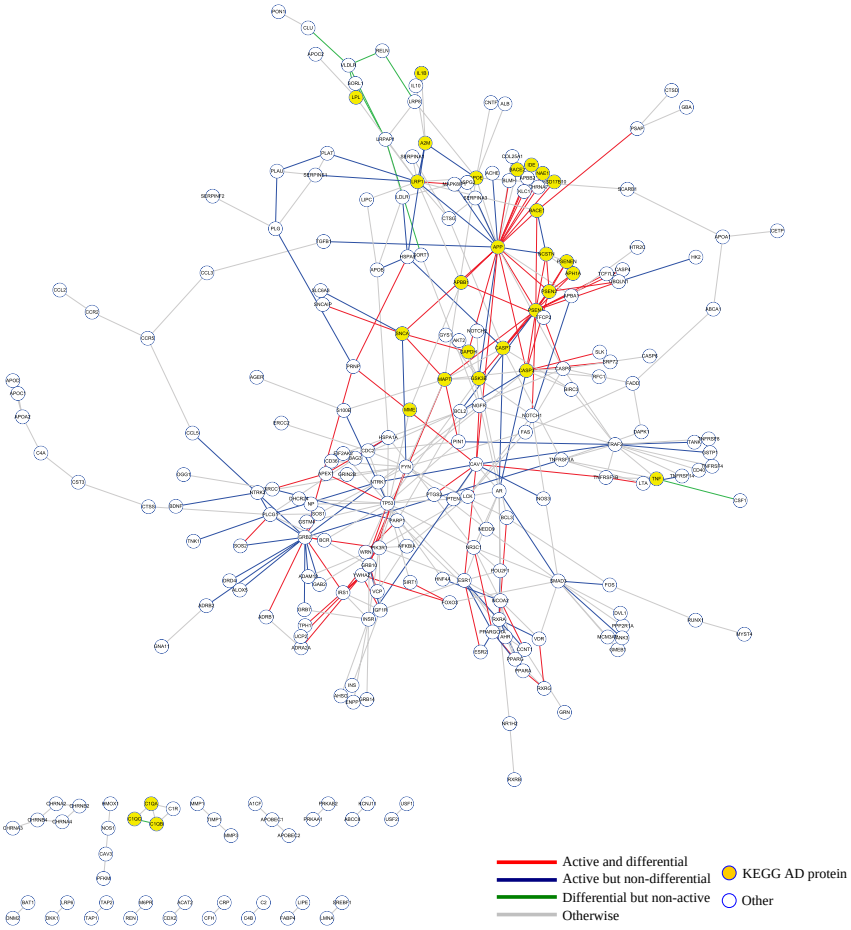


Figure S7.6.1: Identified active pathway of VCX in the ensemble AD protein-protein interaction network from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

