Coexpedia Tutorial

Contents

Data content of Coexpedia

Co-expression links inferred from GEO data

- Coexpedia contains co-expression links inferred from microarray data of the main data depository, Gene Expression Omnibus (GEO).

- Human

  We analyzed 2,622 GEO series which contains at least 12 samples , comprising 181,142 samples based on 5 platforms:
  - Affymetrix Human Genome U133A Array (GPL96)
  - Affymetrix Human Genome U133 Plus 2.0 Array (GPL570)
  - Affymetrix Human Genome U133A 2.0 Array (GPL571)
  - Affymetrix HT Human Genome U133A Array (GPL3921)
  - Affymetrix Human Gene 1.0 ST Array [transcript version] (GPL6244)

- Mouse

  We analyzed 2,468 GEO series which contains at least 12 samples, comprising 76,002 samples based on 5 platforms:
  - Affymetrix Mouse Expression 430A Array (GPL339)
  - Affymetrix Mouse Genome 430 2.0 Array (GPL1261)
  - Affymetrix Mouse Gene 1.0 ST Array (GPL6246)
  - Affymetrix Mouse Genome 430A 2.0 Array (GPL8321)

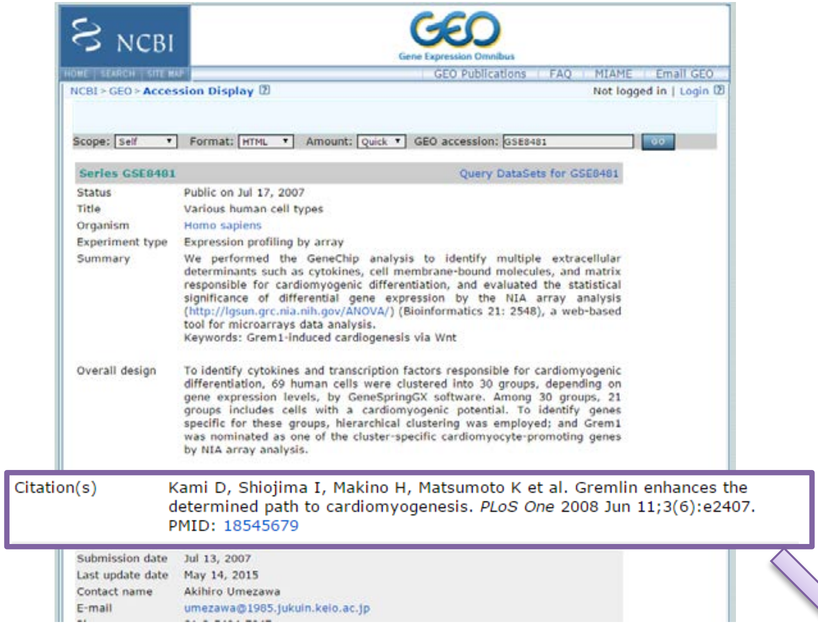
- We used R packages ‘affy’ and ‘oligo’ to obtain and normalize raw gene expression values and normalized them using MAS5 and RMA normalization.

- Finally, we selected 384 and 248 co-expression networks from each GEO series for human and mouse.
  - 384 human GSEs(GEO Series) are from HumanNet v2 project (unpublished data).
  - 183 mouse GSEs from MouseNet v2 (Eiru Kim *et al.* Nucleic Acids Res. 2015) and additional 63 mouse GSEs are selected.

- The constructed co-expression networks of each selected GEO series are consisted of co-expressed gene pairs which have log-likelihood scores (LLS) as edge weights.(Lee *et al.*, Science 2004).

Associated biomedical context information

A GEO series(GSE) has PubMed information if it is based on publication.



Series GSE8481 Query DataSets for GSE8481

Status	Public on Jul 17, 2007
Title	Various human cell types
Organism	Homo sapiens
Experiment type	Expression profiling by array
Summary	We performed the GeneChip analysis to identify multiple extracellular determinants such as cytokines, cell membrane-bound molecules, and matrix responsible for cardiomyogenic differentiation, and evaluated the statistical significance of differential gene expression by the NIA array analysis (http://lgsun.grc.nia.nih.gov/ANOVA/) (Bioinformatics 21: 2548), a web-based tool for microarrays data analysis. Keywords: Grem1-induced cardiogenesis via Wnt
Overall design	To identify cytokines and transcription factors responsible for cardiomyogenic differentiation, 69 human cells were clustered into 30 groups, depending on gene expression levels, by GeneSpringGX software. Among 30 groups, 21 groups includes cells with a cardiomyogenic potential. To identify genes specific for these groups, hierarchical clustering was employed; and Grem1 was nominated as one of the cluster-specific cardiomyocyte-promoting genes by NIA array analysis.
Citation(s)	Kami D, Shiojima I, Makino H, Matsumoto K et al. Gremlin enhances the determined path to cardiomyogenesis. *PLoS One* 2008 Jun 11;3(6):e2407. PMID: 18545679
Submission date	Jul 13, 2007
Last update date	May 14, 2015
Contact name	Akihiro Umezawa
E-mail	umezawa@1985.jukuin.keio.ac.jp

PubMed articles may have several Medical subject heading (MeSH) terms.

PLoS One. 2008 Jun 11;3(6):e2407. doi: 10.1371/journal.pone.0002407.

Gremlin enhances the determined path to cardiomyogenesis.

Kami D[1], Shiojima I, Makino H, Matsumoto K, Takahashi Y, Ishii R, Naito AT, Toyoda M, Saito H, Watanabe M, Komuro I, Umezawa A.

⊕ **Author information**

Abstract

BACKGROUND: The critical event in heart formation is commitment of mesodermal cells to a cardiomyogenic fate, and cardiac fate determination is regulated by a series of cytokines. Bone morphogenetic proteins (BMPs) and fibroblast growth factors have been shown to be involved in this process, however additional factors needs to be identified for the fate determination, especially at the early stage of cardiomyogenic development.

METHODOLOGY/PRINCIPAL FINDINGS: Global gene expression analysis using a series of human cells with a cardiomyogenic potential suggested Gremlin (Grem1) is a candidate gene responsible for in vitro cardiomyogenic differentiation. Grem1, a known BMP antagonist, enhanced DMSO-induced cardiomyogenesis of P19CL6 embryonal carcinoma cells (CL6 cells) 10-35 fold in an area of beating differentiated cardiomyocytes. The Grem1 action was most effective at the early differentiation stage when CL6 cells were destined to cardiomyogenesis, and was mediated through inhibition of BMP2. Furthermore, BMP2 inhibited Wnt/beta-catenin signaling that promoted CL6 cardiomyogenesis.

Publication Types, MeSH Terms, Substances

Publication Types

Research Support, Non-U.S. Gov't

MeSH Terms

- Cell Differentiation/drug effects
- Dimethyl Sulfoxide/pharmacology
- Heart/embryology*
- Humans
- Immunohistochemistry
- Intercellular Signaling Peptides and Proteins/physiology*
- Reverse Transcriptase Polymerase Chain Reaction

