Functional annotation of genetic variants

i. Functional enrichment

ii. Candidate gene prioritization

Anil Jegga

Biomedical Informatics

Slides: **http://anil.cchmc.org/grn**

MG-8011

Sept 14, 2015

Cincinnati Children's | UNIVERSITY OF Cincinnati

http://anil.cchmc.org/grn

Lectures, Tutorials, & Workshops

Functional annotation of genetic variants- 2015:

- **Description**: This lecture is delivered as part of the "Advanced Fundamentals of Human Genetics" course (see details below) and will focus on computational approaches for functional enrichment of genes and gene lists and disease candidate gene prioritization. This 1-hour lecture mainly aims to give an overview of databases and servers/tools which can assist in functional interpreation of variants.
- **Course Title**: Advanced Fundamentals of Human Genetics
- **Course Number**: MG 8011
- **Course Directors**: Drs. Lisa Martin, Ge Zhang and Bill Nichols
- **Lecture/Topic Title**: Functional annotation of genetic variant
  - **Presenter**: Anil Jegga, Associate Professor, Division of Biomedical Informatics, CCHMC
  - **Date**: September 14, 2015 **Time**: 11:00 AM - 12:00 Noon
  - **Location**: Cincinnati Childrens Hospital and Medical Center
  - **Download the presentation**: pdf

I have a list of co-expressed mRNAs (Transcriptome)….

Identify the underlying biological theme

What are my genes "enriched" for?

- Gene Ontology
- Pathways
- Phenotype/Disease Association
- Protein Domains
- TFBS and microRNA
- Protein Interactions
- Expression in other tissues/experiments
- Drug targets
- Literature co-citation…

Annotation Databases
Gene Ontology, Pathways

Genome-wide Promoters
Putative Regulatory
Signatures

DNA Repair
XRCC1
OGG1
ERCC1
MPG….

Angiogenesis
HIF1A
ANGPT1
VEGF
KLF5….

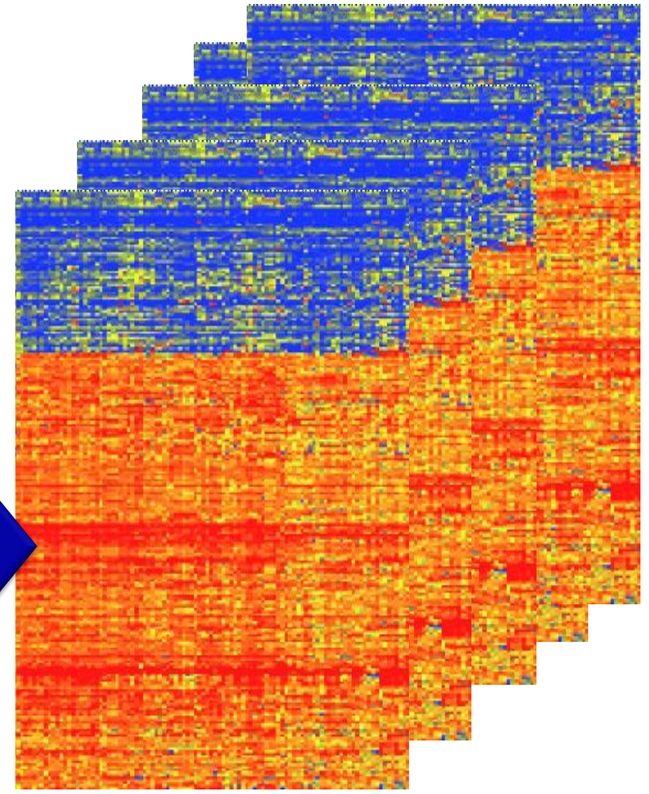
E2F
RB1
MCM4
FOS
SIVA…..

PDX1
GLUT2
PAX4
PDX1
IAPP….

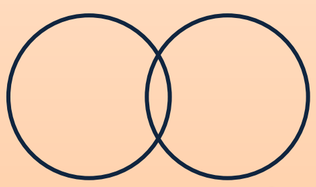
p53
CDKN1A
CTSD
CASP
DDB2….

Gene lists associated with similar
function/process/pathway

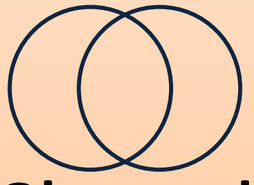
Expression Profile - Gene Lists



Enrichment Analysis



Expected

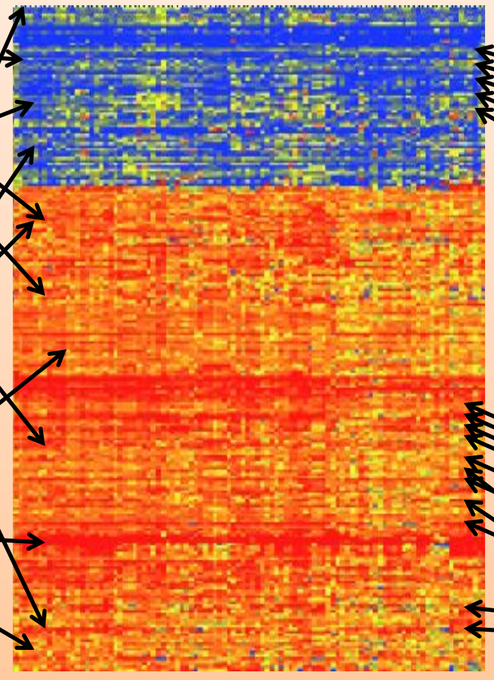


Observed

P53
CTSD
CASP
DDB2….

DNA Repair
XRCC1
OGG1
ERCC1
MPG….

Random Distribution

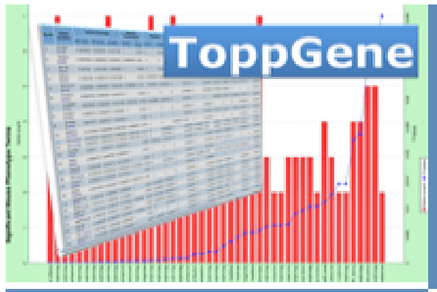


E2F
RB1
MCM4
FOS…

Angiogenesis
HIF1A
ANGPT1
VEGF…..

Significant Enrichment

ToppGene Suite (http://toppgene.cchmc.org)



ToppGene Suite

A one-stop portal for gene list enrichment analysis and candidate gene prioritization based on functional annotations and protein interactions network

- Home
- Links
- Database details
- Supplementary
- Help
- Publications
- Terms of Use
- Contacts

Supported by:

Computational Medicine Center

- **ToppFun**: Transcriptome, ontology, phenotype, proteome, and pharmacome annotations based gene list functional enrichment analysis

  Detect functional enrichment of your gene list based on Transcriptome, Proteome, Regulome (TFBS and miRNA), Ontologies (GO, Pathway), Phenotype (human disease and mouse phenotype), Pharmacome (Drug-Gene associations), literature co-citation, and other features.

- **ToppGene**: Candidate gene prioritization

  Prioritize or rank candidate genes based on functional similarity to training gene list.

- **ToppNet**: Relative importance of candidate genes in networks

  Prioritize or rank candidate genes based on topological features in protein-protein interaction network.

- **ToppGenet**: Prioritization of neighboring genes in protein-protein interaction network

  Identify and prioritize the neighboring genes of the seeds in protein-protein interaction network based on functional similarity to the "seed" list (ToppGene) or topological features in protein-protein interaction network (ToppNet).

1. Free for use, no log-in required.
2. Web-based, no need to install anything (except for applications to visualize or analyze networks)
3. Validated and published

ToppGene Suite (http://toppgene.cchmc.org) - ToppFun

ToppFun: Transcriptome, ontology, phenotype, proteome, and pharmacome annotations based gene list functional enrichment analysis

Select your gene identifier type, paste your sets below or select example set, then submit.

Entry Type: Entrez ID

Example gene sets: HGNC Symbol Entrez ID
(click on "HGNC Symbol" or "Entrez ID" to use the example training and test set of genes)

Training Gene Set:

```
259
5265
350
335
335
1558
1571
229
462
125
3240
5105
5265
3273
2244
2158
5053
125
1356
3827
383
```

Clear | Submit Query

1. Supports variety of inputs
2. Supports symbol correction
3. Eliminates any duplicates
4. Drawback: Supports human and mouse genes only

Input Gene List (81 / 97)

Entered	Human Symbol	Gene ID
259	AMBP	259
5265	SERPINA1	5265
350	APOH	350
335	APOA1	335
1558	CYP2C8	1558
1571	CYP2E1	1571
229	ALDOB	229
462	SERPINC1	462
125	ADH1B	125
3240	HP	3240
5105	PCK1	5105
3273	HRG	3273
2244	FGB	2244
2158	F9	2158
5053	PAH	5053
1356	CP	1356
3827	KNG1	3827
383	ARG1	383
5004	ORM1	5004
2168	FABP1	2168
325	APCS	325

Genes Not Found

Entered	Status
335	Duplicated
5265	Duplicated
125	Duplicated
1571	Duplicated
1571	Duplicated
1373	Duplicated
1356	Duplicated
462	Duplicated
2243	Duplicated
3827	Duplicated
125	Duplicated
229	Duplicated
6822	Duplicated
2328	Duplicated

ToppGene Suite (http://toppgene.cchmc.org) - ToppFun

Feature	Correction	p-Value cutoff	Gene Limits
☑ All	FDR	0.05	1 ≤ *n* ≤ 2000
☑ GO: Molecular Function	FDR	0.05	1 ≤ *n* ≤ 2000
☑ GO: Biological Process	FDR	0.05	1 ≤ *n* ≤ 2000
☑ GO: Cellular Component	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Human Phenotype	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Mouse Phenotype	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Domain	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Pathway	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Pubmed	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Interaction	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Cytoband	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Transcription Factor Binding Site	FDR	0.05	1 ≤ *n* ≤ 2000
☑ Gene Family	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Coexpression	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Coexpression Atlas	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Computational	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ MicroRNA	FDR	0.05	1 ≤ *n* ≤ 2000
▶ ☑ Drug	FDR	0.05	1 ≤ *n* ≤ 2000
▼ ☑ Disease	FDR	0.05	1 ≤ *n* ≤ 2000
☑ CTD			
☑ Clinical Variations			
☑ GWAS			
☑ OMIM			

☐ Group results within a category by source.

Home | Modify Query | Start

1. Gene list analyzed for as many as 18 features!
2. Single-stop enrichment analysis server for both regulatory elements (TFBSs and miRNA) and biological themes
3. Back-end has an exhaustive, normalized data resources compiled and integrated
4. Bonferroni correction is “too stringent”; FDR with 0.05 is preferable.
5. TFBS are based on conserved cis-elements and motifs within ±2kb region of TSS in human, mouse, rat, and dog.
6. miRNA-targets are based on TargetScan, PicTar and miRrecords/Tarbase.

ToppGene Suite (http://toppgene.cchmc.org)

GO Biological Process

Annotations:	13,313
Genes:	18,482

Updated Aug 31, 2015

GO Cellular Component

Annotations:	1,529
Genes:	18,865

Updated Aug 31, 2015

GO Molecular Function

Annotations:	4,723
Genes:	18,326

Updated Aug 31, 2015

Human Phenotype

Annotations:	7,271
Genes:	4,141

Updated Dec 5, 2014

Mouse Phenotype

Annotations:	9,074
Genes:	7,992

Updated Aug 31, 2015

Pathways

Annotations:		3,633
	BioSystems: BIOCYC	319
	BioSystems: KEGG	362
	BioSystems: Pathway Interaction Database	186
	BioSystems: REACTOME	1,400
	BioSystems: WikiPathways	229
	GenMAPP	67
	MSigDB C2: BioCarta	217
	MSigDB C2: SigmaAldrich	10
	MSigDB C2: Signaling Gateway	8
	MSigDB C2: Signaling Transduction KE	28
	MSigDB C2: SuperArray	1
	PantherDB	152
Feb 24, 2015	Pathway Ontology	321
	SMPDB	333
Genes:		10,567

Domains

Annotations:		15,281
	Gene3D	610
	InterPro	8,171
	PROSITE	1,566
	Pfam	4,115
	ProDom	138
	SMART	681
Genes:		16,924

Pubmed

Annotations:		662,625
	GeneRIF	391,321
	Pubmed	271,304
Genes:		31,489

Updated Aug 31, 2015

1. Database updated regularly
2. Exhaustive collection of annotations

Interactions

Annotations:	16,249
Genes:	16,250

Updated May 13, 2015

Cytoband

Annotations:	2,354
Genes:	34,661

TFBS

Annotations:	615
Genes:	9,770

miRNA

Annotations:		4,085
	MSigDB	313
	MicroRNA.org	2,200
	PITA	677
	PicTar	178
	TargetScan	249
	miRTarbase	324
	miRecords_TarBase	144
Genes:		19,844

Gene Families

Annotations:	151
Genes:	6,751

Coexpression

Annotations:		9,016
	GeneSigDB	3,515
	MSigDB C2: Aristoteles University of Thessaloniki	5
	MSigDB C2: Broad Institute	2,962
	MSigDB C2: Columbia University	1
	MSigDB C2: Dana-Farber Cancer Institute	16
	MSigDB C2: Giannina Gaslini Institute	2
	MSigDB C2: Johns Hopkins University School of Medicine	5
	MSigDB C2: Laboratoire CarMeN	2

ToppGene Suite (http://toppgene.cchmc.org) - ToppFun

Results

Go To Start Page

Input Parameters [Show Detail]

Training Results [Show All] [Download All] [Sparse Matrix]

1: GO: Molecular Function [Display Chart] [Show Detail]

2: GO: Biological Process [Display Chart] [Show Detail]

3: GO: Cellular Component [Display Chart] [Show Detail]

4: Human Phenotype [Display Chart] [Show Detail]

5: Mouse Phenotype [Display Chart] [Show Detail]

6: Domain [Display Chart] [Show Detail]

7: Pathway [Display Chart] [Show Detail]

8: Pubmed [Display Chart] [Show Detail]

9: Interaction [Display Chart] [Show Detail]

10: Cytoband [Display Chart] [Show Detail]

11: TFBS [Display Chart] [Show Detail]

12: Gene Family [Display Chart] [Show Detail]

13: Coexpression [Display Chart] [Show Detail]

14: Computational [Display Chart] [Show Detail]

15: MicroRNA [Display Chart] [Show Detail]

16: Drug [Display Chart] [Show Detail]

17: Disease [Display Chart] [Show Detail]

Input Parameters [Hide Detail]

Number of genes in training set:	81
Number of genes in test set:	0
Correction and Cutoff:	

category	Correction	Cutoff	Min	Max
GO: Molecular Function	Bonferroni	0.05	1	1500
GO: Biological Process	Bonferroni	0.05	1	1500
GO: Cellular Component	Bonferroni	0.05	1	1500
Human Phenotype	Bonferroni	0.05	1	1500
Mouse Phenotype	Bonferroni	0.05	1	1500
Domain	Bonferroni	0.05	1	1500
Pathway	Bonferroni	0.05	1	1500
Pubmed	Bonferroni	0.05	1	1500
Interaction	Bonferroni	0.05	1	1500
Cytoband	Bonferroni	0.05	1	1500
TFBS	Bonferroni	0.05	1	1500
Gene Family	Bonferroni	0.05	1	1500
Coexpression	Bonferroni	0.05	1	1500
Computational	Bonferroni	0.05	1	1500
MicroRNA	Bonferroni	0.05	1	1500
Drug	Bonferroni	0.05	1	1500
Disease	Bonferroni	0.05	1	1500

Random sampling size in analysis:	0
Minimun feature count in test set:	2
Analysis took:	2 seconds
Analysis finished at:	Sun Sep 27 16:45:06 EDT 2009

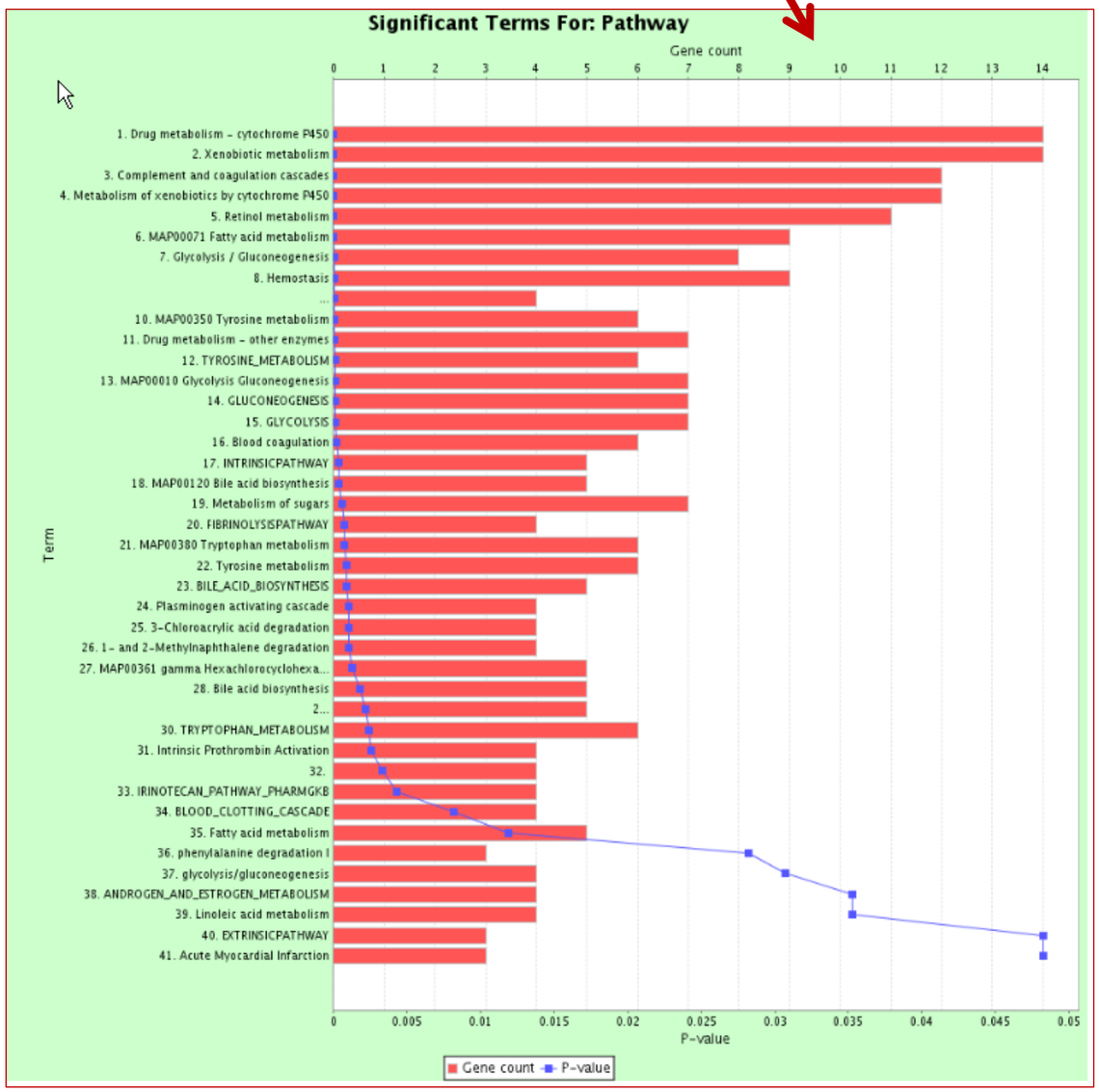
2: GO: Biological Process [Display Chart] [Hide Detail]

	ID	Name	Source	P-value	Term in Query	Term in Genome
1	GO:0009605	response to external stimulus		0	27	893
2	GO:0007596	blood coagulation		0	12	115
3	GO:0006629	lipid metabolic process		0	25	874
4	GO:0044255	cellular lipid metabolic process		0	23	720
5	GO:0050817	coagulation		0	12	119
6	GO:0007599	hemostasis		0	12	120
7	GO:0009611	response to wounding		0	20	542
8	GO:0042060	wound healing		0	13	185
9	GO:0050878	regulation of body fluid levels		0	12	151
10	GO:0055114	oxidation reduction		0	19	624
11	GO:0019752	carboxylic acid metabolic process		0	18	570

ToppGene Suite (http://toppgene.cchmc.org) - ToppFun

2: GO: Biological Process [Display Chart] [Hide Detail]

	ID	Name	Source	P-value	Term in Query	Term in Genome
1	GO:0009605	response to external stimulus		0	27	893
2	GO:0007596	blood coagulation		0	12	115
3	GO:0006629	lipid metabolic process		0	25	874
4	GO:0044255	cellular lipid metabolic process		0	23	720
5	GO:0050817	coagulation		0	12	119
6	GO:0007599	hemostasis		0	12	120
7	GO:0009611	response to wounding		0	20	542
8	GO:0042060	wound healing		0	13	185
9	GO:0050878	regulation of body fluid levels		0	12	151
10	GO:0055114	oxidation reduction		0	19	624
11	GO:0019752	carboxylic acid metabolic process		0	18	570



response to external stimulus; GO:0009605

	Entrez Gene ID	Gene Symbol	Gene Name	Original Symbol
1	126	ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	126
2	335	APOA1	apolipoprotein A-I	335
3	350	APOH	apolipoprotein H (beta-2-glycoprotein I)	350
4	2158	F9	coagulation factor IX	2158
5	5950	RBP4	retinol binding protein 4, plasma	5950
6	197	AHSG	alpha-2-HS-glycoprotein	197
7	2243	FGA	fibrinogen alpha chain	2243
8	213	ALB	albumin	213
9	2244	FGB	fibrinogen beta chain	2244
10	629	CFB	complement factor B	629
11	3158	HMGCS2	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial)	3158
12	5444	PON1	paraoxonase 1	5444
13	1361	CPB2	carboxypeptidase B2 (plasma)	1361
14	3078	CFHR1	complement factor H-related 1	3078
15	5265	SERPINA1	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1	5265
16	3827	KNG1	kininogen 1	3827
17	325	APCS	amyloid P component, serum	325
18	2538	G6PC	glucose-6-phosphatase, catalytic subunit	2538
19	4153	MBL2	mannose-binding lectin (protein C) 2, soluble (opsonic defect)	4153
20	735	C9	complement component 9	735
21	462	SERPINC1	serpin peptidase inhibitor, clade C (antithrombin), member 1	462
22	3273	HRG	histidine-rich glycoprotein	3273
23	5340	PLG	plasminogen	5340
24	5004	ORM1	orosomucoid 1	5004
25	316	AOX1	aldehyde oxidase 1	316
26	3053	SERPIND1	serpin peptidase inhibitor, clade D (heparin cofactor), member 1	3053
27	1356	CP	ceruloplasmin (ferroxidase)	1356

ToppGene Suite (http://toppgene.cchmc.org) - ToppFun

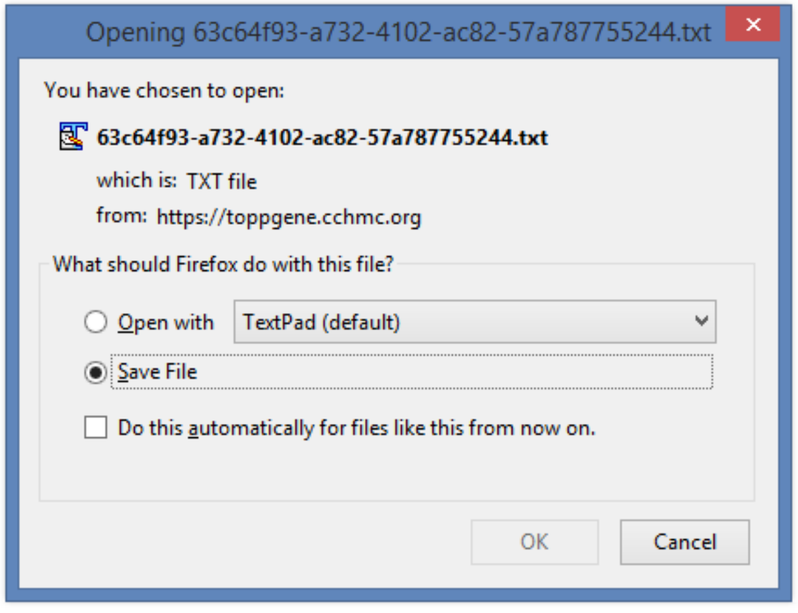
Input Parameters [Hide Detail]

Number of genes in training set:	7
Number of genes in test set:	0

Correction and Cutoff:

category	Correction	Cutoff	Min	Max
GO: Molecular Function	FDR B&H	0.05	1	2000
GO: Biological Process	FDR B&H	0.05	1	2000
GO: Cellular Component	FDR B&H	0.05	1	2000
Human Phenotype	FDR B&H	0.05	1	2000
Mouse Phenotype	FDR B&H	0.05	1	2000
Domain	FDR B&H	0.05	1	2000
Pathway	FDR B&H	0.05	1	2000
Pubmed	FDR B&H	0.05	1	2000
Interaction	FDR B&H	0.05	1	2000
Cytoband	FDR B&H	0.05	1	2000
Transcription Factor Binding Site	FDR B&H	0.05	1	2000
Gene Family	FDR B&H	0.05	1	2000
Coexpression	FDR B&H	0.05	1	2000
Coexpression Atlas	FDR B&H	0.05	1	2000
Computational	FDR B&H	0.05	1	2000
MicroRNA	FDR B&H	0.05	1	2000
Drug	FDR B&H	0.05	1	2000
Disease	FDR B&H	0.05	1	2000