The identified pathway underlying KEGG AD proteins

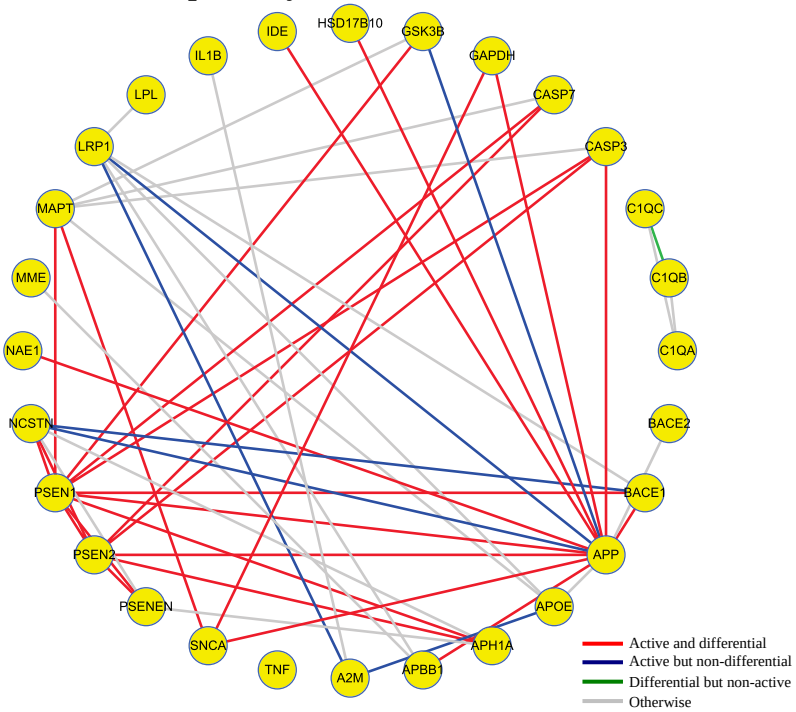


Figure S7.6.2: The active pathway underlying KEGG AD proteins in VCX from disease to control. The meaning of the edge color is the same as that in Figure S2.1.1.

S8. More discussion about the hub proteins

In our proposed algorithm, we have implemented an edge-extension scheme to grow the active pathway from the high-scored edges. The edges with higher ranks are more likely to be chosen in the significant subnetwork. We apply Fisher's method to combine the p-values of gene expressions of the two connected proteins in protein network and p-value of their correlation together to score the edge. That is to say, the rank of the edge's score in the weighted protein-protein interaction network will not be affected by the degree of the two proteins, and the score on an edge has no direct relationship with hub proteins. To an extreme example in following Figure S8.1, one protein is a hub (Node 5) and it has the largest number of partners in the network. If the scores of its connected edges are all very low-ranked, our algorithm does not have the preference to choose to the hub proteins in the significant subnetwork. If there are more high-scored edges in the right road-like part, the hub protein (Node 5) would not be chosen in the identified active pathway.

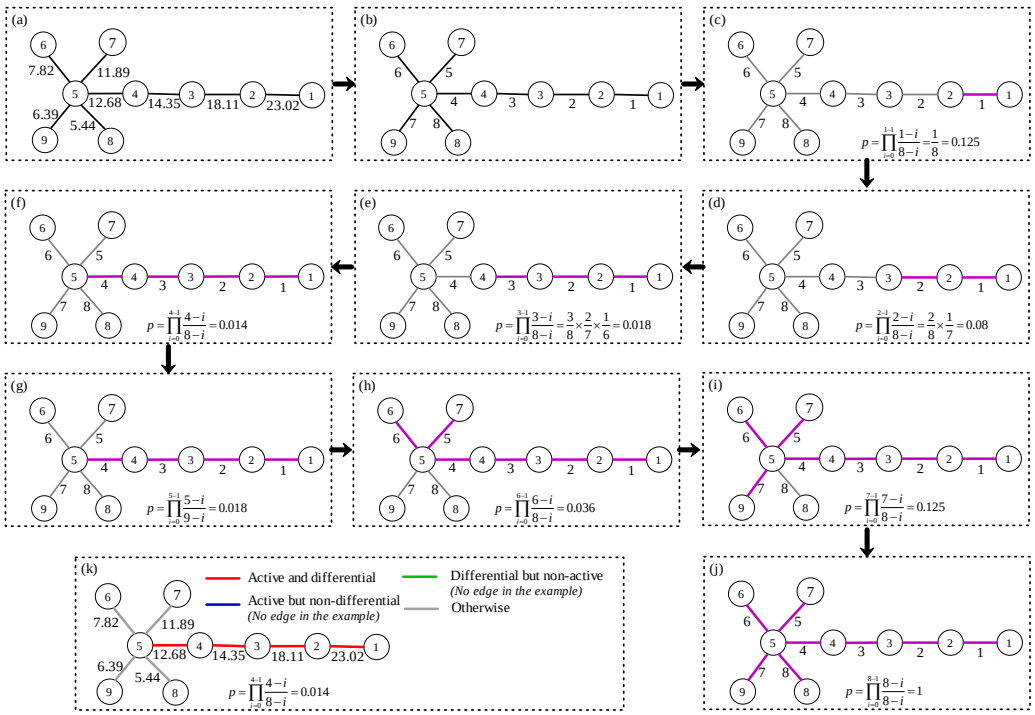


Figure S8.1: An example showing that there is no preference in our algorithm to select hub protein in the active pathway.

