



Linking Biological Pathways and Networks to Disease

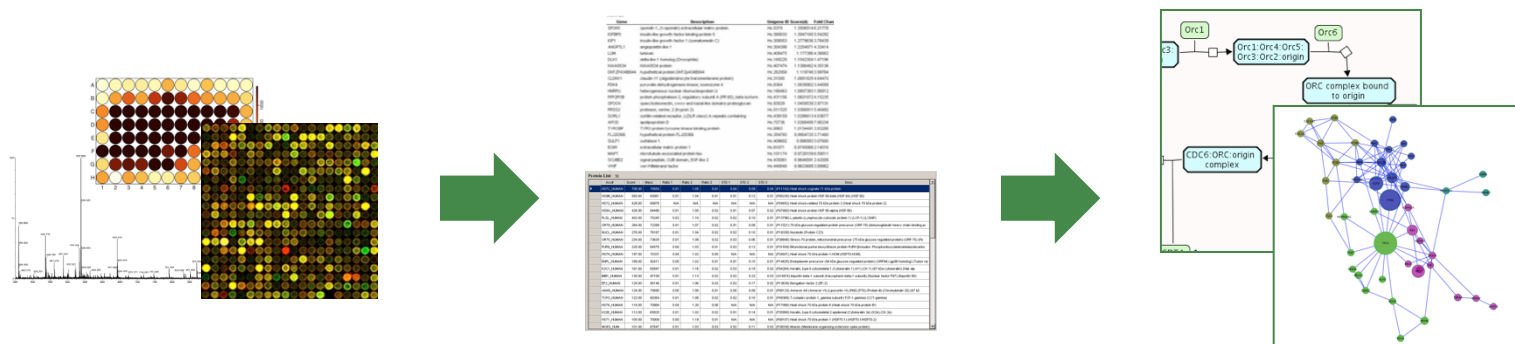
Robin Haw
7th September 2014
BioNetVisA Workshop/ECCB'14

www.reactome.org

What is Reactome?



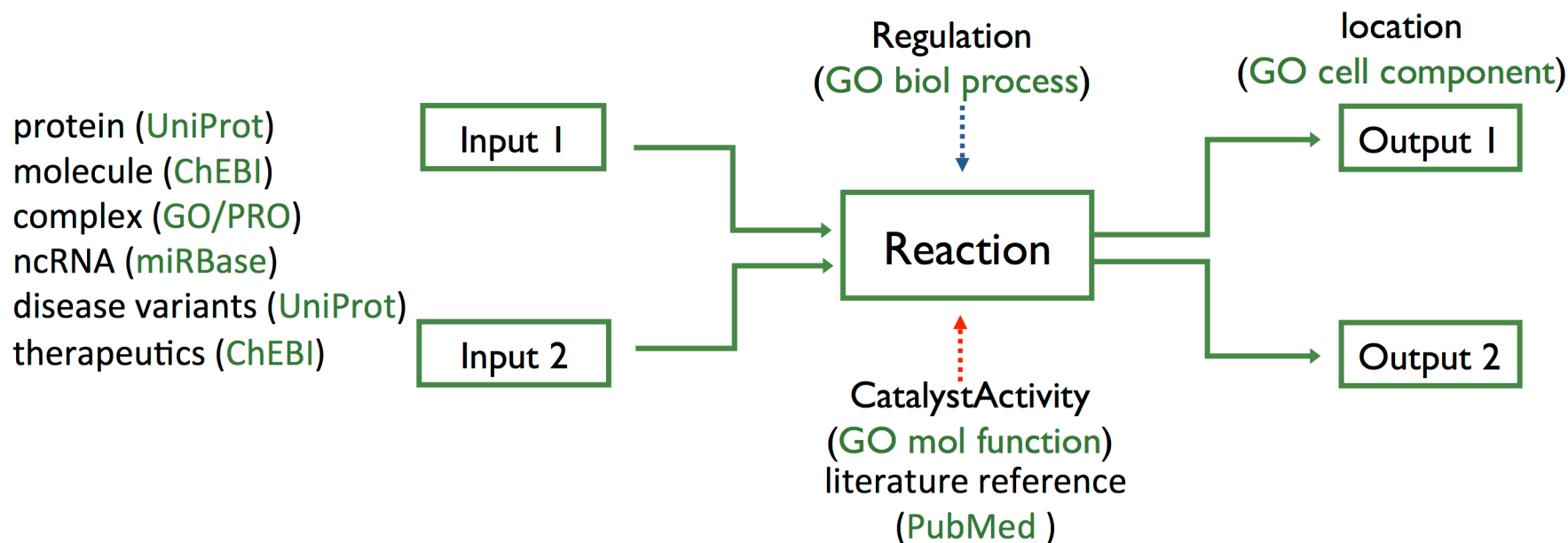
- Open source and open access pathway database
 - 1500+ pathway modules encompassing many areas of human biology
 - Expert authored, manually curated and peer-reviewed.
 - Every pathway is traceable to primary literature.
- Extensively cross-referenced to external bioinformatics databases.
- Computationally inferred pathways for 19 model organisms.
- Provides tools and datasets for browsing and visualizing pathway data.



www.reactome.org

The Reaction

- Reactome is a Reaction Network Database
 - explicitly describe biological processes as a series of biochemical reactions and events.
 - represents many events and states found in biology.



Reactome Homepage



The screenshot shows the Reactome homepage with a dark blue header featuring the Reactome logo and a molecular pathway diagram. Below the header is a navigation bar with links: About, Content, Documentation, Tools, Community, Download, and Contact. A search bar on the right contains the text "e.g. O95631, NTN1, signa" and a "Search" button. The main content area is divided into two columns. The left column contains six large buttons: "Browse Pathways" (with a tree icon), "Analyze Data" (with a bar chart icon), "Reactome FI Network" (with a network icon), "User Guide" (with a person icon), "Data Download" (with a download arrow icon), and "Contact Us" (with an envelope icon). Below these buttons is an "About Reactome" section with a description of the database and its goals. The right column features a "Reactome News" section with three tweets. The first tweet is from @reactome, dated 1h, about pathway data used in a study. The second tweet is from @intact_project, dated 28 Jan, about a registration for a course. The third tweet is from @reactome, dated 13 Jan, about pathway data used in a proteomics study. Below the tweets is a "Tweet to @reactome" input field. At the bottom of the page is a footer with a grid of links organized under the categories: About, Content, Documentation, Tools, Community, Download, and Contact. Social media icons for Facebook, Twitter, and YouTube are also present.

REACTOME
A CURATED PATHWAY DATABASE

About Content Documentation Tools Community Download Contact

e.g. O95631, NTN1, signa Search

Browse Pathways

Analyze Data

Reactome FI Network

User Guide

Data Download

Contact Us

About Reactome

Reactome is a free, open-source, curated and peer reviewed pathway database. Our goal is to provide intuitive bioinformatics tools for the visualization, interpretation and analysis of pathway knowledge to support basic research, genome analysis, modeling, systems biology and education.