Random sampling size in analysis:	0
Minimun feature count in test set:	2
Analysis took:	0 seconds
Analysis finished at:	Sun Sep 13 12:16:08 EDT 2015



Training Results [Expand All] [Download All] [Sparse Matrix] Display pValues and Scores as Scientific (4 significant digits) Table row limit 50

1: GO: Molecular Function [Display Chart] 52 annotations before applied cutoff / 18326 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0003700	transcription factor binding		1.021E-11	3.118E-10	1.415E-9	5.308E-10	7	496
2	GO:0044212	transcription regulatory region DNA binding		2.196E-11	3.118E-10	1.415E-9	1.142E-9	7	553
3	GO:0000975	regulatory region DNA binding		2.399E-11	3.118E-10	1.415E-9	1.247E-9	7	560
4	GO:0001067	regulatory region nucleic acid binding		2.399E-11	3.118E-10	1.415E-9	1.247E-9	7	560
5	GO:0000977	RNA polymerase II regulatory region sequence-specific DNA binding		1.214E-10	1.211E-9	5.495E-9	6.315E-9	6	298

Show 41 more annotations

2: GO: Biological Process [Display Chart] 831 annotations before applied cutoff / 18482 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0003206	cardiac chamber morphogenesis		3.938E-13	2.575E-10	1.880E-9	3.272E-10	6	117
2	GO:0035051	cardiocyte differentiation		6.198E-13	2.575E-10	1.880E-9	5.151E-10	6	126
3	GO:0003205	cardiac chamber development		1.034E-12	2.864E-10	2.091E-9	8.591E-10	6	137
4	GO:0003211	cardiac ventricle formation		1.511E-12	3.139E-10	2.292E-9	1.256E-9	4	10
5	GO:0003207	cardiac chamber formation		3.561E-12	5.918E-10	4.321E-9	2.959E-9	4	12

Show 45 more annotations

3: GO: Cellular Component [Display Chart] 9 annotations before applied cutoff / 18865 genes in category

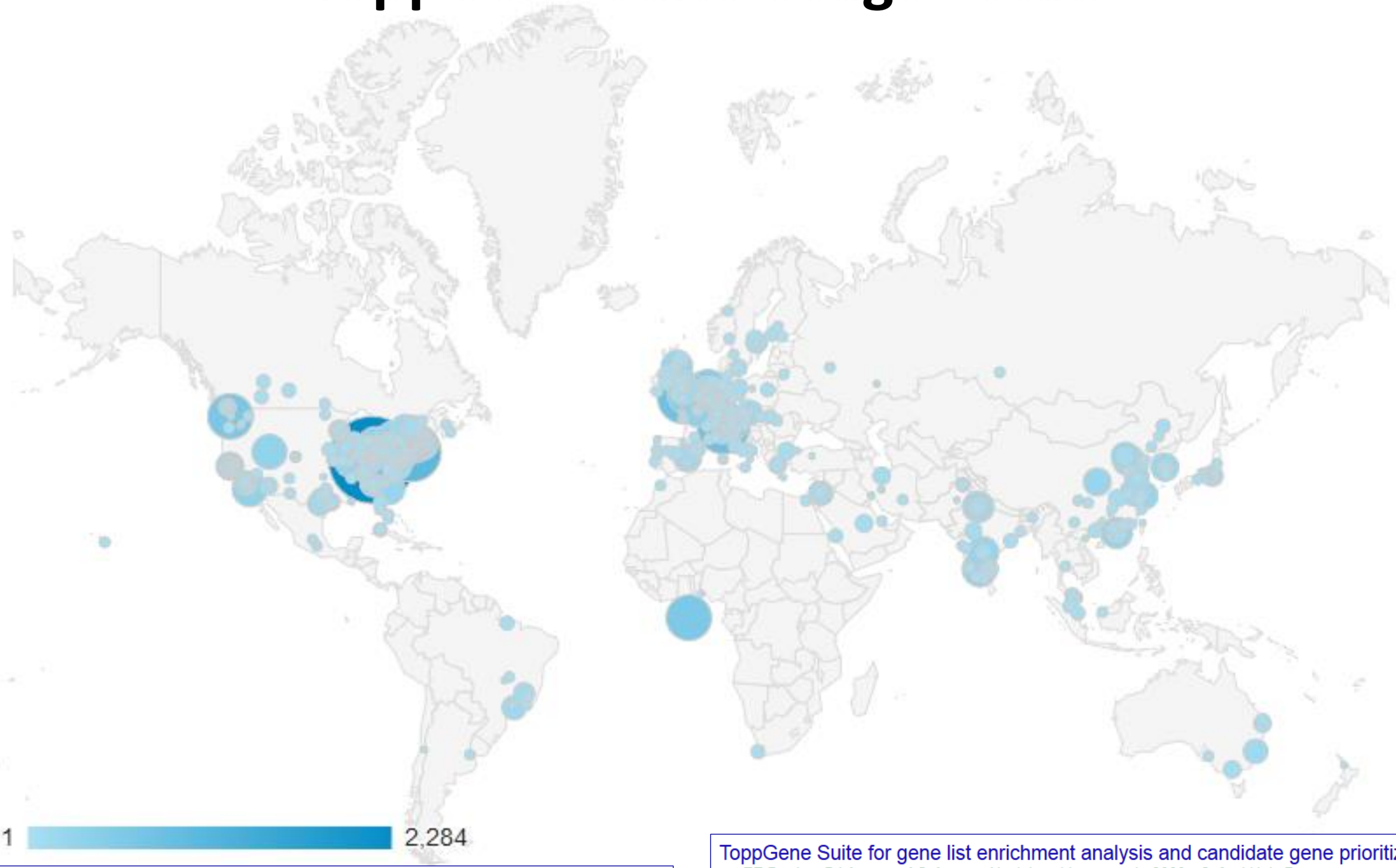
	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0000790	nuclear chromatin		7.070E-7	6.363E-6	1.800E-5	6.363E-6	4	228
2	GO:0044454	nuclear chromosome part		3.642E-6	1.551E-5	4.387E-5	3.277E-5	4	344
3	GO:0000785	chromatin		5.753E-6	1.551E-5	4.387E-5	5.178E-5	4	386
4	GO:0000228	nuclear chromosome		6.892E-6	1.551E-5	4.387E-5	6.203E-5	4	404
5	GO:0044427	chromosomal part		4.748E-5	8.546E-5	2.418E-4	4.273E-4	4	659

Show 3 more annotations

4: Human Phenotype [Display Chart] 277 annotations before applied cutoff / 4141 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	HP:0006705	Abnormality of the atrioventricular valves		5.536E-5	5.859E-3	3.634E-2	1.534E-2	3	101
2	HP:0045017	Congenital malformation of the left heart		6.345E-5	5.859E-3	3.634E-2	1.758E-2	2	14
3	HP:0004383	Hypoplastic left heart		6.345E-5	5.859E-3	3.634E-2	1.758E-2	2	14
4	HP:0001961	Hypoplastic heart		9.474E-5	6.560E-3	4.069E-2	2.624E-2	2	17

ToppGene Suite Usage - Stats



[HTML] Improved human disease candidate gene prioritization using mouse phenotype
J Chen, H Xu, BJ Aronow, AG **Jegga** - BMC bioinformatics, 2007 - biomedcentral.com
Background The majority of common diseases are multi-factorial and modified by genetically and mechanistically complex polygenic interactions and environmental factors. High-throughput genome-wide studies like linkage analysis and gene expression profiling, tend ...
Cited by 125 Related articles All 15 versions Cite Save More

ToppGene Suite for gene list enrichment analysis and candidate gene prioritization
..., EE Bardes, BJ Aronow, AG **Jegga** - Nucleic acids research, 2009 - Oxford Univ Press
Abstract ToppGene Suite (http://toppgene. cchmc. org; this web site is free and open to all users and does not require a login to access) is a one-stop portal for (i) gene list functional enrichment,(ii) candidate gene prioritization using either functional annotations or network ...
Cited by 388 Related articles All 14 versions Cite Save

[HTML] Disease candidate gene identification and prioritization using protein interaction networks
J Chen, BJ Aronow, AG **Jegga** - BMC bioinformatics, 2009 - biomedcentral.com
Background Although most of the current disease candidate gene identification and prioritization methods depend on functional annotations, the coverage of the gene functional annotations is a limiting factor. In the current study, we describe a candidate gene ...
Cited by 206 Related articles All 24 versions Cite Save More

ToppGene Suite Usage – Top users

(Aug 12, 2014- Sept 11, 2015)

Country	Sessions	% New Sessions	New Users	Bounce Rate	Pages / Session	Avg. Session Duration
	34,770 % of Total: 100.00% (34,770)	30.30% Avg for View: 30.21% (0.29%)	10,535 % of Total: 100.29% (10,505)	20.83% Avg for View: 20.83% (0.00%)	6.55 Avg for View: 6.55 (0.00%)	00:08:17 Avg for View: 00:08:17 (0.00%)
1. United States	15,323 (44.07%)	30.54%	4,679 (44.41%)	20.59%	6.95	00:07:56
2. United Kingdom	2,591 (7.45%)	22.35%	579 (5.50%)	14.78%	6.55	00:09:48
3. China	2,230 (6.41%)	29.06%	648 (6.15%)	22.33%	5.96	00:10:19
4. Italy	2,151 (6.19%)	26.73%	575 (5.46%)	19.39%	6.30	00:08:40
5. India	1,755 (5.05%)	34.36%	603 (5.72%)	21.82%	6.01	00:08:09
6. Netherlands	1,235 (3.55%)	19.35%	239 (2.27%)	11.74%	7.45	00:09:24
7. Canada	1,094 (3.15%)	26.23%	287 (2.72%)	18.28%	5.76	00:07:53
8. Germany	1,094 (3.15%)	33.36%	365 (3.46%)	23.22%	5.34	00:06:38
9. France	740 (2.13%)	40.81%	302 (2.87%)	17.57%	7.39	00:09:13
10. Spain	695 (2.00%)	23.88%	166 (1.58%)	15.54%	5.57	00:08:14
11. Belgium	535 (1.54%)	19.63%	105 (1.00%)	16.26%	6.25	00:09:30
12. Israel	449 (1.29%)	24.50%	110 (1.04%)	17.82%	9.02	00:09:20
13. Sweden	421 (1.21%)	26.84%	113 (1.07%)	17.34%	7.91	00:09:43
14. Brazil	408 (1.17%)	35.29%	144 (1.37%)	19.12%	7.76	00:09:34
15. Japan	390 (1.12%)	33.33%	130 (1.23%)	19.74%	7.68	00:10:39
16. South Korea	388 (1.12%)	50.26%	195 (1.85%)	27.84%	6.04	00:07:26
17. Australia	366 (1.05%)	40.71%	149 (1.41%)	19.67%	6.34	00:06:02
18. Hong Kong	314 (0.90%)	19.43%	61 (0.58%)	12.10%	5.91	00:06:09
19. Austria	226 (0.65%)	12.39%	28 (0.27%)	81.86%	2.13	00:02:57
20. Switzerland	219 (0.63%)	31.96%	70 (0.66%)	13.24%	7.63	00:07:26

Are there any other tools similar to these?

DAVID (https://david.ncifcrf.gov)

Database for Annotation, Visualization and Integrated Discovery

DAVID Bioinformatics Resources 6.7
National Institute of Allergy and Infectious Diseases (NIAID), NIH

Home | Start Analysis | Shortcut to DAVID Tools | Technical Center | Downloads & APIs | Term of Service | Why DAVID? | About Us

Shortcut to DAVID Tools

Functional Annotation
Gene-annotation enrichment analysis, functional annotation clustering , BioCarta & KEGG pathway mapping, gene-disease association, homologue match, ID translation, literature match and more

Gene Functional Classification
Provide a rapid means to reduce large lists of genes into functionally related groups of genes to help unravel the biological content captured by high throughput technologies. More

Gene ID Conversion
Convert list of gene ID/accessions to others of your choice with the most comprehensive gene ID mapping repository. The ambiguous accessions in the list can also be determined semi-automatically. More

Gene Name Batch Viewer
Display gene names for a given gene list; Search functionally related genes within your list or not in your list; Deep links to enriched detailed information. More

Recommending: A paper published in *Nature Protocols* describes step-by-step procedure to use DAVID!

Welcome to DAVID 6.7

2003 - 2015

Search

The Database for Annotation, Visualization and Integrated Discovery (**DAVID**) v6.7 is an update to the sixth version of our original web-accessible programs. DAVID now provides a comprehensive set of functional annotation tools for investigators to understand biological meaning behind large list of genes. For any given gene list, DAVID tools are able to:

- Identify enriched biological themes, particularly GO terms
- Discover enriched functional-related gene groups
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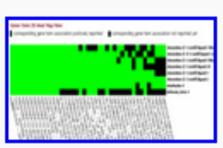
- Highlight protein functional domains and motifs
- Redirect to related literatures
- Convert gene identifiers from one type to another.
- And more


Screen Shot 1


Screen Shot 2


Screen Shot 3

https://david.ncifcrf.gov/home.jsp

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DAVID (https://david.ncifcrf.gov)

Upload | List | Background

Upload Gene List

Demolist 1 Demolist 2

Upload Help

Step 1: Enter Gene List

A: Paste a list

Clear

Or

B:Choose From a File

Browse...

Step 2: Select Identifier

AFFY_ID

Step 3: List Type

Gene List

Background

Step 4: Submit List

Submit List

Annotation Summary Results

Help and Tool Manual

Current Gene List: demolist1 — 171 DAVID IDs

Current Background: Homo sapiens — Check Defaults ☑ Clear All

⊞ Main Accessions (0 selected)

⊞ Other Accessions (0 selected)

⊟ Gene Ontology (3 selected)

☐ GOTERM_BP_1	79%	136	Chart
☐ GOTERM_BP_2	76%	131	Chart
☐ GOTERM_BP_3	74%	127	Chart
☐ GOTERM_BP_4	69%	119	Chart
☐ GOTERM_BP_5	60%	104	Chart
☑ GOTERM_BP_ALL	79%	136	Chart
☐ GOTERM_CC_1	70%	121	Chart
☐ GOTERM_CC_2	61%	106	Chart
☐ GOTERM_CC_3	55%	95	Chart
☐ GOTERM_CC_4	50%	86	Chart
☐ GOTERM_CC_5	38%	65	Chart
☑ GOTERM_CC_ALL	70%	121	Chart
☐ GOTERM_MF_1	75%	129	Chart
☐ GOTERM_MF_2	69%	119	Chart
☐ GOTERM_MF_3	60%	103	Chart
☐ GOTERM_MF_4	56%	97	Chart
☐ GOTERM_MF_5	45%	78	Chart
☑ GOTERM_MF_ALL	75%	129	Chart

⊞ Protein Domains (3 selected)

⊞ Pathways (3 selected)

⊞ General Annotations (0 selected)

⊞ Functional Categories (3 selected)

⊞ Protein Interactions (0 selected)

⊞ Literature (0 selected)

⊟ Disease (1 selected)

☑ GENETIC_ASSOCIATION_DB	13%	23
☐ OMIM_DISEASE	18%	32

Combined View for Selected Annotation

Functional Annotation Clustering new!

2D View

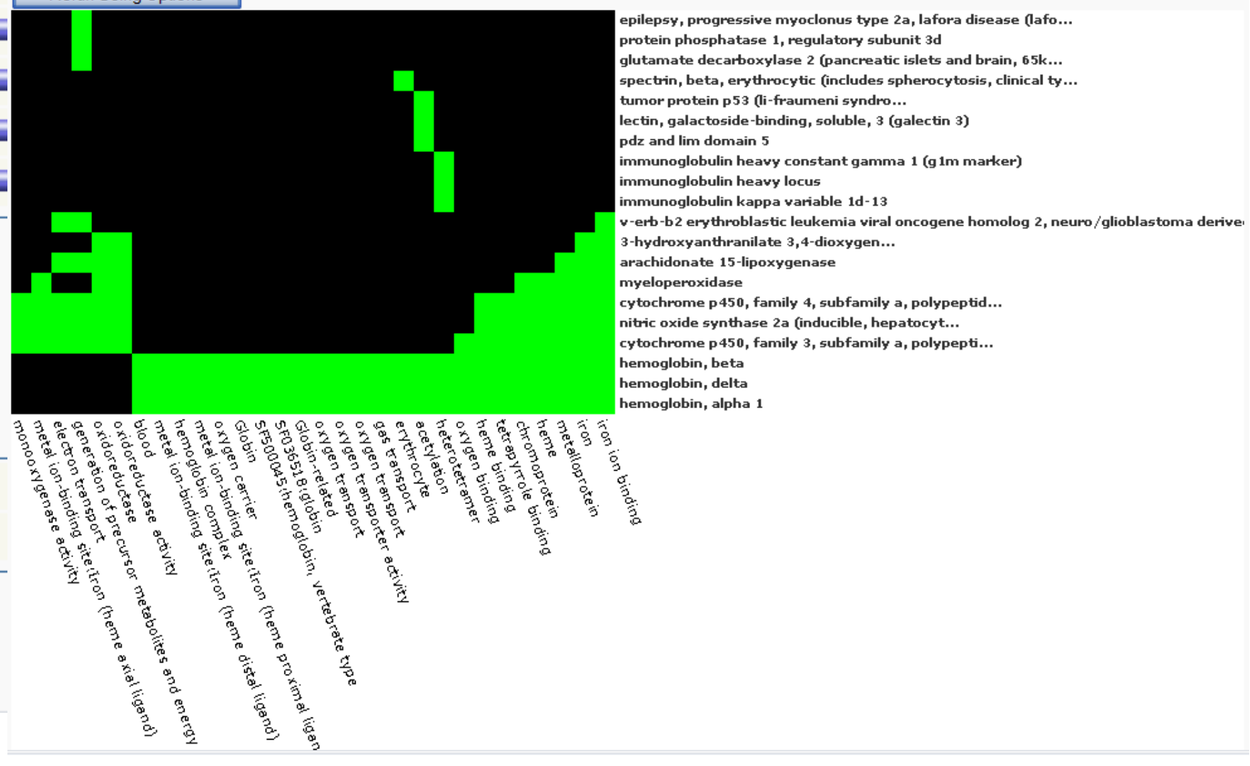
Help

corresponding gene-term association positively reported ■ corresponding gene-term association not reported yet

Download File ViewEditor

Options

Rerun Using Options



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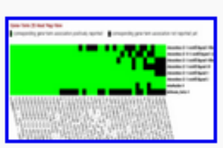
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DAVID (https://david.ncifcrf.gov)

Convert NCBI Entrez Gene IDs to RefSeq Accession Numbers

Upload List Background

Upload Gene List

Demolist 1 Demolist 2

Upload Help

Step 1: Enter Gene List

A: Paste a list

Clear

Or

B:Choose From a File

Browse...

Step 2: Select Identifier

AFFY_ID

Step 3: List Type

Gene List

Background

Step 4: Submit List

Submit List

Gene ID Conversion Tool

Submit your gene list to start conversion!

The Cross-Conversion of Gene ID Types:

- Entrez Gene ID
- Affy ID
- GenBank Accession
- Genpept Accession
- NCBI GI
- PIR Accession
- PIR ID
- PIR NREF ID
- RefSeq Genomic Accession
- RefSeq mRNA Accession
- RefSeq Protein Accession
- RefSeq RNA Accession
- Unigene
- UNIPROT Accession
- UNIPROT ID
- UNIREF100 ID
- Official Gene Symbol new!
- Not Sure new!

Upload List Background

Upload Gene List

Demolist 1 Demolist 2

Upload Help

Step 1: Enter Gene List

A: Paste a list

3493
3512
10562
3535
5284

Clear

Or

B:Choose From a File

Browse...

Step 2: Select Identifier

ENTREZ_GENE_ID

Step 3: List Type

Gene List

Background

Step 4: Submit List

Submit List

us how you like the tool

chnical notes of the tool

Contact us for questions

DAVID (https://david.ncifcrf.gov)

Upload | List | Background

Gene List Manager

Select to limit annotations by one or more species Help

- Use All Species -
HOMO SAPIENS(68)
UNKNOWN(4)
UNIDENTIFIED(1)

Select

List Manager Help

Uploaded List_1

Select List to:

Use | Rename | Remove | Combine

Show Gene List new!

View Unmapped Ids

Convert the gene list being selected in left panel to REFSEQ_MRNA

Submit

Gene ID Conversion Tool Result

Right-click to Download the result Help

Submit Converted List to DAVID as a Gene List | Submit Converted List to DAVID as a Background

Gene Accession Conversion Statistics Help

Conversion Summary		
ID Count	**In DAVID DB**	**Conversion**
60	Yes	Successful
8 IDs	Yes	None
0 IDs	No	None
0 IDs	Ambiguous	Pending
Total Unique User IDs: 68		

Summary of Ambiguous Gene IDs		
ID Count	**Possible Source**	**Convert All**

All Possible Sources For Ambiguous IDs		
Ambiguous ID	**Possibility**	**Convert**

From	To	Species	David Gene Name
202	NM_001624	HOMO SAPIENS	ABSENT IN MELANOMA 1
72	NM_001613	HOMO SAPIENS	ACTIN, ALPHA 2, SMOOTH MUSCLE, AORTA
72	NM_001615	HOMO SAPIENS	ACTIN, ALPHA 2, SMOOTH MUSCLE, AORTA
27299	NM_014479	HOMO SAPIENS	ADAM-LIKE, DECYSIN 1
125	NM_000667	HOMO SAPIENS	ALCOHOL DEHYDROGENASE 1A (CLASS I), ALPHA POLYPEPTIDE
125	NM_000668	HOMO SAPIENS	ALCOHOL DEHYDROGENASE 1A (CLASS I), ALPHA POLYPEPTIDE
126	NM_000669	HOMO SAPIENS	ALCOHOL DEHYDROGENASE 1A (CLASS I), ALPHA POLYPEPTIDE
126	NM_000668	HOMO SAPIENS	ALCOHOL DEHYDROGENASE 1A (CLASS I), ALPHA POLYPEPTIDE
125	NM_000669	HOMO SAPIENS	ALCOHOL DEHYDROGENASE 1A (CLASS I), ALPHA POLYPEPTIDE

What if I want to compare several gene lists at a time?