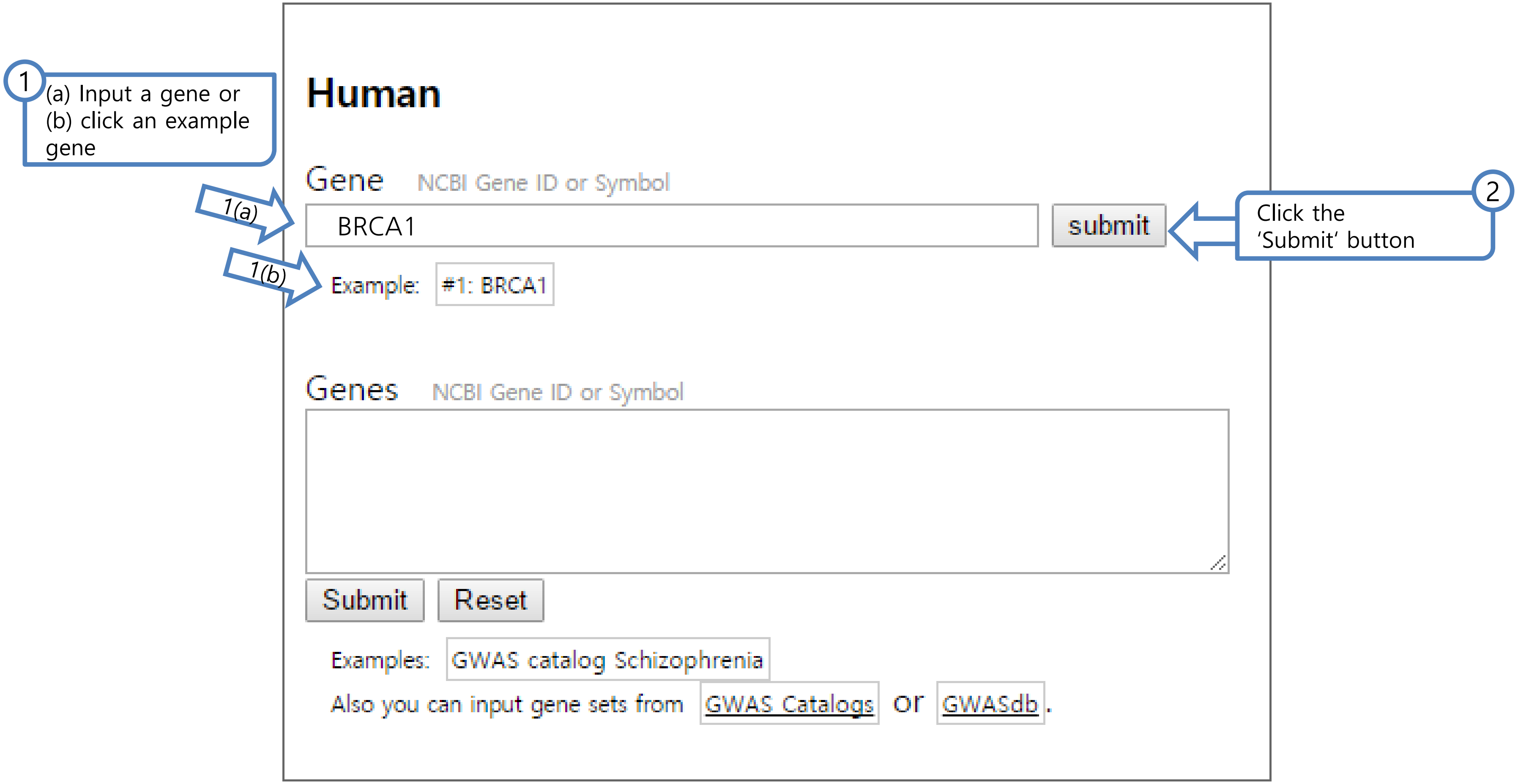
"co-expressed gene pairs ←→ GSE ←→ PubMed ←→ MeSH"

All co-expression links are associated with biomedical information by MeSH terms.

How to search Coexpedia

Search using a single gene

This is a useful option if you want to **identify co-expressed genes of a query gene** and the associated **functions** (GO biological process) and **phenotypes** (Disease Ontology for human, Mammalian Phenotype for mouse) **of the query gene**.



① (a) Input a gene or (b) click an example gene

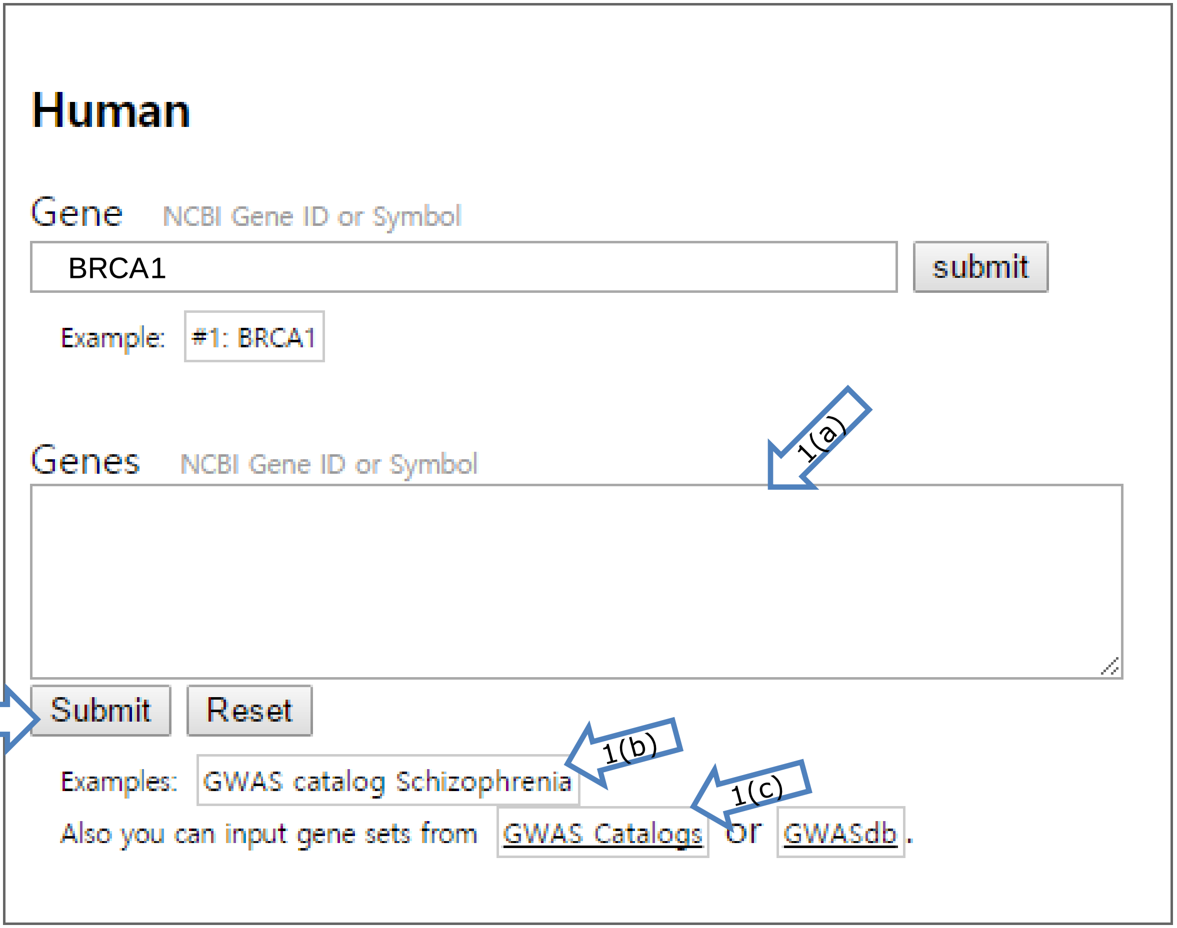
② Click the 'Submit' button

Gene: BRCA1

Also you can input gene sets from GWAS Catalogs or GWASdb.

Search using multiple genes

- This is a useful option if you want to **know which genes are co-expressed among multiple query genes** and **what are their** associated **functions** (GO biological process) and **phenotypes** (Disease Ontology for human, Mammalian Phenotype for mouse).
- Coexpedia provides the **pre-compiled gene lists** from two major databases of GWAS candidate genes: GWAS catalogs and GWASdb.



Human

Gene NCBI Gene ID or Symbol

BRCA1

Example: #1: BRCA1

Genes NCBI Gene ID or Symbol

Examples: GWAS catalog Schizophrenia

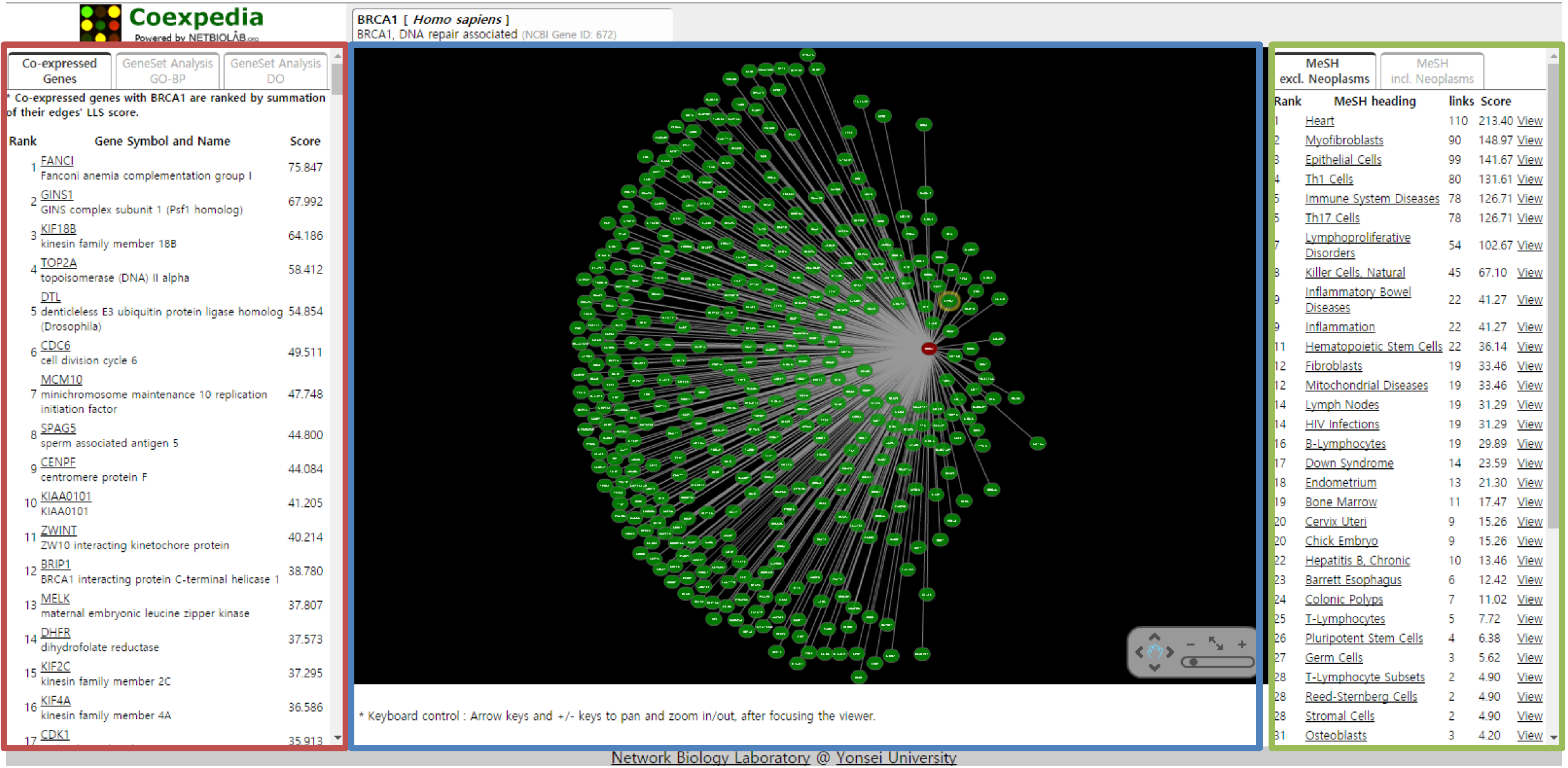
Also you can input gene sets from GWAS Catalogs or GWASdb.