Reactome News

New for 2014: Version 47 Released

reactome @reactome 1h
Pathway data from @reactome used in study of transdifferentiation of lung cancer from ADC to SCC in mice goo.gl/Gn6UBm #usereactome
Expand

IntAct at EBI @intact_project 28 Jan
Registration for 2014 Networks & Pathways course now open - learn to analyse large datasets ebi.ac.uk/training/cours...
t: Retweeted by reactome
Expand

reactome @reactome 13 Jan
Reactome pathway data used in proteomics study of whitefish larvae from differing salinity environs,
Tweet to @reactome

About
About Reactome
News
Reactome Team
Scientific Advisory Board
Other Reactomes
License Agreement
Reactome Disclaimer

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Community
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Reactome Events
Reactome Training
Reactome Publications
Papers Citing Reactome
Resources Guide
Mailing List

Download

Contact

f t You Tube

www.reactome.org

Full-text Search Tool

- Supports accurate and efficient querying of the Reactome knowledgebase, including protein, set, complex, chemical compound, reaction and pathway annotations.

Search results for *PTEN*

Showing 20 of 66

Species

- ☒ Homo sapiens (66)
- ☐ Drosophila melanogaster (70)
- ☐ Danio rerio (62)
- ☐ Rattus norvegicus (30)
- ☐ Bos taurus (14)
- ☐ Caenorhabditis elegans (14)

More...

Types

- ☐ Protein (29)
- ☐ Reaction (23)
- ☐ Pathway (9)
- ☐ Set (3)
- ☐ Complex (1)
- ☐ RNA Sequence (1)

Compartments

- ☐ cytosol (52)
- ☐ plasma membrane (21)
- ☐ extracellular region (4)
- ☐ endoplasmic reticulum lumen (1)

Reaction types

- ☐ activates (1)
- ☐ binds (1)
- ☐ dephosphorylates (1)

Protein

(5 results from a total of 29)

- [PTEN \(Homo sapiens\)](#)
Primary external reference: UniProt [PTEN: P60484](#)
- [PTEN S170N \(Homo sapiens\)](#)
Primary external reference: UniProt [PTEN: P60484](#)
PTEN missense mutation that results in the substitution of serine at position 170 with asparagine affects the
- [PTEN H123Y \(Homo sapiens\)](#)
Primary external reference: UniProt [PTEN: P60484](#)
PTEN missense mutation that results in the substitution of histidine at position 123 with tyrosine affects the
- [PTEN G129E \(Homo sapiens\)](#)
Primary external reference: UniProt [PTEN: P60484](#)
PTEN missense mutation that results in the substitution of glycine at position 129 with glutamic acid affects the
- [PTEN G129V \(Homo sapiens\)](#)
Primary external reference: UniProt [PTEN: P60484](#)
PTEN missense mutation that results in the substitution of glycine at position 129 with valine affects the conserved

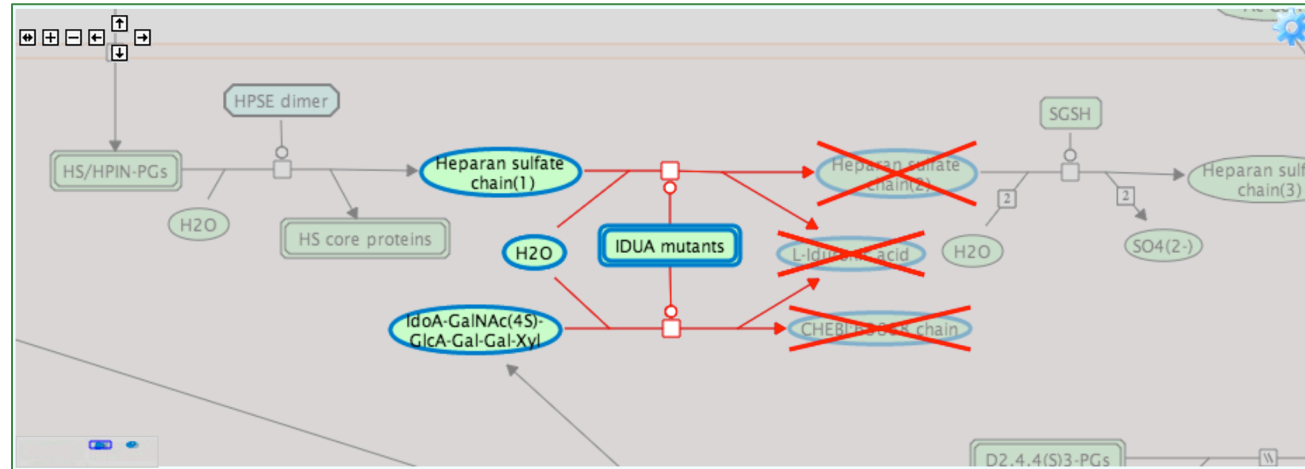
RNA Sequence

(1 results from a total of 1)

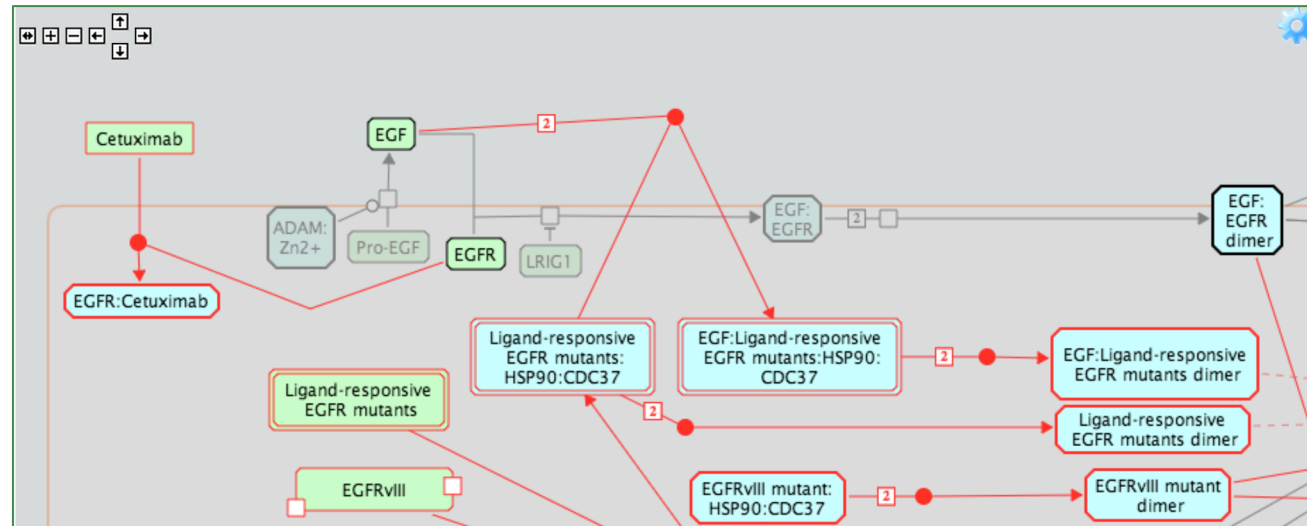
- [PTEN mRNA \(Homo sapiens\)](#)
Primary external reference: ENSEMBL : [ENST00000371953](#)

Disease Pathway Curation

Metabolic disorders
e.g. mucopolysaccharidoses



Complex disorders
e.g. EGF pathway in cancer



SBGN Pathway Browser

- Google-map style pathway diagrams

REACTOME

Pathways for: Homo sapiens

Event Hierarchy:

- The citric acid (TCA) cycle and respiratory electron transport
- Pyruvate metabolism and Citric Acid (TCA) cycle
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 - isocitrate + NADP+ => alpha-ketoglutarate + CO2 + NADPH
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 - Respiratory electron transport, ATP synthesis by chemiosmotic c
 - Metabolism of nucleotides

Overview | Molecules | Structures (0) | Expression | Processes | Downloads

Citric acid cycle (TCA cycle) Species: Homo sapiens

DOI
10.3180/REACT_1785.1

Stable Identifier
[REACT_1785.3](#)

Summation

In the citric acid or tricarboxylic acid (TCA) cycle, the acetyl group of acetyl CoA (derived primarily from oxidative decarboxylation of pyruvate, beta-oxidation of long-chain fatty acids, and catabolism of ketone bodies and several amino acids) can be completely oxidized to CO2 in reactions that also yield one high-energy phosphate bond (as GTP or ATP) and four reducing equivalents (three NADH + H+, and one FADH2). The NADH and FADH2 are then oxidized by the electron transport chain to yield nine more high-energy phosphate bonds (as ATP). All reactions of the citric acid cycle take place in the mitochondrion.

Eight canonical reactions mediate the synthesis of citrate from acetyl-CoA and oxaloacetate and the metabolism of citrate to re-form oxaloacetate. Six additional reactions are included here. Three reversible reactions, the interconversions of citrate and isocitrate, of fumarate and malate, and of malate and oxaloacetate are annotated in both their canonical (forward) and reverse directions. The synthesis of succinate from succinyl-CoA can be coupled to the

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Protein structures from PDBe

REACTOME

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 - NADPH + NAD+ + H+ [cytosol] => NADP+ + NADH + H+ [mitochondrial matrix]
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Protein ☐ Small molecule ☐ Complex ☐

Overview | Molecules | Structures (5/5) | Expression | Processes | Downloads

UniProt: P10515 DLAT Chain: A Resolution: 8.80 Coverage: 0.37 PDB Range: [1, 239] UniProt Range: [409, 647]

3b8k

► All other structures for P10515

UniProt: P08559 PDHA1 Chain: C Resolution: 1.90 Coverage: 0.93 PDB Range: [5, 365] UniProt Range: [30, 390]

2oz1

► All other structures for P08559

Expression data from the Gene Expression Atlas

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Diagram: The diagram illustrates the Citric Acid Cycle (TCA cycle) and its regulation. Key components include:

- pyruvate dehydrogenase complex**: Converts pyruvate to Ac-CoA, releasing CO2 and NADH.
- Citrate Synthase Holoenzyme**: Catalyzes the formation of Citrate (CIT) from Ac-CoA and Oxaloacetate (OA), releasing CO2 and NADH.
- ACO2**: A regulatory protein involved in the cycle.
- ISCIT**: Isocitrate, which is converted to alpha-ketoglutarate (alpha-KG) by the IDH3 complex, releasing CO2 and NADH.
- IDH3 complex**: A regulatory complex involved in the cycle.
- ADP**: A regulatory molecule involved in the cycle.
- CO2**: A byproduct of several reactions in the cycle.

E-MTAB-513 RNA-Seq of human individual tissues and mixture of 16 tissues (Illumina Body Map)
 Organism(s): *Homo sapiens*
 Reference(s): 22496456 22955988 23258890

Showing 1 of 1 genes found:

Gene	adipose	adrenal	brain	breast	colon	heart	kidney	leukocyte	liver	lung	lymph node	ovary	prostate	skeletal muscle	testis	thyroid
CS																

Analyzing OMICS data with Reactome Tools

- Pathway Mapping and Overrepresentation Analysis
 - What pathways are represented in my dataset?
- Expression Overlay onto Pathways
 - Which pathways are expressed in my dataset?

REACTOME

Pathways for: Homo sapiens

Event Hierarchy:

- Apoptosis (74/161) FDR: 1.44E-15
- Binding and Uptake of Ligands by Scavenger Receptors (6/11) FDR: 1.44E-15
- Cell Cycle (126/532) FDR: 1.44E-15**
- Cell Cycle Checkpoints (75/118) FDR: 1.44E-15
- Cell Cycle, Mitotic (115/461) FDR: 1.44E-15**
- Mitotic G1-G1/S phases (89/135) FDR: 1.44E-15**
- G0 and Early G1 (12/25) FDR: 8.7E-5
- G1 Phase (14/38) FDR: 2.52E-4**
- G1/S Transition (81/109) FDR: 1.44E-15
- S Phase (86/123) FDR: 1.44E-15
- Regulation of DNA replication (58/75) FDR: 1.44E-15
- Mitotic G2-G2/M phases (18/124) FDR: 2.03E-1
- M Phase (48/287) FDR: 3.21E-3
- M/G1 Transition (66/82) FDR: 1.44E-15
- Regulation of mitotic cell cycle (41/82) FDR: 6.66E-1
- Chromosome Maintenance (22/79) FDR: 1.73E-4
- Meiosis (14/85) FDR: 1.3E-1
- Cell-Cell communication (4/138) FDR: 1.0E-1
- Cellular responses to stress (33/236) FDR: 1.12E-1
- Cellular response to hypoxia (3/25) FDR: 4.81E-1
- Detoxification of Reactive Oxygen Species (4/29) FDR: 1.44E-15
- Cellular response to heat stress (6/37) FDR: 3.17E-1

1/5: 10h_control

Overview Molecules Structures Expression Analysis (964) Processes Downloads

Results for: UNIPROT (964) Type: Expression [Data: Probeset]

Pathway name	Entities found	Entities Total	Entities ratio	Entities pValue	Results FDR	Reactions found	Reactions total	R
Phenylalanine and tyrosine catabolism	7	9	0.001	5.41E-5	2.16E-4	8	10	
Cyclin D associated events in G1	14	38	0.005	6.31E-5	2.52E-4	7	11	
G1 Phase	14	38	0.005	6.31E-5	2.52E-4	7	11	
Intrinsic Pathway	9	17	0.002	9.29E-5	3.72E-4	16	16	

Result Mapping

241-260 of 964

Reactome supports Open Data Standards



Standard graphical languages for representing biological processes and interactions



SBML level 2.4

Open access interchange format for computer models of biochemical pathways, reactions and networks.



BioPAX

BioPAX level 2 & 3

Standard language that aims to enable integration, exchange, visualization and analysis of biological pathway data.



PSICQUIC level 2.5

PSICQUIC is an effort to standardize the access to molecular interaction databases.

PSI-MITAB is the data exchange format.