ToppCluster (http://toppcluster.cchmc.org)

Cincinnati Children's Biomedical Informatics

ToppCluster

A multiple gene list feature enrichment analyzer for the dissection of biological systems

Navigation
- Main
- Alternative Entry Methods

Information
- Disclaimer
- Documentation
- Supplementary

ToppGene
- Database Info
- Links

Paste input list Load Sample Data

Symbols are HGNC Symbol

Cluster Name Kidney

remove

Genes

ALDH8A1
LOC340094
LOC134147
SLC36A2
DZIP1
EHHADH
BTC
TMEM12
LOC388588
DNASE1L3
KLHDC7A
BBOX1
HOXD10
GLDC
AQP2
WDR72
KCNK5
VNN1
LOC441748
LOC348174
GATM
EMX1
DKFZP586D0919
EMX2
UNC5CL
BTBD5
HNF4G
LOC285733
PPARGC1A
DHDH

Symbols are HGNC Symbol

Cluster Name

remove

- HGNC Symbol
- HGNC Symbol and Synonyms
- Entrez ID
- Ensembl ID
- RefSeq
- Uniprot

CYP3A4
ALDH8A1
JUB
CYP3A5
A2M
CYP3A7
AQP9
MASP2
EHHADH
CYP2D6
TMEM12

ToppCluster (http://toppcluster.cchmc.org)

Options

Feature	Correction	p-Value cutoff	Gene Limits
All	Bonferroni	0.05	1 ≤ n ≤ 1500
GO: Molecular Function	Bonferroni	0.05	1 ≤ n ≤ 1500
GO: Biological Process	Bonferroni	0.05	1 ≤ n ≤ 1500
GO: Cellular Component	Bonferroni	0.05	1 ≤ n ≤ 1500
Human Phenotype	Bonferroni	0.05	1 ≤ n ≤ 1500
Mouse Phenotype	Bonferroni	0.05	1 ≤ n ≤ 1500
Domain	Bonferroni	0.05	1 ≤ n ≤ 1500
Pathway	Bonferroni	0.05	1 ≤ n ≤ 1500
Pubmed	Bonferroni	0.05	1 ≤ n ≤ 1500
Interaction	Bonferroni	0.05	1 ≤ n ≤ 1500
Cytoband	Bonferroni	0.05	1 ≤ n ≤ 1500
TFBS	Bonferroni	0.05	1 ≤ n ≤ 1500
Gene Family	Bonferroni	0.05	1 ≤ n ≤ 1500
Coexpression	Bonferroni	0.05	1 ≤ n ≤ 1500
Computational	Bonferroni	0.05	1 ≤ n ≤ 1500
MicroRNA	Bonferroni	0.05	1 ≤ n ≤ 1500
Drug	Bonferroni	0.05	1 ≤ n ≤ 1500
Disease	Bonferroni	0.05	1 ≤ n ≤ 1500

Chose Toppcluster output format: Network Generator

Network Generator

Interactive

- Comma Separated Values
- GenePattern Format (GCT)
- Tab Separated Values
- HTML Table
- Network Generator

Batch

- Comma Separated Values
- Tab Separated Values
- Clustered Data (Zipped)
- PDF Heatmap

Gene Sets

Kidney
303 known - 59 unknown

Original	Human Symbol	Entrez ID
ALDH8A1	ALDH8A1	64577
LOC340094	LOC340094	340094
SLC36A2	SLC36A2	153201
DZIP1	DZIP1	22873
EHHADH	EHHADH	1962
BTC	BTC	685
LOC388588	LOC388588	388588
DNASE1L3	DNASE1L3	1776
KLHDC7A	KLHDC7A	127707
BBOX1	BBOX1	8424
HOXD10	HOXD10	3236
GLDC	GLDC	2731
AQP2	AQP2	359

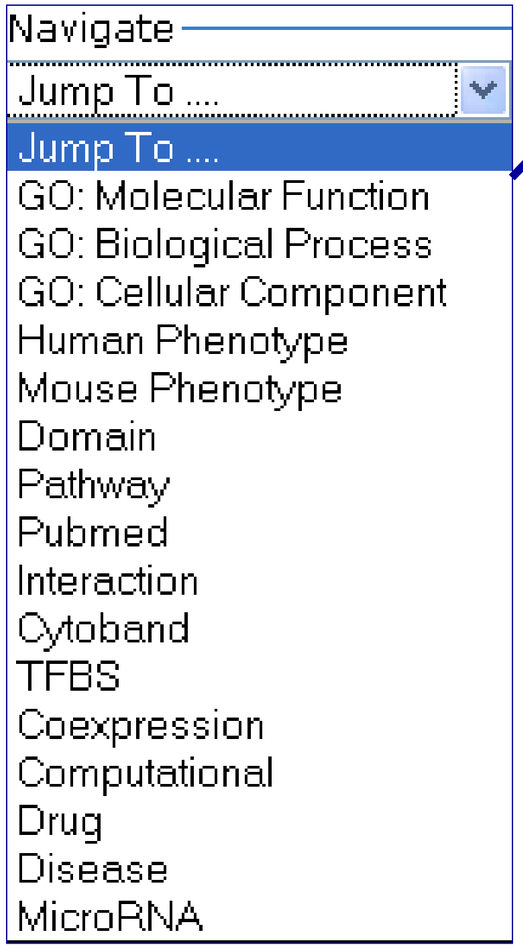
Liver
279 known - 30 unknown

Original	Human Symbol	Entrez ID
CYP3A4	CYP3A4	1576
ALDH8A1	ALDH8A1	64577
JUB	JUB	84962
CYP3A5	CYP3A5	1577
A2M	A2M	2
CYP3A7	CYP3A7	1551
AQP9	AQP9	366
MASP2	MASP2	10747
EHHADH	EHHADH	1962
CYP2D6	CYP2D6	1565
RFXAP	RFXAP	5994
DNASE1L3	DNASE1L3	1776
HEMGN	HEMGN	55363
AGTR1	AGTR1	185

Pancreas
134 known - 46 unknown

Original	Human Symbol	Entrez ID
APOBEC2	APOBEC2	10930
EDN3	EDN3	1908
SYT5	SYT5	6861
SLC44A4	SLC44A4	80736
C14orf50	C14orf50	145376
CDH22	CDH22	64405
TTR	TTR	7276
ERO1LB	ERO1LB	56605
FBXO27	FBXO27	126433
GPR44	GPR44	11251
PPP1R1A	PPP1R1A	5502
GP2	GP2	2813
CPA2	CPA2	1358
PLA2G1B	PLA2G1B	5319

ToppCluster (http://toppcluster.cchmc.org)



Navigate: Jump To .... | Links: Back to Start, Shareable Link | Highlighting: Highlight genes, Clear | Network Generator: Select nodes to be included in the network Then click next, Next »

Category	ID	Title (or Source)		Kidney_logP	Liver_logP	Pancreas_logP	Kidney_GeneSet
GO: Molecular Function				pValues			
GO: Molecular Function	GO:0048037	cofactor binding	☑	☑ 3.8132	☑ 10.0000		ACADSB AGXT2 ALDH6A1 CHDH DDC DMGDH EHHADH FMO1 GCSH GLDC GPT HAO2 HNF4A MIOX MOSC2 NOX4 OGDHL PAH
GO: Molecular Function	GO:0004252	serine-type endopeptidase activity	☑		☑ 10.0000	☑ 3.3520	
GO: Molecular Function	GO:0005215	transporter activity	☑	☑ 10.0000	☑ 3.0795		ABCC6 AQP2 ATP6V0A4 ATP6V0D2 ATP6V1G3 CLCNKB CLDN16 CUBN FXYD2 FXYD4 HCN3 KCNJ1 KCNJ15 KCNJ16 KCNK5 LOC153328 LRP2 OSTBETA PDZK1 RBP5 SCNN1G SLC10A2 SLC12A1 SLC12A3 SLC13A1 SLC13A2 SLC13A3 SLC16A12 SLC16A7 SLC16A9 SLC17A1 SLC17A3 SLC1A1 SLC22A2 SLC22A6 SLC22A7 SLC22A8 SLC23A1 SLC23A3 SLC26A7 SLC27A2 SLC28A1 SLC2A2 SLC2A9 SLC30A2 SLC34A1 SLC36A2 SLC3A1 SLC4A4 SLC4A9 SLC5A11 SLC5A12 SLC5A2 SLC5A8 SLC6A13 SLC6A19 SLC6A3 SLC7A13 SLC7A9 SLCO4C1 TRPM6
GO: Molecular Function	GO:0017171	serine hydrolase activity	☑		☑ 10.0000	☑ 2.7787	
GO: Molecular Function	GO:0031406	carboxylic acid binding	☑	☑ 2.1541	☑ 10.0000		DMGDH DPYS FOLR3 FTCD GCSH GLDC HNF4A NR1H4 PAH PCK1 SLC1A1
GO: Molecular Function	GO:0016491	oxidoreductase activity	☑	☑ 2.0183	☑ 10.0000		ACADSB ADH6 ALDH6A1 ALDH8A1 BBOX1 CHDH CYP17A1 CYP27B1 CYP4V2 DAO DHDH DIO1 DMGDH EHHADH FMO1 GLDC HAO2 HGD HSDL1 MIOX MOSC2 NDUFC1 NOX4 OGDHL PAH PIPOX PRODH2
GO: Molecular Function	GO:0005496	steroid binding	☑	☑ 1.5055	☑ 10.0000		AGXT2 CALB1 DDC GLDC GPT HNF4A HNF4G KL MOSC2 NR1H4
GO: Molecular Function	GO:0001871	pattern binding	☑		☑ 10.0000		
GO: Molecular Function	GO:0008324	cation transmembrane transporter activity	☑	☑ 10.0000			ATP6V0A4 ATP6V0D2 ATP6V1G3 CLDN16 FXYD4 HCN3 KCNJ1 KCNJ15 KCNJ16 KCNK5 SCNN1G SLC10A2 SLC12A1 SLC12A3 SLC13A1 SLC13A2 SLC13A3 SLC17A3 SLC1A1 SLC22A2 SLC22A8 SLC23A1 SLC28A1 SLC2A2 SLC2A9 SLC30A2 SLC36A2 SLC4A4 SLC5A11 SLC5A2 SLC6A13 SLC6A19 SLC6A3 TRPM6
GO: Molecular Function	GO:0016705	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	☑		☑ 10.0000		

Network Generator

Warning: because of the network size, some options like layout, preview and PNG have been limited or hidden.

Summary

2126 checked boxes
2016 nodes in an ABSTRACTED network.
2600 nodes in a GENE LEVEL network.

Method

- (•) **ABSTRACTED** A Feature to Cluster network where the score is used as the edge weight..
- ( ) **GENE LEVEL** A gene-based network where each gene connects from a Cluster to a Feature.

Method Options

- [ ] Create a Category node linked to all features of that category

File Format

- (•) **XGMML** An XML based format compatible with Cytoscape. (more information)
- ( ) **TEXT** A Simple Text Format.
- ( ) **GEXF** An XML based format compatible with Gephi. (more information)

Begin

Network Generator

Summary

279 checked boxes
265 nodes in an ABSTRACTED network.
660 nodes in a GENE LEVEL network.

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Layout Algorithm

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- ( ) Fruchterman-Reingold.
- ( ) Spring.
- ( ) Circle.
- ( ) Meyer's Self-Organizing.

File Format

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Begin Preview

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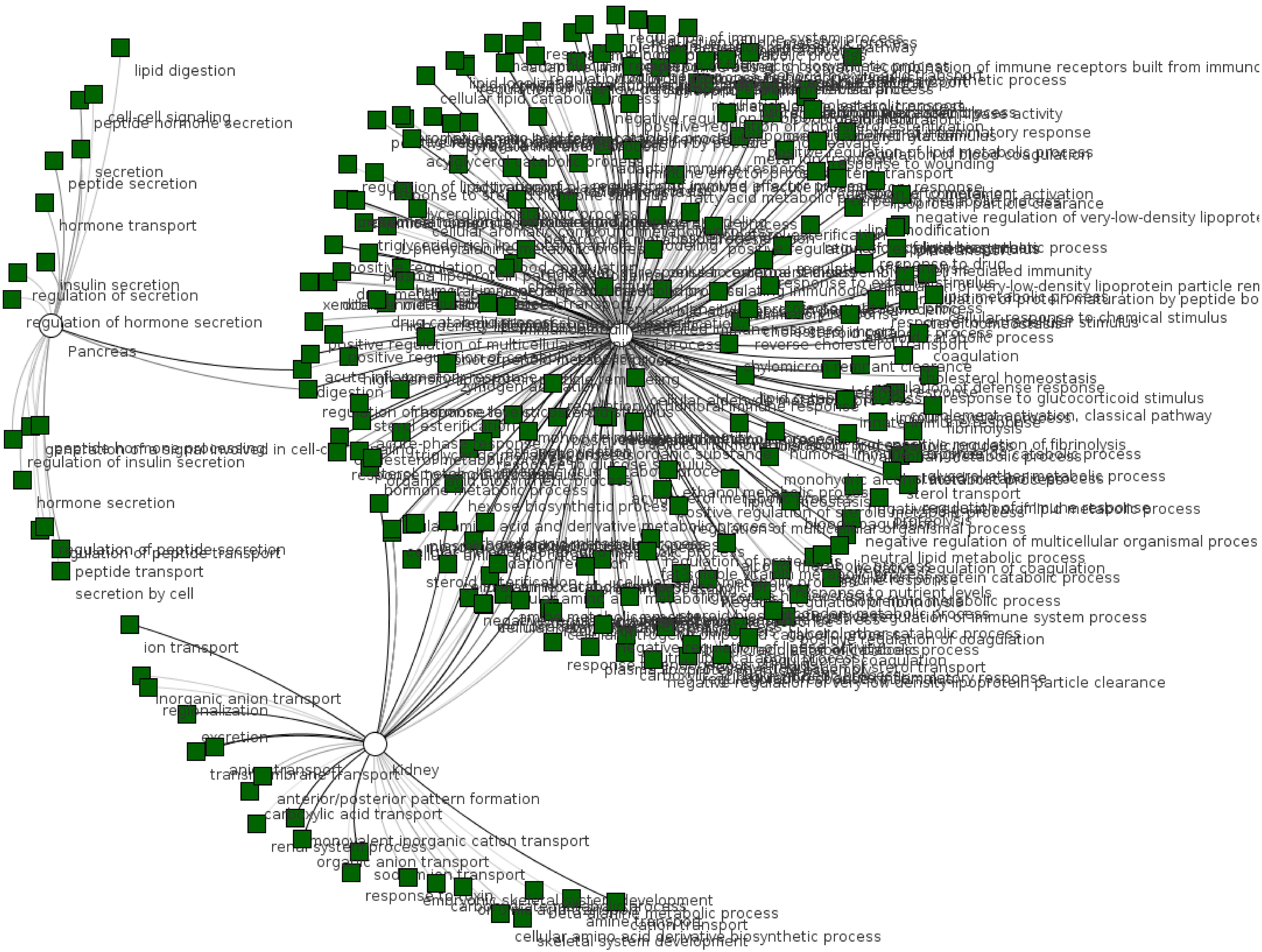

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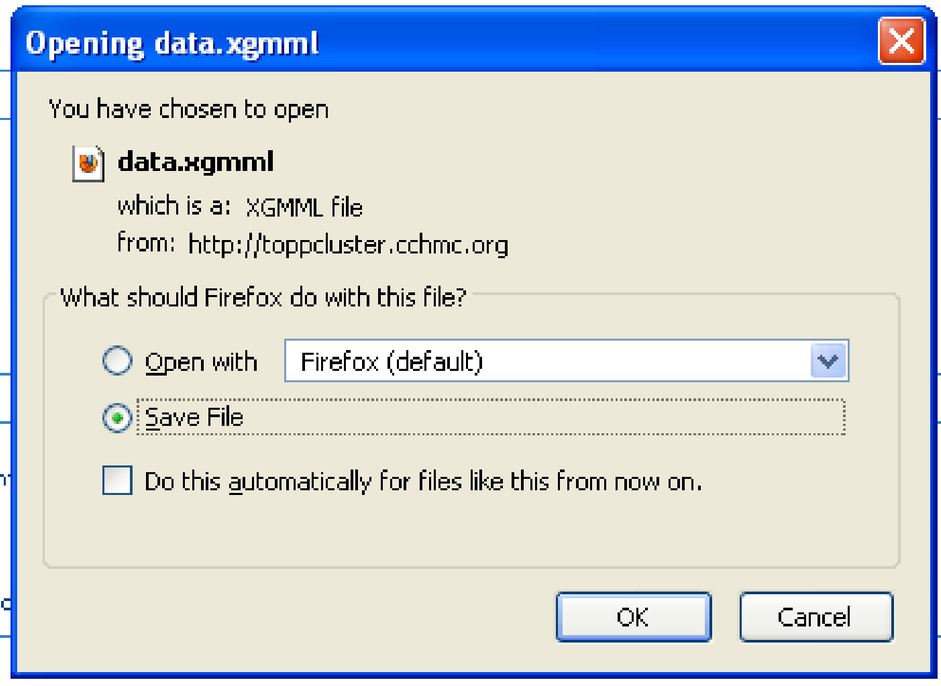
- **GEXF** An XML based format compatible with Gephi. (more informatic

Begin **Preview**

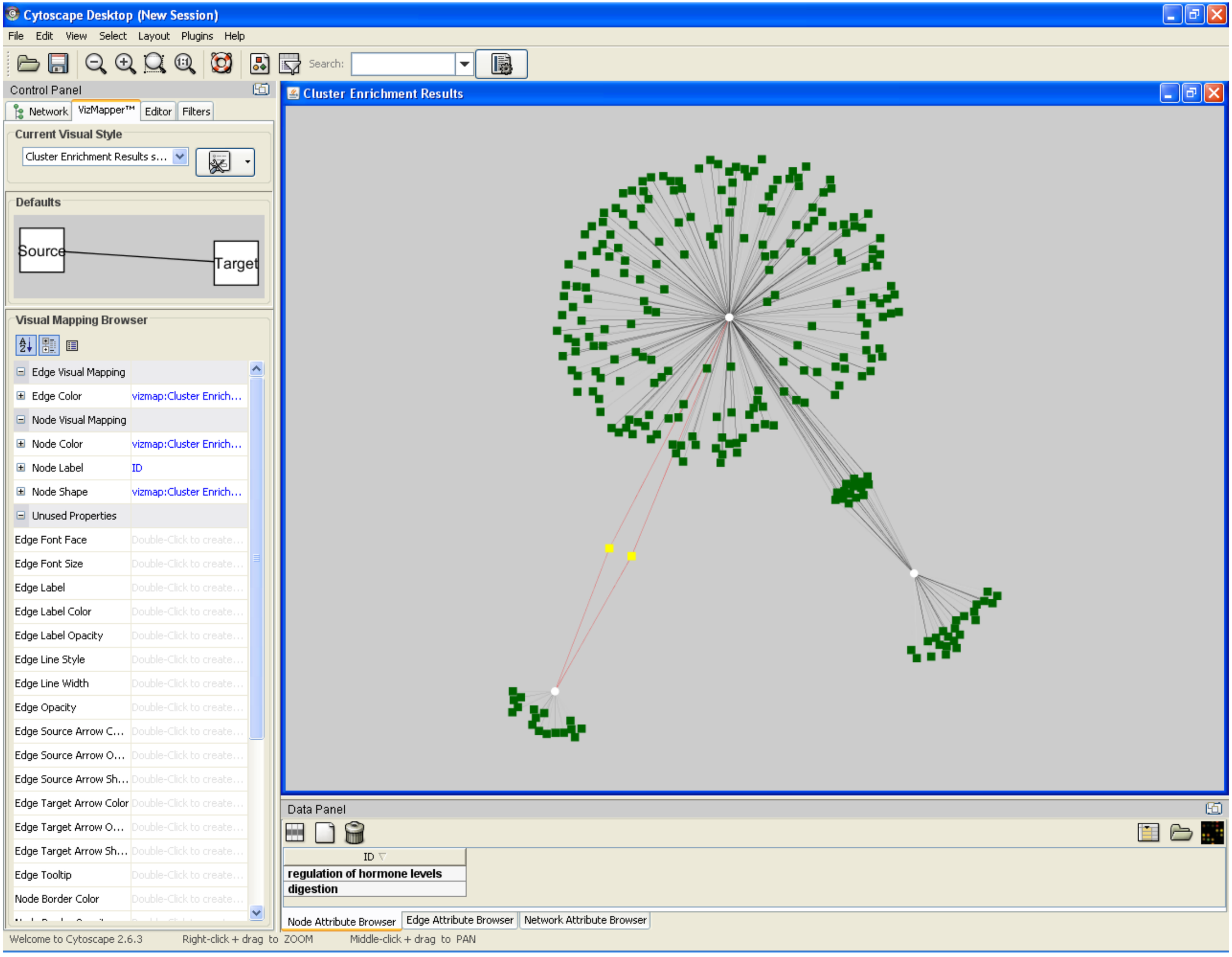


Cytoscape (http://cytoscape.org)

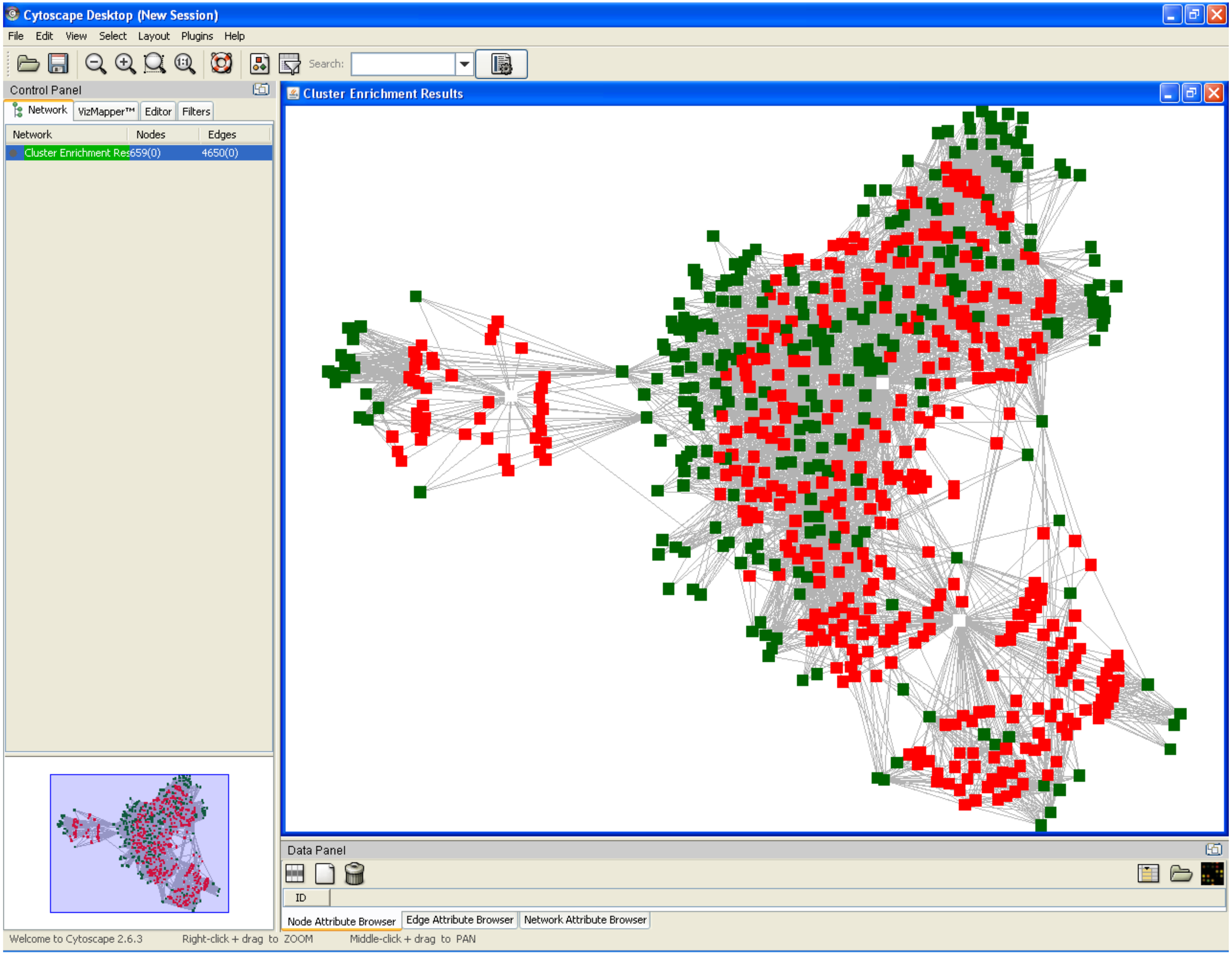
Gephi (http://gephi.org)

Should be installed on your computer and the downloaded files should be imported into these applications

Cytoscape Network (Abstract View)



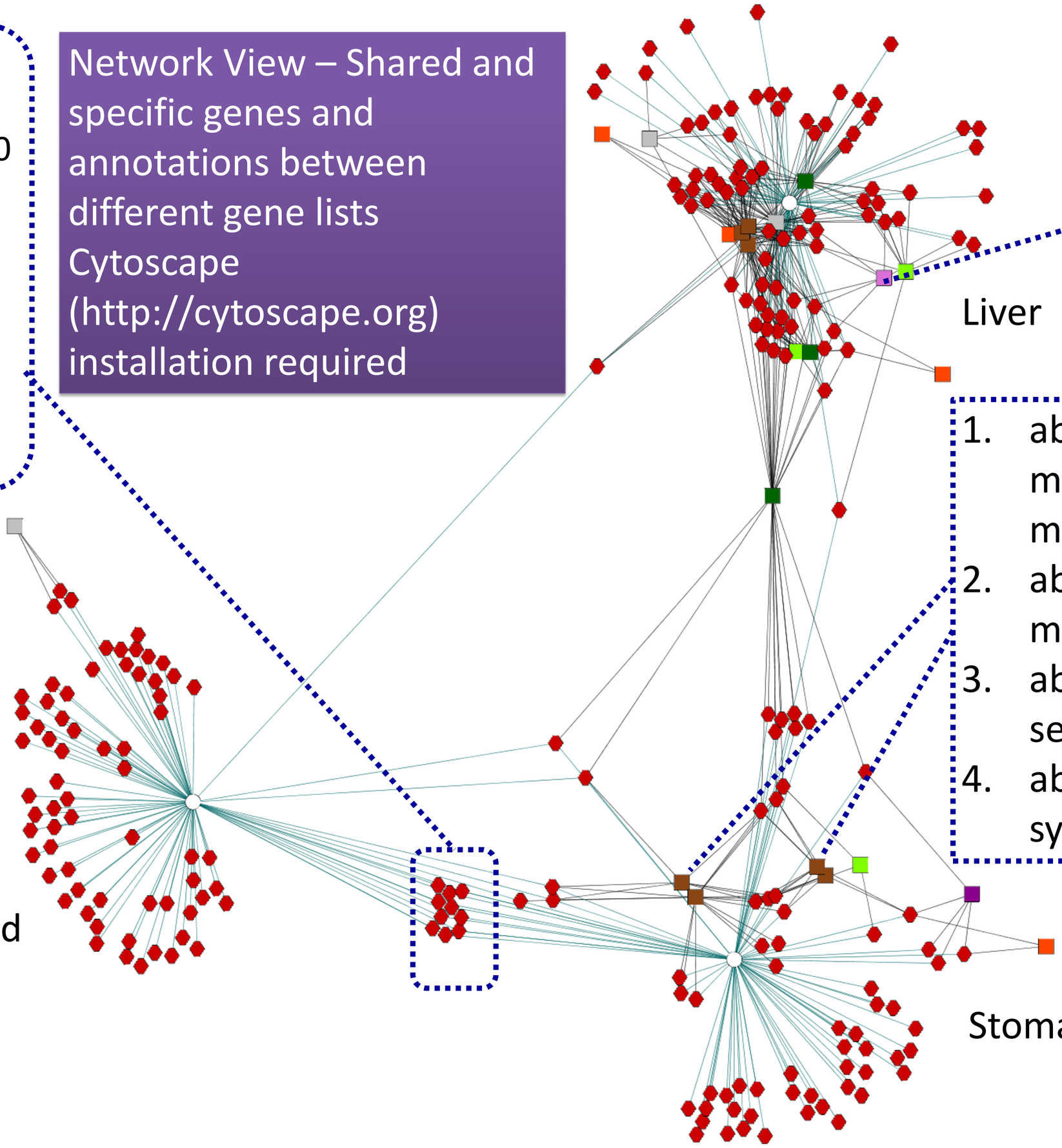
Cytoscape Network (GeneLevel View)