① (a) Input genes , (b) click an example genes, or (c) select the gene set from GWAScatalog/ GWASdb.

② Click the 'Submit' button

How to interpret your search results

Search results (human BRCA1)



BRCA1 [*Homo sapiens*]
BRCA1, DNA repair associated (NCBI Gene ID: 672)

* Co-expressed genes with BRCA1 are ranked by summation of their edges' LLS score.

Rank	Gene Symbol and Name	Score
1	FANCI Fanconi anemia complementation group I	75.847
2	GINS1 GINS complex subunit 1 (Psf1 homolog)	67.992
3	KIF18B kinesin family member 18B	64.186
4	TOP2A topoisomerase (DNA) II alpha	58.412
5	DTL denticleless E3 ubiquitin protein ligase homolog (Drosophila)	54.854
6	CDC6 cell division cycle 6	49.511
7	MCM10 minichromosome maintenance 10 replication initiation factor	47.748
8	SPAG5 sperm associated antigen 5	44.800
9	CENPF centromere protein F	44.084
10	KIAA0101 KIAA0101	41.205
11	ZWINT ZW10 interacting kinetochore protein	40.214
12	BRIP1 BRCA1 interacting protein C-terminal helicase 1	38.780
13	MELK maternal embryonic leucine zipper kinase	37.807
14	DHFR dihydrofolate reductase	37.573
15	KIF2C kinesin family member 2C	37.295
16	KIF4A kinesin family member 4A	36.586
17	CDK1	35.913

* Keyboard control : Arrow keys and +/- keys to pan and zoom in/out, after focusing the viewer.

Rank	MeSH heading	links	Score	
1	Heart	110	213.40	View
2	Myofibroblasts	90	148.97	View
3	Epithelial Cells	99	141.67	View
4	Th1 Cells	80	131.61	View
5	Immune System Diseases	78	126.71	View
5	Th17 Cells	78	126.71	View
7	Lymphoproliferative Disorders	54	102.67	View
8	Killer Cells, Natural	45	67.10	View
9	Inflammatory Bowel Diseases	22	41.27	View
9	Inflammation	22	41.27	View
11	Hematopoietic Stem Cells	22	36.14	View
12	Fibroblasts	19	33.46	View
12	Mitochondrial Diseases	19	33.46	View
14	Lymph Nodes	19	31.29	View
14	HIV Infections	19	31.29	View
16	B-Lymphocytes	19	29.89	View
17	Down Syndrome	14	23.59	View
18	Endometrium	13	21.30	View
19	Bone Marrow	11	17.47	View
20	Cervix Uteri	9	15.26	View
20	Chick Embryo	9	15.26	View
22	Hepatitis B, Chronic	10	13.46	View
23	Barrett Esophagus	6	12.42	View
24	Colonic Polyps	7	11.02	View
25	T-Lymphocytes	5	7.72	View
26	Pluripotent Stem Cells	4	6.38	View
27	Germ Cells	3	5.62	View
28	T-Lymphocyte Subsets	2	4.90	View
28	Reed-Sternberg Cells	2	4.90	View
28	Stromal Cells	2	4.90	View
31	Osteoblasts	3	4.20	View

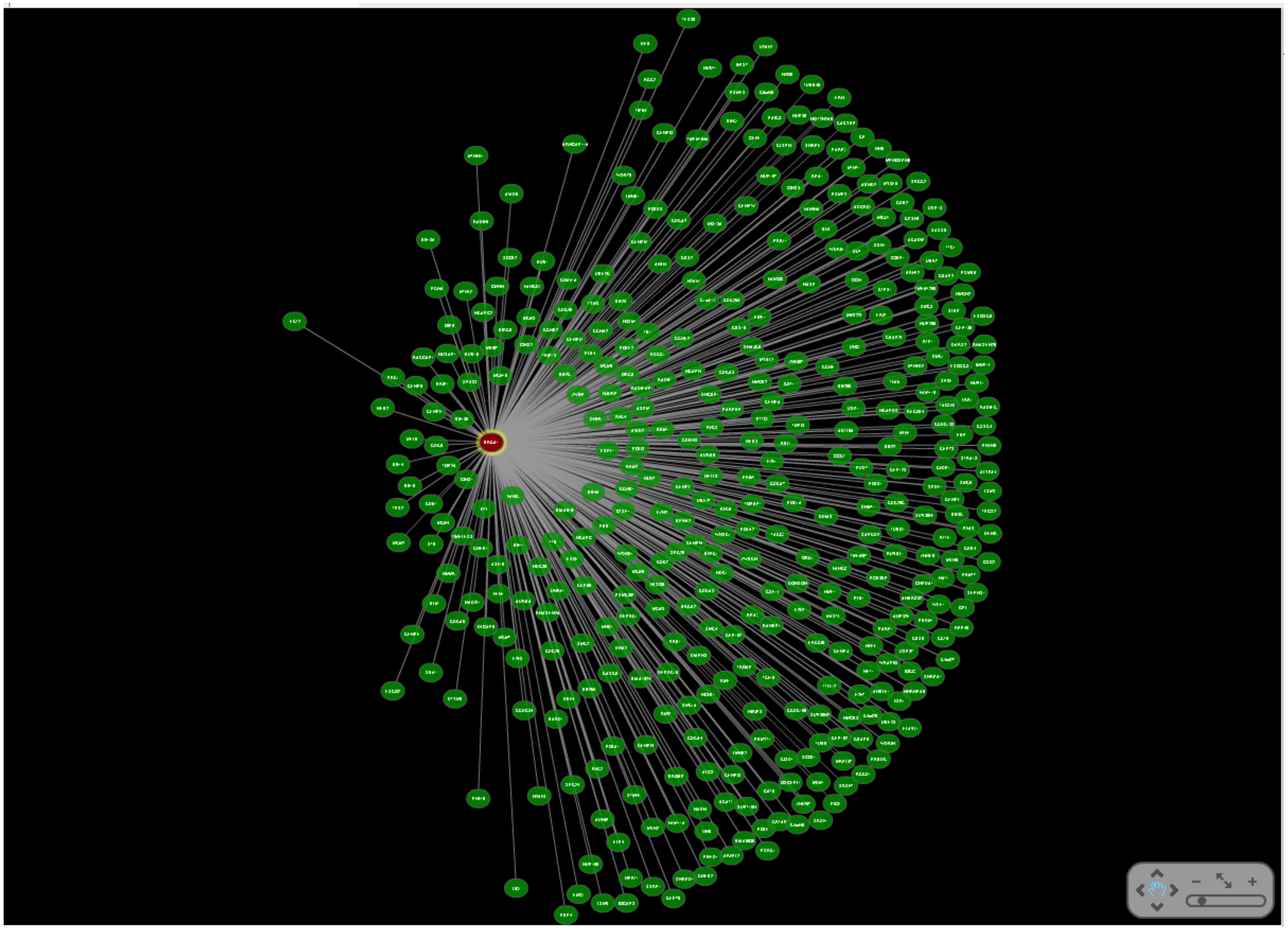
Network Biology Laboratory @ Yonsei University

Co-expressed genes and associated functions (GO-BP) and phenotypes (DO)
Sorted by score (sum of log likelihood scores from all co-expression links)

Network Viewer (Cytoscape Web)
The query gene is represented as red node. The co-expression links are highlighted for the selected MeSH term.
Closer genes to the query gene have higher scores.