Reactome Web Services

```
<?xml version="1.0" encoding="UTF-8" standalone="no"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version4" level="2" version="4">
  <model id="pathway_977225" name="Amyloids" metaid="0">
    <notes><p xmlns="http://www.w3.org/1999/xhtml">Amyloid is a term used to describe typically ext
proteins, sometimes known as plaques. Abnormal accumulation of amyloid is amyloidosis, a te
and tissues, particularly neurodegenerative diseases such as Alzheimer's, Parkinson's and H
predominantly of amyloid fibrils, rigid, nonbranching structures that form ordered assembl
betasheet structure where the sheets run parallel to the direction of the fibril (Sawaya et
left-handed twist (Nelson Eisenberg 2006). At least 27 human proteins form amyloid fibril
proteins have nonpathological functions; the trigger that leads to abnormal aggregations di
well understood but in many cases the peptides are abnormal fragments or mutant forms arisi
that the initial event may be aggregation of misfolded or unfolded peptides. Early studies
widely accepted model that assembly was a nucleation-dependent polymerization reaction (Tepl
be more complex, with multiple 'offpathway' events leading to a variety of oligomeric struc
(Roychoudhuri et al. 2008). An increasing body of evidence suggests that these oligomeric f
the neurotoxic effects of Amyloid-beta (Roychoudhuri et al. 2008), alpha-synuclein (Winner et
2009, Meraz-Rios et al. 2010). Amyloid oligomers are believed to have a common structural mo
protein involved and not present in fibrils (Kayed et al. 2003). Conformation dependent, ag
that there are 3 general classes of amyloid oligomer structures (Glabbe 2009) including annu
responsible for the widely reported membrane permeabilization effect of amyloid oligomers.
precedes the appearance of plaques in mouse models (Ferretti et al. 2011). </p><p xmlns="ht
are often associated with other molecules, notably heparan sulfate proteoglycans and Serum
universally associated and seem to stabilize fibrils, possibly by protecting them from degr
</annotation>
  <p xmlns="http://www.w3.org/1999/xhtml">SBML engine: JsBml<p
description"><glyph class="macromolecule" id="entityVertex
x="273.0" y="267.0"/><glyph class="unit of information">
x="56.0" y="289.0" y="255.0"/><glyph/><glyph/><glyph clas
bbox h="36.0" w="90.0" x="282.0" y="675.0"/><glyph/><glyph clas
bbox h="45.0" w="168.0" x="930.0" y="468.0"/><glyph class
"APCS(20-223), Ca2+/"><callout target="entityVertex_71936
x="114.0" y="537.0"/><glyph/><glyph/><glyph class="unspe
"Amyloid_fibril"/><bbox h="36.0" w="133.5" x="354.0" y="1
"entityVertex_7193683"><label text="Amyloid_fibril_main"/
class="simple chemical" id="entityVertex_7193684"><label
glyph/><glyph class="complex" id="entityVertex_7193685"><l
y="933.0"/><glyph class="annotation" id="entityVertex_719
Serum amyloid P-component homopentamer, HSPG2(22-4391), G
y="969.0"/><callout/><bbox h="24.0" w="760.0" x="2450.5"
"entityVertex_7193686"><label text="HSPG2_22_4391"/><bbox
information" id="entityVertex_7193686_mt"><label text="mt
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y="930.0"/><glyph class="annotation" id="entityVertex_719
homopentamer"/><callout target="entityVertex_7193687"><p>
x="1115.5" y="990.0"/><glyph/><glyph/><glyph class="unspe
"Double_stranded"/><bbox h="36.0" w="183.0" x="915.0" y="
label text="Serum"/><bbox h="57.6" w="175.5" x="1671.0" y
"entityVertex_7193689_annotation"><label text="Serum amy
callout target="entityVertex_7193689"><point x="1846.5" y
/><glyph/><glyph class="process" id="reactionVertex

```

Reactome Web services

Our new RESTful API provides outside users with direct access to pathway data in Reactome. The Reactome pathway analysis tools are also available for integration into third party websites.

- RESTful API is available to access the Reactome data (Note: The RESTful API has been moved to reactomews.oicr.on.ca for better performance.). For details about this API, please see this document: [Reactome RESTful API](#).
- SOAP based Web Services API is available to access the Reactome data. For details about this API, please follow the following links:
 - [Simple Description for the Reactome Web Services API](#).
 - Training Materials for the Reactome Web Services API
 - [Reactome SOAP WS User's Guide in PDF \(1M\)](#).
 - [Reactome SOAP WS Tutorial in Power Point Slides \(2M\)](#).
 - [Reactome SOAP WS Tutorial in Flash Movie \(640 x 480\) \(11M\)](#).
 - [Reactome SOAP WS Tutorial in Flash Movie \(800 x 600\) \(12M\)](#).

Pathway Analysis Service

Provides an API for pathway over-representation and expression analysis as well as species comparison tool

[Contact the developer](#)
Creative Commons Attribution 3.0 Unported License

download : download

Show/Hide | List Operations | Expand Operations | Raw

GET	/download/{token}/entities/found/{resource}/{filename}.csv	Downloads those identifiers found for a given analysis and a certain resource
GET	/download/{token}/entities/notfound/{filename}.csv	Downloads a list of the not found identifiers
GET	/download/{token}/pathways/{resource}/{filename}.csv	Downloads all hit pathways for a given analysis

identifier : identifier

Show/Hide | List Operations | Expand Operations | Raw

GET	/identifier/{id}	Analise the identifier over the different species in the database
GET	/identifier/{id}/projection	Analise the identifier over the different species in the database and projects the result to Homo Sapiens

identifiers : identifiers

Show/Hide | List Operations | Expand Operations | Raw

species : species

Show/Hide | List Operations | Expand Operations | Raw

token : token

Show/Hide | List Operations | Expand Operations | Raw

[BASE URL: <http://www.reactome.org/AnalysisService/api-docs> , API VERSION: 1.0]

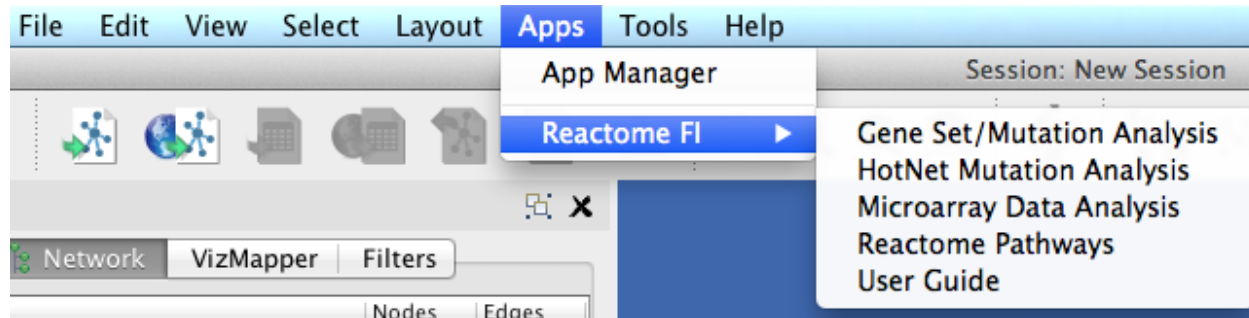
Amyloid SBML file:

<http://reactomews.oicr.on.ca:8080/ReactomeRESTfulAPI/RESTfulVWS/sbmlExporter/977225>

Analysis Service: <http://www.reactome.org/AnalysisService/>

ReactomeFIViz Cytoscape app

- View Reactome Pathway Diagrams in Cytoscape
 - Perform pathway-based data analysis
- Create Gene Networks based upon the Reactome FI Network
 - Perform network-based data analysis



- Install ReactomeFIViz from Cytoscape App Store
- Choose Plugins, Reactome FI.