Cytoscape Network (GeneLevel View)

EHF
COL15A1
LOC100130100
IGHA1
LTF
IGKC
IGL@
FAM129A
ATP8B1
IGLC2

Network View – Shared and specific genes and annotations between different gene lists Cytoscape (http://cytoscape.org) installation required



V$HNF1

Liver

1. abnormal gastric mucosa morphology
2. abnormal stomach morphology
3. abnormal digestive secretion
4. abnormal digestive system physiology

Salivary Gland

Stomach

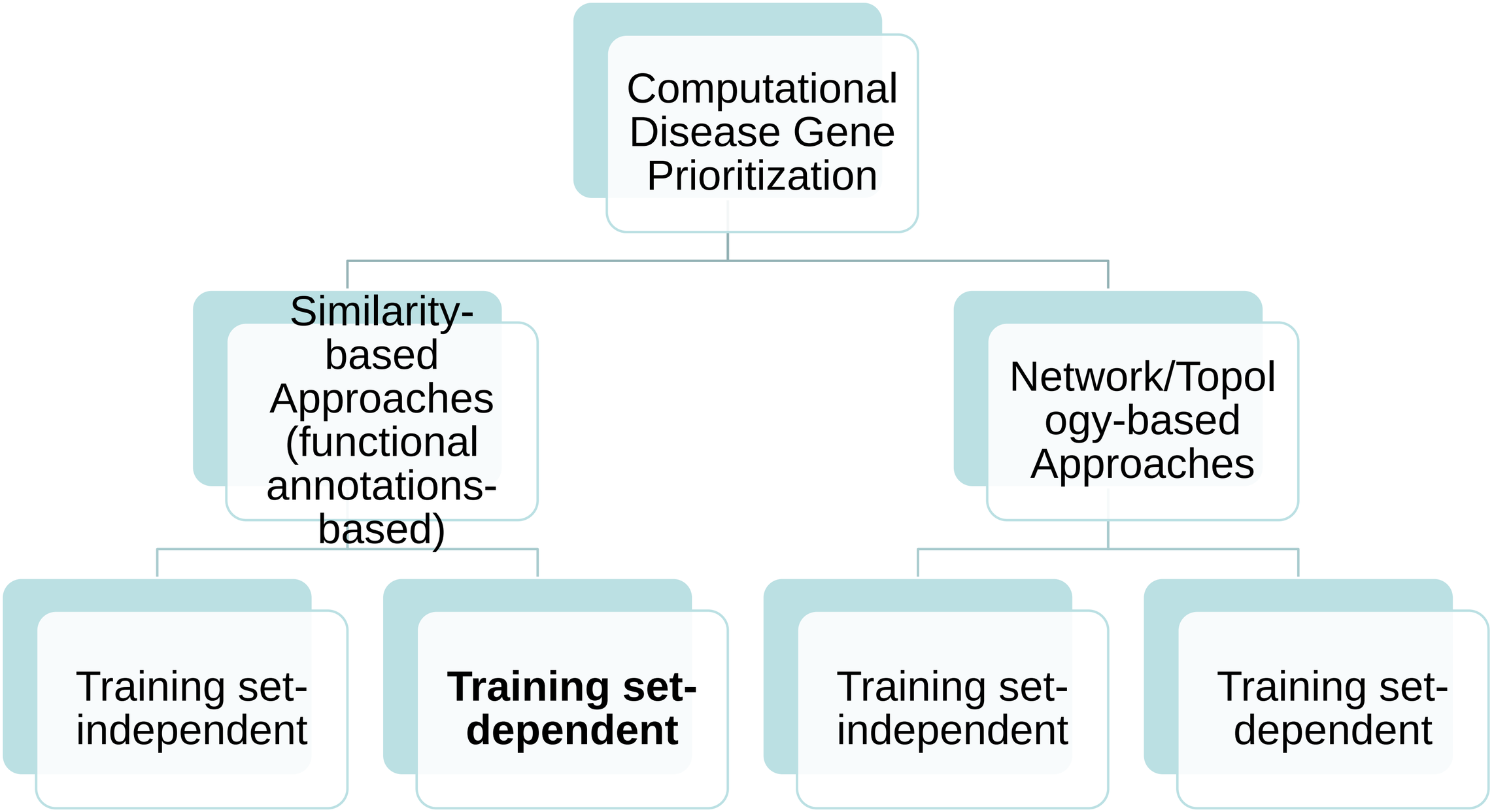
Disease Candidate Gene Prioritization

What, Why, & How

Computational Disease Gene prioritization

- **What**: Computationally assigning likelihood of gene involvement in generating a disease phenotype
- **Why**: Narrows down the set of genes to be tested experimentally – saves time/resources.
- **How**: “Guilt by Association” - Gene “priority" in disease is assigned in a more “informed” way taking into account a set of relevant features or annotations (e.g., gene expression, function/processes, pathways, model organism phenotype, etc.) - Functional Similarity-based methods

Broad Classification



- Protein-Protein Interactions
- Protein Associations (Functional Linkage)

Functional annotation-based candidate disease gene prioritization

- *Guilt by association* - Reliable predictions about the disease involvement of a gene can be made if several of its partners (e.g., genes with correlated expression profiles or protein interactants or genes involved in same biological process or pathway) share a corresponding annotation.
- Incorporating the prior information or knowledge about a disease (e.g., known disease genes) is critical.
- Challenge: Gather, normalize, and integrate heterogeneous data from multiple sources (and keeping them current).

Functional annotation-based candidate disease gene prioritization – General workflow

- Step 1: List of candidate genes (**Test Set**) to prioritize - linkage regions, chromosomal aberrations, association study loci, differentially expressed gene lists or genes identified by sequencing variants, or the complete genome
- Step 2: **Seed** Genes or **Training Set**: Prior knowledge about the disease - known disease genes, or disease-relevant keywords, or biological processes or pathways.
- Step 3: **Prioritization** methods: Which one to select/use?
- Step 4: **Assessment** - Are the selected training/seed genes, keywords and tools suitable? Can reliable predictions be made using these?
- Step 5: Use multiple tools or multiple sets of seed gene or keywords - **Combine** the results to obtain a **consensus** result

What constitutes a “good” seed gene set?

- **Relevancy**: Review each gene - Domain experts especially for selecting keywords (e.g., disease-relevant phenotypes)
- **Size Matters**: Neither too small nor too large.
  - Too small - may be insufficiently informative
  - Too large - too heterogeneous pattern to be useful.
    - Break them down into multiple random sets
    - Filter them based on additional features (e.g., genes associated with a BP term + MP term)
  - Ideally 6 – 30

What constitutes a “good” seed gene set?

- **Robustness**: How robust are the ranking results using a particular seed set?

Cross-validation - Assess whether a set of seed genes provides a coherent pattern

- Create multiple sets of seed genes or keywords covering complementary phenotypic aspects of the disease and assess their performance separately.
- Negative control seed genes: Use genes for other unrelated diseases as training set.
  - Top-ranking candidates are same with negative control seed genes – suggests some systematic bias and prioritization results are probably unreliable

Other Quality Control Measures

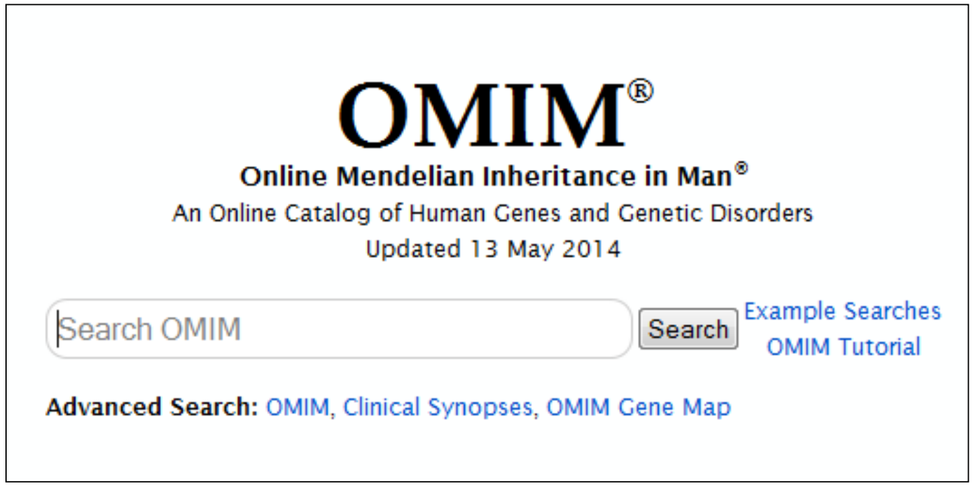
Tool A ranks my "favorite" gene on/among top –
Therefore tool A is the BEST!!!

- **Smaller Test Sets**: Perform prioritizations both on the actual set of candidates and on the whole genome *OR* on a larger set that includes the smaller set of candidates.
  - Are the top-ranking candidates from the small subset rank within the top 5–15% of the whole genome?
  - If not, the prioritization might not have been able to capture enough information to identify good candidates
- **Functional Coherence**: What are the enriched terms for the top ranked candidates? Do they match expectations for the biological process or phenotype of interest?

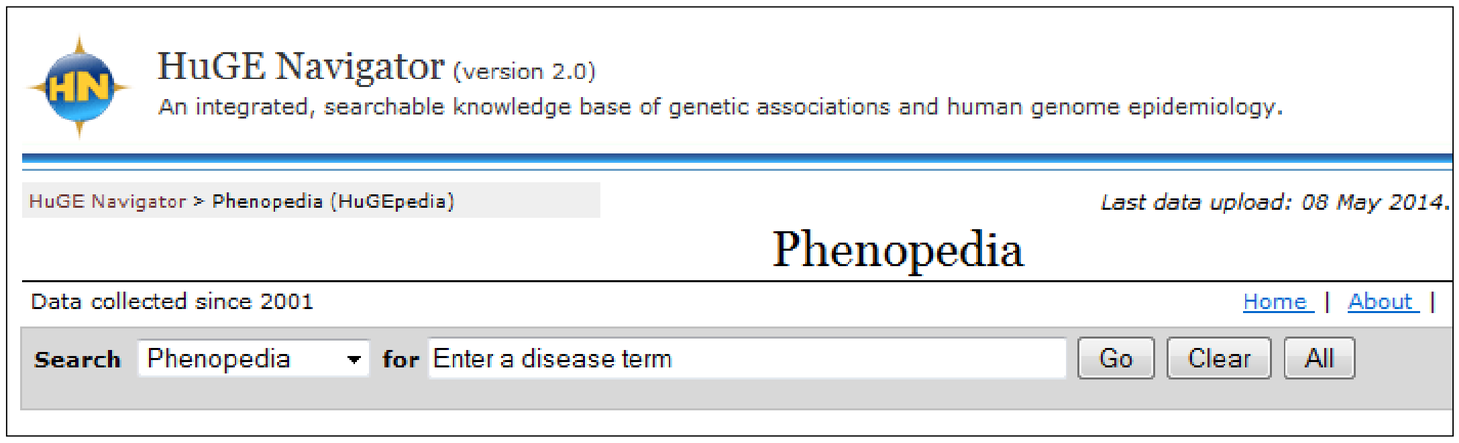
Moreau & Tranchevent, 2012

Resources commonly used for compiling seed set

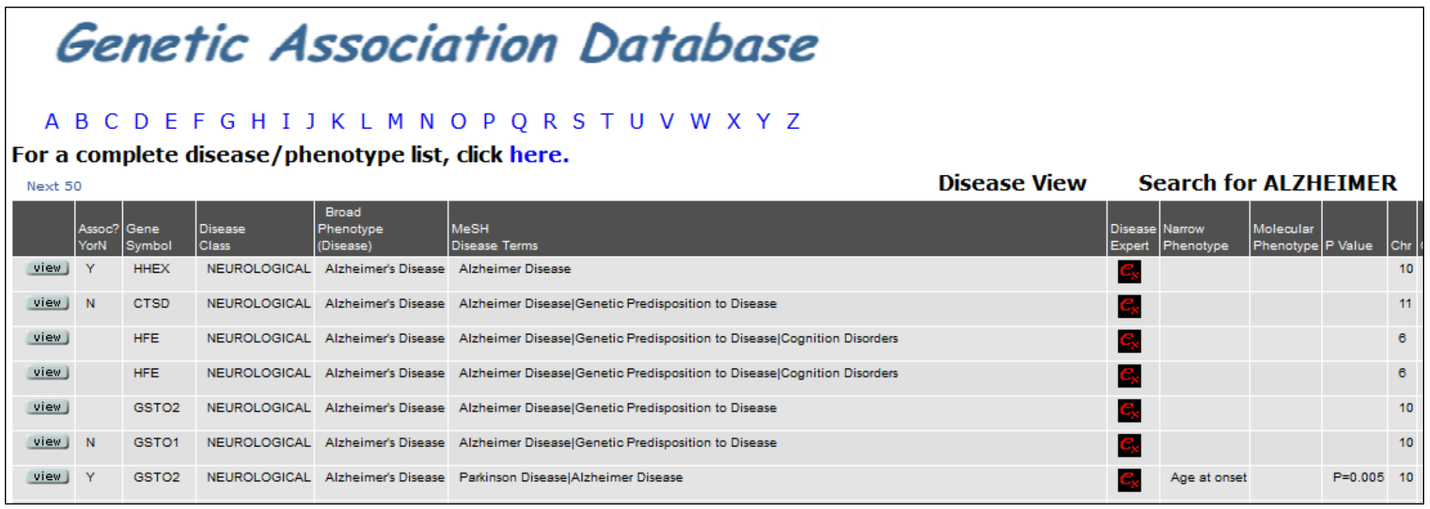
OMIM: http://omim.org



Phenopedia: http://hugenavigator.net

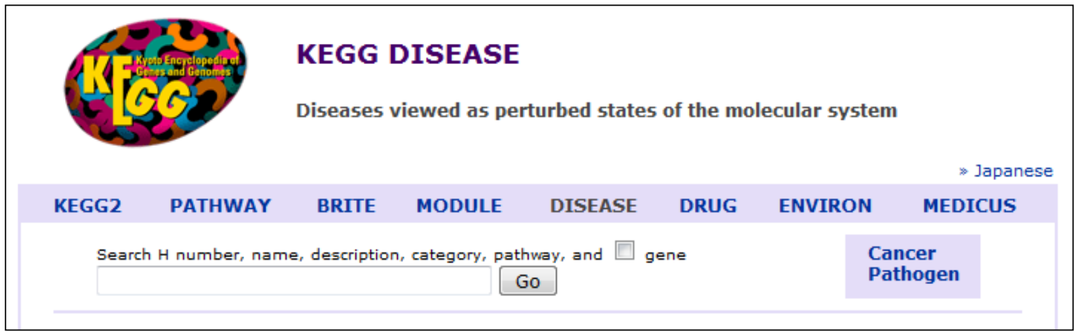


GAD: http://geneticassociationdb.nih.gov



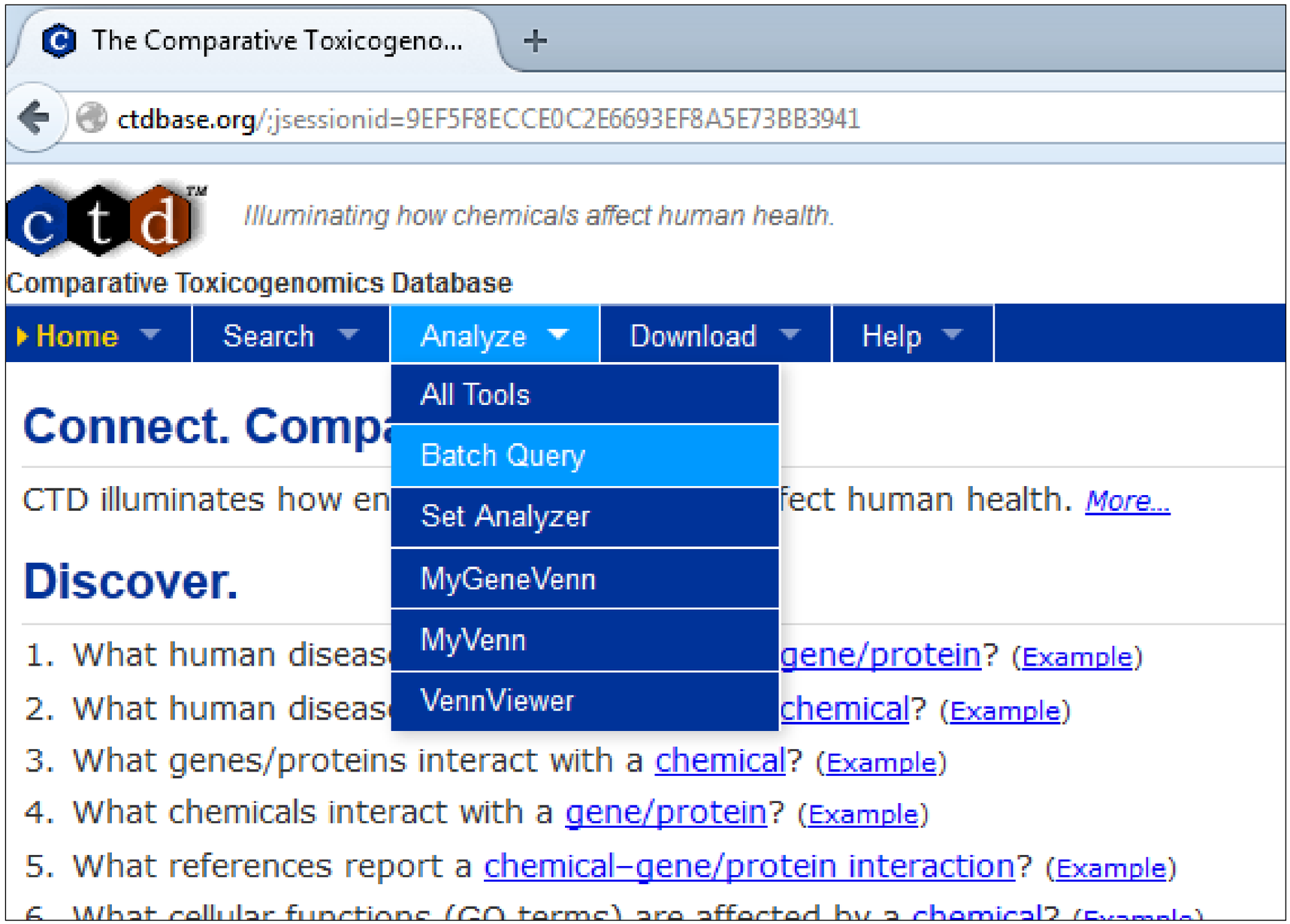
	Assoc? YorN	Gene Symbol	Disease Class	Broad Phenotype (Disease)	MeSH Disease Terms	Disease Expert	Narrow Phenotype	Molecular Phenotype	P Value	Chr
view	Y	HHEX	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease					10
view	N	CTSD	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease|Genetic Predisposition to Disease					11
view		HFE	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease|Genetic Predisposition to Disease|Cognition Disorders					6
view		HFE	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease|Genetic Predisposition to Disease|Cognition Disorders					6
view		GSTO2	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease|Genetic Predisposition to Disease					10
view	N	GSTO1	NEUROLOGICAL	Alzheimer's Disease	Alzheimer Disease|Genetic Predisposition to Disease					10
view	Y	GSTO2	NEUROLOGICAL	Alzheimer's Disease	Parkinson Disease|Alzheimer Disease		Age at onset		P=0.005	10

KEGG Disease: http://www.genome.jp/kegg/disease/



Additional resources for compiling seed set

Comparative Toxicogenomics Database: http://ctdbase.org



Comparative Toxicogenomics Database: http://ctdbase.org

Batch Query

1 Select your input type

- Chemicals (MeSH® names, synonyms, or IDs, or CAS RNs)
- Diseases (MeSH or OMIM names, synonyms, or IDs)
- Genes (NCBI symbols or IDs)
- Gene Ontology terms (GO names, synonyms, or IDs)
- Pathways (KEGG or REACTOME names or IDs)
- References (PubMed® IDs or DOIs)

2 Provide query terms (up to 4,000)

Return-, tab- or |-delimited

Or **upload** a tab-separated file:
Browse... No file selected.
Identifiers column: 1

3 Choose data to download

Data
- Chemical–gene interactions
- Chemical associations
- Gene associations: Curated
- Disease associations: Inferred
- Pathway associations
- Gene Ontology associations

Format
- TSV (tab-separated values)
- CSV (comma-separated values)
- JSON
- XML

Download Clear

1 Select your input type

- Chemicals (MeSH® names, synonyms, or IDs, or CAS RNs)
- Diseases (MeSH or OMIM names, synonyms, or IDs)
- Genes (NCBI symbols or IDs)
- Gene Ontology terms (GO names, synonyms, or IDs)
- Pathways (KEGG or REACTOME names or IDs)
- References (PubMed® IDs or DOIs)

2 Provide query terms (up to 4,000)

Return-, tab- or |-delimited

Or **upload** a tab-separated file:
Browse... No file selected.
Identifiers column: 1

3 Choose data to download

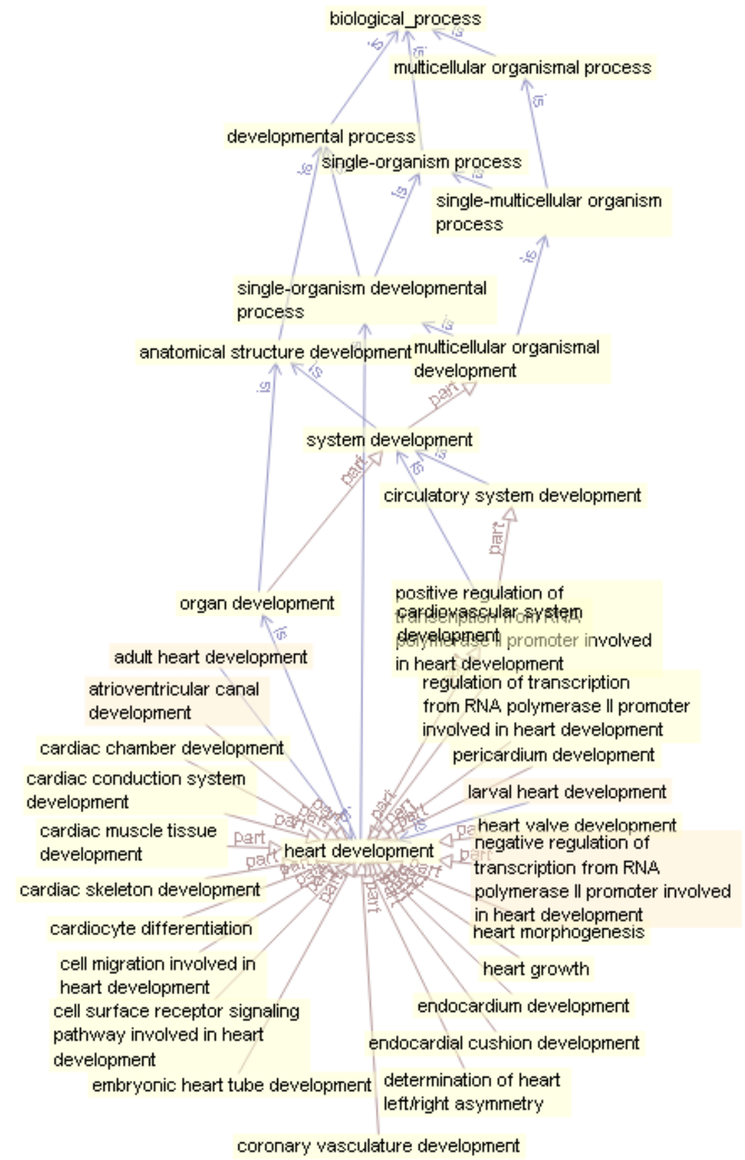
Data
- Chemical–gene interactions
- Chemical associations: All / Curated / Inferred
- Gene associations: All / Curated / Inferred
- Disease associations: Inferred
- Pathway associations
- Gene Ontology associations