This provides evidence that our scoring scheme of edge and the algorithm to identify the active pathways bias are not biased of choosing the hub proteins. In real protein-protein interaction networks, we think that the possibility of a hub protein tends to be included in a significant subnetwork is that hub protein may have more chance to be highly coexpressed with its partners because it has more

partners than the other proteins. It would connect to the high-scored edges with more possibility. Furthermore, we correlate the degree of a protein and the scores of its incident edge. The results are shown in the following Figure S8.2 (a) which shows there is no clear correlation. We use two methods to find the high-scored edges. The first one is to get the edge with the maximal score in all the node's incident edges ('Maximum'). The second one is to get the average value of the scores on its incident edges. We find that the proteins with high degree (hubs) weakly tend to related to high scores. Moreover, we identified the distributions of degree in the AD-related protein-protein interaction network and that in the identified active pathway in EC region. We find that the distribution of degree in 'AD protein interactions' has not been changed obviously compared to that in 'Active pathway in EC'. In these identified pathways, most of hub proteins as well as the nodes with low degree are also contained in the active pathway. This provides evidence for the importance of these hub proteins. In Taylor's work (Nature Biotechnology, 2009), the authors focused on these hubs of protein network and study the dynamics of modules connected and derived by these hub proteins. They classified them into intermodular hubs and intramodular hubs. These topological important proteins are used to correlate with the breast cancer outcome. In our method, we aim to identify the active pathways in AD brain regions by growing from the highest-scored edges. The protein degree has no influence to the edge score and then the bias of degree does not exist in our method.

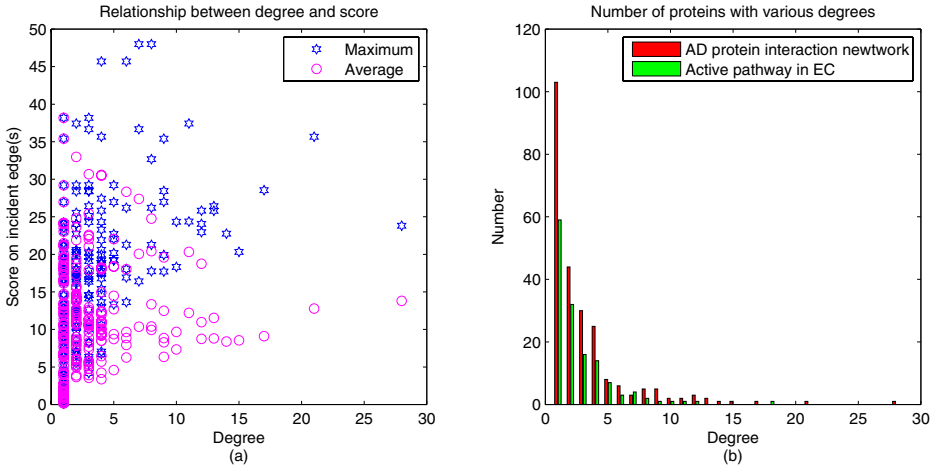


Figure S8.2: (a) Statistics of relationship between degree of node and its incident score of edge. (b) Degree distribution in AD protein interaction network and the identified active pathway in EC region.

S9. Gene expression profiles of AD proteins in six brain regions

The gene expression in six brain regions would imply the regional expression patterns. Temporarily, we identified the differential expression information of AD genes. The results are shown in Figure S9.1 and Table S9.1. In future, we can identify and analyze the whole AD dysfunctional transcriptome in various brain regions.