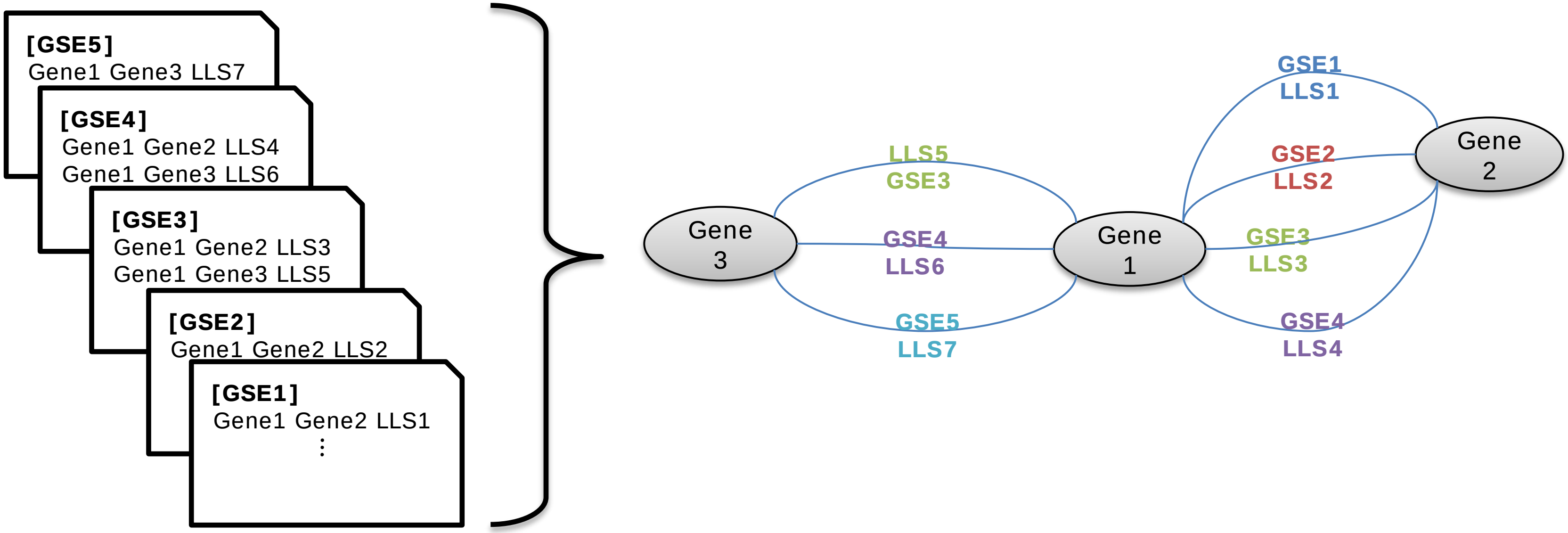
Enriched MeSH terms among the co-expressed genes were sorted by score (sum of log likelihood scores from all links)
Clicking "View" will show a MeSH specific network.

Network viewer



Network Viewer of a queried gene and its co-expressed neighbors, or Co-expressed queried genes using CytoscapeWeb (Adobe Flash Plugin needed).
Mouse-over to the genes or the MeSH headings on the left and right sidebars to highlight nodes(genes) or edges (links).

Relationships among information



[GSE5]
Gene1 Gene3 LLS7

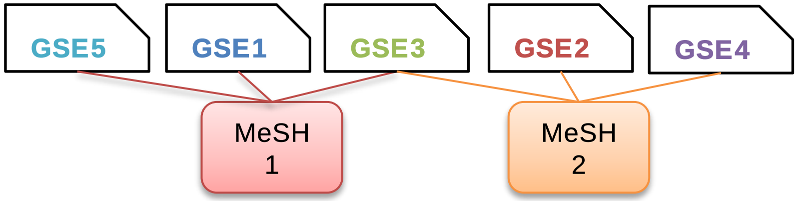
[GSE4]
Gene1 Gene2 LLS4
Gene1 Gene3 LLS6

[GSE3]
Gene1 Gene2 LLS3
Gene1 Gene3 LLS5

[GSE2]
Gene1 Gene2 LLS2

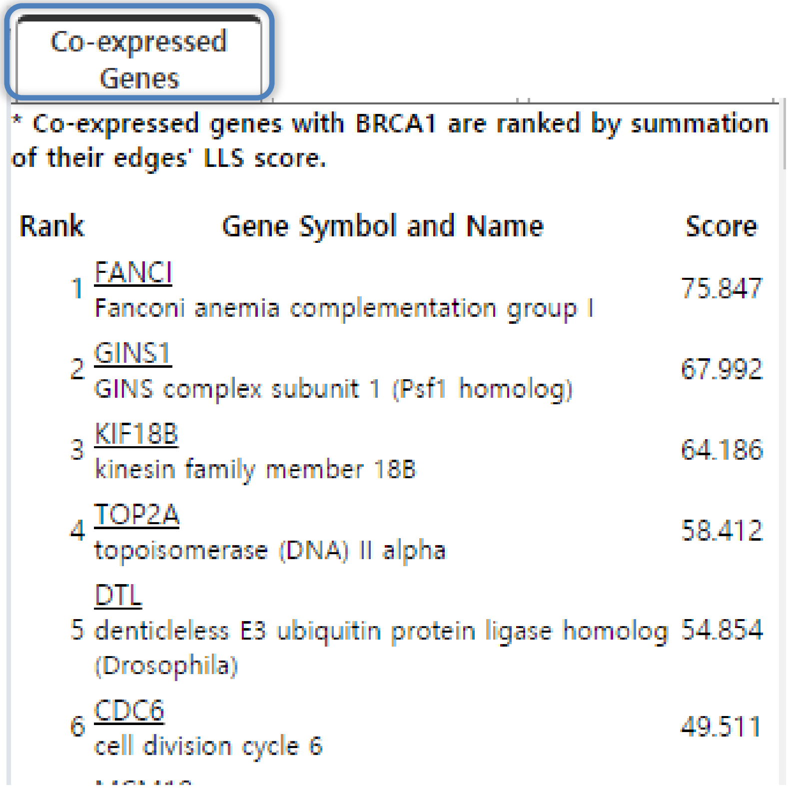
[GSE1]
Gene1 Gene2 LLS1
⋮

Co-expressed gene pairs (edges) of each GSEs have LLS scores.
Each gene pairs can have more than one LLS scores from multiple GSEs.



The relationship between GSEs and MeSH headings.

Co-expressed genes (left sidebar, first tab)



* Co-expressed genes with BRCA1 are ranked by summation of their edges' LLS score.

Rank	Gene Symbol and Name	Score
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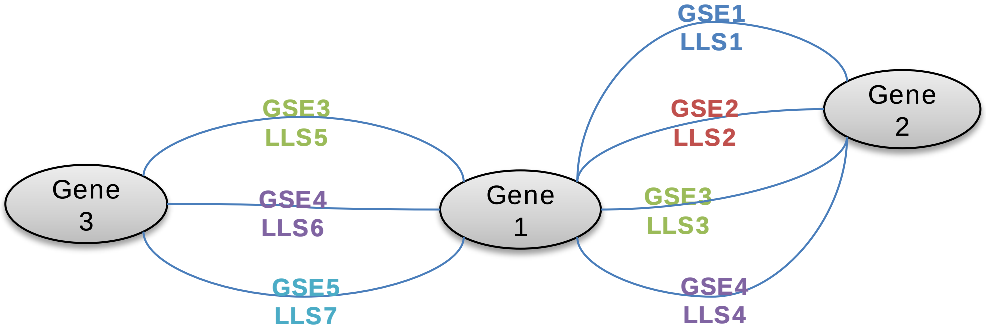
4	TOP2A topoisomerase (DNA) II alpha	58.412
5	DTL denticleless E3 ubiquitin protein ligase homolog (Drosophila)	54.854
6	CDC6 cell division cycle 6	49.511

'Co-expressed Genes' on the left sidebar displays Co-expressed genes of the query gene. They are ordered by the sum of the scores of their queried neighbors (Neighbor sum).



Rank genes by 'Neighbor sum'.