Format
- TSV (tab-separated values)
- CSV (comma-separated values)
- JSON
- XML

Download Clear

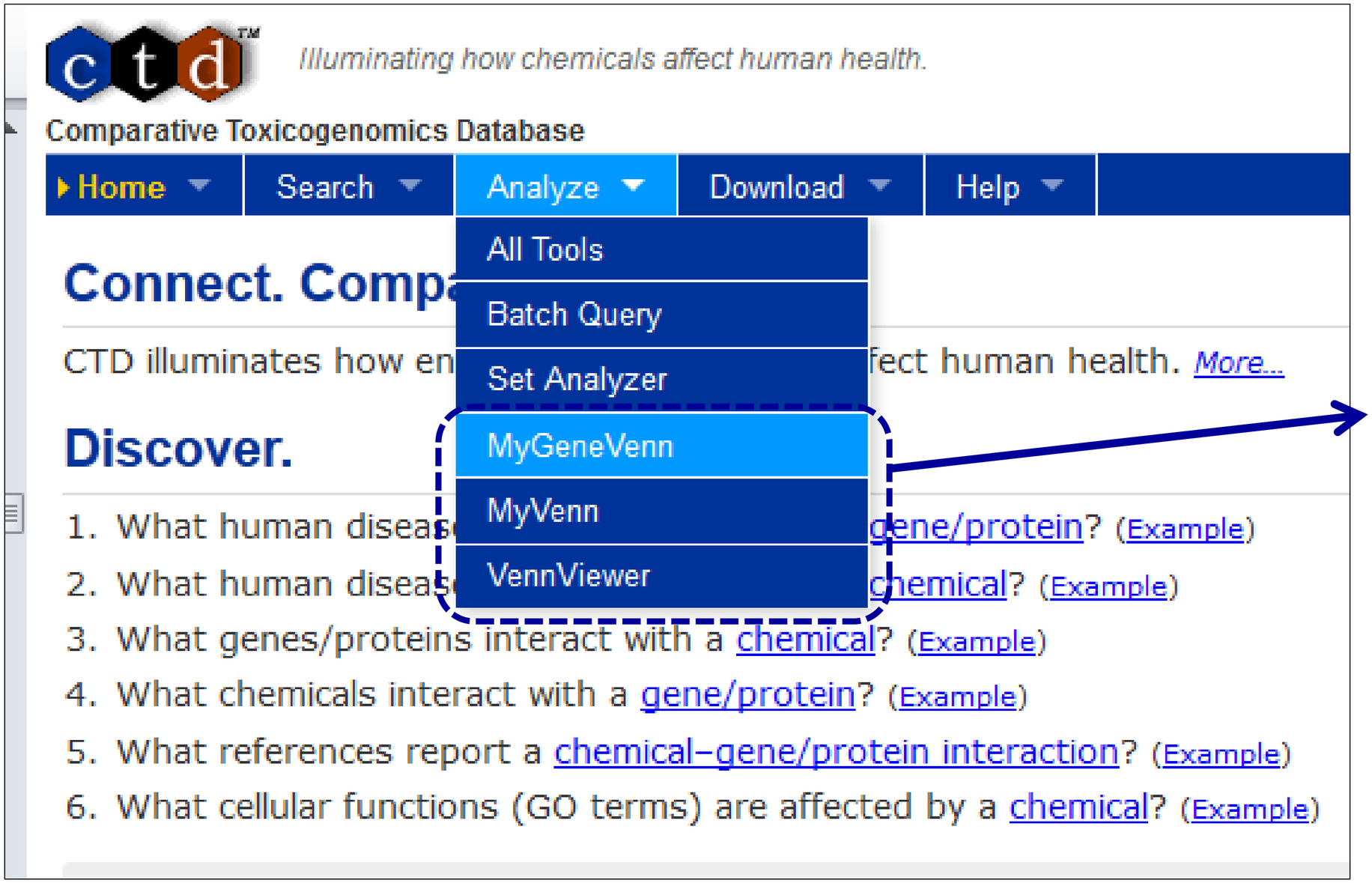
Comparative Toxicogenomics Database: http://ctdbase.org

# Input	GeneSymbol	GeneID	Ontology	GoTermName	GoTermID
go:0007507	TBX20	57057	Biological Process	aortic valve development	GO:0003176
go:0007507	EFNA1	1942	Biological Process	aortic valve morphogenesis	GO:0003180
go:0007507	GATA3	2625	Biological Process	aortic valve morphogenesis	GO:0003180
go:0007507	NOTCH1	4851	Biological Process	aortic valve morphogenesis	GO:0003180
go:0007507	TBX20	57057	Biological Process	aortic valve morphogenesis	GO:0003180
go:0007507	TWIST1	7291	Biological Process	aortic valve morphogenesis	GO:0003180
go:0007507	FHL2	2274	Biological Process	atrial cardiac muscle cell development	GO:0055014
go:0007507	MYH15	22989	Biological Process	atrial cardiac muscle cell development	GO:0055014
go:0007507	NKX2-5	1482	Biological Process	atrial cardiac muscle cell development	GO:0055014
go:0007507	NKX2-6	137814	Biological Process	atrial cardiac muscle cell development	GO:0055014
go:0007507	ISL1	3670	Biological Process	atrial cardiac muscle cell differentiation	GO:0055011
go:0007507	RBM24A	405801	Biological Process	atrial cardiac muscle tissue development	GO:0003228
go:0007507	RBM24B	562236	Biological Process	atrial cardiac muscle tissue development	GO:0003228
go:0007507	BMP10	27302	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	MYH6	4624	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	PITX2	5308	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	PROX1	5629	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	TNNT2	7139	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	TNNT2A	58071	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	WNT2	7472	Biological Process	atrial cardiac muscle tissue morphogenesis	GO:0055009
go:0007507	MYH6	4624	Biological Process	atrial cardiac myofibril assembly	GO:0055004
go:0007507	MYL7	58498	Biological Process	atrial cardiac myofibril assembly	GO:0055004
go:0007507	ANK2	287	Biological Process	atrial septum development	GO:0003283
go:0007507	DAND5	199699	Biological Process	atrial septum development	GO:0003283
go:0007507	GJA5	2702	Biological Process	atrial septum development	GO:0003283
go:0007507	NPHP3	27031	Biological Process	atrial septum development	GO:0003283
go:0007507	TBX5	6910	Biological Process	atrial septum development	GO:0003283
go:0007507	CFC1	55997	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	CFC1B	653275	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	CYR61	3491	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	GATA4	2626	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	GJA5	2702	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	HEY2	23493	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	ISL1	3670	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	NKX2-5	1482	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	NOTCH2	4853	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	SMO	6608	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	TBX20	57057	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	TBX5	6910	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	ZFPM1	161882	Biological Process	atrial septum morphogenesis	GO:0060413
go:0007507	ACVR1	90	Biological Process	atrial septum primum morphogenesis	GO:0003289
go:0007507	GATA4	2626	Biological Process	atrial septum primum morphogenesis	GO:0003289
go:0007507	SOX4	6659	Biological Process	atrial septum primum morphogenesis	GO:0003289
go:0007507	WHSC1	7468	Biological Process	atrial septum primum morphogenesis	GO:0003289
go:0007507	GATA4	2626	Biological Process	atrial septum secundum morphogenesis	GO:0003290
go:0007507	WHSC1	7468	Biological Process	atrial septum secundum morphogenesis	GO:0003290
go:0007507	GJA1	2697	Biological Process	atrial ventricular junction remodeling	GO:0003294
go:0007507	GJA5	2702	Biological Process	atrial ventricular junction remodeling	GO:0003294
go:0007507	PDLIM7	9260	Biological Process	atrial ventricular junction remodeling	GO:0003294
go:0007507	TBX5A	30071	Biological Process	atrial ventricular junction remodeling	GO:0003294
go:0007507	TBX3	6926	Biological Process	atrioventricular bundle cell differentiation	GO:0003167
go:0007507	ACTC1A	408256	Biological Process	atrioventricular canal development	GO:0036302
go:0007507	FOXN4	121643	Biological Process	atrioventricular canal development	GO:0036302
go:0007507	GATA4	2626	Biological Process	atrioventricular canal development	GO:0036302
go:0007507	HAS2	3037	Biological Process	atrioventricular canal development	GO:0036302
go:0007507	MMD	23531	Biological Process	atrioventricular canal development	GO:0036302
go:0007507	PTPN11	5781	Biological Process	atrioventricular canal development	GO:0036302



Ontological tree – Children nodes and their annotations also used

Comparative Toxicogenomics Database: http://ctdbase.org



Explore the Venn utilities – Handy for generating/comparing annotated gene lists (seed set selection)

NCBI MedGen - http://www.ncbi.nlm.nih.gov/medgen

NCBI Resources How To Sign in to NCBI

MedGen MedGen Search

Limits Advanced Help

MedGen MedGen Search

Advanced Help

Limits

Search Field Tags

Field: All Fields

Chromosomes clear

1	7	13	19	MT
2	8	14	20	Unknown
3	9	15	21	
4	10	16	22	
5	11	17	X	
6	12	18	Y	

Show only clear

- Found in *GeneReviews*
- With genetic testing
- Associated with a gene

Record Category clear

- Disease Focus
- Clinical Features

Vocabulary clear

GTR HPO MeSH NCI OMIM

Clear Search

NCBI's portal to information related to Medical Genetics. Terms from the NIH Genetic Testing Registry (GTR), UMLS, HPO, ClinVar and other sources are aggregated into concepts and their gene annotations where available.

NCBI MedGen - http://www.ncbi.nlm.nih.gov/medgen

Alzheimer's disease (AD)

MedGen UID: 1853 • Concept ID: C0002395 • Disease or Syndrome

Synonyms: AD; Alzheimer dementia (AD); ALZHEIMER DISEASE, FAMILIAL, 1, AUTOSOMAL RECESSIVE; Alzheimer sclerosis; Alzheimer syndrome; Alzheimer's disease; Alzheimer-type dementia (ATD); dementia; Dementia; Early-Onset F Alzheimer Disease; familial Alzheimer disease (FAD); Presenile and senile dementia; Primary Senile Degenerati Dementia

Modes of inheritance: Heterogeneous
Autosomal dominant inheritance

SNOMED CT: AD - Alzheimer's disease (26929004); Alzheimer disease (26929004); Alzheimers disease (26929004); Alzheime disease (26929004)

Genes: PAXIP1; SORL1; PLAU; NOS3; MPO; HFE; ACE; BLMH; APP; APBB2; A2M

Cytogenetic locations: 10q22.2; 11q24.1; 12p13.31; 17q11.2; 17q22; 17q23.3; 21q21.3; 4p14-13; 6p22.2; 7q36.1; 7q36.2

OMIM: 104300

Molecular resources

- OMIM
- RefSeqGene
- View A2M variations in ClinVar
- View APBB2 variations in ClinVar
- View APP variations in ClinVar
- View BLMH variations in ClinVar
- View ACE variations in ClinVar
- View HFE variations in ClinVar
- View MPO variations in ClinVar
- View NOS3 variations in ClinVar
- View PLAU variations in ClinVar
- View SORL1 variations in ClinVar
- View PAXIP1 variations in ClinVar

Genetic Testing Registry

- Deletion/duplication analysis (2)
- Mutation scanning of select exons (1)
- Research (1)
- Sequence analysis of the entire coding region (14)
- Targeted variant analysis (4
- See all (20)

- Disorder of nervous system
  - Disorder of the central nervous system
    - Disorder of brain
      - Delirium, Dementia, Amnestic, Cognitive Disorders
        - Cognitive disorder
          - Dementia
            - Alzheimer's disease
              - Alzheimer disease, type 6
              - Alzheimer disease, type 7
              - Alzheimer disease, type 8
              - Alzheimer disease, type 9
              - Alzheimer disease, type 10
              - Alzheimer disease, type 11
              - Alzheimer disease, type 12
              - Alzheimer disease, type 13
              - Alzheimer disease, type 14
              - Alzheimer disease, type 15
              - Alzheimer disease, type 16
            - Early-Onset Familial Alzheimer Disease
            - Late-Onset Familial Alzheimer Disease

Table of contents

NCBI BioSystems - http://www.ncbi.nlm.nih.gov/biosystems

NCBI Resources How To

BioSystems | BioSystems | Search

Limits Advanced

BioSystems | BioSystems | Search

Advanced

Limits

Taxonomic Scope

- Conserved BioSystems
- Organism Specific BioSystems

BioSystem Type

- Pathway
- Structural Complex
- Functional Set
- Signature Module

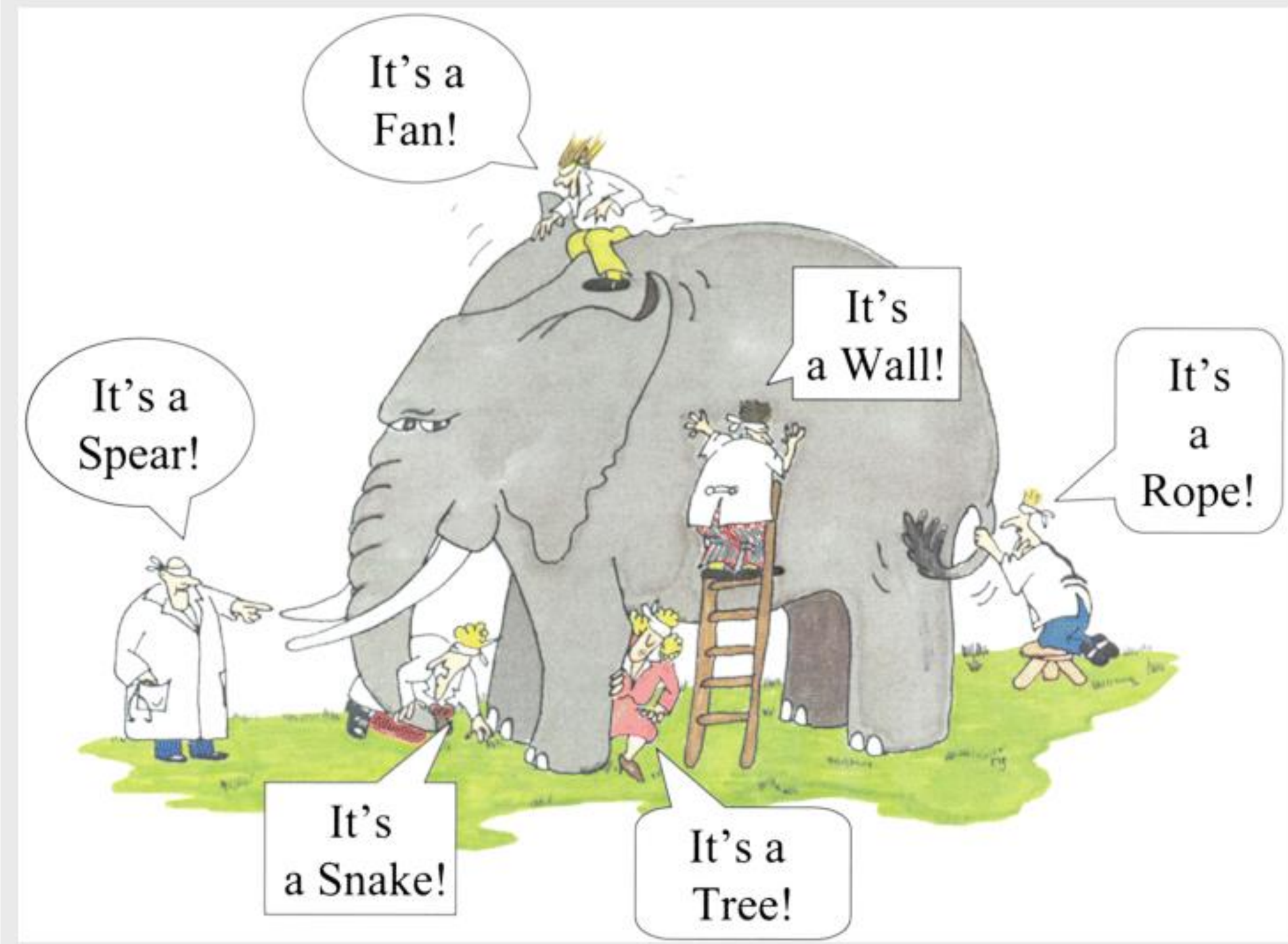
Search Field Tags

- KEGG
- BioCyc & MetaCyc
- Pathway Interaction Database (PID)
- Reactome
- WikiPathways
- Gene Ontology (GO)
- LIPID MAPS

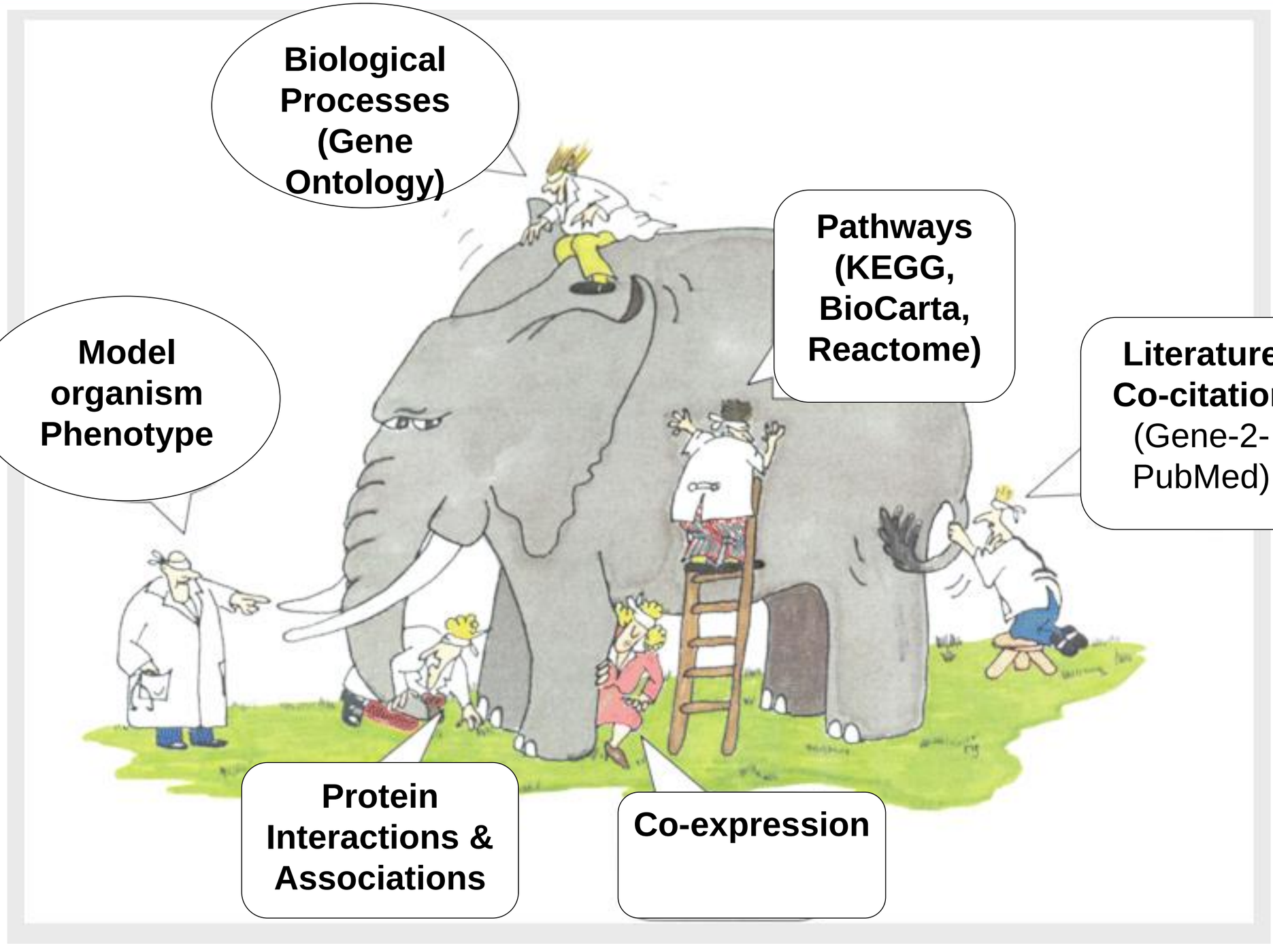
Reset Search

A group of genes that have a pathogenicity or other phenotype associated with them

Functional Similarity – What features to consider?

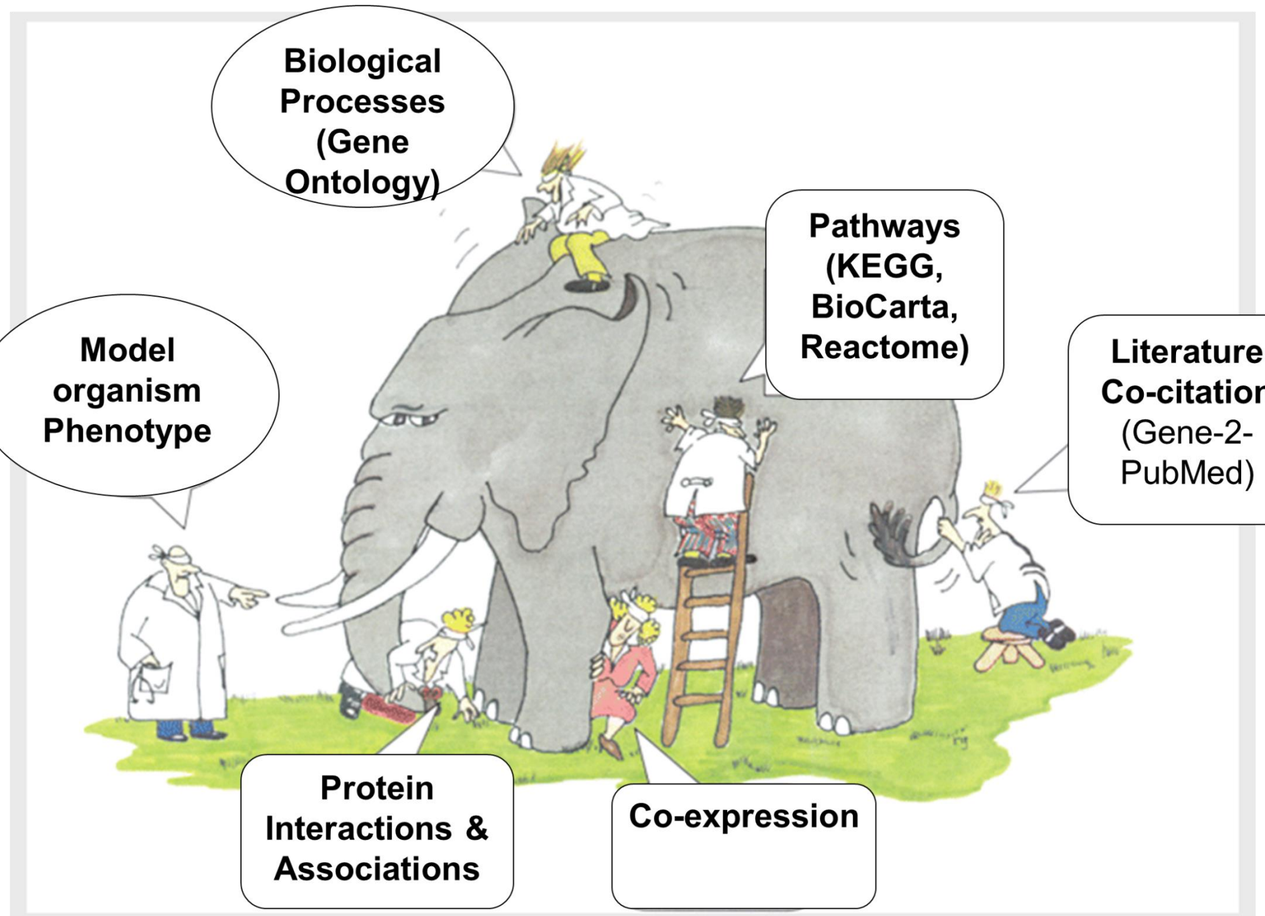


Cartoon: G. Renee Guzlas



- **No single source of data can be expected to capture all relevant relations**
- **Integrate multiple data sources: Better signal-to-noise ratio and improved prediction accuracy**

Cartoon - G. Renee Guzlas
Tranchevent & Moreau



Gene prioritization through genomic data fusion
S Aerts, D Lambrechts, S Maity, P Van Loo… - Nature …, 2006 - nature.com
Abstract The identification of genes involved in health and disease remains a challenge. We describe a bioinformatics approach, together with a freely accessible, interactive and flexible software termed Endeavour, to prioritize candidate genes underlying biological processes ...
Cited by 666 Related articles All 32 versions Web of Science: 425 Cite Save

ToppGene Suite for gene list enrichment analysis and candidate gene prioritization
J Chen, EE Bardes, BJ Aronow… - Nucleic acids research, 2009 - Oxford Univ Press
Abstract ToppGene Suite (http://toppgene. cchmc. org; this web site is free and open to all users and does not require a login to access) is a one-stop portal for (i) gene list functional enrichment,(ii) candidate gene prioritization using either functional annotations or network ...
Cited by 388 Related articles All 14 versions Web of Science: 257 Cite Save

- Guilt-by-association: Approaches differ by the strategy adopted in calculating similarity and by the data sources utilized
- With some exceptions (e.g., ENDEAVOUR, ToppGene), most of the existing approaches mainly focus on the combination of only a few data sources
- For methodological details & validation see:
  - Aerts et al., 2006 Nature Biotech.
  - Chen et al., 2007 BMC Bioinfo.