Reactome Pathways in Cytoscape

- Display Reactome pathways in Cytoscape

The screenshot displays the Cytoscape software interface with the Reactome plugin. On the left, the 'Control Panel' shows a tree view of pathways, with 'Cell Cycle' expanded. A context menu is open over 'Cell Cycle Checkpoints', providing options: 'View in Reactome', 'Show Diagram', 'Search', 'Analyze Pathway Enrichment', 'Expand Pathway', and 'Collapse Pathway'. The main window shows a detailed diagram of the 'Diagram of Cell Cycle Checkpoints' pathway. The diagram illustrates the regulatory network involving BUB3, CDC20, MAD2, and the APC/C complex. The 'Table Panel' at the bottom indicates 'No Network' is loaded. The status bar at the bottom right shows 'Memory: OK'.

Display Reactome Pathways in the FI Network View

- Convert Reactome pathway into Reactome FI network

The screenshot displays the Reactome FI Network View interface. The left panel shows a hierarchical tree of pathways under 'Cell Cycle Checkpoints'. The 'Selected Event Branch' section highlights the 'Cell Cycle Checkpoints' pathway. Below this, a detailed pathway diagram is shown, featuring nodes such as 'phospho-Cdc25C 14-3-3 protein complex', 'RPA complexed to ssDNA', 'Rad17-RFC complex', 'CONB-p-T14-CDK1', and 'Rad9-Hus1-Rad1 complex'. The right panel, titled 'FI Network for Diagram of Cell Cycle Checkpoints', displays a network graph with numerous green nodes and connecting edges. The bottom panel, 'Table Panel', contains a table with the following data:

isReact...	shared name	Pathwa...	clustering...	Reacto...	name	dataSe...
true	FI Network for Diagram of Cell...	69620			FI Network f...	Pathway...

At the bottom of the Table Panel, there are tabs for 'Node Table', 'Edge Table', and 'Network Table'.

Pathway Enrichment Analysis

- Perform enrichment analysis and colourize pathway/network diagrams

The screenshot displays the Reactome Pathway Enrichment Analysis software interface. The main window is titled "Reactome Pathway Enrichment Analysis" and features a "Control Panel" on the left, a "Table Panel" at the bottom, and a central network diagram.

Control Panel: Includes tabs for "Network", "VizMapper", "Filters", and "Reactome". The "FDR" filter is set to ">=0.1". The "Selected Event Branch" shows "Cell Cycle (FDR: 1.000e+00)" and "Cell Cycle Checkpoints (FDR: 9.009e-01)".

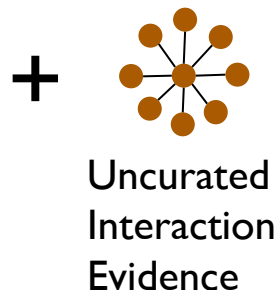
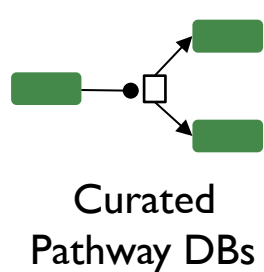
Table Panel: Displays a table of results with columns: ReactomePathway, RatioOfProteinIn..., NumberOfProteins..., ProteinFromGen..., P-value, FDR, and HitGenes. The table is filtered by FDR 1.0.

ReactomePathway	RatioOfProteinIn...	NumberOfProteins...	ProteinFromGen...	P-value	FDR	HitGenes
p53-Independent DNA D...	0.0080	52	1	0.6014	8.947e-01	CHEK2
p53-Independent G1/S D...	0.0080	52	1	0.6014	8.947e-01	CHEK2
Ubiquitin Mediated Degr...	0.0080	52	1	0.6014	8.947e-01	CHEK2
Post-translational protei...	0.0271	177	3	0.6061	8.972e-01	F7,GGCX,PIGU
Mitotic G2-G2/M phases	0.0178	116	2	0.6081	8.976e-01	YWHA,PPP2R1A
Disease	0.1452	948	16	0.6136	9.011e-01	BCR,KRAS,ACA...
Assembly of collagen fibril...	0.0083	54	1	0.6153	9.010e-01	COL6A3
Cell Cycle Checkpoints	0.0181	118	2	0.6174	9.009e-01	CHEK2,MCM8

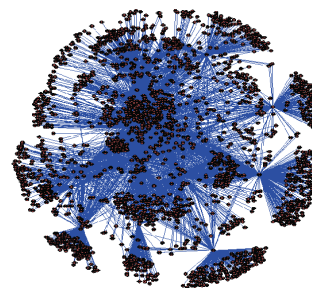
Gene Set Loading Dialog: A dialog box titled "Gene Set Loading" is open, prompting the user to "Choose a gene set file:" (hs_geneNames.txt) and "Specify file format:" (One gene per line).

Network Diagram: A network diagram titled "FI Network for Diagram of Cell C" shows a cluster of green nodes (PSMC3, PSMA8, PSMA3, PSMB11, PSMC5, PSMC4, PSMB8) connected to a central node (ATM). ATM is connected to CHEK2, MDM2, and TP53. CHEK2 is highlighted with a purple border.

Network Module Based Analysis of Disease OMICS Datasets



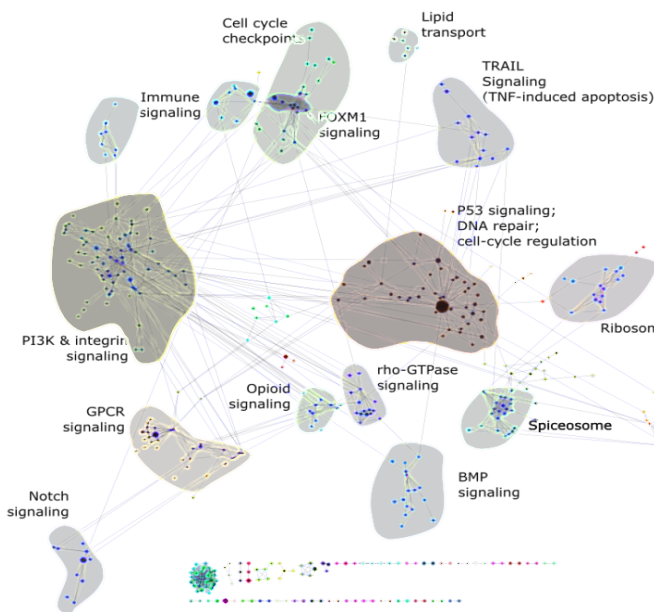
Machine Learning



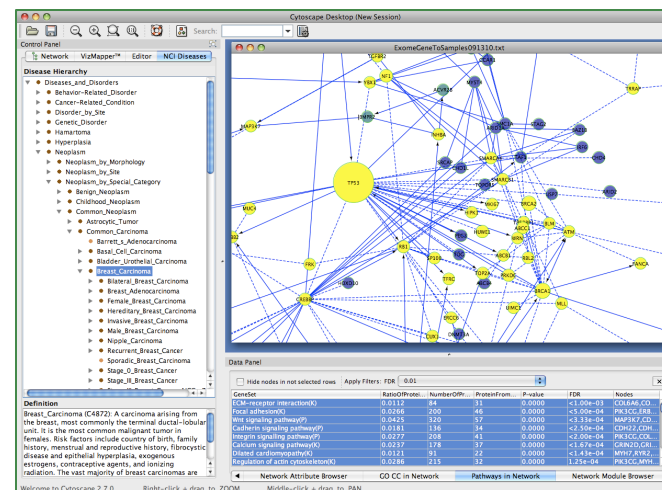
**Reactome Functional
Interaction Network**
(~11K proteins; ~270K
interactions)