In KEGG AD proteins

EC	HIP	MTG	PC	SFG	VCX	
0	0.87	0	0.68	0	0.23	A2M
0.95	0.19	0	0.02	0.02	0.15	NCSTN
0.96	0.98	0.82	1	0.98	0.92	BACE1
0.06	0	0	0	0	0.01	BACE2
1	1	1	1	0.59	0.95	GAPDH
0.99	0	0.47	0.65	0.42	0.36	GSK3B
1	1	0.01	0.94	0.32	0.23	HSD17B10
0.98	0.99	1	0.94	0.95	0.41	APBB1
0.21	0.97	1	0.76	0.86	0.95	IDE
1	0.9	0.05	0.99	0	0.02	APOE
0.04	0.08	0.01	0.64	0.24	0.99	APP
0.06	0.01	0.24	0.13	0.98	0.7	IL1B
0.01	0.86	0.98	1	0.92	0.75	LPL
0.83	0.02	0.98	0.29	0.15	0	LRP1
0.99	0.16	0.99	0.8	0.36	0.52	MAPT
0.09	0.21	0.93	0	0.98	0.06	MME
0	0.25	0	0.02	0.1	0.13	APH1A
1	1	0.99	1	0.98	0.94	PSENEN
0.62	1	0.38	1	0.96	1	PSEN1
0.99	1	1	1	1	1	PSEN2
0.83	1	1	1	0.97	0.99	SNCA
0.55	0.46	0.91	0.63	0.1	0.02	C1QA
0.36	0.89	1	0	0.88	0.49	TNF
1	0.67	0.25	0.95	0.46	0.26	C1QB
0.4	0.45	0.1	0.24	0	0.05	C1QC
0.93	0.53	0.08	0.25	0.06	0.92	CASP3
0.02	0.18	0	0.56	0	0.09	CASP7
0.9	1	1	1	0.93	0.97	NAE1

Figure S9.1: Differential gene expression status of KEGG AD genes. The values are the p-values of Welch's upper-tailed t-test from control to disease in six brain regions individually. The red rectangle indicates that the gene is significantly expressed (p-value < 0.05).

Table S9.1: Differential expression status of the AD genes in six brain regions. The value means the same as that in Figure S9.1.

Gene	EC	HIP	MTG	PC	SFG	VCX
TANK	0.04	0.16	0.24	0.96	0.76	0.99
CDX2	0.59	0.13	1	0.1	0.89	0.28
NCOA2	0	0	0.99	0.02	0.25	0.3
GMEB1	1	0.08	0.98	0.09	0.7	0.84
CETP	0	0.03	0.05	0.24	0.67	0.08
PPARGC1A	0.36	0.96	0.97	1	1	0.99
APOBEC2	0	0.02	0.03	0.01	0.7	0.12
CHRNA2	0.16	0.82	0.59	0.08	0.92	0.01
CHRNA3	0.64	0	0.18	0	0.78	0.09
CHRNA4	0.97	0.2	0.98	0.07	0.29	0.02
CHRNA7	1	0.7	1	1	0.98	0.99
CHRNB2	0.98	0.99	0.94	0.25	0.35	0
CHRNB4	0.62	0.01	0.7	0	0.74	0.01
CLU	0.88	0.97	0.04	1	0.06	0.01
SERPINA3	0	0.28	0.06	0.15	0.01	0.45
CCR2	0.01	0.86	0.97	0	0.87	0.01
CCR5	0.03	0	0.01	0.01	0.87	0.09
CNTF	0.05	0.86	1	0.03	0.62	0.01
CRP	0.07	0.03	0.99	0.31	0.65	0.01
PARP1	1	1	1	1	0.86	0.94
CSF1	0.26	0	0.5	0	0.17	0
CST3	1	0.94	0	0.97	0.01	0.02
ADRA2A	0.63	0.94	0.17	0.87	0.74	0.68
CTSD	1	0.87	0.39	0.98	0.89	0.22
CTSG	0.09	0.28	0.12	0.06	0.81	0.3
CTSS	0.01	0.11	0	0	0.52	0.01
ADRB1	0.15	0.01	0	0.07	0.02	0.33
ADRB2	0	0.4	0.01	0.4	0	0.63
DAPK1	0.61	1	0.94	0.95	0.51	0.95
DHCR24	1	1	1	1	0.99	0.97
AGER	0.74	0.07	0.96	0.4	0.08	0.11
DNM2	0.77	0	0.19	0	0.19	0.01
DRD4	1	0.02	0.72	0.2	0.63	0.29
DVL1	1	0	0	0	0	0
ABCA1	0	0.4	0.06	0.09	0.01	0.01
AHR	0.61	0.02	0.02	0.03	0.1	0.59
AHSG	0.57	0.02	0.99	0.69	0.92	0.06
A2M	0	0.87	0	0.68	0	0.23
ERCC2	1	0.94	0.98	0.02	0.82	0.7
AKT2	0.94	0.09	0.08	0	0.01	0.12
ESR1	0.55	0.12	0.71	0.02	0.27	0.02
ESR2	0.01	0.13	1	0.01	0.59	0.06
ALB	0.02	1	1	0.43	0.9	0.48
FABP4	0.08	0.98	0.97	0.02	0.98	0.19
DKK1	0.03	0.12	0.45	0.96	0.84	0.91