Cincinnati Children's

UNIVERSITY OF Cincinnati

ENDEAVOUR

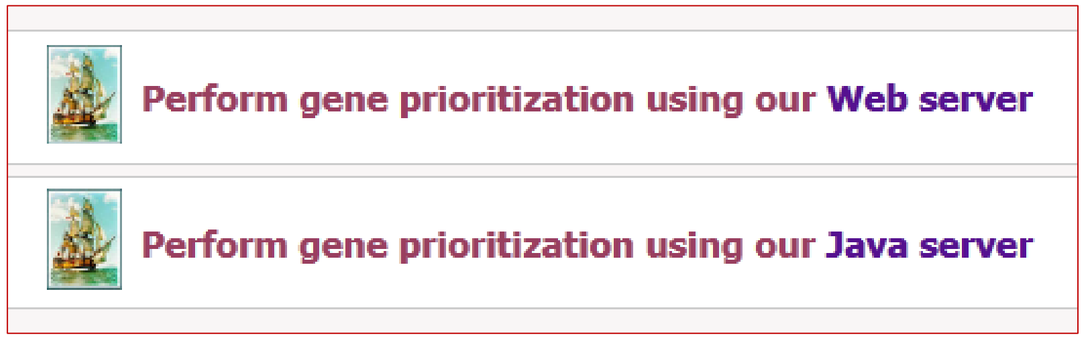
Select All None

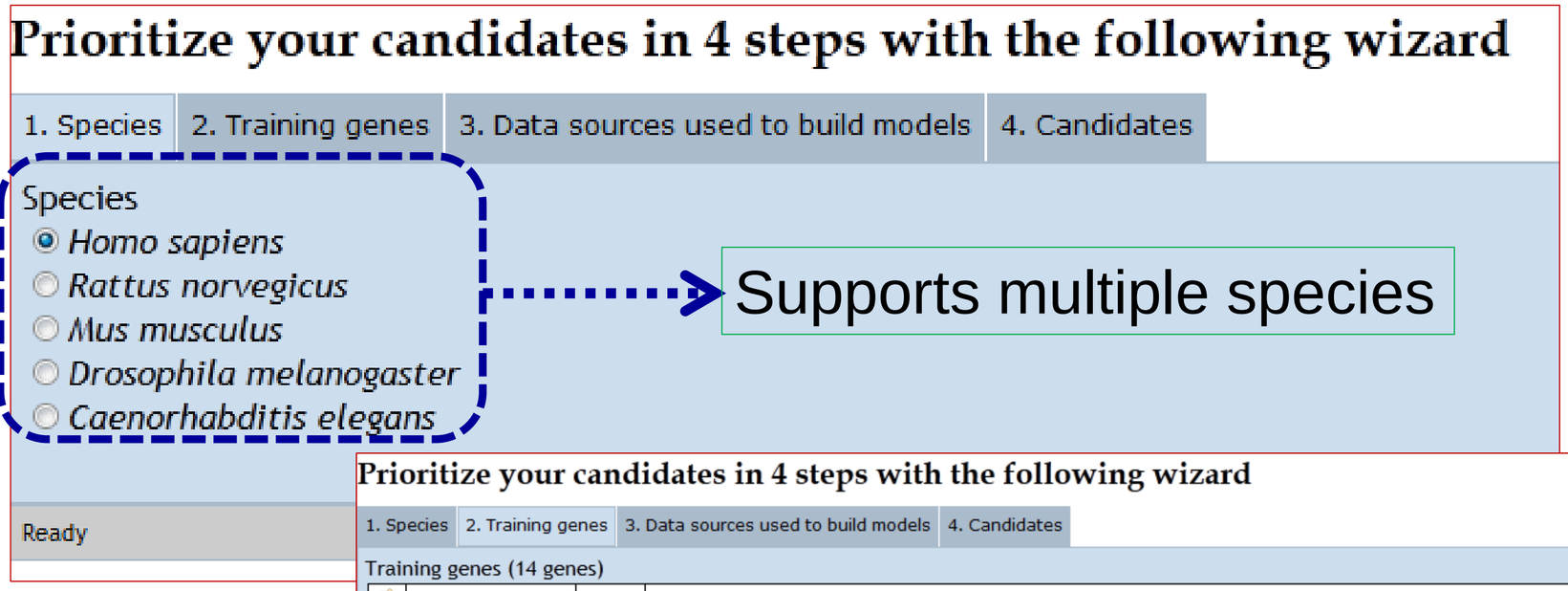
- Annotation - EnsemblEst
- Annotation - GeneOntology
- Annotation - Interpro
- Annotation - Kegg
- Annotation - Swissprot
- Blast
- CisRegModule
- Expression - SonEtAl
- Expression - SuEtAl
- Interaction - Bind
- Interaction - BioGrid
- Interaction - Hprd
- Interaction - InNetDb
- Interaction - Intact
- Interaction - Mint
- Interaction - String
- Motif
- Precalculated - Ouzounis
- Precalculated - Prospectr
- Text

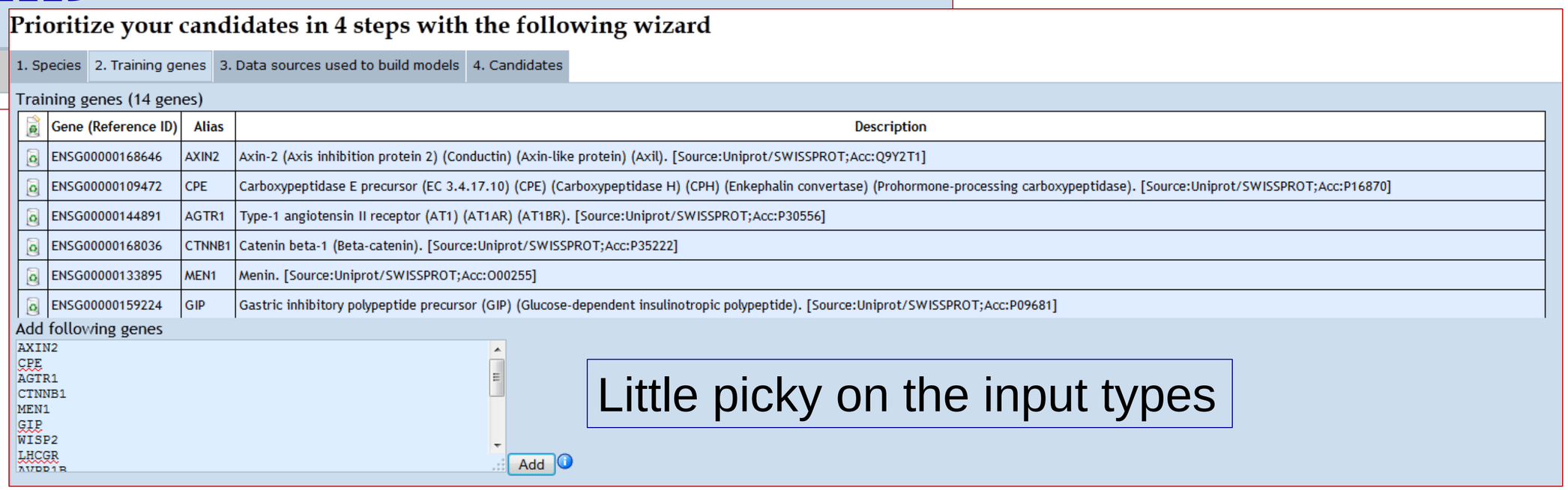
ToppGene

- All
- GO: Molecular Function
- GO: Biological Process
- GO: Cellular Component
- Human Phenotype
- Mouse Phenotype
- ▼ Domain
  - Gene3D
  - InterPro
  - PROSITE
  - Pfam
  - ProDom
  - SMART
- ▼ Pathway
  - BioSystems: BIOCYC
  - BioSystems: KEGG
  - BioSystems: Pathway Interaction Database
  - BioSystems: REACTOME
  - BioSystems: WikiPathways
  - GenMAPP
  - MSigDB C2: BioCarta
  - MSigDB C2: SigmaAldrich
  - MSigDB C2: Signaling Gateway
  - MSigDB C2: Signaling Transduction KE
  - MSigDB C2: SuperArray
  - PantherDB
  - Pathway Ontology
  - SMPDB
- ▼ Pubmed
  - GeneRIF
  - Pubmed
- Interaction
- Cytoband
- Transcription Factor Binding Site
- Gene Family
- ▼ Coexpression
  - GeneSigDB
  - MSigDB C2: Aristoteles University of Thessaloniki
  - MSigDB C2: Broad Institute
  - MSigDB C2: Columbia University
  - MSigDB C2: Dana-Farber Cancer Institute
  - MSigDB C2: Giannina Gaslini Institute
  - MSigDB C2: Johns Hopkins University School of Medicine
  - MSigDB C2: Laboratoire CarMeN
  - MSigDB C2: Michigan State University
  - MSigDB C2: Stanford University
  - MSigDB C2: Steinbeis Transfer Center for Proteome Analysis
  - MSigDB C2: Telethon Institute for Child Health Research
  - MSigDB C2: University Pierre and Marie Curie
  - MSigDB C2: University of Liverpool
  - MSigDB C2: University of Washington
  - MSigDB C6: Broad Institute
  - MSigDB C7: Nick Haining lab (DFCI)
- ▼ Coexpression Atlas
  - Body Map
  - FaceBase_RNAseq
  - FaceBase_ST1
  - Gudmap Mouse MOE430.2
  - Gudmap Mouse ST 1.0
  - Gudmap RNAseq
  - Immgen.org, GSE15907
  - PCBC
  - PCBC_AltAnalyze
- ▼ Computational
  - MSigDb: C4 - CGN: Cancer Gene Neighborhood
  - MSigDb: C4 - CM: Cancer Modules
- ▼ MicroRNA
  - MSigDB
  - MicroRNA.org
  - PITA
  - PicTar
  - TargetScan
  - miRTarbase
  - miRecords_TarBase
- ▼ Drug
  - CTD
  - CTD Marker
  - CTD Therapeutic
  - Drug Bank
  - Stitch
- ▼ Disease
  - CTD
  - Clinical Variations
  - GWAS
  - OMIM

ENDEAVOUR
http://homes.esat.kuleuven.be/~bioiuser/endeavour/index.php







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1. Species | 2. Training genes | 3. Data sources used to build models | 4. Candidates

Select All None

- [x] Annotation - EnsemblEst
- [x] Annotation - GeneOntology
- [x] Annotation - Interpro
- [x] Annotation - Kegg
- [x] Annotation - Swissprot
- [x] Blast
- [x] CisRegModule
- [x] Expression - SonEtAl
- [x] Expression - SuEtAl
- [x] Interaction - Bind
- [x] Interaction - BioGrid
- [x] Interaction - Hprd
- [x] Interaction - InNetDb
- [x] Interaction - Intact
- [x] Interaction - Mint
- [x] Interaction - String
- [x] Motif
- [x] Precalculated - Ouzounis
- [x] Precalculated - Prospectr
- [x] Text

1. Species | 2. Training genes | 3. Data sources used to build models | 4. Candidates

Candidate genes to prioritize (14 genes)

	Gene (Reference ID)	Alias	
	ENSG00000151617	EDNRA	Endothelin-1 receptor precursor (Endothelin A receptor) (E
	ENSG00000183625	CCR3	C-C chemokine receptor type 3 (C-C CKR-3) (CC-CKR-3) (C
	ENSG00000118523	CTGF	Connective tissue growth factor precursor (Hypertrophic c
	ENSG00000163638	ADAMTS9	ADAMTS-9 precursor (EC 3.4.24.-) (A disintegrin and met
	ENSG00000153208	MERTK	Proto-oncogene tyrosine-protein kinase MER precursor (EC
	ENSG00000173598	NUDT4	Diphosphoinositol polyphosphate phosphohydrolase 2 (EC

Add following candidates

EDNRA
CCR3
CTGF
ADAMTS9
MERTK
NUDT4
IGF2
GPR125
F7

Add

- [ ] Full genome

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Console (warnings and errors) clear

```
12:26:10 Updated training genes.
12:35:21 ⚠ no gene for CCNT
12:35:21 Updated candidate genes.
```

« Previous | Launch prioritization

- Little picky on the input types - e.g., gene symbols have to be HGNC approved.
- Supports chromosomal regions, e.g. chr:8p or chr:20p13 – will fetch all the genes in that region
- Doesn't support chromosomal coordinates

Results | Sprint plot | Table | Export | Discard results

Load previously saved results (exported as XML) Browse... No file selected. Load

Download the rankings table

What shared features make a test set gene rank at top or What features are shared between the training/seed set and test set gene are not explicit.

Legend

Note: The top 16 genes are attributed a color in order to easily find the rank of a given gene obtained for each model (selected data source).

ELN Candidates ranking in the top 16 are attributed a random background color.

ELN Candidates with global rank > 16 have a white background color.

ELN Candidates in red color achieved a maximum dissimilarity score (most dissimilar to the training genes).

~~ELN~~ Candidates displayed in a line through font were not scored for the data source (data missing).

Global prioritization	Annotation EnsemblEst	Annotation GeneOntology	Annotation Interpro	Annotation Kegg	Annotation Swissprot	Blast	CisRegModule	Expression SonEtAl	Expression SuEtAl	Interaction Bind	Interaction BioGrid	Interaction Hprd	Interaction InNetDb	Interaction Intact	Interaction Mint	Interaction String	Motif	Precalculated Ouzounis	Precalculated Prospectr	Text
EDNRA	EDNRA	EDNRA	CCR3	EDNRA	GPR125	CTGF	PVRL1	F7	ADAMTS9	F7	GPR125	MERTK	GPR125	GPR125	GPR125	LTBP1	F7	PVRL1	ADAMTS9	CCR3
MERTK	CALCB	CCR3	EDNRA	PVRL1	GPR116	CCR3	ADAMTS9	GPR116	PVRL1	ADAMTS9	EDNRA	EDNRA	CALCB	CALCB	CALCB	EDNRA	GPR116	MERTK	NUDT4	MERTK
PVRL1	CORIN	MERTK	CTGF	CCR3	CCR3	EDNRA	CORIN	CORIN	MERTK	PVRL1	F7	IGF2	EDNRA	EDNRA	EDNRA	CALCB	MERTK	F7	PVRL1	F7
GPR125	NUDT4	GPR125	GPR116	LTBP1	EDNRA	GPR125	LTBP1	NUDT4	F7	MERTK	ADAMTS9	GPR125	CTGF	CTGF	CTGF	CORIN	CCR3	EDNRA	MERTK	CTGF
CCR3	LTBP1	GPR116	GPR125	F7	MERTK	ADAMTS9	CTGF	EDNRA	CALCB	CALCB	PVRL1	F7	LTBP1	LTBP1	LTBP1	IGF2	CTGF	LTBP1	F7	IGF2
F7	CCR3	NUDT4	ADAMTS9	~~CTGF~~	PVRL1	LTBP1	NUDT4	LTBP1	CORIN	CORIN	MERTK	ADAMTS9	CORIN	CORIN	CORIN	ADAMTS9	ADAMTS9	CORIN	EDNRA	PVRL1
CTGF	F7	CTGF	MERTK	~~GPR116~~	F7	MERTK	EDNRA	PVRL1	GPR125	GPR125	CALCB	PVRL1	CCR3	CCR3	CCR3	CCR3	GPR125	IGF2	LTBP1	CORIN
ADAMTS9	GPR125	CORIN	NUDT4	~~GPR125~~	IGF2	GPR116	GPR125	GPR125	IGF2	IGF2	CORIN	CALCB	PVRL1	PVRL1	PVRL1	PVRL1	PVRL1	GPR125	CTGF	EDNRA
CORIN	IGF2	CALCB	CORIN	~~ADAMTS9~~	CTGF	F7	~~CCR3~~	MERTK	EDNRA	EDNRA	IGF2	CORIN	ADAMTS9	ADAMTS9	ADAMTS9	MERTK	NUDT4	CTGF	GPR125	ADAMTS9
IGF2	GPR116	IGF2	CALCB	~~MERTK~~	CORIN	NUDT4	~~MERTK~~	CTGF	CCR3	CCR3	CCR3	CCR3	IGF2	IGF2	IGF2	NUDT4	LTBP1	GPR116	IGF2	LTBP1
LTBP1	ADAMTS9	PVRL1	IGF2	~~NUDT4~~	LTBP1	PVRL1	~~GPR116~~	ADAMTS9	GPR116	GPR116	GPR116	GPR116	F7	F7	F7	GPR125	EDNRA	CALCB	CALCB	GPR125
GPR116	PVRL1	LTBP1	PVRL1	~~CORIN~~	ADAMTS9	IGF2	~~F7~~	CALCB	CTGF	CTGF	CTGF	CTGF	MERTK	MERTK	MERTK	GPR116	CORIN	CCR3	CORIN	NUDT4
CALCB	MERTK	ADAMTS9	LTBP1	~~CALCB~~	CALCB	CORIN	~~IGF2~~	IGF2	NUDT4	NUDT4	NUDT4	NUDT4	GPR116	GPR116	GPR116	CTGF	CALCB	ADAMTS9	CCR3	CALCB
NUDT4	~~CTGF~~	F7	F7	~~IGF2~~	NUDT4	CALCB	~~CALCB~~	~~CCR3~~	LTBP1	LTBP1	LTBP1	LTBP1	NUDT4	NUDT4	NUDT4	F7	~~IGF2~~	NUDT4	GPR116	GPR116

ToppGene – http://toppgene.cchmc.org

ToppGene Suite

A one-stop portal for gene list enrichment analysis and candidate gene prioritization based on functional annotations and protein interactions network

- **ToppFun**: Transcriptome, ontology, phenotype, proteome, and pharmacome annotations based gene list functional enrichment analysis

  Detect functional enrichment of your gene list based on Transcriptome, Proteome, Regulome (TFBS and miRNA), Ontologies (GO, Pathway), Phenotype (human disease and mouse phenotype), Pharmacome (Drug-Gene associations), literature co-citation, and other features.

- **ToppGene**: Candidate gene prioritization

  Prioritize or rank candidate genes based on functional similarity to training gene list.

- **ToppNet**: Relative importance of candidate genes in networks

  Prioritize or rank candidate genes based on topological features in protein-protein interacti

- **ToppGenet**: Prioritization of neighboring genes in protein-protein interaction network

  Identify and prioritize the neighboring genes of the seeds in protein-protein interaction netw

Doesn't support other than human/mouse

Select your gene identifier type, paste your training and test gene sets below or select example sets, then submit.

Example gene sets: HGNC Symbol Entrez ID
(click on "HGNC Symbol" or "Entrez ID" to use the example training and test set of genes)

Symbol Types	HGNC Symbol	HGNC Symbol
Training Gene Set:	AXIN2 CPE AGTR1 CTNNB1 MEN1 GIP WISP2 LHCGR AVPR1B MC2R AVPR1A ADRB1 GIPR AVPR2	Test gene set: EDNRA CCR3 CTGF ADAMTS9 MERTK NUDT4 IGF2 GPR125 F7 LTBP1 GPR116 CORIN CALCB CCNT PVRL1

Clear Submit Query

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Training set (14 / 14)

Entered	Human Symbol	Gene ID
AXIN2	AXIN2	8313
CPE	CPE	1363
AGTR1	AGTR1	185
CTNNB1	CTNNB1	1499
MEN1	MEN1	4221
GIP	GIP	2695
WISP2	WISP2	8839
LHCGR	LHCGR	3973
AVPR1B	AVPR1B	553
MC2R	MC2R	4158
AVPR1A	AVPR1A	552
ADRB1	ADRB1	153
GIPR	GIPR	2696
AVPR2	AVPR2	554

Ignored

Entered	Status

Test set (14 / 15)

Entered	Human Symbol	Gene ID
EDNRA	EDNRA	1909
CCR3	CCR3	1232
CTGF	CTGF	1490
ADAMTS9	ADAMTS9	56999
MERTK	MERTK	10461
NUDT4	NUDT4	11163
IGF2	IGF2	3481
GPR125	GPR125	166647
F7	F7	2155
LTBP1	LTBP1	4052
GPR116	GPR116	221395
CORIN	CORIN	10699
CALCB	CALCB	797
PVRL1	PVRL1	5818

Ignored

Entered	Status
CCNT	Not Found

Find alternatives for missing symbols

Training parameters

Feature	Correction	p-Value cutoff	Gene Limits
All	FDR	0.05	1 ≤ n ≤ 1500
GO: Molecular Function	FDR	0.05	1 ≤ n ≤ 1500
GO: Biological Process	FDR	0.05	1 ≤ n ≤ 1500
GO: Cellular Component	FDR	0.05	1 ≤ n ≤ 1500
Human Phenotype	FDR	0.05	1 ≤ n ≤ 1500
Mouse Phenotype	FDR	0.05	1 ≤ n ≤ 1500
▶ Domain	FDR	0.05	1 ≤ n ≤ 1500
▶ Pathway	FDR	0.05	1 ≤ n ≤ 1500
▶ Pubmed	FDR	0.05	1 ≤ n ≤ 1500
Interaction	FDR	0.05	1 ≤ n ≤ 1500
Cytoband	FDR	0.05	1 ≤ n ≤ 1500
Transcription Factor Binding Site	FDR	0.05	1 ≤ n ≤ 1500
Gene Family	FDR	0.05	1 ≤ n ≤ 1500
▶ Coexpression	FDR	0.05	1 ≤ n ≤ 1500
▶ Coexpression Atlas	FDR	0.05	1 ≤ n ≤ 1500
▶ Computational	FDR	0.05	1 ≤ n ≤ 1500
▶ MicroRNA	FDR	0.05	1 ≤ n ≤ 1500
▶ Drug	FDR	0.05	1 ≤ n ≤ 1500
▼ Disease	FDR	0.05	1 ≤ n ≤ 1500
CTD			
Clinical Variations			
GWAS			
OMIM			

Group results within a category by source.