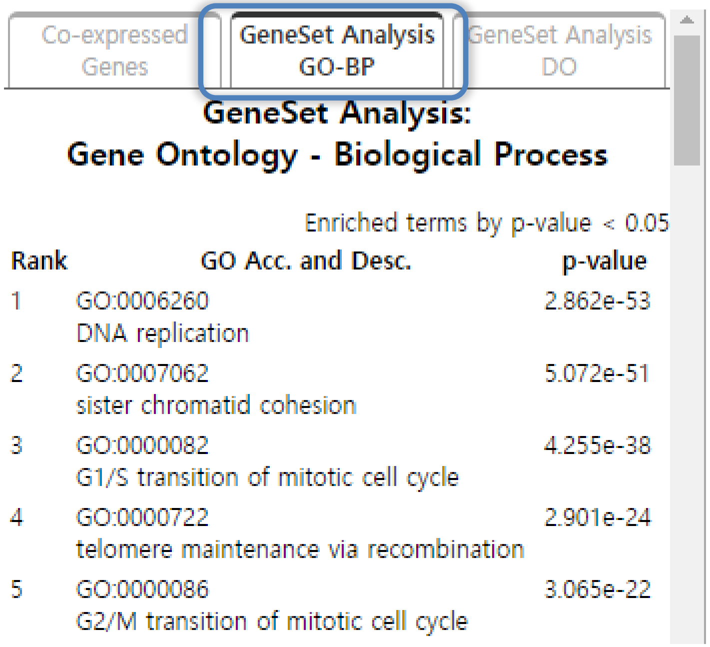
Score of gene1 = LLS1 + LLS2 + LL3 + LLS4 + LLS5 + LLS6 + LLS7

Score of gene2 = LLS1 + LLS2 + LL3 + LLS4

Score of gene3 = LLS5 + LLS6 + LL7

	Descending Order
Gene A	Score
Gene B	Score
Gene C	score

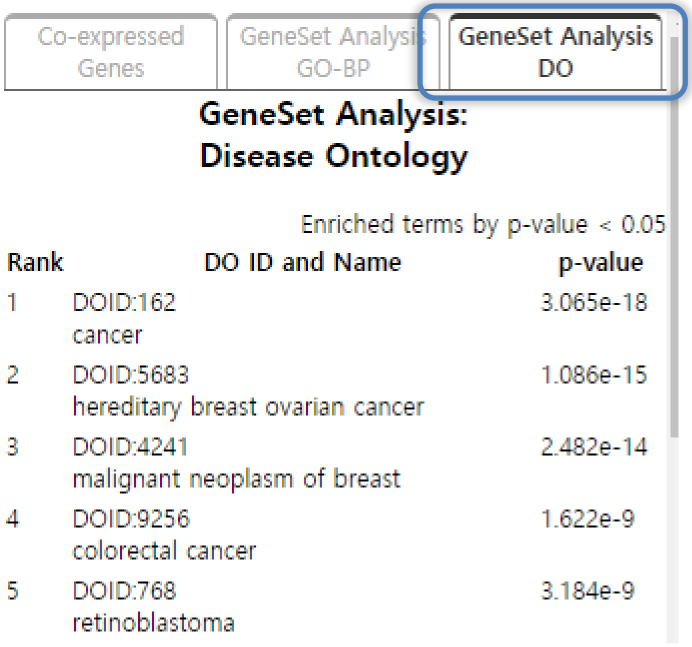
Candidate functions and phenotypes (left sidebar, 2nd and 3rd tab)



GeneSet Analysis:
Gene Ontology - Biological Process

Enriched terms by p-value < 0.05

Rank	GO Acc. and Desc.	p-value
1	GO:0006260 DNA replication	2.862e-53
2	GO:0007062 sister chromatid cohesion	5.072e-51
3	GO:0000082 G1/S transition of mitotic cell cycle	4.255e-38
4	GO:0000722 telomere maintenance via recombination	2.901e-24
5	GO:0000086 G2/M transition of mitotic cell cycle	3.065e-22



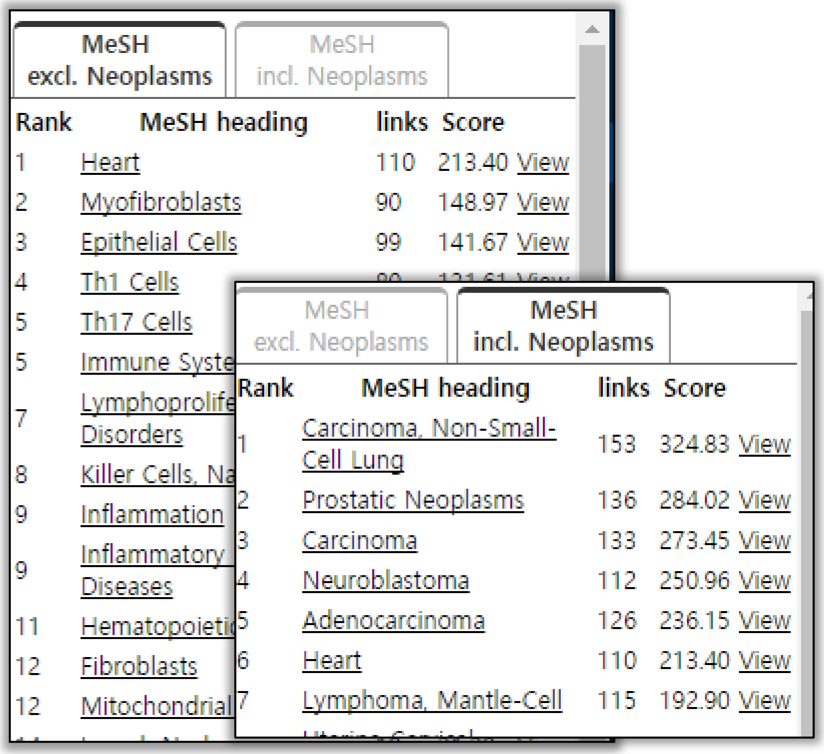
GeneSet Analysis:
Disease Ontology

Enriched terms by p-value < 0.05

Rank	DO ID and Name	p-value
1	DOID:162 cancer	3.065e-18
2	DOID:5683 hereditary breast ovarian cancer	1.086e-15
3	DOID:4241 malignant neoplasm of breast	2.482e-14
4	DOID:9256 colorectal cancer	1.622e-9
5	DOID:768 retinoblastoma	3.184e-9

- Coexpedia also provides Gene Set Analysis of co-expressed genes using annotations of **Gene Ontology - Biological Process (GO-BP)** (reliable evidence codes only; IDA, IMP, IGI, IPI, IEP, TAS) and **Disease Ontology (DO).**
- The query gene, BRCA1, is co-expressed with the genes known to be involved in ‘DNA replication’, ‘sister chromatid cohesion’, ‘G1/S transition of mitotic cell cycle’, and more, which suggest that BRCA1 is likely involved in these functions as well.
- The query gene, BRCA1, is co-expressed with the genes known to be involved in diseases such as ‘cancer’, ‘hereditary breast ovarian cancer’, ‘malignant neoplasm of breast’ and more, which suggest that BRCA1 is involved in such diseases.
- **For mouse**, DO analysis is replaced with **MGI Mammalian Phenotype (MP)** analysis.

Associated MeSH terms (right sidebar, 1st and 2nd tab)



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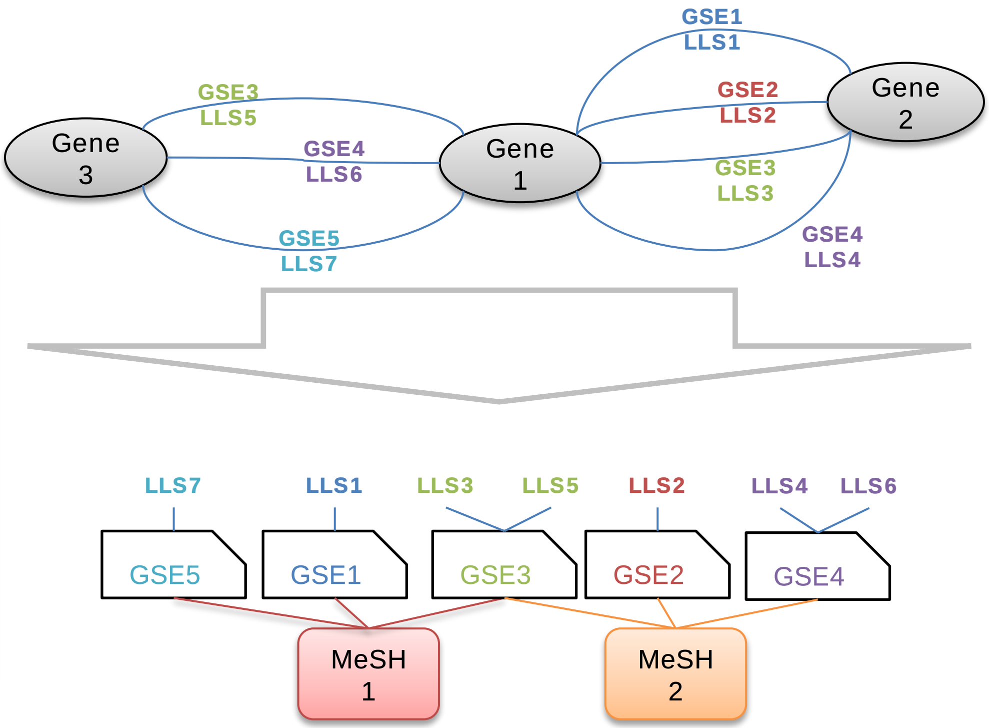
5	Immune Syste			
7	Lymphoprolife Disorders			
8	Killer Cells, Na			
9	Inflammation			
9	Inflammatory Diseases			
11	Hematopoieti			
12	Fibroblasts			
12	Mitochondrial			

Rank	MeSH heading	links	Score	
1	Carcinoma, Non-Small-Cell Lung	153	324.83	View
2	Prostatic Neoplasms	136	284.02	View
3	Carcinoma	133	273.45	View
4	Neuroblastoma	112	250.96	View
5	Adenocarcinoma	126	236.15	View
6	Heart	110	213.40	View
7	Lymphoma, Mantle-Cell	115	192.90	View



MeSH terms are highly biased to cancer (Neoplasms).