FOXO3	0.76	0.08	0.99	0.97	0.37	0.96
NCSTN	0.95	0.19	0	0.02	0.02	0.15
SIRT1	0.01	0.28	0	1	0.03	0.65
MYST4	0.99	0	0	0.05	0	0.56
FOS	0.02	0.76	0.07	0.27	0.07	0.96
BACE1	0.96	0.98	0.82	1	0.98	0.92
ALOX5	1	0.05	0.53	0.05	0.4	0.45
FYN	0.39	0.62	0	0.96	0	0.01
BACE2	0.06	0	0	0	0	0.01
GAPDH	1	1	1	1	0.59	0.95
GBA	1	1	1	0.92	0.7	0.03
GNA11	1	0.1	0	0.27	0	0.55
ANK3	0.19	0.17	0.97	0.97	0.24	0.94
GRB2	1	0.01	1	0.89	0.3	0.99
GRB7	0	0.01	0.02	0	0.03	0.24
GRB10	0	0.87	0.02	1	0.08	0.48
GRB14	0.99	0.19	1	0.96	0.73	0.81
GRN	0.92	0.82	0.73	0.86	0.54	0.01
GRIN2B	0	0.01	0.93	0.26	0.98	0.29
NR3C1	0.23	0.03	0.01	0.63	0.24	0.73
GSK3B	0.99	0	0.47	0.65	0.42	0.36
GSTM4	0.07	0.07	0.03	0.74	0.84	0.03
GSTP1	0.86	0.96	0.39	1	0.31	0.84
GYS1	1	0.88	0.02	0.47	0.42	0.49
A1CF	0.3	0.04	0.39	0	0.61	0.07
UBQLN1	0.99	0.99	1	0.99	0.84	0.99
CFH	0.22	0.63	0.01	0.6	0	0.56
HK2	0	1	0.98	0.1	0.34	0.02
HMOX1	0.02	0.09	0.07	0.53	0.16	0.19
HNF4A	0.93	0.01	0.83	0	0.72	0.1
APBA1	0.59	0.59	0.97	0.01	0.7	0.04
APBB1	0.98	0.99	1	0.94	0.95	0.41
APBB2	0.02	0.64	0.03	0.07	0.65	0.48
APEX1	0.99	1	0.99	1	0.86	1
BIRC3	0.99	0.79	0.11	0.08	0.12	0.02
HSPA1A	0.01	0.65	0	0.31	0	0.38
HSPA5	0.05	0.95	0.17	0.99	0.12	0.99
HSPG2	0.95	0.41	0.92	0.02	0.52	0.04
APOA1	0.84	0.01	0.46	0.05	0.13	0.01
HTR2C	0.97	0.76	0.63	0.91	0.98	0.3
APOA2	1	0.47	0.99	0.03	0.9	0.03
APOB	0.09	0.11	0.06	0.01	0.62	0.01
APOC1	0.75	0.35	0	0	0.01	0.01
IDE	0.21	0.97	1	0.76	0.86	0.95
APOC2	0.61	0.32	0.97	0.2	0.86	0.05
APOD	0.98	0.13	0.12	0.62	0.02	0.09
APOE	1	0.9	0.05	0.99	0	0.02
IGF1R	0	0	0	0.01	0	0.07