Test parameter

Random sampling size: 1500 (6% of genome)

Min. feature count: 2

Home | Modify Query | Start

- Supports synonyms
- Presents suggestions/alternatives for unrecognized entries

Entered	Suggestions
CCNT	CCNT1 - cyclin T1 Human Synonym

Update | Check All

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Training Results [Expand All] [Download All] [Sparse Matrix] Display pValues and Scores as Scientific (4 significant digits) Table row limit 50

1: GO: Molecular Function [Display Chart] 132 annotations before applied cutoff / 18273 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0017046	peptide hormone binding		1.118E-10	1.389E-8	7.589E-8	1.476E-8	5	43
2	GO:0008528	G-protein coupled peptide receptor activity		2.736E-10	1.389E-8	7.589E-8	3.612E-8	6	126
3	GO:0001653	peptide receptor activity		3.157E-10	1.389E-8	7.589E-8	4.167E-8	6	129
4	GO:0042562	hormone binding		1.979E-9	6.529E-8	3.568E-7	2.612E-7	5	75
5	GO:0005000	vasopressin receptor activity		1.251E-8	3.302E-7	1.804E-6	1.651E-6	3	7

Show 45 more annotations

2: GO: Biological Process [Display Chart] 1554 annotations before applied cutoff / 18138 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0007186	G-protein coupled receptor signaling pathway		3.501E-10	5.441E-7	4.312E-6	5.441E-7	10	1057
2	GO:0030819	positive regulation of cAMP biosynthetic process		1.788E-9	6.796E-7	5.387E-6	2.779E-6	5	73
3	GO:0060341	regulation of cellular localization		2.187E-9	6.796E-7	5.387E-6	3.398E-6	9	875
4	GO:0030816	positive regulation of cAMP metabolic process		2.197E-9	6.796E-7	5.387E-6	3.413E-6	5	76
5	GO:0042592	homeostatic process		2.352E-9	6.796E-7	5.387E-6	3.655E-6	10	1284

Show 45 more annotations

3: GO: Cellular Component [Display Chart] 104 annotations before applied cutoff / 18818 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	GO:0005768	endosome		3.932E-6	4.089E-4	2.137E-3	4.089E-4	6	650
2	GO:0005887	integral component of plasma membrane		2.019E-5	7.322E-4	3.827E-3	2.099E-3	7	1341
3	GO:0031226	intrinsic component of plasma membrane		2.589E-5	7.322E-4	3.827E-3	2.693E-3	7	1393
4	GO:0030877	beta-catenin destruction complex		2.816E-5	7.322E-4	3.827E-3	2.929E-3	2	11
5	GO:0031410	cytoplasmic vesicle		8.434E-4	1.754E-2	9.168E-2	8.771E-2	5	1093

Show 5 more annotations

4: Human Phenotype [Display Chart] 321 annotations before applied cutoff / 3811 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	HP:0000850	Cushing syndrome		5.761E-5	1.849E-2	1.174E-1	1.849E-2	2	6
2	HP:0001578	Hypercortisolism		2.101E-4	2.248E-2	1.428E-1	6.745E-2	2	11
3	HP:0004316	Increased cortisol production		2.101E-4	2.248E-2	1.428E-1	6.745E-2	2	11
4	HP:0004421	Elevated systolic blood pressure		7.191E-4	3.521E-2	2.236E-1	2.308E-1	2	20
5	HP:0010514	Hyperpituitarism		9.545E-4	3.521E-2	2.236E-1	3.064E-1	2	23

Show 45 more annotations

5: Mouse Phenotype [Display Chart] 1062 annotations before applied cutoff / 7344 genes in category

	ID	Name	Source	pValue	FDR B&H	FDR B&Y	Bonferroni	Genes from Input	Genes in Annotation
1	MP:0005418	abnormal circulating hormone level		5.911E-8	6.278E-5	4.737E-4	6.278E-5	9	656
2	MP:0000639	abnormal adrenal gland morphology		1.454E-7	6.387E-5	4.819E-4	1.545E-4	5	86
3	MP:0003953	abnormal hormone level		1.804E-7	6.387E-5	4.819E-4	1.916E-4	9	745

Enrichment of Training/seed set:

- Helps in assessing the "quality" of the training set
- Can assist in selecting sub-sets of training set to perform prioritizations (e.g., large training set)

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Test Results [Hide Detail] [Download] [Show Network]

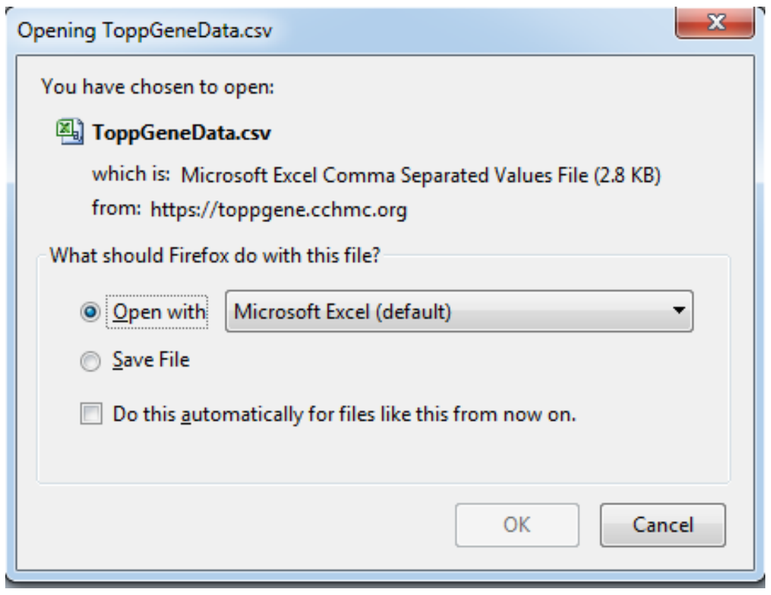
Rank (net)	Gene Symbol	Gene ID	GO: Molecular Function		GO: Biological Process		GO: Cellular Component		Human Phenotype		Mouse Phenotype		Domain		Pathway		Pubmed		Interaction		Cytoband		Transcription Factor Binding Site		Gene Family		Coexpression		Coexpression Atlas		Computational		MicroRNA		Drug		Disease		Average score	Overall P-value
			Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue	Score	pValue		
1	EDNRA	1909	9.135E-1	5.232E-3	1.000E0	6.736E-2	8.078E-1	1.243E-2	1.323E-1	4.644E-2	3.591E-1	4.382E-2	1.142E-1	7.848E-3	9.932E-1	1.000E-6	1.000E0	1.112E-2	2.746E-1	4.055E-2	0.000E0	5.049E-1	0.000E0	4.997E-1			7.117E-1	1.000E-6	2.362E-1	5.886E-3	7.999E-1	1.000E-6	0.000E0	4.997E-1	1.000E0	9.810E-3	2.013E-1	6.540E-3	5.026E-1	8.680E-12
2	IGF2	3481	5.930E-1	4.709E-2	1.000E0	6.736E-2	9.065E-1	6.540E-4	1.000E0	6.540E-4	8.686E-1	1.897E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	1.000E0	1.046E-2	7.393E-1	5.886E-3	0.000E0	5.049E-1	0.000E0	4.997E-1			7.597E-1	1.000E-6	3.295E-1	3.924E-3	0.000E0	5.003E-1	0.000E0	4.997E-1	1.000E0	9.810E-3	8.721E-1	1.308E-3	5.335E-1	3.530E-8
3	CCR3	1232	9.135E-1	5.232E-3	1.000E0	6.736E-2	8.029E-1	1.243E-2			2.507E-1	5.952E-2	1.142E-1	7.848E-3	8.511E-1	2.616E-3	9.931E-1	2.420E-2	0.000E0	5.258E-1	0.000E0	5.049E-1	0.000E0	4.997E-1	0.000E0	4.997E-1	5.732E-1	2.616E-3	0.000E0	5.173E-1	7.999E-1	1.000E-6	0.000E0	4.997E-1	8.654E-1	1.014E-1	0.000E0	5.069E-1	4.254E-1	3.308E-6
4	CTGF	1490	7.846E-1	1.635E-2	1.000E0	6.736E-2	4.245E-1	1.354E-1			3.729E-1	4.251E-2	9.998E-1	6.540E-4	0.000E0	5.154E-1	1.000E0	1.046E-2	0.000E0	5.258E-1	0.000E0	5.049E-1	0.000E0	4.997E-1			6.812E-1	6.540E-4	2.362E-1	5.886E-3	0.000E0	5.003E-1	0.000E0	4.997E-1	1.000E0	1.046E-2	4.526E-1	3.924E-3	4.345E-1	1.498E-5
5	GPR116	221395	6.602E-1	3.009E-2	9.964E-1	1.485E-1	6.169E-1	5.101E-2			3.507E-1	5.298E-2	9.704E-1	2.616E-3	0.000E0	5.154E-1	3.163E-1	1.236E-1			0.000E0	5.049E-1	0.000E0	4.997E-1	0.000E0	4.997E-1	0.000E0	5.154E-1	2.362E-1	5.886E-3			0.000E0	4.997E-1	4.710E-1	1.687E-1			3.630E-1	5.249E-3
6	CORIN	10699	2.504E-1	1.387E-1	1.000E0	6.736E-2	8.981E-1	1.308E-3	1.247E-3	5.494E-2	1.181E-1	7.129E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	9.970E-1	2.093E-2			0.000E0	5.049E-1	0.000E0	4.997E-1			0.000E0	5.154E-1	3.295E-1	3.924E-3	0.000E0	5.003E-1	0.000E0	4.997E-1	7.081E-1	1.308E-1	0.000E0	5.069E-1	2.773E-1	5.666E-3
7	GPR125	166647	6.602E-1	3.009E-2	7.881E-1	2.485E-1	3.164E-1	1.609E-1			1.000E-2	7.848E-2	9.721E-1	1.962E-3			6.835E-1	7.587E-2	0.000E0	5.258E-1	0.000E0	5.049E-1					0.000E0	5.154E-1	0.000E0	5.173E-1			0.000E0	4.997E-1	0.000E0	6.167E-1			3.061E-1	2.118E-2
8	F7	2155	4.430E-1	7.260E-2	1.000E0	6.802E-2	6.354E-1	4.120E-2	2.679E-1	3.859E-2	2.507E-1	5.952E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	1.000E0	1.112E-2	0.000E0	5.258E-1	0.000E0	5.049E-1					0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	9.911E-1	4.774E-2	0.000E0	5.069E-1	2.870E-1	2.533E-2
9	CALCB	797	3.463E-1	9.614E-2	9.987E-1	1.328E-1	0.000E0	6.566E-1					0.000E0	5.095E-1	7.597E-1	5.232E-3	8.666E-1	5.363E-2			0.000E0	5.049E-1	0.000E0	4.997E-1			0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	1.000E0	9.810E-3			3.105E-1	2.890E-2
10	CCNT1	904	8.203E-1	1.373E-2	1.000E0	7.194E-2	5.235E-1	6.671E-2					0.000E0	5.095E-1	0.000E0	5.154E-1	7.583E-1	6.998E-2	4.588E-1	2.158E-2	0.000E0	5.049E-1	0.000E0	4.997E-1			0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	4.071E-1	1.838E-1			3.080E-1	3.093E-2
11	PVRL1	5818	8.505E-1	1.046E-2	1.000E0	7.979E-2	4.833E-1	9.745E-2	8.204E-2	4.905E-2	1.000E-2	7.848E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	9.972E-1	2.027E-2	0.000E0	5.258E-1	0.000E0	5.049E-1	0.000E0	4.997E-1	0.000E0	4.997E-1	0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	8.866E-1	9.810E-2	0.000E0	5.069E-1	2.426E-1	5.302E-2
12	N			-2	9.733E-2	2.976E-1							0.000E0	5.095E-1	0.000E0	5.154E-1	0.000E0	5.618E-1			0.000E0	5.049E-1	0.000E0	4.997E-1	0.000E0	4.997E-1	5.136E-1	2.616E-3	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	6.224E-1	1.445E-1			1.917E-1	9.202E-2
13	M			-2	6.682E-1	3.205E-2	1.247E-3	5.494E-2	5.149E-1	3.728E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	0.000E0	5.618E-1	0.000E0	5.258E-1	0.000E0	5.049E-1	0.000E0	4.997E-1			0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	5.005E-1	1.629E-1	0.000E0	5.069E-1	2.024E-1	9.464E-2
14	L			-1	0.000E0	6.566E-1			2.507E-1	5.952E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	7.945E-1	6.344E-2	0.000E0	5.258E-1	0.000E0	5.049E-1	0.000E0	4.997E-1			0.000E0	5.154E-1	0.000E0	5.173E-1	0.000E0	5.003E-1	0.000E0	4.997E-1	6.978E-1	1.321E-1			2.382E-1	1.203E-1
15	ADA			-1	3.867E-1	1.406E-1			1.000E-2	7.848E-2	0.000E0	5.095E-1	0.000E0	5.154E-1	5.696E-1	9.418E-2			0.000E0	5.049E-1	0.000E0	4.997E-1	0.000E0	4.997E-1	0.000E0	5.154E-1	0.000E0	5.173E-1			0.000E0	4.997E-1	8.444E-2	2.341E-1	0.000E0	5.069E-1	1.750E-1	1.736E-1

Rank (net)	Gene Symbol	Gene ID
1	EDNRA	1909
2	IGF2	3481
3	CCR3	1232
4	CTGF	1490
5	GPR116	221395
6	CORIN	10699
7	GPR125	166647
8	F7	2155
9	CALCB	797
10	CCNT1	904
11	PVRL1	5818
12	NUDT4	11163
13	MERTK	10461
14	LTBP1	4052
15	ADAMTS9	56999

Why is a test set gene ranked at top or What features are shared between the training/seed set and ranked test set gene are presented both as a network and tabular format.

- Select the ranked genes
- Resulting training set, shared annotations, and the ranked gene(s) can be downloaded as an XGMML or GEXF file (Cytoscape/Gephi import)

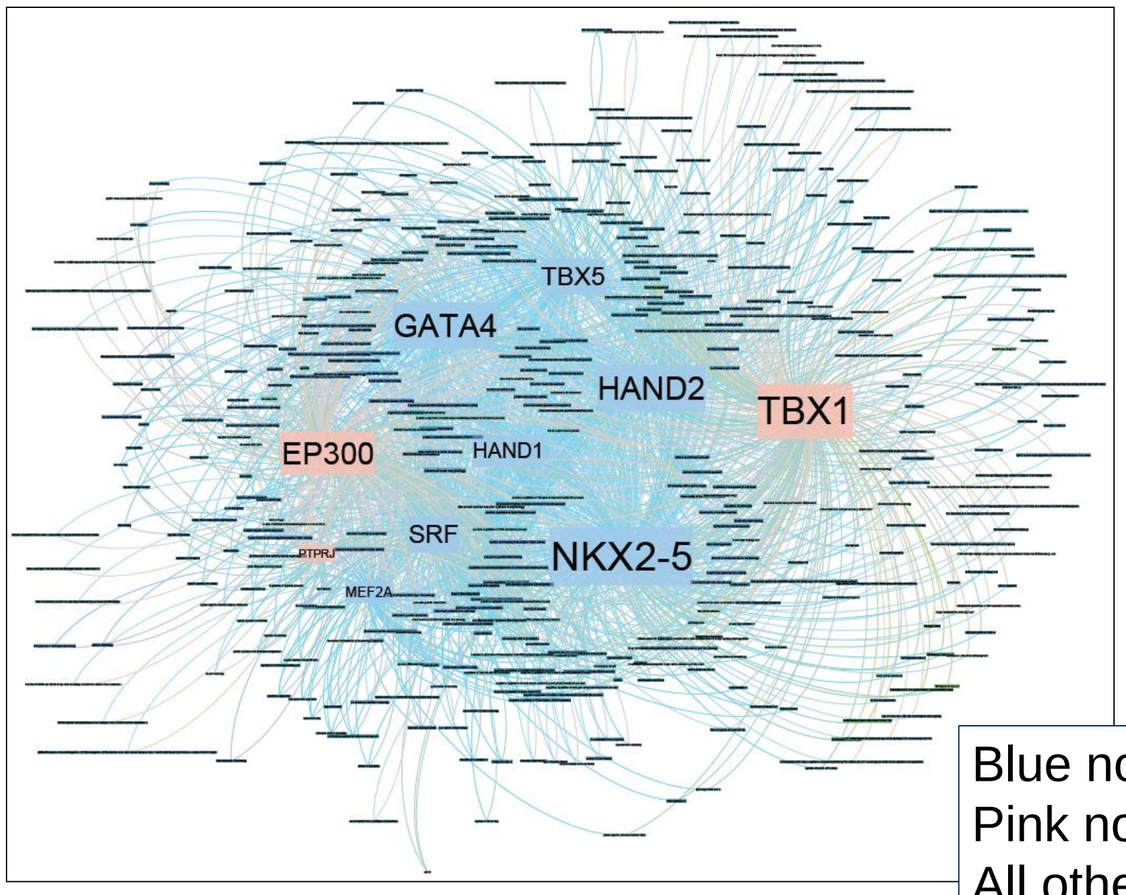
Download the rankings table



Supporting Details

Selected genes shown in **bold**

Feature	ID	Name	Genes
GO: Molecular Function	GO:0008528	G-protein coupled peptide receptor activity	AGTR1 AVPR1A AVPR1B AVPR2 **EDNRA** LHCGR MC2R
GO: Molecular Function	GO:0001653	peptide receptor activity	AGTR1 AVPR1A AVPR1B AVPR2 **EDNRA** LHCGR MC2R
GO: Molecular Function	GO:0004930	G-protein coupled receptor activity	ADRB1 AGTR1 AVPR1A AVPR1B AVPR2 **EDNRA** GIPR LHCGR MC2R
GO: Molecular Function	GO:0004888	transmembrane signaling receptor activity	ADRB1 AGTR1 AVPR1A AVPR1B AVPR2 **EDNRA** GIPR LHCGR MC2R
GO: Molecular Function	GO:0038023	signaling receptor activity	ADRB1 AGTR1 AVPR1A AVPR1B AVPR2 **EDNRA** GIPR LHCGR MC2R
GO: Biological Process	GO:0043084	penile erection	AVPR1A **EDNRA**
GO: Biological Process	GO:0051482	positive regulation of cytosolic calcium ion concentration involved in phospholipase C-activating G-protein coupled signaling pathway	AGTR1 **EDNRA**
GO: Biological Process	GO:0051281	positive regulation of release of sequestered calcium ion into cytosol	**EDNRA** LHCGR
GO: Biological Process	GO:0007620	copulation	AVPR1A **EDNRA**
GO: Biological Process	GO:0007190	activation of adenylate cyclase activity	ADRB1 AVPR2 **EDNRA** GIPR LHCGR
GO: Biological Process	GO:0045762	positive regulation of adenylate cyclase activity	ADRB1 AVPR2 **EDNRA** GIPR LHCGR
GO: Biological Process	GO:0031281	positive regulation of cyclase activity	ADRB1 AVPR2 **EDNRA** GIPR LHCGR
GO: Biological Process	GO:0090183	regulation of kidney development	AGTR1 CTNNB1 **EDNRA**
GO: Biological Process	GO:0051349	positive regulation of lyase activity	ADRB1 AVPR2 **EDNRA** GIPR LHCGR
GO: Biological Process	GO:0007202	activation of phospholipase C activity	AVPR1A AVPR1B **EDNRA**
GO: Biological Process	GO:0010863	positive regulation of phospholipase C activity	AVPR1A AVPR1B **EDNRA**
GO: Biological Process	GO:0045761	regulation of adenylate cyclase activity	ADRB1 AVPR2 **EDNRA** GIPR LHCGR
GO: Biological Process	GO:1900274	regulation of phospholipase C activity	AVPR1A AVPR1B **EDNRA**
GO: Biological Process	GO:0007200	phospholipase C-activating G-protein coupled receptor signaling pathway	AGTR1 **EDNRA** LHCGR



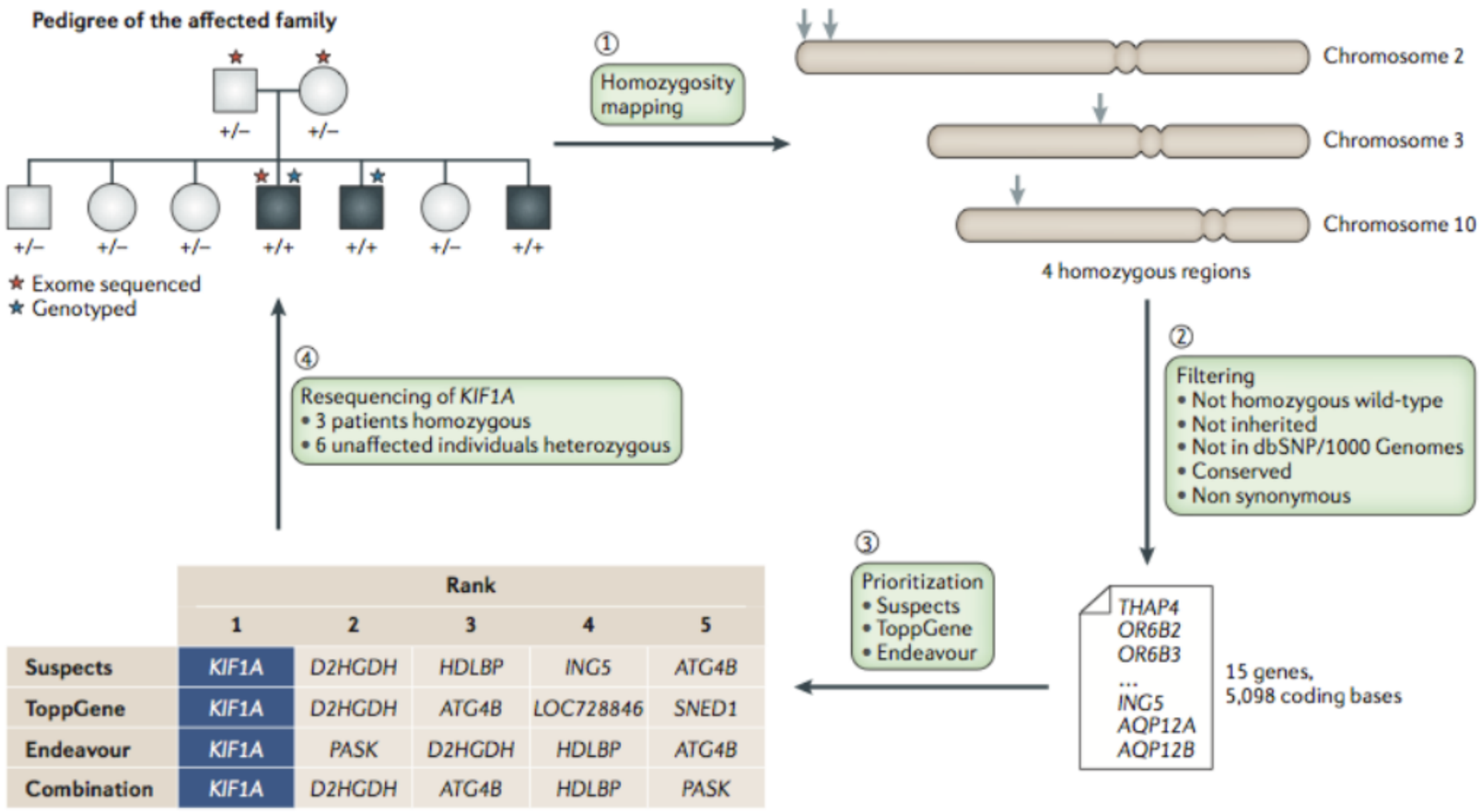
Shared annotations between training set & ranked test set gene

Gene in bold is ranked test set gene; rest are training/seed genes

Blue nodes: Seed genes
Pink nodes: ranked candidates
All other nodes – shared annotations

Combining gene level information with genomic variant information – Few case studies

Exome sequencing and gene prioritization



	Rank				
	1	2	3	4	5
Suspects	*KIF1A*	*D2HGDH*	*HDLBP*	*ING5*	*ATG4B*
ToppGene	*KIF1A*	*D2HGDH*	*ATG4B*	*LOC728846*	*SNED1*
Endeavour	*KIF1A*	*PASK*	*D2HGDH*	*HDLBP*	*ATG4B*
Combination	*KIF1A*	*D2HGDH*	*ATG4B*	*HDLBP*	*PASK*

Nature Reviews | Genetics

CSH PRESS GENOME RESEARCH

Exome sequencing and disease-network analysis of a single family implicate a mutation in *KIF1A* in hereditary spastic paraparesis

Yaniv Erlich, Simon Edvardson, Emily Hodges, et al.

Genome Res. 2011 21: 658-664 originally published online April 12, 2011

Moreau & Tranchevent, 2012

Some more examples of published studies that used Endeavour and/or ToppGene for candidate gene prioritization

Familial Cancer
© Springer Science+Business Media Dordrecht 2013
10.1007/s10689-013-9642-y

Original Article

Whole exome sequencing identifies mutation of EDNRA involved in ACTH-independent macronodular adrenal hyperplasia

Jie Zhu[1], Liang Cui[1], Wei Wang[1], Xing-Yi Hang[2], A-Xiang Xu[1], Su-Xia Yang[1], Jing-Tao Dou[1], Yi-Ming Mu[1], Xu Zhang[1] and Jiang-Ping Gao[1] ✉

The rank of candidate genes in different diseases prediction algorithms

Rank	SUSPECTS	ToppGene	Endeavour
1	EDNRA	EDNRA	EDNRA
2	CCR3	CCR3	GRM1
3	CTGF	PTAFR	GPR125
4	ADAMTS9	GRID2	ACVR1B
5	MERTK	CASR	CCR3
6	NUDT4	GPR18	LGR5
7	IGF2	CALCB	CUL1
8	GPR125	ADCY8	F7
9	F7	GRM1	GRHPR
10	LTBP1	WFS1	PTK2

Exome sequencing and pathway analysis for identification of genetic variability relevant for bronchopulmonary dysplasia (BPD) in preterm newborns: A pilot study

Paola Carrera[a, b], Chiara Di Resta[a], Chiara Volonteri[c], Emanuela Castiglioni[a], Silvia Bonfiglio[d], Dejan Lazarevic[d], Davide Cittaro[d], Elia Stupka[d], Maurizio Ferrari[a, b, c], Marco Somaschini[a], for the
BPD and Genetics Study Group

AJMG AMERICAN JOURNAL OF medical genetics

Research Article

Identification of novel candidate gene loci and increased sex chromosome aneuploidy among infants with conotruncal heart defects

Kazutoyo Osoegawa[1,*], David M. Iovannisci[1], Bin Lin[1], Christina Parodi[1], Kathleen Schultz[1], Gary M. Shaw[2] and Edward J. Lammer[1]

Article first published online: 11 OCT 2013
DOI: 10.1002/ajmg.a.36291

Issue
American Journal of Medical Genetics Part A
Volume 164, Issue 2, pages 397–406, February 2014

Exome Sequencing and Systems Biology Converge to Identify Novel Mutations in the L-Type Calcium Channel, *CACNA1C*, Linked to Autosomal Dominant Long QT Syndrome

Nicole J. Boczek, Jabe M. Best, David J. Tester, John R. Giudicessi, Sumit Middha, Jared M. Evans, Timothy J. Kamp and Michael J. Ackerman

Circ Cardiovasc Genet. published online May 15, 2013;

OPEN ACCESS Freely available online

Exome-Sequencing Confirms *DNAJC5* Mutations as Cause of Adult Neuronal Ceroid-Lipofuscinosis

Bruno A. Benitez[1], David Alvarado[2], Yefei Cai[1], Kevin Mayo[1], Sumitra Chakraverty[1], Joanne Norton[1], John C. Morris[3], Mark S. Sands[2,4], Alison Goate[1,3,4,5], Carlos Cruchaga[1,4]*

Table 3. Gene Ranking Using Bioinformatic/Systems Biology Algorithms

Gene	Rank			
	Endeavour[30]	SUSPECTS[31]	Topp Gene[32]	Total Rank
CACNA1C	1	1	1	1
SLC26A1	3	2	2	2
MAP1A	2	6	3	3
DMRTB1	8	3	4	4
DSCAML1	6	4	6	5
GLTSCR1	5	8	5	6
PPP1R12C	4	7	8	7
MARCKS	7	5	7	8

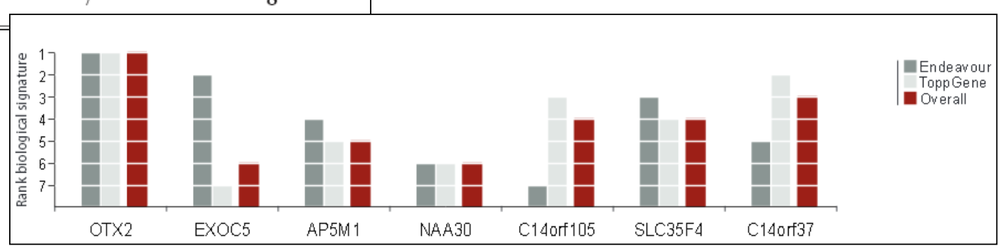
Human Genetics
March 2013, Volume 132, Issue 3, pp 285-292