Therefore, Coexpedia shows associated MeSH terms in two different ways:
‘MeSH excluding Neoplasm’ (1st tab)
‘MeSH including Neoplasm‘ (2nd tab).

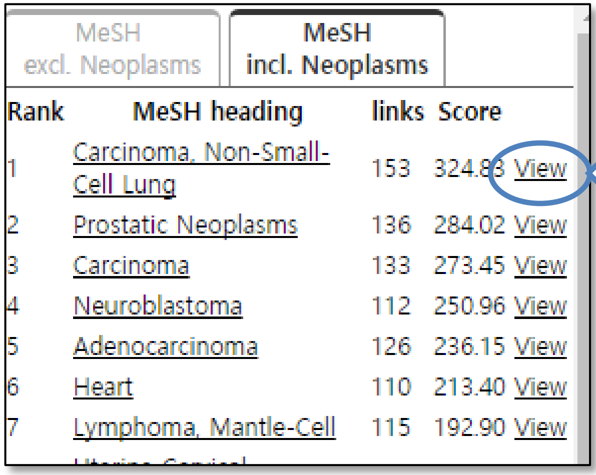
For example, BRCA1 has been known for a major risk genes for human breast cancer. A query for BRCA1 returns ‘Heart’ as the top associated MeSH term, and BRCA1 was recently reported as an essential regulator of heart function and survival following myocardial infarction (*Nat. Commun* 2:593, 2011).

Ranking the MeSH headings:
MeSH headings are ranked by calculating the contribution of their associated GEO series in the total sum of LLS scores.

Score of MeSH1 = Summation Scores from {GSE1 , GSE3, GSE5}
= LLS1 + (LLS3 + LLS5) + LLS7

Score of MeSH2 = Summation Scores from {GSE2 , GSE3, GSE4}
= LLS2 + (LLS3 + LLS5) + (LLS4 + LLS6)

MeSH Viewer



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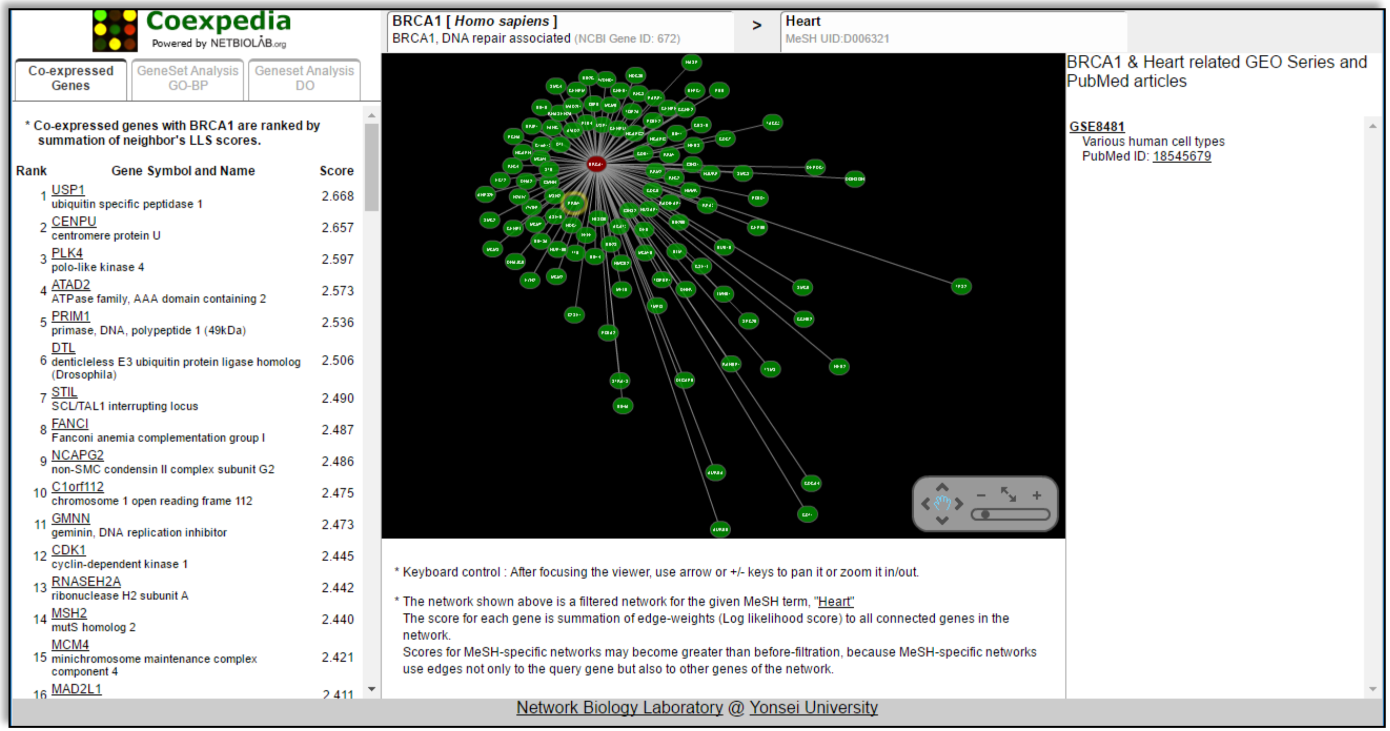
Click **View** to open MeSH Viewer.

This option shows co-expression genes, candidate functions, and phenotypes **in the respect of the selected biomedical context (MeSH term).**



BRCA1 [*Homo sapiens*]
BRCA1, DNA repair associated (NCBI Gene ID: 672)

Heart
MeSH UID:D006321

* Co-expressed genes with BRCA1 are ranked by summation of neighbor's LLS scores.

Rank	Gene Symbol and Name	Score
1	USP1 ubiquitin specific peptidase 1	2.668
2	CENPU centromere protein U	2.657
3	PLK4 polo-like kinase 4	2.597
4	ATAD2 ATPase family, AAA domain containing 2	2.573
5	PRIM1 primase, DNA, polypeptide 1 (49kDa)	2.536
6	DTL denticleless E3 ubiquitin protein ligase homolog (Drosophila)	2.506
7	STIL SCL/TAL1 interrupting locus	2.490
8	FANCI Fanconi anemia complementation group I	2.487
9	NCAPG2 non-SMC condensin II complex subunit G2	2.486
10	C1orf112 chromosome 1 open reading frame 112	2.475
11	GMNN geminin, DNA replication inhibitor	2.473
12	CDK1 cyclin-dependent kinase 1	2.445
13	RNASEH2A ribonuclease H2 subunit A	2.442
14	MSH2 mutS homolog 2	2.440
15	MCM4 minichromosome maintenance complex component 4	2.421
16	MAD2L1	2.411

BRCA1 & Heart related GEO Series and PubMed articles

GSE8481
Various human cell types
PubMed ID: 18545679

* Keyboard control : After focusing the viewer, use arrow or +/- keys to pan it or zoom it in/out.

* The network shown above is a filtered network for the given MeSH term, "Heart"
The score for each gene is summation of edge-weights (Log likelihood score) to all connected genes in the network.
Scores for MeSH-specific networks may become greater than before-filtration, because MeSH-specific networks use edges not only to the query gene but also to other genes of the network.