APP	0.04	0.08	0.01	0.64	0.24	0.99
FAS	0.19	0.93	0.09	0.54	0.14	0.48
IL1B	0.06	0.01	0.24	0.13	0.98	0.7
IL10	0.94	0.74	1	0.02	0.83	0.01
INS	0.66	0.47	1	0.2	0.68	0.03
INSR	0	0.73	0.01	0.98	0.01	0.07
IRS1	0.52	0.83	0.06	0.94	0.34	0.85
AR	0.71	0.87	0.96	0.07	0.94	0.01
KCNJ11	0.98	0.43	0.75	0.27	0.25	0.08
KLC1	0.95	1	0.94	1	0.36	0.86
ACAT2	1	1	0.99	1	0.99	0.94
LCK	0.32	0.17	0.07	0	0.43	0
LDLR	0.86	0.6	0.95	0.03	0.02	0.2
LIPC	1	0.77	0.36	0.07	0.21	0.11
LIPE	0.72	0.01	0.82	0	0.57	0.07
LMNA	0.47	0.38	0.63	0	0.01	0.05
LPL	0.01	0.86	0.98	1	0.92	0.75
LRP1	0.83	0.02	0.98	0.29	0.15	0
LRP6	0.01	0	0	0.4	0	0.31
LRPAP1	1	0.98	1	0.99	0.25	0.9
LTA	0.2	0.37	1	0.03	0.22	0.03
M6PR	0.98	0.99	0.87	1	0.76	0.99
SMAD3	0.43	0.72	0.94	0.72	0.58	0.39
MAPT	0.99	0.16	0.99	0.8	0.36	0.52
ACHE	1	0.27	1	0.33	0.64	0
MME	0.09	0.21	0.93	0	0.98	0.06
MMP1	0.4	0.25	0.79	0.07	0.13	0.04
MMP3	0.3	0.19	0.78	0.15	0.97	0.15
NEDD9	0	0.03	0	0.06	0.54	0.46
NFKBIA	0	0.01	0	0	0	0
NGFR	0.1	0.73	0.98	0.82	0.9	0.01
NOS1	0.63	0.01	0.91	0	0.76	0.3
NOS3	0.98	0.78	1	0.97	0.89	0.07
NP	0.04	0.98	0.05	0.85	0.06	0.78
NTRK1	0.97	0.89	0.95	0.46	0.6	0.04
NTRK2	0	0.21	0	0.93	0.02	0.68
OGG1	0.97	0	0	0.2	0	0
SERPINE1	0.12	0.49	0.97	0.01	0.67	0.02
APH1A	0	0.25	0	0.02	0.1	0.13
ENPP1	0.99	0.01	0.05	0.03	0.66	0
PFKM	1	1	1	1	0.57	0.97
SERPINA1	0.06	0	0.38	0.02	0.64	0.02
PIK3R1	0.01	0	0.88	0.9	0.29	0.97
PIN1	1	0.99	1	0.99	0.55	0.95
PLAT	0.39	0.6	0	0.59	0	0.82
PLAU	0.93	0.02	0.98	0.17	0.29	0.72
PLCG1	0.96	0	0	0	0	0.01
PLG	0.47	0.02	0.98	0.01	0.6	0.04