Project your data
into Reactome FI
Network



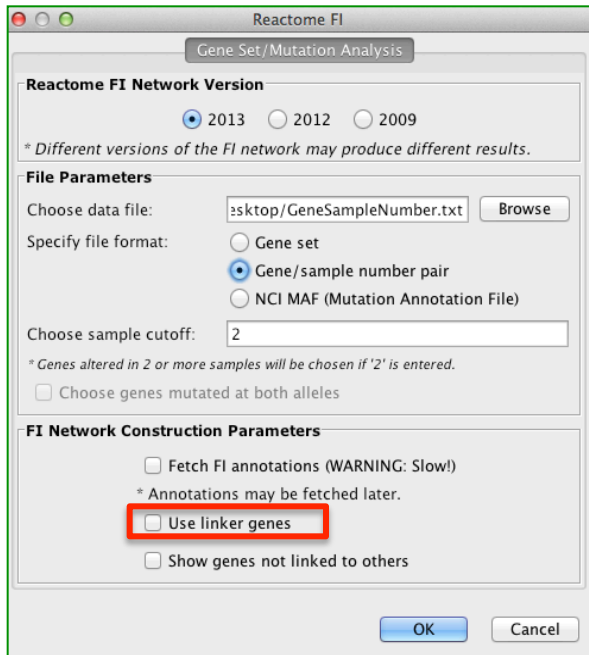
Extract and Cluster,
and Annotate Altered
Genes



Disease “modules” (10-30)

Cytoscape v2.x/v3.x

Using the FI Network - Upload your data



Reactome FI
Gene Set/Mutation Analysis

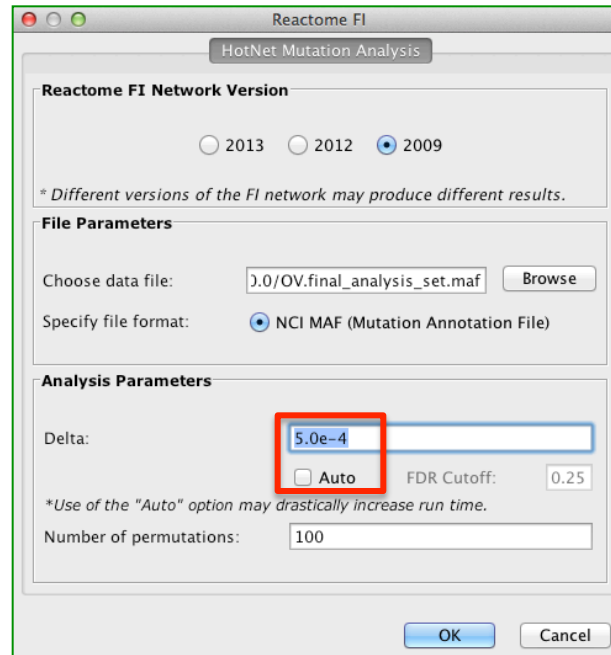
Reactome FI Network Version
☒ 2013 ☐ 2012 ☐ 2009
** Different versions of the FI network may produce different results.*

File Parameters
Choose data file:
Specify file format:
☐ Gene set
☒ Gene/sample number pair
☐ NCI MAF (Mutation Annotation File)
Choose sample cutoff:
** Genes altered in 2 or more samples will be chosen if '2' is entered.*
☐ Choose genes mutated at both alleles

FI Network Construction Parameters
☐ Fetch FI annotations (WARNING: Slow!)
** Annotations may be fetched later.*
☒ Use linker genes
☐ Show genes not linked to others

Gene Set/Mutation Analysis

Use linkers if you have small gene lists.



Reactome FI
HotNet Mutational Analysis

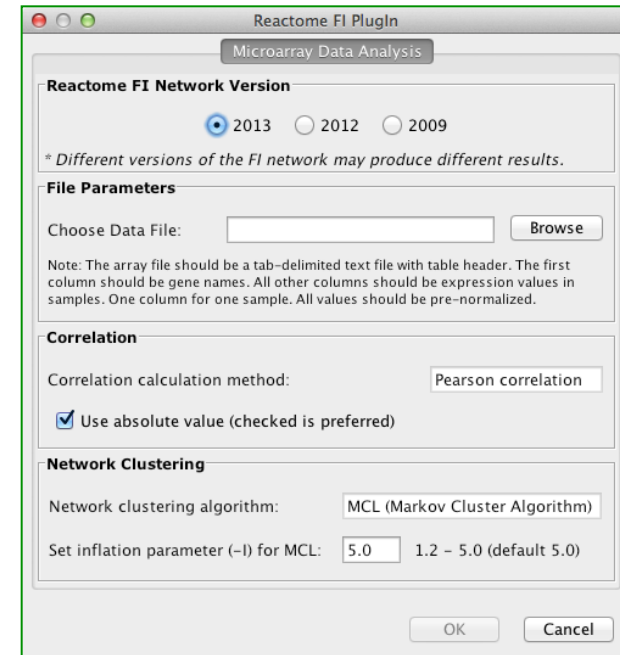
Reactome FI Network Version
☐ 2013 ☐ 2012 ☒ 2009
** Different versions of the FI network may produce different results.*

File Parameters
Choose data file:
Specify file format:
☒ NCI MAF (Mutation Annotation File)

Analysis Parameters
Delta:
☐ Auto FDR Cutoff:
** Use of the "Auto" option may drastically increase run time.*
Number of permutations:

HotNet Mutational Analysis

Select "Auto" if unsure what delta value to use.



Reactome FI Plugin
Microarray Data Analysis

Reactome FI Network Version
☒ 2013 ☐ 2012 ☐ 2009
** Different versions of the FI network may produce different results.*

File Parameters
Choose Data File:
Note: The array file should be a tab-delimited text file with table header. The first column should be gene names. All other columns should be expression values in samples. One column for one sample. All values should be pre-normalized.

Correlation
Correlation calculation method:
☒ Use absolute value (checked is preferred)

Network Clustering
Network clustering algorithm:
Set inflation parameter (-I) for MCL: 1.2 - 5.0 (default 5.0)

Microarray Data Analysis

FI Results Display

- Sub-network is displayed in the Network View panel using an FI specific visual style

The screenshot displays the Reactome FI plugin interface. The main window is titled "Session: New Session" and contains a "Control Panel" on the left and a "Table Panel" at the bottom. The "Control Panel" shows a "Network" tab with a list of networks, including "GWASFuzzyGenes.txt" (82... 96...). The "Table Panel" displays a table of network data for "GWASFuzzyGenes.txt".