Variants in *GATA4* are a rare cause of familial and sporadic congenital diaphragmatic hernia

Lan Yu, Julia Wynn, Yee Him Cheung, Yufeng Shen, George B. Mychaliska, Timothy M. Crombleholme, Kenneth S. Azarow, Foong Yen Lim, Dai H. Chung, Douglas Potoka, Brad W. Warner, Brian Bucher, Charles Stolar, Gudrun Aspelund, Marc S. Arkovitz, Wendy K. Chung

Table S1. Summary of comparison of results from ToppGene and Endeavour gene prioritization analysis

Gene Symbol	Toppgene Results			Endeavour results		Combined score
	Rank Net	Average Score	Overall pValue	Global prioritization score	Rank	
DNAJC5	1	0.7031	7.07E-05	2	0.117	1.5
CDC16	3	0.4483	0.0133049	3	0.167	3
PDCD6IP	5	0.3351	0.0246281	1	0.071	3
NPY1R	2	0.6797	2.30E-04	5	0.249	3.5
LIPJ	4	0.3063	0.015721	4	0.215	4
ZNF717	8	0.1556	0.1493499	7	0.29	7.5
LCMT1	10	0.1008	0.1746657	8	0.312	9
MUC3A	12	0.1445	0.2637284	6	0.256	9
ENPP3	7	0.2334	0.1058833	13	0.531	10
ABCC1	11	0.2423	0.2043685	9	0.337	10
ARHGAP10	9	0.1517	0.1615053	12	0.479	10.5
TNRC6A	6	0.3164	0.0609277	16	0.705	11
LOC100287879	14	-1	0.3513417	11	0.41	12.5
CCDC74B	15	-1	0.3513417	10	0.355	12.5
TTBK2	13	0.1311	0.2709082	15	0.689	14
LOC389906	16	-1	0.3513417	14	0.69	15



OTX2 Duplication Is Implicated in Hemifacial Microsomia

Dina Zielinski[1], Barak Markus[1], Mona Sheikh[1], Melissa Gymrek[1,2,3,4], Clement Chu[5], Marta Zaks[6], Balaji Srinivasan[5], Jodi D. Hoffman[7], Dror Aizenbud[6,9], Yaniv Erlich[1,*,9]

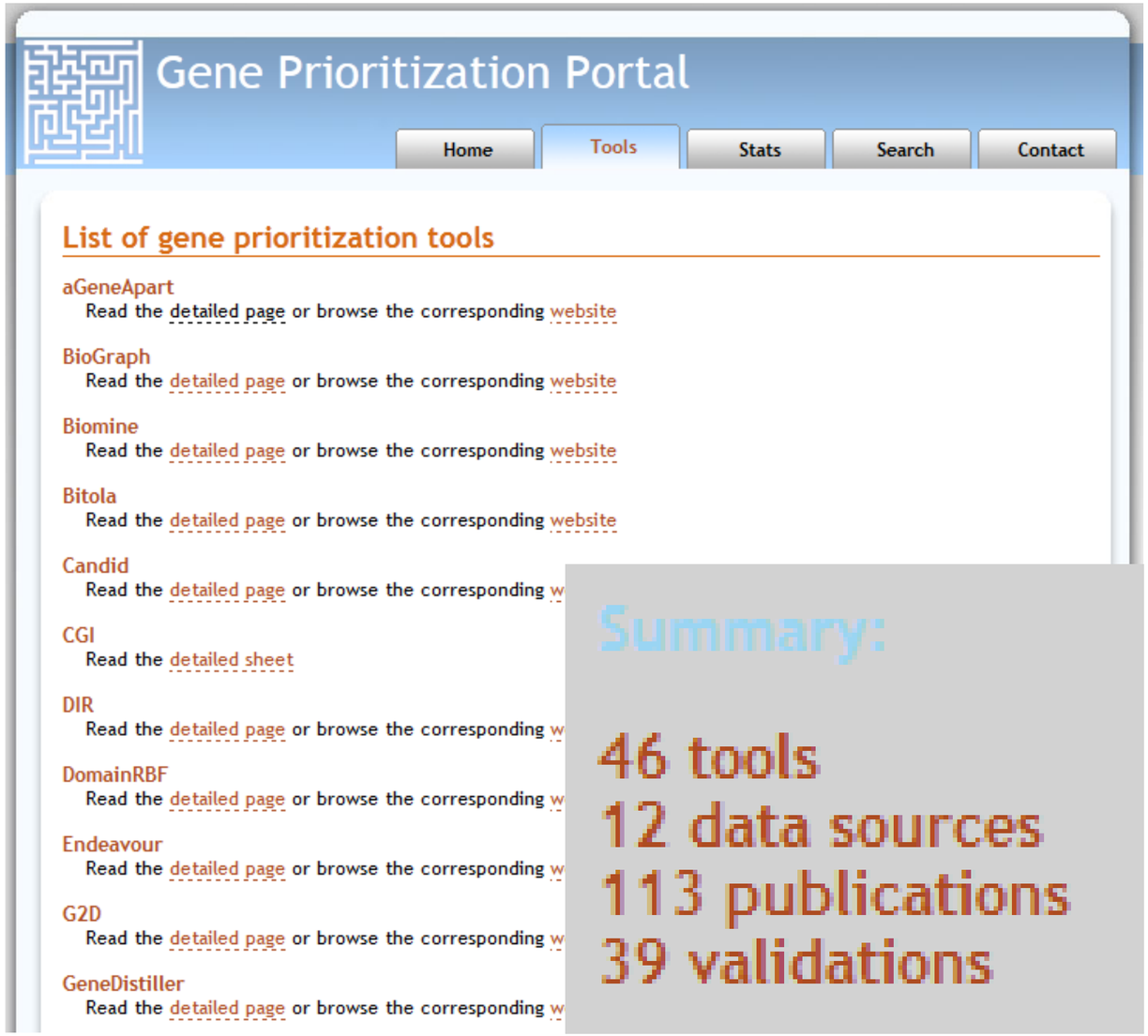
1 Whitehead Institute for Biomedical Research, Cambridge, Massachusetts, United States of America, **2** Harvard-MIT Division of Health Sciences and Technology, MIT, Cambridge, Massachusetts, United States of America, **3** Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, United States of America, **4** Department of Molecular Biology and Diabetes Unit, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **5** Counsyl, South San Francisco, California, United States of America, **6** Rambam Health Care Campus, Haifa, Israel, **7** Division of Genetics, Tufts Medical Center, Boston, Massachusetts, United States of America

Limitations & Points to Remember

- Bias towards the training set: Disease genes yet to be discovered will be consistent with what is already known about a disease and/or its genetic basis – assumption not always true.
- Bias towards selecting better annotated genes: “true” candidate can be missed if it lacks “sufficient” annotations.
- Accuracy depends on the quality (and coverage) of underlying original sources from which the annotations are retrieved.
- Appropriate or “true representative” training set selection: Using larger training sets (>100 genes) decreases the sensitivity and specificity of the prioritization compared to smaller training sets (6 to 30 genes).
- Coding-gene-centric: Complex traits result more often from noncoding regulatory variants than from coding sequence variants

Gene Prioritization Portal

http://homes.esat.kuleuven.be/~bioiuser/gpp/index.php



Cincinnati Children's

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Gene Prioritization Portal

Gene Prioritization Portal

Home | Tools | Stats | Search | Contact

General statistics

This section contains different statistics about the gene prioritization portal. These statistics are automatically retrieved from our frequently updated database and thus they reflect the current state of the art in gene prioritization. Currently, the portal contains :

- 46 gene prioritization tools
- 12 data sources
- 113 gene prioritization related publications
- 39 gene prioritization validations

Data sources statistics

This section contains details about the different datasources and their use by the gene prioritization tools. The following table corresponds to Table 2 of the paper Tranchevent *et al.* (2010). Further details about the data sources can be found below the table.

Tools	Functional annotations	Expression	Regulatory information	Text (co-citation)	Text (functional)	Interactions	Pathways	Sequence	Phenotype	Conservation/homology	Disease probabilities	Chemicals	
aGeneApart					X								1
BioGraph	X				X	X	X					X	5
Biomine	X	X			X	X	X		X	X		X	8
Bitola					X								1
Caesar	X	X			X	X	X			X	X		7
Candid		X			X	X		X		X	X		6
CGI		X				X							2
DGP								X		X			2
DIR		X				X	X						3
DomainRBF								X					1
Endeavour	X	X	X		X	X	X	X			X		8
eResponseNet		X		X		X	X						4
G2D	X			X		X		X					4
GeneDistiller	X	X		X		X	X		X				6
GeneFriends		X											1
GeneProspector					X								1
GeneRank	X	X											2
GeneRanker	X			X	X	X			X				5
GeneSeeker		X			X				X	X			4
GeneWanderer	X	X		X		X	X						5

Inputs / outputs statistics

This section contains details about the different inputs needed by the gene prioritization tools and about the different outputs they produce. The following two tables corresponds to Table 3 of the paper Tranchevent *et al.* (2010). Further details about the inputs / outputs can be found below the tables. The first table describes the inputs of the gene prioritization softwares.

	Training data			Candidate genes		
Tools	Known genes	Keywords	Expression dataset	Region	DEG	Genome
aGeneApart		X				X
BioGraph		X				X
Biomine	X	X			X	
Bitola		X		X		X
Caesar		X		X	X	X
Candid		X		X	X	X
CGI			X			X
DGP						X
DIR	X				X	
DomainRBF		X				X
Endeavour	X	X		X	X	X
eResponseNet	X				X	
G2D	X	X		X		
GeneDistiller	X	X		X		
GeneFriends	X					X
GeneProspector		X				X
GeneRank			X			X
GeneRanker	X	X				X
GeneSeeker		X		X		X
GeneWanderer	X			X	X	
Génie		X			X	X
GenTrepid		X		X	X	

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Gene Prioritization Portal

Detailed view of a gene prioritization tool

Previous tool Back to list Next tool

Name
Pinta

URL
http://www.esat.kuleuven.be/pinta/

Description

PINTA identifies the most promising candidates within a region when only sparse information about the phenotype is available by replacing this knowledge by experimental data on differential gene expression between affected and healthy individuals. Considering the problem from the perspective of a gene/protein network, we assess the relevance of a candidate gene by considering the level of differential expression in its network neighborhood under the assumption that strong candidates tend to be surrounded by differentially expressed neighbors.

Software modes

Web based software	The software contains a web based interface and therefore can be used from a web browser.

Datasources

Functional annotations	Keywords associated to the genes and describing their functions or the ones of the corresponding proteins. Often an organized vocabulary (ontology) is used. The most used annotation source is Gene Ontology.
Expression	Data covering the expression level (usually at the transcript level) of many genes (usually genome-wide) over a wide range of tissues/conditions.
Text (co-citation)	Links between genes obtained by applying text mining techniques in order to find co-citations occurring in the scientific literature.
Interactions	Collection of gene-gene (or protein-protein) interactions coming from biological experiments. Two examples of such data sources are DIP and BioGrid.

Inputs / outputs

Inputs		Outputs
Training data: expression dataset Candidate genes: region Candidate genes: DEG Candidate genes: genome		Prioritized list of candidates Test Statistics

Publications

Nitsch *et al.*, **PINTA: a web server for network-based gene prioritization from expression data**, *Nucleic Acids Res. (2011)*
Show abstract, link to paper

Benchmarks

Nitsch *et al.*, **Candidate Gene Prioritization by Network Analysis of Differential Expression using Machine Learning Approaches**, *BMC Bioinformatics (2010)*
Show abstract, link to paper

Tools used: Pinta.

Critical Assessment

Results of a critical assessment performed on 8 gene prioritization softwares (reference to come). Regular benchmarks are usually run on know data; oppositely this benchmark mimics the discovery of a novel disease gene by performing predictive prioritizations. More precisely, 42 novel disease gene associations were used to benchmark the tools as soon as they were published and therefore before their inclusions in the databases used by these tools.

This plot presents the results of this benchmark for Pinta. Several performance indices are computed: median over the 42 rank ratios, AUC (Area Under the ROC Curve), and True Positive Rates at 10% and 30%.

Disease Gene Prioritization - Network-based strategies

- Candidate genes are ranked based on their topological relevance (e.g., distance) to known disease genes (Training/seed genes) in a network.
  - Protein-protein interactions network (BioGrid, BIND, HPRD, etc.)
  - Protein association network (STRING)
- Random-walk (or PageRank) approaches outperform clustering and neighborhood approaches.

ToppNet (http://toppgene.cchmc.org)

ToppGene Suite

A one-stop portal for gene list enrichment analysis and candidate gene prioritization based on functional annotations and protein interactions network

- **ToppFun**: Transcriptome, ontology, phenotype, proteome, and pharmacome annotations based gene list functional enrichment analysis

  Detect functional enrichment of your gene list based on Transcriptome, Proteome, Regulome (TFBS and miRNA), Ontologies (GO, Pathway), Phenotype (human disease and mouse phenotype), Pharmacome (Drug-Gene associations), literature co-citation, and other features.

- **ToppGene**: Candidate gene prioritization

  Prioritize or rank candidate genes based on functional similarity to training gene list.

- **ToppNet**: Relative importance of candidate genes in networks

  Prioritize or rank candidate genes based on topological features in protein-protein interaction network.

- **ToppGenet**: Prioritization of neighboring genes in protein-protein interaction network

  Identify and prioritize the neighboring genes of the seeds in protein-protein interaction network based on functional similarity to the "seed" list (ToppGene) or topological features in protein-protein interaction network (ToppNet).

Training set (7 / 7)

Entered	Human Symbol	Gene ID
NKX2-5	NKX2-5	1482
MEF2A	MEF2A	4205
GATA4	GATA4	2626
HAND1	HAND1	9421
HAND2	HAND2	9464
TBX5	TBX5	6910
SRF	SRF	6722

Test set (146 / 158)

Entered	Human Symbol	Gene ID
ACVR1	ACVR1	90
ACVR2B	ACVR2B	93
ADAM19	ADAM19	8728
ADM	ADM	133
ADRA1A	ADRA1A	148
ADRA1B	ADRA1B	147
ADRBK1	ADRBK1	156
ALDH1A2	ALDH1A2	8854
ALPK3	ALPK3	57538
ATP6V0A1	ATP6V0A1	535
BMP10	BMP10	27302
BMP2	BMP2	650
BMP4	BMP4	652
BMPR1A	BMPR1A	657
CALCRL	CALCRL	10203
CASP3	CASP3	836
CASP7	CASP7	840
CASP8	CASP8	841
CASQ2	CASQ2	845
CHD7	CHD7	55636
CITED2	CITED2	10370

Graph prioritization parameters

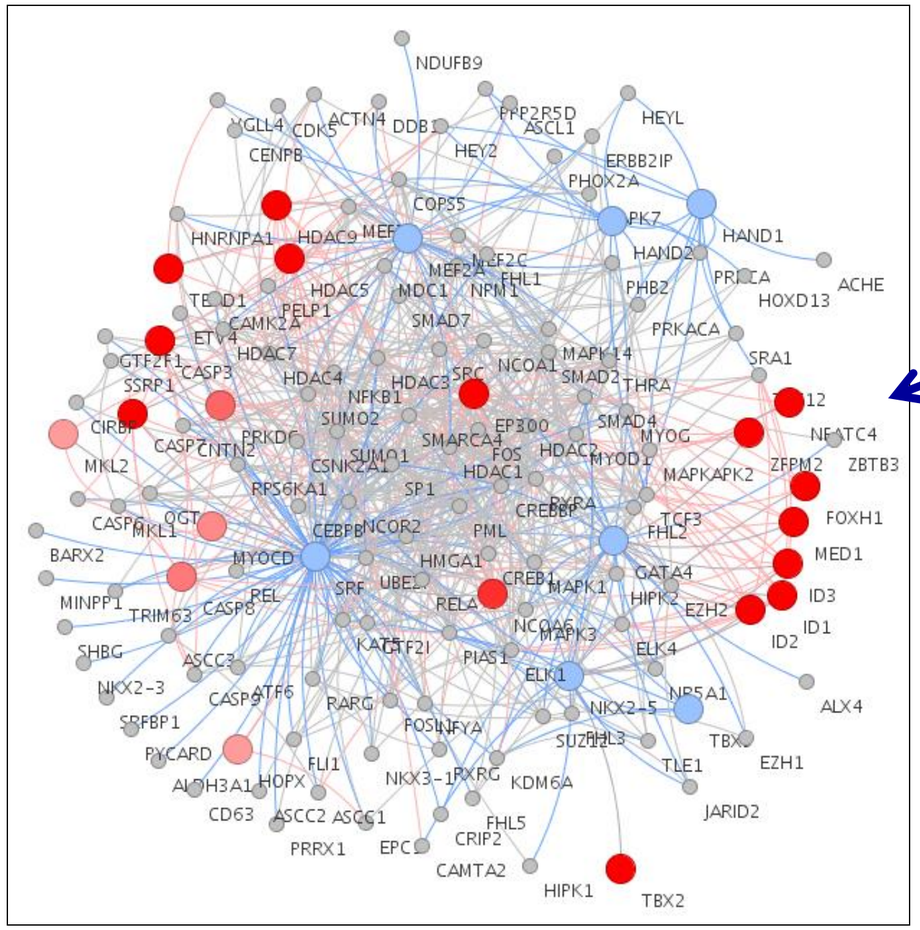
Prioritization method: Page Rank With Priors

Bias (between 0 and 1): 0.3

Training gene neighborhood subnetwork visualization parameters

Neighborhood distance: 1

When training set is big, the training gene neighborhood subnetwork can be huge.



Test Genes [Hide All]

Rank	ID	Name
1	2033	EP300
2	3399	ID3
3	3398	ID2
4	3397	ID1
5	10014	HDAC5
6	8928	FOXH1
7	6909	TBX2
8	836	CASP3
9	7003	TEAD1
10	840	CASP7
11	5469	MED1
12	9734	HDAC9
13	4776	NFATC4
14	23414	ZFPM2
15	23054	NCOA6
16	5591	PRKDC
17	4851	NOTCH1
18	1499	CTNNB1
19	841	CASP8
20	93649	MYOCD

Chen et al., 2009

New tools – Variant prioritization

http://homes.esat.kuleuven.be/~bioiuser/eXtasy/

eXtasy Variant Prioritization

KU LEUVEN

eXtasy: Variant Prioritization by Genomic Data Fusion

What is eXtasy?
eXtasy is a pipeline for ranking nonsynonymous single nucleotide variants given a specific phenotype. It takes into account the putative deleteriousness of the variant, haploinsufficiency predictions of the underlying gene and the similarity of the given gene to known genes in the given phenotype.

Who develops eXtasy?
eXtasy was developed in the Bioinformatics group at the Department of Electrical Engineering of the University of Leuven (part of the iMinds Future Health Department). It was implemented by Alejandro Sifrim and Dusan Popovic under the supervision of Prof. Jan Aerts, Prof. Bart de Moor and Prof. Yves Moreau.

Run eXtasy online:

HPO term(s): (Comma-separated)

VCF file: Browse... No file selected.

Email: (Optional)

Output file name: (Optional)

Submit

http://compbio.charite.de/ExomeWalker

exomewalker

Prioritization of whole-exome data by random-walk analysis of protein-protein interactions

EXOME WALKER is a computational method to prioritise a set of candidates in exome sequencing projects that aim to identify novel Mendelian disease genes. Our approach involves filtering a Variant Call Format (VCF) file according to a number of user-definable criteria, for instance, off-target variants (those that are not located within or close to protein-coding exons) are removed.

Genes are prioritised according to a variant score (predicted pathogenicity, rarity, pattern of variants compatible with the assumed mode of inheritance) and to their vicinity to other genes that belong to the same disease-gene family within the protein protein interaction (PPI) network, using the Random-Walk method as described in Köhler et al. (2008) to determine similarity within the PPI network on the basis of the global characteristics of the network.

1. Upload VCF Data

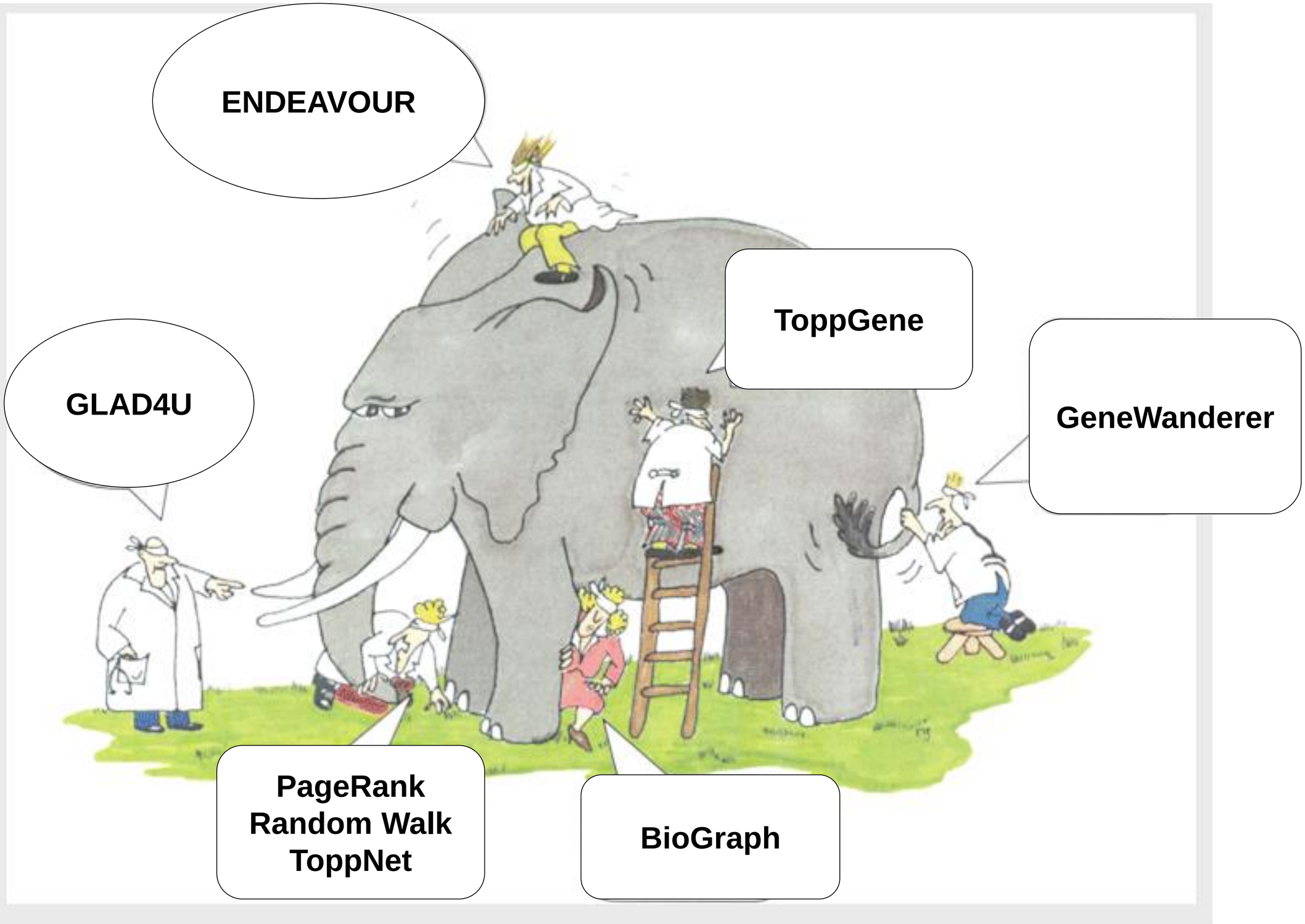
VCF files for single or multiple samples are supported. If you upload a multiple-sample VCF file, you will also be required to enter pedigree data in PED file format. The file suffix must be "VCF" or "vcf".

Choose VCF file: Browse... No file selected.

Send File

References & Further Reading

- Kann MG. 2010. Advances in translational bioinformatics: computational approaches for the hunting of disease genes. Brief Bioinform. 11(1):96-110.
- Piro, R. M. & Di Cunto, F. 2012. Computational approaches to disease-gene prediction: rationale, classification and successes. FEBS J. 279: 678–696.
- ❖ Moreau Y, Tranchevent LC. 2012. Computational tools for prioritizing candidate genes: boosting disease gene discovery. Nat Rev Genet 13: 523–536.
- ❖ Bromberg Y. 2013. Chapter 15: disease gene prioritization. PLoS Comput Biol. 9(4):e1002902.
- Navlakha S, Kingsford C. 2010. The power of protein interaction networks for associating genes with diseases. Bioinformatics 26(8):1057-63.
- Gonzalez MW, Kann MG. 2012. Chapter 4: Protein interactions and disease. PLoS Comput Biol. 8(12):e1002819
- Gilissen C, Hoischen A, Brunner HG, Veltman JA. 2012. Disease gene identification strategies for exome sequencing. Eur J Hum Genet. 20(5):490-7.



Cartoon - G. Renee Guzlas