SERPINF2	0.61	0.32	0.6	0	0.08	0.06
PON1	0.06	0.49	0.99	0.27	0.89	0.05
POU2F1	1	0.02	0	0.45	0.02	0.28
PPARA	0	0.27	0	0.07	0	0.01
PPARG	0.94	0.95	1	1	0.92	0.44
PPP2R1A	0.99	1	1	1	1	0.84
PRKAA1	0.16	0.81	0.23	0.71	0.58	0.94
PRKAB2	0.35	0.06	0.15	0.64	0.12	0.86
PSENEN	1	1	0.99	1	0.98	0.94
EIF2AK2	0.49	0.24	0.81	0.01	0.71	0.23
PRNP	0.21	1	1	1	0.61	0.99
RELN	0.33	0.72	0.04	0.99	0.41	0.94
PSAP	0.72	1	0.4	1	0.39	0.84
PSEN1	0.62	1	0.38	1	0.96	1
PSEN2	0.99	1	1	1	1	1
PTEN	0.48	1	0.86	0.52	0.43	0.16
PTGS2	0.8	0.9	1	0.97	0.94	0.98
BCL2	0	0.21	0.72	0.2	0.01	0.02
REN	0.46	0.43	0.82	0.05	0.68	0.18
RFC1	0.2	0.99	0.84	1	0.34	0.71
BCL3	0.95	0	0.41	0.01	0.01	0.05
BCR	0.99	0.99	0.02	0.99	0.14	0.54
RXRA	0.1	0.07	0.04	0.13	0	0
RXRB	0.92	0.64	0.98	0.03	0.98	0.17
RXRG	0.89	0.15	0.91	0.69	0.28	0.02
BDNF	0.83	0.96	1	1	1	0.98
SORT1	0.38	1	0.96	1	0.47	0.94
S100B	0	1	0	0.99	0.12	0.57
CCL2	0.01	0.37	0	0.05	0.03	0.45
CCL3	0.08	0.98	1	0.3	0.84	0.49
CCL5	0.28	0	0.01	0	0.19	0.02
BLMH	0.17	1	0.99	0.99	1	1
SLC6A3	0.09	0.29	0.9	0.01	0.38	0.02
SNCA	0.83	1	1	1	0.97	0.99
SORL1	0.32	0.96	0.95	0.99	0.32	0.99
SOS1	0.33	0.03	0.35	0.61	0.44	0.91
SOS2	0.12	0	0.51	0	0.08	0
SREBF1	0.27	0.12	0.01	0.06	0	0.13
SRP72	1	0.18	0.15	1	0.57	1
ABCC8	1	0.6	1	0.88	0.1	1
TAP1	0.01	0.45	0	0.15	0	0.03
TAP2	0.28	0.98	0.87	0.8	1	0.95
TCF7L2	0.09	0	0	0.16	0.01	0.8
TFCP2	0.73	1	1	1	1	1
TGFB1	0.82	0.11	0.99	0.01	0.69	0.15
TIMP1	0.14	0.88	0.02	0.08	0	0.09
TNF	0.36	0.89	1	0	0.88	0.49
TNFRSF1A	0	0.85	0	0.01	0	0.02