The "Network View" panel shows a sub-network with nodes and edges. A context menu is open, showing options for "Add", "Delete", "Edit", "Select", "Group", "Apps", and "Preferences". The "Apps" menu is expanded, showing options for "Reactome FI", "Fetch FI Annotations", "Analyze Network Functions", "Cluster FI Network", "Analyze Module Functions", and "Load Cancer Gene Index".

The "Table Panel" displays a table with the following columns: SUID, selected, comm..., shared..., sampl..., isLinker, samples, nodeT..., name, nodeL..., module, nodeT... The table contains data for nodes 170, 237, 100, 101, 96, and 110.

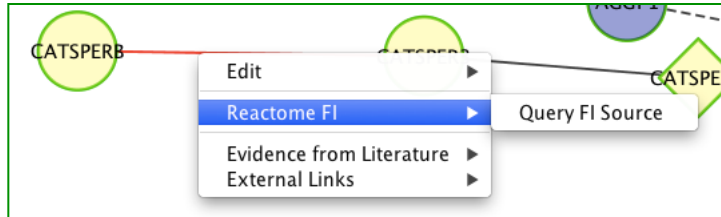
SUID	selected	comm...	shared...	sampl...	isLinker	samples	nodeT...	name	nodeL...	module	nodeT...
170	true	MAGI1	MAGI1		false		MAGI1	MAGI1	MAGI1	Gene	
237	true	SGK2	SGK2		false		SGK2	SGK2	SGK2	Gene	
100	true	ACTN1	ACTN1		false		ACTN1	ACTN1	ACTN1	Gene	
101	true	PTK2B	PTK2B		false		PTK2B	PTK2B	PTK2B	Gene	
96	true	RAF1	RAF1		false		RAF1	RAF1	RAF1	Gene	
110	true	BCAR1	BCAR1		false		BCAR1	BCAR1	BCAR1	Gene	

Memory: OK

The main features of the plug-in are invoked from a popup menu, which can be displayed by right clicking a white space, a node or edge in the the network view panel.

Node and Edge Features

- Query FI Source



Interaction: EGFR - TP53

Reactome Sources

Reactome ID	Type	Data Source
817621	TARGETED_INTERACTION	TRED

Open Reactome Source

Annotated FIs

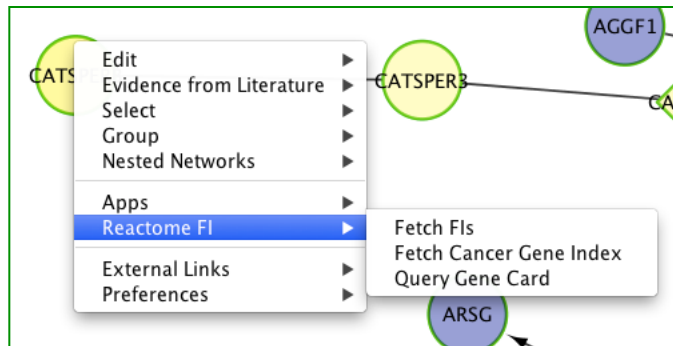
Predicted FIs

Interaction: ATM - ATR

Support Evidence

Predictor	Value
Human Interaction	true
Yeast Interaction	false
Fly Interaction	false
Worm Interaction	false
Geneways Interaction	false
Pavidis Gene Exp	false
Carlos Gene Exp	false
Pfam Domain Interaction	false
GO BP Sharing	true
Score	0.668138487226112

- Fetch FIs for node



FI Partners for ATR

Total FI partners for "ATR": 71

Partners in network: 6

ATM BRCA2 CLASP2 ERBB3 KDR TP53

Partners not in network: 65

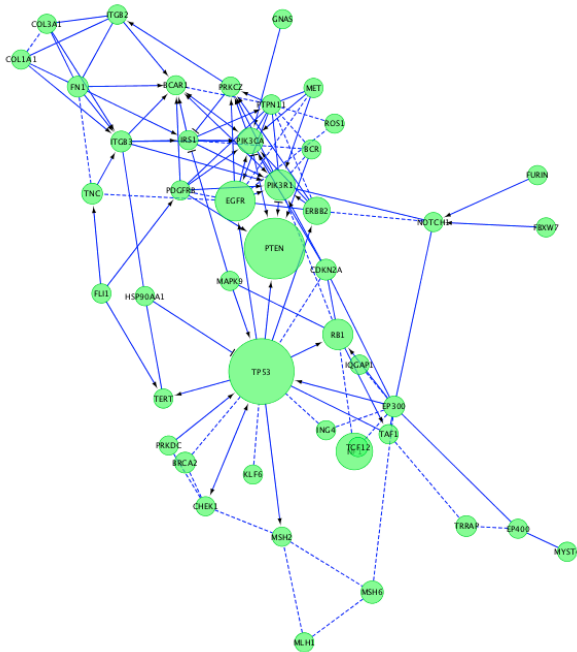
ATRIP	BARD1
BLM	BRCA1
CDC45L	CDC6
CDC7	CDK2

Add selected partner(s) to network

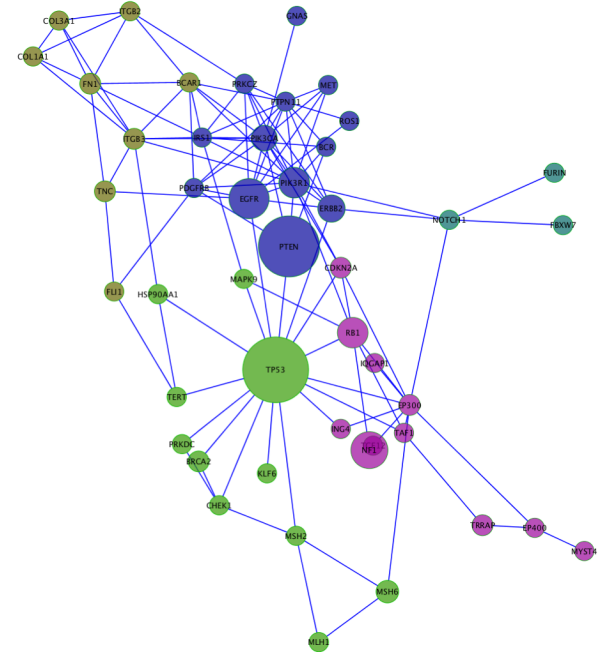
Close

Cluster FI Network

- Runs spectral partition based network clustering ([Newman, 2006](#)) on the displayed FI network.
- Analyze cancer mutation data with HotNet algorithm ([Vandin, 2012](#))
- Apply MCL graph clustering algorithm to networks derived from microarray data ([micans.org/mcl/](#))
- Nodes in different network modules will be shown in different colours (max 15 colours).



Fetch FI Annotations
Analyze Network Functions ▶
Cluster FI Network
Analyze Module Functions ▶
Load Cancer Gene Index



Analyze Module Functions

- Pathway or GO term enrichment analysis on individual network modules.
 - Use filter to remove small network modules
 - Filter by FDR

The screenshot shows a context menu for 'Reactome FI'. The menu items are: Add, Delete, Edit, File, Group, Apps, Reactome FI, Layout, and Select. The 'Reactome FI' item is expanded, showing a sub-menu with: Fetch FI Annotations, Analyze Network Functions, Cluster FI Network, Analyze Module Functions (highlighted), and Load Cancer Gene Index. To the right of this sub-menu is a list of enrichment analysis options: Pathway Enrichment, GO Cell Component, GO Biological Process, GO Molecular Function, and Survival Analysis.