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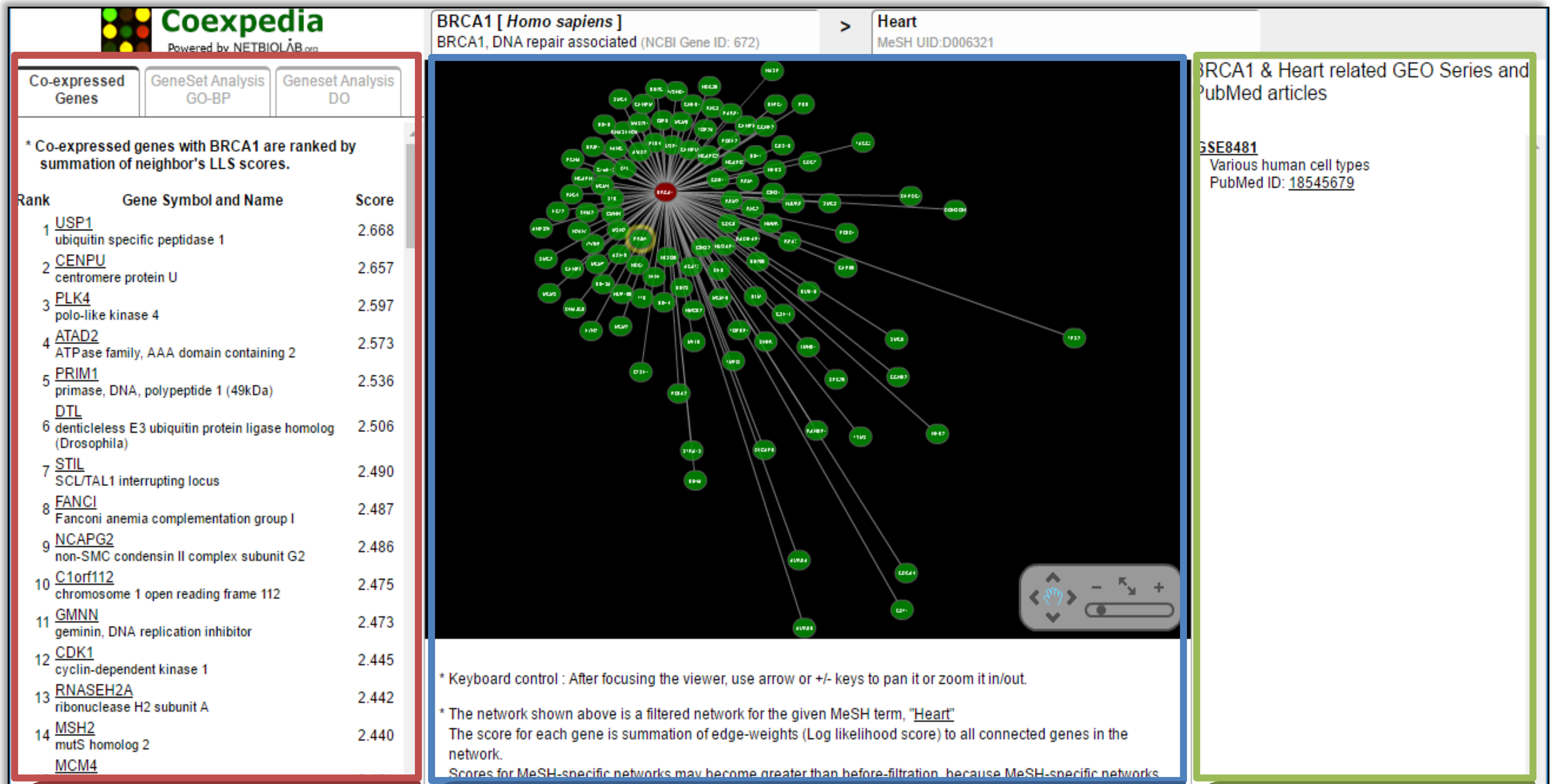
Search results (human BRCA1 → Heart)



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8	FANCI Fanconi anemia complementation group I	2.487
9	NCAPG2 non-SMC condensin II complex subunit G2	2.486
10	C1orf112 chromosome 1 open reading frame 112	2.475
11	GMNN geminin, DNA replication inhibitor	2.473
12	CDK1 cyclin-dependent kinase 1	2.445
13	RNASEH2A ribonuclease H2 subunit A	2.442
14	MSH2 mutS homolog 2	2.440
	MCM4	

* Keyboard control : After focusing the viewer, use arrow or +/- keys to pan it or zoom it in/out.

* The network shown above is a filtered network for the given MeSH term, "Heart"
The score for each gene is summation of edge-weights (Log likelihood score) to all connected genes in the network.
Scores for MeSH-specific networks may become greater than before-filtration, because MeSH-specific networks

RCA1 & Heart related GEO Series and
ubMed articles

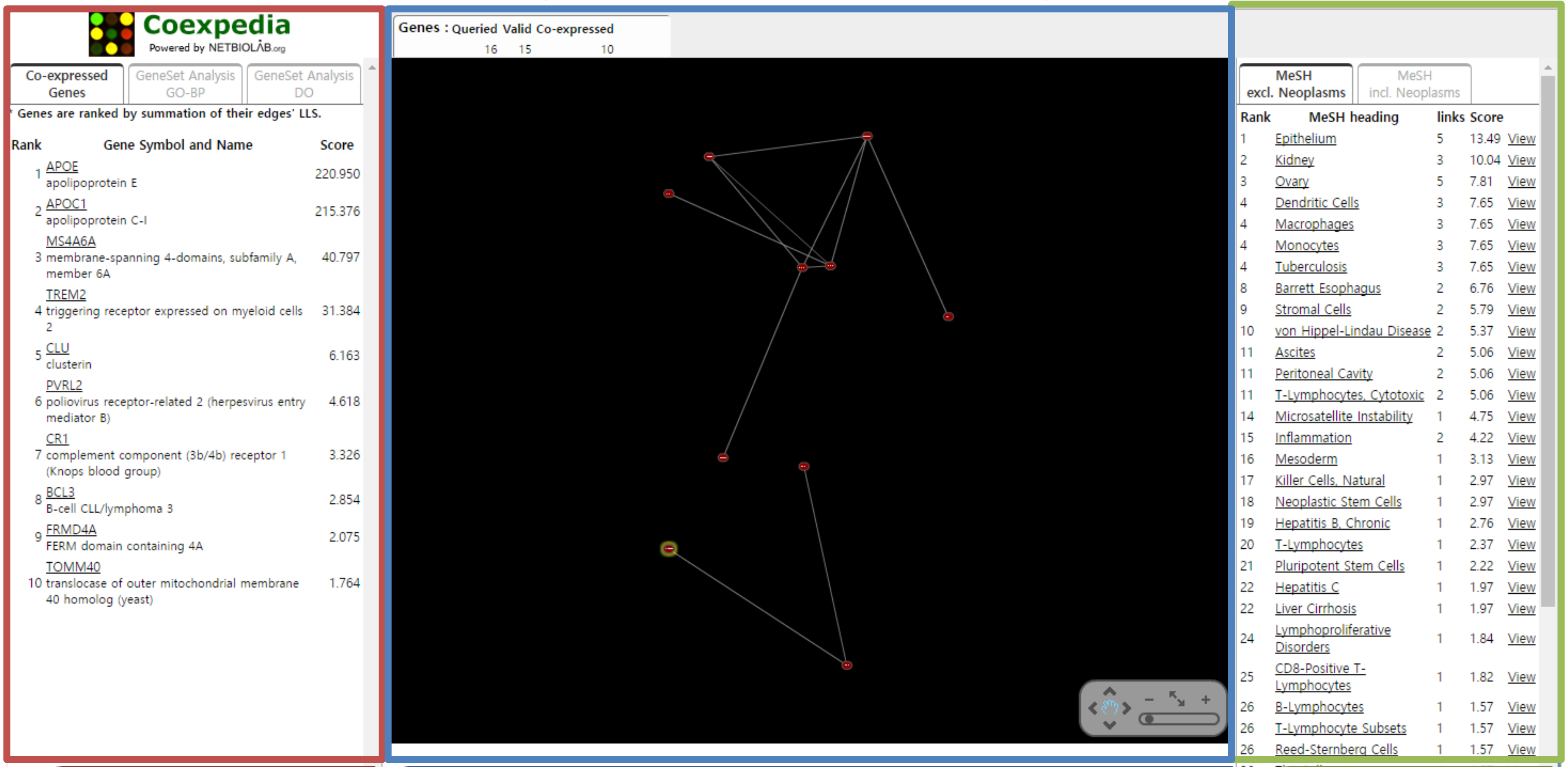
SE8481
Various human cell types
PubMed ID: 18545679

Co-expressed genes, candidate functions, and phenotypes in the context of ‘Heart’.

A network of co-expressed genes in the context of ‘Heart’ (Cytoscape Web)

Microarray GEO Series and PubMed articles that support the MeSH term, ‘Heart’.

Search results (human Schizophrenia candidate genes from GWAS)



* Genes are ranked by summation of their edges' LLS.