TNFRSF1B	0.09	0.16	0	0.11	0	0.03
C1R	0.15	0.77	0.46	0.03	0.04	0.23
TP53	0.05	0.16	0.17	0	0.16	0.01
TPH1	0.94	0.99	1	0	0.89	0
C2	0.46	0.58	0.98	0.04	0.48	0.26
TRAF2	0.59	0.72	0.98	0.27	0.05	0.13
C4A	0.12	0.33	0	0.01	0	0.03
C4B	0.12	0.33	0	0.01	0	0.03
TNFRSF4	1	0.81	1	0.04	0.79	0.01
UCP2	0.92	0	0	0	0.15	0.02
NR1H2	1	0.9	1	0.96	0.54	0.19
USF1	0.49	0.86	1	0.27	0.84	0.14
USF2	0.21	0	0.06	0.01	0.02	0
VCP	0.57	0.95	0.67	0.99	0.62	0.98
VDR	0.9	0.63	0.99	0.01	0.86	0.02
VLDLR	0.86	0.98	1	0.99	0.98	1
WRN	0.7	0.64	0.36	0.98	0.9	0.99
XRCC1	1	0.99	1	0.6	0.93	0.91
YWHAZ	1	1	1	1	0.94	1
LRP8	0.11	0.99	0.58	0.99	0.17	0.94
BAT1	0.86	0.23	0	0.06	0.02	0.61
ADAM12	0.01	0.49	0.03	0.01	0.3	0.03
CASP3	0.93	0.53	0.08	0.25	0.06	0.92
CASP4	0.19	0.77	0.99	0.21	0.27	0.02
CASP6	0.04	0	0	0	0	0.02
CASP8	0	0.01	0.57	0	0.52	0.02
COL25A1	0.62	0.4	1	0.02	0.74	0.04
CAV1	0	0.11	0	0.13	0	0.94
CAV3	0.12	0.97	1	0.27	0.91	0.13
RUNX1	0.95	0.01	0.94	0	0.41	0.03
TNK1	0.3	0.16	0.8	0.6	0.42	0.26
TNFRSF14	1	0	0	0.02	0	0.1
FADD	0.86	0.87	0.96	0.91	0.98	0.67
MCM3AP	0	1	0.94	0.83	0.84	0.81
CCNT1	0.96	0	0	0	0.01	0.11
TNFRSF8	0.91	0.98	0.98	0.41	0.95	0.21
MAPK8IP1	0.99	0.09	0.8	0	0.11	0
CD36	0.99	0.93	1	0.01	0.84	0
SCARB1	1	0.02	0	0.01	0	0.03
BAG3	0	0.1	0	0.45	0	0.04
CD40	0.18	0.03	0.17	0.02	0.41	0.03
SNCAIP	0.97	0.34	0.04	0.14	0.09	0.02
SLK	0.55	0.98	0.04	0.99	0.64	0.99
CDC2	0.08	0.64	1	0.33	0.99	0.18
GAB2	0	0.64	0	0.99	0.28	0.03
APOBEC1	0	0.02	0.73	0	0.32	0.15
HSD17B10	1	1	0.01	0.94	0.32	0.23
C1QA	0.55	0.46	0.91	0.63	0.1	0.02

C1QB	1	0.67	0.25	0.95	0.46	0.26
C1QC	0.4	0.45	0.1	0.24	0	0.05
CASP7	0.02	0.18	0	0.56	0	0.09
NAE1	0.9	1	1	1	0.93	0.97
NOTCH1	0.02	0.17	0.11	0.11	0.01	0.01
NOTCH2	0	0.63	0	0.03	0	0

S10. Active pathways in the whole human protein-protein interaction network

We have implemented our algorithm to the complete PPI network to identify the active pathways. We found that our methods can identify some of the AD proteins which are included in the active pathways. So far, our knowledge about AD is only limited in these AD proteins. In this work, we analyzed the active pathways in these proteins with focus on the active pathways underlying KEGG AD proteins to interpret our results. To interpret the rest of the protein interactions as well as the pathways beyond the collected AD proteins is an interesting research direction. The following Table S10.1 shows the number of these identified active pathways and the number of AD proteins and interactions which are involved in these active pathways. The details of the active pathway are available at: http://www.aporc.org/doc-files/ADR/src/activepathwayinwholeppi.xls. For comparison, we also identified the active pathways by jActivemodules. The results are also shown in Table S10.1.

Table S10.1: The number of edges/nodes in these active pathways identified from the whole human protein-protein interaction network. Also the number of edges and nodes of these active pathways are involved in AD related proteins as well as in KEGG AD proteins are also shown. There are 7,496 proteins with gene expression information and 22,276 interactions in these proteins. We identified the active pathways in various regions individually. For example, in EC region, there are 2,070 edges and 1569 nodes are involved in the active pathway. There are 156/86 interactions/proteins of the 381/243 AD proteins/interactions are involved in the active pathway respectively.

	EC	HIP	MTG	PC	SFG	VCX
In whole protein-protein interactions (22276/7496)						
Our method	2070/1569	2089/1613	2010/1436	2090/1548	2065/1573	2130/1614
jActiveModules	2032/738	2038/809	2451/885	2856/1062	1254/508	1022/389
Underlying AD proteins (381/243)						
Our method	152/98	170/110	165/103	155/94	157/101	118/87
jActiveModules	48/50	54/77	33/43	48/58	29/36	23/28