The screenshot shows the 'Data Panel' interface. At the top, there is a checkbox 'Hide nodes in not selected rows' and a filter 'Apply Filters: FDR 0.01'. Below this is a table with columns: Module, GeneSet, RatioOfProteinIn, mModule, and Nodes. The table lists various biological processes and their associated protein ratios and module sizes. A dropdown menu for 'Module Size' is open, showing a list of values from 7 to 15, with '10' selected. The table data is as follows:

Module	GeneSet	RatioOfProteinIn	mModule	Nodes
0	Translation(R)	0.0158		RPL18,RPL17,RPL36...
0	Influenza Life Cycle(R)	0.0249		RPL18,RPL17,RPL36...
0	Ribosome(K)	0.0117		RPL18,RPL17,RPL36...
0	Metabolism of protei...	0.0267		RPL18,RPL17,RPL36...
1	M Phase(R)	0.0128		ITGB3BP,MAD1L1,CC...
1	Aurora B signaling(N)	0.0052		AURKC,AURKB,CDCA...
1	Signaling by Aurora k...	0.0125		AURKC,AURKB,CDCA...
2	Glucose Regulation of...	0.0197	148	NDUFB4,NDUFA2,ND...
2	Parkinson's disease(K)	0.0176	132	NDUFB4,NDUFA2,ND...
2	Alzheimer's disease(K)	0.0223	168	NDUFB4,NDUFA2,ND...
2	Huntington's disease(K)	0.0246	185	NDUFB4,NDUFA2,ND...
2	Oxidative phosphoryl...	0.0178	134	NDUFB4,NDUFA2,ND...
2	Electron Transport C...	0.0101	76	NDUFB4,NDUFA2,ND...
2	Metabolic pathways(K)	0.1489	1120	NDUFB4,NDUFA2,ND...
3	Antigen processing a...	0.0104	78	KLRC2,KIR2DS1,HLA...
3	Immunoregulatory int...	0.0153	115	KIR2DS1,HLA-B,HLA...
3	Natural killer cell me...	0.0182	137	KLRC2,KIR2DS1,HLA...

At the bottom of the panel, there are tabs for: Node Attribute Browser, Edge Attribute Browser, Network Attribute Browser, MCL Module Browser, and Pathways in Modules.

Clustering of TCGA Breast Cancer Mutations

Hugo_Symbol

BAI2
LRRC41
C1orf173
SSX2IP
NTNG1
PGLYRP3
FCRL5
FBXO28
OR2M2
MKX
.....

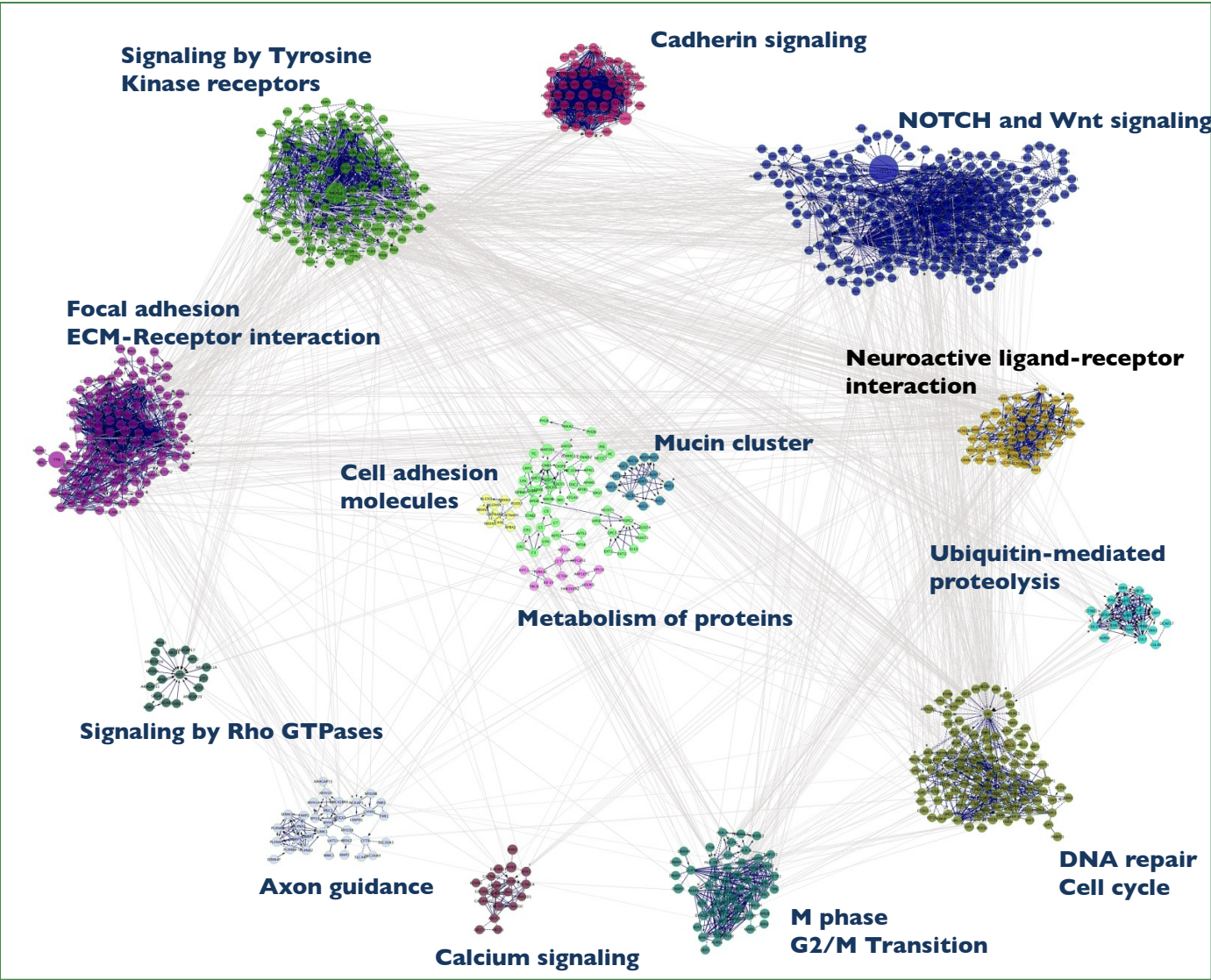
Variant_Classifi

Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Silent
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio
Missense_Mutatio

Matched_No/Match_

TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01
TCGA-04-1331-10A-01

NCI MA



BAM_file	Sequencer
	X
	X
	X
	X
	X
	X
	X
	X
	X
	X

Conclusions

- Reactome is a highly reliable, curated database of biological pathways.
- Web site provides tools and datasets for visualizing pathway data and interpreting your experimental data.
- ReactomeFIViz Cytoscape app provides a powerful way to visualize and analyze cancer and disease data sets.
- All data and software are open to public; no licensing required.

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