Rank	Gene Symbol and Name	Score
1	APOE apolipoprotein E	220.950
2	APOC1 apolipoprotein C-I	215.376
3	MS4A6A membrane-spanning 4-domains, subfamily A, member 6A	40.797
4	TREM2 triggering receptor expressed on myeloid cells 2	31.384
5	CLU clusterin	6.163
6	PVRL2 poliovirus receptor-related 2 (herpesvirus entry mediator B)	4.618
7	CR1 complement component (3b/4b) receptor 1 (Knops blood group)	3.326
8	BCL3 B-cell CLL/lymphoma 3	2.854
9	FRMD4A FERM domain containing 4A	2.075
10	TOMM40 translocase of outer mitochondrial membrane 40 homolog (yeast)	1.764

Genes :	Queried	Valid	Co-expressed
	16	15	10

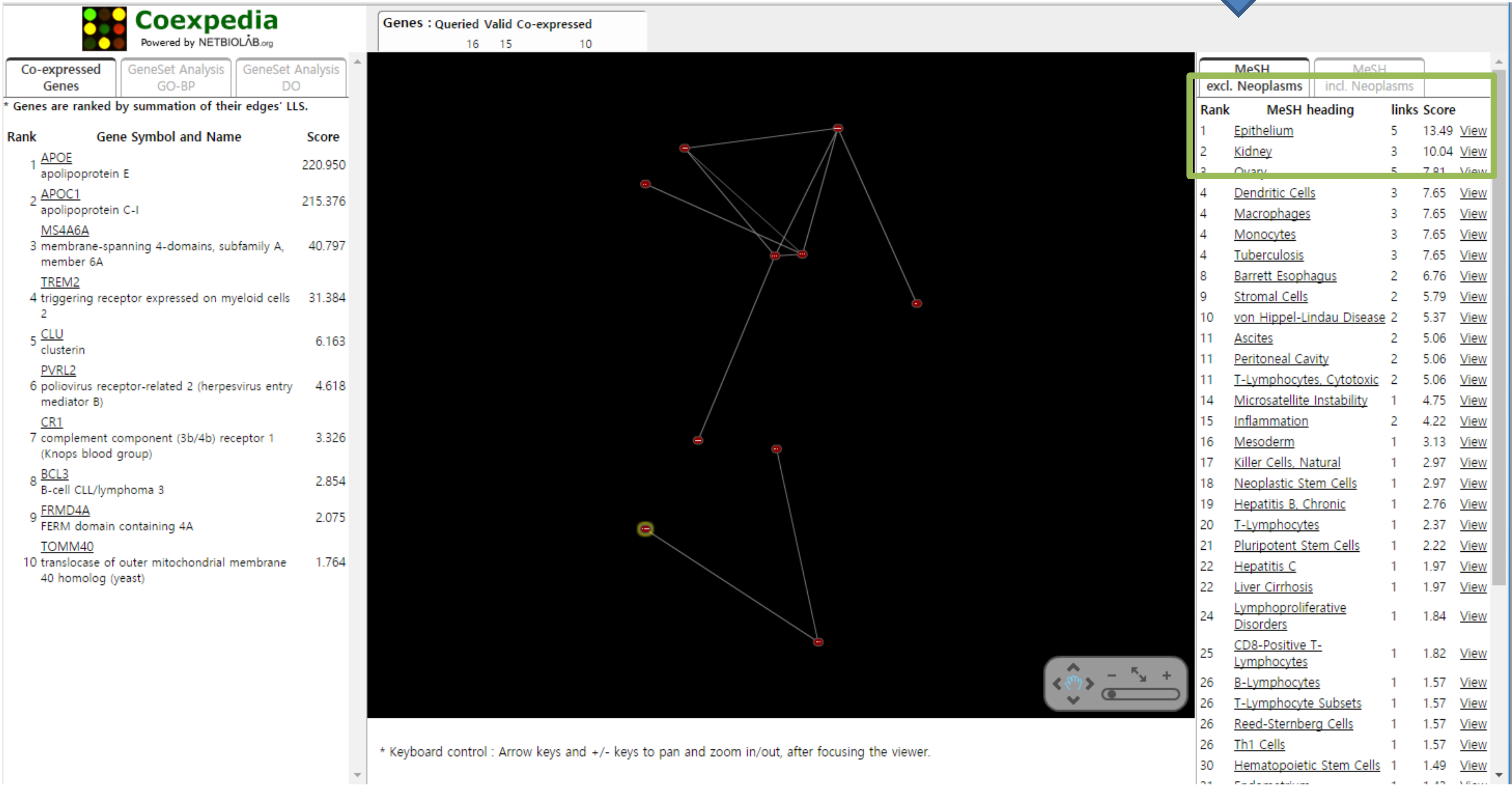
Rank	MeSH heading	links	Score	
1	Epithelium	5	13.49	View
2	Kidney	3	10.04	View
3	Ovary	5	7.81	View
4	Dendritic Cells	3	7.65	View
4	Macrophages	3	7.65	View
4	Monocytes	3	7.65	View
4	Tuberculosis	3	7.65	View
8	Barrett Esophagus	2	6.76	View
9	Stromal Cells	2	5.79	View
10	von Hippel-Lindau Disease	2	5.37	View
11	Ascites	2	5.06	View
11	Peritoneal Cavity	2	5.06	View
11	T-Lymphocytes, Cytotoxic	2	5.06	View
14	Microsatellite Instability	1	4.75	View
15	Inflammation	2	4.22	View
16	Mesoderm	1	3.13	View
17	Killer Cells, Natural	1	2.97	View
18	Neoplastic Stem Cells	1	2.97	View
19	Hepatitis B, Chronic	1	2.76	View
20	T-Lymphocytes	1	2.37	View
21	Pluripotent Stem Cells	1	2.22	View
22	Hepatitis C	1	1.97	View
22	Liver Cirrhosis	1	1.97	View
24	Lymphoproliferative Disorders	1	1.84	View
25	CD8-Positive T-Lymphocytes	1	1.82	View
26	B-Lymphocytes	1	1.57	View
26	T-Lymphocyte Subsets	1	1.57	View
26	Reed-Sternberg Cells	1	1.57	View
26				

Query genes are sorted by score (sum of log likelihood scores from all co-expression links). The top ranked gene is the hub gene.
Other tabs will show associated functions (GO-BP) and phenotypes (DO)

Network Viewer (Cytoscape Web)
Among input query genes, only co-expressed genes are visualized in the viewer (A total of 16 genes for Schizophrenia were submitted, but only 10 genes that co-express with each other are shown in the network view). The co-expression links are highlighted for the selected MeSH term.

Enriched MeSH terms among the co-expressed genes were sorted by score (sum of log likelihood scores from all links)
Clicking “View” will show a MeSH specific network.

If we submit 16 genes associated with Alzheimer by GWASdb, ‘Kidney’ comes as second most associated MeSH term, implicating association between Alzheimer and kidney disorder. Indeed, multiple studies reported chronic kidney disease as a risk factor of Alzheimer diseases (reviewed in *Alzheimer’s Research and Therapy* 7:29, 2015).



Genes : Queried Valid Co-expressed

16 15 10

* Genes are ranked by summation of their edges' LLS.

Rank	Gene Symbol and Name	Score
1	APOE apolipoprotein E	220.950
2	APOC1 apolipoprotein C-I	215.376
3	MS4A6A membrane-spanning 4-domains, subfamily A, member 6A	40.797
4	TREM2 triggering receptor expressed on myeloid cells 2	31.384
5	CLU clusterin	6.163
6	PVRL2 poliovirus receptor-related 2 (herpesvirus entry mediator B)	4.618
7	CR1 complement component (3b/4b) receptor 1 (Knops blood group)	3.326
8	BCL3 B-cell CLL/lymphoma 3	2.854
9	FRMD4A FERM domain containing 4A	2.075
10	TOMM40 translocase of outer mitochondrial membrane 40 homolog (yeast)	1.764

* Keyboard control : Arrow keys and +/- keys to pan and zoom in/out, after focusing the viewer.

Rank	MeSH heading	links	Score	
1	Epithelium	5	13.49	View
2	Kidney	3	10.04	View
3	Ovary	5	7.81	View
4	Dendritic Cells	3	7.65	View
4	Macrophages	3	7.65	View
4	Monocytes	3	7.65	View
4	Tuberculosis	3	7.65	View
8	Barrett Esophagus	2	6.76	View
9	Stromal Cells	2	5.79	View
10	von Hippel-Lindau Disease	2	5.37	View
11	Ascites	2	5.06	View
11	Peritoneal Cavity	2	5.06	View
11	T-Lymphocytes, Cytotoxic	2	5.06	View
14	Microsatellite Instability	1	4.75	View
15	Inflammation	2	4.22	View
16	Mesoderm	1	3.13	View
17	Killer Cells, Natural	1	2.97	View
18	Neoplastic Stem Cells	1	2.97	View
19	Hepatitis B, Chronic	1	2.76	View
20	T-Lymphocytes	1	2.37	View
21	Pluripotent Stem Cells	1	2.22	View
22	Hepatitis C	1	1.97	View
22	Liver Cirrhosis	1	1.97	View
24	Lymphoproliferative Disorders	1	1.84	View
25	CD8-Positive T-Lymphocytes	1	1.82	View
26	B-Lymphocytes	1	1.57	View
26	T-Lymphocyte Subsets	1	1.57	View
26	Reed-Sternberg Cells	1	1.57	View
26	Th1 Cells	1	1.57	View
30	Hematopoietic Stem Cells	1	1.49	View